Foreword: Dry Age-Related Macular Degeneration

This special issue of *Investigative Ophthalmology & Visual Science* was developed to give readers a concise update on the current state of investigation and understanding of dry age-related macular degeneration (AMD). Certainly, anti-VEGF therapies have revolutionized the treatment of neovascular AMD and reduced the likelihood of severe vision loss from wet AMD. However, with these therapies, AMD still primarily is being treated late in the disease process, and it remains a leading cause of irreversible blindness in older adults.

This special issue is anchored by six invited articles that help provide a conceptual framework for thinking about development, progression, and treatment of dry AMD. A multicenter collaborative team, including Sean Garrity, David Sarraf, K. Bailey Freund, and Srinivas Sadda, sets the stage with a comprehensive review of "Multimodal Imaging of Nonneovascular Age-Related Macular Degeneration."[1] In this review, the investigators discuss how multiple imaging techniques have had crucial roles in developing a better understanding AMD pathophysiology as well as providing metrics for disease classification and following disease progression and response to treatment.

A thorough understanding of drusen development and evolution, how drusen transition to retina and RPE atrophy, and the cellular mechanisms of geographic atrophy progression would no doubt help in developing novel treatments that could be used earlier in the disease and prevent vision loss. Christine Curcio of the University of Alabama at Birmingham, provides two reviews for the special issue. In "Antecedents of Soft Drusen, the Specific Deposits of Age-Related Macular Degeneration, in the Biology of Human Macula,"[2] Dr. Curcio discusses how subretinal drusenoid deposits (SDDs) mirror the topography of rod photoreceptors in the human macula and proposes that soft drusen and basal linear deposit (BLinD) together represent a similar deposition that is related to foveal cones. In her companion review, "Soft Drusen in Age-Related Macular Degeneration: Biology and Targeting Via the Oil Spill Strategies,"[3] she discusses evidence that major components of soft drusen/BLinD are lipoprotein particles containing apolipoproteins B and E that are secreted by the RPE in the physiologic lipid-recycling process. She proposes that targeting this "oil spill" has the potential to slow progression to geographic atrophy and neovascular AMD.

Cody Fisher and Deborah Ferrington of the University of Minnesota contribute a "Perspective on AMD Pathobiology: A Bioenergetic Crisis in the RPE"[4] to the special issue. In this perspective, they discuss multiple avenues of AMD-associated mitochondrial disruption that compromise mitochondrial function in RPE cells. They also discuss a model of metabolic uncoupling that alters bioenergetics in the retina and drives AMD pathology.

"A Perspective of AMD Through the Eyes of Immunology"[5] is presented by David Copland, Sofia Theodoropoulou, Jian Liu, and Andrew Dick of Bristol and London, UK. This article provides the view that active immune cellular and tissue pathways are necessary for maintaining proper tissue health, but when these immune responses are perturbed or exaggerated, the resulting chronic inflammation is destructive and contributes to cell pathology in dry AMD.

Finally, Mandeep Singh of the Wilmer Eye Institute and Robert MacLaren of the University of Oxford provide a perspective entitled "Stem Cell Treatment for Age-Related Macular Degeneration: the Challenges."[6] In this article, the investigators review completed and ongoing stem cell trials for AMD, discuss the obstacles that must be overcome for such therapies ultimately to be successful, and provide a vision for future ocular stem cell endeavors.

These invited reviews and perspectives are complimented by 15 original research articles submitted to *IOVS* specifically for the Dry AMD special issue. Among these are articles detailing retinal imaging and dark adaptation techniques that can be used to monitor disease progression and follow interventions. Other studies are presented that investigate the importance of choroidal blood flow in AMD as well as the status of geographic atrophy following autologous choroidal grafting. Basic science studies in the issue evaluate AMD-related RPE transition and propose new mouse models for AMD. Additional studies evaluate reading speed in patients with geographic atrophy, the proteomic landscape in AMD, and the association between AMD and osteoporosis.

We would like to thank the authors of the invited articles for their work in providing the reviews and perspectives for the special issue and the many reviewers for their assistance in the publication process of the original research articles. We also would like to thank Don Hood, Editor-in-Chief of *IOVS*, for his support and guidance with this issue, as well as Jon Mallett, Gayle Claman, Marco Stoutamire, Debbie Chin, and the *IOVS* staff for their enthusiasm and hard work in bringing the special issue to the reader.

We hope that the blend of invited and original research articles in this special issue will serve as a "go-to" read for an updated take on dry AMD. We also know that significant challenges remain before we understand the complexities that drive AMD. We suggest that while we understand highly relevant pathways that become dysfunctional, some of which are outlined in this issue, we do not understand the magnitude of their contribution nor the timing of dysfunction during the development and progression of AMD. Thus, we hope that the articles in this special issue will serve to stimulate new ideas that will advance our understanding of this sight-threatening disease.

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