



feature

Multifaceted roles of ultra-rare and rare disease patients/parents in drug discovery

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Individual parents and patients are increasingly doing more to fund, discover and develop treatments for rare and ultra-rare diseases that afflict their children, themselves or their friends. They are performing roles in business development that would be classed as entrepreneurial; and their organizational roles in driving the science in some cases are equivalent to those of principal investigators. These roles are in addition to their usual positioning as advocates. Through their efforts and those of the collaborative networks that they have developed, they could be positioned to disrupt the usual course of drug discovery. This can be illustrated using three different ultra-rare disease parent/patient advocate groups and the diseases for which they are developing treatments. This represents an alternative model for pharmaceutical research.

Disrupting pharmaceutical research

In the 21st century, many of us take the phenomenal advances in medicine for granted. Rarely a day goes by without some defining press release on a major health-related discovery, a treatment, a device or some research

finding that promises to banish a disease to the footnotes of medical history. For example, in 2012 eight treatments for cancers alone were approved by the FDA [1], and some of these are considered rare diseases. Although facts and figures about rare diseases are increasingly visible, the definition varies by country. Rare diseases are defined as those that affect fewer

than 200,000 (prevalence less than or equal to 67/100,000, USA) or fewer than 50,000 (prevalence 1/2000, UK). An ultra-rare disease affects substantially fewer patients, less than or equal to 6000 (prevalence 2/100,000, USA) [2–4]. According to the National Organization for Rare Disorders (NORD) and others there are only 250 treatments [5,6] for the nearly 7000 rare

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TABLE 1

'Blockbuster drugs' for rare diseases. Treatment costs can vary based on year and data source

