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Orphan Diseases: State of the Drug Discovery Art

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Summary

Since 1983 more than 300 drugs have been developed and approved for orphan diseases. However, considering the development of novel diagnosis tools, the number of rare diseases vastly outpaces therapeutic discovery. Academic centers and non-profit institutes are now at the forefront of rare disease R&D, partnering with pharmaceutical companies when academic researchers discover novel drugs or targets for specific diseases, thus reducing the failure risk and cost for pharmaceutical companies. Considerable progress has occurred in the art of orphan drug discovery and a symbiotic relationship now exists between pharmaceutical industry, academia and philanthropists that provides a useful framework for orphan disease therapeutic discovery. Here, the current state-of-the-art of drug discovery for orphan diseases is reviewed. Current technological approaches and challenges for drug discovery are considered, some of which can present somewhat unique challenges and opportunities in orphan diseases, including the potential for personalized medicine, gene therapy and phenotypic screening.

Keywords

Orphan disease; Drug discovery; Personalized medicine; Gene therapy; Rare disease

Introduction

In 1982, the US congress passed the Orphan Drug Act which was signed into law by President Ronald Reagan in 1983, giving tax and exclusivity incentives to companies that invest in drug development programs for rare diseases – defined as diseases affecting fewer than 200,000 patients [1,2]. This law ended up serving as a model for Japan, which passed the Orphan Drug Law in 1993, and the European Union (EU), which passed its own Orphan Drug Legislation in 1999 [3]. Interestingly, although the Orphan Drug Act was the pioneer, the definition of an orphan disease is not universal, as the European Union (EU) considers a disease with a prevalence of 5 or fewer cases per 10,000 individuals to be orphaned [2]. These laws have had both a positive and an unintended negative effect on the approach of the pharmaceutical industry to rare disease drug development and marketing. Although rare disease oriented therapies were not expected to yield great profit, in recent years, the pricing set by pharmaceutical companies for some efficient rare genetic disease drugs – including

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some types of cancers – have approached “blockbuster” status (with annual sales close to 1 billion US dollars) and have been recently called “niche-buster” drugs [4]. In fact, since the Orphan Drug Act, more than 300 drugs have been developed and approved for orphan diseases; whereas fewer than 10 drugs had been approved by the Food and Drug Administration (FDA) in the 10 years prior to the passing of the Act [2]. Neither the Hatch-Waxman Act of 1984 – passed by the US congress with the goal to encourage the marketing of generic medicines and reduce healthcare cost – nor the Biologics Price Competition Act of 2009 – signed into law by president Barrack Obama in 2010 – have managed to mitigate the high prices of orphan disease drugs. It is noteworthy to mention that this is partially due to the high rate of failure of drug development and the costs associated with a high failure rate. For instance, for a specific disease, approximately 250 new chemical entities (NCEs) out of 10,000 may make it to animal testing, and only 5 to 10 of these may get tested in humans where only 1 or 2 of these investigational new drugs (INDs) may be marketable [5]. Pharmaceutical companies also attempt to recuperate their investment in an orphan drug through high prices since they cannot obtain profits through volume of sales as they would with drugs that target wider-spread diseases such as diabetes, asthma or high cholesterol. Taking that into account for example, treatment with the Genzyme drug imiglucerase, an enzyme replacement therapy developed to treat Gaucher's disease, might cost as much as US \$400,000 per year for an adult patient [6]. Similar costs are observed for treatment of patients with Genzyme's Aldurazyme, an enzyme replacement therapy made to treat Mucopolysaccharidosis Type I. Consequently, one of the biggest criticisms of the Orphan Drug Act is the high cost of treatment.

