Defense Health Agency
2023.B Small Business Technology Transfer (STTR)
Proposal Submission Instructions

INTRODUCTION

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

Proposers responding to a topic in this Broad Agency Announcement (BAA) must follow all general instructions provided in the Department of Defense (DoD) STTR Program BAA. DHA requirements in addition to or deviating from the DoD Program BAA are provided in the instructions below.

The DHA Program participates in up to three DoD STTR BAAs each year. Proposals not conforming to the terms of this BAA will not be considered. Only Government personnel will evaluate proposal submissions.

Specific questions pertaining to the administration of the DHA STTR Program and these proposal preparation instructions shall be directed to:
DHA 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.

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.

PHASE I PROPOSAL GUIDELINES

The Defense SBIR/STTR Innovation Portal (DSIP) is the official portal for DoD 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 STTR Program BAA.

Technical Volume (Volume 2)

The technical volume is not to exceed **20 pages** and must follow the formatting requirements provided in the DoD STTR Program BAA. Do not duplicate the electronically-generated Cover Sheet 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 Sheet and Cost Volume are excluded from the 20-page limit. 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-compliant and score it accordingly.

Content of the Technical Volume
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. Refer to the instructions provided in the DoD STTR Program BAA for full details on content of the technical volume.

Cost Volume (Volume 3)
The Phase I amount must not exceed **$250,000**. Costs must be separated and clearly identified on the Proposal Cover Sheet (Volume 1) and in Volume 3.

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 STTR 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)
DHA STTR will accept a Volume Five (Supporting Documents) as required under the DoD STTR Program BAA.

Fraud, Waste and Abuse Training Certification (Volume 6)
DoD requires Volume 6 for submission. Please refer to the Phase I Proposal section of the DoD STTR Program BAA for details.

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. All DHA STTR Phase I awardees from this BAA will be allowed to submit a Phase II proposal for evaluation and possible selection. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the DHA STTR PMO. Submission instructions are typically sent in month five of the Phase I contract. The awardees will receive a Phase II window notification via email with details on when, how and where to submit their Phase II proposal.

Small businesses submitting a Phase II Proposal must use the DoD SBIR/STTR electronic proposal submission system (https://www.dodsbirsttr.mil/submissions/login). This site contains step-by-step instructions for the preparation and submission of the Proposal Cover Sheets, the Company Commercialization Report, the Cost Volume, the Technical Volume, Supporting Documents, and Fraud, Waste, and Abuse certificate.

The DHA STTR Program will evaluate and select Phase II proposals using the evaluation criteria in the DoD STTR Program BAA. Due to limited funding, the DHA STTR 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 STTR 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. Do not include blank pages, duplicate the electronically- generated Cover Sheets 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-compliant and score it accordingly.

DISCRETIONARY TECHNICAL AND BUSINESS ASSISTANCE (TABA)
The DHA STTR 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 STTR Program has a Technical Assistance Advocate (TAA) 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 STTR Program BAA.

Proposing firms will be notified via email to the Corporate Official 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 STTR Office at usarmy.detrick.medcom-usamrmc.mbx.dhpsbir@health.mil. Please note 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 STTR Program BAA for procedures to protest the Announcement.
As further prescribed in FAR 33.106(b), FAR 52.233-3, Protests after Award shall 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 and II awardees will be informed of contracting and Technical Point of Contact upon award.

ADDITIONAL INFORMATION

RESEARCH INVOLVING HUMAN SUBJECTS, HUMAN SPECIMENS/DATA, OR ANIMAL RESEARCH
The DHA STTR Program highly discourages offerors from proposing to conduct Human Subjects, Human Specimens/Data, or Animal Research during Phase I due to the significant lead time required to prepare regulatory documentation and secure approval, which could substantially delay the performance of the Phase I award. While technical evaluations will not be negatively impacted, Phase I projects requiring Institutional Review Board approval may delay the start time of the Phase I award. If necessary regulatory 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 and Animal Research Oversight (OHARO) provides formal authorization. Written approval to begin a research protocol will be issued from the USAMRDC OHARO, under separate notification to the recipient. Written approval from the USAMRDC OHARO 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.

