

CHEMICAL AND BIOLOGICAL DEFENSE PROGRAM SBIR 15.2 Proposal Submission

General Information

In response to Congressional interest in the readiness and effectiveness of U.S. Nuclear, Biological and Chemical (NBC) warfare defenses, Title XVII of the National Defense Authorization Act for Fiscal Year 1994 (Public Law 103-160) required the Department of Defense (DoD) to consolidate management and oversight of the Chemical and Biological Defense (CBD) Program into a single office – Office of the Assistant Secretary of Defense for Nuclear, Chemical and Biological Defense Programs. The Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD), Defense Threat Reduction Agency (DTRA) provides the management for the Science and Technology component of the Chemical and Biological Defense Program. Technologies developed under the Small Business Innovation Research (SBIR) Program have the potential to transition to the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) if the appropriate level of technology maturity has been demonstrated. The JSTO-CBD Science & Technology programs and initiatives are improving defensive capabilities against Chemical and Biological Weapons of Mass Destruction. The SBIR portion of the CBD Program is managed by the JSTO-CBD.

The mission of the Chemical and Biological Defense Program is to ensure that the U.S. Military has the capability to operate effectively and decisively in the face of chemical or biological warfare threats at home or abroad. Numerous factors continually influence the program and its technology development priorities. Improved defensive capabilities are essential in order to mitigate the impact of Chemical and Biological Weapons. The U.S. military requires the finest state-of-the-art equipment and instrumentation available that permits our warfighters to detect to warn and avoid contamination, if possible – and to be able to sustain operations in a potentially contaminated environment. Further information regarding the DoD Joint Chemical and Biological Defense Program is available at the DoD Counter-proliferation and Chemical Biological Defense homepage at <http://www.acq.osd.mil/cp>.

The overall objective of the CBD SBIR Program is to improve the transition or transfer of innovative Chem-Bio technologies to the end user – the warfighter – in addition to commercializing technologies within the private sector for mutual benefit. The CBD SBIR Program targets those technology efforts that maximize a strong defensive posture in a biological or chemical environment using passive and active means as deterrents. These technologies include chemical and biological detection for both point and stand-off capabilities; individual and collective protection; hazard mitigation (decontamination); information systems technology to include but not limited to modeling and simulation and operational effects & mitigation; medical pre-treatments (e.g., vaccine development and delivery); medical diagnostics & disease surveillance; and medical therapeutics (chemical countermeasures and biological countermeasures).

Submitting Your Phase I CBD SBIR Proposal

Your entire proposal submission (consisting of a Proposal Cover Sheet, the Technical Volume, Cost Volume, and Company Commercialization Report) must be submitted electronically through the DoD SBIR/STTR Proposal Submission system located at <https://sbir.defensebusiness.org/>. A hardcopy is NOT required and will not be accepted by the Chemical and Biological Defense SBIR Program. Hand or electronic signature on the proposal is also NOT required.

The Proposal Technical Volume must be 20 pages or less in length. The Cover Sheet, Cost Volume and Company Commercialization Report do not count against the 20-page Proposal Technical

Volume page limit. Pages in excess of this length will not be evaluated and will not be considered for review. The proposal must not contain any type smaller than 10-point font size (except as legend on reduced drawings, but not tables).

You must prepare a Company Commercialization Report through the Proposal Submission site and it will be included with your electronic submission; however, the Company Commercialization Report does not count against the proposal page limit. Update your commercialization information if you have not done so in the past year. Note that improper handling of the Commercialization Report may result in the proposal being substantially delayed and that information provided may have a direct impact on the review of the proposal. Refer to Section 5.4.e of this program solicitation for detailed instructions on the Company Commercialization Report.

If your proposal is selected for award, the technical abstract and discussion of anticipated benefits will be publicly released on the Internet; therefore, do not include proprietary or classified information in these sections. Note also that the DoD Web site contains timely information on firm, award, and abstract data for all DoD SBIR Phase I and II awards archived for several years. This information can be viewed on the DoD SBIR/STTR Web site at: <http://www.acq.osd.mil/osbp/sbir/>.

The CBD SBIR Program uses a Phase I Option to enhance the Phase I to Phase II transition process; the Phase I option may be exercised to fund interim Phase II activities while a Phase II contract is being negotiated if selected for a Phase II award. The maximum dollar amount for a Phase I proof-of-concept/feasibility study is \$100,000. The Phase I Option, which must be proposed as part of the Phase I proposal, covers activities over a period of up to three months and at a cost not to exceed \$50,000. All proposed Phase I Options must be fully costed and should describe appropriate initial Phase II activities, which would lead, in the event of a Phase II award, to the successful demonstration of a product or technology. **The CBD SBIR Program will not accept Phase I proposals which exceed \$100,000 for the Phase I effort and \$50,000 for the Phase I Option effort.** Only those Phase I efforts selected for Phase II awards through the CBD SBIR Program's competitive process will be eligible to exercise the Phase I Option. To maintain the total cost for SBIR Phase I and Phase II activities at a limit of \$1,150,000, the total SBIR funding amount available for Phase II activities from a resulting Phase II contract will be \$1,000,000.

Companies submitting a Phase I proposal under this solicitation must complete the Cost Volume using the on-line form, within a total cost of \$100,000 over a period of up to six months (plus up to \$50,000 for the Phase I Option over a period of up to three months). Phase I and Phase I Option costs must be shown separately.

