Advancing Therapeutic Development for Dry Age-Related Macular Degeneration (AMD): Workshop in Brief

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Age-related macular degeneration (AMD) is the leading cause of blindness among white Americans and others of European descent, with lower prevalence among those of Asian, Latino, or African ancestry. The overall prevalence of AMD is approximately 8.7 percent worldwide and is expected to rise to 196 million people worldwide by 2020 and 288 million by 2040 (Wong et al., 2014). AMD typically affects people age 50 and older, and the prevalence increases with age, particularly after the age of 75.

Paul Sieving, Director of the National Eye Institute (NEI) of the National Institutes of Health (NIH) noted that AMD is one of the leading causes of suffering as individuals grow older, yet there are currently no treatments available for the most common form of AMD, dry AMD. Advancements in drug discovery and development have been limited and slow due to issues surrounding disease characterization, surrogate endpoints, and clinical trial design, according to Cynthia Grosskreutz, Global Translational Medicine Head for Ophthalmology at Novartis Institutes for Biomedical Research, Inc. Given the urgency of developing new treatments for this common disease, the Institute of Medicine's Forum on Neuroscience and Nervous System Disorders convened a workshop on November 15, 2014, to bring together key stakeholders from industry; academia; NIH, including NEI; the U.S. Food and Drug Administration (FDA), and patient advocacy groups to discuss opportunities for advancing drug development for dry AMD.

Phenotypic and Genotypic Heterogeneity

AMD affects the macula, resulting in a loss of central vision, noted Emily Chew, Deputy Director of the Division of Epidemiology and Clinical Applications at NEI. Two forms of AMD exist: the most common, dry (non-exudative) type, and the wet (exudative) type. Dry AMD typically progresses from an early, mostly asymptomatic phase—observed only by an ophthalmologist as pigment irregularities of the retinal pigment epithelium (RPE) and the presence of small deposits comprised of lipids and proteins called drusen—through intermediate and then the later stages of geographical atrophy (GA) and neovascularization (Luthert, 2010). The discussions at this workshop focused primarily on GA.

Chew noted that several schema for characterizing and grading the phenotypic characteristics of AMD have been developed. In an effort to develop standardized classifications in the field, the Arnold and Mabel Beckman Initiative for Macular Research established a committee of AMD experts that employed a modified Delphi process to develop a clinical classification scheme. The committee is in the process of developing a second, more scientific system that incorporates results from imaging studies and other technologies (Ferris et al., 2013; see Table 1). Development of these systems also involved analysis of data from the Age-Related Eye Disease Study (AREDs), stated Chew.

Chew showed how retrospective fundus photographs from AMD patients suggest that drusen are a precursor to GA. These photographs demonstrate that as the disease progresses, small drusen converge into large confluent drusen with hyperpigmentation (See Figure 1). This is usually followed by hypopigmentation. In some cases, drusen regress in size as refractile deposits appear, stated Chew. Progression from large confluent drusen to GA takes

TABLE 1 Proposed AMD Clinical Classification

Classification of AMD	Definition (lesions assessed within 2 disc diameters of fovea in either eye)
No apparent aging changes	No drusen No AMD-RPE abnormalities*
Normal aging changes	Drusen <63Q (drupelets) No AMD-RPE abnormalities*
Early AMD	Medium drusen (63-125Q) No AMD-RPE abnormalities*
Intermediate AMD	Any Large Drusen (>125Q) Any AMD-RPE abnormalities*
Late AMD	Either or both: Neovascular AMD Any geographic atrophy

* Thought to be related to AMD (at least medium drusen).

SOURCE: Chew presentation, November 15, 2014; adapted from Ferris et al., 2013.

approximately 6.5 years, during which time the patient experiences gradual visual loss, dark adaptation abnormalities, difficulty reading, and problems with face recognition, she added.

Alternatively, the neovascular form of AMD may develop, probably in response to pro-angiogenic factors, said Chew. Another characteristic often seen in the eyes of AMD patients are reticular pseudodrusen, a yellowish-white material that appears as material under the retina organized in ill-defined networks of broad interlacing ribbons. Chew noted that retinal pseudodrusen are a sign of retinal dysfunction and appear to be a risk factor for late AMD, although they may also occur in individuals who do not have AMD.