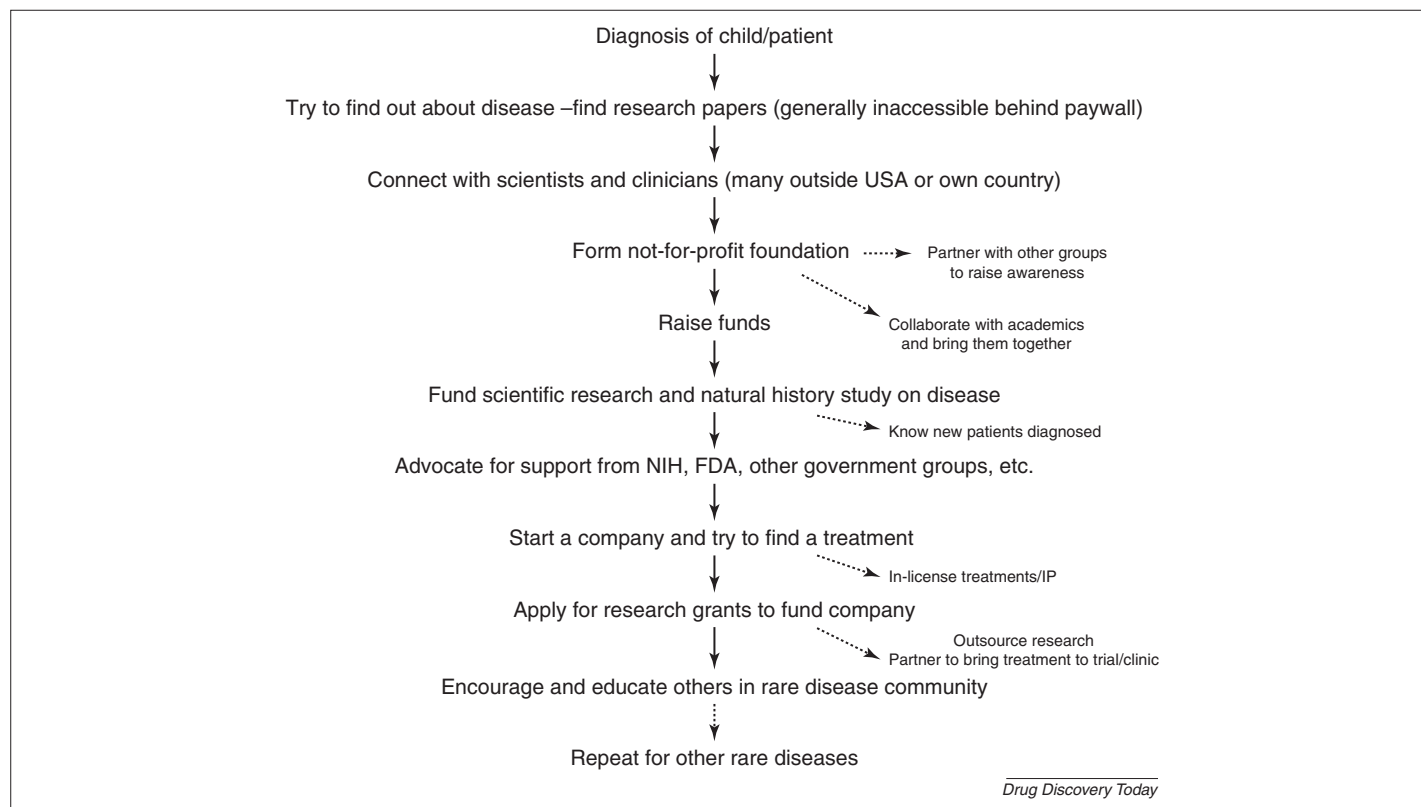
Drug	Therapeutic, disease, mechanism of action	Disease incidence	Treatment cost per year	Company	Forecast sales 2012 (Reuters)
Soliris	A monoclonal antibody treatment for a progressive disease that destroys red blood cells [paroxysmal nocturnal hemoglobinuria (PNH)] and a second condition that damages the kidney and other vital organs [atypical hemolytic uremic syndrome (aHUS)] to inhibit complement-mediated thrombotic microangiopathy	PNH has an annual rate of 1–2 cases per million. aHUS has 3.3 cases per million in Europe [65]	US\$409,500 [66], US\$440,000 [67]	Alexion Pharmaceuticals (USA)	US\$1.1 billion
Cerezyme	Enzyme-replacement therapy that helps break down fatty clumps that build up in cells in patients with Gaucher disease, damaging the liver, spleen and bones	1 in 20,000 live births [68]	US\$200,000 [69]	Sanofi (France)	US\$830 million
Myozyme	Enzyme-replacement treatment for Pompe disease, an inherited neuromuscular disorder that causes progressive muscle weakness	1 in 140,000 for infantile and 1 in 60,000 for adult [70]	US\$300,000 [71]	Sanofi (France)	US\$580 million
Elaprase	Enzyme-replacement treatment for Hunter syndrome, a genetic disease that primarily affects males, causing serious physical and mental problems	1 in 130,000 male live births in the UK [72]. Approximately 2000 people afflicted with Hunter syndrome worldwide	US\$375,000 [73]	Shire (UK)	US\$495 million
Fabrazyme	Enzyme-replacement treatment for Fabry disease, designed to counter damaging symptoms including kidney failure, heart problems and stroke	1 in 40,000 to 1 in 120,000 live births [74]	US\$200,000 [66]	Sanofi (France)	US\$352 million
Cinryze	A C1 esterase inhibitor that prevents dangerous swelling and painful attacks in people with hereditary angioedema	1 in 10,000–50,000 people [75]	US\$350,000 [66]	ViroPharma (USA)	US\$330 million
Vpriv	Enzyme-replacement treatment Gaucher disease	1 in 20,000 live births [68]	>US\$200,000 [76]	Shire (UK)	US\$310 million
Kalydeco	Treats a rare form of the lung disease cystic fibrosis in patients with a particular genetic mutation G551D in cystic fibrosis transmembrane conductance regulator (CFTR)	1100 people in Europe [77] and 1200 in the USA have this mutation [78]	US\$294,000 [79]	Vertex Pharmaceuticals (USA)	US\$260 million
Naglzyme	Enzyme-replacement treatment Maroteaux–Lamy syndrome, which causes short stature, stiff joints and breathing problems	Estimated to occur in 1 in 250,000–600,000 newborns [80]	US\$365,000 [73]	Biomarin Pharmaceuticals (USA)	US\$233 million

disorders, impacting 25–30 million Americans, whereas by contrast the FDA [7] describes over 400 drugs and biologics developed for rare diseases. It is unfathomable to think that there probably would not have been even this number of treatments without the incentives of the 1983 orphan drug act [8]. In 2012, President Obama signed into law the FDA Safety and Innovation Act which includes Section 908 the 'Rare Pediatric Disease Priority Review Voucher Incentive Program'. The act extends the voucher program that has been in place for neglected tropical disease drug development since 2007. Companies receive a voucher for a faster FDA review for a future product once they have a drug approved for a rare pediatric disease. This represents a valuable 'prize' that is also

