Defense Health Agency (DHA)
2024.2 Small Business Innovation Research (SBIR)
Proposal Submission Instructions

INTRODUCTION

The Defense Health Agency (DHA) SBIR Program seeks small businesses with strong research and development capabilities to pursue and commercialize medical technologies.

Proposers responding to a topic in this BAA must follow all general instructions provided in the Department of Defense (DoD) SBIR Program BAA. DHA requirements in addition to or deviating from the DoD Program BAA are provided in the instructions below. Only Government personnel will evaluate proposals submitted under this solicitation cycle.

Proposers are encouraged to thoroughly review the DoD Program BAA and register for the DSIP Listserv to remain apprised of important programmatic and contractual changes.

- The DoD Program BAA is located at: https://www.defensesbirsttr.mil/SBIR-STTR/Opportunities/#announcements. Be sure to select the tab for the appropriate BAA cycle.
- Register for the DSIP Listserv at: https://www.dodsbirsttr.mil/submissions/login.

Specific questions pertaining to the administration of the DHA SBIR Program and these proposal preparation instructions should be directed to:

DHA SBIR Program Management Office (PMO) Email: usarmy.detrick.medcom-usamrmc.mbx.dhpsbir@health.mil

For technical questions about a topic during the pre-release period, contact the Topic Author(s) listed for each topic in the BAA. To obtain answers to technical questions during the formal BAA period, visit the Topic Q&A: https://www.dodsbirsttr.mil/submissions/login.

PHASE I PROPOSAL GUIDELINES

The Defense SBIR/STTR Innovation Portal (DSIP) is the official portal for DoD SBIR/STTR proposal submission. Proposers are required to submit proposals via DSIP; proposals submitted by any other means will be disregarded. Detailed instructions regarding registration and proposal submission via DSIP are provided in the DoD SBIR Program BAA.

Technical Volume (Volume 2)

The technical volume is not to exceed **20 pages** and must follow the format and content requirements provided in the DoD SBIR Program BAA. Do not duplicate the electronically-generated Cover Sheet or put information 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 Sheet and Cost Volume are excluded from the 20-page limit. Technical Volumes that exceed the 20-page limit will be deemed non-compliant and will not be evaluated.

Cost Volume (Volume 3)

The Phase I Base amount must not exceed $250,000 over a 6-month period of performance. Costs must be clearly identified on the Proposal Cover Sheet (Volume 1) and in Volume 3.

Please review the updated Percentage of Work (POW) calculation details included in the DoD Program BAA. DHA will occasionally accept deviations from the POW requirements with written approval from the Funding Agreement Officer.

Travel must be justified and relate to the project needs for direct Research Development Test & Evaluation (RDT&E) Technology Readiness Level (TRL) increasing costs. Travel costs must include the purpose of the trip(s), number of trips, origin and destination, length of trip(s), and number of personnel.

Company Commercialization Report (CCR) (Volume 4)
Completion of the CCR as Volume 4 of the proposal submission in DSIP is required. Please refer to the DoD SBIR Program BAA for full details on this requirement. Information contained in the CCR will be considered by DHA during proposal evaluations.

Supporting Documents (Volume 5)
All proposing small business concerns are REQUIRED to submit the following documents to Volume 5:

1. Contractor Certification Regarding Provision of Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment
2. Disclosures of Foreign Affiliations or Relationships to Foreign Countries

Please refer to the DoD Program BAA for more information.

Fraud, Waste and Abuse Training (Volume 6)

PHASE II PROPOSAL GUIDELINES

Phase II proposals may only be submitted by Phase I awardees. Phase II is the demonstration of the technology found feasible in Phase I. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the DHA SBIR PMO typically in month five of the Phase I contract.

Due to limited funding, the DHA 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 Commercialization Strategy describing feasible approaches for transitioning and/or commercializing the developed technology in their Phase II proposal. This plan shall be included in the Technical Volume.

The Cost Volume must contain a budget for the entire 24-month Phase II period not to exceed the maximum dollar amount of $1,300,000. Budget costs must be submitted using the Cost Volume format (accessible electronically on the DoD submission site) and shall be presented side-by-side on a single Cost Volume Sheet.

DHA SBIR Phase II proposals have six volumes: Proposal Cover Sheets, Technical Volume, Cost Volume, Company Commercialization Report, Supporting Documents, and Fraud, Waste, and Abuse.

