50 1970 2020 ANNIVERSARY

DISCOVERY
THE DISCOVERY EYE FOUNDATION

Thanksgiving 2020

The Discovery Eye Foundation supports cutting-edge research related to sight-threatening eye diseases and their treatments.

Supporting vision-saving research at the University of California, Irvine's Gavin Herbert Eye Institute since 2002.

Treatment Accelerator Program Will Speed Path to Patients

In celebration of our 50th anniversary, DEF is launching a program called **Treatment Accelerator Program (TAP).** This new, ground-breaking program is designed to accelerate the speed at which novel, commercially viable treatments for eye diseases reach patients.

DEF already provides important funding to jumpstart promising basic bench research. Recently, we identified a funding gap for projects that need completion of their pre-clinical and proof-of-concept studies. This vital information is required before the projects can move to the next step on their path toward clinical trials and on to patients.

DEF will be able to provide critical bridge funding for these promising studies.

With donors' participation in **TAP,** DEF will be able to provide critical bridge funding for these promising studies. Researchers who receive **TAP** support will be expected to demonstrate commercial viability that will improve the chances of obtaining money from angel and venture funders and/or government grants.

Researchers who are awarded **TAP** grants will need to generate data and demonstrate potential commercial viability by:

- Completing their pre-clinical studies
- Showing proof of concept in appropriate laboratory models
- Illustrating a road to commercialization
- Obtaining vital patent coverage for the product

Several DEF-supported projects that are being worked on currently will be eligible to apply for **TAP** grants, including treatments for dry AMD, glaucoma and diabetic retinopathy, as well as a treatment to prevent future coronavirus pandemics.

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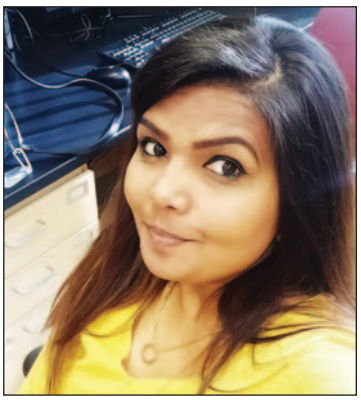
Meet the Researcher Dr. Lata Singh



The first time Lata Singh, PhD, saw an eyeball, it scared her so much that she almost fainted. The eye had been removed from a one-year-old baby who suffered from retinoblastoma, a rare form of cancer of the retina. “Eyes are the most precious organ of the body,” Singh says. “It was hard to imagine a baby without eyesight.” At that very moment, she decided to make ocular-cancer research her life’s work.

From New Delhi, Singh always knew she wanted to be a doctor, but she decided to become a research scientist in order to improve overall human health. She’d never planned to come to the U.S., but she longed for exposure to cutting-edge research, and a chance meeting with DEF Research Director Dr. Cristina Kenney set the stage.

Singh had just started her PhD program in New Delhi and was attending her first conference, the 2013 ARVO (Association for Research in Vision and Ophthalmology) meeting in Seattle. When she saw Kenney, Singh asked her to look at a research poster. “Dr. Kenney was so fascinating, and her research work was so interesting, that I thought to share my research on retinoblastoma with her, and she appreciated my work,” Singh says.

Five years later, they met again at ARVO. By then, mitochondria had become a cornerstone of Singh’s research, and she wanted to reconnect with Kenney, one of the world’s leading mitochondrial researchers. Singh asked Kenney about working at her lab at UC Irvine, but financial circumstances precluded that from happening.

Thanks to a research grant from DEF the following year, Singh was able to become a postdoctoral fellow working with the personalized cybrid models for which Kenney’s lab is renowned. Singh characterized the mitochondrial DNA and cellular defects in cybrids with mitochondria from patients with chronic lymphocytic leukemia (CLL), retinoblastoma, uveal melanoma and other forms of cancers. She also investigated the responses of cancer drugs on the cybrid models.

“I am very thankful to DEF for helping me pursue my dream of improving the outcomes for cancer patients,” Singh says.

Due to go back to India to take a government faculty post in mid-March, when her grant ended, Singh had to remain in the U.S.

