USHER 1F COLLABORATIVE

NEWSLETTER
Fall 2024

Frank Gentile, PhD

BOARD MEMBER SPOTLIGHT:

Frank Gentile, PhD

Frank Gentile, PhD, is one of our original board members and has become an invaluable asset to Usher 1F Collaborative. We took the opportunity to learn more about Frank and to share why Usher 1F Collaborative has become such an important cause to him.

Frank is a chemical engineer. He received his BE in chemical engineering from the Cooper Union in New York, NY, followed by a PhD in chemical engineering from the Massachusetts Institute of Technology (MIT). Subsequently, he completed a post-doctoral fellowship at the Swiss Federal Institute of Technology in Zurich, Switzerland.

Frank's first job in biotechnology was as a scientist at CytoTherapeutics, eventually managing all clinical programs including the company's ALS and chronic pain phase I and II clinical trials. Jobs at Reprogenesis and Millenium Pharmaceuticals followed, and then he left biotech for capital management, investing in both private and public biotech and medtech companies. His experience culminated in becoming Venture Partner at Third Rock Ventures in Boston, where he helped start companies such as Decibel, Maze, and Casma. He left Third Rock to become first full-time COO and then CEO at Casma Therapeutics, where he remains. Casma develops therapies for neurological conditions.

With his background, it is no wonder that Frank has been an invaluable member of our board, serving not only as an expert scientist who helps evaluate our research grant proposals but also as a bridge between the academic and commercial biotech arenas, helping us in our work to advance our research from the lab to the clinic.

Frank has been married for 38 years to his wife Erin, and they have three children, Stefan, a post-doc in molecular biology and bioengineering at the Broad Institute of MIT and Harvard, Ben, a film and documentary director, and Sam, an occupational therapist.

We asked Frank questions about his involvement with and dedication to Usher 1F Collaborative.

1. **What is your connection to Usher 1F Collaborative and what brought you onto the board as one of its first members?**
   I was asked to be on the board by Elliot Chaikof, one of the founders of the Usher 1F Collaborative. Elliot and I were classmates at MIT where we were both in the PhD program in chemical engineering doing research in polymer science and engineering. Elliot and his co-founder, Melissa Chaikof, wanted a board member with biotechnology industry experience, and given my background in approved product development, private investing, and starting biotech

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companies, they believed I could be useful in helping to make targeted investments in scientific and clinical programs for the Collaborative.

2. **Why is finding a cure for the vision loss of Usher 1F important to you and what motivates you to continue to work with us?**
   As a child and young person, I was very close to my paternal grandfather. He twice immigrated to the US for employment opportunities, once when he was seventeen and again in his 30s during the Great Depression. In 1944, he was blinded in a farm accident in southern Italy. He died in 1992 at the age of ninety. While he was quite functional, I saw how devasting a permanent loss of vision was for him and his entire extended family. I always wanted to work in the area of vision loss, and while I was an investor, one of my best public company investments was in Regeneron Pharmaceutics, a company that developed a drug called Eylea, a novel approach to wet age-related macular degeneration, a common cause of blindness in older adults. During my time at Third Rock Ventures, I worked on starting Decibel Therapeutics, a company focused on hearing loss, which is also a hallmark of Usher 1F. (Coincidentally, Decibel was purchased by Regeneron). Again, I came to realize how painful hearing loss is, especially in young children and how underserved this area was by biotech and pharmaceutical companies. Thus, these personal and professional experiences make me very motivated to do everything I can to help the Usher 1F Collaborative in its mission to find therapies and even a cure for vision loss in these very young people.

