DEFENSE THREAT REDUCTION AGENCY
Government Call
HDTRA1-16-24-FRCWMD-Call
Amendment 4
January 2019

Research and Development Directorate (RD)
Chief Scientist and Innovation Department (RD-ST)

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

Original Posting Date: December 2016

TABLE OF CONTENTS

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 may be 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 address for each of the DTRA technical POCs for Thrust Areas 1-7 is provided in Section 9. Coordination of research ideas and efforts must be accomplished via these email addresses, except in cases where a topic specifically states that pre-coordination is not required. Pre-coordination must include 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 email address in Section 9. For an effort to be considered pre-coordinated, a reply email with the disposition will be sent to the applicant from the relevant email address in Section 9. Pre-coordination may not be accomplished with email addresses other than those

listed in Section 9. DTRA may not review white papers without prior coordination. Please note that attachments to e-mails may not be reviewed.

DTRA may remove, add, or update topics at any time without notice by publishing an amendment to this Call. Once a topic has closed or been removed via an amendment, white papers responsive to that topic will no longer be accepted for review. 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), DTRA Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/), 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 may be used to carry out a portion of the research and/or effort. DTRA will review and consider the proposed subawards for all applications 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; 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.

[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.

- 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 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.

The predominance of efforts, including all submissions to the thrust areas and some submissions to topics posted in Section 10, **must be** coordinated with the relevant technical point of contact (POC) for the appropriate thrust area prior to submission of a white paper; an e-mail for the DTRA technical POCs for Thrust Areas 1-7 are provided in Section 9. Coordination of research ideas and efforts must be accomplished via these email addresses, except in cases where a topic specifically states that pre-coordination is not required, 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 email address in Section 9 and a reply email from the relevant email address in Section 9 with the disposition to the applicant. Pre-coordination may not be accomplished with email addresses other than those listed in Section 9. DTRA may not review white papers without prior coordination. Please note that attachments to e-mails may not be reviewed.

Applicants should note that there is extremely limited funding available for the general thrust areas. White papers will only be accepted from the coordinated abstracts under very limited circumstances.

Topics may be posted in Section 10 that may not require pre-coordination of an abstract. Please review the topics carefully.

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

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 RESTRICTED or CLASSIFIED materials to the

Call or to the proposal submission website. All submissions must be completely UNRESTRICTED and UNCLASSIFIED; submissions must not contain For Official Use Only (FOUO) or Official Use Only (OUO) information or be marked as such. Unclassified, unrestricted 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. 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 are not pre-coordinated as required
- 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 the DTRA Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/) (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 Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/).

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 assume that 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 any dollar values detailed for average award amounts 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 the DTRA Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/) (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 Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/) (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 the DTRA Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/) (MS Word format). The SOW must include the following deliverables:

    - Recipient must comply with The Public Access Directive Type Memorandum, DTM-17-002 Public Access to the Results of DoD Intramural Basic Research Published in Peer Reviewed Scholarly Publications, January 10, 2017 (http://www.dtic.mil/whs/directives/corres/pdf/DTM-17-002.pdf).

    - 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 Basic and Fundamental Research Community Portal (https://www.dtrasubmission.net/portal/) and complete it in its entirety for **each** foreign institution participating in the project. Additional instructions for completing the PRAT may be found within the file. The 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 completely UNRESTRICTED and UNCLASSIFIED; submissions must not contain FOUO or OUO information or be marked as such.

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 Call 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; extensions for topic-based proposal submissions will be considered under extremely limited circumstances. Full proposals may be evaluated at any time after submission. 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".

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: Engility Corporation (Advisory & Assistance Services) and their subcontractors, Infinity Technology LLC, Quanterion Solutions Inc., Kforce Government Solutions Inc., KCK Inc., CACI,, , SBG Technology Solutions and their subcontractors, and Terremark Worldwide Inc. Each contract contains OCI provisions and/or includes contractual requirements for non-disclosure of proprietary contractor information or data/software marked with restrictive legends. The applicant, 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 may 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 may 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 Areas 1, 2, 3, 4, 5, and 6 have no specific topics at this time.

Thrust Area 7 has nine (9) topics —Topics I1-I9—detailed below. Submissions to the general thrust area description for this thrust area, in accordance with the requirements detailed in this CALL. are also welcome.

Great care must be taken to select the appropriate topic from the "Thrust Area" drop-down menu when setting up the Cover Sheet at www.dtrasubmission.net, as the thrust area selection dictates how each submission will be reviewed:

- If NOT submitting to one of the specific topic numbers detailed below, select the applicable **Thrust Area 1 through 7** from the Thrust Area drop-down menu on the Cover Sheet
- If you ARE submitting to one of the specific topic numbers detailed below, select the applicable **BR Thrust Area 7 I1 through I9** from the Thrust Area drop-down menu on the Cover Sheet

*****BASIC RESEARCH TOPICS I1-I9*****

In accordance with Section 5.1, the requirement for abstract pre-coordination is waived for Topics I1-I9; this topic does NOT require pre-coordination of an abstract prior to the submission of white papers. All other pre-coordination requirements remain in effect.

The white paper deadline for Topics I1-I9 is 4 March 2019. **WHITE PAPERS FOR THESE TOPICS MUST BE SUBMITTED BY 11:59 PM (MIDNIGHT) EST ON 4 March 2019.** White papers submitted to Topics I1-I9 may not be considered if they are received after this deadline.

Responses to Topics I1-I9 must address ONLY basic research (Budget Category 6.1). 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]

Topics I1-I9 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.

