DEFENSE HEALTH PROGRAM (DHP)
15.1 Small Business Innovation Research (SBIR)
Proposal Submission Instructions

Revised Closing Date: February 25, 2015, at 6:00 a.m. ET

The DHP SBIR Program seeks small businesses with strong research and development capabilities to pursue and commercialize medical technologies.

Solicitation, topic, and general questions regarding the SBIR Program should be addressed according to the DoD Program Solicitation. For technical questions about the topic during the pre-release period, contact the Topic Authors listed for each topic in the Solicitation. To obtain answers to technical questions during the formal Solicitation period, visit http://www.dodsbir.net/sitis.

PHASE I PROPOSAL SUBMISSION

Follow the instructions in the DoD Program Solicitation at www.dodsbir.net/solicitation for program requirements and proposal submission.

SBIR Phase I Proposals have four Volumes: Proposal Cover Sheets, Technical Volume, Cost Volume and Company Commercialization Report. The Technical Volume has a 20-page limit including: table of contents, pages intentionally left blank, references, letters of support, appendices, technical portions of subcontract documents (e.g., statements of work and resumes) and any other attachments. Do not include blank pages, duplicate the electronically generated cover pages or put information normally associated with the Technical Volume in other sections of the proposal as these will count toward the 20-page limit.

Only the electronically generated Cover Sheets, Cost Volume and Company Commercialization Report (CCR) are excluded from the 20-page limit. The CCR is generated by the proposal submission website, based on information provided by you through the Company Commercialization Report tool. Technical Volumes that exceed the 20-page limit will be reviewed only to the last word on the 20th page. Information beyond the 20th page will not be reviewed or considered in evaluating the offeror’s proposal. To the extent that mandatory technical content is not contained in the first 20 pages of the proposal, the evaluator may deem the proposal as non-responsive and score it accordingly.

Companies submitting a Phase I proposal under this solicitation must complete the Cost Volume using the on-line form, within a total cost of $150,000 over a period of up to six months.

The DHP SBIR Program will evaluate and select Phase I proposals using the evaluation criteria in Section 6.0 of the DoD Program Solicitation. Due to limited funding, the DHP SBIR Program reserves the right to limit awards under any topic and only proposals considered to be of superior quality will be funded.

Proposals not conforming to the terms of this solicitation, and unsolicited proposals, will not be considered. Awards are subject to the availability of funding and successful completion of contract negotiations.

PHASE II PROPOSAL SUBMISSION
Beginning with SBIR Phase II’s resulting from a 13.1 Phase I award, invitations are no longer required.

All Phase I awardees from this Solicitation will be allowed to submit an initial Phase II proposal for evaluation and selection. The details on the due date, content, and submission requirements of the initial Phase II proposal will be provided by the DHP SBIR Program Office either in the Phase I award or by subsequent notification. All SBIR Phase II awards made on topics from solicitations prior to FY13 will be conducted in accordance with the procedures specified in those solicitations.

Small businesses submitting a Phase II Proposal must use the DoD SBIR electronic proposal submission system (http://www.dodsbir.net/submission/). This site contains step-by-step instructions for the preparation and submission of the Proposal Cover Sheets, the Company Commercialization Report, the Cost Volume, and how to upload the Technical Volume. For general inquiries or problems with proposal electronic submission, contact the DoD SBIR/STTR Help Desk at [1-800-348-0787] or Help Desk email at [sbirhelp@bytecubed.com] (8:00 am to 5:00 pm ET).

Section 4(b)(1)(ii) of the SBIR Policy Directive permits the Department of Defense and by extension the DHP SBIR Program, during fiscal years 2012 through 2017, to issue a Phase II award to a small business concern that did not receive a Phase I award for that Research/Research & Development. The DHP SBIR Program will NOT be exercising this authority for Phase II awards. In order for any small business firm to receive a Phase II award, the firm must be a recipient of a Phase I award under that topic.

The DHP SBIR Program will evaluate and select Phase II proposals using the evaluation criteria in Section 8.0 of the DoD Program Solicitation. Due to limited funding, the DHP SBIR Program reserves the right to limit awards under any topic and only proposals considered to be of superior quality will be funded.

Small businesses submitting a proposal are required to develop and submit a technology transition and commercialization plan describing feasible approaches for transitioning and/or commercializing the developed technology in their Phase II proposal. DHP SBIR Phase II Cost Volumes must contain a budget for the entire 24 month Phase II period not to exceed the maximum dollar amount of $1,000,000. These costs must be submitted using the Cost Volume format (accessible electronically on the DoD submission site), and may be presented side-by-side on a single Cost Volume Sheet. The total proposed amount should be indicated on the Proposal Cover Sheet as the Proposed Cost.

DHP SBIR Phase II Proposals have four Volumes: Proposal Cover Sheets, Technical Volume, Cost Volume and Company Commercialization Report. The Technical Volume has a 40-page limit including: table of contents, pages intentionally left blank, references, letters of support, appendices, technical portions of subcontract documents (e.g., statements of work and resumes) and any attachments. Do not include blank pages, duplicate the electronically generated cover pages or put information normally associated with the Technical Volume in other sections of the proposal as these will count toward the 40 page limit.

Technical Volumes that exceed the 40-page limit will be reviewed only to the last word on the 40th page. Information beyond the 40th page will not be reviewed or considered in evaluating the offeror’s proposal. To the extent that mandatory technical content is not contained in the first 40 pages of the proposal, the evaluator may deem the proposal as non-responsive and score it accordingly.

**DISCRETIONARY TECHNICAL ASSISTANCE**

In accordance with section 9(q) of the Small Business Act (15 U.S.C. 638(q)), the DHP SBIR Program will provide technical assistance services to small businesses engaged in SBIR projects through a network
of scientists and engineers engaged in a wide range of technologies. The objective of this effort is to increase DHP SBIR technology transition and commercialization success thereby accelerating the fielding of capabilities to Soldiers and to benefit the nation through stimulated technological innovation, improved manufacturing capability, and increased competition, productivity, and economic growth.

The DHP SBIR Program has a Technical Assistance Advocate (TAA) available to provide technical assistance to small businesses that receive Phase I and Phase II contracts.

**PHASE II ENHANCEMENTS**

The DHP SBIR Program has a Phase II Enhancement Program, which provides matching SBIR funds to expand an existing Phase II contract that attracts investment funds from a DoD Acquisition Program, a non-SBIR/non-STTR government program or Private sector investments. Phase II Enhancements allow for an existing Phase II DHP SBIR contract to be extended for up to one year per Phase II Enhancement application, to perform additional research and development. Phase II Enhancement matching funds will be provided on a one-for-one basis up to a maximum $500,000 of SBIR funds. All Phase II Enhancement awards are subject to acceptance, review, and selection of candidate projects, are subject to availability of funding, and successful negotiation and award of a Phase II Enhancement contract modification.

**RESEARCH INVOLVING ANIMAL OR HUMAN SUBJECTS**

The DHP SBIR Program discourages offerors from proposing to conduct Human or Animal Subject Research during Phase I due to the significant lead time required to prepare the documentation and obtain approval, which will delay the Phase I award.

All research involving human subjects (to include use of human biological specimens and human data) and animals, shall comply with the applicable federal and state laws and agency policy/guidelines for human subject and animal protection.

Research involving the use of human subjects may not begin until the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office (HRPO) approves the protocol. Written approval to begin research or subcontract for the use of human subjects under the applicable protocol proposed for an award will be issued from the U.S. Army Medical Research and Materiel Command, HRPO, under separate letter to the Contractor.

Non-compliance with any provision may result in withholding of funds and or the termination of the award.

**FOREIGN NATIONALS**

If the offeror proposes to use a foreign national(s) [any person who is NOT a citizen or national of the United States, a lawful permanent resident, or a protected individual as defined by 8 U.S.C. 1324b (a)(3) – refer to Section 3.5 of this solicitation for definitions of “lawful permanent resident” and “protected individual”] as key personnel, they must be clearly identified. For foreign nationals, you must provide country of origin, the type of visa or work permit under which they are performing and an explanation of their anticipated level of involvement on this project. Please ensure no Privacy Act information is included in this submittal.
<table>
<thead>
<tr>
<th>DHP15-001</th>
<th>Lateral Canthotomy and Cantholysis Training System</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHP15-002</td>
<td>Mobile Virtual Interactive Presence Capability for Combat Casualty Care</td>
</tr>
<tr>
<td>DHP15-003</td>
<td>Virtual Medical Concierge Application</td>
</tr>
<tr>
<td>DHP15-005</td>
<td>Methodologies and Techniques for Balancing Usability and Security for Medical Devices in an Integrated Clinical Environment</td>
</tr>
<tr>
<td>DHP15-006</td>
<td>Rapid Detection of Borrelia burgdorferi (Lyme disease) from Ticks</td>
</tr>
<tr>
<td>DHP15-007</td>
<td>Small Molecule to Combat Multidrug-Resistant Bacteria</td>
</tr>
<tr>
<td>DHP15-008</td>
<td>Predictive Capability for Infectious Diseases</td>
</tr>
<tr>
<td>DHP15-009</td>
<td>Ultimate Passive Dosimeter</td>
</tr>
<tr>
<td>DHP15-010</td>
<td>Oxygen Separation from Air to Provide Supplemental Oxygen for Injured Soldiers</td>
</tr>
<tr>
<td>DHP15-011</td>
<td>Modeling and Simulation of the Blood Platelet Storage Lesion</td>
</tr>
<tr>
<td>DHP15-012</td>
<td>Real-Time Small-Volume Blood Sampling and Analysis for Coagulopathy of Trauma Analytes</td>
</tr>
<tr>
<td>DHP15-013</td>
<td>Optimization of Cryoprotectants, Cryotherapeutics, and Protocols for Cryopreservation of Large Tissue Systems</td>
</tr>
<tr>
<td>DHP15-014</td>
<td>Optimal Rewarming Solutions for Cryopreserved Tissue Systems</td>
</tr>
<tr>
<td>DHP15-015</td>
<td>Objective Measurement Tool for Detection and Monitoring of Noise-Induced Hearing Loss</td>
</tr>
<tr>
<td>DHP15-016</td>
<td>Novel Intraocular Visualization Tool</td>
</tr>
</tbody>
</table>
DHP SBIR 15.1 Topic Descriptions

DHP15-001 TITLE: Late Canthotomy and Cantholysis Training System

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Develop a simulation-based system to provide psychomotor skills training to advanced health care providers in the performance of a Lateral Canthotomy and Cantholysis (LCC) procedure, a method of preserving eyesight.

DESCRIPTION: Over the past twelve years of conflict, eye injuries have held at a rate of 5-10% of combat casualties, attributed to the enemy’s use of explosive devices. Many of these injuries result in a compartment syndrome of the orbit, easily decompressed through the use of a simple procedure called a Lateral Canthotomy and Cantholysis (LCC). The injury is most often caused by blunt trauma, when bleeding into the retrobulbar space causes an increase in intraocular pressure resulting in ischemia to the retina and optic nerve. The LCC is recommended as the treatment of choice in the Clinical Practice Guidelines issued by the Army Institute of Surgical Research and Joint Trauma System. The procedure can be easily performed by a pre-hospital advanced health care provider, thus decreasing intraocular pressure and potentially saving the patient’s vision. The LCC procedure is currently taught and employed primarily by Ophthalmologists and occasionally Emergency Medicine (EM) physicians at Role III facilities. However, the majority of forward deployed organic and Professional Filler System (PROFIS) providers do not have the Ophthalmology or EM background, skills, and knowledge to perform this procedure. The US Army Center for Pre-Hospital Medicine (CPHM) at Fort Sam Houston, TX, provides pre-deployment medical training to providers of all levels as mandated by HQDA EXORD 096-09, Mandatory Pre-Deployment Trauma Training (PDTT) for Specified Medical Personnel. Although the LCC procedure is mandated by the HQDA EXORD 096-09, CPHM does not currently have an LCC training device for the development of psychomotor skills prior to entering into the animal model phase of training. In addition, no current civilian equivalent training model exists for CPHM to adopt. As a result, there is a training void in the US Army and this relatively simple procedure has not been employed by advanced providers. Furthermore, it is cost prohibitive to use cadavers for the number of students attending CPHM each year, and is not logistically feasible to train all providers in Emergency Medicine or Ophthalmology. Consequently, the US Army is currently seeking ways to train providers on treating combat wounded service members on the modern battlefield with respect to the ability to execute this simple vision saving procedure. This eyesight saving skill must be practiced and rehearsed for military providers’ competency development.

Research conducted under this effort should focus on the development and evaluation of a low-cost, simulation-based head/eye training model to teach and practice the LCC procedure. The proposed training product should:

- Support established training objectives.
- Provide a capability to judge proficiency performance.
- Support practice of both cognitive and psychomotor skills.
- Have the ability to produce or simulate proptosis.
- Allow for fast reset.
- Ability to train multiple providers.
- Include palpable anatomical landmarks to determine proper location for injections and incisions.
- Include simulated facial bone fractures/crepitous to augment physical exam and scenario training.

