New and Evolving Rare Diseases Research Programs at the National Institutes of Health

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Key Words

Biospecimens · Common data elements · Orphan drugs · Patient advocacy groups · Patient registries · Rare and genetic diseases research · Research network · Undiagnosed diseases

Abstract

Research emphasis on rare diseases and orphan products remains a major focus of the research Institutes and Centers of National Institutes of Health (NIH). NIH provides more than USD 31 billion annually in biomedical research and research support. This research is the basis of many of the health advances in rare and common diseases. Numerous efforts and a major emphasis by the public and private sector initiatives have resulted in an increase of interventions and diagnostics for rare diseases. Newer translational research programs provide a more systematic and coordinated approach to rare diseases research and orphan products development. The approach that is offered requires extensive public-private partnerships with the pharmaceutical industry, contract research organizations, philanthropic foundations, medical and scientific advisory boards, patient advocacy groups, the academic research community, research and regulatory scientists, government funding agencies, and the public. Each program is unique and requires lengthy planning and collaborative efforts to reach programmatic goals.

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Introduction

Research emphasis on rare diseases and orphan products remains a major focus of the research Institutes and Centers (ICs) of National Institutes of Health (NIH). NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. NIH provides more than USD 31 billion annually in biomedical research and research support. This research is the basis of many of the health advances in rare and common diseases. NIH provides support and conducts scientific research and research training in all 50 states and the District of Columbia in the US and around the world. More than 2,500 universities, hospitals, nonprofit research institutions, and large and small biopharmaceutical and medical device companies receive support and services for research and development activities.

Approximately 25 million people in the US are affected by an estimated 6,000 rare diseases or conditions leading to significant morbidity and mortality. A rare disease is defined through the Orphan Drug Act and Amendments to the Act as a condition affecting fewer than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the product in the US [1, 2].

The goals of the NIH are to foster fundamental creative discoveries, innovative research strategies and their applications as a basis for ultimately protecting and improving health; to develop, maintain, and renew scientific human and physical resources to prevent disease; to expand the knowledge base in medical and associated sciences and to exemplify and promote the highest level of scientific integrity, public accountability and social responsibility in the conduct of science. The research community and the public have become very familiar with many of the existing and traditional NIH extramural research and training grant programs and intramural research and training programs at the NIH Clinical Research Center Hospital. Other sources of useful information readily accessible to the rare diseases community include ClinicalTrials.gov, PubMed and the Genetic Testing Registry. Less well known are the numerous dedicated programs initiated in the past 10 years, such as the Rare Diseases Clinical Research Network (RDCRN), the Genetic and Rare Diseases Information Center (GARD), the Undiagnosed Diseases Program, the Therapeutics for Rare and Neglected Diseases Program (TRND), and many other initiatives developed specifically to emphasize translational research efforts of leading research discoveries to improved diagnostics and interventions.

The National Center for Advancing Translational Sciences

The National Center for Advancing Translational Sciences (NCATS) is the newest of the 27 ICs at the NIH. This Center was established in December 2011 to catalyze the translational science process to enable new treatments and cures for disease to be delivered to patients faster. NCATS is the home to many of these programmatic efforts [3]. NCATS provides innovative and collaborative cross-cutting approaches in translational science that are applicable to the entire scientific community of basic, clinical and translational research investigators and programs. NCATS continues to serve in a catalyst role to enable other parts of the research system to work more effectively. NCATS complements and does not compete with the commitments and responsibilities of other NIH ICs, the private sector and the non-profit community. NCATS Staff and Programs encourages and stimulates significant collaborations among numerous government agencies, academic research investigators, the biopharmaceutical and medical device industries, and patient advocacy groups who are signifi-

cant contributors to successful translation of research discoveries to potential interventions for the prevention, diagnosis, or treatment of rare, neglected and common diseases.

