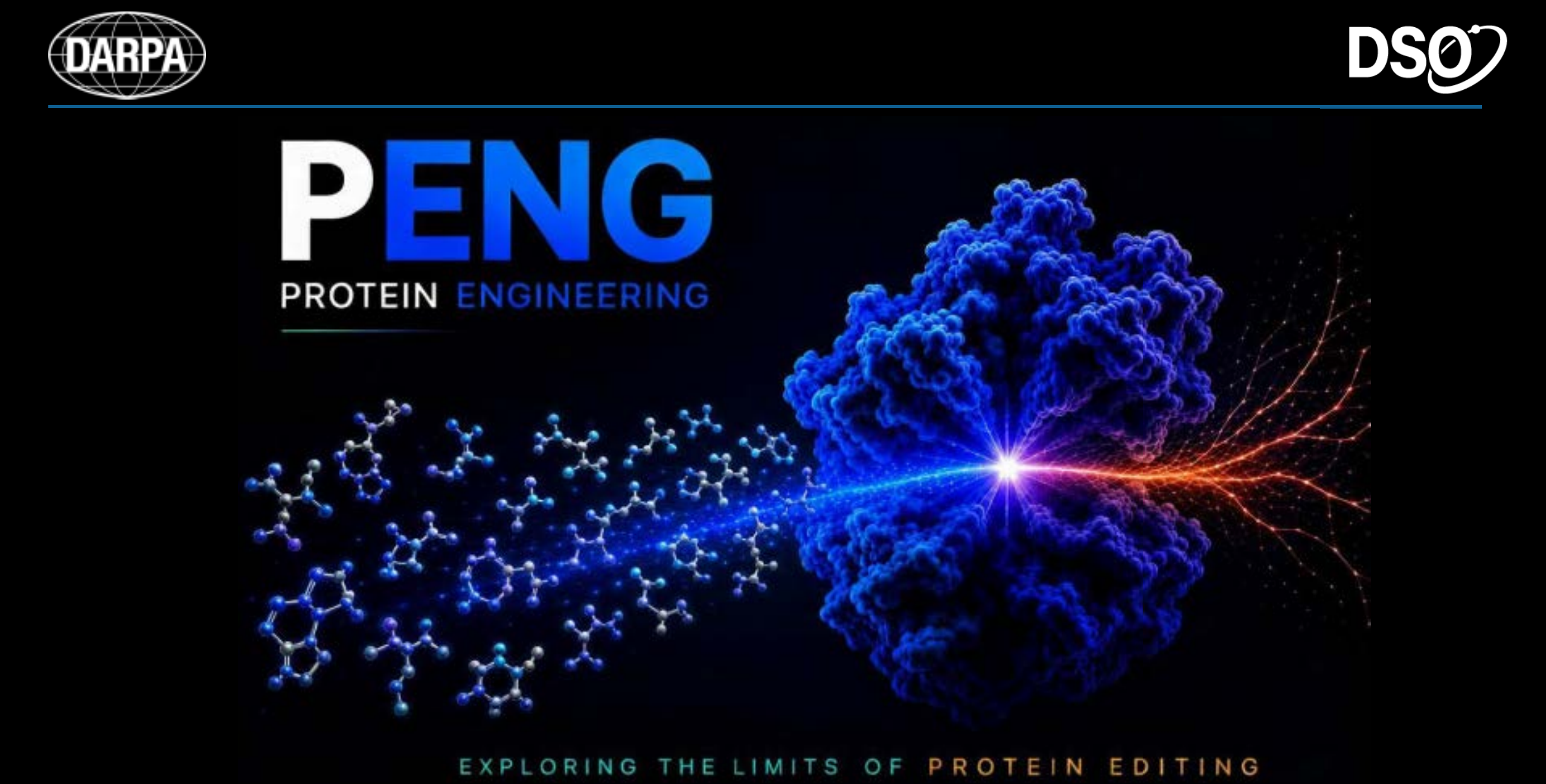


Source: DARPA | Artist-directed image with AI assistance

Protein ENGineering (PENG)

