NIH-Extracellular RNA Stage 2 Applicant Webinar

August 24, 2018

We will start @ 2:05 PM ET

NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

Webinar Logistics

WebEx

- We will not be posting this webinar after, however the slide decks will be made available on the Common Fund Website: https://commonfund.nih.gov/exrna

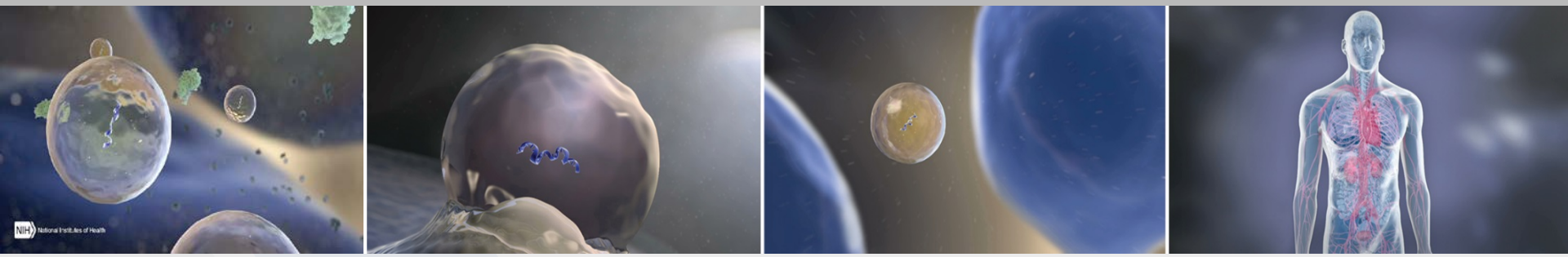
- All participants are muted
  - Please submit using the **Q&A box**
  - All questions submitted to exrnacommunication@mail.nih.gov during the webinar will be answered in the order they were received during the Q&A portion.
  - These questions are intended for us to answer the group at large
  - If you have a specific question for a specific person, please reach out to them directly.

- A list of commonly asked FAQs are posted and will be updated on the Common Fund Website: https://commonfund.nih.gov/exrna/faq

- **Do not disclose project-specific details, any project specific questions should be addressed to the pertinent Program Officer offline.**

Agenda

- **Introduction & WebEx overview** – 3 min; Kayla Valdes, NCATS
- **Common Fund overview** – 5 min; Trish Labosky, Common Fund, OD/OSC
- **Funding announcement overviews** – 5 min each; Kevin Howcroft, NCI; Danilo Tagle, NCATS
- **Review procedure** – 5 min; Maqsood Wani, CSR
- **Cooperative agreement overview & application deadlines** – 5 min; Kayla Valdes, NCATS
- **Q&A session** – 60 min



Common Fund Overview

Trish Labosky, Ph.D.

Program Leader

Office of Strategic Coordination

Division of Program Coordination, Planning, and Strategic Initiatives

Office of the Director, NIH

National Institutes of Health
Office of Strategic Coordination - The Common Fund

One Hundred Ninth Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Tuesday, the third day of January, two thousand and six

An Act

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

TITLE I—NIH REFORM

Origins of the Common Fund

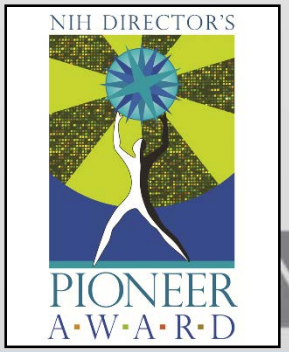
2004: NIH Roadmap is launched

2006: Congress unanimously reauthorizes NIH

Establishes the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within Office of the Director and the NIH Common Fund to provide a dedicated source of funding to enable *trans*-NIH research

Criteria for Common Fund Programs

- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic**: Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health
- **Cross-cutting:** Program areas must cut across missions of multiple NIH Institutes and Centers, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach
- **Unique:** Must be something no other entity is likely or able to do



