

**DEFENSE THREAT REDUCTION AGENCY
Government Call**

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Amendment 6

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Research and Development Directorate (J9)

Basic and Applied Sciences Department (J9BA)

**Fundamental Research to Counter Weapons of
Mass Destruction (C-WMD)**

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1. Introduction and Scope

1.1. This government call is an endeavor focused on the fundamental research needs of DTRA for entities not eligible under the current Fundamental Research Broad Agency Announcement, HDTRA1-14-24-FRCWMD-BAA. DTRA has the mission to safeguard America and its allies from WMD and provide capabilities to reduce, eliminate, and counter the threat and effects from chemical, biological, radiological, nuclear, and high yield explosives (CBRNE). DTRA seeks to identify, adopt, and adapt emerging and revolutionary sciences that may demonstrate high payoff potential to C-WMD threats.

1.2. This call solicits ideas and topic-based white papers for long-term challenges that offer a significant contribution to: the current body of knowledge, the understanding of phenomena and observable facts, significantly advance revolutionary technology, new concepts for technology application, or that may have impact on future C-WMD threat reduction or capabilities.

A portion of this effort is expected to be devoted to awards for science, technology, engineering and mathematics education programs with a C-WMD focus; such as, but not limited to postdoctoral fellowships, stipends, degrees, visiting scientist programs, student exchange programs, and development of accredited C-WMD curricula.

1.3. Contracted Fundamental Research includes research performed under grants, contracts (awards), or OTAs that are (a) funded by budget Category 6.1 (Basic Research), whether performed by universities or industry or (b) funded by budget Category 6.2 (Applied Research) performed on-campus at a university. Further, fundamental research means basic and applied research in science and engineering by any eligible performer for which the results ordinarily are published and shared broadly within the scientific community. Fundamental research is distinguished from proprietary research and from industrial development, design, production, and product utilization, the results of which ordinarily are restricted for proprietary or national security reasons. Fundamental research provides for science and technology (S&T) research and early applied development. It seeks to lower performance risk to a manageable level and facilitate transition and funding to capability end-state programs.

1.4. White papers may be evaluated at any time after submission and invitations for full proposal submission may occur any time after white paper evaluation. Note that proposal invitations will be limited to available program funds. The Government reserves the right to award any combination of approaches which offer the best overall value to the Government and to oversee any and all processes and approaches once ongoing.

2. Purpose and Research Thrust Areas/Topics

2.1. DTRA seeks unclassified, fundamental research across seven major functional C-WMD research thrust areas. Specific research topics that align to one or more thrust areas are presented in [Section 10](#). Otherwise, white papers and proposals shall be written against the thrust area descriptions.

The seven thrust area descriptions are outlined below. **All non-topic-based research ideas, i.e. those submitted to the general Thrust Area description, must be pre-coordinated with the relevant technical POC for each Thrust Area;** an e-mail for the DTRA technical POCs for Thrust Areas 1-7 are provided in [Section 9](#). White papers that are not in response to a published topic or received

without pre-coordination of an abstract via the e-mail addresses in [Section 9](#) will not be reviewed by DTRA.

2.1.1. Thrust Area 1: Science of WMD Sensing and Recognition: The science of WMD sensing and recognition advances fundamental understanding of materials that demonstrate measurable changes when stimulated by radiation or particles from WMD in the environment. This research thrust involves exploration and exploitation of interactions between materials and various photons, molecules, nuclear radiation and/or particles. This research thrust also involves the exploration and exploitation of signatures of these interactions with materials, including those signatures which are actively stimulated. These interactions and the specific form of recognition they provide are used for subsequent generation of information that provides knowledge of the presence, identity, and/or quantity of material or energy in the environment that may be significant. Thrust Area 1 is currently not interested in research focusing on the sensing of explosives or the detection of Improvised Explosive Devices (IEDs). DTRA will not review any non-topic-based Thrust Area 1 white papers without prior coordination of the idea with the Thrust Area 1 e-mail address ([Section 9](#)). Applicants should note that there is extremely limited funding available for Thrust Area 1. White papers will only be encouraged from the coordinated abstracts under very limited circumstances.

2.1.2. Thrust Area 2: Network Sciences: The fundamental science of network science results from the convergence of computer, information, mathematical, network, cognitive and social science. This research thrust expands our understanding of physical and social networks and advances knowledge of adversarial intent with respect to the acquisition, proliferation, and potential use of WMD. The methods may include analytical, computational or numerical, or experimental means to integrate knowledge across disciplines and improve rapid processing of intelligence and dissemination of information. DTRA will not review any non-topic-based Thrust Area 2 white papers without prior coordination of the idea with the Thrust Area 2 e-mail address ([Section 9](#)). Applicants should note that there is extremely limited funding available for Thrust Area 2. White papers will only be encouraged from the coordinated abstracts under very limited circumstances.

2.1.3. Thrust Area 3: Science for Protection: Fundamental science for protection involves advancing knowledge in physical, biological, and engineering sciences to protect life and life-sustaining resources and systems. Protection includes both passive and active defense against threats. Approaches include hardening of infrastructure and facilities to protect against blast, nuclear events, or other CBRNE effects; protection of personnel, including physical defenses as well as advanced biological and chemical countermeasures or filtering; fundamental research to improve understanding defenses to non-traditional agents and threats; novel and significant active defense against WMD, including science to support innovative robotics for countering WMD; detecting, identifying and characterizing the origin and spread of CBRNE agents or threats; methods to measure and assess the effects of WMD; new approaches to understand uncertainty and reduce risk; new principles for decontamination of personnel or equipment/facilities, and other mitigation or restoration; and, shielding of systems or networks. DTRA will not review any non-topic-based Thrust Area 3 white papers without prior coordination of the idea with the Thrust Area 3 e-mail address ([Section 9](#)). Applicants should note that there is extremely limited funding available for Thrust Area 3. White papers will only be encouraged from the coordinated abstracts under very limited circumstances.

2.1.4. Thrust Area 4: Science to Defeat WMD: Fundamental Science for significantly improving energetic materials for use against WMD facilities and systems, for deeper penetration to deny the

adversary sanctuary of WMD, for predictable modeling of counter-WMD munitions and simulation of in-theater scenarios with accurate lethality calculations, for minimizing collateral effects when engaging WMD and for exploiting vulnerable pathways, infrastructure etc. to eliminate the threat of WMD. DTRA will not review any non-topic-based Thrust Area 4 white papers without prior coordination of the idea with the Thrust Area 4 e-mail address ([Section 9](#)). Applicants should note that there is extremely limited funding available for Thrust Area 4. White papers will only be encouraged from the coordinated abstracts under very limited circumstances.

2.1.5. Thrust Area 5: Science to Secure WMDs: Fundamental science to support securing WMD includes: identification of phenomena that enable significant advancements in support of arms control; environmentally responsible innovative processes to neutralize or dispose of CBRNE materials and components; discovery of revolutionary means to secure components, materials, and weapons, including sciences for more robust nuclear security practices; science to enhance monitoring, compliance and verification technologies in support of existing, emerging and new treaties; exploration of principles to improve nuclear test detection and analysis; investigation of fundamental and novel techniques and emerging science areas that support new approaches to developing a strategy for countering WMD development, deployment, or use; forensics; and, studies of scientific principles that lead to novel physical methods to disrupt WMD proliferation pathways. DTRA will not review any non-topic-based Thrust Area 5 white papers without prior coordination of the idea with the Thrust Area 5 e-mail address ([Section 9](#)). Applicants should note that there is extremely limited funding available for Thrust Area 5. White papers will only be encouraged from the coordinated abstracts under very limited circumstances.

2.1.6. Thrust Area 6: Cooperative Counter WMD Research with Global Partners: Cooperative fundamental research to reduce the global threat of WMD in collaboration with a broad range of global research partners. This Thrust Area involves exploratory basic and applied research that will address opportunities to reduce, eliminate, and C-WMD across the CBRNE spectrum. Efforts in this area will develop strong international relationships which will foster a smooth transition of program ownership to the partnering country. The goal is to improve international collaboration to detect, characterize, and report WMD, and to advance partner nation sustainment through a culture of long-term cooperation and scientific responsibility for such programs. Multidisciplinary, multinational research in science, technology, engineering, and mathematics development will be conducted to promote transparency through quality research publications and continual dialogue between scientists/engineers and young researchers. DTRA will not review any non-topic-based Thrust Area 6 white papers without prior coordination of the idea with the Thrust Area 6 e-mail address ([Section 9](#)).

The Cooperative Biological Engagement Program (CBEP), a component of the DoD Cooperative Threat Reduction (CTR) Program, recognizes the danger to U.S. and global health security posed by the risk of outbreaks of dangerous infectious diseases, whether natural or manmade. Consistent with the national and departmental strategies, CBEP strives to address this risk by promoting best practices in biological safety and security, improving partner country capacity to safely and rapidly detect and report dangerous diseases, and establishing and enhancing international research partnerships. The desired end state for CBEP engagements is the development of sustainable partner country capabilities to:

- Employ responsible bio-risk management best practices and principles,

- Conduct a modern and effective disease surveillance mission,
- Comply with World Health Organization (WHO) International Health Regulations (IHR) and World Organization for Animal Health (OIE) reporting guidelines, and
- Promote the One Health Concept.

The goal of CBEP international research partnerships is to promote transparency through quality research leading to peer-reviewed publications, to sustain scientific and professional dialogue, and to foster an international culture of responsible and ethical conduct in biological research. These partnerships are focused on developing cooperative research between U.S. and global partner academic communities to:

- Improve international collaborations to detect, characterize, and report disease outbreaks,
- Prevent, diagnose, and treat illness,
- Train partner country researchers in the conduct of ethical research, and
- Advance partner country sustainment of global health security initiatives.

