Protean

Dr. Michael Feasel

Protean Proposer's Day

20 FEB 2026

[**proh**·tee·uhn] Adj. meaning "versatile", "capable of assuming many forms", or "dynamic." Protean has positive connotations of flexibility, versatility and adaptability.

Protean Team

The Protean Team

- Dr. Michael Feasel, Program Manager
- Ms. Emilee Lee, Financial and Administrative Support
- Dr. Corinne Beier, Technical Support
- Dr. Steven Guard, Technical Support
- Dr. Zach Poss, Technical Support
- Mr. Elvis Montes, Program Security Support

Contracting Support

- Katie Freeman, Contracting Officer (KO), DARPA

All correspondence to: ProteanTherapeutics@darpa.mil

We need complete protection against an increasingly broad threat landscape

Problem: Yesterday's limited medical countermeasures do not protect against today's infinite threat landscape.

Threat Exposure:

https://www.jbsa.mil/News/News/Article/2047407/army-medical-department-board-test-auto-injectors-gets-feedback-from-soldiers/

Yesterday: Delay Lethality

Today's Outcome:

https://www.wpr.org/health/northeastern-wisconsin-hospitals-are-feeling-strain-remarkable-surge-covid-19-cases

Future Theatres Require:

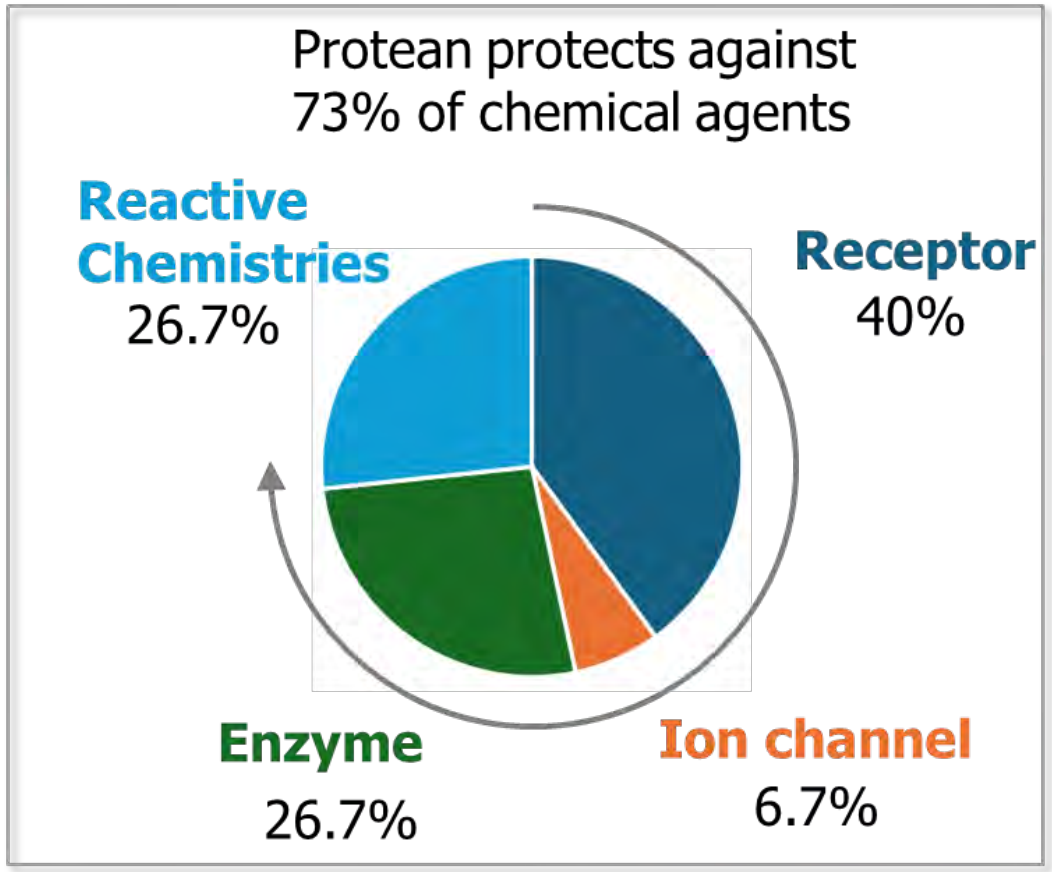
iStock.com/Credit: zabelin

https://www.asahi.com/ajw/articles/15676329

Protean will PROTECT THE TARGET

Vision: Entire classes of CB agents no longer pose any threat.

