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Perspective

Inherited Retinal Degenerations: Current Landscape and Knowledge Gaps

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Introduction

Inherited retinal degenerations (IRDs) represent a diverse group of progressive, visually debilitating diseases that can lead to blindness in which mutations in genes that are critical to retinal function lead to progressive photoreceptor cell death and associated vision loss. IRDs are genetically heterogeneous, with over 260 disease genes identified to date.[1] The development of treatments and cures to modify the rate of disease progression has been limited to date, with some success of neurotrophic factor therapy and gene therapies reported from clinical trials.[2–11] The best example of treatment success is gene augmentation therapy for IRD caused by mutations in the *RPE65* gene, which recently received US Food and Drug Administration (FDA) approval, which in fact represented the first FDA-approved gene therapy (GT) for any genetically inherited disease.[4–9] Recent developments in the IRD field have advanced understanding of the mechanisms responsible for vision loss, creating new opportunities to intervene in the course of disease by developing new therapeutic approaches. In 2013, a Delphi-style gathering of IRD experts led to the identification, by consensus, of top priorities to advance therapeutic efforts for IRDs, including the need for systematic genotyping, improved standardization of visual function testing, development of more rigorous and widespread data collection protocols, and increased data sharing.[12] This document summarizes more recent advances in the IRD field and outlines specific knowledge gaps. These knowledge gaps present oppor-

tunities for further investigation to enable development of therapies that may slow down or prevent vision loss, or restore vision, in affected patients.

Atrophic age-related macular degeneration (AMD) is included among the target inherited retinal diseases of interest because first, understanding AMD may contribute to understanding of inherited macular diseases, and second, understanding of the genetics and mechanism of inherited macular degenerations may contribute to understanding of AMD.

Recent Advances in IRD Research

The development of treatments for IRDs requires basic and translational research that leads to improved understanding of the nature and causes of these diseases. Brief summaries of recent advances in IRD research are included here.

Genetic Causes of Disease

Notable progress has been made identifying the genetic causes of IRDs, with over 260 disease genes identified to date.[1] By sequencing the coding regions of these disease genes via panel based genetic testing, it is currently possible to identify the genetic cause of disease for approximately two thirds of patients with IRDs[13–15] and up to 85% of children with IRDs.[16] Additional mutations can be identified using whole genome sequencing.[17] Active research programs in multiple centers are directed toward identifying the genetic causes of disease in the one third of patients who do not have identifiable mutations in the presently known IRD disease genes. This includes discovery of additional novel disease genes, and identification of noncoding mutations, including structural variants (SVs) in the genome.[18] Additionally, the identification and characterization of modifier genes, which themselves do not cause disease but "modify" the disease severity caused by other disease causing mutations is in its infancy, but has great potential for identifying new targets and approaches for treatment. Lastly, it may be worthwhile to evaluate patients with unilateral disease for somatic mutations[19,20] or other potential causes of retinal degeneration such as posterior uveitis,[21] acute zonal occult outer retinopathy,[22] or medication toxicity.[23,24]

Disease Pathogenesis

Identification of the genetic causes of IRDs has led to improvements in our understanding of retinal biology in general, and in some cases to our understanding of disease pathogenesis. For example, several cell death mechanisms including apoptosis and necrosis have been shown to be activated in different genetic forms of IRD.[25,26] Delineation of the genetic causes of syndromic ciliopathies has led to improved understanding of photoreceptor cell structure, and the importance of cellular transport processes such as intraflagellar transport in IRDs.[27,28] Studies of the noncell autonomous nature of cone cell death in rod-cone degenerations has led to recognition of metabolic and oxidative stress in photoreceptor dysfunction and death.[29,30] These studies have also identified supportive factors such as RdCVF and NRF2 that could be used to develop nongene specific treatments that may be beneficial to groups of disorders that are caused by mutations in a variety of different genes and that could potentially also help at later stages of the disease process.

