DARPA-PS-26-129 & DARPA-SN-26-102 Protein ENGineering (PENG)
Frequently Asked Questions (FAQs)
as of 8/19/2026

42Q: Regarding eligibility questions around non-U.S. persons:

42A: Please refer to pages 16-17 of the solicitation. Eligibility applies to the organization itself and the Principal Investigator (PI). Green Card holders and Lawful Permanent Residents are considered U.S. Persons.

41Q: Does "add/subtract PTMs" in FAQ 26A cover modifications that have no natural writer, eraser, or reader and that act directly on the protein's behavior, rather than serving as a recognition mark for endogenous machinery?

41A: Strategies that rely solely on adding or subtracting PTMs - even novel or synthetic modifications that directly alter protein behavior - are excluded. To be considered responsive, proposed technologies must possess the capability to directly modify the endogenous protein's structure (i.e., altering the polypeptide backbone or sequence).

40Q: Are solutions that include editing of endogenous target transcripts in scope? Or must all proteins targeted for editing be produced from unmodified native transcripts?

40A: Editing the mRNA without editing the protein amino acid sequence or structure of the protein itself is not in scope of this program.

39Q: Are systems which focus on covalently binding a protein domain to a side chain of the endogenous target protein in scope?

39A: Attaching a new amino acid is in scope if it involves physically editing the endogenous protein's backbone structure to alter its function, rather than serving as a standard post-translational chemical tag. Systems that focus on covalently binding to an endogenous target protein are only in scope if the technology possesses the capability to edit the underlying protein sequence. Post-translational modifications (PTMs) may be included as a component of a larger proposed solution – for example, as a mechanism to tune the half-life of the edited protein. Please see 41Q for exclusion criteria regarding PTM-only approaches.

38Q: Scope of Accessible Protein Domains: Would a technology be considered responsive if it can edit the cytoplasmic tail of a transmembrane protein but cannot edit the protein's extracellular or luminal domains?

38A: Protein edits must be productive, functional edits with a purpose. The editing technology should be able to produce a functional and stable protein post editing.

37Q: Scope of Targetable Proteins: Would a technology be considered responsive if it can edit any position within proteins that are associated with ribosomes but cannot edit fully folded proteins that are not associated with ribosomes?

37A: If the technology can edit a protein prior to folding with subsequent chaperone assisted folding to produce a stable, functional, edited protein this would be within scope of the program.

36Q: Distinction from Conventional Gene Editing: Does DARPA require the functions enabled by the proposed protein-editing technology to be functions that cannot be achieved through conventional gene-editing approaches?

36A: The program aims to develop technology to achieve protein editing, not genome editing, the performer may choose to validate their editing approach through any number of available technologies as validation of product.

35Q: Definition of Generalizability and Amino Acid Editing: Specifically, would a technology that cannot add, delete, or replace amino acids within an existing polypeptide chain be considered non-responsive? Conversely, is the ability to add or delete multiple amino acids within a polypeptide chain an explicit requirement for program responsiveness?

35A: A responsive proposal must demonstrate the fundamental capability to directly edit the endogenous protein. Technologies limited to attaching chemical tags (e.g., PROTACs) do not meet this standard and fall under the solicitation's exclusion criteria. Furthermore, the ability to perform multiple edits within a single protein is an explicit requirement of the program; performers are expected to meet or exceed the multiplexing and complexity metrics defined for both Phase 1 and Phase 2.

----------⬆⬆⬆New Q/A⬆⬆⬆----------

34Q: What is the expected funding level per team, and how is it distributed across Phase 1A, Phase 1B, and Phase 2?

34A: Proposers should provide a ROM for the work they plan to do to complete the milestone deliverables in each phase. Funding levels per team and phase are not fixed and will differ based on each team’s proposed tasks to complete the required milestone deliverables. Proposers invited to submit a full proposal will be evaluated on Cost Realism.

33Q: Phase 2 is described as moving "from tissue models to complex cellular systems.” What is the intended Phase 2 biological endpoint, and is in vivo animal demonstration expected or required?

33A: Phase 2 biological endpoint is not a fixed target and should be as ambitious as possible while still supported by the technology proposed and developed. Minimally the proposed effort must lay out a plan to meet the end of Phase 2 Multiplexing & Complexity which is, “Produce functioning protein with >3 edits/ protein and in >3 cell types/organoid system, which demonstrates different effect from endogenous protein” pg. 6 of the Solicitation.

