Program Solicitation
Rapid Inhibitor Discovery and Development pipeLine

RIDDL Program
BIOLOGICAL TECHNOLOGIES OFFICE
DARPA-PS-25-03

November 15, 2024

PROGRAM SOLICITATION OVERVIEW INFORMATION

- **Federal Agency Name** – Defense Advanced Research Projects Agency (DARPA), Biological Technologies Office (BTO)
- **Funding Opportunity Title** – Rapid Inhibitor Discovery and Development pipeLine (RIDDL)
- **Announcement Type** – Initial Announcement
- **Funding Opportunity Number** – DARPA-PS-25-03
- **Dates**
  - Posting Date: November 15, 2024
  - Questions Due Date: December 2, 2024
  - Full Proposal Due Date and Time: December 20, 2024, 4:00 pm. ET

- The Defense Advanced Research Projects Agency (DARPA) is soliciting innovative proposals to develop and demonstrate rapid methods to identify and optimize novel molecules that exhibit inhibitory effects on gene editing technologies. Of particular interest are commonly used gene editors such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated proteins (CRISPR-Cas) nucleases; gene editing technologies beyond CRISPR-Cas systems are also of interest to keep pace with the rapidly advancing field and promote the safe, controlled use of these technologies. The Rapid Inhibitor Discovery and Development pipeLine (RIDDL) program explicitly seeks transformative approaches that enable the rapid discovery, design, and development of novel inhibitors with enhanced activity, specificity, utility, and potency for gene editing technologies. These approaches could serve as a rapid response to counteract the accidental or intentional misuse of gene editing technologies. Novel inhibitor activity will be assessed in vitro over the course of the program to demonstrate the efficacy of the prototype discovery and development pipelines. The pipelines, as well as a subset of top-performing molecules at scaled-up quantities, will be transitioned for testing and evaluation by Department of Defense (DoD) stakeholders. Research that generates incremental improvements to the existing state-of-the-art is specifically excluded.
- **Multiple awards are anticipated**.
- **Total Funding** – DARPA has approximately $17M total for performer awards and anticipates making multiple awards.
- **Types of instruments that may be awarded** – Other Transaction for Prototype
- **Technical Point of Contact** – Dr. Shannon Greene, Program Manager
- **Agency Contact**

  The Solicitation Coordinator for this effort can be reached at:
  RIDDL@darpa.mil
  DARPA/BTO
  ATTN: DARPA-PS-25-03
  675 North Randolph Street
  Arlington, VA 22203-2114
- **Attachments**
  A. Proposal Summary Slide Template
  B. Proposal Instructions and Volume I Template (Technical and Management)
  C. Proposal Instructions and Volume II Template (Cost)

D. MS Excel™ DARPA Standard Cost Proposal
E. MS Excel™ Risk Register
F. Model Prototype Other Transaction (OT) Streamlined, Fixed
G. Schedule of Milestones and Payments

PROGRAM SOLICITATION
Defense Advanced Research Projects Agency (DARPA)

1. PROGRAM INFORMATION

1.1. Background

The rapidly evolving field of advanced genome editing tools has created the ability to modify genetic material in a manner that is precise, rapid, cost-effective, and broadly accessible. CRISPR-Cas technologies represent one of the most widely adopted tools in the genome engineering toolkit, which already consists of a diverse set of molecules, including meganucleases, transposons, recombinases, protein nucleic acids, zinc-finger nucleases, and Transcription Activator-Like (TAL) effector nucleases. From the initial discovery and demonstration of CRISPR-Cas gene editing technologies, the field has rapidly expanded both in the number and types of CRISPR-Cas systems via advanced computational discovery pipelines[1].

The advancement of CRISPR-based genome editing technologies has revolutionized the field of biotechnology and genetic engineering. However, concerns regarding the precision, specificity, and control of CRISPR-Cas systems remain. One promising avenue to address these concerns is the discovery or design of novel inhibitors. These molecules have the potential to inhibit and tune regulation of CRISPR-mediated genome editing by limiting unintended, off-target edits and enabling spatiotemporal control of gene editing activity, thereby enhancing its safety, efficacy, and utility.

Previous DARPA investments in the Safe Genes program demonstrated discovery of potent protein inhibitors for a wide array[2] of CRISPR-Cas technologies, including enzymatic inhibitors capable of acting at sub-stoichiometric levels[3]. Safe Genes performers also developed platforms for discovery of small molecule inhibitors of CRISPR-Cas systems[4,5]. Taken together with work from other groups in the literature describing nucleic acid-based inhibitors[6-8], multiple classes of molecules that exhibit anti-CRISPR activity have been demonstrated, providing significant depth and breadth for novel inhibitor discovery. The RIDDL program seeks to leverage these prior efforts to develop tools for rapid discovery, optimization, and validation of potent inhibitors for gene editing technologies.