Selection of Phase I proposals will be based upon the evaluation criteria discussed in Section 6.0 of this program solicitation. The CBD SBIR Program reserves the right to limit awards under any topic, and only those proposals of superior scientific and technical quality in the judgment of the technical evaluation team 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.

CBD Program Phase II Proposal Guidelines

Phase II is the demonstration of the technology that was found feasible in Phase I. The Reauthorization of the SBIR/STTR Program (see Note 1) has resulted in significant changes to the Phase II proposal submission process. Phase I awardees may submit a Phase II proposal without invitation; however, it is strongly encouraged that a Phase II proposal not be submitted until sufficient Phase I

progress can be evaluated and assessed based on results of the Phase I proof-of-concept/feasibility study Work Plan and at a recommended five months from date of contract award. **All Phase II proposal submissions must be submitted electronically through the DoD SBIR/STTR Proposal Submission system at <https://sbir.defensebusiness.org/>.** At the proposal submission website, Phase II proposals MUST be submitted to ‘CBD SBIR’ regardless of what DoD contracting office negotiated the Phase I contract. Additional instructions regarding Phase II proposal submission process including submission key dates will be provided to Phase I awardees after Phase I contract award and also can be found at <https://www.cbdsbir.net/PhaseII.aspx>.

All proposers are required to develop and submit a commercialization plan describing feasible approaches for marketing and manufacturing the developed technology. Proposers are required to submit a budget for the entire 24 month Phase II period. During contract negotiation, the Contracting Officer may require a Cost Volume for a base year and an option year; thus, proposers are advised to be aware of this possibility. These costs must be submitted using the Cost Volume format (accessible electronically on the DoD SBIR submission site), and the two-years 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. At the Contracting Officer’s discretion, Phase II projects may be evaluated for technical progress prior to the end of the base year, prior to extending funding for the option year.

The CBD SBIR Program is committed to minimizing the funding gap between Phase I and Phase II activities. All CBD SBIR Phase II proposals will receive timely reviews and be eligible for interim funding (refer above for information regarding the Phase I Option). The CBD SBIR Program typically funds a cost plus fixed fee Phase II award, but may award a firm fixed price contract at the discretion of the Contracting Officer.

Key Dates

15.2 Solicitation Pre-Release	24 April 2015 – 25 May 2015
15.2 Solicitation Open/Close	26 May 2015 – 24 June 2015 (submission deadline: 6:00 am Eastern Time on closing date)
Phase I Evaluations	June - July 2015
Phase I Selections	No Later Than 23 September 2015
Phase I Awards	December 2015 (see Note 2)
Phase II Proposal Submission	Recommend proposal submission no earlier than approximately five months from date of Phase I contract award. Additional instructions regarding Phase II proposal submission process including key dates will be provided to Phase I awardees after Phase I contract award and also can be found at https://www.cbdsbir.net/PhaseII.aspx .

(Note 1) On December 31, 2011, the President of the United States signed into law the National Defense Authorization Act for Fiscal Year 2012 (Defense Reauthorization Act), Public Law 112–81. Section 5001, Division E, of the Defense Reauthorization Act contains the SBIR/STTR Reauthorization Act of 2011 (SBIR/STTR Reauthorization Act), which extends both the SBIR and STTR Programs through September 30, 2017.

(Note 2) Subject to the Congressional Budget process.

CBD SBIR PROPOSAL CHECKLIST

This is a Checklist of Requirements for your proposal. Please review the checklist carefully to ensure that your proposal meets the CBD SBIR requirements. **Failure to meet these requirements will result in your proposal not being evaluated or considered for award.**

- _____ 1. The Proposal Cover Sheet along with the Technical Volume, Cost Volume, and Company Commercialization Report were submitted via the Internet using the DoD's SBIR/STTR Proposal Submission Web site at <https://sbir.defensebusiness.org/>.
- _____ 2. The proposal cost adheres to the CBD SBIR Program criteria specified.
- _____ 3. The proposal is limited to only **ONE** solicitation topic. All required documentation within the proposal references the same topic number.
- _____ 4. The Project Abstract and other content provided on the Proposal Cover Sheet does not contain any proprietary or classified information and is limited to the space provided.
- _____ 5. The Technical Volume of the proposal, including the Option (if applicable), includes the items identified in Section 5.3.c of this program solicitation.
- _____ 6. The Proposal Technical Volume must be 20 pages or less in length. The Cover Sheet, Cost Volume and Company Commercialization Report do not count against the 20-page Proposal Technical Volume page limit. Pages in excess of this length will not be evaluated and will not be considered for review.
- _____ 7. The Company Commercialization Report is submitted online in accordance with Section 5.4.e. This report is required even if the company has not received any prior SBIR funding.
- _____ 8. The proposal must not contain any type smaller than 10-point font size (except as legend on reduced drawings, but not tables).