Access to Information on Research and Training Projects

Developing an awareness of the individual research projects can be a difficult task for the patients, families and patient advocacy groups. This essential information can be found more easily by the rare diseases community by searching useful databases. Two in particular are highlighted in this report: the Research Portfolio Online Reporting Tools for research projects and training and the Research, Condition, and Disease Categorization (RCDC) process provide ready access to research projects related to rare diseases and orphan products.

The first of these, the Research Portfolio Online Reporting Tools is now readily accessible and contains historical and current information in addition to carrying out its scientific mission to provide continually updated information from funded grants. This website provides access to reports, data and analyses of NIH research activities, including information on NIH expenditures and the results of NIH supported research. In 2012, NIH provided support for 63,504 grants. The majority, 51,313, were research project grants. There were 5,202 Small Business Innovation Research and 645 Small Business Technology Transfer grants. Training of existing researchers and the next generation of researchers remains a major emphasis at NIH with 4,438 individual training and 813 institutional training awards. Many of these relate to specific rare diseases [4].

Included in this database is information from international research collaboration supported by the NIH research ICs and major initiatives of the Fogarty International Center. This Center supports and facilitates international research collaborative research initiatives conducted by US and international research investigators, building partnerships between health research institutions in the US and abroad, and training the next generation of scientists to address global health needs. In 2012, NIH research ICs provided more than USD 225 million for 479 research project grants, research centers, training, and research and development contracts. Individual grant awards and collaborative research projects with investigators from the US are available to international scientific research teams.

Identifying Rare Diseases Research and Orphan Products Development Research

The NIH informs the research community and the public about the specific research and training projects in biomedical research through the RCDC reports. RCDC provides information from more than 230 categories of disease, condition or research areas. RCDC provides a complete list of all NIH-funded projects related for each category in a searchable database [5]. General categories such as research projects with a focus on genetics, pediatrics, stem cell research, and clinical research are provided. In addition, disease-specific categories such as amyotrophic lateral sclerosis, Batten disease, Huntington's diseases, dystonia, fragile X syndrome, and others are provided. The RCDC data for rare diseases and orphan drugs categories from the fiscal year 2012 reveals that NIH provided approximately USD 3.623 billion for 9,400 rare diseases research projects from a total budget of USD 25.504 billion total for grants, contracts, training, and research facilities construction. This figure represents an increase of USD 94 million or 2.7% from 2011 support levels [6]. A subcategory of the rare diseases category is the orphan drugs emphasis. Nearly USD 809 million supported 1,650 research projects in this category. This was an increase from USD 749 million in 2011 or an 8% increase above the funding levels for the fiscal year 2012 [7].

Common Fund Initiatives

The NIH Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programs that require participation by at least 2 NIH ICs or would otherwise benefit from strategic planning and coordination. The requirements for the Common Fund encourage collaboration across the ICs while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short-term, exceptionally high-impact, trans-NIH programs. The Common Fund is coordinated by the Office of Strategic Coordination in the Division of Program Coordination, Planning, and Strategic Initiatives within the Office of the Director.

The NIH Common Fund programs provide a flexible approach to address emerging scientific opportunities and key roadblocks in biomedical research that impede basic scientific discovery and its translation into im-

Table 1. Scientific focus areas of selected NIH Intramural Research Program principal investigators

Biomedical engineering and biophysics
Cancer biology
Cell biology
Chemical biology
Chromosome biology
Clinical research
Computational biology
Developmental biology
Epidemiology
Genetics and genomics
Health disparities
Immunology
Microbiology and infectious diseases
Molecular biology and biochemistry
Molecular pharmacology
Neuroscience
Social and behavioral sciences
Stem cell biology
Structural biology
Systems biology
Virology

proved human health. In addition, these programs utilize these resources to stimulate progress across multiple biomedical specialty research fields.

Common Fund programs are expected to transform how broad health research is conducted by providing limited term investments in strategic areas to stimulate further research through IC-funded mechanisms. After the initial funding period with appropriate evaluation, the NIH ICs determine the need to continue the existing programs and are expected to provide resources to extend the activities [8].