---

[1] Altae-Tran et al., Uncovering the functional diversity of rare CRISPR-Cas systems with deep terascale clustering. Science. **2023**, 382 (6637), eadi1910 DOI:10.1126/science.adi1910
[2] Marino *et al*., Anti-CRISPR protein applications: natural brakes for CRISPR-Cas technologies. *Nat. Methods* **2020**, 17(5), 471-479.
[3] Knott *et al.*, Broad-spectrum enzymatic inhibition of CRISPR-Cas12a. *Nat. Struct. Mol. Biol.* **2019**, 26 (4), 315-321.
[4] Maji *et al.*, A High-Throughput Platform To Identify Small-Molecule Inhibitors Of CRISPR-Cas9. *Cell*. **2019**, 177, 1067-1079.
[5] Lim, *et al*., A general approach to identify cell-permeable and synthetic anti-CRISPR small molecules. *Nat. Cell Biol.* **2022**, 24, 1766-1775.
[6] Zhao, *et al.*, Development of aptamer-based inhibitors for CRISPR/Cas system. *Nucleic Acids Res.* **2020**, 49(3), 1330-1344.
[7] Barkau, *et al.*, Rationally Designed Anti-CRISPR Nucleic Acid Inhibitors of CRISPR-Cas9. *Nucleic Acids Ther.* **2019**, 29 (3), 136-147.
[8] Camara-Wilpert, *et al*., Bacteriophages suppress CRISPR–Cas immunity using RNA-based anti-CRISPRs. *Nature*. **2023**, 623, 601-607.

Beyond CRISPR-Cas technologies, some recent discoveries, such as Obligate Mobile Element Guided Activity (OMEGA) effector TnpB[9] and Fanzor[10], have further broadened the menu of RNA-guided DNA endonucleases that can be programmed for gene editing purposes. These new editor systems provide further opportunity to explore development of platform technologies for discovery of inhibitors to emerging gene editing technologies. Specifically, RIDDL will develop platform technologies for highly potent inhibitors of gene editors capable of arresting nuclease activity for multiple classes, types, and species of editors. By harnessing advanced computational discovery capabilities such as clustering[11] and deep learning, RIDDL will develop a platform for 24-hour turnaround discovery and development of inhibitors of novel, emergent gene editor technologies. If successful, the RIDDL program will develop a pipeline capable of fielding validated inhibitors in less than 24 hours, enhancing the safety of gene editing technologies and providing rapid response capabilities in the event of accidental or intentional misuse of gene editing technologies.

Ethical, Legal, and Societal Implications (ELSI)

DARPA maintains its commitment to ensuring that efforts funded under this Program Solicitation adhere to ethical and legal regulations currently in place for Federal and DoD-funded research. The RIDDL program is informed by independent Ethical, Legal, and Social Implications (ELSI) experts to help DARPA proactively identify potential issues related to this work.

1.2. Technical Approach

The RIDDL program is agnostic to the methods and approaches employed for discovery or design of novel inhibitors as long as they are potentially transformative. Proposals should focus on selecting diverse CRISPR-Cas systems, updating the CRISPR-Cas system space as novel variants are discovered or designed to keep pace with the state of the art, suitable for demonstrating inhibition and potency. Proposers are highly encouraged to include recently discovered CRISPR-Cas orthologs. Proposals must include inhibitors for CRISPR-Cas systems, specifically Cas9 and Cas12; however, molecules that can inhibit other nucleases are encouraged. Potential approaches to development of novel inhibitors include, but are not limited to:

- Bioinformatic, biochemical, computational, or genetic methods to discover new inhibitors
- High-throughput biochemical, chemical, and/or genetic screens
- Directed evolution
- Multivalent molecules
- Hybrid synthetic-biological materials
- Fusion proteins with enzymatic activity
- Small molecules

[9] Karvelis *et al*., Transposon-associated TnpB is a programmable RNA-guided DNA endonuclease. *Nature*. **2021**, 599, 692-696.
[10] Saito *et al.*, Fanzor is a eukaryotic programmable RNA-guided endonuclease. *Nature*. **2023**, 620, 660-668.
[11] Pinilla-Redondo, *et al.*, Discovery of multiple anti-CRISPRs highlights anti-defense gene clustering in mobile genetic elements. *Nat. Comm.* **2020**, 11, 5652.