CBD SBIR 15.2 Topic Index

CBD152-001	Adjustable Focus Lenses for Respiratory Protection
CBD152-002	Smart Split Neck Seals for Respiratory Protection
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CBD152-004	Exploiting Microbiome and Synthetic Biology to Discover and Produce Naturally Occurring Antibiotics
CBD152-005	High Sensitivity, Low Complexity, Multiplexed Diagnostic Devices
CBD152-006	Signal Processing for Layered Sensing

CBD SBIR 15.2 Topic Descriptions

CBD152-001 TITLE: Adjustable Focus Lenses for Respiratory Protection

TECHNOLOGY AREAS: Chemical/Bio Defense, Biomedical, Human Systems

OBJECTIVE: To develop adjustable optical correction technology for respiratory protective mask lenses

DESCRIPTION: Current respiratory protection systems require optical inserts for wearers requiring optical correction. Use of optical correction inserts limit optical compatibility with night vision goggles and weapon systems due to the added eye relief. One reason individual high index lenses are not used is because they cost seven times more than vision correction inserts. Additionally, polycarbonate lenses have distortions for diopters above positive 6 and below negative 6. Logistics associated with optical inserts are costly due to the need for stocking inserts because inserts may require yearly exchange based on annual vision exams. Similarly, stocking custom lenses to accommodate every soldier is not logistically possible or cost effective. Technology is needed that can provide on-the-fly adjustable focus lenses to accommodate all wearers. The vision correction could be adjusted as a wearer's vision changes. Ideally, these lenses could be built into the respiratory protection system and would reduce overall eye relief. There are many technology concepts for adjustable focus eyeglasses. However, none have been demonstrated to work in a respiratory protective mask system and none are able to cover the entire range of optical correction needed by the military (-9 to 9 diopters). The current effort would develop novel adjustable focus lenses to allow wearers to focus on both near and distance objects with one lens. The adjustable focus lenses should be able to be integrated into the existing Avon Protection Systems, Inc. M50 respirator, should be lightweight, and should change focus quickly. All methods of incorporating the lens into the respirator system will be considered (i.e., the lenses could be included in the respirator during or after manufacture). The lenses must be able to withstand a large range of temperature and environmental extremes and must be resistant to chemical, biological, and non-traditional threat agents.

PHASE I: Demonstrate a lab scale prototype/breadboard system that provides adjustable vision correction from -5 to +5 diopters. Demonstrate a response time of

PHASE II: Refine optical performance. Demonstrate adjustable vision correction from -9 to +9 diopters. Provide a means for the user to easily change the optical correction. Demonstrate the technology can quickly change and maintain the optical correction until the user decides to change it again. Demonstrate a response time of < 1 sec. Demonstrate performance using human subject volunteers. Field of vision, optical distortion, haze, and clarity should be the same or better than the current M50 mask. Demonstrate the technology can be integrated into the M50 respirator.

PHASE III: Complete optical refinement. Optimize fabrication process to demonstrate large-scale production capabilities. Demonstrate ability of technology to be incorporated into a facemask. Demonstrate that the technology is durable and suitable for military combat applications.

PHASE III DUAL USE APPLICATIONS: Potential alternative applications include optical correction in industrial, international, and commercial respiratory protection systems.

REFERENCES:

1. Li Q, Mathine D, Valley P, et al., Switchable electro-optic diffractive lens with high efficiency for ophthalmic applications. Proc Nat Acad Sci 103(16):6100-6104 (2006).
2. <https://www.adlens.com/product/adjustables/>

3. <http://www.gizmag.com/go/5516/>
4. https://www.ted.com/talks/josh_silver_demos_adjustable_liquid_filled_eyeglasses
5. <http://www.allaboutvision.com/lenses/variable-focus.htm>
6. <http://www.avon-protection.com/military/m50.htm>

KEYWORDS: individual protection, respiratory protective mask, lenses, optical correction, adjustable focus lenses

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CBD152-002 **TITLE:** Smart Split Neck Seals for Respiratory Protection

TECHNOLOGY AREAS: Chemical/Bio Defense, Sensors, Human Systems

OBJECTIVE: To develop Smart Split Neck Seal technology to improve current and future neck seal reliant respiratory protection system designs

DESCRIPTION: Current respiratory protection neck seal systems do not incorporate smart sensing technologies. Current neck seal systems are simply basic circular rubber cut-outs and are required to be constructed of one continuous piece of material. Many wearers find traditional neck seals to be uncomfortable. Respiratory protection systems utilized for fixed wing aircraft pilots (e.g. JSAM-FW, AR-5, and AERP), as well as escape purposes (e.g. JSCESM and NIOSH CBRN escape hoods) utilize neck seals as a primary protective barrier. These one piece neck seals may only be donned by pulling the system over the head and down onto the neck. This donning methodology limitation greatly impacts the overall system design, its ability to be worn concurrent with other forms of head-borne PPE, and wearer acceptance. Innovative technology is needed that can allow for a smart split neck seal design that allows for donning versatility, improved comfort, and the provision of user feedback regarding seal performance. Application of smart technology to a neck seal will provide an additional option for wearers with facial hair and/or spectacles (optical correction), would assist in avoiding seal collisions with concurrently worn headgear (e.g. helmet chin straps), and would allow for optional overlapping neck seal wrap designs as opposed to the current continuous neck seal that must be donned over the head. Sensor technology that would continually assess the integrity of the seal but does not require the presence of a specific threat challenge is desired. This sensor would help balance comfort with protection in ensuring that a hermetic neck seal is maintained around the entire circumference of the neck while concurrently ensuring the pressures at the neck are not excessive leading to discomfort. Many types of flexible electronics and pressure-sensitive devices have been constructed from thin films, micro-electromechanical systems (MEMS), and nanowires. However, none have been demonstrated to work in a respiratory protective mask seal system. The current effort would develop not only a novel split neck seal design but also an innovative sensor technology to enhance the sealing of the respiratory protective mask. The sensor would ensure the mask seal maintains proper pressure with the neck skin surface to prevent breakage of the mask seal. In addition, the sensors would be utilized to ensure that both sections of the two piece seal design adequately adhere to one another to form a continuous hermetic sealing surface. The resultant system must be hygienic, durable, and easy to clean. The sensor should be able to be integrated with the seal of the mask, should be lightweight, and should not impact the flexibility or extensibility of the sealing surface. The system must be able to withstand a large range of temperature and environmental

