ORIA

ADVANCING EYE RESEARCH

ORIA RESEARCH FUNDING & IMPACT 2019

$13million

in research funding since 1986

36

grants awarded in the last 3 years

The Ophthalmic Research Institute of Australia (ORIA) is a not-for-profit organisation dedicated to promoting research into the causes of eye disease and the prevention of blindness. The ORIA was founded in 1953 by a group of eye doctors concerned with the need to advance eye research in Australia. Since then, ORIA has distributed millions of dollars to advance eye research.

The ORIA has a wide focus on supporting research into all major eye diseases, as opposed to focusing on a single eye disease.

Research grants are made available annually through ORIA's available funds, which are sourced through bequests and donations from individuals and organisations. A large proportion of these funds have come from people whose sight has been saved as a result of advances in eye care, and who wish to express their appreciation in a tangible way.

Research grants awarded each year have enabled many ophthalmologists and vision scientists working in university departments to improve the diagnosis and treatment of eye diseases through clinical research.

The ORIA conforms to the highest corporate governance standards with its fully audited annual financial statements and reports publicly available.

RESEARCH FUNDING 2019

Name	Title	Grant	Amount
Dr Fred Chen	Antisense oligonucleotide mediated modulation of CNOT3 to treat RP11	Esme Anderson	$50,000
Dr Stuart Keel	Artificial intelligence based screening of eye diseases	ORIA New Investigator	$49,617
Prof Justine Smith	Dengue Virus Infection of Retinal Pigment Epithelium	Richard and Ina Humbley	$49,954
Dr Vivek Gupta	Rexinoid and Retinoid X receptors in glaucoma	Ivy May Stephenson	$49,967
Prof Robert Casson	Photobiomodulation for retinitis pigmentosa	Hardie Anselmi	$49,800
Prof Alex Hewitt	Investigating the role of a novel locus associated with the development of Giant Cell Arteritis	R & L Lowe Grant	$49,846
Dr Elaine Chong	Descemetorhexis for Fuchs'Endothelial Dystrophy	ORIA grant	$49,898.60
Dr Guei-Sheung Liu	Switchable Gene Therapy for Controlled Intervention in Neovascular Blindness	ANZRS	$49,920
Dr Yuyi You	Optic nerve damage in neuromyolitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS)	ORIA/RANZCO NSW Branch	$45,380
Prof Stephanie Watson	The cellular mechanism of UV damage to the corneal epithelium	ORIA Grant	$50,000
Dr WengOnn Chan	A novel calpain antagonist in retinal detachment	ORIA New Investigator	$47,500
Dr Mark Hassall	AAV gene therapy for ganglion cell neuroprotection in glaucoma	ORIA New Investigator	$49,879.38
Dr Nilisha Fernando	Examining the therapeutic potential of microRNAs to regulate inflammasome activation in retinal degenerations	ORIA New Investigator Grant	$49,977

Blocking the genes that cause blindness

Dr Fred Chen, Centre for Ophthalmology and Visual Science (Lions Eye Institute), The University of Western Australia

Retinitis pigmentosa (RP) is an inherited eye condition that causes the light-sensitive cells at the back of the eye to slowly degenerate. RP affects 1 in 3,000 people worldwide and there are 8,000 patients in Australia. Although more than 100 genes may cause RP, a gene called PRPF31 is one of the most commonly implicated.

