Getting Ready for Research as a Rare Disease Patient Advocate

Christopher P. Austin, M.D.
Director, NCATS

NORD RareLaunch Research Ready Workshop
December 3, 2020

Changing the Narrative:
Rare Diseases Are a Public Health Issue

- ~7000 diseases
  - ~80% genetic
  - ~60% onset in childhood
  - ~250 new rare diseases identified every year
- Individually rare, cumulatively common
  - Definition varies by country: US <200,000; Japan <50,000; EU <1/2,000
  - Total prevalence ~8% (US ~25 million)
- High costs in direct patient care, loss of productivity
- Accurate diagnosis often requires 5-15 yrs
- Only 5% of rare diseases have a regulatorily approved treatment
  - ~400 diseases; at current rate 2000 years before treatments for all rare diseases
- Solution: transition from “one disease at a time” to “many diseases at a time” approach
  - Commonalities among diseases
  - Platform technologies for diagnosis and treatment

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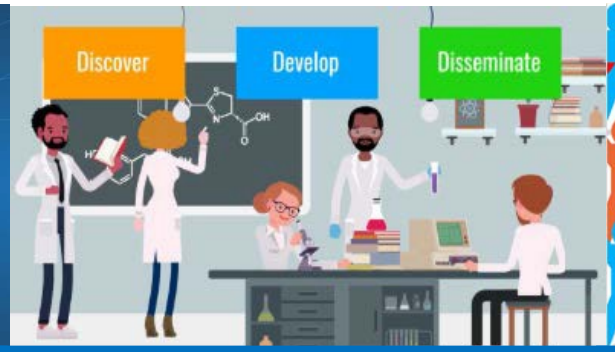
NCATS Office of Rare Diseases Research

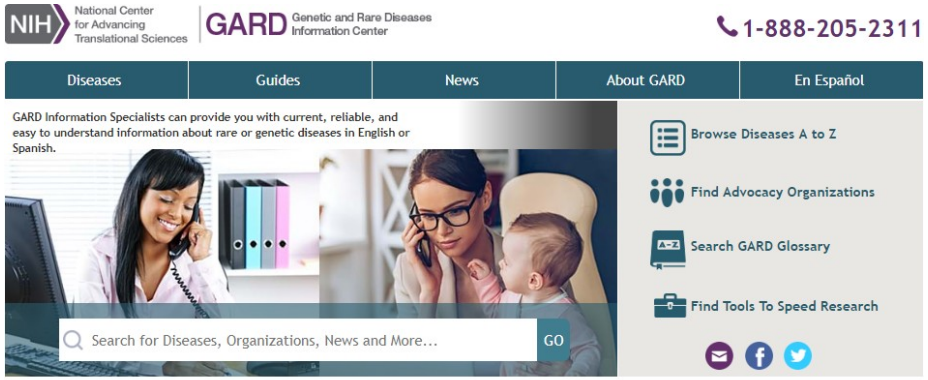


Knowledge/Data	Research/Collaboration	Community Engagement
GARD Cluster	Rare Diseases Clinical Research Network	Rare Diseases Day at NIH
Genetics & Rare Diseases (GARD) Information Center	NCATS Scientific Conference Grants	Rare Diseases Are Not Rare! Challenge
Rare Diseases Registry Program (RaDaR)	Bench to Bedside Grants	Gene Therapy Meeting Series
NCATS Toolkit for Patient-focused Drug Development	Clinical Trial Readiness Grants	International Collaboration IRDiRC
Impact of Rare	PaVe-GT	
Diagnostic Odyssey	Shared Molecular Etiologies Grants	

Anne Pariser, M.D.
Director
anne.pariser@nih.gov

NCATS "Many Diseases at a Time" Research Programs

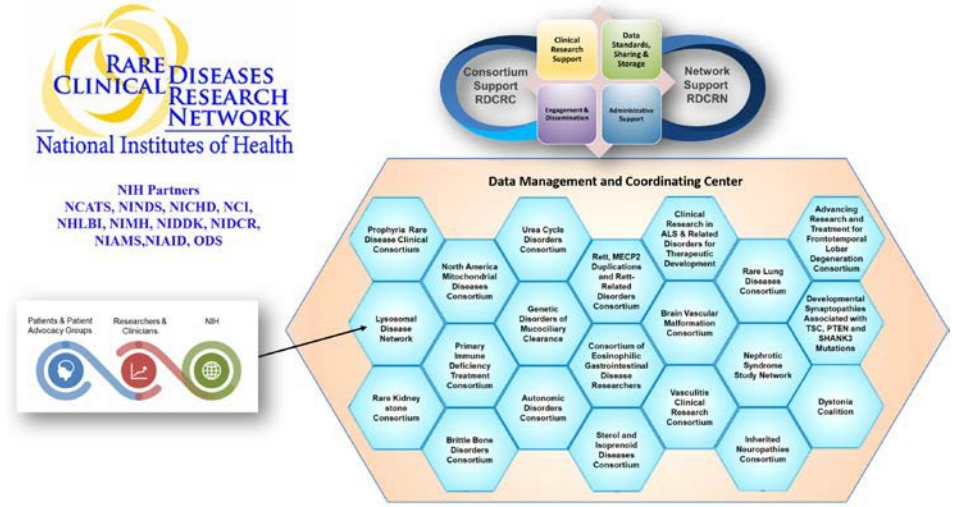
Providing Information and "Big Data"



Empowering Patients as Research Partners

Developing Interoperable Registries

Natural History and Interventional Studies



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NCATS “Many Diseases at a Time” Research Programs

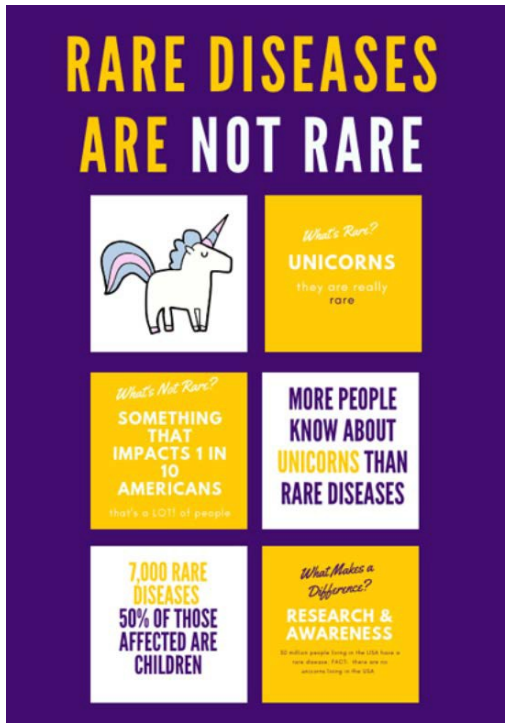
Partnering to Change Perceptions

Challenge.gov
Government Challenges, Your Solutions

Challenges About Agency Toolkit Contact

NCATS Rare Diseases Are Not Rare! Challenge

Share innovative ways to communicate to educate people about rare diseases through social media or art



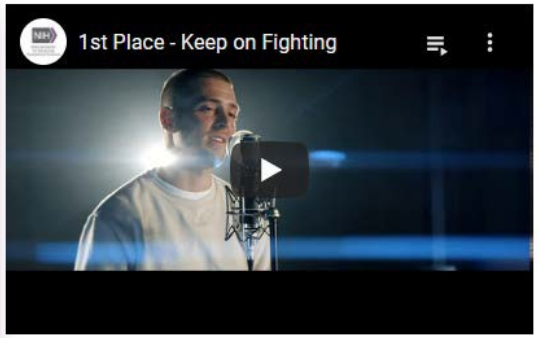
First Place 2018
Nancy Netherland

First Place 2020

“Keep on Fighting”

Jacob Thompson

“When I was 24 years old, about 2 years ago, I was diagnosed with the rare disease known as Friedreich’s Ataxia (FA). When my dreams of playing a sport in college ended, I needed something else to apply myself to. This began my journey as a hip-hop and spoken word artist. When I was diagnosed, it felt as though my dreams for the future had died. In many instances, I felt like giving up on my journey as an artist. Instead, I now have a new vision for my art: both to encourage those who are challenged, whether with rare disease or in general, and to raise awareness for rare disease.”