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

WAIVERS
In rare situations, the DHA STTR Program allows for a waiver to be incorporated allowing federal facility usage for testing/evaluation. A waiver will only be permitted when it has been determined that no applicable U.S. facility has the ability or expertise to perform the specified work. The DHA STTR Program has the right of refusal. If approved, the DHA STTR Program will assist in establishing the waiver for 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 APAN 15-01 requirements that will be included in the Phase II submission instructions.

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 non-profit 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 STTR 23.B Topic Index

DHA23B-001 TITLE: To Develop a Technological Solution for Automated Detection of Circulating and Exosomal miRNAs

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Military Operational Medicine

OBJECTIVE: To develop a reliable, rapid, sensitive, multiplex method to quantify the levels of small RNA molecules such as exosome and circulating microRNAs (miRNA) in biological samples to explore their potential as diagnostic and prognostic tools.

DESCRIPTION: The volume of in vitro diagnostics continues to grow steadily due to increased availability of easy-to-use devices, thus making it possible to deliver less costly care closer to the patient site in a shorter time relative to the central laboratory services. A novel class of small non-coding RNA molecule microRNAs have recently gained attention in healthcare management for its potential as biomarkers for human diseases. MicroRNAs (miRNAs) are evolutionary conserved, ~18–24 nucleotides long non-coding RNA, playing a significant role in controlling human gene expression by post-transcriptional gene regulation or silencing.

Each miRNA can regulate up to 200 predicted target genes, and one mRNA may be influenced by multiple miRNAs. miRNAs are abundant in many cell types, exosomes, and even occur as extracellular circulating molecules in blood and other biological fluid. A growing number of reports have shown that subsets of miRNAs may have clinical relevance as biomarkers. These biomarkers can be used to indicate presence of a pathology and even the stage, progression, or genetic link of pathogenesis (1). In certain situations, one miRNA biomarker may be sufficient to identify a health outcome such as acute injuries to Warfighters in the operational environment; however, in other cases, a well-defined panel of miRNAs is necessary for increased diagnostic sensitivity and/or specificity such as traumatic brain injury (TBI), post-traumatic stress disorder (PTSD) etc. These investigations have been undertaken in preclinical animal models and in human cohorts. For example, multi-omics investigation of PTSD patients' blood samples identified a diversified panel including miRNAs (miR-133a-3p, miR-192-5p, mir-424-3p and miR-9-5p) (2). Data from our lab have also shown exosome derived miRNA are involved in chronic neuropathic pain (3) as well as early impacts of irradiation was underscored by the large number of miRNAs in total body radiation pre-clinical model (4). However, the most widely used methods for analyzing miRNAs, including Northern blot-based platforms, in situ hybridization, reverse transcription qPCR, microarray, and next-generation sequencing involves cascade of operations including sample processing, miRNA quantification can be cumbersome and crippled by serious flaws at all stages of the process. In addition, these methods require that the low abundance miRNA be several folds greater than background to give a significant result. Therefore, the current topic is about the possibility and feasibility to develop a reliable, rapid, sensitive, multiplex method to quantify the levels of exosome and circulating miRNA in biological samples. The ultimate goal is to translate technological developments into diagnostic and prognostic tools.

1) The development of a robust and portable device.
2) To conduct an integrated sample collection-to-assay-to-detection architecture including exosomal and cell-free miRNA.
3) The amount and character of sample requirements. Consider minimally invasive clinical samples, such as blood, urine, saliva.
4) Device should have multiplexing capability and should be flexible to adapt new miRNA panels.
5) The sensitivity and specificity of the assay should be addressed.
6) The robustness and simplicity of the method.
7) The simplicity of software for analysis and interpretation of the data.
8) Minimal use of specialized equipment and reagents.
9) Low turn-around time to result
10) Assay cost

