NEI-Supported Age-Related Macular Degeneration Research: Past, Present, and Future

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Received: March 23, 2020
Accepted: April 8, 2020
Published: June 30, 2020

Keywords: age-related macular degeneration; clinical trial; genetic diseases

Citation: Wright C, Mazzucco AE, Becker SM, Sieving PA, Tumminia SJ. NEI-supported age-related macular degeneration research: past, present, and future. Trans Vis Sci Tech. 2020;9(7):49, https://doi.org/10.1167/tvst.9.7.49

Purpose: To review past and current National Eye Institute (NEI)–supported age-related macular degeneration (AMD) activities and initiatives and preview upcoming coordinated efforts for studying AMD.

Methods: We conducted and summarized a portfolio analysis and literature review of NEI intramural and extramural AMD activities.

Results: The NEI supports a broad range of AMD research, both by individual independent investigators as well as through networks and consortia. The International AMD Genomics Consortium, Age-Related Eye Disease Study, Age-Related Eye Disease Study 2 (AREDS2), and Comparison of AMD Treatments Trial legacy work probed the complex genetics, clinical presentation, and standards of patient care, respectively. The NEI AMD Pathobiology Working Group identified gaps and opportunities for future research efforts. The AMD Ryan Initiative Study and clinical trials testing the efficacies of minocycline to modulate retinal microglia activity and induced pluripotent stem cells–derived retinal pigmented epithelium (RPE) patch implants to rescue photoreceptor cell death are among the future directions for NEI-supported AMD research. Finally, NEI commissioned the creation of AREDS2 participant-derived induced pluripotent stem cell (iPSC) lines linked to their associated genomic and phenotypic datasets. These datasets will also be linked to the data obtained using their associated iPSC-derived cells (RPE, retina, choroid) and made publicly available.

Conclusions: Investments by NEI for AMD research will continue to provide invaluable resources to investigators committed to addressing this complex blinding disease and other retinal degenerative diseases.

Translational Relevance: NEI now stands poised to expand the resources available to clinical investigators to uncover disease mechanisms and move experimental therapies into clinical trials.

Introduction

Until relatively recently our understanding of age-related macular degeneration (AMD) was limited principally to clinical characterization, and patients diagnosed with the disease had no clinical interventions available to slow or reverse visual decline. Recent advances in imaging, genetics, and therapeutics have given researchers and clinicians a clearer understanding of the natural history of the disease, allowing for the generation of hypotheses regarding cellular events critical to disease pathogenesis and progression. Advances in drug development have also led to the development and application of vision-saving antiangiogenic agents for use in the clinic. Unfortunately, despite the myriad technological and scientific advances in AMD research, many AMD patients,
particularly those with geographic atrophy, have no treatments available to preserve their vision. Furthermore, many events in early disease pathogenesis remain unclear,, stymieing efforts to produce therapeutics that could halt disease progression to a late stage in which most vision loss occurs.

AMD is the leading cause of vision loss among Americans at least 60 years of age. Worldwide, 200 million people are affected by AMD, with approximately 10% at an advanced disease stage, and the prevalence may double by 2050. The two late-stage forms are dry AMD or geographic atrophy and wet AMD or choroidal neovascularization. Both types can progress to severe vision loss but by different mechanisms. The pathology primarily involves photoreceptors, the retinal pigmented epithelium (RPE), Bruch’s membrane (BM), and the choroidal circulation.

To address this public health need, the National Eye Institute (NEI) has championed several major efforts to both understand and treat AMD. From 2008 to 2017 the NEI spent more than $1 billion (adjusted for inflation) to conduct studies that have played an instrumental role in understanding AMD pathology. These investments, summarized here, established common clinical staging for AMD, demonstrated a prevention strategy for progression to advanced disease, and laid the foundation for a comprehensive understanding of the genetic underpinnings of the disease. Following on these advances, NEI is initiating new projects aimed at bringing together investigators, datasets, and innovative approaches to surmount translational barriers and develop new therapeutics for patients.

**Legacy Work: Breakthroughs By NEI-Funded Researchers**

**Mapping a Genetic Constellation**

The main risk factor for AMD is aging. Other risk factors include the use of tobacco, genetics, the degree of pigmentation, arterial hypertension, ultraviolet rays, and consumption of a non-balanced diet. The importance of genetics in AMD etiology was not appreciated until the 1990s when twin studies and epidemiology provided suggestive evidence, and several research groups began collecting clinically well-characterized cases and controls, sibling pairs and available families.

