Spring 2020

visionary

Hope in sight™

Hope in Sight GIVING DAY on World Sight Day OCTOBER 8

Help us get closer to a cure for inherited eye diseases

Give hope to people with vision loss and blindness

CENTRE FOR Eye Research Australia

HOPE IN SIGHT GIVING DAY

Help us bring hope on World Sight Day.

Each year on World Sight Day, CERA joins countless others around the world raising awareness about blindness and vision impairment.

This year's theme – Hope in Sight – resonates deeply with our mission. It speaks to the optimism we feel that our research can create a better future for people experiencing vision loss and blindness.

Gene and cell therapy are two emerging technologies offering new hope for patients who were once considered untreatable. Inside, you can read about the exciting research CERA is leading in these areas.

The people affected by vision loss are at the forefront of our research goals. On page 8, you'll meet sisters Kate and Nicole Barrett. They have an inherited retinal disease that gene therapy has the potential to treat in the future.

Life-changing breakthroughs for people like Kate and Nicole are within our reach. Now is a critical time to ramp up our efforts.

On World Sight Day, we're running our inaugural Hope in Sight Giving Day to raise funds for our promising gene therapy research. For every $1 you give, CERA receives $3 through matched donations.

Save the date – **October 8** – and please donate to bring us closer to finding a cure for inherited eye diseases.

Keith Martin

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New frontiers

Rapid improvements in biotechnology are creating a new era in research, treatment—and possibly, reversal—of blinding eye diseases.

In barely a decade, studies in eye health have undergone a revolution. New techniques and discoveries in gene and cell therapy mean there is now hope for people who are losing their vision from diseases once considered untreatable.

Many blinding eye diseases are caused by a gap or 'mistake' in the blueprint for making our eye's building blocks. Gene therapy can fix faults in this genetic code, or DNA, which stop the cell working properly.

"Gene therapy is a way of changing what cells do," says Professor Keith Martin, Managing Director of CERA and Head of Ophthalmology at the University of Melbourne. The instructions are delivered into the cell by using a modified 'safe' virus, which can't cause infection, but is effective at getting genes into a cell.

"It's a bit like a text message," he says. "The virus contains information which is taken up and read by the cell, which then does what it's told to do."

Cell therapy transfers healthy cells from donors to patients, or reprograms a patient's own cells into stem cells, and then into eye-specific cells, to repair vision.

Gene therapy for IRDs

Inherited retinal diseases (IRDs) are the most common cause of severe vision loss in working age adults.

"This can be devastating, and until recently there has been no obvious hope of a cure," says Dr Tom Edwards, CERA's Principal Investigator in Retinal Gene Therapy Research.

There are hopes gene therapy can deliver the breakthrough. A gene therapy

(Continued page 4)

