NCATS Partnerships with NIH Common Fund

January 2016 Joint NCATS Advisory Council and Cures Acceleration Network Review Board

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ASSOCIATE DIRECTOR FOR SPECIAL INITIATIVES

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

NATIONAL INSTITUTES OF HEALTH

NCATS

NIH National Center for Advancing Translational Sciences

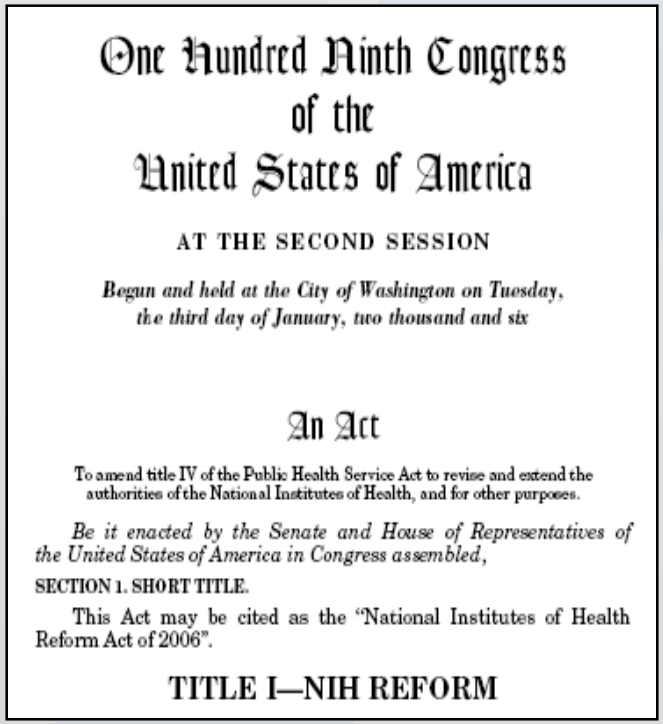
Outline

- NIH Common Fund Overview
- NCATS Partnerships with Common Fund
- Examples:
  - » Extracellular RNA Communication program
  - » Undiagnosed Diseases Network program

Origins of the Common Fund

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



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

Established 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 **goal-driven trans-NIH research**

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

Common Fund Enables a Different Approach to Science and Science Management

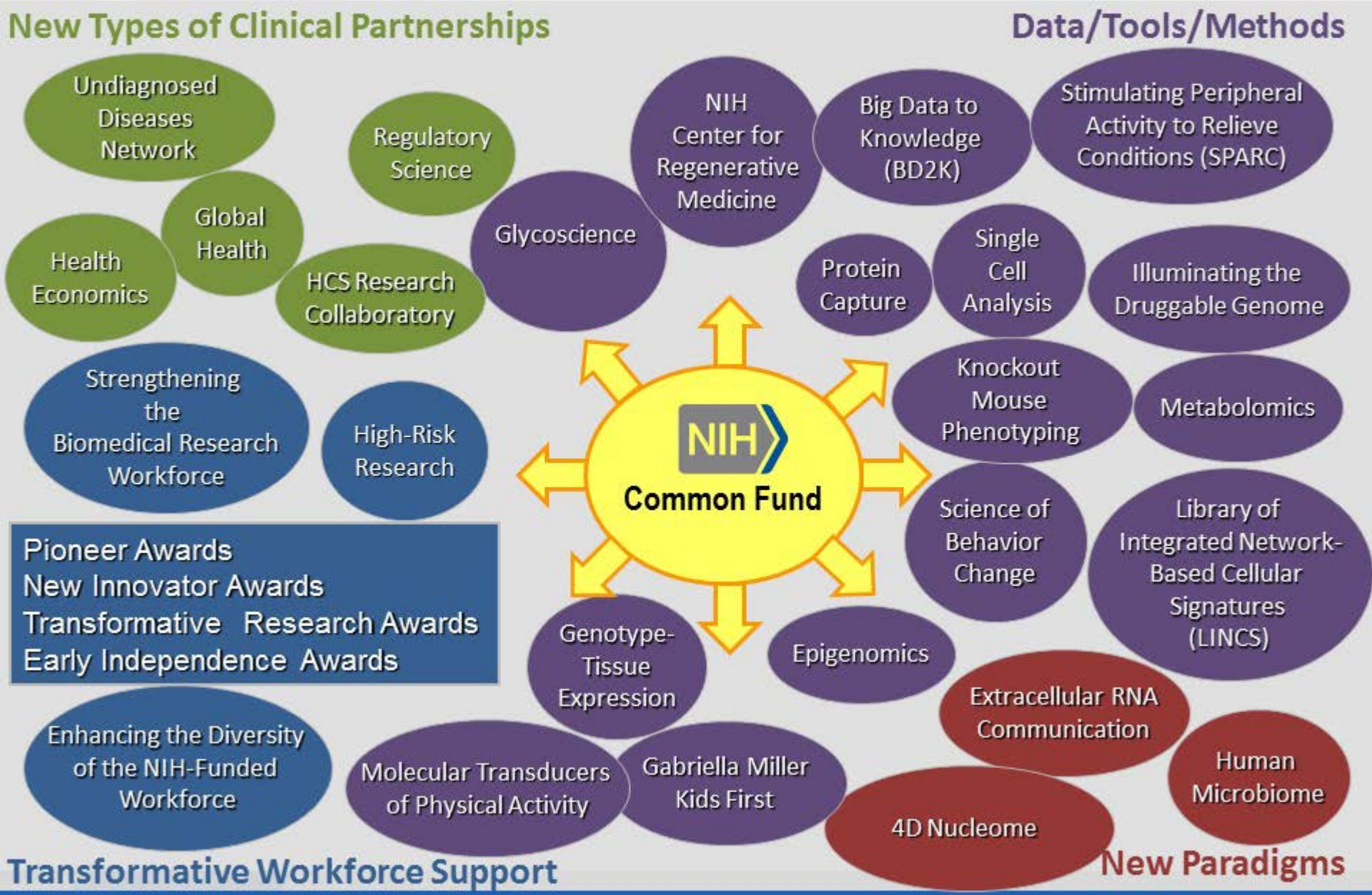
Transformative: Programs are expected to have **exceptionally high and broadly applicable impact.** They should be relevant to many diseases. They should set new standards for research or clinical practice, create entirely new approaches to research or clinical care, or establish new biological paradigms.

