# Advancing Therapeutic Strategies for Inherited Retinal Degeneration: Recommendations From the Monaciano Symposium

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Although rare in the general population, retinal dystrophies occupy a central position in current efforts to develop innovative therapies for blinding diseases. This status derives, in part, from the unique biology, accessibility, and function of the retina, as well as from the synergy between molecular discoveries and transformative advances in functional assessment and retinal imaging. The combination of these factors has fueled remarkable progress in the field, while at the same time creating complex challenges for organizing collective efforts aimed at advancing translational research. The present position paper outlines recent progress in gene therapy and cell therapy for this group of disorders, and presents a set of recommendations for addressing the challenges remaining for the coming decade. It is hoped that the formulation of these recommendations will stimulate discussions among researchers, funding agencies, industry, and policy makers that will accelerate the development of safe and effective treatments for retinal dystrophies and related diseases.

Keywords: retinal dystrophy, gene therapy, cell therapy, disease phenotypes, outcome measures

Over the past 3 decades, global research efforts have unveiled the genetic complexity of the group of rare disorders collectively referred to as retinal dystrophies. Causative mutations for dozens of retinal dystrophies have now been identified, resulting in the discovery of multiple new genes, biological pathways necessary for photoreceptor cell function, and pathogenetic mechanisms involved in retinal degeneration. This work has opened the way for clinical trials of advanced forms of therapy, including gene replacement and cell transplantation. However, the rapid pace of growth, the vastness of the research base, and the genetic and phenotypic diversity of retinal dystrophies present significant challenges for coordinating research efforts for which a unified view of priorities has not been articulated.

With the goal of identifying the key steps needed to advance the development and delivery of effective treatments for retinal dystrophy, an international group of clinicians and scientists with expertise spanning the field convened in October 2013 at Tenuta di Monaciano, the Piperno family estate near Siena, Italy. To focus the meeting content and discussions, a Delphi-like process involving the collection and analysis of responses to a premeeting survey was used. This survey asked participants to prioritize lists of open questions focused on the following: identifying the most compelling therapeutic targets, refining and expanding therapeutic strategies, solving infrastructure needs and streamlining regulatory processes, identifying the patients who could benefit from treatment, and formalizing outcome measures. Building on survey outcomes, targeted presentations, structured group discussions, and multivoting

during the meeting, the participants identified five priority areas for moving the field forward: (1) understanding the pathogenetic mechanisms underlying retinal dystrophies, (2) providing access to genetic testing for patients, (3) understanding the natural history of retinal dystrophic diseases, (4) defining the window of opportunity for therapeutic intervention, and (5) improving outcome measure testing and standardization. A detailed view of the goals and mechanisms needed to advance these priority areas is now presented and placed in the context of the current status of retinal dystrophy research, and addresses issues specific to gene therapy, cell therapy, patient selection, safety, and efficacy.

## THE DISEASE LANDSCAPE AND THERAPEUTIC OPTIONS

The retinal dystrophies are a genetically and phenotypically heterogeneous group of disorders affecting the function and viability of photoreceptor cells. Syndromic and nonsyndromic forms of retinal dystrophies with autosomal, X-linked, and mitochondrial inheritance are observed. Phenotypic categories include RP, rod-cone dystrophy, cone or cone-rod dystrophy, macular degeneration, Leber congenital amaurosis (LCA), congenital stationary night blindness, and other more complex phenotypes with extraocular involvement, such as Bardet-Biedl and Usher syndromes.[1] At the time of the Monaciano Symposium, 244 retinal dystrophy genetic loci had been mapped, and 204 causative genes had been identified affecting multiple biochemical pathways and mechanisms (RetNet, https://sph.uth.edu/RetNet). In the rod and cone photoreceptor cells, these include phototransduction, outer segment structure, connecting cilium structure and transport, inner segment protein and vesicle trafficking, chaperone function, lipid metabolism, transcription and RNA splicing, retinal development, and synaptic function. In the RPE, affected mechanisms include visual cycle reactions, phagocytic activity, membrane trafficking, and ion transport.[2] Certain mutations also affect the function of secondary retinal neurons, Müller cells, and ganglion cells (RetNet).

Such a complex genetic landscape represents a significant challenge for identifying therapeutic targets suitable for demonstrating proof-of-concept and developing approved therapeutics. This requires weighing multiple considerations relative to the genetic nature of the disease, mutation prevalence, disease severity, and age-of-onset, as well as the cell-type(s) and biological mechanism(s) involved. Additional factors affecting the design of preclinical studies include the availability of suitable animal models, the nature of the intervention (gene, cell, or pharmacological), the mode of delivery (systemic, intravitreal, or subretinal), and the potential for clinically quantifiable outcome measures. In addition, treatment options will likely differ for early versus advanced disease. For early- to mid-stage disease, the focus will be on rescuing retinal-cell function and maximizing retinal-cell survival by using strategies involving pharmaceuticals, nutritionals, gene therapy, and cell therapy approaches. For late-stage disease, the focus is predicted to shift toward strategies involving retinal-cell replacement, optogenetics, prosthetics and electronic devices, and potentially combinatorial therapies that optimize the host environment relative to specific interventions.

Although the experts in attendance recognized the potential importance of each of these approaches in the future management of retinal dystrophy patients, a premeeting survey of the participants identified gene therapy and cell therapy as key areas for discussion at the Monaciano Symposium. The ensuing conversations focused on defining the next steps needed to accelerate the development and delivery of gene therapy and cell therapy to a broad cross section of retinal dystrophy patients in the next decade and beyond.

## GENE THERAPY

Gene therapy has tremendous potential for treating diverse forms of retinal dystrophy, particularly when using viral vectors engineered for delivering transgenes to specific classes of retinal cells (reviewed in Refs. 3 and 4). For early-stage disease where the genetic cause is known, possible uses of vector-mediated transduction include replacing a defective gene with a corrected version, knocking down the expression of a defective gene with or without adding back a corrected version, introducing a DNA element that controls gene expression, correcting a mutation that misdirects splicing, or delivering a suppressor that promotes termination-codon read-through. Gene therapy also has the potential to deliver neurotrophic and antiapoptotic factors, modulators of oxidative stress, chaperones that may reduce protein aggregation, and agents that promote recombination repair of DNA. For late-stage disease, optogenetic approaches are being developed to deliver light-sensing signal-transducing proteins to the retina at a point when photoreceptor cells can no longer be preserved or repaired (reviewed in Ref. 5).

