HEALR FAQ

Technical Program Scope

1. **Do matrix metalloprotease (MMPs) fall within the purview of the HEALR program?**
2. **Do partly or fully-biological options, as opposed to small molecules alone, fall within the purview of the HEALR program?**
3. **The "classical" PROTACS are small molecule chimeras. Would a chimeric protein or peptide be acceptable (i.e., a protein that binds a microbial target and host defense system?**
4. **Are DNA-based approaches (such as transgene delivery) for expressing the targeting chimera in scope?**
5. **Are immunomodulatory approaches that are synergistic with the targeting chimeras in scope?**
6. **We envision a system that will not involve ubiquitin or other tag transfer. Would that still be acceptable?**
7. **Must the bacteria be targeted, or could other bacterial proteins be targeted?**
   Yes (to all of the above). The HEALR program is not target or approach prescriptive; proposals must address each of the three TAs, target one or more of the pathogens/biothreats listed in the BAA, and describe how program objectives of developing an effective therapeutic will be met.

8. **What are the restrictions, if any, on the use of macromolecules (e.g., phage tail fibers) for pathogen-binding head of the chimeric molecule?**

   None.

9. **Does a responsive strategy require that the treatment be a chemical?**

   No.

10. **Is a single agent approach necessary, or are combination approaches acceptable, including combination approaches with existing therapeutics?**

    Combination approaches are acceptable provided they address each of the three TAs, target the pathogens/biothreats listed in the BAA, can meet the program objectives of developing an effective therapeutic, and clearly demonstrate that the HEALR component of the combination is essential and substantially enables and/or enhances the therapeutic outcomes.

11. **Is targeting a host response in scope for this program?**

    No, meeting the program metrics laid out in the BAA requires the proposer to target the pathogen rather than a host response.

12. **How will using host machinery to destroy individual intracellular proteins generate an effective therapeutic? How would this system engage proteins within the bacterium?**

    We anticipate that performers will carefully identify and select essential pathogen proteins (or other biomolecular targets) that if effectively engaged and degraded by cellular machinery would result in the desired therapeutic outcome. This is an integral component of TA1 and of the program more generally.

13. **How will the HEALR program generate effective countermeasures against extracellular vs. intracellular pathogens?**

    The BAA lists intracellular and extracellular pathogens of interest to the HEALR program. We anticipate intracellular and extracellular pathogens will require different degradation or deactivation pathways to address. For example, exclusively extracellular pathogens would not be addressable by conventional PROTACs approaches, but could be address by emerging newTACs strategies such as LYTACs.

Technical Program Approach

14. **Does the system have to be catalytic in nature?**

    The system is not required to be catalytic. The proposed work should include tasks that elucidate system turnover and kinetics.

15. **What is the expectation on preexisting data that needs to be part of an application vs a strong well equipped team with a novel idea?**

    Proposals created around a strong concept that is well described and justified based on precedence in the literature are welcome. It is understood that less developed/more novel strategies will have less preliminary data.

16. **Will a specific animal model of infection be used in Phase 2 and 3 demos, or can we utilize our own model?**

    Proposers should specify the animal model(s) and provide information and justification that supports use of the selected model. DARPA will not select the animal model.

17. **Must we kill the bacteria or we can focus on disabling them?**

    Either approach is acceptable provided the approach targets bacteria/bacterial components and therapeutic outcome is achieved.

18. **The mechanism of action for some PROTACs is not well worked out. How well worked out does the biology have to be known for a proposed idea?**

    A complete understanding of the mechanism of action is not a requirement for the proposal, but the proposed work should include tasks to elucidate mechanism of action.

19. **Must the ligand be a new moiety?**

    No, it may be an existing moiety. The HEALR program is not target or approach prescriptive; proposals must address each of the three TAs, target one or more of the pathogens/biothreats listed in the BAA, and describe how program objectives of developing an effective therapeutic will be met.

20. **Is there a preference for targeting intracellular vs extracellular machinery?**

    There is no preference for targeting intra- vs extracellular machinery. The proposed degradation or deactivation route should be appropriate to the selected pathogen.

21. **How should we develop metrics for pathogens not included in Table 2?**

    Table 2 is intended to provide examples of the level of detail that proposers should provide in the metrics they propose. That is, the proposer must provide robust metrics based on the approach and bacteria (selected from Table 1) selected.

22. **Is there a need for high throughput screening in the program?**

    No. The HEALR program is not target or approach prescriptive; proposals must address each of the three TAs, target one or more of the pathogens/biothreats listed in the BAA, and describe how program objectives of developing an effective therapeutic will be met.

Pathogen Selection

23. **Where can I find a list of the pathogens of interest for the DoD?**

    The list of HEALR pathogens can be found in Table 1 of the BAA.

24. **Are viruses considered to be "microbes" under this BAA or are you only considering anti-bacterial systems?**

    Viruses are not included in the pathogen list for HEALR. Pathogens on this list can be found in Table 1 of the BAA.

25. **Are pathogens not included in the BAA acceptable targets?**

    No. Proposers are required to select target pathogens from the list provided in Table 1 of the BAA.

26. Is there any prioritization of the pathogens on the list in the BAA?

No.

27. Do multiple species count as multiple targets, or must multiple targets be specified by genera?

Targets should be selected at the genera level. For example, in Table 1 in the BAA, *Burkholderia spp.* are listed as a target. Different *Burkholderia* species would not be counted as multiple targets.