Research to restore vision and prevent blindness

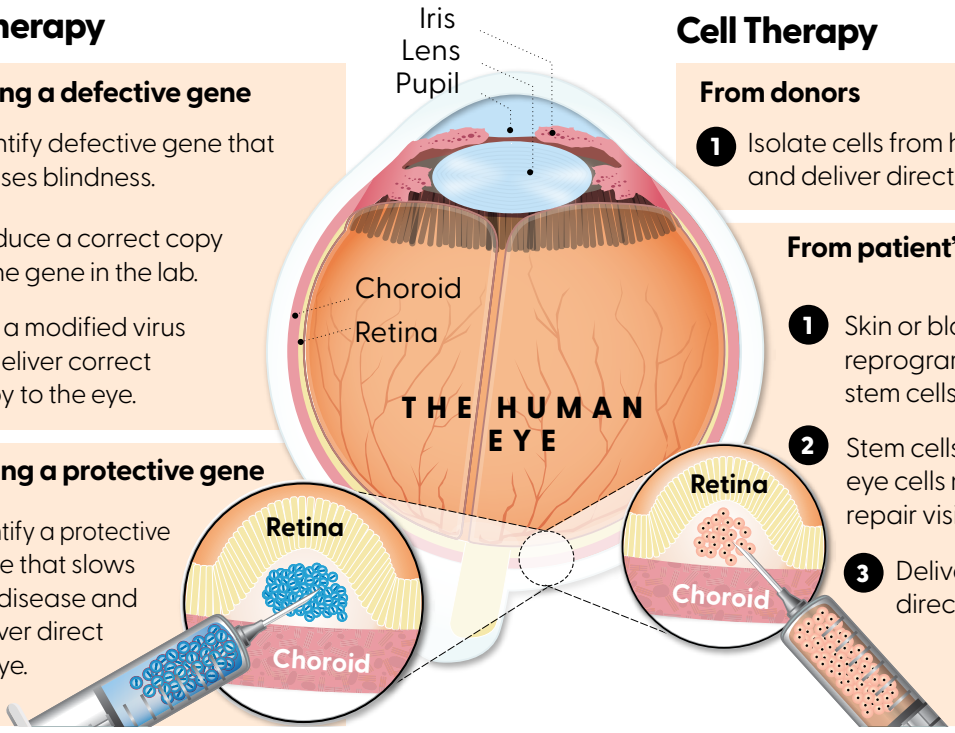
Gene Therapy

Correcting a defective gene

1. Identify defective gene that causes blindness.
2. Produce a correct copy of the gene in the lab.
3. Use a modified virus to deliver correct copy to the eye.

Identifying a protective gene

1. Identify a protective gene that slows the disease and deliver direct to eye.



Cell Therapy

From donors

1. Isolate cells from healthy donors and deliver directly to eye.

From patient's own cells

1. Skin or blood cells reprogrammed into stem cells.
2. Stem cells turned into eye cells needed to repair vision.
3. Deliver healthy cells directly into eye.

developed in the United States for a form of retinitis pigmentosa has recently been approved and will be an 'ice breaker' for other similar therapies to follow, says Dr Edwards.

There are many types of IRDs, each of which is caused by a spelling mistake in the DNA code of critical genes.

"There are over 250 genes implicated in causing IRDs," says Dr Edwards, "and so as a first step, it's important to identify what gene is causing the disease."

Once the faulty gene is identified, a specialised virus can be used to deliver a working copy of the affected gene to the retina. "This strategy is currently being applied to IRDs, but more common diseases such as age-related macular degeneration and glaucoma may be targeted in a similar manner in the future," says Dr Edwards.

Dr Edwards' team is currently investigating a gene therapy that replaces a single misspelt gene with a correct copy for reintroduction into the retinal cells.

Preclinical results are very encouraging, and there is growing conviction they are on the right track.

Glaucoma and AMD

Glaucoma causes a gradual loss of vision and is estimated to affect more than 80 million people. It is more common as we age, and also has a strong inherited component. If glaucoma is diagnosed early, it can be treated effectively in most cases. But untreated glaucoma leads to optic nerve damage and irreversible blindness.

Glaucoma is a challenging prospect for gene therapy because of its genetic complexity.

Instead of replacing a faulty gene, the CERA team is focusing on making the optic nerve stronger and more resistant to damage.

"We've developed what we think is a good candidate for gene therapy for glaucoma, and we're now planning clinical trials in the next 18 months," says Professor Martin.

Gene therapy is also being explored for the dry form of age-related macular degeneration (AMD), for which there is

currently no cure. CERA has been selected as one of the international sites for a new gene therapy for AMD that was developed in the United Kingdom.

"If this treatment is successful and safe, we hope it will lead to being able to start treating people earlier, before the disease has caused significant loss of vision," says Professor Robyn Guymer AM, CERA's Deputy Director and Head of Macular Research.

Engineering corneal tissue

CERA has also begun engineering corneal tissue in the laboratory, which could help millions of people regain their sight.

Damage to the cornea, the clear window at the front of the eye, is a leading cause of blindness throughout the world. While corneal transplantation of donor tissue is common in Australia and the United States, there is a major shortage of donor tissue elsewhere, leaving an estimated 6.5 million people without access to this sight-saving operation.

"Many countries don't have eye banks to safely collect corneal tissue, and in other places there can be a cultural block against donations," says Professor Mark Daniell, Head, Corneal Research at CERA.

The team has successfully grown cells from donated corneal tissue and is now working on creating corneal cells out of stem cells taken from blood or skin. Specific cell markers are used to identify and confirm the cultured cell is in fact a corneal cell.

"We are using a technology called 'single cell RNA gene expression analysis' that basically looks at every piece of DNA within the cells and can provide an absolutely characteristic fingerprint of every single cell," he says.

Professor Martin's research is supported by UK charity Fight for Sight, Dr Edwards' research is supported by the Marjorie M Kingston Trust and the Annemarie Mankiewicz-Zelkin Fellowship Fund.

Melbourne a global centre

Melbourne is poised to become a global centre for gene and cell therapies, says Professor Martin (pictured above).

