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# Retinitis Pigmentosa - Chasing the Cure

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## Editorial

As evidenced by several papers, scientists continue to explore diverse treatment options for Retinitis Pigmentosa (RP) which is an inherited retinal degenerative disease that eventually causes blindness and has no cure. According to the NIH projection, RP affects approximately 1 in 4000 people in the United States and worldwide. RP is characterized by photoreceptor cell death and is caused by heritable defects in rod photoreceptors. In RP, the retinal periphery enriched in rod cells is the most severely affected causing tunnel vision and night blindness. However, central vision that relies mostly on cone cells is preserved until the late stages of RP. The heterogeneity of this disease poses a challenge to the development of targeted therapies for RP, as over 60 genes are linked to RP and it is inherited in three different forms: 1) Autosomal Dominant RP (ADRP), 2) Autosomal Recessive RP (ARRP), and 3) X-linked RP (XLRP). While gene therapy using viral vectors is one of the prominent RP therapeutic strategies, other promising treatment options include stem cell transplantation, vitamin A palmitate supplementation, retinal prosthetic systems, transcorneal electrical stimulation therapy, and subretinal silicone implants. 2

In recent times, CRISPR as a cutting-edge genome editing technology has propelled to the forefront of translational ocular research and has been successfully applied to rescue retinal cells in varied retinal degenerative diseases including RP, macular degeneration, Leber Congenital Amaurosis (LCA), and glaucoma. Based on the type of mutation contributing to RP pathogenesis i.e., Loss-of-function, Dominant-negative, or Gain-of-function mutation, various gene editing approaches could be used. CRISPR-Cas9-mediated precise gene editing has allowed scientists to perform allele-specific knockout of *Rho* (Rhodopsin) gene in the dominant form of RP in *in vitro* and *in vivo* research. For instance, in a murine RP model, CRISPR-Cas9 technology was used to disrupt the mutated P23H *Rho* allele thereby preserving the wild-type functional *Rho* allele and subsequent photoreceptor cell preservation. Similarly, selective targeting of the mutant P23H allele prevented photoreceptor cell loss in *Rho*-P23H knock-in mice. Substantive improvement in visual function and retinal health has also been observed via CRISPR-mediated targeted disruption of the S334ter allele in an *in vivo* rodent model.

It is noteworthy that amalgamation of CRISPR-Cas9 with other gene therapy techniques has considerable potential to advance the understanding of RP and to protect retinal cells. For example, a combination of CRISPR-Cas9 and Homology-Independent-Targeted-Integration (HITI) techniques proved efficacious in preserving photoreceptor outer nuclear layer and visual function in rats. In addition, CRISPR technology combined with iPSCs has been used successfully to develop RP disease models for better understanding of disease mechanisms and drug screening. RP patient-derived iPSCs have been used to study RP pathophysiology *in vitro* and to screen potential protective vitamins and drugs. Moreover, X-linked RP-causing mutations in the *RPGR* gene were repaired using iPSCs acquired from RP patients. CRISPR's potential of precise target-specific genome editing, facile design of guide RNAs, and ease of use has led to the current 3

upsurge in CRISPR-Cas9 technology as a promising tool for RP gene therapy. Interestingly, the CRISPR gene editing technique can be further tweaked for development of new therapies for RP. Variants of the canonical CRISPR-Cas9 system such as CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) techniques allow transcriptional silencing and activation of genes respectively and provide an advantage of reversibility in CRISPR gene editing.

With the advent of precision medicine and cutting-edge genome engineering tools such as CRISPR-Cas9, the future of RP therapy seems promising. In the quest for the cure of RP, some of the crucial goals for ongoing efforts will be to examine the additive effects of combination therapies in pre-clinical models of RP and advancement of ground-breaking bench research to clinical trials.