

Summary of the Inaugural PRPH2 and Associated Retinal Diseases Workshop

FOCUS ON THE PRPH2 GENE: DAY 1, MARCH 30

Introductions

The Inaugural PRPH2 and Associated Retinal Diseases Workshop brought together 110 patients, families, scientific experts, and retinal-industry professionals in La Jolla, California, from March 29-31, 2023, to build research momentum and community to overcome vision loss from retinal diseases caused by mutations in the gene *PRPH2*. Hosted by the Nixon Visions Foundation, the Foundation Fighting Blindness, and Shiley Eye Institute at University of California, San Diego (UCSD), the event featured science presentations and discussions from global *PRPH2* experts who covered a wide range of topics — from gene structure and expression, to disease models and manifestations, to therapeutic opportunities.

The event also served as a launching point for a funding initiative sponsored by the Nixon Visions Foundation and the Foundation Fighting Blindness that will provide multiple annual grants to scientific teams addressing high-impact gaps in the field.

Jason Menzo, chief executive officer at the Foundation Fighting Blindness, underscored in his opening remarks that both strengthening relationships and building community were also important goals of the workshop.

The original inspiration for the event came from Brandon Nixon and his wife, Janine, who was recently diagnosed with cone-rod dystrophy caused by a mutation in the *PRPH2* gene. “It was a beautiful morning in September 2020 when Janine couldn’t see the boats on the lake during vacation,” said Brandon during his welcome address to attendees. “We wondered how this happened so fast. Janine didn’t see the theft in process.” Though she had been told by doctors several years earlier that she had tiny spots on her retinas, they told her not to worry about them.

“We realized Janine would lose more central vision — the ability to drive and see the faces of future grandchildren — though today she navigates these hills and valleys with great strength,” Brandon said. “So we embarked on making a difference — to advance science, connect patients and families, and provide emotional support. This conference is our start and never has there been a more promising time in history for driving research.”

Claire M. Gelfman, PhD, chief scientific officer, Foundation Fighting Blindness, along with Radha Ayyagari, PhD, Shiley Eye Institute, UCSD, and Shyamanga Borooah, MBBS, PhD, Shiley Eye Institute, UCSD, served as workshop co-chairs.

PRPH2 PATIENT SURVEY OUTCOMES AND PATIENT PERSPECTIVES

THE *PRPH2* Survey

Todd Durham, PhD, senior vice president, clinical & outcomes research at the Foundation Fighting Blindness, presented results from a survey on the diagnostic journey and impacts from those affected by *PRPH2* mutations.

The 117 respondents whose surveys were included in the results were obtained from the Foundation's My Retina Tracker Registry and other marketing resources, Retina International, and the University of Melbourne.

The mean age of respondents was 58 years old. Most respondents were from the US (90), Switzerland (12), and Australia (10).

Key survey results included:

- The average age of first visual symptoms was 36 years.
- The average age of first diagnosis of a retinal disease was 44 years.
- The average age when *PRPH2* was identified as the associated gene was 51 years.
- 79 percent of respondents had more than one affected family member.
- 80 percent of respondents 50 years old or younger still drive.

The clinical diagnoses of respondents:

Clinical diagnosis	Number
Pattern dystrophy	35
Retinitis pigmentosa	27
Don't know	17
Cone-rod dystrophy	12
Macular dystrophy	9
Stargardt disease	7
Other	6
Macular degeneration	2
Central areolar choroidal dystrophy	1

Impact of retinal disease on patients' daily lives in order of significance (81 total respondents):

Impact	# of respondents
Inability/difficulty driving	31
Reading print	26
Night blindness	16
Recognizing faces	10
Light sensitivity	10
Loss of central vision	9
Loss of peripheral vision	8
Blind spots	7

Work	6
Using computers	6
Floaters, streaks, or other visual phenomena	6

Patient Perspectives

Putting Down the Baseball Bat

In high school, Damon Lembi was a standout baseball player and was drafted twice — by the Atlanta Braves and the New York Yankees. But instead, he played baseball in college at Pepperdine and Arizona State University. Growing up, he saw his father struggle with vision loss from a retinal disease and was aware that he might develop the condition, as well. He ultimately took over his dad’s Learnit business, a company providing workforce development resources.

Damon’s vision seemed okay until 2016, when at the age of 43, he started noticing blind spots in his vision when playing tennis and basketball. Subsequently, his eye doctor told him he had the retinas of an 80-year-old. Genetic testing revealed that a mutation in *PRPH2* was the culprit. Over the last year, his vision loss has progressed.

Damon is heartbroken that he can’t teach his son to play baseball. “But I focus on what I can control,” he said. “Regardless of my vision, my kids will grow up with the best dad.”