Early genetic studies (1999–2005) indicated possible linkage and association signals on many human chromosomes and two major loci at 1q31 and 10q26. In 2005, several independent research groups demonstrated the value of genome-wide association studies (GWAS) for complex disease with identification of AMD risk genes. The groups identified a common variant in the complement factor H (CFH) gene located on chromosome 1q as a risk factor for developing AMD. CFH plays a role in the intrinsic inflammatory cascade of the immune system. It may also regulate retinal development.

A study that included participants from the NEI-sponsored Age-Related Eye Diseases Study (AREDS) found individuals with the CFHY402H variant are 7.4 times more likely to develop AMD. The study was based on whole genome analysis of participants from the NEI-sponsored AREDS, a major clinical study that closely followed nearly 5000 patients with varying stages of AMD. As a result, in 2010 NEI convened the International AMD Genomics Consortium (IAMDGC, also known as AMDGene) that included scientists from 18 research groups in 14 countries. The first study conducted by this consortium was a meta-analysis of multiple GWAS datasets representing more than 8000 individuals with AMD and 50,000 controls. Further analyses by this consortium included data from over 17,000 advanced AMD cases and more than 60,000 controls of primarily European ancestry, resulting in the next big leap in AMD genetics. The group identified 19 genetic loci linked to AMD susceptibility, with seven previously unreported loci near the genes COL8A1/FILIP1L, IER3/DDR1, SLC16A8, TGFBR1, RAD51B, MIR548A2, and B3GALTL. The genetic risk score analysis of all variants (including the seven new ones) was able to distinguish the affected from unaffected individuals in all samples.

A major highlight of this study was the appreciation of distinct cellular pathways that contribute to pathology of advanced AMD. In addition to complement and immune dysregulation, the genetic studies provided direct evidence of the importance of cholesterol transport and lipoprotein metabolism, extracellular matrix, and angiogenesis signaling pathways, as recognized in previous investigations. A key issue at this juncture was dissecting causality from genetic association studies. There was a concurrent search for causal variants at the GWAS loci by targeted resequencing that led to identification of rare and likely causal variants at complement genes Arg1210Cys in CFH, Gly119Arg in CFI, and Lys155Gln in C3.
Creating Phenotyping Standards

The AREDS was a natural history study designed to determine whether daily intake of certain vitamins and minerals could reduce the risk of cataract and advanced AMD. AREDS was launched in 1992, to evaluate a combination of vitamins E and C, beta-carotene, and zinc, known as the AREDS formulation. AREDS had multiple goals: to establish high-quality phenotyping standards in patients, and to determine whether a vitamin formulation using antioxidants, zinc, and beta-carotene could reduce the rate of disease progression to late AMD in 5 years by 25%. AREDS enrolled 4757 persons with various degrees of lens opacity and AMD. Participants in the study were given one of four treatments: (1) zinc alone; (2) antioxidants alone; (3) a combination of antioxidants and zinc; or (4) a placebo. The supplements evaluated by the AREDS trial contained 500 mg vitamin C; 400 international units vitamin E; 15 mg beta-carotene; 80 mg zinc as zinc oxide; and 2 mg copper as cupric oxide (copper was added to the AREDS formulations containing zinc to prevent copper deficiency, which may be associated with high levels of zinc supplementation). NEI collaborated with Bausch & Lomb, who provided the formulation evaluated by AREDS. The clinical trial was designed as a 5-year study but was extended (up to 10 years) for long-term follow-up.

The data showed that individuals at high risk of developing advanced stages of AMD lowered their risk by about 25% when treated with a high-dose combination of vitamin C, vitamin E, beta-carotene, and zinc. In the same high-risk group, which included people with intermediate AMD or advanced AMD in one eye but not the other eye, the nutrients reduced the risk of vision loss caused by advanced AMD by about 19%. For those study participants who had either no AMD or early AMD, the nutrients did not provide an apparent benefit. The supplements had no significant effect on the development or progression of age-related cataract. After completion of the AREDS trial, all participants were given the option to receive the AREDS formulation as part of a five-year follow-up study.