NIH Collaboratory
Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

Limited Competition: RFA-RM-18-026 Data Management and Resource Repository (DMRR) on Extracellular RNA (U54)

RFA-RM-18-026

Kevin Howcroft on behalf of John Satterlee
(satterleej@nida.nih.gov)

National Institutes of Health
Office of Strategic Coordination - The Common Fund

Limited Competition: **Eligibility is limited to the awardees of RFA-RM-12-010**

Purpose: **The overall programmatic goal of the DMRR is to integrate the efforts of all funded components of the ERCC and serve as a community-wide resource for exRNA standards, protocols, and data.**

U54 Components:

- **Data Coordination Component (DCC):** Complete coordination/archiving activities for Stage 1 ERCC data
- **Data Integration and Analysis Component (DIAC):** Complete analysis of Stage 1 ERCC data
- **Scientific Outreach Component (SOC):** Maintain/update exRNA Atlas website; Stage 2 outreach activities
- **Administrative Core:** Facilitate Stage 2 phone and biannual in person consortium meetings

If you have questions about applying, please contact John Satterlee, satterleej@nida.nih.gov

Advancing Extracellular RNA (exRNA) Communication Research: Improved Isolation and Analysis of exRNA-Carrier Subclasses (UG3/UH3 Clinical Trial Not Allowed)

RFA-RM-18-027

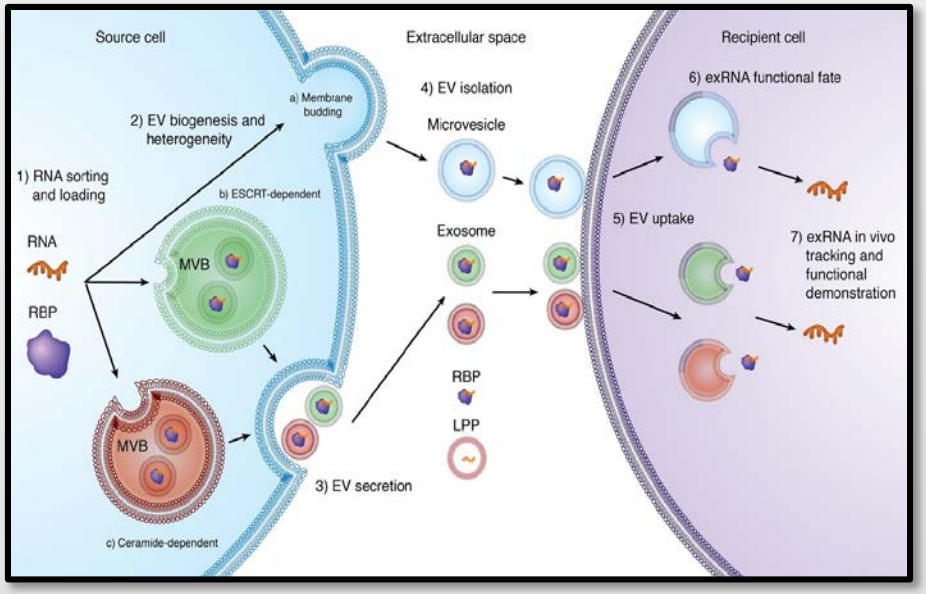
Kevin Howcroft

(Howcrofk@nih.gov)

National Institutes of Health
Office of Strategic Coordination - The Common Fund

Current Barrier to Isolation and Analysis of exRNA-Carrier Subclasses

- An array of carrier vehicles of varying complexity transport exRNAs.
- Current separation approaches are time consuming and do not adequately discriminate vesicle-associated and non-vesicular exRNAs or capture all carrier subclasses.



- Ideally, a protocol(s) for separating exRNA-carrier complexes should be (1) rapid and reproducible, (2) yield highly enriched carrier-specific exRNAs with no cross-contamination, and (3) have the capacity for high-throughput isolation and characterization of carrier-specific genomic, proteomic, and lipidomic signatures.

