Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

CRISPR-Based Genome Surgery for Retinitis Pigmentosa

September 2018

Tsai et al. set out to develop a universal gene therapy tool, based on CRISPR (clustered regularly interspaced short palindromic repeats) technology, to treat retinitis pigmentosa arising from mutations in rhodopsin. Their novel ablate-and-replace strategy appeared to ameliorate disease progression in a preclinical model, suggesting that it may have clinical potential as well.

This experimental study included 2 types of mutation knock-in mouse models: *Rho*^{P23H} and *Rho*^{D190N}. The experiment's premise was that autosomal-dominant *Rho* mutations cannot be remedied solely by conventional gene replacement or augmentation; a cure is possible only if the mutant allele is corrected or destroyed while the wild-type allele is kept intact.

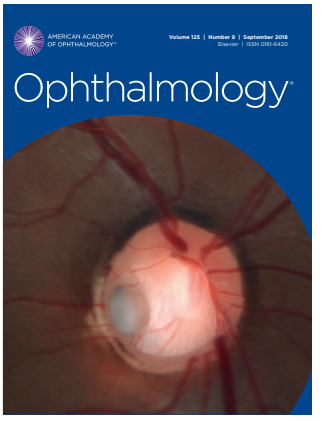
Thus, for this study, the authors applied 2 sets of adeno-associated viruses (AAVs) simultaneously: One ablated the endogenous *Rho* gene by an improved CRISPR-based strategy while the other delivered exogenous complementary DNA expressing the wild-type Rho protein. For comparison purposes, a proportion of eyes received gene replacement only. Electroretinographic and histologic analyses were performed, and an unpaired 2-sided t test was used to compare mRNA levels and electroretinographic responses.

Three months after administration of gene therapy, the outer nuclear layer (ONL) of eyes that received ablation plus replacement was 17% to 36% thicker than the ONL of eyes that had replacement only.

Electroretinographic findings demonstrated that the combination of gene ablation and replacement resulted in superior preservation of a- and b-waves in both murine models.

To the authors' knowledge, their findings represent the first electrophysiologic evidence of the efficacy of CRISPR-based therapy for postmitotic neurons. The ablate-and-replace strategy can be applied in a mutation-independent manner and therefore may be a fiscally practical means to overcome allelic heterogeneity in many autosomal-dominant disorders.

Minor changes could be made to the dual AAV toolset to create a human version suitable for clinical trials. Ultimately, this strategy may permit universal treatment of patients, regardless of allelic status.



A 2-D Markov Model May Predict the Course of Glaucoma

September 2018

The ability to detect glaucoma and predict its course is crucial for effective management. **Song et al.** previously introduced a state-based 2-D continuous-time hidden Markov model (2-D CT HMM) to represent the pattern of detected glaucoma changes using structural and functional information simultaneously. In the present study, their goal was to determine the predictive performance of the model for detecting glaucomatous change in a real-world clinical setting, using retrospective longitudinal data.

The model proved promising for this purpose: Information from 1 visit signaled the clinical picture through 5 subsequent visits.

This longitudinal retrospective study included 134 patients (134 eyes) who had been diagnosed with or suspected of having glaucoma. The hidden state dimensions were thickness of the circumpapillary retinal nerve fiber layer by optical coherence tomography (structural) and the visual field index (VFI; functional).

In a second version of the model, mean deviation was substituted for VFI. The average follow-up period was 4.4 years, and the average number of visits was 7.1.

A subset of the data (107 of 134 eyes; 80%), obtained from all visits except the final one, was used to train the model (training set). The validation set comprised data for the other 27 eyes. Prediction accuracy was represented

as the percentage of correct predictions versus actual recorded states. The researchers also measured deviations of the predicted long-term detected change paths from the actual detected paths.

Results showed that the accuracy of glaucoma changes predicted for the training set was comparable to that of the validation set (57% and 68%, respectively).