transferable and has real value (potentially in the US\$100 millions of dollars). Subsequently, pharmaceutical companies have a renewed interest in rare diseases. Because of the relatively small number of patients affected by rare diseases, the high cost of drug development [9,10] and the need to see a return on their investment, companies can charge considerably more for these treatments. This is usually well over US\$100,000 per year and hence they can, in turn, become profitable drugs and potentially blockbusters if additional approvals for further indications can be added (although this is not always possible). A recent analysis suggests there are at least nine rare disease drugs with sales between US\$200 million to over US\$1 billion (Table 1). In addition to this, their

potentially faster path to approval, and the opportunity to potentially repurpose or reposition for other indications, makes rare disease treatments an increasingly attractive proposition. Indeed, another recent analysis has suggested that orphan drug sales could reach US\$127 billion by 2018 and represent 15.9% of prescription sales [11]. Whether these predictions will come to fruition remains to be seen, but it is clear there is more focus on rare diseases than at any previous time.

We should also look at rare diseases from a different perspective. The patient or the parent of a child with a rare or ultra-rare disease is usually faced with a dilemma upon diagnosis: wait for a treatment to come along or do something about it themselves. The latter option

**FIGURE 1**

Rare disease parent/patient odyssey. This schematic lists some of the common elements that Jonah's Just Begun (JJB) Hannah's Hope Fund (HHF) and Hereditary Neuropathy Foundation (HNF) have pursued.

would sound like an incredible, almost impossible, task fraught with ethical and social issues because pharmaceutical drug discovery and development is a massive long-term risky investment [9,10,12]. Regardless of the perceived low odds of success, parents and patients are increasingly taking matters into their own hands, and taking the latter option in an effort to accelerate research and attempt to discover a treatment for their disease. We could call this the rare and ultra-rare disease parent/patient odyssey, because for many they take a similar common pathway that incorporates many elements of entrepreneurial and scientific skillsets as well as advocacy. Fig. 1 describes some of the common elements experienced. This is also

happening predominantly in the absence of traditional venture capital funding [13], therefore requiring creative ways to fund cost-effective science. For example, parents and patients are forming rare and ultra-rare disease foundations and raising money to fund research themselves through grass-roots efforts. The mechanism for doing this is predominantly charitable giving and what we now term 'crowdfunding' from those that are unaffected and might also have an interest in finding a cure for their disease. Crowdfunding of science is also occurring with individual scientists who are dissatisfied with the current academic peer review and grant funding mechanisms [14,15]. Some parents and patients are even founding virtual pharmaceutical com-

panies to handle their intellectual property. Such patient or parent involvement is a step beyond what we all know from the AIDS/HIV advocacy of the 1980s. These efforts are being led by individuals that are going many steps further than solely raising awareness of the disease and are doing everything possible to make scientific progress happen and not waiting for the big pharmaceutical companies to do it for them.

Much has been written about the role of patient and disease advocates and foundations in drug discovery and development [16–18]. There are probably hundreds if not thousands of such rare disease organizations [19]. Although the efforts of the large disease foundations such as the Cystic Fibrosis Foundation, Multiple

TABLE 2

Illustrative examples of other parent/patient advocates leading drug discovery for rare diseases (limited to small foundations or companies)

Disease	Foundation/company	Refs
Niemann–Pick type C	Addi & Cassi Fund, Solution Therapeutics	[81,82]
Duchenne muscular dystrophy	Charley's fund, Nash Avery Foundation, Dart Therapeutics, Cure Duchenne, Parent Project Muscular Dystrophy	[83]
Pompe disease, Fabry disease, Gaucher disease, other lysosomal storage disorders (LSDs)	Amicus Therapeutics	[84]
Sanfilippo disease type A	Lysogene (launched by Alliance Sanfilippo and partnership with AFM-Telethon)	[85]

Myeloma Research Foundation, Muscular Dystrophy Association, AFM-Telethon (French Muscular Dystrophy Association), the CHDI Foundation, Inc. Michael J. Fox, Myelin Repair Foundation and others gain the bulk of the exposure and public support, they are essentially 'drug developers', using the prevailing big pharmaceutical industry model with very large funds (US\$10s–100s millions) at their disposal. Three examples are now presented of rare and ultra-rare diseases in which the co-authors (J.W., L.S. and A.M.) as a patient or parent have taken on the search for a treatment for the disease, becoming a founder, an entrepreneur, a *de facto* disease expert and a source of scientific knowledge above and beyond what is in the current literature for their diseases. Small rare disease groups are typically less visible compared with the bigger rare disease foundations, and yet such diseases and groups and others (Table 2) are at the forefront of a new wave in disruptive innovation [20,21]. By no means is this article an exhaustive analysis of all such efforts or rare or ultra-rare organizations as a whole, but it should inspire further interest and raise awareness to increase ultra-rare and rare disease research. To date, these efforts involving tiny groups and proportionally much smaller investments compared with the well-known disease foundations have gone undocumented.