Funding Opportunity Purpose

The overarching goal is to develop and evaluate innovative separation tools, technologies, and approaches that will enable the scientific community to rapidly and reproducibly sort complex biofluids into homogenous carrier populations of EVs, (including EV subsets), RNPs, and LPPs, and that also support high-throughput isolation and analysis of their extracellular RNA content and associated molecular cargo.

Essential Elements – UG3/UH3 Mechanism

The UG3 Phase:

- Will support feasibility and proof of principle studies.
- Studies should focus on identifying and validating biophysical attributes that can be applied to separating distinct exRNA carrier populations with high fidelity and establishing thresholds for purity (i.e., percent contamination from other carrier vehicles).
- Projects can use *in vitro* cell culture media and human or animal model biofluids.
- Molecular tools as well as genetic and/or barcoding-based systems that allow assessment of separation performance (i.e., recovery, purity, functional output) of specific carrier subclasses are also encouraged.

Essential Elements Cont.

While one integrated separation protocol is preferred, UG3 investigators will need to be flexible in the design and execution of their specific proposals through collaboration with other UG3 groups in identifying the optimum protocol(s) for each carrier subclass and to develop best practices specific for each carrier type.

Essential Elements Cont.

While one integrated separation protocol is preferred, UG3 investigators will need to be flexible in the design and execution of their specific proposals through collaboration with other UG3 groups in identifying the optimum protocol(s) for each carrier subclass and to develop best practices specific for each carrier type.

Following NIH administrative review, the UH3 Phase will support activities to optimize, refine, and scale-up of validated separation technologies and *must include the use of human biofluids.*

Essential Elements Cont.

While one integrated separation protocol is preferred, UG3 investigators will need to be flexible in the design and execution of their specific proposals through collaboration with other UG3 groups in identifying the optimum protocol(s) for each carrier subclass and to develop best practices specific for each carrier type.

Following NIH administrative review, the UH3 Phase will support activities to optimize, refine, and scale-up of validated separation technologies and *must include the use of human biofluids.*

Precise quantitative milestones should be proposed for UG3 and UH3 phases, including a clearly identified Go/No-Go transition milestones for completion of the UG3 phase at the end of Year 2 and transition to the UH3 phase

Essential Elements Cont.

The UH3 Phase:

- UH3 projects will support the optimization, validation, and scale-up of separation tools/technologies/approaches using one or more human biofluids.
- Determining the exRNA cargo associated with each highly purified carrier class and comparing these datasets against previously deposited exRNA Atlas datasets (http://exrna-atlas.org/) to determine the contribution of each carrier subclass to the bulk exRNA recovered from each biofluid.
- Cataloging other cargo constituents associated with each exRNA vehicle subclass.

Budget

- Should not exceed $500,000 total costs per year for the UG3 Phase, and $1M total costs for the UH3 Phase.

- Each applicant must set-aside approximately **10%** (Direct Costs) of year 2-4 funds to establish a collaboration(s) with a group(s) who will independently validate and provide an assessment of the potential utility of the tools/technologies/approaches.

Review Criteria

Significance: Does the UH3 phase include at least one human biofluid? Are the methods scalable?

PIs: Track record in exRNA isolation, technology innovation, managing complex projects, and working collaboratively.

Innovation: Will the proposed separation strategy/strategies improve the state of the art either by enabling purification of carrier types in a way that has previously not been possible or by dramatically improving (by at least 5-fold) our ability to purify carrier types with respect to increased purity, increased speed, or decreased cost?

Approach: Are appropriate, quantitative milestones provided for the UG3 and UH3 stages clearly defined?