The difference between predicted and actual detected paths of change remained similar throughout follow-up, with deviations actually decreasing (improving) over time. Because the sample size also declined with time, larger studies are needed to confirm the findings.

The 2-D CT HMM has the advantage of demonstrating nonlinear relationships between structural and functional degeneration. It may benefit glaucoma management by providing visually intelligible cues of changes in structure, function, or both. The model's ability to detect changes according to patient-specific data may pave the way for a new personalized-medicine approach to glaucoma assessment and treatment.

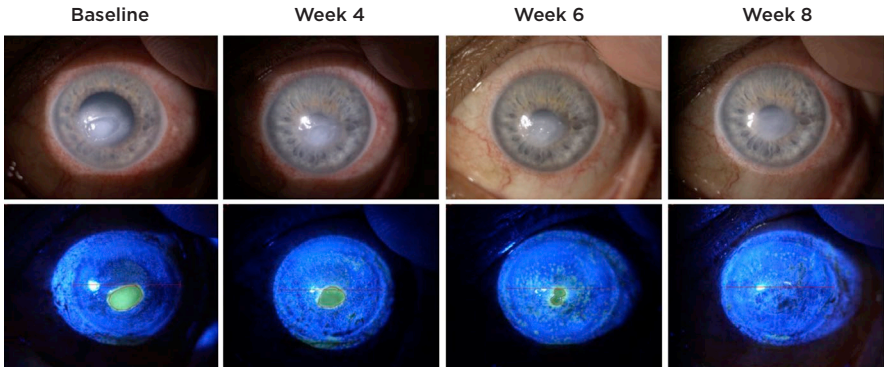
Neurotrophic Keratitis: Topical rhNGF Is Safe and Effective

September 2018

Bonini et al. assessed the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treatment of moderate to severe neurotrophic keratitis (NK). Their results affirmed earlier safety findings and demonstrated the healing and neuroprotective effects of rhNGF in patients with this disease.

This multicenter phase 2 study was vehicle controlled, randomized, and double masked.

Patients with moderate (stage 2) or severe (stage 3) NK in 1 eye were eligible to participate. Those who met all inclusion criteria (N = 156) were assigned randomly (1:1:1) to receive rhNGF 10 µg/mL, rhNGF 20 µg/mL, or vehicle. The dosage for each study arm was 6 drops per day for 8 weeks. Follow-up ensued for at least 48 weeks.



KERATITIS TREATMENT. *This patient—who had an oval, acentral, neurotrophic corneal lesion—was treated with 20 µg/ml rhNGF. Photographs taken from baseline through week 8 under diffuse white light (top row) and cobalt-blue light (bottom row) illumination.*

The main measure of efficacy was corneal healing, defined as total lesion-area diameter <0.5 mm by fluorescein staining. Assessments were made by centralized masked readers at week 4 of follow-up (primary endpoint) and again at week 8 (key secondary endpoint). Corneal healing also was assessed post hoc, using a more conservative measure (0-mm stained lesion area and no other visible staining). The primary variable for safety assessment was the incidence of adverse events.

By the 4-week follow-up, corneal healing had occurred in 54.9% of the 10-µg/mL rhNGF group, 58% of the 20-µg/mL rhNGF group, and 19.6% of the vehicle-control group. By week 8, the respective rates of corneal healing were 74.5%, 74%, and 43.1%, respectively.

Post hoc analysis by the more conservative measure also demonstrated significant differences, at both time points, between active treatment and vehicle control. More than 96% of patients whose cornea healed from rhNGF treatment remained free of recurrence throughout follow-up.

Few patients experienced adverse events (AEs), most of which were local, mild, and transient, and did not require cessation of treatment. The highest incidence of AEs was in the control group.

Findings of this study indicate that the benefits of rhNGF outweighed the risks for patients with moderate to severe NK.