extremes and must be resistant to chemical, biological, and non-traditional threat agents. Lastly, the split neck seal system with the seal sensor should not add more than thirty dollars to the cost of the system in which it is intended to be integrated.

PHASE I: Investigate material sealing methodologies (e.g. ferrofluids, advanced closure systems, etc.) that would allow for the development of a split neck seal design with a hermetic closure. Identify seal performance and wearer comfort metrics for the neck while wearing a full facepiece respirator that seals to the neck. Identify appropriate sensor technology for the proposed split seal design. Demonstrate that selected material sealing technology provides a hermetic seal to the geometry of the neck (e.g., on a headform) and to itself (as a neck closure). A negative pressure between 10 to 15 cmH₂O shall be applied to the neck seal and maintained for 30 sec with less than a 2.5 cmH₂O drop in pressure.

PHASE II: Refine seal performance and develop sensor. Develop sensor technology identified in Phase I. Provide a functioning prototype sensor. The developed sensors should detect a seal performance change of less than or equal to 2% within a time period of 0.2 seconds (e.g. for a pressure sensor, detect a pressure change of less than or equal to 2% of the identified pressures). Apply the developed sensors to actual neck seal geometries to demonstrate performance. Concepts for a split seal design, seal performance indicator, and for electronic user adjustable and automatic fit control shall be demonstrated. Demonstrate the technology can quickly identify repeated seal breaks occurring in the same region. Develop ability to store baseline pressures acquired during a successful fit test. Develop and demonstrate indicator technology to warn user of seal breaks and/or differences in fit from the baseline. Provide a capability for visualization of the potential leak location. Provide pre-production prototype of both face and neck seal respirators with embedded Smart Seal technology. Provide a means for self-calibration of the sensor and seal technology. Demonstrate the flexibility of the existing sealing surface does not change by more than 2% due to the sensor technology. Total weight of the sensors, housing, and electronics including power source should not exceed 50 g. Demonstrate that the system can be electronically adjusted by the wearer to improve fit and that an automatic fit control option is provided and these controls are capable for achieving suitable fit and fit adjustment during simulated workplace protection factor testing.

PHASE III: Complete system refinement. Optimize fabrication process to demonstrate large-scale production capabilities. Demonstrate ability of the technology to be incorporated into a full facepiece respirator prototype. Demonstrate the technology is durable and suitable for military combat applications.

PHASE III DUAL USE APPLICATIONS: Potential alternative applications include industrial, international, and commercial respiratory protection systems as well as protective clothing seals and closures.

REFERENCES:

1. <http://www.sciencedaily.com/releases/2007/04/070402215004.htm>
2. <http://www.sciencedaily.com/releases/2010/09/100912151550.htm>
3. <http://www.sciencedaily.com/releases/2010/09/100913141537.htm>
4. <http://www.unexplained-mysteries.com/news/259903/scientists-build-tiny-terminator-style-muscle>
5. <https://www.ferrotec.com/technology/ferrofluid/>

KEYWORDS: individual protection, respiratory protective mask seal, neck seal, pressure sensor, flexible sensor, MEMS

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CBD152-003 TITLE: Development of Mycotoxin Medical Countermeasures

TECHNOLOGY AREAS: Chemical/Bio Defense, Biomedical

OBJECTIVE: The lack of mycotoxin medical countermeasures represents a critical technology gap for the Department of Defense (DoD). Development of mycotoxin medical countermeasures would be useful to broaden DoD biodefense capabilities. These countermeasures would also have strong commercialization potential in both the government and the private sector because natural 'outbreaks' of mycotoxin poisoning are common and widespread globally.