After gleaning helpful information about his condition from the Foundation Fighting Blindness, he became a partner with the Foundation, donating training courses for its staff of more than 60.

Eye of the Beholder

Tim Smith grew up watching several of his family members, including his dad, struggle with vision loss from retinitis pigmentosa (RP). When he was diagnosed with the condition at the age of 38, he knew what to expect.

Early in life, Tim also knew he wanted to do something visual. He enjoyed photography and painting, studied art and design, earned a master of business administration, and went on to design brands for several large companies.

In 2014, genetic testing revealed a *PRPH2* mutation was causing his vision loss. That happened to be when he stopped driving, though he has retained good central vision since the diagnosis. He signed up in the My Retina Tracker Registry, hoping to get in a clinical trial.

Tim became president of the Cincinnati-Northern Kentucky chapter of the Foundation Fighting Blindness in 2007 after seeing so many kids affected during the Foundation’s VisionWalk fundraiser. He also serves as board vice chair of the Cincinnati Association for the Blind and Visually Impaired.

Tim and other visually impaired artists organized Eye of the Beholder, an event in which they sell art on a virtual gallery to raise money for the Foundation. The fundraiser was successful, so much so for Tim that he sold the same painting of Lake MacDonald in Glacier National Park twice. He was happy to paint the picturesque image a second time to accommodate the demand.

“Some of the worst things that have happened to us have become our best,” he said in closing. “I think this is it.”

RETINA BIOLOGY AND IRDS: THE BASICS

A Science Introduction

Claire Gelfman, PhD, chief scientific officer at the Foundation Fighting Blindness, kicked off the science program by providing an overview of retinal degenerative diseases, the retina, *PRPH2*, and potential therapeutic approaches.

Inherited retinal diseases (IRDs) affect approximately 200,000 people in the US and more than 4 million globally. More than 10 million people in the US have age-related macular degeneration (AMD) with approximately 150 million affected globally.

PRPH2 (peripherin-2) is a protein important for the structure and formation of both rods and cones. Rods are the photoreceptors that provide peripheral and night vision. Cones provide visual acuity, color perception, central vision, and vision in well-lit settings.

PRPH2 is one of the more common genes associated with IRDs — it is associated with 3 to 5 percent of IRD cases — and can lead to many diagnoses including: cone-rod dystrophy, macular degeneration, and RP. Most people with *PRPH2*-associated vision loss inherit the mutated gene in an autosomal dominant fashion.

The *PRPH2* gene, its RNA, and the protein it produces are all targets for potential therapies. Gene agnostic approaches —including neuroprotection, anti-oxidants, and optogenetics — are also potential treatment options.

CLINICAL PERSPECTIVES

PRPH2: Genetics and Genotype-Phenotype Relationships

Radha Ayyagari, PhD, the Viterbi Family Chair of Ophthalmic Genetics and professor at Shiley Eye Institute, UC San Diego, began the conference’s discussion of the varied and complicated genetics and clinical manifestations of the *PRPH2* gene.

Located on chromosome 6, *PRPH2* encodes a protein comprising 346 amino acids (the protein building blocks). Approximately 300 mutations in *PRPH2* have been identified. The mutations in *PRPH2* can be classified as:

- missense (single letter) changes leading to an abnormal, non-functional, or toxic protein;
- truncating changes leading to a shorter protein;
- Insertions and/or deletions leading to changes in protein levels or complete loss of protein.

The clinical spectrum of *PRPH2* is vast and can include:

Retinitis pigmentosa	Pattern dystrophy
Leber congenital amaurosis	Central areolar choroidal dystrophy
Cone dystrophy	Butterfly dystrophy
Cone-rod dystrophy	Best disease
Macular dystrophy	Age-related macular degeneration
Foveal dystrophy	Stargardt disease

One challenging aspect of *PRPH2*-associated disease is that a single mutation in the gene can cause multiple phenotypes (disease presentations) in the same family or different families. There is also wide variance in severity and age of onset even within the same family.

While *PRPH2*-associated disease inheritance is usually dominant and occasionally recessive, it can also be digenic (i.e., caused by mutations in two genes) in which a mutation in the *ROM1* gene is also necessary for the disease to occur. That is, family members with only the *PRPH2* mutation do not develop vision loss.

Dr. Ayyagari noted three *PRPH2* collaboration opportunities for scientists:

- *PRPH2* Collaborative Network
- ARVO Special Interest Group (June 13, 2023)
- Clinical Genome (ClinGen) supported curation of *PRPH2* variations

Clinical Features of *PRPH2*-Associated Disease

Shyamanga Borooah, MBBS, PhD, associate professor of clinical ophthalmology at Shiley Eye Institute, UC San Diego, presented and reviewed images for the different ways that *PRPH2* mutations affect the retina. Ultimately, his work will help researchers better understand disease progression and identify potential endpoints for clinical trials.