The etiology of AMD appears to be strongly influenced by both genetic and environmental factors, said Johanna Seddon, Director of the Ophthalmic Epidemiology and Genetics Service and Professor of Ophthalmology at Tufts University. A study of twins enrolled in the National Academy of Sciences–National Research Council World War II Veteran Twin Registry established that genetic factors explain between 46 percent and 71 percent of the overall severity of AMD (Seddon et al., 2005). According to Seddon, nongenetic factors that play important roles include cigarette smoking, diet, and obesity. The interaction of lifestyle and genetic factors likely contributes to the development and progression of AMD through a variety of genetic pathways that are only beginning to be understood, she added.

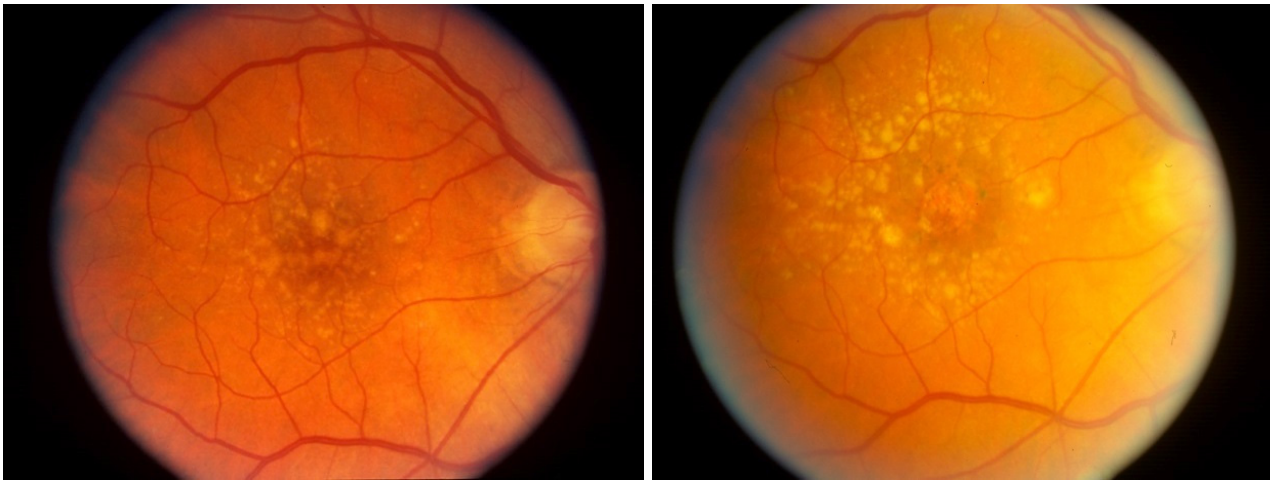

FIGURE 1 Clinical example of GA development. Baseline (left), onset of GA (right).

SOURCE: Chew presentation, November 15, 2014.

Cardiovascular, immune, and inflammatory biomarkers associated with AMD point to mechanisms that may explain the influence of environmental factors on AMD progression, noted Seddon. These biomarkers include C-reactive protein, a marker of inflammation, and homocysteine, an amino acid that adversely affects the vascular endothelium. Other genetic factors have been linked to AMD through Genome Wide Association Studies, she added. According to Seddon, several studies indicate that genes involved in complement regulation, lipid metabolism, extracellular matrix remodeling, and angiogenesis are associated with advanced AMD. Further studies with next-generation sequencing methods have identified rare variants of genes in the complement pathway that might have an even stronger effect on AMD progression, she added. Predictive modeling of disease progression indicates that a combination of rare and common variants might improve the accuracy of risk assessment. Seddon stated that these models may be used as inclusion criteria for clinical trials and may help explain differences in treatment response.

