EYES WIDE OPEN

Scientific advances in gene therapy, stem cell research and artificial intelligence could all offer future treatments for glaucoma.

WORDS BY KERRY VAN DER JAGT

As swift and as silent as a black panther, the 'sneak thief of sight' struck. Glaucoma had been circling for some time and finally it pounced, reducing my vision and ability to see clearly.

One of the world's leading causes of irreversible blindness, glaucoma affects more than 60 million people globally. It is mainly caused by too much fluid pressure inside the eye, which in turn exerts pressure on the optic nerve, leading to damage. Glaucoma occurs when the nerve cells that form the optic nerve fall susceptible to the constant pressure. It cannot be cured, but in most cases it can be controlled.

Unfortunately, even with the best treatments, a small percentage of people still go blind in at least one eye over the course of their disease.

Recent advances, such as gene therapy, stem cell research and artificial intelligence are opening up new frontiers for glaucoma treatment, including the potential to restore sight.

HOW IS GLAUCOMA DETECTED?

A glaucoma test usually includes the following:

- Optic nerve check
- Slit-lamp examination
- Eye pressure check
- Visual field assessment as glaucoma affects the peripheral (side vision) first.

Glaucoma Australia recommends all Australians aged 50 and over have a comprehensive eye exam every two years. If you have a family history of glaucoma or are of Asian or African descent, the recommendation is every two years from the age of 40. *glaucoma.org.au*

And if that's not sci-fi enough, the vector being used to deliver the corrected genes is a modified virus. A virus for good, not evil.

The start of my own glaucoma journey was unremarkable, involving regular checks and eye drops to reduce the elevated pressure.

But after I was struck with an 'acute angle-closure' event, where the intraocular pressure rose quickly and suddenly, leaving me with significant (and permanent) loss of vision in one eye, I sought the guidance of a leading glaucoma specialist, Dr Colin Clement.

Of the two main sub-types of primary glaucoma – open-angle and angle-closure – mine is the second, less-common kind, caused by a narrow angle between the iris and cornea.

EARLY DETECTION

"The key to successful outcomes in glaucoma is to diagnose early and to treat early," says Dr Clement.

"This is because with effective treatments you can prevent further loss of the nerve tissues, but you can't get any of the nerve tissue back that you have lost."

As Dr Clement proceeds with my eye examination he seems to fade, no longer anchored in his consulting chair, in his office, where models and charts of eyeballs bob like schools of colourful fish.

Rather, he's entered a realm of vessels and chambers in which an optic nerve carries visual information to the brain, allowing it to receive electrical signals and interpret them as images. It's a realm in which specialised cells, each one the result of genetic combinations that have been exchanged and rearranged for countless generations, hold secrets to ancestors long past.

And where the tiniest flaw can cause the biggest problem.

In my case, an inherited narrowness of the drainage angle of my eyes has lead to angle-closure glaucoma, a disease that robbed both my mother and grandmother of their sight. Having cared for my mother as she gradually lost her independence was heartbreaking and terrifying. Shared moments of disappointment and grief would make us both weep.

Traditionally, people with glaucoma are treated with eye drops, laser treatments and sometimes complex surgery. However, a new class of surgery, called 'minimally invasive glaucoma surgery' or 'MIGS', is adding a cache of cutting-edge treatments to the surgeon's arsenal.

As my eye pressure was still considered too high and unstable for my set of conditions, I was deemed a suitable candidate for the revolutionary titanium stent known as iStent inject. At just 360 micrometres in length, it is one of the smallest medical devices to be implanted in the human body.

"The benefit of the iStent inject is that it works using the natural outflow pathways of the eye," says Dr Clement. "It does this by allowing the eye to control pressure in the way it normally would, but more efficiently. The advantages of this procedure is that it is very safe, with minimal disruption to the eye and it has no impact on the patient from a visual point of view."

While advances in MIGS surgery are leading to improvements in glaucoma management, researchers are unlocking exciting possibilities for earlier detection, better treatments and potentially the restoration of sight.

Professor Keith Martin is managing director of Melbourne's Centre for Eye Research Australia (CERA) and head of ophthalmology at the University of Melbourne. He is working to develop innovative new treatments to repair the optic nerve.

"The focus of my research is to not only prevent people from going blind, but also to restore useful vision that has been lost," he says.

Professor Martin explains that the eye is a fantastic candidate for gene therapy. "It is both small and geographically isolated, meaning that what we put into the eye doesn't spread around the body. We can look at what is happening in the eye at single-cell resolution and we can tell very quickly if these treatments are working."

Glaucoma has a genetic component, but only a small number of people with glaucoma have a single defective gene problem. "And that tends to be the glaucoma that comes on very early in life, sometimes in babies or in young people," says Professor Martin. "For those with a first-degree family member affected – that's a brother or sister or a mother or a father – then the lifetime risk of developing glaucoma is about one in four."

