Reproducible Cells and Organoids via Directed-Differentiation Encoding (RECODE)

PROGRAM SOLICITATION
NSF 21-608

REPLACES DOCUMENT(S):
NSF 21-532

National Science Foundation

Directorate for Engineering
Division of Chemical, Bioengineering, Environmental and Transport Systems
Division of Civil, Mechanical and Manufacturing Innovation

Directorate for Biological Sciences
Division of Molecular and Cellular Biosciences
Division of Integrative Organismal Systems

Preliminary Proposal Due Date(s) ***(required)*** (due by 5 p.m. submitter's local time):

November 22, 2021

Full Proposal Deadline(s) (due by 5 p.m. submitter's local time):

March 31, 2022

IMPORTANT INFORMATION AND REVISION NOTES

Any proposal submitted in response to this solicitation should be submitted in accordance with the revised *NSF Proposal & Award Policies & Procedures Guide*(PAPPG) (NSF 22-1), which is effective for proposals submitted, or due, on or after October 4, 2021.

SUMMARY OF PROGRAM REQUIREMENTS

General Information

Program Title:

Reproducible Cells and Organoids via Directed- Differentiation Encoding (RECODE)

Synopsis of Program:

The National Science Foundation (NSF) Divisions of Chemical, Bioengineering, Environmental and Transport Systems (CBET), Integrative and Organismal Systems (IOS), Molecular and Cellular Biosciences (MCB), and Civil, Mechanical, and Manufacturing Innovation (CMMI) seek proposals that elucidate mechanisms of, and develop strategies to, direct the differentiation of undifferentiated cells into mature, functional cells or organoids. Projects responsive to this solicitation must aim to establish a robustly validated and reproducible set of differentiation design rules, mechanistic models, real-time sensing, control, and quality assurance methods, and integrate them into a workable differentiation strategy. They must also deepen our fundamental understanding of how cells develop and differentiate, to provide insights into mechanisms, molecular machinery, dynamics, and the interplay between cells and their environment, such as cell-cell/cell-microbe and cell-extracellular matrix (ECM) interactions and use this understanding to manipulate cells purposefully. Investigators can choose any undifferentiated cell type from any animal species, including human cell types, as a starting point and choose any appropriate functional product (cell, organoid, etc.) with real-world relevance. The use of non-model systems (e.g., non-human or non-murine systems) is encouraged as is the exploration of non-medical targets. Functional products can span a diverse range of systems (cardiovascular, nervous, immune, etc.). The RECODE program aligns with NSF's commitment to the development of capabilities in biotechnology that advance the U.S. Bioeconomy.

The process of differentiation involves a multiplex combination of signaling molecules, receptors, promoters, markers, and chemical and mechanical regulators that dynamically interact to direct cell development and behavior. While individual inducers of native differentiation have been identified and employed to create specialized cell types, we generally lack fundamental understanding of the roles of biochemical and environmental regulators necessary for synthetic induction of differentiation along a predetermined path and the ability to actively monitor and manipulate that path dynamically. Such control of differentiation will be valuable to answer mechanistic questions about basic biological processes that govern physiological function and development of specific cells, tissues, and organs, as well as mechanisms for processes

involved in immunity (e.g., symbiosis versus disease, immunological responses to infection).The control of differentiation will also enable the realization of enhanced biomanufacturing, leading to novel products, biomaterials, and significant improvements in individualized medicine, environmental control and monitoring, adaptive sensing, as well as the scalable and reproducible application of 3D organoids in drug testing.

The convergence of many disciplines is necessary to answer the fundamental questions and devise the tools needed to realize truly deterministic cell induction and differentiation strategies. As such, investigators are encouraged to form interdisciplinary teams with expertise in engineering, computation, sensing, systems and synthetic biology, developmental biology, stem cell biology, mechanobiology, cell physiology, microbiology, immunology, and biophysics. Proposals will not be responsive to this solicitation if they address only one aspect of the differentiation process or aim to create a functional living product without improving our understanding and control of the mechanisms that underlie developmental processes. Collaborative proposals, of a duration up to 4 years, with budgets up to $1,500,000 **total will** be considered. Proposed budgets must be justified by the project scope and need for complementary expertise. The solicitation will support teams of three or more PI/co-PIs and senior personnel with complementary expertise. Proposals with only one PI or one PI with one other senior personnel are not permitted and will be returned without review. Reflecting the need for thoughtful collaboration and planning required for these projects, Preliminary Proposals are required to be submitted prior to submission of a full proposal.

Topics that reside clearly within the boundaries of a single NSF core program are outside of the scope of this solicitation. Specifically, projects centered around the exploration of individual stages/mechanisms of differentiation in isolation or production of engineered cells, tissues, organ-on-a-chip systems, or organoids without developing an understanding of differentiation rules are not responsive to this solicitation.

Cognizant Program Officer(s):

Please note that the following information is current at the time of publishing. See program website for any updates to the points of contact.

- Stephanie George, ENG/CBET, telephone: (703) 292-7825, email: stgeorge@nsf.gov
- Evan Balaban, BIO/IOS, telephone: (703) 292-8421, email: ebalaban@nsf.gov
- Laurel C. Kuxhaus, ENG/CMMI, telephone: (703) 292-4465, email: lkuxhaus@nsf.gov
- Steven W. Peretti, ENG/CBET, telephone: (703) 292-7029, email: speretti@nsf.gov
- David Rockcliffe, BIO/MCB, telephone: (703) 292-7123, email: drockcli@nsf.gov
- Aleksandr L. Simonian, ENG/CBET, telephone: (703) 292-2191, email: asimonia@nsf.gov
- Steven M. Zehnder, ENG/CBET, telephone: (703) 292-7014, email: szehnder@nsf.gov

Applicable Catalog of Federal Domestic Assistance (CFDA) Number(s):

- 47.041 --- Engineering
- 47.074 --- Biological Sciences

Award Information

Anticipated Type of Award: Standard Grant or Continuing Grant

Estimated Number of Awards: 4 to 7

Anticipated Funding Amount: $6,100,000 to $11,100,000

Estimated program budget, number of awards and average award size/duration are subject to the availability of funds.

