ALL ABOARD THE RESEARCH TRAIN

Some of the most intriguing sessions at our retina conferences are the ones that have us scratching our heads and asking, "What is the unifying diagnosis?" That question is often followed by, "My colleague is a rockstar for diagnosing that case." For most of us, these once-a-year cases that come through our practices stand out vividly amid thousands of routine intravitreal injections and postoperative evaluations.

Patients with inherited retina diseases (IRDs) often present as a diagnostic challenge because of variable presentations and because of the difficulties we may encounter when ordering and interpreting genetic testing. Furthermore, patients with syndromic forms have other systemic comorbidities that need to be addressed, and we don't have approved therapies for the vast majority of these conditions.

Researchers at the National Institutes of Health recently published findings in *JAMA Ophthalmology* detailing what seems to be an early-onset variant of Sorsby fundus dystrophy.[1] Unlike those with a typical Sorsby presentation, patients with this rare variant reportedly present with scotomas and macular changes but preserved central vision and no choroidal neovascularization. Genetic testing revealed heterozygous variants located in the TIMP3 signal peptide sequence, leading the team to conclude that they had discovered a novel form of macular dystrophy.[1]

Imagine if a patient with this variant walked through your door with an atypical presentation of diffuse maculopathy that genetic testing showed was caused by TIMP3 signal peptide defects. You would be documenting all your findings and eagerly drafting a case presentation for the next conference. You may also be phoning a friend or two—I know I would be. That patient is going to have a lot of questions about their diagnosis and visual prognosis, and we don't have great answers for them.

The senior author of the aforementioned study, Robert B. Hufnagel, MD, PhD, director of the Ophthalmic Genomics Laboratory at the National Eye Institute, noted in a press release that he hopes the discovery will lead to novel therapies for patients with this new IRD.[2]

Statements like that used to be little more than lip service, but times have changed. Patients with *RPE65*–associated retinal dystrophy have access to a gene therapy, and researchers are working hard to expand the list of approved therapies in the coming years.

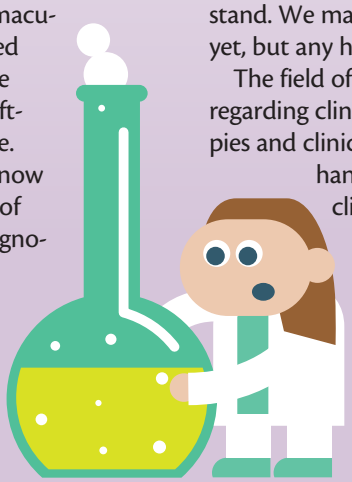
The field of gene therapy research—even its clinical use—is exploding. Of the 15 FDA-approved cellular and gene therapies (not including cord blood), nine were approved in the past 2 years.[3] Most of these are in the field of oncology, with the notable exception of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for the treatment of *RPE65*–associated retinal dystrophy.

Myriad trials are moving forward in the retina space, with plenty of ups and downs to keep us on our toes. Some phase 1/2 trials continue to show promise, but the field was dealt a few hard blows when three trials recently failed to meet their primary endpoints.

That doesn't mean researchers are giving up. Far from it. Traditional gene augmentation strategies already seem like well-trodden approaches with the advent of CRISPR/Cas9 systems that can open up new therapeutic avenues such as the regulation of gene expression, base and prime editing, and multiplexed genome targeting. The work being done is impressive and will likely lead to ground-breaking therapies in the near future.

This issue of *Retina Today* examines where these advances stand. We may not have anything concrete to offer patients yet, but any hope we can give them will be well received.

The field of retina is a fast-moving train with a lot to digest regarding clinical trial successes and failures and novel therapies and clinical approaches. We could all use some shorthand of it all, particularly when it comes to IRD clinical research. I hope this issue fits the bill. ■



AARON NAGIEL, MD, PHD

1. Guan B, Huryn LA, Hughes AB, et al. Early-onset TIMP3-related retinopathy associated with impaired signal peptide. [Preprint published online June 9, 2022] *JAMA Ophthalmol*.
2. National Institutes of Health. NIH researchers discover new genetic eye disease. Accessed June 16, 2022. www.nih.gov/news-events/news-releases/nih-researchers-discover-new-genetic-eye-disease
3. US Food and Drug Administration. Approved cellular and gene therapy products. Accessed June 16, 2022. www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

SPOTLIGHT ON UVEITIS:

This issue also contains a subfocus on uveitis to help you manage this equally challenging condition. Similar to patients with inherited retinal diseases, those with uveitis present with any number of subtle or not-so-subtle examination findings, which can complicate their diagnosis and treatment. The clinical tips and tricks in this issue may come in handy the next time a patient with uveitis needs extra care to get their disease under control. Our expert authors tackle pediatric uveitis, OCT biomarkers, and how to manage patients without a local uveitis referral.