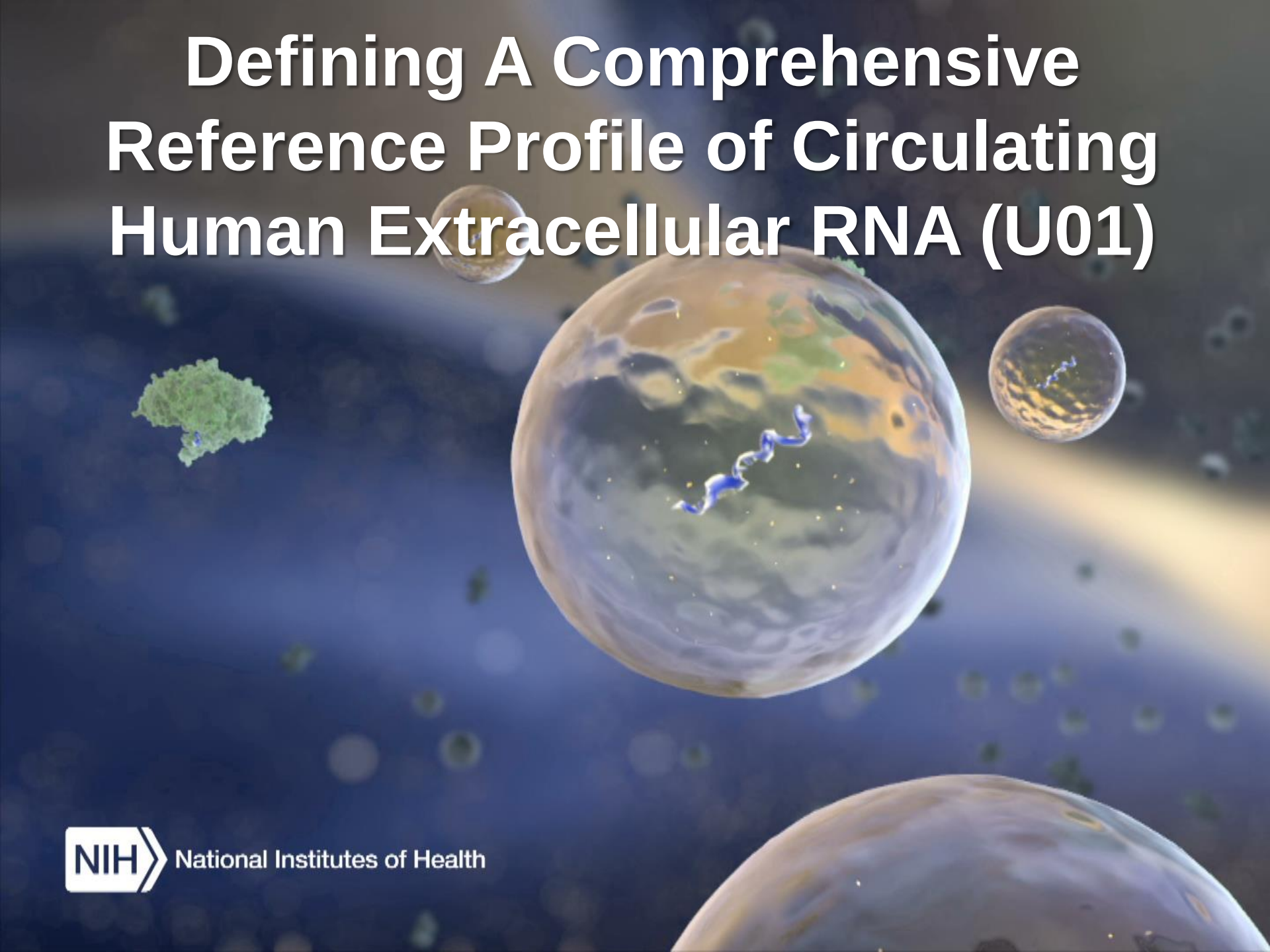
Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)



NIH National Institutes of Health

What's the Common Fund?

OUR VISION

The intent of NIH Common Fund programs is to provide a strategic and nimble approach to address key **roadblocks** in biomedical research that impede basic scientific discovery and its translation into improved human health. In addition, these programs capitalize on **emerging opportunities** to catalyze the rate of progress across multiple biomedical fields.

Common Fund programs are expected to transform the way a broad spectrum of health research is conducted. Initiatives that comprise Common Fund programs are intended to be **catalytic** in nature by providing limited term investments in strategic areas to stimulate further research through IC-funded mechanisms.

Changes Brought by the Reform Act

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".