Ultimately, the techniques, procedures, and approaches must be sustainable for the partner country, and linked with appropriate training, to promote global health security, reinforce norms of safe and responsible conduct, obtain timely and accurate insight on current and emerging risks, and transform the international dialogue on biological threats.

CBEP research projects are not determined by or limited to specific biological agents, but must be aimed at measurably supporting threat reduction objectives that:

- Secure and consolidate collections and associated research of U.S. Select Agent Pathogens and Toxins to a minimum number of secure facilities,
- Improve partner country biosafety and security (BS&S) standards to prevent sale, theft, diversion, or accidental release of biological weapons (BW) related materials, technology, and expertise,
- Improve disease surveillance by enhancing partner capability to detect, diagnose, and report U.S. select agents and toxins, potential pandemics, and emerging/re-emerging pathogens of security interests,
- Enhance understanding of endemic pathogens to allow differentiation of natural occurring disease from those occurring by accident or nefarious intent (e.g. bio-terror attacks),
- Facilitate partner country's/region's research engagement through robust research collaborations employing state-of-the-art analytical methods,
- Enhance host country capabilities to comply with WHO IHR (2005) and OIE reporting guidelines,

- Ensure developed capabilities are designed to be sustainable within each partner country's/region's operating budget,
- Eliminate BW related infrastructure and technologies.

Examples of CBEP research areas of interest include: Biosurveillance, Pathogen Characterization, Assay Adaptation and Optimization, Microbial Ecology within a Public Health Context, and Preventative Strategies and Countermeasures. Medical countermeasure development (i.e., development of diagnostic tools, vaccines, therapeutics) is supported by many other U.S. government or international agencies and is generally not supported by CBEP; however, research projects may inform medical countermeasure development and support validation and verification testing (e.g., as part of proficiency testing, pilot studies/testing, or exercises, etc.). Additionally, CBEP does *not* generally support research with common disease agents such as HIV/AIDS, malaria, and tuberculosis where other U.S. agencies have dedicated missions to do so; however, the program may choose to capitalize on opportunities to leverage research on these diseases to further CBEP goals.

CBEP is interested in collaborative research partnerships between U.S. institutions and foreign research partners in any if the following regions: Countries of the Former Soviet Union (FSU) (specifically Armenia, Azerbaijan, Georgia, Kazakhstan, and Ukraine), Africa (specifically East Africa and the Southern African regions), Southeast Asia (including Indonesia, Malaysia, Cambodia, Laos, Thailand, Vietnam, Philippines, Timor-Leste, and Brunei), and Middle Eastern /South Asian countries (including Afghanistan, Pakistan, India, and Iraq). Note that research ideas should be submitted such that the U.S. institution(s) partner with the foreign institution(s) to develop a collaborative research project.

2.1.7. Thrust Area 7: Fundamental Science for Chemical and Biological Defense: Fundamental science for chemical and biological (CB) defense includes science and technology research that advances knowledge in physical and life sciences to defend and counter chemical and biological weapons of mass destruction (WMD) that could be used against our Nation's warfighters. Fundamental research efforts enable capabilities such as development of improved detection devices for traditional and nontraditional chemical agents; development of diagnostics for existing and emerging infectious disease threats; increasing knowledge and improved capabilities for development of new or improved medical and material countermeasures to CB threats for both pre- and post-exposure scenarios; enhanced personal protection against, modeling of, prevention of, or decontamination of CB threats; and providing effective elimination strategies via non-kinetic approaches for threat agent destruction, neutralization and/or sequestration. DTRA will not review any non-topic-based Thrust Area 7 white papers without prior coordination of the idea with the Thrust Area 7 e-mail address ([Section 9](#)).

2.2. DTRA may remove, add or update topics at any time without notice by an amendment to this Call. Once a topic has been removed, white papers responsive to that topic will no longer be reviewed. DTRA will not provide additional information regarding the posting of future topics, including dates for posting, the potential for a topic to be repeated in out years, the potential for similar topics to be posted, and/or topic details in advance of issuance of an amended Call.

2.3. This Call, in addition to any amendments issued in conjunction with this Call, will be posted to the DTRA Submission Website (www.dtrasubmission.net), the DTRA Basic and Fundamental

Research Community Portal (www.dtrasubmission.net/portal) and to the DTRA website (www.dtra.mil).

2.4. The DTRA Basic and Fundamental Research Community Portal (www.dtrasubmission.net/portal) is available to all applicants. Information available at the portal includes, but is not limited to, the following: a detailed timeline for this Call, templates that may be used when preparing white papers and invited proposals, and an update on the status of submission(s).

3. Award Information

3.1. Resulting awards from this announcement will be Interagency Agreements/Interagency Orders and/or Military Interdepartmental Purchase Requests (MIPRs). The final number of projects and funds allocated will be determined after proposals are received and evaluated.

3.2. Awards may range from small dollar value (e.g., ~\$25K) up to \$1M annually (average award values include both direct and indirect costs).

3.3. The predominance of awards made under this Call will be made with applied research or Cooperative Threat Reduction (CTR) category funds.

3.4. Funding for participation in this program is highly competitive and the cost of proposed research should strictly be maintained in the award amounts outlined for each topic, if one is provided, or in [Section 3.2](#).

3.5. Efforts for Thrust Areas 1-7, including topics associated with these Thrust Areas, may be proposed for up to five (5) years. Awards may be for a base period of one (1) year with four (4) additional years as possible options, a base period of two (2) years with three (3) additional years as possible options, or a base period of three (3) years with two (2) additional years as possible options. Proposals that outline scope and effort for any base and option combination are acceptable.

3.6. Subawards.

3.6.1. Subawards in the form of subcontracts may be used to carry out a portion of the research and/or effort. DTRA will review and consider the proposed subcontracts for all applications on a case-by-case basis.

3.6.2. Subawards in the form of MIPRs and Interagency Agreements/Interagency Orders will be addressed by DTRA on a case-by-case basis.

3.6.3. Subawards in the form of subgrants are not allowed.

3.6.4. For submissions made to Thrust Area 6 (to include the Thrust Area 6 topics), there is no limitation on the dollar value of the subaward(s). Applicants are reminded that priority is given to projects with the main locus of activity in the region-of-interest, so budgets should be allocated accordingly. Preference will be given to proposals where the subaward component to the region-of-interest represents more than half of the award value (as measured in U.S. dollars).

3.7. The Government will not provide any hardware or software to execute the proposed research.

3.8. The Government reserves the right to fund all, some, or none of the proposals submitted; may elect to fund only part of any or all proposals; and may incrementally or fully fund any or all awards under this Call. All awards are subject to the availability of funds.

4. Eligibility

4.1. The following entities are eligible to submit white papers and proposals to this Call:

- Federal laboratories to include DOD, DOE (National Labs), DHS (NBACC, PIADC), HHS (CDC, NIH), and USDA (ARS, APHIS).
- DoD degree-granting academic institutions that are Federal government organizations, e.g. United States Military Academy at West Point, The Air Force Institute of Technology, etc.
- DoD sponsored Federally Funded Research and Development Centers (FFRDCs) specified in the Defense Federal Acquisition Regulation Supplement (DFARS) 235.017-1 (<http://farsite.hill.af.mil/VFDFARA.HTM>) and click on 'DFARS Part 35'
- Other FFRDCs with authorization from its sponsoring agency in accordance with FAR 35.017-1.

4.2. There is no limit on the number of white papers and invited proposals that an applicant Principal Investigator (PI/Co-PIs) may submit in response to this Call.

5. Submission Information

5.1. General Application and Submission Information. This Call contains all information required to submit a white paper and invited proposal. Submissions for this Call will be conducted in two phases. Phase I is for receipt of white papers. Phase II is for receipt of invited proposal applications. Invitation to the Phase II proposal submission will be based on the evaluation results of the Phase I white paper and the availability of funds.

All non-topic-based and some topic-based white paper research ideas **MUST** be coordinated with the technical POC via the e-mail addresses in [Section 9](#) prior to the submission of the white paper. Pre-coordination includes a response welcoming the white paper; emailing an abstract without receipt of an invitation response is not sufficient for submission of a white paper.

For convenience, Microsoft (MS) Word and MS PowerPoint templates for Phase II proposal submissions are provided on the DTRA Basic and Fundamental Research Community Portal (www.dtrasubmission.net/portal) for applicant use. Applicants are encouraged to use the templates for preparing submissions; however, use of the templates is not required. Note: there is not a template available for the white paper.

5.1.1. All applicants interested in submitting white papers and proposals must register on the DTRA proposal submission website, <http://www.dtrasubmission.net>, prior to submission of a white paper(s) and proposal(s). Each institution may establish procedures for the management of registration and submission of white papers and proposals. Detailed registration instructions are available at the website. Failure to register in accordance with instructions will prevent submission of the required documents and render applicants ineligible for participation in this Call. Prior registration at any other

proposal submission site other than at <http://www.dtrasubmission.net> does not fulfill registration requirements for participation in this Call.

5.1.2. White papers and proposals must be submitted electronically through the DTRA proposal submission website, <http://www.dtrasubmission.net>. Do not submit any classified materials to the Call or to the proposal submission website. Unclassified proposals submitted by any means other than the DTRA proposal submission website (e.g., hand-carried, postal service mail, commercial carrier, or e-mail) will not be considered. Detailed submission instructions are available at the website.

5.1.3. Applicants are responsible for ensuring compliant and final submission of their white papers and/or invited proposals, and can verify the submission of the white paper and/or proposal package with the electronic receipt that appears on the screen following compliant submission of a proposal to the DTRA proposal submission website.

5.1.4. Using the DTRA proposal submission website, all applicants must prepare cover sheets for each Phase I white paper and invited Phase II proposal submitted. All data point requirements must be completed in every cover sheet. Once the cover sheet is saved, the system will assign a unique proposal number for each Phase I submission and a different unique proposal number for each invited Phase II submission. Cover sheets may be edited as often as necessary until the white paper and/or proposal is submitted.