At the end of 10 years, about 70% of the AREDS participants were taking the AREDS formulation. The investigators found that participants who had been assigned to the AREDS formulation in the original trial were 25% to 30% less likely to develop advanced AMD than those who had originally been assigned to placebo. Among participants at the highest risk for AMD, 34% who had taken the AREDS formulation in the trial progressed to advanced AMD, compared to 44% who had taken the placebo.

This study provides evidence that inexpensive antioxidant supplements can reduce vision loss by 25% and spare more than 300,000 individuals from significant vision loss.

Blood taken from participants involved in AREDS has yielded genetic associations for the development of advanced AMD. The first discovery of an important polymorphism in the gene regulating CFH, and its association with AMD was made using AREDS data. Numerous additional genes have been demonstrated to be highly associated with advanced AMD, and these
findings have largely been accomplished using AREDS data combined with other data sets. The focus of analysis in AREDS, beyond the clinical trial results, was to provide a better understanding of the natural history and risk factors for both cataract and AMD. For cataract, the researchers published a classification system for grading lens opacity severity along with an analysis of the reproducibility of this cataract grading system. Also, within the cohort of AREDS patients at high risk for progression to advanced AMD there was no evidence of clinically important increased risk of AMD progression after cataract surgery. These data have reassured patients with both cataract and AMD that they can choose cataract surgery when it is limiting their visual function without increased risk of AMD progression. A second focus of the AREDS data analysis was on progression of atrophic AMD. Individuals with drusenoid retinal detachments are at high risk of vision loss and the development of central geographic atrophy. This group turned out to also be at higher risk for development of choroidal neovascularization than had been previously appreciated. The group demonstrated that geographic atrophy (GA) develops in the exact retinal areas that are involved with large drusen more than 90% of the time and that on average it takes about six years from the onset of the large drusen to the eventual development of GA in that area, with a typical progression sequence being the development of large drusen, followed by areas of hyperpigmentation and eventual hypopigmentation that eventually, but not always, leads to GA. This full sequence from large drusen to GA occurs relatively infrequently with the more common sequence being the disappearance of the large drusen with either some relative hypopigmentation in that area or no definite visible change to the underlying retina and retinal pigment epithelium.

Additional data analysis has quantified the risk of progressing to GA based on the severity of large drusen and associated pigmentary abnormalities. This finding was expanded by demonstrating that the development of medium size drusen appears to be the hallmark of the initiation AMD. The presence of small drusen alone appears to be necessary, but not sufficient, for developing AMD. Focusing on factors that lead to progression as well as developing outcome variables for early stages of AMD will be critical as we attempt to find ways to prevent development of AMD. On average, after development of bilateral medium size drusen, it takes five years to develop large drusen and an additional five plus years on average to develop late AMD. Using AREDS data a model was developed to estimate the risk of progression to advanced AMD depending on phenotypic, genetic and environmental risk factors. The most predictive risk factors are the presence of large drusen or pigmentary changes in one or both eyes, with added risk depending on genetic status and personal risk factors such as smoking history and amount of body fat. These data can be helpful in discussing risks with individual patients and also in identifying eligibility criteria for “at-risk” cohorts for clinical trials. AREDS researchers continued to expand understanding of the association of dietary risk factors, especially lutein and dietary omega-3 long-chain polyunsaturated fatty acid intake, in observational cross-sectional and incidence analyses from AREDS, and increased the ability to associate phenotypic changes with genetic polymorphisms.

In 2006, NEI initiated the Age-Related Eye Disease Study, Age-Related Eye Disease Study 2 (AREDS2) study. AREDS2 was designed as a multi-center, randomized trial designed to assess the effects of oral supplementation of macular xanthophylls (lutein and zeaxanthin) or long-chain omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) on the progression to advanced AMD. In prior observational studies, increased dietary intake of some or all of these nutrients had been linked to a reduced risk of advanced AMD.

A secondary goal of AREDS2 was to determine if changing beta-carotene and zinc levels in the original AREDS formulation affected the risk of advanced AMD. The investigators tested the effects of eliminating beta-carotene, which some studies have shown may increase the risk of lung cancer in smokers. Only participants who were non-smokers or former smokers were eligible to receive beta-carotene in AREDS2. The investigators also tried lowering the dose of zinc. In the original AREDS study, the dose was set high because a previous small trial had found that high-dose zinc was beneficial for AMD. However, some nutritionists were concerned the dose was too high.