### RPE65 Proof-of-Concept

Clinical trials in individuals with LCA type-2 provided the first proof-of-concept for gene-replacement therapy in retinal dystrophy patients.[6-9] As of this writing, clinical trials of six adeno-associated viral (AAV) constructs encoding RPE65 have been initiated in the United States, United Kingdom, Israel, and France (Table 1), with outcomes reported for three of the trials. More than 50 patients have been treated by subretinal injection, with the first patient being treated more than 6 years ago. No vector-related safety issues have been reported, and patients who experienced treatment efficacy achieved gains in full-field and local light sensitivity, pupillary light reflex, mobility-maze performance, and visual acuity.[6-11] Ongoing follow-up studies are focused on ascertaining whether the functional gains of the treated area are stable over time and whether treated retinal areas maintain better retinal thickness than adjacent areas. First indications for the protocols and constructs used so far suggest that treatment does not arrest retinal degeneration and that photoreceptor cell loss is unabated.[11] Additional studies are focused on uncovering the causes of these limitations, evaluating outcomes in young children and after treating the second eye of previously treated subjects, and devising strategies to obtain more complete coverage of the retina.

### Ongoing and Anticipated Trials

Following the preliminary successes of *RPE65*-gene-replacement trials for LCA type-2, clinical trials have been initiated and, in some cases, results have been reported, for gene therapy studies targeting additional forms of retinal disease (Table 1). This work builds on pre-clinical studies involving the use of AAV-based vector constructs for autosomal recessive RP due to mutations in *MERTK* (RP38)[12,13]; for choroideremia due to mutations in *CHM*[14,15]; and for Leber hereditary optic neuropathy, a mitochondrial disease caused by mutations in *ND4*.[16-19] In addition, equine infectious anemia virus (EIAV)-based and other lentiviral vector constructs are being tested for Stargardt disease due to mutations in *ABCA4*,[20,21] and for Usher syndrome type 1B due to mutations in *MYO7A*.[22,23] Additional diseases for which gene-replacement strategies

TABLE 1. Registered Clinical Trials of Gene Therapy for Retinal Diseases

| Disease (Gene) | ClinicalTrials.gov Identifier | Vector Name | Locations | Key Publications |
|---|---|---|---|---|
| LCA2 (RPE65) | NCT00481546 | rAAV2-CBSB-hRPE65 | University of Pennsylvania; University of Florida Health Shands Hospital | Bainbridge et al., 2008[6]; Maguire et al., 2008[7] |
|  | NCT00516477; NCT00999609; NCT01208389 | AAV2-hRPE65v2; AAV2-hRPE65v2; AAV2-hRPE65v2 | Children's Hospital of Philadelphia, University of Iowa | Cideciyan et al., 2008[8]; Hauswirth et al., 2008[9]; Simonelli et al., 2010[10]; Cideciyan et al., 2013[11] |
|  | NCT00643747 | rAAV 2/2.hRPE65p.hRPE65 | Moorfields Eye Hospital |  |
|  | NCT00749957 | rAAV2-CB-hRPE65 | Oregon Health and Science University; University of Massachusetts-Worcester |  |
|  | NCT00821340 | rAAV2-hRPE65 | Haddasah Medical Organization |  |
|  | NCT01496040 | rAAV2/4.hRPE65 | Nantes Hospital |  |
| RP38 (MERTK) | NCT01482195 | rAAV2-VMD2-hMERTK | King Khaled Eye Specialist Hospital | Deng et al., 2012[12]; Conlon et al., 2013[13] |
| Choroideremia (CHM) | NCT01461213; NCT02077361 | rAAV2.REP1 | Moorfields Eye Hospital; University of Alberta | Vasireddy et al., 2013[14]; MacLaren et al., 2014[15] |
| LHON (ND4) | NCT01267422 | rAAV2-ND4 | Tongji Hospital, Huazhong University of Science and Technology | Marella et al., 2010[16]; Yu et al., 2012[17] |
|  | NCT02064569; NCT02161380 | rAAV2/2-ND4 – GS010; scAAV2-P1ND4v2 | Centre Hospitalier Nationale d'Ophthalmologie des Quinze-Vingts; Bascom-Palmer Eye Institute | Chadderton et al., 2013[18]; Lam et al., 2014[19] |
| Stargardt Disease (ABCA4) | NCT01367444; NCT01736592 | StarGen (EIAV-ABCA4) | Oregon Health and Science University; Centre Hospitalier Nationale d'Ophthalmologie des Quinze-Vingts | Kong et al., 2008[20]; Binley et al., 2013[21] |
| Usher1B (MYO7A) | NCT01505062; NCT02065011 | UshStat (EIAV-MYO7A) | Oregon Health and Science University; Centre Hospitalier Nationale d'Ophthalmologie des Quinze-Vingts | Hashimoto et al., 2007[22]; Zallocchi et al., 2014[23] |

using AAV constructs have shown strong outcomes in preclinical studies, and for which clinical trials are anticipated, are listed in Table 2. These include X-linked retinoschisis due to mutations in *RS1*,[24-26] X-linked RP due to mutations in *RPGR*,[27,28] achromatopsia due to mutations in *CNGA3* or *CNGB3*,[29-32] and RP due to mutations in *PDE6B*.[33] For autosomal dominant RP due to mutations in *RHO*, RNA-replacement strategies are being developed that involve RNA-targeted gene silencing, which can be coupled with delivery of silencing-resistant RNA to maintain normal levels of protein expression.[34-36] Optogenetic gene therapy is being explored for advanced RP using eNpHR (halorhodopsin)-encoding constructs to express hyperpolarizing chloride pumps in cone cells.[37]

## Future Considerations

Continued progress in the development of gene-therapy approaches for treating retinal dystrophies will require addressing multiple challenges specific to each disease and for each gene. Key questions for guiding the development of disease-appropriate therapies include the following: Is there a viable cell population being targeted that is able to transmit signal to the visual cortex? Does the targeted protein perform a function that is amenable to gene-replacement therapy? What is the optimal dosage? Will toxicity issues occur if the introduced gene is not regulated in the natural way? Is the disease autosomal recessive and/or caused by haploinsufficiency of the affected protein, and therefore potentially correctable by augmentation of the gene product? Is the disease autosomal dominant and caused by a new activity of the mutant protein (e.g., gain of function and/or dominant negative interactions) that will require alternate or modified gene-replacement strategies?

