Invincible Vision

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Helen Keller Prize for Vision Research

Nomination for Richard Yang

1. Introduction

"I was once trapped in the mire of despair and helplessness. The rarity of the disease meant neglect and indifference in the medical field, as if we had been abandoned in a medical wasteland, with no clear path and little hope. However, Mr. Yang's arrival was like a ray of dawn breaking through the darkness, dispelling the haze that loomed over us. He brought unprecedented hope and unity, rekindling the flame of life amidst despair." These heartfelt words from my wife, a patient with a rare blinding disease, encapsulate the profound impact that Mr. Yang has had—not only on her life but on the lives of countless others in the rare disease community.

We have known Mr. Yang for almost 10 years. We witnessed his devotion to vision research, as well as numerous challenges he has encountered as a patient-turned-researcher. His actions remind us all of the power of courage, perseverance, and empathy in the face of adversity.

2. Impact Beyond the Laboratory

(1) **Bringing Hope to Patients Dedication Beyond Measure:** After being diagnosed with Bietti's Crystalline Dystrophy (BCD), a rare genetic disease that leads to gradual vision loss, Mr. Yang took the extraordinary step of dedicating his life to advancing gene therapy research. Aware that his own remaining time with little left functional vision was limited, he embarked on an ambitious journey, teaching himself the intricacies of genetics and collaborating with renowned scientists like Dr. Stephen Tsang. Despite facing immense personal and financial challenges, including using his life savings and children's education funds, Mr. Yang's determination never wavered. His story of selflessness and sacrifice has become a beacon of hope for patients worldwide, demonstrating that even in the face of overwhelming odds, progress is possible.

His commitment to this cause has been recognized by patients across the world. Kirstin from Louisiana, a BCD patient, describes Mr. Yang as a "rare gem in the scientific community" whose tireless work has brought renewed hope to those affected by this devastating disease. She speaks to the profound isolation of vision loss—watching the world fade while feeling forgotten by the medical establishment. Yet, she notes that Mr. Yang's efforts have illuminated a path forward, offering both tangible scientific advancements and the assurance that patients are not alone in their fight.

(2) **Resilience in the Face of Hardship:** Besides physical disability and financial difficulty, Yang's research journey was far from smooth. Failed experiments, inconclusive results, and technical challenges were constant hurdles. These hardships often pushed Yang on the verge of collapse. Yet, through these setbacks, he exhibited remarkable resilience, refusing to let failure deter him. Late nights spent researching on potential pathways and biomarkers, analyzing data and discussing with collaborators to troubleshoot experiments were a testament to his unwavering dedication. His perseverance serves as a powerful reminder to all of us that even the smallest glimmer of hope can illuminate the darkest paths.

(3) **Promoting Patient Unity Inspiring Patient Engagement**: Mr. Yang's courage and relentless pursuit of solutions deeply resonated with the global patient community. His pioneering spirit sparked a movement of shared stories, mutual support, and proactive engagement among patients. What once were isolated struggles have transformed into a united effort to confront and overcome the challenges posed by BCD.

Mira from Copenhagen, Denmark, another BCD patient, describes how Mr. Yang's work has bridged the gap between complex scientific research and the patients who rely on it. She highlights how his ability to explain cutting-edge developments in gene therapy has empowered the BCD community, equipping them with knowledge and renewed optimism. Beyond the science, his persistence and accessibility have given patients a tangible sense of hope for the future.

(4) **Inspired the Establishment of Organizations to Gather Strength**: Inspired by Mr. Yang's resilience, we came together to establish Invincible Vision, a rare disease patient organization that now serves as a global platform. Based in California, this organization raises awareness, secures research funding, and provides emotional and practical support to patients and their families. Through educational talks, meet-ups, and advocacy initiatives, Invincible Vision has become a source of strength and solidarity, proving that unity can empower even the most vulnerable communities.

3. Scientific Contributions and Impact on Vision Research

Demonstrated by the following three papers he published as the sole author or co-first author, Mr. Yang made significant contributions to vision science by advocating for transparent science, analyzing animal model flaws, pioneering a precision medicine approach for gene therapy, and utilizing genomic database to more accurately estimate disease epidemiology. Although these papers used BCD as an example, they have far-reaching implications beyond BCD, in particular papers 1 & 2 below.

