

Molecule-Directed Therapies for Retinal Disease

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Recent progress in understanding of molecular mechanisms underlying disease progression has led to the development of new therapeutic approaches to treating degenerative diseases of the retina based on identified molecular targets (Jacobson & Cideciyan, 2010). These include drugs that target specific molecules and gene replacement or supplementation strategies that use virus-derived vectors or encapsulated cells to provide missing gene products or neuroprotective factors.

Therapies targeting vascular endothelial growth factor, VEGF, or its receptor, including DNA aptamers (pegaptanib) and monoclonal antibodies (ranibizumab and, as an off-label use, bevacizumab), have been widely and successfully used for treatment of AMD (Folk & Stone, 2010; Gehrs et al., 2010). These drugs were designed to inhibit the neovascularization that accompanies the “wet” form of AMD. These treatments have been developed on the basis of many years of basic research into the molecular mechanisms of angiogenesis and its regulation. Sustained delivery of anti-angiogenic molecules using viral vectors (see below) has also been tested in animal models, with some promising results.

Extensive basic research and work with animal models have also set the stage for new molecular therapies targeting inherited retinal degeneration. The greatest progress in treatment of recessive disease using a gene replacement strategy has been achieved with vectors derived from recombinant adeno-associated virus, rAAV (Alexander & Hauswirth, 2008). The only components of the parent virus, which even in native form is nonpathogenic, contained in these vectors are the protein capsids surrounding the viral genome, and inverted repeat sequences at the termini of the single-strand recombinant DNA inserted for therapeutic purposes. Over 60

clinical trials have been conducted using rAAV (Mitchell et al., 2010) in a range of tissues, but one of most successful outcomes has been achieved in the treatment of the blinding disease Leber's congenital amaurosis (LCA). A clinical trial (one of three that are ongoing) using rAAV encoding RPE65 to treat patients with LCA (Simonelli et al., 2010) has demonstrated both safety and efficacy. This work was preceded by extensive studies of rAAV gene replacement in rodent and dog models of RPE65 deficiency. Recruitment is under way for a clinical trial using rAAV to treat Leber hereditary optic neuropathy, caused by a defect in the mitochondrial gene LHON gene (Lam et al., 2010). Successful treatment of animal models of achromatopsia, a disease featuring lack of cone-mediated vision, with rAAV supplying a functional gene encoding one of the cone CNG channel subunits, sets the stage for clinical trials of this approach to treating the most common cause of achromatopsia in humans (Komaromy et al., 2010). The use of lentiviral and adenoviral vectors for retinal therapy has also been proposed and tested in some animal models. A clinical trial was conducted using adenovirus for treatment of retinoblastoma (Ildelfonso et al., 2010).

Whereas gene replacement therapies require a unique viral construct for each rare disease gene, neuroprotective strategies could potentially be more widely efficacious. For example, rAAV-mediated delivery of the ER resident chaperone Grp78/BiP in a rat model of retinal degeneration produced a neuroprotective effect, apparently through reducing apoptosis driven by the unfolded protein response (Gorbatyuk et al., 2010). Another chaperone-type protein, HSP90, has been used to treat an animal model of RP (Tam et al., 2010). Yet another molecular therapy that has been tested in animals is the use of light-regulated ion channels to restore light sensitivity to retinal neurons (Lagali et al., 2008). Transplantation of cells that can replace missing retinal photoreceptors or RPE cells is yet another area of active study (Lamba et al.,

2010; Liao et al., 2010). Finally, induced pluripotent stem cells have been reported to be capable of producing cells with RPE and photoreceptor phenotypes (Parameswaran et al., 2010).