Eligibility Information

Who May Submit Proposals:

Proposals may only be submitted by the following:

- Institutions of Higher Education (IHEs) - Two- and four-year IHEs (including community colleges) accredited in, and having a campus located in the US, acting on behalf of their faculty members. Special Instructions for International Branch Campuses of US IHEs: If the proposal includes funding to be provided to an international branch campus of a US institution of higher education (including through use of subawards and consultant arrangements), the proposer must explain the benefit(s) to the project of performance at the international branch campus, and justify why the project activities cannot be performed at the US campus.
- Non-profit, non-academic organizations: Independent museums, observatories, research labs, professional societies and similar organizations in the U.S. associated with educational or research activities.

Who May Serve as PI:

Principal Investigators (PI) must be at the faculty level, tenured or tenure-track, as determined by the submitting organization.

If the proposal is submitted by a non-profit, non-academic organization, the lead PI must meet all of the following requirements: (1) the PI has a continuing appointment that is expected to last for the duration of a RECODE grant; (2) the appointment has substantial research responsibilities; and (3) the proposed project is related to the PI's job responsibilities as well as to the mission of the department or organization. In addition, a minimum of two collaborating Senior Personnel (e.g., co-PIs, Collaborating PIs) must participate. At least one member of the project team (PI or co-PI) must have a full-time, tenured or tenure-track faculty appointment within a College/Department of Engineering.

Investigators at federal agencies and federally funded research and development centers (FFRDCs) may participate only as unpaid collaborators. FFRDC and federal agency scientists cannot serve as lead PI to be eligible for NSF funding. Non-NSF sponsored FFRDCs are required to provide a letter of support from their agency.

For cooperative projects involving U.S. and foreign organizations, support will only be provided for the U.S. portion. Researchers from a

foreign organization cannot be PIs OR co-PIs and must be listed as "non-funded Senior Personnel." Researchers from a foreign organization cannot be supported by subawards. A letter of collaboration from their organization is required per PAPPG Chapter II.C.2.j.

Limit on Number of Proposals per Organization:

There are no restrictions or limits.

Limit on Number of Proposals per PI or co-PI: 1

An investigator may only be a PI, Co-PI, or other Senior Personnel on one RECODE proposal. Please be advised that if an individual's name appears, in any of the above-mentioned capacities, on more than ONE proposal, all submittals after the first proposal (based on time-stamp) will be returned without review. No exceptions will be made.

Awardees on active RECODE grants may not serve as a PI, co-PI, or other Senior Personnel on a RECODE proposal until the active award is closed.

Proposal Preparation and Submission Instructions

A. Proposal Preparation Instructions

- **Letters of Intent:** Not required
- **Preliminary Proposals:** Submission of Preliminary Proposals is required. Please see the full text of this solicitation for further information.
- **Full Proposals:**
  - Full Proposals submitted via FastLane: *NSF Proposal and Award Policies and Procedures Guide* (PAPPG) guidelines apply. The complete text of the PAPPG is available electronically on the NSF website at: https://www.nsf.gov/publications/pub_summ.jsp?ods_key=pappg.
  - Full Proposals submitted via Grants.gov: *NSF Grants.gov Application Guide: A Guide for the Preparation and Submission of NSF Applications via Grants.gov* guidelines apply (Note: The *NSF Grants.gov Application Guide* is available on the Grants.gov website and on the NSF website at: https://www.nsf.gov/publications/pub_summ.jsp?ods_key=grantsgovguide).

B. Budgetary Information

- **Cost Sharing Requirements:**

  Inclusion of voluntary committed cost sharing is prohibited.

- **Indirect Cost (F&A) Limitations:**

  Not Applicable

- **Other Budgetary Limitations:**

  Not Applicable

C. Due Dates

- **Preliminary Proposal Due Date(s) *(required)*** (due by 5 p.m. submitter's local time):

  November 22, 2021

- **Full Proposal Deadline(s)** (due by 5 p.m. submitter's local time):

  March 31, 2022

Proposal Review Information Criteria

Merit Review Criteria:

National Science Board approved criteria. Additional merit review criteria apply. Please see the full text of this solicitation for further information.

Award Administration Information

Award Conditions:

Standard NSF award conditions apply.

Reporting Requirements:

Standard NSF reporting requirements apply.

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I. INTRODUCTION

Stem cells offer tremendous potential for the alleviation and possible cure of many diseases caused by cellular or tissue malfunctions, including aberrant development, aging, or inappropriate immune responses arising from biotic or abiotic stress or genetic dysfunction. It is critical that differentiation be directed to a desired endpoint, whether that be a functioning differentiated cell, organoid, or tissue. The National Academies of Science, Engineering and Medicine published a report in 2017 entitled "Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies: Proceedings of a Workshop." This report indicates that reproducibility is a critical attribute when developing cell-based therapies, and that we currently do not have sufficient fundamental knowledge of cell activity to reliably produce cells with consistent efficacy. The report also highlights the need to identify appropriate markers of efficacy and to develop sensors capable of tracking those markers during manufacturing. While the focus of this workshop was manufacture of Chimeric Antigen Receptor (CAR) T cells specifically, the same requirements and gaps hold true for other biotechnologies involving induction of stem cells and research leveraging stem cell-derived products. Individual researchers are beginning to address these issues for different stem cells and end points; however, there is not a connected community of researchers looking at the entire range of fundamental questions that would be necessary to develop repeatable strategies for reproducible generation of stem cell-derived products.

The Reproducible Cells and Organoids via Directed Differentiation Encoding (RECODE) solicitation seeks proposals that elucidate mechanisms of and develop strategies for directed differentiation from undifferentiated cells to mature functional cells or organoids with specified activity. This solicitation parallels NSF's investment in *Understanding the Rules of Life (URoL): Predicting Phenotype*, NSF's Big Idea focused on predicting the set of observable characteristics (phenotype) of an organism based on its genetic makeup and the nature of its environment. This solicitation incorporates this NSF Big Idea to understand and accomplish the intentional and guided differentiation of an undifferentiated cell into other cell types, organoids, or tissues with predetermined activities and functions. This program also reflects NSF's commitment to supporting fundamental biotechnology research that advances the U.S. Bioeconomy. Finally, the RECODE program is an integration and extension of the activities supported by the Engineering and Biology directorates to involve cross-directorate programs that share an interest in understanding basic principles and control of cell differentiation mechanisms.