The imaging techniques used in his studies included optical coherence tomography (OCT), which uses light to capture health and changes in the retinal layers, and fundus autofluorescence to image the front of the retina to highlight areas of lipofuscin/drusen accumulation and atrophy. He also showed images from microperimetry which shows retinal sensitivity at many points within the macula — it is essentially a visual field test for the macula.

In a small study in his clinic, four *PRPH2* patients had a mean baseline area of atrophy of 25.67 mm², which increased 7.3 mm² per year (as measured by fundus autofluorescence). The study is being expanded to 50 patients.

Dr. Boroogh showed several types of clinical phenotypes using OCT and fundus images. They included: pattern and butterfly macular dystrophies, vitelliform (egg yolk) macular dystrophy, Stargardt disease-like phenotype, central areolar choroidal dystrophy (CACD), and retinitis pigmentosa-like phenotype.

He concluded by saying that classification of disease will evolve with new imaging technologies and that subclassifying phenotypes will help identify reliable markers of disease progression.

Longitudinal Analysis of Outcome Measures in *PRPH2*-Associated Retinal Dystrophy

Fred Chen, MBBS, PhD, associate professor, Lions Eye Institute, University of Western Australia, and University of Melbourne, conducted a baseline natural history study of 35 individuals from 24 families with *PRPH2* mutations. Follow-up evaluations were performed on 12 individuals from 10 families with a mean follow-up of 4.7 years. The goal of the study was to identify potential functional and structural outcome measures that could be used in clinical trials for emerging therapies.

To determine rate of progression, Dr. Chen evaluated visual acuity, macular sensitivity, area of atrophy, size of atrophic lesion, and macular volume.

He concluded that visual acuity and macular sensitivity were unreliable as endpoints due to slow decline and patients' improved learning of the tests. Change in macular volume has the greatest potential as an endpoint. Changes in lesion size and atrophic area may also be useful measures in some patients.

Outer Retinal Bands in *ABCA4*- and *PRPH2*-Retinopathy Using OCT

Rachael Heath Jeffrey, BAppSc, MChD, MPH, at Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, Australia, used optical coherence tomography (OCT) to compare the volume decline in outer retinal bands (layers) in patients with *PRPH2* mutations and others with *ABCA4* mutations (Stargardt disease). Her goal was to find a structural biomarker to distinguish disease caused by mutations in the two genes as *PRPH2* patients are often misdiagnosed as having Stargardt disease.

Using OCT, Dr. Heath Jeffrey characterized four bands in the retina with Band 1 as the innermost retinal band and Band 4 as the outermost. Her study evaluated the volume of the bands in 45 patients with *PRPH2*-associated retinal disease, 45 with *ABCA4* (Stargardt disease), and 45 controls (no disease).

Dr. Heath Jeffrey found that the ratio of Band 2 to Band 4 could differentiate disease among patients with *PRPH2* disease, *ABCA4* disease, and controls. The Band 2/Band 4 ratio was 1.0 in *PRPH2*, 0.6 in *ABCA4*, and 0.8 in controls.

Her conclusion was that the Band 2/Band 4 ratio may be useful in distinguishing patients with *PRPH2*-associated disease and Stargardt disease prior to genetic testing.

KEYNOTE LECTURE

The Role of PRPH2 in Retinal Health and Disease

Muna Naash, PhD, professor of biomedical engineering, University of Houston, started her research career studying *PRPH2* (aka *peripherin-2*) in 1992 and has dedicated many years of her career to understanding the role of PRPH2 in the development and health of rods and cones, creating relevant animal models, and evaluating gene therapies in the models.

As other workshop presenters noted, PRPH2 plays a critical role in the development of rod and cone outer segments which absorb light to make vision possible. However, rods and cones have different PRPH2 protein requirements. Dr. Naash said that cones require protein from only one normal copy of *PRPH2* whereas rods require protein from two normal copies. She believes that knocking down (turning off) only the mutant copy of *PRPH2* would provide enough protein from the normal copy to preserve cones and their function. (Remember, each cell in the body has two copies of every gene. Most people with *PRPH2* retinal disease have dominant disease, one normal and one mutated copy.)

Dr. Naash also noted that the gene *ROM1* plays an important modifying role in *PRPH2*-associated disease.

Her lab created a mouse model of PRPH2 retinal disease caused by the Y141C mutation — a mutation that leads to high phenotype variability in people. Patients with the mutation can have pattern dystrophy, macular dystrophy, or retinitis pigmentosa (RP). Her lab determined that elimination of the ROM1 protein changes disease from pattern dystrophy to RP.

