Spring 2022

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Australia

HOPE IN SIGHT
GIVING DAY
13 October 2022

Join the fight on World Sight Day

It has been incredible to see exactly how far research has taken us.

It was not too long ago many conditions – including inherited retinal diseases (IRDs) and age-related macular degeneration (AMD) – were considered completely untreatable.

But now, thanks to years of hard work and collaboration in order to fully understand the mechanisms behind these diseases, we are closer than ever before to many new and improved therapies.

Our teams were part of a long-term collaboaration to identify the genetic profiles of people with AMD and glaucoma in order to predict the treatments most likely to be effective for them (page 6).

We're also closer to bringing a potential gene therapy for one of the most common IRDs in Southeast Asia to a clinical trial (page 12).

And we're connecting with people living with these diseases to make sure new treatments can reach them as soon as possible (page 8).

This includes Jasmine Mercieca, who is sharing her experience of living with retinitis pigmentosa to encourage others to support vision research.

On World Sight Day – Thursday 13 October 2022 – CERA is holding the third Hope in Sight Giving Day to raise funds to support this research. For every dollar you donate, we receive $2 in matched donations from generous, anonymous donors who have chosen to support our work – tripling the impact of your gift.

Your donation will support all our research teams as they run world-leading clinical trials and lab-based research to find treatments for previously untreatable diseases. Please save the date – 13 October 2022 – and together we can continue on this journey of discovery.

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*All of the photography in this publication complies with COVID 19 restrictions. Some of the images were taken in 2019 before the pandemic.

Jasmine, with her parents Frank and Grace.

Jasmine's vision for success

Photo: Anna Carlile

Jasmine hasn't let her diagnosis of an inherited retinal disease stand in the way of her ambitions.

Like other nurses in Melbourne's busy hospitals, Jasmine Mercieca is working hard to help save lives.

"I like working in a fast-paced environment where you can have the biggest impact," she says.

The only difference to many of her peers is that Jasmine has retinitis pigmentosa – a type of inherited retinal disease (IRD) that causes progressive, irreversible vision loss.

Living with an IRD

IRD is an umbrella term for a range of genetic eye diseases that cause retinal cells to stop functioning properly, leading to progressive vision loss.

More than 300 genes are associated with inherited retinal diseases. Genetic errors can be passed down from parent to child – but they do not always result in vision loss.

This means an IRD can happen when there is no known history, as it did in the Mercieca family.

"At first, my parents felt a bit guilty, thinking they gave me the inherited disease," she says.

At the same time, Jasmine says the whole family was behind her from day one: "Even when I see my specialist, everyone wants to be in the room."

(Continued Page 4)

"I'm excited to tell my story and be part of CERA's research because, even if it doesn't help me, there's a chance it will help other people."

– Jasmine Mercieca

For her mother, Grace, the diagnosis came as a surprise: "We took her to find a cool, new pair of glasses for her first day of high school. The optometrist noticed something right away and referred us to a specialist. That's when we found out she had retinitis pigmentosa."

Grace says that, coming from traditionally private families, this was a difficult process for her and husband Frank: "We all got tested, but we've never been able to find the link."

Jasmine feels lucky her condition didn't affect her much during her teens: "When you're younger, you're not thinking about your future. As I get older, it's scary because I realise this is happening now."

Even in its earliest stages, retinitis pigmentosa still impacts her daily life: "If I'm tired or looking at a screen a lot, my eyes get quite dry and itchy, and my vision can go very blurry.

"My peripheral vision also isn't amazing, so I can't drive a car. It's frustrating because there is no public transport where I live, and I can't travel independently."

Retinitis pigmentosa affects Jasmine mostly at night and in dimly lit environments: "Last night, I asked Hayden, my partner, to pass my phone. When I thought he was ignoring me, I said: 'Give me my phone!' And he replied: 'It's right in front of you!'"

No career barrier

Fortunately, Jasmine's vision is no barrier to being a nurse.

Her career inspiration came just after completing high school. At the time, she

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Looking forward: Jasmine with her sister Nicole.

was studying environmental science while also caring for her 92-year-old grandfather. "Nurses would visit to make sure he took his insulin and general care of himself. It made such an impact, I decided to study nursing instead," she says.

