DRAFT--February 23, 1999
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PROGRAM OF COUNTERMEASURES TO CHEMICAL/BIOLOGICAL BIOTERRORISM

---TRANS-TEXAS INITIATIVE---

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EXECUTIVE SUMMARY

INTERDISCIPLINARY PROGRAM OF COUNTERMEASURES TO CHEMICAL AND BIOLOGICAL AGENTS
Trans-Texas Initiative

Contributors to the Effort:
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Texas Tech University/Texas Tech University Health Sciences Center (TTU/TTUHSC)
University of Texas-Southwestern Medical School
University of Texas at Austin, TX
University of Texas at Galveston, TX
Department of Justice-South Texas
Texas Department of Health
Emergency Preparedness First Responders-Austin, TX
Institute for Defense Analysis-Alexandria, VA.
The Center for Professional Development and Training (CPDT) at Department of Defense (DoD)

Overview of Statement of Work: The attached document provides descriptions of specific projects and interdisciplinary teams of expertise to provide real solutions to current inadequacies in civilian biodefense capabilities and training.

Purpose: The Purpose of the Trans-Texas initiative is:

- To conduct basic and applied research, education, and training to improve defense to chemical/biological bioterrorism.
- To provide administrative oversight, scientific resources, and a central facility at TIEHH/Reese Center aimed at improving countermeasures to chemical/biological terrorism and training. This facility is envisioned as a *permanent resource for the American public* that will draw expertise from academia, government, military, industry, and the private sector.
- To provide a prototype capability that can be a) implemented in a national threat condition, b) used as a test bed or c) serve as a springboard for other regional or national efforts.

Focus: Drawing from multiple disciplines and pools of expertise, particularly in Texas (universities, government, the public sector), a working infrastructure will be developed for interdisciplinary research and training in countermeasures to CB agents.

Approach: There are four thrust components required:
1) scientific validation of a possible biological/chemical incident (including air/fluid sampling, determination of pathogen virulence factors/pathogenicity islands and signatures, multi-array sensors);
2) physical and medical countermeasures for use on regional/national scale or on small groups of affected persons (c.g. rapid diagnosis, pharmaceuticals, vaccines, triage, quarantine, epidemiology and transport)
3) communication so that appropriate action is taken by authorities with minimal social disorganization;
4) development of an integrated system (integration of sensors into systems; conversion of data to information including data fusion and iconography).

With the above thrusts it will be possible to develop novel education and training with on-site, virtual reality capabilities, distributed information systems (DIS) and advanced distributed systems (ADS), as well as operational needs evaluation.
The components needed for successful response to biological or chemical attack in the continental U.S. or outside the continental U.S. include persons with expertise in the scientific validation of an incident (e.g.

development of tools to capture and concentrate air and liquid samples, rapid multi-array sensors, establishing a relevant data base, data fusion, data presentation); communication (informing appropriate governmental persons, health care persons and the general public about the incident); creation of technologies for the rapid diagnosis of infected people in exposed populations, development of novel compounds that can defeat bacterial, viral and fungal agents; health care and triage related to the care of affected persons using antibiotics, vaccines, medical evacuation including telemedicine capability; developing a system that can integrate the detection and responses in a coordinated manner; developing novel materials and body cover to protect individuals threatened with biological or chemical agents.

Such an integrated team can assist the relevant government agencies in addressing, comprehensively, the challenges of social and response disorganization that might be anticipated during and immediately after a biological/chemical incident. The team can offer an analytical element to appropriate authorities and thereby strengthen the framework of national security.

A trans-Texas team, with expertise in all these areas has been assembled. The team includes researchers at Texas Tech University-Lubbock, the University of Texas-Austin, UT-Southwestern Medical School, Department of Justice-South Texas, Texas Department of Health, Emergency Preparedness First Responders-Austin Texas, the University of Texas -Galveston. In addition the Institute for Defense Analyses (IDA), Alexandria Virginia will also be an active part of the team. The IDA role will be to provide linkage and support to assure that the research conducted within this program maintains a focus on the national security community and the specific challenges addressed. This is a traditional role for IDA, and has been one fulfilled by the Institute since it was founded. The contribution of this group will be: highlighting, focusing and extending research that shows exceptional promise for limiting disorganization and re-establishing structure; for managing the health and casualty impact of terrrorist incidents involving CB agents; and identifying areas which require further investigation. Finally, The Center for Professional Development and Training (CPDT), which has had a role in training at the DoD, will contribute to the education, training, and outreach component of this initiative.
The proposed trans-Texas initiative provides a prototype capability that can be a) implemented in a national threat condition, b) used as a test bed, or c) serve as a springboard for other regional or national efforts.

Budget (2 years):

Total Budget	**$ 40 M**
State/University Contribution	$ 6.5 M
Other	$ 6.5 M
Federal Request for CB Research	$12.0 M
Federal Request for Operations and Training	$15.0 M

Key Points:

- ✔ 60-member interdisciplinary faculty task force initially organized through TIEHH in the summer of 1998
- ✔ Admiral Elmo Zumwalt, Jr. (retired) was briefed on January 25th, 1999 at Texas Tech
- ✔ Trans-Texas team has assembled maximum research and training talent in the region
- ✔ Dr. Steven Kornguth has been acting as mediator with University of Texas campuses, Texas Dept. of Health, and with DARPA
- ✔ TIEHH/Reese Center boasts centralized geographic location, regionally and nationally
- ✔ Year-round operational capability at Reese Center (former airforce pilot-training base) with permanent buildings to facilitate on and off-site education, training, and response capability
- ✔ Modern facilities for toxicological research at The Institute of Environmental and Human Health
- ✔ Integrated University system, including medical and law school
- ✔ Strong track record of interdisciplinary work, with universities, government, military, and community groups
- ✔ Texas Department of Health and community support
- ✔ Secure facility
- ✔ Room for development and expansion
- ✔ State-of-the-art communication capability for medical and training outreach
- ✔ Supercomputer on-site with virtual reality laboratory
- ✔ Accountability in research with experience in quality assurance and Good Laboratory Practice (GLP) studies

PROGRAM OF COUNTERMEASURES TO CHEMICAL/BIOLOGICAL BIOTERRORISM

---TRANS-TEXAS INITIATIVE---

1. The Need:

Developments in the continental US and the international scene have alerted the defense community to the threat of biological and chemical agents on civilian and military populations. Operation Desert Shield and Desert Storm yielded new understanding regarding the effect of a perceived chemical/biological (CB) threat on social and military organization. The events associated with the Aum Shin Rykyo movement in Japan revealed the potential capability of non-nation state terrorist groups to mount a serious threat.

The September 6th issue of the New York Times (article by Judith Miller) reportcd the outcome of a meeting of 200 officials, held in August 1998 in Washington DC. A summary of the group assessment was given to Janet Reno by the Justicc Departmcnt's Office for State and Local Preparedness Support. C. H. Straub of the Department of Justice approved the summary. Justice Officials then met with Richard Clarke, the President's coordinator for anti-terrorism activities. On Friday January 22, 1999, President Clinton addressed the National Academy of Scienees and called for funding a national effort to thwart biological warfare attempts in the continental U.S. (level of funding $1.4 billion dollars). The budget submitted to Congress on February 1, 1999 identified a need for $250 million to support National Guard efforts to develop threat response capability to biological or chemical agents. An organizational structure that effeetively and seamlessly provides coordination among the response agencies (local community first responders, DoJ, FEMA, DoD) was identified for further development.

2. Approach:

To meet the national need, four focus areas will require development and integration:

1) ***scientific validation*** of a possible biological/chemical incident (including air/fluid sampling, determination of pathogen virulence factors/pathogenicity islands and signatures, multi-array sensors);

2) ***physical and medical countermeasures*** for use on a regional/national scale or on small groups of affected persons (e.g. rapid diagnosis, pharmaceuticals, vaccines, triage, quarantine, epidemiology and transport);

3) ***communication*** so that appropriate action is taken by authorities with minimal social disorganization; and,

4) ***integrated system development*** (integration of sensors into systems; conversion of data to information including data fusion and iconography).

With the above thrusts it will be possible to develop novel education and training with on-site, virtual reality capabilities, distributed information systems (DIS) and advanced distributed systems (ADS), as well as operational needs evaluation.

In the event of an actual CB attack, the components needed for a successful response include persons with expertise in the scientific validation of an incident (e.g. development of tools to capture and concentrate air and liquid samples, rapid multi-array sensors, establishing a relevant data base, data fusion, data presentation); communication (informing appropriate governmental persons, health care persons, the media, and the general public about the incident); creation of technologies for the rapid diagnosis of infected people in exposed populations, development of novel compounds that can defeat bacterial, viral and fungal agents; health care and triage related to the care of affected persons using antibiotics, vaccines, medical evacuation including telemedicine capability; developing a system that can integrate the detection and responses in a coordinated manner; developing novel materials and body cover to protect individuals threatened with biological or chemical agents.

It is important to have good cooperation between the civilian and military sector in strengthening the biodefense infrastructure. An integrated team of civilian experts can assist relevant government agencies in minimizing social and response disorganization that might be anticipated during and immediately after a CB incident. They can also offer an analytical element to appropriate authorities and thereby broaden the framework of national security. More importantly, a civilian leadership role in research and training will improve credibility, foster a leadership role for the community, and improve cooperation (and ultimately, outcome) in the event of a catastrophic CB event.

A trans-Texas team, with expertise in all these areas has been assembled. The team includes researchers at Texas Tech University-Lubbock, the University of Texas-Austin, the University of Texas-Southwestern Medical School, the Department of Justice-South Texas, the Texas Department of Health, the Emergency Preparedness First Responders-Austin Texas, and the University of Texas -Galveston. The Department of Defense's Center for Professional Development and Training (CPDT, Dr. Jerry Davis, Director) will provide a valuable resource for developing a regional training program. Finally, the Institute for Defense Analyses (IDA, Alexandria, Virginia) will provide linkage and support to assure that the research conducted within this program maintains a focus on the national security community and the specific challenges addressed. This is a traditional role for IDA, and has been one fulfilled by the Institute since it was founded. The contribution of this group will be:

- highlighting, focusing and extending research which shows exceptional promise for limiting disorganization and re-establishing structure
- managing the health and casualty impact of the CB incident; and
- identifying areas that require further investigation.

The proposed trans-Texas initiative provides a prototype capability that can be a) implemented in a national threat condition, b) used as a test bed or c) serve as a springboard for other regional or national efforts.

3. Deliverables and Timetables

Sensor components:

Sample collectors, multi-array sensor components and pattern array detectors will be ready for technology demonstration at 12-18 months after initiation of funding. The sample collector will be the task of TTU, the multi-array of UT-Austin and the pattern array of UT-Austin.

Integration of the sensor components into a system will be ready for technology demonstration at 18-24 months after funding (UT-Austin).

A database of background levels of selected B agents (e.g. Anthrax, Ebola) will be established within 12-18 months of funding (UT-Austin and TTU).

Identification of key pathogenicity islands for sensor proof of principle will be ready for technology demonstration in 18 months after initial funding (UT-Austin and TTU).

Preparation of unusual immune reactants will be ready for demonstration at 18-24 months (Southwestern Medical Center).

Medical Triage:

Rapid detection of B agents in fluid samples of human or animal subjects will be ready for technology demonstration 18 months after funding begins (TDOH).

Protocols for transporting exposed persons to medical facilities and first responder actions will be ready for demonstration at 18 months after funding (Emergency Response Group-Austin).

Development of antivirals, antibacterials to interdict development of disease after exposure will identify promising new materials for testing in 18 months (Southwest Med Ctr., UW, TTU, and UT-Galveston).

Testing of new materials, body covering and drugs for B agent defense in BL 3, BL 4 facilities will be ready in 24 months (TTU, UT-Galveston).

Testing of physical decontamination equipment in BL 3, BL 4 facilities will be ready in 24 months (TTU, UT-Galveston).

Communications:

Novel protocols for establishing fluid hierarchical command patterns during each time period following a CB event will be ready for testing in 18-24 months (UT-Austin, DoJ, First Responder teams-Austin, TTU).

Strategies for interfacing communications to security, medical triage and the public will be ready for testing in 18-24 months (UT-Austin).

Systems:

Databases for threat agents will be integrated into a model with sensors and platforms to permit rapid assessment of threat situations at 24 months (UT-Austin).

Visual display systems and iconographic models will be ready for technology demonstration in 24 months (UT-Austin)

4. Specific Components of each of the Four Major Thrust Areas

1) Scientific validation:

The time interval between exposure of persons to a biological agent and the development of clinical signs is between 17 hours to 72 hours for many agents of concern. During this critical period, two types of developing technologies will be important to characterize the underlying epidemiology and design rational countermeasures to limit the spread of disease. The first requirement is the development of multi-array sensors and detectors (point and stand-off) that can detect and identify B threat agents rapidly and with high accuracy. Prototype detection devices are comprised of a sample capture device (air/fluid), a microfluidics system, probes that bind B agent material with high affinity and selectivity, and a data fusion display component. The current knowledge base indicates that antigenic, genomic and combinatorial probes can be designed that will yield a highly selective and specific sensing system. Among the targets to be probed are surface antigens on the B agent, and virulence/pathogenicity island factors in the genome. Since most threat agents occur naturally in the world, a database must be developed that will establish threshholds in particular environments. Signals above the threshhold imply a state of danger/concern. The sensors must have sufficient false positive and false negative elements to provide fidelity in the detection and identification task. The systems of greatest utility will detect and identify biological or chemical agent in less than 30 minutes. The sensor/detector systems must be field hardened and able to perform in temperature ranges from –20 to 110 degrees F. The probe must retain functionality when attached to the sensor surface. The data from the detectors/sensors must be fused and presented in a coherent manner, i.e. as information, to a responsible center of action.

