DEPARTMENT OF HEALTH AND HUMAN SERVICES

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# Development of Novel Therapeutics for the Treatment of Rare and Neglected Diseases

Witness appearing before the

**Senate Appropriations Subcommittee on**

**Agriculture, Rural Development, Food and Drug Administration,**

**and Related Agencies**

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Good afternoon, Mr. Chairman and distinguished Members of the Subcommittee:

Thank you for the invitation to speak to you this afternoon about the National Institutes of Health (NIH) activities to promote the development of novel therapeutics for the treatment of rare and neglected diseases. In particular, I am pleased to talk to you about some of the exciting scientific opportunities that we are pursuing and the strong partnerships that we and others at the NIH have built with the Food and Drug Administration (FDA) over many years to facilitate the efficient development of treatments for patients afflicted with these devastating diseases.

Over the last 60 years, the research and drug development infrastructure of the United States, contributed to by the public and private sectors, has produced medicines that have reduced suffering and death from many diseases, including heart disease, diabetes, osteoporosis, many types of cancer, and infections such as AIDS and pneumonia. However, due to the high cost of developing a new drug, most drug development resources are focused on diseases that are highly prevalent in the developed world. While this focus has contributed greatly to the public health of the nation, it has left many in the United States who suffer from rare diseases (those defined by the Orphan Drug Act as affecting fewer than 200,000 Americans), and many more in developing nations who suffer from neglected diseases, without treatments. In fact, of the 7,000 human diseases, over 90% are classified as “rare” or “neglected” (1, 2). Collectively, these affect more than 25 million people in the U.S.

Biopharmaceutical companies are reticent to take on rare and neglected disease studies due to the historically high rate of failure and the relatively low return on investment. The recent contraction of the biopharmaceutical sector has further exacerbated this problem.

The success of the research performed and funded by NIH over the last 50 years, and especially over the last decade, has brought us to the point where basic scientific discoveries can be more rapidly and efficiently translated into medical treatments. Thanks to the Human Genome Project and related initiatives, the genetic basis of over 2,000 rare diseases is now known, and the infectious organisms that cause neglected tropical diseases are understood in unprecedented detail (see, for example, [3]). Over the years, NIH has supported basic research and the

elucidation of biological pathways as a means to understand human health and disease. Since much basic mechanistic research remains to be done in these areas, it is critical that NIH continue to support these avenues of scientific inquiry. NIH also recognizes the opportunity and the imperative to pursue translational initiatives to apply basic scientific knowledge to health needs. Our conviction is that these more applied projects will accelerate diagnostic and treatment development, particularly for rare and neglected diseases.

The Molecular Libraries Initiative, funded by the NIH Common Fund, for example, has made tools and resources accessible to academic researchers that were previously only available in large pharmaceutical companies. Specifically, scientists at universities and medical centers have been provided access to industry-style assay development, high-throughput screening, and medicinal chemistry infrastructure not previously available in academic settings. In doing so, this program has produced more than a hundred chemical "probe" compounds that are used to study rare and neglected diseases in cellular or animal models. These compounds are traditionally referred to as "small molecules" – they are organic chemicals made up of carbon, hydrogen, nitrogen, oxygen, and a few other atoms in a wide variety of combinations, and can be thought of as chemical "shapes" that can interact with a host of cellular targets. Such compounds are the first steps toward drug development, but the development of small molecules suitable for testing in humans requires an additional 3-4 years of development.

The academic sector currently lacks the infrastructure and expertise required for the pre-clinical pharmaceutical development needed to transform a chemical research probe into a candidate compound suitable for testing in patients. Individual NIH Institute and Center programs have been established to move candidate compounds further down the development path—the Neuroscience Blueprint Neurotherapeutics program, the NINDS Spinal Muscular Atrophy Project, NCI's Experimental Therapeutics (NExT) program, and the NIAID BioDefense Product Development Program are but a few examples. These programs, as critical as they are, together address fewer than 100 individual diseases.

Announced in May 2009, the Therapeutics for Rare and Neglected Diseases initiative, abbreviated TRND, is a collaborative research program that builds on efforts across NIH to

develop candidate compounds for clinical testing en route to developing therapeutics for rare and neglected diseases. TRND is a trans-NIH program overseen by the Office of Rare Diseases Research in the Office of the Director, NIH, and administered by the National Human Genome Research Institute. Building on the Molecular Libraries Initiative, TRND will empower academic investigators to pursue pre-clinical work through high-throughput resources not previously available outside the biopharmaceutical sector. In most cases, the starting point for TRND will be a chemical "probe," or compound, known to have some biological effect in laboratory models of a given rare or neglected disease. The end-point deliverable will most often be a candidate compound with sufficient data for an Investigational New Drug (IND) application to the FDA.

