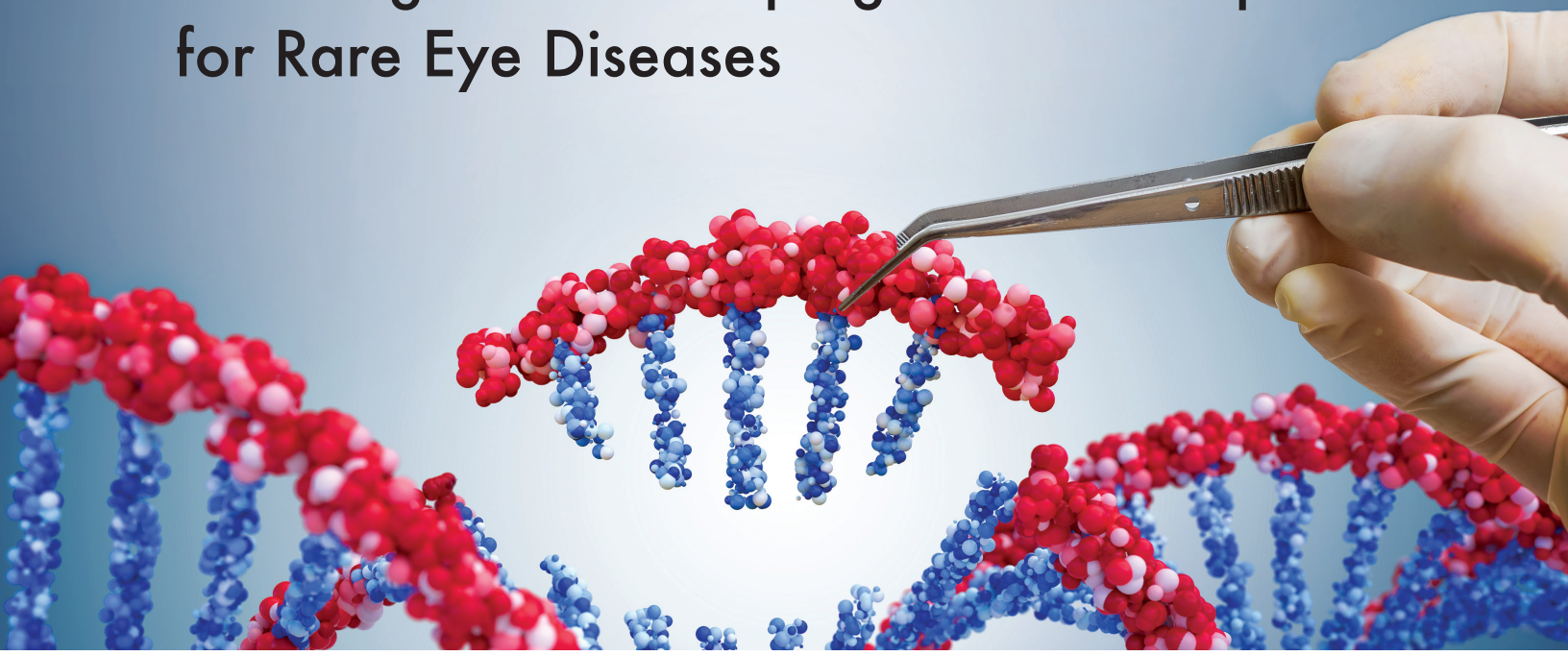
MORE THAN MEETS THE EYE

Challenges in Developing Gene Therapies for Rare Eye Diseases



An overwhelming majority of rare diseases are the result of a single-gene defect, making them a potential target in the hunt for treatment. The U.S. Food and Drug Administration (FDA) has approved just 4 gene therapies to date, but with more than 900 investigational new drug applications for ongoing clinical studies related to gene therapies in the works,[1] the time for these therapeutics to take center stage is fast approaching.

One of those 4 approved gene therapies is for the treatment of biallelic RPE65 mutation-associated retinal dystrophy—a rare eye disease that can cause vision loss that may result in blindness. Spark Therapeutics' Luxturna (voretigene neparvovec-rzyl) was the first gene therapy approved for a genetic disease and the first and only pharmacologic treatment approved for an inherited retinal disease (IRD).

With that approval, gene therapy began to carve out a spot for itself in the world of ophthalmology. Despite potentially transforming the way ophthalmologists treat certain diseases, the road to more approvals in this space is hindered by many of the same issues faced by rare disease communities as a whole—extremely small patient populations, a lack of referrals, and questions regarding cost and funding.

THE TROUBLE WITH RARE

Ophthalmology as a whole is unique in that the organ you are examining is right in front of you. You can look into it—you can see the optic nerve, the retina—and perform a number of different imaging and tests that can help determine pathology.

Despite that ease of access, ocular diseases, particularly rare ones, are not always at the forefront of the ophthalmologist's mind. Most practices focus on optometry, routine diagnosis, and surgical skills, and an emphasis on clinical genetics and genetic counseling is lacking, says Harsha Rajasimha, MS, PhD, Founder and Chairman, IndoUSrare and Jeeva Informatics, who has previous experience at the National Eye Institute as a genomics data scientist.

Particularly for IRD, he said, the lack of genetic referrals is worrisome.

The diagnostic odyssey is not unique to rare eye diseases. The small number of patients with IRD, some with populations of only a few hundred, means that many ophthalmologists simply don't have the expertise or knowledge to make a diagnosis or recognize that a referral is needed.