The second requirement is for instruments and procedures that allow rapid diagnosis of infected and non-infected individuals in areas of concern. This is critical to effectively contain the infectious transmission and to judiciously use treatment personnel and material. Instruments that can continuously screen thousands of individuals immediately after exposure and formulate a differential diagnosis before the appearance of clinical symptoms will be essential. The diagnostic unit must be small, capable of minimally invasive assessment (using saliva or blood), and able to fingerprint an individual to assess infection-state and the nature of the pathogen.

2) Physical Protection Against B agents and Medical Countermeasures Following Exposure

Appropriate physical and medical countermeasures need to be identified and rapidly implemented after any CB event. Physical management encompasses individual/group protection, interior and exterior decontamination equipment, as well as confinement and barrier methods to reduce the passage of agent. Such physical protection may be in the form of body coverings that bind or otherwise inactivate B agents. Medical management encompasses development of novel vaccines including superantigens, development of compounds that interdict the development of disease after exposure to biological agents, management of traumatic injury and subsequent infection, quarantine and evacuation of affected persons, and telemedicine strategies. Knowledge developed in these areas will be used to develop a logistical

plan of pharmacological countermeasure delivery and use. The delivery of vaccine to combat viral epidemics has been proven to be a critical issue in limiting the development of clinical disease in exposed individuals. Anti-viral and antibacterial materials are currently being developed that may interdict development of clinical disease in persons exposed to biological agents. The ability to extend life from seven days to four weeks after exposure to virulent Ebola virus, for instance, would permit initiation of vaccination after exposure to agent. Effective planning for the storage, release, and delivery of pharmaceutical agents is an essential element of the total response to any CB attack. Research and transition programs directed toward these ends would markedly reduce the threat of biological attack and provide protection. Conventional medical treatment of exposed persons, including long-term medical management, can then be initiated.

a) Physical Management

Physical management will focus on the protection of individuals and the environment after a CB attack has occurred. After any initial exposure, additional medical/early response personnel would be required to deal with surviving populations, persons killed by the event, contaminated equipment and facilities. The worst-case scenario is one in which entry into the primary area of contamination results in lethal exposure of individuals. Using existing and developing technologies, complete protection of response personnel and support equipment will be required to minimize further casualties, and area cleanup will be of critical importance to prevent further contamination/exposure. The three physical management research areas will involve:

- development of individual protection equipment that is suitable for short-term use and is inexpensive. The International Textile Center and the Leather Research Institute at TTU can serve the complementary role of developing novel body coverings that inactivate or deny access to B agents.
- selection and development of appropriate containment and barrier materials/designs to prevent the spread of CB agents.
- identification of optimal combinations of therapeutic drugs, to minimize acute and chronic health effects
- development of technologies (UV radiation, ions, electrons, and temperature) for optimal decontamination/sterilization of contaminated areas, based on known properties of specific CB agents.

b) Medical Management

The primary areas of medical management are the development of:

- novel antiviral, bacterial and fungal compounds that protect exposed individuals from secondary organ infection;
- vaccines and superantigens that can reduce the number of infectious particles in vivo;
- diagnosis and triage strategies to limit further spread of disease during medical care and evacuation; and
- long-term medical management that requires the development of new therapeutic approaches

for individuals that survive an initial exposure.

The knowledge developed in these areas will be used to develop a logistical plan of pharmacological countermeasure delivery and use. The delivery of vaccine to combat viral epidemics has been proven to be a critical issue in limiting the development of clinical disease in exposed individuals. Current anti-viral and antibacterial materials are being developed that may interdict development of clinical disease in persons exposed to biological agents. The ability to extend life from seven days to four weeks after exposure to virulent Ebola virus will permit initiation of vaccination after exposure of persons to agent. Effective planning for the storage, release, and delivery of pharmaceutical agents is thus an essential element of the total response to any CB attack.

The TTU Medical Center at Lubbock, TX can provide a facility to test medical triage strategies. Kathi West, the federal Department of Justice person in South Central Texas, will provide expertise in victim support. The federally funded Emergency First Response team (Fire, Police, EMS) and the Texas Department of Health (TDOH, Dr. Michael Perrotta was a member of the IOM panel report on Chemical and Biological Terrorism) are active participants in this component and will provide rapid validation of the nature of the B agent.

3) Communications

To improve communication, paradigms need to be developed that permit coherent evaluation of incoming data as well as dissemination of the resulting information to at least three groups: a)first responders including police, fire, victims assist persons from DoJ, and health care providers; b)national security forces including FBI, National/Coast Guard, and the DoD; and c)the general public (including the media). The information must be coherent, conform to prior training modalities, and be credible.

4) Integrated Systems

This aspect of the project addresses the capability to collect data from either local or dispersed sensor arrays and then processing this data in timely and accurate ways to produce useful information. A particular capability that may apply to the emergency preparedness area is the ability resident in a well-developed Fire support Automated Test System to provide simulation and stimulation for absent units. This capability facilitates the stress testing of distributed command and control systems without the expense of extensive field deployment of actual units. It may be a very good candidate for doing proof of concept testing for distributed biological and chemical sensor arrays. The integrated systems approach determines steady state levels of materials in the environment that behave as agents from the perspective of the sensor. A critical component is identification of the background noise level. It addresses the incorporation of a sensor suite (multi-array) into a functional system that may convert data to information. It includes the iconographic display of threat situations in a manner that is coherent to a field commander or civilian leader. The operational requirements of the TADMUS program are relevant to the need for an integrated system.

The development and implementation of mathematical, statistical, and computer models are integral to all aspects of this Trans-Texas initiative. Attempts to predict possible CB scenarios without strong modeling technologies places too much reliance on expensive, time-consuming large-scale testing. A simulated CB event unfolding at exact real time speed, on the other hand, will be useful for visualization and training key personnel in advance of a threat. Such real-time modeling will make use of available virtual reality technology. Models enable the evaluation of many different contingencies during an actual crisis, based on different planning and decision making strategies, and given different values of unknown parameters (CB agents and their concentrations, wind shifts, population movements, etc.)

State-of-the art models are invaluable tools for decision-makers and strategists to predict quickly:

- whether a CB threat actually exists and, if so,
- what populations are at risk
- the level of risk
- when the initial casualties occur
- how long the risk persists
- how it spreads, and
- how the risk is mitigated.

Models are also necessary to determine where and how countermeasures should be most effectively deployed and which countermeasures will be most appropriate in a given scenario.

In order to effectively detect, contain, and/or counteract the use of chemical/biological weapons, expertise and resources will be pooled to develop, improve, and integrate four categories of models:

- Models of the physical environment (dispersion models and meteorological models) to predict the spread and fate of agents in the air, water, and/or soil, in a variety of systems (rural to urban; large-scale and small-scale) and under a variety of environmental conditions;
- Toxicological models to predict the expected spread of agents through the food chain, and predict toxicity in humans, domestic animals, wildlife, and plants;
- Physiological models to predict how an agent enters, moves, is stored, and is excreted by various organisms; and
- Epidemiological models to understand and predict the course of morbidity and mortality in populations under various conditions. These models are important tools for determining whether CB events are natural or criminal in nature.

Education and Training

As emphasized in a recent conference (Medical and Health Care Response to Bioterrorism, February 16 -17, 1999, in Crystal City, VA), there is a critical need for properly educated and trained personnel to prepare for and respond to a potential bioterrorist attack. This training will be strongly influenced by the technological approaches taken in the above four thrust areas.

Initially, the development of training scenarios and modules will be based on past real-life accidents/disasters. However, increasingly, there will be reliance on the intelligence community to prepare for future scenarios. The training component will focus on the following areas:

- detection (early problem-recognition, prompt diagnosis, timely coordination with necessary "outside" support);
- case or site investigation techniques;
- appropriate triage techniques;
- safety and protective mechanisms training;
- physical containment and remediation;
- medical management (public health/preventive medical intervention);
- strategic planning (including leadership, logic and decision-making);
- standard operating procedures and emergency plan development;
- public and community preparedness training; and
- psychological support techniques.

Detailed Description of Proposed Efforts

The proposed program focuses on designing effective civilian countermeasures for biowarfare and bioterrorist attacks. The Institute for Environmental and Human Health (TIEHH) at Texas Tech University (TTU/TTUHSC)-Lubbock, the University of Texas-Austin (UT), the University of Texas-Southwestern Medical School-Dallas, and the University of Texas–Galveston bring complementary expertise to this task. TTU has excellence in epidemiological and toxicological research, medical research, optical detection and electrophoretic separation technologies, textile research and basic mechanisms in infectious diseases. The Institute of Environmental and Human Health (TIEHH), recently established at TTU/TTUHSC, has leading technology in information display systems for rapid-time modeling and risk assessment capabilities. To meet regional/national demands, unique resources and infrastructure exist at Reese Center (formerly Reese Air Force Base) for on-site and virtual reality training. The UT has excellence in communications systems and research, sensor technology, public policy, and pathogenicity factors. Moreover, UT-Galveston has recently received funding approval for a BSL-4 laboratory, which will be invaluable for testing and validation of novel countermeasures. The UT has excellence and extensive funding in systems applications for defense needs (Advanced Research Laboratory) and has an element of the Army War College (Institute of Applied Technology). Both of the latter elements have secure facilities. UTSW contributes expertise in developing platform technologies for detection and diagnosis of pathogens as well as a track record in developing new approaches to prophylactic and therapeutic vaccines and other immuno-modulatory techniques. The proposed efforts for each of the identified four thrust areas are described below, and parsed by University and IDA task.

1. Scientific validation of biological/chemical incidents (sampling strategies and sensors)

B agent molecules that may serve as probe targets: The detection of biological threat agents is dependent upon recognition of specific genomic, antigenic and other chemical characteristics of the threat agent. An understanding of specific molecular domains of the biological agent most suited for probe analyses follows understanding of specific epitopes on the organism, genomic features including virulance factors and pathogenicity islands, and high affinity binding molecules present on the organism.

TIEHH/TTU/TTUHSC Contribution--Lubbock

Human populations, livestock and staple plants represent the primary target of a bioterrorist attack. The food chain is one of the primary pathways for contamination leading to elimination of crops and livestock and local or global food shortages. In order to develop and validate working models of environmental contamination, laboratory-controlled studies will be required to measure agent- and dose-specific effects in plants and animals. In this effort, TIEHH has organized a team of biologists, environmental scientists, chemists, toxicologists, engineers, medical researchers, epidemiologists, mathematicians and statisticians that will serve as a ready resource for understanding the nature and spread of infectious and/or toxic agents.

Initially, this understanding will focus on agents listed in the Australia Group List (AG list) that

are currently considered plausible for strategic and tactical military operations. Included in this group are chimeric agents (e.g., agents developed by genetic engineering techniques) that have the potential to evade detection and prevent countermeasures while retaining or enhancing toxicological potency. These agents will increase in plausibility for bioterrorist use; it has already proven possible to express toxin genes from pathogens, *Vibrio cholerae* and *Pseudomonas aeruginosa*, in innocuous strains of *Escherichia coli*. Equally sinister strategies can be easily envisioned. Therefore, one avenue of research will be directed toward determining which chimeric agents present a signficant threat and develop probes for these agents. Bioterrorism targeted at the environment will not to be overlooked in this analysis. Plant genetic engineers in the new state-of-the-art Plant Stress Laboratory at TTU (Dept of Agriculture collaboration) will consider possible bioterrorist agents targeted at food or other economic crops.

UT Contribution

The Payne laboratory is interested in the genetics and physiology of bacterial pathogens. In particular, they are interested in the factors associated with emergence of gram negative pathogens such as *Vibrio cholerae* and *Escherichia coli* O157:H7. Factors that distinguish these pathogens from closely related, but non-pathogenic, strains include production of toxins, synthesis of invasins and colonization factors, and expression of high-affinity iron transport systems. Genes encoding these virulence factors are almost exclusively encoded on extrachromosomal or potentially transmissible elements such as plasmids, bacteriophages, transposons or pathogenicity islands. This suggests that rapid identification of emerging infectious agents may depend more upon identification of specific virulence determinants than upon identification of a bacterial species.