CERA works closely with the University of Melbourne and the Royal Victorian Eye and Ear Hospital, bringing together strengths in vision research, clinical trials, surgical infrastructure and clinical practice. CERA already has a major clinical trials centre, and has worked with other local experts to set up a new ocular genetics clinic within the hospital.

"It's all about having the right people with the right skills, the best systems and equipment in place to support patients with inherited eye diseases.

"We see the potential for collaboratively developing more gene therapies, running the clinical trials and then delivering these gene therapies to patients," says Professor Martin.

"This is not a generation away," says Professor Martin. "It's already happening."

Picture: Anna Carlile

Genetic detectives

CERA's clinical genetics team is zeroing in on the causes of inherited eye diseases, then devising new treatments and screening tools to preserve vision and prevent blindness.

Inherited eye diseases are common and complex. Inherited retinal diseases, for example, are the leading cause of blindness in people of working age, with glaucoma the most common in older people. As with age-related macular degeneration (AMD), we know that the number of people affected by glaucoma will grow as our population ages.

Understanding the genetic basis for these blinding diseases is key to finding a cure or a way to prevent vision loss, says Professor Alex Hewitt, Head of Clinical Genetics at CERA.

Inherited eye diseases can be caused by a fault or 'mistake' in a single gene, or in several genes.

"The faulty gene is a sole event, a bit like a single car accident," says Professor Hewitt, "and there are common complex genetic diseases that are more like a general traffic jam and congestion around the city."

CERA's clinical genetics team investigates the genes responsible for common inherited eye diseases like glaucoma and retinitis pigmentosa and rare diseases such as Leber's Hereditary Optic

←

Looking for clues: Researchers Dr Helena Liang, Professor Alex Hewitt, Linda Clarke, Lisa Kearns and Dr Sandra Staffieri.

Neuropathy (LHON). Where the genes or gene variants are identified, the next goal is to edit, delete or repair these faults or explore another way to stop a disease progressing.

The team also translates its findings into screening tools and gene therapies that can be tested and proven in the clinic.

Rapid developments

Revolutionary discoveries in genetic engineering have now made it possible to modify DNA, says Research Fellow Dr Sandy Hung.

It may sound space age, but the invention of the CRISPR gene editing system in 2012 was in fact inspired by a natural process found in bacteria.

The CRISPR gene editing system finds, attacks and destroys an enemy virus by cutting away the DNA of the virus.

"Scientists modified this molecular machinery to target any sequence of DNA, including sequences containing disease-causing mutations in human cells," says Dr Hung.

CRISPR enables researchers to target specific genetic mutations, and delete or correct them.

Dr Hung and the team in Professor Hewitt's laboratory are currently using a CRISPR base editing system to target and change the point mutation in the DNA sequence, as part of their research into LHON.

"When you cut the entire DNA strand you might not get the modification or cellular repair you want," says Dr Hung. Refining and developing these tools is a major part of the team's work.

"Better tools are coming out all the time."

From the lab to the clinic

Earlier this year, CERA was part of a research collaboration which discovered 107 genes that increase a person's risk of developing glaucoma. "For the first time we've been able to clearly show that particular genetic 'loads' have different likelihoods of developing glaucoma," says Professor Hewitt.

CERA worked with the QIMR Berghofer Medical Research Institute and Flinders University, as well as ophthalmologists and patients around the country. And there are more genes to be identified.

By comparing the genomes of people with and without the disease, through a process called Genome Wide Association Scanning, the team is searching for more genes that contribute to disease risk.

They are also investigating the cells that regulate pressure in the eye, which is a major risk factor for developing glaucoma.

The team has now begun developing a test to identify an individual's glaucoma risk, and hopes to have it ready for clinical use within the next two years. Down the track, it could be used for population-wide screening.

"This research is very exciting," says Professor Hewitt. "It's hard to predict what the next breakthrough will be, but we're certainly motivated to understand why some people get disease, and what we can do about it."

Professor Hewitt's research is supported by the National Health and Medical Research Council and the Ophthalmic Research Institute of Australia.
Dr Hung's research is supported by the Mito Foundation.

Hope in sight

Future horizons: Nicole and Kate look forward to research breakthroughs.

As advances in gene and cell therapies spark optimism among people with inherited retinal diseases, a new study is identifying patients suitable for future trials.

Sisters Kate and Nicole Barrett were born 18 months apart and have always been there for each other.

Retinitis pigmentosa – an inherited retinal disease (IRD) that causes progressive, irreversible vision loss - runs through their relationship.

Kate, 35, was diagnosed at six and told she would be blind by 13. When that didn't happen, she was told she would be lucky to make it to 20.