(1) **Advocating for Transparent Science in Rare Disease Research:** In his outspoken article, *A Patient Advocating for Transparent Science in Rare Disease Research*, Mr. Yang critically evaluates three knockout mouse models for BCD, exposing critical flaws such as not mimicking BCD in humans, flawed experimental design, and missing critical data. Further, he discusses how animal model flaws and nontransparent science can misguide medicine regulators and drug developers, delay or frustrate orphan drug development, or waste limited resources for rare disease research. His analysis highlights systemic challenges that extend far beyond BCD. By calling for greater transparency and rigor in rare disease research, Mr. Yang not only advances the field of BCD research but also emphasizes the need for safeguarding research standards across the entire rare disease spectrum, potentially benefiting millions of patients worldwide. Since many ocular diseases are rare disorders, Yang's paper is also an invaluable contribution to vision science beyond BCD.

(2) **Advancing Precision Medicine for BCD Gene Therapy with Patient-Specific Cellular Models**: In *Evaluating Precision Medicine Approaches for Gene Therapy in Patient-Specific Cellular Models of Bietti Crystalline Dystrophy*, Mr. Yang and his collaborators present groundbreaking findings in BCD patient-specific iPS-RPE model:

- Treating Light-induced Oxidative Stress and Retinal Damage in BCD: This was the first proof-of-concept study to show that AAV-CYP4V2 gene therapy can treat light-induced RPE damage in BCD. Additionally, this study identified quantifiable biomarkers like reactive oxygen species (ROS), 4-hydroxy 2-nonenal (4-HNE) levels, and RPE cell death rates to assess therapeutic efficacy of BCD gene therapy.

- Highly Representative Results: This study established BCD patient-specific iPSC-based models of different ethnic backgrounds with distinct mutations to generate highly representative results and assess individual variations.

- Genotype-Phenotype Correlations: Given the wide genotype and phenotype variability among patients, BCD is an ideal disease for studying patient individual differences. This study observed significant variability in cellular

phenotypes among BCD iPS-RPE subjects of divergent CYP4V2 mutations, which outlined genotype-phenotype correlations in BCD patient-specific cell disease models.

- Personalized Preference for Different AAV Treatments and Tailored Gene Therapy: Importantly, results from this study show that different AAV serotypes achieved significant variability in treatment efficacy in iPS-RPE cells of patients with different CYP4V2 mutations. In addition, no AAV vector works best for all patients. These results highlight the need for individualized treatment strategies for AAV-mediated gene augmentation therapy. This is a big step forward from the "one vector for all patients" approach conventionally used in gene therapy R&D.

Significantly, this study not only advanced BCD gene therapy research but also set a precedent for precision medicine approach in developing gene therapy for other ocular diseases, emphasizing the necessity for personalization in healthcare to accommodate individual diversity.

(3) **Unveiling the Genetic Landscape of BCD**: A Global Analysis: In *An In-Depth Single-Gene Worldwide Carrier Frequency and Genetic Prevalence Analysis of CYP4V2 as the Cause of Bietti Crystalline Dystrophy*, Mr. Yang and his collaborators conducted the first worldwide BCD genetic prevalence analysis by utilizing the gnomAD database. This landmark study:

- Estimated that over 19 million individuals worldwide are healthy carriers, with approximately 67,000 affected by biallelic mutations.
- Advocated that although BCD is more common in the East Asian population, the prevalence of BCD should not be overlooked outside of East Asia since thousands of biallelic individuals are expected in the African, European, Latino, and South Asian populations.
- Revealed that the most common CYP4V2 mutations are different among various populations. Hence, it would be helpful to include patients from multiple worldwide populations in future clinical trials aiming to better assess the clinical benefits to patients with different CYP4V2 mutations.

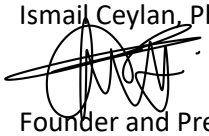
4. Conclusion

Mr. Yang's journey has resonated deeply with patients worldwide, bringing hope and strength in their darkest moments. His relentless pursuit of solutions demonstrates that even the most challenging adversities can be met with courage and purpose, inspiring others to confront their own challenges with renewed determination. His story proves that patients with disabilities can play a proactive role in vision research—not just as beneficiaries, but as key drivers of progress.

Mr. Richard Yang exemplifies the spirit of Helen Keller, transforming personal adversity into remarkable contributions to science and advocacy. Through his groundbreaking research, tireless dedication, and profound impact on the rare disease community, he has made an enduring difference—not only in advancing genetic medicine but also in uplifting the lives of patients and families across the globe. It is with great conviction that I nominate Mr. Yang for the Helen Keller Prize for Vision Research to recognize his extraordinary achievements and to inspire continued efforts to bring hope, unity, and transformative progress to those living with blinding diseases.

