Broad Agency Announcement
Broad-Spectrum Antagonists For Editors

B-SAFE Program

BIOLOGICAL TECHNOLOGIES OFFICE

HR001124S0032

June 14, 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 (BTO)
- **Funding Opportunity Title –** Broad-Spectrum Antagonists For Editors (B-SAFE)
- **Announcement Type –** Initial Announcement
- **Funding Opportunity Number –** HR001124S0032
- **Assistance Listing Number:** 12.910 Research and Technology Development
- **Dates/Time - All Times are Eastern Time Zone (ET)**
  - Posting Date: June 14, 2024
  - Industry Day: June 28, 2024
  - Proposal Abstract Due Date: July 15, 2024 at 4:00 p.m.
  - Question Submittal Closed: July 29, 2024 at 4:00 p.m.
  - Proposal Due Date: August 12, 2024 at 4:00 p.m.

- **Anticipated individual awards** - Multiple awards are anticipated.
- **Types of instruments that may be awarded** - Procurement Contracts, Cooperative Agreements, or Other Transactions Research and Prototype.
- **NAICS Code**: 541715
- **Agency contact**
  - Points of Contact
    The BAA Coordinator for this effort may be reached at:
    B-SAFE@darpa.mil
    DARPA/BTO
    ATTN: HR001124S0032
    675 North Randolph Street
    Arlington, VA 22203-2114

Section I: Funding Opportunity Description

The Defense Advanced Research Projects Agency (DARPA) is soliciting innovative proposals to identify and optimize novel molecules that exhibit inhibitory effects on Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated proteins (CRISPR-Cas) gene editing processes. The Broad-Spectrum Antagonists for Editors (B-SAFE) program explicitly seeks transformative approaches that enable the discovery or design of novel inhibitors of gene editing technologies with enhanced activity, utility, and breadth of coverage. Novel inhibitor activity will be assessed *in vitro* over the course of the program, and a subset of top-performing molecules will be selected for scale-up at quantities sufficient for testing and evaluation by Department of Defense (DoD) stakeholders. In concert, DARPA is interested in exploring methods to rapidly discover inhibitor molecules for novel gene editing technologies beyond CRISPR-Cas systems to keep pace with the rapidly advancing field and promote the safe, controlled use of these technologies. Research that generates incremental improvements to the existing state-of-the-art is specifically excluded.

1.1 PROGRAM OVERVIEW

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. Versatile molecules capable of robust, potent inhibition of multiple CRISPR-Cas systems are of particular interest to DARPA.

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

[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.

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[6,7], multiple classes of molecules that exhibit anti-CRISPR activity have been demonstrated, providing significant depth and breadth for novel inhibitor discovery. The B-SAFE program seeks to leverage these prior efforts to develop tools for discovery, optimization, and validation of broad-spectrum inhibitors for gene editing technologies.

Beyond CRISPR-Cas technologies, some recent discoveries, such as Obligate Mobile Element Guided Activity (OMEGA) effector TnpB[8] and Fanzor[9], have further broadened the menu of RNA-guided DNA endonucleases that can be programmed for gene editing purposes. These new editor systems provide an opportunity to explore development of platform technologies for discovery of inhibitors to emerging gene editing technologies. Specifically, B-SAFE 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[10] and deep learning, B-SAFE will also develop a platform for 24-hour turnaround discovery and development of inhibitors of novel, emergent gene editor technologies.

1.2 TECHNICAL APPROACH

The B-SAFE 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 breadth of inhibition and potency. Proposers are highly encouraged to include recently discovered CRISPR-Cas orthologs. Initially, the program focus is on DNA nucleases (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

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

- Hybrid synthetic-biological materials
- Fusion proteins with enzymatic activity
- Small molecules
- Modified nucleic acids and mimetics
- Peptide nucleic acids

The B-SAFE program is also agnostic to the method(s) in 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 include inhibition of both Cas9 and Cas12 enzymes

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

1.3 TECHNICAL AREAS

The B-SAFE program includes two Technical Areas (TAs) that will run concurrently for the duration of the program. Proposals must address Technical Area 1 (TA1) as described within this section. Proposals may also address Technical Area 2 (TA2). Proposals that only address TA2 will be deemed non-conforming and will not be considered for review.