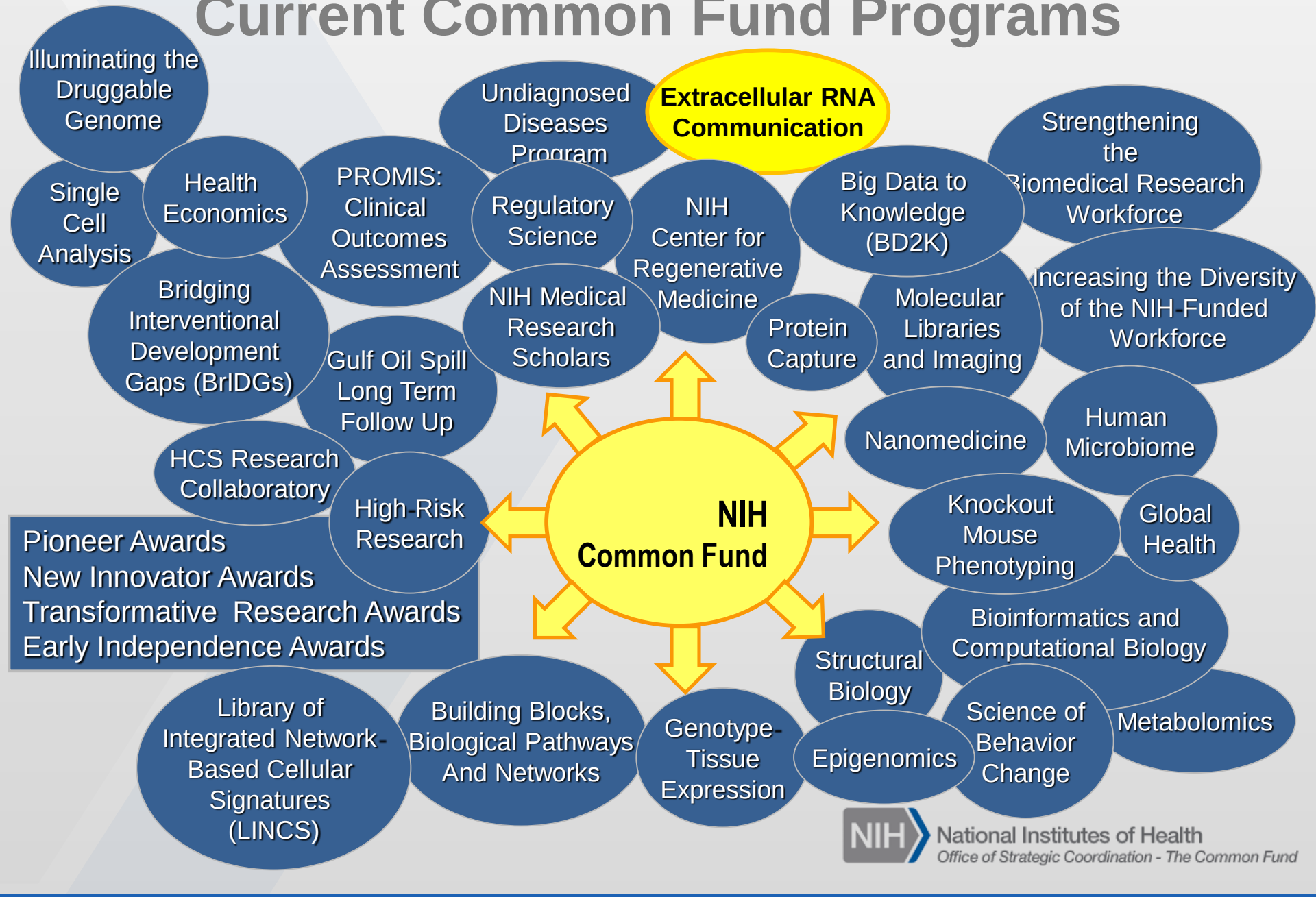
TITLE I—NIH REFORM

2004: NIH Roadmap is launched

December 9, 2006: Congress unanimously passes a reauthorization bill affirming importance of NIH and its vital role in advancing biomedical research to improve the health of the Nation

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

Current Common Fund Programs



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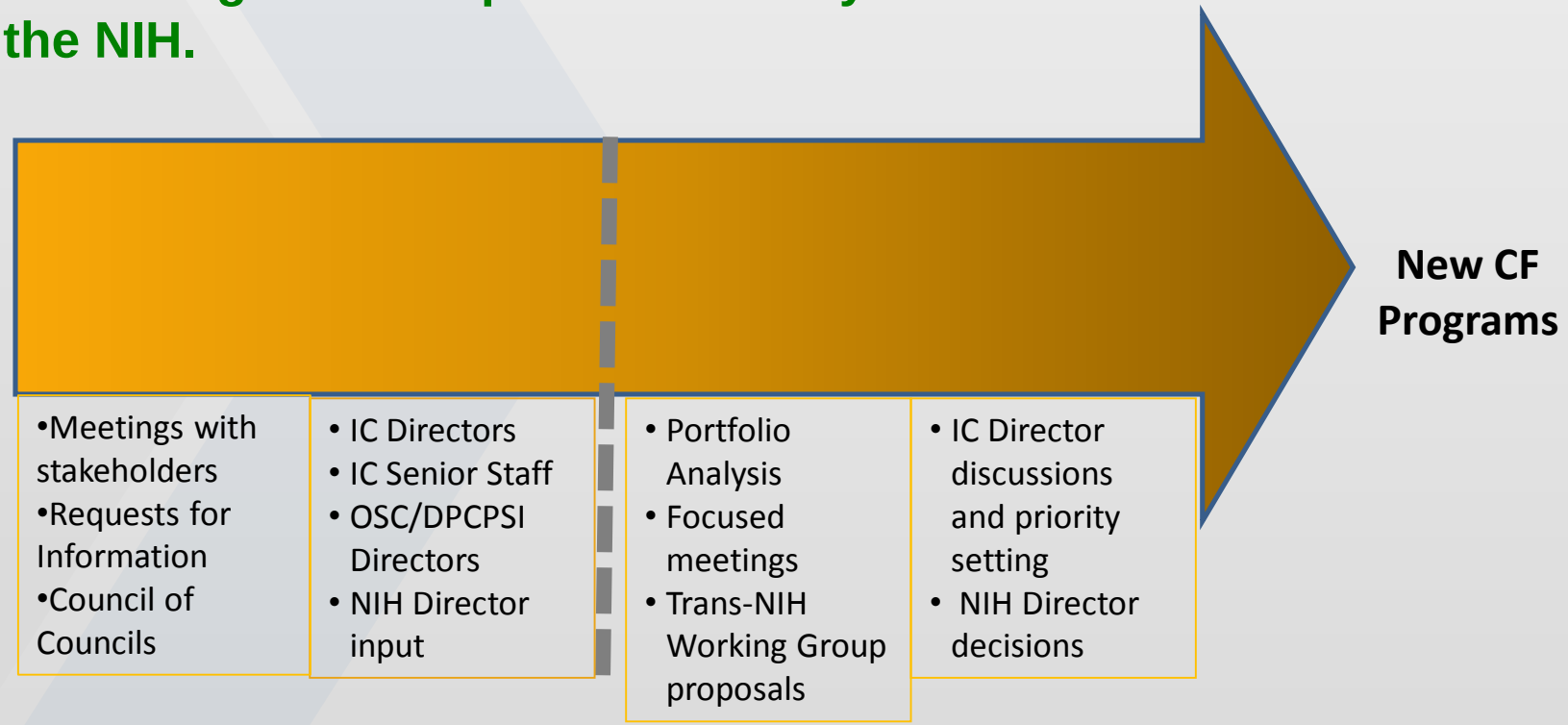
http://commonfund.nih.gov/

Why is the CF supporting an Extracellular RNA Communication program?

It emerged from a comprehensive strategic planning process that sought to identify areas where strategic investments could have a transformative impact – discoveries, data, and technologies are expected to catalyze further work across the NIH.



Criteria for Common Fund Programs

- **Transformative:** Fundamental discoveries, exRNA catalogs, technologies, and clinical strategies are expected to transform our understanding of intercellular signaling and offer entirely new approaches to clinical practice.
- **Catalytic**: The work of this program is expected to provide foundational information that will catalyze many more projects across the NIH
- **Synergistic:** This research should not simply be additive - it should deliver tools, datasets, and methods to enhance the whole field.
- **Cross-cutting:** Results should be very widely applicable
- **Unique:** Must be something no other entity is likely or able to do, coordinating with international efforts as needed to achieve greatest impact

CF Programs Build "Foundations" to Catalyze Research

- **New Approaches to Foster Innovation and Build Multi-Disciplinary Research Teams**
  - High-Risk High-Reward (Pioneer, New Innovator, Transformative Research, Early Independence Awards)
  - Nanomedicine
  - Interdisciplinary Research (Transitioned program)
- **New Tools, Infrastructure, and Data to Support or Establish New Fields of Study**
  - Human Microbiome Project
  - Metabolomics
  - Epigenomics
- **New Technologies and Approaches to Overcome Barriers to Progress in a Field**
  - Structural Biology
  - PROMIS: Patient Report Outcomes Management System
  - Regulatory Science – Tissue Chip for Drug Screening

Extracellular RNA Communication Program

Opportunity to explore new paradigms of intracellular and inter-species communication based on the release, transport, uptake, and regulatory role of exRNAs

What are the effects of extracellular RNAs on human health and disease?

