Broad Agency Announcement
Hermes

BIOLOGICAL TECHNOLOGIES OFFICE

HR001124S0025

April 19, 2024

This publication constitutes a Broad Agency Announcement (BAA) as contemplated in Federal Acquisition Regulation (FAR) 6.102(d)(2) and 35.016 and 2 CFR § 200.203. Any resultant award negotiations will follow all pertinent law and regulation, and any negotiations and/or awards for procurement contracts will use procedures under FAR 15.4, Contract Pricing, as specified in the BAA.

Overview Information:

- **Federal Agency Name** – Defense Advanced Research Projects Agency (DARPA), Biological Technologies Office
- **Funding Opportunity Title –** Hermes Program
- **Announcement Type –** Initial Announcement
- **Funding Opportunity Number –** HR001124S0025
- **Assistance Listing Number:** 12.910 Research and Technology Development
- **Dates/Time - All Times are Eastern Time Zone (ET)**
  - Posting Date: April 19, 2024
  - Industry Day: April 8, 2024
  - Proposal Abstract Due Date: May 3, 2024. 4:00 p.m.
  - Question Submittal Closed: May 21, 2024, 4:00 p.m.
  - Proposal Due Date: June 4, 2024

- **Anticipated individual awards** - Multiple awards are anticipated.
- **Types of instruments that may be awarded** - Procurement Contracts, Cooperative Agreements, or Other Transactions for Prototypes.
- **NAICS Code**: 541714
- **Agency contact**
  - Points of Contact
    The BAA Coordinator for this effort may be reached at:
    HermesBAA@darpa.mil
    DARPA/BTO
    ATTN: HR001124S0025
    675 North Randolph Street
    Arlington, VA 22203-2114

Section I: Funding Opportunity Description

Introduction

The Defense Advanced Research Projects Agency (DARPA) is soliciting innovative proposals to develop systemic drug delivery platforms for medical countermeasures (MCMs). The Hermes program is explicitly seeking transformative approaches enabling the development of delivery platforms with systemic biodistribution, exceptional endosomal escape efficiency, and minimal toxicity. Successful proposals will include a detailed description of the proposed delivery platform including 1) screening pipeline, 2) reporter systems for monitoring biodistribution and expression in animal models, 3) methods to monitor immunogenicity/toxicity, and 4) chosen therapeutic and/or prophylactic cargo and justification. Systemic delivery platforms developed under the Hermes effort will be transferred to U.S. Government stakeholders for further development.

Program Overview

Although efforts to develop novel medical countermeasures (MCMs) have provided critical resources to enable warfighter readiness and counter existing and emerging biothreats, current delivery platforms hinder the efficacy and rapid deployment of these therapeutics. Unlike traditional small molecule pharmaceuticals, biologics are large, complex molecules that can be exceptionally effective, but are challenging to administer and deliver in sufficient quantities to requisite cell and tissue types throughout the body. Many delivery platforms result in preferential liver accumulation, thus limiting the accessibility and effectiveness of MCMs in alternative cell and tissue types.[1] In addition, the rapid clearance of biologics from the bloodstream poses another obstacle—the immune system's vigilant response leads to the swift elimination of these large molecules, reducing their concentration and therapeutic efficacy. Developing new delivery technologies that expand access to multiple cell and tissue types concurrently, along with accommodating the increasing complexity of MCM cargo, is critical to strengthen and augment biosecurity preparedness. By developing versatile, efficient, and accessible delivery platforms, the Department of Defense (DoD) will create new capabilities to protect the warfighter from the emerging threat landscape.

Previous DARPA efforts such as the Pandemic Prevention Platform (P3) and the PRemptive Expression of Protective Alleles and Response Elements (PREPARE) programs resulted in the development of highly efficacious monoclonal antibodies[2] and novel clustered regularly interspaced short palindromic repeats (CRISPR)-based MCMs[3], respectively, against viral, bacterial, and chemical threat agents. In addition, these programs advanced the state of the art (SOA) of nucleic acid-based delivery platforms, but further fundamental research and development is required. By developing versatile, efficient, and accessible delivery platforms,

[1] Kim, J., Eygeris, Y., Ryals, R. C., Jozić, A., & Sahay, G. (2023). Strategies for non-viral vectors targeting organs beyond the liver. Nature Nanotechnology, 1-20.

[2] Zost, S. J., Gilchuk, P., Case, J. B., Binshtein, E., Chen, R. E., Nkolola, J. P., ... & Crowe Jr, J. E. (2020). Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature, 584(7821), 443-449.

[3] Rotolo, L., Vanover, D., Bruno, N. C., Peck, H. E., Zurla, C., Murray, J., ... & Santangelo, P. J. (2023). Species-agnostic polymeric formulations for inhalable messenger RNA delivery to the lung. Nature Materials, 22(3), 369-379.

