Introducing Artur V. Cideciyan and Samuel G. Jacobson, the 2018 Recipients of the Proctor Medal

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Samuel G. Jacobson, MD, PhD, and Artur V. Cideciyan, PhD, both Professors of Ophthalmology at the University of Pennsylvania’s Scheie Eye Institute, Philadelphia, Pennsylvania, have had a longstanding passion for scientific research that dates back nearly three decades when they met at the newly established Center for Hereditary Retinal Degenerations at Bascom Palmer Eye Institute, University of Miami. They began combining their talents in medicine and bioengineering to unravel longstanding mysteries about the blinding inherited retinal disorders (IRDs) that, at the time, did not have known molecular bases or any efficacious therapies. Their stepwise investigations of disease mechanisms by quantitative noninvasive testing led to the discovery of previously undiagnosed retinal degenerations, and these diseases were so well clarified by them that it became possible to move toward their molecular genetic bases. Subsequently, their ever-expanding knowledge around IRDs allowed them to test mechanistic hypotheses through small treatment trials. This was the initiation of an era of improving visual outcomes for IRDs. Fast-forward to 1995 when they were recruited along with their group to the University of Pennsylvania. Their scientific collaborators across the United States and worldwide expanded, and the goal of treatment of the long-considered incurable forms of inherited blindness became almost imaginable. The coinvestigators then initiated the first National Institutes of Health/National Eye Institute (NIH/NEI) program to embark on trying to treat an IRD using gene delivery to the retina. This successful clinical trial of a type of childhood blindness has led the field toward further gene-based therapies for other previously unapproachable blinding diseases. Their pathway from the bench to the bedside is important to illustrate as it provides a roadmap for future clinical studies and trials.

Converging on incurable IRDs from different backgrounds—ophthalmology and bioengineering—Samuel Jacobson and Artur Cideciyan recognized that progress toward therapy needed more in-depth documentation of these diseases. For example, they dissected the waveforms from noninvasive electrophysiologic recordings of patients with retinitis pigmentosa (RP) and proposed that a component of the abnormal vision in these mainly photoreceptor diseases also involved dysfunction of the inner retina. A mathematical model of the waveforms was published thereafter.¹ The observation of inner retinal dysfunction was followed years later by recognition that the retina can remodel as a consequence of loss of photoreceptors. Extensive work to the present day in animal models has sought the sequence of this neural reprogramming and rewiring that undoubtedly is affecting the potential for treatment efficacy. When molecular diagnostics were still in their infancy and diseased cell identification remained mysterious, they sought the cellular basis of an X-linked form of retinal degeneration by image analysis of a pathognomonic funduscopic feature in heterozygotes (carriers)—pinpointing the cone photoreceptors as a site of early disease.² This product of exquisite clinical evaluation antedates the major revolution in en face and cross-sectional retinal imaging that now defines routine clinical investigations.

Pursuit of the mechanism(s) of human IRD led Cideciyan and Jacobson to the discovery of a unique autosomal recessive retinal disorder with a major change in photoreceptor populations. They used photoreceptor function measurements (psychophysical and electrophysiological) to decipher the unusual features of the disease and postulated it was due to an abnormality in photoreceptor development. They later contributed to the molecular characterization of the causative nuclear receptor gene and delineation of the retinal cell fate pathway. The findings are now part of the lexicon for human retinal diseases and photoreceptor development pathways.³⁴ The discovery led to a generation of basic research into the pathways that lead to mammalian photoreceptor fate determination.

Before the advent of noninvasive optical imaging of the retina, human histopathology of eye donor retinas played a major role in understanding the retinal structural basis of the visual loss in these difficult-to-fathom diseases. Two rare retinal degenerations, both autosomal dominant, became amenable to “treatment” as a result of data from histopathology: Sorsby’s fundus dystrophy (SFD; now TIMP3 disease)⁵ and a disorder named by Jacobson and Cideciyan as late-onset retinal degeneration (L-ORD; now C1QNT5 disease⁶). Thickened sub-RPE deposits across the retina in these two entities led to testing the hypothesis that these retinas were suffering from a “nutritional night blindness” and that an oral dose of vitamin A could alter function positively. Rod vision in both conditions was improved by the short-term use of high doses of oral vitamin A and whetted the taste of the Proctor awardees for treatments that could improve vision and not only slow the natural history of the disease.