Sincerely,

Ismail Ceylan, PhD



Founder and President, Invincible Vision

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January 29, 2025

Helen Keller Prize for Vision Research - Nomination for Richard Yang

To Whom It May Concern,

I nominate Richard Yang, J.D. for the 2026 Helen Keller Prize for Vision Research. His work in gene therapy for Bietti Crystalline Dystrophy (BCD) is groundbreaking. Richard is not just a patient. He is a dedicated researcher. We met in 2016 when he came to me as a patient. His retinas were already badly damaged. Instead of just seeking help, he asked me to work with him on BCD gene therapy. He had already studied the disease and suggested we use patient-derived iPS-RPE models. The 2014 knockout mouse model had failed, and Richard wanted a better approach. I agreed.

Richard's work is personal. BCD has blinded his sister. He fights for a cure to help others avoid the same fate. Our research led to a major study: *"Evaluating Precision Medicine Approaches for Gene Therapy in Patient-Specific Cellular Models of Bietti Crystalline Dystrophy"* (PMID: 39171529). Richard was a lead author. His ideas shaped the study.

Richard suspected lipid peroxidation drives BCD. He tested free fatty acids in BCD iPS-RPE cells and found high levels of omega-3 and omega-6 PUFAs in these cells. He linked light exposure to PUFA breakdown, which causes cell death. He identified 4-HHE and 4-HNE as key biomarkers. These measure BCD damage and treatment success.

He also helped show that AAV.CYP4V2 reduces lipid peroxidation and cell death, providing the first proof that gene therapy can fight BCD damage. Unlike most gene therapy trials that use one AAV vector for all patients, Richard tested different AAV.CYP4V2 vectors to see what worked best for each patient. He found that different people respond differently. Some did better with AAV2, others with AAV5. This showed that gene therapy should be tailored to each patient.

Richard has worked under incredible hardship. He is legally blind and must use assistive technology to read and write. He has no salary and funds his research with personal savings. He knows this therapy won't help him, but he fights for others.

Richard's work is bold, smart, and driven by real need. He deserves the Helen Keller Prize for Vision Research.

Cordially,

Stephen H. Tsang, M.D. Ph.D

Stephen H. Tsang, MD, PhD
Laszlo Z. Bito Professor of Ophthalmology
Columbia University Irving Medical Center

NAME:
Richard R. Yang, J.D.

POSITION/TITLE:
Founder, CEO & Head of R&D, Reflection Biotechnologies Limited

EDUCATION:
Peking University, Beijing, China
B.S. in Chemistry, 1996

University of Michigan, Ann Arbor, Michigan, USA
Juris Doctor, 1999

A. Personal Statement

I am a patient-turned-researcher. My sister and I suffer from Bietti Crystalline Dystrophy (BCD), a rare retinal degeneration. My sister became completely blind long time ago. In addition to affecting two patients, BCD puts a heavy burden on everyone in our family. Currently, there is no approved treatment for BCD.

My involvement in vision research begain more than two decades ago when I enrolled as a patient in a NEI-led global study on BCD. The study lead to the discovery that BCD is caused by mutations in the novel *CYP4V2* gene in 2004. Many BCD patients including myself were excited by this milestone, hoping that finding the genetic. cause of BCD can advance treatment research. We waited eagerly. However, ten years have passed since 2004, still there was no news about treatment research for this rare blinding disease,

Meanwhile, my vision has deteriorated to the point that I had to rely on assistive technology to read and write. Instead of waiting, I decided to put matters into my own hands and to initiate and drive BCD gene therapy research as a patient. In the process of going blind, I founded Reflection Biotechnologies (ReflectionBio) with personal savings and apply the *By Patients, For Patients* ® approach for patients to play a proactive role in scientific research to help ourselves and others. Due to the limited budget, I had to drive everything by myself at ReflectionBio. Leveraging on my undergraduate scientific training, I began to read every paper I can find on BCD and gene therapy. In addition, I set up research collaborations on BCD gene therapy and genetic prevalence with Dr. Stephen Tsang and Dr. Dror Sharon, respectively.

In the middle of my research journey, as of three years ago, my left eye and right eye vision already deteriorated to finger count and hand motion, respectively. In addition, I was running out of energy and savings. I felt I was about to collapse. Both mentally and physically. So I seriously thought about stopping all of our research efforts. But in the end, I decided to persevere because of two reasons. First, my family, collaborators and several fellow BCD patients have supported me in various ways. I felt an obligation to advance our work to publication so to show our progress and results to the public and the patient community. Second, more than 90% of rare diseases do not have any treatment available. Like BCD, many blinding diseases also rare and do not have any approved treatment. Hence, if we can

demonstrate that a legally blind patient can help make some progress in vision research, it may bring hope to patients suffering from other rare blinding diseases.