The rhNGF treatment also holds promise for other ophthalmic conditions with neurodegenerative components, such as glaucoma, macular degeneration, and retinitis pigmentosa.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Natural History of Geographic Atrophy

September 2018

In geographic atrophy (GA) clinical trials, a change in a GA measure is usually selected as a primary outcome for evaluating treatment efficacy. However, estimates of GA progression rates in untreated eyes vary widely. **Shen et al.** evaluated the natural progression pattern of GA secondary to nonexudative age-related macular degeneration (AMD) in untreated eyes. They found that the radius of GA lesions increases linearly with time, with a high level of correlation across a wide range of studies.

For this review—believed to be the first meta-analysis on the topic—the authors included 25 studies with data from 2,942 eyes. They analyzed the data using the area linear model, the radius linear model (RLM), and the area exponential model. Of these 3 models, the RLM—in which GA radius grows linearly with time—proved to have the strongest predictive performance. A horizontal translation factor was added to account for the fact that participants entered into the individual studies at

different time points in the history of their disease.

The results showed that GA radius continues to increase at a constant rate of 0.163 mm per year and that this growth rate is consistent across different age groups. The RLM also predicted the age of onset of GA as 67.4 ± 5.2 years.

Thus, the authors calculated, if a patient with GA presents at 67.4 years, the radius of the GA lesion would be 3.26 mm (20 x 0.163) 2 decades later. This is consistent with observations from clinical experience, as patients with GA often have lesions that occupy most of the area within the arcades at the latest stages of their disease.

The authors noted that this analysis only had data in GA sizes ranging from 2.46 to 20.3 mm^2; thus, they said, they do not know if a similar fit is present for GA sizes outside of this range. Nonetheless, they suggested that the RLM be used in future clinical trials designed to evaluate the effect of a treatment on GA progression.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Inner Nuclear Layer Thickness, Metamorphopsia, and Tangential Retinal Displacement

September 2018

Metamorphopsia is a common early feature of macular diseases such as central serous chorioretinopathy, age-related macular degeneration, and epiretinal membrane (ERM). In a retrospective clinical study, **Ichikawa et al.** looked at inner nuclear layer (INL) thickness in relation to metamorphopsia and tangential retinal displacement in ERM. They found INL thickness to be a useful biomarker for metamorphopsia, as well as an indicator of tangential retinal displacement in ERM.

The study was a consecutive interventional series of 50 patients (50 eyes) who received surgery for ERM. M-charts were used to measure metamorphopsia. Measurements of INL thickness, outer retinal layer (ORL) thickness, and distances between the intersections of 2 sets of retinal vessels were obtained from Spectralis optical coherence tomography (Heidelberg Engineering) and infrared images.

Outcomes of interest were correlations of INL and ORL thickness with M-chart scores and retinal displacement distances.

The authors noted strong correlations between preoperative INL thickness and the metamorphopsia scores obtained preoperatively and 3 months postoperatively. Moreover, INL thickness at baseline and its change from baseline to 3 months correlated significantly with vertical retinal displacement observed 3 months postoperatively (both $p < .001$). Neither preoperative nor postoperative ORL thickness was found to correlate with preoperative or postoperative metamorphopsia scores.

Therefore, the authors proposed the utility of INL thickness as a biomarker for the degree of metamorphopsia both before and after ERM surgery. Their findings suggest that changes in the inner retinal layer, which cause distortion of Müller cells, play a large role in the development of metamorphopsia, thus providing further evidence that Müller cells function as optical fibers in the retina. However, the precise mechanisms by which retinal layer shrinkage generates metamorphopsia have not been determined.

Even when ERM surgery is successful, many patients will experience aniseikonia and metamorphopsia afterward. Hence, the authors recommend exploration of more efficient ways to correct irregular positions of retinal Müller cells.