## Challenges and Potential Barriers

Other challenges to advancing gene therapy include needed improvements in vector capacity, as well as strategies to increase the number of transduced cells. Vectors based on AAV2- and EIAV-constructs currently predominate in studies of retinal gene therapy, due in part to their low immunogenicity and long-term expression (reviewed in Refs. 4 and 38). The AAV-based vectors have several advantages for use in retinal gene therapy, as they are nonintegrating and can efficiently transduce postmitotic cells. However, the cargo capacity of AAV (4.7 kb) largely restricts its use to the delivery of relatively small genes. There are a number of recessive genes with high mutation prevalence that are likely too big for delivery by AAV, including *ABCA4*, which is mutated in Stargardt disease[39]; *CEP290*, which is commonly mutated in LCA[40]; and Usher syndrome genes, including *MYO7A* and *USH2A*.[41-44] One workaround being pursued is the use of dual AAV vectors to deliver partial cDNAs that assemble the full-length coding sequences in vivo via trans-splicing.[45] Alternatively, EIAV can accommodate much larger cargo (up to 8 kb), and is being pursued as an approach for treating Stargardt disease (*ABCA4*-related retinopathy),[21] as well as Usher syndrome type 1B.[23] However, more work is needed to determine whether the clinical applications for EIAV are limited by its relative inefficiency in transducing postmitotic photoreceptors,[38] along with concerns regarding its integration capacity. Another alternative under development is the use of nonviral methods for gene delivery, such as DNA-containing nanoparticles.[46]

As currently used, subretinal injection of viral vectors can specifically target RPE and photoreceptor cells. However, bleb size limits the dose and size of the transduced area, the

TABLE 2. Anticipated Clinical Trials of Gene Therapy for Retinal Diseases

| Disease (Gene) | Vector Type | Key Publications |
|---|---|---|
| X-linked retinoschisis (*RS1*) | AAV-RS1 | Zeng et al., 2004[24] |
| | | Min et al., 2005[25] |
| | | Byrne et al., 2014[26] |
| X-linked RP (*RPGR*) | AAV-RPGR-ORF15 | Hong et al., 2005[27] |
| | | Beltran et al., 2012[28] |
| Achromatopsia (*CNGA3*) | AAV-CNGA3 | Michalakis et al., 2010[29] |
| | | Pang et al., 2012[30] |
| Achromatopsia (*CNGB3*) | AAV-CNGB3 | Komaromy et al., 2010[31] |
| | | Carvalho et al. 2011[32] |
| Aautosomal recessive RP (*PDE6B*) | AAV-PDE6B | Petit et al., 2012[33] |
| Autosomal dominant RP (*RHO*) | AAV-RHO RNA suppression and replacement constructs | O'Reilly et al., 2007[34] |
| | | Millington-Ward et al., 2011[35] |
| | | Mao et al., 2012[36] |
| Advanced RP | AAV-eNpHR (halorhodopsin) | Busskamp et al., 2010[37] |
| Optogenetics targeting cone photoreceptor cells | | |

procedure requires a high level of clinical skill, and there are potential risks of complications and damage to foveal cone cells.[47] These risks may sum to an unacceptable level in cases in which significant retinal damage already exists. In addition, the long-term consequences of the retinal detachment that is transiently induced by subretinal administration of viral vectors have not yet been established. The alternative surgical approach, intravitreal injection, does not require the same level of expertise, avoids retinal detachment, and can potentially distribute viral particles across the entire retina.[4,48] However, factors including the dilution of AAV in the vitreous and the necessity for it to traverse the inner limiting membrane and nerve fiber layer appear to contribute to the limited transduction of RPE and photoreceptor cells observed in healthy retinas.[49] In some cases, the dystrophic retina is apparently more permeable to AAV, even in young animals not yet exhibiting retinal degeneration, as increased transduction of multiple cell types was observed after intravitreal delivery of AAV vectors in mouse models of retinoschisis caused by mutations in *RS1*,[26,50] as well as a rat model of RP caused by the S334 mutation in *RHO*.[51] Recent studies using directed evolution[52] and rational design[53] have resulted in the development of new AAV vectors with improved ability to penetrate the healthy mouse retina from the vitreal side. In addition, studies in baboons treated by intravitreal injection of AAV2-quad-smCBA-GFP showed effective transduction of foveal cones located where the inner retina is exceptionally thin.[53] Moving forward, further improvements are needed to increase the efficiency of vector penetration and improve targeting to extrafoveal photoreceptors and additional cell types. Some level of caution may be warranted in developing this approach, however, as there are reports of viral transduction extending outside the eye to sites including the optic nerve, brain, and other tissues after intravitreal injection,[54,55] and there is also a concern that inflammation may persist in the eye after higher viral doses.[56]

The rare nature of most retinal dystrophies, coupled with the genotypic and phenotypic heterogeneity observed in patients, means that only a relatively small number of individuals might benefit from treatments targeting specific gene mutations. This raises issues relative to whether the costs of developing such therapies can be recovered after market authorization, and how to encourage investment in therapies for rare diseases that may involve only a single administration. These issues are actively being debated, and may require developing alternatives to traditional drug-pricing models.[57]

## CELL THERAPY

Cell transplantation is a potential regenerative strategy for diverse forms of retinal degeneration in which replacement cells and/or tissues may benefit advanced-stage disease. The target population could potentially extend beyond individuals with inherited forms of retinal degeneration (an estimated 200,000 persons in the United States),[58] to include millions of individuals worldwide who are affected by AMD, diabetic retinopathy, and glaucoma, although diseases primarily or exclusively affecting the outer retina may pose fewer challenges for therapy development. As a natural anatomical gap, and by virtue of its relative immune privilege and accessibility to surgical intervention, the subretinal space is a highly attractive site for cell transplantation. Depending on the disease and treatment goals, it may be desirable to transplant RPE, rod and/or cone photoreceptor cells.

