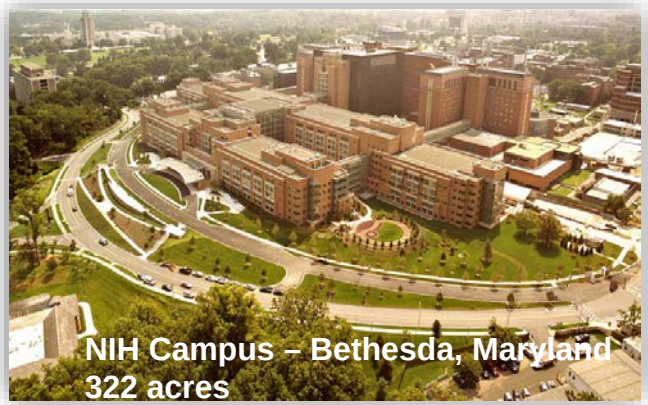
NIH's Investments in Research Innovation: Program Snapshots

Stephanie Morris, Ph.D.
National Institutes of Health

2018 Biophysics Program Review
Air Force Office of Scientific Research
April 16-20, 2018

National Institutes of Health (NIH): 27 Institutes and Centers

NHGRI NIA NIDA



NINDS NIDCD NIMH

NEI NIAAA CIT

NINR NLM NIDDK

FIC CSR NIBIB

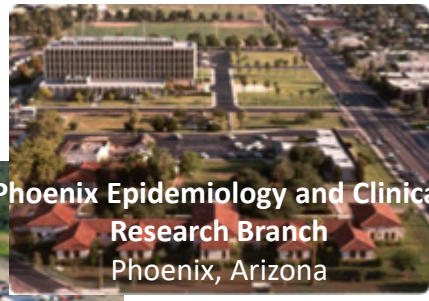
NIGMS NICHD CC

NIMHD NIDCR NIEHS

NIAMS NCCAM NIAID NCI NHLBI NCATS

NIH Budget ~$33.1 Billion (FY17)

- *~80% of budget for extramural support*
- *~10% internal NIH labs and Clinical Center*
- *~50,000 competitive grants and contracts*



NIH Office of the Director

- Central Office of the NIH
- Responsible for setting NIH policy and for planning, managing, and coordinating programs and activity of all the NIH components: *Research, Funding, and Coordination, Communications*, *Policy*, and *Administration and services*.
- Research, Funding and Coordination Component
  - Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
    - Mission: Identifying emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research
    - **Office of Strategic Coordination**

Outline

- Innovation in Technologies for Cancer
  - Nanotechnology
    - NCI Alliance for Nanotechnology in Cancer Program
- Cross-Cutting Trans-NIH Programs
  - NIH Common Fund
    - Somatic Cell Genome Editing Program

National Cancer Institute's (NCI's) Mission

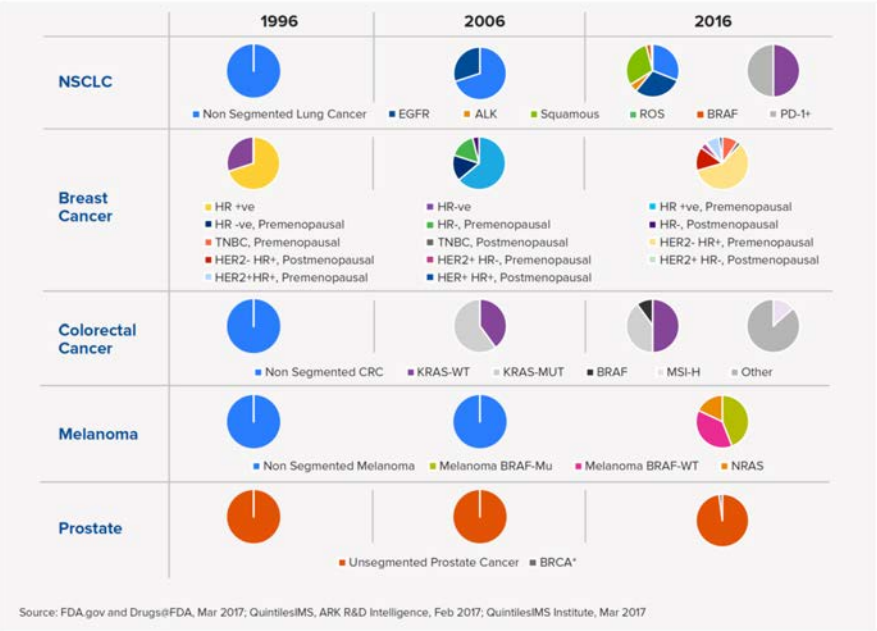
To help people live longer, healthier lives by supporting research to reduce the incidence of cancer and to improve the outlook for patients who develop cancer

www.cancer.gov

For funding, application information: grants.nih.gov

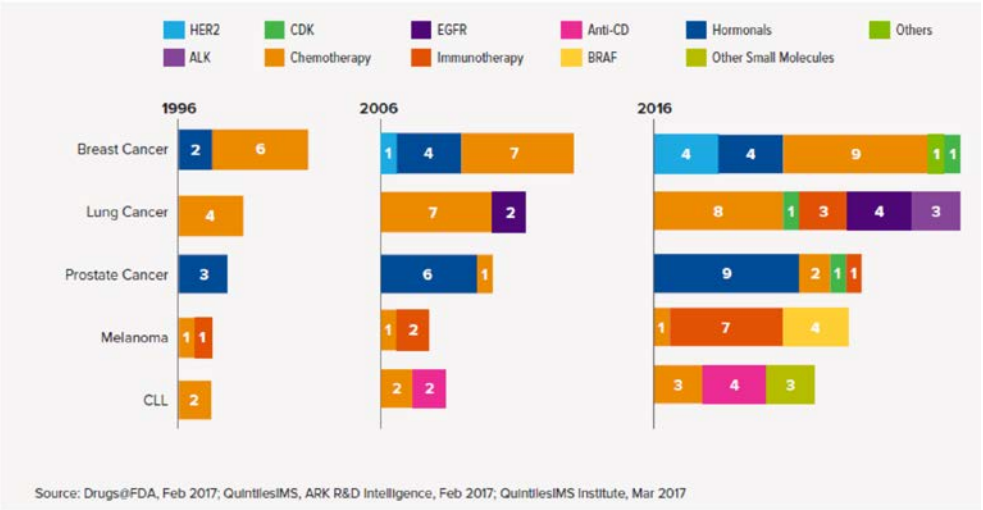
Cancer and Increasing Number of Targets

- Progressively redefined over the past 20 years – from organ-specific to pathway specific
- Due to epigenomics, genomics, and proteomics projects such as:
  - Epigenomics Mapping Consortium
  - The Cancer Genome Atlas
  - Clinical Proteomic Tumor Analysis Consortium
- Learning more about tumor heterogeneity and classification of tumor subtypes; shared molecular abnormalities between completely different cancers are being discovered