- Modified nucleic acids and mimetics
- Peptide nucleic acids

The RIDDL program is also agnostic to the method(s) by which inhibitors arrest genome editing activity. Novel inhibitors may utilize a wide variety of mechanisms of action, including but not limited to the following:

- Inhibiting DNA binding
- Inhibiting cutting activity
- Inhibiting conformational changes required to initiate nuclease activity
- Enzymatic degradation of CRISPR-Cas complexes or components
- Cleaving crRNA
- Inhibiting CRISPR-Cas RNA biogenesis
- Inhibiting formation of CRISPR-Cas complexes with guide RNA

Proposers are expected to provide detailed information on the *in vitro* assays (including cell culture approaches if applicable) to be employed to determine gene editing activity and modulation of that activity. Key information such as assay robustness, sensitivity, dynamic range, concentrations, alternative assay approaches and substrates, throughput, evaluation of off-target effects, *in vitro* testing for toxicity, along with appropriate positive and negative controls should be articulated in depth. In addition, proposals should provide details on the number of candidate inhibitors and the chemical diversity that will be sampled. Proposers should also provide a viable plan to scale up high-performing candidates for future development and technology transfer. Scale-up activities should produce sufficient material for follow-on advanced research and development activities (e.g., milligram to gram scale for small molecules, microgram to milligram scale for proteins and nucleic acids).

Specifically excluded are proposals that involve:

- Engineering Cas variants with modulated activity and their cognate inhibitors with enhanced specificity
- Approaches that include animal subjects research
- Approaches that include human subjects research
- Solely *in silico* approaches without corresponding wet lab validation
- Approaches that do not develop inhibitors for Cas9 enzymes and Cas12 enzymes

Proposals which include any of the approaches described above may be deemed nonconforming and may be rejected without further review.

Proposals should focus on the development of a rapid discovery platform for inhibitors of novel, emerging gene editor systems, including Cas9 and Cas12, and including those generated by deep-learning language models[12]. Objectives include (a) discovery pipeline for inhibitors of novel editing systems; (b) *in vitro* models and assays to test and validate candidate molecules; and (c)

[12] Madani, et al., Large language models generate functional protein sequences across diverse families. *Nat Biotechnol.*, **2023**, 41, 1099-1106.

demonstration of potent inhibition of novel gene editing systems.

Discovery Pipeline for Inhibitors of Novel Editing Systems. Proposers must develop methods for rapid discovery of inhibitors for novel gene editing systems upon identification of a new, emerging editor. Proposers should clearly articulate methods for discovery and discuss strengths and mitigation plans for technical risks. For example, for AI/ML algorithms, proposals should discuss parameters and details such as cost function used during training, convergence properties/stopping criteria, training data augmentation procedures, input data pre-processing/cleaning steps, input data quality control, characteristics of training/test data, procedures for detailing with missing data, availability of data for training, methods for updating the algorithm after deployment.

In Vitro Models and Assays. Test and evaluation of inhibitors to newly discovered editing systems will require rapid development of model systems and assays. Proposers should describe the methods by which model systems would be developed to assess novel gene editor activity, off-target effects, and toxicity, as well as the development of tests for quantitative detection of inhibition. Newly discovered editors (e.g., OMEGA, Fanzor, etc.) as well as computationally designed editors (e.g., OpenCRISPR) may be used as test cases to describe development of models and analysis.

Inhibition of Novel Gene Editors. The ideal discovery pipeline would be able to rapidly nominate lead candidates and test the ability of those candidates to inhibit novel gene editors. Proposals should describe the ability of the pipeline to demonstrate discovery of and specific inhibition of a novel editor.

1.3. Acquisition Strategy

RIDDL is using a modified acquisition approach to lower the administrative burden of entry, reduce program risk, foster competition, and enable performing teams get to work quickly. This RIDDL Program Solicitation (PS) solicits proposals covering all the outlined tasks in a 30-month period. Offerors will submit a full proposal in accordance with the instructions in this solicitation. The Government will review conforming proposals, and selected proposers may be awarded an Other Transaction (OT) for Prototype agreement.

1.4. Program Structure

As shown in Figure 1, RIDDL is divided into three sequential phases: Phase I (Base) for 10 months; Phase II (Priced Option 1) for 10 months; and Phase III (Priced Option 2) for 10 months. Proposers must present a plan for no more than 30 months that includes a comprehensive approach to meeting all program metrics and objectives. Progression from Phase I to Phase II and from Phase II to Phase III is dependent on demonstrated success in meeting program metrics and objectives, as described in Section 1.5. Unless noted otherwise elsewhere in this PS, milestones included in this section are intended to be illustrative; proposers should note that the government does not require these milestones and encourages maximum creativity, innovation, and flexibility in defining appropriate milestones for the work proposed.

