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

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1. Introduction and Scope

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.

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.

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.

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

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. **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.

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.

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

The seven thrust area descriptions are outlined below.

2.1. **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.

2.2. **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.

2.3. **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.

2.4. **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.

2.5. **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.

2.6. **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 counter 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 goals of CBEP international research partnerships are 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, and
- 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 of 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.

2.7. **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 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).

3. Award Information

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. Awards may range from small dollar value (e.g., ~$25K) up to $1M annually (average award values include both direct and indirect costs). Awards made under this Call will be made with basic research, applied research or Cooperative Threat Reduction (CTR) category funds. 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.

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.

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. Subawards in the form of subgrants may be allowed for MIPRs and will be considered on a case-by-case basis. Subawards in the form of MIPRs and Interagency Agreements/Interagency Orders will be addressed by DTRA on a case-by-case basis.

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).

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

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

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

- Federal laboratories to include DoD, Department of Energy (DoE) (National Labs), DHS (NBACC, PIADC), HHS (CDC, NIH), and USDA (ARS, APHSIS).
- 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 FFRDCs specified in DoD FAR Supplement 235.017-1 (http://farsite.hill.af.mil/vfdfara.htm and click on 'DFARS Part 35'). DoD-sponsored FFRDCs shall review FAR 35.017(a)(2) to ensure compliance with the requirement for an Organizational Conflict of Interest (OCI) Risk Mitigation Plan that shall accompany the proposal submission.[1]
- DoE-sponsored FFRDCs provided that authorization is obtained from the DoE sponsor. DoE-sponsored FFRDCs shall review FAR 35.017(a)(2) to ensure compliance with the requirement for an OCI Risk Mitigation Plan that shall accompany the proposal submission.[1] In accordance with FAR 17.503(e), DoE Order 481.1C and DoE Acquisition Regulation DEARS 970.1707-3, DoE-sponsored FFRDCs must provide a copy of the written certification from the DoE sponsor authorizing its performance of the proposed effort. The DoE sponsor must provide written certification that the proposed work:
    1) is consistent with or complimentary to missions of DoE and the facility to which the work is to be assigned,
    2) will not adversely impact programs assigned to the facility, and
    3) will not create a detrimental future burden on DoE resources.
- National Aeronautics and Space Administration (NASA)-sponsored FFRDCs provided that authorization is obtained from the NASA sponsor. NASA-sponsored FFRDCs shall review FAR 35.017(a)(2) to ensure compliance with the requirement for an OCI Risk Mitigation Plan that shall accompany the proposal submission.[1]

There is no limit on the number of white papers and invited proposals that an applicant Principal

[1] The conflict of interest policy in DFARS 235.017-1 pertains to personal conflicts of interest by board members of FFRDCs and not organizational conflicts of interest.

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 website (www.dtra.mil) 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.

All applicants interested in submitting white papers and proposals must register on the DTRA proposal submission website, 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 www.dtrasubmission.net does not fulfill registration requirements for participation in this Call.

White papers and proposals must be submitted electronically through the DTRA proposal submission website, 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.

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.

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.

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.

5.2. 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)

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.

The white paper and most parts of the proposal must be uploaded in a Portable Document File (PDF) format compatible with Adobe Acrobat ® version 9.1 or earlier. The cost proposal portion of the proposal must be uploaded in MS Excel. 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.

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. 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 8½ 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 I White Paper Re-Submission and Content. On a limited basis a second white paper may be submitted without pre-coordination of an abstract. These re-submissions will be based on the review of the original white paper and will be allowed when changes to the project scope, technical approach, and/or cost are envisioned for any potential full proposals. Revised white papers must conform to the standards for the white papers detailed in Section 5.3. At minimum, the revised white paper should address the issues and questions detailed in the debrief summary.

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

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 8½ 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.dtra.mil (MS 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.
- ***Programmatics***. 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; base and option years should be clearly labeled. Additional details that are required include the following:
  - ***Sample Repository.*** Thrust Area 6 narratives ONLY must also clearly identify how the applicant plans to maintain samples collected during the proposed research effort, along with relevant metadata, for at least 12 months after the project end date. The format for the Sample Repository is at the discretion of the applicant.
  - ***Protection of Human Subjects.*** For full discussion, see Section 5.9. If the proposed research does involve human subjects or materials, applicants are asked to: a) justify the use of human subjects, b) outline the human use, and c) include the source of the human subjects or materials involved in the research. Applicants shall submit 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.
  - ***Animal Use.*** For full discussion, see Section 5.10. If the proposed research involves animal use, applicants are asked to justify the use of animals. Any proposals involving animal studies or animal work must include 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. 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.

- ***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.

Cost Proposal. The cost proposal must include two separate documents: a cost summary and a detailed cost portion. The cost proposal must also include detailed cost submissions for all subcontractors and consultants.

The cost summary 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 detailed cost proposal. A **template** for the cost summary may be found online at the DTRA website (www.dtra.mil).

The detailed cost proposal will include the following three sections: (1) tabular cost breakdown by cost element and SOW tasks based on 12-month increments; (2) narrative to support the requirements in each cost element; and (3) subcontractor cost breakdown, if applicable. Applicant format is acceptable provided it includes all required elements. The cost proposal shall include the same level of detail for each subcontractor or consultant as required of the prime applicant. The exception is any proprietary subcontract or consultant cost data (e.g., indirect rates) that may be submitted directly to the Government at time of negotiation.

The detailed 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,

and/or 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.

- 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.

Note that dollar values in this Call include both direct and indirect costs. The detailed cost proposal does not have a page limit and may be provided in the applicant's preferred format. The cost summary and the detailed cost proposal must be uploaded as separate MS Excel files.

Supplemental Information. The supplemental information must consist of the following individual PDF uploads or as a fillable field, as noted:

1) **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.dtra.mil (MS PowerPoint format). The inclusion of the DTRA logo is not required.

2) **SOW:** The SOW does not have a page limit, but should be approximately 3-5 pages in length for incorporation into an award document. 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. A template for the SOW format may be found online at the DTRA website (www.dtra.mil) (MS Word format).

   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. The SOW format/guidance is as follows:

   - ***Objective:*** Brief overview of the specialty area. Describe why the research is being pursued and what knowledge is being sought.
   - ***Scope:*** Include a statement of what the SOW covers including the research area to be investigated, objectives/goals, and major milestones and schedule for the effort.
   - ***Background:*** The applicant must identify appropriate documents, including publications that are applicable to the research to be performed. This section includes any information, explanations, or constraints that are necessary in order to understand the hypothesis and scientific impact on capabilities needed to reduce, eliminate, and counter the threat, and also

mitigate the effects of WMD. It may also include previously performed relevant research and preliminary data.

- ***Tasks/Scientific Goals:*** This section contains the detailed description of tasks which represent the research to be performed that are contractually binding. Thus, this portion of the SOW should be developed in an orderly progression and presented in sufficient detail to establish the methodology and feasibility of accomplishing the overall program goals. The work effort should be segregated by performance period for all tasks to be performed and anticipated milestones realized in that year (e.g., Year 1, Year 2, etc., should be detailed separately). Identify the major tasks in separately numbered sub-paragraphs. Each major task should delineate, by subtask, the research to be performed by year and number each task using the decimal system (e.g., 4.1, 4.1.1, 4.1.1.1, 4.2, etc.). The sequence of performance of tasks and achievement of milestones must be presented by project year and task in the same sequence as in the Project Narrative/Technical Proposal. The SOW must contain every task to be accomplished to include a detailed schedule.

  The tasks must be definite, realistic, and clearly stated. Use "the awardee shall" whenever the work statement expresses a provision that is binding. Use "should" or "may" whenever it is necessary to express a declaration of purpose. Use active voice in describing work to be performed. Do not use acronyms or abbreviations without spelling out acronyms and abbreviations at the first use; place the abbreviation in parenthesis immediately following a spelled-out phrase. If presentations/meetings are identified in your schedule, include the following statement in your SOW: "Conduct presentations/meetings at times and places specified in the grant schedule."

- ***Deliverables:*** A **template** for the SOW format may be found online at www.dtra.mil (MS Word format). The SOW must include the following deliverables:

  - Recipient must comply with any DoD Directive Type Memorandum on Public Access to the Results of DoD Intramural Basic Research Published in Peer Reviewed Scholarly Publications.

  - Annual Technical Review: Awardees will attend an annual technical program review meeting.

  - 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 on or about 1 May of each year on how the report is to be submitted. Templates and specific instructions will be provided each year in advance of the submission deadline.

    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, Participants and Other Collaborating Organizations, Impact, and Changes/Problems.

- Annual Quad Chart(s): An updated quad chart must be submitted annually. A template will be provided each year in advance of the submission deadline (1 July).
- Annual Metrics: Metrics must be submitted annually. DTRA will provide instructions each year in advance of the submission deadline (1 July). Note that the metrics are not cumulative. The first submission shall only include actions that occurred from the Period of Performance start date up to submission deadline. Each subsequent report shall only include actions that occurred during the 12-month period following the previous year's submission.
- 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. Standard Form (SF) 298, Report Documentation Page, must be used. 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://www.gsa.gov/portal/forms/download/116146. 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).
- Final Metrics: A final metrics submission is required. A template and specific instructions will be provided in advance of the submission deadline. The final metrics file should be submitted along with the Final Technical Report. The fields contained in the final metrics file are analogous to those of the annual submissions. The final metrics file shall contain only data from the last annual reporting period until the end of the award's funded Period of Performance.
- 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 any format deemed appropriate by the applicant.
  - Access to all samples collected and data generated during the course of the project for at least 12 months after the project end date.

3) **Other Supplemental Information (submitted as a single PDF upload):**

- For FFRDCs, a statement of any potential OCI, or a confirmation of no conflicts, must be provided. For DoE-sponsored FFRDCs, the DoE sponsor written certification must be included.

- A statement of Intangible Property Assertions.
- 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.

4) **Authorized Offeror Personnel (fillable field):** 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.

5) **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 and/or 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.

6) **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 DTRA website (www.dtra.mil) 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 completed PRAT file(s) should be emailed as a Portable Document File (PDF) format to HDTRA1-FRCWMD-C@mail.mil within two (2) weeks of the full proposal submission. Do not attempt to upload the PRAT to the submission site.