Partnering to Share Knowledge

Rare Disease Day at NIH 2020

NCATS, FDA Co-Host Workshop on Gene Therapy for Rare Diseases

Translational Science Highlight

- NCATS and the Food and Drug Administration are collaborating to identify bottlenecks to gene therapy development and share best practices for advancing gene therapies, a promising approach to treating many different rare diseases.

“We are now at the point of translating the potential of gene therapy — which has been around for a while — into a reality for patients,” said NCATS Director Christopher P. Austin, M.D.

These new advances in gene therapies have truly been a long time in coming. The first human study that involved gene therapy, a type of treatment to replace or fix a defective gene in a patient, began in 1990 at the NIH Clinical Center. Nearly 30 years later, in 2017, the Food and Drug Administration (FDA) approved the first three gene therapies for use in the U.S. One of those three is for an inherited disease; the others alter a patient’s own cells to fight two forms of cancer.

Inspired by this scientific progress, in August 2018, NCATS and the FDA co-hosted a two-day workshop about gene therapy for rare diseases. Many of these diseases are caused by a mutation in a single gene, so gene therapy holds great promise as an effective treatment approach.

Led by NCATS’ Office of Rare Diseases Research and the FDA’s Center for Biologics Evaluation and Research (CBER) staff, the workshop brought together representatives from NIH, the FDA, academia, industry and patient organizations to discuss using gene therapy to treat rare diseases. Discussion topics included recent scientific advances; challenges in manufacturing the viruses, called vectors, that are used to deliver gene therapy products; and how to increase the number of available treatments.

“We really are having this meeting at the right time,” said FDA CBER Director Peter Marks, M.D., Ph.D. He noted that hundreds of potential gene therapy treatments are now entering the clinic for testing in people. In July 2018, the FDA released draft guidance on several topics related to gene therapy, such as manufacturing and long-term follow-up of people who receive these agents.

Advancing the Science

Exciting scientific advances discussed at the meeting included research in animal models and studies showing new advances in humans.

Jay Chiorini, Ph.D., of the NIH National Institute of Dental and Craniofacial Research, shared his research on using gene therapy to make salivary glands work better. Most people who have radiation treatment for head and neck cancer temporarily or permanently lose the ability to make saliva. Without it, eating becomes painful, and people may lose their teeth and have other dental problems. Using gene therapy in mini-pigs that were treated with radiation, Chiorini has been able to show some improvement in how the salivary glands worked. This approach has now entered the clinic, and he has so far enrolled 12 people in a study designed to test different gene therapy doses to find out whether the approach is safe in humans.

“We are often faced with the fact that mouse studies don’t

NCATS Director Christopher P. Austin, M.D., at the Growing Promise of Gene Therapy Approaches to Rare Diseases Workshop in August 2018.

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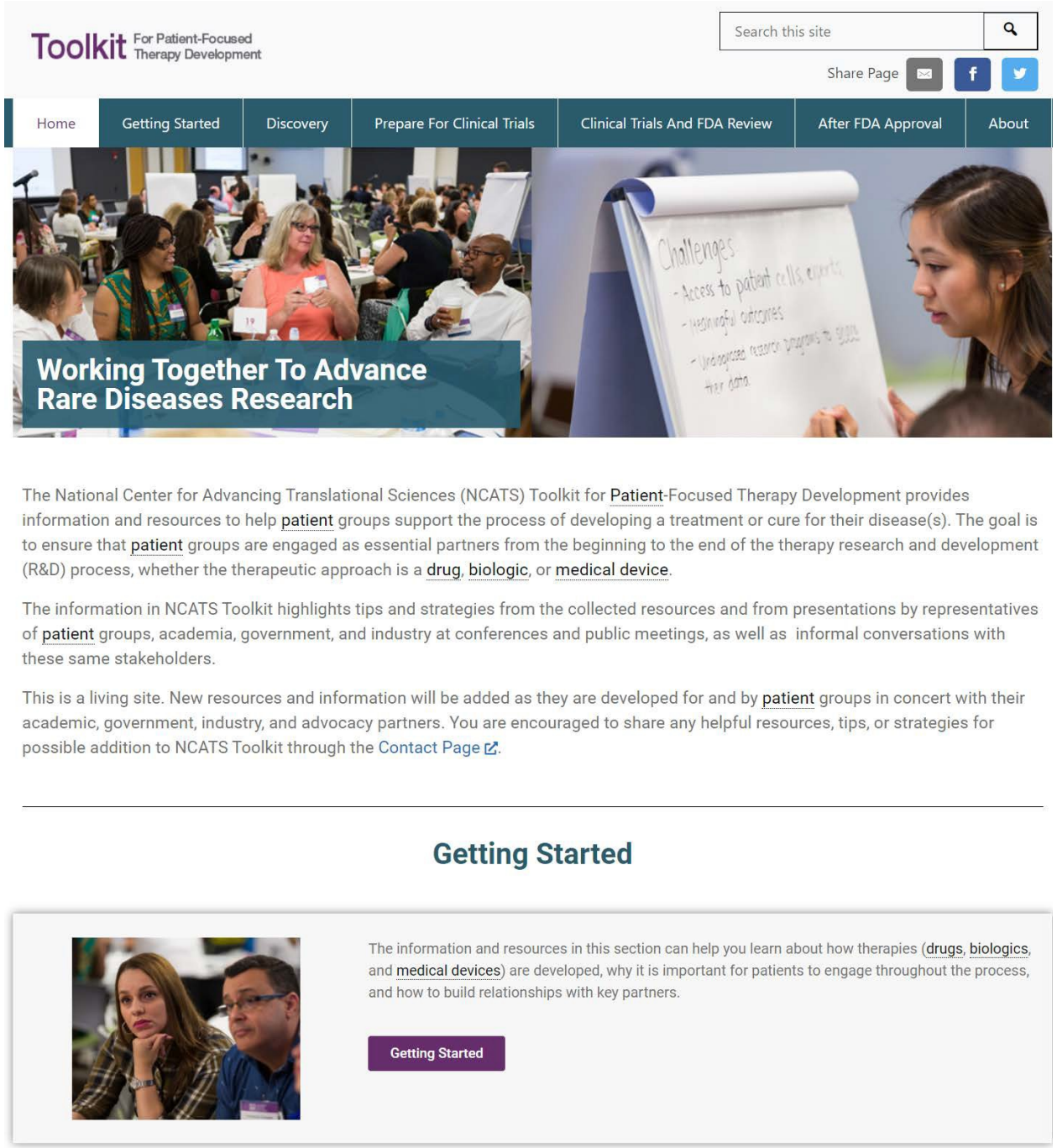