Recently, two high-affinity iron transport systems were characterized in *Shigella* and pathogenic *E. coli*. These systems allow the bacteria to grow in the iron-restricted environment of the mammalian host. One of these encodes a receptor and associated transport proteins for the use of heme as an iron source. The other system consists of biosynthetic enzymes for production of a secreted, high-affinty iron chelator (siderophore) and the cognate receptor and transport proteins. The heme transport genes are found in a pathogenicity island-like locus that is present in many pathogenic *E. coli* and *Shigella* but absent from non-pathogenic strains. The siderophore genes were mapped to a distinct pathogenicity island in *Shigella* and some *E. coli*; in other *E. coli* strains, these genes are plasmid encoded. Acquisition of these and other pathogenicity determinants by a relatively non-pathogenic strain could lead to the emergence of significant new pathogens.

In characterizing these systems, the research team has developed a series of DNA probes to detect these loci. Examining a large number of bacterial strains for the presence of these and other virulence factors provides information on the evolution and acquisition of these genes and provides a basis for design of sensors, countermeasures, epidemiological searches and training as discussed below.

Air/Fluid Sample Capture Systems: The systems to be developed for technology demonstration include air/fluid sampling systems to concentrate any B agents in a volume, a processing

component to release chemical, antigenic or genomic signatures of B agent, a platform to interface sensing elements with released material and finally a transducing system that provides a signal that B agent has been detected. The platform incorporates sensor elements, micro-fluidics and either optical or electrical systems for processing event recording. The systems incorporate all these components with a data fusion and display system that may be remote from the sensor.

TIEHH/TTU/TTUHSC Contribution--Lubbock

Purnendu Dasgupta and his group (TIEHH/TTU) have expertise in the design of sample capture and fluorescence sensing devices. Cyclonic samplers with additional water spray or supersaturated vapor introduction will be designed to collect highly efficient, high volume aerosol samplers that will collect biologicals or chemicals present in the aerosol form in the atmosphere. The effluent from these samplers will contain the original aerosols in a dissolved or suspended form and will be passed through bundles of recently developed capillary liquid core waveguides (LCW) that are coated internally with fluorogenic immunoagents developed by UT. Clusters of such tubes, each specific for a different pathogen are staggered around a central tubular light source. The emission from any positive reaction is guided by the LCW to a terminal optical fiber and the bundle of fibers then are addressed by a detector. For lower-cost rapid yes/no responses, a miniature photo multiplier tube detector is used while a CCD array (see below) is used for antigen specific detection. The transverse illumination of the liquid core waveguide results in overwhelming rejection of the excitation light while the fluorescence emission propagates without loss. This provides highly sensitive fluorescence detection in a very simple configuration.

In a parallel and complementary effort, the effluent from the sampler will be subjected to free zone electrophoresis. Recent evidence indicates that conditions can be arranged to permit whole cells to be separated this way and identified on a preliminary basis based on the charge/mass ratio, functioning in essence as a liquid phase time-of-flight mass spectrometer in a compact miniature package. Detection will be accomplished by laser-induced fluorescence of tryptophan and other fluorescent moieties native to cells and also possibly by in-situ fluorescence tagging. We anticipate close cooperation with UT immunosensing endeavors in both of these efforts.

Sensor design

UT contribution

The Brent Iverson and George Georgiou group has expertise in immunodetection systems and protein engineering. This group, currently funded by DARPA, is focused on creating a set of complementary approaches to protein engineering, thereby providing a means of changing dramatically the specificity and increasing the affinity of antibodies. Emphasis has been placed on high throughput and automation.

The first approach attacks the problem of antibody design in a linear fashion: a large set of mutant antibodies having single amino acid substitutions in residues critical for antigen recognition are generated by employing a high throughput *in vitro* mutagenesis protein synthesis methodology. The effect of each amino acid substitution in binding is determined quantitatively, thus giving rise to a very extensive database of how amino acid replacements modulate affinity and fine specificity. Because the entire procedure is based on simple pipetting, the technique is

currently being adapted to automation using a robotic workstation. This approach is particularly useful for modulating antibody specificity.

The second approach uses a more exponential strategy in which large antibody libraries involving multiple mutations per antibody protein are generated and expressed on the surface of *E. coli* bacteria. These libraries are incubated first with a fluorescent-labeled hapten or antigen, and then with any bacteria. Those cells expressing antibodies that bind the labeled hapten or antigen are isolated in a high throughput and quantitative manner using fluorescence activated cell sorting (FACS). This latter approach is effective for obtaining affinity improvements even for antibodies that already have a high affinity.

Finally, the group has shown that combining the best multiple mutants isolated in independent library screens can work in an additive way to generate extremely high affinity hybrid mutant antibodies. These patented technologies can make antibodies better than those found in nature, and this will improve the performance of any device that uses antibodies for detection. In related work, our molecular biology tools are also being applied to create antibody fragments that are modified in such a way that fluorescent detection is greatly enhanced.

A separate component involves the synthesis of intermediate size molecules, having a molecular weight between small organics and proteins. The issue being addressed is folding; new folding molecular scaffolds are needed to develop effective combinatorial libraries. Except for the rare cases where target proteins already possess a peptide-binding site, flexible peptides will not be able to provide high affinity and specificity. What is needed is a relatively rigid molecular scaffold that is smaller than proteins. The first generation of "aedamers", folding synthetic molecules based on aromatic electronic donor acceptor interactions, has been synthesized in the Iverson/Georgiou laboratory. These were the first reported class of large (large by organic chemistry standards, tiny by protein standards), abiotic folding molecules. This work complements the antibody work in preparation or developing a library of aedamers to determine specific binding to identifiable biological targets.

The Anslyn group will use synthetic chemistry, including combinatorial chemical syntheses to create libraries of unnatural biopolymers. They developed a variety of alternative solid-state oligomer preparation methods using building blocks made of peptides, and two unnatural oligomers: thiourea- and guanidinium-based. These chemical linkages are readily adapted to the most common method for the development of chemical libraries, known as split synthesis, in which the compounds are assembled in a stepwise manner using a bead or resin particle. The method involves the sequential addition of monomers to each bead, but the order of addition is completely random. New building blocks (monomers) are added and the process is continued until the desired library has been created. Such libraries are characterized by "one bead, one compound". Even a relatively short sequence can lead to the creation of a chemically diverse set of compounds that are localized at the surfaces of the polymer beads. For example, ten synthetic steps using the three monomers yields 3^{10} or 59,049 different bead types. Each single bead to be used in these sensing strategies will have its own distinct recognition specificity, independent and different than all its neighbors. It has been shown that this approach will create receptors and sensors for surface saccharides and proteins on bacteria and viruses, as well as medium/small molecule such as toxins.

A large number of chemical/biological agents of interest to the military and civilian communities will be sensed by the described array sensors including both small and medium size molecules.

In order to sense, identify, and quantify the presence of various bacteria and viruses using the proposed micro-machined sensor, two strategies will be explored. First, small molecule recognition and detection will be exploited. Since each bacteria and virus possesses a unique and distinctive concentration of the various cellular molecules: DNA, proteins, metabolites, and sugars, the fingerprint of each organism is expected to be unique. Hence, the "flotsam and jetsam" from whole bacteria/viruses will be exploited for such analyses.

The DNA in the bacteria "flotsam and jetsam" is one of the least complicated components to analyze. The Anslyn group will attach DNA to the resin beads. These oligonucleotides can either be targeted to specific bacteria whose genome is known by making strands complementary to the known bacteria DNA sequences. However, probably more powerful is the use of oligonucleotide libraries. Libraries can be used to target pathogens that have not been thoroughly characterized or new bioengineered pathogens whose genomes are not known. Each recognition DNA strand will be terminated with biotin using standard methods. The biotin will be used for facile assembly of the nucleotide strand to a bead coated with avidin. The signaling strategy will rely upon the dye method developed by the research group. A dye will be attached that is sensitive to the local pH or dielectric constants of the interior of the bead. Several dyes that are pH and solvent sensitive can be purchased with biotin already attached. Self-assembly of the dyes to a bead coated with avidin leads to a "taste bud" loaded both with the oligonucleotide receptor and a signaling moiety.

The detection of viruses, bacteria, and biological macromolecules is challenging since the concentrations of these target species are often in the subnanomolar range. The targets are frequently labile, and analytes are present against a background of numerous interferants. Hence, there is a need for exceptionally strong binding between receptors and their analytes. The individual binding constants between one receptor and one surface saccharide or protein can reasonably be expected to be on the order of 10^5 M^{-1} or higher. However, it is anticipated that the new beads will possess on the order of 10^4 receptors on their surfaces. In turn, the virus coats have several to hundreds of their specific coat-proteins displayed, and bacteria similarly display large numbers of their surface saccharides. Since binding constants are multiplicative, the interaction of two or more bead-based receptors with two or more surface-entities will likely result in binding constants of 10^{10} M^{-1}, and even higher with larger numbers of interactions. Essentially, beads will be developed that display cell adhesion properties toward both bacteria and viruses.

It should be emphasized that although some beads may be purposefully designed to bind certain pathogens, most structures will possess nonspecific functional groups so that they can be trained to recognize unknown bioengineered pathogens. Like the human tongue, the "fingerprint" response evoked from the simultaneous interactions occurring at multiple sites will be used to identify the species present in the unknown samples. Pattern recognition routines will be exploited to deconvolute contributions from the various contributing species.

One of the features associated with the proposed sensor array is the capacity to standardize each sensor suite via exposure to various analytes/pathogens followed by storage of the patterns. Therefore, there is no need to know the identity of the actual chemical structure on each resin bead. Only the characteristic pattern for each sensor array is important. In fact, it is likely that for many applications it will be less time consuming to place the various beads into their

respective holders without taking precautions to characterize the location and chemical sequence of the taste bud elements. Each sensor array will require standardization for this type of application. On-site calibration for new or unknown toxins is possible with this type of array.

The Micromachined Platform: One of the critical issues for the practical application of microelectronic fabrication techniques to microsensors is the scale limitation (in all three dimensions) for both minimum and maximum feature sizes. For the chemical/biological agent sensor arrays proposed here, the need for structures with significant size in the third dimension is acute. The beads used for synthesis are typically 50 - 100 microns in diameter, and may actually change size (e.g., swell or shrink) when the chemical environment changes. The beads are polystyrene-polyethylene glycol (PS-PEG) microspheres that are covalently derivatized with a variety of strategically chosen chemical indicator (i.e. "reporter") molecules. The choice of a PS-PEG matrix is based on its wettability by aqueous solutions and the availability of well developed literature methods for its derivatization. Unlike prior fiber optic analysis of remotely acquired optical information, (i.e. fluorescence and reflected light) which require elaborate optical filtration schemes, direct determination of changes in the absorption and emission properties provides the ability to make parallel analyses for analyte determination and quantification.

To analyze these changes the UT research team is fabricating "micro test-tubes" using a combination of bulk and surface micromachining to provide the necessary confinement for the sensing beads. A conventional bulk micromachining step is used to form a pyramidal pit in a silicon substrate, sized to allow a sensing bead to rest inside it, and a transparent cover plate placed on top to keep the bead in place. Illumination can then be applied to one side, while a photodetector is placed on the other. Light originating from the bottom side of the silicon wafer passes through the colored bead and provides the illumination source to visualize the bead structure. The etched substrate and bead combination provides an assembly whose optical properties are well matched for spectral analyses.

The fabrication of micromachined "test-tubes" will allow immobilization of the sensing beads, and provide optical access, proper illumination, wavelength filtering, and optical detection. For optical detection, one possible approach would be to place the micromachined bead array directly over a commercially available CCD array. This hybrid assembly would be relatively simple, while allowing separate optimization of the analyte sensing and photodetection sections of the system. It should also be possible to directly integrate both simple polysilicon-based photodetectors and optical filters into the bottom membrane of the micromachined wells. Here it will be necessary to carefully consider the various performance trade-offs between monolithic and hybrid assemblies. The interface to microfluidic components is also possible, producing a complete sampling/sensing system.

Recent advances in the development of efficient and inexpensive charge-coupled devices (CCD) made the choice of such array detectors for optical sensing applications quite appropriate (Borman, S.; "Array Detectors are Transforming Optical Spectroscopy", Chemical and Engineering News, March 18, 1996 pages 33-34). Indeed, the commercialization of a number of products that use charge-coupled devices (CCDs) as the active optical sensors (video cameras, laser printers, electronic cameras and a variety of scientific instruments) bodes well for their use in this particular application. Furthermore, CCD detectors have begun to transform the field of

optical spectroscopy and optical imaging applications. These systems have been produced with excellent spatial resolution, ultra-high sensitivity and large dynamic ranges. For example, CCDs have the capacity to detect gray scales of one part in 256,000, compared with one part in 256 for the human eye. Consequently, one can go outside at noon and use a CCD camera, which is focused at infinity in blue sky, and visualize the stars! Furthermore, the high sensitivity characteristics of scientific CCD's have allowed researchers to study the fluorescence behavior of single molecules.