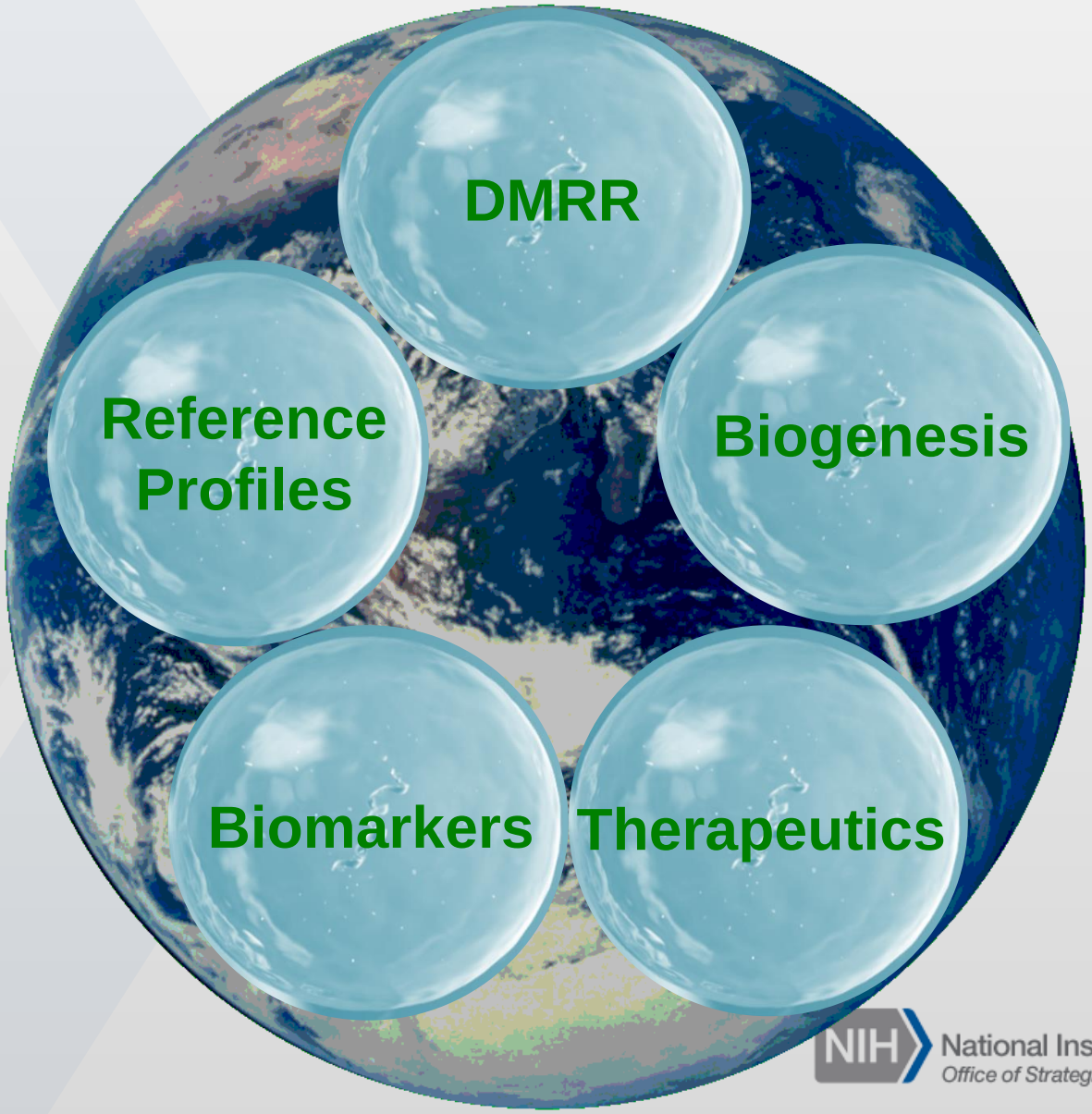
micro

Lin Zhang
Xiangying
Qun Chen
Junfeng Zh

Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes

Lydia Alvarez-Erviti[1,2], Yiqi Seow[1,2], HaiFang Yin[1], Corinne Betts[1], Samira Lakhal[1] & Matthew J A Wood[1]

Extracellular RNA Communication Program



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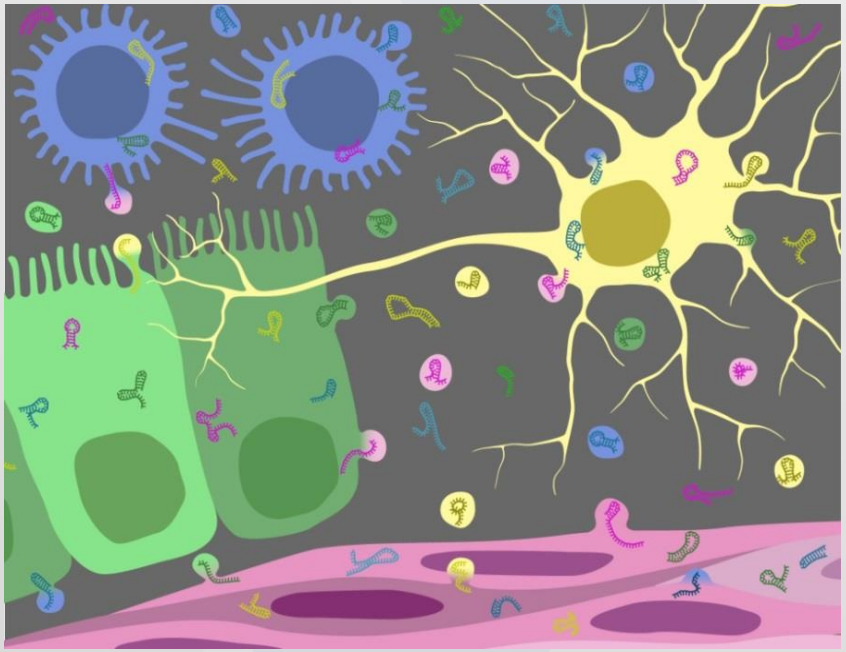
Extracellular RNA (exRNA) Communication Program Overview

Goals: *To discover fundamental biological principles and mechanisms of exRNA generation, secretion, and transport; to identify and develop a catalog of exRNA found in normal human body fluids; and to investigate the potential for using exRNA in the clinic as therapeutic molecules or biomarkers of disease.*



RNAs can be exported from cells in extracellular vesicles, or bound to lipids or proteins, circulate through the body and affect distant cells

- **NIH investment of $130 million over six years**
- **Awards made through a cooperative agreement mechanism**
- **Trans-NIH Scientific Project Team comprised of 25 NIH staff representing 17 NIH Institutes or Centers**
- **Transformative and cross-cutting research will synergistically promote and advance individual missions of NIH Institutes and Centers to benefit human health**
- **Program oversight through an External Scientific Panel of internationally recognized leaders in the field of extracellular RNA**
- **Program governance through a Steering Committee**
- **Kick-Off Meeting – September 26-27, 2013**

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Extracellular RNA (exRNA) Communication Program Overview

Common elements shared by all exRNA RFAs:

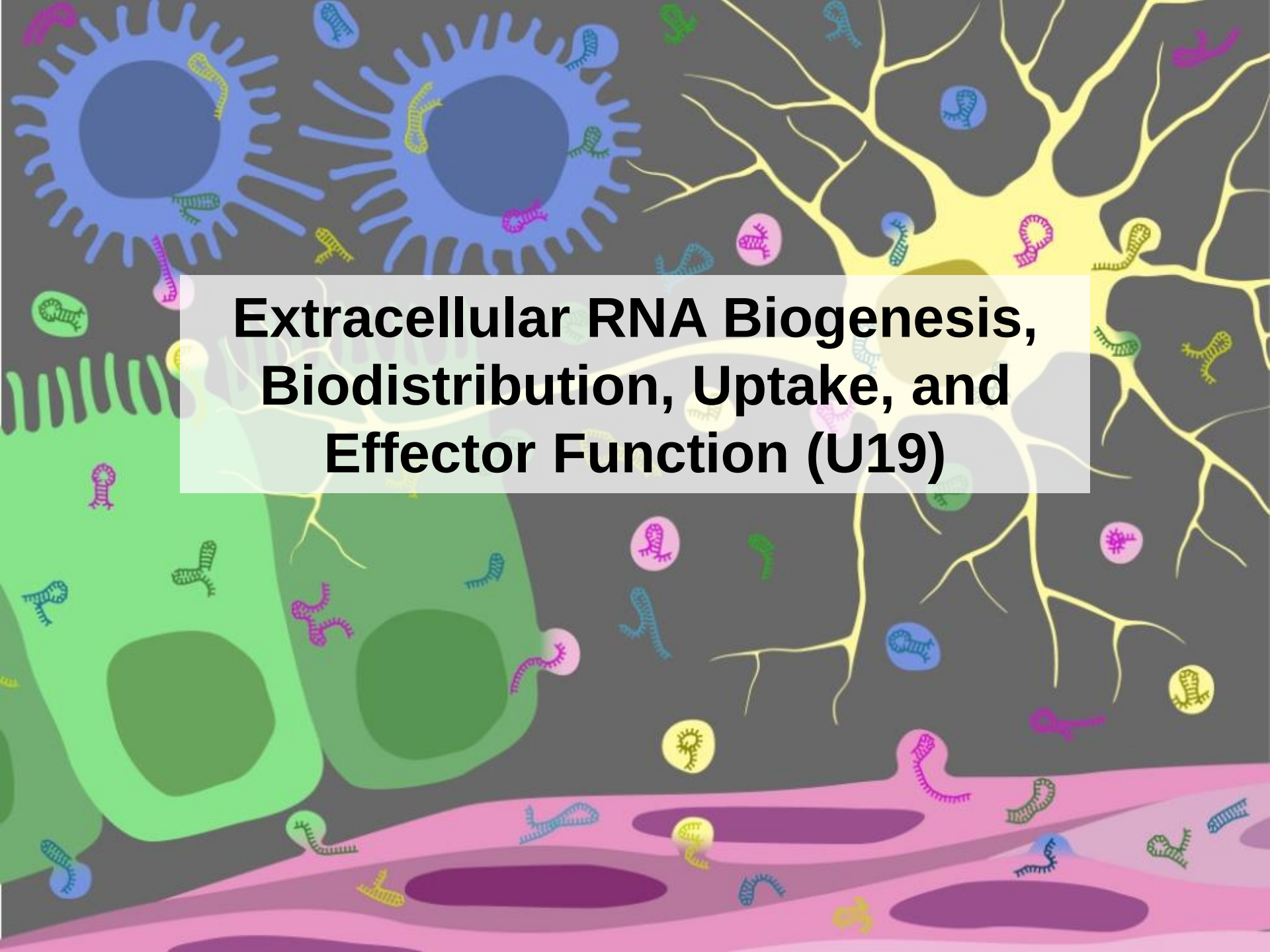
- Applications should involve multidisciplinary teams
  - Multi-PI leadership plans may be required
  - Applicants may collaborate with PIs already in the Consortium
- Milestones-driven awards
- Awardees from all 5 initiatives will form a consortium
  - Determine fundamental principles associated with exRNAs
  - Provide ready access of newly developed tools and resources to consortium members
  - Facilitate dissemination of data and technologies to the general research community
  - Data release/sharing
- Applications from foreign institutions are acceptable

Extracellular RNA Communication Consortium (ERCC)

- **ERCC Program Goal**: to catalyze emerging scientific opportunities in Extracellular RNA Communication research leading to basic scientific discoveries and translation to improve human health.
- **Key aims**:
  - To discover fundamental biological principles about the mechanisms of exRNA generation, secretion, and transport
  - To identify and develop a catalog of exRNA found in normal human body fluids
  - To investigate the potential for using exRNAs in the clinic as therapeutic molecules or biomarkers of disease
  - To disseminate data, resources and best practices to general scientific community in a timely manner

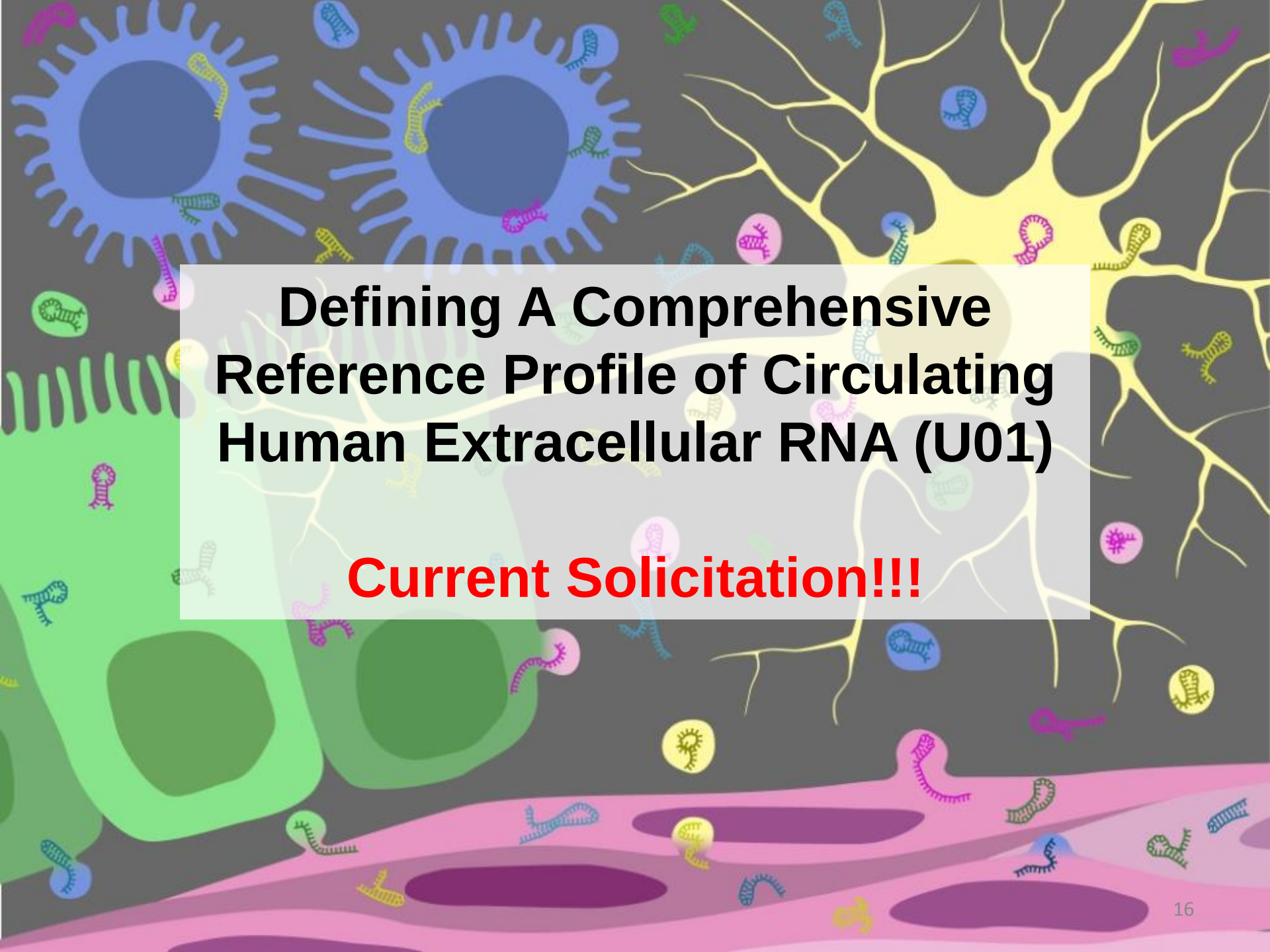
Cooperative Agreements (U mechanism)