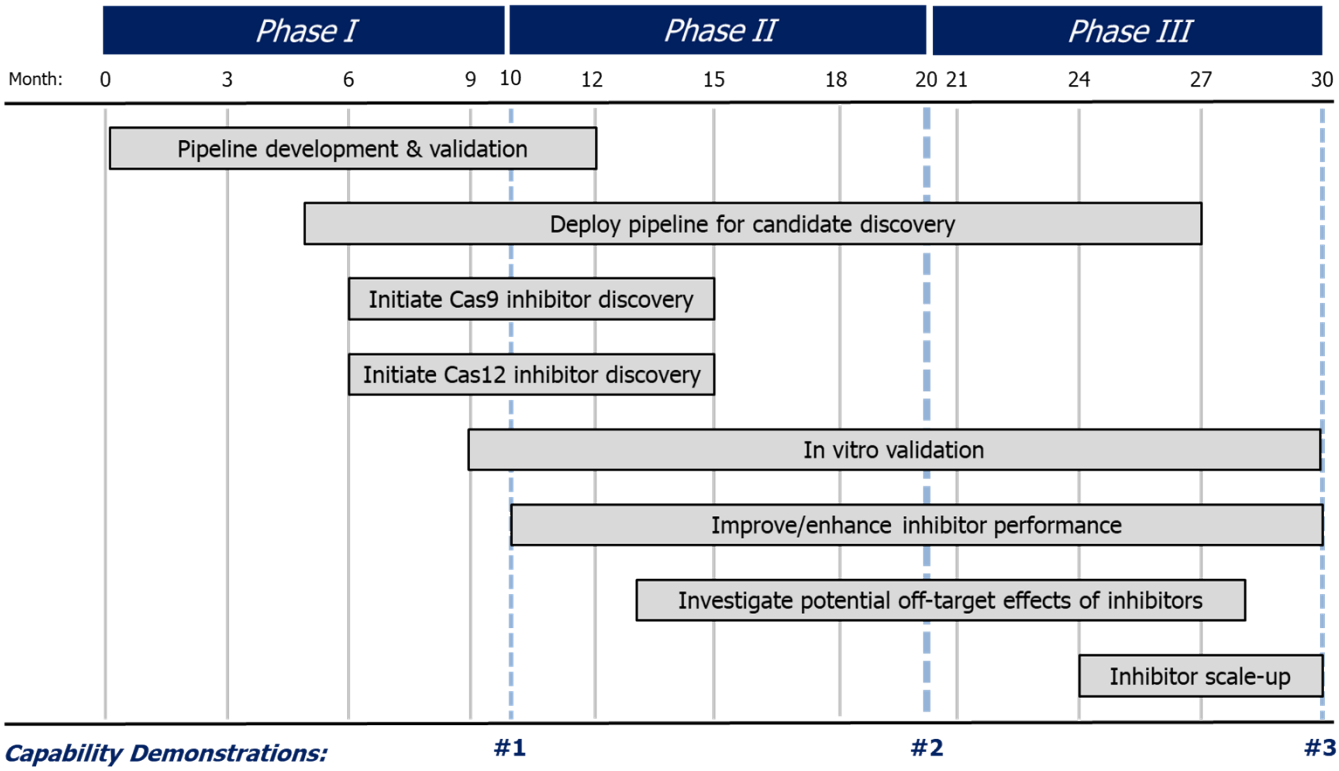

Figure 1: RIDDL schedule

Phase I (Base, 10 months; Months 1 – 10)
During the 10-month Phase I, performers will establish discovery and test platforms.

The capstone of Phase I is Capability Demonstration (CD) 1 (see Section 1.6), during which performers will perform a benchmarking demonstration of the rapid discovery pipeline. Additional milestones may include:

- Establish discovery platform
- Develop models for gene editor inhibitor discovery
- Demonstrate functionality of platform components
    - Initial proof of concept of inhibitor discovery
    - Establish initial *in vitro* reporter system for novel gene editors

Phase II (Priced Option 1, 10 months; Months 11 – 20)
During the 10-month Phase II, performers will improve the pipeline developed in Phase I by identifying potential inhibitors for novel gene editors and developing *in vitro* systems to test those inhibitors.

The capstone of Phase II is CD 2 at Month 20 (see Section 1.6). Additional milestones may include:

- Demonstrate platform ability to discover new inhibitors
- Establish flexible *in vitro* system to test novel inhibitors and editors

- Establish quantitative assays for measuring editor activity and inhibition
- Initial proof of concept of detection of novel gene editor inhibition

Phase III (Priced Option 2, 10 months; Months 21 – 30)
During the 10-month Phase III, performers will demonstrate the ability of their platforms to rapidly produce highly potent inhibitors. Performers will validate discovery pipeline candidates and *in vitro* models to demonstrate inhibition of novel gene editors.