### RPE Transplantation

Transplantation efforts aimed at repopulating the RPE have the potential to benefit a wide range of diseases in which this cell layer is lost, damaged, or rendered nonfunctional. Cells derived from native RPE have been used in numerous transplantation studies aimed at improving the survival and function of photoreceptor cells (reviewed in Ref. 59). In addition, multiple protocols using embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) have been developed to produce differentiated RPE from a number of species (reviewed in Ref. 60). These include approaches involving embryoid body or neurosphere formation followed by adherent culture, and approaches involving spontaneous differentiation of over-grown ESC-adherent cultures (reviewed in Refs. 61 and 62). A number of preclinical studies have evaluated outcomes after transplantation of ESC- or iPSC-derived RPE, delivered either as individual cells[63–66] or as membrane-attached cells or sheets.[67,68] In addition, adult human RPE stem cells grown on a matrix have been tested as an alternative RPE source.[69] Outcomes in a recent phase I/II clinical trial of subretinal delivery of human ESC (hESC)-derived RPE cell suspensions in patients with Stargardt macular dystrophy or AMD (NCT01344993, NCT01345006; ClinicalTrials.gov) showed no adverse events related to transplanted tissue,[70,71] and some subjects experienced improvements in visual acuity and quality-of-life measures. A second trial using the same source of cells is ongoing (NCT01469832). Recently, a sheet of iPSC-derived RPE cells was transplanted for the first time into the subretinal space of a patient with exudative AMD (www.riken.

jp/en/pr/topics/2014/20140912_1/). Future challenges will include optimizing the transplantation procedure itself potentially by involving the use of matrices or scaffolds, understanding and modulating immune responses to the transplanted cells, and scaling up production methods and the number of transplanted cells.

## Photoreceptor Cell Transplantation

Many forms of retinal dystrophy are due to mutations in genes encoding rod photoreceptor proteins, causing rods to die well before cones; however, it is the subsequent death of cone photoreceptors that results in the major visual handicap associated with these diseases. Thus, a major motivation behind efforts to establish rod photoreceptor transplantation therapy is the prediction that adding back rods will promote the survival of cones.[72] In preclinical studies, sources of donor cells included rod precursor cells from freshly dissociated retinas,[73] as well as retinal progenitor cells derived from ESCs.[74,75] Conditions have been established that promote the integration and in vivo differentiation of, and functional rescue by, transplanted rod photoreceptor cells[76,77] and the integration and maturation of retinal progenitor cells derived from ESCs or iPSCs.[78,79] A major challenge for rod photoreceptor transplantation is the potential need for large numbers of cells per patient. It is not yet known how many rods would need to be replaced to increase cone cell survival, or whether transplantation of both rod and cone photoreceptors would be required to benefit end-stage disease. If rod transplantation alone is sufficient to mediate increased cone survival, this approach may benefit patients who retain residual foveal cone vision. Alternatively, diseases resulting in cone loss with relative preservation of rod function (e.g., cone dystrophies) may be candidates for cone photoreceptor replacement. Potential advantages of targeting cone-based disorders for cell replacement include the earlier production of cone cells in vitro, as well as the theoretically smaller number of cells required for treatment.[80,81]

## Clinical Considerations

Despite its great potential, significant risks may be associated with retinal-cell transplantation, including loss of remaining vision due to potential surgical damage, inflammatory responses, immune rejection, and/or induction of proliferative vitreoretinopathy. The development of effective transplantation-based therapies will benefit from incorporating sound theory, clinical correlation, computational science, and cell culture methods, and may use studies in small animal, large animal, nonhuman primate, and human iPSC (hiPSC)-based models of retinal dystrophy.[82,83] Defining the therapeutic window of opportunity is predicted to require studies that rigorously evaluate multiple issues relative to disease pathology. In the final stages of retinal degeneration, inner retinal cells are also lost and extensive retinal remodeling occurs[84] that could limit useful vision even if the transplanted cells effectively integrate with host retina. Furthermore, as the photoreceptor cell layer becomes more degenerated, the transplanted cells will be more disorganized and have shorter outer segments.[73,77] Thus, determining the optimal timing for treatment will likely require considering disease status as gauged by psychophysical and other measures of visual sensitivity, acuity, performance, and navigational ability, as well as by imaging technologies that can provide microanatomical in vivo measures of retinal layer thickness and lamination integrity, cell counts, and pathology (discussed in the section "Advanced Imaging Technology" below). Studies also may be needed to determine the efficacy of combinatorial therapies (e.g., addition of growth factors) in improving

perioperative cell survival, once individual monotherapies have gained regulatory approval. Additional clinical considerations include dose finding, appropriate duration of follow-up, and monitoring for transplant rejection.

## Preparing for Transplantation Therapy

Clinical development of hESC- and hiPSC-based therapeutics is a complex undertaking that will benefit from an interdisciplinary approach involving biologists, bioengineers, materials scientists, and clinicians working together to tackle a host of scientific, medical, and ethical issues. New tools and technologies will likely be needed to improve bioprocessing and production using Good Manufacturing Practices (GMP) in order to ensure quality, stability, reproducibility, tracking, scalability, enrichment, and delivery of therapeutic-grade cells. Preclinical proof-of-concept studies will benefit from selection of animal models appropriate for evaluating connectivity in the macula, biodistribution, and immune responses, efforts critical for establishing mode of action, potency, and safety. To help define the potential applications of hESCs versus hiPSCs for treating various manifestations of retinal disease, decision tree protocols may be a useful strategy. In addition, a better understanding of intraretinal immunomodulatory pathways and mechanisms will likely play an important role in expanding the applicability of these treatments. There also will be a host of regulatory issues to surmount, including issues concerning starting materials (cell line derivation and history), manufacturing processes (expansion, differentiation, purification), process validation to exclude unintended consequences, characterization, and quality control (identity, purity, potency, tumorigenicity, stability). Finally, guidelines relative to issues of ethics and public acceptance, and business models for commercial development should help accelerate progress.

## Clinical Trials

As most forms of gene and cell therapy available in the next decade will be experimental, human studies will be largely confined to officially sanctioned clinical trials funded by major sponsors that can provide unbiased scientific evidence. Phase I clinical trials are first-in-human studies designed to evaluate safety, determine a safe dosage range, and identify side effects. Phase II trials evaluate both safety and treatment effectiveness. Phase III trials confirm efficacy in larger numbers of subjects with wider ranges of disease. Phase IV trials are typically postmarketing studies that further evaluate safety, benefits, and optimal use of treatments. Proper trial design is of utmost importance, as broad acceptance of the findings of a clinical trial depends on its design, end points, and conduct.[85] Appropriate recruitment of trial subjects is a critical consideration; subjects must meet specific inclusion/exclusion criteria to ensure they are suitable to participate, be willing to comply with the study protocol, be given an opportunity to understand the trial, and have the ability to give informed consent.