LCDR Robin Bonomi, M.D., Ph.D.
Program Manager, Defense Sciences Office

Briefing Prepared for Proposers Day

August 10, 2026

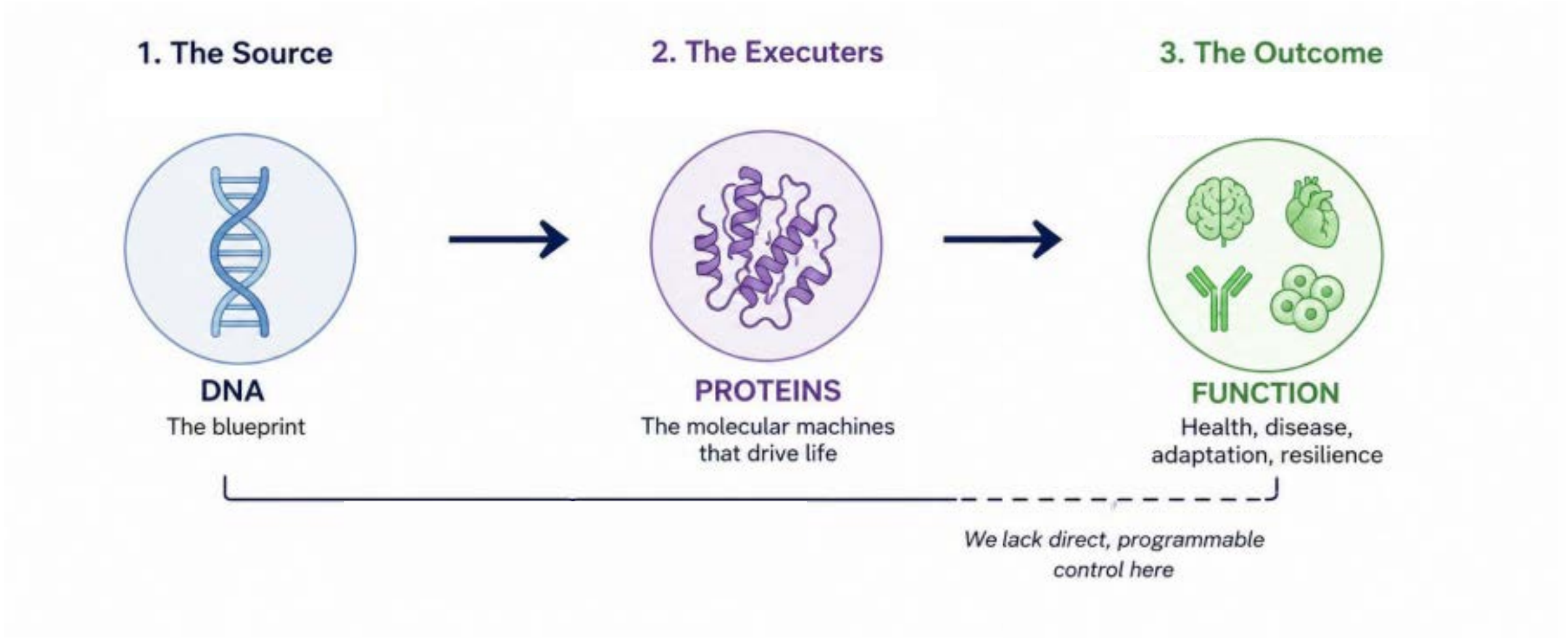
Clarification

If there is any discrepancy between what is presented today and the Program Solicitation (PS), the PS takes precedence

Opening comments

- The Proposer's Day briefing is intended to provide an orientation to the Protein ENGineering (PENG) Program Solicitation and is solely for information purposes.
- The Program Solicitation supersedes anything presented or said by DARPA at the Proposer's Day.
- Proposals will only be evaluated in accordance with the instructions provided in the Program Solicitation. Review the Program Solicitation carefully prior to Abstract submission.
- Examples in this briefing (e.g., technologies, use cases) are chosen for ease of illustration only and do not constitute endorsement of any particular approach.

DNA is an indirect lever of biological function



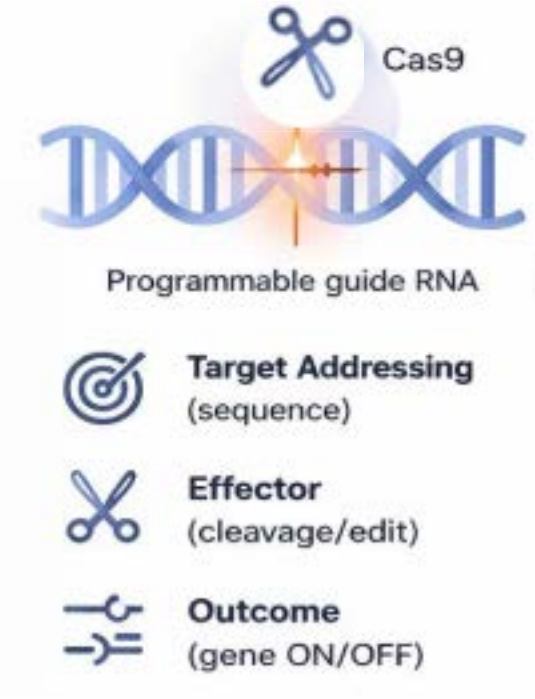
Source: DARPA | Artist-directed image with AI assistance