The two technical areas are:

1. Technical Area 1 (TA1): **Inhibitors for DNA Editors**. Discovery, development, optimization, and validation of broad-spectrum inhibitors for CRISPR-Cas DNA gene editors (i.e., Cas9 and Cas12 species).
2. Technical Area 2 (TA2): **Discovery Platform for Inhibitors of Novel Editors.** Design and implementation of a discovery platform for inhibitors of novel gene editing systems (e.g., Fanzor, OMEGA) and RNA editing systems (e.g., Cas13[11]).

TA1. Inhibitors for DNA Editors
Proposals to TA1 should focus on the development of broad-spectrum inhibitors against CRISPR-Cas DNA nucleases (i.e., Cas9 and Cas12 species). As CRISPR-Cas technologies are among the most flexible and easily programmable genome editors widely used and because DNA editors are among the most well-characterized of these, DARPA's initial focus is on DNA editors. Technologies that are capable of broader inhibition (e.g., DNA and RNA editors, zinc finger nucleases, etc.) are encouraged but not required. TA1 objectives include (a) discovery, design, and screening of novel inhibitors; (b) optimization of lead candidates; and (c) *in vitro* demonstration of potent, broad-spectrum inhibition of gene editing systems.

Discovery, Design, and Screening of Novel Inhibitors. Proposers must develop approaches to discover, design, and screen candidate inhibitors that will be developed as part of TA1. Discovery methods may include but are not limited to, computational methods[12], high-throughput screening (HTS) of molecular libraries, and rational design. It is anticipated that refinement may be necessary after initial screening of inhibitor candidates to reduce off-target effects.

Optimization of Lead Candidates. Optimization efforts should focus on improving activity and stability, while increasing broad-spectrum inhibition, and decreasing unwanted off-target effects. Molecules capable of sub-stoichiometric and/or catalytic inhibition are strongly preferred. Methods that elucidate the mechanism of action of lead candidate inhibitors are also preferred. Inhibitors should be highly potent and capable of completely negating editing activity, with no off-target or toxic effects. Approaches in which insights gained from optimization efforts are fed back into an iterative discovery pipeline are encouraged.

In Vitro Demonstration of Broad-Spectrum Inhibition. DARPA prefers solutions that can demonstrate integration of discovery, screening, optimization, and validation of lead candidates

[11] Wandera et al., Anti-CRISPR prediction using deep learning reveals an inhibitor of Cas13b nucleases. *Molec. Cell*. **2022**, 82, 2714-2726
[12] Duan et al., Structure-guided discovery of anti-CRISPR and anti-phage defense proteins. *Nat. Comm.* **2024**, 15, 649.

for development of highly potent, broad-spectrum inhibitors that retain activity against all known DNA editors and can be modified to inhibit novel or newly discovered DNA editors. The ideal inhibitor system would be capable of complete inhibition of all Cas9 and Cas12 enzymes with only a single molecule. Platforms capable of minimizing the number of molecules required to inhibit all Cas9 and Cas12 enzymes are preferred.

Proposals should describe the complete workflow from candidate discovery to optimization to validation.

TA2. Discovery Platform for Inhibitors of Novel Editors.
Proposals also addressing TA2 should focus on the development of a discovery platform for inhibitors of novel, emerging gene editor systems beyond Cas9 and Cas12, including those generated by deep-learning language models[13]. TA2 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) 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. Discovery pipelines that identify in parallel both novel Cas proteins and inhibitors will be considered.

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, toxicity, as well as development of tests for quantitative detection of inhibition. Newly discovered editors (e.g., OMEGA, Fanzor, etc.) 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 as well as the ability to add additional editors to a pool for broad inhibition (e.g., modification of an existing inhibitor that acts against five editors to include inhibition of a sixth).