Her father, Frank, says Jasmine has always wanted to help make a difference: "She even used to volunteer in the local area planting trees."

Though naturally proud, Frank was also slightly surprised about her choice of career: "Jasmine used to be too scared to even get a needle," he says laughing.

Since graduating in 2021, Jasmine says she's thriving in the challenging and rewarding world of theatre nursing: "The pandemic has put pressure on junior staff, like myself, to really step up. But I'm loving it and wouldn't do anything else."

Natural history study

Jasmine is part of the VENTURE natural history study, led by CERA and the University of Melbourne, and says her family actively encouraged her to participate. "Mum is always texting my specialist, asking whether there's anything I can get involved in."

Until recently, someone diagnosed with an IRD was told that progressive and irreversible vision loss was inevitable. However, with rapid advances in gene and cell therapy research, there is hope for the future.

VENTURE study leader Associate Professor Lauren Ayton says her team aims to create a database containing information about people's vision, genetic profile and availability to take part in clinical trials: "This means that when new clinical trials are available, we will have people ready to take part, giving Australians access to world-leading treatment options as soon as possible."

Hope in sight

While it's scary living with the uncertainty of not knowing how fast her vision loss may progress, Jasmine says the support of loved ones, like Hayden, brings hope: "There are people out there who'll care about you unconditionally – and won't mind that your eyes are a little bit crap."

Grace says her daughter is determined to not let retinitis pigmentosa rule her life: "It's only now she wants to be involved in these trials because, even a few years back, she was in denial."

Jasmine has had time to reflect and is now at peace with having retinitis pigmentosa: "That's why I'm excited to tell my story and be part of this research because, even if it doesn't help me, there's a chance it will help other people. So why wouldn't I do it?"

Hope in Sight Giving Day – 13 October 2022

➜ **Register to donate now at charidy.com/HopeInSight**

➜ Every dollar you donate means three dollars will go to support our work to fight inherited retinal disease.

Photo: Anna Carlile

Charting a path

CERA is part of a collaboration paving the way towards new, precision treatments for AMD and glaucoma by identifying the genetic signatures of each disease.

Genes, the biological instructions that tell cells how to operate, play a crucial role in the human body.

However, genes are also fundamental to many diseases, and specific genes are often associated with particular disorders.

Identifying the genes linked to a condition can guide researchers to improve current treatments, as well as the development of whole new therapies.

This idea has driven the research of CERA's Principal Investigator Clinical Genetics Professor Alex Hewitt.

"We have been building a program of research where we're interested in stem cell studies to model disease at a very large scale to do screening for future clinical trials," says Professor Hewitt.

"This work is the culmination of contributions from many research teams around Australia, and we are grateful for our close collaborations, particularly with Professor Alice Pébay, who is based at the University of Melbourne and Professor Joseph Powell from the Garvan Institute of Medical Research."

By transforming one type of cell into another, Professor Hewitt and his collaborators hope to one day match people living with age-related macular degeneration (AMD) and glaucoma to new, emerging treatments.

AMD identified

AMD – the progressive deterioration of the macula which can lead to the loss of central vision – is an important target for research.

While the 'wet' version of the condition can be stabilised with regular injections, there is currently no treatment for 'dry' AMD.

With a wave of potential new treatments now coming close to clinical trials, identifying genes associated with the disease can

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Identifying genes: (from left) Dr Helena Liang and Professor Alex Hewitt from CERA's Clinical Genetics team.

point researchers towards the treatment most effective for any individual patient.

To find these genes researchers compare healthy tissue to that of someone affected by the disease, but collecting samples would typically require a very invasive procedure.

Instead, the team took skin samples from both healthy people and those with late-stage AMD.

Both sets were reprogrammed to become induced pluripotent stem (IPS) cells, which were then guided to become retinal pigment epithelium cells – the cells affected in AMD.

Comparing 127,600 cells revealed 439 molecular signatures associated with AMD, with 43 of those being potential new gene variants.