Intramural Research Program at the NIH and the Clinical Center Hospital

Approximately 1,200 principal investigators conduct biomedical or behavioral research within the Intramural Research Program at NIH and at 5 other research campus facilities other than those at the main campus of NIH. The NIH Clinical Center facilities include the Mark Hatfield Clinical Research Center and the Warren Grant Magnuson Clinical Center, provide patient care and opportunities for advancing clinical research through protocols initiated by the staff and trainees.

One of the frequently asked questions relates to the establishment of research partnerships with the NIH Intramural Research Program scientists. Each research investi-

gator is associated with a particular institute or center. There are opportunities for research collaborations and they are not limited to the NIH campus research activities. Many of the NIH investigators work extensively with scientific colleagues both nationally and internationally. The rare diseases community can now search on specific research areas or specific investigators and their areas of interest. The general scientific focus areas are provided in table 1 [9].

The Bench-to-Bedside Research Program

The Bench-to-Bedside Program was initiated at the NIH Clinical Center in 1999 to encourage collaboration between basic scientists and clinical investigators from different NIH institutes and laboratories in the Intramural Research Program. Recently, the program was expanded to include research teams comprised of NIH intramural and extramural collaborators and grantees from academic research centers, healthcare organizations and private industry. Since 2006, 74 extramural institutions have been involved in Bench-to-Bedside research projects. In addition to rare diseases, other areas of interest include HIV/AIDS, minority health and health disparities, and women's health. Institutions are eligible for collaborative research efforts with NIH Intramural Research Programs. Selection criteria for these awards include the quality of the science in the proposed project, the potential for becoming an active clinical trial, and the potential for leading to a new medical treatment or better understanding of the disease process.

Since 1999, about 700 principal and associate investigators have collaborated on over 200 research projects. Rare Disease Research has supported these 2-year rare diseases awards since 2003 and contributes to research advances including collaborations with ICs in supporting rare diseases. Bench-to-Bedside program grants administered by the NIH Clinical Center. The Office of Rare Diseases Research (ORDR) provided support for several different diseases including neurofibromatosis, Williams syndrome, endolymphatic sac tumors, chronic graft-versus-host disease, bronchiolitis obliterans, Li-Fraumeni syndrome, hemophagocytic lymphohistiocytosis, leukemia, Niemann-Pick C, and other diseases [10].

Undiagnosed Diseases

Obtaining the correct diagnosis for many rare diseases can be difficult, costly and often requires many years and frequent visits to physicians and clinics who find the dis-

eases both challenging and frustrating. Not all diseases manifest themselves with characteristic symptoms at one time. In the 1989 report of the National Commission on Orphan Diseases, 15% of patients reported it took more than 5 years to obtain the correct diagnosis. Another 31% reported the time to correct diagnosis was between 1 and 5 years. Approximately 6% of the questions received by NIH's GARD related to information about undiagnosed diseases [11, 12].

In the US, it has been estimated that approximately 6% of the general population suffers from a rare disorder. Often times, these individuals go for long periods of time without a diagnosis. To aid these individuals, and to make progress in uncovering, understanding and treating these disorders, the NIH established an Intramural Research Program on undiagnosed diseases in 2008, known now as the Undiagnosed Diseases Program. The Program was developed with resources from the ORDR, National Human Genome Research Institute, and the NIH Clinical Research Center Hospital. Building on the success of this program in diagnosing both known and new diseases, the Common Fund's Undiagnosed Diseases Network (UDN) will aim to achieve this type of cross-disciplinary approach to disease diagnosis in additional academic medical centers the US.

The NIH Common Fund's UDN will promote the use of genomic data in disease diagnosis and will engage basic researchers to elucidate the underlying disease mechanisms so that treatments may be identified. The program also will train clinicians in the use of contemporary genomic approaches to aid in disease diagnosis. The NIH expects to provide approximately USD 145 million in Common Fund support over the next 7 years for the UDN. The goal of the Common Fund Program is to catalyze the field of rare diseases research so that the national centers can continue to help patients, make discoveries and train the physicians and scientists needed to tackle these challenging medical problems and treat the patients affected by rare and common disorders. [Undiagnosed Disease Program references 11–13.]

