Advantages of ocular regeneration research

It is my pleasure to serve as the guest editor for this special eye series of *Annals of Translational Medicine* entitled "Novel Tools and Therapeutics in Eye Regeneration." This special series is very timely since there has been a recent increase in the momentum of translational research in ocular regeneration. This increase stems partially from the success of ocular gene therapy. The US Food and Drug Administration (FDA) approval of voretigene neparvovec-rzyl (Luxturna; Spark Therapeutics) in January 2018 to treat inherited retinal diseases associated with mutations in the gene *RPE65* is the first gene therapy to be approved by the FDA for clinical use. Its approval was based on very compelling positive results of the clinical trials showing improvement in visual function in individuals with previously untreatable progressive severe vision loss (1).

Conducting translational regenerative research in the eye has many advantages which likely contributed to the success of gene therapy for ocular use. The most obvious is the optically clear media of the eye that makes vision possible. The clear ocular media also allows direct *in vivo* visualization and examination of the various tissues in the eye, including the cornea, retina and optic nerve head in live humans and animals. The clear ocular media also allow various *in vivo* optical imaging tools to be developed for clinical and preclinical application. Sher *et al.* summarized in this series the various imaging tools that have been used for clinical and preclinical work on retinal regeneration (2). It provides a nice background on the topic. These imaging tools allow non-invasive *in vivo* histologic analysis of ocular tissue such that morphologic changes associated with various ocular disorders and the effects of therapy can be appreciated in vivo. Ultrahigh resolution imaging possible using adaptive optics and optical coherence tomography (OCT) can result in analysis of the retina at near cellular level. Novel development of these ultrahigh resolution *in vivo* imaging tools has led to the ability to conduct functional testing of the retina at subcellular level. This is exemplified in the optoretinogram discussed by Dr. Jonnal in this series (3). Optoretinogram is an *in vivo* retinal imaging method using adaptive optics and OCT to evaluate subcellular changes within the photoreceptor cells associated with change in photoreceptor function. This novel technology could be the most sensitive retinal functional testing tool to date.

Another advantage of conducting translational research for eye disease is the availability of well-established animal models of common ocular conditions associated with vision loss. In this series, Park *et al.* provide us with a comprehensive overview of animal models of corneal endothelial dysfunction that can be used for development of novel therapies (4). The cornea is the most anterior, superficial tissue in the eye. Optical clarity of the cornea is important for preserving vision. Corneal endothelial diseases affect corneal clarity and are major causes of vision loss. For the retina, dysfunction resulting from retinal ischemia or degeneration results in profound vision loss which is often irreversible. This series includes a review of animal models of diabetic retinopathy, a leading retinal vascular cause of vision loss in adults. As summarized by Quiroz and Yazdanyar, none of the animal models completely simulate human disease, but various aspects of this retinopathy can be studies using these models (5). In this series, one of the more commonly used diabetic retinopathy murine model i.e., streptozocin-induced diabetic retinopathy model, is used by Cheung *et al.* to show that intravitreal injection of human CD34+ bone marrow stem cells result in preservation of the retinal vessels (6). The findings are important since a phase I/II clinical trial is currently underway exploring the safety and efficacy of intravitreal injection of autologous CD34+ stem cells for vision loss associated with retinal vein occlusion, another leading retinal vascular cause of vision loss (www.clinicaltrials.gov).

Various animal models also exist for retinal degeneration, and new models continue to be developed and characterized. In this series, Salpeter *et al.* report on a novel murine model of retinal degeneration associated with neuronal ceroid lipofuscinosis type 8 and compares the retinal changes to that noted in humans with the same condition (7). A more commonly used model of retinal degeneration, Royal College of Surgeon (RCS) rat, is characterized by slowly progressive diffuse retinal degeneration which is hereditary and analogous to retinitis pigmentosa, a diffuse retinal degenerative condition seen in humans. In this series, Park *et al.* from Seoul National University collaborated with our researchers at University of California Davis to show efficacy of intravitreal and subretinal injection of CD34+ stem cells from bone marrow in preserving retinal function in a rat model of diffuse retinal degeneration (8). The results show that the regenerative effects of CD34+ stem cell is not limited to retinal vascular disease as demonstrated by Cheung *et al.* (6).

Disorders of the optic nerve, such as glaucoma, are also leading causes of vision loss and blindness that cannot be treated at the current time. In this series, Fague *et al.* provides an overview of animal models optic nerve damage and degeneration

which can be used to develop regenerative therapy for optic nerve disorders (9). Such regenerative therapies that limit or reverse optic nerve degeneration can have high impact on vision in millions of people. The technology may also pave way to developing novel regenerative therapies in non-ocular neuronal tissue.

Another major advantage of eye research for developing regenerative therapy is the small and enclosed nature of the eye. This allows local administration of novel therapies to be conducted easily and with potential maximum therapeutic effect. Intravitreal injections of drugs are commonly administered in the clinic. Commonly injected drugs are those that inhibit vascular endothelial growth factor (VEGF), a growth factor mediating angiogenesis associated with neovascular complications of macular degeneration and diabetic retinopathy. These drugs usually need to be reinjected, often indefinitely. In this series, Chung *et al.* provide a review of a gene therapy approach to inhibit VEGF in the eye that is being explored in preclinical and early phase clinical trial (10). Long-term intraocular inhibition of VEGF via gene therapy could limit the number of treatments needed for patients with macular degeneration and diabetic retinopathy.

Intraocular administration of various novel regenerative therapies, including various gene therapies and stem cell therapies, are being explored in preclinical and early phase clinical trials for retinal regeneration. The successful FDA approval of Voretigene neparvovec-rzyl as gene therapy for *RPE65* related retinal degeneration has heralded the development of gene therapies for other inherited retinal disorders. In this series, Nuzbrokh *et al.*, provide a comprehensive up to date review of the gene therapy research for inherited retinal disorders, including multiple clinical trials that are on-going or recently completed (11). Most gene therapies, including the FDA approved gene therapy, Voretigene neparvovec-rzyl, is commonly administered subretinal in the operating room (1). However, intravitreal and suprachoroidal delivery options also are being explored. Similarly, clinical trials have started exploring intraocular administration of stem cells for retinal regeneration. In addition, to intravitreal injection of autologous CD34+ stem cells, intravitreal and subretinal injection of fetal and pluripotent stem cells are being explored in clinical trials (12). An up-to-date review of clinical trials exploring pluripotent stem cells is provided by Ahmed *et al.* in this series (13).

Finally, it is important to note that the changes in the eye can often be a manifestation of systemic disease. In this series, Smit-McBride and Morse provide a review of research being done on microRNA in diabetic mellitus and associated retinopathy (14). Specific microRNAs have been associated with diabetic retinopathy and could be used as biomarkers or future therapeutic targets.

This special eye series includes review and original articles of novel tools and therapies being developed for ocular regeneration. This area of research is very broad and cannot be completely covered in this single series. The goal of this eye series is to provide some overview of the latest research being done in the area of ocular regeneration in order to highlight the broad potential in this field. As a practicing ophthalmologist specializing in disorders of the retina, I have a personal interest in research being conducted for retinal disorders that blind many of my patients. Thus, the series may appear a bit skewed towards retinal research. However, this possible bias may be justified by the fact that leading causes of untreatable blindness currently are conditions affecting the retina or retinal ganglion cells that constitute the optic nerve.

In closing, I would like to thank my many colleagues who contributed to this research series. Despite the disruption of professional and personal daily life by the unanticipated emergence of the COVID-19 pandemic during the past year, each contributor did an outstanding job covering the various topics. This eye series would not have been possible without each of their contributions.

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