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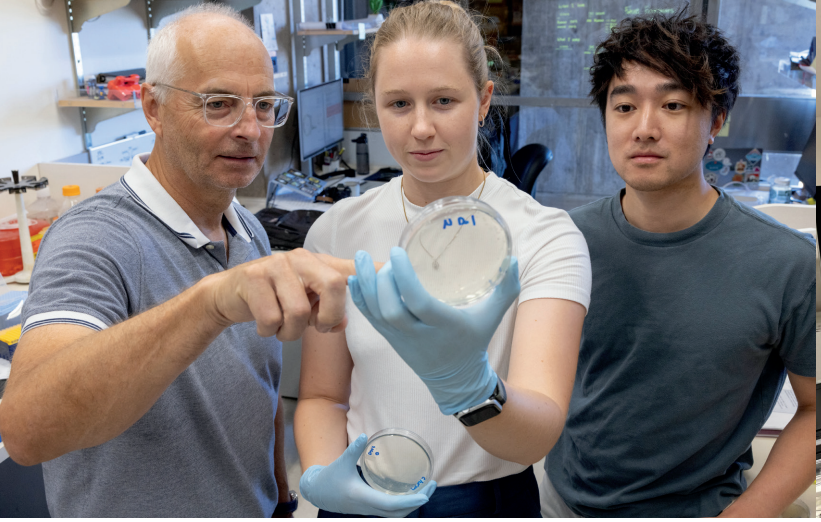
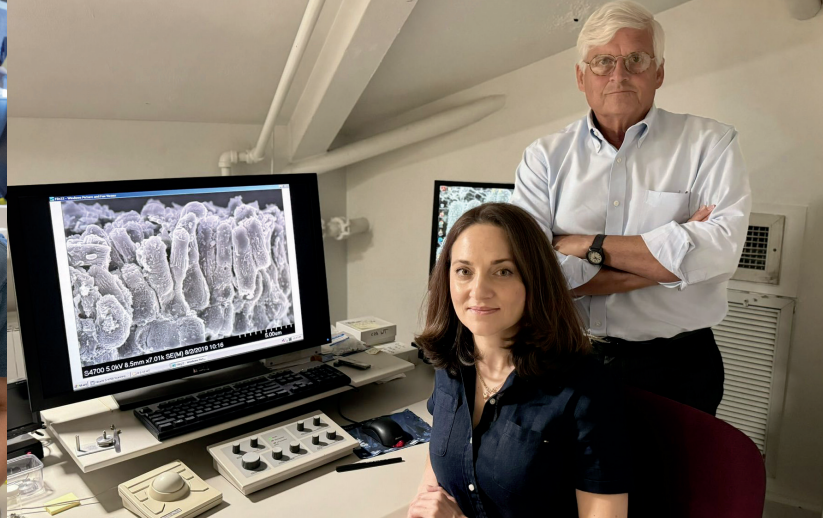
3. **What makes Usher 1F Collaborative unique and enhances its chances for success?**
   There are three things that make the Usher 1F Collaborative unique. First, while there are many such groups focused on raising funds and awareness for specific rare genetic diseases of children, few have the benefit of having a world class physician-scientist as one of their founders. Not only can such a founder help evaluate various research projects for scientific rigor and feasibility, but he or she can also attract other world class researchers to put their talents to work in finding therapies and a cure. Elliot Chaikof is such a founder, and as just one example of how the Collaborative has benefited from his leadership position at Harvard Medical School (HMS), the Collaborative attracted David Corey, a professor at HMS who developed a novel approach to gene therapy for large gene constructs, which is required with existing technology to treat Usher 1F. I do not believe other groups have those kinds of networks.

   Second, Elliot and Melissa Chaikof have created a Board of Trustees for the Collaborative that is a combination of other parents of children with Usher 1F, an adult with Usher 1F, folks that have experience in similar charities, and people who can help evaluate scientific proposals. In this manner, a high percentage of every dollar raised by the Collaborative goes to great researchers with a singular focus of being able to translate scientific discoveries into therapies. The return on investment we have made has led the Collaborative, in a brief period of time, to be on the cusp of a first clinical trial for a therapy for Usher 1F.