Technical advances in the modeling of disease have facilitated improved understanding of pathophysiology and basic mechanisms of IRDs to identify novel targets for therapy and provide proof of concept for therapeutic strategies. The use of induced pluripotent stem cells (iPSCs) to model disease has provided a platform to study IRDs that do not have a relevant animal model or for which the human mutations have not been recapitulated in an animal model.[31] Further, iPSC models have proven useful in establishing proof-of-concept when an animal model is absent. For example, the use of iPSC to validate gene augmentation as a therapeutic strategy for choroideremia has resulted in FDA approval of a phase I/II clinical trial (NCT02341807).[32]

Disease Progression

Consensus guidelines for the care of patients with IRDs can be viewed at the American Academy of Ophthalmology Clinical Education Guidelines portal.[33] Recent developments that have advanced the retinal degenerations field in clinical structure and function have related to novel technologies that enables improved assessment of retinal structure and function. Optical coherence tomography (OCT) provides noninvasive, objective assessment of retinal structure. The axial resolution is 5 μm with commercially available OCT systems,[34] and the outer retinal layers including the outer nuclear layer, the external limiting membrane, the inner segments, the inner segment/outer segment junction or ellipsoid zone (EZ), the outer segments, and the retinal pigment epithelium (RPE) can be measured in eyes with IRD. Numerous studies have established a relationship

between visual field parameters and structure on OCT.[35–40] The objective, quantitative, and high-resolution nature of OCT measures combined with correlation to functional measures has created interest in using the EZ area as a potential clinical trial outcome measure.[41] In addition, swept-source OCT penetrates deeper into the choroid to facilitate optical coherence tomography angiography (OCTA),[42] which may provide insight into how retinal and choroidal vasculature is affected in eyes with different forms of retinal degeneration. Choroidal abnormalities may play a role in disease pathogenesis in conditions like choroideremia and gyrate atrophy, and may be a target for potential drug delivery.

Since photoreceptors degenerate in IRDs with consequent visual loss, imaging photoreceptors in living eyes noninvasively could provide insight into rod and cone structure during disease progression and in response to experimental therapies. However, most clinical imaging modalities do not have adequate resolution to visualize individual photoreceptors at the cellular level. Adaptive optics is a strategy to measure aberrations in light exiting the eye that reduce image resolution and prevent images of photoreceptors at the cellular level.[34,43–45] Adaptive optics scanning laser ophthalmoscopy (AOSLO) captures confocal light wave-guided by photoreceptors with intact inner and outer segments,[44,46,47] while split-detector AOSLO images nonconfocally wave-guided light, to visualize cones with only inner segments.[48–55] Split detector systems can also be used to see inner retinal structures[56] and RPE cells using dark field imaging.[57] Adaptive optics systems are not widely available but are valuable research tools to improve understanding of photoreceptor survival in eyes with IRD, and may have potential as a sensitive, objective outcome measure of safety and efficacy in clinical trials for IRD patients.[58]

Continuing a long history of studies of the course of disease for specific IRDs,[59–67] several multicenter natural history studies have been initiated, including the ProgStar[68–74] and RUSH2A trials sponsored by the Foundation Fighting Blindness Clinical Research Institute. These studies have required standardization of equipment and procedures among sites. Registries for patients with rare inherited eye diseases represent an important development that provides a valuable resource for research into genotype-phenotype correlations and for investigators seeking to identify patients who may be eligible to participate in clinical trials.[75] My Retina Tracker®, now the largest patient-driven registry in the IRD community, continues to amass genetic data that is accessible to researchers globally.[75]

Neuroprotective Agents

Therapies that may slow photoreceptor degeneration due to a range of genetic causes have also been investigated. Vitamin A and docosahexaenoic acid have been demonstrated to provide modest reductions in the rate of disease progression in patients with retinitis pigmentosa (RP).[2,3,76–82] Oral valproic acid was reported to slow visual field progression in a case series of RP patients,[83] but a randomized clinical trial of valproic acid treatment in patients with autosomal dominant RP showed no significant difference between patients treated with valproic acid and placebo (https://www.clinicaltrials.gov/ct2/show/results/NCT01233609?term=01233609&rank=1&sect=X01256#all).

