

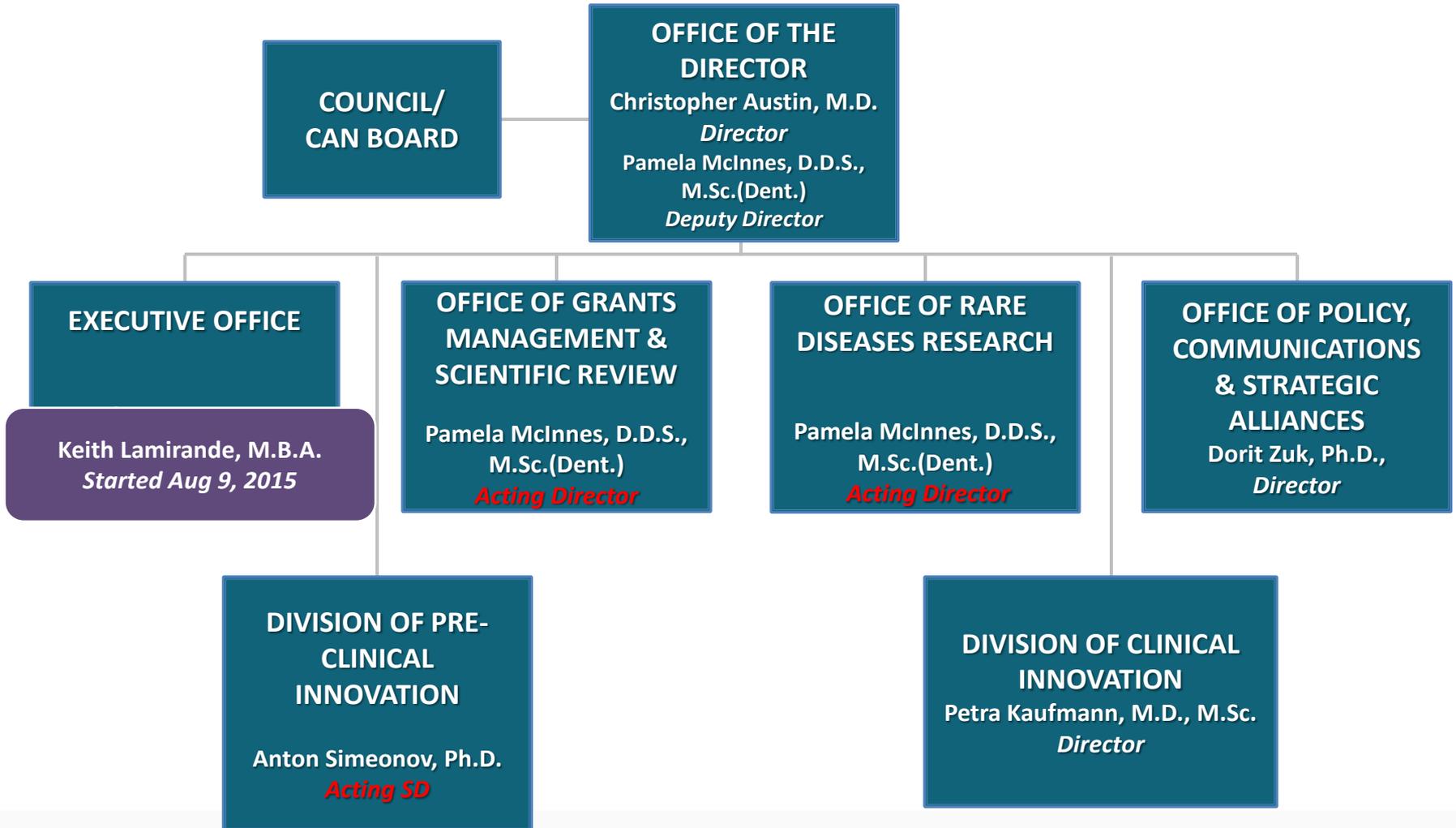
Director's Report

NCATS Advisory Council and CAN Review Board

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
SEPTEMBER 3, 2015

NCATS

Organizational Update



Welcome to Keith Lamirande

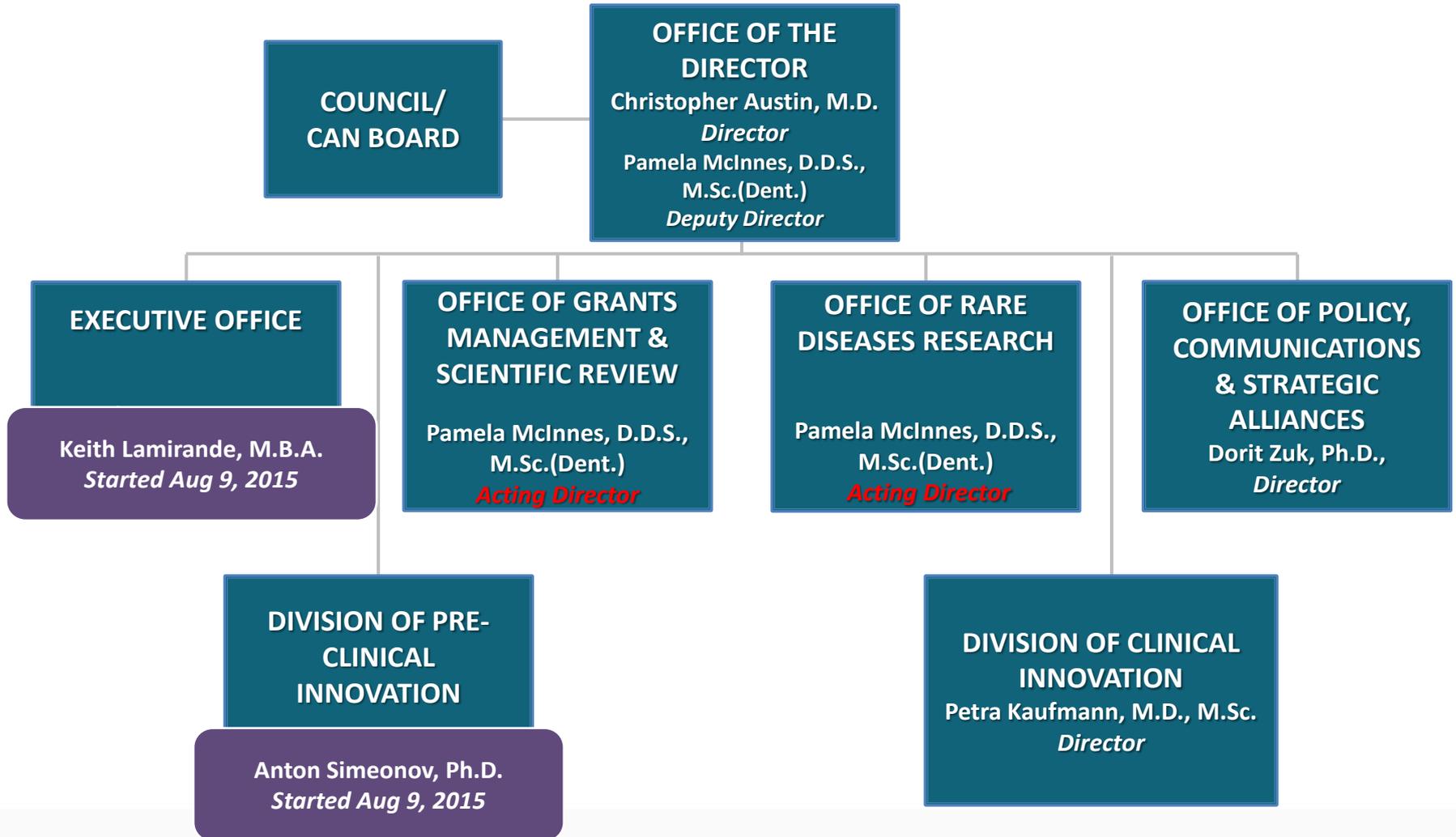