The capstone of Phase III is CD 3 at Month 30 (see Sect. 1.6). Additional milestones may include:

- Demonstrate rapid end-to-end discovery of novel inhibitors
- Demonstrate rapid establishment of *in vitro* systems to test novel inhibitors and editor systems
- Demonstration of methods to quantify off-target effects and toxicity *in vitro*.

Execution of technology transition plan and active support to stakeholders

- Establish portable, reproducible bioinformatic pipelines
- Establish portable databases/training sets
- Establish stable stocks of reporter cell lines for *in vitro* assays

At the end of the program, it is anticipated that performers will transition technologies developed under the RIDDL program to Government stakeholders for further testing, evaluation, and development. **Proposals must include a technology transfer package plan to share data, protocols, computational pipelines, top-performing inhibitor(s), reagents, *in vitro* test systems, and all other materials needed to actively support technology transition to Government stakeholders during this final phase of the program.** Plans that also enable transition to private industry are encouraged.

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

Table 1: RIDDL notional deliverables by Phase

Phase	Deliverable	Frequency
I, II, and III	Technical Report	Monthly
I, II, and III	Financial Report	Monthly
I	CD 1 Report	End of Phase 1
II	CD 2 Report	End of Phase 2
II	Transition Plan	End of Phase 2
III	CD 3 Report	End of Phase 3
III	Technology Transfer Package	End of Phase 3
End of program	Final Technical Report	End of PoP

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

Table 2: Anticipated RIDDL program meetings

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

1.5. Program Tasks, Goals and Metrics

For the Government to evaluate the effectiveness of a proposed solution in achieving the stated program objectives, proposers are required to define specific and quantitative performance metrics for each task and subtask in support of the selected technical approach. Anticipated program milestones are specified below in Table 3. However, proposers should note that the Government has identified these milestones with the intention of bounding the scope of effort, while affording maximum flexibility, creativity, and innovation in proposing solutions to the stated problem.

Quantitative performance metrics may vary for each proposer-selected application and system. Proposers to the RIDDL program are required to define ambitious, specific, and quantitative metrics in support of program goals, including intermediate metrics (e.g., every 3-6 months or sooner) to help further evaluate technical progress. Some exemplary milestones for proposers to consider are included in Table 3 below but are not meant to be prescriptive. Proposed metrics will be finalized during 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.

Table 3: RIDDL example metrics table

Metric	Required	Preferred
Potency/Stoichiometry	Highly potent, >99% inhibition	Highly potent, catalytic/enzymatic
Durability	>24h	>7 days
Safety	No off-target effects, no immunogenicity, no toxicity	
Speed 1.0 (from novel editor to candidate inhibitor discovery)	<3 days	<1 day
Speed 2.0 (from novel editor to *in vitro* model)	<7 days	<3 days
Speed 3.0 (from novel editor to validated safety)	<14 days	<7 days
Functional candidate inhibitors for a given novel editor	>3	>6

The agility and speed of the proposed platforms to adapt to new editors will be a factor in evaluation of performance.

1.6. Capability Demonstrations

Performance metrics should focus on improvements to speed of inhibitor nomination, specificity, safety, and potency of inhibitors, including, but not limited to, the following categories:

- Specificity of inhibition
- Potency of inhibition (e.g., percentage of editor activity decreased)
- Speed of inhibitor discovery, nomination, and validation

Proposers must clearly indicate their target performance metrics for CD. These metrics must describe the benchmark by which performance will be measured, defined in quantitative and qualitative terms. Successful completion of all capability demonstrations should result in a robust, rapid discovery pipeline for highly potent (>99% inhibition) inhibitors to novel editors.

Examples of proposed performance metrics that must be provided by each proposer team are shown in Table 4, below.

Table 4: Notional B-SAFE capability demonstration performance metrics

Metric	**CD1**	**CD2**	**CD3**
Potency	>50%	>75%	>99%
Specificity	>70%	>80%	>90%
Time to inhibitor candidate identification	<1 week	<72 hours	<24 hours
Time to lead inhibitor downselect based on *in vitro* assay	<2 weeks	<1 week	<72 hours
Number of effective lead inhibitor candidates	>1	>3	>6
Throughput (# of novel editors screened in parallel)	1	5	10

The CDs are scheduled to take place at the end of Phase I, Phase II, and Phase III, as shown in Table 5 below.