11) Capable to differentiate between exosome-derived vs cell-free miRNA

PHASE I: To establish feasibility for a quantitative molecular diagnostics technology based on the detection of exosomal and cell free circulating miRNA using readily available clinical or pre-clinical samples. Current in vitro approaches require extensive preparation involving extraction, reverse transcription of miRNA into cDNA, amplification followed by data analytics. To devise specific technological bricks to release these low molecular weight RNA molecules before proceeding to detection and analysis. Here, we are seeking experimental evidence of the proof-of-concept explaining methodologies to detect multiplexed miRNA panel (exosomal and/or circulating) from a single input of biomatrix of choice with minimal human handling. The proposed device should be able to conduct the entire process starting from the biomatrix collection to analysis in a rapid fashion. Molecular diagnostics assay will have a potential for more sensitive, more accurate, and more objective clinical judgments. Use of human or animal subjects is not intended, nor expected, in order to establish/achieve the necessary proof-of-concept in Phase I. Further noting, animal or human use research shall not occur during Phase I as the period of performance does not allow enough time for required approvals to be received. In addition, descriptions of data analysis and interpretations concept and concerns should be outlined. Phase I should also include the detailed development of Phase II testing plan.

PHASE II: The Phase I proposed protype shall be validated in Phase II. During this Phase, technology should undergo testing using a panel of miRNA (exosomal and circulating) for evaluation of the operation and effectiveness of utilizing an integrated system. A complete demonstration from biomatrix to detection of miRNA quantification is expected. Accuracy, reliability, and usability should be assessed. The device should be easy to use and interpret. The testing should be controlled and rigorous. Statistical power should be adequate to document initial efficacy and feasibility of the assay. This phase should also demonstrate evidence of commercial viability of the tool. Any information about risk and its mitigation should be discussed. 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. Lastly, shall develop a clear regulatory strategy on how FDA clearance will be obtained.

PHASE III DUAL USE APPLICATIONS: The product developed is intended to be suitable for use and potential procurement by all Military Services and for civilian. The dual-use technology would be applicable via securing funds from other sources. The successful transition path of the technology is expected to include close engagement with military medical acquisition program managers during product commercialization to ensure appropriate product applicability for military field deployment. This assay format should also be seamlessly integrated into the device for its potential be used as monitoring tool for short- or long-term health assessment. Once developed and demonstrated, the technology can be used for identification of risk, diagnostic, prognostic, monitoring and/ or
predictive biomarkers for diseased state. The broader/commercial impact of this project will be to enhance current diagnostic and prognostic tools for early detection of disease.

REFERENCES:

1. Hanna Johora, Hossain Gazi S., Kocerha Jannet. The Potential for microRNA Therapeutics and Clinical Research. Frontiers in Genetics 2019 https://www.frontiersin.org/articles/10.3389/fgene.2019.00478
2. Dean, K.R., Hammamieh, R., Mellon, S.H., Abu-Amara, D., Flory, J.D., Guffanti, G., Wang, K., Daigle, B.J., Gautam, A., Lee, I. and Yang, R., 2020. Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. Molecular psychiatry, 25(12), pp.3337-3349.
3. Sosanya NM, Kumar R, Clifford JL, Chavez R, Dimitrov G, Srinivasan S, Gautam A, Trevino AV, Williams M, Hammamieh R, Cheppudira BP, Christy RJ, Crimmins SL. Identifying Plasma Derived Extracellular Vesicle (EV) Contained Biomarkers in the Development of Chronic

Neuropathic Pain. J Pain. 2020 Jan-Feb;21(1-2):82-96. doi: 10.1016/j.jpain.2019.05.015. Epub 2019 Jun 19. PMID: 31228575.
4. Chakraborty N, Gautam A, Holmes-Hampton GP, Kumar VP, Biswas S, Kumar R, Hamad D, Dimitrov G, Olabisi AO, Hammamieh R, Ghosh SP. microRNA and Metabolite Signatures Linked to Early Consequences of Lethal Radiation. Sci Rep. 2020 Mar 25;10(1):5424. doi:

KEYWORDS: miRNA, Biosensors, exosomes, Biomarkers, non-coding RNA, small RNA, microfluidics,

DHA23B-002 TITLE: To develop an In Vitro Diagnostic (IVD) Platform for Rapid Detection of Multiplexed Multi-omics Biomarker Panel From Minimally Invasive Biomatrix

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Military Operational Medicine

OBJECTIVE: To meet an innovation gap in rapidly detecting multiplexed multi-omics library of gene-epigene-protein-metabolite from single input of minimally invasive biomatrix in austere condition.