Advancing Extracellular RNA (exRNA) Communication Research: Towards Single Extracellular Vesicle (EV) Sorting, Isolation, and Analysis of Cargo (UG3/UH3 Clinical Trial Not Allowed)

RFA-RM-18-028

Danilo Tagle
(danilo.tagle@nih.gov)

National Institutes of Health
Office of Strategic Coordination - The Common Fund

Current Barriers to Characterizing Extracellular Vesicle Subpopulations

- EVs are Heterogeneous in size, origin, and molecular cargo (including exRNAs species)

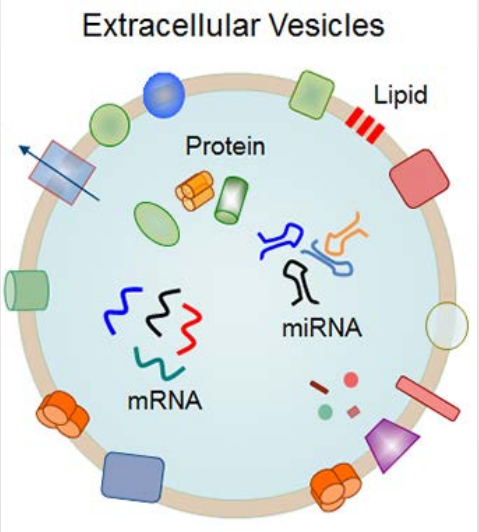
- Current methods for isolating EVs from complex biofluids are limited & do not clearly define cell-of-origin/target cell of exRNA cargo:
  - Unable to sort EVs by cell or tissue of origin
  - Not permissive to single EV isolation and analysis
  - Lack ability to determine origin of EVs from various tissues or cell types

- Ideally, a protocol(s) for isolating single vesicles should be:

  1) rapid and reproducible,

  2) yield highly enriched EV subpopulations from a single source cell or tissue with no cross-contamination, and

  3) have the capacity to analyze and catalog exRNAs present in the single EVs from various cell and tissue types.



RM18-028 Funding Opportunity Purpose

Develop and demonstrate innovative technologies and reagents towards isolating single EVs and to characterize the exRNA cargos associated with specific EV subpopulations based on cell of origin and their intended target cell.

Research Strategy - UG3 Development Phase

- Will support studies that generate novel technologies for EV subpopulation isolation that are:
  - Rapid and reproducible
  - Highly enriched EV subpopulations with little cross contamination
  - Analyze and catalog exRNAs associated with different subpopulations, cell of origin, & intended target cell
  - Track EV subpopulations

- Applications may propose to use:
  - Physiologically relevant human 3D cell models
  - Tissue types derived from primary biopsies
  - Animal models
  - Human biofluids

- Technologies proposed may include:
  - Molecular tools
  - Genetic or barcoding-based systems
  - Identify EVs based on biophysical attributes

- Proposals must:
  - Justify how technology will improve current standards by at least 5-fold
  - Address how technology will increase purity, increased speed, or yield for EV isolation.
  - Incorporate data sharing strategies

Research Strategy - Transition to the UH3 Optimization Phase

UG3 projects that have met the scientific milestones and other requirements (listed below) will be eligible for transition to the second UH3 Optimization Phase pending NIH administrative review.

- Potential for meeting the goal of moving towards single-EV characterization.
- Evidence of collaboration within and outside the Consortium
  - Interacting with the DMRR
  - Timely dissemination of resources/tools to scientific community
- Availability of funds.
- Program priorities.
- **IMPORTANT**: Consistent with recent NIH guidance on rigor and reproducibility in research (https://grants.nih.gov/reproducibility/index.htm), the most important milestone for the transition will be independent validation of any separation tools/technologies/approaches. To achieve this milestone, each applicant must set-aside approximately **10%** (Direct Costs) of year 2-4 funds to establish a collaboration(s) with a group(s) who will independently validate and provide an assessment of the potential utility of the tools/technologies/approaches.

Research Strategy - UH3 Optimization Phase

Will support studies focused on:

- Optimizing, refining, and scale-up validated EV isolation technologies
- Cataloging exRNAs present in complex human biofluids, their respective cell of origin, and intended target cell
- Developing cGMP-compatible methodologies

Applicants must:

- Apply developed technology using complex human biofluids
- Compare results to previously deposited exRNA Atlas datasets (http://exrna-atlas.org/) with the goal of determining the exRNA cell of origin and intended target cell.