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. Technical Volumes that exceed the 40-page limit will be deemed non-compliant and will not be evaluated.

DISCRETIONARY TECHNICAL AND BUSINESS ASSISTANCE (TABA)
The DHA SBIR Program does not participate in the Technical and Business Assistance (formerly the Discretionary Technical Assistance Program). Contractors shall not submit proposals that include Technical and Business Assistance.

The DHA SBIR Program has a Transition Lead who provides technical and commercialization assistance to small businesses that have Phase I and Phase II projects.

EVALUATION AND SELECTION
All proposals will be evaluated in accordance with the evaluation criteria listed in the DoD SBIR Program BAA.

Proposing firms will be notified of selection or non-selection status for a Phase I award within 90 days of the closing date of the BAA. Non-selected companies may request feedback within 15 calendar days of the non-select notification. The Corporate Official identified in the firm's proposal shall submit the feedback request to the SBIR Office at usarmy.detrick.medcom-usamrmc.mbx.dhpsbir@health.mil. Feedback is provided in an official PDF via email to the Corporate Official identified in the firm proposal within 60 days of receipt of the request. Requests for oral feedback will not be accommodated. If contact information for the Corporate Official has changed since proposal submission, a notice of the change on company letterhead signed by the Corporate Official must accompany the feedback request.

NOTE: Feedback is not the same as a FAR Part 15 debriefing. Acquisitions under this solicitation are awarded via "other competitive procedures". Therefore, offerors are neither entitled to nor will they be provided FAR Part 15 debriefs.

Refer to the DoD SBIR Program BAA for procedures to protest the Announcement. As further prescribed in FAR 33.106(b), FAR 52.233-3, Protests after Award should be submitted to:

Ms. Samantha L. Connors SBIR/STTR Chief, Contracts Branch 8
Contracting Officer
U.S. Army Medical Research Acquisition Activity
Email: Samantha.l.connors.civ@health.mil

AWARD AND CONTRACT INFORMATION
Phase I awards will total up to $250,000 for a 6-month effort and will be awarded as Firm-Fixed-Price Purchase Orders.

Phase II awards will total up to $1,300,000 for a 24-month effort and will typically be Firm-Fixed-Price contracts. If a different contracting type is preferred, such as cost-plus, the rational as to why must be included in the proposal.

Phase I/Phase II awardees will be informed of contracting and Technical Point of Contact/Contract Officer Representative upon award.

ADDITIONAL INFORMATION

RESEARCH INVOLVING HUMAN SUBJECTS, HUMAN SPECIMENS/DATA, OR ANIMAL RESEARCH
The DHA SBIR Program highly discourages offerors from proposing animal or human use research during Phase I due to the significant lead time required to prepare documentation and secure approval, which could substantially delay the performance of the Phase I award.

Prior to contract award when an IRB is indicated, proposers must demonstrate compliance with relevant regulatory approval requirements that pertain to proposals involving human subjects, human specimens, or research with animals. If necessary, approvals are not obtained within two months of notification of selection, the decision to award may be terminated.

Offerors are expressly forbidden to use, or subcontract for the use of, laboratory animals in any manner without the express written approval of the U.S. Army Medical Research and Development Command (USAMRDC) Animal Care and Use Review Office (ACURO). Written authorization to begin research under the applicable protocol(s) proposed for this award will be issued in the form of an approval letter from the USAMRDC ACURO to the recipient. Modifications to previously approved protocols require re-approval by ACURO prior to implementation.

Research under this award involving the use of human subjects, to include the use of human anatomical substances or human data, shall not begin until the USAMRDC's Office of Human Research Oversight (OHRO) provides formal authorization. Written approval to begin a research protocol will be issued from the USAMRDC OHRO, under separate notification to the recipient. Written approval from the USAMRDC OHRO is required for any sub-recipient using funds from this award to conduct research involving human subjects. If the Offeror intends to submit research funded by this award to the U.S. Food and Drug Administration, Offerors shall propose a regulatory strategy for review.

*NOTE: Exempt animal or human research use shall also reflect 'yes' on the proposal coversheet for USAMRDC ACURO and OHARO records.

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

FEDERAL FACILITY USE

The DHA SBIR Program highly discourages small business concerns (SBCs) from subcontracting to a federal facility and/or utilizing for testing due to the significant lead time required to secure approval, which could substantially delay the performance of the award.
Use of federal facilities is prohibited without an approved waiver from the DHA SBIR/STTR Office.