From Target to Therapy

Genetic studies have yielded a number of biological pathways that could be targeted for drug development, yet the pathobiology of the disease remains poorly understood and is likely multifactorial, stated Grosskreutz. Several workshop participants noted that treatment may require engagement of multiple targets. Challenges in the preclinical space include the paucity of good animal models and the difficulty of assessing pharmacokinetics in the target tissue, noted Grosskreutz. Other hurdles exist with regard to the tractability of clinical trials. In addition, Grosskreutz stated that slow disease progression results in long trials, and heterogeneity in the rate of progression requires large numbers of patients. She noted that clinical trials for GA typically use a 12-month endpoint (visual acuity) and thus, even if no other roadblocks are encountered, typically require about 11 years to move from first-in-human Phase I studies through confirmatory Phase III studies leading to a new drug application. For a novel compound requiring extensive preclinical studies, the drug development pathway could stretch to 18 or more years she added. Several workshop participants noted that expediting drug development will require staged development and sequential de-risking of the drug development pathway. For example, Grosskreutz suggested speedier, small-scale proof of concept (Phase IIa) studies to enable a preclinical hypothesis to be tested to determine a compound's therapeutic benefit, lack of benefit, or toxicity. Reducing variability in such trials will require better endpoints with higher sensitivity for detecting change or larger numbers of patients, she added. Enriching the study population for individuals at high risk of rapid progression, or accepting less statistical power, e.g., through higher tolerance of type I or type II errors, might enable more rapid determination of whether to move forward, noted Grosskreutz. According to a few workshop participants, testing multiple dosing regimens in a Phase IIa trial as well as in the confirmatory Phase III trial might also expedite drug development. Grosskreutz noted that more sensitive anatomic and functional endpoints, and ideally a surrogate marker, are also needed for confirmatory trials. These endpoints should reflect changes that are clinically meaningful, she added.

Anatomical and Functional Endpoints

Assessing the presence and progression of GA from an anatomical perspective requires quantifying the total area affected as well as the location of atrophy, particularly relative to the foveal center, said Cynthia Toth, Professor of Ophthalmology at the Duke University School of Medicine. Various complementary *in vivo* imaging methods are used, including color photography using multi-spectral visual or infrared or wide field imaging, flurorescein angiography, fundus autofluorescence (FAF), and optical coherence tomography (OCT). According to Toth, each of these methods has strengths and weaknesses; the challenge lies in extracting qualitative and quantitative data and mapping these data to a patient's genotype and disease history.

Color fundus photography is the classical endpoint used in many trials and natural history studies but suffers from poor reproducibility and interference from cataracts, said Toth. Fluorescein angiography requires intravenous injection, making it useful for examining leakage but impractical for large studies. FAF allows for automated

measurements; however, blue light FAF may be affected by natural darkening at the foveal center, she added. In addition, blue FAF is uncomfortable for some subjects because of bright illumination of the retina. Wide field autofluorescence is a newer method not yet fully tested to determine its usefulness for clinical studies. Toth noted that OCT has shown promise in evaluating both retinal and choroidal morphology in GA. It allows examination and quantification of changes in the retinal layers, including the loss of photoreceptors and RPE. Toth added that it will be important to further define the relationship between FAF and OCT regarding the extent of retinal atrophy. In addition, she noted the need to better define anatomic descriptors of retinal changes in eyes with GA that are reproducible across larger populations.

With a long tradition of research, the availability of standardized protocols, and demonstrated correlation with success in daily activities, David Birch, Chief Scientific and Executive Officer of the Retina Foundation of the Southwest, noted that the gold standard functional measure for assessing AMD progression has been best corrected visual acuity (BCVA). An electronic version of the Early Treatment for Diabetic Retinopathy has made it quicker and easier to assess BCVA and has been widely used in clinical trials. However, Birch stated that visual acuity lacks sensitivity for assessing AMD in early stages. Noting that people with GA have increased visual impairment in dim light, a low luminance visual acuity (LLVA) test was developed simply by placing a neutral density filter in front of the eye. Low luminance deficit has been shown to predict subsequent visual loss, and LLVA captures foveal functional deficits better than BCVA in intermediate and advanced AMD, but not control patients, said Birch. He noted that another technique, microperimetry, performs even better in assessing central retinal sensitivity in early stages of AMD, yet a few workshop participants noted that microperimetry tests may be redundant (particularly mesopic microperimetry) and burdensome for patients. However, Birch noted that scotopic microperimetry has shown promise. The technique is used to measure rod sensitivity, which has shown to be anatomically affected early in AMD. Dark adaptometry represents another approach with diagnostic potential; however, its use has been limited because of substantial patient burden. According to several participants, many of these functional assessments might be used for proof of concept and to test mechanisms of action of drugs in clinical trials, even if the assessments themselves do not become FDA-approved endpoints.