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

1.4 PROGRAM STRUCTURE

As shown in Figure 1, B-SAFE 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. With sufficiently compelling data demonstrating completion of program metrics, proposers may request to begin at a later phase (e.g., Phase II) or advance through the phases more rapidly at the discretion of DARPA. Notional 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.

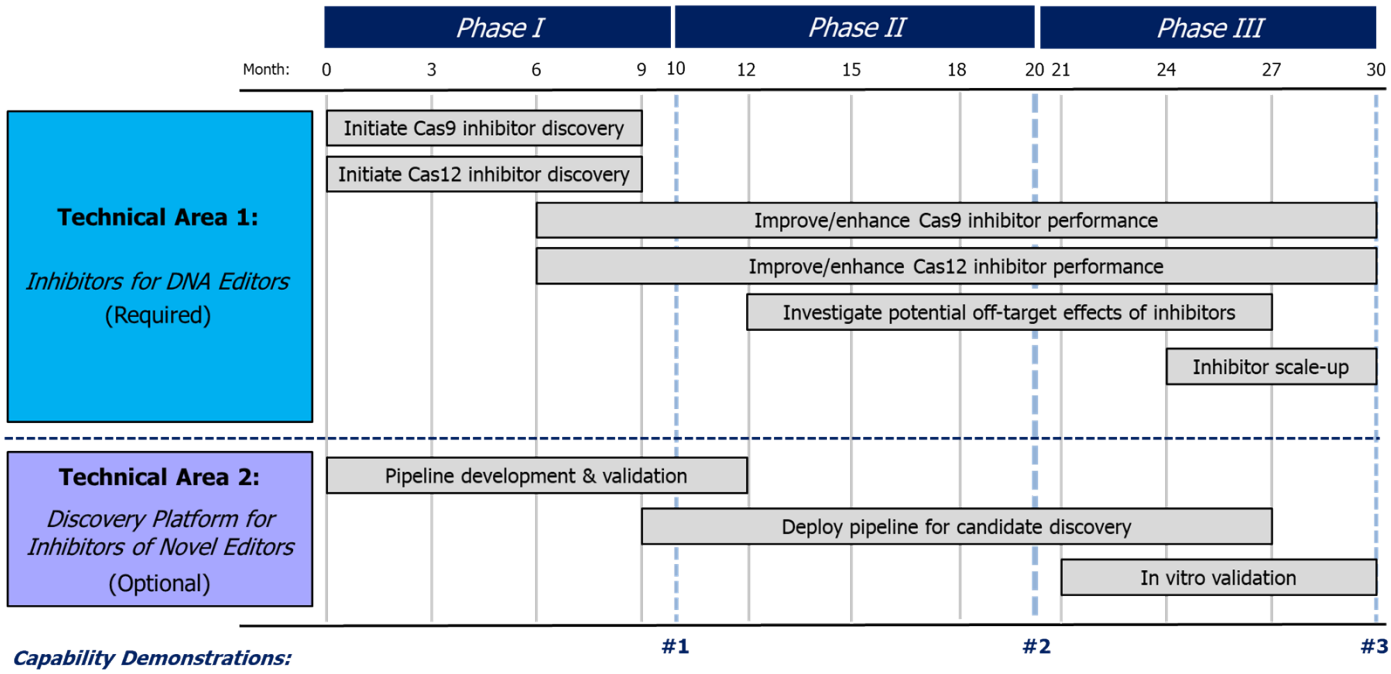

Figure 1: B-SAFE schedule

Phase I (Base, 10 months)
During the 10-month Phase I, performers will establish discovery and test platforms. For TA1, performers will establish *in vitro* models for screening candidate inhibitors against a broad array of CRISPR-Cas enzymes, covering as much of the known library of enzymes as possible. Quantitative assays to determine the degree of inhibition and breadth of inhibition will also be established. For TA2, performers will establish the discovery pipeline for inhibitors of novel editing systems.