The Rare Diseases Clinical Research Network

The NIH ORDR in collaboration with 8 NIH Institutes (NICHD, NHLBI, NIDDK, NIAMS, NINDS, NIDCR, NCI, and NIAID) continues to manage the Rare Diseases Clinical Research Network (RDCRN) Program, which consists of 17 distinct clinical research consortia and 1 Data Management Coordinating Center. Most consortia

have formed collaborations with international sites in 14 countries, including Australia, Austria, Belgium, Canada, England, France, Germany, Iceland, India, Italy, the Netherlands, Scotland, Spain, and Switzerland. The RDCRN Contact Registry which enhances participation in clinical trials and disseminates information has approximately 11,000 registrants from 90 countries for more than 200 rare diseases.

Currently there are 86 active clinical studies involving over 225 clinical research sites. Seventy-six clinical studies have been opened and 37 new clinical study protocols are in various stages of development since August 2009, during the second award cycle of the RDCRN. Ten clinical studies are now closed because targeted patient accrual has been completed, and they are in the final data analyses phase. To date, more than 21,000 patients have been registered to the 119 RDCRN protocols with 15,000 patients enrolled since 2009. There are approximately 95 patient advocacy groups associated with the research activities of the individual consortia. Most of the ongoing studies are longitudinal or natural history studies. Pilot studies, phase I, II and III studies, are also conducted in the RDCRN with funds provided from various sources. There are 13 protocols which involve collaborations with the biopharmaceutical industry. Industry participation in the RDCRN and sponsorship of studies is encouraged [14, 15].

Training in the RDCRN

Consortia in the RDCRN are required to have an active clinical research training component for new and usually younger investigators. This required component is beginning to reach the expected potential of having the trainees complete their research fellowships, move to a different academic institution and open a new research site as part of the consortia. The individual consortia are expected to offer a unique environment for clinical research in rare diseases for new investigators, postdoctoral or clinical fellows, junior faculty or established scientist investigators to redirect their research careers to emphasize rare diseases research. Support from the academic institution or other outside organizations is allowed and encouraged. There has been a total of 174 trainees in both 5-year periods and 134 trainees in the current cycle of RDCRN.

Many patient organizations have established a program priority to provide research support to younger investigators to establish a research interest of their disease and to develop results from smaller pilot studies that will prove

useful in the competition for larger multiple year grants that provide more stable funding. Generating interest with a particular disease can lead to a very rewarding career as new information is discovered and shared with others.

Genetic and Rare Diseases Information Center

Established by the ORDR and the National Human Genome Research Institute in 2002 to respond to the many different questions received about rare and genetic disorders, the GARD focuses on these disorders and complements the information provided by the NIH National Library of Medicine, institutes and centers, other patient advocacy groups and foundations, and information from the pharmaceutical, biotechnology, and medical device industries.

The GARD provides information on over 6,400 rare and genetic conditions via active links to over 6,900 terms in the database on the website. Particular attention is directed to the development of information that is known about the disease; what research studies are actively recruiting patients or have completed recruitment, some with study results available in ClinicalTrials.gov; what genetic testing services and tests are available from CLIA-certified and research laboratories; how patients gain access to patient advocacy groups and their information; and the most recent advances and results from studies in the published literature.

The arrival of internet services and ready access to information about rare diseases has provided patients and patient organizations with frequent informational updates and access to research studies and advances. To assure the release of useful information, the GARD embarked on a program to utilize their resources more effectively. Starting in 2008, responses provided to queries received from the public and healthcare providers are now archived and available for easy reference in the website. This decision reduced the number of questions to the information center but has dramatically increased the visitors to the information centers who are searching for disease-specific information. Phone inquiries remain the largest number of connection to the GARD with nearly 41% of inquiries. E-mail messages account for nearly 34% of personal inquiries. The website results in 24% of in-person contacts with the GARD. Approximately 200,000 visitors each month visit the GARD website. The number of visitors from mobile media applications continues to increase, and it is important to consider these methods of gaining access to information to expand access even more [16].