Catalytic, Short Term and Goal-driven: Programs must achieve - not just work toward - a goal. They have deliverables - data sets, tools, technologies, approaches, or fundamental principles of biology, etc – that can be achieved within 5-10 years.

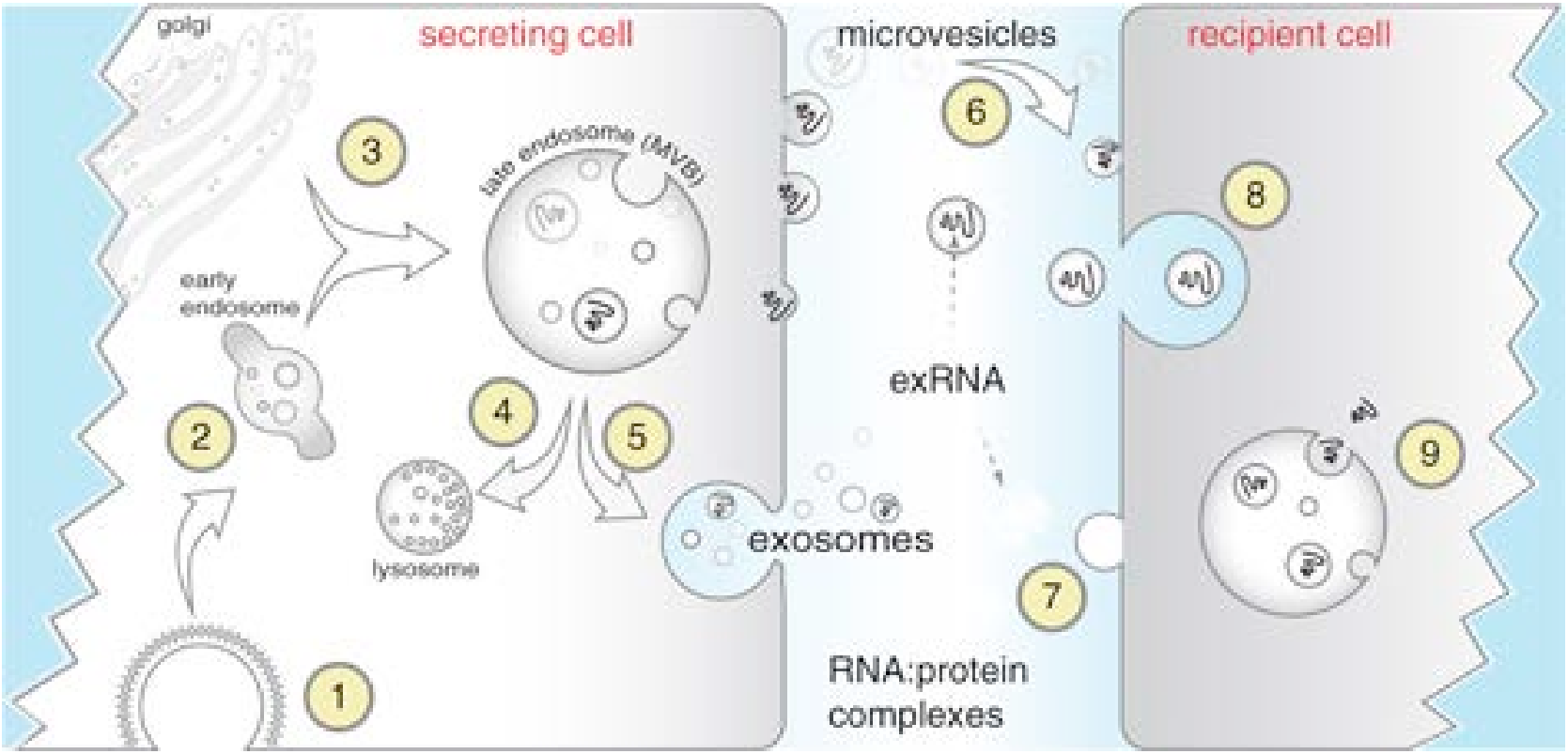
Synergistic/Enabling: Programs should be **valued-added** to the NIH Institutes and Centers, with the output enabling the mission of NIH.

Novel: Programs should provide new solutions to specific challenges.

Current Common Fund Programs (FY16)