Advances in high-throughput screening have accelerated the pace of identifying cellular targets and candidate neuroprotective agents. Oxidative damage has been implicated in photoreceptor degeneration,[84] and N-acetylcysteine (NAC)[85] and N-acetylcysteine amide (NACA)[86] have been shown to prevent retinal degeneration in preclinical studies of RP. A clinical trial of NAC in RP patients is in progress (NCT0306302). Nonspecific neurotrophic factor therapy with ciliary neurotrophic factor (CNTF) has been shown to slow photoreceptor degeneration in a number of animal models, but did not demonstrate visual function benefit in human clinical trials of patients with early or advanced RP.[87] However, neurotrophic factors that reduce photoreceptor susceptibility to oxidative stress and promote cone outer segment regeneration, such as rod-derived cone viability factor (RdCVF) show promise in preserving cone photoreceptors in eyes with RP in preclinical models,[88] and clinical trials are planned in patients with RP. Various protein kinase inhibitors have also been shown to slow retinal degeneration in various mouse and rat models of IRD.

Gene and Genetic (Gene-Specific) Therapies

Based on progress in understanding the genetic causes of IRDs, significant effort has been directed toward developing gene augmentation therapies for specific genetic forms of IRD. Reports of success of clinical trials of gene augmentation therapy for *RPE65*- and *CHM*-associated retinal degeneration suggest the great potential of gene therapies for the treatment of IRDs.[10,89,90] The recent FDA approval of gene augmentation therapy for *RPE65*-associated IRD is an important milestone and suggests that similar approaches can be used for the treatment of

many other genetic forms of IRD. For example, preclinical studies support the broad use of gene therapies for the treatment of IRDs, with proof-of-concept of benefit reported in at least 24 genetic forms of disease.[91–113] Genome editing, including CRISPR-based therapies, and genetically directed pharmacologic therapies, including antisense oligonucleotides, premature termination codon read-through strategies, base editing, and RNA editing are also promising approaches for genetic forms of disease that may be not amenable to gene augmentation therapies.[84,112,114–120]

Regenerative Medicine

Building on data from studies of retinal development, there is now great interest in the use of retinal stem cells for the study and treatment of IRDs. Recent studies show that instead of or in addition to integration of donor cells into the host retina, transplanted photoreceptor precursors into animal models of retinal degenerative disease demonstrated transfer of cytoplasmic material from donor to recipient photoreceptors.[59,121–126] Transplanted donor cell integration and material transfer between transplanted and host cells may both underlie the therapeutic benefits associated with transplantation therapy. It may also be possible to take advantage of material transfer between cells for therapeutic purposes, such as stimulation of host Müller cells to differentiate into photoreceptor cells.[127]

Another approach to transplantation involves iPSC-derived organoids, which enhances the possibility of autologous transplants.[128,129] Retina organoids can be used for disease modeling, as well as for therapeutic purposes.[130,131] There are many efforts underway to develop in vitro models of degenerative retinal disease, which will enable high throughput screening of possible therapies, as well as facilitate understanding of disease mechanisms. The National Eye Institute announced the 3-D retina organoid challenge (https://www.nih.gov/news-events/news-releases/nih-solicits-next-generation-retina-organoids-prize-competition). Erin Lavik, Sc.D., won the "ideation phase" of this competition. Lavik's team proposed using a method to screen print tissue models. Her group will create layers of the various types of retinal neurons that can be derived in a lab from adult stem cells. The method would allow the layers to be correctly oriented to mimic the structure of the human retina.

Approximately 20 early phase clinical trials (www.clinicaltrials.gov) involving cell-based therapy for degenerative retinal disease are underway. Therapeutic targets include the advanced atrophic form of AMD,[132] choroidal neovascularization associated with AMD, Stargardt disease, RP, and atrophy associated with high myopia. Therapeutic cells under study in these trials include autologous bone marrow-derived stem cells, human retinal progenitor cells, embryonic stem cell-derived RPE, iPSC-derived RPE, and human CNS stem cells.[133]

As a note of caution, there is evidence of severe visual loss including complete blindness after ocular injection of autologous adipose derived "stem cells" from unregulated clinics in the United States.[134] There were no clinical trials that supported these treatments and, thus, it remains of utmost importance to wait for the results of formal clinical trials that test the safety and efficacy of these emerging new treatments before patients should undergo any such treatment in a clinical setting.

