



Developing Treatments for Dry Age-Related Macular Degeneration (AMD) A Workshop

November 15, 2014

National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., N.W., Washington, DC

Background: There is strong interest across many stakeholders to increase progress around developing treatments for dry age-related macular degeneration (AMD), which for the context of this workshop is limited to geographic atrophy. Currently, there are no treatments available for the dry form of AMD. Advancements in drug discovery and development in dry AMD have been limited and slow due to issues surrounding disease characterization, surrogate endpoints, and clinical trial design. Given the pressing need for progress in the field, this workshop will bring together key stakeholders from industry, government agencies like NIH and FDA, academia and patient advocacy groups to discuss opportunities for advancing drug development for dry AMD.

Meeting Objectives:

Participants will be invited to:

- Consider scientific opportunities and challenges in speeding drug development for early intervention
- Examine the evidence needed to use clinical endpoints and potential biomarkers as surrogate endpoints in clinical trials, and how to generate that evidence
- Discuss opportunities to improve current and develop new clinical design methodologies
- Explore tangible next steps towards accelerating drug development

8:30 a.m. Opening Remarks & Meeting Goals

MATTHEW MCMAHON, *CO-CHAIR*
Senior Advisor for Translational Research
National Eye Institute

DAVID MICHELSON, *CO-CHAIR*
Vice President
Clinical Neuroscience and Ophthalmology
Merck Research Laboratories

SESSION I: CURRENT LANDSCAPE AND CHALLENGES IN DRUG DEVELOPMENT

Session Objectives: Examine the current therapeutic landscape and explore the challenges that limit drug development. Discuss how the state of the science of basic research is lacking and identify potential mechanisms for accelerating the development process.

8:35 a.m. Dry AMD Phenotype and Genotype

- What is the burden of disease (e.g., functional challenges)?
- What are the defining phenotypic characteristics of the disease?

- Drusen
- Pseudodrusen
- Atrophic AMD
- Geographic atrophy
- What is the impact of phenotypic heterogeneity?

EMILY CHEW
Deputy Director
Division of Epidemiology and Clinical Applications
National Eye Institute

- What is the impact of genotype on disease progression?
- How does genotype improve the understanding disease progression?

JOHANNA SEDDON
Director, Ophthalmic Epidemiology and Genetics Service
Professor of Ophthalmology
Tufts University

9:00 a.m. Drug Development in Dry AMD: From Target to Therapy

- What is the path from target to drug and how could staged development and sequential de-risking improve the process?
- What is required for a viable proof of concept (predictivity, feasibility)?
- What is the confirmatory study (population, duration, endpoint)?
- Where are the gaps today?

CYNTHIA GROSSKREUTZ
Global Translational Medicine Head for Ophthalmology
Novartis Institutes for Biomedical Research, Inc.

9:20 a.m. Panel discussion with Industry Representatives

- What tools and technologies could enable more rapid target identification?
- What advances are needed to enable a staged approach to therapeutic development?
- What are the roles of industry, government, and academia in accelerating therapeutic development?

CYNTHIA GROSSKREUTZ
Global Translational Medicine Head for Ophthalmology
Novartis Institutes for Biomedical Research, Inc.

JASON EHRLICH
Group Medical Director, Ophthalmology
Genentech, Inc.

CEDRIC FRANCOIS
Co-Founder & Chief Executive Officer/President
Apellis Pharmaceuticals, Inc.

MICHAEL SCHWARTZ
Senior Director, Project Leader for GA
GlaxoSmithKline

JASON SLAKTER
Chief Medical Officer, Ohr Pharmaceutical, Inc.
Founder & Director, Digital Angiography Reading Center

9:50 a.m. BREAK

**SESSION II: EVALUATING ANATOMICAL AND FUNCTIONAL ENDPOINTS AND
PATIENT REPORTED OUTCOME MEASURES**

Session Objectives: Explore challenges and opportunities associated with developing anatomical and functional endpoints and evaluate patient reported outcome measures. Consider how standardization of endpoints and patient outcome measures might facilitate progress for drug development. Discuss mechanisms by which standardization could be achieved and consider how alternative modalities could be applied to interpret and evaluate endpoints and measures.

10:05 a.m. Session Objectives

CYNTHIA OWSLEY, *SESSION CO-CHAIR*
Vice Chair of Clinical Research
Department of Ophthalmology
University of Alabama at Birmingham

PHILIP ROSENFELD, *SESSION CO-CHAIR*
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami

10:10 a.m. **Anatomical and Functional Endpoints: Challenges and Opportunities**

Rapporteur: SRINIVAS SADDA
Professor of Ophthalmology
Director, Doheny Image Reading Center
Doheny Eye Institute
David Geffen School of Medicine
University of California – Los Angeles

10:10 a.m. Anatomical Endpoints

CYNTHIA TOTH
Professor of Ophthalmology
Duke University School of Medicine

10:25 a.m. Functional Endpoints

DAVID G. BIRCH
Chief Scientific & Executive Officer
Director, Rose-Silverthorne Retinal Degenerations Laboratory
Retina Foundation of the Southwest

10:40 a.m. Group discussion

- How have anatomy and function been correlated?
- What strategies are being used to measure lesion growth (e.g., imaging)?
- How could evaluation of surrogate endpoints be standardized?
- How could other tools be applied to visualize endpoints?
- What is the predictive value of anatomical and functional markers for clinical outcomes?