5.6. Phase II Full Proposal Re-Submission and Content. A revised proposal may be requested based on the review of the original proposal. Revised proposals will be requested when changes to the project scope, technical approach, and/or cost are required before the proposal could be further considered for an award. Applicants whose proposals are of interest to DTRA may be contacted to provide additional information or to make requested revisions prior to the final decision on funding. This request for further information may include revised budgets or budget explanations, revised SOWs, and other information, as applicable, to the proposed award. Applicants who are not responsive to Government requests for information in a timely manner, defined as meeting Government deadlines established and communicated with the request and not making satisfactory updates as requested, may be removed from award consideration. Applicants may also be removed from award consideration if the applicant and the Government fail to negotiate mutually agreeable terms within a reasonable period of time.

Re-submissions should be made in accordance with the instructions provided in the notification email. Proposal revisions must conform to the original submission requirements as detailed in Section 5.5.

All submissions must be UNCLASSIFIED.

5.7. Marking of White Paper and Full Proposal for 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.

5.8. 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).

5.9. Protection of Human Subjects. If the proposed research involves human subjects or materials,

applicants are asked to: a) justify the use of human subjects, b) outline the human use, and c) 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.

All research under any award made under this BAA involving human subjects must be conducted in accordance with 32 CFR 219, 10 U.S.C. § 980, and DoD Instruction 3216.02, and, as applicable, 21 CFR parts 11, 50, 56, Good Clinical Practice, the ICH, as well as other applicable federal and state regulations. Awardees 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 U.S.C. § 980).

DTRA Directive 3216.01 of June 9, 2010, modified March 18, 2015, established the DTRA Human Subjects Protection Program, set forth the policies, defined the applicable terms, and delineated 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 DTRA Research Oversight Board (ROB) has reviewed and approved the proposed protocol. Contractors 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 IRB to include consent forms for any planned research using human subjects to the DTRA ROB for its review through the contracting officer's representative (if assigned) or the contracting officer. The ROB review is separate from, and in addition to, local IRB review.

A study is considered to involve human research subjects if: 1) there is interaction with the subject (even simply talking to the subject qualifies; no needles are required); and 2) if the study involves collection and/or analysis of personal/private information about an individual, or if material used in the study contains links to such information.

Written approval to begin research or to subcontract for the use of human subjects under the proposed protocol will be provided in writing from the DTRA ROB, through the contracting officer. Both the contractor and the Government must maintain a copy of this approval. 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 Principal Investigator;
- 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; or

- changes in perceived or measured risks or benefits to volunteers that require changes to the study.

Research pursuant to such modifications or amendments must 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. The contractor or subcontractor must provide documentation of continued IRB review of protocols for ROB review and approval in accordance with the Contract Data Requirements List. Research changes must be reviewed by the IRB and ROB in advance unless necessary to eliminate apparent and immediate hazards to the subject(s).

A clause regarding human subjects research will be included in all contracts involving human subjects research. Non-compliance with any provision of this clause may result in withholding of payments under the contract pursuant to the contract's payments clause(s) and/or contract termination pursuant to the contract's termination clause(s). The Government shall not be responsible for any costs incurred for research involving human subjects prior to protocol approval by the ROB.

5.10. Animal Use. If the proposed research involves the use of live nonhuman vertebrate animals, applicants 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) is planned. 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 is available on the ACURO website (http://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.acuro). 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 Instruction 3216.01, dated September 13, 2010, provides policy and requirements for the use of animals in DoD-funded research based on Army Regulation (AR) 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 Instruction 3216.01 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.

5.11. 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 grants awarded 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: https://www.gpo.gov/fdsys/pkg/CFR-2002-title32-vol3/pdf/CFR-2002-title32-vol3-sec626-18.pdf for a copy of 32 CFR 626.18, Biological Defense Safety Program.)

For projects that will employ the use of chemical agents, either neat agent or dilute agent, the applicant must provide approved Facility Standard Operating Procedures that conform to Federal, State and local regulations and address the storage, use and disposition of these chemical materials.

5.12. 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://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf). 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.
- 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.

6. Submission Dates and Times

Coordination of abstracts may be accomplished at any time that this CALL is in effect, unless otherwise stated as part of a specific topic. Once an applicant has been notified that a white paper is welcomed, the white paper should be submitted within 60 days. If the white paper is not submitted within 60 days, DTRA reserves the right to require the applicant to re-initiate the process with another abstract coordination. White papers may be submitted anytime this CALL is in effect (as long as it occurs within the 60 day window following pre-coordination of the abstract), unless otherwise stated as part of a specific topic. 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 may be limited to available program funds.

The due date for the Phase II invited proposal submissions will be provided in the letter of invitation. The applicant will not be allowed less than 45 days to prepare a full proposal submission; there is no

penalty for early submissions. An extension for submission of the Phase II proposal submission may be requested by emailing the administrative email address in Section 9 prior to the deadline for the proposal submission. Full proposals may be evaluated at any time after submission, but generally are reviewed within 60 days. Proposals may not be reviewed if they are received after the deadline. Please note 15 U.S.C. 260a establishes daylight saving time as the standard time during the daylight saving period.

Applicants are responsible for submitting invited proposals so as to be received by the DTRA submission site by the time and date 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.

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.

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. Scientific and Technical Merit. The objective of this criterion is to assess the extent to which the applicant presents ideas that are innovative and/or unique with the potential for high payoff in the science area and details a comprehensive technical approach based on sound scientific principles. Innovation will be judged contextually against the white paper's/proposal's scope, goals, and setting. To the extent possible, the technical risks, including those of biosafety and security, to accomplish the research or project should be identified with appropriate mitigation/management details.

   For Thrust Area 6 white papers/proposals, innovation will also be considered with respect to partner country capabilities.

2. Value to Mission Goals. The objective of this criterion is to assess the extent to which the applicant demonstrates an understanding of the C-WMD research or mission challenges and the contribution to the C-WMD research or mission needs of that thrust area/topic. White papers/proposals must detail research or a project that is responsive to the thrust area/topic as presented in this solicitation. This criterion also addresses the benefit of the proposed effort on enabling knowledge, technology, or capabilities over current methods and/or practices and on the transition potential that is appropriate to the proposed effort. Applicants must also demonstrate an impact of the proposed effort on the institution's ability to perform research relevant to reducing the global WMD threat; and/or to train, through the proposed effort, students and/or partner scientists

in science, technology, engineering and/or mathematics.

Thrust Area 6 white papers/proposals must demonstrate an understanding of the CBEP priorities and mission. As such, the degree to which the proposed collaborations may lead to long-term partner country self-sufficiency and sustainment of the jointly developed capabilities will be considered.

3. Capability of the Personnel and Facilities to Perform the Proposed Effort. The objective of this criterion is to assess the extent to which the applicant's team has the requisite expertise, skills and resources necessary to perform the proposed program. This includes an assessment of the team's management construct, key personnel, facilities and past technical experience in conducting similar efforts of the proposed scope. Applicants must demonstrate that their team has the necessary background and experience to perform this project. Facilities should be detailed with discussion of any unique capabilities pertinent to the research. Subcontractors may include Government facilities or Agencies; however the unique expertise or specialized facilities provided through their inclusion must be clearly presented and the validity of the proposer-Governmental relationship must be clearly documented.
4. Cost Realism Evaluation. The objective of this criterion is to establish that the proposed costs are reasonable, realistic, and justified for the technical approach offered and to assess the applicant's practical understanding of the scope of the proposed effort.

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.

Each white paper and invited proposal submitted to a general TA will be reviewed on a rolling basis; topic-based submissions will be reviewed as a batch following receipt deadlines. All applications will be reviewed based on the merit and relevance of the specific white paper/proposal as it relates to the DTRA program, rather than against other white papers/proposals for research in the same general area.

White paper (Phase I) evaluation will be based on the two (2) equally weighted criteria of (1) Technical/Scientific Merit and (2) Value to Mission Goals. The criteria will be scored as Outstanding (O), Good (G), Acceptable (A), Marginal (M) or Unacceptable (U). Any criterion scored as "Unacceptable (U)" will render the white paper "Not Selectable," and the white paper will not be considered further.

The full proposal evaluation will be based on the four criteria listed above. The first three criteria will be scored Outstanding (O), Good (G), Acceptable (A), Marginal (M) or Unacceptable (U). The fourth criterion will be scored as either Acceptable (A) or Unacceptable (U). Any criterion scored as "Unacceptable (U)" will render the proposal "Not Selectable," and the proposal will not be considered further.

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. 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.

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. It is the intent of DTRA to use non-government personnel to assist with the review and administration of submittals for this Call. All invited proposals will be reviewed by subject matter experts (peer reviewers) who are non-government personnel.

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 or otherwise marked with restrictive legends. Existing DTRA contractors include but may not be limited to the following: TASC-an Engility Company (Advisory and Assistance Services) and their subcontractors, JAB Innovative Solutions LLC, Tenica and Associates LLC, and TFAB Ground Systems LLC (contract specialist support) and their subcontractors, SBG Technology Solutions (automated solicitation proposal management system [ASPMS] support) and their subcontractors, and Terremark Worldwide Inc. (ASPMS support). Each contract contains OCI provisions and/or includes contractual requirements for non-disclosure of proprietary contractor information or data/software marked with restrictive legends. Theapplicant, by submitting a white paper or proposal, is deemed to have consented to the disclosure of its information to the aforementioned contractors under the conditions and limitations described herein.

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.

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

8. Award and Notification Information

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. 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.

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.

All notifications will be made from notification@dtrasubmission.net. Emails sent to this email address will not receive a response. A debrief summary will be provided as part of all notification e-mails. If for any reason there is a delivery failure of these e-mail notices, DTRA will not further attempt to contact the applicants.

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.

9. Agency Contacts

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.

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: Network Sciences

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 6 has no specific topics at this time. Submissions to the general thrust area description in accordance with the requirements detailed in this BAA are welcome.

Thrust Areas 1, 2, 3, 4, 5, and 7 have specific topics detailed below. Submissions to the general thrust area descriptions for these thrust areas in accordance with the requirements detailed in this Call are also welcome. However, great care must be taken to select the appropriate Basic Research (BR) Topic G1-19 from the drop down menu when completing a cover sheet.

BASIC RESEARCH TOPICS

In accordance with Section 2, the requirement for abstract pre-coordination is waived for these topics; these topics do NOT require pre-coordination of an abstract prior to the submission of white papers.

The white paper deadline for these topics is 1 February 2017. NOTE: An amendment to this Call will be posted on 2 February 2017 removing these topics. WHITE PAPERS FOR THESE TOPICS MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 1 FEBRUARY 2017. White papers may not be considered if they are received after this deadline.