Program Timeline and Budget: UG3/UH3 Mechanism

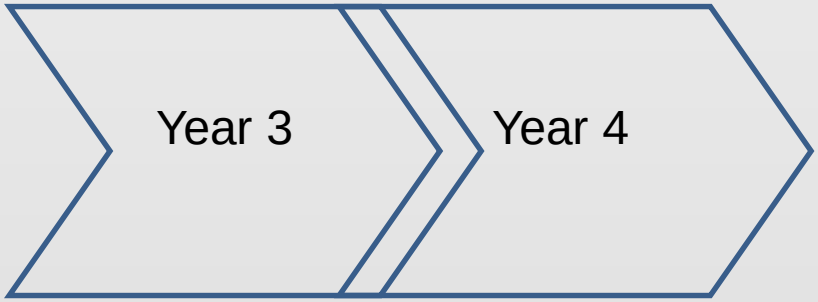
UG3: Development Phase

- Develop protocol(s) for isolating single vesicles
  - improve (at least 5-fold) on current standards (yield & purity)
  - High-throughput

UH3: Optimization Phase

- Optimize approach
- Must use human biofluids.
  - Catalog of exRNAs
  - Identify cell of origin
  - Identify target cell
- Create scale-up using cGMP-compatible methodologies.

UG3: $300K* direct costs per year in FY19-20



UH3: $650K* direct costs per year in FY21-22

UG3/UH3 Transition

- Programmatic review by NIH
- Successful achievement of negotiated milestones
- Evidence of collaboration

*Required set-aside approximately **10%** (Direct Costs) of year 2-4 funds to establish a collaboration(s) to independently validate tools/technologies/approaches.

Specific FOA Review Criteria

Significance: Does the UH3 phase include at least one human biofluid? Are the methods scalable?

PIs: Track record in exRNA isolation, technology innovation, managing complex projects, and working collaboratively.

Innovation: Will the proposed separation strategy/strategies improve the state of the art either by enabling sorting of EV subpopulations in a way that has previously not been possible or by dramatically improving (by at least 5-fold) our ability to purify EV subpopulations with respect to increased purity, increased speed, or decreased cost?

Approach: Are appropriate, quantitative milestones provided for the UG3 and UH3 stages clearly defined?

U.S. Department of Health & Human Services

NIH Center for Scientific Review

Overview of Scientific Review Process

Maqsood Wani, Ph.D.
Chief, Cell Biology IRG
Center for Scientific Review, NIH

Review – who will review my application?

- Reviewed in Center for Scientific Review (CSR)
- Special Emphasis Panels (SEP) – no need to look up and request a standing study section. One-time panels held to review applications on special topics.
- Include only temporary members
- Meeting rosters will be posted online 30 days before the review meeting - https://public.csr.nih.gov/StudySections/SpecialEmphasis/

Review Information

- Refer to Section V of the FOA – “Application Review Information”
- Read Criteria.
- Pay special attention and address “Specific to this FOA” review questions.

Overall Impact and Review Criteria

- **Overall Impact**: The reviewers will assess the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria (as applicable for the project proposed).
- Five Scored Review criteria: Significance, Investigator(s), Innovation, Approach, Environment
- Additional Review Criteria: Protections for Human Subjects, Vertebrate Animals, Biohazards

Overview of Cooperative Agreements and Multi-phase Milestone Applications (UG3/UH3)

National Institutes of Health
Office of Strategic Coordination - The Common Fund

Cooperative Agreements: U Mechanism

- Used when **substantial programmatic involvement is anticipated between the Federal agency and the recipient** during performance of the assisted activity.
- Supports and stimulates the recipients' activities by involvement in and working jointly with the award recipients in a **partnership role**; it is not to assume direction, prime responsibility, or a dominant role in the activities. The dominant role and prime responsibility reside with the awardees of the project as a whole.
- The Cooperative Agreement Terms and Conditions of Award in each FOA clearly outlines the roles and expectations of the PD/PI and NIH Program Staff.
- This information will also be in the Notice of Award (NoA)