Hermes will enable the DoD to move beyond the current paradigm of one drug, one formulation. The goal of the Hermes program is to overcome the challenges associated with broad, intracellular delivery of biologics to diverse cell and tissue types by developing new delivery modalities that provide systemic distribution with limited negative side effects.

To advance the DoD's ability to respond to current and emerging biothreats, Hermes will address the following drug delivery challenges: (1) developing novel platforms and formulations capable of encapsulating large, complex cargos with limited immunogenicity; and (2) effective biodistribution to, and expression in, multiple cell and tissue types concurrently. The Hermes program will produce flexible platforms capable of delivering diverse types of cargo to multiple cell and tissue types to prepare for any biothreat. Next generation delivery platforms developed during the program should offer unprecedented efficiency with minimal toxicity and immunogenicity. Delivery vehicles developed under the Hermes program must be capable of delivering nucleic acids, but approaches that are also compatible with proteins, small molecules, and/or combinations of these cargos are strongly preferred.

Successful proposals must provide a detailed scientific and technical justification for a drug delivery platform capable of broad, systemic distribution to, and transfection of, multiple cell and tissue types concurrently, that includes the following:

- A comprehensive discovery pipeline including appropriate reporter systems for assessing biodistribution, endosomal escape, and functional expression of therapeutic and/or prophylactic cargo.
- Detailed methods and approaches evaluating immunogenicity and toxicity of formulated delivery platforms, along with approaches to mitigating toxicity.
- Ability of chosen drug delivery platform to achieve program metrics and compatibility with scalable, current Good Manufacturing Practice (cGMP) manufacturing.
- Rationale for chosen cargo and description of how chosen cargo will contribute to the overall goals of the program.

Specifically excluded are proposals that involve:

- Approaches that include human subjects research (HSR).
- Final delivery modalities that rely on intravenous administration. Proposals that incorporate intravenous administration as a comparator method or development model are allowed, but DARPA is primarily interested in delivery modalities that would enable field forward capabilities.
- Immunostimulatory or immunogenic approaches.
- Approaches that only incrementally improve on the current state of the art of nucleic acid delivery.
- Delivery platforms that, with further development through the course of the program, are not capable of packaging nucleic acids greater than 5kb.
- Tissue/cell type specific delivery modalities that cannot be co-formulated/co-administered into a single product.
- Approaches that are not amenable to cGMP regulations enforced by the FDA.
- Integrative delivery platforms (e.g. lentiviral vectors for gene therapy)

Technical Approach

Current biological threats, such as Ebola virus[4] or Rift Valley Fever virus[5], are notorious for broad tissue tropism that contributes to the wide range of disease symptoms, morbidity, and mortality observed during infection. In addition, recent disruptive technology advancements in the fields of synthetic biology and artificial intelligence have facilitated the design and development of novel biological threats that may emerge quickly, potentially demanding a rapid response before a deep understanding of affected tissues or cells is available. The sheer number of potential tissues that are targets for current, and potentially novel, biological threats necessitates a versatile delivery platform capable of reaching various cell and tissue types concurrently throughout the body. Additionally, threat-agnostic delivery platforms could be integrated with existing pipelines for pandemic response—enabling coverage of a range of pathogenic threats with different tropisms. To effectively prepare for the emergence of any biological threat, the Hermes program seeks to develop a versatile threat agnostic MCM platform capable of delivering diverse cargos to broad cell and tissue types to protect the warfighter.

Foundational investments related to the delivery of nucleic acid-based cargos have resulted in new prophylactic and therapeutic capabilities such as mRNA lipid nanoparticle (LNP) based COVID-19 vaccines. However, high immunogenicity of the LNP delivery vehicles limits broad therapeutic potential beyond vaccine applications. Development of new capabilities enabling the high-efficiency introduction of diverse cargos to include large nucleic acid cargos, functional antibodies, and enzymes to a broad range of cell and tissue types would create new therapeutic avenues towards biological threats that are currently inaccessible. The realization of these capabilities would potentially transform a wide variety of non-biodefense applications to include novel therapeutics for cancer, autoimmune disorder, and gene therapies. Significant investments towards these goals are already advancing delivery technologies to specific tissues, including the development of engineered virus-like particles[6], selective organ targeted LNPs[7], and ligand conjugated LNPs for hematopoietic stem cell editing[8]. In contrast to current approaches focused on disease-centered strategies tailored for delivery to specific cell and tissue types, Hermes seeks to develop platform capabilities capable of widespread delivery of diverse cargos in a disease agnostic manner. Performers may utilize a variety of approaches to address delivery and formulation considerations for MCM cargo, including but not limited to:

- Lipid-based formulations

[4] Furuyama, W., & Marzi, A. (2019). Ebola virus: pathogenesis and countermeasure development. Annual review of virology, 6, 435-458.

[5] Ikegami, T., & Makino, S. (2011). The pathogenesis of Rift Valley fever. Viruses, 3(5), 493-519.