Responses to these topics must address only basic research. Basic research is the systematic study directed toward greater knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind. It includes all scientific study and experimentation directed toward increasing fundamental knowledge and understanding in those fields of the physical, engineering, environmental, and life sciences related to long-term national security needs. It is farsighted, high payoff research that provides the basis for technological programs.[2]

These topics are interested in research projects that span from those that focus on exploratory aspects of a unique problem or a high-risk approach to those that involve a comprehensive program with interdisciplinary areas. Consistent across all proposals should be the focus on innovative research with the potential for high impact to C-WMD science.

White papers and proposals submitted to these topics must have a single lead organization and single submission for the white paper and the invited proposal. Awards will be made by a single award to the lead institution. Subawards are the responsibility of the award recipient.

Basic Research-Thrust Area 1-Topic G2: Energy-Efficient Physical and Algorithmic Methods for Detection, Localization, and Isotope Identification

Award Amounts for this topic are anticipated to be between $150,000 and $350,000 per year (total dollar value = direct and indirect costs). Larger value efforts (i.e., $350, 000 per year) that are university led, include multiple PIs (at either a single or at multiple organizations), and provide training opportunities are encouraged. In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Capabilities in the detection of nuclear materials in mobile scenarios are limited by power-consumption of sensor-supporting electronics for signal amplification, processing, and algorithmic computation. Algorithm computation becomes a nebulous area of research employing

[2] DoDI 3210.1, September 16, 2005

many techniques and many levels of fidelity spanning between gross-count alarms for initial detection and isotope identification. To minimize size, weight, and power for mobile detection systems, these computational methods must be transitioned to embedded, chip-scale, hardware. Thus, basic research is sought to explore the theoretical minimum amount of electrical power necessary to achieve algorithmic output from spectroscopic sensor data for a given physical architecture. This data may include spectral histograms or list-mode data received event by event. Solutions to decrease power consumption may be found in both algorithmic and physical approaches.

Impact: Advancements in fundamental science may foster future technologies and analysis methodologies that require fewer power resources, help discriminate between background response and signatures of interest, and enhance range-of-detection of illicit nuclear materials. These advancements will also engender processes that extend both the minimal detectable activity and minimal rate of false alarms and false identifications. It is desirable to advance knowledge of embedded computational techniques that minimize power resources and size of supporting electronics. Scientific and technical approaches should enable smarter sensor components and reduce communication resources for exfiltration in a global network by means of transmitting high-fidelity information as opposed to raw sensor data.

Objective: This topic seeks research to foster physical and algorithmic methods that make computational capability more power-efficient in embedded systems. More efficient systems will provide smarter sensing instrumentation on the ground, producing higher information density output and communicating higher-level information while consuming fewer power resources. Successful results may be applicable across multiple uses including ground or airborne radiation/nuclear detection networks, mobile or fixed. Possible research areas may include, but are not limited to:

- Conducting theoretical, computational, or experimental studies of fundamental computational methods to reduce the number of math operations required to achieve algorithmic output for mobile detection and isotope identification with minimal false alarm rates.
- Exploring chip-scale architectures and assemblies that may reduce the power consumed to execute algorithmic calculations, including the reduction of clock-cycles and memory.
- Enhancing understanding of sensor signal fidelity in time and space to exploit minimal effort in computation in distinguishing radiological features of interest from background signatures.
- Investigate additional approaches beyond algorithms to find efficiencies in lowering power for radiation detection analyses; e.g., power saving advances with neuromorphic computing, low-power concepts analogous to advances demonstrated with the introduction of GPUs, or other novel approaches.

Note: Submissions proposing a repackaging of existing processing systems will not be considered.

Basic Research-Thrust Area 2-Topic G4: Behavior Regime Analysis and Model Order Reduction (MOR) for Nuclear Weapons Effects (NWE)

Award Amounts for this topic are anticipated to be between $150,000 and $350,000 per year (total dollar value = direct and indirect costs). Larger value efforts (i.e., $350, 000 per year) that are university led, include multiple PIs (at either a single or at multiple organizations), and provide training opportunities are encouraged. In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Current state of the art analysis methods for NWE do not have sufficient flexibility to meet the wide range of mission needs. Analysis methods currently used for NWE generally fall into one of two general categories: either very high fidelity first principles-based approaches with long computation time (resource heavy high fidelity or completely intractable) or very simple with short computation time (resource light with low fidelity or simply a look-up table). Current missions require analysis methods with flexible levels of fidelity and corresponding resource usage (manpower and computation appropriate), that vary on a continuum between the very high and very low fidelity methods available now. Specific research on determination of various behaviors at regime boundaries and simplified characterizations of NWE would help fill in the capability space with more appropriate fidelity approaches better suited to DTRA missions.

Impact: Advances in the understanding of NWE in various regimes of behavior and the development of NWE characterizations with adjustable fidelity in different regimes, would allow for the appropriate scaling and implementation of theory, modeling, and simulation tools to better meet analysis for mission needs to support national decision makers. Analysts are currently forced to rely on NWE analysis tools with fidelities that may be inappropriate to the problems decision makers confront. NWE analysis tools of varying fidelity could be better matched to mission needs. This flexibility would in turn allow NWE analysts to provide better quality results with greater confidence to national decision makers at appropriate levels of complexity, resource usage and uncertainty.

Objective: The objective of this topic is to fill in the NWE analysis capability space between very high fidelity and very simple methodologies. Development of simplified characterizations of NWE and of research to understand NWE regime behavior focusing on boundary behavior will allow for appropriate fidelity approaches to be developed. Research for this topic may focus specifically on single NWE or be more broadly applicable to multiple NWE. Possible research areas may include, but are not limited to:

- Reduced state and mission-appropriate fidelity of NWE focusing on exploration of physical behavior similitudes and scaling.
- NWE regime determination (phase transition analysis) focusing on boundary behavior (phase changes and emergent behavior).
- Rules of thumb for NWE modeling obtained from ab-initio and/or data driven modeling. Easy user friendly visualization of complex phenomena using these rules
- Surrogate modeling and Simplified Order Modeling (SOM) for NWE that may include kernel PCA, ICA, maximum likelihood, semi-empirical, machine learning, adaptive data driven modeling, and other methods and approaches for reduced order modeling (parametric and non-parametric) are welcomed.

Investigators should propose their own NWE high fidelity model to work with, for example, Boltzmann transport, Navier-Stokes, Maxwell's equations, reaction-diffusion equations, etc. Investigators may also propose a model order reduction methodology that builds hybrid semi-empirical

modeling schemes based upon data-driven modeling of some more difficult to calculate terms in first principles calculations. Regardless of approach, all investigators may request unclassified data sets for use in the research. The end result is to have a methodology to create a continuum of modeling approaches of various levels of fidelity, various levels of tractability, various levels of computational scaling, and various levels of transferability in between regimes for a given NWE simulation system (e.g. simulation of a fireball). The resultant approaches will provide a wider selection of theory, modeling and simulation solutions for the analyst to choose from.

Basic Research-Thrust Area 3-Topic G5: Formation, Evolution, and Conductivity of X-Ray Generated Warm Dense Plasma

Award Amounts for this topic are anticipated to be between $150,000 and $350,000 per year (total dollar value = direct and indirect costs). In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Satellites are a critical part of DoD communication, reconnaissance, and guidance systems. The majority of these satellites are powered by photovoltaic arrays due to their superior combination of cost, weight, stability, and risk. In order to work effectively solar arrays need to have a large surface area exposed to sun light. The large exposed surface area makes them potentially vulnerable to prompt radiation from a high altitude nuclear explosion. The large surface area of modern solar arrays also means that adding even transparent thin films for protection can add significant weight, and the need for direct sunlight exposure in non-concentrator designs precludes shielding-based protection strategies. While surface charging, displacement damage, and total ionizing dose have been studied in solar arrays, the effects of prompt cold X-rays are not well understood.

Prompt X-ray exposures with pulses of less than 100 nanoseconds and with photon energies below ~1 keV can generate high-density surface plasmas due to the vaporization and ionization of the first few microns of surface materials. This warm dense plasma can span the dielectric surfaces and couple the biased solar cells to each other, to spacecraft structures, or to the space plasma itself. The formation and temporal behavior of the plasma, as well as the effective conductivity and coupling to exposed conductors, are not well understood or modeled.

For example, formation of a highly conductive plasma layer has been observed in experiments using the Omega laser at the University of Rochester Laboratory for Laser Energetics. X-rays pulses of ~2 nanoseconds were created using standard laser pulse widths and targets at the Omega laser system. Langmuir probes biased at 10-30 V and solar cells biased at 100 V were used to measure the effects of plasma blow-off. The fluence at the probes and cells of X-rays with energies below ~1 keV ranged from 0.003 – 0.03 Joule/cm^2. In almost all cases, the probes and solar cells exhibited the effects of a conductive surface plasma that allowed discharges with voltage drops <10 V.

Impact: This effort will increase understanding of the potential impacts of prompt X-rays on satellite solar array performance, reliability, and lifetime though fundamental physics modeling of the

formation, time evolution, and conductivity of warm dense surface plasmas generated by prompt X-rays. This will lead to more cost-effective designs for future survivable solar arrays.

Objective: This topic seeks research to study the fundamental physics of the generation, temporal evolution, and properties of the warm dense plasma that can be generated by X-ray exposures. Experimental, theoretical, modelling, and computational efforts that fundamentally describe, predict, and replicate the phenomenon are of interest. Efforts should be focused on discovering the fundamental science that explains the formation and evolution of warm dense surface plasmas and physical and electrical properties of the plasma and its electrical connection to conductive surfaces, not on engineering approaches that seek to develop new methods for mitigation or new solar array designs. This topic is also not interested in solar array ESD (electrostatic discharge) due to natural space environments. Possible research areas may include, but are not limited to:

- The time-dependent interaction of x-rays (with a range of effective blackbody temperatures from 100 to 1000 eV) with both metallic and insulating materials typical of solar arrays that drive the formation warm dense surface plasmas
- Time dependent warm dense surface plasma evolution and conductivity
- The nature of electrical conduction properties of the two solid conductors bridged by surface plasma generated in the aforementioned range for discharges driven by the voltages and currents typically generated by a solar array
- Thermal and electrical transport between cold metals and warm dense surface plasmas
- Changes in x-ray absorption during material blow-off and plasma generation
- Macroscopic property of effective conductivity across an insulating surface and the transition to a sustained arc

Experimental data may be available as Government-Furnished Information during the period of performance of the award for model validation.