NCATS Toolkit for Patient-Focused Therapy Development

- One-stop shop for tools and advice for advancing research programs
- Brings together resources from many organizations
- Developed with and for patient groups wanting to get started in the research process

https://rarediseases.info.nih.gov/toolkit

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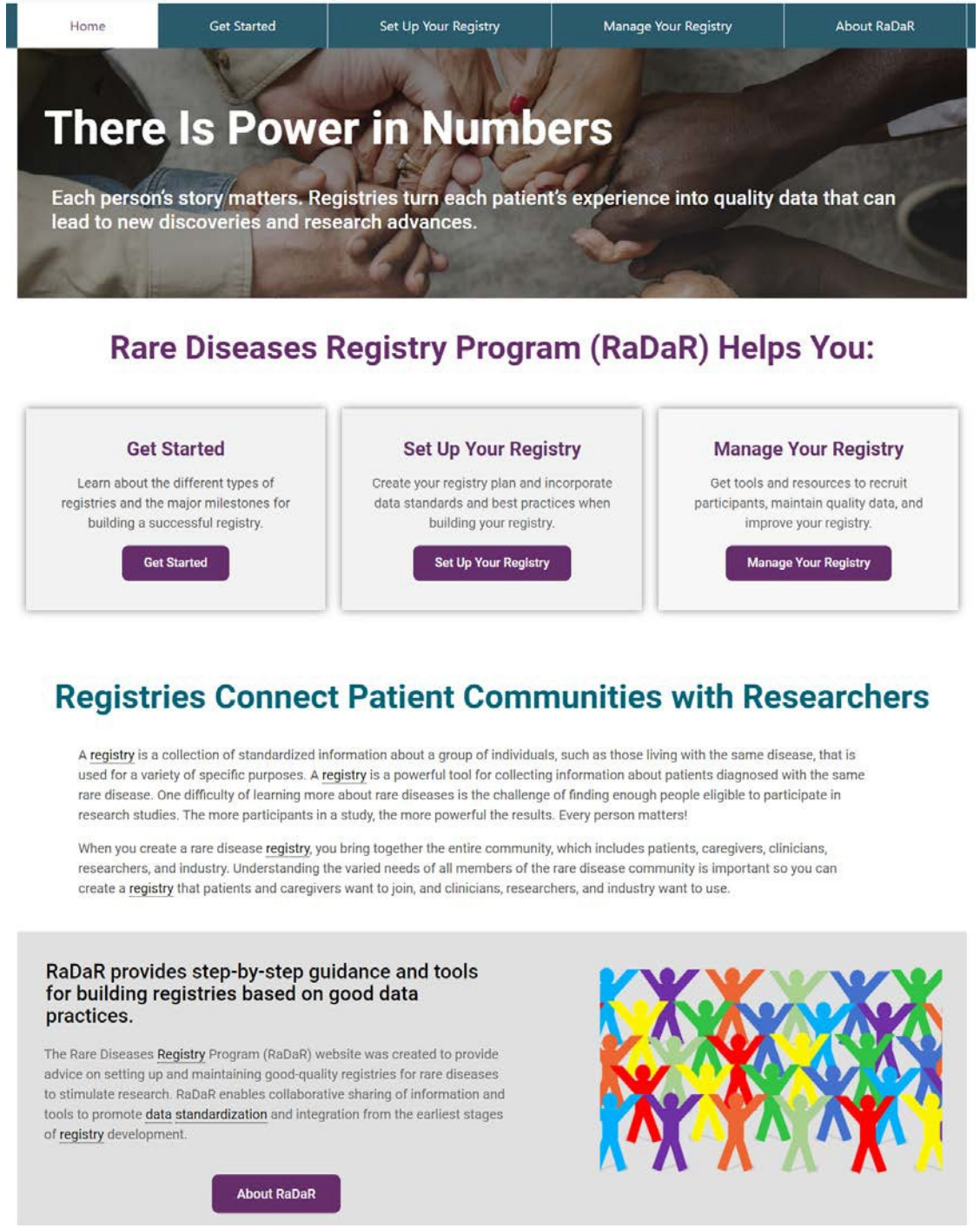

NCATS RaDaR (Rare Diseases Registry) Program

- Tools and advice for building patient registries
- Developed with and for patient groups wanting to get started in developing a registry and natural history study

https://registries.ncats.nih.gov/

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Genetic and Rare Diseases Information Center (GARD)

- Since 2003 the preeminent source of patient-focused information on all rare diseases
- Includes web-based information and consultation phone line
- Now being completely redesigned with new IT and informatics capabilities

https://rarediseases.info.nih.gov/

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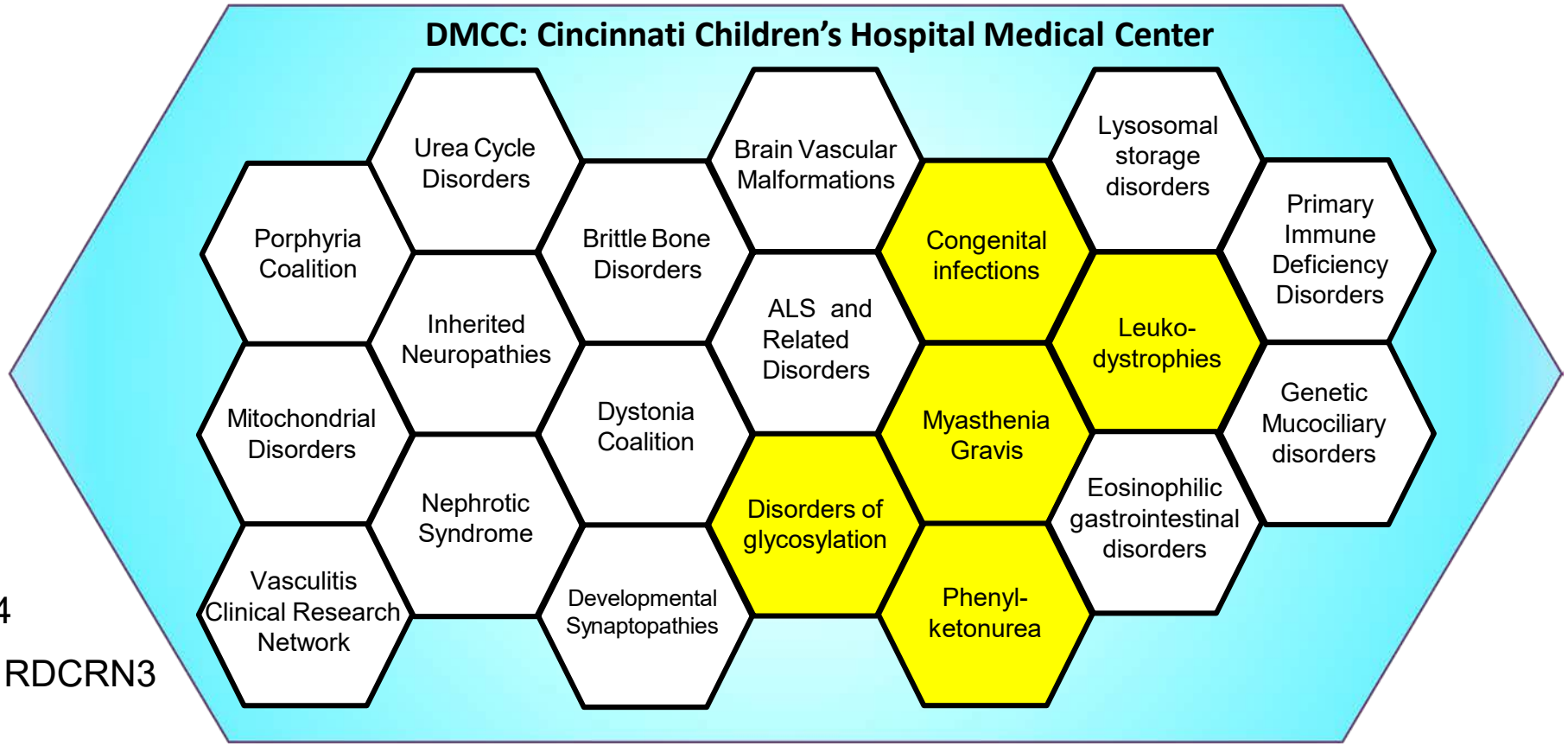
RARE DISEASES
CLINICAL RESEARCH NETWORK