An SBC whose proposed work includes federal facility use is required to provide a written justification, uploaded to the Supporting Documents (Volume 5), that includes the following information:

1. An explanation of why the SBIR/STTR research project requires the use of the federal facility, including data that verifies the absence of non-federal U.S. facilities, in support of the overall mission and research area.
2. Evidence that there is no applicable U.S. facility that has the ability or expertise to perform the specified work.
3. Why the Federal Agency will not and cannot fund the use of the Federal facility or personnel for the SBIR/STTR project with non-SBIR/STTR money.

The DHA SBIR Program has the right of refusal. Companies that fail to meet requirements specified above will be at risk of delay to award or funding.

If the proposal is selected, the U.S. Army Medical Research Acquisition Activity (USAMRAA) will assist in establishing the waiver for DHA SBIR/STTR Office approval. If approved, the proposer will subcontract directly with the federal facility and not a third-party representative.

Transfer of funds between a company and a Military Lab must meet the following APAN 15-01 requirements (the full text of this notice can be found at https://usamraa.health.mil/SiteAssets/APAN%2015-01%20Revised%20Feb%202018.pdf):

(1) The DoD Intramural Researcher must obtain a letter from his/her commanding officer or Military Facility director authorizing his/her participation in the Extramural Research project. This letter must be provided to the Extramural Organization for inclusion in the proposal or application.

(2) The DoD Intramural Researcher must also coordinate with his/her local RM office (or equivalent) to prepare a sound budget and justification for the estimated costs. Where there are no DoD-established reimbursement rates [e.g., institution review board (IRB) fees, indirect cost rates, etc.], the Military Facility's RM office (or equivalent) must provide details of how the proposed rates were determined. The DoD Intramural Researcher must use the budget and justification form enclosed in APAN 15-01 when developing the estimated costs and provide it to the Extramural Organization for inclusion in the proposal or application.

(3) The Extramural Research proposal or application must include a proposed financial plan for how the Military Facility's Intramural Research costs will be supported [i.e., directly funded by DoD, resources (other than award funds) provided by the Awardee to the Military Facility, or award funds provided by the Awardee to the Military Facility (in accordance with the requirements below)].

(4) The DoD Intramural Researcher should also coordinate with his/her technology transfer office.

INTERNATIONAL TRAFFIC IN ARMS REGULATION (ITAR)

For topics indicating ITAR restrictions or the potential for classified work, limitations are generally placed on disclosure of information involving topics of a classified nature or those involving export control restrictions, which may curtail or preclude the involvement of universities and certain nonprofit institutions beyond the basic research level. Small businesses must structure their proposals to clearly identify the work that will be performed that is of a basic research nature and how it can be segregated from work that falls under the classification and export control restrictions. As a result, information must also be provided on how efforts can be performed in later phases, such as Phase III, if the university/research institution is the source of critical knowledge, effort, or infrastructure (facilities and equipment).

END

DHA SBIR 24.2 Topic Index

DHA242-001 TITLE: Fast and Wide Multiplexing Omics Assay Platform to be Eligible for Far Forward Use and to Meet the Criteria to Get Certification of Waiver (COW) Status from Clinical Laboratory Improvement Amendments (CLIA)

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Combat Casualty Care

OBJECTIVE: To develop an in vitro diagnostic (IVD) platform with fast and wide multiplexing capability. This tool should be able to detect at least 25 multi-omics targets in a rapid and automated fashion from single input of minimally invasive biomatrix with an insignificant risk of an erroneous result.

DESCRIPTION: Recent advancements in the field of hardware miniaturization and nanotech based manufacturing industry essentially made a significant change in the conventional molecular testing landscape. The prospect of detecting multi-target profile in the clinical set up with a high precision has becoming more feasible, which is also reflected in the latest list of FDA approved detection kits [1]. Current trend in the commercial pipeline could be highlighted by the following IVD platform, namely FoundationOne CDx (F1CDx), which received FDA approval in 2020; its latest version, namely PGDx is enabled to detect the genetic aberrations linked to multiple types of cancers. These tests deploy Next Gen Sequencing (NGS) platform to detect substitutions, insertions and deletions, and copy-number alterations in 300-500 genes [2]. Such capability, namely one platform that can diagnose multiple diseases is highly beneficial in battlespace since Role 1/ 2 facilities have limited real estate. The advantages of this platform will be magnified should the technology meet the following criteria- “simple laboratory examinations and procedures that have an insignificant risk of an erroneous result.” This is essentially the criteria to get a COW from CLIA testing. None of the available IVD platform that can detect multiple targets can meet the criteria to get CLIA waiver. Present solicitation seeks to bridge this knowledge gap. Note: It’s not necessary for a solicitor to get COW from CLIA within this project timeframe; however, these guidelines should be used as a benchmark to monitor the success criteria.

