

Looking to the Future of Gene Therapy in Ophthalmology



In a symposium ahead of the AAO Annual Meeting, speakers updated attendees on the status of the field.

BY KOUROUS A. REZAEI, MD

The inaugural Future is Now: Leaders in Ocular Gene Therapy Meeting, focusing on gene therapy in ophthalmology, took place in San Francisco before the AAO Annual Meeting in October. Biotech firms, large pharmaceutical companies, physicians, scientists, and personnel from regulatory, manufacturing, and venture capital were represented at the meeting, with more than 30 speakers on the roster. The sessions were co-moderated by Adrienne Graves, PhD, former CEO of Santen; Eugene de Juan, MD, founder and managing partner of ForSight Labs; Karl Csaky, MD, PhD, T. Boone Pickens Director and Chief Medical Officer, Retina Foundation of the Southwest; and Kourous A. Rezaei, MD, course director.

Innovators of the next generations of transformative treatment approaches for ocular diseases showcased their latest work, offering glimpses of what ophthalmologists, especially retina specialists, may have in their armamentarium in the near future. The spectrum of diseases discussed ranged from orphan inherited retinal diseases (IRDs) with no regulatory-approved treatment options to wet age-related macular degeneration (AMD). In the case of AMD, treatment options exist, but real-world experience does not reflect the levels of success seen in clinical trials due to the burdens associated with repeated

THE FIELD OF GENE THERAPY FACES TWO MAJOR HURDLES: MANUFACTURING ISSUES AND THE COST OF TREATMENTS.

injections. In this area, it is hoped that gene therapies can ease some of those burdens.

The breadth of the data presented, mostly in early-stage clinical trial phases, suggested the potential for a paradigm shift in how patients with ocular diseases may be treated in the next decade. Some of the meeting's highlights are recapped below.

ADENO-ASSOCIATED VIRAL DELIVERY IN GENE THERAPY

Guangping Gao, PhD, president of the American Society of Gene and Cell Therapy and a professor of microbiology and physiological systems at the University of Massachusetts Medical School in Worcester, Massachusetts, spoke about the use of adeno-associated virus (AAV) delivery of gene therapy for eye diseases. He presented in detail the biologic steps involved, from AAV transduction to protein expression inside the target cells. These steps include internalization, early and late endosome formation, and other steps leading to protein expression.

Ken Mills, president and CEO of

RegenxBio, highlighted the potential of subretinal AAV gene therapy for VEGF-related retinal diseases, including wet AMD. Aaron Osborne, chief medical officer for Adverum Biotechnologies, discussed an intravitreal approach with that company's therapeutic candidate for wet AMD. Susan Hill, chief business officer for Gyroscope Therapeutics, discussed her company's gene therapy approach to geographic atrophy in dry AMD, targeting the complement cascade. Magali Taiel, MD, vice president for clinical development at Gensight, which is developing a novel gene therapy for Leber hereditary optic neuropathy, presented preclinical data on the effect of intraocular gene therapy on the contralateral eye.

PIPELINE UPDATE

Tuyen Ong, head of the ophthalmology franchise at Biogen; Sue Washer, president and CEO of Applied Genetic Technologies Corporation; Glenn Sblendorio, MBA, president and CEO of Iveric bio; Christine Placet, CEO of Horama; and Kali Stasi, MD, PhD,



The Future Is Now: Leaders in Ocular Gene Therapy Meeting packed the house before this year's AAO Annual Meeting. EyewireTV was on location to interview a number of speakers from the event. Visit Eyetube to see Eyewire's Ranna Jaraha conduct interviews from the meeting floor.

translational medicine director at the Novartis Institutes for Biomedical Research, each presented updates regarding their companies' gene therapy pipelines for orphan IRDs. They highlighted their companies' innovative treatment approaches for patients who have no approved treatment options.

Some of the orphan IRDs these companies are addressing include X-linked retinoschisis, achromatopsia, rhodopsin-mediated retinitis pigmentosa, *BEST1*-related retinal diseases, and various genetic mutations in retinitis pigmentosa.

LARGE PHARMA AND GENE THERAPY

Pete Adamson, vice president and head of the retinal dis-

ease area stronghold for Janssen; Francisco J. López, MD, PhD, executive medical director of clinical development, ophthalmology, for Allergan; and Christopher Brittain, MBBS, BSc, MBA, MRCOphth, global head of ophthalmology clinical development for Genentech/Roche, each discussed the role of ocular gene therapy in the portfolios of the large pharmaceutical companies they represent.