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50 Years of DEF-Supported Retinal Degeneration Research

DEF has been generously supported by individuals and families who have retinal diseases in one or more family member. These retinal diseases include age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME) and retinitis pigmentosa (RP). In the early 1970s, having any one of these retinal diseases likely meant a future with severe vision loss. Numerous advances have been made in the diagnosis and treatment of these retinal diseases, and for the past 50 years, DEF has been supporting the researcher-scientists and clinician-scientists on the front lines with patients. Here are some highlights from the past half-century:

Diagnosis

For many years, retinal specialists could diagnosis the type and severity of retinal diseases only using dilated eye exams to capture retinal images and fluorescein angiography on film. This approach yielded information about the structure but did not provide much information about the health of the cells, the vasculature or the structures beneath the retina. In the 1990s, digital imaging with Optical Coherence Tomography (OCT) was introduced to give pseudo-color images, which allowed non-invasive methods to evaluate retinal vessels and structures. These techniques give better resolution and allow evaluation of the far periphery of the retina, where some diseases occur. DEF supported studies with the Optos camera and Heidelberg Spectralis instruments, and these techniques are now the standard of care for patients. More recently, DEF has supported studies using color-vision changes to identify and follow patients with early AMD.

Etiology and Biochemical Changes

AMD involves biochemical/molecular changes in the complement, lipid, angiogenesis and inflammation pathways. Since 2009, DEF-supported researchers have shown that mitochondria of AMD patients are damaged and not functioning properly. Moreover, using the cybrid AMD model, they have shown the damaged AMD mitochondria can be rescued by various drugs/agents. Research worldwide is pursuing drugs to improve mitochondrial functions in retinal degenerations.

Genetics

Some 15%–20% of patients with AMD have family members with the disease. Since the mid-2000s, DEF has supported researchers conducting genetic studies to identify the nuclear gene defects associated with AMD. To date, there are more than 52 variants in 34 nuclear genes associated with AMD. DEF has supported work demonstrating that some mitochondrial DNA (mtDNA) haplogroups are associated with high risk of developing AMD, while other mtDNA haplogroups are protective against AMD. Most recently, researchers funded by DEF are applying Next Generation Sequencing (NGS) to identify the low-level mtDNA variants associated with the development and progression of AMD. This genetic information can be correlated with the clinical outcomes and responses to medications for many AMD patients.

Each of these steps forward has improved vision and outcomes for retinal degenerations.

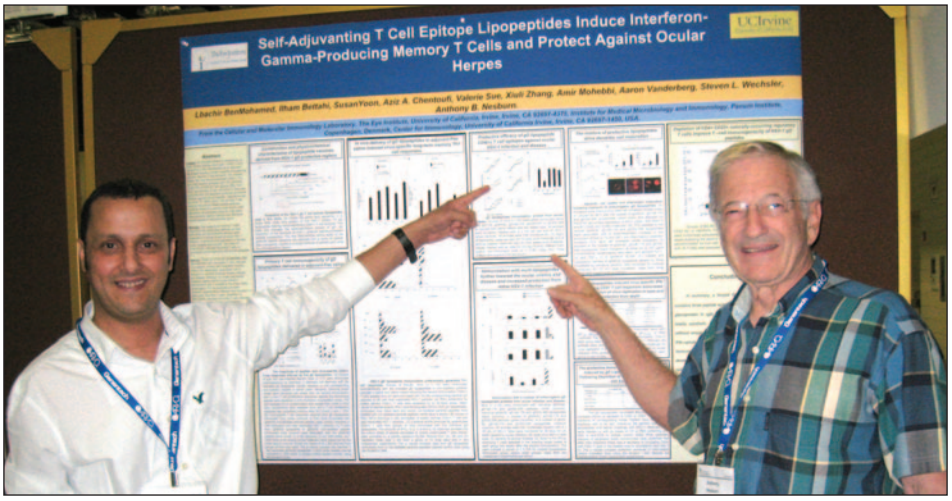
Treatments

DEF has supported the development of stem cells to treat RP and, hopefully, AMD and DR/DME. A powerful mitochondria-targeting drug is in pre-clinical trials to demonstrate its efficacy on retinal degeneration models. DEF-supported researchers are also collaborating with established ophthalmic companies to test the responses to their drugs in the AMD cybrid cells and human retinal cell lines *in vitro*.

Each of these steps forward has improved vision and outcomes for retinal degenerations, including AMD. The biggest gap in knowledge is how to treat patients with the dry form of AMD. DEF continues to fund studies to find therapies for this disease.

A History of DEF-Supported Virology Research

The researchers at DEF have always had a strong interest in diseases caused by viruses, particularly the blinding disease caused by Herpes simplex virus (HSV). While at Harvard Medical School, Dr. Anthony Nesburn, the medical director of DEF, participated in the discovery of the very first antiviral medication, idoxuridine, which successfully treated acute human ocular HSV infections.