Reducing the dimensional challenge of the CB threat space



https://www.opcw.org/chemical-weapons-convention/annexes/annex-chemicals/annex-chemicals

How many targets are there?

- Immediate relevance: ~12
- Related with broader relevance: ~200

Example Agents

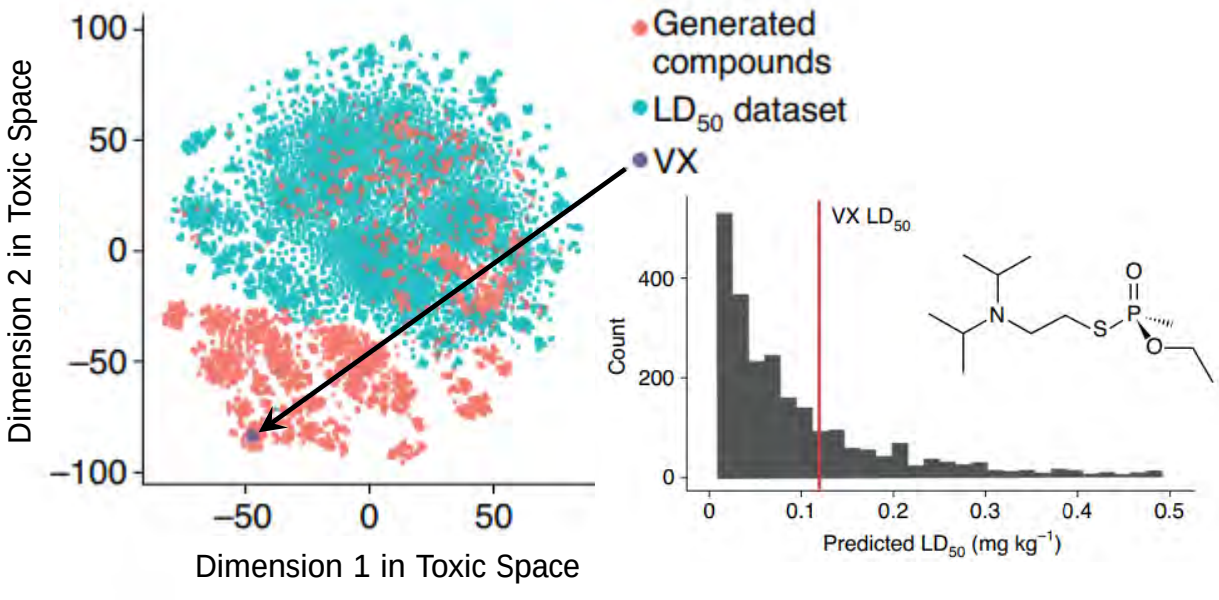
- Receptor
  - PBAs, Bioregulators
- Ion Channel
  - Saxitoxin, Tetrodotoxin, RCAs, Bioregulators
- Enzyme
  - Nerve agents: G-, V-, A-series, Bioregulators
- Reactive Chemistries
  - Mustard, Lewisite, Chlorine

Protean will pursue biological targets of CB threats rather than single agents or downstream symptoms

DARPA has the opportunity to change the chemical warfare equation

Dual-Use of AI Drug Design - A Wake-Up Call: Nerve agents number in the ***tens of millions***

40,000 new chemical agents predicted in 6 hours
Many more lethal than VX



Urbina et al. 2022 *Nature Machine Intelligence*

DARPA Impact

- MCMs that protect protein targets 10,000x more protective than SoA
- Achieves coverage of >95% of nerve agent threat space
- Renders nerve agents non-toxic: access to denied areas and sustained operations

Protecting a ***single*** protein enables elimination of nerve agents as an entire class of threat