- Identifying new epigenetic, genetic, and protein cancer targets
  - Increasing number of biomarkers
  - Increasing number of treatment options
- Adapting emerging technologies that enable these discoveries, as well as new treatments/diagnostics

Number of Treatment Options (Selected Tumors, 1996-2016)



NCI Center for Strategic Scientific Initiatives

"To create and uniquely implement exploratory programs focused on the development and integration of advanced technologies, trans-disciplinary approaches, infrastructures, and standards to accelerate the creation of publicly available, broadly accessible, multi-dimensional data, knowledge, and tools to empower the entire cancer research continuum for patient benefits."

IMAT Innovative Molecular Analysis Technologies

2003, 2007, 2011, 2013, 2014

CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER

2005, 2010, 2015

PHYSICAL SCIENCES in ONCOLOGY

2008, 2013*

NCI Alliance for Nanotechnology in Cancer

2004, 2008, 2014#

THE CANCER GENOME ATLAS

2005, 2008

Cancer Target Discovery & Development (CTD²)

2010

https://cssi.cancer.gov/

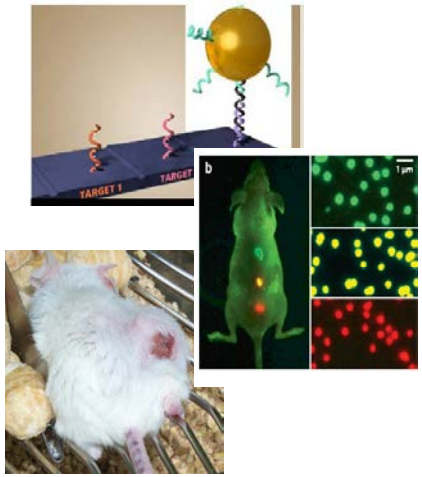
Provocative Questions Initiative

2011, 2014

Dates indicate approval(s) by NCI Board of Scientific Advisors; Program moved to: *NCI Division of Cancer Biology, #NCI Division of Cancer Treatment and Diagnosis

Cancer Nanotechnology: The Opportunity

- Properties of materials at nanometer scale allow for the creation and use of functionalized structures, devices, and systems with novel properties
- Combination of innovation in nanomaterials and cancer biology allows to develop new interventions for cancer



Therapeutics and Delivery

- Nanoparticle-based delivery vehicles and therapeutics
  - New molecularly targeted drugs and delivery of nucleic acids; CRISPR systems
  - Use in functional validation of cancer targets
  - Photodynamic therapy
  - Mechanical cell disruption using magnetic particles
  - immunotherapeutics
- Treatment Monitoring

Detection and Diagnosis

- Techniques to monitor and capture circulating tumor cells from blood
- Modular diagnostics – work with bodily fluids, such as blood, serum, urine, or saliva
- Multifunctional capabilities – one platform capable of detecting nucleic acid and protein

Bringing Nanotechnology to Cancer Research and Oncology: NCI Alliance for Nanotechnology in Cancer Network

Utilize multidisciplinary team science to bring together physical scientists, chemists, engineers with cancer biologist and oncologists to develop nanotechnology-based solutions to cancer

http://nano.cancer.gov

2005 CaNanoPlan Published

NCL Launches

Phase I (Pilot) Awarded

Evaluation and Update (2007)

- Scientific Output
  - Over 600 pubs
- Clinical Translation
  - 50 companies
  - Over 200 patent apps
  - 8-10 clinical trials

Program Renewed

2010 CaNanoPlan Published

Phase II Kick-Off

TONIC Consortium with industry formed

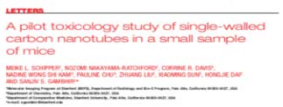
Evaluation and Update (2013)

- Scientific Output
  - Over 1500 pubs
- Clinical Translation
  - Over 75 companies
  - 300 patent apps
  - 17 clinical trials

Program Renewed

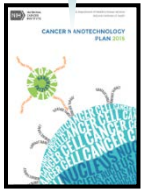
Phase III Kick-Off

2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015



Nano Diagnostics

Nano Therapy



2015 CaNanoPlan Published

Phase III Alliance

Moving practical cancer interventions forward (*translational focus*)…

Centers of Cancer Nanotechnology Excellence (CCNEs) are expected to develop nanotechnology-based comprehensive solutions to significant problems in cancer biology and/or oncology and produce cancer care relevant applications with clinical utility.