Cover Sheet Information: The following information is required to complete a Cover Sheet for each white paper and proposal:

- Thrust Area or Topic Number under which white paper/proposal is being submitted for consideration
- Title of proposed effort, which must be different than the thrust area/topic title
- Applicant Institution name and address (this is based on the registrant submitting the proposal, and should be the institution, not the individual)
- Cost per year of performance
- Information on other submissions of same proposed effort
- Contact Information for PI and Business Points of Contact – Name, Title, Phone, Fax and E-mail
- Identification of proprietary information included in proposal submission (page numbers)
- Technical Abstract. The project abstract should be concise (less than 250 words) and provide a summary of the proposed work and demonstrate relevance to the topic being addressed. The abstract should not contain any proprietary data or markings.
- Key Words/Phrases (limited to 8 key words)

The Cover Sheet is automatically populated with the following information based on the registration process:

- DUNS, CAGE and Tax ID numbers, as entered during registration (cannot be changed)
- Applicant, as entered during registration (cannot be changed)
- Address (can be updated)

5.1.5. If multiple proposals are being submitted by the same institution, separate cover sheets must be generated for each white paper and invited proposal as the required documents must be uploaded with the associated cover sheet. All documents submitted to the DTRA proposal submission website are considered works in progress and are not eligible for evaluation until the applicant submits the final proposal package for consideration. Applicants are responsible for ensuring compliant and final submission of their white papers and proposals; applicants can verify the submission of the white paper and proposal package with the electronic receipt that appears on the screen following submission of a white paper and proposal to the DTRA proposal submission website.

5.1.6. The white paper and all parts of the proposal must be uploaded in a Portable Document File (PDF) format compatible with Adobe Acrobat ® version 9.1 or earlier. Files must not exceed 2 Megabytes of storage space (uncompressed). Movie and sound file attachments or other additional files will not be accepted. Perform a virus check before uploading proposal files. If a virus is detected, it may cause rejection of the file. Uploaded files must not be password protected or encrypted.

5.2. DTRA will not review any of the following:

- White papers that attempt to address multiple thrust areas/topics.
- White papers that are submitted to topics that have been removed.
- Proposals for Phase II submissions that were not invited.

5.3. Phase I White Paper Submission and Content. Interested applicants are required to submit a four-page white paper.

5.3.1. White Paper Narrative Format: The white paper itself should provide sufficient information on the research being proposed (e.g., the hypothesis, theories, concepts, approaches, data measurements, and analysis, etc.) to allow for an assessment by a technical expert.

Any pages submitted for the white paper that exceed the limit of four pages will not be read or evaluated. References may be provided at the discretion of the applicant but will be considered as part of the four-page limit. A page is defined as 8 1/2 x 11 inches, single-spaced, with one-inch margins in type not smaller than 12 point Times New Roman font. The thrust area/topic with the name should be included as a header on the white paper and in the text of the white paper. The white paper must be provided in portrait layout.

At minimum, the white paper should address the following:

- Potential scientific impact to provide greater knowledge or understanding of the fundamental aspects of phenomena and of observable facts, including how the research contributes to the C-WMD science needs outlined in the thrust area/topic.

- The impact of the research on C-WMD science must be clearly delineated.
- Cost estimate by year and total dollars required to accomplish the research as presented in the white paper (no details or breakout of costs is required). Note that dollar values in this Call include both direct and indirect costs.
- Potential team and management plan, including details on student involvement.
- Multidisciplinary white papers should carefully detail each of the institutions/departments involved and the contribution that will be made by each of the investigators.
- Do NOT include corporate or personnel qualifications, past experience, or any supplemental information with the white paper.
- Thrust Area 6 white papers must also include a description of the extent and duration of the relationship/collaboration between the universities/institutes/entities, and/or scientists.

5.4. Phase II - Full Proposal Submission and Content. The full proposal must be prepared in three separate volumes: Technical Proposal, Cost Proposal, and Supplemental Information.

5.4.1. Technical Proposal: The technical proposal must not exceed 20 pages (including references). If the proposal exceeds 20 pages, only the first 20 pages will be reviewed. A page is defined as 8 ½ x 11 inches, single-spaced, with one-inch margins in type not smaller than 12 point Times New Roman font. The proposal must be provided in portrait layout. A **template** for the technical proposal format may be found online at www.dtrasubmission.net/portal (Microsoft Word format).

The technical proposal must include the following components:

- **Abstract.** The project abstract should be concise (less than 250 words) and provide a summary of the proposed work and demonstrate relevance to the topic being addressed. The abstract should not contain any proprietary data or markings.
- **Objective.** A clear and concise objective of the proposed project.
- **Background.** Provide the necessary technical and scientific background to support the scientific and/or technical merit of the proposed project.
- **Programmatic.** Describe your organization's management plan for the proposed project; list supporting and collaborating centers, and the roles/responsibilities of each identified subawardee supporting the project. Authors of multidisciplinary proposals must take great care to clearly outline the scientific contribution from each investigator.

Thrust Area 6 narratives **must** also describe the extent and duration of the relationship/collaboration between the universities/institutes/entities and/or scientists. Teams with pre-existing collaborative research relationships and those which propose to establish new collaborations will be considered, provided teams can supply documentation to demonstrate that an operational framework exists to support the proposed work.

- **Relevance.** Describe the relevance of the proposed project in terms of advancing the state of the science and the anticipated scientific impact on capabilities to potentially reduce, eliminate, counter, provide greater knowledge or understanding of the threat, and mitigate the effects of WMD fundamental aspects of phenomena and of observable facts.
- **Credentials.** Describe the PI's qualifications and the organization's qualifications to perform the proposed work. Summarize the credentials of the primary performing center, and supporting academic and industrial partners to perform the work. Describe specific examples of equipment and/or facilities available to perform the proposed work. Focus on information directly relevant to the proposed work.
- **Work to be Performed.** Provide details of the work to be performed by task and subtask. Tasks must be grouped by project year.

Thrust Area 6 narratives **must** also clearly identify how the applicant plans to develop (if necessary) and maintain a sample repository with relevant meta-data for each sample collected during the proposed research for at least 12 months after the project end-date. Note that annual sample repository information must be submitted using a DTRA-specified format (for an example, please see the Document and Template Library online at the DTRA Basic and Fundamental Research Community Portal (www.dtrasubmission.net/portal)).

- **Performance Schedule.** Provide a table of tasks and sub-tasks and the duration of performance of each in a Gantt or other suitably formatted chart.
- **References.** List any relevant documents referenced.

5.4.2. Cost Proposal: The Cost Proposal should contain cost estimates sufficiently detailed for meaningful evaluation with a break-down of costs on an annual basis and by task. Note that dollar values in this Call include both direct and indirect costs. A narrative supporting the costs should also be included. The Cost Proposal does not have a page limit and may be provided in the applicant's preferred format. The Cost Proposal must be uploaded as a separate Portable Document File (PDF) compatible with Adobe Acrobat ® version 9.1 or earlier. A PDF is requested to ensure formatting remains consistent and appropriate.

The Cost Proposal should include the following information:

- Individual labor categories or persons (principal investigator, graduate students, etc.), with associated labor hours and unburdened labor rates.
- Benefits and labor burden costs.
- Subcontract costs and type (the portion of work to be subcontracted and rationale). Submit a detailed description of the proposed subcontracted effort(s) and the projected cost(s). Note that separate cost proposals should be provided and incorporated into Volume II for any subcontracts.

- Consultant fees (indicating daily or hourly rate) and travel expenses and the nature and relevance of such costs. Note that separate cost proposals should be provided and incorporated into Volume II for any consultants.
- Travel costs and the relevance to stated objectives; number of trips, destinations, duration, if known and number of travelers per trip. Travel cost estimations should be based on the U.S. Joint Travel Regulations (JTR).

Applicants shall plan and budget for travel to accommodate the two meetings outlined as follows:

- **National/International Conferences/Workshops/Symposia:** Applicants are strongly encouraged to attend a nationally/internationally recognized conference, workshop, or symposium in the field of research each calendar year (1 at minimum). Research should be presented as soon as adequate data are available to support posters and presentations. Conferences/workshops/symposia should be attended by the PI and students supporting the research, as appropriate.
- **Annual Technical Review:** Applicants will plan to attend an annual technical program review meeting. For planning purposes the review will be for five days and will be held in Northern Virginia. DTRA encourages graduate students to attend the Annual Technical Review.
- Publication and report costs.
- Estimate of material and operating costs.
- Cost of equipment, based on most recent quotations and itemized in sufficient detail for evaluation. Clearly delineate any computer or IT equipment purchases.
- Communications and publications costs not included in overhead.
- Other Direct Costs.
- Indirect costs.

5.4.3. Supplemental Information must contain the items detailed as follows:

- **Quad chart:** A quad chart for the effort must be uploaded. The quad chart must be presented on 1 page. The quad chart must not contain any proprietary data or markings. The quad chart must be provided in landscape layout. A **template** for the quad chart format may be found online at www.dtrasubmission.net/portal (Microsoft PowerPoint format). The inclusion of the DTRA logo is not required.
- **SOW:** A SOW defining the major tasks and timelines for the effort must be uploaded. SOW does not have a page limit, but should be approximately 3-5 pages in length for incorporation into the award. The SOW should not contain any proprietary data or markings. Pages should be numbered and the initial page should have a date (document date) shown under the title (the title of the SOW should match that of the proposal). The SOW must be provided in portrait layout. The proposed

SOW must accurately describe the research to be performed. The proposed SOW must also contain a summary description of the technical methodology as well as the task description, but not in so much detail as to make the SOW inflexible. A **template** for the SOW format may be found online at www.dtrasubmission.net/portal (Microsoft Word format).

The SOW must include the following deliverables:

- Annual Research Performance Progress Report(s): Annual reports will be due no later than 1 July of each year (or 12 months after award for 1 year base awards). Awards effective after 31 January will not require an Annual Report until 1 July of the following year. DTRA will provide instructions not later than 1 May of each year on how the report is to be submitted.