Table 5: Capability Demonstration Schedule

Capability Demonstration (CD)	Program Phase	Program Month
CD1	Phase I	10
CD2	Phase II	20
CD3	Phase III	30

2. PROGRAM SOLICITATION AUTHORITY

This PS may result in the award of an OT for Prototype agreement, which can include not only commercially available technologies fueled by commercial or strategic investment but also concept demonstrations, and development activities that can significantly improve commercial technologies, existing Government-owned capabilities, and/or concepts for broad defense and/or public application(s). The Government reserves the right to award an OT for Prototype agreement under 10 U.S.C. § 4022 or make no award at all. In all cases, the Government agreements officer shall have sole discretion to select the award agreement type, regardless of agreement type proposed, and to negotiate all agreement terms and conditions with selected proposers. The OT agreement will not require cost sharing unless the proposer is a traditional defense contractor who is not working with a non-traditional defense contractor to a significant extent.

2.1. PS Procedure

In response to this solicitation, and after verifying eligibility, proposers are asked to submit a 25-page proposal as described in Section 4.2. Specific evaluation criteria used by DARPA to evaluate proposals can be found in Section 4.3. After evaluation, DARPA will decide which proposers will be selected to participate in the program. The Government will not pay proposers responding to this PS for the costs associated with proposal development.

DARPA will use the following process to facilitate the RIDDL source selection:

a. **Questions and Answers (Q&A) (Informational Only):** DARPA will post a consolidated Q&A document. The Q&A document will be available online at https://www.darpa.mil/work-with-us/opportunities.
Questions can be sent to RIDDL@darpa.mil. DARPA will respond to any relevant question(s) prior to the final proposal due date and post consolidated Q&A at the DARPA Opportunities page (https://www.darpa.mil/work-with-us/opportunities).

b. **Full Proposal (Required)**: The Government will review all conforming proposals (see Section 4.4), which will not be made public or provided to other proposers. Proposers must only propose an OT for Prototype with fixed payable milestones. (Note – Milestones represent a completed event. Milestone schedule is based on key observable events in the critical path to accomplish program objectives. Payments are released by successful performance of observable technical events. Fixed payable milestones are payments based on successful completion of the milestone accomplishments agreed to in the milestone plan. A Schedule of Milestones and Payments is included as Attachment G.)

3. ELIGIBILITY INFORMATION

3.1. Eligible Applicants

3.1.1 Federally Funded Research and Development Centers (FFRDCs), University Affiliated Research Centers (UARCs), and Government Entities

For Federally Funded Research and Development Centers (FFRDCs), University Affiliated Research Centers (UARCs), and Government entities interested in participating in the RIDDL program or proposing to this PS should first contact the Agency Point of Contact (POC) listed in the Overview section prior to the proposal due date to discuss eligibility.

3.1.2. Other Applicants

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.

3.2. Organizational Conflicts of Interest (OCI)

An organization cannot simultaneously provide scientific, engineering, technical assistance (SETA), advisory and assistance services (A&AS), or similar support to DARPA and also be a performer on a DARPA research program.

If a prospective proposer believes a conflict of interest exists or may exist (whether organizational or otherwise) or has questions on what constitutes a conflict of interest, the proposer must send their contact information and a summary of the potential conflict via the specific e-mail address identified in this PS before time and effort are expended in preparing any submission documentation.

4. GUIDELINES FOR PROPOSALS

4.1. General Guidelines

a. Do not include elaborate brochures; only include information relevant to the submission requirements or evaluation criteria.

b. Use of a diagram(s) or figure(s) to depict the essence of the proposed solution is permitted.

c. All proposals shall be unclassified.

d. Proposers are responsible for clearly identifying proprietary information. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary" or "Company Proprietary." NOTE: "Confidential" is a classification marking used to control the dissemination of U.S. Government National Security Information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

e. Questions regarding proposals can be sent to RIDDL@darpa.mil by December 2, 2024.

f. Submit full proposals by December 20, 2024, 4:00 p.m. ET

g. Submissions sent through other mediums, channels, or after the prescribed Program Solicitation deadline will not be considered, reviewed, or evaluated.

4.2. Full Proposal

a. Full proposals are due December 20, 2024, 4:00 p.m. ET as stated in the Overview section. **Attachments A, B, C, D, E, F, and G** contain specific instructions and templates and constitute a full proposal submission. Please visit Proposer Instructions and General

Terms and Conditions for specific information regarding submission methods through the Broad Agency Announcement Tool (BAAT).

b. Attachment A: Proposal Summary Slide Template

c. Attachment B: Proposal Instructions and Volume I Template (Technical and Management)

d. Attachment C: Proposal Instructions and Volume II Template (Cost)

e. Attachment D: MS Excel™ DARPA Standard Cost Proposal

f. Attachment E: MS Excel™ Risk Register

g. Attachment F: Model OT for Prototype Agreement*:* Proposers must complete and submit the Model Prototype Other Transaction (OT) provided as Attachment F as part of the Proposal package. DARPA has provided the model OT in order to expedite the negotiation and award process.