Nature has found a way

Proteins can acquire new toxin resistance without losing their critical function

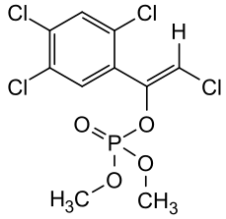
250x protection

Enzyme

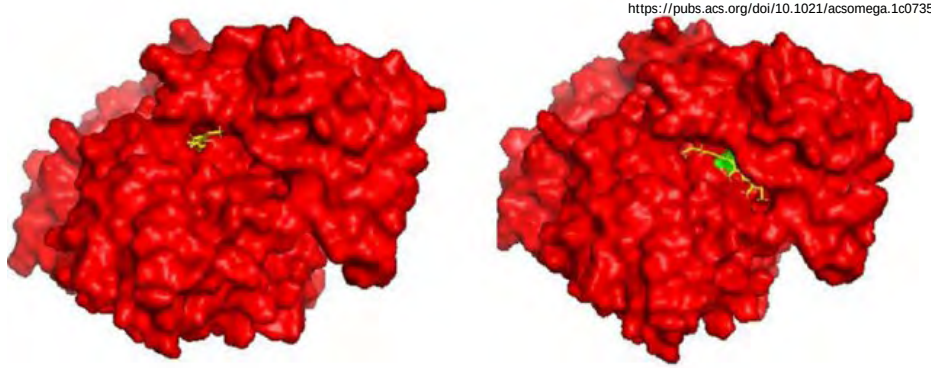
https://virginiamercury.com/2018/08/13/an-asexual-swarming-tick-has-invaded-virginia/

Cattle tick

Pesticide



https://pubs.acs.org/doi/10.1021/acsomega.1c07359



Wild type protein
Susceptible

Mutant protein
Resistant

200x protection

Ion channel

https://en.wikipedia.org/wiki/Herpestes

Mongoose

https://en.wikipedia.org/wiki/Indian_cobra#/media/File:Indian_Cobra,_crop.jpg

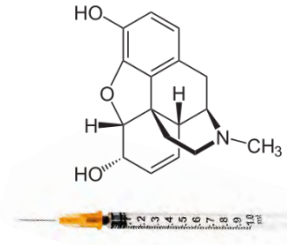
Cobra

https://www.freepik.com/premium-vector/human-anatomy-human-body-silhouette_343275413.htm

30x protection

Receptor

Arg181Cys
mutation

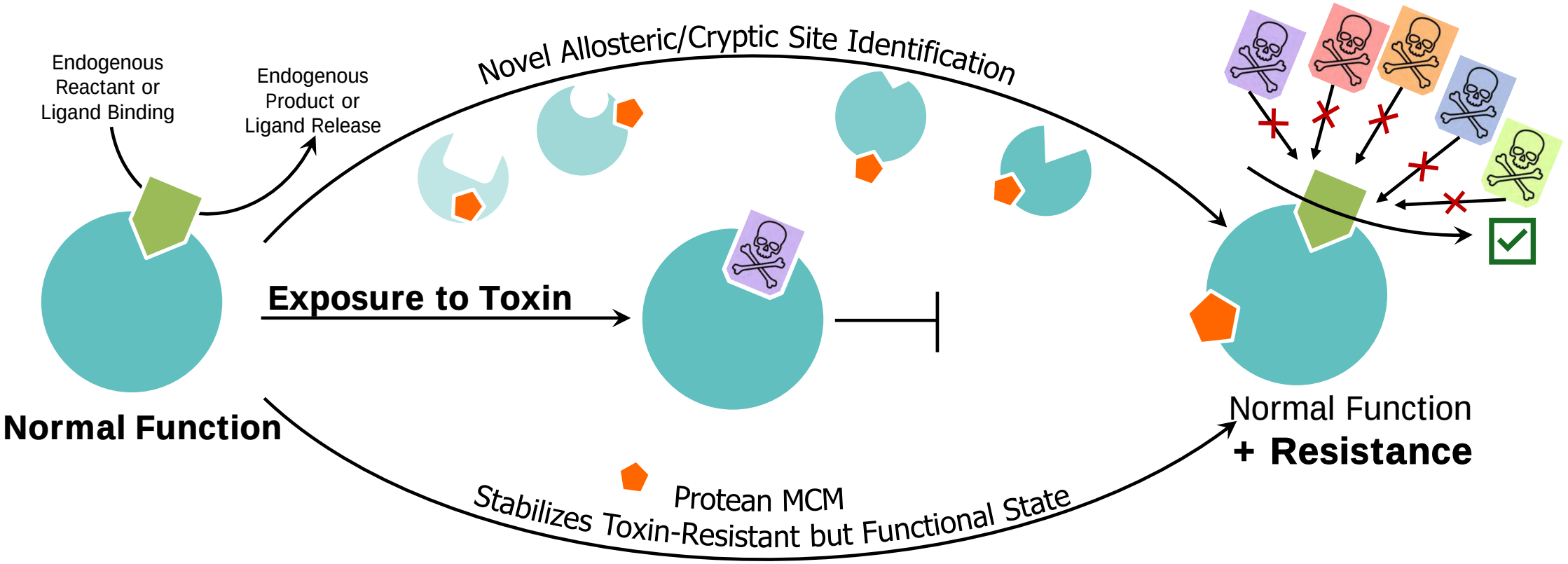


Opioids

Examples from nature are evidence of *genetic* rescue

Protean Hypothesis

"Protean hypothesizes that the key to overcoming this hurdle lies in elucidating the structure, dynamics, and binding pockets that regulate protein function" RA pg.4