DESCRIPTION: High throughput multi-omics readout and Systems integration galvanize our understanding about the molecular interplay and their roles in manifesting phenotypes. This interactive molecular landscape encompasses different layers of omics, namely epigenomics, transcriptomics, proteomics and metabolomics1, which operate in synchronized fashions to carry out biological functions. For instance, an epigenetic information flows through transcriptomics and proteomics layers to modulate metabolite landscape. Evidently, disease pathophysiology leaves footprints in any or all these layers of omics; hence a robust panel of disease biomarkers should include candidates from every layer of omics. Indeed, the current trend in biomarker discovery is progressively shifting from finding a single biomarker to a group of multi-omics biomarkers that can collectively define a clinical event2. A growing number of studies have identified multi-omics markers for psychological diseases like PTSD3,4 and somatic illnesses like rectal and prostate cancer1. Rapid probing of multi-omics molecular landscape is expected to enhance the diagnostic performance2, however such capability is yet to be fully materialized. This is the core innovation gap that we are poised to address here.

To develop this capability, the pilot prototype of IVD platform will detect multiplexed multi-omics PTSD biomarkers3,4 as a proof of its capability. We will ensure maximum flexibility in this prototype development process, so that the prototype could be easily repurposed in future to diagnose additional diseases including, but not limited to sepsis, TBI, infection, exposure to CBRN and cancer.
Diseases like PTSD is a good target for developing the pilot prototype due to two primary reasons. First, PTSD adversely impacts entire system; hence holistic screening of multi-omics landscape is imperative for PTSD subtyping, biomarker discovery and predicting comorbidities. For instance, DNA methylation markers were reported to biotype PTSD patients3. Moreover, multi-omics PTSD blood diagnostic markers included differentially methylated contigs (cg01208318, cg20578780, and cg15687973), miRNAs (miR-133a-1-3p, miR-192-5p, and miR-9-1-5p) and metabolites (gammaglutamyltyrosine)4. Although, we are yet to identify most robust panel of biomarkers for PTSD diagnosis and bio typing, a trend is rather apparent- the final product is likely to have representations from different omics layers, and this trend essentially justifies the proposed STTR program. The second reason to select PTSD is because many of its biomarkers are available in public domain3,4, ensuring an easy access to the Phase I awardees.

A web search of SBIR.gov (dated January 25, 2023) found existing solicitations to develop multiplexed multi-omics tools to primarily reconstruct the cellular motifs with high resolution; all these prototypes are expected to be used in sophisticated laboratory settings and preclude any pursuit to make these assays rapid, automated and operatable in austere condition. There are several ongoing STTR efforts to rapidly screen individual omics layer in a field-rugged platforms. Clearly, there is a vast innovation and capability gap in developing a platform enabled to support rapid detection of pan-omics panel in austere condition. Present proposal is poised to meet this innovation gap.

PHASE I: Provide experimental evidence of the proof-of-concept explaining methodologies to detect multiplexed multi-omics panel from a single input of biomatrix of choice. The expectation is that the biomatrix should be minimally invasive, such as blood, saliva, urine etc. We further expect that the proposed IVD platform should be able to conduct the entire process starting from the biomatrix collection to analysis in a rapid fashion.