DESCRIPTION: Mycotoxins are toxins produced by several species of fungi. Exposure to these toxins can result in incapacitation or even death of the exposed subject. From a biological warfare perspective, mycotoxins are relatively easy to produce in large quantities and many of them have nearly effortless accessibility. For these reasons, mycotoxins present a real threat to the warfighter. Trichothecene (T-2), a type of mycotoxin, can be delivered via food or water sources, droplets, aerosols, or smoke from various dispersal systems and exploding munitions. T-2 toxin has allegedly been used as a biological weapon in the past. For example, due to its high thermal stability, T-2 toxin has been baked into bread, yet maintains activity. T-2 toxin is also extremely resistant to ultraviolet light inactivation. As with virtually all toxins, T-2 toxin is far more toxic when inhaled rather than through oral, dermal, or injection exposure. Aflatoxin is a fungal toxin that commonly contaminates maize and other types of crops during production, harvest, storage or processing. Exposure to aflatoxin is known to cause both chronic and acute hepatocellular injury. In Kenya, acute aflatoxin poisoning results in liver failure and death in up to 40% of cases. Similar to the case for T-2 toxin, aflatoxins have high thermal and ultraviolet radiation resistance to inactivation, making them prime candidates for weapons of mass destruction (WMD) or weapons of mass casualties (WMC). The development of mycotoxin medical countermeasures, specifically against aflatoxins and T-2 toxin, addresses current technology requirements as defined by the Joint Requirements Office for Chemical and Biological Defense (JRO-CBD) and the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD). Currently there are no FDA approved medical countermeasures available for either aflatoxin or T-2 mycotoxin exposure. These toxins are debilitating and sometimes lethal on their own. Reports in the open literature suggest that concurrent exposure of mycotoxins in combination with other toxins (or pathogens), results in the increased susceptibility to toxin induced organ damage/failure and to increased mortality than what is observed when either toxin is given alone.

PHASE I: Offerors must propose proof of concept experiments to demonstrate neutralization or attenuation of mycotoxins (of particular interest is aflatoxin or T-2 toxin in a lethal in vitro model). Demonstration of efficacy in some form of an in vivo model is also acceptable, but not required for Phase I. Technologies of interest include, but are not limited to, antibodies (human antibodies are strongly preferred), small molecules, aptamers, and other novel approaches. Repurposing of FDA approved drugs or drugs with successful completion of FDA Phase I clinical trials are also to be considered. Exit criteria for successful completion of Phase I research would be the demonstration of efficacy at low molar concentration in in vitro studies or a 50% increase in survival in any animal model (assuming the animal model has already been developed and an animal use protocol approved). Information garnered from Phase I experiments may be more qualitative than quantitative.

PHASE II: With successful completion of Phase I experiments, Phase II would further evaluate the medical countermeasure (MCM) in a small mammal study. In these studies the MCM would be

administered to animals with mycotoxin only exposure and to mycotoxin plus another toxin such as Staphylococcal enterotoxin A (SEA) or Staphylococcal enterotoxin B (SEB). The animal model should be of sufficient size and scope to demonstrate a statistically significant increase in long-term survival in animals receiving the MCM. The SBIR Phase II studies shall design experiments in a manner that facilitates the collection of non-clinical GLP pharmacokinetic (PK) and pharmacodynamic (PD) data. The PK and PD information will be of paramount importance to inform subsequent Phase III studies.

PHASE III: Phase III studies would further refine the animal model and the compound/drug dosing regimen. The goal would be to work towards FDA approval of a MCM for one or more mycotoxins to include aflatoxin(s) and/or T-2 toxin(s). FDA licensure/approval is not necessary for the project to be deemed successful. However, an objective demonstration of MCM efficacy in at least an animal model relevant to the human condition, and/or successful completion of an FDA approved clinical trial, with accompanying efficacy demonstrated in an animal model is required for success to be declared. One means for the offeror to document progress in the right direction is through a Technology Readiness Assessment (TRA) of the technology using the harmonized Quantitative Technology Readiness Level (Q-TRL) guidance document as described by the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). A second means for demonstrating success is the establishment of funding and partnering with commercial companies (if necessary) to bring the product to market.

PHASE III DUAL USE APPLICATIONS: Successful MCM products directed towards mycotoxins clearly have broad dual use applicability. Acute mycotoxin intoxication is a common occurrence throughout much of the world, usually due to the growth of mycotoxin producing fungi on grains stored under conditions conducive to fungal contamination.

REFERENCES:

1. Centers for Disease Control and Prevention. Outbreak of Aflatoxin Poisoning – Eastern and Central Provinces, Kenya, January-July 2004. *MMWR* 53(34); 790-793, September 3, 2004.
2. Central Intelligence Agency Library, Reports, General Reports, Iraq WMD 2004, Biological Warfare. Published April 22, 2007, last updated April 23, 2007. https://www.cia.gov/library/reports/general-reports-1/iraq_wmd_2004/chap6.html, accessed 16 December 2014.
3. DeGrasse, Jeffrey, A. A Single-Stranded DNA Aptamer that Selectively Binds to *Staphylococcus aureus* Enterotoxin B. *PLOS One*, vol. 7, no. 3, 2012.
4. GlobalSecurity.org, Weapons of Mass Destruction (WMD), Biological Weapons Program. <http://www.globalsecurity.org/wmd/world/iraq/bw-program.htm>, accessed 16 December 2014.
5. Joint Project Manager Medical Countermeasure Systems Broad Agency Announcement (BAA) for Medical Chemical Biological Radiological and Nuclear (CBRN) Countermeasure Developmental Studies. Attachment 1 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Harmonized Q-TRL List for Medical MCMs, MCS-BAA14-01, December 2013.
6. Kankkunen, P., Rintahaka, J., Aalto, A., Leino, M., Majuri, M.L., Alenius, H., Wolff, H., and Matikainen, S. Trichothecene mycotoxins activate inflammatory response in human macrophages. *J. Immunol.* 182: 6418–6425, 2009.
7. Kim, Y.B., and Watson, D.W. A Purified Group A Streptococcal Pyrogenic Exotoxin. *J. Exp. Med.* vol. 131 no. 3, 611-628, 1970.