Glaucoma detailed

The team have also used the same technique with people affected by primary open angle glaucoma.

Retinal ganglion cells – which transmit visual information from the eye to the brain via the optic nerve – are essential for vision.

In glaucoma, the gradual damage and death of these cells leads to a progressive, irreversible decline in sight.

By comparing stem cell models of the retinal ganglion cells of people with primary open angle glaucoma to those without the disease, the team uncovered more than 300 novel genetic features.

"Glaucoma is often an inherited condition, and comparing diseased retinal ganglion cells with healthy one is an effective way to increase our understanding of the mechanisms that contribute to vision loss," says Professor Hewitt.

Professor Hewitt says the research provides hundreds of new targets for researchers developing new drugs to treat glaucoma.

"Current therapies are limited to slowing vision loss by reducing pressure in the eye – but they do not work for all patients and some people continue to lose many retinal ganglion cells and vision despite having normal eye pressure.

"The rich source of genetic information generated by this research is an important first step towards developing new treatments that go beyond lowering eye pressure, and can reverse damage."

Read the research

Daniszewski et al. (2022) Retinal ganglion-cell specific regulation in primary angle open glaucoma, *Cell Genomics*
doi: 10.1016/j.xgen.2022.100142

Senabouth et al. (2022) Transcriptomic and proteomic retinal pigment epithelium signatures of age-related macular degeneration, *Nature Communications*
doi: 10.1038/s41467-022-31707-4

CERA is grateful to the generous philanthropy of the Joan and Peter Clemenger Foundation and estate of the late Philip Neal, which funded the essential infrastructure to support our IPS cell research.

Venturing forward

Photo: Anna Carlile

A registry gathering vital information on people with inherited retinal diseases will help drive research and improve access to clinical trials.

Jane Cherry's path to being diagnosed with retinitis pigmentosa at the age of 32 was rapid and unexpected.

"I knew from my early 20s I couldn't see well at night, but I'd never heard of retinitis pigmentosa so couldn't make the connection as to why," says Jane.

"No-one in my family had the disease, so I was completely shocked by the diagnosis. I didn't know what it was or what would be next for me."

She received her diagnosis following genetic testing at the Ocular Genetics Clinic at the Royal Victorian Eye and Ear Hospital, but for many others the process is not always as swift.

Retinitis pigmentosa is part of a group of genetic eye diseases collectively known as inherited retinal diseases (IRDs).

IRDs are caused by genetic mistakes, which damage the light-sensing cells of the retina at the back of the eye, leading to progressive, irreversible vision loss.

New hope

Less than a decade ago, someone with an IRD would be told to prepare for a future of declining vision, and little research into them was done.

However, advances in genomic research have enabled more people to find out what is causing their vision loss and be matched with emerging treatments.

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Searching for IRDs: Clinical optometrist Bhaj Grewal at work.

Jane (right) – who now serves on the Board of Retina Australia and the Retina International Youth Council – says receiving a genetic diagnosis was invaluable.

"Knowing what I had didn't necessarily change the outlook for me – but it did arm me with more information."

Jane is one of more than 250 Australians taking part in the Victorian evolution of inherited retinal diseases natural history registry (VENTURE study) – a collaboration between CERA and the University of Melbourne.

The study – led by Associate Professor Lauren Ayton, Head of the Vision Optimisation Unit at the University of Melbourne, and Dr Tom Edwards, Principal Investigator Retinal Gene Therapy at CERA – aims to drive research into IRDs and give more people with the condition the opportunity to take part in research.

Holistic approach

VENTURE takes a holistic approach to improving understanding of IRDs, how they progress and their impact.

Participants receive an examination which includes testing the function of their retina and asking them about their vision and optional genetic testing.

The VENTURE team works closely with CERA's Retinal Gene Therapy Unit, which conducts clinical trials of gene therapies and other innovative new treatments.

Currently, the team is running clinical trials for people with Usher Syndrome and Stargardt's disease, testing an investigational gene therapy for dry age-related macular degeneration and planning upcoming trials for other IRDs.

VENTURE also works with patient advocacy groups to better understand how people with IRDs and their families can be supported.