Program Structure

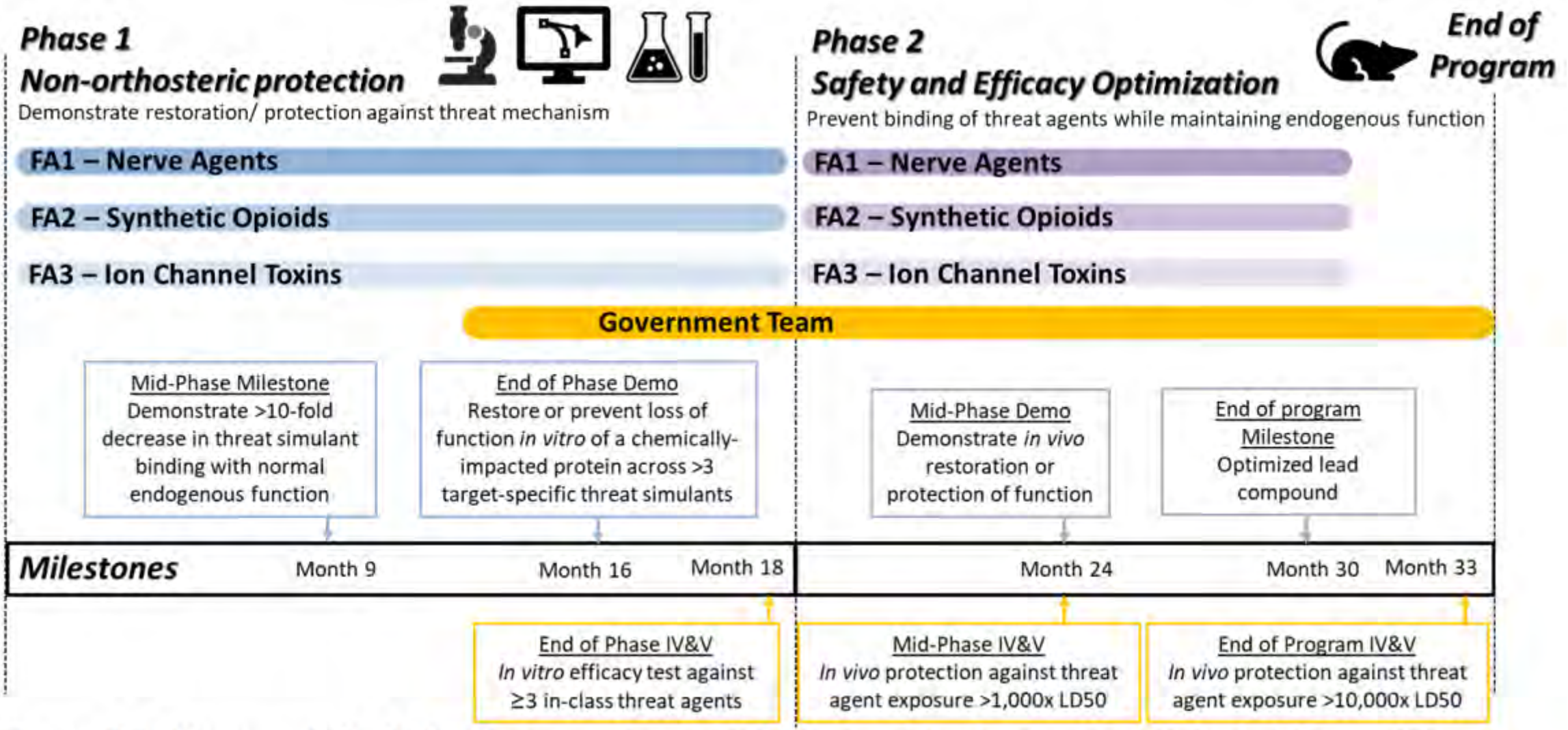
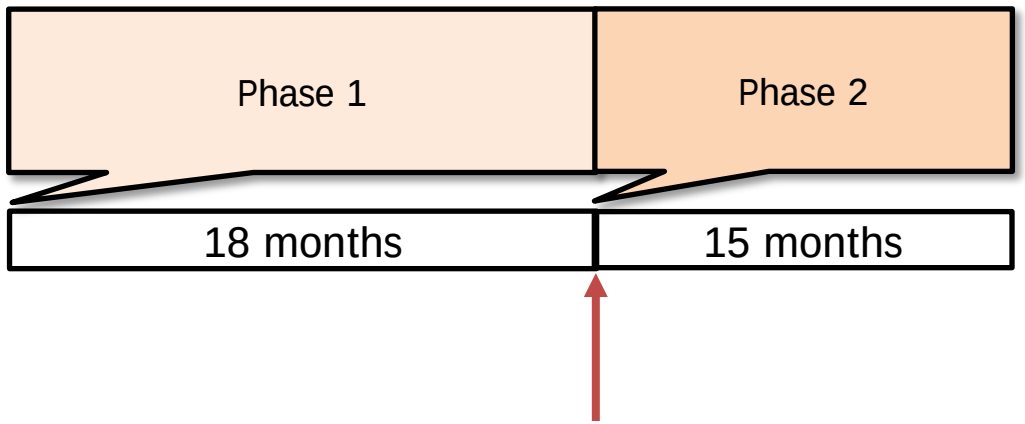