32Q: Will platforms be evaluated on how quickly and reliably they convert a target specification into a working, validated editor, or on the form the editor takes? Where does DARPA draw the line between a per-target design step that is part of a programmable platform and one that constitutes a point-solution? What evidence would establish that a platform falls on the programmable side?

32A: The physical form of the editor or overall strategy of the editor will not be evaluated beyond its ability to meet the program metrics. The platform designed and prototype developed for protein editing should be either very quickly adaptable to different proteins or the editor itself is capable of editing different proteins. For example, in Phase 1B after the DARPA-chosen proteins are revealed, performers will be evaluated on their ability to adapt their editing platform to a new set of proteins. In Phase 1B, performers will have 3 and 5 months to show initial adaptability (see MS6) and “demonstrate functional editing of 2 of the 3 DARPA-chosen proteins” (see MS7). See Phase 1B Milestones 6 and 7 on pg. 8 for details.

31Q: In Phase 1B, will DARPA specify the required edit and the functional outcome for each of the three chosen proteins, or will performers propose the edit and endpoint for a DARPA-specified target? Will all teams receive an identical target set, or will targets be selected to match each team's declared platform? Will the required edit chemistries be of types the performer has already demonstrated in Phase 1A, applied to new targets, or should performers anticipate being asked for edit types they have not previously executed?

31A: In phase 1B, where the protein and edit are specified by DARPA at the controlled unclassified information (CUI) level, performers should expect to perform edits they have not previously executed in phase 1A. DARPA will specify the required edit and functional outcome.

30Q: The Phase 2 metric requires "viable edited protein in system stable for > 3 weeks." What is required to persist for 3 weeks? We read this three ways: (a) an individual edited protein molecule survives more than 3 weeks, requiring the edit to extend the target's half-life well beyond typical mammalian protein turnover; (b) the editing system remains active for more than 3 weeks, continuously re-editing newly synthesized target so an edited population is maintained at steady state; or (c) the biological effect of the edit persists for more than 3 weeks, regardless of the lifetime of any individual edited molecule. Which is intended? Does dilution by cell division

count against the metric? And if depletion or inactivation of the target is the intended functional outcome, how is stability assessed?

30A: Three-week viability would be a goal that the protein remains intact post-editing and the system remains alive post-editing. Exact time points for these metrics may adjust within the program if relevant to the protein in question. Dilution due to cell division would not be counted against a metric. Depletion of a protein alone (i.e., targeted degradation) would not be considered in scope. Inactivation could be measured and a functional edited target, to mean that the protein remains inactivated from its endogenous function for a sustained period of time.

29Q: What does "reversible" mean in the context of this solicitation? That the edit itself can be erased on demand (e.g., phosphorylation/dephosphorylation), that the phenotype washes out through natural protein turnover, or only that the editor makes no heritable genomic change?

29A: Reversible editing on demand is not part of the required scope for this program. The ability to tune half-life in a multiplexed editing capability to allow for variation in protein duration is advantageous, particularly towards phase 2. Editing without heritable genomic change is required.

28Q: The Phase 1A generalizability requirement is specified along a structural-fold axis (globular, transmembrane, fibrous), and the metrics table does not address target localization. Does DARPA expect performers to demonstrate editing of extracellular, membrane-associated, and intracellular targets, or is fold diversity the sole required axis of generalizability? Would a platform whose Phase 1A targets span three structural families but sit predominantly in one compartment class be responsive? If compartment coverage is expected, is it required within Phase 1A or does it enter at Phase 1B/Phase 2?

28A: Editing proteins spanning structural families within one cellular compartment space would be responsive in phase 1A. This is correct that spanning compartments in phase 1A is not required. Phase 1B may include some spanning of different compartments and advancement might be better suited for those who are positioned with capabilities to edit intracellular capacity as opposed to all extracellular or membrane bound.

27Q: Is development of the delivery mechanism within scope of the program and evaluated as part of the technical approach, or is delivery treated as an assumed capability with evaluation focused on targeting, chemistry, and multiplexing? Both application of purified editor as protein and transient intracellular expression of a genetically encoded editor appear consistent with the program's framing, are both in scope? Relatedly, the exclusion criteria rule out "simply delivering new synthetic proteins or transgenes as standalone workarounds;" we read that as excluding replacement of the target's function, not as excluding delivery of the editing machinery itself by protein or nucleic-acid means. Is that correct?

