

A Rare Decade Where Magic Could Happen

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*GUEST EDITORIAL***A Rare Decade Where Magic Could Happen**

Rare Disease Day takes place every year on the last day of February. This day was established in Europe in 2008, and is now observed in more than 80 nations. To put it in perspective, statistics from Globalgenes.org show that approximately 7000 different types of rare diseases and disorders exist, with more being discovered each day. About 30 million people in the U.S. are living with rare diseases, which is approximately 10% of the population. In addition, it is estimated that 350 million people worldwide suffer from rare diseases. If all of the people with rare diseases lived in one country, it would be the world's third most populous country. It is notable that, in the U.S., a condition is considered "rare" if it affects fewer than 200,000 people. Most alarmingly, according to the Every Life Foundation for Rare Diseases, 95% of rare diseases lack a single treatment approved by the U.S. Food and Drug Administration (FDA).

The Orphan Drug Act of 1983 marked the beginning of success stories of transformative therapies. Recognizing the scarcity of treatments for rare diseases, the Orphan Drug Act of 1983 provided incentives including grants and tax credits to companies involved in developing products for rare disease diagnosis, prevention, or treatment. Over the last 30 years, more than 400 medicines representing 447 separate indications have been approved to treat rare diseases, compared to fewer than 10 in the 1970s. As of September 15, 2013, the FDA has granted the orphan drug designation to 2899 potential therapies. These data point to the strong impetus from the industry and academia to develop therapies for rare diseases. In fact, in the last 5 years nearly one-third of all new drug approvals in the U.S. were for rare diseases.

One of the areas of severe unmet need is in the lives of children born with a genetic disease. The NIH estimates that 50% of individuals affected by rare diseases are children, making rare diseases a particularly deadly and debilitating concern for children worldwide. Encouragingly, a third of the treatments with orphan designation are for children. The Orphan Drug Act, the Best Pharmaceuticals for Children Act

(BCPA), and the Pediatric Research Equity Act (PREA) have resulted in a wealth of useful information about dosing, safety, and efficacy in pediatric patients.

An interesting fact is that about 80% of rare diseases are genetic in origin, and thus are present throughout a person's life, even if symptoms do not appear immediately. For example, lysosomal storage and other metabolic disorders could be genetic, while certain forms of cancer accounting for more than one-third of all rare disease medicines in development, and Alzheimer's are also considered rare. Others include neurological conditions, infectious diseases, and autoimmune disorders.

With the sequencing of the human genome and the analysis of functional proteins that play critical roles in the body, biopharmaceutical research is developing important new tools for treating genetic diseases. For patients with a genetic defect, their cells are unable to produce critical proteins that their bodies need in order to function properly. Rather than provide the missing protein or enzyme over a lifetime, the more transformative approach of gene therapy aims at permanently fixing the defect, creating potential for the patient's own cells to make the needed proteins.

Diagnosis of some of the rare diseases itself has been rare, with an average of a 5 year span just for diagnosis. The burden of misdiagnosis or nondiagnosis cannot be ignored, which could lead the patient further away from getting timely help. Simply receiving a diagnosis of a rare disease often becomes a frustrating quest, as many doctors may have never before heard of or seen the disease. Researchers are increasingly able to identify targeted patient populations, allowing clinicians to discover whether a patient is developing or will develop an illness much earlier. Specific rare disease patient populations are not only small in number, but could be geographically dispersed and often include children, posing an even greater challenge. The biopharmaceutical sector is working with patient advocacy organizations to identify and advance better ways to connect patients to biopharmaceutical and academic researchers conducting clinical trials.

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Nevertheless, even with the current challenges, now is a time of great progress and hope. The coming decade is set to explore the efficacy of several transformative and revolutionary therapies that could magically reverse the fate of individuals affected by rare conditions. On the forefront is gene therapy, with a promise to present a cure for complex genetic disorders, several of which currently require multitude of invasive, expensive treatments for the patient's lifetime. Glybera, the first gene therapy drug to be approved in Europe for lipoprotein lipase deficiency was priced at \$1.4 million per dose. Although priced to simply replace a lifetime of therapy with one dose has raised concerns, how future gene therapy drugs would be priced is yet to be seen.

Improved manufacturing capacities, hand-in-hand with higher vector yields, could help offset some of these costs. It is estimated that a 1–2 order of magnitude increase in gene therapy vector manufacturing would be needed over the next few years to support commercial supply requirements for many of the promising disease indications. Translating the rapid advances made in academia in the areas of viral vector expression, and improved analytical methods for prod-

uct and impurity quantification, would be essential to advancing these therapeutics. Improved gene therapy expression cassette design could ensure improved manufacturability. Along with highly purified and well-characterized drugs meeting rigorous quality specifications, this could help advance the increasing number of gene therapy clinical programs to later-phase clinical trials and towards market approval.

Biopharmaceutical research is entering an exciting new era with a growing understanding of the human genome. The ongoing advances in the design and development of therapeutics for the multitude of new rare disease targets offer hope for patients confronting a rare disease.

Disclaimer: The views presented above are of the author and not necessarily the views of any entity or organization. Dr. Kondragunta received her PhD under the joint supervision of Drs. Moreira and Rao.

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