## Identifying Patients of a Specific Genotype

Although diagnostic tools are now available that can identify disease-causing mutations in many retinal dystrophy cases with Mendelian inheritance,[58] finding patients with a genotype of interest, and who also meet specific phenotypic criteria, remains a significant challenge for clinical trial design. The difficulty begins with determining which tests are most appropriate for obtaining a genetic diagnosis for any given patient, as there is an expanding spectrum of phenotypes associated with each disease gene (RetNet). Then, interpreting the results of genetic testing can require evaluating the

significance of variation in multiple genes, including variants of unknown significance.[86] Furthermore, the cost and time required for actually getting test results are highly variable. For research studies, there is no cost to the patient, but results are not always made available or can be significantly delayed, and need to be confirmed by an accredited diagnostic laboratory before they can qualify an individual for inclusion in a clinical trial requiring a specific genotype. For diagnostic testing laboratories, results are typically returned in a few weeks to several months. However, the costs of these tests can be prohibitive, as not all health insurance companies cover molecular genetic diagnostic testing, coverage can be limited to certain scenarios, and the use of out-of-network laboratories can impose significant copays. Health care providers can help facilitate approval of molecular genetic diagnostic testing by drafting letters of necessity, but these do not guarantee success. Thus, improving and facilitating access to testing, and reducing the costs of testing, would be major steps toward ensuring that all patients obtain a molecular genetic diagnosis.

### Identifying Well-Phenotyped Patients

A second challenge is the identification of patient cohorts with mutations in a specific gene who are appropriate for inclusion in a study. Patients who self-identify may have a genetic testing report, but limited phenotypic data, and such individuals may not always be aware of clinical trials. For patients in databases curated by individual institutions, there may be challenges with respect to data sharing, as well as geographic limitations. For patients in databases compiled by testing laboratories, detailed phenotypic information may not be available. One important resource is the eyeGENE database maintained by the National Eye Institute (www.nei.nih.gov/eyegene/). At the time of the Monaciano Symposium, 4736 people were enrolled, including 4055 people affected with retinal dystrophies, including 159 genetically confirmed X-linked retinoschisis (*RS1*), 249 choroideremia (*CHM*), 450 probable Stargardt disease (*ABCA4*), 80 dominant RP (*RHO*), and 239 X-linked RP (216 *RPGR* and 23 *RP2*) patients (Kerry Goetz, MS, National Eye Institute, written personal communication, 2013). However, eyeGENE offers testing for only certain categories of diseases and only limited phenotypic data are available. Another resource is the Foundation Fighting Blindness, which established a National Retinal Degenerative Disease Registry in 1992 for individuals with retinal degeneration and their families. This database has collected information from more than 11,000 participants, including patients with both inherited and acquired retinal disease, and in 2014 the registry migrated over to a new enhanced, user-accessible online system known as My Retina Tracker (https://www.myretinatracker.org/). The database enables participants to build a personal retinal health record, allows them to enter, store, retrieve, review, and update their information at any time, and provides the option to invite their physicians to enter clinical data. Access to the database is limited to participants, the Foundation Fighting Blindness registry staff, and qualified researchers who have been approved to access de-identified data.

### Improving Understanding of Disease Progression

A further challenge relates to identifying patients who can benefit from treatment, and whose disease progression in the absence of treatment can be reliably predicted. One concern is that significant disease progression often occurs in many patients before diagnosis, resulting in missed opportunities to evaluate early-disease kinetics and to treat early-stage disease. Beyond simple considerations of early- versus late-stage disease, another major concern relates to the variability in phenotypic expression associated with mutations in a given

retinal dystrophy gene. A case in point is Stargardt disease, which can exhibit extensive phenotypic variability among individuals with the same mutation, and even among affected members of the same family.[87] Another example is X-linked RP due to mutations in *RPGR* that can result in either rod-cone or cone-rod patterns of vision loss, as well as significant differences in the rate of disease progression that are difficult to predict a priori.[88,89] In the absence of phenotypic features predictive of progression rates at early ages, rigorous studies of disease natural history, large numbers of patients, and multicenter trials will play an important role in reliably evaluating the efficacy and duration of therapy.

## Evaluating Outcomes

The phenotypic diversity intrinsic to retinal dystrophies presents significant and varied challenges for diagnosing and evaluating therapeutic outcomes in different diseases. For example, disease progression in RP is relatively slow and central vision remains intact, but studies in a canine model of autosomal dominant RP caused by a rhodopsin mutation showed that light toxicity may play a factor in disease progression.[90] In patients with disease that affects the macula, such as Stargardt disease, poor fixation can negatively affect testing performance.[91,92] In achromatopsia patients, poor visual acuity and nystagmus also contribute to poor fixation, and although disease progression is slow,[93,94] the continued presence of foveal cones will likely define the therapeutic window. This phenotypic diversity suggests that identifying meaningful outcome measures will require understanding both the function and pathophysiology associated with mutations in each gene, with one important approach being natural history studies of affected individuals.

### When to Measure Outcomes

One of the challenges to measuring efficacy during a clinical trial is determining the time points at which performing outcome measurements will provide the most meaningful information; for example, regarding how quickly patients will respond to treatment and how durable any benefit may be. In the case of *RPE65* gene therapy, some patients at 10 days after surgery reported a bright region in their visual field that corresponded to the location of the subretinal vector bleb, which was confirmed by dark-adapted static perimetry and sometimes resulted in the development of an "ectopic fovea" several months later.[47] On the other hand, new or regained visual function might take several months to be fully perceived by gene therapy patients due to slow cortical adaption. Studies of red-green colorblind squirrel monkeys treated with AAV5-hROps2.1-hROps showed that a behavioral response to a red stimulus required 5 to 6 months to develop,[95] suggesting that delayed perception of visual gains could be a general feature of gene therapy trials. It is also expected that the optimal timing for outcome measurement will differ for therapies aimed at restoring the function of genes involved in light perception compared with those for which the main outcome may be slowing of retinal-cell death. A further consideration for photoreceptor cell-replacement therapy will be establishing the conditions and the length of time required for photoreceptor precursors to mature and become light-sensitive.[76,96]

### How to Measure Visual Function

Determining the reproducibility, reliability, and practicality of available outcome measures for detecting therapeutic benefit will be an important focus for future efforts to standardize measures of treatment efficacy. Objective measures of visual

function include ERGs, pattern VEPs, pupillometry, and functional magnetic resonance imaging. Electroretinography has long been the definitive measure of visual function, with clinical standards established by the International Society for Clinical Electrophysiology of Vision (ISCEV).[97] Multiple ERG configurations have been devised, including the flicker ERG, ON-OFF ERG, photopic negative response, pattern ERG, focal ERG, and multifocal ERG that provide a wide array of precise information about the responses of different retinal-cell types (rod, cone, bipolar, and ganglion cells) in the macula and peripheral retina. Comparisons between laboratories, and across visits, are enabled through the use of standardized protocols that accommodate signal variability. However, recent studies have shown that ERGs may lack the sensitivity needed to detect improvement that is functionally significant for patients, as seen in the *RPE65* gene-therapy trials.[6] Specialized ERG techniques, for example submicrovolt cycle-by-cycle flicker ERG,[98] may help in overcoming some of these limitations.