27A: Correct, designing a new “drug” that is a protein or other protein-mimetic and delivering it to a cell or in vivo system, is not the scope of this program. Development of a targeted delivery system in and of itself, without editing capability, is not in scope. Delivery considerations and approaches may be part of the technical design, particularly in phase 2.

26Q: The solicitation excludes strategies that "merely attach chemical tags (e.g., PROTACs) without further editing the endogenous protein." We read this as excluding non-catalytic binders that recruit endogenous machinery, not as excluding the design and delivery of enzymes that install modifications directly. Is that correct? Specifically, is a designed enzyme that site-selectively installs a PTM on a target (for example phosphorylation, acetylation, methylation, or ligation of a ubiquitin-like modifier) in scope?

26A: Using a designed enzyme that selectively alters a protein would be in scope. If the only change to a protein is to add/subtract PTMs, this would not be considered a full protein edit in the capacity that the program is targeting.

25Q: How should proposers compute "edits/machine," and what is the physical entity in the denominator? The metric could be read several ways. For example: the number of target molecules edited per editor molecule at a single site; the number of distinct sites a single editor molecule acts on without being modified, whether on the same protein or across different proteins; or the number of distinct sites the platform can address when the editor is redesigned or reconfigured for each one, where any individual editor may be single-turnover. Which reading is intended? Which reading will be used in evaluation?

25A: Both will be looked at and balanced understanding the difficulty to achieve both goals together in one system.

24Q: How does DARPA define "edit" for this program? Is the criterion a change to the primary sequence or backbone, any covalent modification of the endogenous protein by designed catalytic machinery, or any programmed change in the protein's functional state? The multiplexing metric requires performers "produce functioning protein," so does every edit have to yield a retained functional product? Or does subtractive editing (e.g. proteolysis) that produces the desired biological outcome count?

24A: The goal is to create a functional protein with a slightly different function from the original. The product should not be a degraded protein, multiple methods for this currently exist.

23Q: Are national labs eligible to participate?

23A: Per Section IV in the solicitation, National Labs, like Federally Funded Research and Development Centers (FFRDCs), are allowed to participate following these guidelines: “(1) FFRDCs must clearly demonstrate that the proposed work is not

otherwise available from the private sector. (2) FFRDCs must provide a letter, on official letterhead from their sponsoring organization, that (a) cites the specific authority establishing their eligibility to propose to Government solicitations and compete with industry, and (b) certifies the FFRDC's compliance with the associated FFRDC sponsor agreement's terms and conditions. DARPA, under this solicitation, will not award separate contracts to FFRDCs as prime or subawardees but will instead leverage their existing sponsors' agreements."

"Proposals that include a UARC, FFRDC, Government entities, or National Laboratory as a subcontractor may also be deemed non-conforming unless: (1) their role is clearly defined in the technical proposal with a point of contact, and (2) a rough order of magnitude cost is provided in the technical proposal only—cost proposals must exclude their funding, as DARPA will not fund them through the prime. It is important to note that if funded, these organizations will be required to share their work and findings with other performers also supporting the same program."

22Q: How can an organization check on whether they have an organizational conflict of interest in doing business with DARPA?

22A: 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 to the specific email address identified in the program solicitation before time and effort are expended in preparing any submission documentation. See page 16/ SECTION IV: SPECIAL CONSIDERATIONS AND ELIGIBILITY REQUIREMENTS of the program solicitation for more specifics.

21Q: Will there be some way to meet other potential PENG team members?

21A: Teaming profiles and contact info of general attendees (who opted in to sharing) were sent to all PENG Proposers Day registrants after the event.

20Q: Can the approach require modification of the endogenous protein, or does the editing capability require functionality on an endogenous, unmodified, protein?

20A: Systems should be capable of editing endogenous proteins without prior modification for increased susceptibility to edits.

19Q: Would it be considered in scope to design a bespoke protein as part of a system for making a specific protein edit?

19A: If there is a generalizable protein platform capable of editing multiple proteins, this would be considered.

18Q: Is cleavage/degradation of the endogenous protein an acceptable "edit?"

18A: The edited product needs to be a functional protein.

17Q: Are any transient modifications at the RNA level in scope?

17A: The program is geared to protein editing for the proteins themselves. RNA editing without changing the amino acid sequence directly of an endogenous protein, would not be considered in scope for this program. Transient modifications to RNA are allowed if used as a delivery mechanism to introduce and/or build the protein editing machinery itself.