The Adam Heller group (UT) has well recognized expertise in amperometric enzyme microelectrodes and microflow systems. Biochemical events are directly transduced in these systems to electrical currents. Consequently, the devices are much smaller and sensitive than those offered by competitors. The enabling technology is that of non-oxygen consuming gold or carbon enzyme microelectrodes, some as small as 10 micrometers in diameter, made without leachable electron transporting mediators. Because these microelectrodes have no leachable components, they are suitable for use in microfluidic channels with fast flow. They were designed for fabrication into arrays. The research team also has capabilities in ruggedized thermostable systems. This technology could prove particularly valuable for (a) thermally stabilized detectors, of particular relevance to nerve gas detection (i.e. detection of acetylcholine esterase inhibitors). Though such detectors are known and in use, this particular detector will not need to be stored or shipped refrigerated and could be easily "ruggedized". (b) rapid separationless validation of nanoliter quantities of PCR-amplified DNA necessary for the detection of biological warfare agents. Validation, rather than amplification, can define the time to the delivery of confirmed information. Amplification on a chip in less than 2 min has been recently reported by others, but the reported validation methods still involve slower electrophoretic separation followed by photon based detection. The proposed amperometric method is separationless, allowing validation in a microfluidic channel in less than 1 min using 1 nL of the PCR product solution. (c) Direct amperometric detection of a single mutation in as few as 40,000 copies of 18 basepair and larger oligonucleotides through enzyme-amplified amperometric measurement of the hybridization temperature.

The Advanced Research Laboratory at UT (ARL:UT) is a Navy sponsored University Affiliated Research Center (UARC) that has maintained a special relationship with DoD for over 50 years. This group has developed active and passive sensors in the following areas:

- Acoustic-- single element and arrays of sensors in the frequency band from approximately 50 HZ to several 100 KHZ.
- Seismic-- P, S and interface (Rayleigh, etc.) wave detection capability.
- Electromagnetic-- a wide variety of rf, millimeter and microwave sensors for both terrestrial and space based applications

The ARL has top secret facility clearance capability with the capability to manage special access programs. The ARL: UT has extensive fabrication capabilities and routinely develops and integrates large-scale systems.

ARL: UT has extensive capability to collect data from either local or dispersed sensor arrays and then process this data in efficient ways to produce information. These capabilities reinforce many important areas of research and represent a premier technical capability at ARL: UT. A particular capability that may apply to the emergency preparedness area is the ability resident in

the Fire support Automated Test System to provide simulation and stimulation for absent units. This capability facilitates the stress testing of distributed command and control systems without the expense of extensive field deployment of actual units. It may be a very good candidate for doing proof of concept testing for distributed biological and chemical sensor arrays.

Intelligent Sensors: Systems requiring large numbers of complex sensors distributed over a geographic area generally require intelligent sensors to be practical. Otherwise, these complex sensors will consume excessive communications resources to deliver the raw data to the analysis site plus will provide overwhelming quantities of data for the available number of human analysts. Signal Physics Laboratory has extensive experience developing intelligent sensors. The function of intelligent sensors is to autonomously acquire data and then intelligently analyze the data to perform functions such as detection and classification. In the case of biological warfare, the detection function might constitute the recognition that a pathogen of interest is present at levels above acceptable levels and the classification might identify which of several possible pathogens is present. Intelligent sensors always operate in the presence of confounding information, such as naturally occurring pathogens. To be most effective, these sensors need information about normally occurring backgrounds. These naturally occurring backgrounds are generally complex. In the case of pathogens, the backgrounds may vary with parameters such as geography, season, and atmospheric conditions among others. Further, simple metrics such as mean levels may provide insufficient characterizations of the background environment for use by intelligent sensors.

Signal Physics Laboratory (SPL) has extensive experience acquiring and analyzing background data to provide baseline information to support the design of intelligent sensors. SPL's resources include experimentalists experienced in acquiring baseline data sets, analysts familiar with characterizing complex data sets, and resources such as analysis software for handling and manipulating extensive data sets.

MultiSource Information Fusion: Systems employing large numbers of distributed sensors can overwhelm the decision maker(s), even when the individual sensors are intelligent and provide only the minimum amount of information needed from the individual sensor. This problem is only exacerbated in dynamic scenarios when decisions are time critical. Signal Physics Laboratory has experience and expertise at assimilating diverse information from distributed, frequently dissimilar sensors, and deriving information (vice data) necessary for decision-makers and performing these functions in time critical scenarios.

Pathogen Agglomeration: Many pathogens have dimenions of 1-10 microns. Particles in this size range are difficult to capture or contain by many conventional methodologies, and yet pose the greatest threat for inhalation exposure. One of the concepts for dealing with pathogens includes introducing agents that agglomerate the pathogens to larger dimensions, simplifying their containment by standard means. Signal Physics Laboratory is currently working to develop the technology to reduce airborne emissions from coal fired power plants through the application of acoustic agglomeration. In the case of coal fired power plants, particulates of the 1 to 10 micron dimension are of concern. They constitute a health threat and yet are difficult to control

by conventional means, such as electrostatic precipitators and bag houses. At this point of time, there seems little doubt that acoustic agglomeration is technically feasible for the reduction of airborne emissions from coal fired power plants. The technology could be adapted to increase the sensitivity of pathogen detection, or alternatively, as a simple means of containment.

TIEHH/TTU/TTUHSC Contribution--Lubbock

Rapid Detection of Air-borne Mycotoxins: The David Straus group (TIEHH/TTUHSC) has an interest in the rapid detection of mycotoxins. There are a significant number of small toxins produced by fungal growths, with molecular weights in the range of approximately 500 Daltons, which are known or anticipated to be available for use in biological warfare theatres or terrorist scenarios. Indeed, it is thought tricothecine mycotoxins (yellow rain) have already been used in Southeast Asia and Afghanistan. These toxins can be grown with relative ease and can therefore pose an enormous public health threat via airborne transport upon their atmospheric release. For example, *Aspergillus* species have been shown to produce mycotoxins (aflatoxins) that can cause liver cancer in experimental animals. At the present time, methods are not sensitive enough to detect these small mycotoxins rapidly in the air. The goal of their group is to demonstrate the viability and capability of existing advanced technology instruments as practical air monitoring techniques(s) and/or system(s) for obtaining instantaneous, peak, and cumulative concentration data for rapid detection of specific airborne mycotoxins.

The group will experimentally use high-speed Fourier Transform Infrared Spectroscopy (FTIR) as the primary advanced technology instrument to be evaluated. In FTIR, infrared radiation is passed through an interferometer (optical mirror system) and a gas sampling cell which produces a frequency interference spectra of which each segregated spectrum is representative of an elemental or molecular compound which partially comprises the composite mixture. FTIR technology already exists to detect low concentrations of gases in the air. Mass Spectrometry (MS) will be utilized as the secondary advanced technology instrument, for validation and certification, in order to determine the principal viability and capability of FTIR for the following purposeful objectives:

- energetic characterization or spectral fingerprinting of certain specific mycotoxins;
- on-line detection and concentration assessment of characterized specific mycotoxins, in sole airborne contaminant releases (sensitivity and accuracy); and,
- on-line detection, speciation, and concentration assessment of characterized specific mycotoxins in airborne mixtures of known and anticipated chemical constituents and/or other characterized specific mycotoxins (sensitivity and accuracy).

Currently, both FTIR and MS, under controlled conditions, are being effectively utilized in the detection of very low concentrations of bad actor, spectrally-characterized volatile chemical compounds and atmospheric gases, for the purposes of early warning in chemical release situation in US chemical operations and semiconductor cleanroom wafer fabrication operations. However, there are virutally no available published data regarding the spectral identification of mycotoxins, proteins, enzymes, etc., and, there are virtually no available published data regarding the use of either FTIR or MS technology in the detection of airborne concentrations of mycotoxins.

FTIR technology was selected as the primary advanced technology instrument for evaluation because of its prior demonstrated accuracy, utilization history for volatile organic and inorganic compounds, suitability for extractive and non-extractive applications, and potential for robust construction. The development of this technology will allow us to detect, in a rapid manner, the presence of airborne fungal toxins which will allow the authorities to take appropriate and timely action.

Field Deployable Systems: The Molecular Toxicology Section at TIEHH/TTU/TTUHSC, led by Richard Dickerson, has identified the need to rapidly determine exposure to and identify biological agents as a result of warfare or terrorist attacks. Present methodology that results in accurate identification is either too slow or too insensitive to be used in emergency situations. Many of the techniques that are rapid lack the ability to discern specific agents which does not allow effective treatment.

This need may be fulfilled by an automatic semi-continuous western blotting apparatus. The totally self-contained device would weigh less than 10 lbs. and occupy less than 0.25 ft^3. It would have the capacity to sample ambient air, identify viral and bacterial agents, and notify the non-skilled operator in 15 minutes of the presence of an agent. Moreover, such devices could be equipped with a miniaturized transmitter and placed along the front of a military advance or near suspected civilian targets of bioterrorism. The technical and design criteria of such a device are described below.

For airborne biological agents such as anthrax, research suggests that as few as 100 spores are sufficient to produce clinical disease. Such a dose must be administered over a short period of time since gradual exposure allows clearance by phagocytic cells in the lung and airways. The resting minute volume is 6 L/min and the alveolar ventilation is 4.2 L/min. This rate may dramatically increase during prolonged exertion or battlefield stress. Under such situation, the minute volume may reach 125-170 L/min. Settling of virus particles or spores is reduced in such situations due to the increased velocity of air in the alveoli. In these conditions, it is not unreasonable to expect that an agent concentration of one particle per liter may cause disease and should be used at the minimal detection limit.

The first step in an effective detection system is designing a filter that effectively traps the agent, does not impede airflow, and allows testing directly on the filter. A nitrocellulose or PVDF filter with the correct pore size based on agent size is promising. The expected agents are anthrax, plague, tularemia, brucella, smallpox (variola), Venezuelan equine encephalitis and the viral hemorrhagic fevers such as Ebola, Lassa, and Hanta. Anthrax (*Bacillus anthracis*) occurs as 3-5 μm rods and as 1-μm spores. Plague (*Yersinia pestis*) occurs as gram negative rods in the same size range as anthrax. Tularemia (*Francisella tularensis*) is an aerobic rod that is smaller than anthrax (0.5 μm by 0.2 μm). The viruses range in size from 40 nm (VEE) to 300 nm (smallpox). Thus, an effective filter must trap particles as small as 40 nm (0.04 μm) yet pass sufficient air containing non-biological particles to achieve a reasonable sample size without plugging. The incorporation of a suitably sized prefilter may alleviate potential problems. It is envisioned that the device would contain a sampling port protected by a glass fiber prefilter under which a continuous ribbon of PVDF with 0.03 μm pores will be intermittently transported. Initial design calls for a 3-minute sampling period. The unit will contain a small vacuum pump to draw ambient air through the prefilter and sample ribbon.

The ribbon can be forward approximately 1 cm for subsequent blocking, washing and rinse steps. The sample spot first be exposed to six antibodies; each labeled with a unique fluor. One antibody will be specific for anthrax spores, one for plague cell wall protein, one for tularemia cell wall protein, one for smallpox, one for Venezuelan equine encephalitis, and the last one will be an antibody that we will select to identify *arenaviridae* (Lassa) and *filoviridae* (Marburg, Ebola). With additional fluors at unique emission wavelengths, antibodies that would recognize *hunyaviridae* (Hanta) and brucella could be added.

After rinsing, the last station will consist of a fluorescent diode array detector. Any emitted light beyond background will trigger both audible and visual alarms. The visual alarm will designate which agent was detected while the audible alarm will notify the operator to check the visual.

The apparatus will contain enough ribbon and supplies for seven days of operation before it will need to be reworked. The construction will be resistant to shock to enable the units fitted with radio transmitters to be air dropped.

UTSW Contribution

Researchers at the Center for Biomedical Inventions have developed a new technology for making microarrays, using Digital Optical Chemistry (DOC). Using arrays of tiny mirrors under computer control, chips containing libraries of DNA, peptides or chemicals can be made rapidly and cheaply. They will detect pathogens without specific knowledge about the pathogen biology. Fluorescence, surface plasmon resonance and MALDI-TOF detection technologies are under development. These technological platforms complement those under development at UT-Austin and can integrate both approaches.

Institute for Defense Analyses Contribution

One role of IDA in this effort will transition results of the research effort into items of interest to the military. A second role will be to offer the researchers support based on the IDA corporate knowledge and experience in inserting technologies into military systems. IDA also brings cross-disciplinary expertise in scientific, military operations, policy and organizational matters. IDA brings a background inherent in many attempts to operationalize new concepts into practical devices and procedures. The issues of concern include ruggedness, size, logisitics and compatibility with existing systems including C4ISR.

2. Physical and Medical Countermeasures to Biological Agent Events

A. Physical Countermeasures:

TIEHH/TTU/TTUHSC Contribution--Lubbock

The development and application of mathematical, statistical, and computer models are integral to all aspects of this project. Attempts to predict possible CB scenarios without strong modeling technologies could place too much reliance on expensive, time-consuming large-scale testing; an actual CB incident might not be manageable without real-time and faster modeling efforts. A simulated CB event unfolding at exact real time speed will be very useful for visualization and training key personnel in advance of a threat. Such real-time modeling will make use of virtual

reality technology available at Reese Center (Lubbock, TX) with the capability of using any existing database. Faster than real time speed (rapid) models enable the evaluation of many different contingencies during an actual crisis, based on different planning and decision making strategies, given different values of unknown parameters (CB agents and their concentrations, wind shifts, population movements, etc.)