Nanoparticles as a Therapeutic Approach to Deliver PRPH2 to the Retina

Dr. Naash reviewed her lab's use of nanoparticles for *PRPH2* delivery in gene augmentation therapies. Nanoparticles are tiny synthetic particles that have many uses including drug and gene delivery. While human-engineered viruses (such as AAV) are typically and effectively used in retinal gene therapies, nanoparticles have two potential advantages: 1) They can deliver a gene of any size and 2) They may be less likely to cause inflammation.

Dr. Naash showed structural rescue of a mouse with RP caused by a *PRPH2* mutation using a nanoparticle gene therapy. Her goal is to deliver gene therapy intravitreally versus subretinally, the latter of which is more invasive. However, intravitreal delivery presents challenges in getting the therapy to the cells that need it. She proposed the use of sulfotyrosine or hyaluronic nanospheres for effective intravitreal delivery of PRPH2.

Dr. Naash's goals for further developing *PRPH2* gene therapies include: improving efficacy with intravitreal delivery, improving distribution of protein expression, and improving knockdown technology for gain-of-function mutations. She also hopes to expand the research community's understanding of how PRPH2 affects cell health and function.

PRPH2 BASIC SCIENCE AND MODELS

The Atomic Structures of PRPH2 and ROM1

James Birtley, PhD, is a structural and molecular biologist who currently runs a cancer lab for Epsilogen in London.

Dr. Birtley began his talk by emphasizing the importance of knowing the structure of PRPH2 and ROM1 proteins in order to develop treatments for related disease. To help attendees appreciate his point, he said that if one had a broken down car, having a detailed map of the engine structure would be much more help in fixing it than just a picture of the car.

PRPH2, he said, is required for proper rod and cone shape and structure. Professor Piet Gros, Utrecht University, and Dounia El Mazouni, Gros' PhD student, detailed the structure of PRPH2 and ROM1, suggesting that the proteins had multiple roles in the development of photoreceptor shape and structure.

Dr. Birtley said that the benefits of knowing protein structure of PRPH2/ROM1 include:

- Understanding function of the amino acids (protein building blocks)
- Providing clues why mutations can be pathogenic
- Understanding range of diseases caused by mutations
- Reducing the need for mouse models
- Providing targets for small molecule treatments

He provided examples of a variety of *PRPH2* mutations and how they cause disease. For example, the Arg172Trp mutation may lead the PRPH2 protein to aggregate or disrupt protein-protein interactions necessary for disc formation in the outer segments of photoreceptors. The Tyr141Cys mutation is likely to lead to a less stable protein. The Lys153DelG is likely to lead to less stable interaction between PRPH2 and ROM1.

The Photoreceptor Outer Segment: How to Build a Sensory Ciliary Organelle

Vadim Arshavsky, PhD, is the Helena Rubinstein Foundation Distinguished Professor in the Department of Ophthalmology at Duke University. In his presentation, he described how photoreceptor outer segments are formed and the essential role of *PRPH2* in that process.

Outer segments are the light-sensing protrusions in photoreceptors. They contain a large stack of discs which contain proteins and other molecules that are critical for vision. Dr. Arshavsky described an outer segment as being like "800 ping-pong balls that have been stepped on and flattened, then stacked one on top of another, then stuffed in a sock."

His work led to the discovery that the suppression of ectosomes, which is necessary for outer segment development and maintenance, is performed by PRPH2. (Ectosomes are vesicles that exchange various proteins and genetic material between cells.)

In a mouse model in which the *PRPH2* protein was knocked out, ectosome release was not suppressed and outer segments did not form.

***ROM1* as a Regulator of Phenotypic Heterogeneity in *PRPH2*-Associated Disease**

Shannon Conley, PhD, assistant professor, University of Oklahoma Health Sciences Center, has studied mutations in *PRPH2* for more than 20 years.

One question she has conducted extensive research to answer is: Why is there so much variability in the vision loss of people with retinal diseases caused by *PRPH2* mutations, even for those people with the same mutation?

Much of her work has focused on the protein encoded by the *ROM1* gene, which is a binding partner and potential modifier of *PRPH2*. She found that removing the *ROM1* protein leads to milder phenotypes. Her studies of *ROM1* removal were conducted in the following *PRPH2* disease mouse models:

- Macular dystrophy caused by the R172W mutation: Cone function did not improve with *ROM1* removal. Rods were not abnormal before or after *ROM1* removal.
- Retinitis pigmentosa, pattern dystrophy, and Stargardt-like disease caused by the K153del mutation: Rod function did improve when *ROM1* was reduced. Cone function didn't improve, though age-related loss of cone function was slowed.
- Pattern dystrophy caused by the C213Y mutation: No improvement in rod or cone function when *ROM1* removed.

Dr. Conley's colleague Lea Bennett, PhD, is creating patient-specific retinal organoids (mini-retinas in a dish) from *PRPH2* (P210R) patient blood cells to study cellular and molecular changes in humans.