Associate Director for Administration
NCATS Executive Office



Started August 9, 2015



Organizational Update



Welcome to Anton Simeonov

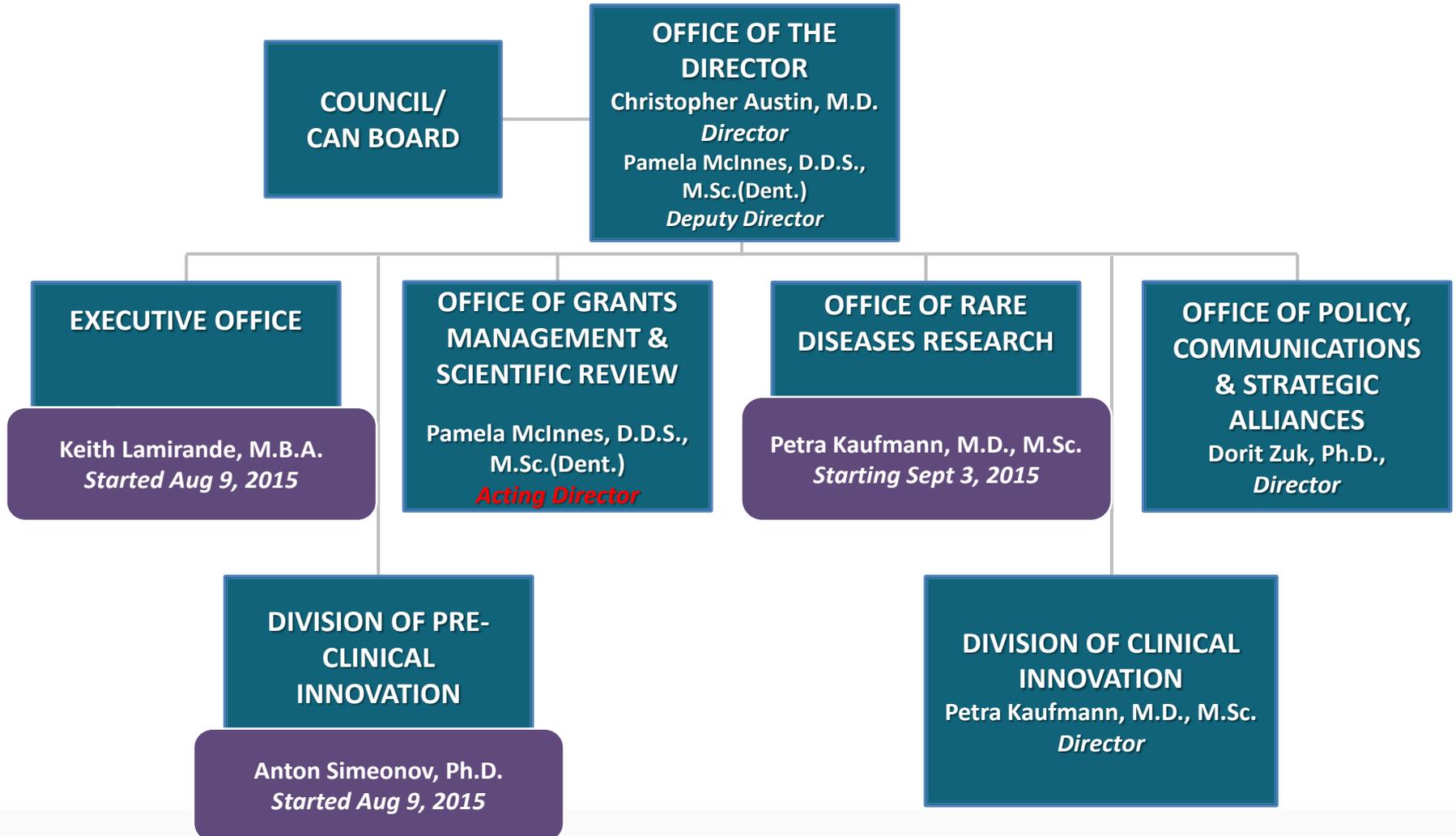
Scientific Director
NCATS Division of Pre-Clinical Innovation