Corneal Ectasia and Chronic Stevens-Johnson Syndrome

September 2018

In a recent case series, corneal ectasia was an incidental finding in patients with Stevens-Johnson syndrome (SJS), an inflammatory disease affecting skin and mucous membranes. Subsequently, **Maharana et al.** assessed topographic changes in patients with chronic SJS and concluded that corneal ectasia is a common but often-missed contributor to poor visual acuity.

This prospective observational study included 30 eyes of 15 consecutive patients (median age, 26 years; 11 males) with chronic SJS who were referred to a cornea clinic. In all cases, SJS was caused by medication-induced hypersensitivity reaction. The median time from disease onset to assessment was 7 years (range, 1-27 years).

The authors used a Scheimpflug system (Pentacam-HR, Oculus) for enhanced detection of corneal ectasia. Repeat imaging was performed until a good scan was obtained. Primary outcomes were best-corrected distance visual acuity (BCDVA), maximum corneal curvature (Kmax), anterior and posterior elevations, thinnest pachymetry, and Sotozono severity score. Final analyses were performed on 21 eyes.

At presentation, median BCDVA was 0.8 logMAR units, Schirmer score was 0 mm, and Sotozono score was 11. Tomography revealed corneal ectasia (Kmax >48 D) in 76.2% of eyes (mean Kmax, 58.37 ± 14.89 D). Front and back elevations on Belin/Ambrósio ectasia display were 42 µm (range, 10-176 µm) and 267 µm (range, 15-2,392 µm), respectively. Mean pachymetry was 377.76 ± 165.05 µm (range, 133-448 µm). The point of maximum ectasia was peripheral in 57.1% of eyes, central in 23.8%, and both peripheral and central in 19.1%. Spearman correlations indicated that deterioration of BCDVA and elevation of Kmax were linked to higher Sotozono severity scores. Associations between disease severity and presentation time, thinnest pachymetry, or anterior/posterior elevations were not significant.

According to the authors, their findings suggest that higher Sotozono scores denote more severe ectasia and that posterior elevation ≥15 µm signals early ectasia. However, validation is needed.

To properly manage SJS and its long-term effects, they advocate checking for corneal ectasia in all patients with the syndrome, especially if reduced visual acuity seems disproportionate to disease severity.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Is Pediatric Atopic Dermatitis Associated With Cataract?

August 2018

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that affects up to 20% of children in industrialized countries. Although the condition has been linked to various ocular complications, whether pediatric AD is associated with cataract is unknown. **Jeon et al.** investigated this matter in a Korean pediatric population. They found that, although the association appears to be rare, pediatric AD carries a higher-than-normal risk for cataract surgery.

For this population-based retrospective longitudinal study, the authors extracted nationally representative data from the Korean National Health Insurance Service database for a 12-year period (2002-2013).

Each incident case of AD or severe AD in a person <20 years of age was matched to 4 controls, using propensity scores derived from age, sex, residential area, and household income. Main outcome measures were incidence probabilities of cataract development and cataract surgery for patients with AD and controls, which were compared using Kaplan-Meier methods and log-rank tests. Cox proportional hazard models, fitted for cataract and cataract surgery, were applied to determine risk factors in the matched cohort.

Among the 34,375 patients with incident AD (mean age, 3.47; 47% female), severe AD was present in 3,734 (10.9%). The total number of matched controls was 137,500. The incidence of cataract development was similar for the AD and control groups (0.216% vs. 0.227%) and for patients with severe AD and their controls (0.520% vs. 0.276%).

Cataract surgery was performed more frequently in the AD cohort than in the control group (0.075% vs. 0.041%) and more often in patients with severe AD than their controls (0.221% vs. 0.070%). Severe AD was associated with cataract development and the need for cataract surgery.

The authors concluded that the absolute risk of cataract is rare, with or without AD. However, their findings suggest that patients with AD are more likely to require surgery for cataract and that this is particularly true for those with severe AD.

Trends in Traumatic Pediatric Acute Ocular Injury

August 2018

Understanding national trends in pediatric eye injury may guide efforts to prevent ocular trauma.