PHASE I: Design/develop an innovative concept for a simulation-based training system to perform an LCC procedure. The effort should clearly analyze the scientific, technical, and commercial merit, as well as feasibility of using a low-cost medical simulator for training advanced medical providers of all levels in Army Combat Medical Training Programs. Proposed work should include research into feasibility of developing the capability and describing the overall concept. The effort should seek innovative and novel ideas to provide a hands-on, low-cost, and realistic simulation solution. The offeror shall identify innovative technologies being considered; technical risks of the approach selected; costs, benefits, and schedule associated with development and demonstration of the prototype.
PHASE II: Develop and demonstrate a prototype system from the recommended solution in Phase I that provides realistic and meaningful interaction for hands-on treatment. The offeror shall consider projection of costs to manufacture, maintain and resupply, as well as the equipment lifecycle. The evaluation of the proposed system by the user community at a military installation is required. The offeror shall conduct usability evaluations to assess the system in terms of: benefit to training, ease of use, anatomical accuracy, physiological accuracy, realism, and motivation to use. Data from these studies shall be provided, analyzed, and presented in a final report.

PHASE III: Follow-on activities are expected to be aggressively pursued by the offeror to demonstrate the application of this system to civilian hospitals, residency training programs, and other military medical personnel. The offeror shall focus on transitioning the technology from research to operational capability and shall demonstrate that this system could be used in a broad range of military and civilian medical training applications by physicians and physician assistants in austere medical environments with emphasis on meeting training objectives at the US Army Center for Pre-Hospital Medicine (CPHM) at Fort Sam Houston, TX.

REFERENCES:


KEYWORDS: Medical Modeling and Simulation, MM&S, Combat Trauma, Pre-Deployment Training, Lateral Canthotomy/Cantholysis, LCC, Orbital Compartment Syndrome, Maxillofacial Trauma, Eye Trauma

DHP15-002  TITLE: Mobile Virtual Interactive Presence Capability for Combat Casualty Care

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: The objective of this topic is to develop and demonstrate video overlay capability of virtual augmented reality technology, also known as VPAAR, on a mobile Android Smart device (also known as an End User Device (EUD)) over a military tactical network. A medic at the point of injury will use the built-in EUD camera to transmit the image of the casualty to a forward Medical Treatment Facility (MTF), like a Battalion Aid Station (BAS). The mobile VPAAR technology will allow a Medical Officer, at the MTF to see on his EUD or capable computer exactly what a medic sees at the point of injury, and then the Medical Officer can introduce his hands into the virtual field. The Medic sees the Medical Officer’s hands as a ghostly image on his Nett Warrior EUD and possibly on a heads-up display. EUDs (Android Smart phones or tablets) are being deployed and evaluated by the PEO Soldier Program Manager Soldier Warrior. The Nett Warrior program is an integrated dismounted situational awareness (SA) and mission command (MC) system for soldiers use during combat operations. USAMRMC Telemedicine and Advanced Technology Research Center (TATRC) is working in cooperation with PEO Soldier and PM MC4 to develop and demonstrate medical applications and wireless medical sensors to be displayed on Nett Warrior EUDs. At the point of injury, a medic will collect the casualty’s physiological data from wireless sensors, and will subsequently enter medical information on an electronic Tactical Combat Casualty Care (TCCC) card application on the Nett Warrior EUD. The Nett Warrior EUD will then transmit the electronic TCCC card via the military tactical network (Joint Tactical Radio System (JTRS) and/or Multi-Access Cellular Extension (MACE) 4G LTE) to a forward medical treatment facility. The intention of this topic is to utilize virtual augmented reality interactive presence to enable a medic to transmit live video from the point of injury to a medical officer at a forward medical treatment facility from a Nett Warrior EUD to a receiving MTF EUD or capable laptop/computer. Using video overlay, the medical officer can use virtual augmented
interactive hands to point to the area of concern, ensuring that the medic can see and understand the medical officer’s instructions.

DESCRIPTION: This topic seeks the development of a mobile virtual interactive presence capability prototype for use on any mobile device over a military tactical network to enable medical officers to provide visual guidance to first responders in a casualty care stability assessment. The intent is to provide the first responder, medic and en route care medic with the capability to transmit near real-time medical information to the next level of care, which will provide and improve medical situational awareness. Actionable information can better prepare the next medical treatment facility to provide appropriate patient care.

This topic seeks a mobile solution from existing Windows laptop/computer virtual augmented interactive presence for surgical assistance. The research and development will focus on software development for the current and future Nett Warrior EUD versions. The combat medic or corpsmen on the battlefield are starting to use Nett Warrior EUDs that connect wirelessly to medical sensors on patients to generate vital signs data. The vital signs data is then transcribed into an electronic TCCC card application on the Nett Warrior EUD which is then transmitted to a PM MC4 laptop on the military tactical network to be uploaded in the Armed Forces Health Longitudinal Technology Application – Tactical (AHLTA-T) and finally downloaded into the patient’s permanent electronic medical record. Current and future development is to develop wireless medical sensors that are integrated and viewable on Nett Warrior EUDs. The Nett Warrior EUDs on the military tactical network will transmit the electronic TCCC card and streaming video in near real time.

This research will incrementally advance the state of the art in pre-hospital combat casualty care assessment, monitoring, and intervention at the point of injury (POI) and on attended en route casualty evacuation vehicles. The final demonstration should show proof-of-concept feasibility for medical data from an Android EUD to be transmitted over a military tactical network to a Battalion Aid Station (BAS).

PHASE I: Research solutions for technical challenges for a virtual augmented reality interactive presence capability compatible with mobile Android devices, ensuring that the resulting data package stream is small enough to transmit over a limited bandwidth military tactical radio network. Phase I deliverables should include a final report, breadboard demonstration, and Phase II design plans, plus an exploration of commercialization potential with civilian emergency medical service systems development and manufacturing companies. Also, a plan for partnerships with government and private industry for the transition and commercialization of the production version of the product developed.

PHASE II: From the Phase I design, develop a ruggedized prototype and demonstrate the virtual augmented reality interactive presence on mobile Android devices; the prototype device can be initially demonstrated on civilian broadband wireless communications networks, knowing that the goal of the prototype is to work over military tactical networks. The prototypes maybe evaluated and tested by medics during a U.S. Army CERDEC Command, Control, Communications, Computers, Intelligence, Surveillance and Reconnaissance (C4ISR) Ground Activity Event exercise. Continue commercialization planning and relationship development with military and civilian end users to conduct proof-of-concept evaluations in Phase III. Begin to execute transition to Phase III transition and commercialization in accordance with the Phase II commercialization plan.

PHASE III: Refine and execute the commercialization plan included in the Phase II Proposal. After Phase III development, the final production model of the virtual interactive presence software capability must be ruggedized for shock, dust, sand, and water resistance to enable reliable, uninterrupted operation in combat vehicles on the move, to include operation and storage at extreme temperatures, and must also be easily installable on Android devices. Size and weight are important factors. The ultimate goal of the system would be to enable the assessment of patient medical stability and to alert first responders in time for preemptive medical care to be performed to save the life of the patient. Additionally, the data bandwidth must be small enough to transmit medical data over military tactical radios. Quantitative values for acceptable operational and storage temperatures and power requirements should be planned to comply with applicable MIL-SPECs (available online).

Execute proof-of-concept evaluation in a suitable operational environment (e.g. Advanced Technology Demonstration (ATD), Joint Capability Technology Demonstration (JCTD), Marine Corps Limited Objective Experiment (LOE), Army Network Integration Exercise (NIE), etc). Present the prototype project, as a candidate
for fielding, to applicable Army, Navy/Marine Corps, Air Force, Coast Guard, Department of Defense, Program Managers for Combat Casualty Care systems along with government and civilian program managers for emergency, remote, and wilderness medicine within state and civilian health care organizations, and the Departments of Justice, Homeland Security, Interior, and Veteran’s Administration. Execute further commercialization and manufacturing through collaborative relationships with partners identified in Phase II.

REFERENCES:
http://reboot.fcc.gov/c/document_library/get_file?uuid=8ac18153-1b96-4e14-958c-9538a7fc272c&groupId=19001

http://www.abstractsonline.com/plan/ViewAbstract.aspx?mID=2885&sKey=7fc33465-d67b-4f60-a795-fc877c8cfd9b%ccKey=a647460e-6ae3-4131-9429-bb4f23a501e0&mKey=%7B36FB8B6A-932F-4EDB-A20A-A9448F2863D0%7D

3. Virtual interactive presence and augmented reality (VIPAR) for remote surgical assistance;

KEYWORDS: combat casualty care, virtual augmented reality interactive presence, tactical military network, combat medic, telemedicine, medical informatics, mobile device

DHP15-003 TITLE: Virtual Medical Concierge Application

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Demonstrate a prototype medical concierge application that will improve patient, employee, and visitor engagement with Military Health System Military Treatment Facilities (MTFs). Pilot the prototype at Walter Reed National Military Medical Center (WRNMMC).

DESCRIPTION: Various leaders at Walter Reed National Military Medical Center have set forth the need for a medical concierge application to support improved operations for patients and visitors. Upon arrival at MTFs, many patients and visitors are challenged with finding parking, remembering which clinic or provider they are going to see, navigating the medical complex, and determining the follow-on actions after completion of an appointment (lab tests, pharmacy, and other consult schedules).

From the staff’s perspective, patients are frequently late or absent, they do not have their forms filled out in advance, and they are unhappy with their overall experience at the MTF. While many MTFs provide great care and patient educational content, they have difficulty disseminating it.

A cost-effective demonstration of information dissemination available through apps on smart mobile phones, tablets, and perhaps even Google Glass is needed. These apps would be downloaded to mobile devices and provide information on where a patient needs to go and what they need to know. The application should employ sensor beacons throughout the hospital to provide context-sensitive aware information that is specific to the patient. Upon arrival at the hospital, the patient would be guided to an open parking spot. He/she would then be given walking directions from the garage or parking space to the appropriate clinic, where he/she would be automatically checked in. Upon completion of an appointment, he/she would automatically be advised on how to get to the lab, pharmacy, or other department for follow-on work, and when their next appointment will occur. Based on the nature of the appointment, the patient would automatically be supplied with relevant patient educational material including appointments for future education seminars or videos. A wide array of guest services would be available through the app. Patients could be asked to complete satisfaction surveys on their mobile device. Staff would have their own applications, including the ability to create staff surveys concerning key management issues.
The concierge application provides a unique opportunity to exploit low-cost distribution of patient, visitor, and staff context sensitive information via a mobile application. It could be promoted through a “tell-a-friend” on-line marketing function. Cost benefits include fewer late and missed appointments and improved operational efficiencies through pre-filled patient forms. The application could also provide near-real time analytics on the customer experience at MTFs and automatically create profiles of customer likes and dislikes. The application could also integrate with existing or planned patient self-help applications, diagnoses checkers, and tele-health applications in the U.S. Army m-Care platform; DHA Tricare On Line Portal, or others supporting the Medical Home concept.

In order to promote DOD medical relevance, the Government will make available several development, integration, and test labs with various degrees of access to DOD medical systems, patient test data, and development tools.

These Government Labs will be made available on a competitive and reimbursable basis, solely at the discretion of the SBIR recipients, to provide access to military health systems and patient test data which might be useful in the research, and to assure DOD medical relevance.

The availability of these labs will be dependent on the Government Lab attaining a SBIR waiver to permit SBIR funds transfer to fund the cost of the lab during the research period of performance.

The existing Government Labs that may be available, depending on demand and other project requirements at the time of award, are:

1. U.S. Army Medical Research and Materiel Command (USAMRMC), Telemedicine and Advanced Technology Research Center (TATRC), Early Stage Platform (ESP), Fort Detrick, MD
2. Pacific Joint Interoperability Test Center (P-JITC), Maui, HI
3. Defense Health Agency (DHA), Development and Test Center (DTC), Richmond, VA

Note that these labs have access to DOD medical systems, but differ in their development tools and access to patient data for use in research.

Pricing would be negotiable, based on the actual requirements in the proposal.

Each SBIR vendor may desire to discuss their requirements with each of these 3 labs, and make a competitive decision based on their particular situation, during contract negotiations for Phase I and/or Phase II, depending on their proposal. Pending negotiations with the SBIR proposers or recipients, and the Government Lab’s attainment of a SBIR Waiver, the costs of the government lab would be withheld from the SBIR award and provided to the Government Lab to cover operating costs.

In lieu of using these labs, the SBIR proposer would need to propose how it would be tested in DOD equivalent Medical Device and Electronic Health Systems and patient data.

PHASE I: This Phase will demonstrate the feasibility of producing a virtual medical concierge application and will outline Phase II success criteria. Delivered as a report, required Phase I deliverables will include: conceptualization and design of a virtual medical concierge application in consultation with U.S. Army Telemedicine and Advanced Technology Research Center (TATRC) and Walter Reed National Military Medical Center; system performance goals and associated metrics; a draft concept of operation for the medical concierge system; and identification of health IT integration points, such as the scheduling system, and various DOD components forming the current Electronic Health Record While planning for the development of the prototype system, it must be shown to fit into overall Military Health System (MHS) architecture for existing or planned appointment, secure messaging, and pharmacy re-fill systems ensuring that it is both interoperable with existing information systems and based on common standards to support the necessary exchange of data and applications.