II. PROGRAM DESCRIPTION

The RECODE solicitation will support activities that substantially advance our capability to direct cell differentiation to a specific functional endpoint through the integration of synthetic biology, advanced sensing and control, and cellular and tissue modeling. Studies that not only use these approaches to test ideas in differentiation but also concomitantly confront new challenges in the contributing scientific areas within the framework of cell differentiation will also be considered. The proposed research should go well beyond that typically supported by a single core NSF program in the participating Directorates. A key objective of this solicitation is to encourage sustained collaboration among the diverse fields of engineering, biology, and biophysics necessary to develop a holistic differentiation control framework. To that end, proposed research submitted in response to this solicitation is expected to bridge the topics supported by the Division of Chemical, Biological, Environmental, and Transport Systems Engineering Biology and Health programs, as well as related programs in the Divisions of Molecular and Cellular Biosciences, Integrative Organismal Systems, and Civil, Mechanical, and Manufacturing Innovation. Proposals are expected to be submitted by multidisciplinary teams of no less than three investigators. At least one member of the project team (PI or co-PI) must have a full-time, tenured, or tenure-track faculty appointment within a college or department of Engineering.

To achieve the above goal, the RECODE solicitation will support projects that address several aspects of the directed differentiation process from a Design-Build-Test-Learn perspective. It is expected that such projects will, of necessity, leverage the expertise and tools relevant to multiple facets of molecular sensing, signal cascades and regulations, synthetic biology, multi-scale modeling, and tissue or organoid formation. Achieving directed differentiation must be the primary goal of the proposed project. Additional appropriate secondary objectives could include, for example, understanding the dynamics, sensing, and control at the reactor to molecular level, developing unique synthetic biology approaches, as well as addressing a social or ethical issue pertinent to designer organoids and cells. Projects are expected to clearly identify a starting undifferentiated cell type and a clear functional endpoint, be it a mature cell type or organoid. Successful proposals embrace a holistic approach to the problem that exploits the strengths of an interdisciplinary team of researchers.

Topics that reside clearly within the boundaries of a single NSF core program are outside of the scope of this solicitation. Specifically, projects centered around the exploration of individual stages/mechanisms of differentiation in isolation, or production of engineered cells, tissues, organ-on-a-chip systems, or organoids without developing an understanding of mechanistic differentiation rules are not responsive to this solicitation. While such projects may have value, they are more appropriately supported by core programs in CBET and other Divisions at NSF. Development of models of cancer is outside of the scope of the RECODE solicitation.

III. AWARD INFORMATION

Anticipated Type of Award: Standard Grant or Continuing Grant

Estimated Number of Awards: 4 to 7

Anticipated Funding Amount:$6,100,000 to $11,100,000

Estimated program budget, number of awards and average award size/duration are subject to the availability of funds.

IV. ELIGIBILITY INFORMATION

Who May Submit Proposals:

Proposals may only be submitted by the following:

- Institutions of Higher Education (IHEs) - Two- and four-year IHEs (including community colleges) accredited in, and having a campus located in the US, acting on behalf of their faculty members. Special Instructions for International Branch Campuses of US IHEs: If the proposal includes funding to be provided to an international branch campus of a US institution of higher education (including through use of subawards and consultant arrangements), the proposer must explain the benefit(s) to the project of performance at the international branch campus, and justify why the project activities cannot be performed at the US campus.
- Non-profit, non-academic organizations: Independent museums, observatories, research labs, professional societies and similar organizations in the U.S. associated with educational or research activities.

Who May Serve as PI:

Principal Investigators (PI) must be at the faculty level, tenured or tenure-track, as determined by the submitting organization.

If the proposal is submitted by a non-profit, non-academic organization, the lead PI must meet all of the following requirements: (1) the PI has a continuing appointment that is expected to last for the duration of a RECODE grant; (2) the appointment has substantial research responsibilities; and (3) the proposed project is related to the PI's job responsibilities as well as to the mission of the department or organization. In addition, a minimum of two collaborating Senior Personnel (e.g., co-PIs, Collaborating PIs) must participate. At least one member of the project team (PI or co-PI) must have a full-time, tenured or tenure-track faculty appointment within a College/Department of Engineering.

Investigators at federal agencies and federally funded research and development centers (FFRDCs) may participate only as unpaid collaborators. FFRDC and federal agency scientists cannot serve as lead PI to be eligible for NSF funding. Non-NSF sponsored FFRDCs are required to provide a letter of support from their agency.

For cooperative projects involving U.S. and foreign organizations, support will only be provided for the U.S. portion. Researchers from a foreign organization cannot be PIs OR co-PIs and must be listed as "non-funded Senior Personnel." Researchers from a foreign organization cannot be supported by subawards. A letter of collaboration from their organization is required per PAPPG Chapter II.C.2.j.

Limit on Number of Proposals per Organization:

There are no restrictions or limits.

Limit on Number of Proposals per PI or co-PI: 1

An investigator may only be a PI, Co-PI, or other Senior Personnel on one RECODE proposal. Please be advised that if an individual's name appears, in any of the above-mentioned capacities, on more than ONE proposal, all submittals after the first proposal (based on time-stamp) will be returned without review. No exceptions will be made.

Awardees on active RECODE grants may not serve as a PI, co-PI, or other Senior Personnel on a RECODE proposal until the active award is closed.

Additional Eligibility Info:

The solicitation will support teams of three or more PI/Co-PIs and senior personnel. Proposals with only one PI or one PI with one other senior personnel are not permitted and will be returned without review. Personnel are strongly encouraged to have complementary expertise in engineering, computation, life science, and physical sciences. No PIs, CoPIs, or other Senior Personnel may be added after the invite of a full proposal without the prior written consent of the cognizant RECODE program officer.