Started August 9, 2015



Organizational Update



Welcome to Petra Kaufmann

Director, NCATS Division of Clinical Innovation and
Office of Rare Diseases Research



Starting September 3, 2015



National Center
for Advancing
Translational Sciences

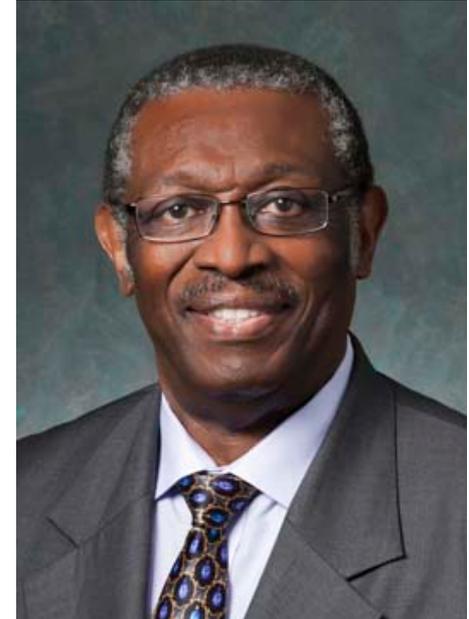
Outgoing CAN RB/Council Members

Thank you!

- Frank Douglas, Ph.D., M.D.

President and CEO

Austen BioInnovation Institute in Akron



- Victoria Hale, Ph.D.

CEO and Founder

Medicines360



New NCATS Video Unveiled

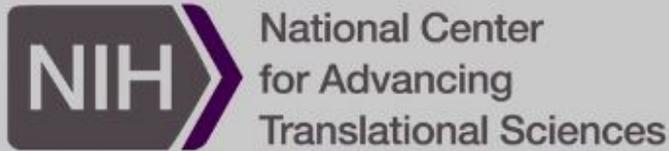
August 11, 2015

- Released latest video:
*A virtual tour of our intramural laboratory facilities
at 9800 Medical Center Drive*
- Featured on our home page
» www.ncats.nih.gov



New NCATS Video Unveiled

August 11, 2015



Inside the NCATS Laboratories



Full video will be playing on loop during lunch



Selected Translational Innovation Highlights

- *Early-stage translation:* chemical probe/lead development for target validation and therapeutic hypothesis testing
- *Mid-stage translation:* preclinical development to first-in-human studies
- *Late-stage translation:* large-scale studies in humans



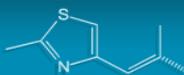
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“Drugging” Novel Targets

nature
chemical biology



nature.com | journal home | archive | issue | research highlights | full text

NATURE CHEMICAL BIOLOGY | RESEARCH HIGHLIGHTS



CANCER

Priority targets

Amy Donner

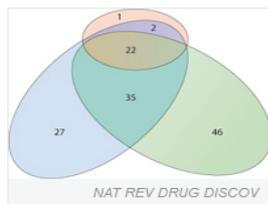
Nature Chemical Biology 9, 138 (2013) | doi:10.1038/nchembio.1189

Published online 15 February 2013

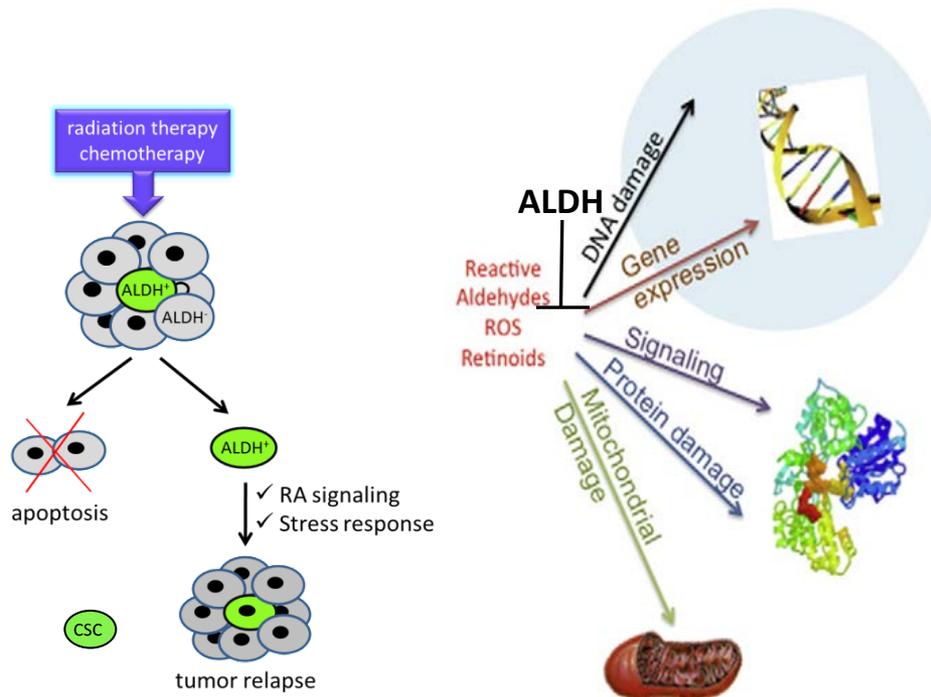
PDF Citation Reprints Rights & permissions Article metrics