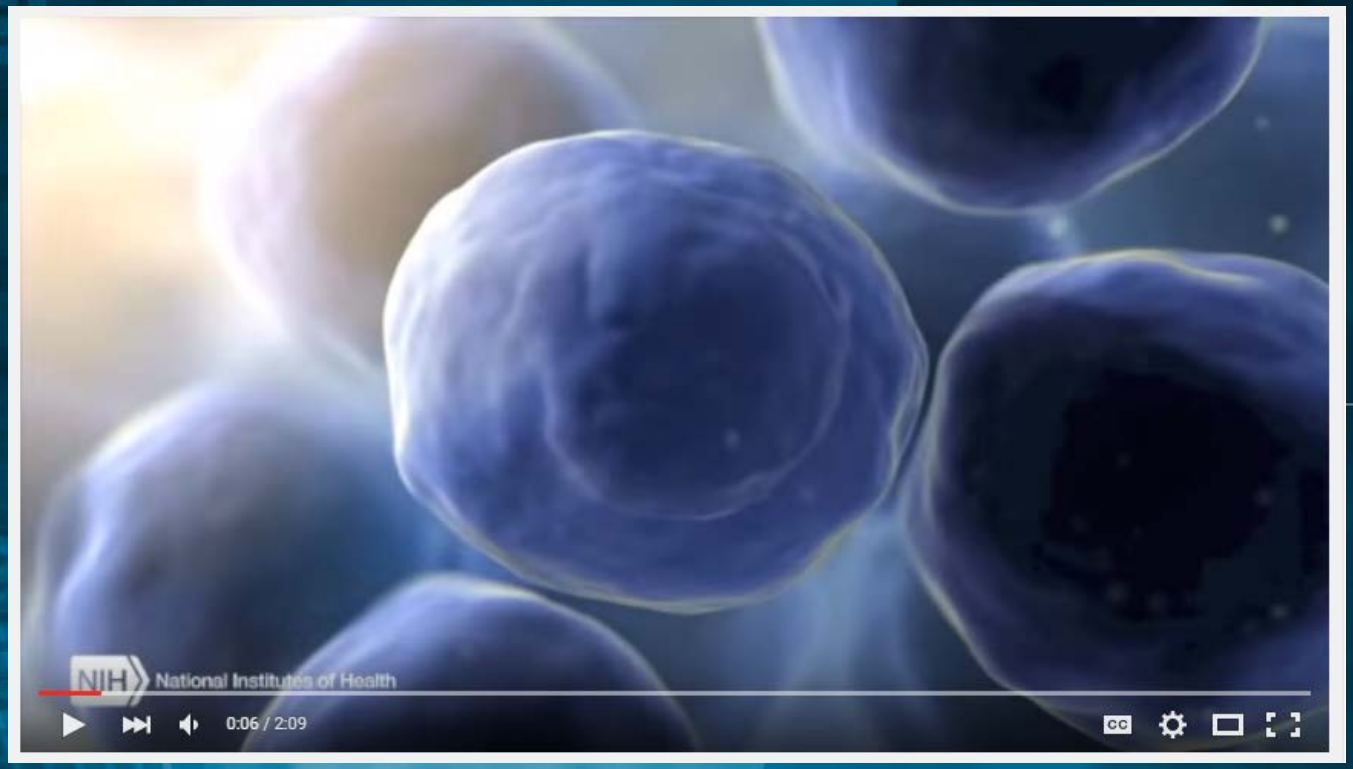


exRNA in Vesicles and Lipoprotein Complexes – A Paradigm Shift



- RNA function is cell autonomous, especially given the levels of RNAse in extracellular fluids and plasma that function to destroy foreign RNAs, most commonly viral RNA. RNA can be secreted and remain stable over long periods of time.
- Recognized signaling molecules are lipids, phospholipids, amino acids, monoamines, proteins, glycoproteins, or gases, such as hormones, neurotransmitters, and cytokines. exRNA mediate cell-to-cell communication.

Extracellular RNA Communication Program

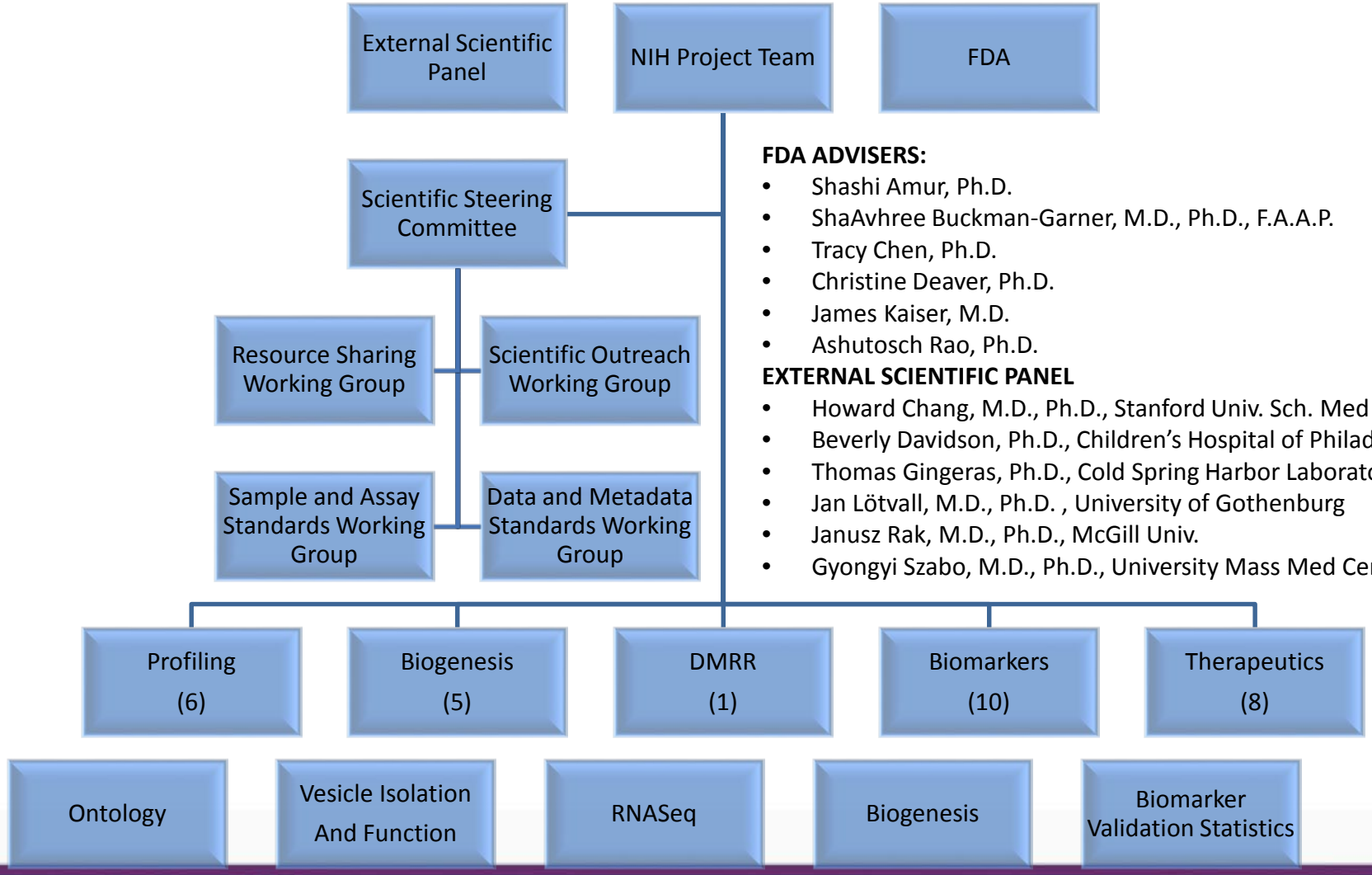


This video is available at https://www.youtube.com/watch?v=bfMg3RhxNm8

NIH Common Fund: 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
- NIH investment of $130 million over six years (2013-2018)