Psychophysical measures of visual function include analysis of visual acuity, contrast sensitivity, kinetic and static perimetry, color vision, and reading speed. Newer techniques include fundus-guided microperimetry and methods to quantitate visual stimulus detection in patients with profound visual impairment, such as the full-field stimulus threshold test.[99] Evaluation of maze-mobility performance also can be a powerful indicator of visual function, but methods need to be developed for quantitating and standardizing outcomes. Other important considerations are quality-of-life issues that may be evaluated by testing (e.g., light-discomfort thresholds) or by developing appropriate patient questionnaires. In selecting which of these measures to use for long-term follow-up, a key issue will be to find effective strategies for dealing with testing variability, as well as age-related changes in visual function experienced by healthy individuals,[100,101] so that these can be accounted for when such measurements occur over a time span of multiple years.

### What Measurements Are Needed?

An important consideration for determining appropriate outcome measures is the significant burden placed on both patients and staff by extensive testing. This is often clearest in the case of children who require sedated ERGs and spectral-domain optical coherence tomography (SD-OCT) involving the presence of a full sedation cart and pediatric sedation team in the examination suite, or testing in an operating room.[102] An important goal will be to determine which functional tests are essential for analysis of clinical outcomes, while at the same time reducing what is requested of patients. Ideal tests should be noninvasive, safe, easy and quick to perform, have high reliability and repeatability, and permit standardization across multiple testing sites using good normative data. It would be useful for researchers and regulatory agencies to establish guidelines that define the tests necessary for evaluating outcomes for specific diseases and types of intervention, and to agree on which tests need repetitive measurement. In addition, testing protocols need to be designed for pediatric patients who cannot reliably perform the tests that adults can. One possibility would be to determine the extent to which questionnaires can play a role in evaluating outcomes in children. Another possibility to consider is whether home-testing protocols can be devised for following patients more closely and reducing testing time in the clinic.

### Advanced Imaging Technology

A number of recent technical advances have made it possible to obtain high-resolution structural information about the retina that has the potential to add rigor and comparative value to analysis of outcomes. Spectral-domain optical coherence tomography (reviewed in Ref. 103), coupled with segmentation analysis (reviewed in Ref. 104), can provide quantitative measures of retinal structures, but more work is needed to determine which measurements will be the most informative. The integration of SD-OCT with confocal scanning laser ophthalmoscopy (SLO) analysis of short wavelength autofluorescence can be used to obtain quantitative measures of lipofuscin accumulation,[105] but advances are needed in standardizing image acquisition and calibration, and to determine whether light toxicity is a concern, especially for patients with certain genotypes.[90,106] Adaptive optics SLO (AO-SLO) is a powerful emerging technology that can image individual cone photoreceptors and the normal cone mosaic.[81,107] Custom-built AO-SLO systems provide the best images, but they are expensive, have long acquisition times, and require expertise that puts them out of reach of most programs. Commercially produced AO-SLOs, as well as flood-illuminated AOs, also are available, and although they have lower resolution, they are easier and faster to use, and data processing can be standardized across multiple laboratories. A key advantage of imaging studies is that they have very high reproducibility and data can be acquired relatively rapidly, safely, and easily. However, imaging studies are currently not widely accepted as clinical trial outcome measures by regulatory authorities, a situation likely to be improved by ongoing efforts to establish meaningful correlations between imaging findings and retinal function, especially with respect to SD-OCT imaging.[103,108]

## PRIORITY AREAS AND RECOMMENDATIONS FOR ADVANCING THERAPY

The remarkable progress made in understanding retinal biology, function, and disease in recent years now places the field in a strong position to develop therapies for retinal dystrophy patients for whom no treatments or cures currently exist. Nevertheless, many major challenges remain, including competition for scarce resources, and regulatory hurdles for obtaining approval to initiate human clinical trials from the Food and Drug Administration in the United States and equivalent agencies elsewhere in the world. With an interest in identifying the key steps needed to move the field forward in the next decade, the participants at the Monaciano Symposium engaged in a structured communication technique to identify their shared priorities and views of needs for the future. Using a Delphi-like process involving anonymous polling of participant opinions before the meeting, and focused small-group discussions and participant voting during the meeting, five major priorities were identified, as well as strategies for achieving the needed improvements, as discussed below.

### Priority 1: Understanding the Pathogenetic Mechanisms Underlying Retinal Dystrophies

Although it is now possible to identify the causative mutations in many forms of retinal dystrophy and to predict their impact on normal cellular function, much less is known about the pathogenetic mechanisms responsible for photoreceptor cell death. This is especially true of defects that decrease the viability of cone cells, directly or indirectly, after loss of rod cells. The development of strategies to improve cone cell survival is a clear therapeutic priority. One potential strategy involves providing rod-derived cone viability factor (RdCVF) lost as a result of rod cell death[109]; preclinical studies in which AAV vectors encoding RdCVF were administered to different

murine models of retinal dystrophy showed improved cone function and delayed cone loss.[110] Potentially targetable secondary mechanisms include pathways linked to autoimmune responses, apoptosis, and other cell death pathways. Delineation of relevant pathogenetic mechanisms is predicted to play an important role in driving innovation and developing novel forms of therapy. The recent development of technology involving the use of patient-derived iPSCs to create disease platforms for evaluating pathogenetic mechanisms and therapeutic outcomes is an exciting advance for these types of studies, and has been used to develop platforms for RP,[111,112] gyrate atrophy,[113] and Best disease.[114] Moving forward, key questions to answer include the following: What are the mechanisms and pathways linking the primary genetic defect to the process of photoreceptor death? Which of these biological mechanisms and pathways are the most accessible therapeutic targets? Which aspects of pathology can be delayed or reversed? What can be done to prevent or delay cone photoreceptor cell death in rod-cone degenerations?

