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 regulatory 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
<table>
<thead>
<tr>
<th>Knowledge/Data</th>
<th>Research/Collaboration</th>
<th>Community Engagement</th>
</tr>
</thead>
<tbody>
<tr>
<td>GARD Cluster</td>
<td>Rare Diseases Clinical Research Network</td>
<td>Rare Diseases Day at NIH</td>
</tr>
<tr>
<td>Genetics &amp; Rare Diseases (GARD) Information Center</td>
<td>NCATS Scientific Conference Grants</td>
<td>Rare Diseases Are Not Rare! Challenge</td>
</tr>
<tr>
<td>Rare Diseases Registry Program (RaDaR)</td>
<td>Bench to Bedside Grants</td>
<td>Gene Therapy Meeting Series</td>
</tr>
<tr>
<td>NCATS Toolkit for Patient-focused Drug Development</td>
<td>Clinical Trial Readiness Grants</td>
<td>International Collaboration IRDiRC</td>
</tr>
<tr>
<td>Impact of Rare</td>
<td>PaVe-GT</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Odyssey</td>
<td>Shared Molecular Etiologies Grants</td>
<td></td>
</tr>
</tbody>
</table>
NCATS “Many Diseases at a Time” Research Programs

Providing Information and “Big Data”

Developing Interoperable Registries

Empowering Patients as Research Partners

Natural History and Interventional Studies
NCATS “Many Diseases at a Time” Research Programs

Partnering to Change Perceptions

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 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 Pseudobulbar Palsy (PBP). When my dreams of playing a sport in college ended, I needed something else to apply myself to. This began my journey as a rapper and spoken word artist. When I was diagnosed, I 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; to encourage those who are challenged, whether with rare disease or in general, to raise awareness for rare disease.”

First Place 2018
Nancy Netherland

Partnering to Share Knowledge

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

Nancy Netherland

First Place 2018
San Diego, CA

Advancing the Science

Exploring scientific advances and the meeting included invited talks from three leaders in the field, sharing new advances in human.

Dr. Charles Giller, Chief of the NIH National Institute of Child Health and Human Development, shared his research on gene therapy for rare diseases in globin genes. He pointed out that new technologies for the treatment of rare diseases can help to bring innovative treatments to the clinic. On March 29, 2018, the NIH released a draft guidance on how to develop and bring new drugs to market.

We are always looking for new and innovative ways to help people who suffer from rare diseases.
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
There Is Power in Numbers

Each person’s story matters. Registries turn each patient’s experience into quality data that can lead to new discoveries and research advances.

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/
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/
• 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

DMCC: Cincinnati Children’s Hospital Medical Center

Porphyria Coalition
Inherited Neuropathies
Mitochondrial Disorders
Urea Cycle Disorders
Brain Vascular Malformations
ALS and Related Disorders
Dystonia Coalition
Disorders of glycosylation
Nephrotic Syndrome
Developmental Synaptopathies
Phenylketonuria
Vasculitis Clinical Research Network
Genetic Mucociliary disorders
Congenital infections
Leuko-dystrophies
Primary Immune Deficiency Disorders
Lysosomal storage disorders
Eosinophilic gastrointestinal disorders
Congenital infections
Leuko-dystrophies
Primary Immune Deficiency Disorders
Lysosomal storage disorders
Eosinophilic gastrointestinal disorders

= new consortium in RDCRN4
= continuing consortium from RDCRN3
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
PaVe-GT: Paving the Way for Rare Disease Gene Therapies

The NCATS-led Platform Vector Geno Therapy (PaVe-GT) pilot project seeks to increase the efficiency of clinical trial startup by using the same gene delivery system and manufacturing methods for multiple rare disease gene therapies. We will make program results and regulatory documents publicly available, with the intention of benefiting future gene therapy clinical trials for very rare diseases.

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 "orphan" 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.
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/
Patient membership on the research team is a “disruptive technology” for rare disease therapy development.
**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**

https://ncats.nih.gov/trnd
Tissues-on-Chips (a.k.a., “microphysiological systems”) in vitro mimics of human organ function

- **Scaffold**
  - Microfluidic cell culture devices

- **Cells**
  - Created with microchip manufacturing methods

- **Structure**
  - Contains continuously perfused chambers

- **Spatial and Temporal Patterning**
  - Seeded by human-derived cells

- **Perfusion**
  - Cytoarchitecture mimics tissue- and organ-level physiology

- **Bioreactor**
  - High-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities

- **Innervation**

- **Host Response**

- **Functional Readout**

- **Computational Design**
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
• **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](https://ncats.nih.gov/translation/maps)

---

**Advancing understanding of translation:**

*The Drug Discovery, Development and Deployment Map*

---

**NATURE REVIEWS | DRUG DISCOVERY**

A dynamic map for learning, communicating, navigating and improving therapeutic development

John Wagner, Andrew M. Dahlem, Lynn D. Hudson, Sharon F. Terry, Russ B. Altman, C. Taylor Gilliland, Christopher DeFeo and Christopher P. Austin

*Nat Rev Drug Discov* (2018);17:150

---

**ARTICLE**

Application of a Dynamic Map for Learning, Communicating, Navigating, and Improving Therapeutic Development

*Clin Transl Sci* (2018); 11:166
The Translational Science Spectrum