The models will be developed as specialized modules that can be integrated to provide a complete picture of any bioterrorist event. The modules will be developed and validated on state-of-the-art personal computers or PC networks. However, because of the complexity, it may be necessary in some cases to utilize a supercomputer to run the integrated model. By incorporating data in real time or faster, responsible individuals will have the capability to explore effective response options to a bioterrorist attack. It is unlikely that a bioterrorist event will disrupt communications capability on a national scale; therefore, the centralized modeling facility at the Reese Center can deliver this ability.

TTU has the capability of developing an integrated modeling environment that will be an effective tool for training and for the development of effective countermeasures in the case of a CBW event. Models of dispersion will be developed based on very large-scale computational models. An interdisciplinary group has been formed, drawing expertise from the College of Engineering in the departments of chemical, electrical and industrial engineering, the Institute of Environmental and Human Health (TIEHH), and departments of mathematics and statistics. The models of dispersion and diffusion will provide data that will allow the models at the scale of ecosystems to run and this will provide data for the epidemiological models. However, the epidemiological models will also provide data on demographics and susceptible populations which will be used to fine tune the dispersion models and the ecological/toxicological models. The physiological models will depend on the above models for initialization in order to know at what level chemical or biological agents are reaching the individual. In turn, the physiological models will integrate with the epidemiological models to provide information on morbidity and mortality which are essential parameters for the epidemiological models.

This entire modeling effort is based upon the availability of a wide variety of computational equipment, ranging from clusters of PCs and workstations to a supercomputer at TIEHH/Reese Center. The Virtual Realty Center at TIEHH/Reese Center will be essential for making the immense amount of data available for use. Massive amounts of data are almost impossible to assimilate unless visualization techniques are employed. Therefore, the very latest equipment and software will be available for the field of visualization. Finally, to make this information accessible, a satellite uplink/downlink will provide outreach for training or support during an actual bioterrorist attack.

Models of the physical environment: The Intelligent Distributed Heterogeneous Physiochemical Transport modeling team focuses on rigorous, first principle based solutions to the conservation equations that govern transport phenomena in dispersing and chemically reacting systems. Their objective is to produce accurate, experimentally verifiable solutions for large simulations of chemical and biological agents dispersing and reacting simultaneously in both rural and urban environments. An objective of this work is to use dispersed heterogeneous parallel computing on-site to produce accurate real-time predictions of chemical and biological substance releases. To realize this objective will involve integrating modeling predictions with the boundary conditions provided by on-site monitors and meteorological information. The intent is to perform these large-scale calculations rapidly, and thereby allow use of measurements from on-

site monitoring equipment to provide progressively more accurate predictions in real time.

An important component of the effort would be to carefully check the accuracy of predictions on model systems. This model verification will involve verifying and tuning models with chemical species identification, concentration, and velocity profile information provided by NMR. Additional model verification will include model verification of full-scale dispersion test preformed at Reese Center at Texas Tech University. The sub-team hopes to engage these extremely large, complex problems that require a high degree of precision to make accurate predictions. Additional constraints to be overcome include computational portability and near real-time simulation speeds. This scale and accuracy will be realized through the use of parallel supercomputing combined with real-time optimization of both the computational structure and the solution algorithm. Applied computational intelligence allows for real-time optimization, and distributed, heterogeneous computing using high performance processors will permit better on-site modeling, visualization, and portability.

The visualization sub-team will provide state-of-the-art three-dimensional animations of the dispersal of various chemical and biological agents. The visualizations will include both experimental data and the results of the modeling predictions and represent the best estimates available of the actual physical events. The intent is to provide a level of visualization that is superior to that currently available from numerical modeling post-processing packages and comparable to the quality seen in commercial movie animations. The interactions of the threat dispersal with various sensors and the effects of their placement and distribution will be visualized and used in various training scenarios at the Reese Center visualization facilities at TIEHH/TTU/TTUHSC.

In addition, it is of paramount importance that site commanders and other incident coordinators be able to visualize best estimates of chemical and biological agent dispersion and be assessed of not only the current situation, but also of probable future dispersions of the chemical and biological agents. These dispersion estimates would be visualized in both two and three dimensions on site with overlays of the local urban or rural structure or environment. The information would be constantly updated by integrating model predictions with local measurements from sensors and with the results of more detailed calculations by satellite links to supercomputing centers and would provide the best possible estimates of current and projected dispersions. TTU/TTUHSC would provide the technology to allow these model predictions using portable heterogeneous parallel distributed computing and advance physiochemical transport modeling of the chemical and biological agents and their interactions with the local environment.

Toxicological models: The Toxicological Model development effort (led by Ken Dixon, TIEHH/TTU) includes the development of Physiologically-Based Pharmacokinetic (PBPK) models based upon and to include effects at all levels of the organism with emphasis on agent concentrations reaching specific organs at both the individual and population levels. The Toxicological Model will also include models of uptake and distribution of chemicals/pathogens of concern to predict the dose to small mammal populations feeding upon vegetation. A Geographic Information System (GIS) will be used to map sources of contamination. Sites will be identified for study by overlaying additional data layers, including atmospheric conditions, population density, and other demographic data.

Because the dynamics of real systems are quite complex, understanding the impact of BW

contaminants on the environment can be enhanced by modeling the system. The adverse effects of multiple toxic variables are directly related to their ability to interfere with the normal functioning of both physiological and environmental systems. The proposed research will focus on the prediction of both acute and long-term effects of chemicals and biological agents of concern on agricultural populations as well as human populations. This requires a mechanistic approach to modeling.

For each expected senario time response paramcters will be expressed as functions of dose to obtain biologically-based dose-response (BBDR). In the case of multiple exposures, the concentration x time (CxT) relationships will be examined. Functional relationships will then be examined between correlated endpoints. This modeling approach will allow future simulation of real-world exposure scenarios. The probability of developmental effects, reproduction, and survival will be incorporated into an individual-based model. Monte Carlo simulations will be run to obtain probabilistic forecasts of population dose responses.

Linear and nonlinear regression, using SAS (SAS Institute Inc.), will be used to develop the dose-response model. The individual-based model will be programmed using MATLAB (The MathWorks Inc.) and C^{++}. The spatial data will be mapped using the ARC/INFO (Environmental Systems Research Institute, Inc.) geographic information system language. The computer simulations will be done using the Unified Transport Model (UTM) developed by Oak Ridge National Laboratory. The basic component of the UTM is the Terrestrial Ecology and Hydrology Model (TEHM) with physically-based subroutines for interception, infiltration, soil-plant water flow storm and groundwater flow. The model simulates runoff, infiltration, soil moisture, and ground water transport for pervious and impervious areas, as well as chemical fate and transport on the land surface, into ground waters, into and through streams, and in well mixed ponds and lakes. The model simulates the effects of toxic chemicals, pesticides, and nutrients on water quality.

Epidemiological models: The goal of bioterrorism is to cause a large amount of morbidity or mortality in a short time span and to have the terrorist event remain undetected for as long as possible. Whether the delivery agent of a bioterrorist agent is chemical or biological, if successful, it should either spread rapidly or go undetected for a long period of time. To understand the nature and spread of various biological agents within a population and to reduce the associated risks, epidemiological models will be formulated, analyzed, and simulated. The epidemiological modeling group (led by Linda Allen, TIEHH/TTU) will develop epidemiological models that follow the growth and spread of a biological agent and the progression of disease throughout a population. Epidemiological modeling will be used as an assessment and training tool to help identify the impact of different biological agents on a particular population, to determine the short-term and long-term risks of different agents, and to test the effectiveness of various treatments and countermeasures in responding quickly and alleviating the effects of the bioterrorist attack.

Epidemiological models for the spread of infectious diseases may be applied to human, plant, or animal populations. In the simplest type of epidemiological model, the host population is subdivided into the following categories: susceptible S, exposed E, infective I, and removed or immune R. Hence, these types of epidemiological models are referred to as SEIR models. In more detailed models, other categories are included such as latent or vaccinated individuals or the population may be further subdivided according to age, physical location, or risk group. The movement of the population through each of these categories can be modeled by systems of

difference or differential equations (ordinary or partial differential equations) which account for the temporal and spatial dynamics of the population.

A two-dimensional spatially-discrete epidemic model of the U.S. population will be developed that models the main population centers, flow rates between the centers, and contact rates within the centers. Flow rates between the cities can be modeled using information about public and private transportation. (A similar model but on a much smaller scale was developed to evaluate the impact of a vaccination program for a measles epidemic at Texas Tech University.)

The qualitative behavior of these SEIR-type models (e.g., conditions required for existence of steady states, stability of these steady states, and asymptotic behavior) can be determined through extensive mathematical analyses. However, extensive computer simulations are also required to determine the quantitative behavior of the model, i.e., the effects of specific biological agents and the diseases that they manifest within a population. Efficient numerical computations require knowledge of the initial and boundary conditions and the values of the parameters in the model. Other experts involved in this initiative will provide expertise for the identification and estimation of critical model parameters for specific biological agents. The initial conditions are specified according to where and to what extent the biological agent is introduced (different scenarios will be hypothesized by the detection group). The boundary conditions are specified according to the agents' ability to spread beyond a particular region (different scenarios for spatial spread can also be hypothesized). There are numerous numerical techniques that will efficiently and rapidly solve large systems of difference and differential equations. Through extensive mathematical analyses and numerical simulations, the progression of the disease through time and space, the amount of morbidity or mortality that occurs, and the effectiveness of various treatments and countermeasures can be quickly and easily evaluated.

Epidemiological models help in the evaluation and assessment of a bioterrorist attack on a particular population. However, epidemiological models integrated with models of the environment, toxicological models, and physiological models will help in the evaluation of the effects on the individual, environment, and ecosystem.

Physiological Modeling: The physiological modeling group (Clyde Martin, director, TTU/TIEHH) has expertise in the development of mathematically based models that are physiologically correct and that are capable of mimicking the function of a single organism, a single organ or a connected set of organs. Well-developed models allow the user to conduct experiments and to insert pathologies that are impossible in a laboratory setting. Excellent examples of such models include the work of Tran and group at North Carolina State University on the metabolism of dioxin in the human body and that group's work on the effect of carbon dioxide on sleep patterns in infants; the work at Cornell on the dynamic modeling of the blood flow in the heart; the work of Martin and group at Texas Tech University on the dynamic models of the eye and their work on the prediction of stress fracture in the tibia; and the work of Dayawansa and group at Texas Tech University on the neural activity in the visual cortex. All of these models share the property that they are physiologically correct and can be modified to include abnormalities of various sorts.

Specific biological and chemical agents will be targeted to develop models that will predict their interaction with specific organs. For chemical agents that are inhaled there is considerable understanding of the mode of action for acute exposure. For sublethal exposures that are close to the detection range, much less is known. Models of the pulmonary-cardiac network will be

developed to understand how the agent is distributed in the body, incorporating all that is known about how the agent and its byproducts are concentrated in various organs. Particular attention will be paid to the effect of very small concentrations at the neural level. Such a model is complicated but its development will be facilitated by the supercomputer at TIEHH/TTU/Reese Center. Probabilistic methods will be used to compensate for low level exposure.

Bacteriological and viral agents present interesting modeling problems but these agents may very well be the agent of choice in a CB event. Bacteriological agents cause both mortality and morbidity. An agent such as bubonic plague is easy to cure if detected early enough. However the treatment is subtle because of the massive number of organisms produced in the human body. The organism must be killed slowly enough to prevent the body from failing due to the problem of eliminating the mass of decomposing bacteria. On the other hand the bacteria must be killed rapidly enough so that the toxin produced by the bacteria does not cause death. Models of the organism within the body and its growth will be developed in the model in such a way that the process of antibiotic treatment may be introduced as a variable. This model will be used to predict the consequences of the speed of the antibiotic regime.

Viral agents present a much different and more difficult modeling scenario and there is virtually no modeling effort in this area. Viral agents act by invasion of cells and this can be modeled. The interaction of the virus with the cellular structure must be understood. This will require close collaboration between the modelers and virologists. This collaboration is possible and will be developed. There is already a very close cooperation between the mathematics, biology, cell biology and pharmacology departments at TTU and TTUHSC. By understanding and developing such models, the research group will be able to predict the effect of various prophylactic agents on viral infection.

Virus particles are often stored in a dormant mode in the body. This is not well understood but is potentially a very important consequence of a CB event. The effects of a viral attack could last for years in the population and cause serious disruption in the community for many decades after the attack. The recurring problems associated with polio are a good example of what may happen. Models do not solve problems, but they do allow the investigation of phenomena that may be difficult or impossible to study in the laboratory. Physiological models work hand in hand with laboratory experiments to suggest important avenues of experimentation, and epidemiological models are useful to predict the effect of an agent on a population.

Individual Protection and Barrier Design: Selected investigators at Texas Tech University are also interested in researching and developing smart fabrics and next-generation protective coverings for personal protection outerwear, medical containment structures and other physical barrier applications. Such unique materials will provide protection in the form of body coverings that can impede, bind-up, neutralize or otherwise inactivate the potential biological and chemical warfare agents. These participants will be coordinated and sponsored through the International Textile Center (Dean Ethridge, director) and the Leather Research Institute (Dennis Shelly, director). These university operating units represent unique and valuable facilities in the region.