Currently, mouse models of retinal dystrophic diseases are the most commonly used platform for studying pathogenetic mechanisms and therapeutic outcomes. However, studies of cone involvement in mouse models of retinal dystrophy have significant limitations, as rodents and most other small animals lack foveae or cone-dense regions,[115] and thus these cones may respond in a way that is not predictive of human therapeutic outcomes. In addition, other structural and biological differences exist that can affect the expression of disease phenotypes, which are not reflected in some mouse models of human disease. These differences are of concern, as most therapeutic approaches are initially tested in rodents, followed by testing in larger animals, typically dogs, pigs, cats, and/or nonhuman primates. Significantly, there are currently no nonhuman primate models of retinal degenerative disease in which to test the effectiveness of targeting rods as a strategy for preserving cones.

Thus, a particular need for moving the field forward is the identification and cultivation of large animal models having eyes that are more similar to humans in terms of anatomy and size, retinal environment, immune systems, and barrier features of the inner limiting membrane. Compared to rodents, larger species also provide improved possibilities for functional analysis, and for major advances in the identification of biomarkers for early-stage retinal dystrophy needed to increase our understanding of disease mechanisms that are therapeutically accessible. To date, such models include naturally occurring dog, cat, chicken, and sheep retinal dystrophy mutants (reviewed in Ref. 116), as well as transgenic rabbits[117] and transgenic swine.[118-121] Exciting new advances in the technology used for genetic engineering, including clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 systems,[122] are expected to greatly expedite the creation of new disease models in a variety of both large and small species. Currently, a major barrier to advancing this research is the high cost of developing and maintaining large animal models that in most cases is too great for single investigators, thus emphasizing the need for major collaborative efforts among basic, medical, and veterinary scientists. Increased funding from both the private and public sectors may be cultivated by improving awareness of the importance of animal models for developing cures for inherited and other forms of blindness.

## Priority 2: Providing Access to Genetic Testing for Patients

Remarkable progress in understanding the genetics of retinal dystrophy has resulted in the identification of more than 200 disease genes that are predicted to be responsible for more than half of all cases (RetNet). However, this wealth of information is only slowly being translated into genetic diagnoses for individual patients, as significant barriers to testing currently exist. This situation exists despite the fact that having a genetic diagnosis is likely to be the single most important factor for gaining access to an approved treatment or clinical trial based on gene therapy. In addition, genetic diagnoses are becoming increasingly important for studies of pharmacologic therapies or otherwise gene- or mutation-specific interventions (e.g., trials of valproic acid for treating dominant RP [NCT01233609; ClinicalTrials.gov] and of 9-_cis_-retinyl acetate [QLT091001] for treating LCA due to mutations in _RPE65_ or _LRAT_ [NCT01014052, NCT01521793, NCT01543906]).[123,124] Furthermore, the opportunity to curate genetic information on a large scale is a singularly important strategy for advancing the classification of mutations and corresponding phenotypes, and for evaluating potential outcomes. It is also predicted to play an important role in identifying causative genes in an era of expanded genetic testing, in which phenotypic matching from a database containing bona fide genotype-phenotype correlations will likely be needed to interpret data from whole exome sequencing.[125] Thus, a critical goal for moving the field forward is to obtain a genetic diagnosis for every patient in the retinal dystrophy population.

Accomplishing this goal will require increased awareness of the fundamental importance of genetic testing, and the development of effective strategies for obtaining the financial resources needed to cover the costs. In some cases, this may involve validating research results that have already been obtained, but which were not often shared with health care providers in the past. Making this research data available going forward could markedly facilitate and reduce the costs of obtaining certified genetic diagnoses. In other cases, effective communication between providers and insurance companies will be needed to obtain approval for benefits that might otherwise be denied or missing. Success in this arena will not be trivial, as it will likely require soliciting help from private, public, and legislative organizations to increase appreciation of the importance of genetic information in developing treatments for diseases that are currently untreatable.

## Priority 3: Understanding the Natural History of Retinal Dystrophic Diseases

A fundamental aspect of designing and implementing trials of novel therapeutics will be the identification of retinal dystrophy patients who could benefit from treatment. Key considerations include the following: What criteria should be used to select the subset of patients who would benefit most from a given therapy? What can be done to facilitate the identification of eligible patients who meet inclusion criteria for specific clinical trials? How could a shared database be used to enhance recruitment of eligible patients for inclusion in specific clinical trials?

Moving this agenda forward will be facilitated by developing detailed understanding of genotype-phenotype correlations in retinal dystrophy, including robust studies of disease natural history. The resource-intensive nature of such endeavors will likely be best accomplished by consortia operating with a high degree of transparency, in which all participants receive credit for their contributions. Phenotypic data collected on a large scale should be merged with existing genetic data in a carefully considered way. This could include the development of an international database useful for identifying patients for clinical trials, as well as the diseases with the most known affected individuals. Significant improvements are needed relative to the criteria and standards currently used for collecting and

depositing patient data so as to overcome the limitations of existing databases. At present, wide variances in database entries severely limit the usefulness of collected data for both research and clinical purposes. Along with genetic information, standard criteria for the phenotypic information to be included should be agreed on by experts in the field. Developing and curating this information centrally has the potential to not only improve understanding of disease natural history, but to also help identify biomarkers for early-stage disease that could facilitate entry of patients into trials at younger ages.

### Priority 4: Defining the Therapeutic Window of Opportunity

Although early diagnosis and treatment are important goals for the future, defining effective therapeutic options for both early- and advanced-stage disease as the field develops will be essential for helping the greatest number of affected individuals. Important unanswered questions include the following: How should treatment strategies differ for early- versus advanced-stage disease? What outcome measures and trial objectives should be used for treating early- versus advanced-stage disease? What information can be obtained that could help match the timing of treatment to the therapeutic window of opportunity? What can be done to slow disease progression and extend the window of opportunity? What strategies are needed to improve the safety and efficacy of delivery of therapeutic agents to diseased retinas? What can we do currently to help patients?