The Annual Report is *not* a cumulative report. The first Annual Report shall only include actions that occurred from the Period of Performance start date up to submission of the first Annual Report. Each subsequent report shall only include actions that occurred during the 12-month period following the previous year's Annual Report.

In brief, awardees should plan to report on the following information in the annual Research Performance Progress Report: Accomplishments, Products, Participating/Collaborating Organizations, Impact and Changes/Problems.

- Annual Quad Chart(s): At the direction of DTRA, an updated Quad Chart must be submitted. DTRA will provide instructions not later than 1 May of each year on how the Quad Chart is to be submitted
- Annual Metrics Survey: At the direction of DTRA, a Metrics Survey must be completed. DTRA will provide instructions not later than 1 May of each year on how the Metrics Survey is to be submitted. Note that the Metrics Survey is not a cumulative survey. The first Metrics Survey shall only include actions that occurred from the Period of Performance start date up to submission of the first Metrics Survey. Each subsequent report shall only include actions that occurred during the 12-month period following the previous year's Metrics Survey. Metric categories include, but may not be limited to the following: Personnel Supported; Publications; Interactions/Transitions; Participation/presentations at meetings, conferences, seminars, etc.; new discoveries, inventions, or patent disclosures; Honors/Awards; courses taught; etc.
- Research Performance Final Report: A comprehensive final technical report is required. The draft document is required forty-five (45) days prior to the end of the Period of Performance and the final document is required ninety (90) days after the expiration or termination of the award. The structure of the report will be provided by DTRA in advance of the draft deadline. In brief, it must document and transition the results of the effort into the DTRA and DoD applied research community. The final report must include Standard Form (SF) 298, Report Documentation Page. Item 13 of the SF-298 should contain a 100 to 200 word abstract summarizing technical progress during the reporting period. The SF-298 may be found on the Internet at: [http://contacts.gsa.gov/webforms.nsf/0/B82C70E2B4C7843185256A2C005F72E0/\\$file/SF298_e.pdf](http://contacts.gsa.gov/webforms.nsf/0/B82C70E2B4C7843185256A2C005F72E0/$file/SF298_e.pdf). The final report will always be sent to the Defense Technical Information Center

(DTIC) and unclassified reports may be made available to the public through the National Technical Information Service (NTIS).

- **Invention Reports:** Invention reports must be filed annually due no later than 1 July of each year. The recipient shall use DD Form 882, Report of Inventions and Subcontracts in accordance with the published instructions for the form **IF** the awardee has a reportable event. Negative reports are not required. The submission of the DD Form 882 is required at the conclusion of all awards.
- Thrust Area 6 proposals require several additional items be included in the SOW. These items are as follows:
 - Submission of annual sample repository information using a DTRA-specified format (for an example, please see the Document and Template Library online at the DTRA Basic and Fundamental Research Community Portal (www.dtrasubmission.net/portal)).
 - Access to all samples collected and data generated during the course of the project for at least 12 months after the project end date.
- **Supporting Documentation:** For Thrust Area 6 proposals ONLY—both general Thrust Area 6 proposals and topics that align to Thrust Area 6. Applicants **must** submit documentation that demonstrates an operational framework to support the proposed work.
 - Specific identification of foreign Principal Investigators (PIs) and number of/job title for other members of the foreign research team. The CVs for the foreign PI(s) should be included.
 - Detailed description of the relationship between the proposed research project and current research efforts at the foreign entity.
 - Description of facilities and any other evidence of suitability of foreign collaborators and sites. In the event that the foreign research component will involve human / other vertebrate animal use, appropriate facilities compliance and certifications documents must be provided.
 - Foreign PI letter of collaboration describing, at minimum, the suitability of the proposed work with respect to ongoing research efforts at the foreign institution, merit of the proposed collaboration, and the expected mutual benefits.
- **Protocol Risk Assessment Tool (PRAT):** For Thrust Area 6 proposals ONLY—both general Thrust Area 6 proposals and topics that align to Thrust Area 6. Applicants **must** download the PRAT from the Document and Template Library online at the DTRA Basic and Fundamental Research Community Portal (www.dtrasubmission.net/portal) and complete it in its entirety for each foreign institution participating in the project. Additional instructions for completing the PRAT may be found within the file. The PRAT(s) should be submitted via email to HDTRA1-FRCWMD-C@mail.mil. Do not attempt to upload the PRAT to the submission site.
- **Other Items (submitted via a form on the submission website):**

- A brief summary of any proposed Human Subjects research or a confirmation that the proposed effort does not include Human Subjects research must be entered.
- A brief summary of any proposed Animal Subjects research or a confirmation that the proposed effort does not include Animal Subjects research must be entered.
- A brief summary of any proposed Biosurety and Select Agent research or a confirmation that the proposed effort does not include Biosurety and Select Agent research must be entered.
- A statement of any potential Organizational Conflicts of Interest, or a confirmation of no conflicts, must be entered.
- A statement of Intangible Property Assertions.
- Authorized Offeror Personnel: Applicants must include the name, title, mailing address, telephone number, fax number, and e-mail address of the company and business point of contact regarding decisions made with respect to the applicant and who can obligate the proposal contractually. Also, identify those individuals authorized to negotiate with the Government.
- A statement outlining any current and pending support related to the proposed effort must be entered. This information must be included for each investigator listed in the proposal. This statement requires that each investigator specify all grants, contracts, and other awards through which he or she is currently receiving or may potentially receive financial support.
- A Cost Summary, which is a form that captures the total costs by year (e.g., direct labor, fringe benefits, subcontract costs, domestic travel costs, foreign travel costs, tuition costs, direct materials and supply costs, direct equipment costs, publication costs, other direct costs and indirect costs). This summary includes total numbers only; supporting detail is included in the Cost Proposal. A **template** for the cost summary may be found online at www.dtrasubmission.net/portal.

5.5. All submissions must be UNCLASSIFIED.

5.6. Marking of White Paper and Proposal and Disclosure of Proprietary Information other than to the Government.

The white paper/proposal submitted in response to this Call may contain technical and other data that the applicant does not want disclosed to the public or used by the Government for any purpose other than proposal evaluation. Public release of information in any white paper/proposal submitted will be subject to existing statutory and regulatory requirements.

If proprietary information which constitutes a trade secret, proprietary commercial or financial information, confidential personal information, or data affecting the national security, is provided by an applicant in a white paper/proposal, it will be treated in confidence, to the extent permitted by law, provided that the following legend appears and is completed on the front of the white paper/proposal: “For any purpose other than to evaluate the white paper/proposal, this data shall not be disclosed

outside the Government and shall not be duplicated, used, or disclosed in whole or in part, provided that if an award is made to the applicant as a result of or in connection with the submission of this data, the Government shall have the right to duplicate, use or disclose the data to the extent provided in the agreement. This restriction does not limit the right of the Government to use information contained in the data if it is obtained from another source without restriction. The data subject to this restriction is contained in page(s) _____ of this White Paper/Proposal.”

Any other legend may be unacceptable to the Government and may constitute grounds for removing the Proposal from further consideration without assuming any liability for inadvertent disclosure.

The Government will limit dissemination of properly marked information to within official channels. In addition, the pages indicated as restricted must be marked with the following legend: “Use or disclosure of the white paper/proposal data on lines specifically identified by asterisk (*) are subject to the restriction on the front page of this white paper/proposal.”

The Government assumes no liability for disclosure or use of unmarked data and may use or disclose such data for any purpose.

In the event that properly marked data contained in a white paper/proposal submitted in response to this Call is requested pursuant to the Freedom of Information Act (FOIA), 5 U.S.C. § 552, the applicant will be advised of such request and, prior to such release of information, will be requested to expeditiously submit to DTRA a detailed listing of all information in the white paper/proposal which the applicant believes to be exempt from disclosure under the Act. Such action and cooperation on the part of the applicant will ensure that any information released by DTRA pursuant to the Act is properly identified.

By submission of a white paper/proposal, the applicant understands that proprietary information may be disclosed outside the Government for the sole purpose of technical evaluation. The Program Coordinator will obtain a written or electronically signed agreement from the evaluator that proprietary information in the white paper/proposal will only be used for evaluation purposes and will not be further disclosed or utilized.

5.7. Export Control Notification. Applicants are responsible for ensuring compliance with any export control laws and regulations that may be applicable to the export of and foreign access to their proposed technologies. Applicants may consult with the Department of State with any questions regarding the International Traffic in Arms Regulation (ITAR) (22 CFR Parts 120-130) and/or the Department of Commerce regarding the Export Administration Regulations (15 CFR Parts 730-774).

5.8. Protection of Human Subjects.

If the proposed research involves human subjects or materials, applicants are asked to justify the use of human subjects and to address the following issues: outline the human use, to include the source of the human subjects or materials involved in the research. As a condition precedent to receipt of DTRA funding, applicants must ensure that the basic rights and welfare of human subjects are protected. Applicants shall submit with the full proposal package written evidence, to include a provisional protocol number and Institutional Review Board (IRB) point of contact information, that a human use protocol has been submitted to and is pending approval by a qualified IRB. Further information may be required if the proposal is successful.

The Common Federal Policy for the Protection of Human Subjects, codified by the Department of Health and Human Services at 45 CFR 46 and implemented by the Department of Defense at 32 CFR 219.

