Collaborative Rare Diseases Research Activities at NIH

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Background

- ~18 - 25 million people in the United States are affected
  - Exact prevalences mostly unknown
  - Good epidemiological studies of prevalence are needed
- Estimated 6%-8% of Population with Global Distribution of Patients
- >7000 Genetic and Acquired Rare Diseases
  - >410 orphan drug approvals in U.S., ~250 diseases
  - >95% of rare diseases have no pharmacotherapy
- Collaborative efforts of the rare diseases community are required for success with use of disease specific committees
  - Academic Research Investigators/ Medical Specialists
  - Federal Research and Regulatory Programs
  - >1100 Patient Advocacy Groups/Philanthropic Foundations
  - Pharmaceutical, Biotechnology, and Medical Device Industries
- U.S. Congressional Rare Diseases Caucus established
Why The Increased Interest in Rare Diseases and Orphan Products?

- Increase in Scientific Opportunities
- Growing Public Recognition that Rare Diseases Represent a Global Public Health Issue Due to Increased Public and Media Interest
- Increased Number of Research Investigators Experienced in Rare Diseases Multi-Center, International Clinical Trials
- Improved Patient Recruitment is Possible With Expanded Roles of Patient Advocacy Groups
- Public-Private Partnerships Increasing
- Increased Industry Interest in Niche Markets
  - Driven by high prices possible and formulary acceptance
- Opportunities for Repurposing of Approved and Investigational Products
- Better Models Available for Research Design with Small Patient Populations
- Expanding Federal, National, and International Interest and Support
- Development of More Directed Research Agenda Leading to Interventions and Diagnostics
Rare Disorders with Identified Molecular Basis

Source: Online Mendelian Inheritance in Man
Rare Diseases Research Activities (NIH)

- **Research, Condition, Disease Categorization (RCDC) for Rare Diseases and Orphan Drugs FY 2011**
  - NIH Rare Diseases – $3.623 Billion (~9400 Research Projects, 2137 rare diseases)
  - NIH Orphan Drugs – $809 Million (~1650 Research Projects)
  - ~12% of NIH Research Budget

- **Clinical Center Bedside to Bench Research Program**

- **Undiagnosed Diseases Program - Expansion Announced Through Common Fund Program**

- **NIH translational resources**
  - NCATS - Therapeutics for Rare and Neglected Diseases (TRND) Program
  - NCI - Experimental Therapeutics (NExT) Program
  - NINDS - Neurological Experimental Therapeutics (NeuroNEXT) Program
  - NICHD - Newborn Screening Translational Research Network; Best Pharmaceuticals for Children Act
  - NHLBI - Centers for Accelerated Innovation
To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.
Catalyzing Collaboration within NCATS Across the Translational Spectrum
Examples of team/network-requiring translational problems

- Predictive toxicology
- Predictive efficacy
- Derisking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- EHRs for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
NCATS Innovation Areas

- Discovery Innovation
  - What to intervene on?
- Preclinical Innovation
  - How to intervene?
- Clinical Innovation
  - Who to intervene on?
- Cross-cutting
  - Rare Diseases
  - Special Initiatives
  - Strategic Alliances
  - Communications, Education
- Operational
  - Scientific Review and Grants Management
  - Administration

Obligatory Collaboration
Galactosemia

- Rare autosomal recessive disorders in which the body cannot properly metabolize galactose

**The Diseases:**

- **Classic Galactosemia** (Galactose-1-phosphate uridyl transferase deficiency)
  - Occurs in ~1 in 30,000 to 1 in 60,000 births
  - Most common, most severe, and lethal if milk and galactose are not quickly removed from infant’s diet.
  - Mental deficits are major clinical outcome shown in health related quality of life surveys: Cognitive function, IQ deficits, ataxia, speech dyspraxia,
  - 75-96% of all women who are homozygous for GALT deficiency have ovarian dysfunction

- **Type II Galactosemia** (Galactokinase Deficiency)
  - Occurs in ~1 in 100,000 births
  - Comparatively mild with severe manifestations not appearing in infancy

- **Type III Galactosemia** (UDP-galactose epimerase deficiency)
  - Very rare and presents similarly to Classic Galactosemia