Modeling Retinal Degenerations Using Patient-Derived Stem Cells

Deepak Lamba, PhD, associate professor of ophthalmology, University of California, San Francisco, reviewed his work in developing retinal organoids to study retinal disease and the development of potential therapies.

The process of developing retinal organoids involves genetically tweaking blood or skin cells so they revert to a pluripotent stem cell state. At this point, they are a clean slate and can be directed to develop into any cell type in the body. Dr. Lamba's lab coaxes them forward to become retinas. The process takes about nine months.

Dr. Lamba showed research he performed on retinal organoids derived from people with severe vision loss at birth caused by Leber congenital amaurosis (*CRX* mutations). *CRX* is an essential gene in retinal development, and by correcting the mutations with CRISPR/Cas9 gene editing, he was able to restore organoid maturation.

His lab also created retinal organoids from patients with retinitis pigmentosa caused by *RHO* mutations and used the organoids to perform screening of potential drug therapies for *RHO* disease.

FIRESIDE CHAT (SANS FIRE) WITH DR. ANGELA BOWMAN

Amy Laster, PhD, senior vice president of science strategy and awards at the Foundation Fighting Blindness, talked with Angela Bowman, PhD, the Foundation's science advocacy lead, about her role in managing the advancement of *PRPH2* research.

As Dr. Laster said, Dr. Bowman is the Foundation's "intellectual CEO" for *PRPH2* and two other genes: *CRB1* and *MYO7A* (the gene responsible for causing Usher Syndrome type 1B). Dr. Bowman played the lead role in planning and organizing the *PRPH2* workshop and wrote an impressively comprehensive landscape report of *PRPH2*. In her research for developing the landscape, she found that the publication that reported on the discovery of *PRPH2*'s association with retinal diseases was funded by the Foundation Fighting Blindness.

Before joining the Foundation, Dr. Bowman was the inaugural executive director of the Washington University in St. Louis Center of Regenerative Medicine and was a research professor in the Department of Developmental Biology. She earned her doctorate in developmental biology from Stanford and conducted post-doctoral research on retinal gene therapy out of Dr. John Flannery's lab at the University of California, Berkeley. Dr. Flannery is also a member of the Foundation's Executive Scientific Advisory Board.

PATIENT RESOURCES AND PANEL DISCUSSION

Ben Shaberman, vice president of science communications at the Foundation Fighting Blindness, led a panel discussion of patient resources — including genetic counseling, clinical trials, and nutrition — with three retinal disease experts:

David Birch, PhD, scientific director and director of the Rose Silverthorne Retinal Degeneration Laboratory, Retina Foundation of the Southwest, said that he believes getting good nutrition through diet is preferred over taking supplements. For people with retinal diseases, that includes eating a diet rich in colorful fruits and vegetables and omega-3 fatty acids (from cold-water fish). Dr. Birch, who studied under vitamin A pioneer Dr. Eliot Berson, also said that high dose vitamin A is now rarely recommended for retinitis pigmentosa.

Dr. Birch also spoke about clinical trials. He noted that while a recent choroideremia gene therapy clinical trial didn't meet its endpoint, people did have vision improvements. Also, the XLRP-RPGR gene therapy trials underway are looking promising. But, overall, we need better trial endpoints to ensure more trial success.

Kari Branham, MS, CGC, Kellogg Eye Center, University of Michigan, is an assistant professor in the Ophthalmology and Visual Sciences Department and a genetic counselor in the Inherited

Retinal Disease Clinic. In addition to helping patients understand genetic testing results, she helps patients and families gain access to low vision, mental health, and educational resources.

She said that gene mutations are classified as benign, pathogenic, or variants of unknown significance (VUS). A VUS can be reclassified when more patients with the variant are identified over time.

When asked about family member testing, she said it is important to know if the member wants to know if they have the disease. Also, counselors are cautious about recommending testing for children if they are asymptomatic and/or there is no intervention for the condition.

Todd Durham, PhD, senior vice president, clinical and outcomes research, Foundation Fighting Blindness, reviewed what researchers and companies consider when designing a clinical trial. He used the acronym PICOT to describe the design elements:

- Participants — determining the preferred patients for the trial given their genetic profile and vision.
- Intervention — determining the correct treatment formulation and dose.
- Control — selecting the correct control for the trial (e.g., placebo, treated eye vs. untreated eye)
- Outcome — selecting an endpoint that will quickly and clearly show if a therapy is working.
- Time — How much time does the trial need to determine if the treatment is working?

Dr. Durham said that the Foundation's My Retina Tracker Registry, which has more than 24,000 registrants, is used by therapy developers to identify potential clinical trial participants and help the research community better understand the impacts of retinal diseases.