Extracellular RNA Communication Consortium



FDA ADVISERS:

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- Janusz Rak, M.D., Ph.D., McGill Univ.
- Gyongyi Szabo, M.D., Ph.D., University Mass Med Center

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

- GOAL: To support data management, data integration and analyses, data deposition, and resource sharing within ERCC.
- Deliverables: Provide community-wide resource for exRNA standards, protocols, and data through the development of an exRNA Portal

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

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

- GOAL: To determine the principles that guide the selection of regulatory RNA molecules for extracellular transport and to determine the function of these extracellular RNAs (exRNAs)
- Includes:

  (1) exRNA biogenesis, (2) biodistribution, (3) uptake of exRNA by target cells, and (4) the physiological impact of delivered exRNA in target cells/ tissues
- Deliverables: Enabling tools, technologies, bioreagents, and analytical approaches that elucidate pathways by which exRNAs are packaged, secreted, transported, and taken up by recipient

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

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

Reference Profiles of Human Extracellular RNA (U01)

- Goal: To develop reference profiles for non-coding extracellular RNAs from diverse set of healthy human body fluids
  - Generate a comprehensive catalog that is inclusive of exRNAs secreted in extracellular vesicles or bound to carriers.
  - Capture of trans-kingdom exRNAs such as those derived from diet or microbiome.
- Deliverable: exRNA Atlas

Reference Profiles of Human Extracellular RNA (U01)

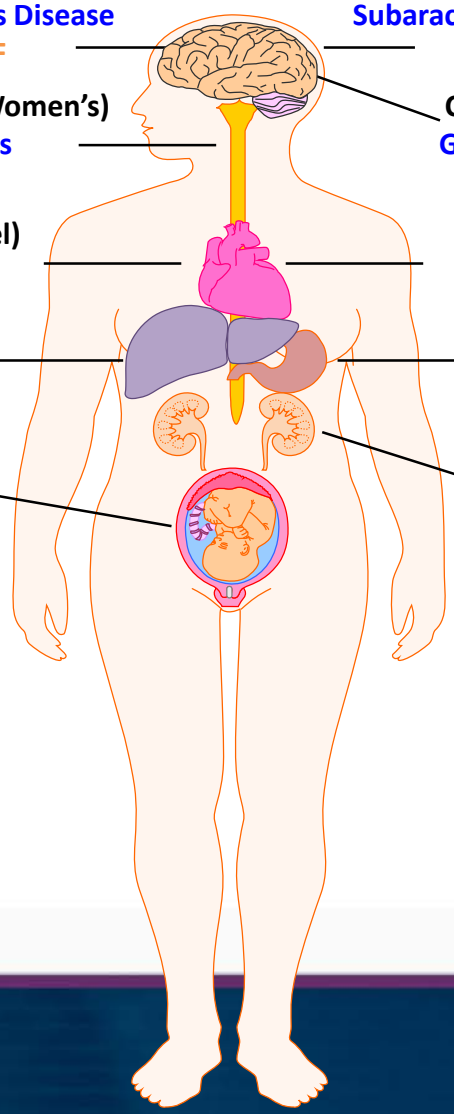
FREEDMAN, JANE E (contact) GERSTEIN, MARK BENDER MUKAMAL, KENNETH JAY ODONNELL, CHRISTOPHER J	**UNIV OF MASSACHUSETTS MED SCH WORCESTER**	**Racial and Ethnic Diversity in Human Extracellular RNA**
GALAS, DAVID J. (contact) NICKERSON, DEBORAH A WANG, KAI	PACIFIC NORTHWEST RESEARCH INSTITUTE	Reference Profiles of Extracellular RNA in 4 Body Fluids of Healthy Humans
GHIRAN, IONITA CALIN	BETH ISRAEL DEACONESS MEDICAL CENTER	Impact of circadian rhythm in obtaining reference profiles of exRNAs in healthy in healthy individuals
LAURENT, LOUISE C	UNIVERSITY OF CALIFORNIA SAN DIEGO	Reference Profiles of ExRNAs in Normal Human Pregnancy
TEWARI, MUNEESH	UNIVERSITY OF MICHIGAN AT ANN ARBOR	Reference Profiles of ExRNA in Biofluids from Well-Defined Human Cohorts
WOODRUFF, PRESCOTT G (contact) ERLE, DAVID J	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA

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

- GOAL: To identify and quantify exRNA-based biomarkers derived from human body fluids
- Utilizes UH2/UH3 Phased Cooperative Agreement mechanism
  - UH2 exploratory and discovery phase
  - UH3 phase for biomarker validation and qualification studies
- MOU with FDA to guide investigators through second phase