Present market is dominated by polymerized chain reaction (PCR)-based detection kits that detect a handful of most eligible molecular targets. Diverging from the current position of IVD market, our proposed platform seeks a more holistic approach to detect all possible actionable targets from minimum inputs and within short turnaround time. Our approach is bolstered by a 2019 market analysis that forecasted a significant gain in diagnostic market share in near future by the wide multiplexing tools with “improved sensitivity and specificity compared with traditional sequencing technologies, as well as faster identification.” [3]

Our objective is to develop a prototype of wide multiplexing capability. It should be able to detect at least 25 targets with high sensitivity and specificity as compared to traditional sequencing technology. Moreover, the prototype should have a small footprint and easy to executable protocol. The protocol should have an automated hands-free process that would allow a single input of minimally invasive biomatrix for a nearly error-free detection. This prototype should be developed with the aim to eventually meet the criteria to get a COW from CLIA. Till date, there are only 40 tests that have been approved for COW status at CLIA website http://www.fda.gov/cdrh/clia and none has wide multiplexing capability.

Our 40-gene panel of sepsis biomarker could be used in the prototype; nevertheless, the best candidate prototype should have maximum flexibility, so that the prototype could be easily repurposed or co-diagnose additional diseases including, but not limited to traumatic brain injury (TBI), infection, and other psychological markers.
A web search of SBIR and STTR solicitations (dated January 23, 2024) found no existing solicitations to develop wide multiplexed tool that will be portable, simple, automated, and can detect a wide spectrum of molecules to facilitate diagnose/monitor/predict multiple diseases.

PHASE I: Phase I will demonstrate the feasibility of a fast and wide multiplexing detection platform; the proof-of-concept should explain methodologies to detect fast and wide multiplexing capability from single input of biomatrix of choice. The expectation is that the biomatrix should be minimally invasive, such as blood, saliva, urine etc. Target biomarkers could be curated from the public domain. Use of human or animal subjects is not intended, or expected, to establish/achieve the necessary proof-of-concept in Phase I.

In summary, our expectations from Phase I are the following:

1. A plan to develop a prototype that can detect at least 25 targets. The final product should be flexible to diagnose multiple diseases, such as sepsis, TBI and pathogenic infection.
2. The expected device should be an automated and portable platform that should be readily used in far forward lab or at bedside with an insignificant risk of an erroneous result.
3. The concept is expected to support an end-to-end methodology e.g., an integrated sample collection-to-assay-to-detection protocol.
4. The concept should show a feasible route to develop wide multiplexing capability with high precision as compared to traditional NGS platform is essential. This metrics should be used/ tested from the beginning of protocol design.

PHASE II: The proof-of-concept generated in Phase I should be transformed into a working prototype during Phase II. Phase II should start with a plan to assay the biomatrix of choice to detect a panel of multi-omics biomarkers. A comprehensive testing is expected to determine the feasibility of the platform to be operated with minimum hands-on time and least supervision. Suitable biomatrix should be finalized. The detection mode (e.g., visual inspection vs. digital record etc.) of endpoint reading should be finalized, and this process should be easily interpretable. We encourage to have a data driven analysis of the proposed capability tested using biomatrix that can inform us about the feasibility of next steps.

In summary, our expectation from Phase II is the following:

1. The input and output modus operandi should be finalized.
2. Assay sensitivity and specificity should be characterized. Screening of limit of detection (LOD) profile in presence of potential confounders and contaminates is expected.
3. A turn-around time should be tested. Herein the assay time includes the sample collection, assay and detection.
4. Potential risk factors and mitigation plan should be discussed.
5. Probable assay cost should be estimated.
6. Plan for a path forward to secure FDA approval.

PHASE III DUAL USE APPLICATIONS: The goal of this phase is to secure an FDA approved product that is intended to be suitable for use and potential procurement for primary use in the field/prehospital environment, including bedside, austere/ far forward, Role 1/2 facilities and prolonged care scenarios. At this phase, target diseases and pertinent biomarkers should be determined. Accuracy, reliability, and usability should be assessed. This testing should be controlled and rigorous. Statistical power should be adequate to document final efficacy and feasibility of the assay.

