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New Financial and Research Models for Pediatric Orphan Drug Development - Focus on the NCATS TRND Program

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Abstract

While there are approximately 7,000 identified human diseases considered as "rare" based on population prevalence or incidence, the cumulative impact runs into the millions of patients globally. Although the genetic underpinnings of more than 2,000 rare diseases have been elucidated, there remains a paucity of therapeutic options, frequently due to lack of commercial interest. Development programs suffer high attrition within the so-called "Valley of Death," in which the risks of scientific failure are still too high to justify the increasing development costs. This problem is common to any drug development campaign, but it is particularly exacerbated in the rare diseases, many of which arise in childhood. To stimulate development of therapeutics for these otherwise underserved patient populations, a number of regulatory incentives and research initiatives have been established. Extended patent protections, expedited regulatory reviews for qualified drug sponsors, and clinical trial grant support aim to foster interest in completing development programs. To stimulate researchers to embark on rare disease drug development campaigns, earlier-stage preclinical research resources have been created, as well, such as the Therapeutics for Rare and Neglected Diseases (TRND) program at the U.S. National Institutes of Health (NIH). TRND is a unique NIH program created to support drug development through formation of public-private partnerships. These partnerships leverage the robust biopharmaceutical industry experience of the TRND staff scientists and the deep disease area expertise of the collaborating partners. Each project adopted into the TRND portfolio aims to satisfy two broad goals: developing a novel therapy for a rare or otherwise neglected disease, and exploring ways to accelerate the drug development process overall so that lessons learned can be disseminated to the wider community undertaking translational research. This article discusses common obstacles and opportunities for therapeutic development, and provides examples of the types of projects TRND has undertaken across a broad range of pediatric rare disorders.

Introduction

There are approximately 7,000 identified human diseases considered as rare based on prevalence. In the United States, the Orphan Drug Act defines a disease as rare if it affects

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fewer than 200,000 patients, while in the European Union a disease is considered rare if it affects fewer than five individuals per 10,000 in the overall population.^[1–3] Despite the general classification as "rare", these diseases affect collectively approximately 25 million patients in the U.S., 30 million in the E.U., and millions more throughout the world.^[4] Fundamental research has discovered the genetic basis of more than 2,000 rare diseases and has identified therapeutic approaches for several.^[5] Whereas non-profit academic laboratories have missions more aligned with the long-term exploration required to elucidate the complex mechanisms underlying individual diseases, the for-profit biopharmaceutical industry sector operates on shorter timelines between discovery and market, and must consider the overall financial potential of each development campaign. Thus, it is understandable that the biopharmaceutical industry has limited commercial interest in developing therapies for rare diseases, particularly those that affect smaller pediatric populations. Nearly 50–75% of rare diseases show onset during childhood,^[6] and approximately 30% of affected children die before the age of five. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide resources to facilitate rare disease drug development,^[7, 8] but the impact has been relatively limited, particularly in the case of pediatric rare diseases. The Therapeutics for Rare and Neglected Diseases (TRND) program^[9] is one effort to stimulate and support such research through formation of collaborative public-private research partnerships, with the goal of more efficient therapeutic development for such conditions.

Crossing the Valley of Death

The journey between a fundamental scientific discovery and a marketed therapy that benefits patients is long (10–13 years), expensive (\$ 1 billion) and has a very high attrition rate (>98%), which has been described many times over in various analyses.^[5, 10–12] For example, the New York Times notes that there were 800,000 medical research publications in 2008, while in the same year FDA approved only 21 new drugs. Conventionally, fundamental research is conducted at academic institutions, and is supported by government agencies, such as the U.S. National Institutes of Health (NIH), with a focus on identifying and validating the biological underpinnings of particular diseases. However, academic investigators often lack sufficient financial resources and expertise to conduct drug development campaigns to capitalize on these fundamental biological insights. Screening for hits, identification/optimization of lead compounds, and clinical trials/development are the traditional domain of the pharmaceutical industry. Because of this division between the academic and commercial spheres, very few fundamental biological discoveries are translated into drug discovery/development campaigns. Perhaps the greatest impediment to translation is that, as a candidate project progresses, and its potential to deliver therapeutic benefit increases, it becomes considerably more expensive to run. Very often, it becomes too expensive before it becomes sufficiently promising, and it dies in the so-called "Valley of Death".