From Jonah's Just Begun-Foundation to cure Sanfilippo to Phoenix Nest

Jonah's Just Begun (JJB) [22] was formed by J.W. in 2010 on behalf of her son Jonah who suffers from the ultra-rare Sanfilippo syndrome type C also known as mucopolysaccharidosis type IIIC (MPSIIIC), and is caused by a deficiency of the enzyme heparan- α -glucosaminide *N*-acetyltransferase (also called acetyl-CoA:heparan- α -D-glucosaminide *N*-acetyltransferase and acetyl-CoA:alpha-glucosaminide *N*-acetyltransferase), which is encoded by the gene *HGSNAT* [23]. Sanfilippo syndrome type C is one of the 50 plus lysosomal storage diseases – a neurodegenerative disease that is fatal [24]. Currently, there is no treatment for it and, because the central nervous system (CNS) is the major affected region and this enzyme is a multispinning transmembrane protein, it is unlikely that enzyme replacement or bone marrow transplant can be effective for treating this disorder. This leaves chaperone therapy and substrate reduction therapy [25,26] as potentially suitable approaches. It was recently shown that the residual enzyme activity of approximately 10% was estimated to be sufficient to prevent storage [27], further suggesting that even a minor increase in enzyme

activity obtained by pharmacologic chaperone therapy (PCT) which could correct protein misfolding, is likely to have an impact on disease pathology and be beneficial for patients. The major challenge however is efficient identification of PCTs. In a short period of time (three years) JJB has been fundraising and partnering with other global Sanfilippo syndrome foundations: JLK Sanfilippo Research Foundation [28], Sanfilippo Sud France, Sanfilippo Barcelona Spain [29]. JJB is now at the forefront of helping to drive the science for Sanfilippo syndrome type C by convening the researchers globally for regular meetings and forming a consortium of scientists, advisors and parents called Helping Advance Neurodegenerative Disease Science (HANDS).

When Jonah was diagnosed at 22 months old he was the youngest child to be diagnosed with Sanfilippo C, three years later and he is still one of the youngest known children with MPSIIIC. A recent study has also identified a two-year-old Korean girl with the disease [30]. Currently, Jonah is asymptomatic: happy, healthy and bright, which suggests with early diagnosis there is an opportunity to follow disease progression and natural history from its initial stages, as well as take preventative steps. His diagnosis stemmed from a fortunate series of circumstances. A switch of pediatricians led to an MRI conducted at New York University (NYU), where they are conducting a clinical trial for the sister disease of Sanfilippo: MPSI. J.W. and her husband Jeremy Weishaar formed JJB [22] after diagnosis in 2010, and in 2012 J.W. and S.E. founded Phoenix Nest [31] to commercialize potential treatments for Sanfilippo.

Because of these research efforts it could be possible to give Jonah and other young children every possibility of seeing a treatment in their lifetime. There are currently approximately 17 children in the USA also afflicted with MPSIIIC and in many cases the disease and symptoms (progressive and severe neurologic deterioration, hearing loss and visceral manifestations) have advanced and are having a devastating effect on their lives. The affected children that live into their 20s behave as if they have Alzheimer's disease; and school-age children are cognitively slipping, barely using any words and some need assistance eating with feeding tubes and constant supervision. For most of these children an illness as simple as the flu could also be deadly. Therefore efforts toward accelerating the search for and development of a treatment are important for all these individuals and their families.

Compared to the money, resources and the decades of research that has gone into drug

discovery for multigene defect diseases like Alzheimer's disease (in 2010 NIH funding was US\$469 million), multiple sclerosis (in 2011 NIH funding was US\$122 million) and Parkinson's disease (in 2011 NIH funding was US\$151 million), relatively little has been invested in the USA for Sanfilippo syndrome research. In comparison there are no published figures for MPSIIIC (or other forms) research funded by the US NIH. Although major multigenic diseases are much more prevalent than MPSIIIC, this monogenic rare disease has had just a fraction of the investment and decades less research but could be treatable. To date, JJB and global sister foundations have initiated six preclinical research projects and work closely with seven laboratories in Canada and across Europe. From the beginning JJB and JLK Sanfilippo Research Foundation made small grants to academic researchers (US\$20,000) that have been helpful because they provide seed funding for projects (e.g. to fund a postdoc) that can then lead to securing larger grants. One could consider this similar to Angel investors. For example, JJB initiated the first ever knockout mouse (also funded by the Canadian Institutes of Health Research), which has given us invaluable insight into the disease progression (Alexey V. Pshezhetsky, pers. commun.). This will give the field of MPSIIIC new hypotheses for treatment options, and provides the parents and patients with some hope for the future.