DTRA anticipates that the predominance of awards made under Topics I1-I9 will be grants. White papers and proposals submitted to Topics I1-I9 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, including all grants and/or contracts, are the responsibility of the award recipient; exceptions will not be made.

Thrust Area 7, Topic I1: In Search of the "lnc": Long Non-Coding Ribonucleic Acids (lncRNA) Role in Pathogenesis

Award Amounts for this topic are anticipated to be between $350,000 and $500,000 for year 1 and up to $1,000,000 per subsequent 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 two (2) years with one (1) additional year as 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. 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 three (3) years will not be considered.

Background: Infections caused by viral or bacterial pathogens are known to significantly up/down regulate various genes which can play a significant role in disease progression. Most of the transcriptomic studies currently sponsored by DTRA have focused on mRNA and their role in disease. Unfortunately, mRNAs represent a very small portion of the transcriptome since over 98% is represented by non-coding RNAs (ncRNAs). LncRNAs represent a class of ncRNAs that are longer than 200 nucleotides and are not well studied nor understood in relation to infectious diseases. LncRNAs are typically expressed at lower levels, but often are implicated to have greater tissue specificity related to biogenesis and epigenetic regulatory factors. LncRNAs are also known to interact with other molecules such as proteins, peptides, DNA, RNA, and even metal ions to form secondary and tertiary structures. By understanding the various lncRNAs interactions this knowledge can potentially be leveraged to understand their role in pathogenesis and to best design and develop novel diagnostic assays.

Impact: Studying lncRNAs potentially offer the ability to elucidate novel biothreat-relevant signatures for diagnosis and potential therapeutic application. It is believed that there is a great potential to best understand the role that lncRNAs play in infection from relevant pathogens to the Chemical and Biological Defense Program (CBDP) with current technologies, capabilities, and

methods currently available. Learning the role that non-coding elements potentially play can greatly enhance the overall knowledge of pathogenesis and virulence that typically lead to adverse clinical symptoms and can impact the Warfighter's combat effectiveness and the greater mission.

Objective: The aim of this topic is to develop proof of concept to determine whether novel diagnostic markers can be discovered from lncRNA research. Specifically, the goal is to understand if lncRNAs play a significant role in pathogenesis and determine the appropriate mechanisms of action. For this basic research topic, the ideal focus is on lncRNAs, which are defined to be greater than 200 nucleotides in length, however, this topic is willing to entertain ncRNAs smaller than 200 nucleotides if their role, function, and mechanism of action can be accurately described. The primary goals and objectives of this basic research effort for the potential 2 year effort will be to:

a) Leverage the appropriate technologies to rapidly discover and identify lncRNAs
b) Determine lncRNA's role in infection and pathogenesis for relevant animal models and/or human infectious disease studies

Please note that only infectious disease studies that are directly relevant to the CBDP will be thoroughly evaluated and considered. These pathogen threats are typically considered to be high-containment microorganisms that are associated with extremely high rates of morbidity and mortality as well as the high risk of transmissibility. Solicitations will be reviewed for experimental design and the necessary studies to elucidate and, if successful, conduct initial verification to showcase the role of lncRNAs in pathogenesis and disease progression.

References:

Hu, Guoku et al. "Molecular mechanisms of long noncoding RNAs and their role in disease pathogenesis" Oncotarget vol. 9,26 18648-18663. 1 Jan. 2018, doi:10.18632/oncotarget.24307

Thrust Area 7, Topic I2: Algorithm Development for Optimization of Biologic Medical Countermeasures

Award Amounts for this topic are anticipated to be up to $400,000 per year through the base period phase to establish proof of concept and, if successful, up to $800,000 per year thereafter (total dollar value = direct and indirect costs). In all cases, the proposed award value should be clearly substantiated by the scope of the effort. Further guidance on scope and cost may be provided in each full proposal invitation.

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. 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.

Note: For this topic, awardees will be required to grant the US Government a licensing agreement to all software and or hardware in perpetuity for all Chemical and Biological Defense Program (CBDP) uses.

Background: Machine learning and artificial intelligence (AI) has advanced greatly in the past decade. Coupled with cheaper computer power, the technology is rapidly moving into diverse areas from natural language processing to autonomous vehicles. The basic underpinnings of the technology

is in the ability to "train" the software to recognize, generate, and analyze patterns from vast amounts of heterogeneous data that may not be readily obvious to the human mind. For example, AI has been successfully used in the field of clinical oncology medicine to accurately read mammograms.[1] The next step is leveraging the potential of AI to drive the next generation of rational drug discovery.[2]

Relevance: The DoD has a unique set of challenges within the CBDP for which AI may be ideally suited to help close gaps in our basic understanding. It is envisioned that a DoD-specific AI drug discovery platform will support the CBDP Agile Medical Platform. Specifically, a DoD-specific AI platform could ultimately be developed that is focused on generating and analyzing biological data specific to monoclonal antibody based therapies, to aid in identifying optimal candidates for advanced development of biological medical countermeasures (MCM) to protect the Warfighter and Nation against biological threat agents. Methods developed that can optimize the antibody for any number or numbers of traits that would accelerate MCM development, by reducing the time and cost, while maximizing efficiency and effectiveness for the DoD are especially of interest. To this end, this topic seeks to solicit groups working in the field of machine learning and algorithm design to help determine if AI/machine learning technology is advanced enough to help define materiel monoclonal antibody based medical countermeasure solutions to the DoD.

Impact: If successful, the work will support the CBDP through improved pathways for moving product through the regulatory process to provide MCMs for the warfighter. It would also support in laying the groundwork for the potential to develop a more encompassing AI drug discovery platform that could be applied across the spectrum of DoD medical areas within the CBDP.