Know your code

Patient registries such as VENTURE are becoming increasingly important, as many emerging treatments depend on knowing the genes that cause vision loss.

So far over two-thirds of VENTURE participants have received genetic diagnoses.

"The point of diagnosis can be a very difficult time for you, your family and friends," Jane says.

"When you have a rare disease, knowing where to find relevant information, the supports available, understanding the benefits of genetic testing and awareness of emerging research are vital."

Project funding

The VENTURE study is supported by the National Health and Medical Research Council, University of Melbourne Driving Research Momentum Fellowship, Melbourne Medical School and CERA strategic grants and philanthropic funding from Retina Australia, the CASS Foundation and Angior Family Foundation.

More information

For more information or to express interest in getting involved in this study, please contact the IRD research team at **IRD@groups.unimelb.edu.au**

Understanding female IRD carriers

Research into X-linked inherited retinal diseases has often focused on men. Now, a study aims to ensure everyone benefits from emerging treatments.

Inherited retinal diseases (IRDs), a broad group of genetic eye conditions caused by changes in a person's genetic code, don't always affect men and women in the same way.

"A majority of female carriers of X-linked IRDs have a near-normal retina, while at the other end of the spectrum is quite severe disease, similar to what males with these conditions experience," says Sena Gocuk, optometrist, CERA researcher and PhD candidate at the University of Melbourne.

The condition of many female carriers is often so mild it's only identified after a male relative has been diagnosed with an IRD.

That's why past research has focused only on men. However, it is now known that some women are much more significantly affected, and can become legally blind even as a carrier.

Operating instructions

Chromosomes are the thread-like structures located inside the nucleus of living cells. They contain the instructions for how those cells should operate – and also determine a person's biological sex.

Females have two X-chromosomes and males have one X and one Y, so certain IRDs can affect the sexes in very different

ways, as Gocuk explains: "Conditions like choroideremia, and some forms of retinitis pigmentosa, are X-linked conditions, meaning they are caused by faults in the X-chromosome."

As men only have one X-chromosome, a single copy of the mutated gene means they'll develop the retinal condition. For women, an X-linked retinal condition may present quite differently – with some having no symptoms and others noting vision changes.

"If a female has one mutated and one normal gene, individual cells randomly decide which of the two X-chromosomes are expressed. Because of that, you get a wide spectrum of disease severities."

Survey and study

During clinical visits, Gocuk will learn more about the eye health of female carriers, with participants receiving genetic testing and counselling, as well as undergoing comprehensive eye examinations to assess their retinas. They can also continue in the study to monitor how their vision changes over time.

In another part of her study, Gocuk is asking female relatives of men with X-linked IRDs to complete an online survey to develop a better understanding of how these conditions affect women.

Gocuk says previous questionnaires that have looked at female carriers of other genetic conditions found many women experience "shock, guilt and anxiety" when male relatives are diagnosed.

"One of my participants became quite teary when speaking about her experiences,

Optometrist and CERA researcher Sena Gocuk

because she has a number of male relatives with retinitis pigmentosa. She knows this research might not benefit her or her children, but she wants to contribute.

"It's been quite rewarding to hear these stories."

As a recipient of the University of Melbourne's Harold Mitchell Postgraduate Travelling Fellowship and a Choroideremia Research Foundation (USA) travel grant, Gocuk is using the funds to travel to the University of Oxford to examine 10-year data from a UK longitudinal study.

This project runs alongside another ongoing study at CERA that is surveying people who are living with an IRD, known as the Victorian evolution of inherited retinal diseases – natural history registry (VENTURE).

Gocuk hopes her research helps lay the groundwork in determining whether more women can benefit from emerging treatments, like gene therapy.

"It would be quite rewarding – and potentially life changing – for female carriers of X-linked eye diseases."

If you think you're a female carrier of an X-linked inherited retinal disease or would like further information, please email Sena Gocuk: sena.gocuk@unimelb.edu.au

Crystal-melting proteins

There are promising results for a potential gene therapy that targets Bietti Crystalline Dystrophy.

A possible treatment for Bietti Crystalline Dystrophy is one step closer to clinical trial following positive results in the lab.