A major focus of our approach to this project is the development of "smart fabrics", materials that react in known ways to the presence of chemical compounds, bacteria, viruses, microorganisms, etc. Special coatings or laminates, perhaps developed from nanoparticles, may enable cost-effective, selective barriers to harmful agents. Treatment with selective adsorbents

and/or fabrics designed with tortuous, porous pathways will also be investigated.

Next-generation coverings are based on innovative designs of new and existing fabric structures. In one scenario, a limited-body covering is envisioned that will allow adequate respiration for the limbs and trunk, allowing the underlying skin to "breathe" but dramatically impeding access of bacteria and viruses to the skin. Existing breathing apparatus technology will be intelligently coupled to this new covering design. Though the primary portal of entry into the human body, for many microbes utilized in biological warfare, is the upper respiratory tract, large areas of exposed skin are also entry points. Viruses (e.g., Variola or Smallpox) are extremely small—in the range of 250-400 nm in diameter. Bacteria are generally much larger than viruses. For example, *Bacillus anthracis*, the causative agent of anthrax, is 2 μm in width and 5 μm in length. However, the spores of *Bacillus anthracis* are only about 1 to 2 μm in diameter and are easily inhaled. We propose to develop a material that will either deny passage of these microorganisms or greatly impede their permeation to the skin surface. It may also be possible to develop a "total outfit" with fully integrated breathing apparatus. Such a design would include a specialized chemical/biological filter for the mouth and nose region, enabling uncompromized inhalation. Such an approach would have significant advantages in deployment to a large civilian population, keeping the number and variety of ancillary equipment in the body-covering regimen to very manageable levels.

Of course, designed materials will have to meet threshold levels of permeation, degradation and breakthrough resistance for chemicals in particulate, liquid and vapor form. Body-covering fabrics must also meet thresholds regarding key physical properties (e.g., strength and durability). Also, the coverings need to be designed and structured either for easy decontamination or easy disposal. For multi-layered garments and coverings, some layers may be decontaminated and others destroyed according to specified protocols.

In addition to woven fabrics, leather is recognized as a unique, extremely versatile fabric that has been used for centuries as clothing and protection outerwear. It is composed of natural fibers (collagen), woven through cellular proliferation and differentiation of the host animal (by nature), that have been chemically and physically manipulated (by human design) to yield a strong, microporous, nondegradable, protein martix. It is a lightweight, conformable material that can be easily shaped, patterned and integrated into complex composite structures. Leather is the most effective, protective coverings toward abrasion and fire, in existence! Leather is proposed as a model fabric for the rational design of next-generation protection outerwear, particularly for protective footwear for military and civilian applications. Both mineral and vegetable -tanned leather has ultimate properties that are highly desirable in such applications. Superior performance characteristics of leather include: tensile strength approaching 5,000 psi, conformability (as stretch-controllable) up to 100+%, flex resistance exceeding 100,000 cycles, water absorbency up to 500% (w/w), low flammability and low thermal conductivity. Knowledge of the relationship between chemical/physical processing of leather and its ultimate properties may greatly facilitate the design of such high-performance footwear. Leather is also proposed as an ideal substrate for the fabrication of natural/synthetic composite biomaterials, having application in next-generation protective defense gear for military/civilian applications. The material properties of leather, a molecularly-engineered form of manipulated collagen, justify its use as a protective covering that is highly workable and customizable for the specific application cited here. For the purpose of biowarfare defense, the laboratory of Dennis Shelly proposes a hair-on hide tannage with a hydrophobic coating on the trimmed hair, providing a

vapor exchange barrier next to the skin. A mineral tannage, such as chromium or aluminum, would render the leather at least somewhat dense to ionizing radiation. The other (flesh) side of this structure could be impregnated (after tanning) with immunoglobulin-containing gel for active and passive neutralization of chemical/biological threats. Woven Kevlar strips and plates will be fastened to the composite structure increasing the overall tensile strength and serving more as body armor. Active transport of respiration products could then be induced through one-way input valves and one-way output valves. Additional adaptations are possible in accord with design considerations and desired performance characteristics.

Another major focus area is in the design of medical-containment structures and other physical barriers that could be rapidly deployed to control the environment and spread of infection after a bioterrorist event. With some modifications, textiles and other materials that meet stringent standards of performance can be developed for use as barrier materials. As with clothing, a barrier design focuses on the directional flow of air, pore-size, and specific chemical properties. These properties can be exploited in the design of medical-containment tents and other "full coverage" structures, doorway and window coverings and other yet-to-be-conceived physical barriers.

The International Textile Center is capable of developing materials that utilize any type of staple or filament fibers and applying either woven or non-woven technology in fabric formation. It is the only university facility possessing such capabilities outside the eastern seaboard of the United States. It is equipped and staffed to conduct the full range of research and development activities, from small-scale testing through large-scale manufacturing. It is housed within a 110,000 sq. ft. facility with exacting control systems for ambient conditions. Its ongoing activities revolve around research, testing, and evaluation of:

- all types of fibers and fiber measurement technologies;
- production techniques and innovations for yarns and fabrics;
- alternative textile processing systems;
- dyeing and finishing; and
- special yarn and fabric treatments.

The Leather Research Institute sponsors faculty-led research projects and conducts institute projects that are directed to "growing" the leather industry in Texas and the US. It supports all segments of the diverse leather industry, from animal husbandry practices that produce better quality hides, to novel tanning techniques for enhanced performance leathers, to creating databases on leather product marketing and consumer preferences. The Texas Panhandle Region produces more wet blue hides (an intermediate stage of leather tanning) than anywhere in the US. The Leather Rescarch Institute is working hard to diversify the leather industry in Texas through basic research, new technology development and timely industry reporting.

An issue of importance to individuals who work with bacteria and viruses on a regular basis, or who may be called for clean-up in the event of an attack, is how functional protective garments are in the areas of comfort and fit. When individuals cannot work comfortably and safely in protective garments over a long period, particularly in the face of emergency time constraints, optimum efficiency levels are not achieved. The public remains at risk for a longer period. Moreover, it is possible to develop a protective garment that can be worn by the general

population in the event of an attack. For the public to accept a garment, that may well become part of a household survival kit, cost and sizing issues must also be investigated. Therefore, the International Textile Center and Leather Research Institute will be collaborating with scientists, not only from the Department of Health and Safety, Microbiology, Pharmacology, and Chemical Engineering, but also those in Merchandising, Environmental Design, and Consumer Economics to design practical body coverings.

In summary, the International Textile Center and Leather Research Institute will be collaborating with scientists and engineers from many parts of the university to develop "smart fabrics" and next-generation protective coverings for personal protection outerwear, medical containment structures and other physical barrier applications. Such equipment will greatly enhance the effectiveness and survivability of military and civilian personnel, including emergency workers and the general population.

Physical Decontamination Strategies: Texas Tech University currently has a funded joint research project between the Departments Chemistry, Electrical Engineering, and Microbiology Departments (Ed O'Hair, director) that addresses the decontamination/sterilization of surfaces utilizing an atmospheric plasma jet. This interdisciplinary team envisions (and is testing) a long linear array of vehicle mounted jet nozzles so that a wide (horizontal to vertical) area could be cleaned at a speed of 2 mph or greater. Such a system would be very practical for the clean up of roads, runways, parking lots, and the exterior of buildings and vehicles. The plasma can be created from nitrogen, air or water, and the jet environment is at a high temperature with wide UV emission spectra and a large percentage delivery of ions and electrons. The present system, as operated, is very effective against biological agents and is expected to be equally effective against chemical agents. At this time the optimization of temperature, UV, and gas mixture has not been established. Once this is known, it will be possible to design and construct a field testable device that can decontaminate or sterilize large surface areas. During the funding period, the research group plans to pursue the development of small more mobile devices that might prove beneficial in the decontamination/sterilization of buildings and equipment.

B. Medical Countermeasures:

UT Contribution:

The development of medical countermeasures to virological, bacterial or fungal attack include the use of compounds that interdict the development of clinical signs of illness in populations exposed to pathogens. Three targets for such interdiction include the entry of virus into secondary organ systems in the host, the intracellular transport of viral nucleic acid and protein, and the assembly of infective viral particles. Steven Kornguth, Professor Emeritus of Neurology and Biomolecular Chemistry at the University of Wisconsin-Madison is PI on a DARPA award to the University of Wisconsin related to such interdiction of viral disease. This group has shown that:

- Epoxy succinyl derivatives (CPI) block entry of reovirus into cells
- These CPI also protect cells infected with reovirus or Ebola virus from death (patent applied for)

- Infectious subvirion particles can be "recoated" by a novel method, utilizing modified sigma 3 protein, and behave as infectious virions (patent applied for)
- A particular peptide sequence (RRKKAAVALLPAVLLALLAP) protects cells from Herpes virus (patent applied for)
- There are defined protein targets of VSV-M protein
- CyA binding to HSP70 is stimulated by Mg and ATP. ED_{50} is 70 nanomolar

The successful demonstration that the CPI block disease manifestation, *in vivo*, in mice exposed to Ebola Zaire, will provide a new opportunity to examine the utility of these compounds in infected persons. Together with the epidemiology group at TTU and facilities anticipated at UT-Galveston for testing, these efforts are expected to lead to several new breakthrough treatments.

UTSW Capability

The Center for Biomedical Inventions has two major efforts relative to BW countermeasures. Stephen Albert Johnston, Director of CBI, is PI on two DARPA grants in this area.

Diagnosis. The rapid diagnosis of infected individuals is a critical part of controlling any BW exposure. The DOC/Microarray technology described above can be applied to diagnosis. The result is a unit that will sample blood or saliva and determine whether a person was infected well before symptoms appear. The pathogen may be identified. Complex libraries of peptide or chemical polymers will fingerprint the components of the fluid to detect changes indicative of infection.

In parallel with Jenny Freeman, Hyperspectral Imaging, a unit will be developed which takes a light image of the skin to detect early signs of infection. This system is non-invasive and allows monitoring in real time.

Vaccines. The CBI has developed technologies that increase the speed at which vaccines can be developed. The Ctr. Developed the gene gun and DNA vaccines. Current efforts include:

- Making vaccines faster acting;
- Targeting and manipulating dendritic cells which are essential in developing immune responses
- Higher throughput vaccine identification using expression library immunization (ELI) allowing the whole genome of pathogens to be searched for maximal vaccine targets

Infection Genomics. The sequence of new pathogens will be sequenced in one day. Using these sequences our technology will be able to produce a vaccine in one day. New molecular biology and machinery have been developed to make oligonucleotides on a large scale.

Supervaccines and Immunomodulation. New techniques are under development that will allow

us to search for vaccines that are more potent and broad based than those currently possible. In addition the CBI and James Lipton at UTSW are developing reagents that manipulate the innate immune response to protect individuals from any pathogen challenge when administered a day prior to or following pathogen exposure.

The University of Texas Medical Branch-Galveston (UTMB-Galveston) Contribution

The University of Texas Medical Branch is a medical center with hospitals and Schools of Graduate Medical Science, Medicine, Nursing, and Allied Health Science. The facilities and resources include those centers of excellence that are currently engaged in research of infectious disease that relate to potential bioterrorism or defensive biological warfare.

The WHO Collaborative Center for Tropical Diseases is comprised of laboratories, insectary, and computational facilities supporting aproximately 35 scientists involved in virology, bacteriology, mycology, and rickettsiology. The Center is housed primarily in the newly renovated Keiller Building where the World Reference Center for Arboviruses and Viral Hemorrhagic Fevers is locatcd. This constitutes the world's largest collection of BSL-w and BSL-3 arboviruses and rodent-associated viruses. Laboratories are certified for work with biosafety level (BSL) 2 and 3 infectious agents. Core facilities include ultrastructure analytic tools, confocal imaging equipment and nucleic acid and peptide synthetic capabilities. The center contains two insectaries for rearing and maintaining pathogen-free colonies and a special BSL-3 insectary equipped with two climate-controlled chambers.

BSL-4 Laboratory. The University has received approval from the University of Texas Board of Regents to construct a BSL-4 facility of approximately 2,000-sq. ft. laboratory space. This facility will permit UTMB scientist and collaborators to carry out experiments with viruses such as those causing hantavirus pulmonary syndrome, arenavirus hemorrhagic fevers, and Crimean-Congo hemorrhagic fever. Challenge experiments with mice, hamsters, guinea pigs, and rabbits will be contained within the facility.

University of Texas Medical Branch- Sealy Center for Structural Biology (Galveston) contains leading edge NMR spectroscopic equipment and X-ray crystallographic capabilities for protein structural studies. This Center has a state-of-the-art, high-speed flow cytometer/cell sorter capable of operating at speeds in excess of 100,000 cells/sec for rare cell analysis - one of the most advanced in the world. Capabilities also include a custom-designed, locally constructed, high-resolution cell sorter (the "HiReCS" system) which is optically split to provide up to three excitation laser beams at two spatial locations providing 6-color fluorescence analysis capabilities. Also on-line are special custom-built, patentcd, high-resolution time-of-flight sizing systems capable of sizing cells and sub-cellular organelles.