CARTER, BOB S (contact) HOCHBERG, FRED H	UNIVERSITY OF CALIFORNIA SAN DIEGO	exRNA Biomarkers for Human Glioma
DAS, SAUMYA (contact) KWONG, RAYMOND Y ROSENZWEIG, ANTHONY SABATINE, MARC S	BETH ISRAEL DEACONESS MEDICAL CENTER	Plasma miRNA predictors of adverse mechanical and electrical remodeling after MI
FREEDMAN, JANE E	UNIV OF MASSACHUSETTS MED SCH WORCESTER	Extracellular RNAs: Biomarkers for Cardiovascular Risk and Disease
HUENTELMAN, MATTHEW J (contact) ADELSON, P. DAVID SPETZLER, ROBERT	TRANSLATIONAL GENOMICS RESEARCH INST	exRNA signatures Predict Outcomes after brain injury
LAURENT, LOUISE C	UNIVERSITY OF CALIFORNIA SAN DIEGO	ExRNAs for Early Identification of Pregnancies at Risk for Placental Dysfunction
PATEL, TUSHAR	MAYO CLINIC JACKSONVILLE	Extracellular non-coding RNA biomarkers of hepatocellular cancer
SAUGSTAD, JULIE ANNE (contact) QUINN, JOSEPH F	OREGON HEALTH AND SCI UNIVERSITY	Clinical Utility of MicroRNAs as Diagnostic Biomarkers of Alzheimers Disease
TUSCHL, THOMAS (contact) SUTHANTHIRAN, MANIKKAM	ROCKEFELLER UNIVERSITY	Clinical utility of extracellular RNA as marker of kidney disease progression
WEINER, HOWARD L	BRIGHAM AND WOMEN'S HOSPITAL	Circulating MicroRNAs as Disease Biomarkers in Multiple Sclerosis
WONG, DAVID T	UNIVERSITY OF CALIFORNIA LOS ANGELES	Clinical Utility of Salivary ExRNA Biomarkers for Gastric Cancer Detection

exRNA UH2/UH3 Biomarker Projects and Their Targets



Saugstad, Quinn (OHSU)
Alzheimer's Disease
CSF

Jensen, Huentelman (TGen)
Subarachnoid Hemorrhage
CSF

Weiner (Brigham and Women's)
Multiple Sclerosis
CSF, Plasma

Carter, Hochberg (UCSD)
Glioblastoma multiforme
CSF

Das, Rosenzweig (Beth Israel)
Myocardial Infarction
Plasma

Freedman U Mass)
Cardiovascular Disease
Plasma

Patel (Mayo)
Hepatocellular Cancer
Plasma

Wong (UCLA)
Gastric Cancer
Saliva

Laurent (UCSD)
High Risk Pregnancy
Preeclampsia
Amniotic Fluid, Serum

Tuschl, Suthanthiran (Rockefeller U)
Kidney Disease
Urine

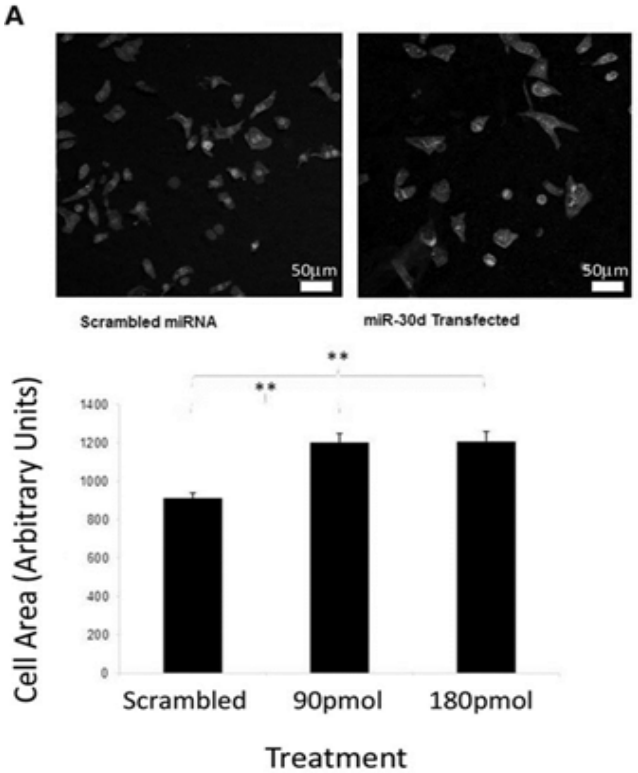
Plasma miRNA Predictors of Adverse Mechanical and Electrical Remodeling After Myocardial Infarction

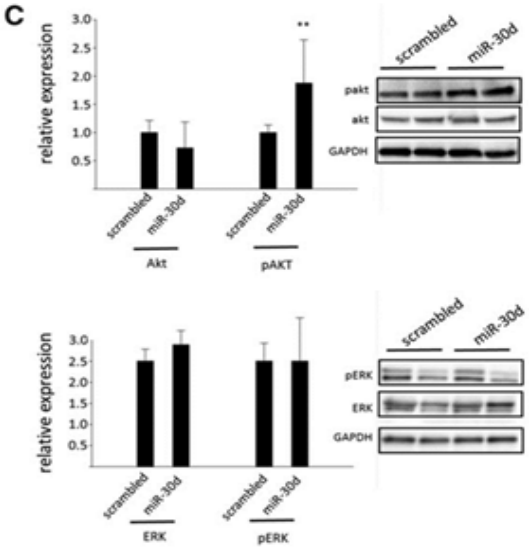
- Half a million cases of heart failure and 300,000 cases of sudden cardiac arrest per year
- These conditions are related to changes in the structure and function of the heart — called remodeling — that follow a heart attack
- Current tests to predict which patients are at risk for these complications are not accurate enough

MI Biomarker project: PI: Saumya Das and Anthony Rosenzweig
Beth Israel Deaconess Medical Center

- Discovered a novel heart failure (HF)-associated microRNA-30d
  Circulation, 2015, 131: 2202-2216
- miR-30d is enriched in the coronary sinus of patients with HF and elevated in myocardial tissue in canine HF
- MiR-30d appears to be regulated by wall stress, novel exRNA biomarker
- Assessment of miR-30d levels in a larger population of patients with HF could constitute a major step forward the disease management

Functional Role of miR-30d





miR-30d mediates adaptative hyperthophy in cultured cardiomyocytes Cultured rat CMs were transfected with either a sham or a miR-30d mimic.

miR-30d effects on hypertrophic signaling pathways. Protein lysates from CMs subjected to miR-30d mimic or scramble transfection for 24 hours were harvested and assessed for levels of phosphorylated (p) and total levels of kinases implicated in cardiac hypertrophy