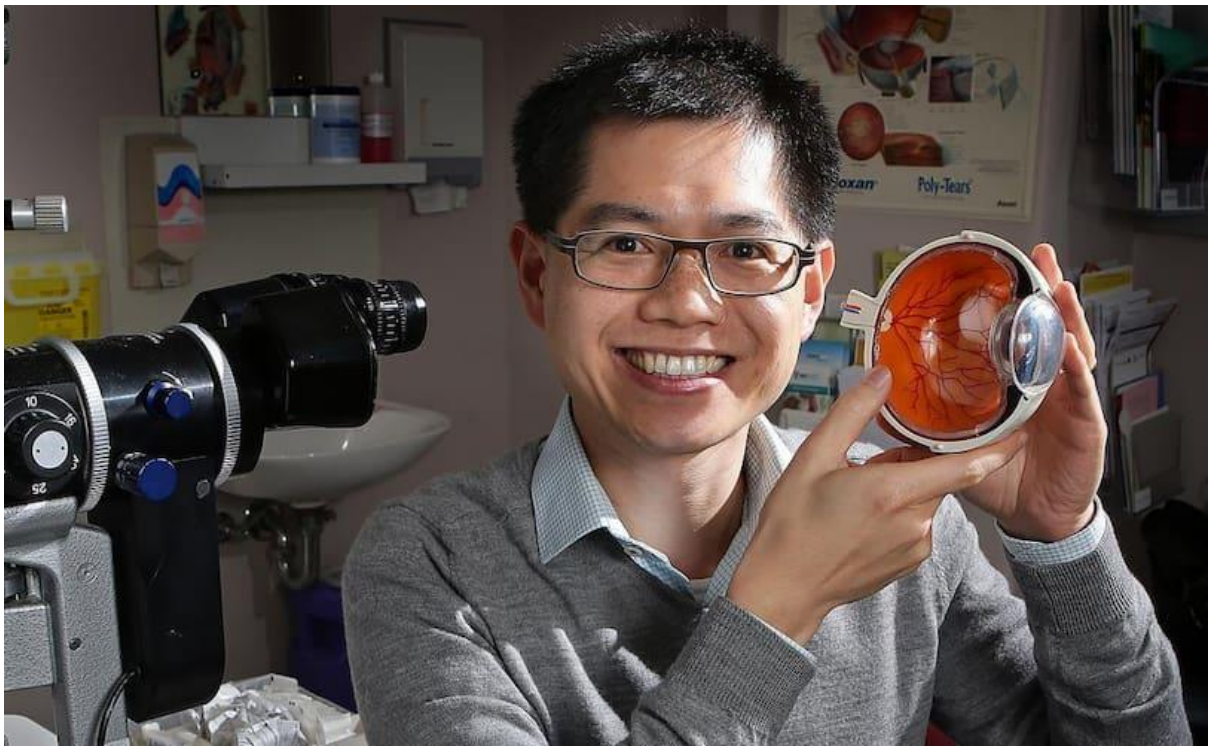
Lead researcher, Dr Fred Chen has studied DNA from families with this gene and found that not all family members (up to 30%) who carry the gene develop RP. This intriguing observation led to the discovery that another gene called CNOT3 is a negative regulator of the PRPF31 gene and is an excellent candidate for new therapeutic strategies. By interfering with CNOT3 function using specially developed RNA fragments, the PRPF31 gene can still function adequately.

“The aim of this study is to induce partial knock-down of CNOT3...and thereby increase PRPF31 expression from the normal allele in retinal cells from patients,” said Dr Chen.

In the laboratory, specially cultured retinal cells from RP patients will then be studied to determine whether gene and cell function improve.

“No treatments are currently available for these diseases,” explains Dr Chen.

“Successful completion of this project will generate essential pilot data to support *in vitro* and *in vivo* pre-clinical animal testing of an Australian made lead drug candidate.”



Harnessing the power of AI for eye disease screening in primary care

Dr Stuart Keel, Centre for Eye Research Australia, University of Melbourne, Victoria