BenMohamed (L) and Nesburn at an ARVO conference

Upon his return to Los Angeles, Nesburn's herpes research was supported by DEF. This allowed him to apply for and receive more than 30 years of funding from the National Eye Institute to expand his work on diagnosis and treatments for ocular HSV.

"Since its inception, DEF always has supported researchers who have contributed knowledge related to HSV genetics, latency, reactivation and vaccine development," Nesburn says.

DEF-supported virology research from the past 50 years has resulted in more than 100 publications in peer-reviewed journals, marking DEF-supported scientists as world authorities in virology. Here are a few highlights:

Biochemical and Molecular Changes

In 1986, Steve Wechsler, PhD, was hired to investigate how HSV infects, disappears and reappears in many patients throughout their lives — the so-called latency and reactivation cycle of HSV that causes blinding corneal disease. Early DEF support helped Wechsler obtain long-term funding. He was the first scientist to describe the molecular mechanisms that allow HSV to become dormant in a person's body. An example of this hiding and reactivating is the lip cold-sore virus that affects millions of people. This same event can occur in the eye, causing scarring and vision loss. Wechsler's findings opened up an entire new field of investigation: understanding and controlling reactivation of the herpes virus.

Treatments

Treatment for the HSV virus can take place once the infection occurs and there are active lesions, using modern antiviral medications that were developed after the original idoxuridine. For many years, DEF supported work to improve antiviral medications to treat herpes infection and prevent the disease caused by virus reactivation. But these medications are expensive and not readily accessible in the third world, where HSV is rampant.

Developing and deploying a vaccine for HSV prevention would be ideal. Lbachir BenMohamed, PhD, an immunologist and vaccine expert from the famous Institute Pasteur in Paris, joined the group and undertook the challenge. His work was initially funded by DEF and has been continually supported by several NIH grants. To date, no herpes simplex vaccine has gained FDA approval. The BenMohamed herpes vaccine, which could protect millions from ocular and even genital herpes, is poised to enter an FDA Phase 1 safety study. The "epitope" technology developed for this herpes vaccine is the approach BenMohamed has used to develop his revolutionary pre-emptive, pan-coronavirus vaccine. *See the back page for more on this.*

A History of DEF-Supported KC Research

DEF was originally founded by Rita and Morris Pynoos, in part, to conduct research and patient education for people with keratoconus (KC). With the help of KC patients and DEF funding, many advances have occurred since DEF was first started 50 years ago. Here are some highlights from the past half-century:

Diagnosis

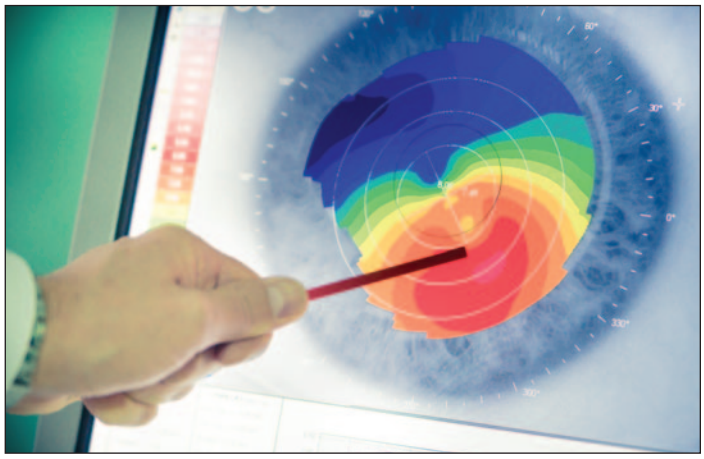
Initially, the only way to determine if someone had KC was to shine images of circles on the front of the cornea and measure if they were regular in appearance. Because of the difficulty of diagnosis, thousands of KC patients went without a diagnosis until the disease became severe enough to be recognized. This changed in the mid-1990s, when instruments were developed that could measure the corneal surface in early-KC patients. Known as "corneal topography," this advancement revolutionized the diagnosis of KC.

Etiology and Biochemical Changes

When DEF began, we knew KC patients had thin corneas, but the biochemical cause was not known. In the late 1990s and early 2000s, DEF-supported researchers investigated the biochemical changes in KC corneas. They found that KC corneas had increased enzyme activities that broke down the sturdy collagen fibrils. This allowed the corneal fibrils to "slip" and stretch out to become thinner. It was then discovered that oxidative stress played a major role in the activation of the degradative enzymes and resultant thinning.