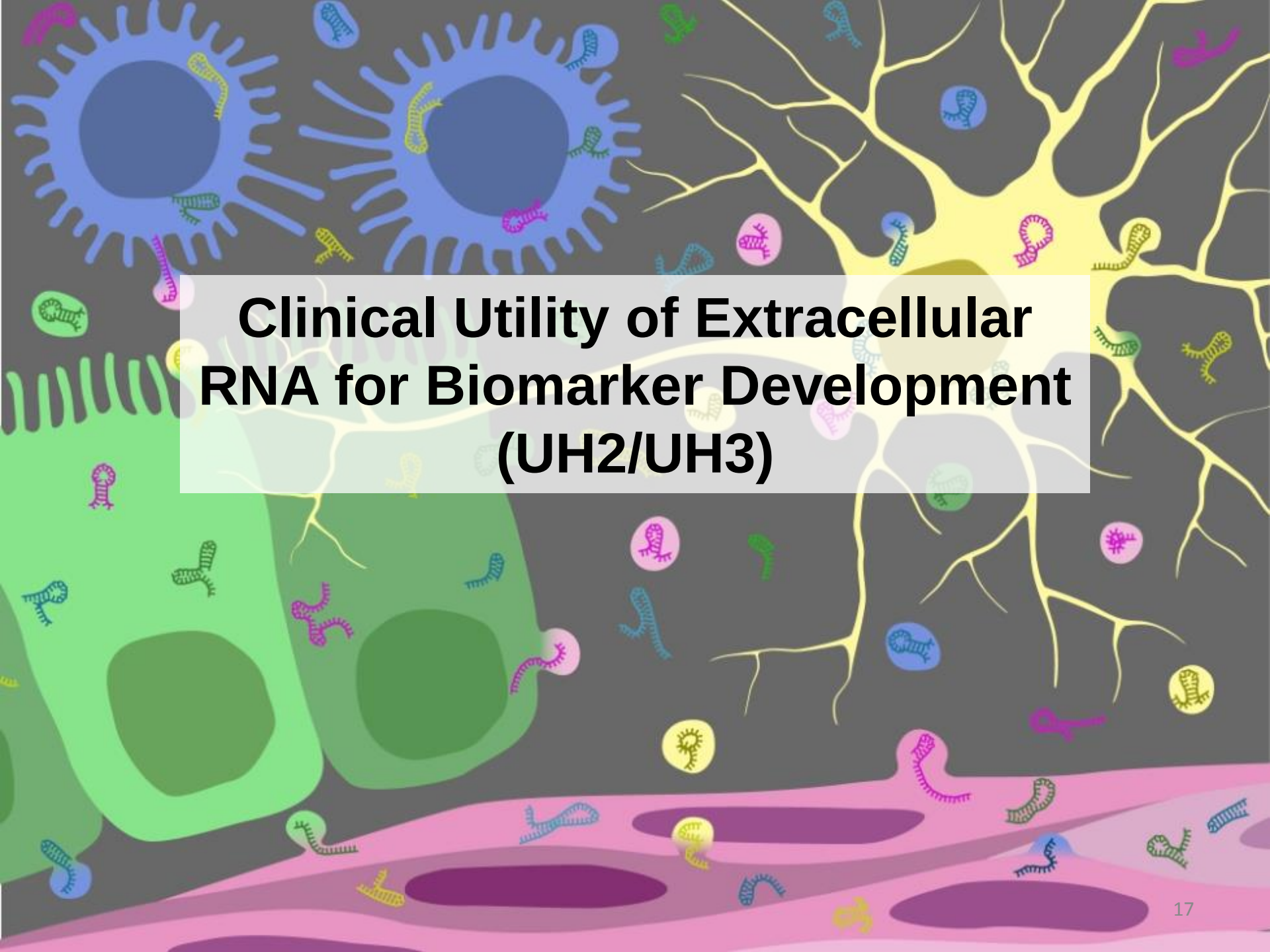
- Neither a grant nor a contract
- Substantial NIH scientific and/or programmatic involvement with the awardee.
- NIH's role is to support and/or stimulate the recipient's activity, but it is not to assume direction, or prime responsibility.
- Milestones-driven research. Meeting these benchmarks will determine continuation of funding through each non-competing renewal.


Extracellular RNA Biogenesis, Biodistribution, Uptake, and Effector Function (U19)

Extracellular RNA Biogenesis, Biodistribution, Uptake, and Effector Function (U19)

PIs	Title	Institution
BLELLOCH, ROBERT	In Vivo Regulated Release and Function of Extracellular Small RNAs	UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
BREAKEFIELD, XANDRA OWENS (contact) CHAREST, ALAIN GOULD, STEPHEN KRICHEVSKY, ANNA MEMPEL, THORSTEN	exRNA released by glioblastoma alters brain microenvironment	MASSACHUSETTS GENERAL HOSP
COFFEY, ROBERT	Secreted RNA during CRC progression biogenesis function and clinical markers	VANDERBILT UNIVERSITY MED CTR
MCMANUS, MICHAEL	Genetic models for exRNA communication	UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
TUSCHL, THOMAS	Definition of Serum Ribonucleoprotein Composition and its Regulation and Function	ROCKEFELLER UNIVERSITY


Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)
Current Solicitation!!!