+

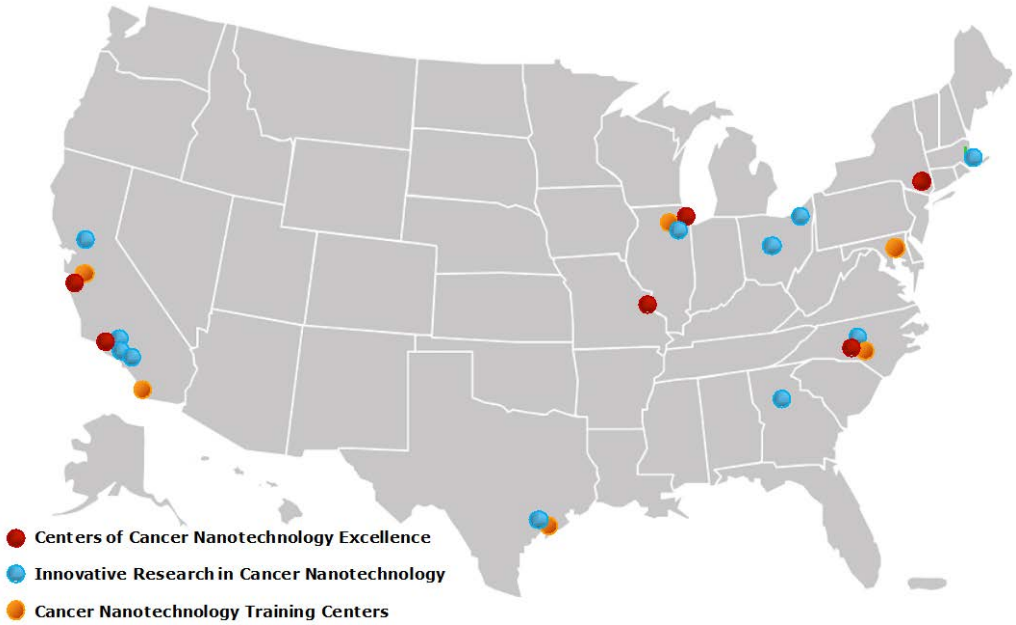
Cancer Nanotechnology Training Centers (CNTCs)

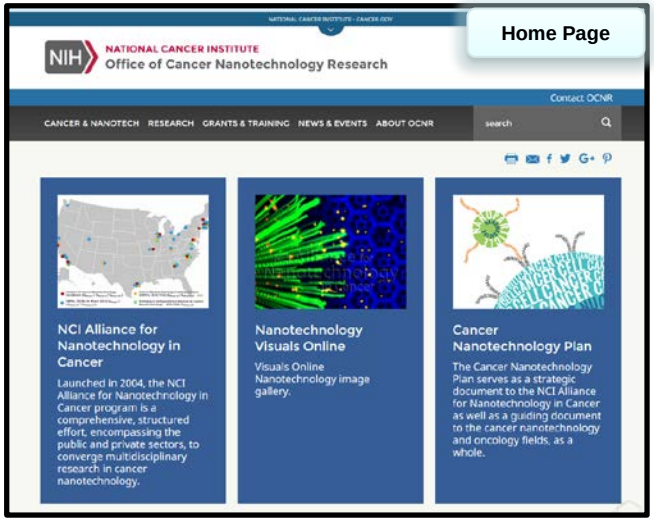
Innovative Research in Cancer Nanotechnology (IRCNs) awards will address major barriers in cancer biology and/or oncology using nanotechnology and emphasize the development of fundamental understanding of the processes pertinent to the use of nanotechnology in cancer.

…while solidifying fundamental knowledge (*to support translation*)

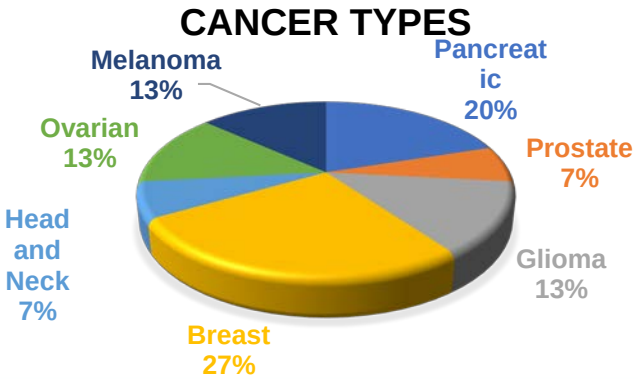
Phase III Awards – September 2017

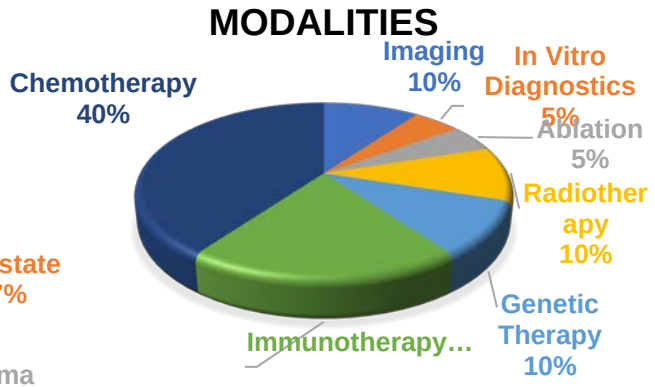
https://www.cancer.gov/sites/ocnr/research/alliance



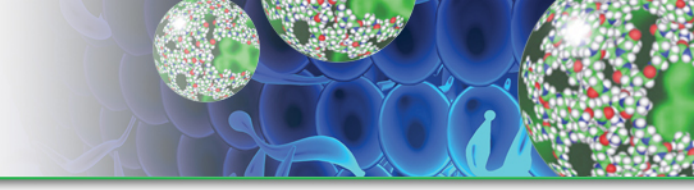


CCNE	IRCN		CNTC
Stanford	UC Davis	UCLA	Stanford
Cal Tech/UCLA	UCLA	Masimo, Inc	Northwestern
Northwestern	U. Chicago	MD Anderson	MD Anderson
Wash. U.	Case Western	Mass. Gen/Harvard	Johns Hopkins
MSKCC/Cornell	Emory U.	Ohio State	UNC Chapel Hill
UNC Chapel Hill	UNC Chapel Hill	Case Western	UC San Diego
		Iowa State	
		UT Southwestern	