Figure 2.2. Program Schedule. FA: Focus Area, T&E: Test and Evaluation, LD50: Lethal Dose, 50%, CB: Chemical and Biological, MCMs: Medical Countermeasures

Period of performance

Proposals must address both phases

- One 18-month Phase 1
- One 15-month Phase 2



- **Phase 2 is an option, contingent on successful demonstration that a chemically compromised protein can be protected or restored by rational intervention *in vitro***

- **Funding for Phase 2 is also contingent on the availability of funds.**

Proposals *MAY* address one or multiple FAs:

- Technical strength of each focus area will be evaluated independently

- FAs can be changed or added prior to submission of the *full proposal* at gate 2.
  - Justification must be provided

- Proposals are recommended to differentiate task/ subtask by FA such that the success of one FA is not dependent on another

- Proposals must propose prophylactic strategies and may optionally also propose therapeutic strategies.

FA1 – Nerve Agents

Preventing Intoxication: “Performers must provide a systematic exploration of ways to intervene in [the intoxication] process, while maintaining binding and downstream activity associated with endogenous ligand(s).” RA pg. 7

By Month 12 performer will:
Demonstrate a >10-fold decrease in threat simulant binding affinity

Performer chosen*. Simulant example for nerve agents: organophosphate-based pesticides

Month 18 Government partner will:
Evaluate *in vitro* efficacy on >3 class specific chemical threats

DARPA chosen. Class specific examples for nerve agents *may* include VX, Sarin, and Novichok agents

*See RA for suggested considerations on choosing simulants and provide justification in your proposal of your choice(s).

FA2 – Synthetic Opioids

Preventing Intoxication: “Performers must provide a systematic exploration of ways to intervene in [the intoxication] process, while maintaining binding and downstream activity associated with endogenous ligand(s).” RA pg. 7

By Month 12 performer will:
Demonstrate a >10-fold decrease in threat simulant binding affinity

Performer chosen*. Simulant examples for synthetic opioids: Morphine, Remifentanil, Fentanyl, Sufentanil

Month 18 Government partner will:
Evaluate *in vitro* efficacy on >3 class specific chemical threats

DARPA chosen. Class specific examples for nerve agents *may* include Ohmefentanyl, Carfentanil

*See RA for suggested considerations on choosing simulants and provide justification in your proposal of your choice(s).

FA3 – Ion Channel Toxins

Preventing Intoxication: “Performers must provide a systematic exploration of ways to intervene in [the intoxication] process, while maintaining binding and downstream activity associated with endogenous ligand(s).” RA pg. 7

Example ion channel toxins you may propose to protect against include but are not limited to pepper spray (OC), tear gas (CS), saxitoxin, picrotoxin, tetrodotoxin and similar ion channel toxicants such as those that can be described as mycotoxins, marine or plant toxins, or venoms.

By Month 12 performer will:
Demonstrate a >10-fold decrease in threat simulant binding affinity

Performer chosen*.

Month 18 Government partner will:
Evaluate *in vitro* efficacy on >3 class specific chemical threats

DARPA chosen. DARPA will select challenge compounds that align with your proposal objectives and test generalizability across ion channels

*See RA for suggested considerations on choosing simulants and provide justification in your proposal of your choice(s).