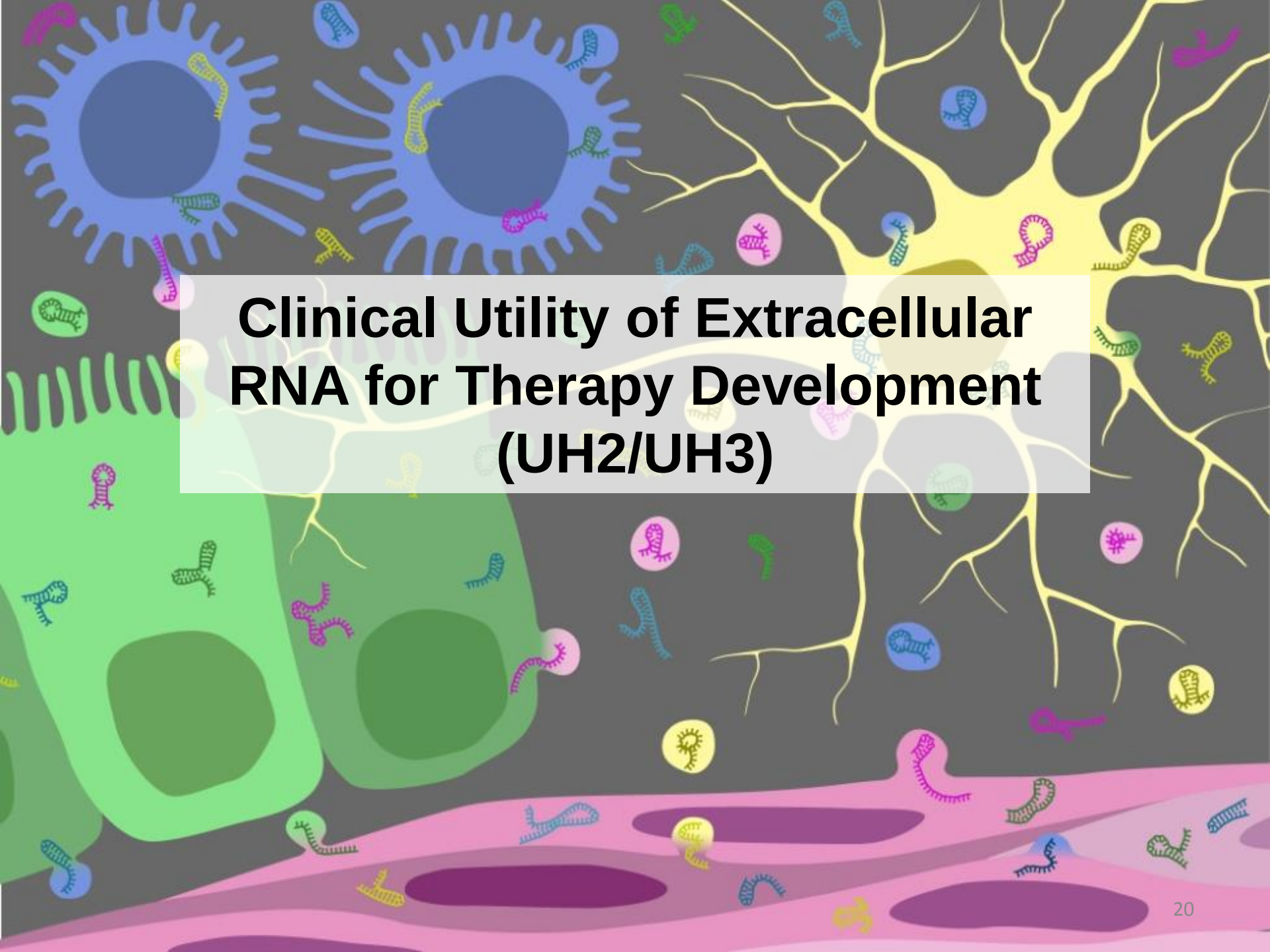
Clinical Utility of Extracellular RNA for Biomarker Development (UH2/UH3)

Clinical Utility of Extracellular RNA for Biomarker Development (UH2/UH3)

PIs	Title	Institution
CARTER, BOB S (contact) HOCHBERG, FRED	exRNA Biomarkers for Human Glioma	UNIVERSITY OF CALIFORNIA SAN DIEGO
DAS, SAUMYA (contact) KWONG, RAYMOND ROSENZWEIG, ANTHONY SABATINE, MARC	Plasma miRNA Predictors of Adverse Mechanical and Electrical Remodeling after MI	BETH ISRAEL DEACONESS MEDICAL CENTER
FREEDMAN, JANE	Extracellular RNAs: Biomarkers for Cardiovascular Risk and Disease	UNIV OF MASSACHUSETTS MED SCH WORCESTER
HUENTELMAN, MATTHEW (contact) ADELSON, P. DAVID SPETZLER, ROBERT	ExRNA Signatures Predict Outcomes After Brain Injury	TRANSLATIONAL GENOMICS RESEARCH INST
LAURENT, LOUISE	ExRNAs for Early Identification of Pregnancies at Risk for Placental Dysfunction	UNIVERSITY OF CALIFORNIA SAN DIEGO
PATEL, TUSHAR	Extracellular Non-coding RNA Biomarkers of Hepatocellular Cancer	MAYO CLINIC JACKSONVILLE
SAUGSTAD, JULIE ANNE (contact) QUINN, JOSEPH	Clinical Utility of MicroRNAs as Diagnostic Biomarkers of Alzheimer's Disease	OREGON HEALTH AND SCI UNIVERSITY
TUSCHL, THOMAS (contact) SUTHANTHIRAN, MANIKKAM	Clinical Utility of Extracellular RNA as Markers of Kidney Disease Progression	ROCKEFELLER UNIVERSITY
WEINER, HOWARD	Circulating MicroRNAs as Disease Biomarkers in Multiple Sclerosis	BRIGHAM AND WOMEN'S HOSPITAL
WONG, DAVID	Clinical Utility of Salivary ExRNA Biomarkers for Gastric Cancer Detection	UNIVERSITY OF CALIFORNIA LOS ANGELES