Basic Research-Thrust Area 3-Topic G6: Modeling Infectious Disease Kinetics and the Host Immune Response

Award Amounts for this topic are anticipated to be between $150,000 and $350,000 per year (total dollar value = direct and indirect costs). Larger value efforts (i.e., $350, 000 per year) that are university led, include multiple PIs (at either a single or at multiple organizations), and provide training opportunities are encouraged. In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: DTRA Reachback provides continuous support and assistance to combatant commands and other customers for all WMD-related matters and natural disasters that involve the release of

CBRN materials.[1] DTRA Reachback is called upon to predict the impact of countermeasures for infectious diseases that could impact military operations or in cases where the military is called upon to assist in humanitarian responses. Additionally, DTRA Reachback is asked to provide guidance for a variety of emerging infectious diseases as well as category A bioagents. In order to provide guidance or answer questions for these heterogeneous populations, it is necessary to consider the impact of differing host factors (e.g. age, gender, genetic, malnutrition) on disease pathogenesis and the host immune response. Models that incorporate the impact of differing host factors can aid DTRA Reachback in predicting the severity of consequences for these heterogeneous populations with and without appropriate medical countermeasures. From the cellular to the tissue level, models have been developed to simulate pathogen infection kinetics and the host immune response.[1-5] Examples include models of viral infection kinetics and sepsis. Some models have begun to incorporate therapeutic treatments, which open the possibility to predicting the performance of different therapeutic dosing regimens,[6] and some researchers have begun modeling the role of host factors such as age on pathogen infection dynamics.[7] Framing such models appropriately poses many challenges, including those associated with determining the appropriate level of abstraction (e.g., whether or not to incorporate specific granulocytes, monocytes, lymphocytes and cytokine/chemokine networks). Quantitatively validating models with experimental data is likewise a significant challenge, as is the computational tractability of modeled systems as they increase in complexity and size. However, before conducting additional targeted experiments, it is prudent to integrate the use of existing *in vitro* and *in vivo* data of disease infection kinetics, host immune response including both cellular (T cell) and humoral (antibodies) arms, and therapeutic treatments.

Impact: This work focuses on modeling pathogen-host interactions. This will provide deeper insights regarding the establishment of infections and help predict the severity of consequences both with and without appropriate medical treatment. Research conducted herein will enable DTRA Reachback to predict the performance of differing therapeutic dosing regimens for heterogeneous populations.

Objective: The overarching research goal is to gain further understanding of infectious disease kinetics and host immune response dynamics by modeling the emergent system behavior (e.g. viral load, immunoglobulin levels, cellular lysis, etc.). Synthesis of existent data is desirable in order to identify critical gaps in knowledge and provide an analytical framework to guide future research. Proposals should utilize, to the extent possible, data generated by previous studies. Proposals that include experimental testing should provide clear rationale for doing so. In particular, approaches that establish validity using a single model system that lends itself to comparisons with other emerging pathogens or Category A agents containing similar host-pathogen dynamics are of interest. Successful programs under this topic should address a majority of the following concerns:

- Develop approaches to incorporate and predict the impact of differing host factors on disease pathogenesis and the host immune response
- Develop approaches to incorporate and predict the impact of differing therapeutic dosing regimens on disease pathogenesis
- Incorporate disparate data sources as well as develop methods to analyze datasets with missing or incomplete data
- Address potential computational tractability issues and, if appropriate, develop methods to overcome these issues
- Verify if parameters in their chosen model or simulation are identifiable[4]

- Delineate and justify assumptions, including those associated with hypothetical cause-and-effect relationships
- Provide rationale for selection of data types (e.g. choice of cell type), choice of system (e.g. human, rat, etc.), selection of therapeutic (e.g. antibiotic), and selection of computational approaches
- Incorporate sensitivity analysis and risk mitigation plans, especially for cases where small changes to assumptions may result in large changes to end-state predictions
- Explain methods that will be used or developed to quantify uncertainties

A multidisciplinary team with strong backgrounds in medical, immunological, and computational sciences is preferred.

References:

1. http://www.dtra.mil/Portals/61/Documents/Shield_spring_2011_12mb.pdf
2. Shi, Zhen Z., Chih-Hang Wu, and David Ben-Arieh. "Agent-based model: a surging tool to simulate infectious diseases in the immune system." *Open Journal of Modelling and Simulation* 2014 (2014).
3. Boianelli, Alessandro, et al. "Modeling influenza virus infection: A roadmap for influenza research." *Viruses* 7.10 (2015): 5274-5304
4. Nguyen, Van Kinh, et al. "Ebola virus infection modeling and identifiability problems." *Frontiers in microbiology* 6 (2015): 257.
5. Pollmächer, Johannes, and Marc Thilo Figge. "Deciphering chemokine properties by a hybrid agent-based model of Aspergillus fumigatus infection in human alveoli." Frontiers in microbiology 6 (2014): 503-503.
6. Schirm, Sibylle, et al. "A biomathematical model of pneumococcal lung infection and antibiotic treatment in mice." *PloS one* 11.5 (2016): e0156047.
7. Uvarovskii, Ted M. Ross, et al. "Effects of Aging on Influenza Virus." J. Virol 88.8 (2014): 4123.

Basic Research-Thrust Area 3-Topic G7: Radiation Effects in 3D and Vertically Integrated Microelectronics

Award Amounts for this topic are anticipated to be up to $1,000,000 per year (total dollar value = direct and indirect costs). All efforts must be multidisciplinary. Preference will be given to multi-institution proposals; however, multiple PIs from a single organization are also eligible to apply. Further preference will be given to teams that have a university as the lead organization, maintain significant amounts of research at one or more universities, and include multiple opportunities for training. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Highly integrated micro/nanoelectronic components in satellites, robots, and unmanned vehicles may be required to operate reliably and predictably in natural and manmade high radiation environments. As the electronics, circuits, and sensors become integrated in three dimensions on the same chip or in the same package, understanding, modeling, predicting, and testing the effects of radiation becomes increasing challenging and complicated.

As micro/nanoelectronic device scaling becomes more technologically challenging and less cost effective, manufacturers are increasingly turning to vertical integration to increase device density, improve efficiency, and add functionality. This three dimensional (3D) integration also adds complexity and cost to the design and fabrication process that could limit adoption. The degree of vertical integration possible is currently limited by the fabrication process (e.g. temperature limits, yield), by chip limits (heat removal, IO), and by the cost-to-benefit ratio. The ideal level of 3D integration is currently unknown and application specific, but there is increasing interest in and availability of vertically integrated devices for space and DoD applications.

There are multiple approaches to achieving 3D integration. Some approaches look to combine different device types, for example MEMS devices using the BEOL (back end of the line) process have been stacked on conventionally fabricated CMOS circuits. Some approaches create multiple layers of the same devices, for example 3D NAND Flash is already commercially available with 32 device layers and V-NAND Flash is available with 48 layers. Other efforts are underway to stack photonic devices or non-silicon devices with silicon CMOS.

A few initial studies have been done on the effects of radiation on stacked devices. One of the first studies by Gouker *et al.* looked at three layers of fully depleted 150nm SOI SRAM fabricated by oxide to oxide wafer bonding. They showed that there were no tier-to-tier effects and radiation effects were comparable between 2D and 3D SRAM. In subsequent studies Re *et al.* showed no additional TID effects in wafer bonded 130 nm bulk CMOS layers due to stacking. Single event effects (SEE) in two 90 nm COTS SRAM stacked dice separated by ~250µm were investigated by Gupta *et al.* They found a negligible increase in predicted proton SEE rates versus a single layer device. While these initial studies are promising for 3D ICs operating in high radiation environments, there are a number of unanswered questions that require further investigation.

Impact: Multi-layer stacked and 3D integrated chips have significant potential benefits for space and DoD applications, including increased power efficiency, increased device density, and added chip level functionality. However, the effect of stacking and integrating multiple technologies and materials on their radiation response is largely unknown.

Objective: This topic seeks, through experimentation and modeling, to develop a fundamental knowledge of the effects of radiation on multiply stacked and 3D integrated micro/nanoelectronic device and circuits. This topic is interested in both innovative and efficient ways to model and test radiation effects in 3D integrated devices as well as the results (underlying physics) of radiation testing and modeling. This topic is NOT interested in developing 3D IC technology. Of particular interest:

- Innovative radiation testing approaches to overcome the limitations of conventional testing facilities to effectively penetrate multiple layers
- Innovative radiation effects modeling approaches to address the challenges of efficiently modeling across multiple layers, both radiation/charge transport and circuit level
- Effect of integrating non-silicon materials and layers on radiation response

- Effect of integrating MEMS, photonic, or sensor devices and layers on radiation response
- Effect of device and layer scaling on radiation response
- Radiation effects in nanowire and gate all around (GAA) devices
- Impact of 3D transmission lines and through silicon vias on radiation response
- Probability and consequences of SEEs across multiple layers
    - Does RHBD need to be three dimensional?
- Impact of radiation strike angle

References:

1. P. M. Gouker *et al*., "Radiation Effects in 3D Integrated SOI SRAM Circuits," in *IEEE Transactions on Nuclear Science*, vol. 58, no. 6, pp. 2845-2854, Dec. 2011.
2. V. Re, L. Gaioni, A. Manazza, M. Manghisoni, L. Ratti and G. Traversi, "Radiation Tolerance of Devices and Circuits in a 3D Technology Based on the Vertical Integration of Two 130-nm CMOS Layers," in *IEEE Transactions on Nuclear Science*, vol. 60, no. 6, pp. 4526-4532, Dec. 2013.
3. V. Gupta *et al*., "SEE on Different Layers of Stacked-SRAMs," in *IEEE Transactions on Nuclear Science*, vol. 62, no. 6, pp. 2673-2678, Dec. 2015.

Basic Research-Thrust Area 4-Topic G8: Dynamic Characterization of Shock Induced Fragmentation and Reactions Involving Reactive Materials upon Impact

Award Amounts for this topic are anticipated to be between $150,000 and $250,000 per year (total dollar value = direct and indirect costs). Larger value efforts (i.e., $250, 000 per year) that are university led, include multiple PIs (at either a single or at multiple organizations), and provide training opportunities are encouraged. In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Reactive materials are solids such as metals and metal oxides that are capable of releasing large amounts of thermodynamic energy very rapidly. The individual constituents are mixed together in solid form and compacted into structures. Impact induced reactions of reactive fragments are caused by high velocity (~1-2 km/s) impact of composite materials of metal components on solid walls. These composite metal pieces generally range in size from millimeters to a few centimeters. Many aspects of the impact process between the composite metal pieces and solid walls, and the constituent spatiotemporal and thermochemical processes are not well characterized, along with the resulting fragmentation, rebound velocities and direction of the resulting fragments, their sizes, their temperature, their ignition, and combustion in air.