Metrics and Milestones Phase 1

Metrics and Milestones for all Focus Areas	
Phase 1:	**6 Months** – Characterize the energetics, kinetics, and mechanisms and validate how each event impacts function. - E.g., Allosteric binding events, cryptic binding site identification, protein dynamics regulatory events, identification of alternate control surfaces - Identify >1 novel distal regulatory sites or modes of regulation within protein target of interest. **12 Months –** Demonstrate a >10-fold decrease in threat simulant binding affinity for its protein target, while ensuring endogenous ligand/substrate binding is minimally impacted (<5x, across all target classes) **16 Months** - Restore or prevent loss of function of a chemically-impacted protein. - Rescue or protection: >10x increase in *ED50 of >3 threat surrogates/simulants for target-specific *in vitro* endpoint. **End of Phase Milestone – 18 Months:** T&E will evaluate *in vitro* efficacy on >3 class specific chemical threats.

Metrics and Milestones Phase 2

Phase 2:	**24 Months** – Demonstrate *in vitro* protection of function to a protein via molecular intervention: 1,000x increase in threat simulant ED50 for in vitro endpoint - Lack of acute toxicity predicted by in vitro ADR panel. **Mid Phase 2 Milestone - 24 Months: (**T&E) LD50 of chemical threat with intervention is >1000x baseline exposure in a rodent model **30 Months** – End of program Milestone – Optimized lead compound - Half-life of intervention ≥ threat agent compound or target-threat adduct. - Prevention of threat agent initiated signaling events in vitro: 10,000x increase in threat simulant ED50 for in vitro endpoint **End of Program Milestone - 33 Months: (**T&E) Demonstrate intervention relieves physiological outcomes of chemical threat exposure in a rodent model. - LD50 with intervention is >10,000x baseline exposure

How does the tasking requirement relate to these metrics?

- Tasking must relate to time sensitive metrics and provide length of performance
- Subtasks organized under major program activities
- Quantitative metrics and Deliverables
  - **THESE NEED TO BE USEFUL FOR MEASURING PROGRESS TOWARDS OVERALL PROGRAM GOALS**
- Cost may be approximated at this stage per task (ROMs are acceptable)

FOR EXAMPLE ONLY

Task 1: Build Spaceship ($cost and time to completion)

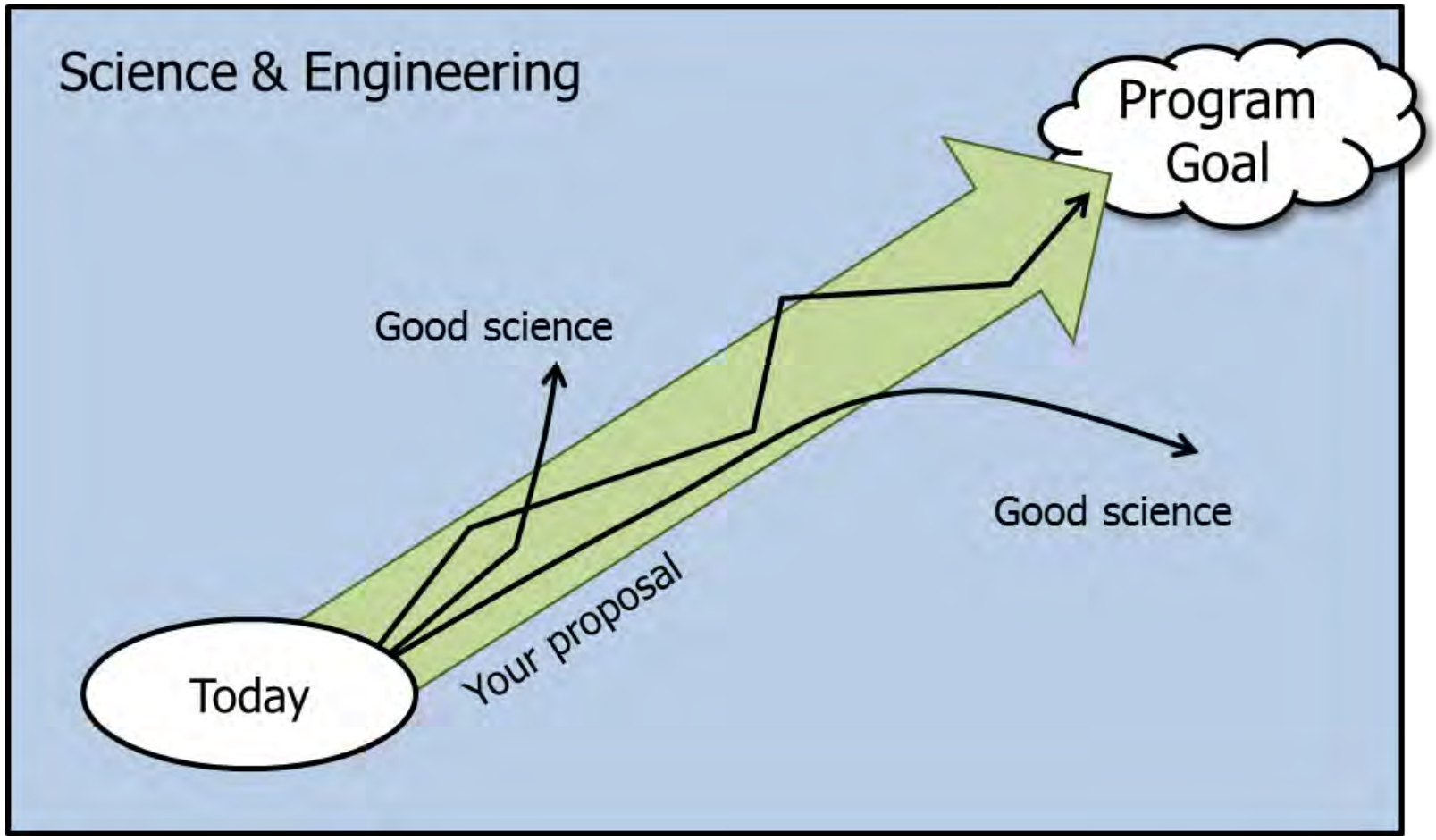
Subtask 1.1: Build Reusable Booster Rocket ($cost and time)