In addition, the difficulties J.W. experienced accessing information on the disease and sharing with others inspired the development of a mobile app to collect social media and open information from the Internet on this and other rare and neglected diseases. The development of Open Drug Discovery Teams has in turn led to increased opportunities to raise awareness of Sanfilippo syndrome [32] and the need for more open, collaborative research on rare diseases. JJB has also been able to work with an actor (Jonny Lee Miller) to raise awareness for the disease and funds via crowdfunding [33].

Hannah's Hope Fund for giant axonal neuropathy

Giant axonal neuropathy (GAN) is a recessively inherited condition that results in progressive nerve death [34]. GAN generally appears in early childhood and progresses slowly as neuronal injury becomes more severe. The GAN gene encodes the protein gigaxonin [35]. Recent studies suggest disturbed cytoskeletal regulation probably involving the proteasome degradation pathway [36] is responsible for formation of aggregates of intermediate filaments, which is

a morphological characteristic of this disease [37]. As the disorder progresses, patients typically become quadriplegics, dependent on a feeding tube and ventilator before dying in the second or third decade. GAN is an ultra-rare disease (with many undiagnosed), but neurologists suspect that some Charcot–Marie–Tooth (CMT) type 2 patients whose causal gene remains unknown might actually have GAN [38] and this would greatly expand the patient population. The majority of GAN patients that have been identified to date have extremely kinky hair. However, there are two confirmed GAN cases with straight hair, further suggesting CMT as a differential diagnosis for GAN. Some pathologic factors in GAN, like neurofilament light chain (NF-L) and peripherin accumulation, are also hallmarks of ALS (Lou Gehrig's disease) [35] and CMT 2E [39]. Abnormal intermediate filament aggregates are also observed in Alzheimer's disease, Parkinson's disease, diabetic neuropathy, spinal muscular atrophy, as well as other diseases [36]. To date, there are no therapeutics for GAN yet a small molecule that clears intermediate filament aggregates could apply to potentially many of these neurologic disorders.

Hannah's Hope Fund (HHF) [40] was founded in 2008 by L.S. and Matt Sames following the diagnosis of their youngest daughter, Hannah. There had been very little research conducted on GAN at the time of Hannah's diagnosis and they were only able to find one scientist in the world who was funded to study the disease. Like J.W., they decided to fight the disease, reasoning that for any disease someone has to be the first and for GAN it would be Hannah. When they told a geneticist they were going to start a foundation and raise money for therapy development for GAN they were told it would take 10 years and US\$10 million before there would be anything for Hannah. Just three years and three months later HHF began funding the University of North Carolina (UNC) at Chapel Hill Gene Therapy Center, and they were in front of the FDA Center for Biologics Evaluation and Research (CBER) for their Pre-investigational New Drug Meeting for GAN gene delivery to the CNS. Children with GAN will probably be one of the first disease communities in the world to receive a therapeutic gene to the spinal cord. GAN could be the first in-human disease where the AAV9 viral vector is used, and is currently being tested in preclinical studies elsewhere [41]. In fewer than five years, HHF has raised US\$5 million through grass-roots support to fund preclinical gene delivery studies and GMP vector manufacture for Phase I and Phase II gene delivery trials. HHF is also working tirelessly to fund basic research

needed to identify the molecular target(s) for treatments in GAN [36].

HHF does not pay indirect costs to institutions, which helps to stretch the money raised. HHF provides seed funding to the laboratories of Robert Goldman and Puneet Opal at Northwestern University. A recent study confirmed giganonin regulates glial fibrillary acidic protein (GFAP; <http://www.ncbi.nlm.nih.gov/gene/2670>) in astrocytes (unpublished correspondence with Dr Robert Goldman and Dr Puneet Opal, Northwestern University). As a member of the cytoskeletal family of intermediate filaments, GFAP is believed to modulate astrocyte motility and shape and could also be involved in glial cell adhesion, myelination and cell signaling [42]. An ultra-rare disease known as Alexander disease (AxD) impacts about 500 patients globally and is caused by dominant nonsense mutations in GFAP. GAN and AxD present Rosenthal fibers as hallmarks of their disease pathology. These new data raise the question of whether or not GAN also has activated astrocytes involved in disease pathogenesis, like AxD and ALS. A study was recently initiated to see if the GAN knockout mouse has astrocyte pathology.