Genetics

For the majority of KC patients, no one else in their family has the disease, and fewer than 10% have more than one family member with KC. When DEF first started, we had no idea about the genes involved. In the late 1990s, investigators began analyzing the DNA of KC patients and their families to identify gene defects that increased the risk for KC. Today, with increased sophistication of sequencing techniques, more than 20 genetic changes have been associated with KC.



Corneal topography with typically steep KC changes

Treatments

Corneal crosslinking (CXL) has revolutionized treatment for KC. In recent years, DEF-supported studies using femtosecond laser technology have been carried out to more precisely deliver the energy required to crosslink the corneal collagen fibrils and improve patient outcomes.

Each of these steps forward has improved the vision and outcomes for KC patients. We still have many unanswered questions about KC. For the past 50 years, DEF has been committed to our KC patients, and we will continue supporting vision-saving KC research.

DOUBLE YOUR GIFT TO DEF!

Does your employer offer matching-gift funds? If so, you can double your gift!

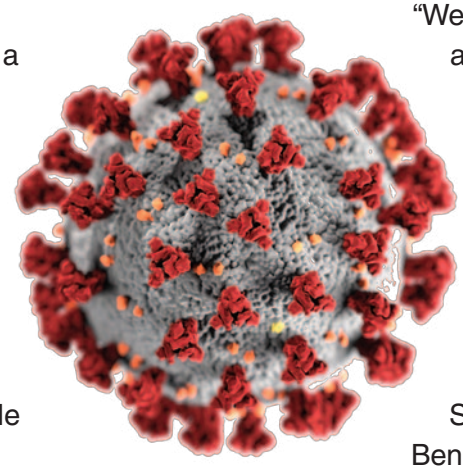
$25 becomes $50 • $100 becomes $200 • $1,000 becomes $2,000

If your employer offers matching gifts, ask for a matching-gifts form. It's as easy as that, and you can double your meaningful gift to support cutting-edge research.

DEF-Supported Herpes Research Could Lead to Coronavirus Vaccine

DEF-supported researcher Lbachir BenMohamed, PhD, a professor and director of the Laboratory of Cellular and Molecular Immunology at UC Irvine's Gavin Herbert Eye Institute, is making progress on a novel "pre-emptive pan-coronavirus" vaccine.

Most research efforts aimed at a COVID-19 vaccine are targeted specifically at the familiar spike protein (pictured), which is believed to be most responsible for the virus' ability to latch on to human target cells. But there are 11 other proteins in the coronavirus. BenMohamed's team is targeting all 12 proteins, in an effort to protect people from all coronaviruses.



"This vaccine is pre-emptive, because there will be another outbreak of another coronavirus," BenMohamed says. "It's not a question of *if*, it's a question of *when*."

The idea for this vaccine approach stemmed from work BenMohamed was already doing to develop a vaccine against herpes simplex (HSV-1), a virus that can affect vision. Twelve years ago, with DEF support, BenMohamed began this research project, which is currently awaiting its Phase 1 clinical trial. According to BenMohamed, COVID-19 also can affect eyes (conjunctivitis may be a sign of infection), so he believes both viruses can be tackled with the same approach.

"As soon as the genomic sequence of SARS-CoV-2 came out, we jumped on it," BenMohamed says. "We started identifying the building blocks and did microsurgery on the virus to identify the regions that are being recognized by T-cells and antibodies."

Those sections of the viral proteins are called epitopes; they evoke an immune response. The lab's vaccine is multi-epitope in nature, using the epitopes from all the proteins within SARS-CoV-2. The results are promising. BenMohamed expects to finish the preclinical stage of laboratory work toward the end of 2020, and begin Phase I clinical trials next year.

If successful, the vaccine would be effective both at preventing cases of COVID-19, by stimulating the body to build immunity against it before infection, and treating the disease in infected people, by stimulating a stronger immune response. This pre-emptive vaccine could also be used for prevention of future coronavirus outbreaks, and the same multi-epitope method might be usable for vaccines against other viral respiratory illnesses, including the flu or pneumonia.

TAP

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"As we celebrate five decades of sight-saving research, this is the perfect time to accelerate patient-oriented research outcomes," Dr. Anthony Nesburn, DEF's medical director, says. "Creating **TAP** to specifically target and accelerate the most promising and commercially viable sight-saving projects to reach real patients will make a marked difference in the lives of those dealing with eye disease."

Singh

(continued from inside)

because of COVID-19. But thanks, again, to DEF, she was given a six-month extension to keep working with Kenney on DEF's COVID-19 project.

"I learned so much from Dr. Kenney, and I don't want to leave her," she says. "But I love my country, and I am excited to go back, and grow from a student to a leader."