Nat. Rev. Drug Discov. 12, 35–50 (2013)

Despite the success of some molecularly targeted drugs, the selection and validation of targets suitable for drug discovery programs remains challenging. Patel *et al.* now report a computational approach to assess biological and chemical space for the prioritization of potential therapeutic targets and apply this approach to cancer. The approach involves the annotation of biologically relevant genes (479, in their cancer example) based on homology to targets of approved drugs, the properties of existing active molecules, three-dimensional structures, druggability, functional class, subcellular localization and other publicly available disease information. The data are then combined to rank potential targets. The authors applied their approach to propose the repurposing of drugs approved for other indications to cancer and to identify new targets. On the basis of these analyses, the authors propose that PPAR γ , DNA methyltransferase 3A and aldehyde dehydrogenase—all drug targets but not indicated for use in cancer—should be evaluated for cancer. In addition, they identify 46 druggable proteins via structure-based



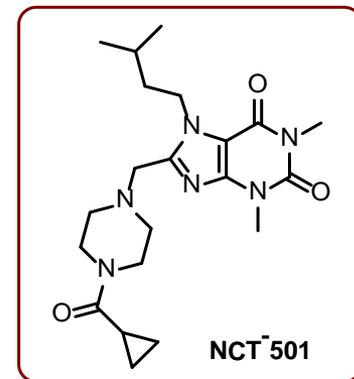
Target: Aldehyde dehydrogenase 1A1
Collaborator: Vasilis Vasiliou (Yale)
Therapeutic Scope: Cancer, Inflammation, Obesity, Development



Chemico-Biological Interactions 202 (2013) 2-10

“Drugging” Novel Targets

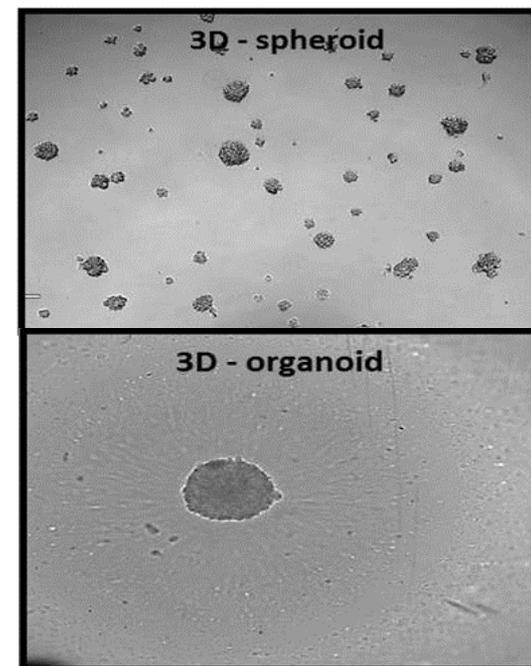
Aldehyde Dehydrogenase



- Developed two highly potent ALDH1A1 inhibitor series

➤ Excellent selectivity and ADME properties

1A1	1B1	3A1	ALDH2	Permeability (PAMPA)	Aqueous Solubility
40 nM	>57 μM	>57 μM	>57 μM	164 (10 ⁻⁶ cm/s)	>60 μg/mL
RLM (T _{1/2})	HLM (T _{1/2})	Caco-2: P _(B-A) /P _(A-B)			Protein Binding
84 min	> 2 h	19.6/19.3 = 1.02			69%



- Demonstrated efficacy in cancer stem cell (3D-spheroid and organoid) models of glioblastoma multiforme brain cancer
- Animal efficacy studies ongoing

J. Med. Chem., **2015**, 58: 5967–5978

NCATS - Lilly Open Innovation Drug Discovery (OIDD) Partnership

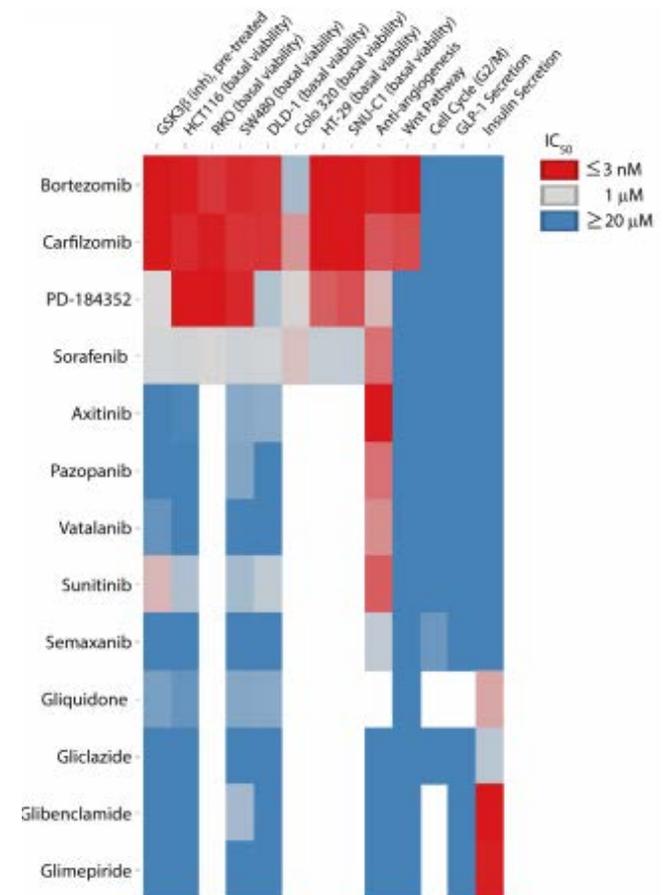
- 2,500 approved drugs from NCATS Pharmaceutical Collection tested in Lilly OIDD assays relevant to
 - » Cardiovascular diseases, diabetes, cancer, endocrine disorders
- All data made public