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**Children ages 16+**

**TABLE 4.** Mean HRQoL Scores (TAAQOL) for Children With Galactosemia and for the General Population

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean Patients With Galactosemia (n = 17)</th>
<th>Mean General Population (n = 350)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor</td>
<td>89.7</td>
<td>93.7</td>
<td>.28</td>
</tr>
<tr>
<td>Fine motor</td>
<td>95.2</td>
<td>97.9</td>
<td>.30</td>
</tr>
<tr>
<td>Pain</td>
<td>75.0</td>
<td>81.0</td>
<td>.47</td>
</tr>
<tr>
<td>Sleeping</td>
<td>77.2</td>
<td>79.5</td>
<td>.70</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>72.4</td>
<td>84.0</td>
<td>.04</td>
</tr>
<tr>
<td>Social function</td>
<td>76.8</td>
<td>89.0</td>
<td>.04</td>
</tr>
<tr>
<td>Daily activities</td>
<td>90.8</td>
<td>84.1</td>
<td>.05</td>
</tr>
<tr>
<td>Sexuality</td>
<td>89.7</td>
<td>90.9</td>
<td>.82</td>
</tr>
<tr>
<td>Vitality</td>
<td>58.8</td>
<td>68.0</td>
<td>.11</td>
</tr>
<tr>
<td>Happiness</td>
<td>67.6</td>
<td>73.3</td>
<td>.25</td>
</tr>
<tr>
<td>Depressive moods</td>
<td>80.4</td>
<td>81.5</td>
<td>.70</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>92.2</td>
<td>86.5</td>
<td>.09</td>
</tr>
</tbody>
</table>

High scores indicate better quality of life. *P < .05.

Bosch et al. *Pediatrics* 2004, 113, e423
Galactokinase as a Target

- Type II galactosemics (GALK deficient) do not suffer from same clinical manifestations and long-term problems associated with Classic Galactosemia.
- Gal-1-p is the product of GALK and is thought to be a major contributor to CG phenotype, but its mechanism is not known.
- GALT-deficient primary patient cells accumulate ~5 mM gal-1p, but GALK deficient and normal cells accumulate ~0.01 mM.
GALK Inhibitor Program at NCATS, in Collaboration with Kent Lai at U. of Utah

Primary Patient Cell Data:
Compound effectively lowers gal-1-p levels in CG patient fibroblasts after galactose challenge

- **RO1 Funding Allows for First Ever Characterization of Animal Model for CG (completed end of January 2013)**
- **In vivo Experiments with NCGC00242658 started beginning of March**

**Kinetics of Gal-1P accumulation & disappearance in three normal (N) and three mutant (M) mice under varying periods of 40% galactose diet. (Expts. #2 & #4)**
Enabling Comprehensive Drug Repurposing

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be “repurposed” for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

Developing new medicines for (rare) blood cancers: The Learning Collaborative

- Bench-to-bedside translation in drug repurposing
- National leadership in medicinal and pharmaceutical chemistry
- Pharma experience

The Learning Collaborative™

- Focus on rare and neglected diseases
- Industrial scale HTS, cheminformatics, medicinal chemistry, drug development capabilities
- Pharma experience

- ~400 active research projects
- Worldwide network of blood cancer experts
- Track record of commercial partnerships
- Pharma experience
Rare Diseases Research Activities (NCATS): Therapeutics for Rare and Neglected Diseases (TRND) Program

- **Model:** Collaboration between NIH intramural labs with preclinical drug development expertise and extramural labs with disease-area / target expertise

- **Projects:**
  - May enter at various stages of development
  - Taken to stage needed to attract external organization to adopt for final clinical development
  - Serve to develop new generally applicable platform technologies and paradigms

- **Eligible Applicants:**
  - Academic, Non-Profit, Government Lab, Small Business, or Large Biotech / Pharma
  - Ex-U.S. applicants accepted

- **Intellectual Property:**
  - Partnerships are creative
  - TRND may generate intellectual property
## TRND Portfolio