- Network of consortia grouped around ≥3 rare diseases
- Natural history, recruitment, intervention trials required
- *Patient advocacy group inclusion required*

NIH Partners:
NCATS, NINDS, NICHD, NHLBI, NIMH, NIDDK, NIDCR, NIAMS, NIAID, ODS



= new consortium in RDCRN4

= continuing consortium from RDCRN3

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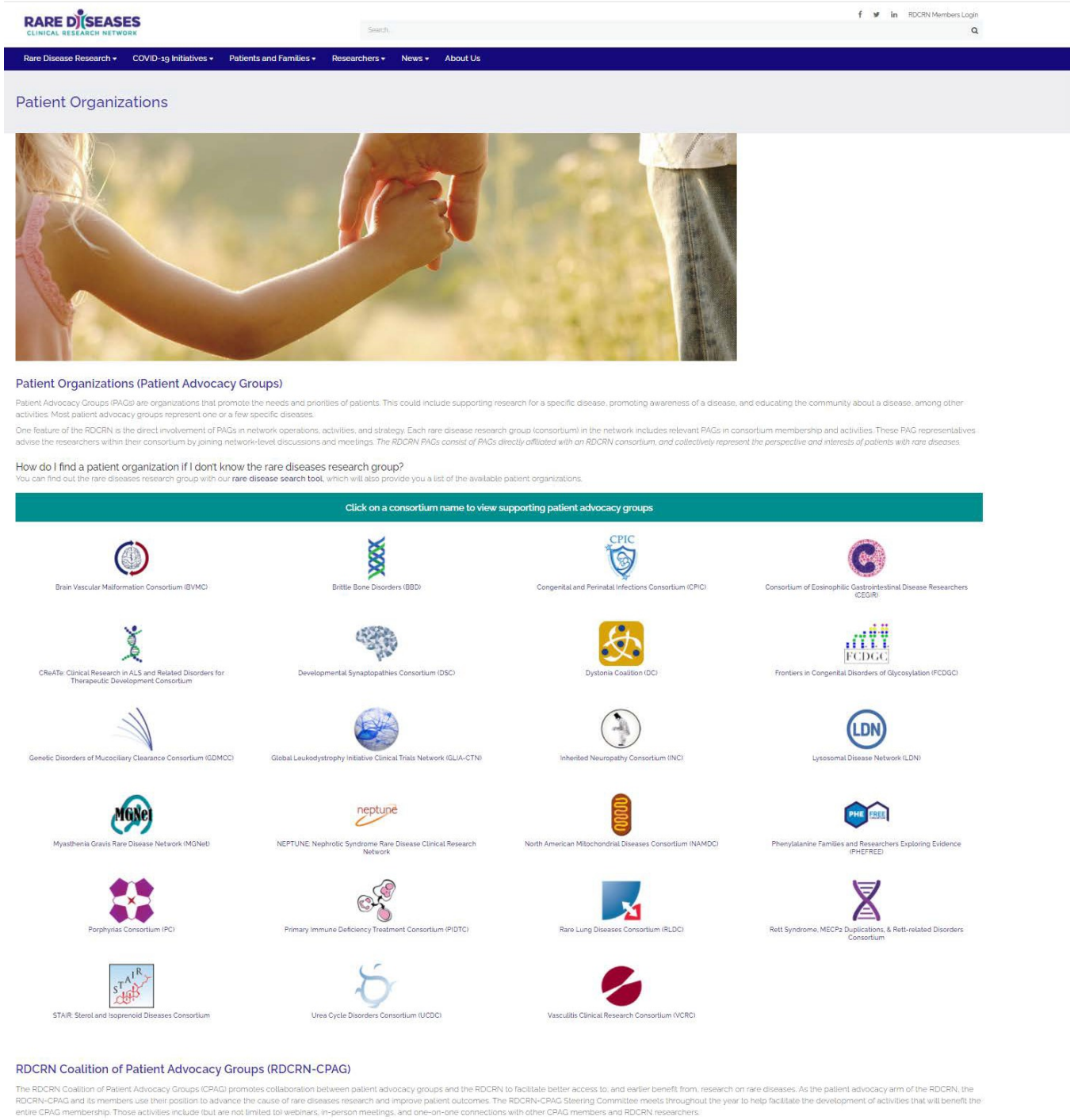

RDCRN Coalition of Patient Advocacy Groups (CPAG)

- Integral part of RDCRN
- Information and strategy sharing among the >300 patient advocacy groups that are part of the RDCRN consortia

https://www.rarediseasesnetwork.org/pags

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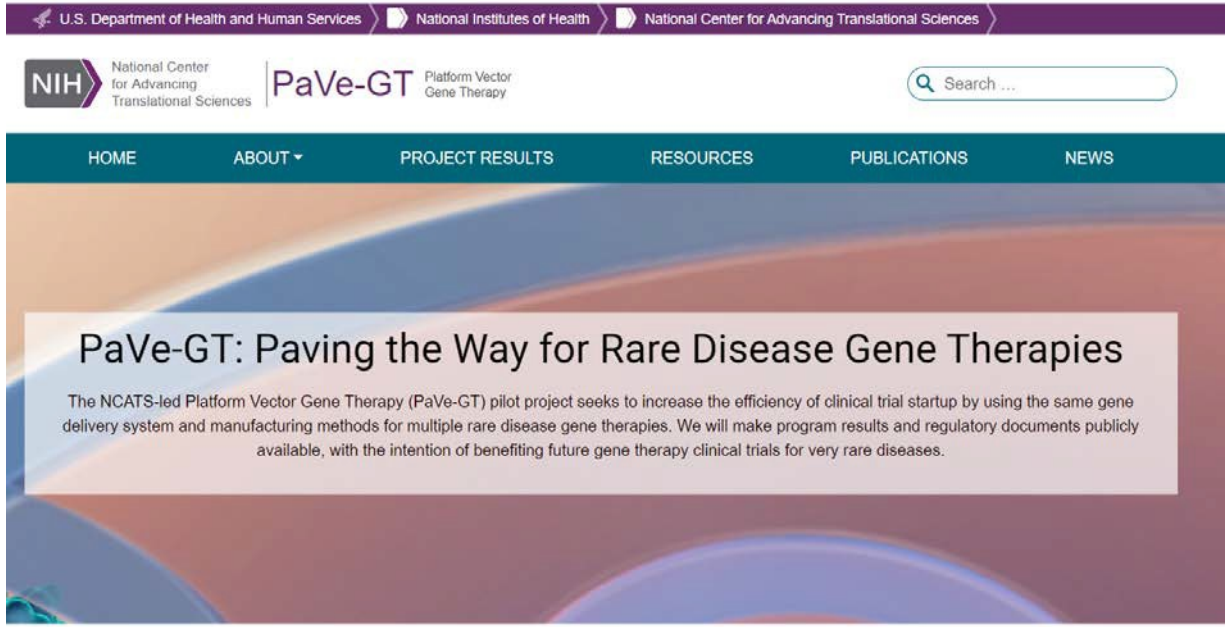

WHY WE NEED PaVe-GT

Approximately 7,000 rare diseases affect 25 million people in the United States, but only about 5 percent of rare diseases have a treatment approved by the U.S. Food and Drug Administration (FDA).