Objective: As a proof of concept, the initial work will be directed towards the optimization of monoclonal antibody biologics. While discovery of antibodies with strong binding is fairly routine, the ability to develop those into feasible drug candidates remains a challenge. Basic understanding of which amino acids can be changed to optimize an antibody to maximize its protection against a biological threat agent of interest to DoD is still a relatively novel research area.

This topic aims to answer fundamental research questions related to addressing whether AI can be utilized to provide information to aid optimizations in rational antibody based drug design, and whether AI can help address issues relevant to the development of antibody based MCMs for biological agents of relevance to DoD:

- Plasma stability / half-life – can we routinely achieve 6 months or greater duration of protection?
- Route of administration – can we optimize for intramuscular injection?
- Shelf-life – can we routinely lyophilize and reconstitute?
- Greater avidity – can we develop countermeasures with increased binding and clearance?
- Aggregation—can we minimize the aggregation potential of monoclonal antibodies?

Other directed applications that optimize manufacturability will also be considered.

The DoD has made significant investments in the development of antibody-based MCMs, and as such, has access to a potential "learning set" of proteins that could aid in the development of a useful algorithm. While not required, there may be some benefits to partnering with groups that have been involved in the design of antibodies against pathogens of interest to the DoD. Further guidance on

potential partnerships/collaborations may be provided with each full proposal invitation.

The end state for this work will be a validated algorithm capable of optimizing an existing antibody for specific biological properties and the accompanying laboratory data to prove its predictability.

Proposals for small molecules will not be considered.

References:

*Tejal A. Patel MD, Mamta Puppala MS, Richard O. Ogunti MBBS, Joe E. Ensor PhD, Tiancheng He PhD, Jitesh B. Shewale BDS, MPH, Donna P. Ankerst PhD, Virginia G. Kaklamani MD, DSc, Angel A. Rodriguez MD, Stephen T. C. Wong PhD, Jenny C. Chang MD, "Correlating mammographic and pathologic findings in clinical decision support using natural language processing and data mining methods," Cancer **123**, 114–121 (**2017**)*

*See for example: https://endpts.com/ai-drug-discovery-success-inspires-a-machine-learning-startup-at-the-mayo-clinic/; https://www.reuters.com/article/us-pharmaceuticals-ai-gsk/big-pharma-turns-to-ai-to-speed-drug-discovery-gsk-signs-deal-idUSKBN19N003 and Eric Smalley, "AI-powered drug discovery captures pharma interest", Nature Biotech, **35**, 604–605 (**2017**) doi:10.1038/nbt0717-604*

*"From machine learning to deep learning: progress in machine intelligence for rational drug discovery", Zhang L, Tan J, Han D, Zhu H, Drug Discov Today. **2017** Sep 4. pii: S1359-6446(16)30436-6. doi: 10.1016/j.drudis.2017.08.010.*

*"druGAN: An Advanced Generative Adversarial Autoencoder Model for de Novo Generation of New Molecules with Desired Molecular Properties in Silico", Kadurin A, Nikolenko S, Khrabrov K, Aliper A, Zhavoronkov A., Mol Pharm. **2017** Sep 5;14(9):3098-3104. doi: 10.1021/acs.molpharmaceut.7b00346.*

*"Machine learning reveals a non-canonical mode of peptide binding to MHC class II molecules", Andreatta M, Jurtz VI, Kaever T, Sette A, Peters B, Nielsen M., Immunology. **2017** Oct;152(2):255-264. doi: 10.1111/imm.12763.*

*"Mathematical Modelling of Immune Parameters in the Evolution of Severe Dengue", Premaratne MK, Perera SS, Malavige GN, Jayasinghe S., Comput Math Methods Med. **2017** ;2017:2187390. doi: 10.1155/2017/2187390.*

*"Learning the Relationship between the Primary Structure of HIV Envelope Glycoproteins and Neutralization Activity of Particular Antibodies by Using Artificial Neural Networks", Buiu C, Putz MV, Avram S., Int J Mol Sci. **2016** Oct 11;17(10). pii: E1710.*

*"A computational method for designing diverse linear epitopes including citrullinated peptides with desired binding affinities to intravenous immunoglobulin", Patro R, Norel R, Prill RJ, Saez-Rodriguez J, Lorenz P, Steinbeck F, Ziems B, Luštrek M, Barbarini N, Tiengo A, Bellazzi R, Thiesen HJ, Stolovitzky G, Kingsford C., BMC Bioinformatics. **2016** Apr 8;17:155. doi: 10.1186/s12859-016-1008-7.*

Thrust Area 7, Topic I3: Identification of Common Molecular Pathways Associated Chemical Warfare Agent (CWA)-Induced Inflammation

Award Amounts for this topic are anticipated to be between $250,000 and $500,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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. 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: Chemical warfare agents (CWAs) are amongst the most brutal weapons of mass

destruction (WMD) created by mankind. CWAs are extremely toxic synthetic chemicals that can be dispersed as a gas, liquid or aerosol or as agents adsorbed to particles to become a powder. These CWAs have either lethal or incapacitating effects on humans. Thousands of toxic substances are known, but only some of them are considered as CWAs based on their characteristics, high toxicity, imperceptibility to senses and rapidity of action after dissemination and persistency, and are listed as scheduled chemicals in the Chemical Weapons Convention. The CWAs possess different characteristics and belong to various classes of compounds with pronounced physicochemical, physiological and chemical properties. While CWAs are known to cause a multitude of physiological insults, a common feature among many CWAs is the ability to provoke inflammation. The goal of this topic is to discover common molecular pathways and/or mechanisms of action for inflammation that results from exposure to a broad range of chemicals – including nerve agents, pulmonary agents, blister agents, and other CBDP-relevant compounds.