[6] An, Meirui, Aditya Raguram, Samuel W. Du, Samagya Banskota, Jessie R. Davis, Gregory A. Newby, Paul Z. Chen, Krzysztof Palczewski, and David R. Liu. "Engineered virus-like particles for transient delivery of prime editor ribonucleoprotein complexes in vivo." *Nature Biotechnology* (2024): 1-12.

[7] Cheng, Q., Wei, T., Farbiak, L., Johnson, L. T., Dilliard, S. A., & Siegwart, D. J. (2020). Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR–Cas gene editing. Nature nanotechnology, 15(4), 313-320.

[8] Breda, Laura, Tyler E. Papp, Michael P. Triebwasser, Amir Yadegari, Megan T. Fedorky, Naoto Tanaka, Osheiza Abdulmalik et al. "In vivo hematopoietic stem cell modification by mRNA delivery." *Science* 381, no. 6656 (2023): 436-443.

- Polymer-based formulations
- Virus-like particles
- Extracellular vesicles
- Viral vectors

Proposed delivery platforms should be minimally capable of delivering any nucleic acid-based cargos (i.e., DNA or RNA) intracellularly, but offerors are encouraged to propose platforms capable of delivering other cargos (e.g., proteins, small molecules, etc.). Systemic delivery may be achieved through a single platform formulation capable of targeting multiple relevant cell and tissue types concurrently, or a co-formulation of multiple delivery platforms with specific targets. The co-formulation approach must be stable and deliverable through no more than two administrations (e.g. two intramuscular injections; or one intramuscular injection and one nebulization; etc.). For clarification on required and desired specifications, see Table 1.

Table 1. Target Product Profile

Parameter	Acceptable ("must have")	Preferred ("nice to have")
Cargo	Delivery vehicles capable of delivering nucleic acids	Delivery vehicles capable of encapsulating protein, nucleic acids, and small molecules
Durability of protection	Maintenance of efficacious dose ≥2 weeks after administration	Confers long-lasting protection for>1 month after administration
Administration	Simple administration (e.g. intramuscular injection, sub-cutaneous injection, nebulization)	Self-administration (e.g. oral, auto-injector, inhaler, patch)
Product Storage Temperature (long-term)	-20°C	4°C or room temperature
Risk/Side Effect	Tolerable reactogenicity and acceptable safety profile; no genomic integration	Safety and reactogenicity comparable to over-the-counter medications (only mild, transient adverse events); no genomic integration
Tissue/cell type specificity	Able to target multiple tissue types (e.g. lungs, liver, gastrointestinal tract, kidney, central nervous system, etc.) if it can be co-delivered/formulated	Systemic delivery achieved with no more than 2 administrations and/or 2 routes
Manufacturability	Formulation compatible with cGMP scale-up	Formulation compatible with simple and rapid production and cGMP scale-up
Demonstration of efficacy	Able to show production of MCM molecules (e.g., relevant expression levels) and activity of molecules (e.g., correct folding, enzymatic activity,	Able to demonstrate efficacy (e.g. survival, weight gain, etc.) of animal models after challenge

	binding/neutralization of target, etc.) that correlates to protection or treatment in appropriate tissues	
Cargo capacity	Capable of packaging large, complex cargo (>5kb nucleic acid, 100kDa protein)	Compatible with any size cargo
Dosing	Compatible with repeated administration (i.e. avoids tolerance, immune response, or compounded affects)	

Proposals that include incremental improvements of well-established delivery technologies, modalities, and formulations are not encouraged.

To meet the program requirements, proposers should employ a delivery platform discovery pipeline to identify and characterize lead candidates. Proposers must sufficiently detail the assays, reporter systems, and benchmarks comprising the pipeline chosen to measure key performance metrics to include cellular uptake and endosomal escape efficiency, cargo half-life/turnover, and biodistribution *in vivo.* For nucleic acid encoded cargo, assays and reporter systems must be capable of quantifying the level and durability of protein expression in different cell and tissue types *in vivo.* To address concerns regarding tolerability, immunological responses, and potential adverse side effects, a detailed plan for assessing immunogenicity and toxicity *in vivo* (e.g. immunohistochemistry, RNA sequencing, anti-drug antibody assay, weight loss, etc.) should be included in the proposal.

Proposers must clearly indicate how their selected delivery formulation approach will address and mitigate risk associated with potential failure modes, such as immunogenicity (adaptive and pre-existing) that would interfere with re-administration/multi-dosing treatment regimens, endosomal escape, toxicity, lack of cell tropism diversity, suboptimal absorption, distribution, metabolism and excretion (ADME) kinetics, cargo size limitations, ultralow temperature storage requirements, and compatibility with established manufacturing and scale-up practices.