Circulation 2015;131:2202-2216

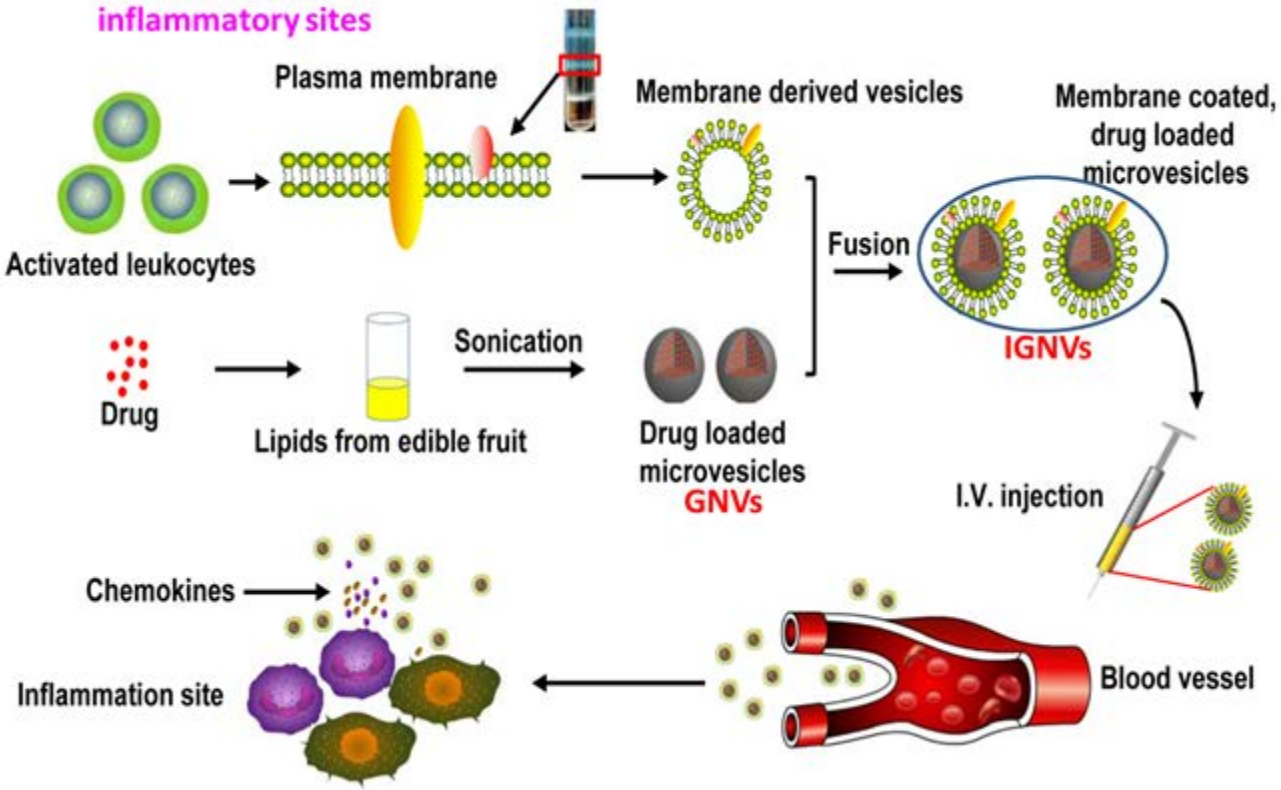
Clinical Utility of Extracellular RNA for Therapy Development (UH2/UH3)

- GOAL: To develop and advance the therapeutic utility of exRNAs, RNA-containing extracellular vesicles (EVs) or exosomes, and/or exRNA-bound to other carrier molecules, such as lipoproteins and RNA-binding complexes.
- Utilizes UH2/UH3 Phased Cooperative Agreement mechanism.
  - UH2 phase consists of proof of concept studies
  - UH3 phase consists of pre-clinical optimization, safety and toxicology studies leading to an IND
- MOU with FDA to guide investigators through second phase

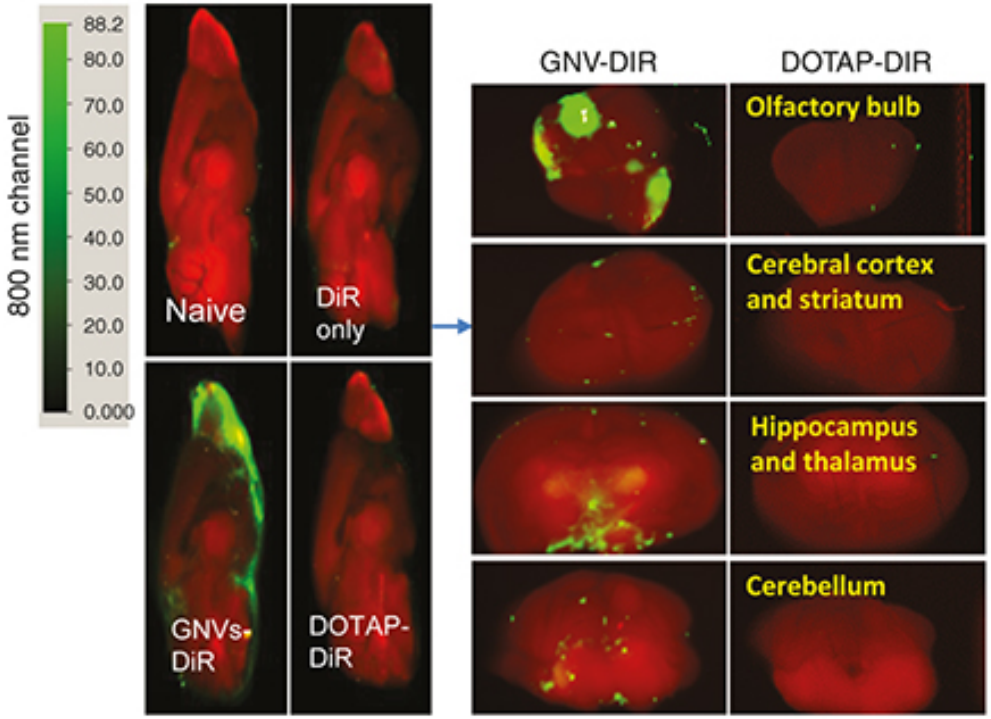
ABDEL-MAGEED, ASIM B	TULANE UNIVERSITY OF LOUISIANA	Targeting Tumor-Derived exRNA-Containing Microvesicles by High Throughput Screeni
ARONIN, NEIL	UNIV OF MASSACHUSETTS MED SCH WORCESTER	Exosome based therapeutics in Huntingtons disease
KRAIG, RICHARD P	UNIVERSITY OF CHICAGO	Exosome RNA-Therapeutics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