Funding could be solicited from CDMRP and BARDA, who usually support such efforts focused to military health. As mentioned previously, the target disease might include those health issues that are nonexclusive to active-duty members. Realization of a dual-use technology applicable to both the military and civilian use could be achieved via making commercial partners with IVD marker leaders like Roche, Inc, Illumina, Inc., Bio-Rad, Inc. etc.The goal of this phase is to secure an FDA approved product that is intended to be suitable for use and potential procurement for primary use in the field/prehospital environment, including bedside, austere/ far forward, Role 1/2 facilities and prolonged care scenarios. At

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REFERENCES:

1. US Food and Drug Administration Website: Nucleic acid-based tests. Page last updated: 11 Sep 2018. Accessed 12 Dec 2023. https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests
2. Sternberg, A. HITTING THE TARGET: Multigene Tests Gain Foothold in More Clinical Settings. Targeted Therapies in Oncology. June 1, 2020; 9 (8), pp 65. https://www.targetedonc.com/view/hitting-the-target-multigene-tests-gain-foothold-in-more-clinical-settings
3. Global Companion Diagnostics Market Report 2019-2024. News release. BUSINESS WIRE; Page last updated: September 24, 2019. Accessed 12 Dec 2023. https://www.businesswire.com/news/home/20190924005792/en/Global-Companion-Diagnostics-Market-Report-2019-2024---Market-to-Reach-7.3-Billion-by-2024-Registering-Massive-Growth---ResearchAndMarkets.com

KEYWORDS: Fast and wide multiplexing, targeted biomarker quantification, CLIA waiver certificate, Far forward lab, minimally invasive biomatrix, simple protocol, automated hands-free protocol

DHA242-002 TITLE: Robotic End-Effector for Combat Casualty Care

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Combat Casualty Care

OBJECTIVE: To develop a novel robotic arm manipulator end-effector that attaches to robotic and autonomous systems to perform diagnostics and intervention medical tasks for combat casualty care.

DESCRIPTION: The robotics industry has majorly advanced in the past few decades due to innovation in the ability to automate industrial and manufacturing tasks. This was focused on the design and function of robotic end-effectors to accomplish industrial tasks such as pick & place, lifting, and spot welding. Recent advancements in Artificial Intelligence (AI) and Machine Learning (ML) have opened the doors for Robotic and Autonomous Systems (RAS) to automate many more fields outside of manufacturing. Automation in the medical field is an emerging area, however it is primarily dominated by software based automated solutions. This is because physical interaction with robotic systems is limited to the functionality of the robotic end-effector, which have almost exclusively been developed for industrial and manufacturing purposes. Current robotic end-effectors rely on a two-finger configuration which is beneficial for simplicity and stability of rigid and structured objects. Additionally, the design of an end-effector is to fit a specific use case and not for general purpose use, limiting their ability to perform more than one task. As the Military Health System (MHS) is aiming to modernizing, it is looking to leverage emerging technologies to increase the capability and capacity of its medical care providers across the continuum of care [1,2]. The main issue remains that robotic end-effectors designed for industrial and manufacturing purposes will not be able to complete the complex and diverse set of tasks that are needed for automating aspects of combat casualty care. This topic calls for the development of novel robotic end-effector designs to specifically assist emerging robotic and autonomous solutions to medical tasks. The goal of the topic is to demonstrate the ability for the novel medically-focused robotic end-effectors to successfully perform a range of diagnostic and intervention patient care tasks. The focus of this SBIR topic is on the design and implementation of the robotic end-effector. Successful demonstration of patient care tasks may be fully teleoperated, as software autonomy is not being assessed, only the functionality of the hardware. This topic allows for any novel design of robotic end-effector and is not limiting to any specific type. In other words, rigid multi-fingered, soft robotics, and any other innovative design is welcome. General constraints to keep in mind are that the robotic end-effector should be safe and strong enough for physical interaction with a patient, such as lifting and repositioning an arm or a leg. The end-effector needs to be general purpose enough to interact and use many different medical objects such as those found in a medic's tool kit, and devices found in fixed hospitals. And lastly the end-effector needs to be dexterous and stable enough to use medical objects in completing various patient care diagnostics and intervention tasks.