Multi-phase Applications

- Applications must be written in a multi-phased manner with clear, quantitative milestones
- Milestones are goals that create go/no-go decision points and must include clear and quantitative criteria for success.
- At a minimum, there should be one defined milestone for each year of requested support.
- Milestones are included in the Type 1 application and are sometimes re-negotiated in the pre-award stage.
- **RM18-027 & RM18-028**: Phase I (UG3) will be two years in length, and Phase II (UH3) is an additional two years in length, for a total project length of four years.
- Competing (Type 1) applications will go through the NIH peer-review and IC Council review processes.

Cooperative Agreements Terms and Conditions of Awards

- Acceptance of the Notice of Award (NoA) indicates the recipients' willingness to work with NIH Program staff during the course of the award.
- To participate in semi-annual meetings and in regular conference calls with NIH program staff and other exRNA grantees.
- To actively seek input from NIH regarding resource needs or expertise needs that may arise during the performance of the project.
- To work within a consortium agreement to meet the goals of the Program.

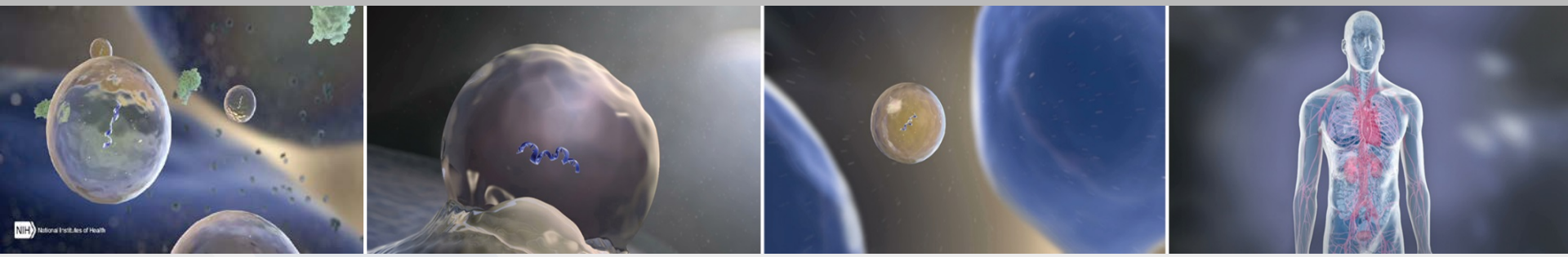
Transition Phases

The transition from one phase to the next (UG3 to UH3 phase) is gauged on the achievement of the negotiated milestones during an administrative review. Some of the following are general points that are considered:

- Successful achievement of the defined milestones for the UG3/UH3 Phase of the project
- Potential for meeting the goals of the Initiative
- Ability to work within a Consortium arrangement with other awardees to meet the goals of the program
- The availability of funds
- Program priorities

Resources

- NIH Grants Policy Statement: https://grants.nih.gov/grants/policy/nihgps/HTML5/introduction.htm
- SF424 (R&R) General Instructions for NIH and other PHS Agencies: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf
- Funding Opportunity Announcements:
  - NIDA RFA (*U54 mechanism):* RFA-RM-18-026
  - NCI/NCATS RFA *(UG3/UH3 mechanism):* RFA-RM-18-027
  - NCATS/NCI RFA *(UG3/UH3 mechanism):* RFA-RM-18-028



Scientific/Research Contact(s)

- **RFA-RM-18-026**
  - John Satterlee, Ph.D.; NIDA
  - Tel.: 301.435.1020
  - Email: satterleej@nida.nih.gov

- **RFA-RM-18-027**
  - Kevin Howcroft, Ph.D., NCI
  - Tel: 240.276.6229
  - Email: Howcrofk@nih.gov

- **RFA-RM-18-028**
  - Danilo Tagle, Ph.D. NCATS
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  - Email: danilo.tagle@nih.gov

- **Peer Review Contact**
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  - Email: wanimaqs@csr.nih.gov