As described in Section 1.6., the capstone of Phase I is Capability Demonstration (CD) 1 at Month 10. Additional milestones may include:
TA1

- Demonstration of discovery platform for novel inhibitors to Cas9 and Cas12
- Demonstration of *in vitro* systems for detection of CRISPR-Cas inhibition
- Demonstration of methods for quantification of key inhibitor characteristics, such as:
    - Potency, efficiency, efficacy
    - Broad-spectrum inhibition

TA2

- 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)
During the 10-month Phase II, performers will continue their TA1 efforts by optimizing lead candidate inhibitors for potency (e.g., ability to inhibit gene editing activity completely) and breadth (e.g., ability to inhibit more than one species or variant of gene editor with a single inhibitor). Optimization efforts could involve a variety of techniques including, but not limited to, directed evolution, medicinal chemistry-inspired optimization based on structure-activity relationships, multivalent systems, and/or enrichment strategies. Optimization efforts should also seek to reduce unwanted, off-target effects and reactivity. TA2 performers will demonstrate 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:

TA1

- Demonstration of both improved potency and breadth of Cas9 and Cas12 inhibitor activity by 50% over Phase 1 results
- Determination of mechanism of action of top-performing inhibitors
- Demonstration of methods for quantification of off-target effects and toxicity

TA2

- 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)
During the 10-month Phase III, performers will demonstrate the ability of their platforms to produce potent, broad-spectrum inhibitors. For TA1, performers will finalize optimization of lead candidate inhibitors, demonstrating highly potent, broad acting inhibition of gene editor activity *in vitro*. A small number of inhibitors should achieve prompt, potent inhibition of nearly

all CRISPR-Cas DNA nucleases (i.e., Cas9 and Cas12) with no off-target effects. For TA2, performers will validate discovery pipeline candidates and *in vitro* models to demonstrate inhibition of novel gene editors. Performers will also demonstrate the ability of the pipeline to extend existing inhibitors to new editors of the same type/class (e.g., inhibition of another enzyme with the same inhibitors or with modifications of the same inhibitors while maintaining inhibition of the previous enzymes).

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

TA1

- Demonstration of 100% improvement in inhibitor efficacy
- Demonstration of 100% improvement in inhibitor breadth of coverage of Cas9 and Cas12 species
- Scale-up of top-performing inhibitor(s) for transition to stakeholders

TA2

- 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 B-SAFE 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.

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

Table 1: B-SAFE notional deliberations by Phase

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

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

Table 2: Anticipated B-SAFE program meetings

1.5 PROGRAM 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 B-SAFE 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. Final metrics are to be negotiated at the time of contracting 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.

	METRIC	REQUIRED	PREFERRED
TA1	Broad-Spectrum	>99% of Cas9 and Cas12 species covered with <6 inhibitors	>99% of Cas9 and Cas12 species covered with ≤2 inhibitors
	Potency/Stoichiometry	Highly potent, >99% inhibition	Highly potent, catalytic/enzymatic
	Durability	>24h	>7 days
	Safety	No off-target effects, no immunogenicity, no toxicity	
TA2	Speed (from novel editor to candidate inhibitor discovery)	<3 days	<1 day
	Speed (from novel editor to *in vitro* model)	<7 days	<3 days
	Functional candidate inhibitors for a given novel editor	>3	>6
	Functional candidate inhibitors for a collection (>8) of editors	>1	>3

Table 3: B-SAFE example metrics table

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

1.6 CAPABILITY DEMONSTRATIONS

Performance metrics should focus on improvements to breadth of inhibition and potency of inhibitors, including, but not limited to, the following categories:

- Number of enzymes inhibited
- Potency of inhibition (e.g., percentage of editor activity decreased)
- Number of inhibitors needed to inhibit the library of CRISPR-Cas enzymes

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 highly potent (>99% inhibition) and broad-spectrum (>99% of all Cas9 and Cas12 enzymes) platforms utilizing only a few inhibitors from efforts in TA1 and a robust, rapid discovery pipeline for inhibitors to novel editors from efforts in TA2.