After years of hard work, our research works were published in three papers listed under Section C. below of which I was a co-first author or the sole author. These papers cover a wide range of research topics such as retinal gene therapy, patient-specific cellular models, precision medicine approach for gene therapy based on individual differences among patients, lipid peroxidation, genetic prevalence, animal model flaws, and advocating for transparent science. As summarized in Section C. below, some of them may have an impact on vision science beyond BCD.

Before ReflectionBio, I had worked for 15 years in law and finance. I began my career in law working at the New York office of Shearman & Sterling. My last job was an Managing Director and the Asia Co-head of Consumer and Healthcare Investment Banking at Jefferies.

B. Positions, Scientific Appointments, and Honors

Head of R&D, Reflection Biotechnologies Limited, 2015 – Present

C. Contributions to Science

Li Y, **Yang RR**, Li YS, Hsu CW, Jenny LA, Kong Y, Ruan MZ, Sparrow JR, Tsang SH. Evaluating precision medicine approaches for gene therapy in patient-specific cellular models of Bietti crystalline dystrophy. JCI Insight. 2024 Aug 22;9(16):e177231. doi: 10.1172/jci.insight.177231. PMID: 39171529; PMCID: PMC11343589.

- Role: co-first author
- Contributions: conceptualization; methodology; data analysis; writing, review and editing of manuscript; resources.
- Designed the AAV.CYP4V2 vectors used in the study.
- Decision to use BCD patient iPS-RPE cells as BCD model for thie study.
- Hypothesized and proved that light-induced lipid peroxidation plays a critical role in the development of BCD.
- Identified quantifiable biomarkers like reactive oxygen species (ROS), 4-hydroxy 2-nonenal (4-HNE) levels, and RPE cell death rates to assess therapeutic efficacy of BCD gene therapy.
- This is the first proof-of-concept study to show that AAV-*CYP4V2* gene therapy can treat light-induced lipid peroxidation and RPE damage in BCD.
- Observed personalized preference for different AAV.CYp4V2 vectors among iPS-RPE cells of different BCD patients.
- Significantly, this study not only advanced BCD gene therapy research but also set a precedent for precision medicine approach in developing gene therapy for other ocular diseases, emphasizing the necessity for personalization in healthcare to accommodate individual diversity.

Hanany M, **Yang RR**, Lam CM, Beryozkin A, Sundaresan Y, Sharon D. An in-depth single-gene worldwide carrier frequency and genetic prevalence analysis of *CYP4V2* as the cause of Bietti crystalline dystrophy. Transl Vis Sci Technol. 2023;12(2):27,

- Role: co-first and co-correspondence author.
- Contributions: conceptualization; methodology; data analysis; writing, review and editing of manuscript.
- This was the first worldwide BCD genetic prevalence study by utilizing the gnomAD database.
- Estimated that approximately 67,000 individuals worldwide are affected by biallelic mutations.
- Estimated BCD incidence rates among different populations:
    - African (1:333K)
    - East Asian (1:32K)
    - European (1: 302K)
    - Latino (1:108K)
    - South Asian (1:1.28M)
- Discovered that the top *CYP4V2* mutations vary among different populations. Thus, it would be helpful to include patients from multiple worldwide populations in future clinical trials aiming to better assess the clinical benefits to patients with different *CYP4V2* mutations.

Yang RR. A patient advocating for transparent science in rare disease research. Orphanet J Rare Dis. 2023 Jan 19;18(1):14. doi: 10.1186/s13023-022-02557-6. PMID: 36658594; PMCID: PMC9854194.

- Role: sole author
- As compared to research on common diseases, rare disease research is not always reviewed with scrutiny, leaving room for what I refer to as nontransparent science.
- This paper evaluated three *Cyp4v3* knockout mouse models of BCD (*Cyp4v3* being the murine orthlog of human *CYP4V2*), probed various forms of nontransparent science and analyzed the flaws in these mouse models.
- Discussed how animal model flaws and nontransparent science can misguide medicine regulators and drug developers, delay or frustrate orphan drug development.
- Importantly, 300 million people worldwide live with at least one rare disease. Mutations in one of more than 200 genes can cause blindness. Many blinding diseases are also rare disorders. Hence, lessons from BCD research could potentially benefit millions of patients suffering from other rare blinding diseases worldwide.