Noninvasive therapeutic approach for treating brain-related disease through intranasal delivery

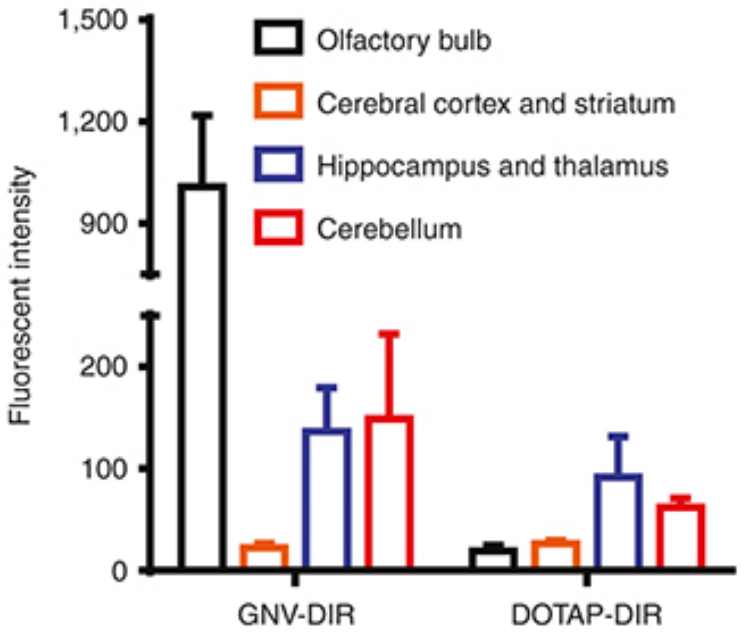
- Grape fruit-derived nanovectors delivering therapeutic miR17 through an intranasal route inhibit brain tumor progression
- PI: Huang-Ge Zhang, University of Louisville



Intranasal administration of GNVs facilitates localization to the brain



12h of postintranasal administration. Representative images from the center of the brain