The recipient shall adhere to DTRA local clause 252.223-9002. The full text of this clause is as follows:

All research under this award involving human subjects must be conducted in accordance with 32 CFR 219, 10 USC 980, and DoDD 3216.02, as well as other applicable federal and state regulations. Awardee must be cognizant of and abide by the additional restrictions and limitations imposed on the DoD regarding research involving human subjects, specifically as regards vulnerable populations (32 CFR 219 modifications to subparts B-D of 45 CFR 46), recruitment of military research subjects (32 CFR 219), and surrogate consent (10 USC 980). DTRA Directive 3216.01 establishes the DTRA Human Subjects Protection Program, sets forth the policies, defines the applicable terms, and delineates the procedures necessary to ensure DTRA compliance with federal and DoD regulations and legislation governing human subject research. The regulations mandate that all DoD activities, components, and agencies protect the rights and welfare of human subjects of study in DoD-supported research, development, test and evaluation, and related activities hereafter referred to as “research”. The requirement to comply with the regulations applies to new starts and to continuing research.

The DTRA directive requires that research using human subjects may not begin or continue until the Defense Threat Reduction Agency’s Research Oversight Board (ROB) has reviewed and approved the proposed protocol. Awardees and subcontractors are required to submit a valid federal assurance for their organization (institution, laboratory, facility) that has been issued by either DoD or the Department of Health and Human Services, and documentation of review of proposed protocols by the local Institutional Review Board (IRB) to include consent forms for any planned research using human subjects to the DTRA ROB for its review through the Action Officer. The ROB review is separate from, and in addition to, local IRB review.

Written approval to begin research or subcontract for the use of human subjects under the proposed protocol will be provided in writing from the DTRA ROB, through the Action Officer. A copy of this approval shall be maintained by both the awardee and the government. Any proposed modifications or amendments to the approved protocol or consent forms must be submitted to the local IRB and the DTRA ROB for review and approval. Examples of modifications/amendments to the protocol include but are not limited to:

- a change of the PI
- changes in duration or intensity of exposure to some stimulus or agent
- changes in the information requested of volunteers, or changes to the use of specimens or data collected
- changes in perceived or measured risks or benefits to volunteers that require changes to the study

Research pursuant to such modifications or amendments shall not be initiated without IRB and ROB approval except when necessary to eliminate apparent and immediate hazards to the subject(s).

Research projects lasting more than one year require IRB review at least annually, or more frequently as required by the responsible IRB. ROB review and approval is required annually. The awardee or subcontractor must provide documentation of continued IRB review of protocols for ROB review and approval in accordance with these Terms and Conditions. Research must not continue without renewed ROB approval unless necessary to eliminate apparent and immediate hazards to the subject(s).

Non-compliance with any provision of this clause may result in withholding of payments under the award and/or award termination. The government shall not be responsible for any costs incurred for research involving human subjects prior to protocol approval by the ROB.

5.9. Animal Use.

If the proposed research involves animal use, applicants are asked to justify the use of animals and to address the following issues: any proposals that include animal studies or animal work must submit detailed information on the animal protocols to be used and verify the location where the studies will be conducted. Animal studies are subject to review and approval for safety and adherence to regulations. As a condition precedent to receipt of DTRA funding, applicants shall submit with the full proposal package written evidence, to include a provisional protocol number and Institutional Animal Care and Use Committee (IACUC) point of contact information, that a vertebrate animal use protocol has been submitted to and is pending approval by a qualified IACUC. Further information may be required if the proposal is successful.

The recipient shall adhere to DTRA local clause 252.235-9002 – Animal Use (Jul 2010). The full text of this clause is as follows:

If the proposed research involves the use of live nonhuman vertebrate animals, offerors are required to justify the use of animals by providing detailed information on the proposed animal use, to include the proposed species and number of animals planned, along with the location(s) where the animal study(ies) are planned. This information, if applicable, must be included in Supplemental Information, of the Phase II full proposal. Additional information will be required if the proposal is selected for award subject to successful negotiations. The Animal Care and Use Review Office (ACURO), a component of the USAMRMC Office of Research Protections (ORP), must review and approve all animal use prior to the start of working with animals. Therefore principle investigators will be required to complete and submit the animal use appendix titled “Research Involving Animals”, after award of the procurement instrument, which can be found on the ACURO website (https://mrmc.amedd.army.mil/index.cfm?pageid=Research_%20Protections.acuro&rn=1). Allow 2 to 4 months for regulatory review and approval processes for animal studies. Applicants are to build this review time into their project schedules.

DoD Directive 3216.1, dated April 17, 1995, provides policy and requirements for the use of animals in DoD-funded research along with Army Regulation 40-33. The DoD definition of animal is any live nonhuman vertebrate. All proposals that involve the use of animals must be in compliance with DoD Directive 3216.1 and AR 40-33. DTRA requires that research using animals not begin or continue until the ACURO has reviewed and approved the proposed animal use. For animals, the provisions include rules on animal acquisition, transport, care, handling, and use in: (i) 9 CFR Parts 1-4, Department of Agriculture rules that implement the Laboratory Animal Welfare Action of 1966

(U.S.C. 2131-2156); and (ii) the “Guide for the Care and Use of Laboratory Animals,” National Institutes of Health Publication No. 86-23.

5.10. Biological Defense Research Program (BDRP) Requirements: BioSurety and Select Agent Use.

Proposals must specify what Select Agent work will be conducted at the applicant’s facility and what Select Agent work will be performed in other facilities. Proposals also must provide the source of the Select Agent(s), any appropriate registration information for the facilities, and specify the Laboratory Bio-safety Level. All Select Agent work is subject to verification of information and certifications. Further information may be required if the proposal is successful.

For those institutions in which PI’s are conducting research with Bio-safety Levels 3 and 4 material, a Facility Safety Plan must be prepared and made available during the project award phase in accordance with 32 CFR 626.18. For subawards to foreign institutions, you must follow either local or U.S. laws (as stated above) depending on which laws provide stronger protection. (DTRA requires that research using Select Agents not begin or continue until DTRA has reviewed and approved the proposed agent use. See URL: www.access.gpo.gov/nara/cfr/waisidx_99/32cfr626_99.html for a copy of 32 CFR 626.18, Biological Defense Safety Program.)

5.11. Dual-Use Potential.

In accordance with National Science Advisory Board for Biosecurity (NSABB) recommendations, DTRA will not support research that, based on current understanding, can reasonably be anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. Research involving select agents and toxins is within scope of the DTRA mission; however, the use of select agents and toxins in certain experimental categories is considered “dual-use research of concern” (DURC) according to U.S. policy (http://oba.od.nih.gov/biosecurity/news_events_oba.html#NSABB). Proposals that contain DURC will not be funded. Dual-use potential will be assessed based on application of the following criteria:

- Use of select agents or toxins. This factor evaluates whether the proposed research involves use of one or more select agents or toxins [as identified by the Select Agent Program under Federal Law (7 C.F.R. part 331, 9 C.F.R. part 121, and 42 C.F.R. part 73)] which pose significant risk of deliberate misuse with potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence. The following are select agents or toxins:
 - a) Avian influenza virus (highly pathogenic)
 - b) *Bacillus anthracis*
 - c) Botulinum neurotoxin
 - d) *Burkholderia mallei*
 - e) *Burkholderia pseudomallei*
 - f) Ebola virus
 - g) Foot-and-mouth disease virus
 - h) *Francisella tularensis*
 - i) Marburg virus
 - j) Reconstructed 1918 Influenza virus

- k) Rinderpest virus
- l) Toxin-producing strains of *Clostridium botulinum*
- m) Variola major virus
- n) Variola minor virus
- o) *Yersinia pestis*

- Scope of proposed experiments. This factor evaluates whether the proposed research involves experiments that will produce, aim to produce, or is reasonably anticipated to produce: (a) Enhanced harmful consequences of the agent or toxin; (b) Disruption of immunity or effectiveness of an immunization against the agent or toxin without clinical or agricultural justification; (c) Conferred resistance by the agent or toxin to clinically or agriculturally useful prophylactic or therapeutic interventions against the agent or toxin, or facilitated ability to evade detection methodologies; (d) Increased stability, transmissibility, or dissemination ability of the agent or toxin; (e) Altered host range or tropism of the agent or toxin; (f) Enhanced susceptibility of a host population to the agent or toxin; or (g) Eradicated or extinct select agents or toxins.

5.12. Representation Regarding the Prohibition on Using Funds under Grants and Cooperative Agreements with Entities that Require Certain Internal Confidentiality Agreements. By submission of its proposal or application, the applicant represents that it does not require any of its employees, contractors, or subrecipients seeking to report fraud, waste, or abuse to sign or comply with internal confidentiality agreements or statements prohibiting or otherwise restricting those employees, contractors, or subrecipients from lawfully reporting that waste, fraud, or abuse to a designated investigative or law enforcement representative of a Federal department or agency authorized to receive such information. Note that: (1) the basis for this representation is a prohibition in section 743 of the Financial Services and General Government Appropriations Act, 2015 (Division E of the Consolidated and Further Continuing Appropriations Act, 2015, Pub. L. 113-235) and any successor provision of law on making funds available through grants and cooperative agreements to entities with certain internal confidentiality agreements or statements; and (2) section 743 states that it does not contravene requirements applicable to Standard Form 312, Form 4414, or any other form issued by a Federal department or agency governing the nondisclosure of classified information.

5.13. White papers and proposals may be withdrawn by written notice received at any time before award. Withdrawals are effective upon receipt of notice by the Program Coordinator via the e-mail address listed in [Section 9](#).

6. Submission Dates and Times

6.1. White papers will be accepted continuously. The due date for the Phase II invited proposal submissions will be provided in the letter of invitation. Proposals will not be reviewed if they are received after the deadline.

6.2. White papers will be reviewed at least quarterly (October, January, March, and July), but may be reviewed on a rolling basis.

6.3. Applicants are responsible for submitting invited proposals so as to be received by the DTRA submission site by the time and dates listed in the letter of invitation for proposals. When sending electronic files, the applicant should allow for potential delays in file transfer from the originator's

computer server to the Government website/computer server. Applicants are encouraged to submit their proposals early to avoid potential file transfer delays due to high demand encountered as the submission deadline approaches.