8. Tai, J.H. and Pestka, J.J. Synergistic Interaction between the Trichothecene T-2 Toxin and Salmonella typhimurium Lipopolysaccharide in C3H/HeN and C3H/HeJ Mice. Toxicology Letters, Vol. 44, Issues 1-2, pgs. 191-200, November 1988.
9. Tai, J.H. and Pestka, J.J. T-2 Toxin Impairment of Murine Response to Salmonella typhimurium: a Histopathologic Assessment. Mycopathologia, vol. 109, issue 3, pp 149-155, March 1990.
10. Wang, N., Mattis, D.M., Sundberg, E.J., Schlievert, P.M., and Krantz, D.M. A Single, Engineered Protein Therapeutic Agent Neutralizes Exotoxins from Both Staphylococcus aureus and Streptococcus pyogenes. Clin Vaccine Immunol, vol. 17 no. 11, 1781-1789, November 2010.

KEYWORDS: Aflatoxin; Heat Stable; Medical Countermeasure; Mycotoxin; Staphylococcal Enterotoxin; Staphylococcus Aureus; T-2 Toxin

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CBD152-004 **TITLE:** Exploiting Microbiome and Synthetic Biology to Discover and Produce Naturally Occurring Antibiotics

TECHNOLOGY AREAS: Chemical/Bio Defense, Biomedical

OBJECTIVE: Identification and development of novel, naturally occurring antibiotics through the use of genomic profiling of the microbiome; identification of gene clusters, and cloning and expression of these clusters using synthetic biological approaches.

DESCRIPTION: The explosion in the “omics” field has allowed for unprecedented genetic identification of some of the billions of bacteria that comprise the world of the microbiome. A potential wealth of information is available through the study of species that have developed sophisticated defense mechanisms to protect themselves from the onslaught of foreign invaders. Recent examples include the microbiome of the new world vulture and in humans. The potential for identification of natural product antibiotics is now within technical reach, and could represent a large family of hitherto unknown naturally occurring antibacterial agents. Furthermore, current data suggest that these natural products are produced from a cluster of genes, and likely represent a variety of agents that have singular and synergistic effects against invading bacteria. Isolation of the natural products, as well as elucidation of the genes involved in their biosynthesis, might provide a number of convergent paths towards the development of new and improved antibacterial therapeutic agents. Another advantage of these types of investigations is the well-established regulatory pathway to FDA approval. The ever-increasing discovery of drug resistant strains, such as methicillin resistant Staphylococcus aureus (MRSA), coupled with the dwindling antibiotic research efforts in pharmaceutical companies, is one reason that Executive Order 13676 was issued in September 2014 to expedite the discovery and development of new antibacterial agents. The Department of Defense (DoD) is increasingly concerned with both multi-drug resistant strains of bacteria, as well as those bacterial threats that could potentially be used as biowarfare agents. In an effort to address these gaps, the DoD is soliciting researchers who will take advantage of recent advances in technology to identify and develop new families of antibiotics derived from the microbiome.

PHASE I: Perform proof-of-concept studies to define the source of the microbiome, the identity of a gene cluster relating to the biosynthesis of antibacterial agents, and in vitro data showing antibacterial effect. It is not expected at this stage that any natural products will be isolated and identified, rather that crude mixtures would be tested to show in vitro activity. The bacterium does not, at this stage, need to be a priority for the DoD, and could be *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, etc. If selected for a Phase II contract, the Phase I Option period should be used to test the crude mixtures of natural products against bacteria of interest to the DoD (*Bacillus anthracis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Francisella tularensis*, and *Yersinia pestis*). The government currently offers a Core testing capability to perform in vitro and/or in vivo screening of compounds (lead, advanced, or licensed) alone or in combination against an extensive panel of biodefense pathogens, as well as a panel of multi-drug resistant (MDR) pathogens, to generate minimum inhibitory concentration (MIC) data at no cost, and with no intellectual property implications to the providing party. Offerors selected for Phase I award will be provided additional information regarding these opportunities.

PHASE II: During Phase II, it is expected the crude mixtures used in Phase I will be purified to homogeneity. Novel chemical entities will be fully defined and characterized. These materials will be further tested for efficacy in in vitro assays. Depending on the complexity of the structure, it may be advantageous to develop a medicinal chemistry program around any novel chemotype discovered. Mechanism of action studies should be commenced to understand the target(s) of these natural products in order to further exploit the compounds as potential therapeutics. It is further anticipated that the cluster of genes responsible for the biosynthesis of these small molecule compounds will be fully identified, and methods for their expression in suitable vectors will be developed. Synthetic biology approaches to constructing bio-factories for the large scale production of these materials could be explored for feasibility. Structure-function and/or structure-activity relationships should be established during this Phase, and the further development of these novel compounds as novel antibacterial agents defined. These studies would encompass a large spectrum of bacterial targets, and identification of broad-spectrum agents should be a priority. By studying and understanding the mechanism of action of these compounds, it may be advantageous to define a multi-pronged therapeutic regime similar to what could be found in nature. The primary deliverable from this Phase of the project will be to demonstrate in vivo efficacy (target >50% survival in a lethal challenge model when initially dosed greater than or equal to 12h post-exposure) of one or more of these compounds against multiple bacteria, including but not limited to agents of interest to the DoD (*B. anthracis*, *B. mallei*, *B. pseudomallei*, *F. tularensis*, and *Y. pestis*). Ideally, these compounds will show characteristics amenable to advancement into pre-clinical and clinical studies.