Mol. Therapy, 2015, 188

Detection of GNV as early as 1.5 h after intranasal administration

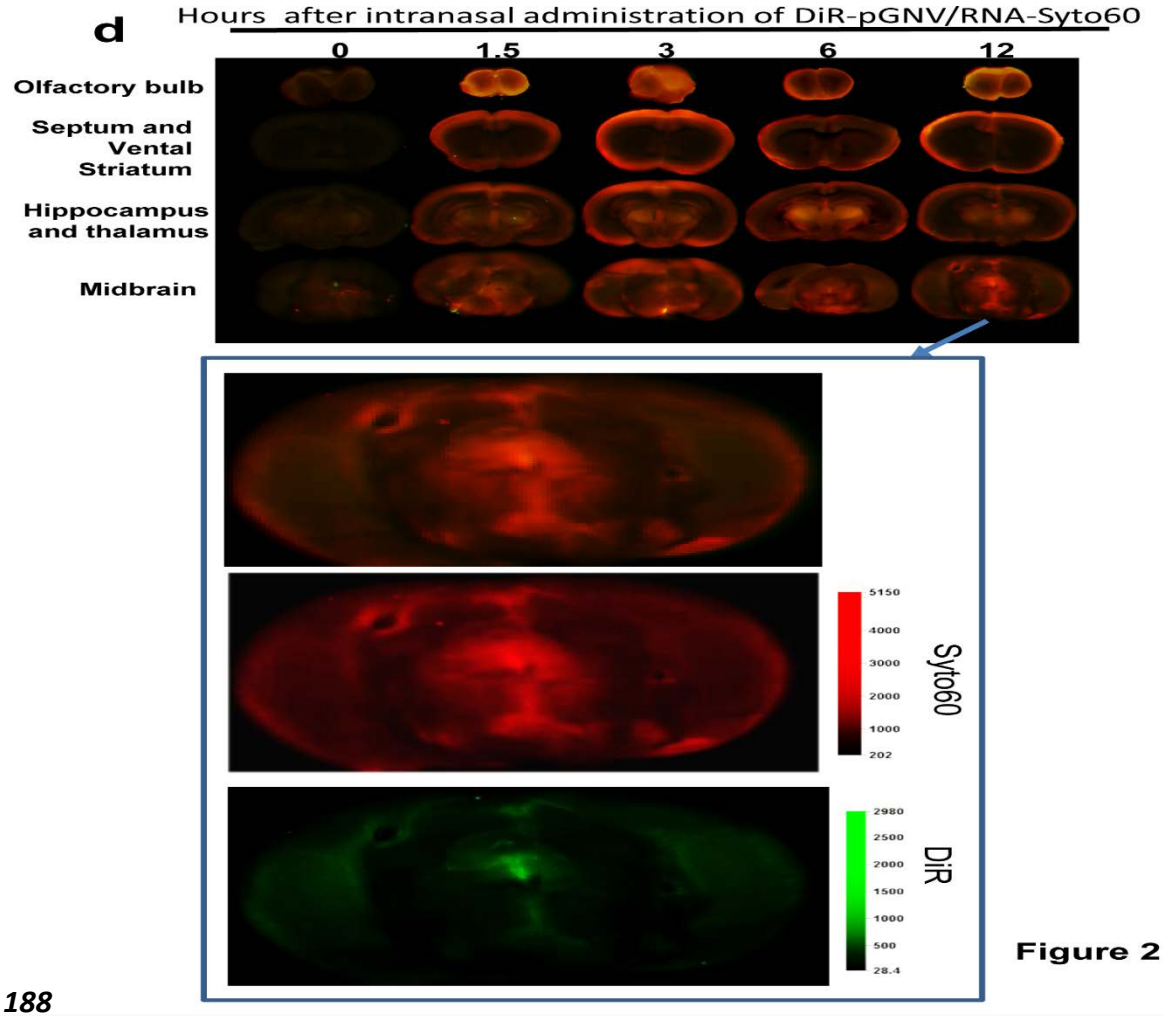


Figure 2

Mol. Therapy, 2015, 188

Intranasal targeted delivery of miR17 encapsulated in FA-pGNVs inhibits GL26 tumor growth

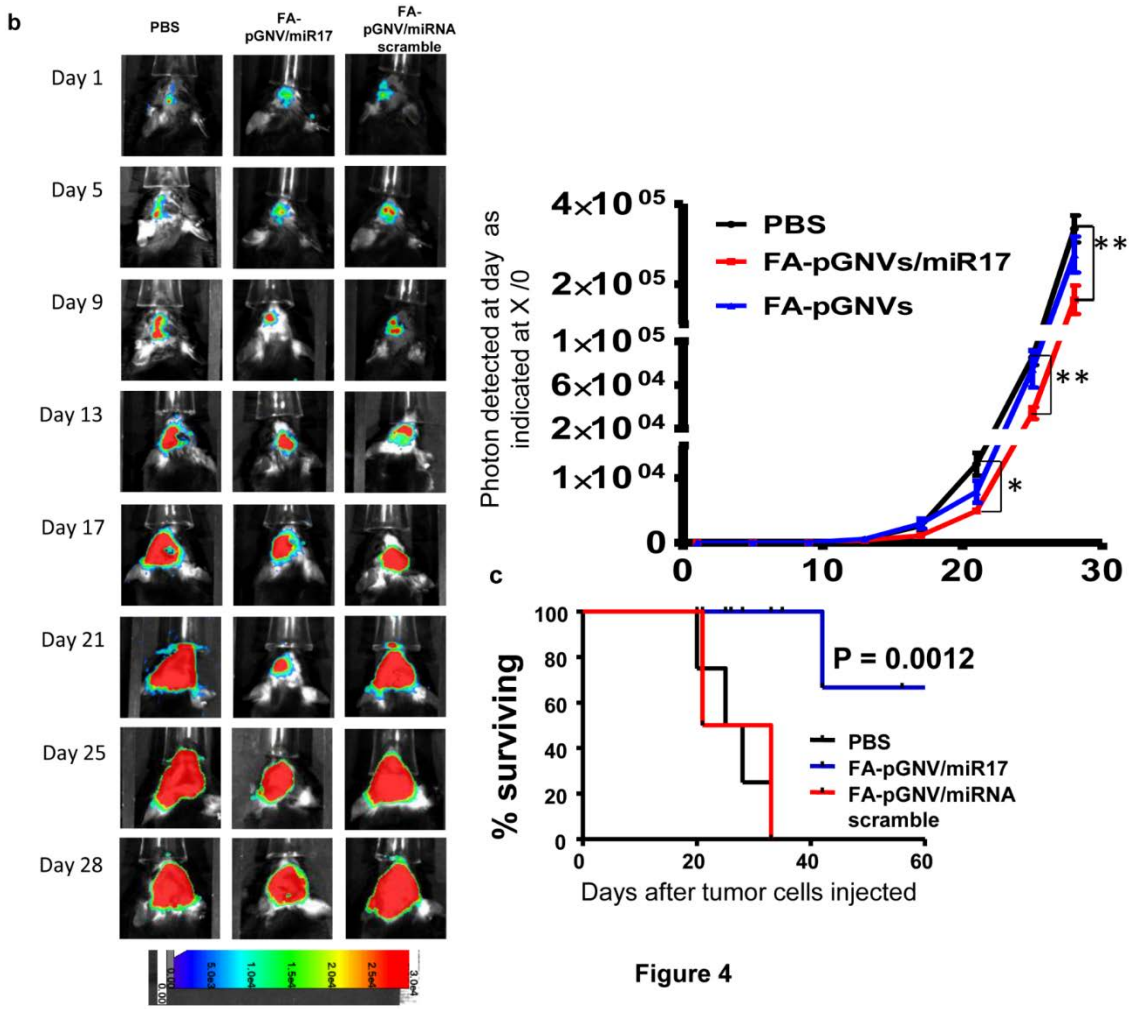


Figure 4

Mol. Therapy, 2015, 188

Clinical Trials Using Plant Exosomes

- ClinicalTrials.gov Identifier: NCT01294072, "Study Investigating the Ability of Plant Exosomes to Deliver Curcumin to Normal and Colon Cancer Tissue"
  - Previous clinical trials conducted with oral curcumin have demonstrated only limited bioavailability even at very high doses of 8-12 grams per day
  - Curcumin is the yellow pigment of turmeric, a natural product with diverse biological activities
  - Principal Investigator: Donald M Miller, MD, Ph.D., James Graham Brown Cancer Center, University of Louisville

- ClinicalTrials.gov Identifier: NCT0166884 "Edible Plant Exosome Ability to Prevent Oral Mucositis Associated With Chemoradiation Treatment of Head and Neck Cancer"
  - Evaluate grape-derived exosomes as an important anti-inflammatory agent to reduce the incidence of oral mucositis during radiation and chemotherapy treatment for head and neck tumors
  - Principal Investigator: Rebecca Redman, MD, James Graham Brown Cancer Center, University of Louisville

Trans-NIH ERCC Project Team

Co-Chairs:
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Pothur R. Srinivas, Ph.D., M.P.H. (NHLBI)

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Sundar Venkatachalam, Ph.D. (NIDCR)