6.3.1. Acceptable evidence to establish the time of receipt at the Government office includes documentary and electronic evidence of receipt maintained by DTRA. Applicants should also print, and maintain for their records, the electronic receipt following submission of a white paper and proposal to the DTRA submission site.

6.3.2. If the invited proposal is submitted to the DTRA submission site after the exact time and date specified in the letter of invitation for the invited proposal, the submission is "late" and will not be considered. Exceptions will not be considered.

6.3.3. Please note 15 USC 260a establishes daylight saving time as the standard time during the daylight saving period.

6.4. If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be submitted to the DTRA submission site by the exact time specified in the letter of invitation for the invited proposal, the time specified for receipt of submissions will be deemed to be extended to the same time of day specified in the Call on the first work day on which normal Government processes resume.

7. Application Review information

7.1. Evaluation Criteria. The evaluation criteria to be used for review of applications are listed below. Only the first two criteria will be used to evaluate white papers; all four will be used to evaluate invited proposals.

1. Technical/Scientific Merit. This area addresses the technical approach and the contribution of the research, educational program, or other effort to advancing the C-WMD technical body of knowledge, providing educational opportunities to the C-WMD workforce, or supporting the DTRA C-WMD mission. It evaluates what activities will be performed, skills required, and/or how it will be accomplished. Two (2) factors will be considered. The first factor (Soundness of Approach) is of higher importance.

- Soundness of Approach. This factor addresses whether the proposal writer clearly identifies and demonstrates an understanding of the C-WMD research or mission challenges and whether the proposed effort has a well-designed methodology or capability, based on sound scientific and engineering principles. The fundamental research objectives should address the stated C-WMD scientific challenge or need, technical risks (mitigated and managed), as well as the plan for maturing and transitioning the results to technology programs, as appropriate.
- Degree of Innovation. This factor addresses the originality of the concept, its scientific merit, its creativity, and/or the novelty of the approach and the potential of the proposed effort to enable technology or advance C-WMD capabilities. The degree of innovation will be judged based on the innovation or originality that is appropriate to the proposed effort.

2. Responsiveness to Thrust Area and Program. This area evaluates the extent to which the proposed effort supports specific Thrust Areas. It also considers the derivative benefit that may be realized by the performer and its organization through performance of the proposed effort. Three (3) factors will be considered: 1) Responsiveness to Thrust Area; 2) Expected Benefits to Program Objectives; and 3) Derivative Benefit. The first factor (Responsiveness to Thrust Area) is of highest importance. The second and third factors are of lesser importance with the second factor (Expected Benefits to Program Objectives) being more important than the third factor (Derivative Benefit).
 - Responsiveness to Thrust Area. This factor addresses the responsiveness of the proposal to the objectives of the specific Thrust Area and the contribution to the C-WMD research or mission needs outlined in the Thrust Area or Topic.
 - Expected Benefits to Program Objectives. This factor addresses the benefit of the proposed effort on enabling knowledge, technology, or capabilities over current methods and/or practices. Net advantages are based on the potential to affect knowledge, technology, or capabilities once it is fully developed or executed and on the transition potential that is appropriate to the proposed effort. The expected benefit will be qualitatively assessed against the effort, cost, and time.
 - Derivative Benefit. This factor considers the impact of plans to enhance the institution's ability to perform research relevant to reducing the global WMD threat; and/or to train, through the proposed effort, students in science, technology, engineering and/or mathematics.
3. Program Capabilities. This area addresses key personnel, facilities, and major equipment required to accomplish the effort. The two (2) factors (Qualifications and Capabilities) are equally weighted.
 - Qualifications. This factor will be scored based on the qualifications, and availability of the proposed PI, co-PIs and other key personnel who are critical in achieving proposed objectives.
 - Capabilities. This factor considers the applicant's current or planned facilities and equipment as appropriate to the proposed effort. Capabilities evaluation will be based on the total capabilities of the individual or assembled team that will be brought to bear as part of the proposed effort.
4. Cost Realism and Reasonableness. This factor considers the adequacy and reasonableness of resources applied to each project task. This includes labor (in terms of time and mix), equipment, other direct costs, fee (if applicable), and indirect costs.

7.2. Review and Selection Process.

The white paper and proposal selection process will be conducted based upon a technical review and includes the use of non-government peer-reviewers.

7.2.1. White paper (Phase I) evaluation will be based on 2 equally weighted criteria described in [Section 7.1](#): Criteria 1. Technical/Scientific Merit and Criteria 2. Responsiveness to Topic which will

each be scored as Green (acceptable), Yellow (acceptable with minor issues), or Red (unacceptable). The Government reserves the right to limit the number of Phase II invited proposals requested depending upon the volume of white papers submitted, the results of the Phase I evaluation, and the specific needs of the Agency.

7.2.2. Invited Proposal (Phase II) Evaluation will be based on the 4 criteria described in [Section 7.1](#). Criteria 1. Technical/Scientific Merit and Criteria 2. Responsiveness to Topic Area and Program are equally weighted and are more important than Criteria 3. Program Capabilities which is more important than Criteria 4. Cost Realism and Reasonableness. All 4 criteria receive a numerical score ranging from 1 (unacceptable) to 5 (outstanding).

7.2.3. Other factors that may be considered during the selection process are the possible duplication with other research currently funded by the Government, program balance across research topics, and budget limitations. Accordingly, proposals may be selected for funding which are not reviewed as highly as others, which are of higher risk and/or which may be of a higher cost.

7.2.4. The Government reserves the right to select all, some, or none of the proposals, or any part of any proposal, received in response to this Call and to make awards without discussions with applicants; however, the Government reserves the right to conduct discussions or request clarifications or updates if determined necessary.

7.2.5. Additional details, including the due date, for Phase II submissions may be provided to applicants in the invitation e-mail.

7.3. Technical and Administrative Support by Non-Government Personnel.

7.3.1. It is the intent of DTRA to use non-government personnel to assist with the review and administration of submittals for this Call.

7.3.2. All invited proposals will be reviewed by subject matter experts (peer reviewers) who are non-government personnel.

7.3.3. Participation in this Call requires DTRA support contractors to have access to white paper and invited proposal information including information that may be considered proprietary. Existing DTRA contractors include but may not be limited to the following: Engility Corporation (A&AS) and their subcontractors, Suntiva Executive Consulting (contract specialist support) and their subcontractors, SBG Technology Solutions, and Terremark Worldwide Inc. Each contract contains organizational conflict of interest provisions and/or includes contractual requirements for non-disclosure of proprietary contractor information or data/software marked with restrictive legends.

7.3.4. All individuals having access to any proprietary data must certify that they will not disclose any information pertaining to this Call including any submittal, the identity of any submitters, or any other information relevant to this Call.

7.3.5. All applicants to this Call consent to the disclosure of their information under these conditions.

8. Award & Notification Information

- 8.1. Applicants of white papers that are not selected for invitation will be notified of the decision by e-mail at all of the addresses provided at the time of submission.
- 8.2. An invitation to submit a proposal will be extended to those applicants whose submissions were selected in Phase I. The invitation will be transmitted via e-mail to all of the e-mail addresses provided at the time of submission.
- 8.3. Applicants will be notified by DTRA of their selection/non-selection for award from the Phase II invited proposals via e-mail to all of the e-mail addresses provided at the time of submission. Notification of proposal selection is not an authorization to begin work.
- 8.4. A debrief summary will be provided as part of all notification e-mails.
- 8.5. All notifications will be made from notification@dtrasubmission.net. Emails sent to this email address will not receive a response. All email correspondence should be directed to the email addresses detailed in [Section 9](#).
- 8.6. The applicants must be aware that it is their responsibility to ensure: 1.) the correct e-mails are provided at the time of submission; 2.) this e-mail notification reaches the intended recipient; and 3.) the e-mail is not blocked by the use of 'spam blocker' software or other means that the recipient's Internet Service Provider may have implemented as a means to block the receipt of certain e-mail messages.
- 8.7. If for any reason there is a delivery failure of these e-mail notices, DTRA will not further attempt to contact the applicants.

9. Agency Contacts

- 9.1. All administrative and programmatic correspondence should be directed to HDTRA1-FRCWMD-C@mail.mil.

Every effort will be made to provide a timely response to all inquiries; however, e-mails may not receive a response. Attachments will not be reviewed.

- 9.2. All non-topic-based and some topic-based proposed efforts must be coordinated with the relevant technical point of contact (POC) for each Thrust Area prior to submission of a white paper; e-mail addresses for the DTRA technical POCs for Thrust Areas 1-7 are provided below.

Pre-coordination of research ideas and efforts must be accomplished via e-mail and includes submission of an abstract (recommend less than 250 words) of the proposed project/effort or a paragraph description of the proposed project/effort to the technical POC and a reply e-mail from the technical POC with their disposition to the applicant. DTRA will not review non-topic-based white papers without prior coordination. Please note that attachments to e-mails will not be reviewed.

Specific technical correspondence regarding the thrust areas as well as the topics corresponding to the thrust areas may be directed to the appropriate e-mail address. Please note that technical correspondence e-mails may or may not be reviewed and responded to; attachments will not be reviewed.

Dialogue that assists the applicants in developing better white papers and invited proposals is encouraged. Questions regarding debriefing summaries for white papers that are invited to full proposals are encouraged.

Thrust Area 1: Science of WMD Sensing and Recognition

E-mail: HDTRA1-FRCWMD-TA1@mail.mil

Thrust Area 2: Cognitive, Information and Network Science

E-mail: HDTRA1-FRCWMD-TA2@mail.mil

Thrust Area 3: Science for Protection

E-mail: HDTRA1-FRCWMD-TA3@mail.mil

Thrust Area 4: Science to Defeat WMD

E-mail: HDTRA1-FRCWMD-TA4@mail.mil

Thrust Area 5: Science to Secure WMD

E-mail: HDTRA1-FRCWMD-TA5@mail.mil

Thrust Area 6: Cooperative Counter WMD Research with Global Partners

E-mail: HDTRA1-FRCWMD-TA6@mail.mil

Thrust Area 7: Fundamental Science for Chemical and Biological Defense

E-mail: HDTRA1-FRCWMD-TA7@mail.mil

10. Topics

Thrust Area 7, Topic A: Rapid Identification and Design of Protective Epitopes for Vaccines

NOTE: An amendment to the Government Call will be posted on 2 February 2016 removing this topic. WHITE PAPERS FOR THIS TOPIC MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2016. White papers will not be considered if they are received after this deadline.