It is also important to note that different biomatrix is enriched by different omics components. For instance, whole blood is the preferred biomatrix for extracting maximum amount of mRNA and DNA, while the cell free serum or plasma is the preferred biomatrix for extracting maximum amounts of proteins and metabolites. Therefore, if an IVD prototype targets blood for molecular extraction, it should be able to handle whole blood and serum/plasma concurrently from single input volume.
Target PTSD biomarkers could be curated from the public domain3,4. Use of human or animal subjects is not intended, or expected, in order to establish/achieve the necessary proof-of-concept in Phase I. At the end of this phase, a working prototype of the device should be demonstrated with reasonable sensitivity and feasibility. In addition, descriptions of data analysis and interpretations concept should be outlined. Phase I should also include the detailed development of Phase II testing plan.
In summary, our expectations from Phase I is the following
1. A plan to develop an IVD device that can detect multiplexed multi-omics biomarker panel to map phenome of interest. For the pilot prototype, we plan to detect multi-omics PTSD biomarkers that are available in public domain. However, the final product should be flexible to diagnose other diseases, such as sepsis, traumatic brain injury, pathogenic infection, exposure to CBRN and cancer.
2. The expected device should be an automated and portable IVD platform enable to be used in far forward lab or at bedside in an energy inexpensive manner.
3. The device is expected to support an end-to-end methodology e.g., an integrated sample collection-to-assay-to-detection protocol.
4. Multiplexing capability of multi-omics panel from single input volume is essential. Should the device select blood as the input biomatrix, the platform should be able to simultaneously handle whole blood and serum/plasma from single input volume.

PHASE II: The knowledge/ prototype generated in Phase I should be ready to be improved 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 mode of endpoint reading should be finalized, and this process should be easily interpretable. Finally, we expect to have clear indications of the prototype's operational capability in real-world situations; some knowledge about the risks, source of confounders and concerns should be outlined, and pertinent mitigation plan should be furnished. 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. This phase should also deliver a plan for commercialization.

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 finalized. 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 commercial production and a plan on how FDA clearance will be obtained.

PHASE III DUAL USE APPLICATIONS: The product developed is intended to be suitable for use and potential procurement for primary use in the field/prehospital environment, including austere, prolonged care scenarios. At this phase, target diseases and pertinent biomarkers should be determined. As mentioned previously, the target disease might not be relevant to the health issues exclusive to active duty members. Realization of a dual-use technology applicable to both the military and civilian use could be achieved via securing funds from third party. Therefore, the successful transition path of the technology is

encouraged to include close engagement with military medical acquisition program managers during product commercialization to ensure appropriate product applicability for military field deployment. 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. FDA submission and approval is a goal for this phase.

REFERENCES:

5. Subramanian I, Verma S, Kumar S, Jere A, Anamika K. Multi-omics data integration, interpretation, and its application. Bioinformatics and biology insights. 2020 Jan;14:1177932219899051.
6. Vincent, J.-L., Bogossian, E. & Menozzi, M. J. C. c. c. The Future of Biomarkers. 36, 177-187 (2020).
7. Yang, R., Gautam, A., Getnet, D., Daigle, B.J., Miller, S., Misganaw, B., Dean, K.R., Kumar, R., Muhie, S., Wang, K. and Lee, I., 2021. Epigenetic biotypes of post-traumatic stress disorder in war-zone exposed veteran and active duty males. Molecular psychiatry, 26(8), pp.4300-4314.
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KEYWORDS: In vitro diagnostic device, multi-omics biomarker detection, multiplexing capability, targeted molecular identification, minimally invasive biomatrix, rapid diagnosis, austere environment-friendly, minimum hands-on time

DHA23B-003 TITLE: Electrodermal Activity for Prediction and Detection of Symptoms Related to the Central Nervous System Oxygen Toxicity Including Seizures

OUSD (R&E) CRITICAL TECHNOLOGY AREA(S): Military Operational Medicine

OBJECTIVE: Develop a means to detect the onset of seizures due to CNS-OT for real-time monitoring of divers immersed underwater.