As Kate's sight declined, she earned qualifications in counselling and criminology, wrote children's history books and had twin girls Abigail and Aurora. She now has a small amount of tunnel vision and guide dog 'Misty' to help navigate the world.

Nicole, 33, was diagnosed at 17. Despite the initial shock, she went on to develop a successful career in occupational therapy. "I am now at the point where I am looking to start a family. I have been able to achieve the things I have wanted to in my career, I'm happy, I've got married and everything is progressing well," she says.

"The most difficult thing is not being able to get a clear prognosis of how the disease will progress. I live from day to day and hope


Pictures: Anna Carlile

my vision stays the same." The sisters are part of a new study between the Centre for Eye Research Australia and the University of Melbourne to learn more about IRDs and identify patients suitable for future trials.

Natural history

Dr Lauren Ayton, who leads the natural history study, says that only five years ago someone diagnosed with an IRD would have been told their disease was untreatable.

But rapid advances in gene and cell therapies mean that treatments to stop vision loss are now being trialled overseas and will soon become available in Australia.

While these treatments could be life changing, researchers don't yet know all of the patients who could benefit or how to find them.

An additional challenge is that with more than 200 different genes associated with IRDs, each treatment is targeted to specific genes and many people do not have an exact diagnosis.

To overcome this problem the researchers are attempting to identify, assess and track the estimated 16 500 Australians with IRD.

As part of the study, people with an IRD will receive a comprehensive eye examination and genetic testing.

"This will enable us to create a database with information about their vision, their genetic profile and whether they are interested in taking part in clinical trials," says Dr Ayton. "As new treatments come up, the patients will be ready to go."

The eventual goal is a national register which would list everyone in Australia suitable for an IRD treatment.

The research has another important outcome – a better understanding of the sub-types of IRD and how they progress.

Kate and Nicole say new gene therapy research gives them hope that in their lifetime there may be a treatment for retinitis pigmentosa, either to stop vision loss or to slow down the rate of loss.

"Even if I don't have the exact genes for the treatments that are being tested (for) now, I hope there will be something in the future," says Nicole.

"It gives everybody hope to know that people are looking into all avenues and looking for a cure."

Kate's wish is simple: "I hope that my sight can stay where it is so I can see my daughters graduate and get married. That would be irreplaceable."

Kate and Nicole are the faces of CERA's Hope in Sight Giving Day on Thursday 8 October. You can donate at **www.charidy.com/HopeinSight**

If you are interested in taking part in IRD research you can email **IRD@groups.unimelb.edu.au**

Rebuilding the retina

Fresh from their role in developing the world's most detailed retinal gene atlas, our cellular reprogramming unit is using this knowledge to develop pioneering new techniques to restore sight.

Our vision depends on a healthy retina, a thin layer of cells at the back of eye that sense light and send messages to the brain via the optic nerve and enable us to see.

In 2019, CERA Principal Investigator Dr Raymond Wong led a team of Australian researchers who developed the world's most detailed retinal gene atlas.

The project, a collaboration between CERA, the University of Melbourne, the University of Queensland and the Garvan Institute of Medical Research, provided unprecedented insights into the genetic signals of retinal cells.

The group examined the complex genetic sequences behind more than 20 000 individual retinal cells. They then captured the precise genetic profile of each of the major cell types within the retina and the genes they 'express' to function normally.

"By creating this genetic map, we can better understand what enables cells to function and contribute to healthy vision, and what genetic signals cause a cell to stop functioning and lead to vision loss," says Dr Wong. "It provides a 'high resolution' map of those molecular genetic signals happening within the cell."

That project has accelerated research underway at CERA to develop new techniques to restore sight.

The loss of light-sensing photoreceptors in the retina can lead to irreversible blindness in diseases such as retinitis pigmentosa, age-related macular degeneration and diabetic retinopathy.

Now Dr Wong and his team are investigating ways to restore them using a technique known as cellular reprogramming.

Targeting the retina's Müller glial cells, the team are hoping to 'reprogram' them by introducing genes which could turn them into photoreceptors.

Switching on genes

"We're growing these cells in the lab, and switching on different sets of genes to see which are the best combinations to turn them into photoreceptors," says Dr Wong.

A gene therapy could ultimately involve injecting reprogramming genes into the eye of the patient to regenerate new photoreceptors, says Dr Wong.

Dr Wong's team is also exploring reprogramming Müller glia cells into retinal ganglion cells which make up the optic nerve that connects the retina to the brain. This work could help patients with diseases such as glaucoma and Leber's Hereditary Optic Neuropathy (LHON).