PHASE II: Based on the Phase I deliverables, develop, integrate, and test a pre-production prototype demonstrating potential military utility in accordance with system performance goals and metrics developed in Phase I. Deliver the pre-production prototype for DoD evaluation at Walter Reed National Military Medical Center with hands-on
assessment in a laboratory setting (System Integration and/or Qualification Testing) by patients, visitors, and hospital staff. By the end of Phase II the Contractor will have demonstrated a militarily and operationally relevant virtual medical concierge application for use at Walter Reed National Military Medical Center, with the scalability and flexibility to be employed for any MTF or commercial health system. Where available, the system should use open, state of the art software and hardware principles, use validated data from reliable sources, reside on DoD IT systems, and provide validated results. The SBIR recipients will deliver a report describing the design and operation of the pre-production prototype capability. The intent of this Phase is for the developer to deliver a well-defined prototype (i.e., a technology, product or service) meeting the requirements of the original solicitation topic and which can be made commercially viable.

PHASE III: Since this is a DHP SBIR topic, ideally the SBIR will develop a system prototype that can improve the consumer health experience in military health care, and will support the overall MHS Strategic Planning goals of accomplishing more with the same or declining levels of resources, while maintaining patient satisfaction and patient safety. The medical concierge may also help recapture workload lost to the civilian health system and paid under TRICARE managed health support contracts.

If the plan is to transfer the prototype to production in the military sector, the Phase III work should produce the necessary security application package to show how the final production platform will comply with the Defense Information Assurance Risk Management Framework (DIARMF) and Networthiness standards. Phase III work should also start the Defense Business Systems Certification approval process if it is anticipated that the prototype will transfer to production in the MHS. Prototypes may not transition to production in an operational system in the MHS unless these certifications have been obtained.

Such a system will likely also be of interest to commercial health organizations that are faced with similar resource issues while trying to maintain a positive consumer experience. If the plan is to transition the prototype for integration with commercial Electronic Health Records, Phase III would be used to plan and execute transition activities unique to commercial systems.

All work, regardless of whether intended for the DOD or civilian health sectors should leverage the HHS Office of the National Coordinator for Health IT’s Standards and Interoperability (S&I) Framework with respect to health data exchange and interoperability.

This SBIR topic provides various ways for interested small businesses to sustain their operations upon completion of the prototype and transition activities. As a software application, either military or civilian health systems users will require modernization efforts as new consumer services are introduced. Unique aspects of the application might also be patented, and licensed to other developers. In the case where an open source version of the virtual medical concierge software might be developed, the SBIR recipient should be prepared to set forth their plan for selling services around this software. Lastly, the virtual medical concierge software might be adapted for use in other industries outside of the medical domain, including hotels and the travel industry. Customer Relationship Management (CRM) is one of the next big areas to master for many industries, and is instrumental for survival in a competitive market. Hence, the topic of this SBIR is very timely.

REFERENCES:
1. Example commercial ExEVirtual Medical Concierge development platform at http://www.fourwindsinteractive.com/markets/healthcare/medical-concierge-services/
3. Example of medical staff items of potential interest in Medical Concierge application, http://www.healthcareoss.com/medical_concierge.php

KEYWORDS: Virtual Medical Concierge Application, Consumer Health, Customer Relationship Management (CRM), Customer Experience, DOD Military Health System, Military Treatment Facilities, Patient Satisfaction
TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Develop a toolset for analyzing the security properties of interconnected medical devices in an Integrated Clinical Environment (ICE) architecture.

DESCRIPTION: Inter-networked computing systems have long been subject to malicious exploits via a range of security vulnerabilities. Recently, embedded cyber-physical systems, power generation and distribution systems, and Supervisory Control and Data Acquisition systems (SCADA) have become targets of cyber-attacks. Security researchers have demonstrated that medical devices are vulnerable to such exploits. This has led the General Accounting Organization (GAO) to issue recommendations to the Federal Drug Administration (FDA) to increase oversight in this area [1]. The U.S. Department of Homeland Security, Industrial Control Systems Cyber Security Response Team (ICSCERT) and FDA have also issued recent safety alerts [2], [3] and [4].

While security is a property of an inter-networked system, medical devices are developed, tested and approved as stand-alone systems. This poses a challenge. Simply adding security controls to individual devices does not guarantee that a device is secure when assembled into a complete system. For other cyber-physical systems, such as aircraft, power systems, and process control systems system integrators are responsible for verifying “system of systems” properties, including security. However, integrated medical systems are typically assembled by hospital information technology (IT) staff. In the case of home-based devices, the patient or a family member assembles the network without such system integration testing, and thus fails to mitigate security risks.

Inter-networked hospital-based medical device research has centered on the ICE standard [5]. This American Society of Testing and Materials (ASTM) International standard defines a layered architecture for interconnecting devices with higher-level control and display functions, including alarm management. This architecture combined with the emergence of portable “apps” in the mobile device world has resulted in the concept of a “Medical Application Platform (MAP)” [6], which proposes that “apps” running on an approved “MAP” would be able to ensure that the resources the application requires are available before it begins to function.

Several problems need to be solved to ensure that the security properties of the system can be assured in a platform-based architecture.

• First, a method to analyze the security properties of the interconnected elements (devices, computing platforms and applications) and determine whether the required security properties are assured is required. This process begins with the definition of a specification language (or extension to an existing language) for security properties, such as the Architecture Analysis & Design Language (AADL) [7]. This specification must include the pre-conditions required by each interconnected element and the security properties provided if those pre-conditions are met. Subsequently, analysis methods and tools must be constructed to determine whether a set of elements can deliver required confidentiality, integrity, and availability levels.

• Second, the failure modes of the components in a MAP/ICE architecture and the impact of those failures on the security properties of the overall system must be understood. Failure sources may come from user interactions, including failed interactions with the security controls as well as from system response to malicious attacks. Error propagation models being developed for MAP/ICE architectures do not currently include these additional fault classes.

• Finally, analysis tools are needed to understand how the overall system can detect and respond to evidence that an attack is underway. Extending the models of application performance to separate essential capabilities from extended features would allow for us to investigate whether the overall system can safely operate with only the essential capabilities in the presence of a detected security attack.

Developing and testing security assessment tools for interconnected medical devices in a DOD environment poses special challenges. Such tools would have to support the security framework defined by the National Institute of
Standards and Technology (NIST), which is governed by NIST Special Publications SP-800-37, SP 800-39, and SP 800-53, and others which may be under development for medical devices. DOD is adopting the NIST framework in lieu of its older and now outdated Defense Information Assurance Certification and Accreditation Process (DIACAP) framework.

In order to promote DOD medical relevance, the Government will make available several development, integration, and test labs with various degrees of access to DOD medical systems, patient test data, and development tools. These Government Labs will be made available on a competitive and reimbursable basis, solely at the discretion of the SBIR recipients, to provide access to military health systems and patient test data which might be useful in the research and to assure DOD medical relevance.

The availability of these labs will be dependent on the Government Lab attaining a SBIR waiver to permit SBIR funds transfer to fund the cost of the lab during the research period of performance.

The existing Government Labs that may be available, depending on demand and other project requirements at the time of award, are:

1. U.S. Army Medical Research and Materiel Command (USAMRMC), Telemedicine and Advanced Technology Research Center (TATRC), Early Stage Platform (ESP), Fort Detrick, MD
2. Pacific Joint Interoperability Test Center (P-JITC), Maui, HI
3. Defense Health Agency (DHA), Development and Test Center (DTC), Richmond, VA

Note that these labs have access to DOD medical systems, but differ in their development tools and access to patient data for use in research.

Pricing would be negotiable, based on the actual requirements in the proposal.

Each SBIR vendor may desire to discuss their requirements with each of these 3 labs, and make a competitive decision based on their particular situation, during contract negotiations for Phase I and/or Phase II, depending on their proposal. Pending negotiations with the SBIR proposers or recipients, and the Government Lab’s attainment of a SBIR Waiver, the costs of the government lab would be withheld from the SBIR award and provided to the Government Lab to cover operating costs.

In lieu of using these labs, the SBIR proposer would need to propose how it would be tested in DOD equivalent Medical Device and Electronic Health Systems and patient data.

PHASE I: Develop a specification language for the security properties in a MAP/ICE architecture. Define the analysis properties to show that confidentiality, integrity and availability can be met by a collection of elements interconnected in a MAP/ICE architecture. Provide a demonstration of an analysis using automated tooling and a subset of the security properties. The performer shall document potential failures of the security functions of the architecture and its elements.

PHASE II: Refine the specification language based on Phase I findings, and extend the analysis tooling to the complete set of security properties. Extend the ICE fault models to incorporate the security faults. Define intrusion detection requirements for MAP/ICE architectures. Demonstrate fault model analysis including attack tolerant system behaviors driven by detected intrusion attempts. Develop and test prototype security assessment tools for interconnected medical devices in a DOD environment that meet the NIST standards governed by NIST Special Publications SP-800-37, SP 800-39, and SP 800-53,

PHASE III: In Phase III, the recipient will explore technology transition routes to commercialization of the developed tool or release it into the open source community. The tool could be potentially released for stand-alone product use or incorporated into other commercial software testing suites. These software testing suites, with the included medical device security assurance tool would be of interest to Medical Device Manufacturers, NIST, FDA, DOD, and commercial health delivery organizations. The market for specialized security tools for medical devices

DHP - 12
could be substantial. Security assurance is part of a broader set of properties that need to be evaluated for any system architecture instance, along with data availability (timeliness, data quality), overall system timing, processor loading, memory, reliability and fault/error response. While many commercial software testing suites provide for these characteristics, they do not currently provide for assessing the unique security aspects posed by medical devices. In the case of an open source release, the recipient may desire to collaborate with the Open Source Electronic Health Record Alliance (OSEHRA), Open Health IT Tools, Alembic/Aurion Foundation, or other open source communities to release the software into the public domain and determine a plan to sell services around the open source license.

REFERENCES:


5. ASTM F2761 - 09(2013); Medical Devices and Medical Systems - Essential safety requirements for equipment comprising the patient-centric integrated clinical environment (ICE) - Part 1: General requirements and conceptual model


KEYWORDS: Medical Device Security, Medical Device Interoperability, Integrated Clinical Environment (ICE), Supervisory Control and Data Acquisition Systems (SCADA), Industrial Control Systems Cyber-Security. Medical Application Platforms (MAP)

DHP15-005 TITLE: Methodologies and Techniques for Balancing Usability and Security for Medical Devices in an Integrated Clinical Environment

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Research and develop new controls for securing in an integrated clinical environment from malicious threats, which minimizes impacts on clinical workflows and usability, and promotes patient safety using a model-based approach.

DESCRIPTION: Tension often exists between security controls and usability needs. For example, end users’ quick access to a medical device or medical software application can be delayed by the need to first authenticate to ensure he/she is legitimate, and is provided the right level of system access. While there has been significant research conducted on the topic of security and usability for general purpose computing [1, 2], little research has been done in the clinical health setting. Mechanisms for authentication, access control, non-repudiation, and data privacy of
connected medical devices need to be evaluated in the context of acute clinical settings and remote care settings. For example, in the case of acute clinical settings, the user may have to wear masks or gloves, impeding system access through traditional means. The acute care setting also presents a need for multi-person care teams to access one or more systems in a timely manner where life is on the line. Remote care settings present different challenges, where the threat envelope is large and security expertise may be low. For medical systems in a deployed military infrastructure, the health care system is part of the overall supply chain, and could be a target of cyber-attack during conflicts. Medical device manufacturers do incorporate usability analysis in their design processes [3, 4], yet it typically only encompasses the behavior of a single device with a single user. How to handle authentication access control, non-repudiation, and data privacy of connected medical devices in non-traditional settings while balancing usability is the focus of this SBIR topic.

Security control decisions concerning usability and clinical workflow are complicated given the complexity of workflow scenarios and medical device combinations. The usability and security of a single device applied in a small set of clinical workflow scenarios is feasible “by hand,” however, computerized workflow models are needed to analyze more complex multi-device workflows. A workflow modeling approach should consider timing properties to be analyzed and should capture the interaction points with a range of candidate security controls. This approach should also model error flows – in particular, errors from interactions with security controls or confusion in their usage.

Such computerized workflow models for integrated medical device systems are only beginning to be conceived. Developing a computerized workflow modeling tool, specifically designed for medical system workflows, would allow key usability/security properties to be explored and assessed with respect to:

• The identification of security controls that balance good security and low workflow impact.
• The impact of disparate security controls across different devices associated with the same patient.
• The development of realistic workflow scenarios where a team of clinicians collectively manage a set of patients.

These specialized medical system workflow models will need to be validated by comparison with human performance in similar situations. Human performance can then be compared to the model predictions in order to calibrate model performance. The results of this research will likely be of interest to the Food and Drug Administration (FDA) Medical Device Act regulators; the Federal Communications Commission (FCC), the National Institute for Standards (NIST), and the Office of the National Coordinator for Health IT. If sanctioned by these medical device government regulators, control-based standards developed through this SBIR will likely become of interest to Medical Device Manufacturers.