RESEARCH ARTICLE

Novel Phenotypic Outcomes Identified for a Public Collection of Approved Drugs from a Publicly Accessible Panel of Assays

PLOS ONE 2015, 10: e0130796. doi:10.1371



NCATS - Lilly OIDD Partnership

Unprecedented systems pharmacology data enabling therapeutic discovery

NCBI
PubChem BioAssay
 PubChem BioAssay [dropdown] [input field] [Search]
 Limits Advanced search

SHRE [social icons]

BioAssay: AID 1117321



Collaborative phenotypic assays for screening drugs in NPC

Phenotypic assays have a proven track record for generating leads that become first-in-class therapies. Whole cell assays that inform on a phenotype or mechanism also possess great potential in drug repositioning studies by illuminating new activities for the existing pharmacopeia. The National Center for Advancing Translational Sciences (NCATS) pharmaceutical collection (NPC) is the largest [more](#) ..

Table of Contents

- [Related Experiments](#)
- [Description](#)
- [Protocol](#)
- [Comment](#)

AID: 1117321 [icon]

Data Source: Cheminformatics & Chemogenomics Research Group (CCRG), Indiana University School of Informatics (NPC_OIDD_Assay_Summary)

BioAssay Type: Summary, Candidate Probes/Leads with Supporting Evidence

Depositor Category: Other

Deposit Date: 2015-03-08

Modify Date: 2015-03-09

Related Experiments

Show more [icon]

AID	Name	Type	Comment
1117322	RKO viability from Cell TiterGlo-IC50	Confirmatory	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117323	SNU-C1 viability from Cell TiterGlo-IC50	Confirmatory	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117324	VEGF stimulated ADSC/ECFC co-culture nuclear area decrease (viability)-IC50	Confirmatory	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117325	nuclear beta catenin stimulation in WNT3A conditioned C2C12 cells-IC50	Confirmatory	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117326	nuclear beta catenin stimulation in WNT3A conditioned C2C12 cells-screen	Screening	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117327	alkaline phosphatase stimulation in WNT3A conditioned C2C12 cells-IC50	Confirmatory	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly
1117328	human p70S6K1 kinase inhibition-screen	Screening	depositor specified assay group: Phenotypic drug screening by Data2Discovery, NCATS, Lilly

Description:

Abstract

Phenotypic assays have a proven track record for generating leads that become first-in-class therapies. Whole cell assays that inform on a phenotype or mechanism also possess great potential in drug repositioning studies by illuminating new activities for the existing pharmacopeia. The National Center for Advancing Translational Sciences (NCATS) pharmaceutical collection (NPC) is the largest reported collection of approved small molecule therapeutics that is available for screening in a high-throughput setting. Via a wide-ranging collaborative effort, this library was analyzed in the Open Innovation Drug Discovery (OIDD) phenotypic assay modules publicly offered by Lilly. The results of these tests are publicly available online at <https://tripod.nih.gov/pd2/> and via the PubChem Database (<https://pubchem.ncbi.nlm.nih.gov/>). Phenotypic outcomes for numerous drugs were confirmed, including sulfonylureas as insulin secretagogues and the anti-angiogenesis actions of multikinase inhibitors sorafenib, axitinib and pazopanib. Several novel outcomes were also noted including the Wnt potentiating activities of rotenone and the antifolate class of drugs, and the anti-angiogenic activity of cetaben.

Selected Translational Innovation Highlights

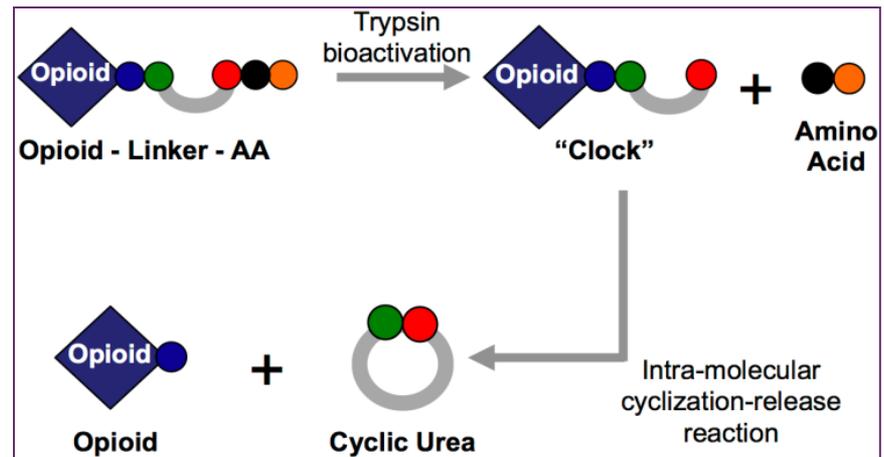
- *Early-stage translation:* chemical probe/lead development for target validation and therapeutic hypothesis testing
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NCATS-NIDA Collaboration

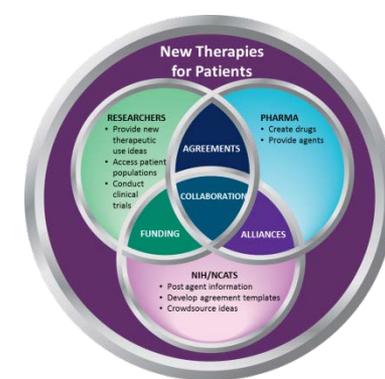
Development of an abuse-resistant oral narcotic

- Prescription Drug Abuse is an urgent national priority
- Abuse-resistant narcotic formulations face scientific and business hurdles
- NIDA partnered with NCATS BRIDGs program and Signature Therapeutics (Palo Alto, CA) to develop oral prodrug formulation of oxycodone
- Novel Project Model
 - MOU between NIDA and NCATS
 - 3-way CRADA
- IND cleared June 2015
- Clinical trial expected to begin August 2015