- **1.1.1:** Booster rocket achieves Low Earth Orbit (LEO) with 1000kg payload. ($cost and time)
- **1.1.2:** Booster rocket returns to Earth intact after launch. ($cost and time)
- **1.1.3:** Booster rocket achieves LEO > 5 times. ($cost and time)

Subtask 1.2: Build Human-Compatible Compartment ($cost and time)

- **1.2.1:** Compartment supports life for > 30 days including oxygen, water, and waste management systems. ($cost and time)

How DARPA thinks about your project



Proposal Requirements

Protean seeks to “develop prophylactics (and optionally therapeutics) that protect protein function against chemical threat challenges over 10,000x LD50s.” *RA, pg 4.*

Successful proposals must provide the following:

1. An approach for discovering novel regulatory points for proposer’s selected protein target.

2. Methods for characterizing the mechanism of chemical intoxication for at least 1 class of threats or surrogates/simulants. Interventions must provide broad protection against chemical threats that share a mechanism of action.

3. Methods for evaluating whether a given protein conformation, binding site or dynamic event contributes to protein function.

4. A well-integrated pipeline for optimization of chemical matter to achieve end-of-program efficacy metrics *in vivo*.

It is up to you to propose a solution.

Proposal Exclusion Criteria

Specifically **excluded** are proposals that involve:

1. Strategies that exclusively develop competitive inhibitors or activators.

2. Strategies designed to absorb or degrade a specific chemical threat, e.g. agent-centric sponges and detoxifying enzymes.

3. Medical countermeasure development that relies on genetic engineering of the host as an intervention.

4. Research that generates incremental improvements to existing MCMs including but not limited to: analogs, formulation, delivery systems.

5. Molecular design strategies that lack novel mechanistic insight. (e.g. black box AI/ML strategies where the internal model structures are unknown)

It is up to you to propose a solution.

Teaming

To fully address the RA you *might* (?) need to team with other entities.