The Model Prototype Other Transaction (OT) Streamlined, Fixed is representative of the terms and conditions that DARPA intends to award for RIDDL and includes the following six (6) attachments:

- Attachment 1 Task Description Document
- Attachment 2 Report Requirements
- Attachment 3 Schedule of Milestones and Payments
- Attachment 4 Agreements Officer's Representative Appointment Memo
- Attachment 5 Property/Equipment
- Attachment 6 Performer Attestation

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 should provide 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.).

Proposers may suggest edits to the model OT for consideration by DARPA and provide a copy of the model OT with tracked changes as part of their proposal package. Please note that DARPA may not agree to suggested edits. The Government reserves the right to remove a proposal from award consideration should the parties fail to reach agreement on OT award terms and conditions. If edits to the model OT are not provided as part of the proposal package, DARPA assumes that the proposer has reviewed and accepted the award terms and conditions to which they may have to adhere and the sample OT agreement provided as an attachment, indicating agreement (in principle) with the listed terms and conditions applicable to the specific award instrument. DARPA explicitly reserves the right to terminate awards if negotiations are not completed in a timely manner.

h. Attachment G: Schedule of Milestones and Payments: Proposers must complete and submit the Schedule of Milestones and Payments provided as Attachment G as part of the Proposal package. Proposers must only propose an OT for Prototype agreement with fixed payable milestones. Note – Milestones represent a completed event. Milestone schedule is based on

key observable events in the critical path to accomplish program objectives. Payments are triggered by successful performance of observable technical events. Fixed payable milestones are payments based on successful completion of the milestone accomplishments agreed to in the milestone plan**.**

4.3. Full Proposal– Process and Basis of Evaluation

- 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; 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 proposed intellectual property restrictions (if any) will not significantly impact the Government's ability to transition the technology.

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.

- **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 sub-awardees 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.).

After completing evaluation of proposals, DARPA will: 1) negotiate a 30-month award; or 2) inform the proposer that its proposed concept/solution is not of continued interest to the Government, and they are no longer considered for the program. If DARPA does not intend to issue an award to a proposer, DARPA will provide feedback to the proposer regarding the rationale for this decision.

4.4. Review and Selection Process

DARPA's policy is to ensure impartial, equitable, and comprehensive proposal evaluations based on the evaluation criteria listed above and to select the source (or sources) whose proposal meets the Government's technical, policy, and programmatic goals. DARPA will conduct a review of each proposal. All evaluations will be based solely on the evaluation criteria in Section 4. Using the evaluation criteria, the Government will evaluate each proposal in its entirety, documenting the strengths and weaknesses relative to the evaluation criteria. Based on the identified strengths and weaknesses, DARPA will determine whether a proposal is selectable. DARPA will not evaluate proposals against each other during the scientific review process, but rather evaluate the proposals on their own merit to determine how well the proposal meets the criteria stated in this PS. DARPA will make an award to a proposer whose proposal is determined to be selectable by the Government, consistent with instructions and evaluation criteria specified in the PS, and based on availability of funding. Given the limited funding available, not all proposals considered selectable may be selected for a potential award. For the purposes of this proposal evaluation process, DARPA defines a "selectable" proposal as follows: Selectable: A selectable proposal is one that the Government has evaluated against the evaluation criteria listed in the PS, and the positive aspects outweigh the negative aspects. For the purposes of this proposal evaluation process, DARPA defines a "non-selectable" proposal as follows: Non-Selectable: A proposal is considered non-selectable when the Government has evaluated it against the evaluation criteria listed in the PS, and the positive aspects do not outweigh the negative aspects.

5. AWARDS

5.1. General Guidelines

Upon favorable review of the proposal and subject to the availability of funds, the Government may choose to negotiate an award an OT for Prototype agreement.

The Government Agreements Officer reserves the right to negotiate directly with the proposer on the terms and conditions prior to execution of the resulting OT agreement, including payment terms, and will execute the agreement on behalf of the Government. Be advised, only a Government Agreements Officer has the authority to enter into, or modify, a binding agreement on behalf of the United States Government.

