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NIH TRND Program: Successes in Preclinical Therapeutic Development

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The Therapeutics for Rare and Neglected Diseases (TRND) program (see: <http://ncats.nih.gov/trnd.html>) seeks to encourage and speed the development of new treatments for diseases of limited commercial interest to the biopharmaceutical industry. Faced with constrained financial resources and the inherent risk of failure during development, industry must make strategic decisions regarding therapeutic commercialization [1, 2]. Often, “rare” diseases of low prevalence, as defined in the Orphan Drug Act, as amended [3, 4], as well as high-prevalence “neglected” diseases (see: http://www.who.int/neglected_diseases/diseases/en/) occurring chiefly among impoverished populations in the developing world go unaddressed. Part of the National Center for Advancing Translational Sciences (NCATS) at the U.S. National Institutes of Health (NIH), TRND represents an important aspect of the NIH commitment to improving health through basic biomedical research and reengineering translational science [5]. TRND contributes to this effort by stimulating collaborations among intramural NIH scientists and extramural academic researchers, nonprofit organizations, and pharmaceutical and biotechnology companies actively developing therapeutic candidates for rare or neglected disease (RND) indications.

Impediments to Translation and Development

The manifold problems of the widely-discussed “Valley of Death” plague any drug development program [6], but their impact is all the more apparent in the RND space. The academic laboratories that generate fundamental mechanistic and clinical insights into rare diseases operate in a very different space than do drug developers. In academia, the incentive structure favors the generation and sharing of new knowledge via publication of peer-reviewed journal articles. Publications may be born of long years of work within a single investigator’s lab, and they may target a relatively narrow band of similarly-focused researchers. Industry, however, needs to commercialize specific therapeutic products on more abbreviated timelines. Commercial potential has traditionally relied on broader market applicability, and efficient development programs leverage large, multidisciplinary, managed teams to advance products through the pipeline. The disparate funding, expertise, and resource models that foster and reward academic versus commercial success are aligned to achieve their own goals, but do not mesh well.

TRND in the Intersection

The TRND program represents an innovative NIH effort to address some of the gaps that exist in RND translation and therapeutic development. Traditional NIH funding mechanisms provide grant-based financial support to applicant investigators to conduct proposed

research projects within the specified disease areas and organ systems of interest to the sponsoring Institute or Center. By contrast, as part of the broader NCATS, TRND solicits projects in a “disease-agnostic” fashion, provided that the proposal addresses an RND indication. Applicants may come from academic settings, biotechnology or pharmaceutical companies, and/or patient advocacy foundations, both within or outside the U.S. Further, rather than receiving a pre-determined amount of funding at the outset, meritorious projects adopted into the portfolio form unique, milestone-driven public-private partnerships with TRND and its staff of experienced drug development scientists. This structure seeks to leverage the strengths and capabilities that each party brings to the collaborative relationship: TRND provides expertise across the range of preclinical and early clinical development, from chemical lead optimization, to pharmacology, through toxicology to regulatory support; the external partners bring deep disease area expertise and knowledge of the specific molecules they seek to develop.

As projects continue to meet scientific milestones, TRND continues its support. The program is designed to generate the data necessary to “de-risk” a therapeutic candidate so that it may become more attractive for adoption by an outside biopharmaceutical or venture capital partner with the capacity to carry the program through full clinical development and final registration of a marketed therapy. A typical exit point from the program is clearance of an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA). In certain circumstances, TRND may support limited early clinical development. If a project fails to meet critical milestones in a timely fashion, it will be discontinued.

In service of the broader NCATS mission to advance translational science (see: <http://www.ncats.nih.gov/about/about.html>), TRND seeks to facilitate and develop new technologies and cooperative models to improve the efficiency of therapeutic development. Individual RND-directed projects exploiting innovative “platform technologies” whose proof-of-concept may benefit a wider range of disease indications are welcome. In addition, TRND is entrepreneurial in its approach to developing novel, potentially multi-party collaborative relationships.