Although scaled or cGMP manufacturing is out of scope in the Hermes program, proposals should include a viable plan for small-scale production of lead drug delivery platforms for delivery to U.S. Government stakeholders and transition partners for follow-on technology development (see Section 1.3), as well as a discussion of future pre-clinical testing and regulatory considerations to enable potential pathway towards future FDA regulatory filings. Proposers are encouraged to incorporate appropriate analytic capabilities for assessing platform characteristics to ensure compliance with FDA regulations and scale-up manufacturing throughout their period of performance.

In addition to technical details, the proposal must describe the organizational structure of the team, including project management, distribution of responsibilities, data capture, curation, and storage, animal use and care, along with project management and reporting structure. Teaming is highly encouraged as desired solutions will likely require integration of expertise from multiple disciplines (e.g. incorporation of a dedicated toxicologist or pathologist). The proposal must also describe a structure to communicate and engage with the Government sponsor, Government stakeholders, and relevant prospective regulatory agencies to facilitate a feasible path towards

future clinical translation, as well as pathways to commercialization of technologies developed during the Hermes program.

Performers will need to demonstrate distribution to and intracellular delivery of therapeutic and/or prophylactic cargo to multiple tissue/cell types concurrently *in vivo*. The cargo may be performer defined based on the expertise and capability of the offeror's team. However, a therapeutic and/or prophylactic agent with a relevant DoD-use case is highly encouraged. Delivery platforms with demonstrated capability for large cargos (e.g. >5kb nucleic acid or >100kDa protein) and/or compatible with multiple types of macromolecules are also highly encouraged and should be considered when proposing. Proposals must clearly describe the reporter systems and chosen cargos and a justification of relevancy to the program goals. Some examples DoD-relevant MCMs could include, but are not limited to:

- Inhibitors of post-entry viral processes for viruses with broad tropism, such as Rift Valley Fever virus, Ebola, poxviruses, etc. expressed in affected tissues (e.g. liver, lung, spleen/lymph nodes, gastrointestinal tract, kidney, vascular epithelial cells, bone marrow, skin, eye, etc.)
- Inhibitors of protein-based toxins such as ricin, Shiga toxin, Anthrax toxin etc. delivered intracellularly to relevant cell and tissue types (e.g. gastrointestinal tract, kidney, lungs, central nervous system, etc.)
- Therapeutics for diseases caused by intracellular bacteria (e.g., legionella, tuberculosis) and parasites (e.g., malaria, Chagas) delivered to diverse cells and tissues (e.g., macrophages, fibroblasts, nervous system, muscular system, lymphatic system, red cells, etc.)
- Delivery of drug products such as leukocyte growth factors, pro-survival anti-neutropenia cytokines, and other supportive therapies to treat injuries and symptoms from acute exposure to ionizing radiation to targets such as endothelial, vascular, gastrointestinal, pulmonary, and related tissues.

The goal of the Hermes program is to develop a systemic drug delivery vehicle for MCM cargos *with exceptional tolerability*. Due to risks associated with balancing systemic efficiency and toxicity, immunostimulatory delivery approaches (e.g. vaccine designs) are considered out of scope of the Hermes program.

Program Structure

The Hermes program is structured in two sequential Phases of increasing technical complexity (see Table 2). Phase I (Base, 20 months) will focus on developing the delivery platform screening pipeline, optimization of lead candidates, and evaluating delivery efficiency of chosen cargo. Phase II (Option, 10 months) and will focus on adapting platforms to deliver a government-defined MCM cargo to demonstrate platform flexibility. Performers will conduct a Capability Demonstration (CD) at the end of each Phase, see Section 1.4. **Progression to Phase II depends on performance towards prior Phase-specific goals as described below.** If the team achieves the outlined metrics prior to the end of the Phase, performers may progress to subsequent Phases at the discretion of DARPA.

Table 2. Program Schedule

Phase I: **20 Months** **(Base)**	**Milestone: Proof of concept for performer-defined cargo** • **Months 0-20: Negotiated intermediate metrics based on individual performer approaches and goals** • **Month 1: Program kickoff** • **Month 17-19: Demonstrate effective, broad delivery of chosen therapeutic and/or prophylactic cargo *in vivo* (CD1)** • **Month 20: CD1 performance review**
Phase II: 10 Months (Option 1)	**Milestone: Delivery of government-defined medical countermeasure** • Months 21- 30: Negotiated intermediate metrics for optimization and testing of lead drug delivery vehicles • Month 21: Notification of MCM cargo and target tissue/cell types by government team • Month 27-29: Demonstrate effective, broad delivery of government-defined MCM cargo *in vivo* (CD2)
Phase II': ~2-6 Months (Option 2)	**Milestone: Small-scale manufacturing for testing and evaluation.** • Month ~24-30: scale-up manufacturing of delivery vehicle sufficient for ~500 doses in mice.