"While not many non-ophthalmologists may have heard of Bietti Crystalline Dystrophy, it's actually one of the most common inherited retinal diseases in Southeast Asia," says Dr Tom Edwards, Principal Investigator at CERA.

"Also, from a scientific point of view, it has a number of features that make it an appealing target for gene therapy."

The research to find an investigational therapy, led by Dr Edwards, ophthalmologist Dr Doron Hickey and their team, has reached a milestone following the publication of their work in the journal *Scientific Reports*.

The paper identifies a viral vector with the capabilities to deliver the therapy, bringing it one step closer to a clinical trial.

Missing proteins

The condition is caused by a fault in the CYP4V2 gene, which provides the instructions that the body uses to create a particular protein in the eye.

This protein has a critical role in breaking down lipids – a type of fatty acid. But for people missing this protein, this process is interrupted.

Crystal melting: Dr Tom Edwards (left) and Dr Sloan Wang.

"Without this protein the lipids do not break down, leading to the crystals that form on the retina that impair vision," says Dr Sloan Wang, Research Fellow in the Retinal Gene Therapy Unit, who led the lab that undertook the work for this project.

"If we can introduce the protein back into the eye, it could be possible to dissolve the crystals."

Special delivery

To do this, the team have taken the missing gene and put it into a viral vector called AAV2.

Their lab research verified that this method is an effective method of delivering the missing gene.

"This type of therapy is called gene supplementation therapy," says Dr Wang.

"The healthy gene that we introduce into the cells starts copying itself, and then starts to produce the protein in the eye."

The effect has the potential to reverse vision loss.

"Then once the crystals are dissolved, we'll then, theoretically, be able to restore a person's vision," says Dr Wang.

The next stage for the research would be testing the treatment outside of the lab.

"We've shown about as much as we can in a laboratory setting – that this treatment has a good prospect of treating the disease," says Dr Edwards.

"The next step would be going ahead with a clinical trial."

Building on the success of his work, Dr Wang was recently announced as a 2022 Graduate Education Fund Scholar by the American Australian Association.

The prestigious scholarship will allow him to study at Yale University for a year, where he will focus on the development of novel viral vectors for future gene therapies.

"There's an old saying about the efficacy of the gene therapy: delivery, delivery delivery," says Dr Wang.

"The deliverer of genes is the foundation of all gene therapies.

"What I will be working on is a way to deliver the gene therapy that is safer, more effective, and with less limitations.

"It'll be interesting to develop those skills and bring them back to CERA."

Dr Edwards says the opportunity reflects Dr Wang's many successes at CERA and is a well-deserved opportunity.

"Sloan has been an outstanding postdoc, and he'll come back from this even better and more accomplished as a scientist."

Read the research

Wang, JH., et. al. (2022) AAV2-mediated gene therapy for Bietti Crystalline Dystrophy provides functional CYP4V2 in multiple relevant cell models. *Sci Rep*
doi: 10.1038/s41598-022-12210-8

A life of service

CERA is grateful to the late Geoff Burfoot for his generous bequest to support vision research.

Throughout his life, Geoff Burfoot was known as a generous man. When he passed away, aged 94, a total of 52 charities benefited from his will.

Close friend and retired Anglican priest Graeme Hodgkinson says Geoff also supported people financially when in need: "The Anglican Church in Tyalgum received a new roof with Geoff's help. He was always willing to share his wealth for a good cause."

Early life

Geoff grew up in Sydney's Upper North Shore and suffered from poor health as a young man.