In order to promote DOD medical relevance, the Government will make available several development, integration, and test labs with various degrees of access to DOD medical systems, patient test data, and development tools.

These Government Labs will be made available on a competitive and reimbursable basis, solely at the discretion of the SBIR recipients, to provide access to military health systems and patient test data which might be useful in the research, and to assure DOD medical relevance.

The availability of these labs will be dependent on the Government Lab attaining a SBIR waiver to permit SBIR funds to fund the cost of the lab during the research period of performance.

The existing Government Labs that may be available, depending on demand and other project requirements at the time of award, are:

1. U.S. Army Medical Research and Materiel Command (USAMRMC), Telemedicine and Advanced Technology Research Center (TATRC), Early Stage Platform (ESP), Fort Detrick, MD

2. Pacific Joint Interoperability Test Center (P-JITC), Maui, HI

3. Defense Health Agency (DHA) Development and Test Center (DTC), Richmond, VA
Note that these labs have access to DOD medical systems, but differ in their development tools and access to patient data for use in research.

Pricing would be negotiable, based on the actual requirements in the proposal.

Each SBIR vendor may desire to discuss their requirements with each of these 3 labs, and make a competitive decision based on their particular situation, during contract negotiations for Phase I and/or Phase II, depending on their proposal. Pending negotiations with the SBIR proposers or recipients, and the Government Lab’s attainment of a SBIR Waiver, the costs of the government lab would be withheld from the SBIR award and provided to the Government Lab to cover operating costs.

In lieu of using these labs, the SBIR proposer would need to propose how it would be tested in DOD equivalent Medical Device and Electronic Health Systems and patient data.

PHASE I: Investigate and demonstrate the impact of a set of typical medical device security controls on the workflow efficiency and safety of an interdisciplinary medical team using a clinical workflow monitoring approach in an integrated clinical environment. Create clinical workflow scenarios that are reasonably complex and address a single patient example (e.g. a patient in a critical care environment after surgery for major trauma) to be used in a demonstration of the model. Performers should provide an evaluation plan that describes how they will determine the validity of modeled results and apply this model to the demonstration.

PHASE II: Extend the model and evaluation plan to cover a wider range of clinical scenarios, including emergency room, operating room, and satellite clinics. Phase II could also include home-based monitoring, under the purview of the Military Health System Medical Home concept, as well as a broader set of device types and security controls. Analyze the scalability of the model to multi-patient scenarios (e.g. modeling an emergency room or a complete intensive care unit). Emergency access functions should also be analyzed. At the end of Phase II, the SBIR recipient will deliver a set of technical implementation guidelines for security control choices that balance usability with security and minimize negative impacts on clinical workflows. These technical implementation guidelines concerning security controls will be delivered in a report. The SBIR recipient will also provide the specific characteristics of the workflow modeling, the workflow monitoring tool developed, the evaluation plan, and a sample of executable software code that could be implemented to control a system of medical devices and electronic health records supporting the clinical scenarios chosen.

PHASE III: In Phase III, SBIR recipients could patent the Workflow Model, any associated workflow modeling tools, the evaluation plan, technical implementation guidelines, and executable medical device control software and negotiate commercial licensing with DOD Defense Health Agency; the Veterans Health Administration; FDA; FCC; NIST; ONC for Health IT, other interested government agencies; medical device manufacturers, or healthcare delivery organizations. As an alternative, any or all of these artifacts might be released into the open source community through organizations such as the Open Source Electronic Health Record Alliance (OSEHRA) or Open Health IT Tools or similar organizations for open sources licensing. Based on negotiations with the types of government and commercial organizations cited, it is possible that hybrid commercial and open source licensing could occur. In the case where these artifacts are released into the open source community, the SBIR Recipient would need to develop and provide a plan to state how it would sell additional consulting, software implementation and/or training services around their workflow model, technical implementation guidelines, and/or software controls.

REFERENCES:

2. See the proceedings of the annual Symposium on Usable Privacy and Security (SOUPS) http://cups.cs.cmu.edu/soups

3. IEC 62366:2007 Medical Devices – Application of Usability Engineering To Medical Devices

4. AAMI HE75:2009 Human Factors Engineering - Design of Medical Devices

KEYWORDS: Medical Device Security, Medical Device Usability, Medical Device Interoperability, Integrated Clinical Environment (ICE)

DHP15-006 TITLE: Rapid Detection of Borrelia burgdorferi (Lyme disease) from Ticks

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: To develop a sensitive, specific, rapid, portable, field friendly assay to determine whether a tick or pool of ticks is infected with the Borrelia burgdorferi bacterium, the causative agent for Lyme disease.

DESCRIPTION: Arthropod borne disease is one of the more significant threats facing the health of our military personnel, which can affect the readiness of our troops both at home and abroad. The spread of disease by these vectors can be averted by a timely and resourceful surveillance and treatment program. One of the resources required by these programs is the ability to rapidly and accurately detect the number of arthropods carrying a pathogen of interest. The Lyme disease bacterium, Borrelia burgdorferi, is spread through the bite of an infected tick (vector/arthropod) and infects more than 20,000 people a year in the United States alone. The bacteria are found inside ticks, and are transmitted during feeding. The blacklegged tick (or deer tick, Ixodes scapularis) spreads the disease in the northeastern, mid-Atlantic, and north-central United States, and the western blacklegged tick (Ixodes pacificus) spreads the disease on the Pacific Coast. The disease can also be found throughout Europe. Since many of our troops are stationed at bases throughout the U.S. and Europe that can potentially expose them to this pathogen, we need a rapid method of detection for an effective surveillance and treatment program.

Most humans are infected with Borrelia burgdorferi through the bites of immature ticks called nymphs. Nymphs are tiny (less than 2 mm) and difficult to see; they feed during the spring and summer months. Adult ticks are larger (up to 3.5mm) and can also transmit Lyme disease bacteria.

A rapid, field-friendly assay is required to break open the ticks, and to detect the Borrelia burgdorferi bacterium. Ticks have a tough exoskeleton, especially adult ticks; breaking them open to acquire bacteria can be difficult. The method developed will need to rapidly break open 1-10 ticks at a time. Since disease surveillance requires a large number of samples (ticks) be collected and processed rapidly, the assay will need be able to process a large number of samples, and should require no more than 30 minutes to obtain results.

The method developed needs to be field-friendly, meaning no cold chain, little to no electricity (if power is needed it should be able to be supplied from a battery or other portable source) and portable, meaning it should weigh less than 3 pounds and be smaller than 1 cubic foot. If ancillary equipment or reagents are required, the same requirements should be followed.

The method developed should be sensitive and specific. Sensitivity needs to be 80% compared to a standard non-molecular assay i.e., Enzyme Linked Immuno-Sorbent Assay (ELISA) and specificity must reach 80%; again compared to non-molecular assays.

PHASE I: The selected contractor shall determine the feasibility of the concept by developing a prototype assay that has the potential to meet the broad needs discussed in this topic. The contractor shall conduct initial laboratory evaluation of the prototype device and provide a written report to the Contracting Officer’s Representative (COR). By the conclusion of Phase I, the selected contractor shall provide a single lot of 100 prototype assays to the COR. The degree to which the prototype assay meets the desired capability outlined above will be evaluated at a government laboratory. Data from this independent evaluation will be used in the determination of the Phase II awardee.
PHASE II: The goal in Phase II is the development of a prototype assay that provides at least 80% sensitivity and at least 80% specificity when compared to current gold standard assays for detecting Borrelia burgdorferi. Once sensitivity/specificity requirements have been met, the selected contractor shall conduct comprehensive laboratory evaluation of the assay performance characteristics (sensitivity, specificity, positive and negative predictive value, accuracy and reliability) and initial field testing. By the conclusion of Phase II, the selected contractor shall provide a single lot of 1,000 prototype assays to the COR. The selected contractor shall also conduct stability testing of the device in Phase II. Stability testing should be conducted under both real-time and accelerated (attempt to force the product to fail under a broad range of temperature and humidity conditions and extremes) conditions. The Walter Reed Army Institute of Research (WRAIR) or US Army Medical Research Institute of Infectious Diseases (USAMRIID) may provide support to facilitate the test and evaluation of the developed device. The selected contractor shall coordinate in advance with the COR for any support required from the WRAIR or USAMRIID.

PHASE III: During this phase, the performance of the assay should be evaluated in a variety of field studies that will conclusively demonstrate that the assay meets the requirements of this topic. By the conclusion of this phase the selected contractor will have completed the development of the assay and successfully commercialized the product. The contractor shall provide a report that summarizes the performance of the assay to the Armed Forces Pest Management Board, and will request that a national stock number (NSN) be assigned. Contractor shall coordinate in advance with the COR for any support required from the WRAIR or USAMRIID. Military Application: Once an NSN has been assigned to the assay, the Armed Forces Pest Management Board will work with appropriate organizations to have the assay incorporated into appropriated "sets, kits, and outfits" that are used by deployed Preventive Medicine Units.

Commercial Applications: This assay will also be available for non-military purposes, such as use by commercial pest controllers or non-governmental organizations (NGOs) in areas of the world where Borrelia burgdorferi/Lyme Disease are endemic. We envision that the contractor that develops the Borrelia burgdorferi assay will be able to market this assay to a variety of commercial, governmental and non-governmental vector control organizations, and that this market will be adequate to sustain the continued production of this device. By the end of this phase, the selected contractor shall make this product available to potential users throughout the world.

REFERENCES:

KEYWORDS: Arthropods, field-deployable, lyme, ticks, Borrelia burgdorferi, rapid, vector, bacteria
DESCRIPTION: This topic seeks the identification and preparation of a candidate small molecule(s) for the treatment of multidrug-resistant bacteria. Ideally, the molecule(s) will broadly target gram-negative and gram-positive classes of bacteria. The successful candidate small molecule could be incorporated 1) into a wound dressing material, 2) into a topical formulation, or 3) into a systemic or local delivery system to specifically target infections. The molecule and delivery system is expected to have no, or minimal, toxicity and should be easily administered by the patient or caregiver.

An increasing number of antibiotic-resistant bacteria have been recognized as a global (2) as well as a military threat. Infections resulting from such bacteria can cause sepsis, cellulitis and skin abscesses, pneumonia, toxic shock syndrome, and endocarditis, with serious cases resulting in organ failure, loss of limbs (via amputation) and death. To date, a number of new antibiotics in various classes have been approved and/or are in various phases of development for the treatment of the spectrum of bacterial infection; however, an antibiotic that can overcome multidrug resistance has not been demonstrated (3). This is largely due to the powerful adaptability of microbes, the misuse of antibiotics, as well as the lower relative rate of return on investment for antibiotics compared to other drugs (4).

Clinical management of multidrug-resistant bacterial infections has become critical components of combat care. Complications due to wound infection are the primary cause of morbidity among patients that suffer combat and non-combat related trauma, and are a leading cause of mortality in patients who survive the first few days after injury (5). The effects of these multidrug-resistant bacteria are even more devastating for burn patients or those who are otherwise immune-compromised (6). Consequently, these infections add an expense of $20-35 billion to the US healthcare system alone (7). Based on the need to control multidrug-resistant infection globally, in particular within high-risk patient populations within the US military, this topic seeks proposals that will develop an innovative small molecule that targets multidrug-resistant bacteria by overcoming current bacterial resistance strategies and/or one that improves the effectiveness of known antibiotics by circumventing existing bacterial countermeasures.

PHASE I: Define and characterize a small molecule(s) that can directly or indirectly treat any single, or any combination of multidrug-resistant bacterial infections stated in the Objective. Proposals should describe the rationale for the appropriateness of candidate lead molecule(s) already identified by initial screening. Screens to simply identify small molecule candidates will not be considered for funding. Proposals should contain: 1) in vitro data against a bacterial panel which includes the resistant strains noted in the Objective, 2) a compound series containing analogues with varying in vitro activity, and 3) a plan and rationale on further analogue development to increase activity. This small molecule should be compatible with incorporation into a wound dressing format, topical formulation, or other delivery system. Required Phase I deliverables will include: 1) demonstration that the study rationale led to 2-3 analogues with increased activity, 2) in vitro metabolic stability (human) performed on a representative sample of the compound series, 3) in vitro toxicity data on a representative sample, and 4) a detailed animal testing plan. No animal/human testing is required during the Phase I (6 month) period.

PHASE II: Further evaluate the efficacy of the small molecule(s) identified in Phase I in a military-relevant in vivo model(s) of multidrug-resistant infection (pre-clinical studies). Evaluate the safety of the molecule with respect to biocompatibility, toxicity and immunogenicity. Required Phase II deliverables will include: 1) demonstration of bactericidal/bacteriostatic activity using the delivery method(s) and formulation(s) identified in Phase I against at least one of the above identified bacterial species within a military-relevant in vivo model of infection, 2) preliminary assessment of effective dose ranges and application frequencies, 3) assessment of the safety and toxicity in vitro, in vivo, or ex vivo, and 4) initial optimization of the most promising molecule formulation, delivery method, and production approach that follows Good Manufacturing Practice (GMP) manufacturing guidelines. In addition, applicants must plan to conduct a pre-Investigational New Drug (IND) meeting with the US Food and Drug Administration (FDA) at the end of Phase II. Department of Defense Research Laboratories (Walter Reed Army Institute of Research (WRAIR), Naval Medical Research Command (NMRC), and United States Army Institute of Surgical Research (USAISR) have validated burn and wound infection animal models and SBIR Phase II Principal Investigators are encouraged to collaborate with these DoD Laboratories.