"Some patients may not ever have genetic testing depending on the eyecare professional they see," said Byron L. Lam, MD a professor at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine. "They could see a doctor who's not aware of the research in this field and not know how to order genetic testing."

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Some ophthalmologists may recognize that a patient has signs of an IRD but not be aware that there are potential treatments or clinical trials available, he added.

CLINICAL TRIAL ISSUES

The lack of proper diagnosis and referral to genetic testing is a major hurdle for those working to enroll patients in gene therapy clinical trials.

Every patient who enters a gene therapy clinical trial has to be a genetically confirmed case, said Dr Lam, who is involved with a number of clinical trials at the Bascom Palmer Eye Institute, including one for AAV8-RPGR retinal gene therapy for patients with X-linked retinitis pigmentosa.

NORD estimates[2] that there are around 100,000 people with retinitis pigmentosa in the United States. Approximately 10% of those patients may have retinitis pigmentosa related to the RPGR gene, making the population to conduct clinical trials in very small, especially when you consider how many individuals do not have a proper diagnosis.

When you take into account study criteria (most gene therapy trials look at patients who are moderately affected and not too young, according to Dr Lam), the pool of potential study candidates to pull from is even smaller.

Even then, just because you identified potential participants, it doesn't mean they are going to enroll.

"Gene therapy clinical trials are conducted at specialized trial sites capable of administering them carefully in complex protocols by highly trained clinical investigators," said Dr Rajasimha. "Since these sites are distributed far and few, patients are often required to travel thousands of miles to the nearest trial site to be able to participate."

WORKING THROUGH THE DIFFICULTIES

The difficulties in setting up and enrolling participants in gene therapy trials hasn't seemed to stop the tremendous growth in this area, perhaps because of the vast impact these treatments can have on many underserved diseases.

"The process of discovering and developing these emerging treatments is fast getting streamlined by nimble biotech startups pursuing lentiviral or adeno-attenuated virus based targeted gene therapy delivery," said Dr Rajasimha.

One such company is Ocugen, a clinical-stage biopharmaceutical company with a focus on rare ophthalmic diseases.

Their modifier gene therapy platform includes the product candidate OCU400 (AAV-NR2E3), which has been granted FDA orphan drug designation for the treatment of CEP290 mutation-associated retinal disease and NR2E3 mutation-associated retinal diseases.

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Preclinical data published in *Nature Gene Therapy*[3] demonstrated the efficacy of OCU400 in 5 different animal models related to 5 different human IRDs, illustrating the broad-spectrum therapeutic effects of a single modifier gene therapy.

"One of the biggest advantages of our modifier gene therapy platform is that it has the potential to eliminate the need for individual gene replacement and gene editing strategies and may revolutionize gene therapy treatments for eye diseases," said Shankar Musunuri, PhD, MBA, the CEO and Co-founder of Ocugen. "The platform differentiates itself from gene augmentation by introducing a functional gene to modify the expression of many genes and gene networks by bringing homeostasis to retina with normal function and health, compared with gene augmentation, which targets one individual gene mutation at a time and one disease."

Preclinical studies on OCU400 are currently completing and Phase1/2a clinical trials should begin in 2021, according to Dr Musunuri.

As new gene therapies are just starting to enter the world of clinical trials, others have been on the path for years.

Dr Lam and his team at Bascom Palmer Eye Institute are currently studying a number of gene therapies in various stages of clinical trials, including one for the treatment of X-linked retinitis pigmentosa caused by the RPGR gene mutation.

A Phase 1/2 clinical trial has been completed, and according to Dr Lam, shows that this gene therapy in this particular subtype of retinitis pigmentosa is so far relatively safe and there is some efficacy. An ongoing randomized phase 2/3 clinical trial is underway.

Although many therapies entering or already in Phase 1 trials may be exciting, Dr Lam cautions that many may not make it to Phase 2.

UNANSWERED QUESTIONS

The road to approval may be long and many therapies won't make it but with such a robust pipeline, gene therapy is poised to make an impact on ocular diseases and the patients who suffer from them.

As a patient advocate, Dr Rajasimha is optimistic about the impact gene therapy can have on patients, but also worries that the cost may be immense as well.

"As we have seen from the first few gene therapies, the average lifetime cost per patient has exceeded well over $1M. The big question is, how affordable these gene therapies are going to be for patients? How accessible will they be? Will health insurance cover the costs of these expensive treatment options?" he said, naming a few more hurdles that will need to be overcome after the approval process. "Answers to these questions," he added, "will require some serious will from all relevant stakeholders."

Luckily, it seems like most of those stakeholders are up to the task.

"Gene therapy has the potential to not just address the symptoms of current diseases but could be a cure for rare diseases," said Dr. Musunuri. "In the area of eye disease, gene therapies may stop the progression of the disease, thus allowing a patient to preserve his or her current vision and possibly improve the patient's vision with a single dose therapy for life. The same principle applies to gene therapies for rare diseases in general. The impact to a patient's quality of life is significant, which is what we are all striving for."

References

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3. Li S, Datta S, Brabbit E. et al. Nr2e3 is a genetic modifier that rescues retinal degeneration and promotes homeostasis in multiple models of retinitis pigmentosa. *Gene Ther*. 2020; ;10.1038/s41434-020-0134-z.