DNA: Deoxyribonucleic acid

Accelerating 20 years of discovery into 42 months

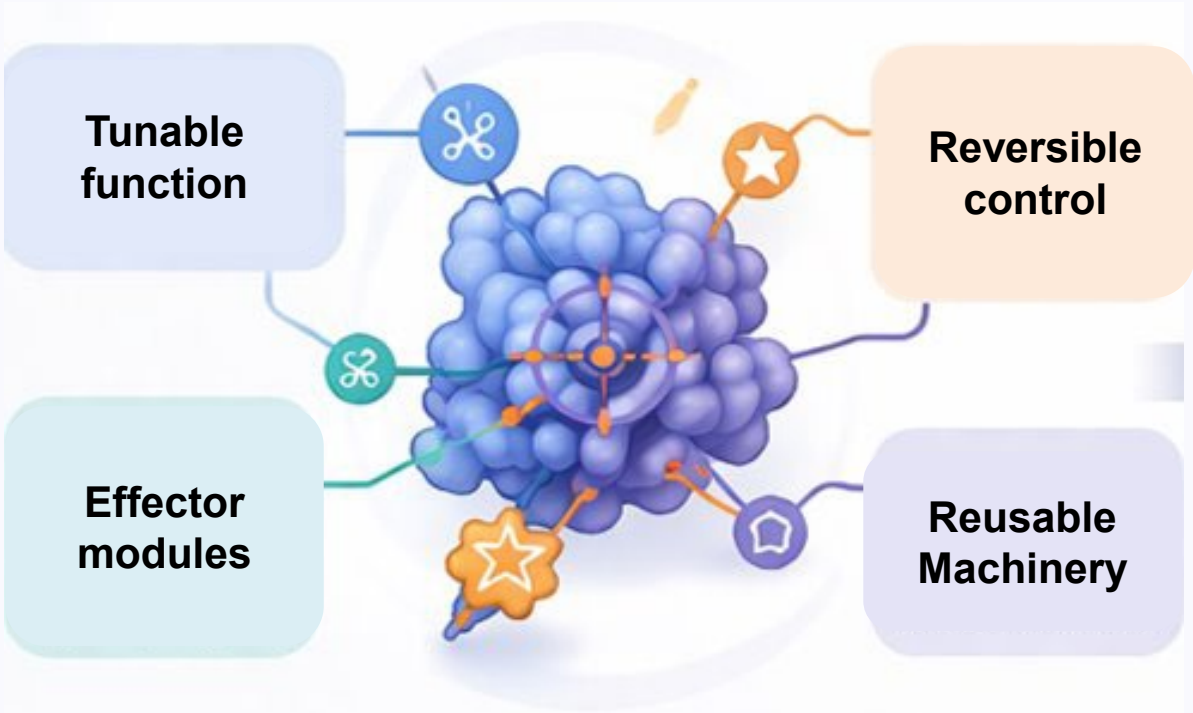
What We Can Do Today

Powerful but permanent and far from functional level



This Program – The Vision

Any Edit in Any Protein to control function



Direct, programmable control of protein structure and function

Source: DARPA | Artist-directed image with AI assistance

Expanding and learning the fundamental limits of protein editing

Transforming proteins from static components into tunable machinery

Proteins power many sectors…

MATERIALS

CHEMICAL SYNTHESIS

SUSTAINABILITY

AGROINDUSTRY

BIOTECHNOLOGY

NUTRITION

…PENG unlocks a common control layer for them all

Source: DARPA | Artist-directed image with AI assistance

Technical challenges currently limit protein editing

Targeting is limited

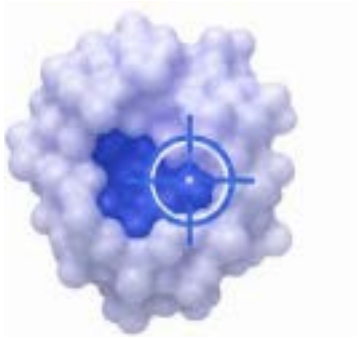
Chemistry is not generalizable

Multiplex editing and tissue scaling is not possible

Exploring limits and developing guidelines for protein engineering

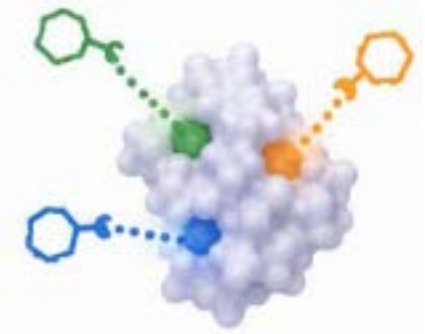
3 key pillars for foundational change

PENG



Find and edit the right protein at the right place

Tools to edit any amino acid and any protein



Edit many sites at the same time

Bridging the gap between genetic information and functional biological control through development of a scalable platform for targeted protein engineering

Source: DARPA | Artist-directed image with AI assistance

To accomplish this:

PHASE 1A: 18 months

Performers will validate their platforms using 3 self-selected protein targets (of different structural classes) with functional outcomes of the proposed edits