The team is also using highly advanced techniques to understand how defective genes contribute to other retinal

degenerative diseases, including age-related macular degeneration (AMD).

These techniques include induced pluripotent stem cells (IPS cells), CRISPR and transcriptomics.

With IPS cells, cells are grown from a person's own skin or blood cells and 'reprogrammed' as a stem cell that can be turned into eye cells as a model to study AMD in the lab.

The team then uses the CRISPR technique to switch on and switch off multiple genes to test their function. Through transcriptomics, which is a readout of gene expression in a cell, the team can see what changes take place and understand how they contribute to AMD.

With research supported by the NHMRC grant, Retina Australia and the Kel & Rosie Day Foundation, Dr Wong and his team are hopeful their work will contribute to restoring people's sight in the future.

"By creating this genetic map, we can better understand what enables cells to function and contribute to healthy vision, and what genetic signals cause a cell to stop functioning and lead to vision loss."

– Dr Raymong Wong

↑ *Changing cells: Researchers Daniel Urrutia Cabrera, Dr Raymond Wong and Crystal Nguyen.*

"This funding gives us the opportunity to get 'proof of concept' and preclinical data on the efficacy of the technology.

"We're very excited about this research," he says. "It could potentially help more than 190 million people with vision impairment."

Donors making a difference

The generosity of CERA supporters is critical in helping our researchers achieve their goal of a world free from vision loss and blindness.

The unprecedented events of 2020 have created great uncertainty in our community, but a donation to eye research can continue to offer hope for people and their families experiencing eye disease.

CERA's Head of Philanthropy and Fundraising Sarah Rainbird says that despite the difficult year, characterised by COVID-19 lockdowns, CERA researchers continued to advance their research.

"We know our supporters are passionate about the transformative potential that our research has to save people's sight and restore vision, and this has inspired our researchers to keep working towards that goal," she says.

"It's been extremely humbling to see donors continue to support us in 2020 – and it's also been critical in helping our researchers keep vital research projects on track and one step closer to discoveries that could lead to new treatments and cures for eye disease."

Donors contribute to CERA's research in many ways. They include through annual fundraising appeals and bequests, and from major gifts made by individuals, families, foundations and sub-funds to specific areas of research.

Donations can be made directly to CERA to support critical research projects. Most bequests can be directed to the CERA Foundation – CERA's endowment established to ensure both the organisation's financial sustainability and the careful, long term management of precious donor funds.

Philanthropic support is also provided by corporate partners who believe in our vision of a world free from vision loss and blindness.

Connecting researchers

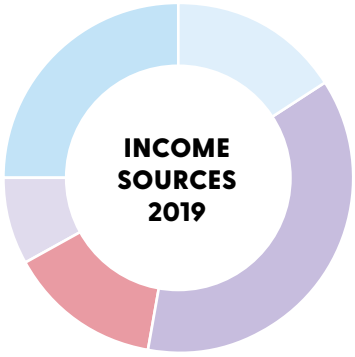
CERA Board member and Board member of the CERA Foundation, Christine Edwards, is an experienced health care executive and former CEO of the Sidney Myer Fund and The Myer Foundation.

She says one of CERA's strengths is how it connects researchers with supporters and helps them understand how their donation is making a difference, by giving people hope for the future.

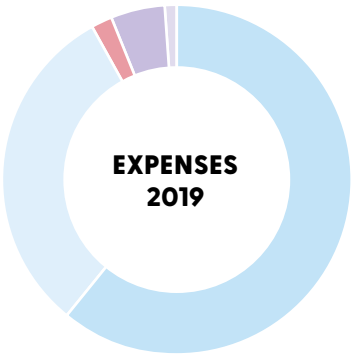
"Donors want an organisation with a strong vision that can deliver on what they say they are going to do," she says.

"They also need to know that the organisation is financially sustainable, and that their donation is going to research and not simply to prop up the bottom line."

CERA's financial statements for 2019 illustrate



37% Clinical trials and contract research
16% Federal and State Government grants
14% Donations and bequests
25% Investment and other income
8% Philanthropic and other grants



61% Research expenses
31% Research support expenses
2% Occupancy expenses
5% Depreciation and amortisation
1% Finance expenses

the major contribution philanthropy makes to our research – with more than a fifth of our income coming from philanthropic sources.

This was more than our researchers received for what was a successful year of applications for competitive research from government schemes such as the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF).