Phase I (Base, 20 months): Proof of concept for performer-defined therapeutic and/or prophylactic cargo *in vivo* (0-20 Months): Phase I is intended to generate a lead drug delivery platform that is capable of intracellular delivery of cargos to multiple cell and tissue types *in vivo*. Performers may define their chosen cargo in Phase I, but the BAA requires delivery of nucleic acids during both Phase I and Phase II. Proposers will screen drug delivery vehicles, or combinations thereof, for lead candidates to progress to *in vivo* testing and optimization. Delivery vehicles should demonstrate the ability to be introduced in animal models (e.g. murine, rat, hamster, rabbit, ferret, non-human primates etc.) through simple administration routes (e.g. intramuscular, intranasal, oral, etc.). Three months prior to the end of Phase I, performers will begin CD1, and a final report representing the outcome of CD1 will be submitted to the government team one month prior to the end of Phase I. Performer advancement to Phase II will be determined by DARPA.

Phase II (Priced Option 1, 10 months): Delivery of government-defined MCM *in vivo* (21-30 Months): The goal of the Hermes program is to develop a threat and cargo agnostic delivery vehicle; thus, performers will be challenged to deliver a government-defined cargo in Phase II. The goal of Phase II will be a demonstration that the delivery vehicle developed in Phase I can be adapted to carry a different cargo and expand targeting to additional tissue/cell types not demonstrated in Phase I. Performers will be notified of the government-defined cargo and the intended target cell and tissue types at the beginning of Phase II, and must initiate CD2 at least 3 months prior to the end of Phase II. During Phase II, performers should demonstrate enhanced performance of the delivery capability (e.g. increase in total cargo capacity, improvement in

intracellular delivery efficiency, etc.) beyond achievements in Phase I. A final report will be due at the end of Phase II.

Quantitative and qualitative metrics must be met at the end of each phase and will be defined at negotiation (as described below in Section 1.4). At the end of the program, it is anticipated that performers will transfer technologies developed under the Hermes program to DARPA and Government stakeholders for independent verification, validation, and DoD-specific test and evaluation. Proposals must include a detailed plan for data storage, curation, and sharing with the Government, along with a plan to document protocols, formulations, reagents, and all other materials needed to support technology transition. Transition plans that include technology transition and commercialization to private industry are also highly encouraged.

Priced Option 2: Small-scale manufacturing for testing and evaluation: Pending performance against program metrics and at the discretion of DARPA and government stakeholders, an optional task for manufacturing and transferring small scale material for downstream animal studies could be exercised. Material should be sufficient for a small-scale animal study; the exact quantities produced, and the duration of this Option will be determined in collaboration with DARPA and the Government team based on the proposed technical approach. For budgetary purposes, 500 doses for a mouse model may be used as an estimate. This Option, if exercised, would be executed within Phase II.

Metrics and Milestones

Proposers to the Hermes program must define ambitious, specific, and progressive quantitative metrics in support of program goals and specific to their proposed cargo and drug delivery platform, including intermediate metrics for each Phase of the program to help evaluate technology development progress. **Suggested milestones are included below for proposer consideration but are not meant to be prescriptive.** Due to the diversity of potential solutions to the challenge of intracellular delivery, proposers should define metrics based on the proposer-defined use case and current capabilities. Final metrics are to be determined at time of award negotiation and are subject to DARPA approval. Proposers should note that program metrics may serve as the basis for determining whether satisfactory progress is being made to warrant continued funding of the program.

Proposers should define metrics associated with milestones for each Phase, Capability Demonstration (CD), and overall effort. Although specific program metrics will depend on the chosen cargo, examples of broad qualitative milestones and associated quantitative metrics for the overall program include, but are not limited to:

- Develop high-throughput, combinatorial pipeline screening with delivery formulations *in vivo* or in an appropriate cell, organoid, or tissue system *in vitro.*
- Develop novel reporter systems and demonstrate ability to monitor biodistribution and cargo release in real time.
- Demonstrate formulations that deliver reporters/therapeutic cargos intracellularly and target multiple cells, tissue, and organs concurrently *in vivo*.
    - Metric: Achieve high transfection efficiency (measured at >95% cells) *in vivo* in 5+ tissue types

    - Metric: Achieve sustained *in vivo* expression and/or protection of >3 months before return to a wildtype state (i.e., no genomic integration and undetectable by ADME profiling).
- Demonstrate ability to package large and complex cargos.
    - Metric: Package cargos > 10 kb nucleic acid, >200 kDa protein
- Demonstrate loading of drug delivery vehicle with multiple unique cargo types.
    - Metric: Package at least 2 cargo types (e.g. capable of carrying DNA, RNA, protein, small molecules, etc.) in a single vehicle.
- Demonstrate exceptional safety profile (e.g., minimal adverse effects in a healthy animal model)
    - Metric: Change in weight less than 5%, animals exhibit normal behaviors (e.g., well-groomed, normal posture/gait, explores environment, eats/drinks readily).
    - Metric: No reactivity detected for anti-vehicle antibodies at pg/mL sensitivity for IgG, IgM, IgE for repeated dose testing
    - Metric: No adverse effects in toxicity studies after repeated dose testing
- Administer drug delivery platform through non-invasive administration route (e.g. intramuscular, sub-cutaneous, oral, intranasal).
- Demonstrate exceptional stability of drug delivery platform.
    - Metric: Demonstrate stability at -20°C, or preferably lyophilization and storage at room temperature, for 6 months in real time and 18 months in accelerated aging studies.