Visual Prosthetics

For patients with IRD there have traditionally been no effective treatments to restore vision. In 2013, an epiretinal prosthetic device received human use device (HUD) exemption from the FDA for use in patients with near total vision loss due to RP. Since then, over 200 patients world-wide have received the Argus 2™ device from Second Sight Medical Products, Inc. (Sylmar, CA) with some evidence of improved visual function and performance.[135–139] Other retinal prostheses that target various regions of the visual pathway are under development or are in clinical trials including the electronic retinal implant Alpha AMS,[140,141] Intelligent Retinal Implant System (IRIS V2 (NCT02670980), Suprachoroidal Retinal Prosthesis (NCT01603576), and the PRIMA high-resolution photovoltaic retinal prosthetic system (NCT03333954).

Optogenetics provides the opportunity to confer novel light-sensing properties to inner retinal neurons that normally have nonimage forming light sensitivity such as bipolar cells and retinal ganglion cells. The strategy involves transfecting inner retinal neurons with a gene encoding a light-sensitive protein such as channelrhodoposin-2 or halorhodopsin. Optogenetic proteins can be sensitive to wavelengths of natural light (Allergan RST-001, NCT02556736) or genetically red-shifted to decrease the potential for light damage by bright white light. In this case, an external visual interface (goggles) transforms external light stimuli into signal that activates the transduced retinal ganglion cells with the appropriate (infrared) wavelength (GenSight Biologics GS030, NCT03326336; GenSight Biologics SA, Paris, France).

This combination of GT and electronics could offer cell specificity, as well as stimulation of a large number of neurons via viral vector-based transfection technology, delivered by intravitreal injection. The light-sensing receptors may also be built into actual artificial retina implants.[142,143]

Specific Knowledge Gaps That Should Be Addressed to Advance the Field

The goal of this analysis of gaps in knowledge regarding IRDs is to identify priority areas for research that will accelerate progress toward development of treatments and cures for IRDs.

Genetics of IRDs (GE)

The goals of this Research Priority Area include:

1. Identification of the genetic causality of all forms of IRDs
2. Integrate comprehensive genetic testing into clinical care for patients with IRDs
3. Identify the genetic risk factors for AMD

Identification of the genetic cause of disease is an important part of clinical care for patients with IRDs. Many times, the phenotype of a condition can be ambiguous and molecular genetic diagnosis leads to the accurate clinical diagnosis. A genetic diagnosis can identify potential treatment options for patients, inform them about the potential risk of disease to family members, and identify the potential risk that other organ systems may be affected in syndromic diseases. An important goal in the IRD field is for molecular genetic diagnostic testing to become a routine part of clinical care, and for testing to be accessible, affordable, and accurate.[12] A related goal is to improve the sensitivity of testing such that pathogenic or likely pathogenic mutations causing IRDs are identified in a substantial fraction of cases (at least 95%).

Specific Knowledge Gaps

1. Identify the remaining "elusive" genetic causality of IRDs
   a. Identify remaining IRD disease genes
   b. Identify noncoding mutations in IRD disease genes

As described above, the genetic cause of disease can be found for approximately two thirds of patients via sequencing of the coding regions of known IRD disease genes. The genetic causality for the remaining one third of patients needs to be identified. Based on results of ongoing studies by multiple research groups, it is apparent that the genetic causes of disease in these patients and families will be distributed between novel IRD disease genes and noncoding mutations, including SVs in known disease genes.

2. Incorporate improved sequencing methods into research and diagnostic testing, including long-read sequencing, single-molecule sequencing, advanced methods to detect copy number variants (CNVs) and other types of SVs, and methods to reconstruct extended haplotypes.
3. Improve the ability to determine which rare variants are damaging, potentially pathogenic, and likely disease-causing to resolve variants of uncertain significance (VUSs), using bioinformatics and computational approaches, collaborative data sharing, and functional assays, including in vitro, cell, and animal based assays.
4. Identify genetic modifiers of disease severity through studies of cohorts of patients with mutations in the same gene but varied disease severity. Many IRDs have variable penetrance, age of onset, progression, and clinical consequences. Even patients who share the same disease gene or mutation may differ substantially in penetrance and clinical expression. While in some cases primary genotype-phenotype correlations have been reported, it is hypothesized that additional genetic modifiers of disease severity exist. Identification of genetic factors modifying clinical consequences may reveal shared disease pathways and novel treatment targets.
5. Improve access to molecular genetic diagnostic testing, test result evaluation, and genetic counseling, including improved payment mechanisms and more widespread coverage of testing costs. This includes the adoption of faster, more accurate, and less expensive methods to identify mutations. Further need to improve communication of test results to patients. Genetic counseling is also an important part of care for patients with IRDs, to help navigate the genetic testing process and interpret the results.
6. Improve contribution of anonymous genetic data to public databases. Continue to support patient data registries such as My Retinal Tracker.
7. Identify additional genetic factors contributing to atrophic AMD, with attention to understud-