Impact: Improved understanding of CWA-induced inflammation may point to novel therapeutic targets for intervention. Furthermore, identification of common molecular pathways and /or mechanisms of action for inflammation may enable the design or repurposing of potential therapeutics with broad spectrum action across a range of CWAs. Identification of novel therapeutic targets and or interventions are critical activities for advancing treatments associated with CWA exposure.

Objective: The objective of this topic is to solicit proposals that aim to both:

a) Characterize molecular pathways and/or mechanisms of action for CWA-induced inflammation. Competitive proposals will focus on inflammation from a broad range of CWA, including; nerve agents, pulmonary agents, blister agents, and other CBDP-relevant compounds. Additionally, proposals are expected to consider inflammation across a variety of tissues (e.g. nervous, epithelial, etc.). Activities may also rely upon both established and novel techniques (e.g. in-silico, in-vitro, ex-vivo, and in-vitro).

b) Identify common molecular pathways and/or mechanisms of action for CWA-induced inflammation that may be suggestive of novel targets for therapeutic intervention. An expected emphasis is in the identification of common inflammation-specific molecular elements that span CWAs and tissue type.

Thrust Area 7, Topic I-4: Identification of Novel Methods for Improving the Pharmacokinetic Properties of Proteins

Award Amounts for this topic are anticipated to be between $280,000 and $450,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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. 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: Prophylactic and therapeutic medical countermeasures (MCMs) for chemical and

biological agents currently in development have limited circulatory stability and may elicit an immune response during repeat dosing. Therefore, the goal of this topic is the identification of novel methods for improving the Absorption Distribution Metabolism Excretion (ADME) properties specific to Excretion. This approach can incorporate either humanizing non-human proteins to decrease immunogenicity as well as identifying novel methods for increasing the half-life of biologic based MCMs. The first interest is the stabilization and decreased immunogenicity of antibodies derived from non-human sources (e.g. – murine model). The second area of interest is identification of novel mechanisms to decrease methods of clearance and elimination to improve half-life of biologic MCMs (e.g. – increasing affinity of Fc to FcRN). Prolonged stability of therapeutic antibodies directed against chemical warfare agents (CWAs) or biological warfare agents (BWAs) has the potential to advance both novel and previously developed MCMs.

Impact: This research would be to be able to provide the Warfighter with an improved prophylactic and therapeutic MCMs against CWAs and BWAs. Discovery of novel technologies to improve the ADME properties of biologic MCMs such as antibodies would greatly increase the Warfighters' capability to operate during a biological or chemical attack.

Objective: The objective of this topic is to solicit proposals that aim to both:

a) Identify novel methods for humanizing non-human proteins to decrease immunogenicity and increase stability.

b) Provide solutions to extend the half-life of prophylactic or therapeutic MCMs.

Thrust Area 7, Topic I5: Receptor Mapping Across Humans and Animal Models

Award Amounts for this topic are anticipated to be between $250,000 and $500,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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. 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: A proper understanding of how receptors and enzymes map across humans and laboratory animal models is critical for providing relevant, translatable data necessary to develop safe and efficacious medical countermeasures for the warfighter. Little data exists that comprehensively compares the distribution (blood, brain, lung, heart, liver and kidney, etc.), type, and function of receptors that interact with the various chemical or biological warfare agents (CWAs and BWAs) in humans to those in the various laboratory animal models (mice, rates, guinea pigs, rabbits, ferrets, swine, and non-human primates). Such data would help determine which animal models are suited for studying the various CWAs and BWAs for their signs, symptoms and medical countermeasures. Receptors should include standard chemical weapon target receptors (AChE, GABA, opioid, and other CBDP-relevant chemical classes), as well as off-target receptors that have relatively high interactions with the chemicals of interest. Therefore, the goal of this topic is to utilize receptor mapping to aid in

identifying the appropriate choice of animal models for medical countermeasures development studies as well as reveal potential areas for novel prophylactic and/or therapeutic intervention.

Impact: Understanding how receptors targeted by CWAs map and function across humans and laboratory animal models will allow for more relevant animal model selection in medical countermeasure development.

Objective: The objective of this topic is to solicit proposals that aim to:

a) Define the type and distribution of receptors across humans and laboratory animal models for mice, rats, guinea pigs, rabbits, ferrets, swine, and non-human primates (NHP) to allow for more relevant animal model selection in medical countermeasure development. Targeted tissues in each animal model should include blood, brain, lung, heart, liver and kidney, etc. Receptors should include AChE, GABA, and opioid receptors, as well as off-target receptors that have relatively high interactions with CBDP relevant chemical classes.

b) Characterize the structural and physiological homologies of receptors and enzymes across humans and laboratory animal models for mice, rats, guinea pigs, rabbits, ferrets, swine, and NHP to allow for more relevant animal model selection in medical countermeasure development. Targeted tissues in each animal model should include blood, brain, lung, heart, liver and kidney, etc. Receptor and enzyme families should include AChE, GABA, opioid receptors, as well as off-target receptors that have relatively high interactions with the chemicals or biologics interest.

c) Amongst receptors and enzymes that differ significantly in their homology relative to human (characterized in Objective b, above), describe their relative affinities for (or inhibition by) chemicals of interest to include cholinesterase inhibitors, GABA inhibitors, opioids, biological toxins and other CBDP relevant chemical agents.