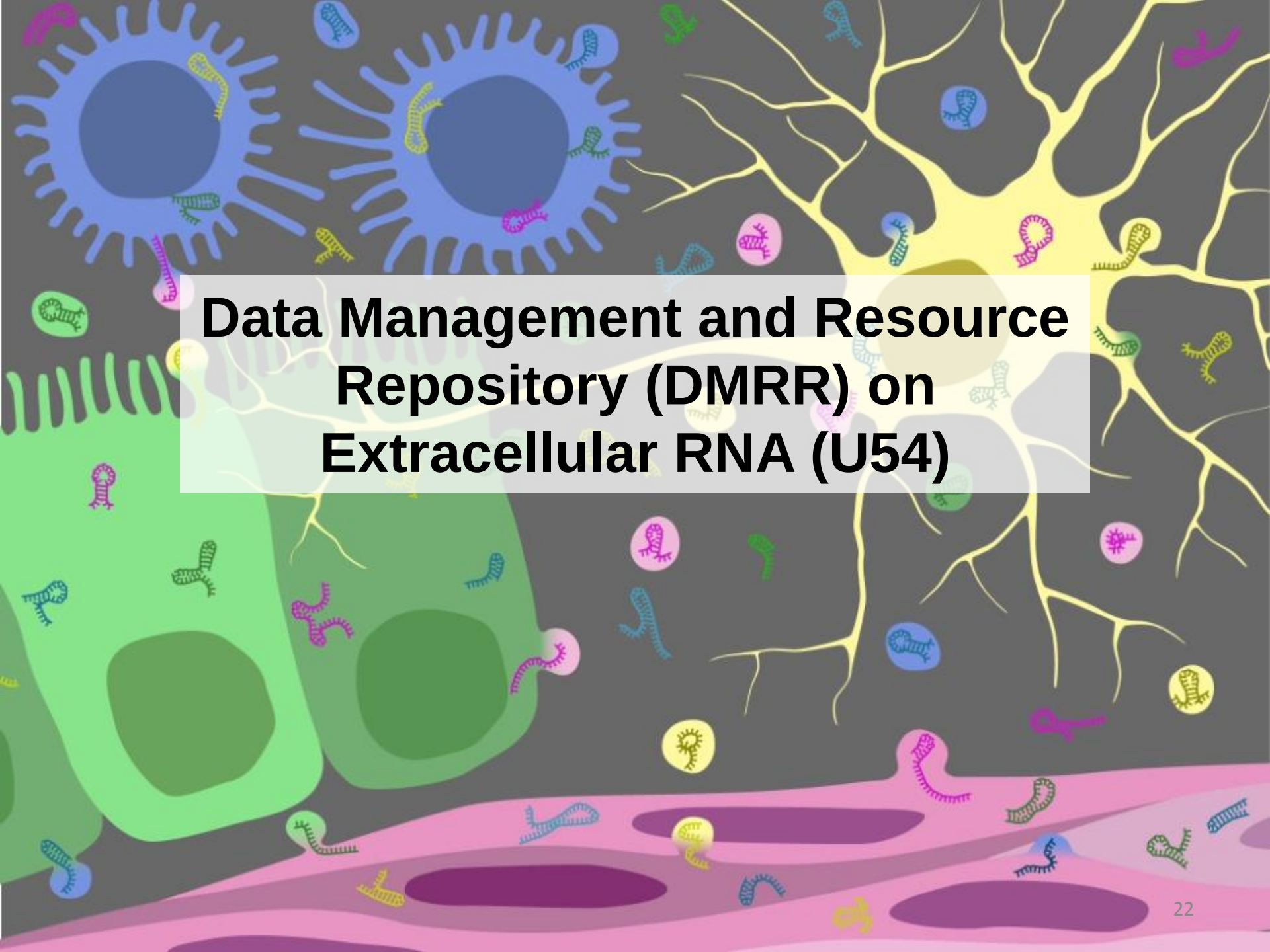
Clinical Utility of Extracellular RNA for Biomarker Development (UH2/UH3)

PIs	Disease	Biofluid
CARTER, BOB S (contact) HOCHBERG, FRED	Glioma	**Plasma, CSF**
DAS, SAUMYA (contact) KWONG, RAYMOND ROSENZWEIG, ANTHONY SABATINE, MARC	Adverse outcome after myocardial infarction	**Plasma**
FREEDMAN, JANE	Cardiovascular disease	**Plasma**
HUENTELMAN, MATTHEW (contact) ADELSON, P. DAVID SPETZLER, ROBERT	IVH and aSAH	**CSF, Plasma**
LAURENT, LOUISE	Placental Dysfunction	**Plasma, Serum**
PATEL, TUSHAR	Hepatocellular cancer (HCC)	**Serum**
SAUGSTAD, JULIE ANNE (contact) QUINN, JOSEPH	Alzheimer's disease	**CSF**
TUSCHL, THOMAS (contact) SUTHANTHIRAN, MANIKKAM	Chronic kidney disease (CKD)	**Urine**
WEINER, HOWARD	Multiple Sclerosis (MS)	**Plasma, Serum**
WONG, DAVID	Gastric cancer	**Saliva**


Clinical Utility of Extracellular RNA for Therapy Development (UH2/UH3)

Clinical Utility of Extracellular RNA for Therapy Development (UH2/UH3)

PIs	Title	Institution
ABDEL-MAGEED, ASIM	Targeting Tumor-Derived exRNA-Containing Microvesicles by High Throughput Screening	TULANE UNIVERSITY OF LOUISIANA
ARONIN, NEIL	Exosome based therapeutics in Huntingtons disease	UNIV OF MASSACHUSETTS MED SCH WORCESTER
KRAIG, RICHARD	Exosome RNA-Therapeutics to Promote CNS Myelination	UNIVERSITY OF CHICAGO
MATIN, AC	HER2-targeted exosomal delivery of therapeutic mRNA for enzyme pro-drug therapy	STANFORD UNIVERSITY
QUESENBERRY, PETER	Regulation of renal and bone marrow injury by extracellular vesicle non-coding RNA	RHODE ISLAND HOSPITAL
SCHMITTGEN, THOMAS (contact) PHELPS, MITCH	Targeted delivery of microRNA-loaded microvesicle for cancer therapy	OHIO STATE UNIVERSITY
SOOD, ANIL K (contact) CALIN, GEORGE A LOPEZ-BERESTEIN, GABRIEL	Novel extra cellular RNA-based combinatorial RNA inhibition therapy	UT MD ANDERSON CANCER CTR
ZHANG, HUANG-GE (contact) GUO, PEIXUAN	Fruit exosome-like particles for therapeutic delivery of extracellular miRNAs	UNIVERSITY OF LOUISVILLE


Data Management and Resource Repository (DMRR) on Extracellular RNA (U54)

Data Management and Resource Repository (DMRR) on Extracellular RNA (U54)

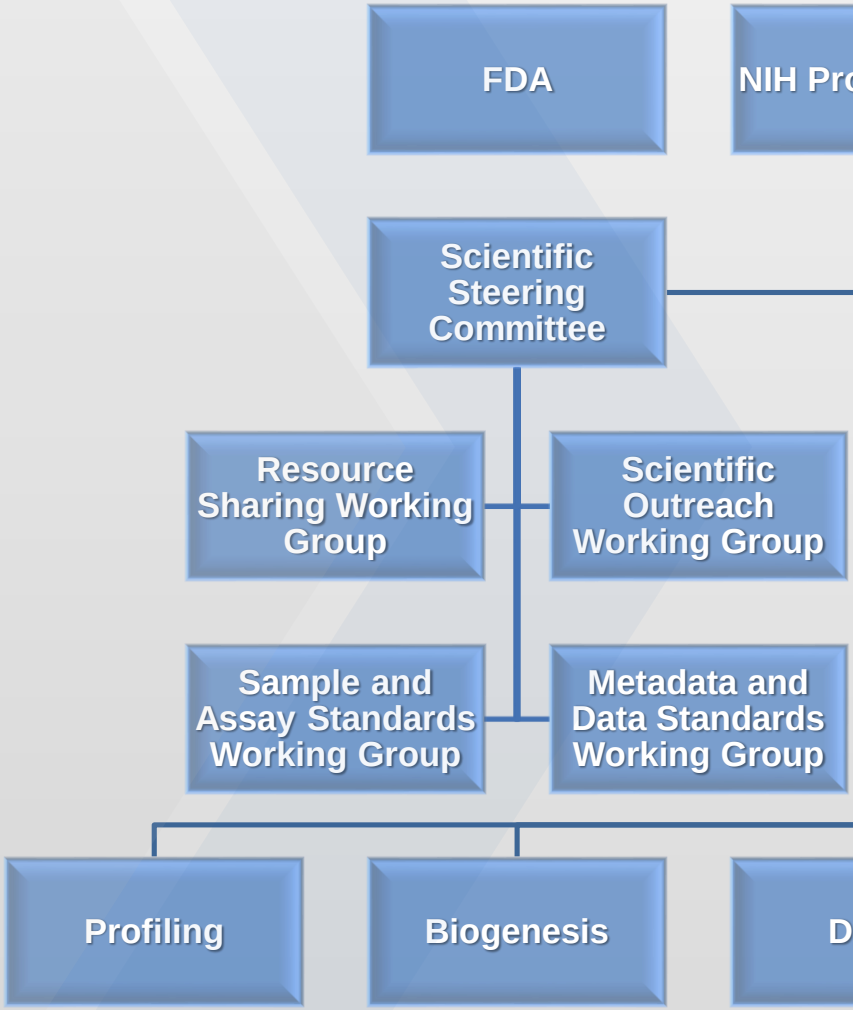
GOAL: The DMRR will integrate the efforts of all of the funded components of the program and serve as a community-wide resource for exRNA standards, protocols, and data through the development of an exRNA Atlas.