Global Rare Disease Patient Registry and Data Repository

The ORDR, NCATS, NIH has launched a pilot project to establish the GRDR. The goal is to establish a data repository of de-identified patient data, aggregated in a standardized manner using Common Data Elements (CDEs) and standardized terminology to be available to all investigators to enable analyses across many rare diseases and to facilitate various biomedical studies including clinical trials in pursuit of developing drugs and therapeutics to improve the healthcare and the quality of life for the many millions of people who are diagnosed with rare diseases. De-identification of patient's data will utilize the Global Unique Identifiers system which could also link patient's data to a biospecimen data set. To assist in testing the different aspects of creating the GRDR repository including implementation of the CDEs and the mapping to standard terminology, patients groups with and without registries were selected to participate in the pilot project [17–20].

In an attempt to harmonize and provide standardization among the different rare disease registries, ORDR had developed a number of resources, available to all. Among them are a set of CDEs that can serve groups establishing their patient registries and existing registries transferring their data to the GRDR repository. Additional disease-specific standards and CDEs are constantly in development in collaboration with other NIH institutes and federal agencies through the NIH CDEs working group and available for use to the community [21]. In addition, the ORDR office has developed an informed-consent-document template for participating in a patient registry that can be used and modified to the specific needs of each registry.

In addition, during the 2-year pilot project, ORDR has developed a web-based open-source software patient registry template that will be released to the public, as a service to the patient organizations and others, to allow and encourage them to establish additional rare disease patient registries. During the pilot project period, guidance and instructions will be available to patient groups to establish a registry and to contribute their de-identified patient data to the GRDR repository and to groups with existing registries to map their de-identified data and export it to the GRDR repository. Currently data is being submitted to GRDR to be available for access by investigators. The GRDR website provides information and useful links to other resources related to patient registries and the rare disease community.

The Rare Disease Human Biospecimen Database

Biospecimens are an essential resource for studying the pathogenesis of diseases and for other biomedical research. However, there are many challenges standing in the way of locating and acquiring a sufficient amount of high-quality specimens for research purposes. For rare diseases these challenges are magnified many times over.

- Rare disease specimens, to the extent that they are available, are widely dispersed across geographical regions and among various government or privately supported biorepositories.
- Many of the rare disease specimens are collected and stored together with specimens of common diseases with no appropriate designation. As a result, the existence of the biospecimens from rare diseases may not be known to investigators.
- Many advocacy groups lack the funds to support individual biorepositories or to participate in existing repositories.

To address some of these issues, the ORDR/NCATS has developed the Rare Disease Human Biospecimen database to serve as a central portal where researchers, professional societies, patient advocacy groups and other interested parties can locate and identify biorepositories and specimens needed for their research with a focus on rare diseases. The Rare Disease Human Biospecimen database website contains a searchable database of human biospecimens collected, stored and distributed by biorepositories in the US and around the world for research use. Searchable fields include: (1) repository name, (2) disease, (3) specimen type, (4) anatomic source, (5) processing method, (6) storage method, and (7) imaging. In addition, it contains a directory of various biorepositories available to the scientific community. The specimen's data and the biorepository directory is updated and expanded periodically to include additional information from existing biorepositories.

Specimens of rare disease listed in this database are labeled and linked to the rare diseases terms in the GARD, which provides extensive medical and educational information about specific rare diseases. Managers of biorepositories associated with patient registries are encouraged to link the patient data to the biospecimens data set in the process of de-identifying the data using the Global Unique Identifiers system or an internal generated ID [22, 23].