This topic does NOT require pre-coordination of abstracts prior to the submission of pre-application white papers.

Average Award Amounts for ***Thrust Area 7, Topic A***:

- Single Scope or Multidisciplinary Awards may be up to \$500,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.

Award Structure for **Thrust Area 7, Topic A:**

- Will be for a base period of one (1) year with up to four (4) additional years as possible options.
- Pre-application white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable.
- Note that pre-application white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: The goal of this topic is to solicit proposals focused on rapid identification and/or design of protective vaccine immunogens or epitopes that may naturally be masked by non-protective immunodominant epitopes. By doing so, it may be possible to optimize vaccine immunogen design to enhance protective responses to the immunorecessive epitopes of pathogens for which there are currently no prophylactic vaccines. There is an increasing body of evidence that viral and bacterial pathogens express immunodominant B-cell and T-cell epitopes that have evolved to act as decoys to mask or subvert potentially protective responses as a means of evading immune surveillance^{1,2}. Such immunogenic but non-protective epitopes are often encoded in regions of the pathogen genome that are highly susceptible to mutation³. Furthermore, protective epitopes themselves are often encoded by regions of hypermutable sequence that allows the pathogen to escape a protective immune response^{3,4}. Efforts to discover immunogenic epitopes for *Burkholderia mallei* and *Burkholderia pseudomallei* in particular has been stymied due to possible decoy antigens or motifs that misdirect or suppress host immune responses and thus serve as poor immunogens in vaccines. Discovering antigenic motifs that facilitate immune evasion, suppression or modulation by *B. mallei* and *B. pseudomallei* are also of interest in this topic. Selective design and presentation of immunogens and specific epitopes may be key in refocusing the immune response to what have thus far been vaccine-resistant pathogens.

Impact: Identification and presentation of protective B and T cell epitopes of significant biothreat pathogens for which there are no or limited prophylactic medical countermeasures is of interest. These epitopes are often immunorecessive or masked by immunodominant responses that are not protective. Selective expression or redesign of these immunogens/epitopes is a key step in the path to rapid development of vaccines to protect the U.S. warfighter.

Objective: The goal of this topic is to solicit proposals focused on the rapid identification and/or design of protective vaccine antigens. Additionally, identification and optimization of the expression of immunorecessive vaccine immunogens or epitopes to overcome the effects of non-protective immunodominance in biothreat pathogens is of interest. This topic will likely involve both *in silico* and *in vivo* analysis, and selection and modification or design of immunogens. Key to this effort will be the validation of immunogens/epitopes of interest in relevant *in vivo* or *ex vivo* models of immunogenicity. Proposals that aim to identify conserved protective epitopes across multiple biothreat agents are also of interest. Pathogens of prioritized interest are as follows:

1. *Burkholderia pseudomallei* and *Burkholderia mallei*
2. *Coxiella burnetii*
3. *Francisella tularensis*
4. Western, Eastern and Venezuelan equine encephalitis viruses
5. Filoviruses (Ebola and Marburg species)

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Thrust Area 7, Topic B: Predictive Computational Modeling of the Immune System to Bridge Animal and Human Immune Responses to Vaccines

NOTE: An amendment to the Government Call will be posted on 2 February 2016 removing this topic. WHITE PAPERS FOR THIS TOPIC MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2016. White papers will not be considered if they are received after this deadline.

This topic does NOT require pre-coordination of abstracts prior to the submission of pre-application white papers.

Average Award Amounts for **Thrust Area 7, Topic B:**

- Single Scope or Multidisciplinary Awards may be up to \$400,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.

Award Structure for **Thrust Area 7, Topic B:**

- Will be for a base period of one (1) year with up to four (4) additional years as possible options.
- Pre-application white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable.
- Note that pre-application white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: The goal of this topic is to develop, refine and validate computational models of immune responses in humans based on those observed in animal models resulting from vaccination or challenge. There are numerous algorithms available for the prediction of T cell epitopes by MHC and supertype as well as both linear and non-linear B cell epitopes¹⁻³. Additionally, software such as Rosetta Antibody has made it possible to predict the structure of an antibody variable region⁴. Beyond the prediction of T- and B-cell epitopes and antibody structure, there is a clear need to develop the capability to predict human cellular and humoral immune responses based on those observed in animal models. While computational epitope prediction is extremely valuable in vaccine development, it does not routinely address the full breadth of functions in the development of any particular immune response. Issues of B cell maturation and somatic mutation, T cell activation and differentiation, host-pathogen interactions, the development of immune memory and cross-species differences in these functions are examples of key gaps that prevent the accurate predictive bridging of immune responses in animals to humans.

Mitigating the absence of predictive immunological bridging across species leads to significant loss of time and efficiency in the process of Animal Rule-based licensure of prophylactic products for

emerging infectious diseases and biothreat agents. Applying immunoinformatics, systems biology, genomic and proteomic databases, and computational modeling capabilities currently available should permit the development of sufficient computational tools to bridge animal and human immunologic data to reduce the uncertainty and burden in designing and selecting vaccine modalities, animal studies and human clinical sample analyses in support of FDA licensure. Ideally, this model could also be validated and applicable to lead vaccine selection and optimization.

Impact: Despite the existence of the FDA's Animal Rule licensure pathway for well over a decade, there has not yet been a vaccine licensed under this mechanism. A major hurdle in this pathway lies in bridging animal and human immune data with sufficient confidence to derive a correlate or surrogate of protection. Further upstream, the computational ability to precisely predict human immune responses based on animal data could also generate a substantial gain in lead selection and optimization time.

Objective: The goal of this topic is to solicit proposals focused on the development of *in silico* computational methods for predicting and/or bridging complex human immune responses, including humoral and cellular immunity, to immunogens/vaccination based on those observed in animal models. Modeling of immune responses to vaccination will likely require, but is not limited to, use of genomic and proteomic databases, immunoinformatics, and systems biology to bridge animal and human immune responses. To establish some degree of reliability, a plan to gather and model animal and human data from FDA licensed vaccines that have an established correlate/surrogate of protection will be imperative. Future plans to model established animal data and DTRA-funded or non DTRA-funded human vaccine trial data may also be included. These aspects may provide some foundations and reliable modeling tools to predict the full breadth of immune responses to vaccine candidates that have not been tested in humans as of yet. The following immunological parameters, albeit additional parameters can be included in proposals, are of interest:

- B and T cell epitope recognition
- Antigen presenting cell profiles
- B cell and T cell profiles including characterization of the BCR and TCR, cellular maturation and differentiation, somatic mutation, and cytokine/chemokine profiles
- Immunological memory, including memory T cell and long-lived plasma cell profiles, and antibody repertoire

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Thrust Area 7, Topic C: Relationship of Soil Environmental “Interactomics” and Environmental Triggers that Result in Increase in Disease Incidents for Biothreat Pathogens

NOTE: An amendment to the Government Call will be posted on 2 February 2016 removing this topic. WHITE PAPERS FOR THIS TOPIC MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2016. White papers will not be considered if they are received after this deadline.

This topic does NOT require pre-coordination of abstracts prior to the submission of pre-application white papers.

Average Award Amounts for **Thrust Area 7, Topic C:**

- Single Scope Awards may be up to \$500,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.
- Multidisciplinary Awards may be up to \$1,000,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.

Award Structure for **Thrust Area 7, Topic C:**

- Will be for a base period of two (2) years with up to one (1) additional year as a possible option.
- Pre-application white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable.
- Note that pre-application white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Due to Next Gen Sequencing (NGS), genomes from virtually all of the bio- and emerging threat bacterial pathogens as well as important near-neighbors, commensal, symbiotic and environmental organisms have now been sequenced. Cladistics analysis of these genomes continues to reveal the relationship and complex ancestral structure of pathogen phylogenetics. The finding that horizontal gene transfer and core and accessory genome recombination and re-assortment have key roles in the fitness of bacterial pathogens has been particularly surprising, even in some organisms previously thought to be “clonal”. Many pathogen near-neighbors turn out also to be phylogenetically diverse. Thus, the concepts of pathogen and virulence factor require contextual views. Recent work on Metagenomics methods, bioinformatics and quality control procedures have steadily improved and can now be employed to explore microbiome and outcomes.

The goal of this topic is two-fold: 1) to identify and characterize relationships, interactions, and dependencies of environmentally-derived bio-threat pathogens with other soil ecosystem and biome elements; and 2) to explore how environmental factors or the reservoir relationships can influence an increase in incidence of disease. Pathogens of specific concern are *Francisella tularensis* and *Burkholderia pseudomallei*. *Francisella tularensis* and *Burkholderia pseudomallei* are highly infectious, aerosolizable pathogens that could potentially pose a threat as biological weapons. Both microbes occur naturally in the environment and are known to cause natural disease incidents in humans and animals.