The University of Texas Medical Branch will provide a capability to rapidly examine the utility of novel anti-viral, anti-bacterial compounds on agents of concern. It will also add immediate capability to explore novel matcrials that may act as barriers to B agents for utility as protective body coverings.

TIEHH/TTU/TTUHSC Contribution--Lubbock

The Reid and Spallholz laboratory at TTUHSC have special expertise in the development of anti-viral and anti-bacterial agents. This research team has recently developed a new technology that is based upon the unique properties of the selenium atom. The primary focus of the team is the development of technologies that utilize selenium free radical chemistry. These technologies exploit the ability of specific organo-selenium compounds to generate superoxide and other free radicals. Selenium is unique in that it is the only element in the periodic chart that can catalyze the formation of superoxide radicals while it is covalently attached to an organic molecule. In vivo, these free radicals are only toxic when they are targeted and become concentrated in a localized environment. Highly localized free radicals can be used to kill viruses and bacteria and yet have no effect on the host in which they are present.

Why is selenium special? Humans consume selenium everyday in their diet (approximately 100 ug/day). Selenium is utilized in the body by incorporation into proteins as part of our anti-oxidant defense. However, selenium at higher concentrations is toxic. This is because many organo-selenium compounds have the ability to catalyze the formation of superoxide radicals that overwhelm the body's defense system. Fortunately selenium can be incorporated into anti-viral and anti-bacterial agents and yet have no unwanted side effects on an individual. This is because the amount of selenium used is less than 1% of that consumed in a daily diet and because unless the selenium is targeted to a specific site this amount of selenium will not have any effect on a mammalian cell. Mammalian cells have the ability to effectively deal with superoxide radicals through the action superoxide dismutase and similar enzymes. These systems are much better han those in bacteria and, of course, viruses have no defense system whatsoever. Selenium compounds can be stored in a dry form for years and then mixed with saline and injected or put into an inhaler for respiratory use.

a. Targeting of Bacteria

Scientists in Dr. Reid's laboratory are testing a new generation of antibiotics based upon the toxic properties of selenium that will target a specific type or subtype of bacteria. As an example, anthrax may be targeted. At the moment antibiotics are very indiscriminate in their ability to target bacteria. Thus, they also kill useful bacteria that exist in our body allowing resistant strains to overcome our defense mechanisms. In the proposed strategy, bacteria will not be able to develop a resistance. This is because the design incorporates natural targeting mechanisms that have been developed by nature over millions of years and to which there is no known bacterial resistance. However, in the unlikely event that bacteria strains did develop resistance it is a simple matter to change the drug design to overcome this resistance.

b. Targeting of Viruses

An organoselenium labeled peptide directed against the HIV (AIDS) virus has recently been shown to inactivate the virus before it can infect a cell. *In vitro* testing demonstrated that a low concentration of a selenopeptide was capable of inactivating 95% of a virulent isolate of HIV in

2 hours (in a longer time more is inactivated). For the purposes of this proposal, pox viruses will be targeted. A drug of this type can be manufactured cheaply and would have a long shelf life at room temperature. Phage expression libraries will be used to select peptides that will bind to the surface of the pox virus. A range of concentrations of selenium will be incorporated into the peptide to produce the drug. Similar drugs can be produced against any virus. These agents represent true anti-viral drugs since they act directly on the virus and not by blocking viral replication as done by present day anti-viral agents. Once the specific drug is produced, the research group will be ready for preliminary toxicity/efficacy testing in animal models.

Mechanisms of Chronic Neurotoxicity by Chemical Agents: The TTU/TTUHSC group (led by Lou Chiodo, and including Howard Strahlendorf, Peter Syapin, Jean Strahlendorf) has an interest in cellular mechanisms of neurotoxicity of sublethal/periodic exposure to organophosphates. Individuals episodically or periodically exposed to low-level neurotoxicants that elicit asymptomatic pathologic effects, potentially represent a population of susceptible individuals predisposed to more serious effects, if subsequently exposed to the same or different toxicant. The nature of this susceptibility needs to be better understood in order to develop appropriate medical countermeasures. Anticholinesterase organophosphates (OPs) potentially have latent chronic toxic effects on the CNS consequential to either a single exposure in which victims are protected from acute lethality or chronic low-level or periodic/episodic exposures. Acute pathology to OP poisoning results from a sequelae of events resulting in intractable convulsions and death if the victim is not treated. However, protection from terminal convulsions may not afford total protection to the central nervous system (CNS) from delayed neural toxicity. Moreover, repeated exposures (episodic/periodic) to sub-acutely toxic levels potentially cause permanent damage to organ systems that may become symptomatic only later in life. This is particularly true for organ systems undergoing development (pre- or postnatal fetus) or with limited or no regenerative capacity, such as the CNS. Because the CNS undergoes substantial development during the early years of life and does not possess the ability to spontaneous regenerate most of its cells, it has been identified as being of special concern for toxin exposure. Adverse changes during a critical window of time in an organism's life can significantly impair performance for the remainder of its life span.

Sub-lethal intermittent or low continuous exposures to OPs also may disrupt a host of homeostatic physiologic functions of neurons and glia in the mature CNS eventually leading to toxic effects and neurodegeneration in selectively vulnerable areas in the CNS. For example, evidence is emerging regarding the Gulf War Syndrome and Post-traumatic Stress Disorder that suggests intracellular genetic cascades can be initiated by transient or periodic exposures to the highly toxic OP chemical warfare agents that temporally precede development of symptoms and related CNS pathophysiology. Another example can be found in the relationship that exists between exposure to OPs and development of Parkinson's disease (PD) and potentially other neurodegenerative neurologic and psychiatric disorders. The primary lesion in PD is progressive degeneration of the dopamine (DA)-synthesizing neurons of the substantia nigra within the mesencephalon, and although the etiology of PD is unknown, OPs as a class have been particularly implicated as risk factors in PD. Based upon their pharmacology and acute toxicology, it is reasonable to assume that OPs can cause neurotoxicity and degeneration of DA neurons, and potentially other critical CNS neurochemical systems. Research into types and potential mechanisms of neurotoxicity and death of neurons is extensive and includes necrotic

and apoptotic characteristics associatcd with excitotoxicity, elevated intracellular free Ca^{2+} ($[Ca^{2+}]_i$), excessive oxidative stress, and lack of neurotrophic factor support. Thus the need to study the neurotoxic consequences of chronic, low-lcvel and episodic exposures to OPs is of paramount importance.

Two sets of experiments are proposed to investigate latent neurotoxic effects of OPs. I*n vitro* neuronal and glial cultures from the mesencephalon, a dopamine (DA)-containing brain area that is critically important for many motor and cognitive behaviors, will be utilized as a prototypical model system to study novel neurodegenerative mcchanisms caused by low-level continuous or episodic exposure to OPs. Prcliminary data exists to show that chronic diisopropylfluorophosphate and chlorpyrifos-oxon (OP insecticides) exposure induces mesencephalic neurodegeneration independent of cholinergic activity. Based on these initial findings, it is hypothesize that low concentrations of OPs induce latent lethal and sub-lethal neurotoxicity to DA neurons by novel mechanisms not appreciably dependent on cholinesterase inhibition. Toxicity is incurred by altering one or more physiologic parameters of the neuron including: intracellular calcium levels, mitochondrial membrane potential, glutathione reserve versus reactive oxygen species, expression of survival- versus death-promoting genes and enhancing susceptibility to further neurotoxic challenges. Furthermore, low-level pesticide exposure disrupts the survival-promoting interaction between glia and ncurons rendering the physiology of DA neurons labile to additional insults. Three specific hypotheses to be tested using OPs are: 1. That chronic or episodic exposure elicits a direct, novel lethal effect on DA neurons. 2. That chronic or episodic exposure to sub-lethal amounts of OPs enhances the susceptibility of DA neurons to other neurotoxic insults. 3. That mesencephalic astrocytes and their products (neurotrophic factors, NTs) protect DA neurons against the direct lethal and indirect toxic sensitizing effects of OP exposure.

A second set of *in vivo* experiments will verify that the neurotoxic effects seen *in vitro* lead to significant deficits in behavior. It is hypothesized that exposure of an organism to OPs during a critical period of CNS development alters the normal maturation of the brain causing permanent deficits in behavior that may not be evident until later in life. Prenatal rat pups will be exposed to low sub-lethal concentrations of OPs *in utero* by dosing pregnant dams at critical gestational windows. Controls will be similarly treated with the vehicle used to deliver the OP. Following birth, animals from treatment and control litters will be allowed to mature. Periodically throughout this postnatal developmental period they will be subjected to a battery of standardized behavioral tests to determine whether there are latent deficits in their motor and cognitive abilities (e.g., learning and discrimination).

Neurodegenerative disorders are insidiously progressive. Current theories relating toxins, particularly OPs, and damage to CNS neurons, consider strongly the point that chronic low-level or periodic/episodic exposures have both lethal effects on some neurons and sub-lethal actions on others that compromise neuronal, and possibly glial, physiology. Because there is a paucity of data regarding the long-term neuropathology of exposure to OPs, it is the purpose of experiments described in this proposal to investigate potential mechanisms of latent neurodegeneration following low-level exposure to thcse compounds. The proposed research will provide significant insight into potential prophylactic and therapeutic interventions, such as NTs and genetic therapies, to avert deleterious latent toxicity and life-long deficits in function.

3. Communications:

There are two components in the communications thrust:

One is the development of strategies to inform different communities (i.e. medical treatment, security, and public) about an event in a credible and effective manner. The second concerns the actual transmission of information to the various entities in a format that allows ready accessibility and comprehension. UT has two efforts in this arena.

The College of Communication, directed by Dean Ellen Wartella, has brought together a team of experts to establish a communication research strategy. This group will provide a range of faculty expertise in diffusion of information both within organizations (media and government) as well as in communities and other populations. Among the faculty brought together are journalism faculty who are expert in understanding the structures of journalistic and other media organizations; public relations faculty who are expert in crisis communication and management; health communication faculty both in this College and UT's School of Public Health in Houston with experience in risk communication within various populations; and media effects researchers who understand how to examine message effects and impacts among different populations. The College has identified a team of appropriate experts to examine the relevant policies for communicating response to a chemical or biological event. This team will examine the structures and policies of government agencies charged with responding to such events; the commercial and public media organizations and their attendant professional associations for establishing diffusion guidelines and information networks; and organizational and message strategies for communicting to the wider public while avoiding mass panic.

The ARL: UT has extensive knowledge with communications network modeling and modulation techniques both at the radio frequency (RF) and network level. Work with COMNET and OPNET will allow for quick modeling of communications infrastructures in various areas to support a national level disaster. Support to Army C4ISR systems provides the background to understand and model challenges at the RF level. The Radio Frequency Mission Planner can also be used to plan worldwide contingency deployments of communications equipments with carrier frequencies between 2 MHz and 30 GHz. As additional research is required, assets within UT and other central Texas universities can be accessed to bring in academic expertise.

Considerable work has already been completed in the efficient rendering of three-dimensional objects. One technique uses tree structures to render only the objects visible to the viewer. Another technique uses adaptive rendering to provide more detail on objects in the foreground and less detail for objects in the background (and more distant from the viewer). Additionally, the group is just beginning to explore creation of "virtual" video in conjunction with the Army objective instrumentation system for the National Training Center (NTC) to substantially reduce the amount of data that must be transmitted. In the NTC work, it is possible to transmit periodic updates of vehicle ID and location and then use artificial terrain in the creation of "video" for the after action review (AAR). The communications channel savings is tremendous. Smurffing techniques can also be used to move the vehicle between the discrete data points. Similarly, minimal data may be transmitted from sensor platforms to a central storage facility and combined there with digital maps for the display of CB strength levels projected onto a digital map. Concentration variations versus altitude (either MSL or AGL) can also be readily created. Dispersals over time due to atmospheric conditions could be calculated and show as simulated time-based video.

4. Systems integration

This task requires that the team bring multiple disciplines and resources together. The primary goal of the integrated effort is to re-establish social organization and function as rapidly as possible after a B/C incident. Supporting goals include the application of needed resources without being wasteful, reinforcing a hierarchy of social organization and services appropriate to societal values and expectations. Intensive and varied applications of information technologies are expected. Most crisis situations are rich in data sets; the data is at best heterogeneous and sometimes contradictory. The key elements are data screening, validation and presentation as coherent information. The development of a specific set of specific tools will be required to realize the end goals stated above.

A single point HTML/JAVA interface to heterogeneous data will be constructed. Sources may be unstructured, semi-structured, or structured data. Unstructured data are flat files such as a collection of messages. Semi-structured data is text messages with some formatting information such as a situation or casualty report. Structured typically refers to information already in a data base with meta data to describe the contents of the database. The data may be stored locally in a single server or geographically distributed with access via various communications paths. In all cases some type of interface is usually developed between the raw data source and a common data interface which is the enterprise or federated schema.