- **Grants Management****
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  - Tel: 301.435.0964
  - E-mail: wilkomg@mail.nih.gov

- **Common Fund**
  - Trish Labosky, Ph.D., OD/OSC
  - Tel: 301.594.4863
  - E-mail: patricia.labosky@nih.gov

**Please check FOA for specific GM contact

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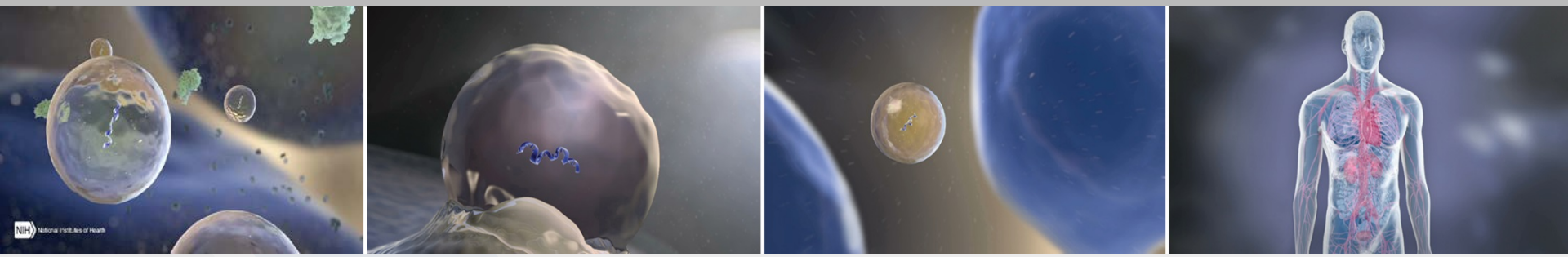
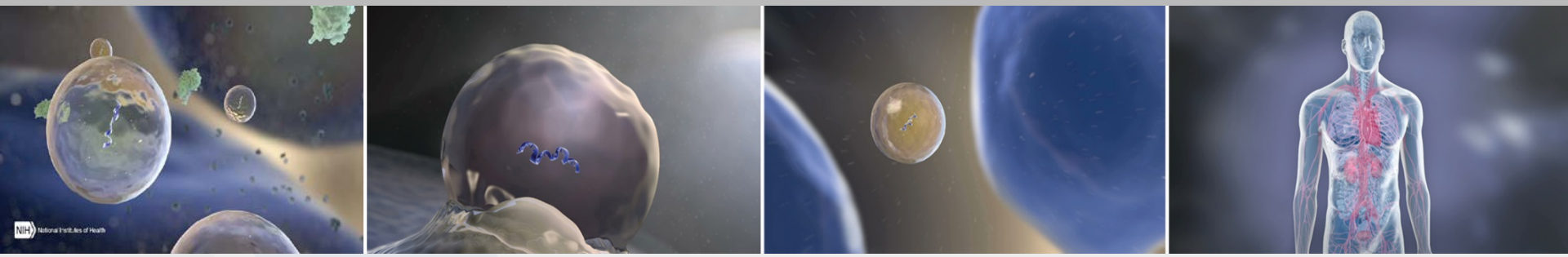


Questions & Answers

- Please submit using the **Q&A box**
- All questions submitted to the exRNA email address (exrnacommunication@mail.nih.gov)during the webinar will be answered in the order they were received.



Instructions for NIH IRP Applicants

Instructions for IRP applicants are in the Common Fund Handbook (NIH access only):
https://osc.cf.cit.nih.gov/CommonFundHandbook/Pages/Chapter_6_Section_C_Intramural_Involvement_in_Common_Fund_Programs.aspx

Some highlights:
IC Scientific Director needs to sign application
IRP can request funds only for project activities – not to support federal staff
If acting as a collaborator, the IRP PI gives a budget request to the ERP PI that gets submitted with the application
The IRP funds go directly from the CF to the IRP as an interagency agreement, not from the CF to the ERP and then to the IRP.