   Third, the Usher 1F Collaborative invested in a natural history study of the disease. This allows us to determine the normal time course of the disease and thus will allow the appropriate evaluation of success for potential therapies. As an example, it was not until a natural history study was conducted in Duchenne Muscular Dystrophy that potent therapies were developed. To have a foundation take on this challenge is nothing short of extraordinary. We have also been able, due to the highly professional operation we have, to encourage the Foundation Fighting Blindness to co-sponsor this Usher 1F natural history study. ◆



Usher 1F Salk team – Samuel Pfaff, PhD, with Claire Williams and Ryan Hsu



Usher 1F Harvard team - Maryna Ivanchenko, MD, PhD, and David Corey, PhD

Usher 1F Collaborative Funds a Promising Research Collaboration

Usher 1F Collaborative is excited to fund a promising research collaboration between our teams at Harvard Medical School, David Corey, PhD, and Maryna Ivanchenko, MD, PhD, and The Salk Institute, Samuel Pfaff, PhD.

The most successful gene therapies to date for inherited retinal diseases entail delivering a new, correct copy of the gene to the retina. The delivery vehicle for the gene is an Adeno-associated Virus (AAV). The corrected gene is inserted into the AAV vector. Most of the Usher syndrome genes are large, including PCDH15, the Usher 1F gene, so won't fit on a single vector. Thus, much of the focus of our funded research has been to develop a method of delivering our large gene to the retina. As we have described previously, Dr. Corey's mini-gene is one such approach and is proving very successful in the lab and in pre-clinical testing.

MUCH OF THE FOCUS OF OUR FUNDED RESEARCH HAS BEEN TO DEVELOP A METHOD OF DELIVERING OUR LARGE GENE TO THE RETINA.

Because we want to have multiple shots on goal in order to increase our likelihood of success, we continue to develop additional approaches. One such approach is a dual vector approach. That is, the gene is split into two parts with each part inserted into an AAV vector. Each vector includes instructions for the parts to reassemble into a full gene once in the eye. Dr. Corey has obtained in his lab results a split gene that is equally as successful to his mini-gene. One drawback to this approach, though, is that it is less efficient than inserting a single gene on one vector.

In May 2022, we received an email from the developer of a new technology for delivering dual vectors for inherited retinal diseases, RNA end-joining (REJ) that promised greatly enhanced efficacy over prior attempts with dual vectors. Lukas Bachmann, a former post-doc in Dr. Pfaff's lab, developed REJ during his time at The Salk Institute. After meeting with Drs. Pfaff and Bachmann, Usher 1F Collaborative's board of directors opted to fund development of this approach for Usher 1F.

In October 2022, Drs. Corey and Pfaff met for the first time when we brought our Usher 1F researchers together for a scientific research conference. The two then agreed to collaborate, with Dr. Corey using his expertise in gene delivery of our Usher 1F gene, along with his mouse model, to test Dr. Pfaff's vectors once complete. Bringing these two esteemed and gifted researchers together is not only an exciting opportunity for Usher 1F Collaborative to advance research for a cure but also illustrates the benefits of fostering collaboration among our research scientists to accelerate this effort. ◆

KHALED LABED:

Seeking the Greatest Gift for His Children

Khaled Labed with Bella and Ismail

Khaled Labed and his wife Souheir Hammani live in Paris, France, with their three children, two of whom have Usher 1F. Khaled and Souheir share an unusual connection through their grandmothers. Both of Khaled's grandmothers along with Souheir's maternal grandmother were sisters. They were of Eastern European Ashkenazi Jewish ancestry. Their family emigrated to Algeria in the 18th century. What they did not know is that Souheir's grandmother and at least one of Khaled's grandmothers carried the most prevalent Usher 1F mutation. While their first child was not affected, their two younger children both have Usher 1F.

In 2015, when they had only one child, Khaled and Souheir moved to Morocco for professional opportunities. In December 2018, they returned to Paris for the birth of their second child, Bella, to be close to their families. Although France has universal newborn hearing screening, they were told the test did not work for Bella but they should not worry, that it was likely an issue with the testing equipment. After returning to Morocco, a few months later Souheir noticed that Bella was unresponsive to sound and did not know her name, and their anxiety grew. They remembered the unsuccessful hearing test. Bella also had delayed gross motor milestones and balance issues, suggesting an affected vestibular system.