Cideciyan and Jacobson took major steps to move from the laboratory into the clinic with the first human gene therapy clinical trial for an IRD: the childhood inherited blindness known as Leber congenital amaurosis (LCA), specifically due to RPE65-mutant dogs⁷. Pivotal experiments that took the field forward were performed on Saturdays, time set aside by them to study the potential effects of gene therapy on naturally occurring dog models of human retinal degenerations. These proof-of-concept experiments always involved limited expectations because failure was the rule in their experience to date. On a day in 2000, however, the three RPE65-mutant dogs studied all showed an interocular asymmetry in retinal electrophysiology; the treated eye had nearly normal signals while the other eye remained severely abnormal. Having checked again and again for artifactual causes of the asymmetry...
and finding none, there were two choices: Either this was an error and a normal animal had reduced electrophysiological activity in one eye, or this was not a mistake and a mutant animal somehow had restored retinal function in one eye. The result was not an artifact, but was the first proof of concept that subretinal gene delivery (using an adeno-associated viral vector) could restore vision to the canine model of a human childhood-onset retinal degenerative disease (specifically LCA) due to a mutation in the *RPE65* gene. It is fair to say that the seminal paper in *Nature Genetics*, 2001, changed the momentum for the retinal gene therapy field. These observations of success with gene therapy were confirmed and extended in this canine mutant, as well as in other naturally occurring or genetically engineered models of the same human disease.

The question Jacobson and Cideciyan next asked was whether the animal models that showed efficacy using gene augmentation were faithful replicas of the human disease. The answer was sought in a seminal paper addressing in detail the disease mechanism in patients with LCA caused by *RPE65* mutations. The answer was a qualified affirmative—qualified because the patients at all ages showed more photoreceptor cell loss, that is, degeneration, than the animal models. Yet, there were patches of remaining retina, and using high-resolution in vivo microscopy and colocalized vision measurements, a dissociation of structure and function was detected. This had to be due to the basic biochemical abnormality of the disease and would be potentially treatable with gene augmentation or with an oral cis-retinoid treatment that Jacobson, Cideciyan, and their collaborators also had shown could ameliorate the biochemical blockade in the retinoid (visual) cycle caused by insufficient Rpe65, the retinoid isomerase. Given a targeted approach not only to the RPE cell by the vector gene, but also at the level of the individual patient to those regions of the retina that retained sufficient photoreceptors to warrant therapy, there was reason to move forward with the first human clinical trial of subretinal gene therapy in a genetic retinopathy. A succession of safety studies, both non-Good Laboratory Practice (GLP) and GLP, was performed with key members of the collaborative group. These pointed to “go” and the Food and Drug Administration (FDA) agreed. Jacobson and Cideciyan jointly headed and implemented the NIH/NEI grant to perform the clinical trial of *RPE65*-LCA. Two other clinical trials, one in the United States and the other in the United Kingdom, by superb clinicians and scientists also began during this time period.

Preliminary and encouraging reports of safety and success of gene therapy by Jacobson, Cideciyan, and colleagues appeared in 2008 and 2009; the other two trials also reported early safety and success. Jacobson and Cideciyan took a major step in pursuit of the goal of treating incurable human IRD in 2012 when data on all 15 patients were reported. The continued progress of all patients in the trial to that date was tracked; due to the meticulous mapping of each subject’s retina by noninvasive photoreceptor imaging it was found that improvements were to different degrees in different patients, and predictably localized to the treated areas of the retina. However, this mapping, along with the detailed natural history of disease studies, showed that the natural rate of photoreceptor degeneration due to *RPE65* mutations was not modified by the gene therapy, and the short-term improvements in visual function start waning in the long term. In this and subsequent studies of the trial subjects after gene therapy, Jacobson and Cideciyan proposed strategies for the next steps to advance the new treatment to even greater and long-lasting clinical benefit for patients with this form of LCA.

The progress achieved by Cideciyan and Jacobson with *RPE65*-LCA established that there can be a successful path from basic science discovery to proof-of-concept research to preclinical safety studies evaluating the human phenotype, all of which are required for successful human clinical trials. This team now has investigated numerous hereditary retinal diseases in collaboration with national and international colleagues to assess the potential for treatment with gene augmentation therapy or other promising therapeutic modalities. These studies have provided them, and the retinal degeneration research community, with the groundwork to move toward clinical trials of still-incurable genetic retinal degenerations. Most of the more recently investigated retinopathies in canine models and human patients are photoreceptor diseases, in contrast to *RPE65* deficiency: X-linked recessive RP due to *RPGR* mutations; autosomal dominant RP caused by rhodopsin mutations; and the severe autosomal recessive retinal–renal disease known as Senior-Loken syndrome caused by *NPHP5* mutations. Progress since 2001 to date has been remarkable: *RPE65*-LCA gene therapy has now been commercialized after FDA approval; *RPGR*-linked RP is now in phase 1/2 clinical trials; and *RHO*-adRP and *BEST1*-Best disease are on the path to FDA-enabling studies. The prospects are indeed very promising.

So what does the future hold? As you will see from their Proctor Award lecture, their horizons are expanding to now assess two new LCA subtypes, the *CE290* ciliopathy, and the phototransduction defect resulting from mutations in *GUCY2D*. Their precise phenotyping and assessment of underlying pathology based on in vivo measures along with their clear appreciation of the molecular mechanisms of the diseases precisely identify the therapeutic targets and provide absolute measures of outcome assessments. We have been fortunate to have worked and interacted with these two superb scientists, and we are especially honored to introduce Artur V. Cideciyan and Samuel G. Jacobson as the 2018 recipients of the Proctor Medal.

References