In July 2012, L.S. was able to obtain the interest of ALS Principal Investigators (PIs) Dr Robert Brown and Dr Marc Freeman (University of Massachusetts Medical School) who are currently breeding the slow Wallerian degeneration (WldS) mouse and sterile alpha and Toll–interleukin receptor motif-containing protein 1 (Sarm1) knockout mouse models (both of which block axon degeneration after injury) with the GAN knockout mouse. This approach will allow them to assess directly whether blocking axon degeneration is beneficial in the context of axon loss in GAN, and potentially other neurodegenerative disorders. If this turns out to be the case, then therapeutics currently being developed to target the Sarm1 pathways might also help patients suffering from GAN.

L.S. is pursuing sublicense agreements for the gene therapy they have in development that HHF has funded. If this therapy is successful, all funds generated will be re-invested in therapy development to treat the peripheral nervous system of children with GAN. L.S. also founded BioGan Therapeutics and is pursuing small business innovation research (SBIR) grants to fund the discovery of small molecule therapeutics that clear intermediate filament aggregates and/or increase axonal transport in GAN. If a larger prevalence of GAN exists (as suggested by the straight-haired GAN cases), there is the possibility to attract venture capital funding for the development of a peripheral

nervous system treatment that could also have broad implications for closely related neurodegenerative disorders that also have intermediate filament aggregates as hallmarks of disease pathology.

The Hereditary Neuropathy Foundation and CMT1A

Approximately 1 in 2500 Americans suffer from CMT so this represents a rare disease with a much higher incidence than GAN and MPSIIIC. Peripheral myelin protein 22 (PMP22) duplication gene phenotype is the most common form of CMT called CMT1A [43]. CMT1A is also called hereditary motor and sensory neuropathy type 1a (HMSN 1a) [44]. There are currently no treatments for any of the CMTs. Symptoms of the disease often present in the first two decades of life [45] with CMT1A patients having reduced compound muscle and sensory action potentials, slow nerve conduction velocities, sensory loss, progressive distal weakness, foot and hand deformities, decreased reflexes and bilateral foot drop similar to all patients who have CMT type 1 [46]. PMP22D patients suffer debilitating sensory and motor neuropathy and about 5% become wheelchair bound. Although there are now more than 51 different genes implicated in CMT, with some forms more severe, the symptoms and electrophysiologic values are similar in several forms of CMT. Autosomal dominant patients are either assigned CMT type 1 (slow nerve conduction velocities and pathologic evidence of a hypertrophic demyelinating neuropathy) or CMT type 2 (relatively normal nerve conduction velocities and axonal degeneration) [47,48]. Underlying disease mechanisms are unique in most forms of CMT, with many point mutations on various genes causing a toxic accumulation of mis-folded proteins [49].

A.M. developed severe onset of CMT in 1995 and later one of her sons was diagnosed with CMT. She founded the Hereditary Neuropathy Foundation (HNF) [50] in 2001 with a mission to bring awareness and new treatments for CMT. HNF has increased awareness through campaigns, a cooperative agreement from the Centers for Disease Control and Prevention and launched the National CMT Resource Center, a portal of resources to support, educate and disseminate materials to the CMT communities. In 2007, HNF formed a therapeutic approach to tackling these debilitating progressive diseases: therapeutic research in accelerated discovery (TRIAD) [51]. The TRIAD model aims to treat CMT by creating partnerships with academia, government, pharmaceutical companies and the biotech industry. HNF created a roadmap that is paving the way to

treatments that will help the thousands of children and families affected with CMT.