In its simplest form, gene therapy for eye disease works by identifying a defective gene that is causing vision loss, producing a correct copy in the lab and reintroducing it to the eye using a specially-engineered virus.

"Viruses have evolved over million of years to become very good at putting their genes into human cells," says Professor Martin. "We're certainly seeing what they [viruses] are capable of at the moment around the world."

In a move that sounds decidedly 'brave new world', scientists are learning to harness this power, tame it and use it to deliver therapeutic treatments to cells within the body.

During gene therapy, the virus' disease-causing genetic material is removed and replaced with either a missing gene or with a gene that can give protection to the cells of the optic nerve. A treatment for a rare optic nerve disease called Leber's Hereditary Optic Neuropathy has commenced clinical trials and is producing promising results.

VITAMIN THERAPY

A world-first clinical trial led by researchers at CERA has shown that vitamin B3 (nicotinamide) could play an important role in protecting against nerve cell damage that leads to blindness. Results of the trial, published in *Clinical and Experimental Ophthalmology* in July, 2020, show significant and early improvement in the visual function of glaucoma patients who received a daily high dose of vitamin B3 in addition to their regular treatment to reduce eye pressure. I know I will not be the only glaucoma patient watching this project as it moves into a collaborative international study.

Other groundbreaking projects at CERA include a new bionic eye prototype, trials to use artificial intelligence (AI) to undertake eye screenings in remote Indigenous communities, and exploring ways a 'scaffolding molecule' called protrudin can help regenerate the optic nerve. "The tools and technologies we have to do these things have advanced more rapidly in the past five years than in the preceding 50 years," says Professor Martin.

Professor Helen Danesh-Meyer is head of the Optic Nerve and Glaucoma Research Unit of the New Zealand National Eye Centre (NZ-NEC) at the University of Auckland. The professor of ophthalmology has been studying ways to protect and support the optic nerve in glaucoma patients.

"One theory we have is that when the optic nerve is stressed by eye pressure, or any other insult, the environment surrounding the optic nerve changes," she says. "It becomes toxic."

Professor Danesh-Meyer explains the process by using the analogy of a pelican surrounded by an oil slick. "The key to saving the pelican is to remove the toxic oil," she says. "Similarly, my view is that to protect the optic nerve, the key is to alter the environment to reduce the level of neuro-inflammation that occurs following optic nerve insult."

Working in collaboration with Professor Colin Green, also from the University of Auckland, Professor Danesh-Meyer has shown (in the controlled laboratory environment) that by altering the level of neuro-inflammation, neuronal rescue can be achieved. "I believe this line of treatment will be critical for the management of glaucoma," says Professor Danesh-Meyer. "The next step is to translate this finding into a clinical trial."

Professor Danesh-Meyer is also actively involved in research using AI to identify patients who are at high risk of developing glaucoma. "If we can identify who is likely to develop glaucoma early, we can initiate an appropriate management strategy to prevent visual loss."

Around 300,000 Australians have glaucoma – with 50 per cent of those undiagnosed and unaware. By age 40, about one in 200 Australians will have developed the condition.

Professor Danesh-Meyer's research into the retinal nerve fibre layer (RNFL) has far-reaching implications for other fields, from predicting the outcome of vision in patients suffering from visual loss caused by brain tumours, to the future management of neurological disorders such as Alzheimer's disease.

Far left: Professor Keith Martin is working to develop innovative new treatments to repair the optic nerve. ***Left:*** Professor Helen Danesh-Meyer is involved in research using AI to identify patients at high risk of developing glaucoma.

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PROTECT YOUR VISION

Having regular eye checks is Professor Danesh-Meyer's most important piece of advice. "Identifying areas of concern early and initiating appropriate treatment in a timely fashion may prevent visual loss," she says. "The key is to respect your eyes – vision is the most precious of all senses!"

As my own battle continues, marked by further vision loss and more invasive surgery, I am nonetheless filled with optimism and gratitude – for a future in which children born with genetic eye defects will know the miracle of sight, and for visionary researchers and practitioners who are forging a new way forward.

"It doesn't matter who I see or what their ethnicity, background or social status is, whether they are homeless or live in a mansion, everyone has beautiful eyes," says Dr Clement. "In my opinion, it is the most wondrous organ in the body." MF

WHO IS MOST AT RISK?

Although anyone can get glaucoma, people in the following categories have a higher risk:

- Over 50s
- Family history
- High eye pressure
- Short- or long-sighted
- High or low blood pressure
- Use of steroids
- Eye injury
- African or Asian descent
- Have diabetes

NOTE: Glaucoma cannot be self-detected, and many people affected by glaucoma may not be aware of any vision loss.

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It's recommended you have a general check-up with your healthcare practitioner every year. Regular checks help you stay healthy and pick up early signs of disease or illness. **mindfood.com/12-point-health-checklist**

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