CCNEs

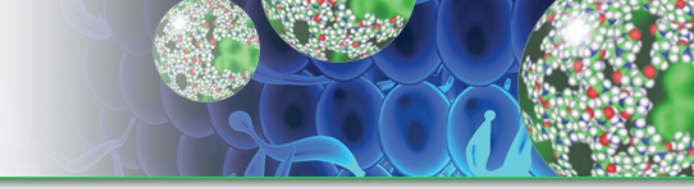


PIs	Tumor types	Overall Scientific Focus	New materials and devices	Drug(s), treatment(s) used in the study
Sam Gambhir and Shan Wang *Stanford University*	NSCLC and prostate	Develop and utilize in vitro nanosensors and in vivo molecular imaging tools to advance methods in earlier detection of aggressive cancers as well as monitoring response to therapies	Multiscale in vitro Dx, self-assembling/dis-assembling NPs (TESLA), US/PA nanobubbles	N/A (measuring response to several therapeutics)
James Heath and Michael Phelps *Caltech/UCLA*	GBM and melanoma	Design and develop nanotherapies and nanotech tools to guide selection of combination cancer immunotherapy and targeted therapy treatments	Polymeric Targeted NPs, in vitro Dx, nanobubble US imaging agents, mol nanotherapeutics	Erlotinib, novel immunotherapy-based solutions (targeted inhibitors, T cell specific)
Chad Mirkin and Leonidas Platanias *Northwestern University*	GBM and prostate	Design, synthesize, characterize, and develop spherical nucleic acid constructs as effective nanotherapeutic, single-entity agents for the treatment of glioblastoma multiforme and prostate cancers.	Spherical nucleic acids (SNAs)—gold, silica, and liposomal nanoparticles	IDH1 siRNA, toll-like receptor agonists, peptide antigens, anti-PD-1, anti-PD-L1
Samuel Achilefu and Gregory Lanza *Washington University*	Multiple myeloma	Primary objective is the development of nanoptherapeutics via unique drug delivery mechanisms and multidimensional treatment paradigms as well as noninvasive imaging methods to monitor subsequent treatment response for multiple myeloma.	Targeted micelles, titanocene (Tc), TiO2	Targeted cMyc-prodrugs, Cerenkov radiation PDT, anti-CD47 mAbs
Michelle Bradbury and Ulrich Wiesner *MSKCC/Cornell University*	Melanoma and glioma	Design, optimize, disseminate and translate a suite of ultrasmall (<10 nm) silica-organic hybrid nanoparticles with tunable size, brightness, and geometry for intraoperative imaging and to improve cancer localization, staging, and treatment, as well as the development of optimized therapeutic platforms	Core shell silica nanoparticles (C'dots)	Gefitinib or dasatinib nanoparticle drug conjugates (Gef-NDC or Das-NDC)
Leaf Huang and Joel Tepper *University of North Carolina*	NSCLC and melanoma	Exploit the host response through nanotechnology-based approaches for cancer disease management and treatment	Polymetformin, lipid-calcium-phosphate, PRINT nanoparticles; micelles	Nucleic acid-based (plasmid DNA, siRNA), Braf inhibitors, varied immune modifiers, anticancer agents (e.g., paclitaxel)

Nanotechnology-based Applications— e.g., *in vitro* nanosensors, in vivo molecular imaging tools to monitor treatment, intraoperative detection tools, and nanotherapies

https://www.cancer.gov/sites/nano/research/alliance/ccne

IRCNs…So Far

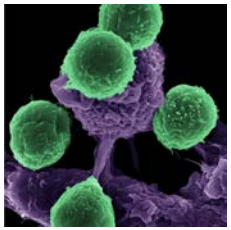


PIs	Tumor types	Project focus	New materials and devices	Drug(s) used in the study
Lily Yang *Emory U.*	Pancreatic	Ultra-small, targeted IONPs to break stroma and treat pancreatic cancer	Theranostic iron oxide with anti-fouling coating	Cisplatin, SN38 (active metabolite of irinotecan)
H-R. Tseng *UCLA*	Prostate	Programmable CTC capture devices to recover viable cells with high selectivity	CTC capture devices	N/A
E. Karathanasis *Case Western U.*	Glioma	Controlled release nanochains to eradicate tumor and stem cells in glioma	Nanochain-liposome constructs	Docetaxel, nitric oxide synthase inhibitor
Sasha Kabanov *UNC*	Triple negative breast	Mechanically deforming NPs for enhanced tumor penetration	Core shell nanogels	Cisplatin, NRT (tyrosine kinase inhibitor)
Kit Lam *UC Davis*	Glioma, breast	'Eye-pod' – eye tumor model to study tumor growth and tumor interaction with NPs	Nanoporhyrins	Doxorubicin
Andre Nel *UCLA*	Pancreatic	Synergistic delivery of GEM/PTX using targeted NPs	Mesoporous silica	GEM/PTX, irinotecan
Wenbin Lin *U. Chicago*	Head and neck	Deep tissue PDT using NPs as highly efficient photosensitizers	Nanoscale metal-organic frameworks (NMOFs)	PDT
Peixuan Guo *Ohio State U.*	Triple negative breast	Optimization of RNA nanoparticles to target TNBC and immunomodulation	RNA nanoparticles	N/A (siRNA and CpG)
D. Lapotko *Masimo Corp.*	Triple negative breast	New therapeutic approach based on intracellular mechanical impact generated by plasmonic nanobubbles	Gold NPs and liposomes	Doxil, Lipoplatin, and Radiotherapy
R. Weissleder *Mass General Hospital*	High and low grade serous ovarian	In vivo imaging analyses of therapeutic nanoparticles (TNP) to address key questions on PK/PD of nanoparticle, the role of TAM, and the prediction of treatment efficacy	Fluorescent companion drugs, dextran, polymeric, albumin bound, and intravital microscopy	Paclitaxel, docetaxel
G. Lopez-Berestein *MD Anderson*	High grade serous ovarian	NPs targeting monocyte-macrophage axis to enhance treatment efficacy	Dual assembly nanoparticles (DANPs)	MCP-1 siRNA, AXL aptamer, paclitaxel, cisplatin, zoledronic acid

Nanotechnology-based Applications—e.g., optimizing photodynamic therapy, understanding nanotherapeutics distribution and eyepod model

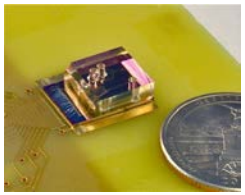
https://www.cancer.gov/sites/nano/research/alliance/ircn