Orphan product exclusivity – exclusive marketing rights for an extended period (7 years in the USA, 10 years in the European Union & Japan, and 5 years in Australia) – is crucial to keep pharmaceutical companies interested in developing drugs for rare disorders. There are many advantages to being designated an orphan drug. Most importantly and enticing to the pharmaceutical industry is the fact that unlike patent requirements that are stringent and require a drug to be novel and non-obvious to someone trained in the art, the only requirements needed for marketing exclusivity of an orphan drug are that the drug be orphan-designated, safe and approved for the indication. Additionally, orphan drug marketing exclusivity starts the day the FDA approves the drug unlike patented drugs where protection starts early in the development process, years prior to FDA approval. An Orphan drug thus often has more years of protected marketing. Furthermore, “obvious” drugs that would typically not be patentable can be designated orphan drugs and protected. Examples such as zinc (for Wilson's disease), caffeine (for apnea of prematurity), albuterol (for prevention of paralysis due to spinal cord injury), and ascorbic acid (for Charcot-Marie-Tooth disease) are among a few non-patentable drugs that can be found in the orphan drug literature [7]. A database including the complete list of orphan drugs designations and their related indication approvals can be queried on the US-FDA website: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.

Without exclusivity rights companies such as Amgen, Genzyme, and Genentech whose first marketed products were orphan drugs would not likely be as successful as they are today. By the same token, without the lucrative incentives allowed to an orphan-product designation, efficient drugs such as those mentioned above as well as drugs for some of the rarest

diseases like severe combined immunodeficiency associated with a deficiency of adenosine deaminase (SCID-ADA) and tyrosinaemia Type-I would not exist [6,8,9]. Hence, there is a symbiotic relationship among orphan disease drug development, patients and pharmaceutical companies. However, few companies actually want to take the risk of investing in Orphan disease drug Research and Development (R&D), thus creating a vacuum in this space. Recently, foundations have gotten involved, filling some of the support gaps for Orphan disease drug R&D through personalized medicine, academic drug discovery and non-profit institutes (Table 1).

I. “Common” Orphan diseases and Personalized Medicine

The USA National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) Office of Rare Diseases Research (ORDR) estimates that approximately 7,000 Rare diseases have been described to date [10]. In this review, we will use “rare” or “orphan” diseases interchangeably. Advances in genomics, pharmacogenomics and epigenomics have allowed better definitions and characterizations of Orphan diseases, especially those that are monogenic. Consequently, there are approximately 250 new orphan diseases described every year [2]. Although the cutoff number of 200,000 people defines Orphan diseases in the USA, a staggering 20 to 30 million Americans currently suffer from some type of orphan disease [11]. To address this need, personalized medicine has become an intricate, although insufficient, part of funding orphan disease drug discovery. Indeed, although more than 300 drugs have been developed for rare diseases in the last 32 years, this number is a relatively small percentage compared to the close to 7000 designated orphan diseases. As revealed by those numbers, despite the measures and incentives offered to companies by the Orphan Drug Act and others for such diseases, hardly any pharmaceutical companies invest in drug R&D for a disease that may afflict as few as 30 people worldwide. Some diseases are so rare that a specialized physician may end up treating only a single patient for a specific disease per year [11]. Despite those odds, companies like Genzyme and Genentech – whose first successful drug targeted an orphan disease – invest in orphan disease drug R&D. The often extraordinary success of many blockbuster drugs was not predicted from a business standpoint. It is interesting to speculate what fraction of orphan drugs reached the market due to the insistence of research management [1].

II. Orphan Disease Drug Discovery Approaches

A group of orphan diseases that has benefited from some successes in academic drug discovery is lysosomal storage diseases (LSDs). These are typically monogenic disorders characterized by lysosomal defects in: enzymatic expression and activity, post-translational modifications and trafficking of enzymes as well as integral membrane proteins and transporters [12,13]. These defects cause accumulation of substrates within the lysosomes, leading to tissue damage through still partially understood mechanisms. The most successful US FDA-approved therapies to date have been those based on enzyme replacement therapy (ERT), which is now considered the standard of care for LSDs. Please see the article by Parenti *et al.* 2015 for a detailed review [14]. Indeed, ever since the successes of ERT administration for Gaucher disease, investigators and the biotech industry have focused on developing ERTs for rare diseases in which enzyme deficiency is the culprit. Subsequently, ERTs have been developed for numerous LSDs and have either been approved or are in

clinical trials for the following diseases: Pompe; Fabry; Muccopolysaccharidoses (MPS) types I, II, IIIA, IVA, VI & VII; Lysosomal acid lipase deficiency; Alpha-mannosidosis; Metachromatic leukodystrophy; Neuronal ceroid lipofuscinosis, late infantile (CLN2); and Niemann-Pick disease type B [14]. However, ERT has a number of limitations such as blood brain barrier permeability, bone penetration and quality of life – route of administration, IV infusion and high cost of treatment. In light of these limitations, other approaches employed by academia, non-profit institutes and some small biotechnology companies include: repurposing of small molecule drugs, development of pharmacological chaperones, phenotypic drug screening, improvement of antibody therapeutics, and advancement in gene therapy.