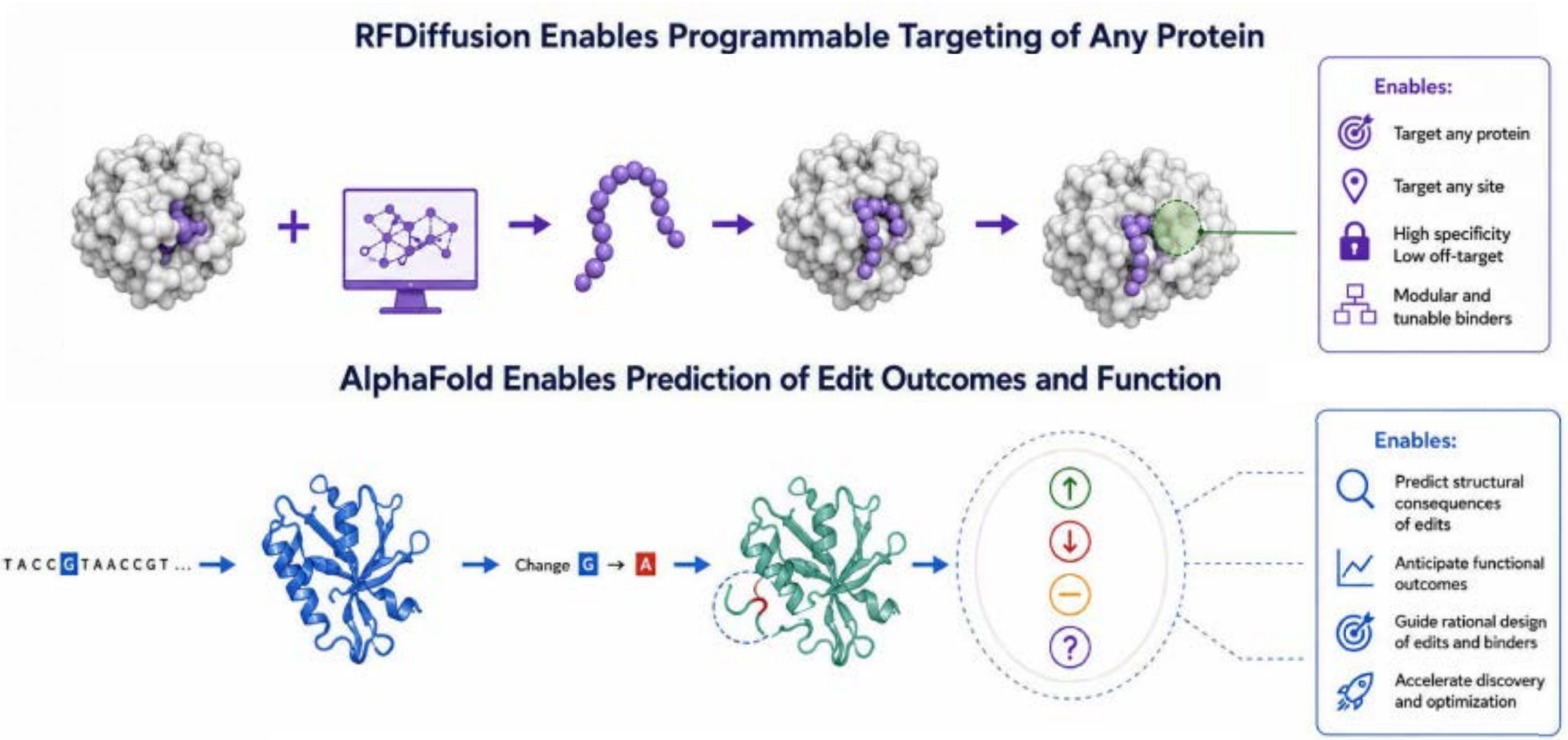
PHASE 1B: CAPABILITY DEMONSTRATION

Performers will edit previously unannounced target proteins under short-notice constraints within complex tissue systems

PHASE 2: 18 months

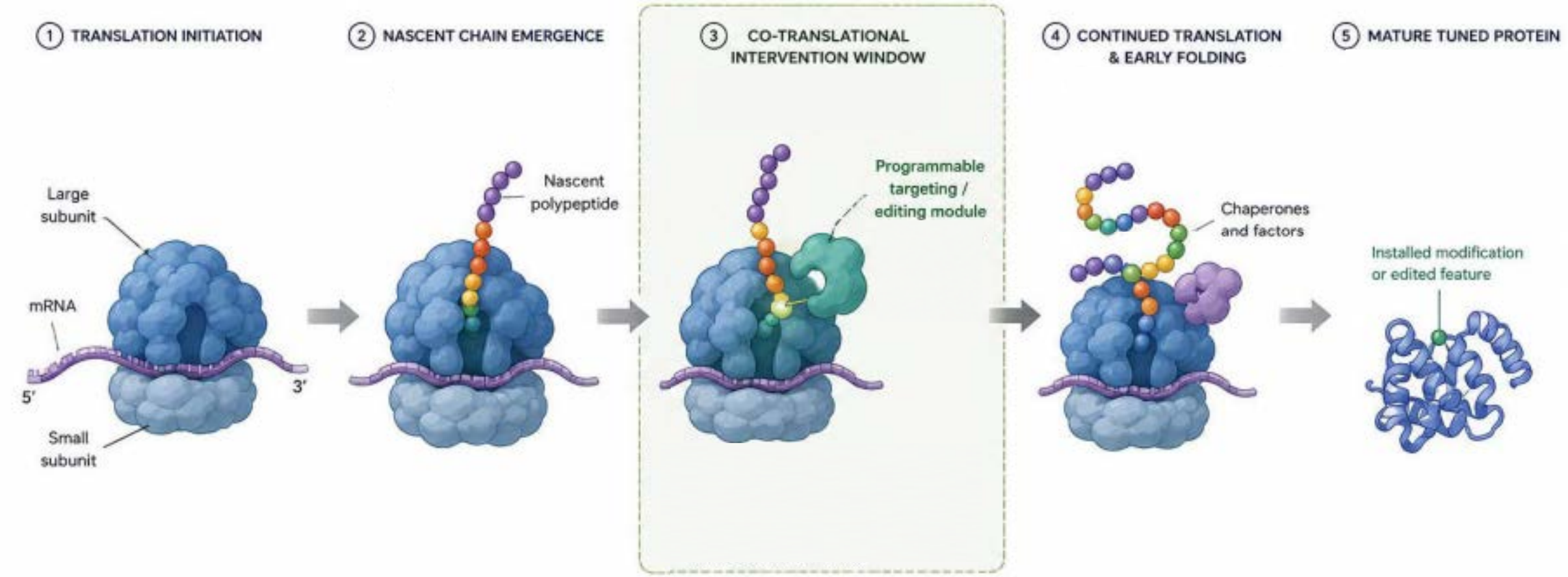
Expanded scope of edits, protein varieties, complexity of tissues and preparing for in vivo transition

