DARPA-EA-24-01-02
Discovering Unknome Function (DUF)

I. ARC Opportunity

The Defense Advanced Research Projects Agency (DARPA) Defense Sciences Office (DSO) is issuing an Advanced Research Concepts (ARC) Opportunity, inviting submissions of Abstracts for innovative exploratory research concepts in the technical domain of Biology. This ARC Opportunity, methods to Discovering Unknome Function (DUF), is issued under the master ARC Exploration Announcement (EA), DARPA-EA-24-01.

ARC Opportunities are designed to allow an individual researcher the opportunity and time to focus on nascent, paradigm-shifting ideas for national security applications. While multiple researchers from the same organization may be proposed, the aggregate level of effort for a proposed research concept must be equivalent to one full-time equivalent (FTE) and 12 months. DARPA expects that the individual(s) working on the proposed idea primarily focus on the effort for the entire period of performance to the maximum extent practical. Only minimal variation to this requirement will be accepted. The maximum period of performance is 12 months. Each ARC award's maximum total value is $300,000, including direct and indirect costs and graduate student tuition, if applicable. Proposed costs are limited to $10,000 or less for materials, equipment, and Other Direct Costs (ODC). Under no circumstances will profit be authorized. While resource sharing is not expected, it may be offered in the proposal. Any proposed resource share must be directly applicable to the effort. Any costs proposed beyond the $300,000 in Government funding will be the performer's responsibility. Travel and publication costs may not be proposed. No subawardees are permitted.

To view the original DARPA Exploration Announcement and the latest amendment issued against Advanced Research Concepts, visit SAM.gov under solicitation number DARPA-EA-24-01: https://sam.gov/opp/54ba5dd6825d4d84a2468e52e341cdef/view. It is incumbent upon the proposer to review DARPA-EA-24-01, any resulting amendments to DARPA-EA-24-01, and Frequently Asked Questions (FAQs) before preparing and submitting an Abstract and/or an Oral Proposal Package (OPP) (if invited). All Abstract submissions to this announcement must adhere to the instructions contained in DARPA EA-24-01.

All technical, contractual, and administrative questions regarding this notice must be emailed to DUF@darpa.mil. This ARC Opportunity is soliciting Abstracts only. DARPA will evaluate Abstracts submitted in response to this ARC Opportunity, as detailed in Section 4 of the latest amendment against DARPA-EA-24-01. If the Government selects an Abstract for an Oral Presentation, the Government will issue an invitation to submit an OPP. The invitation will include the submission instructions and deadline.

All awards made from the ARC Opportunity will be Research Other Transactions (OTs) awarded under the authority of 10 U.S.C. § 4021.

Abstracts submitted to this ARC Opportunity will be evaluated on a rolling basis in accordance with the latest amendment issued against DARPA-EA-24-01. The end of the submission period is four (4) months from release on April 5, 2024, at 4:00 p.m. Eastern Time. No Abstracts will be accepted after the end of the submission period. Proposers are encouraged to submit Abstracts as early as possible. Funding for this ARC Opportunity is limited. Should funding be exhausted, the Government may elect to shorten the overall submission period with an amendment to this ARC Opportunity.

II. ARC Opportunity Description

Despite over 20 years of extensive genome function annotation, certain genes have been neglected (i.e., the Unknome)[1]. Annotating these genes is technically challenging and often goes unfunded. The result is a bias in biological research toward previously studied genes, leaving a large area of fundamental research ripe for scientific discovery.

Cellular processes are inherently complex due to the large number of molecules and interactions, which are often nonlinear and occur at drastically different spatiotemporal scales that can span orders of magnitude[2]. Generating cellular datasets for gene function discovery is thus laborious and time-consuming; this leads to integrated experimental datasets from various strains, cellular states, and laboratory conditions[3]. Consequently, efforts to build useful predictive models of genotype-phenotype relationships are hindered by batch effects in training datasets and unannotated genes that still affect cell phenotype[4-6].

The DUF ARC Opportunity is soliciting ideas to explore the question: Can high-throughput workflows be developed to annotate the unknown function of (non)coding genes?

A. ARC Opportunity Technical Objective

DUF performers will develop reproducible high-throughput gene function discovery workflows using recent technological advances, such as automated cultivation techniques, microfluidics, single-cell multi-omics, bioinformatics, cloud computing, whole-cell modeling, artificial intelligence, machine learning, and computational microscopy. Key technical challenges to be addressed by DUF include high-throughput:

1. Generation of high-quality datasets to hypothesize gene function.
2. Experimental validation of hypothesized gene function.

