Small Business Innovation Research (SBIR) and
Small Business Technology Transfer (STTR)
Opportunity Announcement
HR001120S0019-02
Rapid, flexible manufacturing of DNA molecules for synthetic biology and therapeutic applications

Which program will fund this topic?
SBIR
What type of proposals will be accepted?
Both Phase I and Direct to Phase II (DP2)

Technology Area(s): Biomedical

I. INTRODUCTION

The Defense Advanced Research Projects Agency (DARPA) Small Business Programs Office (SBPO) is issuing an SBIR/STTR Opportunity (SBO) inviting submissions of innovative research concepts in the technical domain(s) of Biomedical. In particular, DARPA is interested in understanding the feasibility of rapid, flexible manufacturing of DNA molecules for synthetic biology and therapeutic applications.

This SBO is issued under the Broad Agency Announcement (BAA) for SBIR/STTR, HR001120S0019. All proposals in response to the technical area(s) described herein will be submitted in accordance with the instructions provided under HR001120S0019, found here: https://beta.sam.gov/opp/b8abeb02f16a4450b2c2f859fc00c177/view.

a. Eligibility

The eligibility requirements for the SBIR/STTR programs are unique and do not correspond to those of other small business programs. Please refer to Section 3.1, Eligible Applicants, of HR001120S0019 for full eligibility requirements.

b. Anticipated Structure/Award Information

Please refer to Section 1, Funding Opportunity Description, in HR001120S0019 for detailed information regarding SBIR/STTR phase structure and flexibility.

If a proposer can provide adequate documentation to substantiate that the scientific and technical merit and feasibility described in the Phase I section of the topic has been met and describes the potential commercial applications, the Direct to Phase II (DP2) authority allows the Department of Defense (DoD) to make an award to a small business concern under Phase II of the SBIR program without regard to whether the small business concern was provided an award under Phase I of an SBIR program. This SBO is accepting both Phase I and DP2 proposal submissions.

For this SBO, DARPA will accept Phase I proposals for cost of up to $225,000 for a 12-month period of performance.

DARPA will accept DP2 proposals for cost of up to $1,750,000. This includes a 24-month base period not to exceed a cost of $1,000,000 and a 12-month option period not to exceed a cost of $500,000. A separately priced option of up to $250,000 may also be proposed for contractors who would like to be considered for participation in the DARPA Embedded Entrepreneur Initiative (EEI). Refer to Section 2.6 of HR001120S0019 for detailed information on EEI.

Proposers should refer to Section 4, Application and Submission Information, of HR001120S0019 for detailed proposal preparation instructions. Proposals that do not comply with the requirements detailed in HR001120S0019 and the research objectives of this SBO are considered non-conforming and therefore are not evaluated nor considered for award.

Phase I proposals shall not exceed 20 pages. Phase I commercialization strategy shall not exceed 5 pages. This should be the last section of the Technical Volume and will not count against the 20-page limit. Please refer to Appendix A of HR001120S0019 for detailed instructions on Phase I proposal preparation.

DP2 Feasibility Documentation shall not exceed 40 pages. DP2 Technical Proposal shall not exceed 40 pages. Phase II commercialization strategy shall not exceed 5 pages. It should be the last section of the Technical Volume and will not count against the 40-page limit. Please refer to Appendix B of HR001120S0019 for detailed instructions on DP2 proposal preparation.

c. Evaluation of Proposals

Section 5, Evaluation of Proposals, in HR001120S0019 provides detailed information on proposal evaluation and the selection process for this SBO.

d. Due Date/Time

Full proposal packages (Proposal Cover Sheet, Technical Volume, Price/Cost Volume inclusive of supporting documentation, and Company Commercialization Report) must be submitted via the DoD SBIR/STTR Proposal Submission website per the instructions outlined in HR001120S0019 no later than **2:00 pm ET, April 20, 2020.**

II. TOPIC OVERVIEW

a. Objective

Develop a rapid and cost-effective synthetic DNA manufacturing capability.

b. Description

There is a critical DoD need to be able to rapidly and efficiently synthesize highly accurate kilobase (kb) pair length DNA constructs for medical countermeasure and synthetic biology applications. Several DARPA programs and technologies (e.g., Living Foundries, PRemptive Expression of Protective Alleles and Response Elements (PREPARE), and Pandemic Prevention Platform (P3)) rely heavily on synthetic DNA and the timely generation, manipulation, and delivery of genetic constructs. Current synthetic DNA production is costly, time-consuming, and requires highly specialized

technical expertise and equipment. Consequently, few commercial suppliers are capable of producing synthetic DNA at a length that is appropriate for DARPA technologies (i.e., >2,500 base pairs) in the days-long turnaround time required for rapid response. First, due to the limited capability base, commercial sources experience significant backlog in synthetic DNA production services, extending research and development timelines dependent on gene-encoded products, and increasing costs for the consumer. Second, current methods for synthesis or assembly of kilobase length constructs are often error prone, requiring manual purification and/or analytics steps to achieve the final product. Third, as demand for synthetic DNA production increases, any achieved throughput increases will need to maintain or even decrease the cost per base pair.