Thrust Area 7, Topic I6: Molecular Cascades for Signaling of Chemical and Biological Warfare Agents

Award Amounts for this topic are anticipated to be between $350,000 and $500,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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 seeks to understand the design, synthesis, and characterization of a signal cascade or amplification scheme that may be incorporated into a stimuli responsive system which reacts and responds to chemical and biological warfare agents (CWAs and BWAs). In recent years, it has been shown that materials can selectively bind to CWAs and BWAs or stimulate a response. For example, aptamers and single domain antibodies have been explored for various assay applications for the detection of BWAs [Turner 2017; U.S. Patent US9310357B2]. Polymers can be synthesized to change shape or depolymerize when exposed to chemical warfare simulants [Sha, 2017; Phillips,

2014], or enzyme systems can be manipulated to elicit a pH or colorimetric change when exposed to CWAs [FLIR, 2017]. In addition, responsive materials have been engineered for detection applications, as in the case of *"molecular beacons" for fluorescent detection of bacterial cells or spores*, or fluorophores released from shape responsive small molecules in the presence of cyanide [Jo, 2013]. However, in all cases, the response generated from the binding event is typically stoichiometric, not amplified sufficiently for live observation, and not amenable for non-assay based applications. A reaction scheme involving materials that bind CWA and BWA and elicit a cascade reaction leading to an amplified response for real-time observation is highly desired.

Impact: Successful novel materials that can be designed and scaled to react to CWA and BWAs can greatly enhance the capabilities of current contamination mapping efforts by enhancing protection and guiding decontamination.

Objective: This research topic seeks to develop a cascade reaction scheme involving a rationally-designed material that can bind to CWA and BWAs, resulting in an amplified response. The research should propose to: 1) Identify chemical and biological stimuli (i.e., signatures) that are unique to specific CWA and BWAs; 2) Iteratively design and synthesize materials that can bind to CWAs and BWAs, resulting in a cascade reaction scheme that leads to a rapid amplified response; and 3) Characterize amplified responses that support the iterative process of design and synthesis to achieve a sensitive response to one unit of CWAs and BWAs. A material or a reaction scheme that produces a change in infra-red or an anti-stokes shift is of particular interest to the agency; however, other acceptable responses include, but are not limited to, colorimetric, fluorescence, and phosphorescence. The amplified signal, or the cascade scheme should be robust and not easily interfered with from environmental factors: temperature, presence or absence of water/humidity, and pH. For example, BWA-responsive materials should be able to bind to specific signatures of the endospore and the vegetative bacteria and agnostic to delivery media (aqueous, solvent, or combination thereof). Ideal BWA-responsive materials would respond to a single colony or plaque forming unit of the BWA, with abilities to differentiate BWA strains through the amplified response or binding event.

Research areas may include, but are not limited to:

a) Studies involving multiplexed approaches for developing stimuli-responsive materials or classes of materials that respond to two or more CWAs or BWAs in the same sample, with the potential to identify CWAs or BWAs by the type of response;

b) Molecular-level interrogation of the interactions between a stimuli-responsive material and specific CWAs and BWAs (to include environmental requirements, specificity, sensitivity, and interference potential);

c) Approaches involving oligonucleotide aptamers or single domain antibodies or derivatives thereof.

A single model CWA or BWA can be used to demonstrate the technique or technology developed under this program; however, it is desired for the technology to be amenable to bind and react with a wide variety of agents. Due to the large body of literature and existing projects supporting responsive materials for CWAs, proposals wishing to study CWA responsive materials must address gaps in existing technologies supporting CWA contamination mapping. Proposals or teams looking to build sensors or devices will not be selected. Strategies and partnerships for live agent testing of designed

system is highly encouraged.

References:

Turner, Kendrick, et al. "Pairing Alpaca and Llama-Derived Single Domain Antibodies to Enhance Immunoassays for Ricin." Antibodies, vol. 6, no. 1, Feb. 2017, p. 3., doi:10.3390/antib6010003.

U.S. Patent US9310357B2: Detection of chemical and biological agents using oligonucleotide aptamers, 2016-04-12. https://patents.google.com/patent/US9310357.

Sha, Sheng-Chun, et al. "Chemical Warfare Simulant-Responsive Polymer Nanocomposites: Synthesis and Evaluation." Journal of Polymer Science Part A: Polymer Chemistry, vol. 55, no. 18, 2017, pp. 3034–3040., doi:10.1002/pola.28580.

Phillips, Scott T., et al. "Amplified Responses in Materials Using Linear Polymers That Depolymerize from End-to-End When Exposed to Specific Stimuli." Journal of Applied Polymer Science, vol. 131, no. 19, Mar. 2014, doi:10.1002/app.40992.

FLIR Agentase C2. 2017. FLIR Systems, Inc. Retrieved Nov. 2, 2018 from https://www.flir.com/globalassets/imported-assets/document/flir-agentase-c2-datasheet-en.pdf.

Jo, Junyong, et al. "Interdigitated Hydrogen Bonds: Electrophile Activation for Covalent Capture and Fluorescence Turn-On Detection of Cyanide." Journal of the American Chemical Society, vol. 135, no. 9, 2013, pp. 3620–3632., doi:10.1021/ja312313f.

Thrust Area 7, Topic I7: An Every-Atom-Counts Approach to Designing Small Cluster Catalysts

Award Amounts for this topic are anticipated to be between $350,000 and $500,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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 has invested considerable resources over the past two decades in the design and development of active materials for the capture and decomposition of chemical agents.