The graphical user interface (GUI) is normally written in a language (such as JAVA) that is easily transportable across platforms. Operator terminals then access the data base server via LAN, classified LAN or dial in modem. Browser and application software on the client terminal then allows exploration of the data, processing/data mining, and presentation. This structure is commonly know as a three tier architecture with the top tier being the client terminal, the middle tier being the enterprise schema and storage and the bottom tier being the data in its native form and perhaps resident at the authoritative source for the data. Use of the Common Object Request Broker Architecture (CORBA) allows appropriate dynamic assignment of functionality at compile time to the various tiers. In reality the three tiers may reside on one to three machines.

Given that various sources of data are now accessible from a single point, various applications can be developed to aid the analysts. Just to explore some possibilities in the chemical/biological world, consider the following scenarios.

1. Suppose 10 known key terrorists are identified in the world. Processing by email addresses and key words, a logical network could be built around each terrorist to identify consultants based on key subjects. For example, looking at emails sent to/from Jones containing plutonium and triggers shows a relationship with Smith, Thomas, and Zachery. Further networks around each of these three could eventually build the network of experts to construct a nuclear weapon.
2. Correlations could be mined between events. For instance, the Federal Building in Oklahoma was bombed on the anniversary of the burning of the Koresh compound in Waco. Is the end of the Texas Federation in West Texas going to trigger a similar event somewhere else in Texas in the future? For example, should security in Austin be increased if the State Legislature is ever in session on the anniversary of FBI agents storming the stronghold in west Texas?

3. By identifying key release points for CB agents in the 50 major cities in the world, they could be correlated with weather and public event information to identify times and places where a large group of people could be affected. For example, a warning might be warranted if weather conditions are such that a release in the desert around Phoenix, AZ would sweep the CB agents across Sun Devil stadium during a Super Bowl or sweep across the Motorola facility affecting hundreds of defense industry workers. Likewise, key release points in Washington, DC might allow dispersion across the capital plaza during a presidential inauguration. Use of terrain and city building information could then be used to model and display dispersion of the agents through the US capital and two and three dimensional displays developed to display the information to decision makers and planners to aid in the determination of actions the prevent/control a potential attack.

Support to the Defense Modeling and Simulation Office and expertise with the DoD High Level Architecture provides a good point of departure for a joint TTU/UT activity. Geographic and computer platform dispersion of the eventual system will be necessary for adequate planning, warning, and response of a major CB event in the US and the world.

A joint medical data warehouse where medical records of service members are stored could facilitate development of algorithms to explore relationships between symptoms, illness, treatments, results, duty stations, age groups, race, ethnic backgrounds, etc. TTU and UT have capabilities in this area. This work could form the basis for identifying susceptible populations in the world that may be particularly vulnerable/immune to various CB agents, due to genetic or environmental factors. Both acute and chronic effects, as well as interactive effects could be explored.

Education and Training: The education and training programs will be designed to teach groups how to plan for, recognize, and appropriately deal with a bioterrorist event. We will employ the most appropriate faculty: in-house, other universities, government (Army War College, FEMA, military, health, agriculture, intelligence, state law enforcement, etc.) and/or contract-private organizations for particular components of the training. The Texas Department of Health has generously offered their support in this effort, and will contribute valuable resources and infrastructure.

Training formats will integrate on-site scenario and lecture formats as well as recent advanced methods in education, such as distance learning. Telemedicine and two-way interactive television will be utilized in training modules and for coordinating key personnel during a crisis. TTUHSC's HealthNet/Telemedicine system, rated as one of the top four such programs in the United States in 1998, will be an integral part of this training program, as well as two-way interactive television access through South Plains College, located at Reese Center.

TIEHH/TTU/TTUHSC Contribution

Texas Tech has been assembling a team of eminent trainers and educators, led by Catherine M. Bens (TIEHH), willing and able to develop an all encompassing training and education program in research that, through modern technology, would reach a broad spectrum of audience types to assist in preparing and responding to chemical or biological threats at both the national and

community levels. Several program areas are proposed:

- National and International Conference Program – to bring together prominent and experienced responders to review the status of national and community preparedness and research, make recommendations, develop proceedings, review Center curricula and contribute in other ways in an on-going effort to evaluate the current understanding and response capability to these type of events.
- To develop a National Training Center, utilizing TTU and outside specialists and educators, resources and facilities to promote preparedness and response through a sound foundation in education, integrated with the current state of the research sciences and coordinated with responding agencies and individuals who might be isolated and unknown without such training and coordination. For example, the Center for Professional Development and Training (CPDT, discussed below) represents a critical resource for this type of specialized training.
- Integration of Education and Training in Research through Technology, including the use of a supercomputer, a Reality Center, Telemedicine, two-way interactive television, satellite broadcasts, etc.
- Development of a National Archive and Repository for Biological and Chemical Emergencies – to bring into one place, in a secure and retrievable manner for researchers, community planners, educators, and historians those documents and other resources which contribute to our current understanding of the threat from chemical and biological weapons.

The Center for Professional Development and Training (CPDT, Dr. Jerry Davis, Director), is a dynamic organization with the mission of education, training and program development for the Department of Defense (DoD). Within the mission scope are several areas of special interest that would facilitate interaction with educational and research institutions:

- Senior Service College Fellowships in Army Acquisition (AAC) and Modeling and Simulation (M&S). The Center has operated the AAC Fellowship since 1992 and operation/administration for the M&S Fellowship since 1997. The Fellows are from Active Duty, National Guard, United States Army Reserve (USAR) and DA civilian ranks. The current class has 11 military officers and one civilian. All Fellows are required to conduct research and write a formal report at the end of their one year stay at UT. The emphasis for most of the Fellows this year is in the area of simulations. A close linkage to Fort Hood has been developed from this topical interest.
- CPDT has a long history of conducting training events in communications, leadership, mentoring and technical subjects. The organization is currently working with military organizations in long range planning and restructure issues. Training is conducted on a national basis with classes offered at military installations.
- CPDT has several other ongoing programs with the AAC. These include a direct relationship with AAC officers and civilians attending the University's Executive Master of Business Administration (MBA) degree and the Executive Master of Science degree in Technology Commercialization. These programs bring together nationally recognized faculty of extensive backgrounds in research and practice with academically outstanding

students who hold responsible positions in a wide variety of organizations. Classes meet on alternate weekends allowing the student to earn the degree while continuing to work full-time. Army officers and civilians selected for these prestigious programs may participate full time or part time in RD&A related projects at CPDT while completing the degree program.

- Simulation activities included work with Simulation Based Acquisition (SBA), modeling the acquisition process and developing a M&S presence at Fort. Hood. CPDT is linked with other M&S organizations at the University that support DoD. University customers have included the Defense Advanced Research Agency (DARPA), the Defense Modeling and Simulation Office (DMSO) and the Army's Simulation, Training, and Instrumentation Command (STRICOM). Past efforts include work on the Synthetic Theater War-1997 (STOW-97) program, the High-Level Architecture (HLA) and command and control (C2) system simulation. Efforts are now underway in applying software agent technology to M&S and the use of software tools for synthesizing command and control behaviors. Our background in synthetic environments, semi-automated forces, and C2 provides a good launching point for simulation of emergency response to a weapon of mass destruction. To make the best use of this technical capability, we believe that a teaming arrangement with the National Simulation Center (NSC) at Ft. Leavenworth would create a powerful combination. The NSC has modeled the emergency response problem and has agreed to work with UT in expanding and adapting the capability in a manner consistent with national priorities. UT would provide key software and M&S expertise as well as disaster management expertise.
- CPDT has worked with the Office of Secretary of Defense for Test and Evaluation (OSD/T&E) in the development of educational materials for Live Fire Testing. Current projects include the possible development of an OSD course to be offered to all services for certification in LFT efforts.

The Center has extensive resources available for collaborations with universities, such as TTU/TTUHSC and UT, for the development and conduct of programs in CB activities. These assets include the use of SSC fellows and other officers working directly on specific CB projects. The close link of the center with the National Guard is a natural link to CB response and mission efforts.

The Institute of Environmental and Human Health (TIEHH) exists as ajoint venture between Texas Tech University and Texas Tech University Health Sciences Center (TTUHSC). TIEHH is located at Reese Center, ten miles west of Lubbock, Texas. This facility offers a unique integrated and accredited academic foundation that would provide extensive support to any education and training program. It offers an interdisciplinary academic and research faculty, as well as, infrastructure necessary to support education and training at the level proposed herein. In addition, it offers unique experience in such areas as long distance learning and specialized archive/library support.

The Reese Center, formerly Reese Air Force Base, is currently being converted into a state-of-the-art research, technology, and industrial park. The former air force base, now known as Reese Center, is located 10 miles west of Lubbock, Texas and houses the infrastructure to facilitate chemical and biological weapons initiatives. This center will enable Texas Tech to expand upon chemical and biological weapons research and realistic and virtual training capabilities. Reese

Center currently holds self-contained (on-site) housing, feeding, classroom, transportation (air and ground), and field-exercise facilities. In addition, The Texas Department of Health and South Plain College (also located at Reese Center) have generously offered their full support in this effort, and will contribute valuable resources and infrastructure. Many buildings and classrooms have recently been modernized.

Virtual Reality Center: The Institute of Environmental and Human Health at TTTU/TTUHSC is establishing a high-performance computer facility interfaced with a "Virtual Reality Center." The Virtual Reality Center would allow opportunities to create virtual modeling experiences to understand dispersion and transport of potential biological and chemical agents and exposure pathways. By having a Virtual Reality Center, seating forty persons, multi-disciplinary teams could be brought together quickly for consults in case of a chemical and biological emergency. This would allow us to provide integrated environmental and human health perspectives in response to chemical and biological emergencies, particularly in a crisis situation. The Virtual Reality environment that will be modeled with the interfaced high-performance computing system will be transportable via satellite uplinks to distant points of communication including the Pentagon. There will also be available satellite downlinks to allow additional opportunities to communicate with other high-performance computing environments, particularly through virtual reality, that will allow real-time consults to be communicated and re-evaluated as data is provided to update the modeling system. At TIEHH, a major toxicology library is being established that can be mined electronically effectively in a real time situation such that toxins and their toxicology, either biological in nature or toxics that may be synthetic chemical in nature will be evaluated from multi-disciplinary perspectives and risk factors can be better understood including transport and dispersion as well as toxicity to humans and the environment. This state of the art technology will be directly applicable for support of field deployable units that may be in the interface of dealing with a chemical and biological emergency and will need better scientific information as a backup in order to more effectively deal with that situation.

Conclusions

The United States needs to develop a more effective capability for response to bioterrorist events. The research outlined above will be pivotal in correcting these deficiencies. The Institute of Environmental and Human Health at TTU/TTUHSC-Lubbock, the University of Texas-Austin, the University of Texas-Southwestern, and the University of Texas at Galveston, along with unique facilities and resources available at these institutions and with local, state and federal agencies, will create for the United States an essential capability that can provide effective response to CB attacks. This will be developed through basic research, new technologies, realistic education and training, and modeling to provide an integrated approach. These facilities and personnel will provide a national center for combating CB terrorism at the local, regional, and national levels.

development of tools to capture and concentrate air and liquid samples, rapid multi-array sensors, establishing a relevant data base, data fusion, data presentation); communication (informing appropriate governmental persons, health care persons and the general public about the incident); creation of technologies for the rapid diagnosis of infected people in exposed populations, development of novel compounds that can defeat bacterial, viral and fungal agents; health care and triage related to the care of affected persons using antibiotics, vaccines, medical evacuation including telemedicine capability; developing a system that can integrate the detection and responses in a coordinated manner; developing novel materials and body cover to protect individuals threatened with biological or chemical agents.

Such an integrated team can assist the relevant government agencies in addressing, comprehensively, the challenges of social and response disorganization that might be anticipated during and immediately after a biological/chemical incident. The team can offer an analytical element to appropriate authorities and thereby strengthen the framework of national security.

A trans-Texas team, with expertise in all these areas has been assembled. The team includes researchers at Texas Tech University-Lubbock, the University of Texas-Austin, UT-Southwestern Medical School, Department of Justice-South Texas, Texas Department of Health, Emergency Preparedness First Responders-Austin Texas, the University of Texas -Galveston. In addition the Institute for Defense Analyses (IDA), Alexandria Virginia will also be an active part of the team. The IDA role will be to provide linkage and support to assure that the research condueted within this program maintains a focus on the national security community and the specific challenges addressed. This is a traditional role for IDA, and has been one fulfilled by the Institute since it was founded. The contribution of this group will be: highlighting, focusing and extending research that shows exceptional promise for limiting disorganization and re-establishing structure; for managing the health and casualty impact of terrorist incidents involving CB agents; and identifying areas which require further investigation. Finally, The Center for Professional Development and Training (CPDT), which has had a role in training at the DoD, will contribute to the education, training, and outreach component of this initiative.
The proposed trans-Texas initiative provides a prototype capability that can be a) implemented in a national threat condition, b) used as a test bed, or c) serve as a springboard for other regional or national efforts.

Budget (2 years):

Total Budget	**$ 28 M**
State/University Contribution	$ 6.5 M
Other	$ 6.5 M
Federal Request for CB Research	$12.0 M
Federal Request for Operations and Training	$ 3.0 M

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