If this translational gap is wide for common conditions, it is even more so for rare diseases – particularly in pediatrics – because of their low prevalence, small commercial potential, and the added complexities of conducting clinical trials in children.^[13] Since initial passage of the Orphan Drug Act in 1983, meant to incentivize development of drugs targeting rare

diseases, FDA has granted orphan status to more than 2,000 therapeutic candidates. Approximately 400 of these orphan products have reached marketing approval in the U.S., though "pediatric only" conditions represent a minority of the total.^[7, 14] Nevertheless, it is promising to note that pediatric indications account for an increasing proportion of orphan product approvals.^[15] This demonstrates the value of the Orphan Drug Act and related legislation and regulations in the U.S. and abroad.^[4, 8, 16–19] Such measures provide support and incentives to focus on developing drugs for rare pediatric conditions, as well as investigating the surrogate endpoints that may facilitate more efficient clinical evaluation of novel agents.

Unfortunately, incentives and mandates alone cannot fully bridge all of the development gaps in the "Valley of Death". Practical considerations like dosing, formulation, and drug delivery are important in general, but can pose additional challenges for the pediatric population specifically. For example, if a child cannot or will not swallow tablets, then the common aim of developing an oral pill formulation will likely fall short of the intended clinical aim. Since children tend to exhibit more sensitivity to the taste of medicines, an adult may tolerate a more bitter-tasting pill or liquid, while a child may not. A recent report from the Pediatric Formulations Task Force of the American Association of Pharmaceutical Scientists discusses many such formulation issues and identifies a number of areas for future research.^[20] In some cases, regardless of the formulations effort brought to bear, oral dosing may be incapable of achieving delivery of sufficient quantity of drug to the target organ, for example, across the blood-brain barrier into the central nervous system. If a suitable oral formulation cannot be developed, a more direct route may be required, such as intrathecal injection. The FDA provides a monograph presenting a range of potential routes of administration that one may consider,^[21] although each will have its own advantages, drawbacks, and technical challenges.

The TRND Program

A key aspect of the mission of the NIH National Center for Advancing Translational Sciences (NCATS) (<http://www.ncats.nih.gov>) is to bridge the translational gap in drug discovery and development. Specifically focused on rare disease drug development is the Therapeutics for Rare and Neglected Diseases (TRND) program (www.ncats.nih.gov/trnd.html). TRND forms collaborations between intramural NIH scientists and external researchers from U.S.-based and foreign academic institutes, the private sector, and non-profit organizations. The majority of TRND scientists have a pharmaceutical industry background, bringing extensive drug development skills and experience. TRND adopts projects in need of preclinical development support, from lead optimization through the Investigational New Drug (IND)-enabling studies required to receive clearance from FDA to enter human trials. Rather than a traditional financial grant mechanism, TRND support comprises unparalleled access to the drug development capabilities, expertise, and clinical/regulatory resources of TRND, through formation of a unique public-private partnership. The common goal of each partnership is to generate data of sufficient quality to support successful IND filing, and generally de-risk the project such that it becomes attractive to an outside biotechnology, pharmaceutical, or venture capital company that will be required to complete the final stages of full clinical development. TRND seeks to adopt therapeutic

candidates that will be transformational for the target patient populations and address otherwise unmet medical needs. This includes diseases for which no therapy exists, as well as those with available treatments that suffer from clear deficits upon which a novel therapeutic can improve.

Outside of the individual development projects, TRND also seeks to develop platform technologies and innovative approaches that can foster greater efficiency in drug discovery and development overall. Thus, TRND's broadest objective is to advance the entire field of drug development and improve success rates. Since its founding in 2009, TRND has developed a broad portfolio of projects targeting a diverse range of rare and neglected diseases, with four projects to-date having reached the clinic.^[22] The majority of the projects adopted by TRND represent pediatric diseases (Table I). The following selected examples highlight the range of support TRND provides.

Niemann–Pick Type C1 Disease (NPC1)

Niemann-Pick Type C1 disease is a fatal genetic disease marked by a failure to metabolize and dispose of cholesterol and lipids. Unesterified cholesterol is important for the remodeling of neural cell plasma membranes, which have a high turnover rate (20% per day in central nervous system neurons).^[23] The NPC1 protein is involved in cholesterol and lipid disposal, but mutations in NPC1 impair its function, leading to toxic accumulation, which results in various symptoms of the disease, including progressively impaired movement and intellectual function. NPC1 has been referred to as a "childhood Alzheimer disease". Many patients die before 10 years of age, and the majority of patients do not survive beyond age 20. There are no FDA-approved therapies for NPC1. The molecule 2-hydroxypropyl- β -cyclodextrin (HPBCD) has been shown to reduce the characteristic cholesterol and lipid accumulation, and prolong survival in animal models of NPC1 disease.^[24]

A major hurdle to developing this therapy is the delivery of HPBCD to the target neural cells. To address this problem, TRND has collaborated with researchers from seven different academic and industrial organizations to develop an innovative solution: a safe, effective system for delivery of HPBCD directly into the CNS of patients. TRND conducted the animal toxicology studies necessary for IND filing, helped to support biomarker studies, and prepared for and participated in two pre-IND meetings with the FDA. Early engagement and ongoing interaction with patient advocacy groups have also provided key inputs toward developing an efficient clinical evaluation strategy. TRND started the first-in-human clinical trials in early 2013.