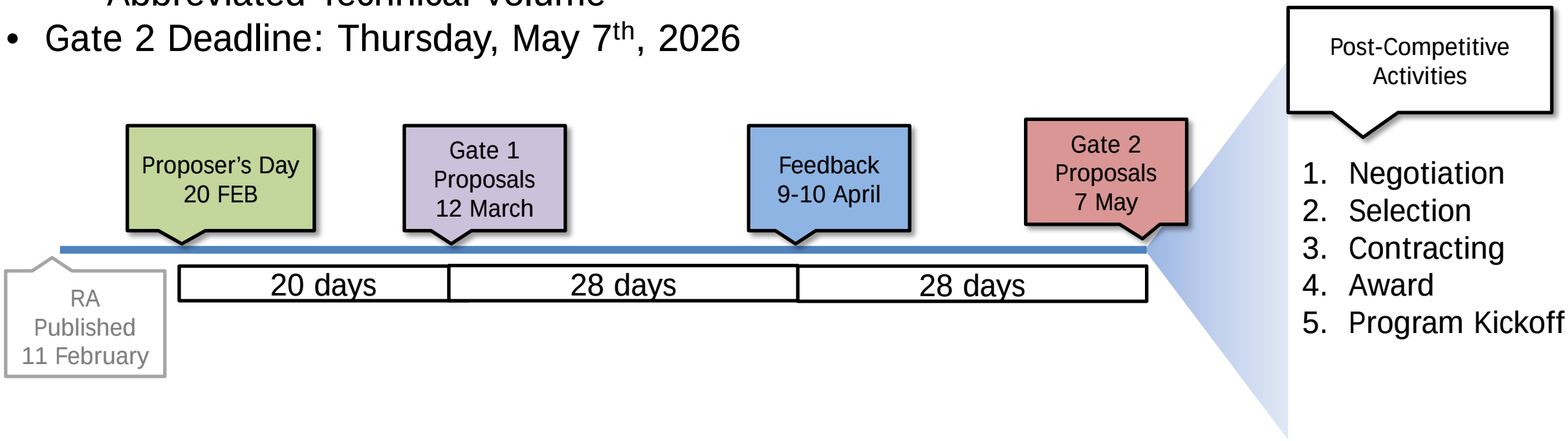
- If you need to build a team across multiple institutions/subcontractors, you must present a convincing research and management plan.
- You must find your collaborators on your own.
- Your team should submit a unified proposal under a single PI.
- This RA is open to educational institutions, government labs, and/or private companies.
- As Controlled Technical Information (CTI) is anticipated for this program, foreign proposers are encouraged to understand U.S. export law and have a plan in place to obtain export licenses when necessary. Possible methods include teaming with a U.S. prime and/or having a U.S. subsidiary/parent company.
- If you are a member of a team, you may join any number of other teams or form your own and submit a proposal as PI.
- Proposals are strongly encouraged to have a project manager for the entirety of the effort.

Acquisition Structure and Gate Process

Dr. Steven Guard

Important Dates (Protean RA)

- Posting Date: Wednesday, February 11th, 2026
- Gate 1 Deadline: Thursday, March 12th, 2026
  - Video Abstracts
  - Abbreviated Technical Volume
- Gate 2 Deadline: Thursday, May 7th, 2026



Gate 1 Materials: Abbreviated Technical Volume

BOTH VIDEO ABSTRACTS AND ABBREVIATED TECHNICAL VOLUMES ARE REQUIRED

- Demonstrate and understanding of the program challenge
- An opportunity to sell the novelty of your solution/ approach.
  - Some concepts can be difficult to capture in text.
  - Sell the reviewer on why it is exciting.
- Provide an understanding of the DARPA mission.
- Introduce key personnel and the value they contribute to the proposed approach.

Abbreviated Technical Volumes should include:

- Cover Page
- Executive Summary Slide
- Technical Approach
  - *Be sure to address all Tasks by Phase.*
  - *Be sure to include milestones*
- Technical Ability:
  - Identify the Principal Investigator (PI)
  - Responsibilities of the team members
- Tasking and Cost
  - ROMs
  - Capture critical program activities

Technical volumes are limited to 5 pages excluding: conflicts of interest, IP, certifications, novelty statements and references

Gate 1 Materials: Video Abstracts

Video Abstracts are your chance to really sell the proposal

10 – Minute format. Video content highly encouraged.

- Demonstrate and understanding of the program challenge
- An opportunity to sell the novelty of your solution/ approach.
  - Some concepts can be difficult to capture in text.
  - Sell the reviewer on why it is exciting.
- Provide an understanding of the DARPA mission.
- Introduce key personnel and the value they contribute to the proposed approach.
- Capture the core concept but is not completely redundant with the written proposal.
- **These videos are likely going to be the first thing your reviewer sees.**

Gate 2 Materials: Full Proposal

GATE 2 SUBMISSIONS ARE BY INVITE ONLY

- Proposers proceeding to Gate 2 of the submission process will receive additional instructions with Gate 1 feedback letters.

- Instructions at this point will include
  - Submission Dates
  - A scheduling request to discuss the proposal with the program manager
  - Detail on submission materials:
    - ❑ Cost proposal templates
    - ❑ Research description documents
    - ❑ Formal guidance specific to the award mechanism of interest: Cooperative Agreements (CA) and Other Transaction for Research (OT-R)

- A meeting will be requested with the Protean Program Manager within 1 week of feedback letter receipt.
  - Discussion of content
  - Recommendations for full proposal material
  - Finalization of FA to be addressed

www.darpa.mil