<table>
<thead>
<tr>
<th>Therapeutic Area / Disease</th>
<th>Collaborator(s)</th>
<th>Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle Cell Disease</td>
<td>Aes-Rx, NHLBI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NME – Small Molecule</td>
<td>Clinical</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>Leukemia &amp; Lymphoma Society, University of Kansas</td>
<td>Repurposed Drug – Small Molecule</td>
<td>Clinical</td>
</tr>
<tr>
<td>Hereditary Inclusion Body Myopathy</td>
<td>New Zealand Pharmaceuticals, NHGRI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NME – Small Molecule</td>
<td>Clinical</td>
</tr>
<tr>
<td>Niemann-Pick Type C1</td>
<td>Johnson &amp; Johnson, Albert Einstein College of Medicine, Univ. of Pennsylvania, Washington Univ., NICHD&lt;sup&gt;c&lt;/sup&gt;, NINDS&lt;sup&gt;d&lt;/sup&gt;, NHGRI</td>
<td>Repurposed Drug - Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>ReveraGen BioPharma</td>
<td>NME – Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Cryptococcal Meningitis</td>
<td>Viamet Pharmaceuticals, Inc.</td>
<td>NME - Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Core Binding Factor Leukemia</td>
<td>NHGRI</td>
<td>Repurposed Drug - Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Neonatal Herpes Simplex</td>
<td>University of Alabama, NIAID&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NME – Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Autoimmune Pulmonary Alveolar Proteinosis</td>
<td>Cincinnati Children’s Hospital</td>
<td>Repurposed Drug - Biologic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Fibrodysplasia Ossificans Progressiva</td>
<td>Massachusetts General Hospital</td>
<td>NME - Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>CoNCERT Pharmaceuticals</td>
<td>NME – Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Creatine Transporter Defect</td>
<td>Lumos Pharma</td>
<td>NME - Small Molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Sarepta Therapeutics</td>
<td>NME – Biologic</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

<sup>a</sup> National Heart, Lung, and Blood Institute; <sup>b</sup> National Human Genome Research Institute; <sup>c</sup> Eunice Kennedy Shriver National Institute of Child Health and Human Development; <sup>d</sup> National Institute of Neurological Disorders and Stroke; <sup>e</sup> National Institute of Allergy and Infectious Diseases
Niemann-Pick Type C Disease: A Collaborative Effort  
Academic, Government, and Industry Public-Private Partnership

Pooled resources: funding and development expertise

- NCATS / TRND centralized project team management
- Multiple NIH Institute-NICHD, NHGRI, NINDS
- Animal models
- Chemistry and manufacturing of clinical trial material
- Biomarkers
- NIH Clinical Center
- Natural history study
- Rare disease advocacy programs

February 2011: 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) selected by TRND as pre-clinical candidate

December 2012: IND filed

February 2013: Phase I initiated and 1st patient dosed
Clinical and Translational Science Awards (CTSA) Program

- Support a national consortium of medical research institutions
- Work together to improve the way clinical and translational research is conducted nationwide
- Accelerate the research translation process
- Provide robust training for clinical and translational researchers
Clinical and Translational Science Awards (CTSA) Program Sites
Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia
A Randomized Controlled Trial

- Published in JAMA October 2012
- Tested a repurposed heart drug in patients with a rare genetic muscle disorder
- Collaboration with NIH’s Rare Diseases Clinical Research Network (RDCRN) and Clinical and Translational Science Awards (CTSA) program at 7 institutions in 4 countries (England, Italy, Canada, United States)
- Recruited enough patients with the rare disease to test the drug in a clinical trial
- RDCRN’s Data Management Coordinating Center collected and managed the data from the 7 sites
- CTSAs provided support for lab tests, electrocardiograms, muscle tests and pharmacy services
- Funded by the U.S. Food and Drug Administration’s Office of Orphan Products Development and by NIH’s National Institute of Neurological Disorders and Stroke (NINDS)
Rare Diseases Research Activities (NCATS): Office of Rare Disease Research

- **Rare Diseases Clinical Research Network (RDCRN)**
  - 17 consortia at 225 institutions worldwide
  - Studying >200 diseases with 83 active protocols, and
  - More than 85 patient advocacy groups participating

- **Genetic and Rare Disease Information Center (GARD)**

- **Scientific Conferences Program**
  - Identify Scientific Opportunities and Establish Research Agendas (1200 Conferences)

- **Global Rare Disease Registry (GRDR) Data Repository**
  - 15 GRDR patient registries + 19 existing registries
  - Ability to conduct pan-disease analysis and recruitment
The Rare Disease Clinical Research Network

Who Are We?