The pursuit of novel partnerships with biopharmaceutical companies and patient advocacy groups will be another hallmark of this program that brings together the necessary expertise and patient communities to realize therapeutic development success in the rare and neglected disease realm. It is expected that in most cases, TRND's candidate compounds will ultimately be licensed to biopharmaceutical companies for clinical development, permitting TRND to focus on the most scientifically challenging stages of pre-clinical drug development. In this way, TRND intends to "de-risk" projects sufficiently to make them enticing to groups outside of NIH to pursue final development, even for less common diseases with limited markets. TRND's scientific activities will include everything from iterative medicinal chemical modification of promising compounds to testing optimized compounds in laboratory disease models; in cases that lack sufficient private-sector interest and present compelling health needs, NIH may even conduct the early clinical trials necessary for safety and efficacy analyses, using the substantial resources of the NIH Clinical Center and the network of 46 Clinical and Translational Science Awards (CTSAs) across the country.

Significantly, beyond delivering candidate compounds for clinical testing in individual rare and neglected diseases, TRND will focus on improving the overall efficiency of drug development for these types of diseases. Currently, drug development is an unavoidably long and failure-prone process, requiring 4-8 years and carrying a failure rate well over 90%. This high-failure rate and extended timeline is due in large part to the unpredictable nature of the biological effects

of new candidate compounds. NIH aims to advance the underlying drug development processes through open and broad dissemination of the information learned in the course of candidate compound development. To achieve this goal, TRND will focus on mechanisms able to cut across traditional disease or organ system boundaries, allowing each drug developed potentially to target the underlying pathology for more than one disease. Successes and failures will be investigated and published, and specific technology development programs addressing the two most common causes of new drug failure—toxicity and efficacy in humans—will be launched.

To expand some of the unrealized potential of earlier drug development projects, an alternative approach—known as drug "repurposing"—will seek to identify drugs for rare or neglected diseases from among those already approved for use in people by FDA or another regulatory agency outside the U.S. The opportunity of this approach is that it potentially allows for rapid therapeutic advances, with a treatment available 1-2 years after the initial tests. The challenge is the relatively small number of compounds (i.e., drugs) that have been approved for human use, and therefore that are available for repurposing (approximately 3,000, compared to 100-1000 times the number of new candidate compounds available). As part of its program to take every approach to speeding the development of new drugs for rare and neglected diseases, TRND will be testing clinically approved drugs for new activities in assays related to 100 rare diseases. This effort will complement TRND's traditional compound development pathway, and will provide information on the critical question of what percentage of rare and neglected diseases can be treated to some extent by the current pharmacopeia.

Since one of the organizing principles of TRND is a *systems* approach to drug development, all rare and neglected disease areas will be suitable for TRND. Because TRND is explicitly designed to address *any* rare or neglected disease, and identify and capitalize on biological/pathway commonalities among these diseases regardless of the organ systems they affect, the program's success will rely and actively draw upon the knowledge and expertise resident in all the NIH Institutes and Centers. TRND will draw many of its projects from extramurally supported investigators as well, and look to them for insights into the molecular pathogenesis of diseases, and for collaborations on pharmacological and animal models for lead optimization and pre-clinical testing. This coordinated and universal approach to rare and

neglected diseases should with time lead to therapeutic strategies for additional diseases not directly studied by TRND.

To launch the scientific program and begin to develop the operational processes necessary for the management of these types of atypical research partnerships, five initial projects—at a variety of stages of development, with different types of collaborators, and with different disease types—have been initiated in FY 2010.

- The first pilot is focused on schistosomiasis and hookworm, which are highly prevalent and neglected tropical parasitic diseases that affect over 500 million people worldwide. This project is an early pre-clinical ("probe optimization") stage project, and involves a collaboration with two extramurally-funded NIH investigators.

- The second project is a mid-stage drug "repurposing" project for a rare disease, Niemann-Pick Type C (NPC), which is allowing the piloting of the later stages of pre-clinical development including formulation, pharmacokinetics, pharmacodynamics, blood-brain barrier penetration issues, and challenging clinical trial design. NPC is a rare pediatric neurodegenerative disease, and the project is a collaboration with both extramural and intramural scientists. Importantly, this project also involves several patient advocacy groups who support and coordinate NPC research.

- A third project is a collaboration with a research-driven disease foundation and extramural collaborators, focusing on repurposing an approved drug for treatment of Chronic Lymphocytic Leukemia. This project is currently at the later "pre-IND" stage of the drug development pathway.