V. PROPOSAL PREPARATION AND SUBMISSION INSTRUCTIONS

A. Proposal Preparation Instructions

Preliminary Proposals *(required)*: Preliminary proposals are required and must be submitted via the NSF FastLane system, even if full proposals will be submitted via Grants.gov.

Preliminary Proposal Preparation Instructions:

Preliminary proposals must be submitted via FastLane in accordance with the instructions below. Preliminary proposals that are not compliant with this solicitation will be returned without review. It is the submitting organization's responsibility to ensure that the proposal is compliant with all applicable requirements. Preliminary proposals should not include separate subaward budgets but should include planned levels for subawards on the budget justification page. Preliminary proposals must contain the items listed below and must strictly adhere to the specified page limitations. No additional information may be provided as an appendix or by links to web pages. Figures and tables must be included within the applicable page limit. All elements of the proposal, including legends and tables, must meet all formatting requirements for font size and characters per inch as specified in the *NSF Proposal & Award Policies & Procedures Guide* (PAPPG).

Preliminary proposals must include the following items:

Cover Sheet: Select the solicitation number from the pull-down list. Check the box indicated for preliminary proposal. Entries on the Cover Sheet are limited to the principal investigator and a maximum of four co-principal investigators. A minimum of two co-principal investigators must be identified. Additional project leaders or senior personnel can be listed on the project summary page and entered into FastLane as senior personnel. At the preliminary proposal stage, avoid the inclusion of individuals without a substantive project role.

Proposal Titles: Proposal titles must begin with RECODE Preliminary Proposal, followed by a colon and the title of the project (i.e., RECODE Preliminary Proposal: Title). If you submit a proposal as part of a set of collaborative proposals, the title of the proposal should begin with Collaborative Research followed by a colon, then RECODE Preliminary Proposal followed by a colon, and the title. For example, if you are submitting a collaborative set of proposals, then the title of each would be Collaborative Research: RECODE Preliminary: Title.

Project Summary: Project Summaries, not to exceed one page, are required for all preliminary proposals and should be prepared in accordance with the guidance in PAPPG Chapter II.C.2.b and the following instructions:

1. In the Overview section, include the title of the project, the name of the PI, the lead organization, and a list of co-PIs and senior personnel, including potential subawardees, together with their organizations.
2. Provide a succinct summary of the *Intellectual Merit*of the proposed project. This should include the transformative nature of the proposed research and strategies for establishing robustly validated and reproducible differentiation design rules.
3. Describe the *Broader Impacts of* the proposed work, including the potential long-term impact of project outcomes and educational activities.
4. At the bottom of the "Broader Impacts" section of the summary, list 4 research keywords that define the project.

Preliminary proposals that do not separately address in the project summary both intellectual merit and broader impacts will be returned without review.

Project Description: The project description of the preliminary proposal is limited to five pages and should include the following three sections:

1. **Vision and Goals** – Describe the vision and specific goals of the proposed research. Starting undifferentiated cell type and targeted biological endpoint must be clearly identified, as must the manner of endpoint validation.
2. **Approach and Methodology** – Describe the approach and methodology that will be used to achieve the vision and goals.
3. **Transformative Impact** – Describe the transformative aspects of the project, including how the collaboration of experts from different disciplines will enable a significant advancement of fundamental knowledge of directed-differentiation and will have strong potential for long-term impact. Include a succinct statement of your anticipated Broader Impacts.

References Cited: Please include your references cited as a separate document from the project description as defined in PAPPG Chapter II.C.2.e.

Biographical sketches: A separate biographical sketch must be provided through use of an-NSF-approved format, for each individual designated as PI, Co-PI or other senior personnel.

Budget: The preliminary proposal must include a budget for each of the years proposed. FastLane will automatically provide a cumulative budget. Preliminary proposals should not include separate subaward budgets if subawards are planned for a full proposal submission. However, the budget justification should include planned levels for subawards to any partner organization. Enter the anticipated total level of subaward support on line G5, Subawards. Collaborative Research budgets from multiple organizations should be prepared per the guidance in PAPPG Chapter II.D.3.b.

Current and Pending Support for the PI, co-PIs, and senior personnel must be included.

In the **Supplementary Documentation** section, include the following:

List of **key personnel involved** (maximum one page), with a description of affiliation, the expertise each person brings to the project, and how this expertise will be applied to achieve convergent research. Each of the key personnel should be named as either PI, co-PI, or Senior Personnel. Avoid listing personnel who do not substantively contribute to the project goals.

In the **Single Copy Documents** section, include the following:

Collaborators and Other Affiliations Information: Proposers should follow the guidance specified in Chapter II.C.1.e of the NSF PAPPG.

Preliminary proposals will be reviewed by panels of outside experts. Based on the reviews, a limited number of organizations will be invited to submit full proposals.

Full Proposal Preparation Instructions: Proposers may opt to submit proposals in response to this Program Solicitation via FastLane or Grants.gov.

- Full proposals submitted via FastLane: Proposals submitted in response to this program solicitation should be prepared and submitted in accordance with the general guidelines contained in the *NSF Proposal & Award Policies & Procedures Guide* (PAPPG). The complete text of the PAPPG is available electronically on the NSF website at: https://www.nsf.gov/publications/pub_summ.jsp?ods_key=pappg. Paper copies of the PAPPG may be obtained from the NSF Publications Clearinghouse, telephone (703) 292-8134 or by e-mail from nsfpubs@nsf.gov. Proposers are reminded to identify this program solicitation number in the program solicitation block on the NSF Cover Sheet For Proposal to the National Science Foundation.

Compliance with this requirement is critical to determining the relevant proposal processing guidelines. Failure to submit this information may delay processing.