More than 4000 people, ages 50 to 85 years, who were at risk for advanced AMD participated in AREDS2 at 82 clinical sites across the country. There were four main treatment arms to the trial: (1) control/AREDS formulation only, (2) lutein/zeaxanthin added to the formulation, (3) DHA/EPA added, and (4) lutein/zeaxanthin and DHA/EPA added. All participants were offered additional treatment with the study formulation used in AREDS. For those who elected to take this additional supplement, which is now considered the standard of care, further randomization occurred to evaluate the possibility of deleting beta-carotene and decreasing the original levels of zinc in the formulation for the treatment of AMD. Adding omega-3 fatty acids did not improve on the AREDS formulation.
The plant-derived antioxidants lutein and zeaxanthin also had no overall effect on AMD when added to the combination; however, they were safer than the related antioxidant beta-carotene. The AREDS2 study also offers the promise of providing researchers with data that may prove invaluable in discovering pathological mechanisms underlying AMD. In particular, the AREDS2 study aims to link genome sequence data to eyes with more severe phenotype data than what was originally included in the original AREDS study. As the largest natural history study of AMD, with 95% follow-up and a large data base of systematically collected data including fundus and lens photographs, it will continue to be an important resource for decades just as the ETDRS data continue to be used today a quarter of a century after the study ended. Complete AREDS2 genetic and phenotypic datasets will be made available to the entire vision research community soon.

Comparing Antiangiogenic Therapeutics

Bevacizumab (Avastin) and ranibizumab (Lucentis) revolutionized the treatment of neovascular AMD (nAMD) by targeting the pro-angiogenic vascular endothelial growth factor-A (VEGF-A) protein. Genentech, the maker of both drugs, originally developed bevacizumab to prevent blood vessel growth that enables cancerous tumors to develop and spread. In 2004, the FDA approved bevacizumab for the systemic treatment of metastatic colon cancer. Genentech later developed ranibizumab, derived from a protein similar to bevacizumab, specifically for injection in the eye to block blood vessel growth in AMD. Although ranibizumab was for years the only anti-VEGF therapeutic approved for the treatment of nAMD, extensive off-label use of the cheaper therapeutic bevacizumab by clinicians prompted NEI to formally study the two drugs in a clinical setting. In 2008, NEI launched the multicenter Comparison of AMD Treatments Trial to both compare the efficacy of bevacizumab and ranibizumab and compare the efficacy of monthly and as-needed administration schedules in nAMD patients. The study reported results for 1185 patients treated at 43 clinical centers in the United States. Patients were randomly assigned and treated with one of four regimens for a year. They received either bevacizumab or ranibizumab monthly or as needed. The trial found that both drugs were equally effective in halting neovascularization and visual function loss in nAMD patients and that both treatment schedules were equally effective in preventing vision loss. These findings enabled clinicians to make better-informed decisions when treating nAMD patients and have allowed for substantial monetary savings to both patients and taxpayers by reducing copays and Medicare reimbursements, respectively.

Current Work: Identifying Robust Biomarkers for Disease Progression

Assessing the State of the Science

In 2015, NEI formed the AMD Pathobiology Working Group, an interdisciplinary group that reports to the National Advisory Eye Council (NAEC) and served to evaluate the state of the science in AMD research and research opportunities in the context of emerging science. The AMD Pathobiology Working Group, composed of nine investigators spanning both basic and clinical areas of expertise, tackled the gaps and opportunities in AMD from multiple perspectives. The AMD Pathobiology Working Group held in-person meetings and made several presentations to the NAEC. They provided, at a high level, biological insight into AMD that may be used in future clinical studies. Feedback from the AMD Pathobiology Working Group has identified several major challenges for the AMD community. For example, the working group stressed that the field does not fully understand how genes and pathways implicated in AMD via genetic studies contribute to the disease process over time and at the cellular level. Also, the working group stressed the need to diagnose, track disease progression, and treat patients at earlier disease stages. Discussion of ways to address these challenges include supporting functional and integrative approaches to put genes and pathways together (e.g., systems biology approaches), improving access to high-quality ocular tissue, and developing biomarkers for early-stage disease changes than can be imaged in vivo in AMD patients.