Relevance of Metal Oxide Research. In the 1990s and early 2000s much work was done in understanding properties of bulk metal oxides in supported/unsupported form to bind and decompose chemical agents at ambient and elevated temperatures. This period of work established an important benchmark as a historical departure from many decades of research on activated carbon chemistry. Insight into the role of the active nature of mixed metal oxides on porous activated carbons provided the motivation to explore these bulk oxides in a more rigorous manner. The results of this research showed important properties and limitations of certain metal systems to bind and decompose chemical agents. Many forms of the bulk oxides were shown to be limited in porosity which reduced accessibility of chemical adsorbates to a high number of active centers. Bulk oxides demonstrated good hydrolytic chemistry at ambient temperatures due to the active nature of the proton on the metal-oxygen center (H-O-M) as well as binding with the Lewis acid metal. At high temperatures (350-900 ^{o}C) these oxides showed increased activity for oxidation of chemical agents. The outcome of this body of work suggested that metal oxide systems of high porosity and accessibility to active centers (M-O-

M) was critical to achieving high chemical adsorption and decomposition of chemical agents.

The emergence of reticulated metal organic frameworks in the middle of the last decade (~2005) provided new motivation to address the technical challenges as learned with bulk metal oxide systems. This era of periodic structures as presented by Metal Oxide Frameworks (MOF) and other related forms was driven by the rapidly emerging science of nanostructured materials in general, such as small metal cluster s (<10 nm) of Au, Ag and Pt in unsupported and supported form. For the past decade DTRA has invested heavily in understanding the structure and activity relationships of MOF. By design (in pristine form), MOFs are highly coordinated structures with high porosity making them attractive candidates for strong binding and active site utilization of adsorbed chemical agents. The chemistry of the MOF, like bulk metal oxides, demonstrate moderate to high hydrolytic chemistry for decomposition of chemical agents. Recently questions emerged regarding the role of defects in MOF structures and have provided additional motivation for understanding design rules regarding adsorption, diffusion and chemical decomposition. An important observation from all of the MOF work regarding chemical activity suggests that they are important platforms for inclusion of guest atoms and clusters that can be designed to enhance binding and decomposition beyond hydrolysis of chemical agents (such as oxidation and dealkylation).

Metal Atoms and Clusters. The next generation of active oxides centers on utilization of highly energetic forms of single atom and small clusters to promote stronger binding and molecular dissociation without the dependency on external energy sources (i.e., thermal, light). The ultimate small-size limit for metal particles is the single-atom catalyst (SAC), which contains isolated metal atoms singly dispersed on supports. SACs maximize the efficiency of metal atom use, which is particularly important for supported noble metal catalysts. Moreover, with well-defined and uniform single-atom dispersion, SACs offer great potential for achieving high activity and selectivity. Heterogeneous catalysis usually occurs at the surface of a solid catalyst, which ideally has a high surface area to volume ratio. For example, smaller metal particles have a higher fraction of surface atoms than do larger metal particles. This fraction not only has an impact on the fraction of metal atoms that are catalytically active (hereafter referred to as metal atom utilization), but also has a substantial effect on selectivity. The metal atom utilization in homogeneous molecular catalysts can reach 100% — a figure that may be orders of magnitude higher than that of heterogeneous catalysts. Heterogeneous catalysts might feature non-uniform aggregates of hundreds and/or thousands of metal atoms, only a small fraction of which are exposed to reactants. For example, the reactive, coordinately unsaturated metal atoms at apices, edges, steps and corners usually represent less than 20% of the total metal atoms. However, the surface free energy of metals increases significantly with decreasing particle size, promoting aggregation of small clusters. Using an appropriate support material that strongly interacts with the metal species prevents this aggregation, creating stable, finely dispersed metal clusters with a high catalytic activity, an approach industry has used for a long time.

Objective: To advance understanding on how to design new forms of highly active materials that exhibit new chemistries to bind, decompose and detoxify chemical agents of interest to DTRA. This topic focuses on advancing the current knowledge in the design of active materials to provide tunable binding properties in order to promote highly efficient molecular dissociation (bond breaking) and detoxification of chemical agents. Specifically the work will concentrate on the design of very small metal oxide clusters (<2 nm) that possess a high surface concentration of undercoordinated metal

centers to promote molecular dissociation through oxidation and dealkylation.

Research areas may include, but are not limited to:

a) Design of sub-nanometer clusters of metal atoms and molecules with strong size-dependent properties to promote active centers for binding and decomposition of chemical agents.

b) Employing theory and surface sensitive techniques to systematically investigate size-dependent properties of metal centers on binding and molecular dissociation of relevant systems (live agent/simulant).

c) Understanding the interactions of ambient chemicals on structure-activity of promising metal systems relevant to binding and dissociation of chemical adsorbates.

d) Investigating the dynamics of metal center aggregation and stabilization under ambient conditions, to include stabilizing substrates and environments to preserve activity of small metal clusters.

References:

Lichen Liu and Avelino Corma Metal Catalysts for Heterogeneous Catalysis: From Single Atoms to Nanoclusters and Nanoparticles, Chem. Rev. 2018, 118, 4981−5079.

Aiqin Wang, Jun Li and Tao Zhang, Heterogeneous single- atom catalysis, Nature Reviews Chemistry volume 2, 65-81, JUNE 2018.

Somorjai, G. A.; Carrazza, J. Structure Sensitivity of Catalytic Reactions. Ind. Eng. Chem. Fundam. 1986, 25, 63−69.

Che, M.; Bennett, C. O. The Influence of Particle Size on the Catalytic Properties of Supported Metals. Adv. Catal. 1989, 36, 55−172.

Ye, R., Hurlburt, T. J., Sabyrov, K., Alayoglu, S. & Somorjai, G. A. Molecular catalysis science: perspective on unifying the fields of catalysis. Proc. Natl Acad. Sci. USA 113, 5159–5166, 2016.