Capability Demonstrations. At the end of each Phase, performers will complete a CD, and proposers must clearly indicate their target performance metrics for each CD. For the first CD, metrics must describe the state of art (SOA) drug delivery platform that will be used to benchmark performance, and must define, in quantitative and qualitative terms, what is considered efficient delivery *in vivo*, and describe how it will be measured (e.g. % fluorescently positive cells, target concentration of protective gene product in tissue). Although the proposal must include current information for the SOA benchmark, proposers should anticipate adjusting benchmarks to keep pace with evolving SOA over the course of the Hermes program. Example metrics for each CD are provided in Table 3.

As described in Table 3 below, performers should define the cargo, target, and indication for CD1. While a DoD-relevant use case is highly encouraged, targets with commercial value or other importance to the performer team may be proposed.

For animal models, offerors may propose to simply provide an efficacious dose as defined by SOA or complete an efficacy study in a relevant animal model. Proposers may select any animal model of choice, but must provide justification for the selection especially if proposing large animal studies (e.g. non-human primates).

Table 3. Example Metrics

	Metric	
	CD1	**CD2**
Cargo	Performer-defined cargo	Government-defined cargo

Capacity	>5kb nucleic acid, >100kDa protein	>10kb nucleic acid, >200kDa protein
Durability	2 weeks	>1 month
Tissue/ Cell type specificity	5+ tissue types*	8+ tissue types*
Testing	*In vivo*	
Administration	Simple**	Self-administration**
Stability	-20°C	4°C or room temperature
% Efficiency	≥2-fold improvement over SOA	≥10-fold improvement over SOA
Reactogenicity/ Immunogenicity / Toxicity	No significant reactogenicity/immunogenicity/toxicity†	

Specific tissue types of interest: Lung, liver, spleen, heart, kidney, gastrointestinal tract, bone marrow, muscle, eye, brain/central nervous system
****Simple administration refers to quick, minimally invasive administration performed by a healthcare provider (e.g. intramuscular injection, sub-cutaneous injection, nebulization), while self-administration refers to oral, auto-injector, inhaler, patch, etc. delivery approaches.***
† As measured by in vivo weight loss, immunohistochemistry, RNA sequencing for innate immune response (for example)

1. GENERAL REQUIREMENTS

1.1 PROPOSING TEAMS

It is expected that proposals will involve teams with expertise to execute the goals of the program. Specific content, communications, networking, and team formation are the sole responsibility of the proposer teams. Proposer teams must submit a single, integrated proposal led by a single Principal Investigator, Program Integrator/Manager, under a single prime contractor that addresses all program phases, as applicable.

DARPA held an Industry Day to facilitate the formation of proposer teams with the expertise necessary to meet the goals of the program and enable sharing of information among interested proposers through the DARPA Opportunities Page and the Industry Day registration website.

1.2 DELIVERABLES

All products, material and otherwise, to be provided to the Government as outcomes from conducted research should be defined in the proposal. Performers need to allot time and budget to fulfill obligations for travel to review meetings and the transmission of report documentation.

Mid-Phase and End of Phase reports: One month prior to the end of each Phase (i.e. EOM19, EOM29), performers must draft and present to DARPA a written report of all research activities and metrics satisfied. This report should contain as much supporting data as possible.

Monthly financial reports: Performers are required to provide financial status updates. The prime Performer shall include information for itself and all subawardees/subcontractors. These reports should be in the form of an editable Microsoft (MS) Excel™ file (template to be provided by DARPA), and should provide financial data including, but not limited to:

- Program spend plan by phase and task
- Incurred program expenditures to date by phase and task
- Invoiced program expenditures to date by phase and task

Monthly technical progress reports: Performers are required to provide monthly research updates in the form of a standardized slide presentation given to DARPA and discussed with the program management team via teleconference. Length and detail level is at the discretion of the Program Manager.

Annual reviews: The Principal Investigator (PI) from each performer team (with additional key personnel at the discretion of the PI) will be required to present research progress in person at program review meetings. The purpose of these reviews is to ensure adequate engagement with the DARPA team to discuss and provide opportunities to discuss progress towards milestones and scientific goals, any ongoing technical or programmatic challenges that must be overcome to achieve the overarching goals of the program.