Open Alliance Opportunity: IRCN Program



Victor Segura Ibarra and Rita Serda, Ph.D.
Houston Methodist

Innovative Research in Cancer Nanotechnology (IRCN) Awards
R01 Mechanism



David Issadore, Ph.D., Hyun Jung Chung, Ph.D., Hakho Lee, Ph.D., and Ralph Weissleder, M.D., Ph.D.
Harvard-MIT

PAR-17-240; $450K direct costs/year/award, up to 5 years of support

Fundamental Understanding of Nano-Bio Interactions

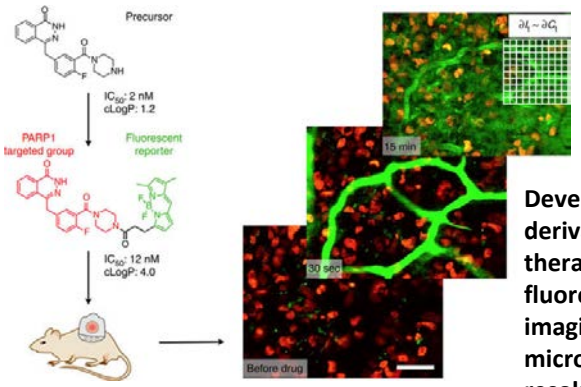
- Projects should be designed to enable multidisciplinary, fundamental research in cancer biology and/or oncology through the use of nanotechnology
  - Mechanisms of delivery to intended cancer targets and characterization of *in vitro* devices
  - Major barriers in cancer biology and/or oncology
  - Innovative use of nanotechnology to solve cancer biology/oncology problems
  - Nanotechnology is expected to provide a better solution than other currently available approaches
- Receipt dates (twice/year): Nov 21, 2017; **May 23, 2018**; Nov 20, 2018; May 23, 2019; Nov 21, 2019; May 21, 2020
- Funded projects become part of the NCI Alliance for Nanotechnology in Cancer Network
- If appropriate, work should aid in clinical translation, but clinical translation is not the ultimate goal of these awards

Imaging of Nanotherapeutic Drug Action

Ralph Weissleder, MD
Massachusetts General Hospital IRCN

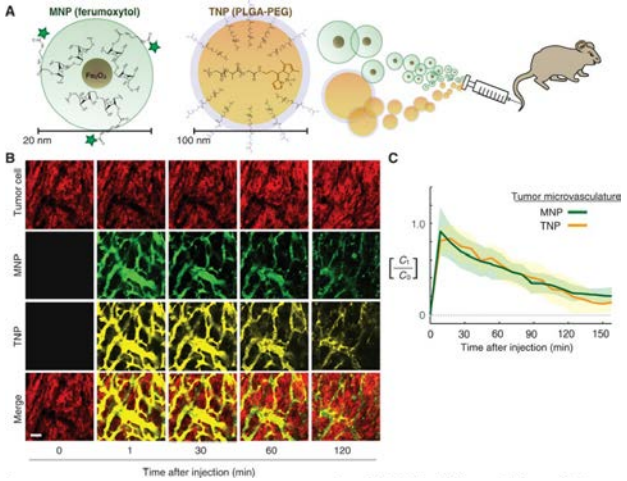
Background

- Project goal is to perform in vivo analyses of therapeutic particles at the single cell level to understand mechanisms of nanoparticle distribution and cellular response.
- Will answer questions concerning nanoparticle delivery to tumors
- Based on previous work on in vivo pharmacokinetic imaging of PARPi as model drug (**right**) and companion MRI NP (MNP) to predict therapeutic NP localization and efficacy (**below**)



Developed fluorescent derivative of PARPi to serve as therapeutically active fluorescent companion imaging drug; in vivo microscopy with subcellular resolution

Despite different sizes and materials, MNP able to predict areas of colocalization in tumor microenvironment with >85% accuracy; microvasculature >95% accuracy



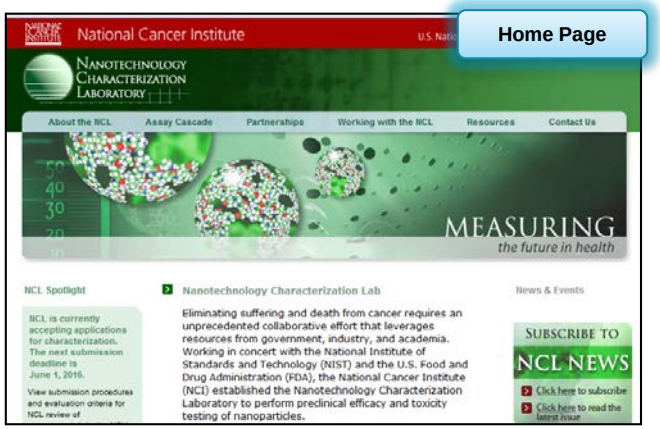
IRCN Project Goals

- Use of intravital microscopy to track clinical therapeutic NPs in vivo; labeled paclitaxel NP (both parts labeled) to quantitate cellular drug concentrations in ovarian cancer and host cells
- Analyze whether targeting enhances tumor cell killing in vivo at single cell level
- Determine if clinical imaging NPs can be clinical surrogates to predict therapeutic NP behavior in vivo—continuation of previous work with MNPs and MRI for testing of therapeutic NPs studies in earlier part of project
- As part of this project, will evaluate NPs from the work of another investigator funded through the Alliance

Thuber et al., *Nature Communications*, (2013)
Miller et al. *Science Translational Medicine.*, (2015)

NCI Translational Support

Nanotechnology Characterization Laboratory (NCL)



https://ncl.cancer.gov

Physicochemical ***In vitro*** ***In vivo***

- Evaluates a wide variety of cancer nanotechnology platforms
- Evaluated over 350 nanomaterials to date; characterize an average of 75 samples per year
- Accept applications for characterization request every quarter
- Provides submitters a preview of what FDA may be concerned with based on past experience