Fortunately, it is becoming increasingly possible to develop gene therapies for rare diseases. A rapidly maturing therapeutic platform — adeno-associated virus (AAV) gene therapy — holds great promise for many rare diseases. AAV gene therapies use a modified version of a virus called adeno-associated virus to deliver a working copy of a defective gene into the cells relevant for a given disease. AAV has been shown to deliver therapeutic genes to cells in the eye, liver, brain, muscle and other organs. In recent years, AAV gene therapies have been approved by the FDA for treating diverse rare diseases, including a retinal disorder and a neurodegenerative condition. For many rare diseases, the limiting factor for developing a gene therapy is not scientific knowledge, but rather operational and financial hurdles, particularly for the thousands of rare diseases that are so rare there is no clear business model for bringing a gene therapy to market. These therapies for diseases of no commercial interest are sometimes referred to as "bespoke" therapies.

In theory, the process of testing new AAV gene therapies for safety prior to human trials could be streamlined because AAV gene therapies for distinct diseases can use the same outer shell, called a capsid, and the same manufacturing methods. If those two factors were kept the same, central questions in preclinical testing, like the biodistribution of a therapeutic, might need to be answered only once for each method of manufacturing an AAV gene therapy, which would save time, money and animal resources. Entire sections of Investigational New Drug (IND) applications might be able to be reused like templates. This approach may be significantly more efficient than using different manufacturing and testing processes for each gene therapy, saving precious time and resources on the road to developing and testing a gene therapy.

The goal of NCATS' PaVe-GT pilot program is to test whether we can significantly increase the efficiency of gene therapy trial startup by using a standardized process, with the same capsid and manufacturing methods, for four different rare diseases. Importantly, we will test this hypothesis in a transparent manner so that results, documents and learnings resulting from the program will be made publicly available and can therefore be used to benefit subsequent AAV gene therapy efforts.

LEARN MORE ABOUT PaVe-GT

https://pave-gt.ncats.nih.gov/

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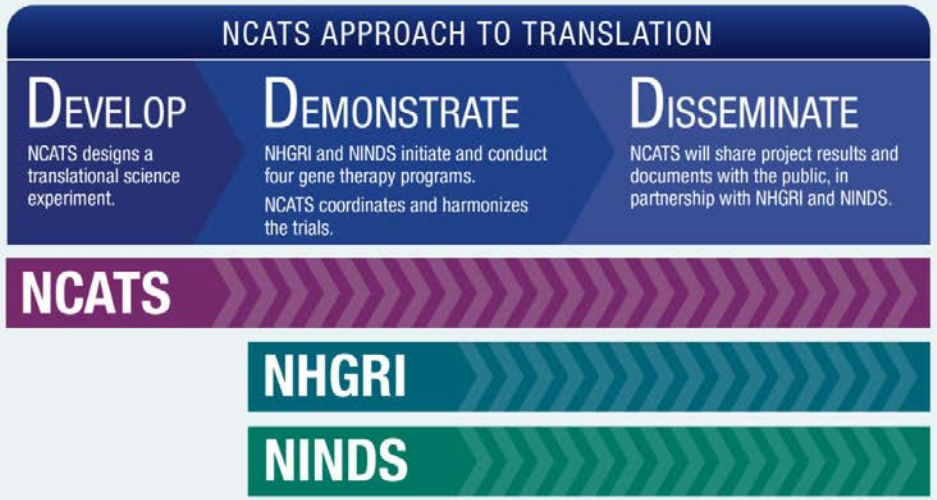
Partners Across NIH: Translational Science Is a Team Sport

The PaVe-GT project is led by NCATS and includes collaborators at different institutes across NIH because surmounting obstacles in translational science requires teamwork that brings together expertise from different fields. Together, the PaVe-GT team will answer a pressing translational science question in AAV gene therapy:

Can researchers significantly increase the efficiency of gene therapy trial startup by using the same capsid and manufacturing methods for different AAV gene therapies, thereby minimizing redundancies in the preclinical development of gene therapies for extremely rare diseases?



GET TO KNOW PaVe-GT

https://pave-gt.ncats.nih.gov/

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Patient membership on the research team is a “disruptive technology” for rare disease therapy development

News & Events
- Releases & Announcements
- Media Coverage
- Grantee & Partner News
- Events

Stories & Publications

Media Resources

Connect with NCATS

NCATS is committed to including diverse patient and community perspectives in all phases of translational science, from basic research to public health implementation. Each year NCATS staff host NCATS Day to facilitate and advance robust dialogue and meaningful collaboration.

NCATS Day 2019:

NCATS Day 2019, held on December 17, featured thoughtful discussion, perspectives and insights into data sharing in the translational science community.

The collection and analysis of data is important for translating research results into new prevention strategies and treatments that can improve human health. Sharing of scientific data helps validate research results, enables researchers to combine data types to strengthen analyses, facilitates reuse of hard-to-generate data or data from limited sources, and contributes to ideas for future research directions. Central to data sharing is the recognized need to make it as available as possible while ensuring the confidentiality and autonomy of research participants.

NCATS is committed to placing patients and their communities at the center of all our efforts and looks for opportunities to include the patient perspective. At NCATS Day 2019, attendees discussed data sharing from different viewpoints, including the research participant, community, researcher, federal funder and industry. Attendees taking part in this vital dialogue heard the important perspectives of stakeholders from diverse backgrounds.

Walkley *et al. Orphanet Journal of Rare Diseases* (2016) 11:161
DOI 10.1186/s13023-016-0540-x

Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

Fostering collaborative research for rare genetic disease: the example of niemann-pick type C disease

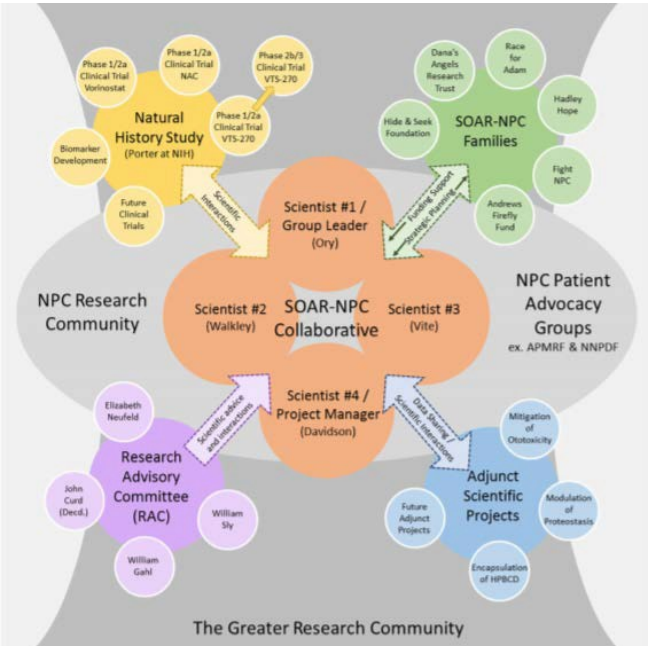
Steven U. Walkley[1*], Cristin D. Davidson[1], Jonathan Jacoby[2], Philip D. Marella[3], Elizabeth A. Ottinger[4], Christopher P. Austin[5], Forbes D. Porter[6], Charles H. Vite[7] and Daniel S. Ory[8]

Abstract

Rare disease represents one of the most significant issues facing the medical community and health care providers worldwide, yet the majority of these disorders never emerge from their obscurity, drawing little attention from the medical community or the pharmaceutical industry. The challenge therefore is how best to mobilize rare disease stakeholders to enhance basic, translational and clinical research to advance understanding of pathogenesis and accelerate therapy development. Here we describe a rare, fatal brain disorder known as Niemann-Pick type C (NPC) and an innovative research collaborative known as Support of Accelerated Research for NPC (SOAR-NPC) which illustrates one pathway through which knowledge of a rare disease and its possible treatments are being successfully advanced. Use of the “SOAR” mechanism, we believe, offers a blueprint for similar advancement for many other rare disorders.