Annual site visits. The government team will visit the performer site at least once per year. Performers should prepare in-depth technical and programmatic updates, as well as facility tours, for the government team during the site visit. Details for the site visit agendas and reports will be in collaboration with the Program Manager and performers.

Final Program Report: When the final funding phase closes out, performer teams must provide a final report summarizing all research activities, outcomes, and molecular mechanisms discovered during the program; publications, research presentations, patent applications that result from the research pursued; and any additional deliverables requested by the Contracting Office for this program.

A notional list of deliverables with Phase delineations is provided below:

Phase	Deliverable	Frequency
I and II	Technical Report	Monthly
I and II	Financial Report	Monthly
I and II	Site Visit Report	Yearly
I	Mid-Phase Report	Month 10
I	CD1 Report	Month 19
I	End of Phase I Report	End of Phase 1
II	CD2 Report	Month 29
II	End of Phase II Report	End of Phase 2
End of program	Final Technical Report	End of period of performance

A notional list of meetings with anticipated locations is provided below:

Meeting Type	Anticipated Location	Frequency
Kickoff	Arlington, VA	Once
Site visit	Performer site	Annually
Hermes Principal Investigator meeting	Arlington, VA	One per Phase
Technical & financial update	Teleconference/videoconference	At least monthly

Section II: Evaluation Criteria

- Proposals will be evaluated using the following criteria listed in ***descending order of importance***: Overall Scientific and Technical Merit; Potential Contribution and Relevance to the DARPA Mission; and Cost and Schedule Realism.

- **Overall Scientific and Technical Merit:**
  The proposed technical approach is innovative, feasible, achievable, and complete. The proposed technical team has the expertise and experience to accomplish the proposed tasks. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks, and planned mitigation efforts are clearly defined and feasible. The timeline for achieving major milestones is aggressive but rationally supported with a clear description of the requirements and risks. The proposer's prior experience in similar efforts must clearly demonstrate an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule. The proposed team has the expertise to manage the cost and schedule.

- **Potential Contribution and Relevance to the DARPA Mission:**
  The potential contributions of the proposed effort bolster the national security technology base and support DARPA's mission to make pivotal early technology investments that create or prevent technological surprise.

  The proposer clearly demonstrates its capability to transition the technology to government and commercial entities. Transition to U.S. Government stakeholders is anticipated at the end of the period of performance. Proposers must therefore include plans and demonstrate capability to transition the reagents, assays, computational pipelines, and other materials to the government. Plans that enable transition to private industry are encouraged. It is important that transition to the research, industrial, and/or operational military communities is done in such a way as to enhance U.S. defense. In addition, the evaluation will take into consideration the extent to which the proposed intellectual property (IP) rights will potentially impact the Government's ability to transition the technology.

- **Cost and Schedule Realism:**

The proposed costs and schedule are realistic for the technical and management approach and accurately reflect the technical goals and objectives of the solicitation. All proposed labor, material, and travel costs are necessary to achieve the program metrics, consistent with the proposer's statement of work and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and proposed subawardees are substantiated by the details provided in the proposal (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs and the basis for the estimates). The proposed schedule aggressively pursues performance metrics in an efficient time frame that accurately accounts for the anticipated workload.

It is expected that the effort will leverage all available relevant prior research in order to obtain the maximum benefit from the available funding. For proposals that contain cost share, the proposer has provided sufficient rationale as to the appropriateness of the cost share arrangement relative to the objectives of the proposed solution (e.g. high likelihood of commercial application, etc.).

- Unless otherwise specified in this announcement, for additional information on how DARPA reviews and evaluates proposals through the Scientific Review Process, please visit: Proposer Instructions and General Terms and Conditions

Section III: Submission Information

- This announcement allows for multiple award instruments types to be awarded to include Procurement Contracts, Cooperative Agreements, and Other Transactions for Prototypes. Some award instrument types have specific cost-sharing requirements. The following websites are incorporated by reference and contain additional information regarding overall proposer instructions, general terms and conditions, and each specific award instrument type.

    - **Proposer Instructions and General Terms and Conditions**: Proposer Instructions and General Terms and Conditions
    - **Procurement Contracts**: Proposer Instructions: Procurement Contracts
    - **Cooperative Agreements:** Proposer Instructions: Grants/Cooperative Agreements
    - **Other Transaction agreements**: Proposer Instructions: Other Transactions

- This announcement contains an abstract phase. Abstracts are strongly encouraged, but not required. Abstracts are due **May 3, 2024 at 4:00 p.m.** as stated in the Overview section. Additional instructions for abstract submission are contained within **Attachments A and B**.

- Full proposals are due **June 4, 2024 at 4:00 p.m.** as stated in the Overview section.

- **Attachments C, D, E, and F** contain specific instructions and templates and constitute a full proposal submission for proposers requesting either a Procurement Contract or Other Transactions for Prototype.
- **Attachments C, D, and F** contain specific instructions and templates and constitute a full proposal submission for proposers requesting a Cooperative Agreement.