Experimental design should include: quality control strategies to minimize database noise (i.e., contamination, point mutations, etc.); well-documented metadata of experimental conditions and cellular states, and biological and technical replicates.

DUF workflows will provide a methodological template for utilization by the scientific community to better understand complex biological systems and shrink the Unknome. Ultimately, this will result in the accumulation of a critical mass of high-quality datasets that will allow the construction of more precise models and improve the rational engineering of systems for biotechnological, biomedical, and biomanufacturing applications.

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1. Rocha, J. J., Jayaram, S. A., Stevens, T. J., Muschalik, N., Shah, R. D., Emran, S., Robles, C., Freeman, M., & Munro, S. (2023). Functional unknomics: Systematic screening of conserved genes of unknown function. PLoS biology, 21(8), e3002222. https://doi.org/10.1371/journal.pbio.3002222
2. King, J., Eroumé, K. S., Truckenmüller, R., Giselbrecht, S., Cowan, A. E., Loew, L., & Carlier, A. (2021). Ten steps to investigate a cellular system with mathematical modeling. PLoS computational biology, 17(5), e1008921. https://doi.org/10.1371/journal.pcbi.1008921
3. de Crécy-Lagard, V., Amorin de Hegedus, R., Arighi, C., Babor, J., Bateman, A., Blaby, I., Blaby-Haas, C., Bridge, A. J., Burley, S. K., Cleveland, S., Colwell, L. J., Conesa, A., Dallago, C., Danchin, A., de Waard, A., Deutschbauer, A., Dias, R., Ding, Y., Fang, G., Friedberg, I., … Xu, J. (2022). A roadmap for the functional annotation of protein families: a community perspective. Database : the journal of biological databases and curation, 2022, baac062. https://doi.org/10.1093/database/baac062
4. Heigwer, F., Scheeder, C., Bageritz, J., Yousefian, S., Rauscher, B., Laufer, C., Beneyto-Calabuig, S., Funk, M. C., Peters, V., Boulougouri, M., Bilanovic, J., Miersch, T., Schmitt, B., Blass, C., Port, F., & Boutros, M. (2023). A global genetic interaction network by single-cell imaging and machine learning. Cell systems, 14(5), 346–362.e6. https://doi.org/10.1016/j.cels.2023.03.003
5. Skalnik, C. J., Cheah, S. Y., Yang, M. Y., Wolff, M. B., Spangler, R. K., Talman, L., Morrison, J. H., Peirce, S. M., Agmon, E., & Covert, M. W. (2023). Whole-cell modeling of E. coli colonies enables quantification of single-cell heterogeneity in antibiotic responses. PLoS computational biology, 19(6), e1011232. https://doi.org/10.1371/journal.pcbi.1011232
6. Stevens, J. A., Grünewald, F., van Tilburg, P. A. M., König, M., Gilbert, B. R., Brier, T. A., Thornburg, Z. R., Luthey-Schulten, Z., & Marrink, S. J. (2023). Molecular dynamics simulation of an entire cell. Frontiers in chemistry, 11, 1106495. https://doi.org/10.3389/fchem.2023.1106495

B. ARC Abstracts

DUF ARC Abstract submitters must clearly articulate a proposed idea to discovering gene function by addressing one or both technical challenges above. Abstracts will include the rationale for their chosen gene(s) of interest, experimental design, and facility resources to support the work. Abstracts should describe how the proposed workflow improves high-throughput gene function discovery and differentiates from current state-of-the-art methods.

Both coding and noncoding genes are suitable for investigation in any cell type and viruses. The best Abstracts will be generalizable to diverse cell types and gene functions.

This ARC Opportunity is intended to be as inclusive as possible; however, proposed ideas should address the appropriate scope, have a clear deliverable at the end of the effort, and include specific practical applications of the research.

Abstracts should describe a research plan, including (1) detailed intermediate technical objectives with evaluation measures and (2) a schedule segmented monthly or quarterly outlining corresponding deliverables.

DARPA will evaluate Abstracts submitted in response to this ARC Opportunity, as detailed in Section 4 of the latest amendment issued against DARPA-EA-24-01. If the Government selects an Abstract for an Oral Presentation, the Government will issue an invitation to submit an OPP. The invitation will include the submission instructions and deadline.

C. Schedule of Milestones

The specific milestones and due dates listed below are common to all Abstracts and OPPs (see above for technical details and Section III.A. below for additional information on milestones). Abstracts selected to submit an OPP will be required to propose milestones associated with the program plan as part of the oral proposal.