The Rare Diseases Clinical Research Network (RDCRN) is made up of distinctive consortia that are working in concert to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities.

Click on the Consortium Name to view the diseases or disorders studied by each consortium. Clicking on a disease or disorder name will take you directly to a description of that disease or disorder.

- Angelman, Rett, and Prader-Willi Syndromes Consortium
- Autonomic Rare Diseases Clinical Research Consortium
- Brain Vascular Malformation Consortium
- Chronic Graft Versus Host Disease Consortium (CGVHD)
- Dystonia Coalition
- NEPTUNE: Nephrotic Syndrome Study Network
- North American Mitochondrial Disease Consortium
- Porphyrias Consortium
- Primary Immune Deficiency Treatment Consortium
- Rare Kidney Stone Consortium
Office of Rare Diseases Research and FDA

- Many workshops and conferences held jointly:
  - Science of Small Clinical Trials Workshop
  - Adaptive Clinical Trial Design Workshop
  - Rare Disease Day
  - Disease-Specific Conferences
  - Rare Disease Clinical Research Network Consortia: Conducting Studies after Receiving Grant Support from the Office of Orphan Products Development

- FDA presence is crucial to enable cross talk on regulatory issues
30th Anniversary of the Orphan Drug Act

- On January 7, the FDA celebrated the Orphan Drug Act by recognizing 30 rare disease heroes
- Two NCATS programs recognized as research heroes
Tissue Chip for Drug Screening: Microsystems Initiative

- Aims to develop tissue chips that mimic human physiology to screen for safe, effective drugs using best ideas in engineering, biology, toxicology
- NIH Investment (Funded Through CAN + Common Fund) = $70M/5 years
- DARPA Investment = $75M/5 years
- FDA Investment = Regulatory and toxicology expertise
- NCATS and DARPA independently manage and fund separate but highly coordinated programs
Tissue Chip Program

**GOAL:** Develop an *in vitro* platform that uses human tissues that will be predictive of efficacy, pharmacokinetics, safety and toxicity of promising therapies in humans and suitable for regulatory science use.

- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
- Physiologically relevant, genetically diverse and pathologically meaningful
- Modular, reconfigurable platform for easy integration
- Tissue viability for at least 4 weeks
- Community-wide access
Discovering New Therapeutic Uses for Existing Molecules Program

Goal:
To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

The pilot initiative:

- Match candidate Agents from 8 pharmaceutical partners with innovative ideas for new indications from the biomedical research community.
  - **NIH provides:** template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, and oversight
  - **Pharmaceutical partners provide:** compounds, biologics, in kind support, and pertinent data
  - **Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to appropriate patient populations
NCATS: Therapeutics Discovery Pilot
NCATS: Therapeutics Discovery Pilot

58 Agents made available for this pilot program by 8 pharmaceutical company partners*

- AbbVie (formerly Abbott)
- AstraZeneca
- Bristol-Myers Squibb Company
- Eli Lilly and Company
- GlaxoSmithKline
- Janssen Pharmaceutical Research and Development, LLC
- Pfizer
- Sanofi

*listed alphabetically
Meeting Our Shared Goals

• NIH is a willing (and founding) partner for IRDiRC
  ➢ Fostering international partnerships across the translational spectrum
  ➢ Sharing data and resources

• An open invitation to access resources at NIH and NCATS
  ➢ Harness capabilities of research networks
  ➢ Novel collaborative approaches
Final Thoughts

- *Make no little plans; they have no magic to stir men's blood...Make big plans, aim high in hope and work.*
  - Daniel H. Burnham
    US architect & city planner (1846 - 1912)

- **Many hands make light work**
  - John Heywood
    English writer (1497-1580), after Ecclesiastes

- *Have a bias toward action - let's see something happen now. You can break that big plan into small steps and take the first step right away.*
  - Indira Gandhi
NIH...

Turning Discovery Into Health