Qiao, B. et al. Single- atom catalysis of CO oxidation using Pt1/FeOx. Nat. Chem. 3, 634–641 2011.

Xiao-Feng Yang, Aiqin Wang, Botao Qiao, Jun Li, Jingyue Liu, And Tao Zhang Single-Atom Catalysts: A New Frontier, In Heterogeneous Catalysis, Accounts Of Chemical Research, 1740–1748, 2013 Vol. 46, No. 8.

Thrust Area 7, Topic I8: Design Rules for a Biomimetic Membrane with Selective Water Permeability

Award Amounts for this topic are anticipated to be between $350,000 and $500,000 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. Further guidance on scope and cost may be provided in each full proposal invitation.

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 seeks to understand the design and synthesis of biomimetic membranes that are selectively water permeable for use as protective barriers to CWAs. Current CWA protective barrier membranes like coated PTFE and butyl rubber offer high protection against CWA, but have low to no moisture vapor transport rates (MVTR). By contrast, in nature biological cells have highly selective

membrane channels (e.g., aquaporins, AQP), that can selectively transport water molecules across membranes at a rate of 3×10^9 s^{-1} per channel [Groot, 2001], and have been impregnated in membranes for filtration applications [McCutcheon, 2017]. There is also a large body of literature describing synthetic water channels that transport water at equal or greater rates than biological channels, but with a significant loss of selectivity [Song, 2018]. For example, researchers have demonstrated synthetic membranes derived from self-assembled block copolymers with high selectivity and high tenability [Mulveena, 2014; Qu, 2015]. Ideally, biomimetic membrane channels might be leveraged to maximize selectivity and MVTR across the membrane while maintaining protection from CWAs. However, a number of knowledge gaps in critical areas must be addressed prior to achieving this, including: 1) Modeling at all length scales to develop a coherent molecular understanding of synthetic channel and membrane properties, provide insight for future materials design, and predict selectivity for water transport (and not CWA); 2) Basic understanding of compatibility of water transport channels in CWA protective polymer and tolerance to various processing conditions; 3) Fundamental understanding of biomimetic channel and membrane structure optimization to control transport properties; 4) Laboratory evaluation of membranes is often conducted with highly idealized mixtures, so separation performance in real applications with complex mixtures needs to be demonstrated; and 5) Lack of systematic understanding of methodologies to incorporate channels and scale promising membranes from the few square centimeters needed for laboratory characterization to the thousands of square meters needed for large applications impedes membrane deployment. Nevertheless, opportunities for biomimetic water-permeable channels and membranes in both existing and emerging technologies, together with an expanding set of membrane materials, hold great promise for the technology to effectively address CWA protection needs.

Impact: Successful design and synthesis of biomimetic, selective, water-permeable channels and their incorporation into substrate membranes could potentially be transformative in bringing new barrier technologies that are breathable, stretchable, and protective against CWA.

Objective: This research topic seeks to develop rational design approaches for robust, predictable and cost effective construction of synthetic membranes containing biomimetic water channels (natural, synthetic, or combination thereof) that can perform selective/facilitated transport of water molecules and air, and ability to block chemical warfare agent. The research should propose an iterative (spiral) approach to understand the opportunities for advancing biomimetic, water-selective, CWA impermeable membranes, to include: 1) novel discoveries in chemistries that lend themselves to scaling in a stimuli responsive system; 2) higher permeability and selectivity of water in membrane applications, without sacrificing CWA protection; and 3) membrane systems that lend itself to scaling. The biomimetic water channels can be derived from ruggedizing existing natural AQP channels or producing *de novo* [Lu, 2018] water selective transmembrane proteins or synthetic channels that can tolerate chemical processing techniques. The biomimetic water channels can also be from completely synthetic materials embedded in a membrane. However, all membranes must be protective against CWA, and therefore strategies and partnerships for simulant (DMMP, 2-CEES) liquid and vapor permeation testing are highly encouraged.

Proposals offering only theoretical approaches (e.g., modeling) will not be entertained.

Research areas may include, but are not limited to:

a) Ruggedizing natural AQP through de novo design for incorporating on protective substrates;

b) Artificial water channels in self-assembled membrane substrates and testing against CWA

c) Other biomimetic mechanisms that could increase MVTR and selectivity without sacrificing protection

References:

Groot, B. L. (2001). Water Permeation Across Biological Membranes: Mechanism and Dynamics of Aquaporin-1 and GlpF. Science, 294(5550), 2353-2357. doi:10.1126/science.1062459

Song, W., Lang, C., Shen, Y., & Kumar, M. (2018). Design Considerations for Artificial Water Channel–Based Membranes. Annual Review of Materials Research, 48(1), 57-82. doi:10.1146/annurev-matsci-070317-124544

Mulveena, R.A., Weidman, J.L.; Jing, B.; Pople, J.A.; Zhu, Y.; Boudouris, B.W.; Phillip, W.A. (2014). Tunable Nanoporous Membranes with Chemically-Tailored Pore Walls from Triblock Polymer Templates. J. Mem Sci, 470, 246-256. doi.org/10.1016/j.memsci.2014.07.021

Qu, S.; Dilenschineider, T.; Phillip, W.A. (2015). Preparation of Chemically Tailored Copolymer Membranes with Tunable Ion Transport Properties. ACS Appl. Mater. Interfaces, 7, 19746−19754. doi.org/10.1021/acsami.5b05592