Portfolio of Successes

Since its creation in mid-2009, TRND has continued to develop and enhance infrastructure, and has adopted 14 collaborative projects into the portfolio (Table 1). Therapeutic candidates comprise both small molecule and biological new molecular entities (NME) that have never been used in patients, as well as molecules previously approved by FDA for use in other diseases, which TRND is helping to develop for new RND indications. Within three years of initiation, three projects resulted in successful IND clearance and have since reached the clinic, with one additional project (as of this writing) poised for IND filing in 2012. Short synopses of the most advanced programs are given below.

Sickle Cell Disease

SCD is a genetic blood disorder that affects millions worldwide. A single mutation in hemoglobin causes red blood cells to become rigid and sickle-shaped, leading to blockage of small blood vessels, decreased blood flow, inflammation, pain, and strokes in children. To date, the only drug approved by the FDA to treat SCD is hydroxyurea (HU). HU is an anti-cancer drug that is only indicated for use in adults, and its modest efficacy in SCD and undesirable side-effects severely limit its use. This limited efficacy lies in the fact that HU does not directly address the underlying molecular defect that causes SCD, despite more than half a century of research since SCD was described as the first disease of molecular origin in man [7]. TRND has partnered with a small biotech company, AesRx, to further

development of their novel anti-SCD compound, Aes-103. This compound represents the first drug candidate to directly target the molecular cause of SCD, directed toward use in both adults and children, in support of a key strategic goal of the National Heart, Lung, and Blood Institute (NHLBI) regarding SCD research and treatment [8].

In less than a year of signing the collaborative agreement with AesRx, TRND completed all pre-clinical toxicology, chemistry, manufacturing and controls, and regulatory studies necessary to support and file an IND application with FDA. Upon clearance by FDA, Aes-103 was moved into Phase I/IIa clinical trials in both healthy volunteers and SCD patients. TRND has established a project team that includes TRND staff, AesRx, and a leading SCD clinical researcher at NHLBI. After TRND adopted AesRx into the portfolio, the company was able to leverage our collaboration to obtain a Massachusetts Life Science Accelerator Grant to support additional studies necessary to complete clinical development of Aes-103 (see: <http://www.aesrx.com/news.html#Patients>).

Chronic Lymphocytic Leukemia

Approximately 15,000 people in the U.S. are diagnosed with CLL each year. This is a slower-progressing leukemia that tends to affect patients over 60 years of age. Standard treatments comprise traditional chemotherapies and antibody-based approaches, but these first-line therapies ultimately fail, leading to recurrence of disease and death. This project represents a multi-party collaboration between TRND, the University of Kansas Institute for Advancing Medical Innovation (IAMI), and the Leukemia & Lymphoma Society (LLS), which we have termed “The Learning Collaborative” [9]. This novel partnership leverages a number of strengths brought to bear by the various partners: TRND brings a rare disease focus to its pharmaceutical development experience, as well as an ability to perform industrial-scale high-throughput screening and informatics in partnership with the NIH Chemical Genomics Center (NCGC) at NCATS; IAMI is a national leader in bench-to-bedside translation and medicinal/pharmaceutical chemistry; and LLS maintains approximately 400 research projects across its worldwide network of blood cancer researchers, and has a history of fostering successful pharmaceutical commercial partnerships.

The TRND project was born of an initial collaboration between NCGC, NHLBI, IAMI, and LLS. The goal of the initial project was to identify a currently-approved drug that could be repurposed subsequently by TRND for use in treatment-refractory CLL. The partners performed a high-throughput screen of over 2,000 small molecule drugs in the NCGC Pharmaceutical Collection to test for differential killing of leukemic B-cells versus healthy donor cells. The rheumatoid arthritis drug, auranofin, was selected as a potent, selective agent, in need of further CLL-specific development. In under a year after adoption, the collaborative team conducted all of the pre-clinical studies and regulatory work necessary for IND filing and clearance. Auranofin is currently in Phase I/IIa clinical trials in patients at three sites, including the NIH Clinical Center, the University of Kansas, and the Ohio State University (see: http://www.lls.org/aboutlls/news/pressreleases/11111_groundbreakingclinicaltrial).