PHASE III: Phase III activities will focus on advancing the most promising candidate(s) towards the clinic and FDA approval. This would include pre-clinical studies such as further animal efficacy studies, pharmacology, toxicology, formulation, and dose ranging studies to determine likely human dosing, routes of administration, as well as manufacturing and all requisite studies to file an Investigational New Drug (IND) application with the FDA.

PHASE III DUAL USE APPLICATIONS: Although the DoD has specific requirements for therapeutics and/or prophylaxis against bacterial agents that can be used as biowarfare agents, it is fully expected that any product derived from this work will have significant and broad commercial applications to the health and safety of the general public.

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KEYWORDS: Antibacterial, Natural Products, Microbiome, Synthetic Biology

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CBD152-005 **TITLE:** High Sensitivity, Low Complexity, Multiplexed Diagnostic Devices

TECHNOLOGY AREAS: Chemical/Bio Defense, Biomedical

OBJECTIVE: To provide a rapid, highly sensitive, logistically simple and easy to use human clinical diagnostic testing technology for use in clinics and forward deployed military medical treatment facilities. Capabilities sought must be effective for the diagnosis of a wide range of disease caused by biological warfare agents and infectious diseases of operational concern.

DESCRIPTION: The U.S. Department of Defense requires infectious disease in vitro diagnostic (IVD) capabilities that are operationally suitable for use in far forward military environments and operationally effective versus a wide range of threats. Current single use disposable Lateral Flow Immunoassay-based diagnostic tests have many desirable operational suitability characteristics (low cost, minimal training, lightweight, results in 15 minutes, eye readable results, and long shelf life at room temperature) but lack sufficient sensitivity to be clinically useful for most infectious diseases. Current nucleic acid amplification-based diagnostic tests provide adequate sensitivity for some diseases but are slow (>30 minutes), more complex, are not compatible with many host response biomarker-based diagnostic approaches and have a high cost per test. The High Sensitivity, Low Complexity, Multiplexed Diagnostic Devices topic seeks to develop novel approaches that will fundamentally improve sensitivity while maintaining desirable operational suitability characteristics. Furthermore, novel approaches will be needed to incorporate multiple analytical approaches into a single platform technology to provide clinical utility across a broad range of etiological agents (i.e., intracellular organisms, parasites, etc.), diseases and clinical sample types and to provide information to support force health protection decision making.

PHASE I: Describe the specific technical approaches that would be pursued for achieving better than state of the art clinical sensitivity ($\geq 90\%$) for acute infections (testing occurs within the first 168 hours after symptom on-set or pre-symptomatically) in an operationally suitable platform for the representative etiological agents/diseases:

- *Yersinia pestis* / Plague (Gram-negative coccobacillus)

- Brucella spp. / Brucellosis (Intracellular, Gram-negative bacteria)
- Alpha viruses / Venezuelan equine encephalitis, Chikungunya (Single stranded RNA)
- Dengue virus with serotype identification / Dengue Fever (single stranded RNA virus)
- Variola major / Smallpox (DNA virus)

The five diseases listed are representative of a larger set of diseases of operational concern to the U.S. military that would be pursued if selected for Phase III transition. One or more of the representative diseases would be selected as the basis for prototype development in Phase II depending on the specific approach proposed. Within Phase I these five representative diseases serve as the basis for offerors to illustrate the innovative elements of their proposed technical approach when applied to a specific real-world problem. For disease specific tests, the description of the technical approach entails a detailed description of assay designs (bio-recognition elements), signal amplification and transduction techniques, selected sample types (least invasive clinical sampling), and sample preparation techniques (if any) for a specific diagnostic intended use that illustrates the contractor's understanding of the disease, the diagnostic problem, and improvements over the current state of the art for the same market. The description should provide details how sufficient inclusivity and specificity will be obtained to inform treatment decisions. Syndromic approaches (through multiplexing) add significantly to clinical utility. Provide an analysis of the envisioned technical approach with respect to the Clinical Laboratory Improvement Act (CLIA) guidelines for CLIA-waived status.

PHASE II: For one or more of the test types investigated in Phase I, develop and deliver prototype IVD device and pilot lot assays (if applicable to the system design) to the Government for independent evaluation. Complete pre-submission meetings with the FDA to inform inclusivity, specificity and syndromic approaches and intended use for the test and CLIA-waived clinical trial design. The degree of innovation will be measured by the offeror's ability to achieve a high clinical sensitivity for a broad range of disease and sample types while retaining operationally desirable characteristics (cost < \$40 per sample analyzed, training time less than 4 hours, system weight with consumables for 40 tests less than 25 lbs., single sample time to result less than 30 minutes, eye readable results, and consumable shelf life greater than 1 year at 25C). By the end of Phase II, the offeror will have produced a pre-production prototype of the diagnostic device, optimized the assay design for performance in the relevant clinical sample types, temperature and shelf life stability, and manufacturability and will be ready to begin pre-clinical trials shortly after Phase III award.