- A fourth TRND project involves a rare muscle-wasting disorder that occurs in mid-life, known as Hereditary Inclusion Body Myopathy. In this instance, the project involves a new candidate compound, but is also at a late stage, requiring only discrete toxicology studies before moving into clinical testing. This project involves a collaboration with an investigator

at the NIH Clinical Center and a biotechnology company, and is allowing TRND to pilot processes to incorporate the unique resources of the NIH Clinical Center and also to work through business issues related to partnering with the private sector.

- The final pilot project focuses on sickle cell disease, and brings together non-profit, intramural and extramural investigators to focus on a new candidate compound at the mid-stage of pathway development.

If TRND is to succeed in achieving its objective to increase the number of therapeutics available to combat rare and neglected diseases, an integral part of the commitment must be regular dialog and coordination with the FDA. To accelerate and enhance TRND activities, a working group of TRND and FDA staff meet monthly to discuss conceptual issues in existing TRND projects, and to develop new ideas to address the principal roadblocks in drug development for these diseases. FDA participants include representatives from the Office of New Drugs and the Office of Translational Science, with expertise in rare disease drug development, toxicology, and policy. The NIH staff includes TRND leadership and individual scientists working on the particular projects being discussed. Separately, TRND is working closely with the FDA Office of Orphan Product Development (OOPD) to coordinate activities and leverage OOPD programs to advance mutual goals.

In addition to these critical staff contacts for TRND, the NIH recently formed a flagship partnership with the FDA. Through a recently announced Joint Leadership Council, co-chaired by NIH Director Francis Collins and FDA Commissioner Margaret Hamburg, the two agencies will work closely together to ensure that sound regulatory considerations are an integral part of research planning. The initiative involves two interrelated scientific disciplines: translational science (the shaping of basic scientific discoveries into treatments); and regulatory science (the development and use of efficient and effective tools, standards, and approaches to develop products and evaluate product safety, efficacy, and quality). Both disciplines are needed to turn biomedical discoveries into products that benefit people. Through research programs in

regulatory science, innovative mechanisms and processes will be explored to devise optimal methods for drug development and review.

This multi-pronged approach for collaboration between FDA and NIH in support of the development of novel products to treat and diagnose rare and neglected diseases will promote the development of new pathways through which safety, quality, and efficacy can be assessed, improving the overall efficiency of clinical research as a whole.

In summary, the NIH, through TRND and other research initiatives across the agency, is poised to make extraordinary advances in the development of potential therapeutics and treatment strategies for rare and neglected diseases. The opportunity to pursue new scientific directions through the availability of resources traditionally restricted to the biopharmaceutical community, and to generate vitally needed alternatives to traditional drug development pathways in partnership with the FDA, presents new hope for the ultimate success of bringing better clinical options to patients afflicted with rare and neglected diseases.

Thank you very much for the opportunity to testify before the Committee this afternoon. I would be happy to take any questions that the panel may have.

**References**


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Christopher Austin is Director of the NIH Chemical Genomics Center (NCGC) and the Therapeutics for Rare and Neglected Diseases (TRND) program at the U.S. National Institutes of Health (NIH), and Senior Advisor to the Director for Translational Research at the National Human Genome Research Institute. The NCGC is an ultrahigh-throughput screening, informatics, and chemistry center that profiles small molecule libraries for biological activity using its qHTS technology, and develops novel compounds as probes of biology and starting points for the development of new drugs for rare and neglected diseases. The NCGC also develops new paradigms to increase the efficiency and genome-wide reach of assay, screening, chemistry, and informatics technologies, and is a partner with NTP, EPA, and FDA in the Toxicology in the 21$^{st}$ Century (Tox21) Program.

In his role as Senior Advisor for Translational Research, Dr. Austin was a principal architect of several large initiatives to translate the human genome sequence into biological function and therapeutics, including the NIH Molecular Libraries Initiative, a multifaceted program of small molecule technologies in the public sector, and the Knockout Mouse Project, which is producing knockout mice for all mouse genes. Most recently, he has developed and launched the new NIH TRND program, which will develop small molecule compounds from the lead to clinical proof-of concept stage for rare and neglected diseases.

Before joining NIH in 2002, Dr. Austin directed research programs genomics-based target discovery, pharmacogenomics, and DNA microarray technologies at Merck, with a focus on neuropsychiatric diseases. Dr. Austin received his A.B. in biology *summa cum laude* from Princeton, and his M.D. from Harvard Medical School. He completed clinical training in internal medicine and neurology at the Massachusetts General Hospital, and a postdoctoral fellowship in developmental genetics at Harvard.