In closing, the panelists discussed clinical trials, reminding the audience that trials are experiments (the treatment might not work), highly selective in patient enrollment (many people don't meet inclusion and exclusion criteria), and are a big time commitment for participants.

DAY 1 SUMMARY AND DISCUSSION

Drs. Ayyagari and Gelfman reviewed some of the day's highlights to close out the first day of the workshop. Their observations included:

Patient experiences were emotional and moving and underscore the importance of the research and development of therapies.

PRPH2 mutations present many challenges due to significant variability of disease severity, age of onset, affected photoreceptor types, and impacts from modifiers such as *ROM1*. Significant disease variability can (and often does) occur within the same family.

Imaging of retinal layers through OCT, measuring thickness of retinal bands, can help clinicians distinguish between *PRPH2*- and *ABCA4*-associated disease.

Drug delivery remains a challenge in getting treatments to the back of the eye. Sulfotyrosine (per Dr. Naash) is an intriguing option for bypassing the cellular barriers for retinal delivery.

Patient-specific retinal organoids are a valuable resource for screening potential therapies.

FOCUS ON THERAPIES: DAY 2, MARCH 31

Finding Hope for a Family's Younger Generations

With an introduction from Dr. Borooah, Lisa Rosado opened the second day of the workshop by sharing her large family's multigenerational story of *PRPH2*-related vision loss.

Lisa said she always dreaded going to the movie theater because she was unable to see anything inside. She also thought she was clumsy because she frequently bumped into people.

But recently, an eye doctor told her she had white spots on her retina — that was the first indication that something was wrong with her eyes. While age-related macular degeneration (AMD) ran in her family, she was only 40-years old when her doctor noticed the retinal abnormality, so Lisa thought she had a lot of time before her vision loss would be significant. Her grandmother was diagnosed with AMD, but didn't go blind until her 80s.

But after a follow-up appointment, Lisa was surprised to receive a diagnosis of retinitis pigmentosa, which happened to be the same diagnosis for her great aunt, who went blind in her 60s.

Lisa shared a five-generation family photo tree that showed at least three generations affected by vision loss. She couldn't be sure, but there may have been other affected family members who didn't feel comfortable talking about their vision issues.

Lisa then showed a family photo that included 22 grandchildren. She wondered who else in that picture might be affected.

Lisa acknowledged that she had felt hopeless as her vision loss has accelerated.

But getting connected to the Foundation Fighting Blindness by Dr. Tomas Aleman, an inherited retinal disease expert at the University of Pennsylvania, has brought her to a new family. She is thankful to be a part of this passionate and resilient community of families and researchers.

In concluding her story, she quoted Helen Keller: "Alone we can do so little. Together we can do so much."

Lisa is the senior director of program management at SEBPO. She collaborates with stakeholders and cross-functional global leaders to define, prioritize, and develop programs that shift organizational value propositions to align with business outcomes.

THERAPEUTIC APPROACHES

Therapeutic Strategies for Autosomal Dominant Retinal Disease, including *PRPH2*

Angela Bowman, PhD, the science advocacy lead at the Foundation Fighting Blindness, reviewed the biological impacts and challenges of dominant disease, as well as potential therapeutic strategies for addressing retinal conditions caused by *PRPH2* mutations. As discussed during previous sessions, most retinal disease caused by *PRPH2* mutations is inherited dominantly.

With a dominant disease, the affected patient only needs one mutated copy of the specific gene even if their other copy is normal. Additionally, they have a 50 percent chance of passing that mutated gene (and often the disease) onto each of their children.

Dominant mutations can be broadly classified as “loss of function” or “gain of function.” With loss of function, the protein expressed by the mutated gene doesn’t do its job. With gain of function, the protein expressed by the mutated gene does something (often harmful) outside of its normal role, and, in some cases, alters the function of the protein expressed by the normal gene copy.

PRPH2 mutations can be loss of function or gain of function. In many cases, researchers don’t know which.

Gene replacement (augmentation) therapies are most suitable for loss-of-function mutations. With these therapies, normal gene copies are delivered to retinal cells using a human-engineered virus (adeno-associated virus), nanoparticles, or other gene delivery method.

Gene knockdown and replace therapies are more relevant for gain-of-function. In these approaches, a molecular tool is used to “knockdown” or reduce the effect of the mutated gene copy. In addition, a normal replacement gene copy is delivered.

The molecular tools for knocking down the mutated copies include:

- siRNA (small interfering RNA) which degrades the RNA (genetic messages) used by cells to make proteins.
- Antisense oligonucleotides (AONs) which alter or mask mutant RNA used for protein production.
- CRISPR/Cas9 gene editing which works like molecular scissors to cut out the mutated region of the gene.