- Full proposals submitted via Grants.gov: Proposals submitted in response to this program solicitation via Grants.gov should be prepared and submitted in accordance with the *NSF Grants.gov Application Guide: A Guide for the Preparation and Submission of NSF Applications via Grants.gov*. The complete text of the *NSF Grants.gov Application Guide* is available on the Grants.gov website and on the NSF website at: (https://www.nsf.gov/publications/pub_summ.jsp?ods_key=grantsgovguide). To obtain copies of the Application Guide and Application Forms Package, click on the Apply tab on the Grants.gov site, then click on the Apply Step 1: Download a Grant Application Package and Application Instructions link and enter the funding opportunity number, (the program solicitation number without the NSF prefix) and press the Download Package button. Paper copies of the Grants.gov Application Guide also may be obtained from the NSF Publications Clearinghouse, telephone (703) 292-8134 or by e-mail from nsfpubs@nsf.gov.

In determining which method to utilize in the electronic preparation and submission of the proposal, please note the following:

Collaborative Proposals. All collaborative proposals submitted as separate submissions from multiple organizations must be submitted via the NSF FastLane system. PAPPG Chapter II.D.3 provides additional information on collaborative proposals.

See PAPPG Chapter II.C.2 for guidance on the required sections of a full research proposal submitted to NSF. Please note that the proposal preparation instructions provided in this program solicitation may deviate from the PAPPG instructions.

The following information SUPPLEMENTS (not replaces) the guidelines provided in the NSF Proposal & Award Policies & Procedures Guide (PAPPG).

Proposal Title: Proposal titles must begin with RECODE, followed by a colon and the title of the project (i.e., RECODE: Title). If you submit a proposal as part of a set of collaborative proposals, the title of the proposal should begin with Collaborative Research followed by a colon, then RECODE followed by a colon, and the title. For example, if you are submitting a collaborative set of proposals, then the title of each would be Collaborative Research: RECODE: Title.

Project Summary: At the bottom of the "Broader Impacts" section of the Project Summary, list 4 research keywords that define the project.

Project Description: In addition to the requirements specified in the PAPPG, the Project Description should clearly:

- Articulate a plan for dynamic regulation of the cellular differentiation process.
- Explain how the proposed research effectively integrates diverse fields (e.g., engineering, life sciences, physical sciences) to dynamically direct the cellular differentiation process.
- Clearly identify a starting cell type and final product (mature cell or organoid).
- Address how the multidisciplinary group of scientists and engineers is appropriate to the project. Do the team members provide distinct, complementary expertise to the project? Are all fields of expertise needed to complete the proposed work represented on the team?
- Describe robust plans for validation and reproducibility of the final product.

These criteria are reflected under Additional Solicitation Specific Review Criteria.

In the **Supplementary Documentation** section, include a list of **key personnel involved** (maximum one page), with a description of the expertise each person brings to the project and how this expertise will be applied to achieve convergent research. Each of the key personnel should be named as either PI, co-PI, or Senior Personnel. Avoid listing personnel who do not substantively contribute to the project goals.

B. Budgetary Information

Cost Sharing:

Inclusion of voluntary committed cost sharing is prohibited.

C. Due Dates

- **Preliminary Proposal Due Date(s) *(required)*** (due by 5 p.m. submitter's local time):

  November 22, 2021

- **Full Proposal Deadline(s)** (due by 5 p.m. submitter's local time):

  March 31, 2022

D. FastLane/Grants.gov Requirements

For Proposals Submitted Via FastLane:

To prepare and submit a proposal via FastLane, see detailed technical instructions available at: https://www.fastlane.nsf.gov/a1/newstan.htm. For FastLane user support, call the NSF Help Desk at 1-800-673-6188 or e-mail fastlane@nsf.gov. The NSF Help Desk answers general technical questions related to the use of the FastLane and Research.gov systems. Specific questions related to this program solicitation should be referred to the NSF program staff contact(s) listed in Section VIII of this funding opportunity.

For Proposals Submitted Via Grants.gov:

Before using Grants.gov for the first time, each organization must register to create an institutional profile. Once registered, the applicant's organization can then apply for any federal grant on the Grants.gov website. Comprehensive information about using Grants.gov is available on the Grants.gov Applicant Resources webpage: https://www.grants.gov/web/grants/applicants.html. In addition, the NSF Grants.gov Application Guide (see link in Section V.A) provides instructions regarding the technical preparation of proposals via Grants.gov. For Grants.gov user support, contact the Grants.gov Contact Center at 1-800-518-4726 or by email: support@grants.gov. The Grants.gov Contact

Center answers general technical questions related to the use of Grants.gov. Specific questions related to this program solicitation should be referred to the NSF program staff contact(s) listed in Section VIII of this solicitation.

Submitting the Proposal: Once all documents have been completed, the Authorized Organizational Representative (AOR) must submit the application to Grants.gov and verify the desired funding opportunity and agency to which the application is submitted. The AOR must then sign and submit the application to Grants.gov. The completed application will be transferred to the NSF FastLane system for further processing.

Proposers that submitted via FastLane may use Research.gov to verify the status of their submission to NSF. For proposers that submitted via Grants.gov, until an application has been received and validated by NSF, the Authorized Organizational Representative may check the status of an application on Grants.gov. After proposers have received an e-mail notification from NSF, Research.gov should be used to check the status of an application.

VI. NSF PROPOSAL PROCESSING AND REVIEW PROCEDURES

Proposals received by NSF are assigned to the appropriate NSF program for acknowledgement and, if they meet NSF requirements, for review. All proposals are carefully reviewed by a scientist, engineer, or educator serving as an NSF Program Officer, and usually by three to ten other persons outside NSF either as *ad hoc* reviewers, panelists, or both, who are experts in the particular fields represented by the proposal. These reviewers are selected by Program Officers charged with oversight of the review process. Proposers are invited to suggest names of persons they believe are especially well qualified to review the proposal and/or persons they would prefer not review the proposal. These suggestions may serve as one source in the reviewer selection process at the Program Officer's discretion. Submission of such names, however, is optional. Care is taken to ensure that reviewers have no conflicts of interest with the proposal. In addition, Program Officers may obtain comments from site visits before recommending final action on proposals. Senior NSF staff further review recommendations for awards. A flowchart that depicts the entire NSF proposal and award process (and associated timeline) is included in PAPPG Exhibit III-1.

A comprehensive description of the Foundation's merit review process is available on the NSF website at: https://www.nsf.gov/bfa/dias/policy/merit_review/.