PHASE III: If successful, Phase II work will result in a novel small molecule that directly or indirectly treats multidrug-resistant bacterial infections. During Phase III, additional experiments will be performed as necessary to prepare for FDA review of an IND application. A plan for protection of intellectual property should be created and executed. The small business should have plans to secure funding from non-SBIR government sources and/or the

DHP - 18
private sector to develop or transition the prototypes into a viable product for sale to the military and commercial markets. The end-state of the research will be the full development of one or more products consisting of an innovative small molecule that prevents or eradicates the growth of multidrug-resistant bacteria and that can be administered to military and civilian patients in a clinically relevant manner. Military application: The therapeutic will be available to military personnel who suffer from multidrug-resistant bacterial infections of wounds related to combat- and noncombat-related trauma. Commercial application: Health professionals could utilize this therapeutic to treat various multidrug-resistant bacterial infections in medical facilities worldwide, reducing morbidity, mortality and global healthcare costs.

REFERENCES:
(1) Zapor et al. 2008. Emergence of Multidrug Resistance in Bacteria and Impact on Antibiotic Expenditure at a Major Army Medical Center Caring for Soldiers Wounded in Iraq and Afghanistan. Infection Control and Hospital Epidemiology 29(7): 660-663.

KEYWORDS: antibiotic, multidrug-resistant, wound care, infection, small molecule, bacteriostatic, bactericidal, antimicrobial

DHP15-008 TITLED: Predictive Capability for Infectious Diseases

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Demonstrate a prototype system that will successfully predict the incidence of human infectious disease. In this context, "predict" is defined as approaches aiming to anticipate the likelihood that a specific infectious disease threat will emerge in the human population; whereas "forecast" refers to approaches that aim to project the likely progression of, and impact of specific mitigation measures on, the trajectory of infectious disease outbreaks.

DESCRIPTION: The prevention of disease is vital to the success of military missions. The US Department of Defense (DoD) has developed a requirement for innovative technologies to support disease prevention strategies. Infectious diseases are a significant threat to the fighting strength of our Armed Forces, and have historically been the major cause of casualties during war (1).

For many diseases today, it is possible to detect and identify biological pathogens (after exposure of personnel) in time to pretreat victims before the onset of symptoms. Prediction (before exposure of personnel) of a disease threat in time to adjust medical planning, operational plans, or mission parameters would be of significant value. These, and related actions, eliminate or mitigate disease vectors before they reach personnel or enhance the ability of personnel to protect themselves from exposure with physical barriers or medical prophylaxis to disease hazards.
Advanced awareness of emerging infectious disease threats would enable DoD decision makers to coordinate timely, science-based disease outbreak prevention, preparedness, and control-and-response capabilities (2).

For diseases of operational significance to the United States military, the DoD is seeking innovative materiel solutions to provide a deployable and easy to use disease prediction capability. It should provide users of varying (but appropriately trained) experience levels at headquarters, command, and unit levels the ability to identify, with selectable geospatial, temporal, and impact (e.g. virulence and transmissibility) parameters, the risk that a particular disease (novel, emerging, re-emerging) will present in the human population. Analytical support should be made available as may be desired by the user; “what-if” analyses applied to disease emergence factors should enable the user to construct emergence scenarios of their own selection; metrics characterizing the level of confidence in prediction model results should be practical, intuitive, and effective. Extensive special training in the use and output of the model should not be required.

Developing and testing security assessment tools for interconnected medical devices in a DOD environment poses special challenges. Such tools would have to support the security framework defined by the National Institute of Standards and Technology (NIST), which is governed by NIST Special Publications SP-800-37, SP 800-39, and SP 800-53, and others which may be under development for medical devices. DOD is adopting the NIST framework in lieu of its older and now outdated Defense Information Assurance Certification and Accreditation Process (DIACAP) framework.

In order to promote DoD medical relevance, the Government will make available several development, integration, and test labs with various degrees of access to DOD medical systems, patient test data, and development tools.

These Government Labs will be made available on a competitive and reimbursable basis, solely at the discretion of the SBIR recipients, so as to gain access to military health systems and patient test data which might be useful in the research, and to provide for DOD medical relevance.

The availability of these labs will be dependent on the Government Lab attaining a SBIR waiver to permit SBIR funds to fund the cost of the lab during the research lab.

The existing Government Labs that may be available, depending on demand and other project requirements at the time of award, are:

1. U.S. Army Medical Research and Materiel Command, Telemedicine and Advanced Technology Research Center, Early Stage Platform (ESP)
2. Pacific Joint Interoperability Test Center (P-JITC), Maui, HI
3. Development and Test Center, Richmond, VA

Note that these labs have access to DOD medical systems, but differ in their development tools and access to patient data for use in research.

For example, the TATRC lab has access to Synthetic Patient test data, which is totally made-up data generated by computer, and does not require any Data Use Agreements or Institutional Review Board Approvals in advance of use. Other labs may have access to de-identified or anonymized test data that will require Data Use Agreements and Institutional Review Board approvals.

TATRC ESP and P-JITC Government Labs are more oriented towards research use; the DTC lab is more oriented towards production system testing, but may be available for early stage research, depending on demand.

Pricing for these labs are based on individual project needs, number of users, how many servers they need, how much storage, and other factors, such as need for test patient data.

Pricing would be negotiable, based on the actual requirements in the proposal.
Typical cost for use of the TATRC ESP lab in the past has ranged from $75K to $300K, but the actual cost for an SBIR should be determined in negotiations with each lab.

Each SBIR vendor may desire to discuss their requirements with each of these 3 labs, and make a competitive decision based on their particular situation, during contract negotiations for Phase I and/or Phase II, depending on their proposal. Pending negotiations with the SBIR proposers or recipients, and the Government Lab’s attainment of a SBIR Waiver, the costs of the government lab would be withheld from the SBIR award and provided to the Government Lab to cover operating costs.

In lieu of using these labs, the SBIR proposer would need to propose how it would access test instances of DOD Medical Systems and patient data.

PHASE I: Demonstrate the feasibility of producing a disease prediction capability, and outline Phase II success criteria, such as prediction timing, geographical focus, and disease selection. Delivered as a report, required Phase I deliverables will include: Conceptualization and design of an innovative disease prediction capability (no restrictions on the number of models comprising the capability exists, but it is envisioned that topic respondents will address one model, for one location/region, and one disease); performance goals and associated metrics; and a draft concept of operation for the capability. Development of any model under this topic must be shown to fit into our biosurveillance portal architecture (additional information will be provided to respondents during this phase regarding the architecture needs), ensuring that it is both interoperable with existing information systems, such as Global Information Grid (GIG) but also Joint effects Model (JEM), Joint Warning and Reporting (JWARN), etc., and based on common standards to support the necessary exchange of data and applications.

PHASE II: Based on the Phase I design and development feasibility report, the performer shall produce a prototype demonstrating potential military utility in accordance with the success criteria developed in Phase I. The performer will then deliver the prototype for DoD evaluation. The performer shall deliver a report describing the design and operation of the prototype. The intent of this phase is for the developer to deliver a well-defined prototype (i.e., a technology, product or service) meeting the requirements of the original solicitation topic and which can be made commercially viable.

PHASE III: By the end of Phase III, the contractor will have demonstrated a militarily and operationally relevant disease prediction capability with the scalability and flexibility to be employed for one or more diseases and geographic regions of interest. Ideally, the capability will be based on open, state of the art software and hardware principles, use validated data from publicly available sources, reside on DoD IT systems, and provide validated results.

Such a system would fulfill a documented capability gap (Capability Development Document for Global Biosurveillance Portal, May 2014), and support the Joint Program Executive Office Chemical and Biological Defense Program (JPEO-CBD). JPEO-CBD is the Joint Services’ single focal point for research, development, acquisition, fielding and life-cycle support of chemical and biological defense equipment and medical countermeasures, and manages contracts for product development from after the proof-of-concept phase through initial fielding to operational units. Further, the system may have commercial market applicability to commercial and governmental health care professionals, and non-governmental and intergovernmental organizations (NGOs and IGOs) implementing public health, humanitarian assistance, and disaster relief projects in the developing world.

REFERENCES:
1. Armed Forces Research Institute of Medical Sciences (AFRIMS), http://www.afrims.org/frmsetabout.html

KEYWORDS: Prediction, infectious disease, forecasting, biosurveillance
TITLE: Ultimate Passive Dosimeter

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: A non-invasive, wearable passive dosimeter that can be stored indefinitely until analysis is required. The ideal product would be able to measure chronic exposures (several days to weeks) of exposure to sub-acute levels of hazardous chemicals in the spectrum of military environments. The intent is to provide a broad screening process for a wide-range of hazards for exposure documentation to gases, volatile and semi-volatile organics, as well as to substances that may need to be captured and analyzed by a variety of different mechanisms such as respirable aerosols.

DESCRIPTION: Historically, sampling to establish exposure has been conducted on relatively controlled events with either active or passive samplers. This approach works with well-established industrial practices. However, there is no current approach that suitably captures exposures during military operations where sampling may be problematic due to logistics of obtaining supplies, power, ruggedness of equipment, and shipping back to analytical labs located far outside of theater. Examples of issues where insufficient personal data was problematic are: Agent Orange (AO) in Vietnam, burn pit exposure1 (BPE) in Iraq, and any number of hazards linked to Gulf War Illness. If a universal sampler was deployed – an analysis may have been able to link health outcomes to exposures. This approach could lead to timely diagnoses which would benefit the exposed individual, reduce liabilities to the DOD, and allow for corrective actions in the future. The goal is to provide a dosimeter at low cost that is rugged, sensitive, specific, small and lightweight, that can integrate doses over time. This dosimeter would provide Individual Longitudinal Exposure Records (ILER) for service members.

Recent literature(2-4) has shown that readily available resins can be worn as wrist bands and have the ability to capture a wide range of organic compounds. We would like to advance this concept by fitting the form and substrate to suit military needs. For example, a wider set of substances would be desirable so the substrate may need to be changed or added to. Ideally, this would create a non-intrusive sampler capable of multiple types of analysis that could be attached to the uniform. We will refer to this as the Ultimate Passive Dosimeter (UPD).

The UPD should allow the captured analytes to have long-term stability. We define stability here as minimizing the loss of compound either to breakdown product formation and/or avoidance of loss due to volatilization.

The UPD must also be able to reversibly release the product for the purpose of analysis. Analysis of the UPD could be by a variety of means, including but not limited to: thermal desorption, headspace analysis, chemical extraction, supercritical fluid extraction, microscopy, etc. Since a single exposed UPD may require a variety of extraction schemes, the ideal material would be uniform and be able to be sectioned for multiple analyses. The sampler should be designed with uniform absorption so that sectioning would provide pieces with equal exposure.

The UPD will require a chemically inert storage device for delivery to the service members and return to the laboratory and should be a consideration in the proposal.

While many compounds can be collected and analyzed without loss, many other compounds are highly reactive and decompose after collection. A secondary consideration should be given to the possibility of embedding derivatizing agents that would allow these compounds to be captured and analyzed. A few classes of target analytes that require modification during collection are: aldehydes, ozone, etc.

PHASE I: The effort in this phase will identify is the most appropriate material and the best geometry that can be the basis of the Universal Passive Dosimeter (UPD). The material(s) will be shown to be free of contaminants. The technical feasibility of the UPD will be determined with respect to a the following classes of compounds: Organophosphates; Nitramines; Pyrethroids; Nitroaromatics; Tetrazoles; Organochlorines: PCBs/PCDFs/PCDDs; PAHs; Carbonyl Compounds; Fuels and Chlorinated solvents. In this phase a limited testing of these classes will be investigated with respect to capture, stability and recovery of the target compounds. Since this is primarily a screening tool, an imperative will be placed on the applicability to a broad set of contaminants as opposed to any
specific set of chemicals or chemical classes. However, the following compounds are of key interest and should be examined: Acrolein; Benzene; Naphthalene; 1,2,4-Trimethylbenzene; Vinyl Acetate; Methylene Chloride; Hexane; Xylene and Acetaldehyde.

Phase I – Performance Parameters: Success will be measured by the number of classes of compounds (described above) that were successfully recovered (minimum 7/10 classes). Of those classes deemed successful it is anticipated that preliminary stability data will be provided.

We also desire Phase I to perform modeling to determine if effective rates of sampling can be established.