PHASE I: The goal of Phase I efforts is to provide evidence in the feasibility of the innovative end-effector design. In Phase I researchers should concentrate on software-based design and simulated capabilities of the proposed solution. Researchers will need to present their computer-aided design (CAD) drawings as well as their end-effector successfully performing patient care tasks in robotic simulation environments. It is suggested that performers should prove feasibility in their design accomplishing 3 of the following described prehospital medical tasks for both direct and in-direct human interaction. In-direct tasks include: 1) placing a pulse oximeter on a patient's finger, 2) assisting in a Bag-Valve Mask procedure by placing and holding the mask on the patient's face, 3) assisting in a Bag-Valve Mask procedure by continuously compressing the bag, and 4) lifting an ultrasound probe and maneuvering it across a patient's torso. Direct
human interaction patient care tasks include: 5) lifting a patient's limb and repositioning it, 6) picking up a catheter and performing a Needle Decompression Thoracostomy, 7) picking up a scalpel and applying enough force and precision to perform the cutting steps of a Fasciotomy. In a feasibility proof-of-concept demonstration the performers should showcase their design's ability to perform 3 of these tasks in a

digital simulation environment (e.g. Gazebo etc.). This effort is not concerned with the creation of high-fidelity digital patient assets and rudimentary digital shapes such as cylinders with similar sizes and weights can be substituted for human anatomy.

PHASE II: In Phase II researchers should implement and fabricate the design demonstrated in Phase I's feasibility test. The goal at the end of Phase II is to have a physical robotic end-effector prototype capable of performing patient care procedures. The designed end-effector must be integrated onto an articulated robot arm platform. The choice of articulated arm platform is left to the researchers and can be either commercial-off-the-shelf or custom made (if previously developed, Phase II effort should not be spent on designing and building a custom articulated arm). Common articulated arms include but are not limited to Universal Robotics, Franka Emika, etc. At the conclusion of the Phase II effort the researchers must demonstrate the capability to teleoperate their robotic system (chosen articulated arm integrated with their novel end-effector) performing all seven of the patient care procedures described in the Phase I description. For the Phase II demonstration a manikin will be used in place of a patient and any representative manikin or medical task trainer will suffice to demonstrate the task completion. These tasks can be completed through teleoperation as there is not an expectation of autonomy in the execution of procedures. There is no need for any human subjects testing to demonstrate capability. The prototype system should be ruggedized enough to operate outdoors (i.e., closed prototype with no loose wires or breadboards). Applicants should describe their approach to the regulatory requirements and describe their strategy to obtain clearance / approval for the end product. Phase II topic proposals should include a strategy on how to obtain regulatory/FDA approval. It could be beneficial to target existing FDA approved medical robotic platforms for prototype end-effector integration for future Phase III efforts into commercialization and regulatory approval.

PHASE III DUAL USE APPLICATIONS: In Phase III the focus should be on interoperability and commercialization for Government and civilian use. If the intention of commercialization is for medical purposes, then the goal of Phase III efforts should be to obtain regulatory/FDA approval of the developed device. Phase III provides an opportunity for additional improvements to the system that enable commercialization and for regulatory approval. These include improvements to make the end-effector more compatible with the most widely used commercial and Government used robotic platforms. Additionally Phase III can allow for additional ruggedization of the prototype to enable better use in outdoor and military domains. Phase III is also an opportunity to look beyond the prescribed seven tasks in Phase II and develop additional capabilities for the novel end-effector, including investigating adding autonomy features. For consideration of Government commercialization, the end-effector should target capabilities of accomplishing robotic-assisted diagnostic and intervention tasks in the battlefield prehospital setting as well as fixed hospital care. This includes the ability to perform patient care tasks for tactical combat casualty care, prolonged field care, and care within evacuation vehicles. In the civilian sector there are many paths for commercial use of the developed end-effector. Similar to the Government sector, evacuation care in the civilian sector could utilize the novel medical end-effector for use in en-route care, specifically in long medical transfers. Rural medical facilities are particularly under resourced in both personnel and specific expertise and could benefit from the use of autonomous or teleoperated robotic systems for various diagnostic and medical interventions. Additionally centers for elderly care and 24/7 assisted living could also benefit from autonomous and robotic systems treating and administering care to their patients beyond the capabilities of today's robotic capabilities.