A multimodal approach including both anatomical and functional measures may be necessary to evaluate progression of disease in clinical trials; however, further phenotype/genotype studies will be needed to determine the best options, said SriniVas Sadda, Professor of Ophthalmology at the David Geffen School of Medicine, University of California, Los Angeles, and Director of the Doheny Image Reading Center. In addition, different types of assessments serve different purposes, he added. For example, functional endpoints may lack sufficient precision for short studies but correlate better with quality of life and thus may be useful in registration trials.

Patient-Reported and Performance-Based Outcome Measures

Several workshop participants noted that patient-reported outcome measures and performance-based tests (PROs and PBTs) have taken on an increasingly important role in clinical trials as regulators and payers demand that any demonstrated anatomic, physiologic, or functional benefits be clinically meaningful for patients. PRO measures typically use rating scales consisting of multiple items that are ranked by the patient according to the level of difficulty, said Robert Massof, Professor of Ophthalmology and Neuroscience at the Lions Vision Research and Rehabilitation Center, and Wilmer Eye Institute at The Johns Hopkins University School of Medicine. For example, the Visual Function 14 (VF-14) is a 14-item questionnaire of functional impairment that asks patients to describe the level of difficulty they experience in activities such as reading small-print labels or recognizing faces. The items on the questionnaire serve as standard references against which each patient is compared. Functional ability is the latent variable that is being measured. Each patient has some level of functional ability, which is termed "person measure," whereas the "item measure" is the average level of functional ability that is required to perform the activity in the questionnaire based on the overall population. The difference between the functional ability of the patient, the patient's interpretation of the item, and what the activity requires is called the functional reserve. Massof noted that if the field is going to measure visual function using questionnaires, the items first have to be

calibrated based on the population of interest. Furthermore, Massof added that it will be important to measure the variable rather than the summation of raw scores, which can be individualized for both the instrument and the patient due to missing data (e.g., skipped items on the questionnaire, which would distort the measure). PBTs, in contrast, provide more objective measures of functional abilities that are important to patients said Gary Rubin, Helen Keller Professor of Visual Rehabilitation at the Institute of Ophthalmology, University College London. For example, a chief complaint of patients with visual impairment is difficulty reading; thus, a number of reading performance tests have been developed, including the MNREAD acuity chart and the International Reading Speed Test. The validity of these tests in predicting reading performance in real-world conditions has been demonstrated by the Salisbury Eye Evaluation study, noted Rubin. These measures may be particularly useful in identifying a state of preclinical disability, he added. The differences in these various outcome assessments point to their utility at different stages of the drug development process. Anatomical and functional tests of vision are useful in understanding mechanisms and monitoring progression and therefore are likely most useful in first-in-human and proof-of-concept studies, while PROs and PBTs can provide complementary information regarding the impact of the disease on the patient, noted Sadda. However, no PROs have been validated for GA at this time.

Clinical Trial Design and Regulatory Requirements

In designing clinical trials for GA treatments, anatomic endpoints offer the lowest variability, noted Wiley Chambers, Deputy Director of the Division of Transplant and Ophthalmology Products, Center for Drug Evaluation and Research, FDA. Moreover, preserving structures needed for visual function, such as photoreceptors, should have a benefit to the patient, said Chambers. He noted that a precedent was set by the FDA when it accepted an anatomic endpoint for the treatment for cytomegalovirus (CMV) retinitis: preservation of an intact photoreceptor border, even in the absence of an effect on visual acuity. Chambers said that functional endpoints may also be acceptable if they enable the sponsor to show either statistically significant improvement or prevention of loss of visual function and that PROs may also be a legitimate endpoint for which the FDA has issued a guidance (FDA , 2009). However, PROs have not yet been used in ophthalmology trials.

Since there appear to be multiple causes of GA, therapy may require tackling multiple targets either with a single or multiple compounds, noted Chambers. The FDA has published a guidance on co-development, which is defined as the development of two novel compounds that are intended to be used together rather than as add-ons to existing therapies (FDA, 2010). This guidance stipulates that each component must contribute to the effectiveness of the combination and outlines a high-level roadmap for clinical studies. Recognizing that co-development adds complexity and thus time to the drug approval process, the FDA has signaled flexibility with regard to study design as well as the amounts and types of data needed for approval of a co-developed therapy (Woodcock et al., 2011).