New NTU Projects Awarded

July 2015



Original Indication	Pharma Partner	Academic Partner	New Indication
Pulmonary <i>COPD, cystic fibrosis, bronchiectasis</i>	AstraZeneca	Allegheny Health Network Research Institute	Type 2 Diabetes
Lung cancer	AstraZeneca	Duke University	Glioblastoma
Chronic pain	Sanofi	UC San Diego	Chagas disease
Solid tumors, e.g., ovarian	AstraZeneca	Massey Cancer Center, VCU	Acute Myeloid Leukemia (AML)

Tissue Chip

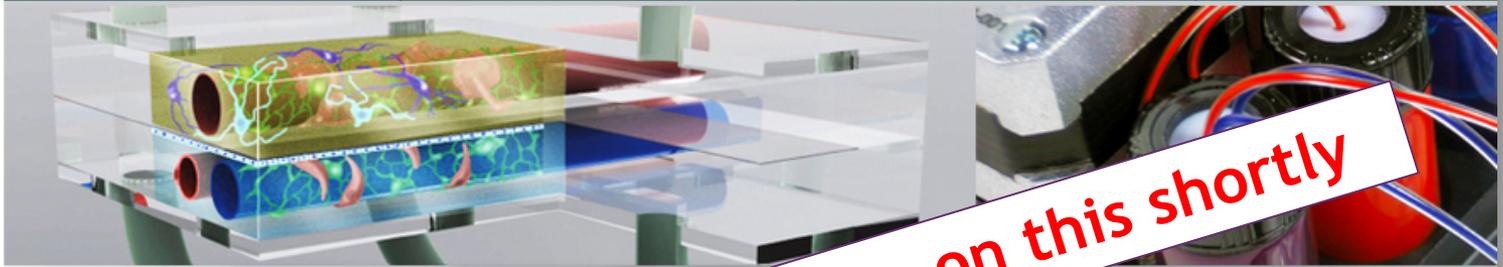


Research

Funding & Notices

News & Media

About Translational Sciences



You will be hearing more on this shortly

Home > About NCATS > NCATS Programs & Initiatives > Tissue Chips > Meet Chip: Female Reproductive System

About Tissue Chip: Meet Chip: Female Reproductive System

Tissue Chip: Female Reproductive System

Tissue Chip Projects

Meet Chip

- > Meet Chip: Brain
- > Meet Chip: Muscle
- > Meet Chip: Heart
- > Meet Chip: Lungs
- > Meet Chip: Liver
- > Meet Chip: Kidneys
- > Meet Chip: Gastrointestinal System
- > **Meet Chip: Female Reproductive System**

From puberty until menopause, the female reproductive system is capable of an amazing feat: growing a new human being. The reproductive system also has many other functions. Every month, the ovary releases an egg, and the uterus sheds and replenishes its lining. The ovaries also make hormones that circulate through the body and affect a woman's health. Scientists need better ways to test how new drugs and other chemicals affect the female reproductive system.

Modeling Ovaries, Uterus and More

Understanding women's health requires more comprehensive knowledge about the workings of the female reproductive system, including monthly menstrual cycles, pregnancy, and production of hormones that affect the entire body, from bone maintenance to blood clotting to sexual health. But there are limits to how much scientists can understand about the workings of the human female reproductive system by studying animals or cells growing in a lab.

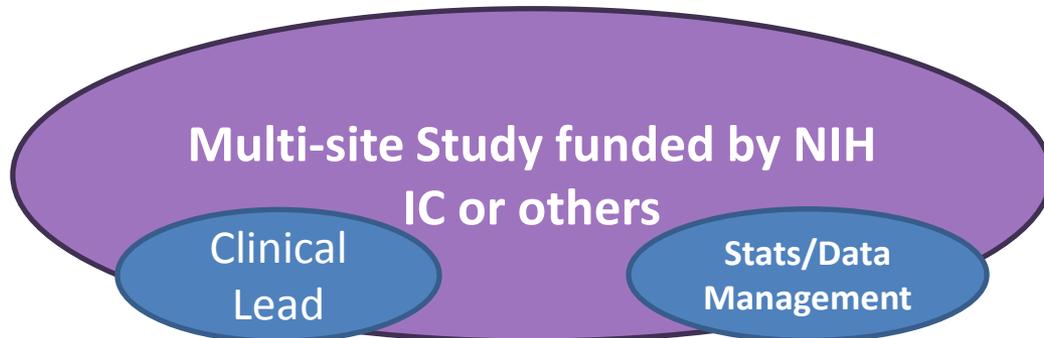
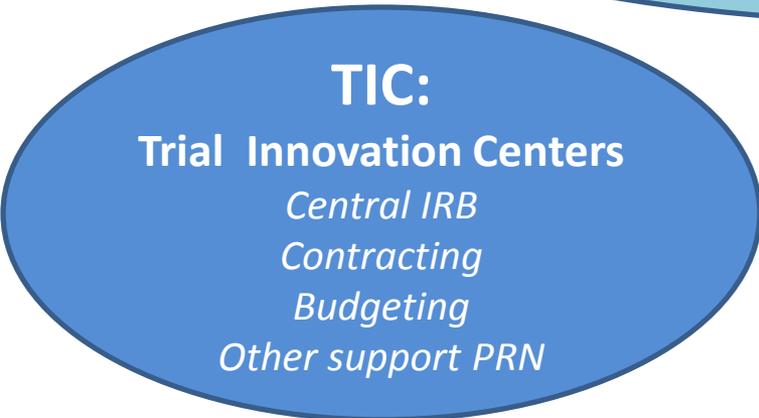


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Evolving the CTSA Program to Transform Clinical Translational Science