Several mutation-agnostic approaches, which are designed to work independent of the mutated gene and its effect on protein expression, are currently in clinical development. They include:

- Neuroprotection for preserving cones and/or rods (e.g., SparingVision).

- Cell-based therapies for preserving or replacing cones and/or rods.
- Optogenetics for harnessing retinal interneurons or ganglion cells to restore vision for people who have lost all rods and cones (e.g., Nanoscope).

A Mutation-Specific Therapeutic Intervention for PRPH2-Associated Retinal Disease

Rob Collin, PhD, a professor at Radboud University Medical Center in the Netherlands, is also the founder and chief scientific officer at Asthera, a Radboud spin-off developing RNA therapies for vision issues.

Dr. Collin said that R142W is the most common *PRPH2* mutation in the Netherlands. His lab evaluated the use of an antisense oligonucleotide (AON), a small piece of genetic material that binds to RNA to alter protein production. In their *PRPH2* experiment, they were able to degrade production of the mutant (R142W) protein in a cell culture using an AON. The normal *PRPH2* protein production was unaltered.

He acknowledged that questions about using this approach for *PRPH2* retinal disease remain:

- What are the best models for testing therapies?
- Which therapeutic strategies are best for different mutations?
- Is degrading the mutant gene copy enough to restore vision?

Advancing Precision Medicine using Gene Editing to Treat Inherited Retinal Diseases

Peter Quinn, PhD, a principal investigator and associate research scientist at Columbia University, introduced the concept of CRISPR/Cas9 gene-editing for treating *PRPH2*-associated retinal diseases. He noted that gene-editing was attractive for shutting down the production of mutant (toxic) proteins which may be desired in many cases of *PRPH2* conditions.

CRISPR/Cas9 therapies use a specially designed RNA molecule to locate the mutation of interest in DNA. The Cas9 enzyme then cuts out or modifies the mutation. In some cases, new DNA is also inserted.

He reviewed three CRISPR/Cas9 gene-editing techniques:

- 1) Nucleases (original CRISPR/Cas9 technology) which work like molecular scissors to cut out the mutation by breaking both strands of DNA. Generally speaking, the approach is less efficient and has more potential side effects than more advanced techniques.
- 2) Base editing which changes a single letter mutation without making double-stranded breaks. Base editing is relatively efficient and safe, but less flexible.
- 3) Prime editing which can delete and insert large genomic regions in DNA with a single-stranded break. This approach provides much more editing flexibility and capability, and is relatively safe.

Dr. Quinn reviewed his lab's effective prime editing of a *PRPH2* mutation, as well as *PRPH2* disease modeling in a dish.

Inhibition of Protein Kinase G to Prevent PRPH2-Mutation Induced Retinal Degeneration

François Paquet-Durand, PhD, from the University of Tübingen and Mireca Medicines, reviewed his development of a small molecule, an inhibitor of toxic protein kinase G, for treating select inherited retinal diseases (IRDs).

In certain IRDs, including those caused by *PRPH2* mutations, the production of protein kinase G is caused by high levels of a phototransduction molecule known as cGMP. For several years, Dr. Paquet-Durand and his team have been working on the identification of a protein kinase G inhibitor as a therapy for relevant IRDs. He identified two lead candidates that have shown promise in preserving vision in mouse models (*PDE6B* and *PRPH2*). The lead candidate, CN238, is being further developed by his company, Mireca. The company also recently acquired a PLGA (nanoparticle) drug delivery technology from pharmaceutical company Graybug to get the therapy to the back of the eye where it should be effective for three to six months after which re-treatment would be needed. Additional work is planned to move a lead kinase G inhibitor into a clinical trial.

EMERGING THERAPIES ROUNDTABLE

SparingVision

Daniel Chung, DO, chief medical officer at SparingVision, reported that the company's lead therapeutic, SPVN06, has been authorized to move into a clinical trial in the US and Paris. The emerging mutation-agnostic gene therapy expresses rod-derived cone-viability factor (RdCVF) for preserving cone vision in people who have lost rods but still have functioning cones — for example, some people with retinitis pigmentosa (RP) caused by *PRPH2* mutations.

As a mutation agnostic therapy, SPVN06 is designed to work independent of the mutated gene causing the retinal disease. The trial will initially enroll RP patients with mutations in *PDE6A*, *PDE6B*, or *RHO*, because those genotypes have been well characterized.

SparingVision is also developing a mutation-agnostic gene therapy, SPVN20, for restoring light sensitivity to cones that have lost their outer segments, the light-sensing protrusions of cones, but still have inner segments, the cone cell bodies. The company hopes to launch a clinical trial for SPVN20 in the next year or so.