Core-Binding Factor Leukemia

Approximately 12,000 new cases of acute myeloid leukemia (AML) and 5,000 new cases of acute lymphoid leukemia (ALL) were diagnosed in the U.S. in 2010. Leukemia is often associated with specific recurrent chromosome translocations and inversions that generate fusion genes, which play critical roles in leukemogenesis. The transcription factors RUNX1 (Runt-related transcription factor 1) and CBF β (core-binding factor β) are two such proteins that form a DNA-binding heterodimer that regulates leukemic gene expression.^[25] With

current treatments, the long-term survival rate for CBF leukemia is only about 40–50%.^[26] TEL-RUNX1 pediatric leukemia has a survival rate of >80%,^[27] but there is significant morbidity associated with the current standard of care. It was hypothesized that inhibitors of the CBF β -RUNX1 interaction would have potential therapeutic effects for all CBF-related leukemias.^[28, 29]

TRND is supporting collaborators at the National Human Genome Research Institute (NHGRI) in developing targeted treatments for the subgroup of CBF β leukemias. The NHGRI researchers identified a series of lead compounds that inhibit CBF β -RUNX1 protein interactions,^[30] demonstrating an ability to reduce leukemic burden in preliminary studies in mouse models of disease. The objective of the TRND/NHGRI collaboration is to optimize the lead compound and identify an ultimate clinical candidate, which will then undergo the IND-enabling studies necessary to progress to proof of concept in early clinical trials.

Creatine Transporter Deficiency (CTD)

Creatine transporter deficiency (CTD) is a rare X-linked condition, broadly classified as an Autism Spectrum Disorder, leading to varying degrees of relatively profound mental retardation, delays in language development, and autism. Approximately 42,000 males in the U.S. are affected by CTD, and there are no approved treatments. CTD results from mutations in the creatine transporter gene, SLC6A8. Over 120 mutations in SLC6A8 have been identified that result in loss of function of the transporter.^[31, 32] Creatine is an important cellular energy source, and the metabolic deficits due to impaired creatine transport are most pronounced in neurons.

TRND is collaborating with Lumos Pharma (<http://lumos-pharma.com/>) to develop a small molecule therapy for CTD. Lumos scientists demonstrated that the creatine structural analog, cyclocreatine, is able to penetrate cells independent of the creatine transporter and serve as an energy source. This analog has been shown to improve performance in behavioral tests in mice with CTD.^[33] TRND is supporting preclinical development, including animal model efficacy and pharmacokinetic studies, development of bioanalytical assays, scale-up and process synthesis, establishment of an oral dosage formulation, and preclinical toxicology and safety pharmacology studies required to submit an IND application. TRND is also initiating a natural history study of CTD to gather information that will be important for developing clinical trial plans.

Fibrodysplasia Ossificans Progressiva (FOP)

Fibrodysplasia Ossificans Progressiva (FOP) is a rare form of Heterotopic Ossification (HO), the formation of ectopic bone in skeletal muscle and other connective tissues. HO represents an important cause of morbidity from joint immobility and pain. FOP is inherited as an autosomal dominant trait, associated with activating mutations in *Acvr1*, the gene encoding the Bone Morphogenetic Protein (BMP) type I receptor, ALK2. FOP patients have only minimal skeletal abnormalities at birth, but traumatic injury or inflammation can trigger extensive HO affecting nearly all skeletal muscles, ligaments, and fascia. Currently there is no effective treatment for FOP patients, and disease progression results in severe restriction of joint function and premature mortality.^[34]

TRND collaborators at Massachusetts General Hospital identified dorsomorphin as the first small molecule able to block BMP signaling, through inhibition of BMP type I receptors.^[35] The researchers developed dorsomorphin derivatives through medicinal chemistry optimization, identifying a lead compound (LDN-193189) with much better potency and selectivity than the parent compound.^[36] LDN-193189 is well tolerated in mice, has low toxicity, and good oral availability. Most importantly, LDN-193189 has shown to be efficacious in a mouse model of FOP disease. Pending an exploratory toxicology study of LDN-193189 in mice, TRND will perform lead optimization or select a replacement compound, followed by scale-up synthesis, development of an optimal oral formulation, pharmacokinetic, ADME and toxicology studies, and IND submission. Phase I tolerability studies in humans may also be conducted.

Conclusion

Development of therapeutics specifically for pediatric diseases lags behind that for the adult population. This is especially noticeable in the rare disease arena, despite the cumulative millions globally affected by such conditions. Individual rare disease populations are often too small to garner significant interest from the biopharmaceutical industry, particularly in light of the relatively high risk of failure in the so-called "Valley of Death". The adult-pediatric disparity is compounded by the added complexities of conducting clinical evaluation of new therapeutics in children. However, efforts are underway to narrow these gaps.