In order to receive an award:

a. Proposers must have a Unique Entity Identifier (UEI) number and must register in the System for Award Management (SAM). Proposers are advised to commence SAM

registration upon notification of entry to the program.

b. Awardees will be required to submit invoices for payment electronically via the Wide Area Work Flow (WAWF) module in the Procurement Integrated Enterprise Environment at https://piee.eb.mil/, unless an exception applies. Registration in PIEE is required prior to any award under this PS. DARPA Contracts Management Office (CMO) personnel will assist those proposers from whom a proposal is requested.

c. Proposers must be determined to be responsible by the Agreements Officer and must not be suspended or debarred from award by the Federal Government nor be prohibited by Presidential Executive Order and/or law from receiving an award.

d. Being asked to submit a proposal does not guarantee that a proposer will receive an award. The Government reserves the right not to make an award.

5.2. Competition Sensitive Information

DARPA policy is to treat all submissions as competition sensitive, and to disclose their contents only for the purpose of evaluation. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation. All DARPA support contractors performing this role are expressly prohibited from performing DARPA sponsored technical research and are bound by appropriate nondisclosure agreements. Input on technical aspects of the proposals may be solicited by DARPA from non-Government consultants/experts who are strictly bound by the appropriate non-disclosure requirements.

5.3. Intellectual Property / Data Rights

The Government expects Government Purpose Rights (GPR) for the technology developed under the RIDDL program but is open to flexible intellectual property (IP) proposals from performers that are advantageous to the Government. IP proposals should, at a minimum allow DARPA to:

- Flexibly brief U.S. Government stakeholders regarding technical progress and accomplishments,
- Allow validation of technical performance, capabilities, and accomplishments by independent technical (potentially non-Government) experts, subject to NDA restrictions,
- Facilitate discussion of technical challenges and applications with the broader technical community – for example, by starting a new DARPA program that attempts to solve a serious technical challenge that limits further progress,
- Support analyses of alternatives, and
- Support transition opportunities, including design and performance data required to support other acquisition activities. These latter activities may require the Government to conduct an independent performance analysis.

5.4. Procurement Integrity Act (PIA)

All awards under this PS shall be treated as Federal Agency procurements for purpose of 41 U.S.C. Chapter 21. Accordingly, the PS competitive solicitation process and awards made thereof must adhere to the ethical standards required by the Procurement Integrity Act.

5.5. Human Subjects Research /Animal Subject Research Use

Proposers that anticipate involving human subjects or animals in the proposed research must comply with the approval procedures detailed at https://www.darpa.mil/work-with-

us/humanresearch to include providing the information specified therein as required for proposal submission.

6. PS DEFINITIONS

"Data" refers to recorded information, regardless of form or method of recording, which includes but is not limited to, technical data, software, mask works and trade secrets. The term does not include financial, administrative, cost, pricing or management information and does not include inventions.

"Other Transaction" refers to the type of OT that may be awarded as a result of this PS. This type of OT is authorized by 10 U.S.C. § 4022 for prototype projects directly relevant to enhancing the mission effectiveness of military personnel and the supporting platforms, systems, components, or materials proposed to be acquired or developed by the DoD, or for the improvement of platforms, systems, components, or materials in use by the armed forces.

"Prototype Project" is described in the DoD Other Transactions Guide (Version 1, Nov. 2018) issued by the Office of the Under Secretary of Defense for Acquisition and Sustainment: https://www.dau.edu/pdfviewer/Source/Guidebooks/Other-Transactions-(OT)-Guide.pdf.

7. ACRONYMS

A&AS: Advisory and Assistance Services
ACURO: Animal Care and Use Review Office
ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicology
ASR: Animal Subject Research
BTO: Biological Technologies Office
C.F.R.: Code of Federal Regulations
CMO: DARPA Contracts Management Office
CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
CRISPR-Cas: CRISPR associated proteins (CRISPR-Cas) nucleases
DARPA: Defense Advanced Research Projects Agency
DoD: Department of Defense
FAQ: Frequently Asked Questions
FDA: U.S. Food and Drug Administration
FFRDC: Federally Funded Research and Development Centers
GPR: Government Purpose Rights
IACUC: Institutional Animal Care and Use Committee
IP: Intellectual Property
NTE: Not To Exceed
OCI: Organizational Conflicts of Interest
OT: Other Transaction for Prototype agreement
PIA: Procurement Integrity Act
PS: Program Solicitation
RIDDL: Rapid Inhibitor Discovery and Development pipeline Program
SAM: System for Award Management
SETA: Scientific Engineering Technical Assistance
SME: Subject Matter Expert
UEI: Unique Entity Identifier
U.S.C.: United States Code
WAWF: Wide Area Work Flow

U.S.C.: United States Code