To achieve these goals, DARPA seeks methods capable of rapidly generating a panel of synthetic DNA meeting the following objectives:

- Each product sequence must be greater than 2,500 base pairs;
- Demonstrate a platform error rate of less than 1 per 5000 base pairs;
- Synthesis of at least 200 unique sequences (Phase I) in under one week;
- Synthesis of at least 500 unique sequences (Phase II) in under one week; and
- Technology and commercial model with a cost per base pair to the consumer comparable to current vendors (see Phase II section below).

c. Phase I

Develop rapid DNA synthesis method(s) capable of generating DNA molecules greater than 2,500 base pairs in length. The synthesis method should be capable of producing 200 unique DNA sequences in less than one week in quantities sufficient for downstream cloning into expression vectors. Within the one-week production timeframe, the synthesized DNA molecules will need to be purified and analyzed for sequence identity relative to the input sequence and any residual impurities. At the end of Phase I, performers will need to demonstrate feasibility for producing 200 unique DNA sequences based on DARPA-defined targets in less than one week.

i. **Schedule/Milestones/Deliverables:**

Phase I fixed payable milestones for this program should include:

- Month 1: Kickoff meeting and initial report on status of DNA synthesis methodology and approach for meeting phase I objectives.
- Month 6: Demonstrate ability to synthesize DNA molecules greater than 2,500 base pairs in length.
- Month 11: Demonstrate ability to synthesize 200 unique DNA sequences of greater than 2,500 base pairs in length.
- Month 12: Final Phase I Report summarizing approach; report summarizing ability to produce 200 unique DNA sequences of greater than 2,500 base pairs in length.

Phase I deliverables: Basic prototype of the DNA synthesis platform and a final report that must include: (1) proposed methods to scale DNA synthesis towards production levels capable of generating more than 500 unique sequences; (2) prototype performance

metrics; (3) results of the capability demonstration; and (4) competitive assessment of the market.

Plans for Phase II should include optimization design goals and key technological milestones to scale no less than 500 and up to 1000 or more unique DNA molecules in one week.

Proposers interested in submitting a Direct to Phase II (DP2) proposal must provide documentation to substantiate that the scientific and technical merit and feasibility described above has been met and describes the potential commercial applications. Documentation should include all relevant information including, but not limited to: technical reports, test data, prototype designs/models, and performance goals/results. For detailed information on DP2 requirements and eligibility, please refer to Section 4.2, Direct to Phase II (DP2) Requirements, and Appendix B of HR001120S0019.

d. Phase II

Develop and demonstrate a flexible, multiplexed platform for the rapid synthesis of DNA molecules based on the basic prototype developed during Phase I. The platform should enable scaled synthesis of at least 500 unique gene sequences but preferably 1,000 unique sequences. Additionally, the platform at scale should generate products at a cost of <$0.01 per base pair. At the end of Phase II, performers will demonstrate the feasibility of producing 500-1000 unique DNA sequences based on DARPA-defined targets in less than one week.

i. **Schedule/Milestones/Deliverables:**

Phase II fixed payable milestones for this program should include:

- Month 12: Demonstrate ability to synthesize unique DNA sequences at a cost <$0.01 per base.
- Month 24: Demonstrate ability to synthesize at least 500 unique DNA sequences greater than 2,500 base pairs with an error rate of less than 1 per 5000 base pairs.
- Option Month 36: Demonstrate ability to synthesize 500-1000 unique DNA sequences of greater than 2,500 base pairs in length on a beta prototype device.

Phase II deliverables: Working prototype of the multiplexed system and a final report that includes: (1) system performance metrics; (2) results of the capability demonstration; and (3) projections for commercial scale manufacturing yield and costs.

e. Dual Use Applications (Phase III)

The commercial applications of synthetic DNA include, but are not limited to, applications for synthetic biology, manufacturing of protein therapeutics, and drug discovery modalities. These technologies create potential for the use of DNA technologies in cancer immunotherapy. DoD/military applications include generation of synthetic biology components required to produce DoD relevant materials and for the manufacturing of DNA-encoded antibodies and vaccines to provide protection against infectious diseases.

f. References

(1) Randall A. Hughes and Andrew D. Ellington. Synthetic DNA Synthesis and Assembly: Putting the Synthetic in Synthetic Biology. Cold Spring Harb Perspect Biol. 2017 Jan 3;9(1).

(2) Palluk S. et. al. De novo DNA synthesis using polymerase-nucleotide conjugates. Nat Biotechnol. 2018 Aug;36(7):645-650. doi: 10.1038/nbt.4173. Epub 2018 Jun 18.

g. Keywords

DNA, manufacturing, synthesis, formulation, delivery, synthetic biology

III. SUBMISSION OF QUESTIONS

DARPA intends to use electronic mail for all correspondence regarding this SBO. Questions related to the technical aspect of the research objectives and awards specifically related to this SBO should be emailed to HR001120S0019@darpa.mil. Please reference BAA HR001120S0019-02 in the subject line. All questions must be in English and must include the name, email address, and the telephone number of a point of contact.

DARPA will attempt to answer questions in a timely manner; however, questions submitted within seven (7) calendar days of the proposal due date listed herein may not be answered. DARPA will post a consolidated Frequently Asked Questions (FAQ) document. To access the posting please visit: http://www.darpa.mil/work-with-us/opportunities. Under the HR001120S0019-02 summary, there will be a link to the FAQ. The FAQ will be updated on an ongoing basis until one week prior to the proposal due date.

In addition to the FAQ specific to this SBO, proposers should also review the SBIR/STTR General FAQ list at: http://www.darpa.mil/work-with-us/opportunities?tFilter=&oFilter=29934. Under the HR001120S0019 summary, there is a link to the general FAQ.

Technical support for the Defense SBIR/STTR Innovation Portal (DSIP) is available Monday through Friday, 9:00 a.m. – 5:00 p.m. ET. Requests for technical support must be emailed to DoDSBIRSupport@reisystems.com with a copy to HR001120S0019@darpa.mil.