A) Small molecule strategies

1) FDA-approved drug repurposing: Repurposing FDA-approved drugs offers several advantages over novel compounds that have not yet been shown to be efficacious and safe in humans. Such compounds allow the possibility of rapid treatment with drugs where the safety profile is well established. Additionally, a re-purposed compound is oftentimes no longer under patent protection and generic versions are available, thus potentially diminishing treatment cost to the patient. The “Rare Diseases Repurposing Database” (Xu and Coté, 2011) describes 236 drugs that have been granted orphan product status although they have not been formally allowed to be marketed for these rare diseases *per se* [15]. Such tools are still rare and screening FDA-approved drugs to assess their potential as treatments for orphan diseases requires tremendous expertise and work.

2) Molecular and pharmacological chaperones: Molecular chaperones (pharmacological chaperones, pharmacoperones) are compounds, usually but not exclusively small molecules, directed toward a protein target which has a folding defect that causes the protein to be defective [16-18]. Molecular chaperones can also increase the activity of truncated proteins, but will typically have little effect on proteins where large truncations have removed major functional domains such as enzyme catalytic sites or transmembrane domains. However, in the case where there is a point mutation or where the most important functional domains remain, a chaperone approach can serve to increase protein function substantially. Pharmacological chaperones have recently emerged as potential treatments for orphan diseases such as the lysosomal storage diseases: Gaucher, Fabry, Pompe and Gangliosidosis. Please see Parenti (2009) for a comprehensive review [16]. As mentioned above, some of the limitations of ERT, the current standard of care for the aforementioned diseases, include: low bio-distribution, low blood brain barrier (BBB) permeability and increased immune response to the corrective enzyme.

Small molecule compound chaperones represent an alternative therapeutic avenue to circumvent these limitations. Consequently, other than their use in lysosomal storage diseases, pharmacological chaperones have been proposed as treatments for loss-of-function genetic diseases such as cystic fibrosis (CF), phenylketonuria (PKU), autosomal dominant retinitis pigmentosa, nephrogenic diabetes insipidus, hypogonadotropic hypogonadism, hyperoxaluria type I [16,19]. These chaperones can ameliorate the disease at different levels, from mutated enzyme trafficking/stability to enzyme conformation/folding and catalytic

activity. There have been disappointments in this approach, such as the recent suspension by Amicus Therapeutics Inc. of the phase II clinical trial for the treatment of Pompe disease with the pharmacological chaperone AT2220 (1-deoxynojirimycin HCl). However, CF has been treated in patients that express the most prevalent F508 mutation of the cystic fibrosis trans-membrane conductance regulator (CFTR) with quinazoline derivatives [20]. These compounds serve as pharmacological chaperones that rescue the misfolding and the trafficking of the F508 mutant protein present in 70% of CF patients [16]. In the case of cystic fibrosis, the most common molecular defect causes the protein to become trapped in the endoplasmic reticulum and degraded before it can reach the plasma membrane. The channel appears to be fully capable of function, but since it cannot reach the plasma membrane, CF develops. The molecular chaperone approach in this disease aims to allow the mutant CF chloride channels to evade endoplasmic reticulum quality control machinery, route to the plasma membrane and function normally. This approach is being pursued heavily as a potential curative treatment. Similar approaches are being pursued for hypogonadotropic hypogonadism [21], lysosomal storage diseases [17] and others.