- a) This topic seeks proposals to develop meta-genomic/proteomic approaches and workflows and provide foundational data and insights into whether factors derived from interactions with specific amoeboid, nematode, fungal, or insect predators create or modulate selective pressures that could result in effects on human virulence. Likewise, proposals should aim to shed light on the relationship between these interactions, the relative fitness measurements, and phenotypic expression of known and novel virulence factors, including multidrug resistance. Little is known about the life cycle of *B. pseudomallei*. Limited study with other soil-dwelling biothreats have shown some unexpected interactions in soil (e.g. *B. anthracis* and *F. tularensis* multiply in the phagocytic amoeba *Acanthamoeba*); but what fitness advantages are gained and how this relates to unique genomic plasticity is unknown. The identification of environmental factors that correlate with presence or absence of these threats and their virulence are needed.
- b) This topic also seeks proposals that will explore how naturally occurring disease foci are correlated to large scale environmental factors that could trigger an increase in disease clusters and transmission. *Francisella tularensis*, the source of recent multiple Tularermia incidents, is known to be present in water ways, soil, arthropods and soil dwelling organisms^{1,5}. The pathognomic correlates of these disease clusters and mechanisms by which the bacteria were distributed over large distances is still largely unknown. *Burkholderia pseudomallei*, the source of the disease Melioidosis, is also found in water and soil, but other reservoirs and environmental factors could be contributing to its virulence and increases in disease incidents as well. There is some evidence that soil with specific characteristics such as a specific soil texture or organic matter content may influence the persistence of *Burkholderia pseudomallei*⁴. Additional research linking the natural reservoirs, including data from meta-genomic/proteomic portion of the study and the literature, with environmental disease causing triggers would give the biosurveillance community an additional set of parameters to help with predicting future outbreaks. Environmental triggers could include enviro-climate data, arthropod growth cycles and data on complex soil relationships

Objectives: Proposals are sought to provide a basic scientific understanding of:

- The experimental identification and characterization of the relationships, interactions, and dependencies of environmentally-derived bio-threat pathogens with other soil ecosystem and biome neighbors.
- The development and utilization of “interactomic” tools to characterize microbiome interactions
- Determination of relationship of “interactome” constituents to virulence, antibiotic resistance, other phenotypic properties
- Identification of the nature of interaction with ecosystem/biome: host, reservoir, co-factor, etc. and what factors enhance risks of ecosystem changes (OneHealth approach).
- Identify the environmental reservoir and triggers that could be leading to increased disease incidents for bacteria of concern to the DoD, specifically *F. tularensis* or *B. pseudomallei*. The goal is to obtain relevant data that would inform predictive outbreak models.
- Explore models and strategies for identifying environmental “hot zones” rapidly, that would inform operations

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Thrust Area 7, Topic D: Feasibility of Interstitial Fluid for Biomarker Analysis and Threat Exposure Monitoring

NOTE: An amendment to the Government Call will be posted on 2 February 2016 removing this topic. WHITE PAPERS FOR THIS TOPIC MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2016. White papers will not be considered if they are received after this deadline.

This topic does NOT require pre-coordination of abstracts prior to the submission of pre-application white papers.

Average Award Amounts for **Thrust Area 7, Topic D:**

- Single Scope Awards may be up to \$350,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.
- Multidisciplinary Awards may be up to \$700,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.

Award Structure for **Thrust Area 7, Topic D:**

- Will be for a base period of two (2) years with up to one (1) additional year as a possible option.
- Pre-application white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable.
- Note that pre-application white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Traditional blood-based analytical methods have many drawbacks, such as the requirement of trained personnel for sample collection, as well as the inability of real-time measurements. Skin patches of microneedle arrays were initially developed for vaccine and drug delivery in the 1990s. These arrays inject products into the dermis or epidermis, depending on the length of the needles. Similar skin patches are now under study as a pain-free means to collect biofluids for analysis. However, it is currently unknown how dermal interstitial space analytes will compare to traditional biological fluids.

Impact: To ensure mission success, warfighters need to remain healthy. Early warning of a possible infection or chemical exposure could allow for a more timely treatment regimen which may increase the ability of warfighters to perform their missions. DTRA/CBA continues its efforts to characterize and develop multiplex biomarker panels on classifiers of human (and animal model) early exposure to biological and chemical agents via differential transcriptomic, regulatory, and proteomic expression methods.

Objective: Proposals are sought to explore interstitial fluid as a sample for chemical and biological agent diagnostics and exposure awareness. Attractive proposals will expand the understanding of the interstitial space and how interstitial fluid samples might compare to the host immuno/exposure profile developed from other biological fluids from animal exposure models, with a focus on host-based markers of insult or infection. Work should not be limited to specific microbial or chemical detection, but should provide a broader inventory of all components that might be informative for chemical or biological exposure awareness. This might include cytokines, mRNAs, small RNAs, antibodies, signaling proteins, inflammation markers, small molecule byproducts, etc., to include kinetics and persistence of such markers.

Thrust Area 7, Topic E: Influence of Respiratory Tract Components and Particle Dispersity in Aerosol Pathogenesis

NOTE: An amendment to the Government Call will be posted on 2 February 2016 removing this topic. WHITE PAPERS FOR THIS TOPIC MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2016. White papers will not be considered if they are received after this deadline.

This topic does NOT require pre-coordination of abstracts prior to the submission of pre-application white papers.

Average Award Amounts for **Thrust Area 7, Topic E:**

- Single Scope Awards may be up to \$350,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.
- Multidisciplinary Awards may be up to \$700,000 per year. Further guidance on scope and cost may be provided in each full proposal invitation.

Award Structure for **Thrust Area 7, Topic E:**

- Will be for a base period of two (2) years with up to three (3) additional years as possible options.
- Pre-application white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable.
- Note that pre-application white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: The goal of this topic is two-fold. The primary goal is to develop improved predictive understanding of the pathogenesis of toxic particulates, namely aerosolized toxic chemicals and peptide/protein toxins, as a function of (a) modulated molecular and cellular populations of the olfactory, respiratory tract and alveoli as well as (b) aerosol particle characteristics including, *e.g.*, composition, topology, and size distribution spanning a range including but also extending beyond 1-10 microns. The secondary goal is to employ this new understanding to enable novel strategies to prototype respiratory pretreatments and drug delivery methods.

Of particular interest is the role within aerosol pathogenesis of phenotype variation among the populations of alveolar macrophages, mucins, and the respiratory microbial ecosystem, as mediated in part by interactions with the alveolar epithelial cells and immune cells within the olfactory, bronchioles and interstitial space between the alveoli and blood vessels. Changes to these respiratory molecular and cellular components is a major determinant in reaction to toxic smokes and toxicant-induced susceptibility to infection^{1,2}, but is not well understood within the context of chemical and biological warfare agents. The highly adaptive nature of the alveolar macrophages³ and their pivotal role in regulation of local immunological homeostasis as well as toxicant scavenging at the primary human/environmental chemical interface makes them a critical node for improved predictive toxicology and development of future medical countermeasures to inhaled chemical and biological threats⁴⁻⁶.

Within the olfactory and bronchioles, mucus is the major ecological niche for the human microbiota, accommodating microbial densities of 10^{11} – 10^{12} cells/mL, a record for any microbial ecosystem documented thus far. The matrix of constituent mucin glycoproteins provides a geometric and diffusive constraint to the distribution of nutrients, toxins, and oxygen⁷. Moreover, recent work has demonstrated the role of particular mucin components in airway defense⁸. An improved understanding of how the respiratory mucus interacts with and regulates the respiratory microbial ecosystem as well as toxic particulates could therefore lead to improved risk assessments as well as radically new strategies for countering aerosolized threats at their primary initial site of intersection with humans.

Currently, inhalational exposure, infection and toxicology parameters are based on data from animal models, often under specific and limited experimental conditions. Generally, experimental conditions employ aerosol particles in the 1-3 μm range, or more broadly in the 1-10 μm range⁹. However, aerosols or airborne droplets can and do cover a wider size range. Few experiments have examined the role of aerosol particle size in pathogenesis, and those experiments have been restricted to a small number of agents of bioterrorism concern. There is growing evidence that particle size plays an important role not only in toxic dose, but also in pathogenesis and related kinetics.

Aerosols are a major focus of the Chemical and Biological Defense Program due to their role within weaponized chemical and biological agents as well as within potential delivery platforms for medical countermeasures to these threats^{10,11}. The mechanisms of action of aerosolized toxicants are diverse, ranging from selective blockage of specific molecular reactions or binding to specific receptors, to those acting at multiple sites or levels¹². Developing toxicant-specific medical countermeasures for all classes of potential toxicants would be prohibitively expensive. Therefore, pre-treatment strategies for broad-spectrum neutralization of diverse toxicants are of interest to the DoD, including those that are in an early stage of development.

Impact: This topic supports Chemical and Biological Defense Program goals by providing insights into inhaled chemical particulates and toxicants of diverse origins and by providing strategies and platforms for medical countermeasure discovery and development. This information will directly inform the advancement of appropriate chemical medical countermeasures, some of which may rely upon an understanding of aerosol-pulmonary interactions, as well as improved risk assessment capabilities.

Objective: The goal of this topic is to solicit proposals aimed at developing improved predictive understanding of the toxicokinetics and pathogenesis of aerosolized toxicants, with a specific focus on (a) modulated molecular and cellular populations of the olfactory, respiratory tract and alveoli as well as (b) aerosol particle characteristics spanning an extended range. The identification of early-stage strategies and platforms for medical countermeasure discovery and development is also encouraged. Proposals that address any or all of the following will be considered:

- Impact of modulated olfactory, respiratory, and alveolar molecular and cell genotypic and phenotypic variation on cellular penetration of inhaled particulates as well as progression of toxicological and pathogenic effects;
- Development of improved predictive *in silico*, *in vitro*, and low-cost *in vivo* assays and correlations between these models, to enable more accurate and rapid screening of acute pulmonary toxicity and partitioning into systemic circulation, as well as improved mechanistic understanding;
- Structure-property relationships correlating particle size, morphology, and physicochemistry with immunogenic and other interactions at the olfactory and epithelial cells of the alveoli and bronchioles.

Proposals that would support or enable development of strategies and platforms for medical pretreatments or countermeasures against multiple aerosolized threats having similar mechanisms of action will receive priority consideration for funding over those that deal with specific threat molecules.

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