Focusing on mechanisms of injury and their association with demographic factors and the risk of vision loss, **Matsa et al.** reviewed prevalence data and noted trends for a 9-year span. During that period, the rate of pediatric ocular injuries associated with visits to the emergency department (ED) decreased substantially and was consistent among demographic characteristics, patterns of injury, and vision-loss risk categories.

For their research, the authors used a stratified U.S. sample of data from ED visits for acute traumatic ocular injury, occurring from 2006 through 2014. The study cohort consisted of 376,040 patients from birth to 17 years of age. Collected data included demographic and clinical characteristics. Temporal trends were explored and compared, including the incidence of ocular injury, risk of vision loss, and mechanism of injury.

Diagnoses were assigned to 1 of 3 risk categories for vision loss, depending on the injury location: high risk (pathognomonic), variable risk (need for injury monitoring), or low risk (vision sparing was anticipated). Data analysis was completed in 2018.

Between 2006 and 2014, the proportion of pediatric acute ocular injuries presenting to EDs declined by 26.1% and was similar across demographic variables, injury patterns, categories of vision-loss risk, and most mechanisms of injury.

Among injuries with a high risk of vision loss, the greatest declines were observed for motor vehicle trauma (−79.8%) and gunshot wounds (−68.5%). Injured children were more often male (63%) and in the youngest age group (birth to 4 years: 35.3%). Injuries commonly resulted from a strike to the eye (22.5%) and affected the adnexa (43.7%). Most injuries (84.2%) were low risk for vision loss; only 1.3% were high risk. Types of injury that increased during the study span involved sports (+12.8%) or household/domestic activities (+20.7%).

The authors suggest further investigation to pinpoint the initiatives that may be contributing to the observed decline in pediatric ocular injury and to identify interventions to reduce the most common injuries and those with high risk of visual impairment.

Genetic Variants Linked to Poor AMD Treatment Outcomes

August 2018

Currently, the most effective treatment for neovascular age-related macular degeneration (AMD) is intravitreal injection of anti–vascular endothelial growth factor (VEGF) drugs. However, visual results vary considerably. **Lorés-Motta et al.** conducted a multicenter genome-wide study aimed at identifying genetic factors associated with this variability. They found that the poorest visual acuity (VA) outcomes correlated with protein-altering variants in the *C10orf88* and *UNC93B1* genes.

Their study included 678 patients with wet AMD for whom genome-wide genotyping data were gathered in the discovery phase. In addition, genotyping was performed in the replication phase for another 1,380 patients with the disease. All participants received a loading dose of bevacizumab or ranibizumab, consisting of 3 injections given monthly. The primary outcome was the change in VA from baseline to completion of therapy.

The mean age of the entire study population was 78 years. All patients in the discovery cohort and most of those in the replication cohort were of European descent.

At baseline, the mean (standard

deviation) VA score was 51.3 (20.3) letters according to the Early Treatment Diabetic Retinopathy Study (ETDRS) system. After the third injection, the mean gain in VA was 5.1 (13.9) ETDRS letters, denoting improvement of 1 full line.

Genome-wide analyses of common single variants showed that 5 independent loci were associated with a p value below 10×10^{-5}. After replication and meta-analysis of the lead variants, rs12138564 in the *CCT3* gene was nominally associated with a better VA outcome (letter gain of 1.7). The gene-based optimal unified sequence kernel association test of rare variants showed genome-wide significant associations for the *C10orf88* and *UNC93B1*, both of which led to poorer outcomes. Patients with a rare variant in *C10orf88* or *UNC93B1* lost a mean of 30.6 letters (6.09 lines) or 26.5 letters (5.29 lines), respectively.

