Orphan Disease Center — Connecting the Dots

Letter from the Director
James M. Wilson, MD, PhD

We included “orphan” in the center’s name to reflect the fact that rare diseases are under-served in research funding for new treatments. Several years ago, the pharmaceutical industry had little to no interest in rare disease products. However, this is beginning to change due in part to the willingness of some insurance companies and government payers to provide high rates of reimbursement for disease-modifying therapies with curative potential.

The ODC aims to ride this wave of interest in rare diseases by catalyzing opportunities for the development of new therapies. In fact, we have become an important nexus between the rare disease communities and drug developers, for fostering relationships and collaborations. In an emerging reciprocal paradigm, we are helping biopharmaceutical companies partner with rare disease communities that support their product concepts. The ODC’s role in these alliances is to recruit patients, establish patient registry and natural history studies, and enlist key opinion leaders. So far, we have established partnerships with companies spanning multiple technology platforms, including gene therapy, genome editing and mRNA therapeutics.

We are excited that industry has estab-lished business models to justify investment in new drug development for rare diseases. However, this is only the tip of the iceberg in terms of unmet need across all rare diseases. In addition, the high costs of rare disease treatments further amplifies health care dispari-ties. We will leave “orphan” in our name until we develop a treatment for each of the 7,000+ rare diseases, and make the treatments accessible to all those living with these diseases. Time to get back to work!

Patient Spotlight:

Angelman syndrome (AS) entered our world unexpectedly 3 years ago when our daughter Quincy was born. Quincy had a beautiful delivery into this world in New York City on March 23, 2014. She was gorgeous and thriving. At about 2 weeks of age she started having significant intestinal symptoms with severe gastric reflux, which did not improve. Having another gorgeous typical older daughter, who was 22 months at the time, we knew this was not normal. At 3 months of age we felt she was not developing at the same pace as her older sister.

After multiple inquiries, we were told she is perfectly fine and she would catch up. At 5 months, with no eye contact, no rolling over, no reaching for toys and the failure to engage with her sister, or us, her mom and dad, we demanded genetic testing. Unfortunately, our hunch was correct. She was diagnosed with this very rare genetic disorder called Angelman syndrome. We were told 4 things: 1) This is catastrophic news. 2) She will never talk. 3) She will never walk. 4) She will be a happy girl and we should take her home and love her. Our 5-month old little girl had every hope and dream stripped from her life at that moment.

Angelman syndrome is a rare neurogenetic disorder affecting approximately 1 in 15,000 individuals. It is most commonly a random occurrence and affects children of all genders and race. Children and adults with AS typically have balance issues, motor impairments, a complete lack of speech, sleep disturbances, and potential-ly debilitating seizures. It is very true that individ-uals with AS will require continuous care for the rest of their lives and will never live independent-ly, if there are not breakthrough therapies.

What people don’t tell you is that these children are inspirational. They are SMART. They are FUNNY. They are incredibly social. They have a whole lot to say with the inability to speak. What the doctors did not tell us was that Angelman syndrome is one of the most unique mono-genetic disorders with one of the most optimistic possibilities for a cure. This is a disorder due to the loss of a single copy of a single gene. Most genes have 2 copies and if one is missing the other one takes over, without any obvious disease being present. With this specific gene the other copy is silenced in the brain. But it is present and healthy. This silencing does not happen until after the child is born, which means their brain has a functional copy of this gene.

We serve the purpose of making science and research accessible to rare diseases.

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Milestones in Rare Disease Drug Development

- Approvals, approvals, approvals... 2017-2018 has been a period of landmark approvals for advanced therapeutic platforms with great promise in rare disease. For example, the FDA approved Luxturna™ (voretigene neparvovec-rxyl), developed by Philadelphia-based Spark Therapeutics in collaboration with researchers at Children’s Hospital of Philadelphia and the University of Pennsylvania, for the treatment of biallelic RPE65 mutation-associated retinal dystrophy, marking the first approval for an AAV in vivo gene therapy in the US. European approval is expected to follow soon, where it will become the second AAV-based product approved. The FDA also approved the world’s first RNAi drug, ONPATTRO™ (patisiran) for the treatment of the polyneuropathy of Hereditary Transthyretin-Mediated (HATTR) Amyloidosis in adults, developed by Alnylam Pharmaceuticals.

- AAV-based in vivo gene therapy shows remarkable progress in rare diseases. As the number of AAV-based in vivo gene therapies in the clinic increases with a multitude of industry and academic-led trials, some of the most advanced projects start to show remarkable efficacy data. AveXis, recently acquired by Novartis, is developing an AAV gene therapy for Type 1 SMA and has been reporting remarkable survival and achievement of developmental milestones by patients. Audentes Therapeutics is following suit with encouraging data for its AAV gene therapy for the treatment of X-Linked Myotubular Myopathy (XLMTM). Finally, the community is expecting the early efficacy reports for the several AAV gene therapies under development for Duchenne’s Muscular Dystrophy.

Our Mission:

Each type of orphan disease affects such a small subset of the population, so the need for research and funding in this area is largely unmet. Our Center, the first of its kind, works closely with patient groups and foundations, Pharma and biotech, and the academic community. We bring a unique set of programs to the table, enabling us to add value at any stage - from building the initial knowledge base to enabling therapeutic development. Through our grants, Programs of Excellence, International Patient Registries, Jump Start programs, and a number of new initiatives, the ODC seeks to drive therapeutic development for rare diseases. We help identify and fund the most promising therapeutics while also tackling obstacles present in rare disease drug development.

Patient Registry

The Orphan Disease Center collaborates with medical informatics company, Pulse Infoframe, to build a suite of rare disease patient registries using cloud-based technology. Our registries collect real-world demographic, clinical, and laboratory data in addition to patient (or caregiver) reported outcomes (PROs) from patients with rare diseases. Data is securely collected through online portals, centralized, and de-identified for use by the broader scientific community. The data collected in these registries is essential for understanding rare diseases and accelerating the development of new treatments.

Current Projects in the Orphan Disease Center International Patient Registry:

- CRIGLER-NAJJAR
- CDKL5 DEFICIENCY DISORDER
- GM1

Visit our website for updates on registry timelines and development orphansocietycenter.med.upenn.edu/patient-registries

Featured Program: Jumpstart

The Orphan Disease Center’s Jump Start program serves to establish and progress research agendas in emerging and neglected rare diseases. The Jump Start program partners with patient groups and families to address gaps by identifying key opinion leaders and introducing new researchers to a disease. The program can help facilitate the development of animal models, establish a patient alliance or a patient registry, and organize symposia.

Research & Development Partners

- Biogen
- Takeda
- Ultragenyx Pharmaceutical
- ZC4H2 Research Foundation
- Champ1 Research Foundation
- Liv4 The Cure