3) Phenotypic drug screening: While many orphan indications result from rare genetic mutations, which can be identified and a target provided, there are others, such as autoimmune disease, with a much more complex biology or completely unknown etiology. In cases such as these, and without a clear molecular target, a phenotypic approach to drug discovery needs to be pursued. Typically, phenotypic screening is avoided due to the challenges of the development process. For example, it is difficult to increase the potency of a compound in a medicinal chemistry effort, if the molecular target is unknown, that is to say, an “optimization” may result in more than one activity in the cell and the resulting activities may offset each other. Despite these drawbacks, phenotypic screening has yielded 28 new molecular entities that were discovered and developed in the years between 1999-2008 [22]. Probably the best use of phenotypic screening is in drug repositioning where currently available FDA-approved drugs are tested to provide a resulting phenotype in the cell. The advantages to this approach is that the drug identified will have known human toxicity and drug-like profiles in humans and the advantages of use can be immediately compared to the disadvantages. Cancer is foremost when it comes to phenotypic screening. The ability of a compound to “melt” cancer cells (cause cell death) is often screened for in academia and industry alike [23]. Vorinostat, an orphan drug for cutaneous T-cell lymphoma, was discovered to induce myeloid differentiation and then subsequently identified as a broad spectrum HDAC inhibitor [24].

4) Personalized medicine: Personalized medicine is the tailoring of medicine to an individual patient. Traditionally this has meant that a patient's disease symptoms and pathophysiology was used to dictate which medicines to deliver. However, in recent times techniques such as DNA and RNA sequencing have allowed the ability to utilize molecular biomarkers to inform treatment options termed a pharmacogenomics approach. For example, in cancers, sequencing the cancer cell may reveal a mutation in a pathway where there is a known drugs to treat such a mutational landscape. This kind of approach is elegant and can save the patient from undergoing harsh treatments that would be predicted to fail, and also potentially uncover novel treatments that would not typically be part of the standard of care.

One of the most promising applications of personalized medicine, yet to be realized, may be in the undiagnosed patient populations where a disease cannot even be ascribed. Syndromes such as these may benefit from a personalized approach where patient symptomatology, treatment outcomes and pharmacogenomics are combined to inform treatment options, especially in cases where no treatment options exist. Indeed, for ultra-rare diseases, a physician may have only a single patient and in such a case rely on experience-based medicine to treat symptoms. The ability to enroll such a patient in a personalized medicine program to identify potential therapeutic avenues could be invaluable and may also provide information for the identification of a new disease, diseased patient population and even biomarkers for disease progression and treatment outcomes [25].

B) Gene Therapy—Monogenic rare diseases hold among the best potential for gene therapy approaches because the gene causing the defect(s) can be directly targeted. Furthermore, in severe diseases such as some aggressive cancers, the potential benefits outweigh the potential drawback of using a gene therapy experimental approach. In LSDs for example, gene therapy can be used to either increase or restore defective enzyme activity in patients' cells and tissues by delivering a wild-type copy of the defective gene, or a re-engineered copy where the defective gene is “corrected” and re-introduced to the patient. A strategy for the former is to systemically deliver, under the control of a ubiquitous promoter, the therapeutic gene in order to allow synthesis of the wild-type protein in the patient. A strategy for the latter is to collect patient bone marrow cells, transduce them *ex-vivo*, and re-introduce the “genetically corrected” cells [14]. This sort of bone marrow transplant may have a reduced risk of immune reaction by the patient. One gene therapy for a rare disorder currently has European approval: alipogene tiparvovec (Glybera) has been approved for lipoprotein lipase deficiency. This US \$1.6 million treatment is likely to become the world's most expensive drug. Long term and side effect are still unclear for this and other gene therapy approaches, making this a risky approach. However, it is not out of the realm of possibility that with the first wave of approvals and improvement in the technology that all single gene rare diseases will be addressed in part with this approach. Among the lysosomal storage diseases, for instance, gene therapy is undergoing clinical trial for the following diseases: Gaucher type 1; Fabry; Metachromatic leukodystrophy (late infantile); Mucopolysaccharidosis II, IIIA & IIIB; Neuronal ceroid lipofuscinosis, late infantile (CLN2); and Pompe disease [14]. This is among the most exciting and active areas for research that could benefit rare disease patients.

