



NATIONAL SCIENCE FOUNDATION
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ALEXANDRIA, VIRGINIA 22314

NSF 18-071

Dear Colleague Letter: Rules of Life (RoL): Design and Engineering of Synthetic Cells and Cell Components (DESYN-C³)

April 18, 2018

Dear Colleagues:

NSF seeks proposals that **jump-start the de novo design of complex, synthetic biological components and cells**. This DCL intends to engage scientists and engineers in the application of Design-Build-Test-Learn and experiment-modeling cycles to create synthetic cells. It is anticipated that the research will lead to new rules relevant for cell metabolism, epigenetics, interaction networks, and organelle function; molecular components and organelles of cells; and strategies for the design and synthesis of cells.

BACKGROUND

Synthetic cellular biomanufacturing has the potential to improve the production of fuels, chemicals, functional biomaterials, and human therapeutics, and to enhance bioremediation and ecological engineering in a profound and sustainable fashion. New therapies and cell-based products depend critically on the development of robust, reliable and reproducible biomanufacturing technologies. The design of these technologies has been enabled by basic science research on biomolecular design and synthesis aimed at understanding biological function, the development and application of chemistry for probing cellular function, and the identification of causal relationships in biological systems (e.g. genotype/phenotype, structure/function). Effective utilization of these science and engineering developments will enable biosystem designers to avoid the constraints of existing biological regulatory systems to create novel, optimized biosynthetic reaction systems that are adaptive and responsive to external stimuli.

The de novo design of synthetic cells will require the convergence of traditional chemistry and chemical engineering activities (chemical synthesis and self-assembly, process synthesis and control, reaction engineering, mass transport, separations) with diverse other research areas, including control theory, synthetic biology, systems biology, biomaterials science,

biochemistry, molecular structure, dynamics, and modeling, chemical biology, and bioorganic and bioinorganic chemistry. This effort will also require advanced nanomanufacturing technologies, such as DNA-enabled nanofabrication, to produce the subsystems (motors, pumps, constrained volume reactors, actuators) that comprise the synthetic cells.

This Dear Colleague Letter (DCL) describes an initial effort to expand and test our current understanding through the design of synthetic cell components (ribosomes, mitochondria, membranes, regulators, molecular machines, etc.) and molecular probes, and their synthesis and integration into "pseudo-cells" that efficiently convert raw materials to useful products. This effort resonates with the high priority placed by the Directorate for Engineering on advanced biomanufacturing and by the Directorate for Mathematics and Physical Sciences on understanding the fundamental science that underlies life processes, and it complements the NSF Ten Big Ideas of [Understanding the Rules of Life](#) and [Growing Convergent Research](#).

The NSF Divisions of Chemical, Bioengineering, Environmental and Transport Systems (CBET), Civil, Mechanical and Manufacturing Innovation (CMMI) in the Directorate of Engineering (ENG), and Chemistry (CHE) and Materials Research (DMR) in the Directorate of Mathematical and Physical Sciences (MPS) seek to support activities that include Conferences, EARly-Concept Grants for Exploratory Research (EAGER), and Research Advanced by Interdisciplinary Science and Engineering (RAISE) grants.

RESEARCH CONCEPT OUTLINE SUBMISSION

Prior to submitting EAGER or RAISE proposals, interested principal investigators (PIs) must prepare research concept outlines. Note, conference proposals (see the *NSF Proposal & Award Policies & Procedures Guide* (PAPPG), [Chapter II.E.7](#)) do not require the submission of a research concept outline. The research concept outlines must include clear statements as to why this project is appropriate for either EAGER funding (see [PAPPG, Chapter II.E.2](#)) or RAISE funding (see [PAPPG, Chapter II.E.3](#)). Research concept outlines must also include the compelling research challenge being addressed and its direct relevance to synthetic cell design. The research concept outline should address the current state of the research challenge and describe an integrated strategy for addressing that challenge.

The research concept outlines must not exceed two pages and must comply with standard proposal margin and spacing requirements (see [PAPPG, Chapter II.B.2](#)). They must contain the following information:

- Title of the DESYN-C³ research.
- Description of and justification for the proposed research.
- Names, and the Departmental and Institutional affiliations of researchers.
- Contact information of the researchers (email and phone number).

- An estimated budget amount (including both direct and indirect costs). A detailed budget is not required for the research concept outline. See the Summary of the Opportunity section below for budget limitations for EAGER and RAISE proposals.

The research concept outline should be emailed to SynCellDCL@nsf.gov and must be submitted by May 17, 2018. Research concept outlines that either do not provide the requested information or do not comply with formatting guidelines may not be reviewed.

RESEARCH CONCEPT OUTLINE REVIEW AND DECISION

PIs submitting research concept outlines that effectively address how self-sustaining (not necessarily self-replicating) "pseudo-cells" exhibiting specific functions can be effectively designed and implemented may be invited to submit a full proposal. Decisions on full proposal submissions will be based on research efforts that could lead to major advances in the design of effective cellular subsystems.

Please note that an invitation to submit a full proposal is not an indication that the proposal will be funded. Full proposals will undergo further internal review by the participating divisions before funding decisions are made. The number of research concept outlines invited to submit a full proposal are subject to the quality of concepts received and available funding (up to 20 may be invited). All funding decisions will be made during fiscal year 2018 (FY 2018).

SUMMARY

NSF will review proposals that propose activities in the following areas:

- Conferences that engage the research communities in identifying the minimal composition (structurally and functionally) of a functional "pseudo-cell": Conference awards will provide up to one year of support for projects that do not exceed \$100,000 in total. Proposals must include the prefix "RoL: Conference: DESYN-C³" in front of the title. There is no deadline for submission of these proposals; however, to be considered for FY 2018 support, proposals should be submitted by June 15, 2018. Conference proposals should follow the guidance in [PAPPG, Chapter II.E.7](#).
- EAGER projects to develop and test the functionality of integrated, natural or synthetic multi-component cell subsystems identified as critical for system function. EAGER proposals encouraged for submission in response to this DCL must include the prefix "RoL: EAGER: DESYN-C³" in front of the title. Please note that the maximum for EAGER awards is \$300,000 for a maximum period of 2 years. Please see the [PAPPG, Chapter II.E.2](#) for further information on EAGER proposal guidelines. Following encouragement to submit, full proposals must be submitted by July 12, 2018.
- RAISE projects encouraged for submission should support innovative research into

"pseudo-cell" functions by multidisciplinary teams. RAISE proposals encouraged for submission in response to this DCL must include the prefix "RoL: RAISE: DESYN-C³" in front of the title. Requests may be for up to \$1,000,000 and up to five years in duration. The award size and duration will be consistent with the project scope. Please see [PAPPG, Chapter II.E.3](#) for further information on RAISE proposal guidelines. Following encouragement to submit, full proposals must be submitted by July 12, 2018.

POINTS OF CONTACT

General and procedural inquiries should be directed to SynCellDCL@nsf.gov.

Specific questions pertaining to this Dear Colleague Letter can be directed to the following cognizant Program Directors:

- Steven Peretti, Program Director, ENG/CBET, speretti@nsf.gov
- Triantafillos (Lakis) Mountziaris, Program Director, ENG/CBET, tmountzi@nsf.gov
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