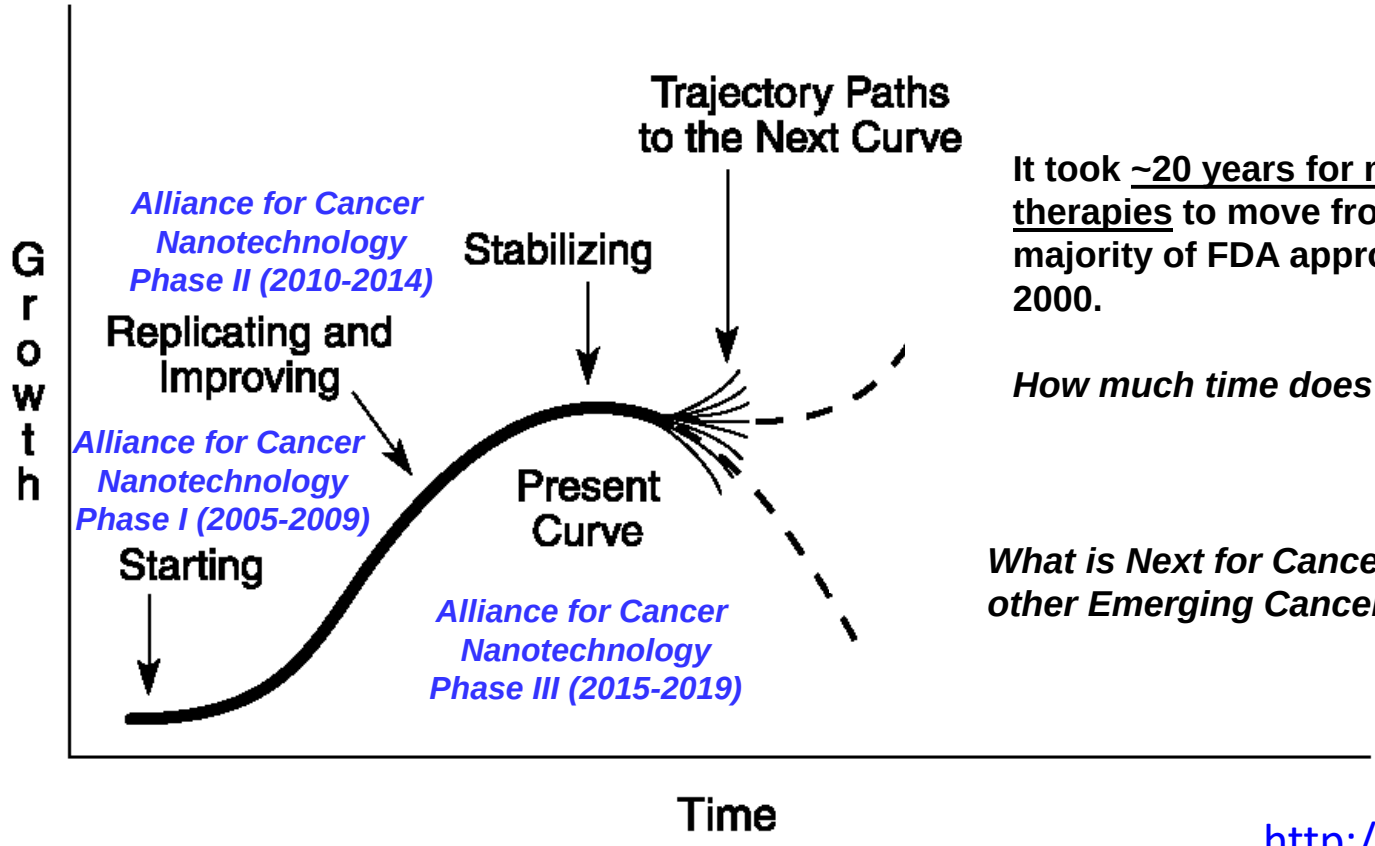
Cancer Nanotechnology Laboratory Data Portal (caNanoLab)

http://cananolab.nci.nih.gov

- Facilitates data sharing to expedite and validate use of nanomaterials in biomedicine
- Provides access to characterization data, protocols, and publications
- In house curator; data submission directly by users (access to data private or public)
- caNanoLab software available for installation of local instances
- Houses 1200+ sample records, 1900 publications, 50+ protocols

Evolution of New Technologies: Always Looking Ahead

Nanomedicine – NCI's Cancer Nanotechnology



It took ~20 years for monoclonal antibody therapies to move from the lab to the clinic – majority of FDA approval occurred after year 2000.

How much time does nanotechnology need?

What is Next for Cancer Nanotechnology and other Emerging Cancer Technologies?

http://nano.cancer.gov

Outline

- Innovation in Technologies for Cancer
  - Nanotechnology
    - NCI Alliance for Nanotechnology in Cancer Program

- Cross-Cutting Trans-NIH Programs
  - NIH Common Fund
    - Somatic Cell Genome Editing Program

Origins of the Common Fund

2004: NIH Roadmap is launched

2006: Congress unanimously reauthorizes NIH

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.

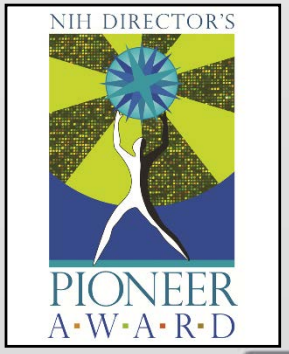
This Act may be cited as the "National Institutes of Health Reform Act of 2006".