PHASE II: Using the results from Phase I, the dosimeter will be developed and validated with respect to the ten (10) classes described above. The validation will demonstrate that an effective sampling rate (ESR) can be established. Additionally, the practical implementation should demonstrate the degree of analyte stability with regard to the collection medium; and recovery. A prototype will be developed that includes the packaging to the deployed airman, as well as, packaging to store the UPD until analysis can be accomplished. This packaging must include sufficient space to provide details that include where the sample was taken, who was exposed and the duration of the UPD exposure.

Phase II – Performance Parameters: Design of a dosimeter or packaging to provide stability for a minimum of 30 days after collection. Stability is defined here as greater than 75% recovery of absorbed materials when received and analyzed by a laboratory.

PHASE III: Follow-up activities are expected to be pursued by the offeror, including government and civilian application and use, i.e. occupational health applications in situations where conventional sampling is difficult or impossible. Commercial application: Commercial benefits include a very efficient process for archiving the exposure of individuals while actively engaged with toxic chemicals. Actively monitoring of archived samples may lead to early diagnosis and lower morbidity from chemical exposure.

REFERENCES:
1. Ring of Fire, Katie Drummond, The Verge, October 2013

KEYWORDS: Chemical Passive Dosimeter, Volatile Analyses, Semi-volatile Analyses, Ease of Deployment, Target Compound Stability, Resin, Chemical Exposure

DHP15-010 TITLE: Oxygen Separation from Air to Provide Supplemental Oxygen for Injured Soldiers

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Develop and demonstrate new techniques to separate/enrich oxygen from air using minimal power to provide supplemental oxygen for injured soldiers under field conditions.

DESCRIPTION: Currently when soldiers suffer a loss of blood due to injury their oxygen carrying capability is compromised. This can lead to permanent disability or death. Army medics do not have whole blood or compressed oxygen available to administer to ameliorate blood loss. Oxygen has been used for more than 25 years as therapy for
extreme blood loss in cases where transfusion has been unavailable. Army medics could rapidly provide live saving care under austere conditions using a device that generates oxygen enriched gas by separation from air at the point of use until patents could be transported to medical facilities. The hand-held device would need to start rapidly and use minimal power.

Ceramic membranes have been used to selectively separate oxygen from air through electrical or pressure differentials with oxygen traversing the membrane as oxygen ions. To date systems based on these technologies have generally been large and consumed significant power often because the ceramic materials have operated at elevated temperatures to achieve acceptable conductivity. Research needs to be conducted that explores new materials with enhanced oxygen conductivity at lower temperatures and new methods of manufacture that enable the production of robust high surface area ceramic membranes that can be integrated into oxygen separating devices.

PHASE I: Design, construct, and evaluate proof of concept device that is capable of generating >1 liter of oxygen enriched gas per minute without the use of consumables such as water. Provide a detailed conceptual design of a light-weight battery powered system capable of generating 10's of liters of oxygen per minute based upon the results generated in the phase I effort. Conceptual design should include consideration of physical shock hardening to ensure function after drop or other physical impact and production cost per unit estimate.

PHASE II: Demonstrate and deliver breadboard device capable of generating >20 liters of 90 % oxygen enriched gas per minute using a BA-5590 battery (~170Wh) for 30 minutes. Device should weigh less than 2 kg and should not require consumables such as water. System ideally would be able to start in less than 5 minutes.

PHASE III: Prototype system would require additional development to include oxygen delivery monitoring, is modulated by pulse oximetry etc. prior to fielding. A point-of-use oxygen generator that does not require consumables such as water would be used in hospital and home use settings. This device could also be used to replace oxygen cylinders that patients must often carry or roll with them to enable movement. These systems could also be used in laboratory and small manufacturing systems to provide oxygen for a variety of processes.

REFERENCES:

KEYWORDS: oxygen, casualty, air, separation, enrich, ceramic, manufacturing processes, fabricate
platelets. Platelets are typically stored or ‘banked’ to improve the processing procedure and determine product quality. Storage of platelets for periods longer than 5-7 days produces a condition known as platelet storage lesion in which platelets become progressively less able to form blood clots [1]. This can, in part, be due to bacterial contamination, but other mechanisms may also contribute to this decline in function. Factors that can reduce the quality of platelet function include the method of isolating and collecting them from a donor’s blood, the chemical compositions of the storage container and the storage media, and the storage temperature. Understanding how these and other factors could adversely affect normal molecular mechanism(s), and thereby causing a dysfunctional state requires a detailed understanding of the kinetics of the molecular pathways that help maintain critical functions. The proteins and metabolites (sugars, amino acids, lipids, glutathione etc.) of stored platelets have been shown to exhibit changing concentration profiles during the storage period [2]. Such a dynamic set of components adds even more complexity to this inherently difficult system. The primary focus of this topic area is to have a kinetic model built that can simulate and determine which metabolic, signaling and other pathways are potentially affected in producing the platelet storage lesion, and to develop a prototype or a commercial software product to help improve the storage of blood components.

PHASE I: In this Phase I study, a kinetic model will be formulated, and a computer program will be developed and demonstrated to simulate one or more indicators of dysfunction that occur in platelets during 5-7 days of storage. These indicators may include, but are not limited to, an increase in glycolysis, an accumulation of lactate, an increase in acidity (drop in pH), changes in pCO2 and pO2, and an increase in reactive oxygen species. The quality of the performance of this program will be evaluated based on how well specific indicators of platelet dysfunction can simulate published experimental and/or clinical data. The effects of temperature and the variables characterizing one or more types of storage media should also be simulated. The results of this work will help the Government determine whether such a kinetic approach at the molecular level is feasible, and whether it would have scientific, clinical and commercial merit. The Phase I deliverable is a prototype computer program (both the source code and an executable version) that can run on a standard laptop PC or on a server that has a user-friendly interface. Results of parametric simulations should help design experimental protocols for model validation and for improved platelet storage.

PHASE II: If one of the Phase I efforts is successful, a future Phase II effort will be used to plan and execute the development of a prototype program or a commercially viable software product for improved blood product storage. Further model improvements and identification of kinetic parameters for model calibration and validation will be conducted. Simulation outcomes will guide the design of experiments to collect data for model validation, better understanding of the mechanisms of platelet storage lesion, and for improving platelet storage protocols. The final software framework and models will then be delivered to the COR for evaluation.

PHASE III: The envisioned end state of this project is the development and marketing of a commercial-grade software tool suitable for application in civilian and military blood banks, and platelet storage equipment manufactures. This software tool could be further extended for model-based optimization of transfusion products and protocols, as well as hemostasis, in combat casualty care. Such a tool will also have civilian applications in hospital intensive care units.

REFERENCES:


KEYWORDS: transfusion; blood platelets; platelet storage lesion; platelet preservation; proteomics; signal transduction
TITLE: Real-Time Small-Volume Blood Sampling and Analysis for Coagulopathy of Trauma Analytes

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Develop a biosensor technology capable of measuring specific analytes in blood, continuously, in real-time. The biosensor must be able to measure multiple analytes that are relevant to coagulopathy of trauma and related phenomenon (e.g. therapeutic agents and protein biomarkers).

DESCRIPTION: Traumatic hemorrhage is associated with the development of trauma induced coagulopathy, as well as a number of responses including an inflammatory response, endothelial dysfunction, and others. These pathophysiologic reactions develop and progress rapidly, and result in increased mortality and morbidity. In order to provide effective treatment under these rapid and dynamic conditions, it is imperative to develop novel biosensor technology capable of measuring multiple analytes continuously in the blood of the patients - in real-time. In the current state-of-the-art, continuous, real-time molecular measurement is only possible for a handful of targets (e.g., glucose, lactose, oxygen), and these existing platforms for continuous measurement are not generalizable for the monitoring of other analytes [1,2]. To address this critical unmet need, the main goal of this project will be to develop a “universal” real-time biosensor capable of continuously tracking a wide range of circulating biomarkers and drugs in living subjects.

The successful implementation of such a biosensor must fulfill the following requirements: First, the sensor must operate continuously, without requirement for sample preparation or processing. Second, it must achieve sufficient sensitivity, selectivity and dynamic range, and demonstrate the ability to resolve temporal changes in analyte concentrations at physiological time-scales (i.e. minutes). Finally, it must be resistant to fouling even after prolonged exposure to complex sample mixtures such as whole blood, and remain stable while operating in this environment for extended periods of time.

PHASE I: The main goal of the Phase I project is to construct a prototype biosensor and demonstrate the feasibility for continuous, real-time measurement of a protein related to thrombin generation or other proteins involved in hemostatic mechanisms. The performer may select the relevant therapeutic agent of their choice. The demonstration must be performed first in vitro using undiluted whole blood as a sample matrix.

The prototype biosensor must meet the following specifications:
• Operate continuously for at least 1 hour.
• The detection must be performed directly in whole blood without sample preparation (i.e. no batch processing).
• Must achieve sufficient sensitivity to detect the therapeutic agent at physiologically relevant concentrations.
• The sensor must be specific to the therapeutic agent and not respond to other molecules.
• Must be able to achieve continuous detection with a temporal resolution at relevant concentrations. Time resolution of less than 10 minutes is highly desirable.
• Must demonstrate that the sensor is stable throughout the operation.

It is highly desirable to demonstrate that the sensor approach is general; that it can be broadly applicable for the measurement of a wide spectrum of protein and small molecules. However, it is not necessary for the performer to demonstrate the detection of more than one analyte during Phase I.

PHASE II: The main goal of the Phase II project is to construct a prototype biosensor and demonstrate the feasibility for simultaneous detection of 3-4 proteins or protein biomarkers, in unprocessed whole blood. Although the performer may select the relevant protein biomarker and small molecule agent of their choice, it is highly desirable that these analytes are directly relevant to the understanding coagulation process or the treatment of coagulopathy.

The prototype biosensor must meet the following specifications:
• The prototype must operate either directly in vivo (of a model animal) or in vitro using unprocessed whole blood without sample preparation (i.e. no batch processing).
• The sensor must operate continuously for at least 2 hours.
• The sensor must achieve sufficient sensitivity to detect the protein biomarkers and small molecule agent at physiologically relevant concentrations.
• The sensor must be specific to the protein biomarker as well as small molecule agent (as applicable).
• Must be able to achieve continuous detection with a temporal resolution that is physiologically relevant to the understanding and treatment of coagulopathy. Time resolution of less than 10 minutes is highly desirable.
• Must demonstrate that the sensor is stable. It is highly desirable to show that the sensor performance remains calibrated and does not degrade during the period of operation.

PHASE III: At this time, no technologies exist at a stage that are ready for commercialization and/or Phase III applications. If/when a technology reaches Phase III, a commercialization plan will be required and developed, under guidance of an appropriate working group overseeing the project if applicable.

REFERENCES:

KEYWORDS: biosensors, molecular detection, diagnostics, real-time measurements, coagulopathy, microfluidics

DHP15-013 TITLE: Optimization of Cryoprotectants, Cryotherapeutics, and Protocols for Cryopreservation of Large Tissue Systems

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Development of novel cryoprotectants, cryotherapeutics, and cryopreservation protocols that will permit clinically effective banking of large complex vascularized composite tissues such as vital organs and limbs.

DESCRIPTION: The development of methods to cryopreserve complex tissues such as organs and limbs without loss of function would revolutionize several areas of medicine and biomanufacturing. Such a capability would alter the practice of transplant medicine, trauma treatment, fertility treatment, and the manufacturing of engineered tissues for regenerative medical applications. A key challenge in this area is the widespread use of dimethyl sulfoxide (DMSO) and similar cryoprotectant compounds. DMSO and related compounds are used in virtually all current cell preservation media and are of great concern due to their toxicity. Any methods to replace or reduce their use or mitigate their effects would transform the cell and tissue banking industries and enable the development of cryopreservation for larger tissues.

The preservation of organs and vascularized composite tissues after donor harvest is a central problem in transplant and reconstructive medicine. The feasibility of many transplant procedures (for solid organs like hearts, limbs, or face) is limited not by the availability of donor tissue but by the transportation time required to deliver donor tissue to the recipient [1],[2]. There is a vast and growing shortage of organs leading to premature death for millions. Costs to society are immense and there is further suffering, death and cost due to required immune suppression and non-ideal organ matching. Cryopreservation of organs can help solve each of these problems. It would also enable doctors to extend the benefits of fertility-related cryopreservation to women by enabling the preservation of whole ovaries. This is particularly important in women who suffer combat-related or civilian trauma or who are undergoing cancer treatment. It would also better enable a greater number of digit, hand, face and limb transplants. Moreover, organ banking will be a valuable complement to and facilitator of tissue engineering and vice versa. Each of these applications will fuel mutual demand for the other. The development of methods to extend the viability of tissues beyond several hours post-harvest would transform the practice of transplantation and reconstructive medicine by making donor tissue available to many more recipients than is currently possible.
Current formulations of cryoprotective agents (CPAs) suffer from several limitations that prevent their use in the clinically-relevant cryopreservation of large complex tissues such as organs and limbs. This topic focuses on three fundamental problems that govern the performance of CPAs in these types of applications: 1) CPA toxicity 2) mass exchange issues and material properties of CPAs (e.g., diffusivity and viscosity) that impact the effectiveness of ice inhibition and the ability of the CPAs to uniformly diffuse into tissues prior to cooling and to diffuse back out of tissues following rewarming, and 3) the ability to intervene therapeutically to mitigate the unwanted effects of CPAs and thermomechanical stress. Further, currently utilized CPAs and cryopreservation strategies typically limit their effects to that of physical and chemical control of the impact of the freeze-thaw process while minimally addressing the molecular-biological driven stress response of cells and tissues to the process [3],[4]. This molecular control aspect continues to gain attention in the research community and has provided a new path in the development of CPA formulations targeting not only improved survival but function as well [5].