Tech challenge 1: programmable targeting



Sources:
Butcher J, et al, bioRxiv 2025
Jumper, et al, Nature, 2021
Abramson, et al, Nature, 2024
DARPA | Artist-directed image with AI assistance

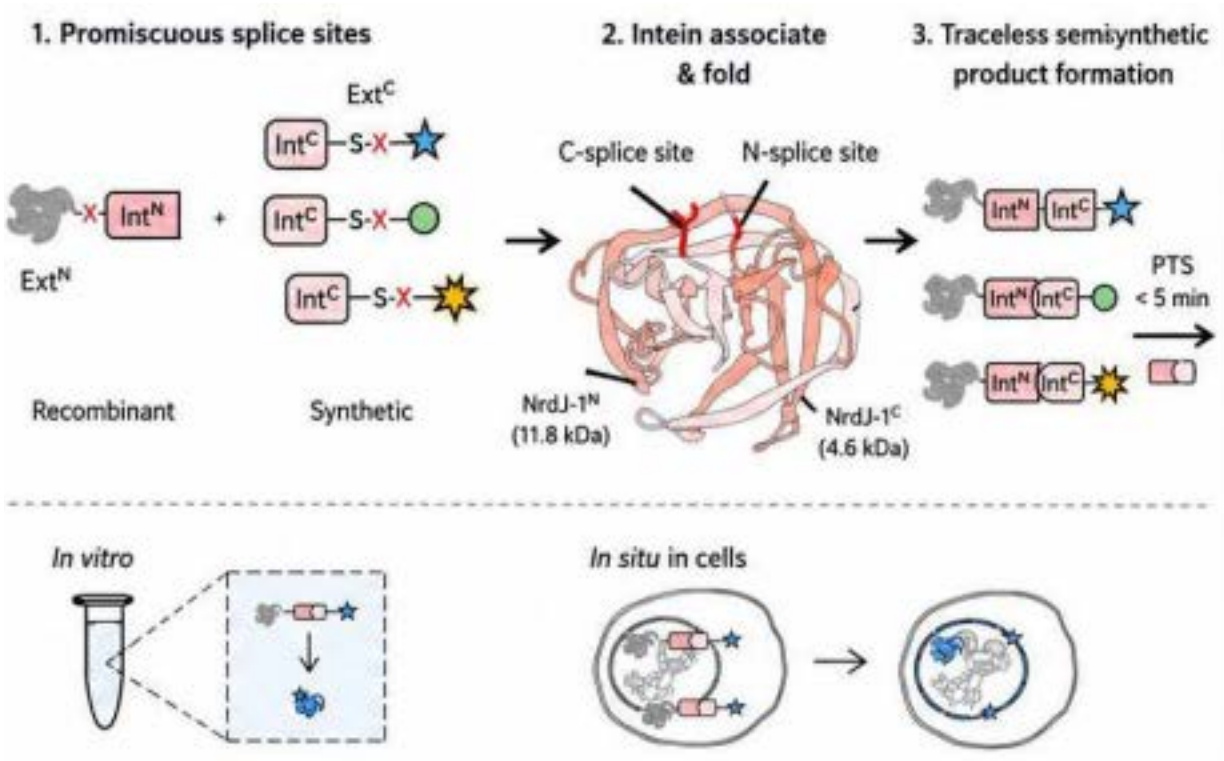
Tech challenge 2: generalizable chemistries and editors



Sources:
Muir, Personal correspondence, 2026
DARPA | Artist-directed image with AI assistance