Lessons from drug development for other diseases can be applied to development of treatments for GA, said William Potter, Senior Advisor at the National Institute of Mental Health. For example, drug development for Alzheimer's disease (AD) has faced similar challenges as those facing the AMD field. In particular, Potter cited the need to intervene early in a slowly progressing disease, the lack of validated measures to detect early disease and clarity with regard to pathophysiology, the apparent need to attack multiple targets, and the lack of effective treatments. As a result of these and other challenges, many Phase III failures have cast a pall over AD drug development, prompting the search for new strategies that might de-risk the process, he stated. In particular, the field has recognized the need for collaborative precompetitive efforts to develop and standardize biomarkers, develop new mechanistic models, and share data from clinical trials.

Philip Rosenfeld, Professor of Ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, noted that the therapeutic goals for dry AMD treatment also resemble those for AD: slowing or preventing impairment. In AD as in AMD, designing efficient clinical trials with smaller populations requires enriching study populations with patients likely to show benefit from the treatment approach. Thus, the selection of enrichment criteria must be based on the primary outcome endpoint selected for the trial, Rosenfeld added. For example, if an anatomic endpoint is used in a GA treatment trial, phenotypic enrichment could be accomplished by selecting subjects on the basis of autofluorescence patterns, disruption or atrophy of

photoreceptors demonstrated with OCT, low luminance deficits, findings from microperimetry or dark adaptation studies, or other markers.

Genotype may also be useful as an enrichment criterion; however, this will require a refined understanding of genotype-phenotype associations, said Gregory Hageman, Director of the Moran Center for Translational Medicine and John A. Moran Presidential Professor of Ophthalmology and Visual Sciences at the University of Utah School of Medicine. Again as in AD, the underlying biology of the disease is complex and only partially understood. Daniel Martin, Chairman of the Cleveland Clinic Cole Eye Institute cautioned that enriching subject populations carries with it certain hazards with regard to the generalizability of outcomes and labeling issues for an approved drug.

Filling the Gaps

The purpose of the workshop was to catalyze discussion and further develop the field's understanding of opportunities to move forward in the development of effective treatments for dry AMD, particularly for GA. A number of key knowledge gaps were identified that have stymied progress. In particular, several workshop participants noted that more longitudinal, natural history, and deep phenotyping and genotyping studies are needed to define the relationship between phenotype and genotype in order to enable shorter and more efficient clinical trials. A few workshop participants noted that an online centralized data repository could facilitate progress in this area but will require commitment across stakeholders to share data even from failed trials.

As seen in other disease areas, several workshop participants noted that this could be facilitated by collaborative efforts between academia, government (e.g., NIH and NEI), industry, and nonprofit organizations. Although a few participants stated that there is a natural hesitancy for both academic and industry partners to share data and knowledge, as drug development becomes more expensive, even this roadblock may be surmountable, noted Matthew McMahon, Senior Advisor for Translational Research at NEI. According to several workshop participants, consortia such as the Critical Path Institute and TransCelerate Biopharma, Inc., have been created to advance innovation and de-risk drug development by working cooperatively in pre-competitive space. For example, they have worked to create clinical data standards and promote data sharing across multiple disease areas. Other areas that could benefit from a consortium approach include the development, validation, qualification of biomarkers, and building a clinical trial network, noted McMahon. Indeed, one such network has already been created in ophthalmology: the Diabetic Retinopathy Clinical Research Network (DRCR.net), said Martin. Funded by NEI, DRCR.net supports multicenter clinical trials through its network of more than 100 participating sites and more than 320 physicians. Martin added that a similar network, or one built on the DRCR.net foundation, could facilitate greater efficiencies in conducting clinical trials.

The infrastructural requirements needed to build large, sharable databases continue to increase in cost, size, and complexity. These issues further support the need for collaboration across multiple stakeholder groups, noted David Michelson, Vice President of Clinical Neuroscience and Ophthalmology at Merck Research Laboratories. Workshops such as this one represent an opportunity to bring key stakeholders together to develop a unified approach on how best to study and develop effective treatments for dry AMD.

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REVIEWERS: To ensure that it meets institutional standards for quality and objectivity, this workshop in brief was reviewed by **Karl Csaky,** Retina Foundation of the Sourthwest; and **SriniVas R. Sadda,** David Geffen School of Medicine, University of California, Los Angeles, and Doheny Image Reading Center. **Chelsea Frakes,** Institute of Medicine, served as review coordinator.

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