Hereditary Inclusion Body Myopathy

HIBM is a rare, fatal muscle-wasting disease that is driven by mutations in a key enzyme in the biosynthetic pathway for sialic acid. Patients are born with enough sialic acid to maintain proper glycosylation and function of their muscles through their 20s or 30s. After this point, the inability to generate new sialic acid causes the disease to manifest. Although the quadriceps muscles of the upper leg are spared the characteristic deterioration, patients lose muscle mass throughout their bodies. Initially, patients lose the ability to walk, with

progressive, pervasive muscle-wasting leading to death. There are no approved therapies for HIBM, and treatment is limited to palliative care. The therapeutic approach of this TRND project is to develop a targeted pathway intermediate, the sugar ManNAc (N-acetyl-D-mannosamine), to effectively skip the defective step in the biosynthesis of sialic acid in muscle cells.

This project came to the TRND program from academic investigators at the National Human Genome Research Institute (NHGRI), in collaboration with New Zealand Pharmaceuticals, the company that will produce the ManNAc product (DEX-M74). TRND supported two pivotal animal toxicology studies necessary to demonstrate drug safety to the FDA, and helped generate required data on the manufacturing processes employed to produce the final drug product. To gather the information required for a clinical trial, TRND began a natural history study of HIBM disease progression at the NIH Clinical Center in 2011. The data generated by TRND fulfilled requirements by FDA to move the investigator's IND into clinical testing, with Phase I trials beginning in September 2012 (see: <http://www.nih.gov/news/health/sep2012/ncats-24.htm>).

Niemann-Pick Type C1 Disease

NPC1 is a fatal genetic disease, characterized by a failure to metabolize and dispose of cholesterol and lipids, causing progressively impaired movement and intellectual function. It strikes in early childhood, and is lethal within a decade of diagnosis. There are no FDA approved therapies for NPC1. HPBCD (2-hydroxypropyl- β -cyclodextrin) appears to reduce the cholesterol and lipid accumulation, and prolongs survival in animal models of NPC1 disease. The goals of this project are to generate the extensive data needed to establish safe, effective dosing for the delivery of HPBCD directly into the brain of patients, and to test the drug for initial safety, efficacy, and biomarker response.

TRND established an interdisciplinary project team of academic and industrial scientists from seven different organizations to move HPBCD forward in pre-clinical development. TRND conducted the animal toxicology studies necessary for IND filing, helped support biomarker studies, and has prepared for and participated in two pre-IND meetings with the FDA. Early engagement and ongoing interaction with patient advocacy groups has also provided key input toward developing an efficient clinical evaluation strategy. TRND is on schedule for IND filing and first-in-human clinical trials, expected to begin in early 2013 (see: <http://www.nnpdf.org/Cyclodextrin.html>).

Trends for the Future

TRND serves the broader NCATS mission to catalyze innovations on the many fronts of translational science. The primary vehicle through which TRND participates in this endeavor is by fostering development of new therapeutics for the treatment of rare and neglected diseases. TRND accomplishes this task by facilitating industry and academic collaborations, and through sharing of scientific and technical knowledge. However, TRND does not limit this sharing and knowledge transfer solely to the current portfolio of projects themselves. Another aspect of the TRND mission is to create forums for discussing key issues, common pitfalls, and potential solutions to common impediments that can arise in RND therapeutic development. This has taken the form of regular, ongoing discussions between the scientists at TRND and specific offices at FDA, as well as larger public meetings involving broader constituencies. One such workshop on natural history studies of rare diseases convened academic, industrial, and regulatory scientists, as well as patient advocates, to focus on the importance of high-quality natural history studies in support of rare disease therapeutic development (see: https://events-support.com/events/Natural_History_Studies).

Successful RND discovery and development in academia more often relies on smaller groups of scientists with more focused “inch wide, mile-deep” expertise, whereas successful RND development in industry tends more toward division of labor and expertise among teams in a “mile-wide, inch deep” mode. While there are clear merits to the methods employed in these different spheres, there is great potential in lowering some of the barriers and operating at their intersection. The successes enjoyed so far by TRND underscore this point, clearly demonstrating the synergy of industry, academia, the patient community, and government working together to address unmet medical needs.

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Table 1

Portfolio of Active TRND Projects

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

^aNational Heart, Lung, and Blood Institute;

^bNational Human Genome Research Institute;

^cEunice Kennedy Shriver National Institute of Child Health and Human Development;

^dNational Institute of Neurological Disorders and Stroke;

^eNational Institute of Allergy and Infectious Diseases