TITLE I—NIH REFORM

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

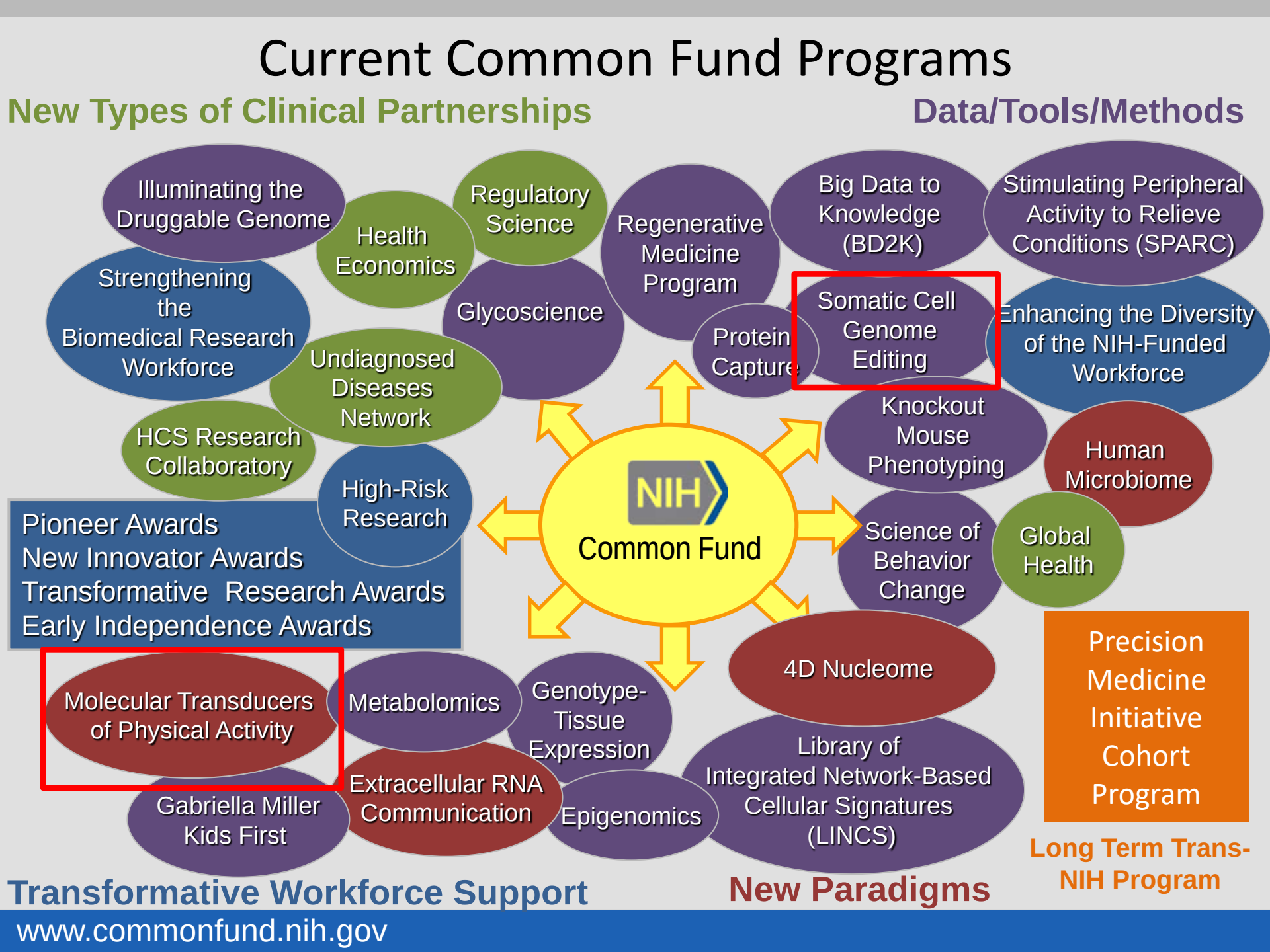
Criteria for Common Fund Programs

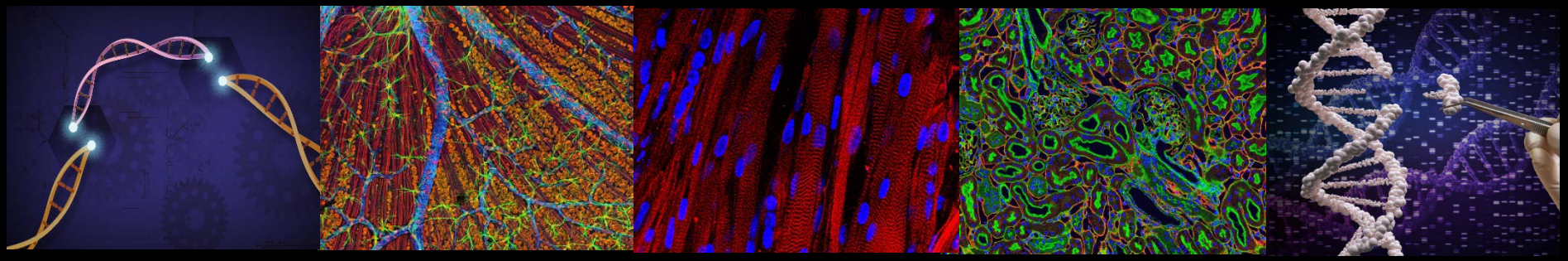
- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic**: Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions 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



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

Current Common Fund Programs



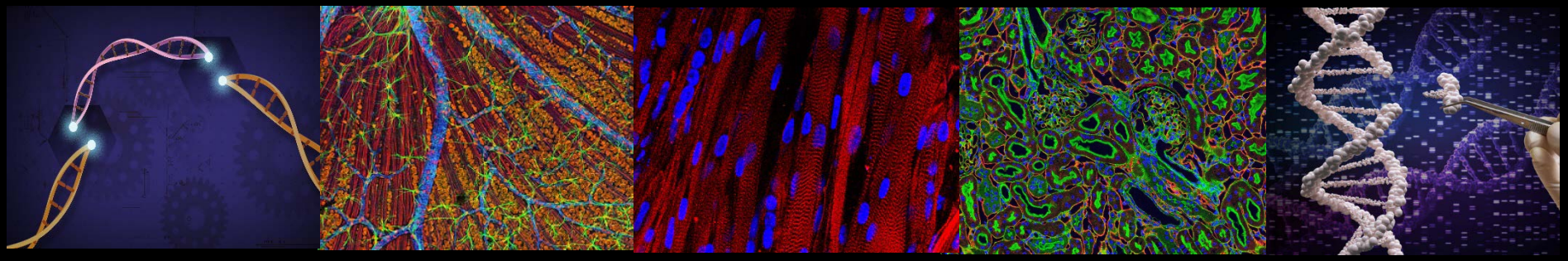


SCGE Program Goals

Lower the Barriers for New Genome Editing Therapies by:

- Testing Genome Editing Reagents and Delivery Systems in Better Animal Models
- Assessing Unintended Biological Effects
- Improving *In Vivo* Delivery of Genome Editing Machinery
- Expanding the Human Genome Engineering Toolkit
- Coordinating Partnerships and Disseminating Information

https://commonfund.nih.gov/editing



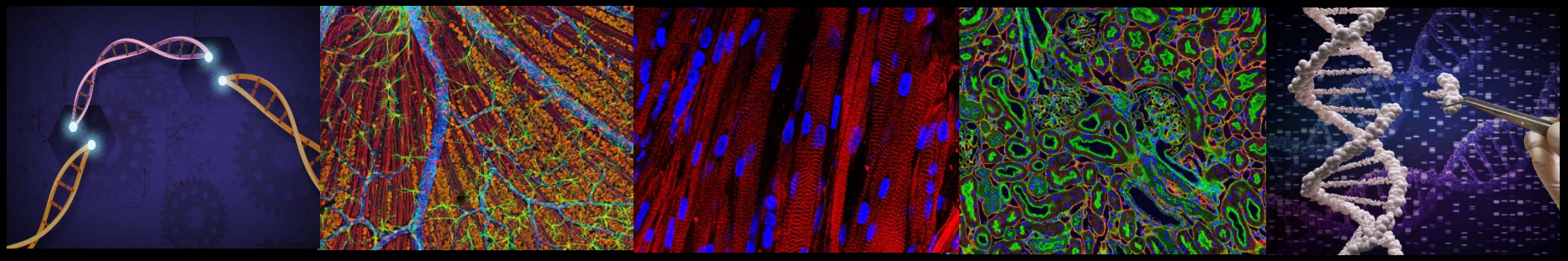
The NIH SCGE Planning Workshop

July 24, 2017

Major Gaps Identified:

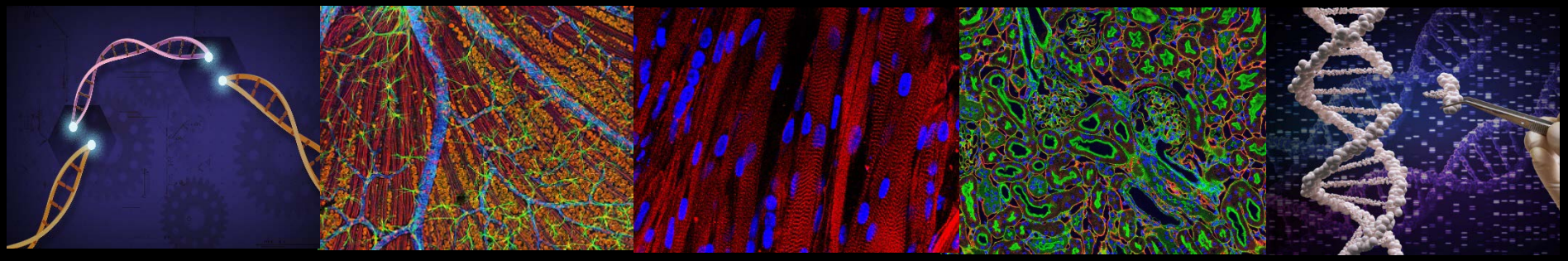
- Relevant human and animal models systems for pre-clinical testing
- Cell- and tissue-specific delivery systems
- Error-free editing machinery (nuclease alternatives)
- Standardized assays for measuring genetic off-target effects
- Long-term cell tracking assays

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



NIH SCGE Working Group

Olivier Blondel, NIDDK
Pj Brooks, NCATS
Tom Cheever, NIAMS
Colin Fletcher, NHGRI
Maria Giovanni, NIAID
Linda M. Griffith, NIAID
Min He, NCI
Keith Hoots, NHLBI
Chamelli Jhappan, NCI
Tim LaVaute, NINDS
Jerry Li, NCI
Nicole Lockhart, NHGRI
Aron Marquitz, OSC/OD
Oleg Mirochnitchenko, ORIP/OD
Stephanie Morris, OSC/OD
Nasrin Nabavi, NIAID
David Panchision, NIMH
Mary Perry, OSC/OD
Betty Poon, NIAID
David Rampulla, NIBIB
John Sheridan, NHLBI
Jeff Struewing, NHGRI
Kayla Valdes, NCATS
Wendy Wang, NCI



SCGE Dissemination & Coordinating Center (RFA-RM-18-018)

- Facilitate interactions and communication between consortium components
- Disseminate a SCGE Toolkit to the research community

large and small animal testing systems (RFA-RM-18-012 & 013)

cell and tissue platforms to detect adverse biological consequences (RFA-RM18-015)

new delivery systems (RFA-RM-18-016)

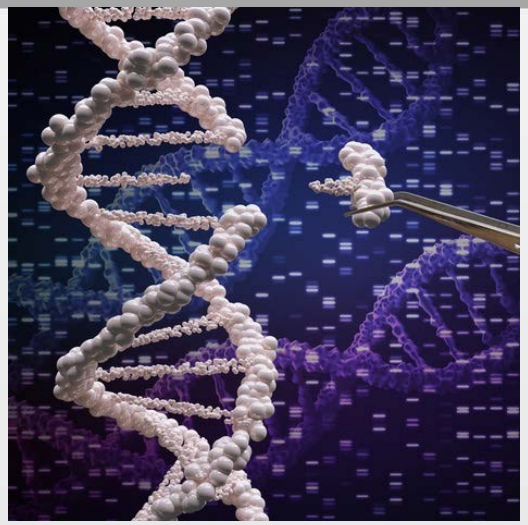
expanding the repertoire of genome editors (RFA-RM-18-017)

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

Potential Impact

- Increased access to IND-enabling technologies
- Accelerated filings of new INDs for gene editing therapies
- Faster approval of gene editing therapies
- New therapeutic approaches for both rare and common diseases

SCGEprogram@nih.gov



Questions?

morriss2@mail.nih.gov