Proposers should also be aware of core strategies that are essential to the fulfillment of NSF's mission, as articulated in *Building the Future: Investing in Discovery and Innovation - NSF Strategic Plan for Fiscal Years (FY) 2018 – 2022*. These strategies are integrated in the program planning and implementation process, of which proposal review is one part. NSF's mission is particularly well-implemented through the integration of research and education and broadening participation in NSF programs, projects, and activities.

One of the strategic objectives in support of NSF's mission is to foster integration of research and education through the programs, projects, and activities it supports at academic and research institutions. These institutions must recruit, train, and prepare a diverse STEM workforce to advance the frontiers of science and participate in the U.S. technology-based economy. NSF's contribution to the national innovation ecosystem is to provide cutting-edge research under the guidance of the Nation's most creative scientists and engineers. NSF also supports development of a strong science, technology, engineering, and mathematics (STEM) workforce by investing in building the knowledge that informs improvements in STEM teaching and learning.

NSF's mission calls for the broadening of opportunities and expanding participation of groups, institutions, and geographic regions that are underrepresented in STEM disciplines, which is essential to the health and vitality of science and engineering. NSF is committed to this principle of diversity and deems it central to the programs, projects, and activities it considers and supports.

A. Merit Review Principles and Criteria

The National Science Foundation strives to invest in a robust and diverse portfolio of projects that creates new knowledge and enables breakthroughs in understanding across all areas of science and engineering research and education. To identify which projects to support, NSF relies on a merit review process that incorporates consideration of both the technical aspects of a proposed project and its potential to contribute more broadly to advancing NSF's mission "to promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defense; and for other purposes." NSF makes every effort to conduct a fair, competitive, transparent merit review process for the selection of projects.

1. Merit Review Principles

These principles are to be given due diligence by PIs and organizations when preparing proposals and managing projects, by reviewers when reading and evaluating proposals, and by NSF program staff when determining whether or not to recommend proposals for funding and while overseeing awards. Given that NSF is the primary federal agency charged with nurturing and supporting excellence in basic research and education, the following three principles apply:

- All NSF projects should be of the highest quality and have the potential to advance, if not transform, the frontiers of knowledge.
- NSF projects, in the aggregate, should contribute more broadly to achieving societal goals. These "Broader Impacts" may be accomplished through the research itself, through activities that are directly related to specific research projects, or through activities that are supported by, but are complementary to, the project. The project activities may be based on previously established and/or innovative methods and approaches, but in either case must be well justified.
- Meaningful assessment and evaluation of NSF funded projects should be based on appropriate metrics, keeping in mind the likely correlation between the effect of broader impacts and the resources provided to implement projects. If the size of the activity is limited, evaluation of that activity in isolation is not likely to be meaningful. Thus, assessing the effectiveness of these activities may best be done at a higher, more aggregated, level than the individual project.

With respect to the third principle, even if assessment of Broader Impacts outcomes for particular projects is done at an aggregated level, PIs are expected to be accountable for carrying out the activities described in the funded project. Thus, individual projects should include clearly stated goals, specific descriptions of the activities that the PI intends to do, and a plan in place to document the outputs of those activities.

These three merit review principles provide the basis for the merit review criteria, as well as a context within which the users of the criteria can better understand their intent.

2. Merit Review Criteria

All NSF proposals are evaluated through use of the two National Science Board approved merit review criteria. In some instances, however, NSF will employ additional criteria as required to highlight the specific objectives of certain programs and activities.

The two merit review criteria are listed below. **Both** criteria are to be given **full consideration** during the review and decision-making processes; each criterion is necessary but neither, by itself, is sufficient. Therefore, proposers must fully address both criteria. (PAPPG Chapter II.C.2.d(i). contains additional information for use by proposers in development of the Project Description section of the proposal). Reviewers are strongly encouraged to review the criteria, including PAPPG Chapter II.C.2.d(i), prior to the review of a proposal.

When evaluating NSF proposals, reviewers will be asked to consider what the proposers want to do, why they want to do it, how they plan to do it, how they will know if they succeed, and what benefits could accrue if the project is successful. These issues apply both to the technical aspects of the proposal and the way in which the project may make broader contributions. To that end, reviewers will be asked to evaluate all proposals against two criteria:

- **Intellectual Merit:** The Intellectual Merit criterion encompasses the potential to advance knowledge; and
- **Broader Impacts:** The Broader Impacts criterion encompasses the potential to benefit society and contribute to the achievement of specific, desired societal outcomes.

The following elements should be considered in the review for both criteria:

1. What is the potential for the proposed activity to
    a. Advance knowledge and understanding within its own field or across different fields (Intellectual Merit); and
    b. Benefit society or advance desired societal outcomes (Broader Impacts)?
2. To what extent do the proposed activities suggest and explore creative, original, or potentially transformative concepts?
3. Is the plan for carrying out the proposed activities well-reasoned, well-organized, and based on a sound rationale? Does the plan incorporate a mechanism to assess success?
4. How well qualified is the individual, team, or organization to conduct the proposed activities?
5. Are there adequate resources available to the PI (either at the home organization or through collaborations) to carry out the proposed activities?

Broader impacts may be accomplished through the research itself, through the activities that are directly related to specific research projects, or through activities that are supported by, but are complementary to, the project. NSF values the advancement of scientific knowledge and activities that contribute to achievement of societally relevant outcomes. Such outcomes include, but are not limited to: full participation of women, persons with disabilities, and other underrepresented groups in science, technology, engineering, and mathematics (STEM); improved STEM education and educator development at any level; increased public scientific literacy and public engagement with science and technology; improved well-being of individuals in society; development of a diverse, globally competitive STEM workforce; increased partnerships between academia, industry, and others; improved national security; increased economic competitiveness of the United States; and enhanced infrastructure for research and education.

Proposers are reminded that reviewers will also be asked to review the Data Management Plan and the Postdoctoral Researcher Mentoring Plan, as appropriate.