A key physical parameter that impacts the outcome of cryopreservation of large tissue systems is the nature of the aqueous state transition in and around cells from liquid water to either an amorphous glassy state or ice [6],[7]. The formation of ice in or between cells can be lethal and is problematic during both the cooling and warming phases of cryopreservation. Previous studies have found that ice formation in hepatocytes can be lethal at levels as low as 2-4% of the total water in the cell [8]. The extent of ice formation depends on factors such as the cooling rate, solute concentrations, and the path of state transition to either ice or an amorphous glassy state. However, a promising method to manage or avoid ice formation when cryopreserving larger tissue systems exists in so-called vitrification [9],[10],[11]. Vitrification, an "ice-free" cryopreservation method, is an effective way to preserve biological matter as it avoids the damage caused by ice growth. This method involves solidification of a liquid into a glassy state without crystallization due to high values of viscosity at low temperatures and can allow for indefinite storage without any biological change.

Water can be supercooled to the homogeneous ice nucleation temperature of 235 Kelvin (K) and can be vitrified by very rapid cooling to below the water glass transition temperature of 136 K when cooled at rates exceeding 105 K/s [12]. However, this rate of cooling has not yet been demonstrated for aqueous systems wider than a few microns. However, cooling rates necessary to achieve vitrification can be reduced greatly by adding CPAs. Successful vitrification of nucleated cells using a cooling rate of only 20 K/min has been demonstrated by using a mixture of several CPAs to minimize toxicity [13]. More recent work has shown that ~10 gram rabbit kidneys can be loaded with vitrifying CPA, cooled to 45°C, and then unloaded by vascular perfusion with consistent subsequent long-term survival [14]. One kidney was successfully cooled below the glass transition temperature with post-transplant function [15]. CPAs discovered to date tend to be toxic in varying degrees for both living cells and tissues, especially at warmer temperatures. Permeability and, as temperature is lowered, viscosity can stand in the way of obtaining uniform distributions of the CPA solutions to all parts of a tissue during the desired short loading and unloading periods. The effectiveness of CPAs often requires that they be used in very high concentrations. Natural antifreeze proteins (AFPs) found in cold-adapted organisms such as some species of fish and frogs may be less toxic but have so far been prohibitively expensive. However, successful cryopreservation in combination with DMSO using relatively inexpensive recombinant insect-derived AFPs has been reported [16].

Various cell and tissue types also exhibit varied tolerance to different types of CPAs. This may require formulations of CPAs optimized for particular tissues. The identification of novel biological targets for the development of cryotherapeutics to mitigate CPA toxicity and chilling injury would open additional possibilities for advancing the field of cryopreservation. Potentially promising paths that are encouraged under this topic, include, but are not limited to:

- Specialty CPAs including disaccharides, ice blockers or modulators and/or natural antifreeze compounds that in addition or in combination are less toxic.
- Applying computational chemistry and/or high throughput testing methods to design, evaluate, and optimize more effective and less toxic cryoprotectant cocktails.
- Adding accessory compounds that mitigate effects of oxidative damage, osmotic stress, and cryoprotectant toxicity (cryotherapeutics), or augment natural healing processes.
- Using modeling, simulation, and estimation, to guide optimal loading and unloading protocols while also optimizing cool down and rewarming protocols.
- Alternative techniques for CPA loading and unloading, such as electroporation, ATP-induced pore formation in cells that carry appropriate receptors, and aquaporins to increase membrane permeability.
• Using hyperbaric protocols to improve loading times and distribution of CPA and other compounds to cells and tissues.
• Identification of critical molecular cell stress response pathways activated during cryopreservation.

Convergence of multiple domains outside of cryobiology may yield important insights that would be useful in solving key challenges. A non-exhaustive list of such domains includes:

• Metabolomics, proteomics, genomics and epigenetics (to better understand and find ways to intervene in toxic reactions to cryoprotectants, osmotic stress and chilling injury).
• Modeling and computer simulations (to better guide rational compound discovery and optimal loading and unloading procedures).
• Thermodynamics of complex biological systems.
• Preconditioning and biological stress responses (to prepare and “harden” cells ahead of potential damage and optimize healing post-insult).
• Hypothermic surgery and resuscitation medicine (to minimize ischemic injury and optimize resuscitation procedures).
• Advanced imaging / phase scanning / diffusion tensor imaging techniques (to image CPA distribution, ice distribution, and stress distribution in 3-dimensional systems).

PHASE I: The performer will carry out early foundational work to develop an understanding of biological pathways that can inform novel candidate CPA formulations, identify targets for cryotherapeutics, and/or molecular/stress modulation, and develop cryo-protocols that would be expected to increase efficacy and minimize damage during cryopreservation of large complex tissues. The performer will propose, or adapt, existing model systems that are suitable to evaluate and clearly demonstrate efficacy and toxicity outcomes. This model or set of models will be used in Phase II. The focus of this phase is on developing the understanding required to rationally develop CPA formulations, identify targets for cryotherapeutics, develop cryo-protocols, and select biological model systems that are suitable for use in Phase II. Computational modeling and simulation of system performance during Phase I is strongly encouraged. Preliminary evaluation and testing of novel CPAs, cryotherapeutics, and cryo-protocols in the selected biological model system is encouraged, but not required. The biological model system may be engineered tissue or tissue derived from an animal. Screening may employ cell-based assays.

PHASE II: The performer will build on the foundational work performed during Phase I to develop and evaluate novel CPA formulations, screen stress modulators and cryotherapeutics, and test cryo-protocols to demonstrate their effectiveness using the biological model system identified in Phase I. Although screening and early evaluation may be carried out in smaller cell-based biological model systems this phase will require demonstration of performance of top CPA(s), stress modulator(s), cryotherapeutic(s), and cryo-protocol(s) in suitable tissue-based engineered constructs, human or animal explants, or an in vivo small animal model, with preference given to larger, more complex model systems. The deliverable in Phase II will be a novel CPA formulation, therapeutic modulator of cryo-injury, model system to evaluate cryo-preservation, or protocol for performing cryo-preservation.

PHASE III: Cryopreservation of complex biological tissues is an open problem with a large potential market in cell banking, organ banking, or storage of engineered tissues and with direct applicability across a full spectrum of medical treatment, diagnostics, and long-term unattended biologically based sensor platforms. Progress in developing methods for large volume tissues will also likely transform current cell and thin tissue banking industries. By providing better protocols and solutions improving cell viability, cell yield, and tissue function, and by providing alternatives to the currently widespread use of dimethyl sulfoxide (DMSO) and other toxic compounds used in virtually all cell preservation media. There is also a significant opportunity to p

DHP - 29
REFERENCES:


KEYWORDS: Cryopreservation, extension of biological function, stasis, organ transplant preservation, tissue engineering, regenerative medicine, vitrification
TITLE: Optimal Rewarming Solutions for Cryopreserved Tissue Systems

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: A capability is sought to solve one of the remaining barriers towards true banking of organs and vascularized composite tissues – optimal rewarming methods of large cryopreserved tissues.

DESCRIPTION: This solicitation calls for the development of optimal warming methods that can be applied to volumetrically large complex biological tissues. While examples of potentially promising methods have been discussed, this call is not limited to those approaches but seeks any and all approaches for the optimal re-warming of complex tissue post cryopreservation.

The preservation of organs and vascularized composite tissues after donor harvest is a central problem in transplant and reconstructive medicine. The feasibility of many transplant procedures is limited not by the availability of donor tissue but by the transportation time required to deliver donor tissue to the recipient. The development of methods to extend the viability of tissues beyond several hours post-harvest would transform the practice of transplantation and reconstructive medicine by making donor tissue available to many more recipients than is currently possible. It is envisioned that cryopreservation methods may also be used to salvage mangled extremities following trauma by permitting their preservation until advanced surgical procedures are available to repair the limb. One aspect of cryopreservation that remains a challenge regardless of the approach is the rewarming phase. This topic focuses on the optimization of solutions and methods for rewarming of cryopreserved tissues.

Cryopreservation through vitrification holds great promise as demonstrated in cells and described in theory for tissues in the mid-1980s [1],[2]. Vitrification involves freezing to a "glassy" rather than crystalline phase, thereby avoiding damaging intra- and extracellular ice crystals that are known to damage cells and tissues in the frozen state. In practice vitrification relies on loading a high enough concentration of a cryoprotectant (CPA) (up to 50% w/w) and cooling rapidly enough such as to reach below the glass transition temperature (Tg) while minimizing or avoiding nucleation of ice. The full realization of this technology could potentially make hand, face, limb, organ, and ovary banking part of medical practice. It would also enable storage of 3D engineered tissues for regenerative medicine. However, practical application in tissues has been difficult to realize due to diffusive heat and mass transfer and phase-change limitations that cause the procedure to fail. For instance, insufficient diffusive loading of the cryoprotective solution, insufficient cooling or warming rates, and thermal gradients that can impose thermal stress can all lead to vitrification failures. These are manifested as ice growth due to devitrification and stress driven fractures and cracking during thawing. More recently some groups have shown promising approaches to address these diffusive limitations in thin tissues, by working with thin veins, blood vessels [3],[4] organs [5],[6],[7] and limbs [8]. This has continued to highlight the promise of vitrification, but also underlines the need to find a way to broaden the ability to work with thicker bulk tissue systems to fully realize the potential of the technology [9].

Assuming sufficiently uniform cryoprotective loading can be achieved as previously reported [1],[10], the most important issues to address relate to uniformity and speed of cooling and thawing rates such that failures such as cracks and devitrification can be avoided. While cracking and fracturing can already occur within smaller tissue systems, these problems only grow as tissues scale up in volume. Thermo-mechanical fractures are created by differential contractions in the tissues; and they may be caused by differences in coefficients of expansion in different tissue types, by thermal gradients, and perhaps by other means. Vitrifiable tissues larger than a few cubic centimeters often develop these large-scale fractures [11].

With regards to devitrification or ice nucleation, several studies suggest that the successful outcome of cryopreservation is often limited by the re-warming, not the cooling step [12],[13]. More specifically, the rates of cooling necessary to achieve vitrification are often orders of magnitude less than those needed to remain vitrified during warming [15]. This is important since approaches to cool to the vitrified state in bulk tissues such as kidneys already exist [1],[10]. Importantly, some ice growth can be compatible with viability and function post cryopreservation, but the level of ice must be held to a very low percentage within the sample [1],[4],[10]. This ice nucleation within a vitrified aqueous phase as the temperature rises above 150 K (or the glass transition temperature of the sample which varies with CPA) is termed devitrification and can lead to large intracellular ice crystal
formation and preservation failure. Avoiding this devitrification is directly related to the warming rates and concentration of added cryoprotectants. Encouragingly, unlike cooling, warming can be accelerated by application of penetrating radiofrequency or microwave energy [15] and other methods such as the use of hyperbaric pressure and warmed gas persufflation have been proposed [16]. The most well recognized attempt at achieving uniform heat generation in cryobiology has been with microwave rewarming [17-23]. Importantly, the study of electromagnetic warming, coupling with magnetic nanoparticles and gas persufflation are all well researched domains, but have thus far had limited applications in cryobiology. Recently, initial success has also been demonstrated with the combination magnetic nano particles and radio frequency (winning the 2013 J.K. Crister Award at the Society for Cryobiology’s 50th Anniversary meeting) [9].

All the methods discussed above have the potential to enable increased speed and uniformity of warming that can help avoid cracking or fracturing and devitrification (i.e. crystallization). The temperature zone where previously-nucleated ice crystals grow most rapidly typically spans tens of degrees Kelvin below the melting temperature, above which ice cannot exist, and below which ice growth is kinetically inhibited by viscosity [24],[25]. Each of the methods mentioned above has the potential to rapidly and uniformly traverse that specific temperature zone of maximum ice growth where risk of devitrification and damage from ice is greatest and increased warming rates are needed the most. Further, any method that enables faster rewarming and hence less devitrification can decrease the needed amount/concentration of cryoprotectants. Since cryoprotectant toxicity increases non-linearly with concentration, even small reductions in concentration can yield large decreases in toxicity [26]. Faster rewarming also decreases the toxic effects of the cryoprotectants as toxicity is directly dependent on the exposure time.

Approaches based on electromagnetic fields (microwave and RF) and/or magnetically susceptible nanoparticles have the advantage that in principle these bulk warming methods can be chosen to couple with the cryoprotectant solution as a function of temperature, thereby slowing the speed of thaw for annealing close to the glass transition temperature [11], but allowing one to speed up to avoid devitrification during subsequent warming. This allows rapid passage through the ice growth temperature zone while also reducing the mechanical stress by annealing and thereby avoiding both devitrification (ice growth) and cracking or fracturing [28].