Although the findings suggest that rare protein-altering genetic variants may signal a poor visual response to anti-VEGF therapy in patients with neovascular AMD, further investigations are warranted. Information gleaned from this study and similar research may help to personalize management.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Oral or IV Corticosteroid Treatment of Optic Neuritis

JAMA Neurology
2018;75(6):690-696

Intravenous (IV) administration of corticosteroids is the standard of care for acute optic neuritis, but it can be costly and inconvenient. In an investigator-masked randomized study, **Morrow et al.** sought to determine whether oral administration of a bioequivalent oral corticosteroid would be as effective as IV administration in the management of this condition. The authors found that recovery of vision was similar for the 2 treatment arms.

Fifty-five adults presenting within 14 days of optic neuritis onset were enrolled in the study, which included a 6-month follow-up period. Participants were assigned randomly (1:1) to receive IV methylprednisolone sodium succinate (1,000 mg) or oral prednisone (1,250 mg) and were unmasked to treatment assignment. Each treatment was administered daily for 3 days. The selected oral dose was based on evidence of its bioequivalence to 1,000 mg of IV methylprednisolone in persons with multiple sclerosis.

IV treatment was administered at a hospital outpatient infusion center—or, when possible, at a hospital outpatient infusion center for the first dose and at home for subsequent doses. Patients in the oral group received 75 tablets of 50-mg prednisone to be consumed at home (25 tablets per day). The primary outcome was recovery of the latency of the P100 component of the visual evoked potential at 6 months. Secondary outcomes were P100 latency at 1 month and best-corrected visual acuity (BCVA) at 1 and 6 months.

The final analysis cohort included 45 patients (23 in the IV group and 22 in the oral group).

At 6 months, mean P100 latency had improved by 62.9 ms (from 181.9-119.0 ms) in the IV group and by 66.7 ms (from 200.5-133.8 ms) in the oral group. Also similar was P100 latency recovery at 1 month and BCVA at months 1 and 6, including low-contrast scores.

The authors concluded that bioequivalent oral doses of IV corticosteroids appear to be suitable treatment for optic neuritis. As demonstrated in other studies, patients are likely to prefer the cost and convenience of oral medication.

First Human Study of Intraocular Robotic Surgery

Nature Biomedical Engineering
Published online June 18, 2018

Edwards et al. have pioneered a first-in-human study of remotely controlled robot-assisted retinal surgery performed through a telemanipulation device. Their findings indicate that such a system, although still in its infancy for human use, has potential to achieve the precision warranted for many intraocular procedures. Specifically, surgical outcomes with the robotic system were comparable to those of manual surgery, but operating time was longer with the new technology.

For this double-armed study, 12 patients who required removal of an epiretinal or inner limiting membrane peel for macular hole repair were assigned randomly to receive robot-assisted surgery or manual retinal surgery (all procedures were conducted with the patients under general anesthesia).

The robotic system used by the investigators (Preceyes) had already been applied successfully in animals. The system combines a motion controller, held by the surgeon, with an instrument manipulator that can be fitted with a host of microsurgical instruments. Features include tremor filtering, adjustable virtual boundary, dynamic motion scaling, and a clutch mechanism that can freeze the position of the instrument inside the eye. In pigs, the system was able to cannulate and deliver drugs into retinal venules of approximately 80 µm in diameter, which would not be possible with manual surgery.

Main outcomes for the present study in humans were surgical success, duration of surgery, and the amount of retinal microtrauma (as a proxy for safety).

Surgical success and the amount of retinal microtrauma were comparable for the 2 study groups. However, dissection time was much longer with robotic surgery (4 minutes, 55 seconds vs. 1 minute, 20 seconds). To simulate potential use for subretinal gene therapy, the authors also used the robotic system to inject recombinant tissue plasminogen activator subretinally in 3 patients who had acute central vision loss caused by subretinal hemorrhage, secondary to age-related macular degeneration. These patients received local anesthesia. The robotic system accomplished the task, effectively displacing sight-threatening hemorrhage in their eyes.

—Summaries by Lynda Seminara