DESCRIPTION: Divers breathing hyperbaric oxygen (HBO2) are at risk for developing Central Nervous System Oxygen Toxicity (CNS-OT), which can manifest as symptoms that might impair a diver's performance, such as headache, nausea, tinnitus, lip twitching, tingling of the limbs, or even more serious symptoms such as seizure or altered consciousness(1,2). Oxygen seizures themselves are not harmful, the environmental conditions greatly influence the risks associated with losing consciousness or convulsing; being underwater could result in the dislodgement of the diver's air supply from his or her mouth, possibly leading to drowning(3,4). Furthermore, the risk of CNS-OT dictates strict diving protocols greatly limiting mission capabilities (depth and duration of a dive are impacted by risk of CNS-OT). Developing a means to detect the onset of seizures due to CNS-OT would provide great safety monitoring that has been absent from risk of CNS-OT in diving. If proven, mitigation strategies to prevent CNS-OT and detection of the consequential seizures in some subjects could reduce risk to divers. The risk of CNS-OT occurrence is highly variable between individuals, making it hard to predict the onset of seizures, and to determine the safety of exposure to HBO2. Being able to establish an individual safe level of exposure would maximize the therapeutic and operational uses of HBO2 in hyperbaric, diving, and submarine medicine (e.g. healing problematic wounds or preventing DCS), by enabling the extension of exposure time in individuals with more neurological tolerance to HBO2. Previous studies have suggested that electrodermal activity (EDA) can be used to predict seizures in rodents exposed to HBO2(5).

PHASE I: Demonstrate feasibility through analysis and limited laboratory demonstrations, a device that is capable of measuring electrodermal activity (EDA) to be worn by: pool swimmers/divers, surface supplied divers, free swimming divers, and patients receiving hyperbaric oxygen treatment in dry chambers. The device shall provide full function and data processing while immersed in salt water and exposed to increased hyperbaric pressures of 100 feet of sea water (FSW) (threshold)/300 FSW (objective) at a temperature range of 32-95 Degrees F, Provide cost-effective designs and reliability estimates, including lifetime expectancy and lifetime cost estimate. The required Phase I deliverables will include: 1) a research plan for the engineering design of the physiologic monitor; 2) a preliminary prototype, either physical or virtual, capable of demonstrating effectiveness of the proof-of-concept design; and 3) a test and evaluation plan to validate accuracy of data collection including identification of proper controls. Important considerations should include location, minimization of motion artifacts, enhanced comfort and wearability (minimization of wired elements), and on-board processing. Device should detect EDA while submerged underwater. Phase I will provide key information about the uses and limitations of the system and could include rapid prototyping and/or modeling and simulation.

PHASE II: Develop, demonstrate, and validate the underwater EDA prototype based on the Phase I design concept. The system should be used under the expected extreme environmental conditions (as cited in the description section) to collect and analyze data and test algorithms against the known physiological alterations during diving activity. Device shall collect data continuously for up to 24 hours at minimum with on-board processing capability to enable feedback to individual. Initial prototype may be designed for use on the body of a diver with or without a wetsuit or drysuit using traditional scuba or rebreather life support. Device should include onboard data processing enabling real-time feedback to diver. No data transmission will be included under the initial development. A lithium battery may be used but alternative power sources that have minimal safety hazards and can function submerged in ocean water should be considered. Initial design may be intended for experimental or training use and need not be adapted for operational use. Phase II deliverable of, at minimum, two prototype units that includes detailed design specifications and technical data package drawings (level 2/3) established through this STTR to ONR that ensures IP protection.

Interest by military customer would be defined by validation through testing and confidence in predictive measures. Successful devices would need to be tested either at a Naval dive unit such as Naval Experimental Diving Unit (NEDU) if possible or another acceptable dive facility, which could include commercial dive centers. If NEDU is preferred, it is advisable to plan well in advance to ensure they are able to accommodate testing schedule.

PHASE III DUAL USE APPLICATIONS: If successful, transition prototype to a functional unit to the US Navy's Naval Sea Systems Command Supervisor of Salvage and Diving (NAVSEA SUPSALV), which maintains diving equipment authorized for Naval use. Operationally relevant conditions will necessitate additional testing and may require greater depths, prolonged data collection, and security considerations.

If successful, the small business shall support the Navy in transitioning the resulting technology for use in operational environments. The small business shall develop a plan to transition and commercialize the technology and its associated guidelines and principles. Private Sector Commercial Potential: This SBIR would provide much needed understanding of objective measures for detecting early signs of neurologic distress and generally monitoring brain health across recreational and commercial diving populations during mixed gas dives for use in hyperbaric treatments by medical professionals.

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