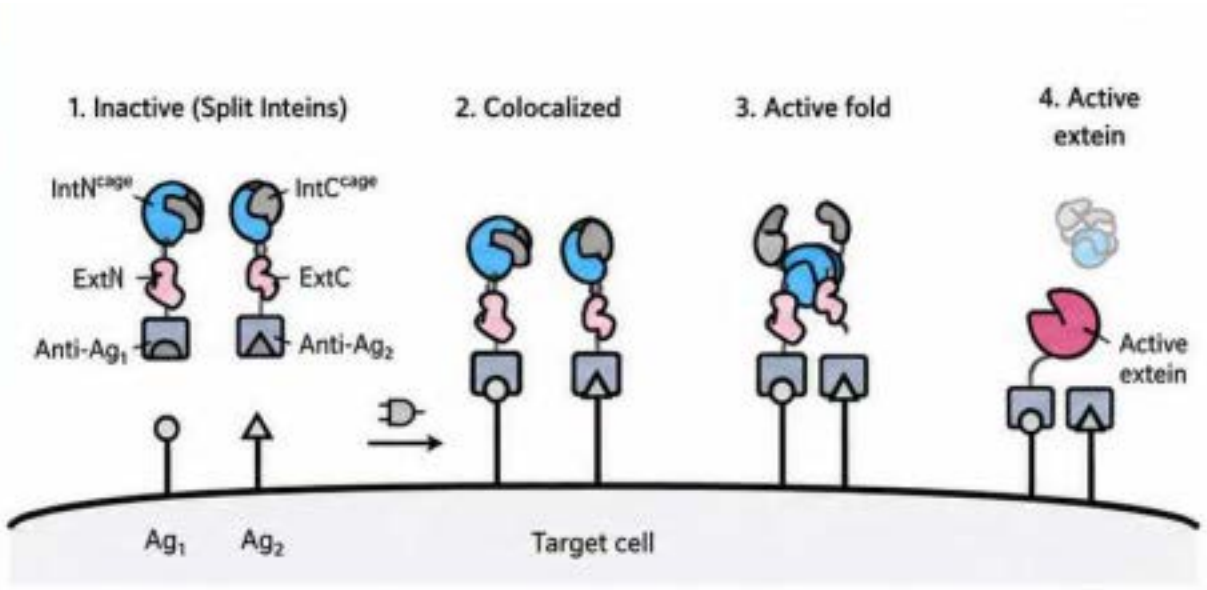
Tech challenge 3: multiplexing at scale in more complex tissues