Keywords: Cyclodextrin, Collaborative science, Drug pipeline, Lysosomal disease, Miglustat, Niemann-Pick C, Patient advocacy, Rare disease, Therapy development, Translational medicine

Fig. 2 SOAR-NPC Collaborative meeting. A face-to-face meeting of SOAR-NPC members as occurred at the Rose F. Kennedy Center at the Albert Einstein College of Medicine on February 26, 2014. Pictured are (*left to right*), Daniel S. Ory, Cristin D. Davidson, Charles H. Vite, Steven U. Walkley, Philip D. Marella and Sean Recke (not shown: Jonathan Jacoby). Individuals shown have consented to having their pictures published



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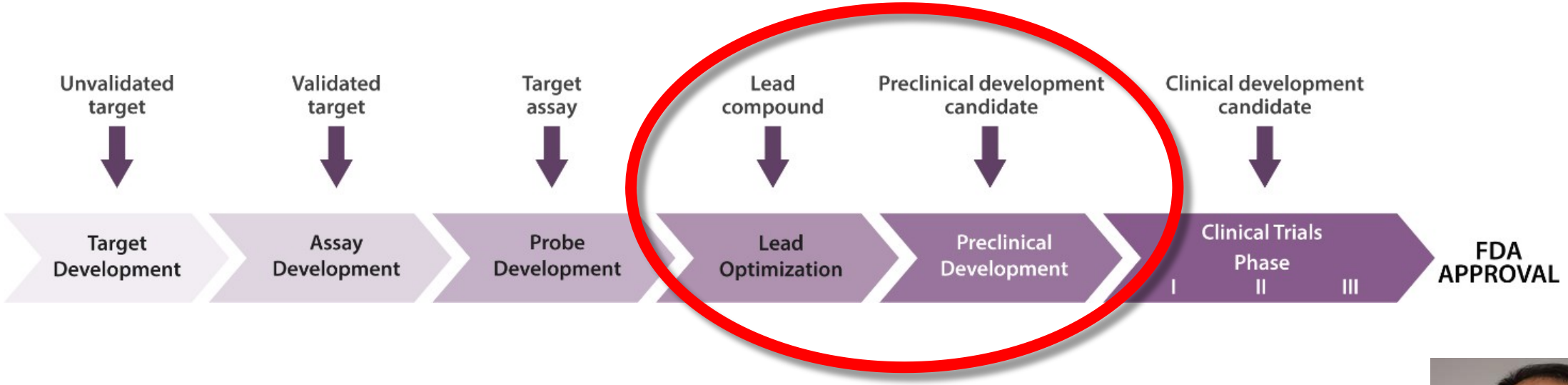
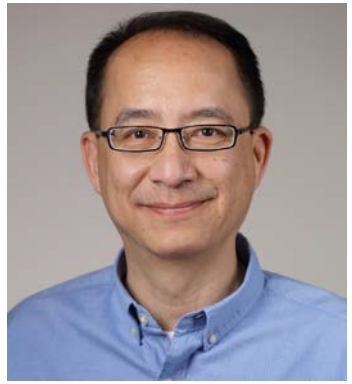
NCATS Therapeutic Development Branch:

Lead candidate to Investigational New Drug (IND) filing with FDA



- IND clearance required to initiate clinical trials
- **IND-enabling studies** typically take 2-5 years and cost average of $4M+
- Few funding mechanisms in this area
- Commercial investment scarce because of high failure rates
- Helping cross the drug development "**Valley of Death**" is TDB's *raison d'etre*



Don Lo, Director
https://ncats.nih.gov/staff/lodc

https://ncats.nih.gov/trnd

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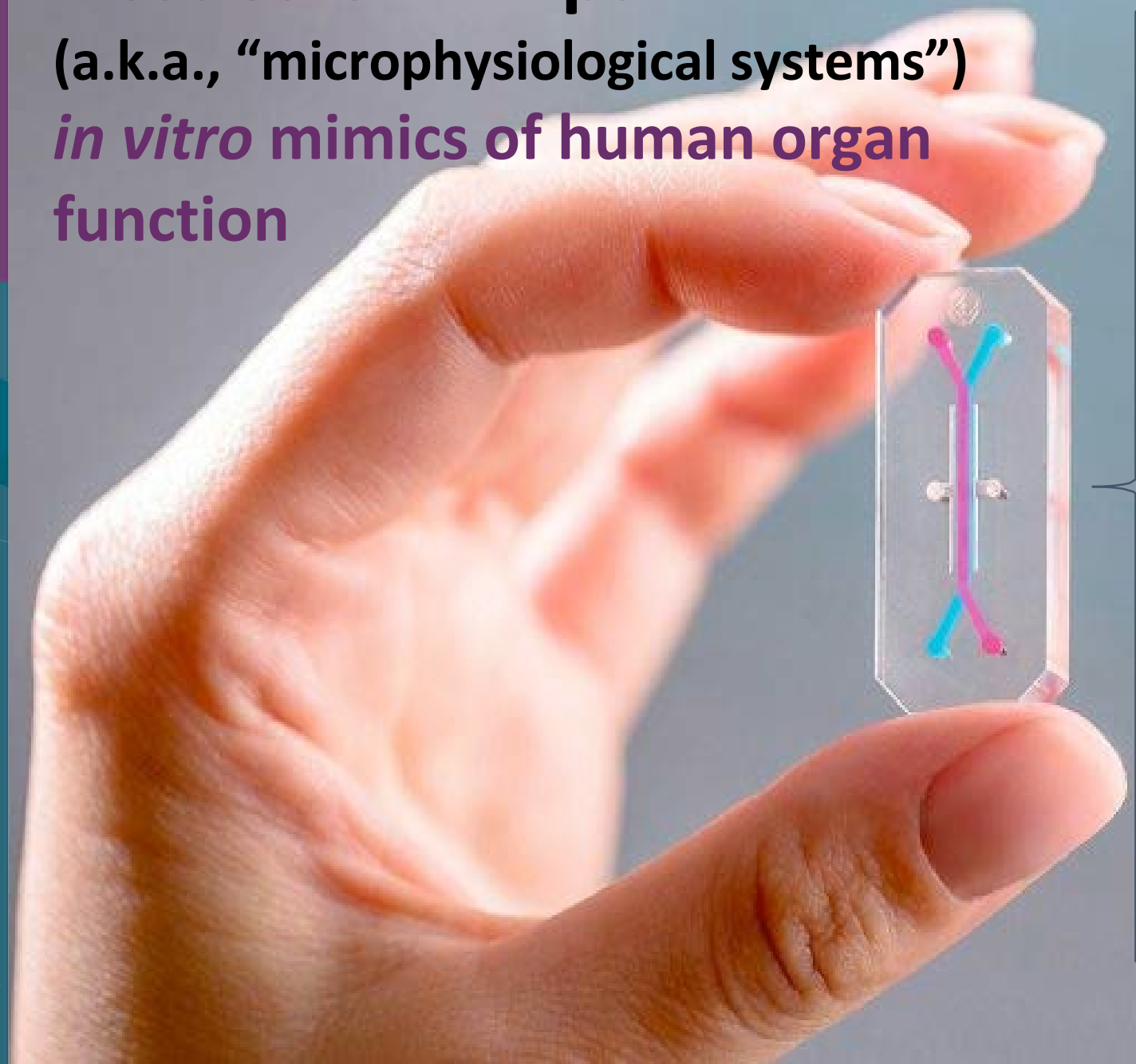
Tissues-on-Chips