- Kick-off meeting: Briefing to include the technical approach and steps forward, including the Design of experiment (DOE) and hypothesized conditions. Submit the DOE including the quality control strategies, metadata template spreadsheet, and replicates.
- Q1 and Q2 Milestones: Briefing to include detailed progress towards all technical objectives, DOE modifications, draft Standard Operating Procedures (SOP), and discussion of next quarter objectives.
- Q3 Milestone: Briefing to include the final DOE and SOP and discussion of a plan to extend the high-throughput workflow to additional genes to be selected by DARPA in the next quarter.
- Final Milestone: Opportunity out brief summarizes the previous total Period of Performance and final report.

D. Reporting Requirements

Performers will be expected to provide, at a minimum, the following reports:

- Monthly technical and financial updates. These updates should include technical progress to plan and a high-level financial summary.
- Quarterly technical report. Each report should detail progress towards all research objectives and should include a master document that refers to associated explanatory

presentation slides, design document, algorithms, models, modeling data and results, model validation data, publications, and software source code with full documentation, as needed. This report should also include a financial summary that spans the prior three (3) months.

- Final technical report. The final report should contain the final SOP(s), data spreadsheet listing metadata and annotated function of all genes that have been hypothesized and/or experimentally verified, the genes' signaling network, and confidence scores.

III. ARC Opportunity Submission Format, Instructions, and Selection

A. Abstract Content and Format

All Abstracts submitted in response to this notice must comply with the content and format instructions in Section 3.1 of the latest amendment issued against DARPA-EA-24-01. The submission must use the template provided as an attachment to DARPA-EA-24-01. Abstracts submitted in response to this ARC Opportunity must be unclassified.

B. Abstract and OPP Submission Instructions

Abstracts submitted in response to this ARC Opportunity and OPPs submitted in response to an invitation should be submitted electronically via the DARPA Submission website at https://baa.darpa.mil. See Section 3.3 of the latest amendment issued against DARPA-EA-24-01 for Abstract and OPP submission instructions.

Technical support for the DARPA Submission website is available during regular business hours, Monday – Friday, 9:00 a.m. – 5:00 p.m. Eastern Time. Requests for technical support must be emailed to BAAT_Support@darpa.mil with a copy to DUF@darpa.mil. Questions regarding submission contents, format, deadlines, etc., should be emailed to DUF@darpa.mil. Questions/requests for support sent to any other email address may result in delayed/no response.

DARPA will acknowledge receipt of complete submissions via email and assign identifying numbers that should be used in all further correspondence regarding those submissions. If no confirmation is received within two (2) business days, please contact DUF@darpa.mil to verify receipt.

No Abstracts will be accepted after the end of the overall submission period listed in Section I above. Abstracts must be submitted per the instructions outlined in this ARC Opportunity *and received by DARPA* no later than this time and date. Proposers are advised that the Abstract submission deadline outlined herein is in Eastern Time.

Abstracts will be evaluated and selected in accordance with Section 4 of the latest amendment issued against DARPA-EA-24-01.

IV. Award Information

Selected OPPs will result in a potential award of a Research OT agreement subject to the proposer's acceptance of the terms and conditions. Proposers must review the model Research OT agreement provided as Attachment I to DARPA-EA-24-01.

The completed Task Description Document, Schedule of Milestones and Payments (templates included in Attachment I), and data rights will be included in the Research OT agreement upon

award.

Given the limited funding available for each ARC Opportunity, not all proposals considered selectable may be selected for a potential award.

V. Eligibility

See Section 6 of the latest amendment issued against DARPA-EA-24-01 for information on who may be eligible to respond to this notice.

VI. Human Subject Research

Abstracts to this ARC Opportunity proposing human subjects research will be considered out of scope and may be disregarded.

VII. Administrative Requirements

Section 7.2 of the latest amendment issued against DARPA-EA-24-01 provides information on administrative requirements that may be applicable for proposal submission as well as performance under an award.

VIII. Frequently Asked Questions (FAQs)

All technical, contractual, and administrative questions regarding this notice must be emailed to DUF@darpa.mil. Emails sent directly to the Program Manager or any other address may result in delayed or no response.

All questions must be in English and must include the name, email address, and telephone number of a point of contact. DARPA will attempt to answer questions publicly in a timely manner; however, questions submitted within seven (7) calendar days of the proposal due date listed herein may not be answered.

DARPA may post an FAQ list under the ARC Opportunity on the DARPA/DSO Opportunities page at (http://www.darpa.mil/work-with-us/opportunities). The list will be updated on an ongoing basis until one (1) week prior to the abstract due date. DARPA will also maintain https://www.darpa.mil/ARC as a resource page with links to all relevant ARC Opportunities and FAQs.