Promiscuous inteins and splices



Ye, et al, BioRxiv, 2026

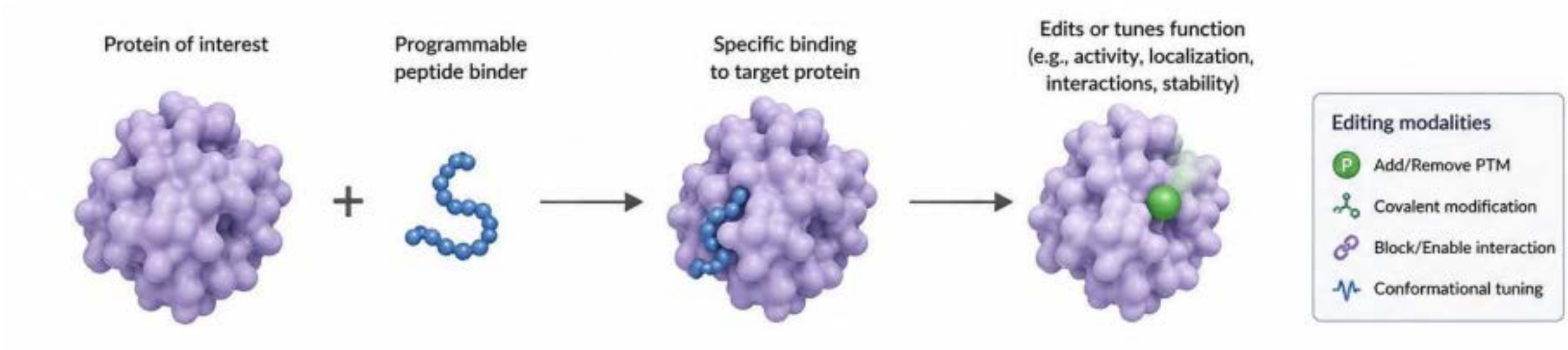
Better targeting in cells



Kofoed, et al, Nature, 2025

Tech challenge 3: multiplexing at scale in more complex tissues

Leveraging understood post translational modifications

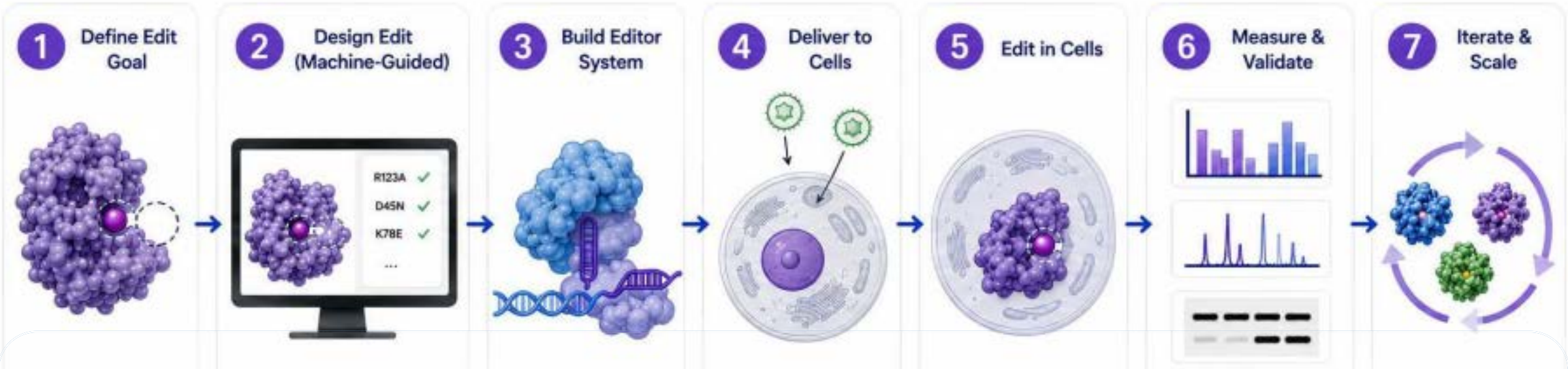


Editing multiple sites on protein to tune half life control

Sources:
Schissel, et al, J. American Chemical Society, 2025
Roe, et al, Nature Chemical Biology, 2025
DARPA | Artist-directed image with AI assistance

PTM: Post-translational modification

From silos to synergy



Comprehensive, integrated platform to unlock protein editing

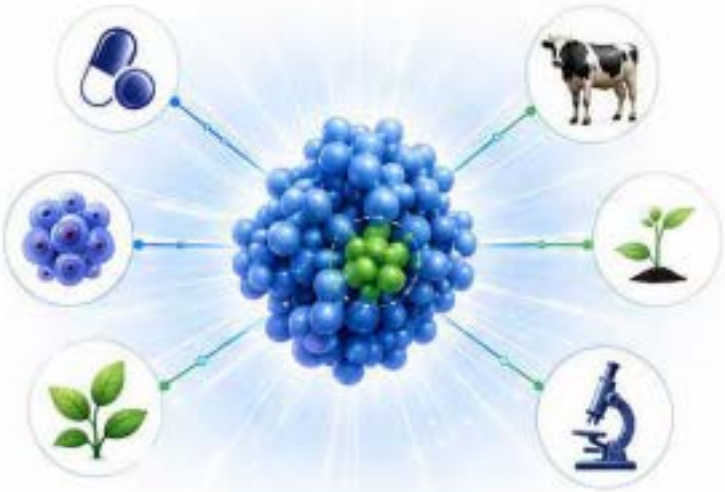
Source: DARPA | Artist-directed image with AI assistance

One program with many opportunities for future applications

Fundamental change to research

New era of therapeutics

Widespread impact



RESEARCH | THERAPEUTICS | REGENERATIVE MEDICINE | AGRICULTURE | INDUSTRY | DISCOVERY

Source: DARPA | Artist-directed image with AI assistance

PENG definitions

Biological systems: Single cell in vitro assays to organoids. Animal use research is allowed but not required to meet program metrics. (Human subjects research is not allowed).

Endogenous proteins: Proteins (>50 amino acids) that already exist, post-synthesis, within a biological system. This includes post-ribosome amino acid chains out to fully folded, transported and embedded functioning proteins.

Editing machinery: Physical system(s) capable of making endogenous protein edits.

Functional edits: Edits to endogenous proteins that impart a different function to that protein.

Generalizable chemistry: Changing, adding, and/or deleting amino acids in endogenous proteins in a repeatable way. Editing is generalizable to many protein types and machinery is reusable.

Programmable targeting: Ensuring editing machinery finds intended protein target site with minimal off-target effects in a complex system.

Multiplexing and complexity: Editing machinery can make multi-site protein edits and function in complex environments.

Future capabilities readiness: System is viable for future transition to in vivo use.

Teaming

- To fully address the Program Solicitation, you may need to team with other entities.
- You must find your collaborators on your own, maybe through Lightning Talks and networking today.
- Each team should submit a unified proposal abstract under a single prime.
- This Program Solicitation is open to educational institutions and/or private companies.
  - Note: UARCs, FFRDCs, Government entities, or National Laboratories should review the solicitation for details on their eligibility.
- Non-U.S. organizations and/or individuals cannot participate in this solicitation.
- Even if you are a member of a team, you may still join any number of other proposal teams or form your own and submit a proposal as PI.

FFRDC: federally funded research and development centers
PI: principal investigator
UARC: university affiliated research centers

PENG abstracts are REQUIRED

Abstracts shall address both Phase 1 and Phase 2 and:

- Provide preliminary technical rationale of how the proposed solution can achieve the program goals and metrics, including, but not limited to, supporting empirical data, relevant literature citations, robust structural modeling, and/or in silico predictions. Any quantitative performance figures must be supported by discussion or biological/computational theory.
- Clearly identify the initial Phase 1 target proteins *(at least three self-selected targets spanning distinct structural protein families)* and provide a clear justification for each, detailing the precise, quantitative functional outcomes of the proposed edits. Proposers must detail the exact analytical validation methods *(e.g., quantitative Mass Spectrometry, Western Blot, or functional assays)* they will use to verify their functional edits.
- Outline preliminary platform specification and methodologies, to include:
  - The proposed generalizable chemistry.
  - The proposed programmable targeting mechanism.
  - The intended complex cellular systems planned for Phase 2 validation.
- Briefly describe the roles of key personnel and provide evidence of the team's ability to execute the proposed research.
- Include a Rough Order of Magnitude (ROM) cost estimate, clearly broken out by Phase 1A (Base), Phase 1B (Capability Demonstration Option), and Phase 2 (Option).