They immediately consulted a pediatrician, who referred them to an ENT clinic to perform a hearing test, which confirmed that Bella was profoundly deaf. Khaled felt as if "the world seemed to collapse beneath our feet." He felt helpless, wondering if his daughter would ever hear him. Wanting to know more, he combed the internet and learned for the first time about cochlear implants. He and Souheir did not waste a moment, opting to return to Paris in order to obtain the best care for their daughter. While there were excellent ENTs in Morocco, due in large part to the work of Lalla Asmaa, the sister of the king of Morocco, who founded an association for the deaf, follow-up care was lacking. In Paris, they obtained a referral to the Necker hospital to get Bella cochlear implants, and she was bilaterally implanted at age 18 months.

> **"WE HAVE STRONG HOPE THAT THIS REMEDY WILL SAVE THE SIGHT OF OUR CHILDREN AND OTHER CHILDREN. IT IS THE GREATEST GIFT THAT SCIENCE COULD OFFER TO ALL OUR CHILDREN."**

While Khaled and Souheir did not yet know Bella's genetic diagnosis, during his online research, Khaled read that Bella's vestibular symptoms were often associated with Usher syndrome, and he became alarmed. "I saw a double penalty, the absence of hearing and vision! It's a nightmare, but I reassured myself that it was not possible!" That this all took place during the height of the Covid pandemic did not make the diagnosis process easy, but the care at the hospital did include genetic testing, which confirmed Usher syndrome type 1F.

Kahled and Souheir's son Ismail was born in December 2023 and also has Usher 1F. He will receive bilateral implants at age nine months in September.

In Paris, in addition to hearing-related care at the

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First Usher 1F Golf, Tennis & Pickleball Outing - A Resounding Success

On June 10, Usher 1F Collaborative held its first Golf, Tennis & Pickleball Outing at the beautiful Mountain Ridge Country Club in West Caldwell, New Jersey. The day also featured cards and mahjong, as well as a dinner reception with live music and an auction. In all, we hosted more than 250 guests and raised $274,000 for Usher 1F research.

The host committee was comprised of board members Josh Cohen, Eric Halper, Jared and Rachel Root, and Heather Rosenstein. They brought together a long list of sponsors and attendees, some who have been dedicated donors for years, and many who learned about Usher 1F for the first time. Also at the event was board president, Melissa Chaikof, her daughter Jessica, who lives with Usher 1F, and board member and Usher 1F ambassador, Dorie Shapiro. Even Sal Vulcano of *Impractical Jokers* made an appearance to "help" our golfers during the Blind Putting Competition.

Jessica Chaikof, Zachary Root, and Dorie Shapiro, all of whom have Usher 1F

The cards room filled with Canasta and Mahjong players

It was a perfect day of camaraderie and competition, all while sharing our mission with our guests and raising critical funds for life-changing research. We plan to return to Mountain Ridge Country Club on June 9, 2025. If you are in the New Jersey – New York area, we hope you join us! ◆

Usher 1F Collaborative board and staff

SEEING FORWARD

OUR 3-YEAR MAJOR-GIFT FUNDRAISING INITIATIVE TO MEET OUR NEXT BOLD GOALS ON A RAPID PATH TOWARD A CURE

FUNDRAISING UPDATE

$0 **$480,000** $3,015,000

updated on October 1, 2024

usher1f.org/seeingforward

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Necker Hospital, Bella and Ismail receive care for their vision and vestibular issues at the Quinze-Vingts National Ophthalmology Hospital and the Institut Imagine for genetics. Bella is a very happy child who communicates orally with her parents. She enjoys wearing her implants and is making great progress. Through Usher 1F Collaborative, the family connected with our other Usher 1F family in France, and sharing their experiences is helpful to both.

When they first received the Usher 1F diagnosis, "We were completely destroyed," says Khaled, "until I learned of the research done by Professor Corey and the existence of your foundation. We have strong hope that this remedy will save the sight of our children and other children. It is the greatest gift that science could offer to all our children." ◆