ied ethnic/geographic populations, and to genetic factors contributing to specific clinical features and endophenotypes, that is, intermediate disease states and associated biomarkers.

Cell and Molecular Mechanisms of Retinal Disease (CMM)

The goals of this Research Priority Area include:

1. Improve our understanding of the mechanisms by which mutations in IRD disease genes cause dysfunction and death of retinal cells so that improved therapies to prevent vision loss can be developed.
2. Delineate pathways that link mutations in multiple different genes to common disease mechanisms and molecular pathways, with the goal of identifying potentially common therapeutic targets that are applicable to groups of genetic forms of IRD.
3. Determine mechanisms and pathways by which modifier genes and environmental factors modulate the disease impact of IRD-causing mutations, since such understanding could also identify new targets and pathways for therapeutic intervention.

Specific Knowledge Gaps

1. Improve understanding of the pathways leading to retinal cell dysfunction and death, including:
   a. The roles of different cell death pathways such as apoptosis, necrosis, and a distinct form of programmed cell death dependent on poly-ADP-ribose (PAR) overactivation termed parthanatos in IRDs
   b. The roles of different cell stresses such as oxidative stress and endoplasmic reticulum stress in IRDs
   c. The roles of inflammation, autoimmunity, and retinal microglia in IRDs
   d. The role of autophagy in IRDs
   e. The role of mitochondria dysfunction and energy metabolism in IRDs
2. Improve understanding of regulation of gene expression in retinal cells
   a. Investigate how gene expression is altered in different genetic forms of IRD and with aging
   b. Identify the regulators that control rod and cone differentiation, which could inform efforts to reprogram rod cells to become more cone-like and vice-versa for therapeutic purposes
   c. Identify the gene expression patterns in all retinal cell types through improved RNA-sequencing methods, including single cell transcriptome analyses
   d. Define role of epigenetic factors in modulating retinal/photoreceptor health and disease
3. Improve understanding of the metabolism of retinal cells, and how this is altered in disease
   a. Identify the unique aspects of photoreceptor and RPE cell metabolism that affect the responses of these cells to genetic disease, and thus are potential therapeutic targets
   b. Improve understanding of the metabolic interactions of retinal cell types
4. Improve understanding of the consequences of therapeutic drug delivery, including retinal detachments for delivery of therapies and impact on photoreceptor synaptic connectivity
5. Develop and characterize additional animal models of IRDs, including:
   a. Genetically modified rodent models of specific genetic forms of IRD
   b. Nonrodent models of retinal degeneration
   c. Cone-rich models of disease
   d. Large animal models of disease
   e. Determine which animal models best model human disease in terms of both mechanism of disease and which are best for predicting therapeutic efficacy and safety
6. Improve understanding of the noncell autonomous aspects of retinal neurodegeneration
7. Establish model systems for the study of macular degenerations, including AMD
   a. Animal and cell models of inherited macular degenerations
   b. Cell-based models of AMD, such as iPSC-derived RPE cells
8. Identify the molecular events responsible for retinal remodeling during different stages of retinal degeneration, including:
   a. Interactions of retinal cells with Müller cells, microglia, and RPE cells
   b. The impact of these interactions on formation or remodeling of synaptic connections
   c. Reactive gliosis and loss/remodeling of inner retinal neurons
9. Determine the mechanisms that maintain synapses between photoreceptor and bipolar

cells, and that promote new synapse formation. Such understanding will be crucial for the development of regenerative medicine-based treatment approaches.