Understanding Early-Stage Disease

For patients to be diagnosed with AMD, drusen >63 μm in diameter must be present; traditionally, the confluence of these drusen determine whether AMD is progressing, i.e. moving from early to intermediate disease stages. Unfortunately, clinicians do not have any biomarkers for predicting progress to either GA or nAMD. The previous identification of reticular pseudodrusen, in conjunction with the advent of modern imaging technologies like OCT, may present clinicians with a potentially informative biomarker. Unlike other drusen, reticular pseudo-
drusen are subretinal deposits of extracellular material that form in the subretinal space of certain AMD patients. Furthermore, earlier work indicates reticular pseudodrusen may have a high degree of correlation with advanced disease stages.

NEI has recently launched a new clinical study called the AMD Ryan Initiative Study, the purpose of which is to unravel the clinical evolution of early AMD and the importance of reticular pseudodrusen in predicting progression to advanced disease. The study will take place across 20 international clinical centers and will enroll 500 patients (200 early AMD patients with bilateral medium sized drusen, 200 patients with reticular pseudodrusen in the absence of large drusen, and 100 age-matched controls without disease) 50 years of age or older. The study protocol includes a blood draw, imaging with color fundus photographs, ultra-wide field color fundus photographs, OCT, scotopic microperimetry, and dark adaptation for participants annually with five-year follow-up.

In addition to evaluating the predictive value of reticular pseudodrusen, the NEI is also conducting a study of dark adaptation in participants with AMD. Because AMD patients have little change in visual acuity in early and intermediate disease stages, the identification of a biomarker for visual function would be invaluable to clinicians. Preliminary work at NEI suggests AMD patients in earlier disease stages, especially those with reticular pseudodrusen, may have impaired dark adaptation compared to age-matched controls. That study is focusing on natural history and is currently still recruiting. In the future, a subset of these study participants will have follow-up testing with vitamin A to probe its effects on the physiology of the visual system.

**Future Work: Target Identification And Therapeutic Testing**

**Expanding DRCR.net to AMD**

In 2002, NEI formed the Diabetic Retinopathy Clinical Research Network (DRCR.net) as a collaborative network for multisite clinical trials for drugs targeting diabetic retinopathy, diabetic macular edema and associated conditions. The Network involves community-based practices, as well as “academic” or university-based centers. It also encourages collaboration with industry to facilitate investigations and pursue opportunities otherwise not possible and to do so in a manner consistent with the Network’s dedication to academic integrity and optimal clinical trial performance.

The Network supports the identification, design, and implementation of multicenter clinical research initiatives focused on retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well. In 2018, the Network expanded its scope beyond diabetic retinopathy to research on other retina disorders, including AMD, and the name was changed to the DRCR Retina Network in April of 2019. The Network currently includes more than 160 participating sites with more than 500 physicians throughout the United States and Canada. Funding for the DRCR.net is through the NEI and The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored cooperative agreement and the current award period is from 2019 to 2023. The DRCR.net is an effective model for planning, organizing, conducting, and reporting collaborative clinical studies. Through DRCR.net, NEI has leveraged federal funding to partner with industry and with foundations to conduct important studies that produce evidence to guide clinical practice and change the care of patients. Expansion of DRCR.net offers an expansive infrastructure comprising retinal special specialists at both community and university-based practices to clinical researchers testing therapeutic interventions for AMD.

**Targeting Inflammation as a Driver of Disease**

AMD has long been understood to possess an important inflammatory component, but currently no anti-inflammatory agents have approval from the Food and Drug Administration (FDA) for treatment of this disease. Gene therapy approaches directly targeting complement activation have also so far failed to significantly slow vision loss, prompting many in the field to look for additional molecular and cellular targets for anti-inflammatory intervention. Microglia, the primary resident immune cell type in the retina that have been implicated in AMD pathobiology, may be a cellular target for approved pharmacological agents. A Phase I/II multi-center trial aiming to repurpose minocycline, an FDA-approved anti-inflammatory agent that modulates microglia, is currently recruiting GA patients. This anti-inflammatory approach dovetails with other complement inhibition efforts in the extra-mural community (e.g., APL-2 inhibition of C3).
Patching Bruch’s Membrane With Retinal Pigment Epithelium (RPE) on a Membrane