As another example, shock induced fragmentation of weapon case metals is generally accepted to

proceed through crack nucleation, growth, coalescence, and culminating in fragmentation; however, limited dimensionality of data collection and *post mortem* sample collection and analysis further limit the understanding of this fundamental process. Limitations in detection capabilities still present a significant hurdle to providing a complete mapping of the spatiotemporal evolution of these processes. Methods that allow observation of the dynamics of these fundamental constituent processes involving reactive fragments are highly desired.

Experimental facilities/tools now couple high intensity and high flux x-ray capabilities with impact drivers (e.g. lasers, gas guns, etc.), so opportunities now exist for directly probing material fracture mechanisms and particle dispersal under extreme loading/unloading conditions. In addition to fragmentation, enhancing the capability to measure processes including the dynamics of metal particle dispersal as well as diagnosing temperature and reaction mechanisms of metals upon impact is desired. Intensity and phase dependent imaging techniques at both x-ray and optical wavelengths may offer the ability to fully characterize some of these processes with a high degree of spatiotemporal resolution. Additionally, time resolved x-ray diffraction (XRD) at high repetition rates would allow for investigating the thermodynamic pathways of metal composite material reactions of interest.

Impact: Currently, hydrodynamic / multiphysics codes far exceed the experimental capabilities to examine the overall complex nature of fragmentation and breakup evolution to particles, high velocity particle transit and finally impact induced reaction involving reactive materials. Being able to characterize the dynamic breakup and reactions of reactive materials upon impact may lead to better understanding of how to utilize casing materials to react with and control agents and agent simulants.

Objective: Overall, the intent is to develop advanced characterization methodologies to measure and visualize the development of fragmentation, particle dispersal, and impact induced reactions of reactive materials. The primary objective of interest is to develop a comprehensive methodology to examine a dense reacting particle flow upon secondary fragmentation of a reactive material hitting an anvil, thereby allowing for characterizing ignition and combustion of metal/metal alloy systems. The secondary objective is to develop methods to characterize the initial fracture behavior (e.g. case breakup) and relate it back to fundamental fracture theory and modeling capabilities. Possible research areas may include, but are not limited to:

- Fully characterize size, size distribution, dispersal and mass of fast moving particles traveling at high velocities (~1-2 km/s) before impact and the resulting fragments after impact
- Characterize conditions for driving ignition and burn of fragments
- Use techniques such as time resolved XRD to characterize ignition and combustion reactions of metals/metal alloys upon impact
- Evaluate *in situ* fragment temperature upon high velocity impact via material or photon based techniques, allowing for measuring reaction thermodynamic pathways
- Utilize intensity and phase dependent techniques (both x-ray and optical) in multiple dimensions to characterize the evolution of processes that include fragmentation and particle dispersal
- Utilize advanced imaging techniques (e.g. plenoptic techniques) to evaluate material failure and transit of particles (including particle velocity vectors) of different sizes and distributions across a 2D plane or 3D volume with high spatiotemporal resolution

References:

1. "Material Development for Enhanced X-ray Detection of Dynamic Material Events under High Loading Rates", SBIR Topic: DTRA-T152-002

Basic Research-Thrust Area 5-Topic G10: Noble Gas Biodetection

Award Amounts for this topic are anticipated to be between $150,000 and $350,000 per year (total dollar value = direct and indirect costs). Larger value efforts (i.e., $350, 000 per year) that are university led, include multiple PIs (at either a single or at multiple organizations), and provide training opportunities are encouraged. In all cases, the proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of three (3) years with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. White papers and proposals that outline scope and effort for different base period and option combinations may also be considered; however, note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Many nation states conduct nuclear activities for legitimate peaceful purposes as well as for acknowledged defense programs within the international norms established by current non-proliferation and arms control treaties or agreements. However, discriminating between legitimate activities and activities prohibited by international agreements, or nefarious nuclear activities conducted by non-state actors, poses significant challenges to current monitoring and analysis methods. Extant nuclear detection technologies often require sample collection near a suspected activity, and transport to an off-site laboratory for analysis, resulting in substantial time-to-answer delays. Other methods rely upon unwieldy sampling architectures with high power requirements that limit the number and location of such detection systems. In the latter case, reliable detection of specific "smoking gun" signatures is further hampered by uncertainties in establishing background levels because of contributions from other processes (e.g., medical isotope production).[1] Collection and detection motifs that would allow greater proximity to suspect activities in order to improve the signal-to-noise ratio and provide near real-time information are desirable to serve a cueing function that can direct more granular collections.

Radioisotopes of noble gases, like xenon, argon, and krypton, are produced in relatively high abundances during nuclear fission and may also be produced by activation of surrounding materials in both nuclear power plants and nuclear explosions. The elevation of noble gas isotope concentration above regional background (e.g., natural xenon atmospheric concentration is estimated to range from about 50 - 100 ppb depending upon the source of the information)[2] provides strong indication of nuclear activity. Therefore, the collection and measurement of these gases may assist in detecting and locating activities associated with the production of materials for nuclear weapons or weapons testing. These elemental gases are chemically inert yet, paradoxically, noble gases display a remarkable spectrum of biological properties, including a number of health-benefiting qualities which make them clinically relevant.[3] Noble gas atom size, and both chemical and physical properties make them available to a variety of biochemical and biophysical reactions. For example, xenon is regularly used in biochemical and structural studies of proteins because of its known affinity for the hydrophobic cavities in macromolecular interiors. X-ray crystallography studies have characterized gas-binding

properties in different domains of model transmembrane proteins to better understand the means by which inert gases produce pharmacological action.[4,5,6] Xenon also has a low blood-gas partition coefficient that affords rapid induction and emergence times which make it a nearly ideal anesthetic agent.[7] Likewise, xenon has analgesic and neuroprotective properties.[2,3,8] It acts as an antagonist to the excitatory N-methyl-D-aspartate receptor, although contributing mechanisms and pathways have not been fully elucidated.[2,9,10] Argon and xenon have been shown to impact inflammation[11] and apoptosis signal transduction pathways induced by the broad-spectrum tyrosine kinase inhibitor staurosporine.[12] Such properties also have been investigated for krypton and argon, albeit to a lesser extent. Despite the extensive prospects for clinical applications of noble gases, fundamental biochemical studies which would provide the basis for broader use are lacking.

The present topic seeks deeper understanding of the means by which biological systems interact with noble gases, with the aim of developing novel collection, separation, concentration and/or detection motifs that can report local elevations of noble gas.

Impact: The fundamental knowledge generated as a result of this research will be broadly applicable to core DTRA capability requirements for detecting, locating, identifying, characterizing and assessing foreign nuclear materials production and weaponization in support of C-WMD operations. In addition, the research could further understanding of the direct and indirect effects of human exposure to certain noble gases, and thus will address Force Protection requirements for conducting operations in contaminated environments. The described work also will contribute to better understanding of the basis for clinically important effects mediated by noble gases and potential applications to mitigate or reverse impacts from traumatic injuries to warfighters. Research likewise will support development of better noble gas recapture technologies. Finally, the development of detection technologies to address a number of diverse mission needs is of paramount interest to the DoD and is critical to developing disruptive technologies that will enable game-changing C-WMD capabilities.

Objective: This topic seeks research to investigate interactions with, and reactions to, xenon by biological systems. Different lines of research could contribute to the overall aims by: (1) identifying macromolecular structures that are uniquely suited to bind xenon and are compatible with emplacement on or in standard detection architectures, or (2) characterizing chemical and physical properties of cellular compartments that could be replicated for development of novel collection and/or detection motifs. Topic focus is on discrete structures and compartments affecting the collection and concentration of xenon rather than on whole-cell or -organism systems. Although such systems may be used as the basis for establishing basic principles on likely modes of interaction, efforts specifically concerned with modifying or engineering whole-cell or –organism systems will not be considered. Possible research areas may include, but are not limited to:

- Experimentally characterize the gas-binding properties of **macromolecules** (e.g., proteins) known to interact with xenon and identify specific domains which demonstrate particular proficiency. Establish the likely basis for such interactions as it relates to specific structures (e.g., side chain residues) within the respective domains. Develop actual or propose hypothetical macromolecules that leverage properties of domains with high binding proficiency, and promote higher binding efficiency beyond the capacity that was experimentally observed in order to increase local concentrations and retention times.
- Identify and characterize **cellular compartments** in which xenon is preferentially sequestered. Establish contributing chemical and/or physical processes and determine retention times. Develop [biotic-abiotic] hybrid or synthetic collection architectures based upon experimental observations

of biological systems as noted above and supported by molecular modeling and simulation where practical, with the specific goal of increasing local concentrations and retention times.

Collaborative efforts between life scientists and nuclear or chemical engineers working in the nuclear industry are particularly encouraged in order to establish relevance of exposure levels to anticipated "real-world" scenarios.

References:

1. Bowyer TW. 2002. Detection and analysis of xenon isotopes for the comprehensive nuclear-test-ban treaty international monitoring system. *J Environmental Radioactivity* 59:139-151**.**
2. Jordan BD, Wright EL. 2010. Xenon as an anesthetic agent. *AANA 78:387-392.*
3. Sanders RD, Ma D, Maze M. 2005. Xenon: elemental anaethesia in clinical practice. *British Medical Bulletin* 71:115-135.
4. Tanwar AS et al. 2013. Importance of hydrophobic cavities in allosteric regulation of formylgycinamide synthetase: insight from xenon trapping and statistical coupling analysis. *PLoS One* 8:e77781.
5. Colloc'h N, Marrasio G, Prangé T. 2011. Protein-noble gas interactions investigated by crystallography on three enzymes – implication on anesthesia and neuroprotection mechanisms. *Current Trends in X-Ray Crystallography* ed. Chandrasekaran A, ISBN: 978-953-307-954-3.
6. Sauguet L et al. 2016. Structural basis for xenon inhibition in a cationic pentameric ligand-gated ion channel. *PLoS One* DOI: 10.137/journal.pone.0149795.
7. Lynch C III, Baum J, Tenbrinck R. 2000. Xenon anesthesia. *Anesthesiology* 92:865-70.
8. Winkler DA et al. 2016. The diverse biological properties of chemically inert noble gases. *Pharmacol Thera* 160:44-64.
9. Weinrich M, Worcester DL. 2013. Xenon and other volatile anesthetics change domain structure in model lipid raft membranes. *J Phys Chem B* 117:16141-16147.
10. Gruss M et al. 2004. Two-pore domain K^+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Mol Pharmacol* 65:443-452.
11. Breur T et al. 2015. Xenon triggers pro-inflammatory effects and suppresses the anti-inflammatory response compared to sevoflurane in patients undergoing cardiac surgery. *Magn Reson Med* DOI: 10.1186/s13054-015-1082-7.
12. Spaggiari S et al. 2013. Antiapoptotic activity of argon and xenon. *Cell Cycle* 12:2636-2642.