REFERENCES:

1. United States Army Futures Command Concept for Medical 2028, https://api.army.mil/e2/c/downloads/2022/04/25/ac4ef855/medical-concept-2028-final-unclas.pdf
2. United States Army Medical Modernization Strategy, https://www.army.mil/e2/downloads/rv7/about/2022_Army_Medical_Modernization_Strategy.pdf

KEYWORDS: Robotics, End-Effector, Medical, Prehospital, Combat Casualty Care, Automation, Innovation, Modernization

DHA242-003 TITLE: Hydrogel-based Drug Delivery Product(s) for Traumatic Brain Injury

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Combat Casualty Care

OBJECTIVE: To develop and validate a biodegradable hydrogel drug delivery system for open-skull fracture or penetrating traumatic brain injury (TBI) designed to seal the wounded environment and facilitate the controlled, continuous release of hemostatic agents to stop intracerebral hemorrhage, antimicrobials to prevent infection, and drugs to prevent brain swelling and herniation.

DESCRIPTION: Traumatic brain injury (TBI) is a significant health issue affecting military service members during both wartime and peacetime. Care for TBI will be particularly challenging for military medics as it will extend over a prolonged period, in far-forward, austere settings. Yet, this prehospital phase of care is vitally important as the first link in the chain to prevent death and to limit secondary injuries for TBI combatants. Currently, no therapeutic intervention is available as neuroprotective treatment for TBI. In the battlefield, supportive measures usually include restoration of blood pressure and tissue oxygenation through resuscitation or control of intracranial hypertension with hypotonic saline. However, all these measures require skilled paramedics and reasonable medical settings, which are often not feasible during combat. Future improvement in combat casualty outcomes depends on closing the gap in prehospital care. One approach is to develop therapeutic products that can be readily available for administrating by a Combat Medic and/or self or buddy-administration to mitigate morbidity and mortality from TBI during prolonged field and enroute care.

Hydrogels are stable, highly malleable, and easily transportable matrixes that can potentially carry multiple therapeutics. They are easy to apply and offer a promising solution for the point-of-injury care for TBI. Moreover, they are ideal for extended release of drugs directly at the site of injury, bypassing the systemic route and thus limiting potential adverse effects (Fernandez-Serra, Gallego, Lozano, & Gonzalez-Nieto, 2020; Ma et al., 2020). The desired end-product would be a combination (biologic + drug) therapy product utilizing an FDA-approved biodegradable hydrogel combined with an FDA-approved drug that has demonstrated significant evidence of therapeutic benefit in the preclinical TBI literature. The product target should be for TBI patients presenting with skull fracture or penetrating wounds to the brain. This system should be designed to seal the wounded environment and facilitate the controlled, continuous release of individual or multiple therapeutics including antimicrobials to prevent infection, antioxidants, and anti-inflammatory drugs to prevent cellular damage, brain swelling, and herniation. The release of the drug(s) should be unidirectional, facilitating drug infusion into the injured tissue while mitigating any seepage into re-sutured skin and/or gauze bandages. A successful awardee will design, develop, and demonstrate the utility of a hydrogel-embedded drug formulation for TBI in pre-clinical studies.

PHASE I: Demonstrate the feasibility of the concept by providing proof-of -concept hydrogel-based drug delivery platform for TBI that has the potential to meet the broad needs discussed in this topic description. Currently there are no FDA-approved, field-capable materiel solutions that can be used for open-head wounds or penetrating brain injuries. The proposed studies should consider the ability of the hydrogel to provide the safe, controlled release of known neuroprotective drugs directly to the injured brain. Accompanying the application should be standard protocols and procedures for its use and integration into ongoing programs.

PHASE II: The Performer will validate the feasibility of the proposed product by completing pre-clinical in vivo exploratory studies in established small (i.e., rat) animal models of TBI to (1) demonstrate the safety of the hydrogel product, (2) validate pharmacokinetic and pharmacodynamics (PK/PD) properties of the hydrogel-embedded drug delivery approach, and (3) demonstrate therapeutic efficacy of the hydrogel-embedded drug(s) for TBI. PK/PD evaluation shall include selectivity, bioavailability, bio-

distribution, half-life, stability, and clearance of the drugs in brain tissue and blood/plasma. Drug candidates of interest include, but are not exclusive to, dexamethasone, acetyl L-carnitine, glyceryl tri-acetate, resveratrol tri-acetate, cyclosporine, n-acetylcysteine, candesartan, and minocycline.