Non-conforming activities

- Rely on permanent genomic editing or transgenic bypass to circumvent editing existing endogenous proteins.
- Consist solely of *in silico* modeling without a planned wet-lab experimental validation component.
- Strictly rely on traditional pharmacology.
- Contain Human Subject Research.
- Fail to address the entire solicitation by offering only partial solutions or addressing only one Phase.
- Proposal submission through mechanisms other than DARPA's Broad Agency Announcement Tool (BAAT), such as through Grants.gov or directly to the PENG@darpa.mil e-mail.

Questions

- Please submit any questions to PENG@darpa.mil
- Answers to the questions will be provided later and posted to the DARPA program page and https://sam.gov/
- Program presentation materials will be posted to the DARPA program page

Key upcoming dates

- FAQ Submission Deadline: **17 August 2026 4:00 PM EST**

- Abstracts Due (required): **24 August 2026 4:00 PM EST**
  - *All abstracts are required to be submitted via DARPA's Broad Agency Announcement Tool.*
  - *Since proposers may encounter technical difficulties or heavy web traffic, DARPA discourages waiting until the day submissions are due to upload the submission.*

- Full Proposals Due (by invitation only): **19 October 2026**

- Expected Start Date: **June 2027**

Closing comments

- Reminder: the Program Solicitation supersedes anything presented or said by DARPA at the Proposers Day.
- Proposals will only be evaluated in accordance with the instructions provided in the Program Solicitation.
- Only a duly authorized Contracting/Agreements Officer may obligate the government.
- **Examples in this briefing (e.g., technologies, use cases) are chosen for ease of illustration only and do not constitute endorsement of any particular approach.**
- Interested performers are expected to be able to articulate a clear and compelling vision for their technology and proposed course of research.
- Teaming is important and today is a great opportunity for networking!

Animal Subject Research

Proposals could potentially include animal use research. Proposers that anticipate involving animals in the proposed research must comply with the approval procedures detailed at https://www.darpa.mil/policies/human-animal-research to include providing the information specified therein as required for proposal submission.

What is animal subject research?

For DARPA research, an animal **IS**

- ✔ A living or dead **vertebrate**
- ✔**A larval fish or amphibian**
- ✔**An egg-laying vertebrate** is only an animal **after hatching**

Dead = killed for the direct purpose of conducting research

An animal is not

- **X** An un-hatched egg
- **X** An invertebrate
- **X** Dead animals or parts of dead animals purchased at grocery stores or slaughterhouses

Review of the protocol

All DARPA animal use protocols must go through two reviews

1st review

Local Level (IACUC Review)

2nd review

DoW Level (Secondary Review)

ACURO review

Required Submission Docs from Performer

- ✓ IACUC approved protocol
- ✓ Evidence of IACUC approval
- ✓ ACURO appendix
  - Available on ACURO's website

Approval Process

- ✓ ACURO reviews docs
- ✓ May ask PI for clarifications
- ✓ Sends to DoW vet for final review and approval

Approval can take 2-3 months

ACURO approval is needed before any funds can used for the purchase and care of animals. Purchase of supplies and equipment is allowed prior to ACURO approval.

Controlled Unclassified Information (CUI)

Controlled unclassified information (CUI)

CUI is unclassified information that is required to be protected under laws, regulations, and government wide policy

- CUI should be protected on NIST 800-171 Rev. 2
- Compliant systems and physical control must be in place to ensure only individuals with a lawful government purpose can access the information
- Reference the CUI categories in the U.S. National Archives Registry

- Phase 1A is expected to be unclassified fundamental research
  - Note: You do not need to be CUI-compliant to submit an abstract, but it is preferred
- The Phase 1B is expected to be CUI. Performers MUST become CUI-compliant prior to the end of Phase 1A to be able to participate in the capability demonstration
- Phase 2 may contain both unclassified and CUI research. Failure to achieve CUI compliance within Phase 1 period may result in no award

Important things to remember for individual users working with CUI:

- Only work on systems you know are approved for CUI
- If sending CUI data, make sure it is encrypted
- Only send/share CUI to approved individuals
- Only send/share CUI through approved means
- Only save CUI in approved folders

CUI disclosure to team members

CUI controlled by DARPA may only be disclosed to **U.S. and non-U.S. persons** if they are a performer on a team selected for the program. Non-U.S. persons must sign an NDA. There must be a valid contract in place with binding CUI direction and guidance.

Becoming system compliant for CUI handling

Performers are required to have their systems secured per NIST SP 800-171, "Protecting Controlled Unclassified Information in Nonfederal Systems and Organizations"

Performers self-certify that IT systems are compliant

- Set up your own system or use a cloud provider
- Compliance will be verified through Supplier Performance Risk System (SPRS)
- Must register and demonstrate SPRS score ≥ 88 within the past 3 years
- https://www.sprs.csd.disa.mil/default.htm
- *DARPA does not accredit your system or review System Security Plans*

www.darpa.mil