Basic Research-Thrust Area 7-Topic G11: Critical Requirements for Effective Single-Dose Vaccines

Award Amounts for this topic are anticipated to be between $750,000 and $1,000,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $1,000,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of one (1) year with up to four (4)

additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: The current immunization schedule for many childhood and adult vaccines in the U.S. consists of multiple doses, with time between priming and boosting ranging from one to several months, or even years. For military operations, however, an ideal vaccine is one that can provide 1+ year of protection after a single dose. While live attenuated vaccines are typically effective as single-dose vaccines due to their ability to replicate, non-replicating vaccines such as subunit, inactivated, or nucleic acid vaccines require one or more boosts. Controlled release of non-replicating vaccines has been identified as a potential single-dose prime-boost technology. An example is an injectable controlled-release microsphere formulation containing vaccine antigen that can be released as a pulse one to six months after injection, and with continuous release of antigen by particulate platforms.[1-3] However, further development of these encapsulation technologies (pulsed and continuous) and translation of their feasibility in animal models and human trials have been hindered for a number of reasons, including antigen thermostability at body temperature over time, encapsulation material and size, antigen loading and dose control, and full characterization of the immune response.

Impact: Safe and protective vaccines that can be administered in one dose would be conducive to military operational deployment. Understanding what is required for an effective single-dose vaccine will support the development of future single-dose vaccine candidates that will be compatible with military operations.

Objective: The goal of this topic is to identify optimal requirements for effective, non-replicating single-dose vaccines by examining the knowledge gaps in controlled-release antigen delivery and ways to enhance timing and duration of antigen exposure. Specifically, research to understand and identify the critical requirements to make single-dose, non-replicating vaccines effective using a viral biowarfare (BW) pathogen, or a non-BW pathogen that has similarities to a viral BW agent as a model is of interest. The pathogen of choice should have the necessary tools (i.e. established animal model, non-replicating vaccine(s) candidate, live attenuated vaccine(s) candidate) available to make sound comparisons between single-dose, multi-dose or live-attenuated vaccine effectiveness, such as Yellow Fever virus. Possible research areas may include, but are not limited to:

- Characterization of the immune response to pulsatile versus continuous antigen release
- The effect of antigen release rate and timing on the magnitude and type of immune response elicited
- Understanding the requirements for enhanced onset to immunity
- Novel methods to control the timing and duration of antigen exposure. This can include, but is not limited to: novel materials and encapsulation techniques, techniques to enhance antigen stability over time at body temperature, and other single-dose technologies that have not established a proof-of-concept

Proposals that detail development and advancement of a vaccine candidate will not be considered. Any proposed in vivo animal studies should be conducted in small animal models, not non-human primates. Moreover, proposed animal studies should use both male and female animals, and include any statistical gender differences. In addition, applicants who are selected for funding under this Topic will be encouraged to share data with other grantees funded under this Topic, as well as those funded under TA7-BR-Topic G14: Generating Cross-Reactive Antibodies Following Single-Dose

Vaccination (Thrust Area 7), detailed below.

References:

1. Walters, Krastev, et al. Journal of Pharmacy and Pharmacology, Vol 67, 400-408, 2014.
2. Alonso, et al. Vaccine, 12: 299-306, 1994.
3. Sanchez, et al. J Pharm Sci, 85(6): 547-52, 1996.

Basic Research-Thrust Area 7-Topic G12: Discovery of Novel Methods to Ameliorate the Effects of Nerve Agent Exposure

Award Amounts for this topic are anticipated to be $350,000 per year (total dollar value = direct and indirect costs); awards are anticipated to be multidisciplinary. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of two (2) years with up to one (1) additional year as a possible option. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Organophosphorus (OP) agents act by inhibition of acetylcholinesterase (AChE) resulting in reduced hydrolysis of the neurotransmitter, acetylcholine, causing overstimulation of the acetylcholine receptor. Physiological responses comprise hypotension, rhinorrhea, wheezing, and diarrhea among other symptoms, with severe exposures leading to death. OP intoxication poses a significant threat to military forces and agricultural workers. In the military, current medical countermeasures constitute: 1) pralidoxime (2-PAM), a charged oxime reactivator of OP-inhibited AChE, 2) atropine, an antimuscarinic agent that blocks the acetylcholine receptor, and 3) diazepam, to treat seizures resulting from excess acetylcholine in the central nervous system by enhancing the inhibitory effects of gamma-aminobutyric acid in the brain. A majority of research within this arena target reactivation of OP-inhibited AChE using oxime-based compounds. Few groups have explored AChE reactivators containing different functional moieties,[1,2] or pursued targets other than AChE and the acetylcholine receptor to treat OP intoxication. Novel approaches to treat OP agent intoxication are desired with focus on a wider spectrum of targets involved in the biological cascade resulting from exposure.

Impact: OP agents continue to be a threat to the Armed Forces and agricultural workers, against which there are no broad spectrum medical countermeasures. Addressing causal agents that lead to symptoms of OP exposure will provide more insight into the short-term and long-term effects resulting from OP intoxication.

Objective: This topic seeks proposals that identify new and innovative methods of treating nerve agent exposure. Core focus should be on elimination or inactivation of causal agents rather than treating the symptoms of OP exposure. Possible strategies may include, but are not limited to:

- Sequestration and/or hydrolysis of excess acetylcholine
- Induced temporary expression of AChE to moderate accumulation of acetylcholine
- Reactivation of AChE inhibited by a broad range of OP agents, through use of non-oxime based reactivators

As an example, the above aims may be achieved via discovery of novel small molecules, peptides, peptidomimetics, or proteins. Proposals detailing new methods of AChE reactivation will be considered if the strategy is novel and unpublished, with the proviso that oxime-based reactivators will not be considered. This topic is not interested in pursuit of acetylcholine receptor inhibitors, AChE inhibitors, new anticonvulsants or GABA receptor modulators.

References:

1. Bhattacharjee, *et al*. "Discovery of non-oxime reactivators using an *in silico* pharmacophore model of oxime reactivators of OP-inhibited acetylcholinesterase" *Eur. J. Med. Chem.* **2012,** *49,* 229-238.
2. Katz, *et al*. "Discovery of New Classes of Compounds that Reactivate Acetylcholinesterase Inhibited by Organophosphates" *ChemBioChem,* **2015,** *16,* 2205-2215.

Basic Research-Thrust Area 7-Topic G13: Environmental Factors and the Viable but Non-Culturable State of Francisella tularensis

Award Amounts for this topic are anticipated to be between $500,000 and $750,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $750,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of two (2) years with up to one (1) additional year as a possible option. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Category A agents *Francisella tularensis, Burkholderia psuedomallei* and *Yersinia pestis* enter into viable but non-culturable (VBNC) state (Sinclair et al., 2008). This state allows bacteria to persist in an environment with unfavorable conditions until they can resuscitate under more favorable conditions. It is unclear what specific environmental factors induce pathogenic bacteria *F. tularensis* to enter into the VBNC state. Other bacteria enter the VBNC state when exposed to certain temperatures, levels of salinity or acidic conditions. It can be projected that these factors also effect *F. tularensis*, but under what levels? A systematic approach of testing the various environmental factors known for inducing the VBNC state in other bacteria would help elucidate under what conditions *F. tularensis* may be persisting in the environment as VBNC bacteria. Additionally, the behavior of *F. tularensis* in the environment while it is in the VBNC state has yet to be explored (Oliver 2010; Li 2014). Bacteria behave differently under stressful conditions while they are entering the VBNC state. For instance, *B. psuedomallei* forms biofilms under nutrient-limited conditions and enters the VBNC state. Certain concentrations of iron and salt also trigger this behavior (Kamjumphol et al., 2015). The formation of biofilms is considered problematic since biofilms protect the bacteria from antibiotics and decontamination, promoting continued persistence in the environment (Oliver 2010). Additionally, bacteria in the VBNC state could have properties allowing it to transport to more favorable conditions, spreading the pathogenic bacteria to new areas, or the bacteria may adhere to various surfaces like clay particles.

Impact: Overall impact of this research includes providing possible targets for detection, understanding how *F. tularensis* could transport to other locations helping explain current disease

incident research, and inform on general persistence of the bacteria in the environment for future prediction models.

Objectives: There are four objectives to this topic:

1) Systematically determine what environmental factors induce *F. tularensis* to enter the VBNC state. Applicants should provide details on measuring the VBNC state and propose a systematic approach to test these factors, including testing their effects individually and combined.
2) Understand *F. tularensis* behavior in the environment while it is in the VBNC state, e.g., can the bacteria form biofilms, do the cells adhere to surfaces such as soil minerals or other organisms like amoebas?
3) Understand what conditions resuscitate *F. tularensis* so that it is viable, e.g., can the *F. tularensis* cell resuscitation from the VBNC state be reliably quantified?
4) Determine which genes, if any, are transcribed while *F. tularensis* is in the VBNC state allowing it to survive.

References:

1. Li, L., N. Mendis, H. Trigul, J. D. Oliver, and S. P. Faucher. The importance of the viable but non-culturable state in human bacterial pathogens. Frontiers in Microbiology. 5:72-91.
2. Kamjumphol, W., P. Chareonsudjai, S. Taweechaisupapong, and S. Chareonsudjai. 2015. Morphological alteration and survival of *Burkholderia pseudolmallei* in soil microcosms. The American Journal of Tropical Medicine and Hygiene. 93: 1058-1065.
3. Oliver, JD. 2010 Recent findings on the viable but nonculturable state in pathogenic bacteria. FEMS Microbiology Reviews. 34:415-425
4. Sinclair R, S. A. Boone, D. Greenberg, P. Keim, and C. P. Gerba. 2008. Persistence of category A select agents in the environment. Applied and Environmental Microbiology. 74: 555-563.