Therapeutics for Rare and Neglected Diseases Program

The Therapeutics for Rare and Neglected Diseases (TRND) program, a key component of the NCATS program, is an intramural research and therapeutics development program for rare and neglected diseases in the Division of Preclinical Innovation. TRND provides preclinical and early clinical development. The TRND program is neither a direct grant nor a contract program, but provides resources to develop collaborative therapeutic development projects. One of the goals is to eliminate barriers to initiating studies in humans. Other goals are to reduce the risks of failure encountered in the drug development process, reduce unanticipated time delays, and decrease costs of advancing basic research discoveries into diagnostics and treatments by bridging the gaps of missing data required for regulatory review purposes. Public and private sector partnerships and investments are frequently required to develop new drugs for patients with rare and neglected diseases. Each project is uniquely different in availability of existing and required data. The goal remains the same for all projects – to identify potential therapeutic compounds for the biopharmaceutical industry to adopt and take into clinical development. Potential partners include the biopharmaceutical industry, academic investigators and institutions, patient advocacy groups, foundations, and NIH intramural research program scientists. Specific projects have been initiated in the following selected therapeutic areas: Niemann-Pick disease type C, hereditary inclusion body myopathy, sickle cell disease, chronic lymphocytic leukemia, core binding factor leukemia, Duchenne muscular dystrophy, cryptococcal meningitis, autoimmune pulmonary alveolar proteinosis, fibrodysplasia ossificans progressiva, schistosomiasis, creatine transporter defect, and neonatal herpes simplex [24].

Bridging Interventional Development Gaps

Bridging Interventional Development Gaps (BrIDGs), previously the NIH Rapid Access to Intervention Development program, was reintroduced under its new name in October 2011 in the NCATS Division of Preclinical Innovation. BrIDGs provides critical resources needed for the development of therapeutic interventions. Similar to the TRND research program, investigators do not receive direct grant funds. The successful applicants receive access to NIH contractors who conduct preclinical studies at no cost to the investigator. Resources are available for

synthesis, formulation, pharmacokinetic, and toxicology services in support of investigator-held investigational new drug applications to the US Food and Drug Administration (FDA).

Contract costs are supported by the NIH Common Fund Program and collaborating NIH ICs. As of November 2012, BrIDGs has generated data to support 12 investigational new drugs accepted by the FDA. Twelve projects have been evaluated in clinical trials. Three BrIDGs-supported agents have entered phase II clinical trials to evaluate the effectiveness and safety. Six agents have been licensed during or after their development by BrIDGs. Selected BrIDGs Projects include the following diseases: atherosclerosis, spinal cord injury, chronic dry eye, AADC deficiency, pancreatic cancer, hypoparathyroidism, β -thalassemia, multiple sclerosis, acute brain trauma, and rheumatoid arthritis [25].

Tissue Chip for Drug Toxicity and Efficacy Screening

To help improve the therapeutic development pipeline, NIH, the Defense Advanced Research Projects Agency, and the FDA are striving to improve the process for screening potential compounds before human use. The Tissue Chip for Drug Screening initiative aims to develop 3-D human tissue chips that accurately model the structure and function of human organs. After development is completed, researchers can use tissue on a chip model to predict whether a candidate drug, vaccine or biological agent is safe or toxic in humans in a faster and more cost-effective way than current methods. Many potentially useful compounds have failed to gain premarket approval efforts due to toxicity despite promising preclinical studies in animal models. Tissue chips are a human, cell-based approach to enable scientists to predict more accurately how effective a therapeutic candidate would be in clinical studies. Eliminating toxic and/or ineffective drugs earlier in the development process would save time and money. These human tissue chips also could possibly predict disease progression, enabling researchers to prevent, diagnose and treat such conditions. Tissue chips combine miniature models of living organ tissues on a transparent microchip. The chips are lined with living cells and are designed to replicate the complex biological functions of specific organs. The Defense Advanced Research Projects Agency has provided support to develop platforms capable of integrating 10 or more organ systems. The FDA will help explore how this new technology might be used to assess drug safety prior to approval for first-in-human studies.