Establishing the best timing and type of therapy, as well as the optimal outcome measures to determine efficacy, will necessitate considering the disease entity as well as disease status. Studies of disease natural history aimed at improving the ability to predict disease course and evaluate outcomes, and prospective studies aimed at better predicting benefit versus risk in individual cases, are expected to be key approaches. In addition, strategies to improve the technology for dealing with large genes, as well as for intravitreal delivery of viral vectors that may be needed for treating retinas rendered fragile by disease, are being developed and will likely expand the population of patients who could potentially benefit. Improvements in treating dominant disease are likely to be linked to advances in basic science, potentially involving high-throughput screening on ESC or iPSC platforms that enable development of small molecule and other therapies. Strategies for helping current patients, including those for whom causative mutations have not been identified, may focus on addressing secondary-injury mechanisms. One key approach may be to treat autoimmune retinopathy secondary to RP.[126,127] For example, cystic changes of the macula present in panretinal degenerations are highly associated with circulating antiretinal antibodies and often respond to immunosuppression or steroids, with positive effects seen as improvement in the visual field size or scotomata.[128]

### Priority 5: Improving Outcome Measure Testing and Standardization

The increasing complexity of testing technologies, combined with growing numbers of patients, test sites, and therapeutic modalities, present significant challenges for evaluating disease status and treatment outcomes. Overcoming these challenges will involve addressing key questions, including the following: What is the reproducibility and reliability of currently available outcome measures for detecting therapeutic benefit? Which functional and structural tests are essential for optimizing the evaluation of outcomes in clinical trials, while at the same time reducing the burden on patients? What additional detection

technologies or paradigms need to be developed to improve the speed and significance of therapeutic outcome measurements? What technologies and testing protocols should be set for pediatric patients who cannot reliably perform tests that adults can?

Following the ISCEV model for standardizing the practice of clinical electrophysiology,[97] a high priority is to standardize the clinical protocols for key new technologies. This could be accomplished by working groups and specialist meetings to establish standardization of testing procedures and data analysis, as well as to engage in technician training. Another priority would be to ensure that all trials use either genotyped patients or patients with a narrowly defined phenotype whose blood should be banked. In addition, disease-specific outcome measures should ideally be incorporated into each study, as well as age-appropriate measures of quality of life. An overarching goal of all such efforts should be to shorten validation times and reduce the testing burden on patients of all ages. Due to the many uncertainties relative to which outcome measures will be required for the approval of new therapies, it will be critical to work with regulatory agencies to develop minimum testing protocols. One important area of needed agreement is in defining mutually acceptable end point criteria that can serve as alternatives to visual acuity testing, which in most cases is predicted to have limited value in assessing therapeutic efficacy. A standardized and streamlined set of clear outcome measures for individual diseases will facilitate establishing clinical trials for new therapies and gaining regulatory approval for their use, and is predicted to significantly raise commercial interest in the field.

## ENHANCING PROGRESS THROUGH COLLABORATIVE AND COLLECTIVE EFFORT

Accomplishing such an ambitious agenda, particularly as it concerns translational efforts directed at rare diseases, will require significant collaborative and collective effort. Unfortunately, many road blocks to collaboration exist, including issues relative to sharing responsibility, funding, credit, and intellectual property; standardizing techniques, protocols, and instrumentation; and overcoming challenges posed by geographic distances, language barriers, patient attitudes, and differences in regulatory environments. It is thus of key importance to identify useful mechanisms of collaboration that will support the needs of advancing future research, as well as the needs of the researchers and patients themselves.

Current efforts to promote collaborative research include investigator-driven initiatives, such as the European Retinal Disease Consortium; funding agency–driven projects, including E-rare grants, National Institutes of Health R24 grants, and the Age-Related Macular Degeneration Consortium; and industry-driven multicenter clinical trials, including those focused on hESC-RPE and gene therapy. Additional large-scale efforts will be needed to establish international databases of correlative phenotype-genotype information, to standardize protocols and outcome measures, and to develop a unified approach for addressing regulatory requirements and facilitating phase I/II clinical trials. With respect to the latter, common regulatory protocols and paperwork could be made available to avoid duplication of effort by each center. On a smaller scale, mechanisms are needed to enhance resource sharing, to coordinate project planning, and to reduce redundancy between individual investigators. Such efforts would be facilitated by developing uniform agreements for collaboration and authorship, secure Web sites to enable data sharing, and dedicated centers with specialized expertise that can be accessed by the scientific community (e.g., animal models,

viral vectors, histology, imaging reading). Progress at the basic science level could be accelerated by open exchange and shared development of techniques, unique resources, animal models, and expertise (both technical and administrative), through targeted workshops, student exchange programs, Web-interactive seminars, private chat sites, and shared databases.

Unfortunately, issues relative to publication and funding are chronic problems associated with collaborative efforts. More flexibility on the part of scientific journals is needed to establish mechanisms for attributing meaningful credit to multiple contributors on publications of collective work. In addition, flexible funding mechanisms and financial models are needed to allocate funds across multiple investigators and centers contributing to the progress of specified projects. Importantly, the field needs a financial strategy that will enable therapeutic coverage for the greatest number of genes and patients. Inevitably this will require grappling with questions including the following: What can be done to reduce the cost of treating patients? What infrastructure requirements will be needed to support large-scale treatment of patients?

Ultimately, sources of increased funding to promote and sustain collaborative research will need to be identified. Such efforts may include lobbying major funding agencies to increase the number and size of multicenter grants, as well as working to incentivize industry to develop mechanisms that better promote collaboration and openness. It also will be important to raise public awareness broadly to attract disease-neutral philanthropy from individuals with the ability to provide major funding for basic and clinical research. Suggested mechanisms for accomplishing these aims include the formation of an international gene therapy consortium for monogenic disorders.[129]

## MOVING FORWARD

The participants at the Monaciano Symposium recognized that addressing the priority areas identified in their discussions will require multiple strategies, including (1) public and private lobbying to raise awareness and increase funding for genetic testing of the retinal dystrophy population; (2) establishing an international database to facilitate access to patients for natural history studies and clinical trials; (3) funding specialist groups to train technicians and set standards for outcomes testing using new technologies; (4) using a consortium approach to define and collect key information needed to improve understanding of retinal dystrophy natural history; (5) improving access to expertise in translational studies through workshops and formation of an advisory board; and (6) developing consortia to increase resource sharing among basic, veterinary, and medical scientists in which everyone is acknowledged and can benefit. Each of these approaches will require concerted effort by specialists in the field, possibly via self-identified and self-organized working groups dedicated to advancing each specific objective. Such collaborative action should provide the best opportunities for innovation in terms of the therapeutic modalities being developed, as well as in the delivery of patient care.

The remarkable progress taking place in retinal dystrophy research will almost certainly result in tools and insights that will have broad applicability to common forms of retinal disease. For example, in addition to mutation-specific treatments for rare retinal dystrophies that are currently being developed, mutation-independent gene therapy and cell therapy approaches are expected to emerge. These treatments may be of broad utility for ameliorating both monogenic disorders and complex conditions in which genetics, environmental factors, and aging all contribute to disease etiology.

Thus, the stakes and motivation for ensuring that retinal dystrophy translational research reaches its full potential have never been greater.

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Investigative Ophthalmology & Visual Science

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