Basic Research-Thrust Area 7-Topic G14: Generating Cross-Reactive Antibodies Following Single-Dose Vaccination

Award Amounts for this topic are anticipated to be between $500,000 and $1,000,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $1,000,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of one (1) year with up to four (4) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: A single-dose vaccine that can protect against multiple bacterial or viral pathogenic strains is a desired, yet challenging goal. It's well established that antibody responses are typically required for protective vaccines, however immunization with a single antigen variant results in strain-specific antibodies, suggesting that vaccination with multiple antigen variants is required to generate

cross-reactive antibodies.[1] Affinity maturation (AM) is a key process that drives the fine specificity of a protective humoral response. Studies to understand how AM takes place in the presence of variants of the same antigen revealed that administration with a cocktail of antigen variants frustrated AM resulting in a low probability of cross-reactive antibody generation, whereas sequential administration of multiple antigen variants can generate cross-reactive antibodies that focus on conserved residues.[2] Controlled-release of antigen after a single dose has been shown to mimic multiple, sequential doses,[3] however how controlled-release of multiple antigen variants affect AM and the generation of cross-reactive antibodies remains elusive. Based on these phenomena and the need for broadly protective single-dose vaccines, this topic seeks to understand how to generate cross-reactive antibodies after a single vaccination and to determine how controlled-release of antigen, or other single-dose technology, can be used to generate a broadly protective humoral response.

Impact: Single-dose vaccines that can protect against multiple pathogenic strains would be conducive to military operational deployment. Understanding how to generate a broadly protective immune response after a single administration will support the development of future single-dose vaccine candidates that will be compatible with military operations.

Objective: This topic seeks research to understand how to generate cross-reactive antibodies after a single-dose vaccination and to determine how controlled-release of antigen, or other single-dose technologies, can be used to generate a broadly protective humoral response using antigens from a viral biowarfare (BW) pathogen, or a non-BW pathogen that has similarities to a viral BW agent. Possible research areas may include, but are not limited to:

- Understanding how controlled-release of multiple variants of the same antigen affect affinity maturation and the generation of cross-reactive antibodies
- Understanding how epitope valence, or concentration, of multiple antigen variants influences AM and the generation of cross-reactive antibodies after a single vaccination
- Identifying other innovative strategies to generate cross-reactive antibodies after a single vaccination

Proposals that detail development of a vaccine candidate will not be considered and any *in vivo* animal studies should be conducted in small animal models, not non-human primates. Moreover, any proposed animal studies should use both male and female animals, and include any statistical gender differences in humoral responses. In addition, applicants who are selected for funding under this topic will be encouraged to share data with other grantees funded under this topic, as well as those funded under TA7-BR-Topic G11: Critical Requirements for Effective Single-Dose Vaccines (Thrust Area 7), detailed above.

References:

1. Liao, *et al.* Nature, 496, 469-476, 2013.
2. Wang, Shenshen et al. Cell, Volume 160, Issue 4, 785-797, 2015.
3. Walters, Krastev et al. Journal of Pharmacy and Pharmacology, Volume 67, 400-408, 2014.

Basic Research-Thrust Area 7-Topic G15: Non-Invasive Cell-Free Nucleic Acid for Companion Diagnostics (NICNAC)

Award Amounts for this topic are anticipated to be between $500,000 and $1,000,000 per year (total

dollar value = direct and indirect costs). The larger value efforts (i.e., $1,000,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of two (2) years with up to one (1) additional year as a possible option. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Given that only a small percentage of the transcribed human genome is actually translated into protein, there has been a surge of interest in the role of the non-coding RNA transcriptome and its contribution to pathogenesis. While RNA sequencing (RNA-Seq) molecular genomic approaches have studied RNA differential expression in several body fluids, most of these studies have focused on analyses of miRNAs and mRNAs. The recent discovery of a significant number of other cell-free small non-coding RNA species suggests an additional pool of potential host biomarkers of exposure to infectious disease pathogens. Some examples of recent discoveries include:

- A significant number of extracellular circular RNAs (cirRNAs) have recently been identified; their biogenesis are formed by back-splicing events in higher eukaryotic cells and are extremely stable in clinical body fluids. However, little is known about how circRNAs are regulated, cleared or foster cell-to-cell communication.[1-3]
- Piwi-interacting RNAs (piRNAs) are small (26–31nt) non-coding cell-free RNA molecules expressed in animal cells that form RNA-protein complexes. Originally described in the germline, there are many piRNA genes in the human genome that are involved in the epigenetic silencing of transposable elements in addition to the transcriptional regulation of genes.[4]
- Some miRNAs are hypothesized to act as signaling molecules via binding to intracellular Toll-like receptors (TLRs); characteristic of immune cells involved in the innate immune system.[5]
- A recent study characterizing extracellular small non-coding RNA in human saliva identified approximately 400 circRNAs in cell-free saliva. The results also indicated that that piRNAs were surprisingly abundant in cerebrospinal fluid (CSF) when compared with other body fluid or intracellular samples.[6]
- "Liquid biopsy" targeting of extracellular sequence mutations as cancer genotyping biomarkers for several somatic mutations derived from malignant tumors.[7]
- Pathogen small RNAs colonizing strains have been discriminated in saliva from strains in patients with bloodstream infections, including patients with sepsis and septic shock using pathogens small RNAs.[8]
- Invasive blood collection, transport, preservation and sample processing, nucleic acid extraction, and assessment of sample quality are major hindrances on time, cost, and applicability of standard molecular diagnostics of early warning biomarkers diagnosis of exposure/disease. Thus, alternative sample matrix (e.g. saliva) as part of a "liquid biopsy" could provide a more subject- and user-friendly system.

Objectives: The goal of this topic is to provide a fundamental scientific understanding of cell-free non-coding RNA (cfNCR) species. Responsive proposals should address the following aims:

1. Discovery, survey and catalogue of presence, state (free versus bound), and range determination of analytical attributes of novel cfNCR species as potential biomarkers of infectious disease and therapeutic targets for companion diagnostics in non-traditional clinical matrices.
    a. Development and enhancement of catalogue of cfNCR species in non-invasively sampled body fluid (i.e. saliva) and investigation into their potential as biomarkers.
    b. Characterization of the normal range/variability of cfNCR species.
    c. Determine most up- or down-regulated RNAs in exposed saliva and corresponding serum (properly preserved bio-banked samples are acceptable).
    d. Perform preliminary determination of the diagnostic/prognostic windows of the biomarkers in non-traditional clinical matrices.
2. Method development and determination by enriched sensitivity, un-biased, broad spectrum analytical approaches. In order to detect down-regulated cell-free RNAs, a high analytical sensitivity (limit of detection) will be required.
3. Determination of a panel of candidate cfNCR circulating and exosomal nucleic acids of both:
    a. Host response to infectious disease (e.g. respiratory tract, GI tract, etc.) and;
    b. RNAs secreted/shed directly from causative infectious agent or surrogate (at least one virus and one bacteria).
4. Identify role/mechanism of ≥ 4 most dysregulated species.
    a. Determination of the mechanisms of host, as well as pathogen-shed, extracellular RNA, and protein/peptide biomarkers generation, secretion, and transport.

References:

1. Salzman J, Chen RE, Olsen MN, Wang PL, Brown PO (2013) Cell-Type Specific Features of Circular RNA Expression. PLoS Genet.
2. Salzman J, (2012) Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types. PLoS ONE.
3. Lasda E, Parker R (2016) Circular RNAs Co-Precipitate with Extracellular Vesicles: A Possible Mechanism for circRNA Clearance. PLoS ONE 11(2): e0148407. doi:10.1371/journal.pone.0148407.
4. Biology of PIWI-interacting RNAs: new insights into biogenesis and function inside and outside of germlines (2012) Genes & Development.
5. Fabbri, M et al. (2012) MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. PNAS.
6. JH Bahn et al. (2015) The Landscape of MicroRNA, Piwi-Interacting RNA, and Circular RNA in Human Saliva. Clin Chem.
7. F Wei, et al. 2014. Detecting EGFR Mutations in Saliva. Am J Respir Crit Care Med.
8. V Bordeau et al. 2016. Staphylococcus aureus Regulatory RNAs as Potential Biomarkers for Bloodstream Infections. Emerg Infect Dis.

Basic Research-Thrust Area 7-Topic G16: Novel Technologies to Target Encephalitic Alphavirus Infections

Award Amounts for this topic are anticipated to be between $500,000 and $750,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $750,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of one (1) year with up to four (4) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: The new-world alphaviruses, including Venezuelan equine encephalitis virus (VEEV), eastern equine encephalitis virus (EEEV), and western equine encephalitis virus (WEEV), cause disease in humans and pose a grave threat to the warfighter as an engineered biological weapon. The susceptibility of humans to aerosol infection evident in reported cases of laboratory infections by VEEV, EEEV, and WEEV raises the level of concern. No licensed vaccines or specific therapies exist to prevent or treat human infections for VEEV, EEEV, or WEEV due in part to the challenges of addressing multiple viral serotypes, the rapid transmission of the viruses to the brain, and associated difficulty of getting a therapeutic across the blood brain barrier (BBB). In an ever-changing threat environment, the "one bug" one drug, pathogen-targeted approach is prohibitively slow and expensive; the warfighter requires a broad spectrum antiviral. Therefore, the goal of this topic is to discover novel, medically relevant technologies such: a) Host protein targets that can lead to a broad spectrum antiviral; and b) Proteins capable of targeting viral dsRNA and treating the encephalitic alphaviruses. All technologies need to be capable of crossing the BBB.

Impact: Identification and development of broad-spectrum antiviral therapeutics derived from host target proteins and proteins targeting viral dsRNA will lead to safe therapeutics that treat the encephalitic alphaviruses. These therapeutics will provide the warfighter with a key medical countermeasure to combat emerging biological threats as there are no current licensed therapeutics for the treatment of alphavirus infection.

Objective: The goal of this topic is to: a) identify host cell proteins that can serve as targets for therapeutics in treating alphavirus encephalitic virus infection; and b) identify and understand proteins capable of targeting long-stranded viral dsRNA to treat alphavirus encephalitic virus infection. The goal of this topic is identification and understanding of the interactions between host cell proteins and alphavirus proteins necessary for replication. Development of therapeutics focused on targeting viral proteins has not produced promising therapeutic candidates in part due to structural complexity and diversity. Focusing on host proteins/pathways required for EEEV, VEEV, and WEEV replication provide an opportunity to develop antivirals capable of treating all encephalitic alphaviruses. Additionally, an added benefit of focusing on host cell proteins should be reduced viral resistance since the proteins being targeted are from the host and not the virus. Previous studies have shown that both DNA and RNA viruses can be inhibited using host protein targets. Applicants should seek to identify and understand host proteins required for replication and interactions with EEV, VEEV, and WEEV viral proteins. Proof of concept will include in vivo testing.