16Q: In terms of generalizability, would development of a “suite” of tools targeting different classes of proteins be in scope for PENG?

16A: The solicitation includes instructions for the inclusion of different protein families in the initial editing phase proposal, as well as ability to generalize to other protein families and sub-cellular location in the program.

15Q: In terms of reversibility, is PENG exclusively interested in turnover/half-life modulation, or are “switching” proteins in scope?

15A: Switching proteins on/off would also be of interest, tunability in a broad sense is of interest at this time.

14Q: Are there specific cell types of interest for editing? (ex. mammalian, bacterial, etc.)

14A: The primary focus is on mammalian cells; however, proposals involving any cell type will be considered.

13Q: How will intellectual property created as a result of this project be treated?

13A: The Government expects unlimited rights for the technology and data developed and/or generated under the program but is open to flexible intellectual property (IP) proposals from proposers that are advantageous to the Government. Please view page 18 in the program solicitation.

12Q: What is the program’s budget and expected grant sizes?

12A: Please see page 13 in the solicitation for more details on cost realism.

11Q: Are cell-free approaches within scope?

11A: These could be considered in scope for phase 1A, however, phase 1B will prefer approaches capable of operating within complex cellular systems.

10Q: Is Dr. Bonomi available for a call or meeting to discuss our approach?

10A: No. Due to scheduling limitations, and in the interest of fairness to all proposers, Dr. Bonomi will not be taking program-related calls and meetings. The best way to receive feedback on an approach is through the submission of a proposal abstract prior to the deadline specified in the PENG solicitation and through the FAQ process.

9Q: Is there a maximum value or budget cap on for a proposal's total value or annual direct costs?

9A: While there is not an explicit value maximum for what funds proposer can request, the cost associated with every proposal will be evaluated for alignment and realism with the work proposed during full proposal evaluations (see Pg. 13 of the solicitation for more detail).

8Q: Do proposers need to register in SAM.gov to submit abstracts to the PENG Solicitation?

8A: You do not need to register in SAM.gov to submit abstracts, but you must register there to receive an award.

7Q: I am working on a concept that appears to sit inside PENG's scope. Can you review my concept and confirm if it's in scope for PENG as you envision it?

7A: DARPA cannot comment as to whether an individual concept is in or out of scope of PENG. Please review the exclusion criteria on pg. 7 of the solicitation for details. Additionally, please note that "Proposals MUST explicitly address each of these metrics… across at least three self-selected targets spanning distinct structural protein families" (pg. 6 of the solicitation).

6Q: Is editing proteins at the genetic level (e.g., bridge recombinase: https://www.biorxiv.org/content/10.64898/2026.04.29.721476v2) in or out of scope?

6A: Genetic editing technologies are out of scope (see Exclusion criteria on pg. 7 of the Solicitation). Proposed research must "physically edit existing proteins" (pg. 4 of the Solicitation).

5Q: Are bacterial, microbiome, and phage systems considered "bench-top laboratory models" for PENG?

5A: Bacterial, microbiome, and phage systems could qualify as simpler biological systems appropriate for Phase 1. However, Phase 2 metrics require increasingly biologically complex systems; the proposer must justify how their system(s) will meet the Multiplexing & Complexity Phase 2 metrics. See Program Metrics on pg. 6 for details.

4Q: Is teaming required? Is there a limit on team size? Is there a recommended team size? Can DARPA facilitate teaming if a proposer cannot address all aspects of the program on their own?

4A: Specific content, communications, networking, and team formation are the sole responsibility of the proposer team.

3Q: Will PENG Proposers Day materials (attendee questions and slide decks) be shared?

3A: Yes. Attendee questions will be part of the program FAQ document. The FAQ and slide decks will be posted to the program page on DARPA's website. Teaming profiles will be sent out to all meeting registrants. Transcripts of Proposers Day will not be shared.

2Q: I do not have a laboratory or an institutional affiliation. I am trying to find out whether this direction is worth pursuing, and if it is, what a realistic path looks like for someone at my stage. What kind of team should I try to join, if one is needed?

2A: Teaming is at your discretion. Per the Special Notice: “Specific content, communications, networking, and team formation are the sole responsibility of the participants. Neither DARPA nor the Department of War (DoW) endorses the information and organizations contained in the consolidated teaming profile document.”

1Q: Do you have time for a short call to answer my questions about the goals of the program?

1A: Thank you for your interest. We will not be taking individual meetings with potential proposers but, please stay tuned for the solicitation release to clarify.