Epidemiology, clinical standardization, genetic analyses, animal models, biomarker identification and discovery approaches to cellular pathways are not the only research approaches NEI is supporting to elucidate AMD pathobiology. Stem cells and regenerative medicine are also tools in this AMD arsenal. In 2013, an NEI intramural team won a National Institutes of Health (NIH) Common Fund Therapeutic Challenge Award to support the development of induced pluripotent stem cell (iPSC)-derived RPE-patches for use in a Phase I/IIa clinical study involving AMD patients. This team accomplished a technological breakthrough in developing the ability to grow RPE on three-dimensional poly lactic-co-glycolic acid–based biodegradable scaffolds to be used in transplantation. The group has also streamlined the manufacturing process to generate transplant-ready clinical-grade RPE cells from AMD patient induced pluripotent stem cells. This team has successfully used an immunocompromised rat model for safety, toxicity, and tumorigenicity studies. A proof-of-concept animal study in the pig using human RPE was also completed with a positive outcome, demonstrating rescue of photoreceptor cells after laser injury to the pig retina.\(^{57,58}\) Based on these two animal models, the group completed preclinical animal toxicity, efficacy, and transplantation device compatibility studies and subsequently obtained FDA approval for a Phase I/IIa investigational new drug trial that will enroll patients for therapeutic intervention (transplantation) by the end of 2020.

Launching a Resource for the AMD Research Community

In a bold effort to build on the AREDS and AREDS2 investments, the NEI has taken the first important steps to correlate clinical disease phenotype in a cellular model with patient genotype and imaging information in the newly created AMD Integrative Biology Initiative. Fundamental to this effort is making available to the research community iPSC and iPSC-derived RPE cells (iPSC-RPE), where the iPS cells come from AREDS/AREDS2 participants with specific genetic risk factors for AMD. Although this project originated in the NEI intramural Research Program, a key component was the establishment of an external committee of experts representing all facets of AMD biology, as well as experts in other nonvision neurodegenerative diseases. This undertaking, done in partnership with the New York Stem Cell Founda-

tion (NYSCF), will involve a cohort of 66 AREDS2 patients (chosen based on known AMD risk alleles). iPSC lines, generated at NYSCF, and the accompanying genomic and phenotypic data will be made widely available to the research community.

Additionally, access to the AREDS2 iPSC cell lines and the patient datasets will be contingent upon data sharing agreements designed to facilitate faster target discovery and other basic research efforts. In addition to iPSC cell line validation, functional analyses of the patient iPSC-RPE in quantitative assays examining drusen-like particles, autophagic pathways, inflammatory cytokine secretion, shape, pigmentation, and other structural features will also enable a comprehensive analysis of RPE physiology paired with genotype information.\(^{59}\) NYSCF has completed the first ten cell lines, and some of the isogenic control lines (2/10) have been completed and are in the process of being validated. By statute, these iPSC lines cannot be directly used in humans or for any diagnostic, prognostic, or treatment purposes. They can, however, be utilized for research purposes. Requestors will be required to submit a research project when requesting the lines. NYSCF and NEI will use common identifiers to link the iPSC lines at NYSCF repository with their respective genomic and phenotypic data on an NIH bioinformatics platform. The data from the AMD Integrative Biology Initiative will be housed on the NEI Data Commons, which will have a link to this initiative. NEI is taking advantage of the NIH Biomedical Research Informatics Computing System (BRICS), which can combine different data sets (clinical, demographic, genetic, images). BRICS has the ability to query, join, filter, and export for analyses. It also allows researchers to contribute new data to the database. BRICS can also be used to identify and request samples based on specific clinical phenotype and genotype criteria. Data including medical history, nutritional history, eye examination, and more will be required to submit a research project when request-

Conclusions

With AMD’s prevalence expected to double by 2050, the public health burden demands a multi-
pronged approach by NEI and the biomedical research community. Although several common complex eye diseases rob patients of vision, NEI’s longstanding investment in AMD research has brought us to the point of being able to direct efforts to make a significant push to develop new therapies. To be successful in treating and preventing AMD, we must tackle the problem along the continuum of supporting basic biology to clinical work and back again. The advent of regenerative medicine and iPSC technologies, coupled with advances in clinical imaging, analytical, and other advanced technology herald a new frontier in vision research.

Acknowledgments

Disclosure: C. Wright, None; A.E. Mazzucco, None; S.M. Becker, None; P.A. Sieving, None; S.J. Tumminia, None

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