Regulatory incentives exist to stimulate pediatric rare disease therapeutic development. For example, the FDA, through the Orphan Drug Act, can provide drug sponsors with tax credits for qualified clinical testing, a waiver of some user fees, and a period of market exclusivity after approval of the drug. The Best Pharmaceuticals for Children Act provides for additional exclusivity protections. Similar incentives exist elsewhere in the world, from Europe, to Asia, to Australia. Researchers have made the case for improved and expanded access to accelerated approval mechanisms for rare diseases,^[37] and recent legislation^[38] has given FDA new tools to expedite approvals for potential "breakthrough therapies" for patients with serious or life-threatening diseases. This should prove particularly beneficial to the pediatric rare diseases, with their dearth of therapeutic options.

Research support funds are also available, such as FDA grants to support clinical safety and efficacy studies for rare disease drugs and devices. Depending upon the clinical phase and scope of the study, these orphan products grants may total up to \$400,000 per year over four years,^[19] mitigating somewhat the high costs of continued development. At preclinical stages, programs such as TRND can provide crucial development resources to advance promising candidates. Our collaborative program seeks not only to support development of discrete therapeutics for the diseases adopted into the portfolio, but also aims to accelerate the field of translational research as a whole. With TRND support, our collaborators are able to demonstrate the safety and efficacy of their candidate therapeutics. These projects should then be sufficiently "de-risked" as to become attractive for adoption by an outside partner. By taking on challenging technical problems and implementing novel approaches to development, our goal is to improve the efficiency of the overall drug discovery and

development process. Having moved four rare disease therapeutic candidates to clinical testing in the relatively short lifetime of the program is encouraging. This is only a milestone on the path to ultimate success, but represents an encouraging start on the journey through the "Valley of Death" to bring treatments to the medically underserved children around the world.

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KEY POINTS

1. The rare/orphan diseases, which individually affect relatively few patients, lack available therapeutic options, despite substantial cumulative impact on the global population.
2. High costs and risk of failure are disincentives to initiating rare/orphan drug development campaigns, particularly for diseases with pediatric onset.
3. Evolving and emerging financial incentives, research support mechanisms, and regulatory pathways aim to mitigate the risks and barriers to rare/orphan drug development.
4. The TRND Program exemplifies a novel, successful approach to forming public-private research partnerships to facilitate and expedite preclinical drug development across a range of rare/orphan therapeutic areas.

TABLE I

Portfolio of TRND projects affecting children

Therapeutic Area / Disease	Collaborator(s)	Agent/Approach	Status
Niemann-Pick Type C1 Disease	Johnson & Johnson, Albert Einstein College of Medicine, Univ. of Pennsylvania, Washington Univ., NICHD, NINDS, NHGRI	Repurposed Drug–Small Molecule; Unconventional drug delivery directly into CNS	Clinical
Sickle Cell Disease	Aes-Rx, NHLBI	NME – Small Molecule	Clinical
Autoimmune Pulmonary Alveolar Proteinosis	Cincinnati Children's Hospital	Repurposed Drug – Biologic	Preclinical
Core Binding-Factor Leukemia	NHGRI	Repurposed Drug – Small Molecule	Preclinical
Creatine Transporter Defect	Lumos Pharma	Repurposed Drug – Small Molecule	Preclinical
Cryptococcal Meningitis	Viamet Pharmaceuticals	NME – Small Molecule	Preclinical
Duchenne Muscular Dystrophy	ReveraGen BioPharma	NME – Small Molecule	
Duchenne Muscular Dystrophy *	Sarepta Therapeutics	NME – Biologic; Exon-skipping technology	Preclinical
Fibrodysplasia Ossificans Progressiva	Massachusetts General Hospital	NME – Small Molecule	Preclinical
Fragile X Syndrome *	Afraxis, Inc.	NME – Small Molecule	Preclinical
Neonatal Herpes Simplex Virus *	University of Alabama, NIAID	NME – Small Molecule; Lipid-antiviral conjugate technology	Preclinical
Schistosomiasis	CoNCERT Pharmaceuticals	NME – Small Molecule	Preclinical
Schistosomiasis and Hookworm Infection *	Rush University; Yale University	NME – Small Molecule	Preclinical

* Indicates a project no longer active in the TRND portfolio.

NHGRI – National Human Genome Research Institute; **NHLBI** – National Heart, Lung, and Blood Institute; **NIAID** – National Institute of Allergy and Infectious Diseases; **NICHD** – Eunice Kennedy Shriver National Institute of Child Health and Human Development; **NINDS** – National Institute of Neurological Disorders and Stroke; **NME** – New molecular entity.