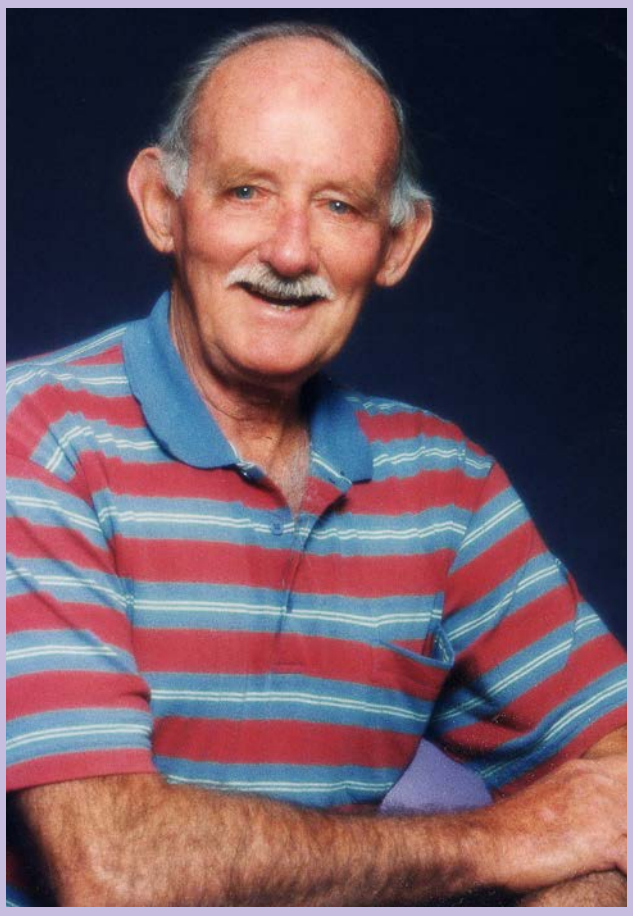
When his doctor recommended a warmer climate, Geoff made the big move to Papua New Guinea (PNG).

He loved his adopted country and joined the Provisional Administration of New Guinea in 1946 as a patrol officer – just after the end of World War II.

Starting in Port Moresby, Geoff served throughout PNG and eventually rose to the rank of Assistant District Officer.

A friend and superior officer from Geoff's time in the service says he had a reputation for being a "man of high morals" and was "different to the run-of-the-mill officers".

In 1961, Geoff cut his leave short to assist in the recovery following the catastrophic eruption of the Mount Lamington volcano.



↑ *Life in service: Geoff Burfoot lived an adventurous life in support of others.*

For nine months, Geoff led patrols into the disaster zone to find villages that had been destroyed – helping locals and burying the dead.

At the same time, Geoff was known as a bit of a character, as a friend explained: "Our kids loved it when Geoff visited. He learned all the traditional dances and performed them with great gusto in front of anyone interested in watching.

"If you visited his house, you never knew how you'd find him. Once I found him hanging from the rafters by his ankles doing exercises. As an entertainer, Geoff had no equal."

Back in Australia

Though Geoff loved his life in PNG, he returned to Australia in 1975 after the Declaration of PNG Independence.

He bought a property in the bush, near the small Northern Rivers town of Tyalgum in NSW and fell in love with the countryside.

Here, Geoff grazed cattle and practised the skills he developed at the Australian Natural Therapy College in Sydney.

Geoff's talents also extended to the kitchen. When Geoff's sister Jo visited from Sydney, Graeme and his wife always got an invitation to dinner.

"He'd ask us what we preferred out of German, English, Japanese and other Asian dishes. He was an expert at cooking any traditional style of meal," Graeme says.

Final years

Geoff's endless generosity was not lost on the people of Tyalgum. And when he could no longer drive, the locals banded together to deliver meals to his property and drive him into town to grab supplies.

"When we parked outside the post office, Geoff would blow the car horn three times at full blast, then wait for the postmaster to come running with his mail and papers. Everyone in town knew when Geoff was picking up his mail," Graeme says.

Graeme says toward the end of Geoff's life, Geoff ate almost every day at the local café, with a special table always reserved: "Woe betide the management if, for any reason, the table was in use by someone else!"

Graeme visited Geoff regularly in his final years and says he was a man of great faith: "We enjoyed a muscat or two each Monday and talked about many subjects. He was well prepared for his passing when the time came."