Additional Solicitation Specific Review Criteria

In addition to the standard NSF merit review criteria of Intellectual Merit and Broader Impacts, reviewers and Program Directors will consider the following additional criteria to evaluate the proposals:

Responsiveness:

- Does the proposal provide a clear, logical, and well thought-out plan for dynamic regulation of the cellular differentiation process?
- Does the proposed research effectively integrate diverse fields (e.g., engineering, life sciences, physical sciences)?
- Does the proposal clearly identify a starting undifferentiated cell type and a final product (e.g., mature cell type or specific organoid)?

Expertise: To what extent is the team of investigators, comprised of a multidisciplinary group of scientists and engineers, appropriate to the project? Have the team members been selected to provide distinct, complementary expertise to the project? Are all fields of expertise needed to complete the proposed work represented on the team?

Validation: Are there robust plans for validation and reproducibility of the final product? Are these plans appropriate for the chosen final product?

B. Review and Selection Process

Proposals submitted in response to this program solicitation will be reviewed by Ad hoc Review and/or Panel Review.

Reviewers will be asked to evaluate proposals using two National Science Board approved merit review criteria and, if applicable, additional program specific criteria. A summary rating and accompanying narrative will generally be completed and submitted by each reviewer and/or panel. The Program Officer assigned to manage the proposal's review will consider the advice of reviewers and will formulate a recommendation.

After scientific, technical and programmatic review and consideration of appropriate factors, the NSF Program Officer recommends to the cognizant Division Director whether the proposal should be declined or recommended for award. NSF strives to be able to tell applicants whether their proposals have been declined or recommended for funding within six months. Large or particularly complex proposals or proposals from new awardees may require additional review and processing time. The time interval begins on the deadline or target date, or receipt date, whichever is later. The interval ends when the Division Director acts upon the Program Officer's recommendation.

After programmatic approval has been obtained, the proposals recommended for funding will be forwarded to the Division of Grants and Agreements for review of business, financial, and policy implications. After an administrative review has occurred, Grants and Agreements Officers perform the processing and issuance of a grant or other agreement. Proposers are cautioned that only a Grants and Agreements Officer may make commitments, obligations or awards on behalf of NSF or authorize the expenditure of funds. No commitment on the part of NSF should be inferred from technical or budgetary discussions with a NSF Program Officer. A Principal Investigator or organization that makes financial or personnel commitments in the absence of a grant or cooperative agreement signed by the NSF Grants and Agreements Officer does so at their own risk.

Once an award or declination decision has been made, Principal Investigators are provided feedback about their proposals. In all cases, reviews are treated as confidential documents. Verbatim copies of reviews, excluding the names of the reviewers or any reviewer-identifying information, are sent to the Principal Investigator/Project Director by the Program Officer. In addition, the proposer will receive an explanation of the decision to award or decline funding.

VII. AWARD ADMINISTRATION INFORMATION

A. Notification of the Award

Notification of the award is made to *the submitting organization* by a Grants Officer in the Division of Grants and Agreements. Organizations whose proposals are declined will be advised as promptly as possible by the cognizant NSF Program administering the program. Verbatim copies of reviews, not including the identity of the reviewer, will be provided automatically to the Principal Investigator. (See Section VI.B. for additional information on the review process.)

B. Award Conditions

An NSF award consists of: (1) the award notice, which includes any special provisions applicable to the award and any numbered amendments thereto; (2) the budget, which indicates the amounts, by categories of expense, on which NSF has based its support (or otherwise communicates any specific approvals or disapprovals of proposed expenditures); (3) the proposal referenced in the award notice; (4) the applicable award conditions, such as Grant General Conditions (GC-1)*; or Research Terms and Conditions* and (5) any announcement or other NSF issuance that may be incorporated by reference in the award notice. Cooperative agreements also are administered in accordance with NSF Cooperative Agreement Financial and Administrative Terms and Conditions (CA-FATC) and the applicable Programmatic Terms and Conditions. NSF awards are electronically signed by an NSF Grants and Agreements Officer and transmitted electronically to the organization via e-mail.

*These documents may be accessed electronically on NSF's Website at https://www.nsf.gov/awards/managing/award_conditions.jsp?org=NSF. Paper copies may be obtained from the NSF Publications Clearinghouse, telephone (703) 292-8134 or by e-mail from nsfpubs@nsf.gov.

More comprehensive information on NSF Award Conditions and other important information on the administration of NSF awards is contained in the NSF *Proposal & Award Policies & Procedures Guide* (PAPPG) Chapter VII, available electronically on the NSF Website at https://www.nsf.gov/publications/pub_summ.jsp?ods_key=pappg.

C. Reporting Requirements

For all multi-year grants (including both standard and continuing grants), the Principal Investigator must submit an annual project report to the cognizant Program Officer no later than 90 days prior to the end of the current budget period. (Some programs or awards require submission of more frequent project reports). No later than 120 days following expiration of a grant, the PI also is required to submit a final project report, and a project outcomes report for the general public.

Failure to provide the required annual or final project reports, or the project outcomes report, will delay NSF review and processing of any future funding increments as well as any pending proposals for all identified PIs and co-PIs on a given award. PIs should examine the formats of the required reports in advance to assure availability of required data.

PIs are required to use NSF's electronic project-reporting system, available through Research.gov, for preparation and submission of annual and final project reports. Such reports provide information on accomplishments, project participants (individual and organizational), publications, and other specific products and impacts of the project. Submission of the report via Research.gov constitutes certification by the PI that the contents of the report are accurate and complete. The project outcomes report also must be prepared and submitted using Research.gov. This report serves as a brief summary, prepared specifically for the public, of the nature and outcomes of the project. This report will be posted on the NSF website exactly as it is submitted by the PI.

More comprehensive information on NSF Reporting Requirements and other important information on the administration of NSF awards is contained in the *NSF Proposal & Award Policies & Procedures Guide* (PAPPG) Chapter VII, available electronically on the NSF Website at https://www.nsf.gov/publications/pub_summ.jsp?ods_key=pappg.

VIII. AGENCY CONTACTS

Please note that the program contact information is current at the time of publishing. See program website for any updates to the points of contact.