And as Ms Rainbird and Ms Edwards both point out – it's those initial contributions from philanthropy that often provide a springboard to NHMRC and MRFF success.

"Many of the successes of our researchers are only possible because of the initial support from loyal and generous donors," says Ms Rainbird.

"They help researchers develop proof of concept for bold ideas that have limited supporting data, and initially may appear too left of field for conventional funding programs."

Indeed, some of the researchers whose work appears in this edition of *Visionary* – including Dr Raymond Wong and Dr Tom Edwards – have received early boosts for their innovative research from philanthropy.

Encouraging innovation

"Philanthropy is sometimes about taking a risk to go into places that government funding can't, won't or shouldn't," says Ms Edwards.

"It's where people feel they can invest in something that will really make a difference and they can be involved in something on the cutting edge that's exciting.

"In the area of gene and cell therapy, there's a real opportunity for donors to consider their early role in this research and to identify with the successes that are involved along the way."

Ms Edwards says the CERA Foundation's (CERAF) governance ensures donors' funds are allocated to projects that will have a clear impact on tackling eye disease and improving eye health.

And, as many of the Foundation's funds come from bequests, the Foundation makes sure that bequestors' wishes are honoured.

"A gift provided by a bequest is both symbolic and significant. It represents somebody's legacy," she says. "It's an enormous responsibility and privilege to ensure it is committed to research that will have an impact."

Generous legacy: The late 'Frankie' Frees with her granddaughter Nicole.

Frankie's generous gift

CERA is grateful to the late Anne Frances 'Frankie' Frees (1929 – 2019) – social worker, gardener and philosopher – for her generous bequest for eye research.

Frankie Frees spent much of her life helping others, despite facing her own challenges.

Born Anne Frances Frees in 1929, she was dubbed 'Frankie' and it stuck, as did her determination and fierce independence.

After losing her husband while in her 40s, Frankie decided to become a social worker. In her 80s, she studied philosophy.

"She went to uni in her fifties and got a degree in social work," Frankie's granddaughter Nicole recalls.

Helping others gave Frankie great satisfaction after experiencing tough times herself. Following her social justice passion, she spent 18 years as a social worker at an adoption agency and in family welfare.

Today, Frankie is survived by her grandson Ben, granddaughter Nicole, daughter-in-law Debra and great grandchildren Chloe and Ashlea. Nicole has fond memories of her Nanna, who told her imaginative stories while babysitting and grew her own vegetables. "She loved her garden," Nicole says. "She was in a gardening club."

"When I was younger, we used to go Christmas shopping and we'd fill up a shoe box with toys. She then sent them to a kid in need."

Eliminating eye disease

Frankie's generosity was legendary, so Nicole is not surprised that she made a generous donation to the Centre for Eye Research Australia Foundation. The Foundation was established to support the long-term sustainability of the Centre for Eye Research Australia (CERA). In 2019 alone the Foundation gifted over $400,000 to advance CERA's mission to eliminate major eye diseases and reduce their impact on people's lives.

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

You can also learn more at **cera.org.au/leave-a-gift-in-your-will**

This World Sight Day, your gift can make *triple* the difference to CERA's life-changing eye research

Save the date – October 8

On World Sight Day 2020 you can be part of our future focussed appeal – the Hope in Sight Giving Day.

Every donation – no matter the size – brings our researchers one step closer to finding a cure for inherited eye diseases.

For ***one day only,*** every dollar donated will be matched with an additional two dollars: $1 from the National Stem Cell Foundation of Australia and $1 from the Centre for Eye Research Australia Foundation.

Triple your donation

All donations made to CERA on October 8 will be tripled by our generous partners

$20 → $60

$50 → $150

$100 → $300

Sign up for Hope in Sight Giving Day alerts

Don't miss out on being part of the future of eye research this World Sight Day. Sign up to our email list for Hope in Sight Giving Day updates and reminders: charidy.com/HopeinSight

Ready to give now?

You can donate to the Hope in Sight Giving Day early and your gift will be counted on 8 October.

Donate securely online through our Hope in Sight Giving Day page: charidy.com/HopeinSight

#HopeinSightGivingDay


CENTRE FOR
Eye Research
Australia
HOPE IN SIGHT
GIVING DAY
HELP us raise
$150,000 for
GENE THERAPY
research
"Gene therapy research offers the best prospect of finding cures for inherited eye diseases that cause blindness."
Dr Tom Edwards
DONATE on 8 OCTOBER and your gift will be TRIPLED by our generous partners.
VISIT charidy.com/HopeinSight
#HopeinSightGivingDay