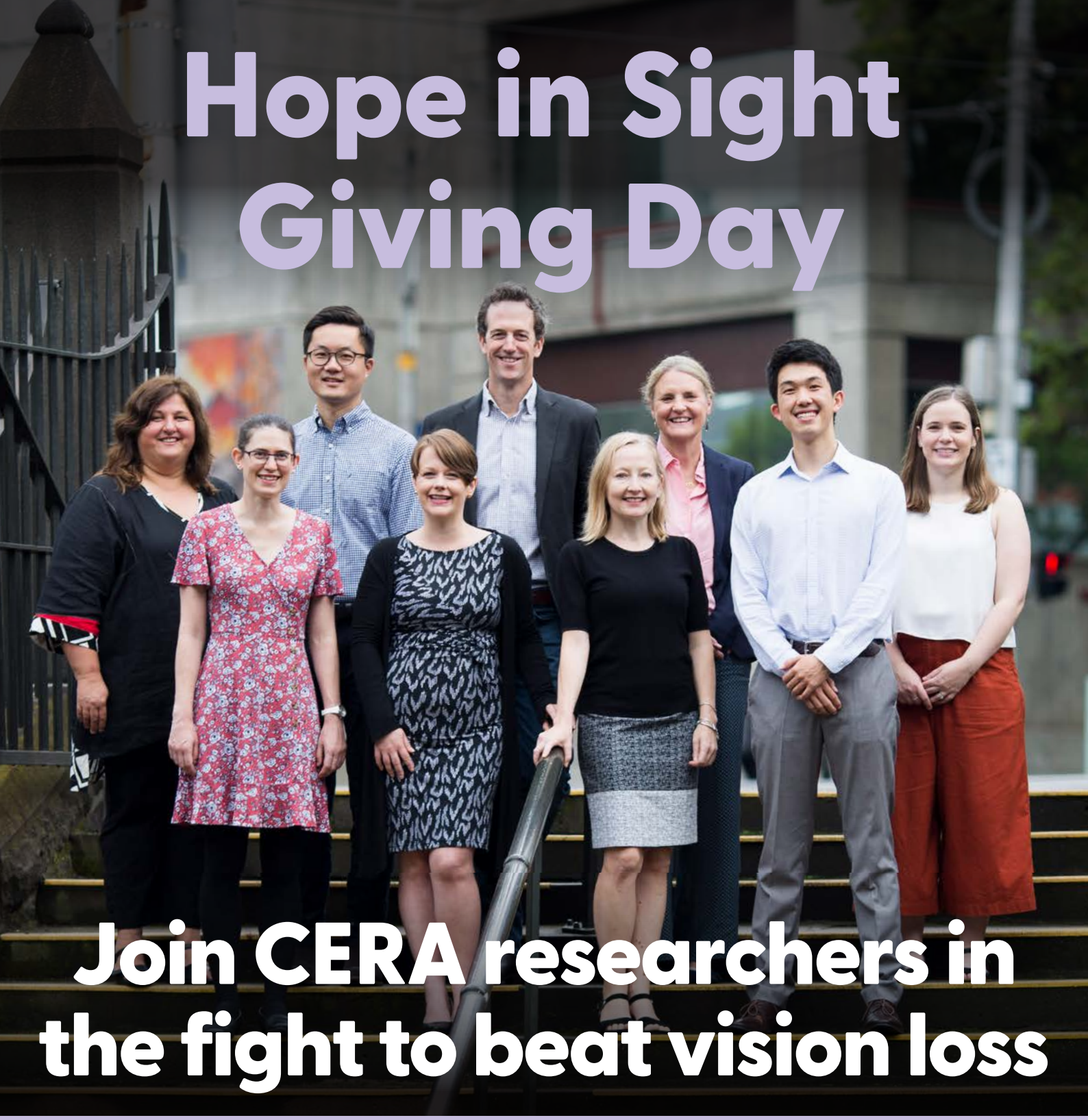
By including a gift in your will to the Centre for Eye Research Australia or the Centre for Eye Research Australia Foundation, your support for new medical discoveries to treat and cure eye diseases can continue.

Your gift will contribute to research projects that are most important to you and will have the greatest impact on eye health in the future.

If you're considering leaving a gift in your will to advance CERA's research, please call our Donor Relations Advisor on **1300 737 757** for a confidential discussion.

For more information, visit **cera.org.au/gifts-in-wills**

Hope in Sight Giving Day



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