It is anticipated that, over the duration of the B-SAFE program, the number of identified Cas9 and Cas12 variants will increase potentially beyond the scope of a performer's ability to generate all variants for testing. Proposals should describe how – given potential protein synthesis limitations – they will employ computational and experimental approaches to assess enzyme inhibition across the evolutionary space. Breadth of inhibition will be assessed in Capability Demonstrations through Government-selected enzyme sequences that have not previously been investigated by the performer teams.

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

Technical Area	**Metric**	**CD1**	**CD2**	**CD3**
TA1	Potency	>50%	>75%	>99%
	Broad-spectrum	>50%	>75%	>99%
	Number of inhibitors	Any number	<8	<3
TA2	Novel inhibitors		Demonstrate discovery	Validate pipeline
	Expansion of inhibition			Adding at least one new USG-defined enzyme to existing inhibitor

Table 4: Notional B-SAFE capability demonstration performance metrics

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

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

Table 5: Capability Demonstration Schedule

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; 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.).

- 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 instrument types to include Procurement Contracts, Cooperative Agreements, and Other Transaction Research and Prototype. 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.

  Proposers must review the following links below:

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

- This announcement contains an abstract phase. Abstracts are required. Additional instructions for abstract submission are contained within **Attachments A and B**.

- Full proposals are due August 12, 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. Please visit Proposer Instructions and General Terms and Conditions for specific information regarding submission methods through the Broad Agency Announcement Tool (BAAT) and grants.gov (as applicable).

- **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)
  - **(required) Attachment E**: Proposal Instructions and Volume II Template (Cost)
  - **(required) Attachment F**: MS Excel™ DARPA Standard Cost Proposal

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), University Affiliated Research Centers (UARCs), and Government entities interested in participating in the **B-SAFE** 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: 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: 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: 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 sub-awardee's effort may be fundamental research. It is also possible that the research performed by a potential awardee is fundamental research while its proposed sub-awardee'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, now FRR-BS "aka FERBS") 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. DARPA will create risk assessments of all proposed senior/key personnel selected for negotiation of a fundamental research cooperative agreement award. The DARPA 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.

- The APEX Accelerators program, formerly known as the Procurement Technical Assistance Program (PTAP), focuses on building a strong, sustainable, and resilient U.S. supply chains by assisting a wide range of businesses that pursue and perform under contracts with the DoD, other federal agencies, state and local governments and with government prime contractors. See https://www.apexaccelerators.us/ for more information.

  APEX Accelerators helps businesses:

  - Complete registration with a wide range of databases necessary for them to participate in the government marketplace (e.g., SAM).
  - Identify which agencies and offices may need their products or services and how connect with buying agencies and offices.
  - Determine whether they are ready for government opportunities and how to position themselves to succeed.
  - Navigate solicitations and potential funding opportunities.
  - Receive notifications of government contract opportunities on a regular basis.
  - Network with buying officers, prime contractors, and other businesses.
  - Resolve performance issues and prepare for audit, only if the service is needed, after receiving an award.

- Project Spectrum is a nonprofit effort funded by the DoD Office of Small Business Programs to help educate the Defense Industrial Base (DIB) on compliance. Project Spectrum is vendor-neutral and available to assist businesses with their cybersecurity and compliance needs. Their mission is to improve cybersecurity readiness, resilience, and compliance for small/medium-sized businesses and the federal manufacturing supply chain. Project Spectrum events and programs will enhance awareness of cybersecurity threats within the manufacturing, research and development, as well as knowledge-based services sectors of the industrial base. Project Spectrum will leverage strategic partnerships within and outside of the DoD to accelerate the overall cybersecurity compliance of the DIB.

  www.Projectspectrum.io is a web portal that will provide resources such as individualized dashboards, a marketplace, and Pilot Program to help accelerate cybersecurity compliance.
- 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 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