11:10 a.m. Summary by the Rapporteur

11:15 a.m. **Patient Reported Outcome Measures**

Rapporteur: SUSAN VITALE
Research Epidemiologist
Division of Epidemiology and Clinical Applications
National Eye Institute

11:15 a.m. Self-Reported Outcome Measures

ROBERT MASSOF
Founder & Director
Lions Vision Research and Rehabilitation Center
Professor of Ophthalmology and Neuroscience
Johns Hopkins University School of Medicine

11:30 a.m. Performance Outcome Measures

GARY RUBIN
Helen Keller Professor of Visual Rehabilitation
Institute of Ophthalmology
University College London

11:45 a.m. Group Discussion

- What daily tasks are important to assess in patients?
- How do self-reported and performance measures correlate?
- How can these measures be used to identify markers of early AMD?
- How can patient reported outcomes support (or supplant) regulatory endpoints?

12:15 p.m. Summary by the Rapporteur

12:20 p.m. LUNCH

**SESSION III: EXAMINING REGULATORY REQUIREMENTS AND
CLINICAL TRIAL DESIGN**

Session Objectives: Examine the regulatory requirements and clinical trial patient selection process for therapeutic studies. Consider issues related to disease prevention, modification, and symptom improvement in trial design. Discuss opportunities to improve current and develop new methodologies that will reduce the number of patients required and establish reasonable timeframes for providing proof of concept and delivering promising therapies.

1:20 p.m. Session Objectives

JASON EHRLICH
Group Medical Director, Ophthalmology
Genentech, Inc.

1:25 p.m. **Regulatory Requirements**

Rapporteur: KARL CSAKY
T. Boone Pickens Senior Scientist
Retina Foundation of the Southwest

1:25 p.m. Regulatory Perspective on Endpoints and Therapeutic Development

WILEY CHAMBERS
Deputy Director, Division of Transplant & Ophthalmology Products
Center for Drug Evaluation & Research
Food and Drug Administration

1:40 p.m. Group Discussion

- How are surrogate markers assessed as substitutes for clinical endpoints?
- What are the performance characteristics (e.g., effect sizes, variability, time to see change) for proposed markers? How does this correlate with clinical endpoints?
- How are definitive clinical endpoints evaluated?
- How are clinical endpoints viewed in terms of suitability for a novel therapeutic?

2:10 p.m. Summary by the Rapporteur

2:15 p.m. **Clinical Trial Design**

Rapporteur: DANIEL MARTIN
Chairman, Cleveland Clinic Cole Eye Institute

2:15 p.m. Lessons Learned from Alzheimer's Disease

WILLIAM POTTER
Senior Advisor
National Institute of Mental Health

2:30 p.m. The Role of Phenotype in Selectively Enriching Patients for Clinical Studies

PHILIP ROSENFELD
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami Miller School of Medicine

2:45 p.m. The Role of Genotype in Selectively Enriching Patients for Clinical Studies

GREGORY HAGEMAN
Director, Moran Center for Translational Medicine
John A. Moran Presidential Professor
Department of Ophthalmology and Visual Sciences
University of Utah School of Medicine

3:00 p.m. Group Discussion

- What methods could be applied to reduce the length of clinical trials and the number of patients required?
- How could the timeframes for following patients (i.e., longitudinal studies) be improved?
- What enrichment strategies may be beneficial to identify patients at risk for developing AMD and how fast the disease is likely to progress?
- What strategies could be developed to reduce the risk of failure in a definitive study?

3:30 p.m. Summary by the Rapporteur

3:35 p.m. BREAK

SESSION IV: POTENTIAL NEXT STEPS

Session Objectives: Discuss a roadmap forward for researchers who have therapeutics in the pipeline. Identify tangible next steps and consider key stakeholders that could facilitate the process toward advancing drug development.

3:50 p.m. **Potential Next Steps**

3:50 p.m. Session Objectives

MATTHEW MCMAHON, *CO-CHAIR*
Senior Advisor for Translational Research
National Eye Institute

DAVID MICHELSON, *CO-CHAIR*
Vice President
Clinical Neuroscience and Ophthalmology
Merck Research Laboratories

3:55 p.m. Group discussion

1. How could a validation trial be implemented?
 - What are the most reasonable and relevant structural and functional endpoints?
 - What alternative surrogate endpoints could be used that would benefit patients and be less severe from a regulatory perspective?
2. How would a centralized data repository of clinical trial data improve drug development?
 - Which stakeholders would be important to engage?
 - What are potential challenges to data sharing?
3. What would be the best way to implement a natural history study?
 - Who would the critical partners be?
 - What would be a reasonable timeline?

4:55 p.m. Final Remarks

5:00 p.m. ADJOURN