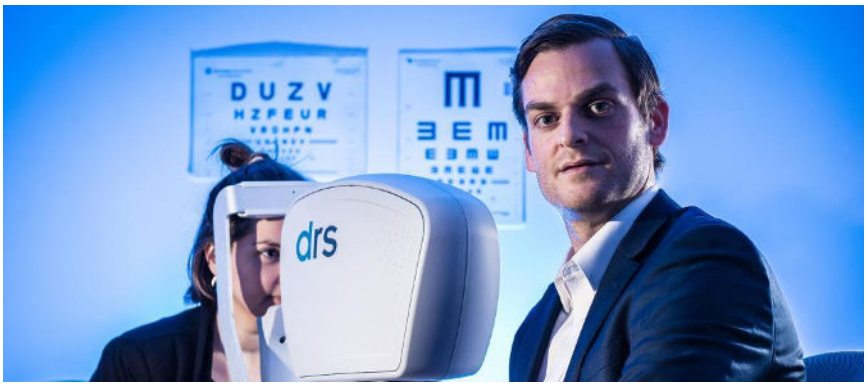
Up to 500,000 adults in Australia have vision impairment or blindness but it is estimated that 80% of vision loss is avoidable through early detection, prevention and treatment strategies. It is therefore very concerning that an estimated 50% of glaucoma and diabetic retinopathy cases in Australia go undiagnosed.

“Identification of eye diseases through a screening program is an important step towards the protection of visual function in the Australian population,” explains Dr Keel.

“Given that GPs are the cornerstone of primary care and 85% of the Australian population visit a GP service at least once every 12 months, they should have a central role to play in the opportunistic screening and identification of eye diseases.”

In this research, Dr Keel and his colleagues will develop an innovative screening system that combines portable retinal photography with AI grading in a portable system, to facilitate detection of diabetic retinopathy, glaucoma, age-related macular degeneration and cataract, in an opportunistic primary care setting. A real-world study of patient acceptability, accuracy and sensitivity will then be undertaken.

“Delays in diagnosis of common eye diseases dramatically increase the burden of vision loss in the Australian community and health care system.

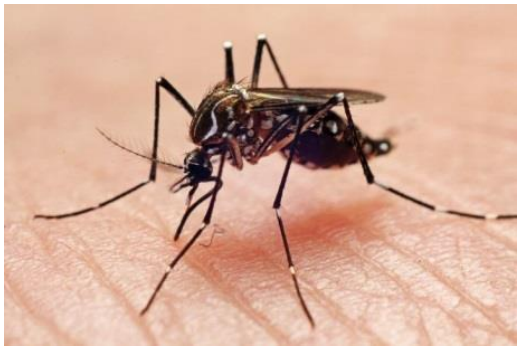


Although retinal photography can increase early diagnosis, the need for expert manual interpretation of the photographs presents a barrier to its wider use. The development of an automated system of interpretation solves this problem, and its integration with an affordable and portable retinal camera offers great potential to increase the uptake of eye disease screening within GP settings,” said Dr Keel.

Understanding vision loss caused by the dengue virus

Prof Justine Smith, Flinders University, South Australia

Worldwide, deaths due to dengue virus infection have increased by around 50% between 2005 and 2015, to 18,400. In Australia, the number of dengue virus infections is at a 20-year high. At present no approved vaccines or anti-viral drugs are available to treat dengue virus.



Dengue virus infection may cause an array of different dengue eye diseases.

"Retinopathy, and particularly pathology involving the macula, is well described and most likely to adversely impact the vision," explains Prof Smith.

"Ultimately any retinal inflammation resolves, but the prognosis of dengue retinopathy is highly variable, ranging from full resolution to permanent vision loss, irrespective of medical interventions to reduce inflammation."

Prof Justine Smith and colleagues at Flinders University have planned a program of laboratory research to investigate exactly how dengue virus interacts with retinal cells at the molecular level. They are particularly interested in the immune response to the virus.

"Defining the interactions between DENV and retinal pigment epithelial cells represents a first step towards developing effective treatment for dengue retinopathy," said Prof Smith.

Finding new molecular targets to prevent glaucoma

Dr Vivek Gupta, Prof Stuart Graham & Dr Mehdi Mirzaei, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW

Even though primary open angle glaucoma is the most common cause of irreversible vision loss the exact mechanisms that cause cellular damage and vision loss are still poorly understood.