General inquiries regarding this program should be made to:

- Stephanie George, ENG/CBET, telephone: (703) 292-7825, email: stgeorge@nsf.gov
- Evan Balaban, BIO/IOS, telephone: (703) 292-8421, email: ebalaban@nsf.gov
- Laurel C. Kuxhaus, ENG/CMMI, telephone: (703) 292-4465, email: lkuxhaus@nsf.gov
- Steven W. Peretti, ENG/CBET, telephone: (703) 292-7029, email: speretti@nsf.gov
- David Rockcliffe, BIO/MCB, telephone: (703) 292-7123, email: drockcli@nsf.gov
- Aleksandr L. Simonian, ENG/CBET, telephone: (703) 292-2191, email: asimonia@nsf.gov
- Steven M. Zehnder, ENG/CBET, telephone: (703) 292-7014, email: szehnder@nsf.gov

For questions related to the use of FastLane or Research.gov, contact:

- FastLane and Research.gov Help Desk: 1-800-673-6188
- FastLane Help Desk e-mail: fastlane@nsf.gov
- Research.gov Help Desk e-mail: rgov@nsf.gov.

For questions relating to Grants.gov contact:

- Grants.gov Contact Center: If the Authorized Organizational Representatives (AOR) has not received a confirmation message from Grants.gov within 48 hours of submission of application, please contact via telephone: 1-800-518-4726; e-mail: support@grants.gov.

IX. OTHER INFORMATION

The NSF website provides the most comprehensive source of information on NSF Directorates (including contact information), programs and funding opportunities. Use of this website by potential proposers is strongly encouraged. In addition, "NSF Update" is an information-delivery system designed to keep potential proposers and other interested parties apprised of new NSF funding opportunities and publications, important changes in proposal and award policies and procedures, and upcoming NSF Grants Conferences. Subscribers are informed through e-mail or the user's Web browser each time new publications are issued that match their identified interests. "NSF Update" also is available on NSF's website.

Grants.gov provides an additional electronic capability to search for Federal government-wide grant opportunities. NSF funding opportunities may be accessed via this mechanism. Further information on Grants.gov may be obtained at https://www.grants.gov.

ABOUT THE NATIONAL SCIENCE FOUNDATION

The National Science Foundation (NSF) is an independent Federal agency created by the National Science Foundation Act of 1950, as amended (42 USC 1861-75). The Act states the purpose of the NSF is "to promote the progress of science; [and] to advance the national health, prosperity, and welfare by supporting research and education in all fields of science and engineering."

NSF funds research and education in most fields of science and engineering. It does this through grants and cooperative agreements to more than 2,000 colleges, universities, K-12 school systems, businesses, informal science organizations and other research organizations throughout the US. The Foundation accounts for about one-fourth of Federal support to academic institutions for basic research.

NSF receives approximately 55,000 proposals each year for research, education and training projects, of which approximately 11,000 are funded. In addition, the Foundation receives several thousand applications for graduate and postdoctoral fellowships. The agency operates no laboratories itself but does support National Research Centers, user facilities, certain oceanographic vessels and Arctic and Antarctic research stations. The Foundation also supports cooperative research between universities and industry, US participation in international scientific and engineering efforts, and educational activities at every academic level.

Facilitation Awards for Scientists and Engineers with Disabilities (FASED) provide funding for special assistance or equipment to enable persons with disabilities to work on NSF-supported projects. See the *NSF Proposal & Award Policies & Procedures Guide* Chapter II.E.6 for instructions regarding preparation of these types of proposals.

The National Science Foundation has Telephonic Device for the Deaf (TDD) and Federal Information Relay Service (FIRS) capabilities that enable individuals with hearing impairments to communicate with the Foundation about NSF programs, employment or general information. TDD may be accessed at (703) 292-5090 and (800) 281-8749, FIRS at (800) 877-8339.

The National Science Foundation Information Center may be reached at (703) 292-5111.

The National Science Foundation promotes and advances scientific progress in the United States by competitively awarding grants and cooperative agreements for research and education in the sciences, mathematics, and engineering.

To get the latest information about program deadlines, to download copies of NSF publications, and to access abstracts of awards, visit the NSF Website at https://www.nsf.gov

- **Location:** 2415 Eisenhower Avenue, Alexandria, VA 22314
- **For General Information** (NSF Information Center)**:** (703) 292-5111
- **TDD (for the hearing-impaired):** (703) 292-5090
- **To Order Publications or Forms:**

  Send an e-mail to: nsfpubs@nsf.gov

  or telephone: (703) 292-8134
- **To Locate NSF Employees:** (703) 292-5111

PRIVACY ACT AND PUBLIC BURDEN STATEMENTS

The information requested on proposal forms and project reports is solicited under the authority of the National Science Foundation Act of 1950, as amended. The information on proposal forms will be used in connection with the selection of qualified proposals; and project reports submitted by awardees will be used for program evaluation and reporting within the Executive Branch and to Congress. The information requested may be disclosed to qualified reviewers and staff assistants as part of the proposal review process; to proposer institutions/grantees to provide or obtain data regarding the proposal review process, award decisions, or the administration of awards; to government contractors, experts, volunteers and researchers and educators as necessary to complete assigned work; to other government agencies or other entities needing information regarding applicants or nominees as part of a joint application review process, or in order to coordinate programs or policy; and to another Federal agency, court, or party in a court or Federal administrative proceeding if the government is a party. Information about Principal Investigators may be added to the Reviewer file and used to select potential candidates to serve as peer reviewers or advisory committee members. See System of Record Notices, NSF-50, "Principal Investigator/Proposal File and Associated Records," and NSF-51, "Reviewer/Proposal File and Associated Records." Submission of the information is voluntary. Failure to provide full and complete information, however, may reduce the possibility of receiving an award.

An agency may not conduct or sponsor, and a person is not required to respond to, an information collection unless it displays a valid Office of Management and Budget (OMB) control number. The OMB control number for this collection is 3145-0058. Public reporting burden for this collection of information is estimated to average 120 hours per response, including the time for reviewing instructions. Send comments regarding the burden estimate and any other aspect of this collection of information, including suggestions for reducing this burden, to:

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