PHASE III: Complete the maturation of all hardware, software and reagent elements of the diagnostic device. Conduct pre-clinical and clinical trials and 510(k) package preparation and submission (as the sponsor) to the U.S. Food and Drug Administration (FDA) for the initial IVD product developed under Phase II. Conduct follow-on developments and FDA clearances of IVD tests for additional known and emerging diseases of operational interest to the U.S. Military. Manufacture IVD devices and assays (as applicable to the technical approach) under Current Good Manufacturing Practices (cGMP) and other quality systems and deliver to the Government for operational use by Warfighters. The Government will provide Government Furnished Information (GFI) and Materials (GFM), when not publically available, to support assay design and testing. The Government will provide access to Biological Safety Level (BSL) 3 and 4 testing facilities when needed.

PHASE III DUAL USE APPLICATIONS: Beyond the diagnostic use for the military population, products of this effort are intended to be used in U.S. and European Union domestic health care markets for in vitro diagnostics. Furthermore, for some agents, the products of this effort may be useful for companion diagnostics to be used in therapeutic development studies and environmental field analytics applications.

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KEYWORDS: infectious disease, in vitro diagnostic, point of care, biological warfare agent, biomarkers

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CBD152-006 **TITLE:** Signal Processing for Layered Sensing

TECHNOLOGY AREAS: Chemical/Bio Defense, Sensors

OBJECTIVE: Demonstrate an analytical approach for the development of comprehensive situational understanding regarding the presence of threats in an operational environment based on multiple signature feeds from networked sensors and threat information.

DESCRIPTION: Asymmetric threats including chemical and biological agents, improvised dissemination devices, and vehicle- and personnel-born improvised explosive devices represent a persistent hindrance to U.S. military operations. Various sensor and surveillance systems develop a capacity to warn of the presence of such threats on a point-by-point basis; however the consumption of these data in the construction of a common operational picture for unit commanders remains an intractable challenge. Even if all of the systems were integrated onto a common networking and communications framework so that early warning data from any individual sensor were available in real time, the capacity to process and analyze such data in order to synthesize situational understanding for leaders is extremely limited. The current state of the art in the chemical and biological sensing paradigm is limited to the correlation of alarm information from networked sensor systems vis-à-vis the actual multimodal fusion of quantized native sensor signals. Enabling technology in information theory and signal processing continues to advance and emerge as a reasonably mature approach toward the consumption of sensor data leading to the development of improved situational understanding based on disparate and unrelated data sources. While the integration and correlation of information has advanced in recent times due in part to improved accessibility of networking and communications architectures, few examples of multimodal data fusion using data from more than one sensor have been reduced to practice. Network bandwidth continues to constrain the content available for such systems to function; however, distributed processing architectures allow for the fusion of quantized native sensor signals at outlying nodes, mitigating to some extent the size of the data stream that must be fused at the central signal processing node. This effort would be expected to demonstrate the unique and invaluable power of a multimodal signal processing tier of raw sensor data as a first tier of a layered sensing architecture that provides an unprecedented depth of information and detection confidence that exceeds the baseline simple correlation approach. The system should demonstrate the management of uncertainty and error (e.g., position, navigation, and timing errors and spurious alarm response signals) at various levels in the architecture, and incorporate the fault analysis and multimodal fusion product along with a representation

of the overall confidence level of the final product in a fashion that is intuitive to non-technical operational decision-makers. Such a demonstration would serve as a validation case for arguments on the implementation of disparate sensing architectures for threat detection and awareness. To date, there remains a significant level of skepticism surrounding the argument that data fusion architectures provide operational benefit.

PHASE I: Execute a comprehensive system study and define best practices models and theory for the correlation and fusion of weighted signal outputs from multiple sensor modalities (including but not limited to: electro-optical/infrared imagery, acoustic, seismic, magnetic, passive infrared motion sensors, chemical and biological agent detectors, radiological detectors, explosives sensors, ground surveillance radar, airborne imagers and LIDAR systems, unmanned aerial vehicle imagery, aerostat imagery) in the presence of bias and other errors, including position and time errors, and faulty sensor operation. Assess the value of follow-on tasking of reconnaissance and surveillance assets. Accommodate real-time threat environment intelligence and meteorological data and apply decision logic that accounts for realistic operational conditions. Provide a system level capability that manages false alarms while maintaining sufficient network-wide sensitivity to the threat condition.

PHASE II: Fabricate, integrate, test, and optimize the performance of a signal processing system that was defined as an outcome of the Phase I Feasibility Study.

PHASE III: A Phase III follow-on effort would effect a system demonstration that could be integrated into a wargame environment or table-top exercise to enable capability and doctrine developers to assess the value of an autonomous layered sensing architecture on battlefield situational understanding. The demonstration would have immediate value for the definition of future warfighter capability requirements while simultaneously maturing the technology readiness level of the multimodal data fusion environment.

PHASE III DUAL USE APPLICATIONS: An integrated multimodal data fusion environment would realize significant market potential in industrial process control and chemical transfer line integrity in engineering plants and medical diagnostics. Environmental, law enforcement, security, and incident/disaster response applications would also lend themselves to the exploitation of multimodal data fusion integration systems and techniques.

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KEYWORDS: Information fusion, sensor network, multimodal information processing, covariance estimation, situation awareness theory, multisensory data fusion

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