Clinical-Structure and Function (CL)

The goals of this Research Priority Area include:

1. To develop and apply new technology to measure structure and function in IRDs.
2. To establish relationships between measures of retinal functional test and retinal structure, with the goals of understanding the relationship between genotype and clinical phenotype.
3. To identify outcome measures or biomarkers to demonstrate change over a relatively short time period spanning no more than 2 to 3 years.

Specific Knowledge Gaps

1. To improve and facilitate new approaches to clinical care for IRD patients and families, including access to care, education of nonexpert clinicians, shared standards for clinical tests, and support for expenses. This includes methods of dissemination to retinal specialists and other eye care professionals of advancements in IRD research.
2. To understand factors modifying penetrance and clinical expression of IRDs.
   a. Continue natural history studies of specific disease-causing genes to document the spectrum of clinical consequences. Evaluate mutation-specific variation within these natural history studies.
   b. Evaluation of possible environmental modifying factors such as diet, smoking, exercise, and sunlight exposure in natural history studies.
3. To identify the earliest manifestations of degeneration.
   a. Identify primary cells affected in response to mutations that cause different IRDs.
   b. To develop and validate reliable outcome measures, endpoints, and/or biomarkers that may be important targets to monitor and modify as initiating processes in degeneration.
   c. Improved understanding of the relationship between photoreceptor structure and functional vision, including how many photoreceptors and other retinal neurons need to be restored to provide useful vision.
   d. Improved evaluation of the retinal periphery: earliest changes often occur in the midperiphery. Current structural imaging methods including OCT and AOSLO are limited primarily to the central retina. Improvements in imaging speed and eye movement compensation may facilitate evaluation of midperipheral disease.
   e. Improved evaluation of rods. Most clinical tests to monitor function are cone mediated, despite the fact that many mutations in RP affect primarily rods. Rod perimetry and microperimetry should be further developed and used to characterize early degeneration. High resolution measures of retinal function during degeneration and responses to therapies need to be developed.
   f. Improved evaluation of the RPE to determine the relationship between RPE and photoreceptor death. Current methods (shortwave length AF or IR AF) only measure substructures within RPE cells (melanosome or lipofuscin) rather than RPE cell number and shape. Newer imaging techniques, such dark field adaptive optics, hold promise for imaging RPE, but need further refinement.
   g. Improved evaluation of retinal and choroidal vasculature: utilize OCT angiography to detect and investigate early vascular abnormalities in the retinal and choroidal circulation to correlate perfusion changes with photoreceptor and RPE degeneration.
   h. Improved image acquisition, processing and analysis, including:
      i. Automated OCT segmentation that can more accurately segment the images specific to IRDs. With increased density of B-scans for en-face imaging, manual correction becomes impractical.
      ii. Better software to easily align multiple structural and functional data such as fundus photography, AF, en face OCT, OCTA, and AO.
      iii. Development of commercially available instruments that can be deployed and used in multicenter trials.
4. Develop Patient Reported Outcome measures (PROs):
   a. Tailored to and validated in specific diseases based on mutation, mechanism, patient age, and stage of progression.

b. Assess impact of treatment on patients who have participated in clinical trials.
c. Natural history studies provide an opportunity to develop and validate PROs for specific diseases.

5. Improved assessments of vision in patients with advanced disease.
   a. Multiluminance mobility tests, pupillometry, and full-field stimulus threshold testing are some examples.

Novel Medical Therapies (NMT)

The goals of this Research Priority Area include:

1. To develop drug therapies that protect retinal function and structure in IRDs.
2. To create and develop improved animal models of human disease to evaluate the effects of NMTs.
3. To develop better functional testing of drug effectiveness.
4. To develop novel drug delivery systems.

Specific Knowledge Gaps

1. Study design rigor to improve repeatability of preclinical studies. Lack of reproducibility is largely responsible for basic science developments not moving forward into translational studies.[144–148]
2. Develop targeted high throughput phenotypic drug screening tools relevant to human IRDs.
3. Develop treatments that target different pathways involved in IRD pathogenesis including but not limited to ER stress, proteostasis, or protein editing, alternative splicing, including antisense oligonucleotides to alter splicing of key exons.
4. Develop treatments that promote regeneration or reprogramming of Müller cells, ganglion cells, or RPE cells.
5. Improved drug delivery: develop platforms for sustained delivery methods and formulations to enable penetration and long-term sustained delivery to target cells with minimal off-target side effects.
6. Advancing therapies to clinical trials
   a. Develop appropriate animal models of human IRD for testing approaches/compounds.
   b. Determine optimal patient population to test pan therapeutic treatments.
   c. Consideration of study of post-mortem samples from patients treated with novel therapies.