Xia L., Andersen, M.F., Hélix-Nielsen C., McCutcheon J.R. (2017). Novel Commercial Aquaporin Flat-Sheet Membrane for Forward Osmosis. Industrial & Engineering Chemistry Research, 56 (41), 11919-11925 doi: 10.1021/acs.iecr.7b02368

Lu, P., Min, D., DiMaio, F., Wei, K.Y., Vahey, M.D., Boyken, S.E., Chen, Z., Fallas, J.A., Ueda, G., Sheffler, W., Mulligan, V.K., Xu, W., Bowie, J.U., Baker, D. (2018). Accurate computation design of multipass transmembrane proteins. Science, 6379 (359), 1042-1046 doi: 10.1126/science.aaq1739

Thrust Area 7, Topic I9: Design of Repellant Permanent Thin Films for Chemical and Biological Agent Resistance

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). In all cases, the proposed award value should be clearly substantiated by the scope of the effort. Further guidance on scope and cost may be provided in each full proposal invitation.

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. 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 chemical and biological agent resistant coatings fail to provide desired levels of contamination prevention. This means warfighters are required to expend significant effort during field decontamination of equipment. Attempts to control penetration of liquids into surfaces often harness the lotus leaf effect. This involves the use of a textured surface providing air-liquid and air-solid interfaces. For these surfaces, increases in pressure, for example applied weight or pressure washing, can lead to liquid intrusion into the textured surface resulting in a defeat of the repellent characteristic. The surface features that produce this effect also tend to be fragile. Alternatives to the lotus leaf effect have been described, including slippery liquid-infused porous surfaces (SLIPS) and slippery omniphobic covalently attached liquids (SOCAL). The liquid-liquid interaction interfaces of these materials address some shortfalls in the lotus effect, but current technologies tend to be temporary, or to weather poorly.

Improved coatings and thin films for agent resistance would decrease the logistical burden associated with decontamination of equipment by warfighters. In order to develop these materials, a fundamental understanding of the surfaces and the physical and chemical properties that assist with resisting contamination is needed. Ideally the thin film would allow for decreased sliding and shedding angles for agents and other contaminants as well as simplified decontamination approaches.

Impact: The research explored in this topic seeks to develop a fundamental understanding of a permanent technology for repelling chemical agents and decreasing the logistics of decontamination. Ideally, chemical and biological warfare agents and other contamination would be shed from coated surfaces, minimizing the need for additional decontamination strategies.

Objective: Proposals are sought for work which seeks to understand the fundamental aspects of coating technologies (or thin films) and how those aspects control penetration and repellency of chemical and biological warfare agents. The technologies should be permanent with a minimum persistence of 18-24 months and be transparent or offer pathways to achieving transparency. The work will include synthesis of the technology and evaluation of wetting by, and retention of, simulants for chemical warfare agents.

Research areas may include, but are not limited to:

a) Determination (theoretical or experimental) of composition impact on chemical agent resistance
    a. Experimental synthesis and characterization of the technologies and measurements at the laboratory scale with chemical warfare agent simulants
    b. Technologies must adhere to a polyurethane base coating
    c. CB warfare agent resistance with no more than 0.4% agent (or simulant) retention by the technology
    d. Technology must be compatible with military decontamination procedures or, ideally, with a water rinse
    e. Must be amenable to use under varying environmental conditions low/high temperatures, low/high humidity, continuous UV exposure, water/mud, and mechanical and thermal stresses etc.
    f. Determination of chemical agent resistance over time (degradation of the thin film) physical, chemical mechanical and environmental
        i. Material should perform at initial metrics for a minimum of 18-24 months aging
        ii. Similar repellant performance in low/high temperatures, low/high humidity, mechanical stress, thermal stress, UV exposure after 18-24 months
b) Evaluation of chemical warfare agent simulant retention and repellency
    a. Technologies must be amenable to varying environmental conditions and provide a minimum resistance to chemical agents
    b. Applied technology layers must be thin while providing desired performance
    c. Thin films must be durable to mechanical and thermal stresses
    d. Determination of agent (simulant) retention/penetration after rinsing with water

The focus of proposals should be on development of thin film or coating technology and its

characterization. Proposals should show preliminary simulant retention or wetting data, or evidence that the technology is capable of providing repellency. Finally, simplicity in the synthetic approach and in coating application is paramount for potential follow-on manufacturing and scaling; successful technologies could be candidates for transition to a product. The potential for development of a one-step spray coating is highly desirable.

References:

L. Wang, T. McCarthy. Covalently Attached Liquids: Instant Omniphobic Surfaces with Unprecedented Repellency. Angewandte Chem.2016, 55, 244-248

C. Zhang, Y. Xia, H. Zhang, N. Zacharia, Surface Functionalization for a Nontextured Liquid-Infused Surface with Enhanced LifetimeACS Appl. Mater. Interfaces 2018, 10, 5892-5901.

J. Wang, K. Kato, A. Biois, T-S. Wong, Bioinspired Omniphobic Coatings with a Thermal Self-Repair Function on Industrial MaterialsACS App. Mater. Interfaces 2016, 8, 8265-8271.

J. Conti, J. De Coninck, M. Ghazzal. Design of water-repellant coating using dual scale size of hybrid silica nanoparticles on polymer surface Appl. Surf. Sci, 2018, 436, 234-241.

P. Irajizad, M. Hasnain, N. Farokhnia, S.M. Sajadi, H. Ghasemi. Magnetic slippery extreme icephobic surfaces. Nat. Commun. 2016, 7, 13395.

X. Feng, L. Jiang. Design and Creation of Superwetting/Antiwetting Surfaces. Adv. Mater. 2006, 18, 3063-3078.