Nanoscope Therapeutics

Aaron Osbourne, MBBS, the chief medical officer and chief development officer at Nanoscope Therapeutics, reported on his company's recently announced Phase 1/2 clinical trial results for its optogenetic therapy for patients with RP.

The emerging treatment, MCO-010, is designed to bestow light sensitivity to bipolar cells in people who have lost most or all of their photoreceptors to conditions such as retinitis pigmentosa. The mutation-agnostic gene therapy enables bipolar cells to express a light-sensitive multi-characteristic opsin, a protein that is able to respond to a broad spectrum of light.

According to the company, MCO-010 enabled 16 of 18 patients to either better navigate a simple multi-luminance mobility course or better identify a shape at two levels of reduced luminance. All patients receiving the high dose had improved visual acuity.

The trial didn't meet its primary endpoint, which was for participants to navigate the mobility course with a mean reduction of two luminance levels from baseline. Nanoscope is talking to the FDA about potential next steps.

The company also has an MCO-010 clinical trial underway for individuals with Stargardt disease.

Opus Genetics

Ash Jayagopal, PhD, chief scientific officer at Opus Genetics, said the company was formed in 2021 by members of the Foundation's RD Fund management team. to address the barriers — including small-scale manufacturing and small patient populations — to developing gene therapies for inherited retinal diseases. The goal is for the company to be a sustainable engine, launching a new clinical trial every year.

Opus has received authorization from the FDA to launch its first clinical trial — for an LCA5 gene therapy.

Dr. Jayagopal said that the design approach for one of its projects, a gene therapy for autosomal dominant retinitis pigmentosa caused by *RHO* mutations, would involve ablating the mutant gene copies and delivering new, healthy *RHO* copies. The approach would be similar to what's needed to address many forms of dominant *PRPH2* retinal disease.

DAY 2 SUMMARY

Hope's a Good Thing, Maybe the Best of Things

David MacDonald grew up watching his father struggle with vision loss. "I was there when he couldn't do the things he wanted to do and he had the socially awkward moments when he couldn't recognize people he knew standing in front of him," he said. "And for the first 32 years of my life, I went through my oblivious phase when I was lucky enough to not realize what he was going through in his life was going to be my life."

But everything changed for David in 2002 when an optometrist in Memphis diagnosed him with a retinal disease. Feelings of helplessness caused him to disengage with the medical community. He stopped driving, stopped playing golf, and stopped recognizing faces. But he also went on with his life and got married and had two kids.

His wife, Kelley, pushed him for many years to go back to the doctor to get genetically tested, but it wasn't until 2018 that he finally did. "My connection to my father was now really clear," he said.

David credits his wife for being motivated to find more information. When their kids were tested and diagnosed with his retinal condition, her motivation grew dramatically. “She became the mama bear,” he said.

December 25, 2021, was a pivotal day for the MacDonalds. That’s when Kelly got a Google alert about the Nixon Visions Foundation. They had a Zoom call with Janine and Brandon shortly thereafter. “It was the first time I spoke with someone who had what I had,” David said. “And the Nixons had a plan.”

David concluded his remarks with a quote from the movie *The Shawshank Redemption*: “Hope’s a good thing, maybe the best of things.”

Building Momentum

In summarizing the past two days, Amy Laster, PhD, senior vice president, science strategy and awards at the Foundation Fighting Blindness, reflected on the impressive progress the workshop made in building community, sharing disease and science knowledge, and paving the way for therapy development. She encouraged the *PRPH2*-focused audience of 110 plus to keep the momentum strong for advancing research. She also asked patients and families to join the *PRPH2* Forum (info@prph2.org) to further build community and gain support.

Dr. Laster highlighted the commitment of the Foundation Fighting Blindness and the Nixon Visions Foundation to building a robust portfolio of *PRPH2* research in the coming years. Her team will soon be calling for research applications to fund at least two *PRPH2* projects in the next year.

Dr. Laster also noted that the Foundation Fighting Blindness recently began funding *PRPH2* research through its Translational Research Acceleration Program (TRAP) for a project at Oregon Health & Science University (OHSU) to develop a *PRPH2* CRISPR/Cas9 prime-editing therapy with nanoparticle delivery.

“We at the Foundation will continue to find all the clinicians and researchers in this space who want to make a difference,” she said in conclusion.

CONCLUDING REMARKS

“We had no idea if we would get 10 people or 20 people. In our wildest dreams it was 50,” Brandon said about his and Janine’s initial expectations for workshop attendance. “And the quality and caliber of all the presenters was off the charts.”

But something else surprised Brandon even more. “I expected the patients and families to strongly connect with the researchers, but I didn’t realize how much those connections would mean to the researchers. That was astounding to see.”

The next *PRPH2* conference should take place in about three years.

In his final, thank you to attendees, Jason Menzo said, "Hope is great, but it's even better when it's married to a plan."