Gene Therapy (GT)

The goals of this Research Priority Area include:

1. To develop and optimize viral and/or nonviral gene delivery systems for use in the treatment of IRDs.
2. To demonstrate efficacy and safety using preclinical models in preparation for human trials.

Specific Knowledge Gaps

1. Develop gene editing approaches that can correct multiple genes/classes of mutations, including:
   a. Treatment of diseases due to mutations in large genes
   b. Treatment of diseases due to dominant gain-of-function mutations
   c. Evaluate and address limitations including efficiency and off target effects
2. Translation from preclinical models to humans:
   a. Identify optimal large animal models for preclinical studies
   b. Identify optimal promoters for expression of therapeutic transgenes at desired levels in appropriate retinal cell types
   c. Genetic isoform/splice variants expression should be carefully evaluated (i.e., Myo7A in mouse versus human)
   d. Inflammation varies by species and by vector (i.e., AAV2 vs. AAV4 or AAV5)
   e. IP issues with specific types of vectors (i.e., AAV8)
3. Careful assessment of GT trial results:
   a. Effects of retinal detachment: characterize photoreceptors and synaptic connectivity after detachment
   b. Evaluate safety and efficacy results
   c. Evaluate the impact of inflammation and autoimmunity on efficacy results
   d. Consideration of study of post-mortem samples from patients treated with GT
4. Improved delivery of treatments on a long-term basis
   a. Because naturally occurring AAV and lentiviral serotypes are unable to cross existing physical barriers in the retina, subretinal injections are the standard method by which

vectors are administered to photoreceptors and RPE cells, the major targets of GT. Subretinal injections have limitations including:
   i. Detachment of the retina away from the underlying RPE
   ii. Delivery of AAV or lentiviral vectors is limited to the area of the retinal detachment
b. Intravitreal injections, which do not require damage or detachment of the retina, represent a less invasive and safer approach by which vector could potentially be delivered across the entire retinal surface, while avoiding complications associated with subretinal injection. Challenges associated with intravitreal injection include:
   i. High intravitreal viral titers may cause inflammation; it is necessary to manage the immune-mediated inflammatory response treatments can induce
   ii. Dense vitreous in young subjects is barrier; improve penetration for panretinal distribution without increasing clearance of vectors

Regenerative Medicine

The goals of this Research Priority Area include:

1. To develop strategies that provide functional rescue or replacement of degenerating or dead retinal cells that can slow and prevent vision loss or restore vision.

Specific Knowledge Gaps

1. Improved production of cells:
   a. Developing cells that will survive in hostile environment of advanced degeneration
   b. Improve understanding of effects of host tissue status on transplant survival and integration
   c. Understand role of and need for adequate immunosuppression; autologous versus xenograft
2. Clarify the mechanism by which transplanted cells can provide benefit to the host retina
   a. Distinguish clearly between material transfer between transplanted and host cells and integration of transplanted cells into the host retina
3. Develop ways to track and improve transplant survival
   a. Demonstrate that stem cells persist after implantation with better means of imaging implanted cells
   b. Distinguish effects of transplant survival from fusion of stem cells with native surviving cells
   c. Consideration of study of post-mortem samples from patients treated with GT
4. Develop ways to reprogram Müller cells and/or RPE cells that persist despite advanced photoreceptor degeneration
5. Identify improved large animal models to determine if xenograft will be safe and effective in patients
6. Learn from ongoing clinical trials and preclinical studies:
   a. Survival of transplants in primates to study fate
   b. Remodeling in eyes that have received transplanted cells in non-human primates

Addressing the knowledge gap detailed above will likely require projects that incorporate components of multiple project areas because the gaps are synergistic. Making progress to address the gaps will require multipronged, multidisciplinary approaches. Many of the gaps listed pertain to more sections than the ones listed above, and impactful research projects will address gaps and problems from multiple different approaches.

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