Only proposals addressing the encephalitic alphaviruses will be considered. Monoclonal antibody proposals will not be entertained.

Basic Research-Thrust Area 7-Topic G17: Organophosphate Poisoning—Novel Detoxifying Mechanisms in Animal Systems

Award Amounts for this topic are anticipated to be $600,000 total (total dollar value = direct and indirect costs). Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of one (1) year with a 6-month possible option. The base period of the effort should be focused on exploration and identification of OP resistant animal species and the option should be focused on determination of the mechanism of OP resistance and proof of concept experiments. Note that white papers and proposals that outline scope and effort that exceed a total of 18 months will not be considered.

Background: Animal species, including many invertebrates, have a robust innate protection mechanism against organophosphate (OP) poisoning, while others have the ability to develop resistance towards OP toxicosis within their respective environment. For example, this phenomenon can be observed in the necessity of repeated OP pesticide application in agriculture.[1,2] Carboxylesterase degradation of the OPs appears to be the most common mechanism of this resistance. The Australian Blowfly, for instance, contains within its hemolymph a type of carboxylesterase which is not only capable of efficiently detoxifying the most common OP containing pesticides, but is also modified by the insect to detoxify newly developed OP pesticides as well.[3] However, additional physiological processes of OP resistance or detoxification might exist in insects or other animal species waiting to be discovered.

The chemical structures and general modes of action of OP pesticides and organophosphate nerve agents (OPNAs) are related. Therefore, if additional novel OP detoxifying mechanisms exist they could eventually be exploited to develop medical countermeasures that are effective against OPNA compounds.

Medical countermeasure development against chemical WMD is a major focus of the Chemical and Biological Defense Program. Thus, a systematic discovery study designed to identify unique endogenous systems that may protect against OPs and possibly OPNAs apart from the carboxylesterase enzyme systems would not only be of general scientific interest but also of great utility. Current systems have severe limitations in therapeutic as well as prophylactic applications. Carboxylesterase enzymatic systems such as PON1, OPAA, and OPH suffer from limitations such as low LD_{50}, inadequate bioavailability (no access to the central nervous system), lack of broad spectrum reactivity against multiple OPNAs, immunogenicity, and high cost of production. Therefore, new approaches are needed.

Impact: Discovery and identification of novel organophosphate protection mechanisms could provide alternative means for medical chemical countermeasure development to address current capability gaps.

Objective: The goal of this topic is discovery of novel mechanisms of OP detoxification leading to survivability. Proposals describing work on known carboxylesterases such as OPH, OPAA, etc., will not be considered. For the purpose of this topic, animal species will be limited to invertebrates that are known to be able to survive high levels of OP exposure. Consideration will be given to proposals that:

- Cogently define those experiments that will lead to a demonstration of proof of concept in the timeframe of the period of performance
    - Studies that make use of modern genetic technologies that will "silence" or significantly knock down the production of the known pathways would be favored
- Include discussion of methods for the identification of the specific pathway(s) or endogenous peptide, protein or natural product leading to survivability
- Indicate strategies for moving forward if the research is successful. For example, how the information discovered will be capitalized on and how it can lead to the development of a medical countermeasure

References:

1. Maxwell DM, Brecht KM, O'Neill BL. *The effect of carboxylesterase inhibition on interspecies differences in soman toxicity*. Toxicol Lett. 1987;39:35–42.
2. Ranson H, et al. *Evolution of supergene families associated with insecticide resistance*. Science. 2002;298(5591):179–181.
3. Jackson CJ, et al. Structure and function of an insect α-carboxylesterase (α*Esterase*7) associated with insecticide resistance. Proc Natl Acad Sci USA. 2013 Jun 18; 110(25): 10177–10182.
4. 4. Kikuchi, Y., Hayatsu, M., Hosokawa, T., Nagayama, A., Tago, K., & Fukatsu, T. (2012). Symbiont-mediated insecticide resistance. Proceedings of the National Academy of Sciences, 109(22), 8618-8622.

Basic Research-Thrust Area 7-Topic G18: Photonic Transducers for Chemical Threat Sensing

Award Amounts for this topic are anticipated to be between $350,000 and $750,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $750,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of one (1) year with up to two (2) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of three (3) years will not be considered.

Background: Spectroscopic sensing techniques offer promise for low-power, low-consumable chemical detection. Recent advances in materials design and fabrication have improved the feasibility of small, multiplexed photonic detection devices. Whispering gallery mode resonators can significantly amplify signals from highly dilute samples due to the recirculation of light via continuous total internal reflection, and these resonators have been demonstrated for chemical detection via absorption methods[1] or through shifts in the refractive index.[2] Expanding the selectivity and availability of these photonic chemical sensing approaches is desired, as detection of low levels of threat compounds in highly cluttered backgrounds remains a significant challenge.

Impact: It is anticipated that the new photonic transduction approaches enabled by this topic will enable more sensitive, selective, and low-cost sensing of chemical threat materials. The comparative

simplicity of a system based on these new approaches may also decrease the overall logistical burden when compared to current detection methods.

Objective: The goal of this topic is to develop and demonstrate the scientific underpinnings and design principles for miniaturized photonic transducers, in order to enable new approaches to chemical threat sensing.

Research areas of interest include:

- Understanding design features to ultimately improve selectivity, sensitivity, and/or affordability compared to current optical or photonic sensing approaches.. Initial analytes of interest are chemical warfare agent simulants/surrogates, precursors, breakdown products, and toxic industrial chemicals.
- Development of the fundamental understanding of the key phenomena and principles of photonic transducers to enable new approaches to chemical threat sensing, such as the effects of size, shape, and composition.

Where possible, relevant data from experiments and related publications should be included and explained. Submissions should include order-of-magnitude estimates of the predicted capability improvements for the proposed approach. Priority will be given to proposals that couple experimental observation with theoretical grounding. Proof-of-concept experimentation is expected; however, this is not an instrument development program and proposals in that vein will not be considered. Approaches aimed at specific applications not relevant to sensing of chemical threats (i.e., biological detection) will likewise not be considered.

References:

1. Todd H. Stievater, Marcel W. Pruesnner, Doweon Park, William S. Rabinovitch, R. Andrew McGill, Dmitry A. Kozak, Robert Furstenberg, Scott A. Holmstrom, and Jacob B. Khurgin, "Trace gas absorption spectroscopy using functionalized microring resonators," *Optics Letters* v. 39 (2014), p. 969.
2. Daniel C. Kim and Robert C. Dunn, "Integrating Whispering Gallery Mode Refractive Index Sensing with Capillary Electrophoresis Separations Using Phase Sensitive Detection*," Analytical Chemistry* v. 88 (2016), p. 1426

Basic Research-Thrust Area 7-Topic G19: Robust and Efficient Catalytic Systems for Degradation of Organophosphorus Nerve Agents

Award Amounts for this topic are anticipated to be between $400,000 and $600,000 per year (total dollar value = direct and indirect costs). The larger value efforts (i.e., $600,000 per year) should be multi-disciplinary. Further guidance on scope and cost may be provided in the debrief summary for full proposal invitations. The proposed award value should be clearly substantiated by the scope of the effort.

The preferred award structure for this topic is a base period of two (2) years with up to three (3) additional years as possible options. However, white papers and proposals that outline scope and effort for only the base period and do not propose options are also acceptable. Note that white papers and proposals that outline scope and effort that exceed a total of five (5) years will not be considered.

Background: Naturally occurring enzymes that are capable of catalytic degradation of OPNAs are

scarce and their use for countermeasure applications is limited due to their high cost, fragility, and inefficiency (especially towards more toxic OPNA isomers). Many organisms have evolved to develop enzymes for survival purposes, and in the process have attained high catalytic efficiencies that approach diffusion limits. However, OPNAs are a recent development and therefore the OPNA-degrading activities of naturally occurring enzymes are relatively low. Different approaches have been undertaken to address these shortcomings (e.g., directed evolution of natural OPNA enzymes and of unrelated enzyme scaffolds redesigned with new catalytic sites). Also, efforts have been undertaken to develop biomimetic abiotic catalysts. Although much progress has been made, the results are still inadequate to meet warfighter needs. Nevertheless, the knowledge provided by these undertakings (including designing catalytic enzymes for OPNA stereo-selective hydrolysis and robust catalytic organometallics, advances in parametric protein design, and the advent of high-throughput enabling methods for screening genomic libraries and for determining 3-D protein structures) have provided a unique opportunity to pursue computational design approaches for catalytic OPNA-degrading catalytic systems and develop deeper understanding for the underlying structure-activity and structure-stability relationships. These insights could enable better biomimetic abiotic or bio-abiotic hybrid catalytic systems for OPNA degradation.

Impact: The success of the research under this topic would enable rational design and production of efficient, rugged, and inexpensive catalytic bio and abiotic systems for OPNA degradation.

Objective: The goal of this topic is to develop and utilize an advanced fundamental mechanistic understanding of high-efficiency hydrolytic and hyper-stable OPNA-degrading abiotic catalysts or bio-abiotic hybrids. The research should be targeted so the results can inform design and construction of catalytic systems for OPNA hydrolysis that are highly efficient, thermostable, small, and functional even when exposed to mixed solvents or reaction byproducts.

Highest consideration will be given to proposals based on an iterative (spiral) approach to understand the underlying structure-activity and structure-stability relationships and can provide confirmation of the developed catalytic system's effectiveness on live agents. Proposals offering only theoretical approaches (e.g., modeling) or approaches to improve existing natural enzymes will not be entertained.

Possible research areas may include, but are not limited to:

- Studies of high efficacy mechanisms of catalytic constructs' interactions with targets (e.g., binding, transition state stabilization, product release)
- Studies of the mechanisms of high catalytic efficiency and hyperstability phenomena of rationally designed biomimetic constructs and beyond on abiotic catalysts, such as completely *de novo* designed small proteins, proteomimetic and organometallic catalysts
- Studies of synergistic combinations of bio and abiotic catalytic systems
- Predictive models with experimental validation for binding and catalysis using modern computational methods
- Design imparting high stability against time, heat, mixed solvents, and reaction byproducts