No need to rebuild trial components each time



Evolving the CTSA Program to Transform Clinical Translational Science

CTSA Hubs

TIC:

Trial Innovation Centers

Central IRB

Co

Building

Other support PRN

You will be hearing more on this shortly



RIC:

Recruitment Innovation Centers

Feasibility Assessment

Recruitment Plan and

Implementation



Multi-site Study funded by NIH

IC or others

Clinical Lead

Stats/Data Management

No need to re-build trial components each time



Innovation Corps (I-Corps) Program

- I-Corps training program aims to accelerate commercialization of biomedical technologies
- NIH-NSF pilot program
 - Developed with SBIR/STTR funding
 - NCATS made 3 supplemental awards to Phase 1 SBIR/STTR awards
- Now creating NSF/CTSA I-Corps Program
 - Applying the I-Corps teaching methodology to the CTSA program via “train-the-trainer” approach
 - Pilot: NCATS will provide funding and access to this program for up to 10 institutions
 - Featured at White House “Demo Day” August 4





Petra Kaufmann, DCI Director
White House Demo Day showcasing NIH I-Corps Program



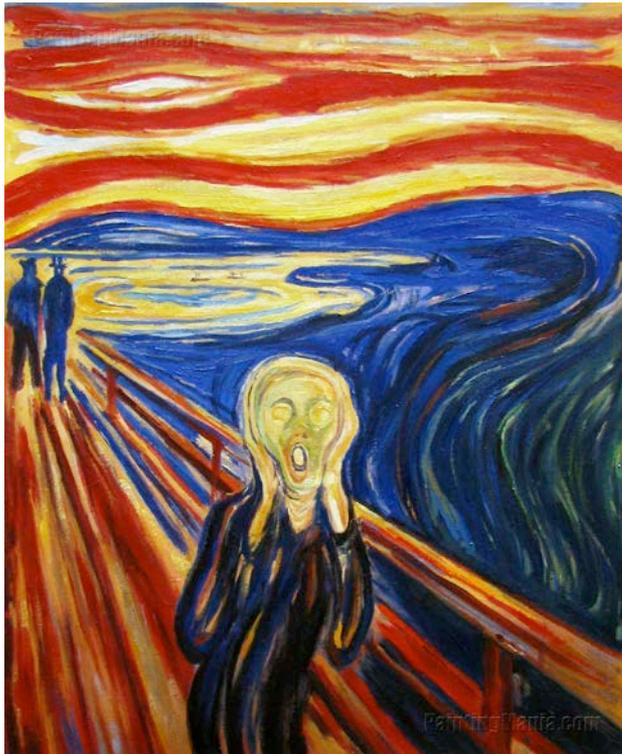
CTSA Common Metrics Initiative

- “Advancing” translational science
 - From Latin *ab* ‘from’ + *ante* ‘before.’
- “The CTSA Program...should use clear, consistent, and innovative metrics...that go beyond publications and number of grant awards”
 - IOM, *The CTSA Program at NIH*, 2013
- “If you can’t measure it, you can’t manage it.”
- “Not everything that can be counted counts, and not everything that counts can be counted.”
- **Conclusions**
 - Measurement is difficult to get right but essential to knowing if advancement is occurring
 - Measurement is a science that must be approached experimentally
 - Measurement must be reiterative, collaborative, and tied to hypotheses and a variety of data types



The Problem

If we fear
(the misuse of)
data/metrics



we end up
flying blind



The Challenge

Building a culture that encourages the use of data/metrics in the strategic management of the CTSA Program



The Vision

The strategic management
of the CTSA Program
by the PIs and NCATS

is

✓ data-driven

and

✓ collaborative...

...to maximize the impact
of the CTSA Program.

The Vision

The strategic management
of the CTSA Program
by the PIs and NCATS

You will be hearing more on this shortly

data-driven
and
✓ collaborative...

...to maximize the impact
of the CTSA Program.

ORDR/NCATS

(NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS)

Dystonia Coalition

Coalition of Patient Advocacy Groups (CPAG)

Porphyria Rare Disease Clinical Research Consortium

PAG

North America Mitochondrial Diseases Consortium

Primary Immune Deficiency Treatment Consortium

Brittle Bone Disorders Consortium

Chronic Graft Versus Host Disease

The Data Management and Coordinating Center

Urea Cycle Disorders Consortium

Brain Vascular Malformation Consortium

Genetic Disorders of Mucociliary Clearance

Consortium of Eosinophilic Gastrointestinal Disease Researchers

Rett, MECP2 Duplications and Rett-Related Disorders Consortium

Sterol and Isoprenoid Diseases Consortium

Autonomic Disorders Consortium

Developmental Synaptopathies Associated with TSC, PTEN and SHANK3 Mutations

The Frontotemporal Lobar Degeneration Clinical Research Consortium

Inherited Neuropathies Consortium

Nephrotic Syndrome Study Network

Rare Lung Diseases Consortium

Lysosomal Disease Network

Rare Kidney Stone Consortium

Vasculitis Clinical Research Consortium

Clinical Research in ALS & Related Disorders for Therapeutic Development



- Collaborative Clinical Research
- Centralized Data Coordination and Technology Development
- Public Resources and Education
- Training

RDCRN-Rare Lung Diseases Consortium (RLDC)

Sirolimus Trial for LAM

- Lymphangiomyomatosis (LAM) is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal
- RLDC conducted Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial
 - PI: Dr. Francis McCormack
 - Collaborative effort between RDCRN-RLDC, Pfizer, and LAM Foundation
- In early 2015 FDA accepted sNDA via priority review
- In March 2015 FDA approved sirolimus for LAM
 - First drug approved by FDA for the treatment of LAM