C) Natural History Studies—Natural history studies (NHS) are necessary in both rare and prevalent diseases to define both disease and disease progression, where patients are followed ideally before the disease is apparent. The course and effects of the disease are documented in order to understand the disease. A major hurdle is the development of biomarker assays that allow monitoring of disease progression. This is of particular interest in orphan diseases as we move to defined patient populations in early clinical development. Such quantitative biomarkers play an important role since the spectrum of the disease may appear very differently in a relatively small patient population and many rare diseases are chronic. There tends to be an inverse correlation with patient population and level of understanding of a disease. Added to this is that with few or no current treatment options, it

is difficult to categorize patients into treatment groups, so especially in rare disorders without any obvious etiology, natural history studies serve to inform a clinical trial and be useful in developing inclusion criteria. In an ideal case, a NHS will help identify biomarkers that can be used as outcome measures to increase the power of a clinical trial. NHS are thus a key component of a drug approval. The added benefit to patients with a rare disease is that due to the requirement to include NHS in an FDA application, a rare disease may actually become much more defined for the patient and for treating physicians to improve treatment options and standard of care [26,27].

III. Challenges

There are numerous challenges in attempting to find treatments for orphan diseases aside from the scarcity of the patient population. Access to patients and patient samples, population size and heterogeneity (age, sex, quality of therapy, etc.), naïve vs. treated patients, mutation severity spectrum, age of onset, and increasing the activity or expression of enzymes (it is much easier to inhibit) are all surmountable challenges, but challenges nonetheless.

A) Pre-Clinical Studies—In prevalent diseases such as Alzheimer's or Parkinson's, cell and animal models are oftentimes generated by teams of scientists to test potential treatments. Although cell models are also frequent in rare diseases, it is much more difficult to encounter animal models in those because of the long lead time and expertise needed to generate them. Many experts rely on *in-vitro* or *ex-vivo* studies to test potential drugs. Indeed, a gold standard model currently used by pharmaceutical companies and academia is skin fibroblast cells isolated from patients. Another frequently used model is lymphocytes obtained from patients, and from which induced pluripotent stem cells (IPSCs) can easily be derived. However, it is difficult to file an investigational new drug (IND) application solely based on *in-vitro* data. The U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) has a set of guidelines that they recommend for exploratory IND applications with limited but well-designed studies [28]. Although these guidelines can be used for an IND application targeting any disease, it provides a streamline approach that is useful for orphan diseases, considering the limited supply of samples. For example, although pre-clinical studies have to describe in detail the chemical properties of the candidate drug, including toxicology, pharmacokinetics, dosage and route of administration, fewer animals, fewer doses and shorter exposures can be used to apply for an exploratory IND compared to the regular one.

B) Clinical Trials—Typical randomized clinical trials are difficult to conduct in orphan diseases due to the scarcity of patients. One also faces possible ethical questions if small cohorts of patients are treated with placebos for an aggressive disease when a possible experimental drug could have saved their lives. A possibility to meet this challenge is to use each patient as his/her own control. These are often “N of 1” trials or multiple cross-over trials [29]. These type of trials have the advantage that each patient is exposed to both placebo and treatment, but it becomes more difficult to extrapolate the results due to intra- and extra-individual variances. Another disadvantage of the cross-over and “N of 1” trial formats is that outcome variables need to be stable or linearly progressive to be certain that

the treatment is working. Surrogate biomarkers have to be determined and quantitative biomarker assays have to be reliable in order to conduct an orphan disease clinical trial.

C) Funding—While the issue of commercial return on investment has been incentivized with legislation and there are several for-profit companies with a robust business model, there remains the issue of funding, especially in early preclinical work. It can take as many resources to uncover the pathophysiology of a rare disease as it would for a common disease such as Alzheimer's. Yet Alzheimer's has a great deal of funding where rare diseases typically do not. There are several efforts to address this disparity, such the National Organization for Rare Diseases (NORD), which has been successful in the past at lobbying the US congress for improvements to the Orphan Drug Act. NORD comprises more than 2000 different organizations representing specific rare diseases, and they provide funds through a small grant program to help develop drugs/treatment for Orphan diseases [11]. Such grants can help with the collection of pilot data in order to apply for larger financial support through the NIH or other mechanisms. The NIH also has programs to help fund rare disease research at higher rates and also the NIH official policy is to not consider the numbers of patients affected when considering funding an application. This helps to balance the funding. Another solution to this problem resides in patient advocacy groups and foundations, which focus on a particular rare disease and often also serve to unite researchers within an area. It has also been encouraging that as in recent years that as several funding sources become more competitive, the rare diseases appear to maintain their funding, and perhaps even gained ground. Along the same lines, the FDA Office of Orphan Products Development (OPD) is the largest funding source for clinical grants that helps bridge the gap between basic research, clinical development and marketing approval [3]. These grants cover portions of Phases I, II and III clinical trials and do not consider pre-clinical development. The OPD grants are especially useful for academic researchers. These academically developed drugs can then be licensed to pharmaceutical companies for commercialization purposes. This method may reduce the final cost of a treatment for patients.