The speakers agreed that major pharmaceutical companies are interested in playing a key role in developing ocular gene therapies, and that their expertise and experience may help guide the field forward. You can watch interviews with some of the members of this and other sections on Eyetube.

THE ROLE OF VENTURE CAPITAL AND OTHER GROUPS

Hannah Chang MD, PhD, of Wu Capital USA; Gilbert H Kilman, MD, managing partner of InterWest Partners; and Cyrus Mozayani MD, co-founder and CEO of Vedere, shared their thoughts on the factors involved in decision-making for funding of early-stage gene therapy companies and some of the challenges that these companies face.

Benjamin Yerxa, PhD, CEO of the Foundation Fighting Blindness, highlighted the crucial role that this nongovernmental organization has played in the recent past by providing funding and help in moving forward the field of gene therapy. He also

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addressed the foundation's future plans in this effort.

CLINICAL TRIAL DESIGN

Jacque L. Duncan, MD, a professor of ophthalmology at the University of California, San Francisco, presented potential endpoint options for clinical trial assessments evaluating therapies in patients with IRDs. Adaptive optics, which allows imaging of retinal photoreceptors at cellular level, was mentioned as a potential tool to use in clinical trials.

K. Thiran Jayasundera, MD, an associate professor at the Kellogg Eye Center of the University of Michigan, discussed the role and importance of reported patient outcomes in clinical trials, noting that the goal of treatment is to help patients function better, and that outcome measure reports will detail how treatment has affected patients.

Nader Halim, PhD, vice president of strategy for Verana Health, discussed the role of electronic medical data in accelerating the progress of clinical trials. Wiley Chambers, MD, deputy director of the Division of Transplant and Ophthalmology Products for the US FDA, discussed the current regulatory climate surrounding ocular gene therapy and the challenges it faces.

THE REAL WORLD AND GENE THERAPY

Mark Pennesi, MD, PhD, division chief for ophthalmic genetics at the Casey Eye Institute of Oregon Health and Science University, presented real-world data on patients being treated with commercially available gene

therapies and discussed the judgment calls involved in choosing patients who may potentially benefit from gene therapy. Christine Nichols Kay, MD, of Vitreo Retinal Associates in Gainesville, Florida, presented real-world experience with diagnostic genetic testing.

SEEKING ADVANCES IN GENE THERAPY

Andreas K. Lauer, MD, chair of the department of ophthalmology at Casey Eye Institute, discussed subretinal surgery and important factors that may help to optimize outcomes in gene therapy surgery. Dr. Csaky noted that, although gene therapy has come a long way since the early 1990s, it still is in its early stages and there is significant room for improvement. Mark Vezina, scientific director for ocular and neuroscience at Charles River Laboratories, discussed the role of pre-clinical models in gene therapy and the similarities and differences in various models of the human eye.

MANUFACTURING AND COSTS

The field of gene therapy faces two major hurdles: manufacturing issues and the cost of treatments. Although ocular gene therapy does not require a high number of vectors for delivery because the treatment is localized, there are still significant bottlenecks and waiting times to secure slots for gene therapy manufacturing. This problem will probably not be resolved in the near future.

"Gene therapy manufacturing has the challenge of catching up with the

expanding demand," said Deborah Wild, chief of staff and vice president of corporate development at Paragon Gene Therapy, a part of Catalent Biologics.

In one discussion session, an audience member noted that making gene therapy available and paying its costs at a global scale will require new reimbursement models. These are generally one-time treatments that potentially offer a cure rather than requiring lifelong treatment. Other speakers noted that reductions in the costs of clinical trials and manufacturing will be necessary to allow these potentially innovative next-generation treatment options to become available to everyone who needs them.

In summary, this debut meeting demonstrated that significant progress has been made in the field of ocular gene therapy, and an interesting and hopeful future awaits us and our patients. ■

The author wishes to thank the meeting sponsors and the Ingalls Development Foundation for supporting the meeting. To learn more, visit OcularGeneTherapy.com.

KOUROUS A. REZAEI, MD

- Chief Medical Officer, Iveric Bio
- Senior Partner, Illinois Retina Associates, Chicago
- Associate Professor of Ophthalmology, Director of Vitreoretinal Fellowship, Rush University Medical Center, Chicago
- Editorial Advisory Board Member, *Retina Today*
- karezaei@yahoo.com
- Financial disclosure: Course Director, Founder (Future Is Now: Leaders in Ocular Gene Therapy Meeting)