In a few short years through funding by HNF, researchers have reached milestones, developing two assays for CMT1A with high-throughput *in vitro* high-content screens and there are promising hits underway (Pragna Patel, pers. commun.). In addition, HNF has contracted with the West Virginia University School of Medicine in collaboration with Dr Brent A. Baker's musculoskeletal pathomechanics research team at the National Institute for Occupational Safety and Health (NIOSH) and the Max-Planck Institute for Experimental Medicine (MPI) to establish two colonies of transgenic CMT1A rats at the Morgantown (WV) branch of NIOSH for the purpose of examining the effects of resistance exercise and neurotropic drugs and small molecule therapies, as well as the combination of interventions, in experimental animals. By targeting individual inherited neuropathies there is a streamlined path toward improving the quality-of-life of those suffering with these diseases. When there is a safe and effective small molecule therapeutic it probably will be possible to move quickly to show safety because clinical outcome measures for CMT have already been established, resulting from a 5-year natural history study on adults and the CMT Pediatric 5 Point Scale, which was recently published [52]. Upon reaching clinical phase the NIH Funded CMT Centers of Excellence, Cedars-Sinai Medical Center/Hereditary Neuropathy Center can be used as well as the Global Clinical Patient Registry for Inherited Neuropathies funded by HNF and HHF. The goals of the clinical registry are: collect information and tissue samples needed by the research community; assist in getting patients properly diagnosed with their specific form of inherited neuropathy; and recruitment of patients for clinical trials.

When there is an effective treatment for CMT1A, not only will patients be able to live and work independently, thus reducing dependence on disability insurance, the cost of ankle foot orthotics (AFOs), surgery, walkers, wheelchairs, scooters, neuropathic pain and antidepressant medications, among others, it will also result in decreased costs to the entire healthcare system.

The need for new tools

To date, a relatively small number of rare diseases has been tackled based on the few hundred approved drugs for over 7000 diseases. This suggests a significant gap. Most of these diseases are thought to be monogenic. If that alone made it simple to generate treatments this would have happened already and clearly it has not. Systematically approaching 7000 rare

diseases requires capturing the relevant information in a useful format. Currently, there is no exhaustive repository for rare diseases available to specifically assist in drug discovery or development efforts. Instead there are databases (and the following are just representative examples) that address rare diseases, with links to underlying genetics [e.g. NIH Office of Rare Disease, National Organization for Rare Disorders (NORD), Online Mendelian Inheritance in Man (OMIM), among others], and others that address foundational support for research and link patients and families to clinical resources (e.g. globalgenes.org). The FDA's Rare Disease Repurposing Database (RDRD) [53] consists of excel tables containing approved orphan drugs. Clearly this lack of a definitive rare disease database is inadequate at present and represents an opportunity. Rare disease researchers require data management facilities for consolidating the underlying genetic and protein causes, and potential treatments of these disparate rare diseases. Bringing them together in a comprehensive database with information that reaches beyond just the underlying gene will be crucial to researchers performing drug discovery on these disparate diseases.

Accelerating rare disease translation

Although there have been several new drugs approved for rare diseases in recent years and many have become profitable for the companies involved (Table 1), there is an urgent need to accelerate discovery and development for thousands of other rare and ultra-rare diseases. CMT1A is a text book case of how groundbreaking fundamental discoveries by academic scientists are not being rapidly translated to therapeutics fast enough. The causal gene duplication defect for the most common form of CMT (PMP22) was identified in 1991 [54,55] and confirmation that the elevated gene dosing resulting in the pathology of the disease was established in 1993, yet the first HTS to search for a small molecule therapeutic was not published until 2012 [56]. This represents a 21 year gap in translation from gene to screen. Equally alarming, as of February 2009, only one genetic disorder of the 43 disorders under the Muscular Dystrophy Association (MDA) umbrella has an FDA-approved therapy in the USA, and that is for Pompe disease (PD). This enzyme-replacement therapy for PD was led by a father with two children with PD who has gone on to become CEO at Amicus Therapeutics, which in turn is researching treatments for this and other rare diseases (Table 1). In Europe only, Firdapse[®] is an approved drug for the symptomatic treatment of

Lambert–Eaton myasthenic syndrome in adults, which comes under the disorders covered by the MDA umbrella.

With GAN, CMT1A and Sanfilippo syndrome there is the opportunity to speed this translation from bench to bedside and rapidly increase the knowledge on these diseases as a result of the advocacy and studies funded in just a few years and with relatively small investments (hundreds of thousands to low millions of dollars) compared with the amounts (many US\$100s millions) that the NIH is funding Alzheimer's disease, multiple sclerosis and Parkinson's disease. Even the efforts at drug discovery and development by large foundations such as the Cystic Fibrosis Foundation's relationship with Vertex, resulting in the recently approved drug Kalydeco[™], required significant investments (US\$75 million). JJB, HHF and HNF were recently awarded research services in the Rare Disease Challenge [57], which should facilitate the ongoing drug discovery projects and those of collaborators. For example, now that the NIH has started to screen for therapeutics for CMT1A this could inspire HNF and others to search for additional compounds active in various assays that have molecular similarity to the hits already identified [56].