Conclusions and Recommendations

While the vast majority of rare diseases have no treatments, the past 20 years have shown that rare diseases represent a ripe area for research and development with a high potential for uncovering novel treatments and achieving commercial success. Rare disease legislation has stimulated these areas and the field appears to be as strong as ever. With emerging technologies and increased understandings of epigenetics, epigenomics and pharmacogenetics, new methods of undertaking therapeutics discovery for orphan diseases are imminent. Epigenetics approaches offer the possibility to modulate (upregulate or downregulate) gene expression with small molecules without the need for gene therapy. Such methods are already being developed and potentially coming to fruition against MPS I and other rare diseases [30,31].

Orphan diseases and especially monogenic diseases etiology and pathogenesis can be more straightforward than polygenic diseases such as Alzheimer's and as a result the drug discovery process can be quite streamlined. Indeed, academic centers are cropping up that

are taking the lead in the drug discovery and development process. The potential upside for companies to enter into rare disease therapeutic areas has been apparent for a number of years, yet there is still a disconnect in public private partnerships, which may be a result of an overall lower number of groups working on any one particular disease. Thus, pushing funding to rare diseases should be a priority and new models for commercial interests funding early work should be considered. With a higher chance for success and legislation in place to ensure commercial benefit, the public private partnerships are likely to be actually more fruitful than the same partnerships would be for common diseases. Disease-specific foundations and patient groups are the obvious facilitators of this kind of interaction and may also serve to provide patient information for clinical trials recruitment.

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Table 1
Academic Centers involved in Orphan disease drug discovery, research and development

A partial list of notable academic drug discovery centers for rare diseases. Approximately 90% of all new indications for previously FDA-approved drugs have resulted from collaborations with academic institutions (including federal laboratories and universities).

Academic Centers / Non-Profit Institutes	Location	Strategies	References
Center for Orphan Disease Research,	University of Pennsylvania Raymond and Ruth Perelman School of Medicine	Fostering collaborations between researchers and clinicians at the University of Pennsylvania and other institutions committed to treating and curing orphan disorders/diseases.	[32]
Boler-Parseghian Center for Rare and Neglected Diseases	University of Notre Dame, Notre Dame, IN, USA	Using drug discovery approaches to discover novel diagnostics and therapeutics for rare diseases; Build partnerships with stakeholders such as pharmaceutical industry, the NIH, patients etc.	[33]
The Manton Center for Orphan Disease Research	Boston Children's Hospital, Boston, MA, USA	Using genomics to better understand rare diseases and to identify drug targets	[34]
The Center for Orphan Drug Research (CODR)	University of Minnesota, College of Pharmacy, Minneapolis, MN, USA	Focusing on FDA-approved drugs and novel drug delivery systems especially for rare neurological diseases in children.	[35]
Telethon Institute of Genetics and Medicine	Pozzuoli, Italy	Using genetics, cell biology, molecular therapy and systems biology approaches to provide the scientific basis for the development of treatments for rare diseases.	[36]
The Center for Therapeutic Innovation	University of Miami Miller School of Medicine, Miami, FL, USA	Using epigenetics and drug discovery approaches to discover therapeutics for orphan and common diseases.	[37]
The Center for Rare Disease Therapies	Keck Graduate Institute of Applied Life Sciences, Claremont, CA, USA	Think tank acting as a “nonprofit catalyst that interacts with government agencies like the FDA's Office of Orphan Product Development, patient advocates such as the National Organization for Rare Disorders and the Pharmaceutical Research and Manufacturers Association (PhRMA).”	[38]
Moser Center for Leukodystrophies	Kennedy Krieger Institute, Baltimore, MD, USA	High-throughput screening of small molecules to identify novel therapeutics for leukodystrophies; Genomics studies, cell-based therapy research as well as newborn screening and patient care.	[39]