1. Scientific Outreach Component
   - ExRNA Atlas website (e.g. data, protocols)

PIs	Title	Institution
MILOSAVLJEVIC, ALEKSANDAR (contact) GALAS, DAVID GERSTEIN, MARK BENDER	Data management and Resource Repository for the exRNA Atlas	BAYLOR COLLEGE OF MEDICINE

   - other data types (e.g. genotype, phenotype) and data from outside program
   - Data deposition (e.g. GEO, dbGAP)
3. Data Integration and Analysis Component
   - Analysis tools and strategies (e.g. exogenous vs endogenous exRNAs)
   - exRNA catalogs
   - Software, tool, and “app” development
   - Help analyze data for integrative consortium papers
   - Help PIs funded by other RFAs analyze their data
4. Administrative Core
   - Facilitating interaction between three U54 components and rest of ExRNA consortium
   - ExRNA program teleconferences and workshops, steering committee meeting

Extracellular RNA Communication Consortium (ERCC)



- **Howard Y. Chang, M.D., Ph.D.**
  Stanford University School of Medicine
- **Beverly Davidson, Ph.D.**
  University of Iowa
- **Jan Lötvall, M.D., Ph.D.**
  University of Göthenburg
- **John Quackenbush, Ph.D.**
  Dana-Farber Harvard University
- **Janusz Rak, M.D., Ph.D.**
  McGill University
- **Gyongyi Szabo, M.D., Ph.D.**
  University of Massachusetts Medical School

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

Funding Opportunity Announcement (FOA):

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

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

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

- A key component of the Extracellular RNA Communications Program will be the generation of reference profiles for exRNAs in normal healthy individuals that may subsequently facilitate disease detection, diagnosis, stratification, interventions, and prediction of therapeutic outcomes.

- Extensive interaction and coordination is envisioned for the awardees of this RFA and the exRNA consortium that is in place currently.

- The initial release of this RFA (RFA-RM-12-011) did not receive a favorable review and no awards were made.

- The RFA was re-released to enable (1) broader outreach, (2) more unbiased and comprehensive approaches to detection of long and short non-coding exRNA from endogenous and exogenous sources, and (3) the use of diverse body fluids as sample sources.

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

KEY DATES:

- **Letters of Intent (LOI) Due October 22, 2013:** A letter of intent is not required, is not binding, and does not enter into the review of a subsequent application.
- **Application Due Date November 22, 2013:** 5:00 PM local time of applicant organization. NOTE: The federal shutdown does not affect November submission dates.

BUDGET:

- $700,000 in Total Costs per year
- Maximum project period is 5 years
- It is anticipated that 3-5 projects will be supported

REVIEW:

- Scientific Merit Review, January- February 2014
- Advisory Council Review, May 2014

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

OBJECTIVES:

- Generate reference profiles of both short and long non-coding regulatory exRNAs, including any environmentally-derived exRNA (e.g. from diet, microbiome),
- Include a diversity of healthy human body fluids such as blood, saliva, urine, breast milk, semen, amniotic fluid, cerebrospinal fluid, ascites and pleural effusions.
- These body fluids should be derived from healthy human subjects to serve as reference data for future analyses of the role of exRNAs in normal biological processes and in disease conditions.
- The profiles should include exRNAs in vesicles and exRNAs bound to carrier proteins such as lipoproteins and Argonaute and also include environmentally derived exRNA species such as from the diet.

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

Responsiveness to the RFA:

- Human exRNA reference profiles MUST include a set of assays that will **enable detection of the full spectrum of potential non-coding regulatory exRNA species** (e.g. short, long, and circular RNAs).

- Applicants should describe their previous experience and current capability regarding **production level** RNA-seq or related relevant assays.

- Applicants **MUST** propose to perform reference profiling on **HUMAN** samples. Applications that propose to perform profiling of non-human samples will not be responsive to this FOA.

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

Responsiveness to the RFA:

- Applicants **MUST** propose to use **EXISTING** human samples that have been appropriately archived, annotated, linked to appropriate metadata, and are amenable to profiling. While prospective sample collection will not be allowed for discovery purposes, a limited prospective collection would be permissible for **VALIDATION** of exRNA profiles discovered in archived samples sets. The cohorts from which samples will be derived should be associated with high-quality phenotypic and other relevant data.

- The sample sets should be reflective of the general U.S. population and include **statistical justification for the number of samples proposed**. Plans for confirmatory or cross validation studies should be included in the application.

Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01)

Responsiveness to the RFA:

- Applicants are encouraged to assemble a **multidisciplinary team** including **experts in exRNA biology, high-throughput sequencing, biostatistics and bioinformatics**. The team should also include investigators familiar with all aspects of the parent studies from which samples are to be derived.

- A fee for service type arrangement NOT responsive. A **collaborative effort** rather than a fee for service type arrangement would be deemed responsive.

Trans-NIH Project Team

Co-Chairs:

Chris P. Austin, M.D. (NCATS)
Story Landis, Ph.D. (NINDS)
Dinah S. Singer, Ph.D. (NCI)

Project Team Coordinators:

Kevin Howcroft, Ph.D. (NCI)
Suresh Mohla, Ph.D. (NCI)
Danilo A. Tagle, Ph.D. (NCATS)

Members:

Alexandra Ainsztein, Ph.D. (NIGMS)
Maureen Beanan, Ph.D. (NIAID)
Philip J. Brooks, Ph.D. (NIAAA/NCATS)
Michelle Freund, Ph.D.(NIMH)
Tina Gatlin, Ph.D. (NHGRI)
Max Guo, Ph.D. (NIA)
Christine A. Kelley, Ph.D. (NIBIB)
Trish Labosky, Ph.D. (DPCPSI)
George A. McKie, D.V.M., Ph.D. (NEI)
Richard Panniers, Ph.D. (CSR)
Matthew Reilly, Ph.D. (NIAAA)
John Satterlee, Ph.D. (NIDA)
Pothur R. Srinivas, Ph.D., M.P.H. (NHLBI)
Robert Star, M.D. (NIDDK)
Margaret Sutherland, Ph.D. (NINDS)
Xenia Tigno, Ph.D., M.S. (NINR)
Sundar Venkatachalam, Ph.D. (NIDCR)

Questions?

- FAQs can be found at http://commonfund.nih.gov/Exrna/faq.aspx

- For individual questions contact:

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National Heart Lung and Blood Institute (NHLBI)
Telephone: 301-402-3712
Email: srinivap@mail.nih.gov