Technical Area 2

28. Is there an emphasis in development of a new way to engage the host machinery as opposed to using E3 ligase?

Yes, TA2 is focused on developing new ways to engage host machinery.

29. TA2 has three types of "new TACs" listed for deactivation, modification and extracellular. Does the proposal need to address all 3 types?

No, these are provided only as examples. A proposal could use some or all of these approaches, or could use other approaches not covered in these examples.

30. Is it acceptable to leverage the bacterial degradation machinery?

Yes, this is one of a number of acceptable approaches to degradation or deactivation of targets. Please refer to the TA2 requirements for more detail.

31. Is it acceptable to employ the commensal microbiome as the "host machinery" degrader/deactivator?

Yes, this is one of a number of acceptable approaches to degradation or deactivation of targets. Please refer to the TA2 requirements for more detail.

Proposal Preparation

32. Does each proposal need to address all three TAs?

Yes.

33. Should the proposal address all three phases of the program?

Yes.

34. How quickly will DARPA provide feedback on the abstract?

Per the BAA, DARPA will attempt to provide feedback on the abstract within 20 days, although we strive to provide feedback as promptly as possible and can often do so in a shorter timeframe.

35. What is a recommended budget?

The amount of resources made available under this BAA will depend on the quality of the proposals received and the availability of funds. Typical DARPA BTO program budgets range from $40-60M over 3-5 years and fund 3-5 awards.

36. Is the administrative program manager expected to be included in the budget? Should this be a full-time position?

All personnel included in the proposal should be included in the budget. Sufficient time should be allocated to all personnel to effectively complete the work required for the program to be successful. The level of effort for an administrative program manager would depend on factors that might include the size of the effort, the number of institutions that must be coordinated, etc.

37. Does the full team need to be assembled by the time of abstract submission?

No, team composition may be adjusted after abstract submission. Only the team composition of the proposal will be considered in evaluating the proposal.

38. Do you have recommendations for teaming? Are inter-organizational teams preferred over intra-organizational?

DARPA programs such as HEALR are complex efforts that require a wide range of expertise to be successful. Successful proposals frequently come from teams in order to tap into a variety of subject areas, and teaming is therefore encouraged. There is no preference for teams within an organization as compared to intra-organizational teams.

39. Will teaming profiles be shared?

Participants in the HEALR Proposers Day will receive a copy of any teaming profiles that were submitted within a week following Proposers Day.

40. Funding is scheduled to begin mid 2021. Why such a long lag?

The program schedule included in the BAA indicates a likely kickoff in mid FY2021. Note that the fiscal year starts in October, so this timeline aims for a kickoff in the first quarter of 2021. This schedule includes time for abstract review, proposal review, and contracting.

41. Does participation in an existing DARPA program have any effect on evaluation of a proposal to HEALR?

No, this is not considered in evaluation of the proposal. However, the work that is proposed must not be duplicative with work under another effort.

42. Are teams able to apply for the EEI program separately from the HEALR program?

This solicitation will only consider applications to the EEI program as part of a HEALR proposal. Current DARPA performers who are interested in learning more about the EEI program should contact their DARPA POCs for more information about opportunities available to them.

43. Are there opportunities for IV&V partnership?

Government organizations that wish to participate in IV&V should reach out separately, per instructions in the BAA.

44. Are there any restrictions on national labs participating?

As stated in Section 3.1.1 of the BAA: "Government Entities (e.g., Government/National laboratories, military educational institutions, etc.) are subject to applicable direct competition limitations. Government Entities must clearly demonstrate that the work is not otherwise available from the private sector and provide written documentation citing the specific statutory authority and contractual authority, if relevant, establishing their ability to propose to Government solicitations and compete with industry. This information is required for Government Entities proposing to be awardees or subawardees."

General Inquiries

45. What motivated the development of this program?

The program seeks to expand the maturing field of protein degradation to develop clinical applications addressing the DoD-relevant problem of bacterial infections.

46. My research is not geared specifically to meet the HEALR program goals. Is there an alternate solicitation that I can respond to?

Yes. DARPA/BTO has an office-wide solicitation (HR001120S0044) for this purpose. Responses are being collected through April 2021. Any innovative ideas can be submitted to the BTO office-wide solicitation at any time.

47. Is Dr. Cohen available for a call or meeting to discuss our approach?

In the interest of fairness to all parties, as Dr.Cohen will likely not have availability in his schedule to honor all requests, we will not be taking any program-related calls/meetings.

Ultimately, the best way to determine the applicability of and level of interest in your approach is through the submission of a proposal abstract. The BAA describes the program, including metrics, in detail. If you have specific questions, please submit them by email to HEALR@darpa.mil. Please be aware that your question and its answer may be published on this FAQ page, after the question has been revised to remove proprietary information.

48. Is proposal abstract submission required to submit a full proposal?

No. Per the BAA – "Regardless of DARPA's response to an abstract, proposers may submit a full proposal. DARPA will review all conforming full proposals using the published evaluation criteria and without regard to any comments resulting from the review of an abstract." That being said, you are STRONGLY encouraged to carefully review the solicitation/FAQ and ask any necessary clarification questions to ensure your approach is responsive to the BAA before expending the effort to prepare a proposal.