VBS FELLOWS' PROGRAM: PRIMER ON INHERITED RETINAL DISEASES

A lecture by Stephen Tsang, MD, PhD, explored progress in this burgeoning field.

BY JAMES LIN, MD

During the Fellows' Program at the 2019 Vit-Buckle Society Meeting in Las Vegas in April, Stephen Tsang, MD, PhD, director of the Electroretinography Service at New York-Presbyterian/Columbia University Medical Center, delivered a talk entitled "Primer on Inherited Retinal Diseases." Dr. Tsang began by highlighting the development of genetic medicine—in particular, how the mutation for sickle cell anemia was identified in 1956, and how, even today, researchers are still seeking to correct this genetic mutation.

The field of ophthalmology has greatly benefited from inroads in molecular genetics, Dr. Tsang noted. In 2017, US FDA approval of a gene therapy to treat degeneration caused by the RPE65 mutation was a milestone in the use of genetic medicine to treat an inherited disorder.

A genomic surgery technique using *clustered regularly interspaced short palindromic repeats* (CRISPR) is a powerful tool that acts like molecular scissors, altering DNA sequences and modifying gene function. CRISPR has become popular since 2013, when it was used successfully to edit the genomes of human cells.

Around this time, a technology similar to CRISPR called *transcription activator-like effector nuclease*, or TALEN, was used to correct a mutation in mouse Crb1, a gene responsible in humans for degenerative retinal disorders in children. Now, CRISPR technology is actively being used in human trials, including one involving treatment for CEP290-related Leber congenital amaurosis.

GENETIC MEDICINE TRIALS

Genetic medicine trials are ongoing for choroideremia, X-linked retinitis pigmentosa, rod monochromatism, age-related macular degeneration, Leber hereditary optic neuropathy, and Stargardt disease. For genome surgery, there are generally two approaches: in vivo and ex vivo. Dr. Tsang discussed the in vivo approach, which involves delivering the genome surgery components directly into the targeted tissue; in the ongoing *CEP290* Leber congenital amaurosis trial, the target is the retina.

The challenge of gene therapy delivery is being researched as well, as many trials currently utilize viral vector delivery, which can increase the risk of off-targeting. One method of gene delivery being explored uses ribonucleoprotein complex, which has less off-targeting and might facilitate FDA approvals.

Dr. Tsang spent some time discussing the challenges of precision medicine and genome sequencing. One challenge is the presence of *variants of unknown significance,* or VUS, which are genetic sequences with purposes still undetermined. CRISPR may be useful to determine the significance of genetic sequences, as it can be used to edit or fix nonsense mutations through a trial-and-error method of inserting specific code sequences. Even with the use of CRISPR technology, there are challenges in determining which sequences can be targeted, particularly because it is easier to ablate than to directly repair. No current trials are directed at repair because this process is inefficient (except in stem cells or immortal cell lines).

A NEW APPROACH

To date, gene therapy trials sanctioned by the FDA have involved the treatment of autosomal recessive (ie, loss-of-function) disorders by supplementation with the wild-type version of the mutant gene in question. For patients with autosomal dominant (gain-of-function) disorders, the best hope for a cure is genome surgery that

AT A GLANCE

- CRISPR gene editing technology is now being used in clinical trials for inherited retinal diseases.
- New methods of gene therapy delivery are being explored to overcome the drawbacks of viral vector delivery.
- A new mutation-nonspecific strategy using CRISPR technology has been developed to perform gene ablation and replacement simultaneously.

RETINA TODAY ON THE ROAD

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repairs or removes the malfunctioning genes at the root of the disease. Currently, the hope for that approach rests in CRISPR gene editing.

The strength of the first-generation CRISPR-based therapy, however—namely its mutation-specificity—is also its greatest weakness. This is because the therapeutic components for each mutation (both the guide RNA and the repair template) must be custom-designed, engineered, tested, and approved for use in humans by the FDA. This presents a considerable and costly challenge for the many autosomal dominant diseases that can be caused by multiple different mutations.

For example, the blinding autosomal dominant disorder retinitis pigmentosa can be caused by any one of 150 different mutations in the rhodopsin gene. Treatment of all patients with retinitis pigmentosa would therefore require that 150 sets of CRISPR components be engineered, validated, and approved by the FDA.

To overcome this limitation, a new mutation-nonspecific strategy using CRISPR technology has been developed. With this technique, a second vector is codon-modified to introduce mismatches by silent mutations, making it resistant to guide-RNA targeting. This dual-vector design ensures simultaneous gene ablation and replacement; that is, no ablation before DNA replacement, an important safety feature.

With rapid developments in precision medicine through genome surgery ongoing, it is hoped that the next generation of retina specialists will be inspired to further advance the treatment of retinal disorders with these new technologies, Dr. Tsang said in closing. ■

JAMES LIN, MD
- Second-Year Vitreoretinal Surgery Fellow, Bascom Palmer Eye Institute, University of Miami, Miami
- jameslin1834@gmail.com
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