(a.k.a., “microphysiological systems”)

in vitro mimics of human organ function



Scaffold

Cells

Structure

Spatial and Temporal Patterning

Perfusion

Bioreactor

Innervation

Host Response

Functional Readout

Computational Design

- Microfluidic cell culture devices
- Created with microchip manufacturing methods
- Contains continuously perfused chambers
- Seeded by human-derived cells
- Cytoarchitecture mimics tissue- and organ-level physiology
- High-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities

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Using tissue chips to model diseases and drug efficacy

Kam Leong, Columbia U
Proteus Syndrome and DiGeorge Syndrome

Danielle Benoit, Lisa Delouise, Catherine Ovitt, U Rochester
Radiation-induced xerostomia

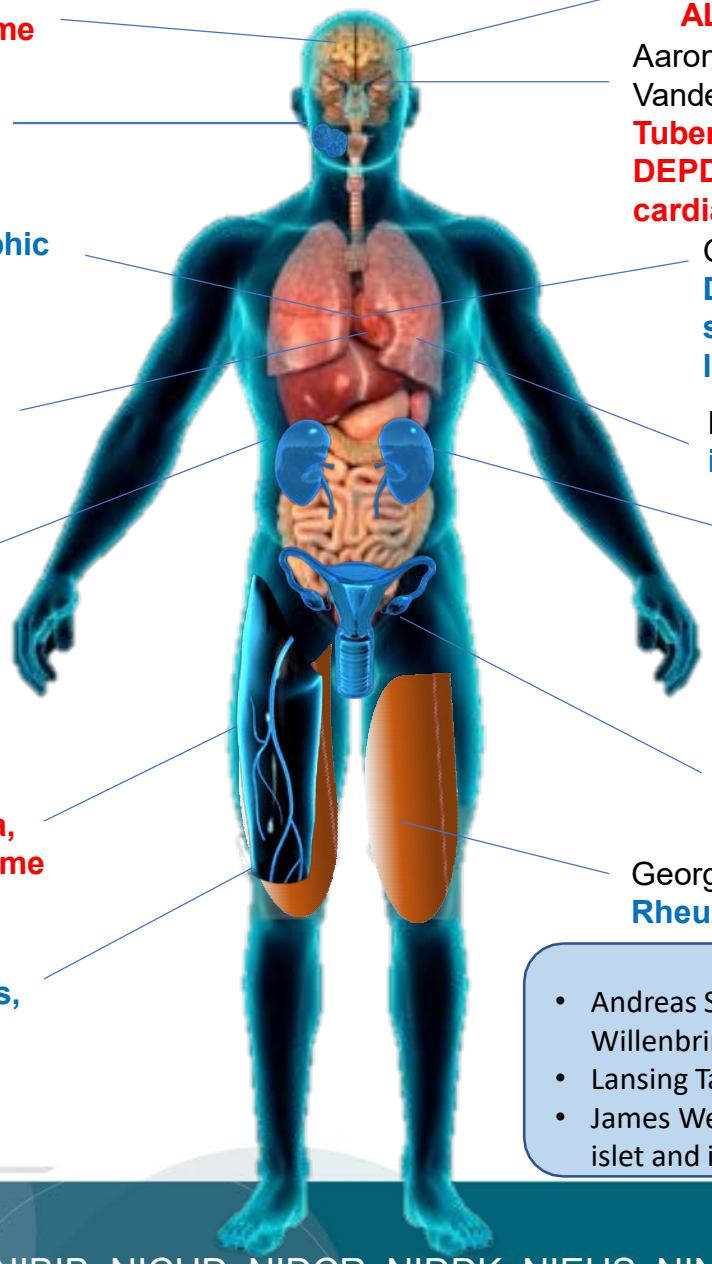
Kevin Kit Parker, William Pu, Harvard U
Barth syndrome, Catecholaminergic polymorphic ventricular tachycardia, Arrhythmogenic cardiomyopathy

Steven George, David Curiel, Stacey Rentschler, UC Davis and WashU **Atrial fibrillation**

Joseph Vincent Bonventre, Luke Lee, Brigham and Women's
Polycystic kidney disease, Focal segmental glomerulosclerosis

Christopher Hughes, UC Irvine
Hereditary hemorrhagic telangiectasia, Port Wine stain, Sturge-Weber syndrome

Rocky Tuan, U Pittsburgh
Osteoarthritis, inflammatory arthritis, adipose-mediated diabetic joint complications



Clive Svendsen, Cedars-Sinai
ALS; Parkinson's Disease

Aaron Bowman, Kevin Ess, John Wikswo, Vanderbilt U
Tuberous sclerosis complex (TSC) epilepsy, DEPDC5-associated epilepsy, & associated cardiac dysfunction

Gordana Vunjak-Novakovic, Columbia U
Dox induced cardiomyopathy; multi-system pathologies involving heart, liver, skin, bone and vasculature

Donald Ingber, Harvard U
influenza infection, COPD

Jonathan Himmelfarb, U Washington
Apolipoprotein L1 mediated kidney disease, drug induced and host-pathogen interaction induced renal thrombotic microangiopathies

Teresa Woodruff, Northwestern U
Polycystic ovarian syndrome

George Truskey, Duke U
Rheumatoid arthritis, atherosclerosis

Type-2 Diabetes Mellitus

- Andreas Stahl, Kevin Healy, Matthias Hebrok, Edward Hsiao, Holger Willenbring, UC Berkeley - Pancreatic islet, liver, adipose
- Lansing Taylor, U Pittsburgh – Vascularized liver and pancreatic islets
- James Wells, Moo-Yeal Lee, Cincinnati Children's Hospital - Liver, pancreatic islet and intestine

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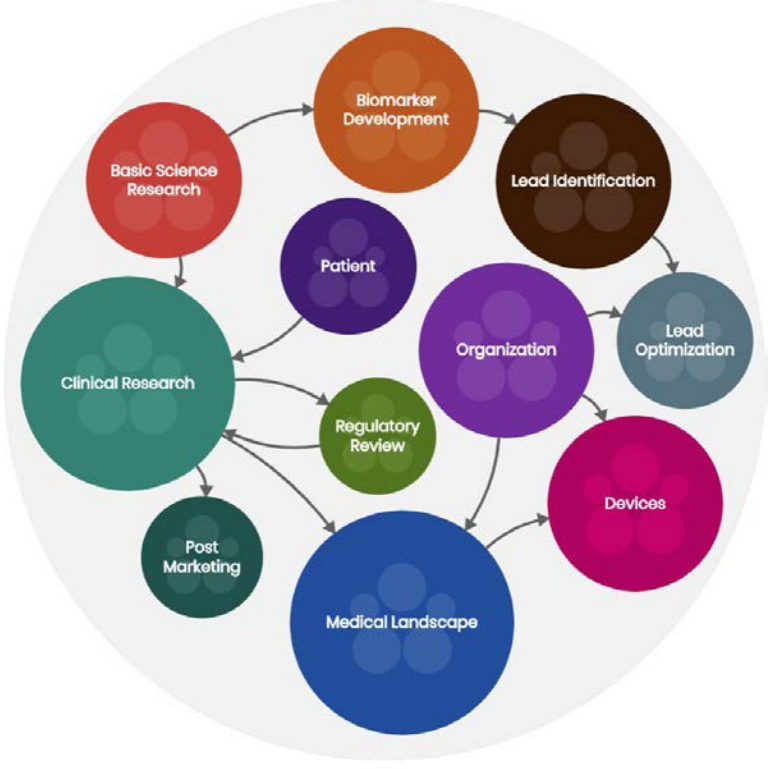
Advancing understanding of translation:

The Drug Discovery, Development and Deployment Map

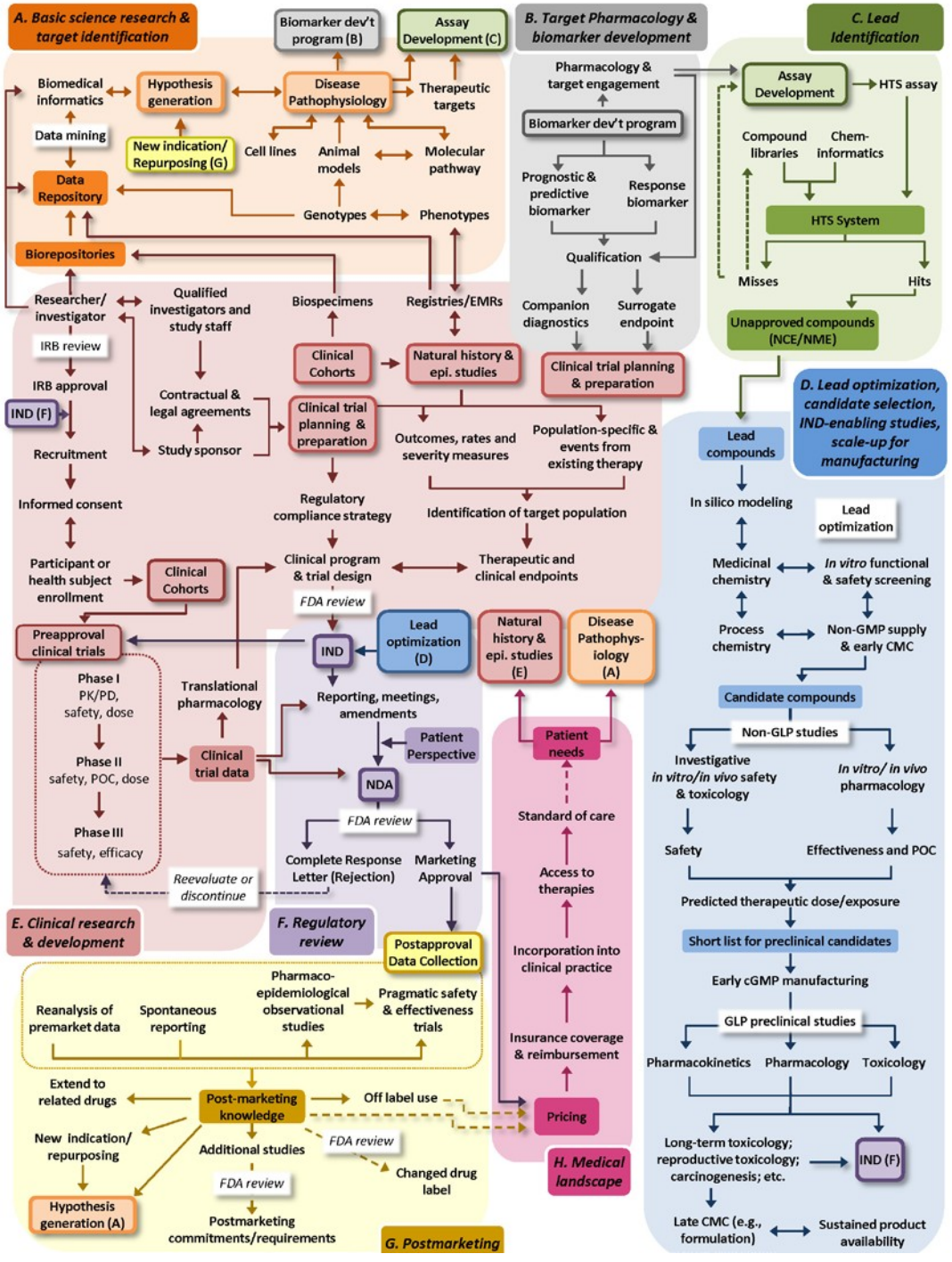
- **Problem**: many stakeholders unaware of complexity of developing therapeutic interventions; systems engineers lack common framework for improvements
- **Solution**: create an accurate portrayal of the translational process to educate stakeholders and identify opportunities for innovation
- **NASEM** Forum on Drug Discovery, Development and Translation developed initial map
- Development continuing to incorporate “GoogleMaps-like” features (“traffic”, “GPS”, programs to assist)
- Freely-available at https://ncats.nih.gov/translation/maps

Drug Discovery, Development and Deployment Map

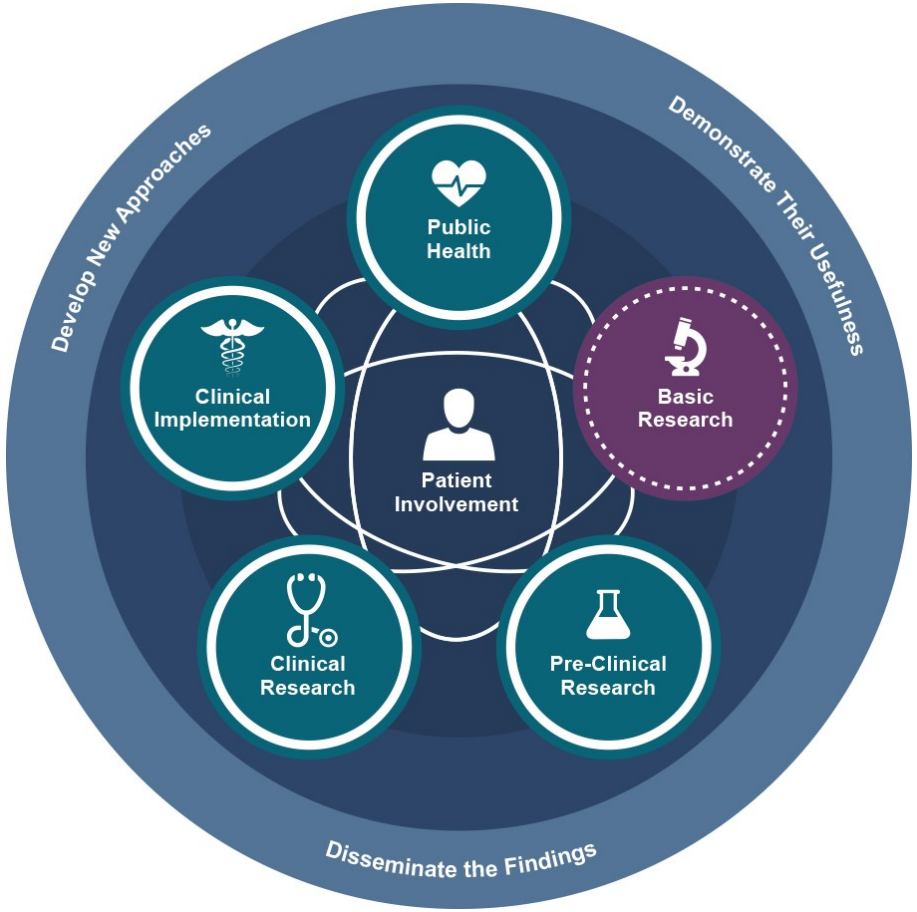
Nature Reviews Drug Discovery 15:150, 2018



https://ncats.nih.gov/translation/maps



The Translational Science Spectrum



NCATS

COLLABORATE. INNOVATE. ACCELERATE.

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