Concluding remarks: there are no obstacles only opportunities

Rare diseases benefit from the probably very small clinical trials (tens to hundreds of patients) so, although these will be expensive, it will still be a fraction of the cost of major diseases. Not all rare diseases and their treatments will result in profitable outcomes and it is important to remember that this can also be the case for major disease treatments that do not become blockbusters. With only 11% (144/1310) of orphan designations being for ultra-rare diseases, big pharmaceutical research companies will probably still not see the profitability in developing a treatment for such diseases and governments will continue to focus on treatments for more prevalent diseases (US\$3.53 billion was spent on rare disease research, representing 11.4% of the NIH budget in 2011) [58]. It is clearly left to the parents and patients like those described, as well as the bigger disease foundations, to drive the science and deliver a treatment to trial and onto the open market. More collaboration and coordination between rare and ultra-rare disease foundations working in similar areas might be needed (for example as seen with the global Sanfilippo foundations). Bringing closely related diseases together will increase the patient population and attractiveness to facilitate venture funding and commercial interest.

Although parent and patient led groups can achieve a great deal they certainly benefit from academic or pharmaceutical scientists donating their time or providing advice. Efforts such as the Rare Disease Challenge [57] could also be catalytic in bringing different types of service vendors into the rare disease realm. All interested individuals are encouraged to connect with such rare disease foundations and offer their services. There is also a need to recruit experienced pharmaceutical researchers that can shepherd and expedite treatments for rare diseases through to clinical trials for these groups. Ultimately, parent and patient led rare disease groups also have to balance when to get involved and when to let their collaborators drive the projects to completion.

One of the co-authors of this paper, S.E. as a scientist recognized that all three of the rare disease groups represented by the co-authors had taken remarkably similar paths with their respective diseases and were effectively citizen (or DIY) scientists [59], with no formal scientific training. There are many excellent examples of rare disease foundations in which parents of children have become advocates, for example Leslie Gordon MD, PhD from Progeria Research Foundation [60], Pat Furlong from Parent Project Muscular Dystrophy [61] and multiple patient families and scientists forming Friedreich's Ataxia Research Alliance [62]. These organizations have become very effective in driving research, yet the lack of formal scientific or medical training should not hold people back in their search for researching or developing treatments. All three groups represented by the co-authors had become knowledgeable of all relevant science ongoing and the intricacies of their diseases, educating themselves to become experts and a resource for others (including scientists). The foundations they have developed are relatively tiny and literally run from their kitchen tables. They are doing more than acting as project managers, hence the suggestion that their roles are a hybrid of advocate, entrepreneur and principal investigator. Additionally, it was recognized that all three have what is lacking in traditional drug discovery culture: a sense of urgency. To these advocate-entrepreneur-scientists, time is valuable because there are lives at stake that are in their own families. They represent the very disruptors [13,52] of biomedical research that should be encouraged as the pharmaceutical industry looks for ways to improve its efficiency, profitability and public relations [20,63]. Perhaps there is a lesson for the pharmaceutical industry

in that they need to include people on their teams for whom the project is more than a career. Even the engagement of those affected by a disease as consultants might help to motivate new ways of addressing research. All three disease groups described can execute rapidly on shoe-string budgets. They use various fundraising approaches (employing social networks and the Internet) to receive donations that are then used to fund academic scientists to perform the research they need to push their goals forward. Some of their support can come from other patients investing in their own search for future treatments and represents crowdfunding.

The three disease groups also have an innate ability to view failures as stepping stones to better things, harnessing the reality that more knowledge is power. In essence, these groups developed their own preclinical research approaches (described above) that mirrored the recent suggestion to develop a generalized approach [64]. We have attempted to show how one can pursue rare and ultra-rare disease research on a very small budget with very few resources of your own other than determination, an ability to connect with scientists and fundraising ability. Therapeutic development should and can be cost and time efficient. Other parents and patient advocates can increasingly take a similar direction to those described herein because currently there are few other available options to find treatments for rare and ultra-rare diseases. Waiting for big pharma to take on their cause is not an option.

Conflicts of interest

J.W. is founder of Jonah's Just Begun-Foundation to cure Sanfilippo and Phoenix Nest. L.S. is founder of Hannah's Hope Fund and BioGan Therapeutics. A.M. is founder of Hereditary Neuropathy Foundation. S.E. works for Collaborations in Chemistry, and is co-founder of Phoenix Nest. Since writing this article he has also become a consultant for JJB, HHF and HNF.

Authors' contributions

All authors contributed to the literature review and the writing of this article. All authors read and approved the final manuscript.

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