Phase II Deliverables

1. The Performer shall submit to DoD technical data and results of experiments demonstrating proof-of-concept and safety of candidate hydrogel + drug formulation(s) in defined small (i.e., rat) animalmodels of TBI non-GLP laboratory studies.
2. The Performer shall submit a Regulatory Development Plan to include identification of the formalregulatory pathway, records of any informal FDA communications guiding their recommendedpathway, referenced hydrogel 510K device already FDA cleared/approved, novel combination withdrug Target Product Profile (TPP) and/or Indication for Use (IFU), projected FDA meeting types, andtop three risks or questions proposed to settle with FDA interactions. The Performer shall provideevidence of FDA interactions confirming whether the novel combination of previously FDA clearedhydrogel + drug may or may not require additional Phase 1 safety studies and/or additional pre-clinicalstudies required by the Agency prior to further clinical development.

PHASE III DUAL USE APPLICATIONS: The Performer shall focus on transitioning the technology from pre-clinical research, through FDA regulated trials, to operational capability and should demonstrate that this system could be used in a broad range of military and civilian medical facilities including by Combat Medics or by buddy administration in austere medical environments. The Performer shall develop a Transition Plan to demonstrate their strategy to infiltrate civilian markets and align to a military operational requirement. The Performer shall discuss technical risks of the approach, costs, benefits, and plan for further development. The Performer shall interface with the U.S. Army Acquisition Medical Research and Development Command (MRDC) Advanced Development Team early to ensure the product aligns to military-relevant use requirements outlined in the current Concepts of Operations. Performers shall integrate the criteria for transitioning to Advanced Development and into the plan. The Performer's Transition Plan shall also demonstrate need for the product by civilian sector stakeholders. Performer shall conduct analysis for commercial viability, via market research data, for possible use in prehospital setting, to include first responders, paramedics, and ambulance transport, and hospital settings. Phase III will require a detailed plan to test the hydrogel + drug product developed in Phase I-II in a larger animal model (pigs, dogs, macaques, etc.), as well as human studies. All research involving animals shall comply with the applicable federal and state laws and agency policy/guidelines for animal protection. Considerations should include material and process documentation, and verifiable data sets on animal samples. The detailed plan shall cite the FDA interactions from Deliverables in Phase II and discuss the steps required for transition from pilot lots of prototypes towards manufacturing process amenable to (cGMP-compliant) pilot lot production. GLP safety and toxicity studies in animal model systems, studies to evaluate the pharmacokinetics and pharmacodynamics (PK/PD), and study specifics for stability and shelf-life studies shall also be discussed in the plan.

The Performer's transition plan shall propose a Clinical Development Plan for FDA regulated Phase 2 and 3 clinical trials to include optimal dosing concentration and regimen determination demonstrated via PK/PD studies, clinical trial synopsis, targeted TBI population, power analysis, and primary outcome measure for efficacy.

The Performer's transition plan shall discuss Product Development Plan to include manufacturing readiness to support Phase 2 and 3 clinical trials, drug packaging and distribution partnerships, results of release and stability studies completed, and a plan for scaling to GMP certified manufacturing partners if not already established.

Lastly, the Performer's transition plan shall discuss the business case to include commercial partner alliance(s), intellectual property protections, patent status, any licensing agreements and plans for commercialization. Private industry can be sought for production of using Good Manufacturing Practice (GMP) processes, either by the small business or under license. Ideally, the Performer will be the regulatory sponsor for clinical studies necessary to demonstrate selective, targeted delivery to the brain, as well as clinical safety and efficacy. The Performer is encouraged to submit proposals to competitive applications to acquire and leverage additional funding sources (i.e. Congressional Directed Medical Research Program/CDMRP, Joint Warfighter Brain Health (JWBH), Combat Casualty Care Research Program (CCCRP), Medical Technology Enterprise Consortium (MTEC) and/or private investiture) adequate to support all development activities and ensure commercial availability and sustainability for the developed product(s).

REFERENCES:

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2. Ma, X., Agas, A., Siddiqui, Z., Kim, K., Iglesias-Montoro, P., Kalluru, J., . . . Haorah, J. (2020). Angiogenic peptide hydrogels for treatment of traumatic brain injury. Bioact Mater, 5(1), 124-132. doi:10.1016/j.bioactmat.2020.01.005

KEYWORDS: Hydrogel, traumatic brain injury, penetrating brain injury, extended drug release, TBI, skull fracture