Several selected projects include the following: intestinal organoids with an enteric nervous system, induced pluripotent stem cell-derived skin constructs, circulatory system and integrated muscle tissue, cardio-pulmonary system, intestinal organoids, a 3-D model of human brain development for studying gene/environment interactions, human induced pluripotent stem cell and embryonic stem cell-based models for predictive neural toxicity and teratogenicity, an integrated in vitro model of perfused tumor and cardiac tissue, gastrointestinal organotypic culture system, a 3-D biomimetic liver sinusoid construct for predicting physiology and toxicity, 3-D osteochondral microtissue to model pathogenesis of osteoarthritis, 3-D human lung model to study lung disease and formation of fibrosis, a tissue-engineered human kidney microphysiological system, and a neurovascular unit on a chip for chemical communication, drug and toxin responses [26, 27].

Discovering New Therapeutic Uses for Existing Molecules – The New Therapeutic Uses Program at NCATS

This collaborative pilot Common Fund program is designed to develop partnerships between pharmaceutical companies and the biomedical research community to identify new therapeutic uses for existing compounds for rare and common diseases that have already entered the marketplace or have previously been involved in clinical trials. NIH has awarded 9 grants to evaluate new therapeutic uses for 8 drugs made available by pharmaceutical firms. The path to drug approval is usually very long and difficult with multiple opportunities for failure along the way. As a result, many potential compounds never become available to patients because they do not receive marketing approval from the FDA due to safety concerns or lack of effectiveness. Also, for most products, the full range of potential uses is never explored in clinical trials, even though considerable data exists from preclinical, toxicity and toxicology studies as well as clinical data related to the safety of the compounds. The NCATS' New Therapeutic Uses program identifies potential new uses for compounds that have undergone significant research and development by industry. By using compounds that already have cleared several key regulatory steps, it is possible to accelerate the pace of therapeutic development.

Eight drug companies including AbbVie (formerly Abbott), AstraZeneca; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline; Janssen Re-

search & Development, LLC; Pfizer; and Sanofi US provided 58 compounds for the pilot program. NIH requested potential new uses for these partially developed compounds. In June 2013, NIH awarded USD 12.7 million to fund 9 projects through this NCATS-led pilot program. These cooperative agreement awards will link academic research investigators with a selection of pharmaceutical industry compounds to explore new treatments for patients in 8 disease areas, including Alzheimer's, calcific aortic valve stenosis, Duchenne muscular dystrophy, lymphangioleiomyomatosis, peripheral artery diseases, smoking cessation, and schizophrenia. The NIH Common Fund provides funding for the pilot phase of these awards. To avoid additional delays, NIH developed model template agreements to facilitate the legal and administrative negotiations process for participation by multiple organizations.

Scientific expertise for the cooperative agreements is provided by 7 other NIH ICs, including the National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute on Aging; National Institute of Alcohol Abuse and Alcoholism; National Institute on Drug Abuse; National Institute of Mental Health; and National Institute of Neurological Disorders and Stroke. The library of potential compounds is available at the NCATS website [28, 29].

Conclusion

Numerous efforts and a major emphasis by the public and private sector initiatives have resulted in an increase of interventions and diagnostics for rare diseases. Newer translational research programs provide a more systematic and coordinated approach to rare diseases research and orphan products development. The approach that is offered requires extensive public-private partnerships with the pharmaceutical industry, contract research organizations, philanthropic foundations, medical and scientific advisory boards, patient advocacy groups, the academic research community, research and regulatory scientists, government funding agencies, and the public. These partners are referred to as the Rare Diseases Community. NIH has initiated new programs and expanded existing programs to provide the collaborative efforts required to stimulate product development or provide necessary data that prevents a product from moving to the next stage of product development for rare and neglected diseases. More resources are becoming readily available to bridge data gaps that currently exist and impede the

translation of research discoveries. These resources are available through the traditional grants and contracts to investigators to complete the necessary work or through services and support for the studies to develop the necessary data to meet regulatory requirements. As research resources become increasingly more scarce, well-planned comprehensive initiatives are needed to explore the existing data, the data needed to be acquired for regulatory purposes, and the required financial and personnel resources to enable the transition of research discoveries to

diagnostics, prevention and treatment interventions with all of the involved partners. Each program is unique and requires lengthy planning and collaborative efforts with responsible program teams to reach our goals.

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