Policy and Legislative Updates



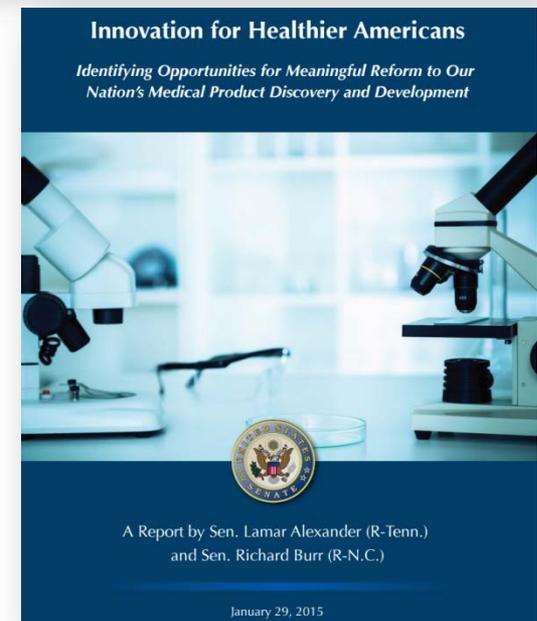
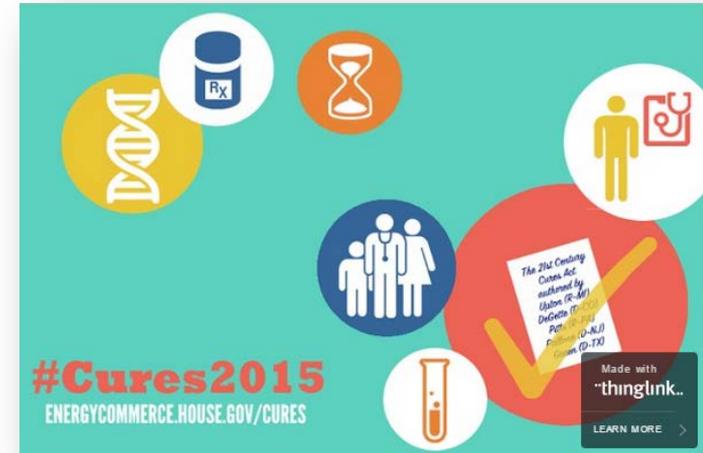
FY 2016 Budget Request

- On February 2, 2015, President Obama released the FY 2016 budget
 - NIH: request for \$31.3B, increase of \$1B over FY15
 - NCATS: request for \$660.1M, increase of \$27.4M over FY 2015
 - NCATS' Congressional Justification (CJ) and appropriation status is available at:
<https://ncats.nih.gov/about/center/budget>
- House and Senate appropriation bills approved by committees, but never voted on by full chambers
- Continuing Resolution (CR) may be needed to keep government running after September 30



Congressional Authorizing Activities

- House: “21st Century Cures” (H.R. 6)
 - July 10: passed by large majority (344-77)
 - NIH “Innovation Fund” set at \$8.75 billion, over five years
- Senate: “Innovation for Healthier Americans”
 - Hearings held in Spring
 - NCATS participated in April hearing
 - Draft bill may be released in Fall



FOR IMMEDIATE RELEASE
September 2, 2015

Contact: HHS Press Office
202-205-0143

HHS announces proposal to update rules governing research on study participants

Proposed changes enhance protections for individuals involved in research, while modernizing rules and improving efficiency

The U.S. Department of Health and Human Services today announced proposed revisions to the regulations that govern research on individuals who participate in research.

The current regulations that protect individuals who participate in research, which have been in place since 1991, are followed by 18 federal agencies and are often referred to as the Common Rule. They were developed at a time when research was predominantly conducted at universities, colleges and medical institutions, and each study generally took place at a single site. The expansion of research into new scientific disciplines, such as genomics, along with an increase in multisite studies and significant advances in technology, has highlighted the need to update the regulatory framework. Notably, a more participatory model of research has also emerged, with individuals looking for more active engagement with the research enterprise.

In July 2011, HHS issued an [Advance Notice of Proposed Rulemaking](#) to seek the public's input on updating the Common Rule. The [Notice of Proposed Rulemaking](#) (NPRM) issued today reflects that input and requests comments for HHS to consider as it drafts the final rule.

The protection of research participants is of paramount importance. Medical advances would not be possible without individuals who volunteer to participate in research. This NPRM proposes to modernize the current regulations by enhancing the ability of individuals to make informed decisions about participating in research, while reducing unnecessary burdens by streamlining the regulatory requirements for low-risk research.

Changes proposed in the NPRM issued today include:

- Strengthened informed consent provisions to ensure that individuals have a clearer understanding of the study's scope, including its risks and benefits, as well as alternatives to participating in the study.
- Requirements for administrative or IRB review that would align better with the risks of the proposed research, thus increasing efficiency.
- New data security and information protection standards that would reduce the potential for violations of privacy and confidentiality.
- Requirements for written consent for use of an individual's biological samples, for example, blood or urine, for research with the option to consent to their future use for unspecified studies.
- Requirement, in most cases, to use a single institutional review board for multisite research studies.
- The proposed rule would apply to all clinical trials, regardless of funding source, if they are conducted in a U.S. institution that receives funding for research involving human participants from a Common Rule agency.

To view the NPRM, [click here](#). HHS will take public comment on this NPRM for 90 days, beginning Sept. 8.



Strategic Planning underway

- NIH Strategic Plan
 - Dr. Lawrence Tabak will update Council on the process to date
- NCATS Strategic Plan
 - Dr. Dorit Zuk will update Council on NCATS planning activities



Strategic Planning underway

- NIH Strategic Plan

- Dr. Lawrence Tabak will update Council on the process to date

- NCATS Strategic Plan

You will be hearing more on this shortly

- Dr. Zuk will update Council on NCATS planning activities



Discussion