- Please visit Proposer Instructions: General Terms and Conditions for general Terms and Conditions for all requested contract types. Visit Proposer Instructions: Procurement Contracts for submission instructions for proposers requesting Procurement Contracts. Visit Proposer Instructions: Other Transactions for submission instructions for proposers requesting Other Transactions. Visit Proposer Instructions: Grants/Cooperative Agreements for submission instructions for proposers requesting Cooperative Agreements. (Proposers requesting Procurement Contracts or Other Transactions for Prototype must submit proposals through the Broad Agency Announcement Tool. If requesting a Cooperative Agreement proposals must be submitted through grants.gov.)

- **BAA Attachments**:
  - **(required) Attachment A**: Abstract Summary Slide Template
  - **(required) Attachment B**: Abstract Instructions and Template
  - **(required) Attachment C:** Proposal Summary Slide Template
  - **(required) Attachment D**: Proposal Instructions and Volume I Template (Technical and Management)
  - **Attachment E**: Proposal Instructions and Volume II Template (Cost) **(required for proposers requesting Procurement Contracts or Other Transactions for Prototype)**
  - **(required) Attachment F**: MS Excel™ DARPA Standard Cost Proposal Spreadsheet

Section IV: Special Considerations

- This announcement, stated attachments, and websites incorporated by reference constitute the entire solicitation. In the event of a discrepancy between the announcement, attachments, or websites, the announcement shall take precedence.

- All responsible sources capable of satisfying the Government's needs, including both U.S. and non-U.S. sources, may submit a proposal that shall be considered by DARPA. Historically Black Colleges and Universities, Small Businesses, Small Disadvantaged Businesses and Minority Institutions are encouraged to submit proposals and join others in submitting proposals; however, no portion of this announcement will be set aside for these organizations' participation due to the impracticality of reserving discrete or severable areas of this research for exclusive competition among these entities. Non-U.S. organizations and/or individuals may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances.

- As of the time of publication of this solicitation, all proposal submissions are anticipated to be unclassified.

- Federally Funded Research and Development Corporations (FFRDCs) and Government entities interested in participating in the **Hermes** program or proposing to this BAA should first contact the Agency Point of Contact (POC) listed in the Overview section prior to the Abstract due date to discuss eligibility. Complete information regarding eligibility can be found at Proposer Instructions and General Terms and Conditions.

- As of the date of publication of this solicitation, the Government expects that program goals as described herein may be met by proposed efforts for fundamental research and non-fundamental research. Some proposed research may present a high likelihood of disclosing performance characteristics of military systems or manufacturing technologies that are unique and critical to defense. Based on the anticipated type of proposer (e.g., university or industry) and the nature of the solicited work, the Government expects that some awards will include restrictions on the resultant research that will require the awardee to seek DARPA permission before publishing any information or results relative to the program. For additional information on fundamental research, please visit Proposer Instructions and General Terms and Conditions.

- Proposers should indicate in their proposal whether they believe the scope of the research included in their proposal is fundamental or not. While proposers should clearly explain the intended results of their research, the Government shall have sole discretion to determine whether the proposed research shall be considered fundamental and to select the award instrument type. Appropriate language will be included in resultant awards for non-fundamental research to prescribe publication requirements and other restrictions, as appropriate. This language can be found at Proposer Instructions and General Terms and Conditions.

- For certain research projects, it may be possible that although the research to be performed by a potential awardee is non-fundamental research, its proposed subawardee's effort may be fundamental research. It is also possible that the research performed by a potential awardee is fundamental research while its proposed subawardee's effort may be non-fundamental research. In all cases, it is the potential awardee's responsibility to explain in its proposal which proposed efforts are fundamental research and why the proposed efforts should be considered fundamental research.

- DARPA's Fundamental Research Risk-Based Security Review Process (formerly CFIP) is an adaptive risk management security program designed to help protect the critical technology and performer intellectual property associated with DARPA's research projects by identifying the possible vectors of undue foreign influence. The Security and Intelligence Directorate (SID) team will create risk assessments of all proposed Senior/Key Personnel selected for negotiation of a fundamental research grant or cooperative agreement award. The SID risk assessment process will be conducted separately from the DARPA scientific review process and adjudicated prior to final award. For additional information on this process, please visit Proposer Instructions: Grants/Cooperative Agreements.

- DARPAConnect offers free resources to potential performers to help them navigate DARPA, including "Understanding DARPA Award Vehicles and Solicitations", "Making the Most of Proposers Days", and "Tips for DARPA Proposal Success". Join DARPAConnect at www.DARPAConnect.us to leverage on-demand learning and networking resources.

- DARPA has streamlined our Broad Agency Announcements and is interested in your feedback on this new format. Please send any comments to DARPAsolicitations@darpa.mil