While the intent of the call is to improve vitrification in large tissue systems, there will be simultaneous benefit at all scales in cryopreservation and vitrification. Development of new technology in this space would likely capture substantial commercial value in the existing cell and thin tissue banking industries. For instance, increasing the uniformity and speed of thawing will extend the abilities of almost any cryopreservation solution in the field, and therefore its use on any system large or small. Specifically, faster warming will allow the molarity of cryopreservation solutions to be reduced thereby allowing less toxic solutions to be developed and used [10]. This will be a large step forward in cryopreservation that will have lasting impact in both cellular and tissue-based regenerative medicine.

Beyond the physical challenges associated with rapid and uniform warming of frozen or vitrified tissues, another significant challenge to current organ and cell transplant procedures is the control of ischemia/reperfusion (I/R) injury that occurs as a result of re-warming, re-oxygenation, and the resultant reactivation of biochemical functions. It is known that hypothermia causes tissue damage which influences the extent of I/R injury, thereby directly impacting organ/graft rejection [30]. What is less appreciated is the role I/R injury plays in cell and tissue demise following cryopreservation. Given that all cells, tissues, and organs undergoing freezing and thawing are subjected to prolonged exposure to hypothermic conditions all these biologics are impacted to a degree by I/R injury upon rewarming and implantation [31]. This is true for both hypothermically stored and cryopreserved products. The rewarming process can result in the creation of a delayed I/R injury environment resulting in continued compromise of cell retention, decreased tissue quality and function, as well as, the initiation of an immune response yielding delayed engraftment [32],[33]. As such, there is a compelling need for the development of strategies to mitigate this molecular biochemical response within tissues during the thawing and recovery process. The development of new strategies (reagents and protocols) designed to reduce the level of I/R related damage would provide for improving cell survival, function and engraftment of tissues and organs post-thaw [34]. This would not only impact organ cryopreservation but would also be beneficial for current and future cell and tissue banking industries, such as cell therapy products and vascular grafts, as well as offering the potential to improve more traditional organ transplantation protocols by providing a post-storage pre-implantation tissue recovery process.
PHASE I: The performer will demonstrate successful development of warming methods that minimize vitrification failures due to ice formation and mechanical (i.e. thermal) stresses thereby allowing for reduced molarity and different types of CPAs to be evaluated. This should then allow protocol development that reduces toxicity while maximizing viability of tissue systems post-preservation. Proposals may include devices, protocols, or reagents among others. Phase I can be used to demonstrate feasibility on suitable model systems rather than working directly with complex vascularized tissue systems. The deliverable of Phase I will be a technical report and does not need to be a product or device.

PHASE II: The performer will demonstrate the utility of the approach from Phase I by successfully vitrifying a large complex vascularized tissue system. The approach described in the technical report from Phase I will be scaled up to system sizes that allow bulk tissues to be vitrified. The tissues of interest include complex and vascularized tissue systems such as muscle and/or blood vessels, although larger systems are also of interest (i.e. animal limbs, digits, or organs). Demonstration that the large tissue achieved vitrification by some quantitative form of imaging (EM – freeze substitution, computed tomography, or other) is highly encouraged. Thermal analysis to demonstrate the avoidance of crystallization and cracking during thawing within the sample is encouraged (gross morphology, histology, EM, or other). In Phase II biological assessments that demonstrate viability and function of the tissue post-vitrification are required. Demonstration of the ability to reduce CPA toxicity by selecting less toxic CPAs and/or reducing CPA molarity as a result of the methods developed while still achieving vitrification will be a key feature of successful projects. It is expected that device(s) and methods will be developed under Phase II funding. This will form the basis for further translation and commercialization in Phase III.

PHASE III: Cryopreservation of complex biological tissues is an open problem with a large potential market and with direct applicability across the full spectrum of medical treatment, diagnostics, and long-term unattended biologically based sensor platforms. The effort should address the commercialization of the underlying technology. Potential paths to commercialization may benefit from potential future funding under programs administered through USAMRMC such as USAMMDA or CDMRP. It must describe one or more specific Phase III military applications and/or supported S&T or acquisition programs as well as the most likely path for transition of the SBIR from research to operational capability. For example, the proposal might relate the use of cryopreservation solutions, protocols or equipment to the potential use in the treatment of particular diseases or conditions of military interest. Specific commercial applications might include cell banking, organ preservation, research tools, diagnostics, or other applications where extended cell viability would be useful. Specific defense applications include preservation of engineered tissues to support long-term storage and shelf-life extension. The performer or a suitable partner will pursue development of the approach to permit the cryopreservation of successively larger tissues and organs. This award mechanism will bridge the gap between laboratory-scale innovation and entry into a recognized FDA regulatory pathway leading to commercialization.

REFERENCES:


KEYWORDS: Cryopreservation, rewarming, ischemic, injury, extension of biological function, stasis, organ transplant preservation, tissue engineering, regenerative medicine, vitrification

DHP15-015 TITLED: Objective Measurement Tool For Detection and Monitoring of Noise-Induced Hearing Loss

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: Develop objective measurement tool for the detection of noise-induced hearing loss and a smart algorithm for monitoring.

DESCRIPTION: Noise is a major occupational and environmental hazard, causing hearing loss, annoyance, sleep disturbance, fatigue, hypertension, and negatively impacting quality of life. Military personnel are commonly exposed to high levels of noise, with associated hearing loss and tinnitus common service-connected disabilities among U.S. Veterans. Currently, hearing loss is detected primarily through significant threshold shifts on pure-tone audiograms. However, such measures are known to be insensitive to the earliest (pre-clinical) signs of noise-induced auditory damage. Developing objective measures, including otoacoustic emissions (OAEs), provide more sensitive measures of the earliest signs of auditory damage compared to pure-tone audiometry. Such non-invasive, quick, boothless, portable, technician-deliverable measures hold the potential for improved diagnostic and monitoring capabilities in isolation or in combination with currently available technologies. Furthermore, military members have limited access to care while in remote settings or deployed where many of these noise-related injuries are sustained and where testing would require completion in less than ideal conditions or extraction from the area. Characterization of the initial auditory injury is essential for early identification and individualized treatment, as well as for quantifying auditory risk/vulnerability in populations at large. Characterizing those individuals and groups at increased risk of noise-induced hearing loss can improve and customize prevention strategies (e.g., education, hearing protection devices, periods of auditory rest, pharmaceutical interventions, etc.).

Although a variety of commercial OAE systems are available for screening and for diagnostic purposes, there are several limiting factors for use in a noise-exposed population that are incompatible with automatic monitoring or characterization of auditory risk. An innovative solution for detection and monitoring of noise-induced hearing loss is needed. A rugged, portable, sensitive, and reliable OAE system capable of quick, binaural, remote testing in less than optimal circumstances (outside of a sound booth) is not available. For noise-exposed ears, reliable,
reproducible measures are particularly important to capture and compare repeated measurements incorporated into a smart algorithm for monitoring.

PHASE I:  Define a conceptual approach for a diagnostic tool and smart monitoring algorithm that meets the intent of the SBIR topic for objective detection and monitoring of noise-induced hearing loss. The Phase I deliverable is a technical report, outlining the approach, establishing feasibility, and including a detailed analysis defining the predicted performance of the end product.

PHASE II:  Produce and evaluate the prototype system defined by the Phase I design. Quantifiable performance measures for the measurement tool should be determined that are sufficient to assess the ability to provide objective measure(s) and evaluate monitoring capabilities. Conduct a pilot study in humans to assess initial effectiveness of the tool. Develop a plan and cost/time estimate for additional development and clinical study activities required to achieve Food and Drug Administration (FDA) and other regulatory approvals required to make the technology commercially available for military clinical use. Phase II deliverables include a developed prototype system, technical reports documenting the appropriate performance measures for the measurement tool, pilot clinical study; and a proposed roadmap addressing additional activities, cost and time required to make the technology commercially available.

PHASE III:  Technology innovations developed through this SBIR will have dual use application for detection and monitoring of noise-induced hearing loss in the DoD/VA and private sectors. Phase III will focus on integrating the portable OAE system into the DoD/VA medical treatment facilities and remote testing locations. The system should be available for wide dissemination for clinical use and will be compatible with networks and telemedicine data flows within the DoD/VA community.

REFERENCES:


KEYWORDS: Noise-induced hearing loss, early detection, otoacoustic emissions, monitoring, telemedicine, binaural
chorioretinectomy, anatomic and functional outcomes remain poor [2,3]. In many cases, severely scarred corneas preclude adequately visualizing the retina and other intraocular structures to allow optimal surgical repair. In such instances, traditional surgical visualization strategies for retinal surgery typically require the use of a keratoprosthesis, a temporary plastic device that replaces a damaged cornea to provide clarity and surgical access to the retina [4]; conventional vitrectomy techniques using non-contact viewing systems are then employed to perform the surgery. A traditional corneal transplant is then performed at the conclusion of surgery. However, corneal transplants in such situations are at a high risk for failure. Indeed, when performing this technique in injured U.S. servicemembers, a 75% rate of corneal graft failure and eventual blindness occurred [5].

An alternative method includes the use of an ophthalmic micro-endoscope, but this technique requires an advanced degree of surgical skill, since the surgeon sacrifices 3D stereoscopic visualization while operating via a 2D monitor. As intraocular tissues are literally only microns in scale—and ocular surgical error is unforgiving—such techniques necessarily require significant skill and constant practice. Consequently, such advanced equipment and techniques are usually found only in select medical centers. Novel intraocular visualization strategies that allow sophisticated and highly detailed intraocular visualization and navigation are necessary to improve surgical outcomes following complex ocular trauma, particularly in situations where conventional intraocular visualization is compromised or limited, such as with scarred and opacified corneas. Potential solutions need not be limited to reliance on conventional optics and illumination wavelengths, and could include modalities such as intraocular ultrasound, alternative light wavelengths, and the like. The desired end product, however, is intended to provide the surgeon an intraocular view that will permit state-of-the-art, sophisticated intraocular surgery; as such, an intraocular diagnostic instrument alone is insufficient. Rather, an instrument that affords the surgeon a highly detailed and precise view of the intraocular operative field and that is compatible with contemporary ophthalmic surgical techniques and requirements is required.

With this in mind, eventual technical requirements will include: optical resolution of 50microns or better in all axes; components no larger than 18gauge (smaller is better); compatibility with intraocular lasers; compatibility with the intraocular surgical environment (eg, saline, intraocular gasses, immersible in silicone oil); and ability to be used in either a stationary configuration (ie, “chandelier” visualization) or a maneuverable configuration (ie, “wand” visualization). While stereoscopic 3D capability is not required, it is highly desired, with stereoscopic discrimination of at least 20 arc seconds. Illumination schema need not be limited to conventional visible light, but if incorporating it, must be either compatible with conventional intraocular ophthalmic light sources or, if illumination is an integrated component, must be technically comparable to existing ophthalmic light sources (eg, brightness, color temperature, thermal temperature, etc). A critical requirement will be the ability to accurately discriminate (or allow discrimination of) various ocular tissues and structures such as (but not limited to) the crystalline lens and suspensory zonules, ciliary body, ciliary processes and sulcus, retina (pars plana, pars plicata, neurosensory retina, etc), retinal vessels, fibrovascular tissue and scarring, intraocular foreign bodies, and subretinal hemorrhage and fibrosis.

PHASE I: Develop a conceptual model and demonstrate feasibility of proposed novel tool for intraocular visualization and navigation that will meet the above requirements through benchtop and/or preclinical testing. In Phase I solicitor must demonstrate proof of concept for an 18gauge (or smaller) instrument that will provide initial visual resolution of 100microns in all axes (2D or 3D), as well as allowing navigation and placement of microsurgical instruments to within 100 microns of an intended target or depth (100 micron accuracy in all axes, including depth). Identify a Phase II plan to further develop, refine and validate the technology so as to meet the more stringent technical requirements as described above, as well as a planned regulatory pathway.

PHASE II: Develop, demonstrate, and validate system prototypes of an 18gauge (or smaller) visualization instrument to meet all technical requirements specified in Description, above. Improve and demonstrate resolution to 50microns (or better), and surgical accuracy to 50microns (or better). Develop plan for FDA approval, including demonstration of ocular safety if employing unconventional imaging modalities.

PHASE III: The technology developed under this SBIR effort will have applicability to both civilian and military ophthalmic surgery and other micro-surgical specialties, particularly in conditions in which conventional visualization is compromised, such as trauma or advanced disease states. Depending upon the technology proposed, the technology may also have broad applicability for other forms of micro- and minimally-invasive medical procedures in both military and civilian settings, such as oculoplastic surgery, neurosurgery, interventiona
radiology, reproductive medicine, and micro-endoscopic and micro-vascular medicine. Non-medical applications may include military and industrial customers interested in advanced imaging capabilities in small confines where direct viewing is not possible (micro-imaging), or in other low-visibility scenarios (not necessarily restricted to a micro-environment).

REFERENCES:


KEYWORDS: visualization, ocular surgery, eye trauma, retina surgery, minimally invasive surgery, microsurgery