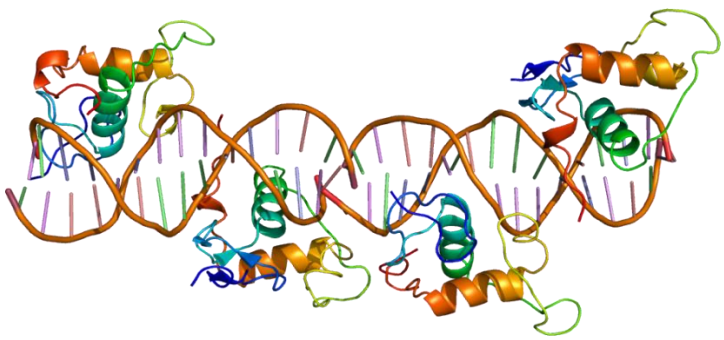
Dr Gupta, Prof Graham and Dr Mirzaei from Macquarie University, Sydney will focus their research on better understanding the role of rexinoid and retinoid X receptors in the development of glaucoma.

“Our pilot studies have provided substantial evidence that the Retinoid X Receptors (RXR) are well expressed in the retina and the RXR network is negatively affected in glaucoma, in both human retina as well as in mouse models of glaucoma,” the researchers explained.

The research team hypothesise that the RXR network is important in maintaining the health of retinal ganglion cells. They hope that by gaining a better understanding of the biology of the retina and RXR network molecular mechanisms will lead to new therapeutic targets for glaucoma treatment.

Using an animal model, this project will look at the effects of activating and blocking RXR on healthy retina and retina affected by glaucoma. The research will also target RXR pharmacologically using endogenous rexinoid.

“Current glaucoma management is limited to lowering the IOP which we know is not enough as many patients continue to progress despite treatment. Therefore, it is extremely important to better understand mechanisms underlying RGC loss and to develop therapeutic strategies which can protect against this,” said the researchers.



► FIGURE retinoid XR receptor

Harnessing the power of light to prevent blindness

Prof Robert Casson, University of Adelaide, South Australia

Photobiomodulation (PBM) uses light from a laser in the far-red to near-infrared spectrum (630-1000 nm) to irradiate tissue in a non-destructive way. There is evidence that PBM influences energy metabolism at the cellular level and may activate the mitochondrial electron transport chain.

Prof Casson and his colleagues have conducted pilot studies in an animal model with exciting results.

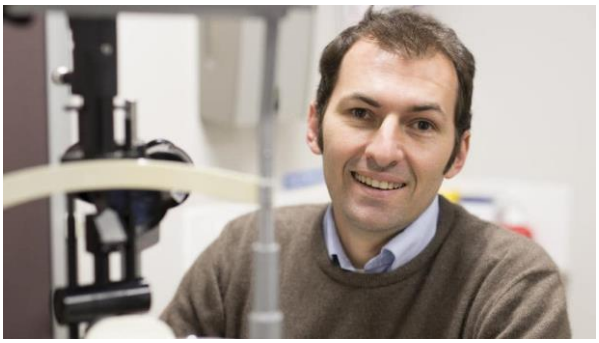
“In 2017, we used the laser in an attempt to prevent secondary cone photoreceptor degeneration in a rodent model of severe retinitis pigmentosa (RP). The reproducible rescue of cones was extraordinary,” said Prof Casson.

“A safe, effective, non-invasive treatment for RP would be a major medical breakthrough, improving both vision and quality of life for individuals suffering from a blinding disease that currently has no treatment,” he said.

The next steps in this exciting research are to determine exactly how PBM exerts its action on the retina. Cone cells from an animal model will be grown in the laboratory and then studied to determine whether PBM protects the cells from oxidative stress and metabolic insults.

Decoding the genetic risk for giant cell arteritis

Prof Alex Hewitt, Centre for Eye Research Australia, Melbourne, Victoria

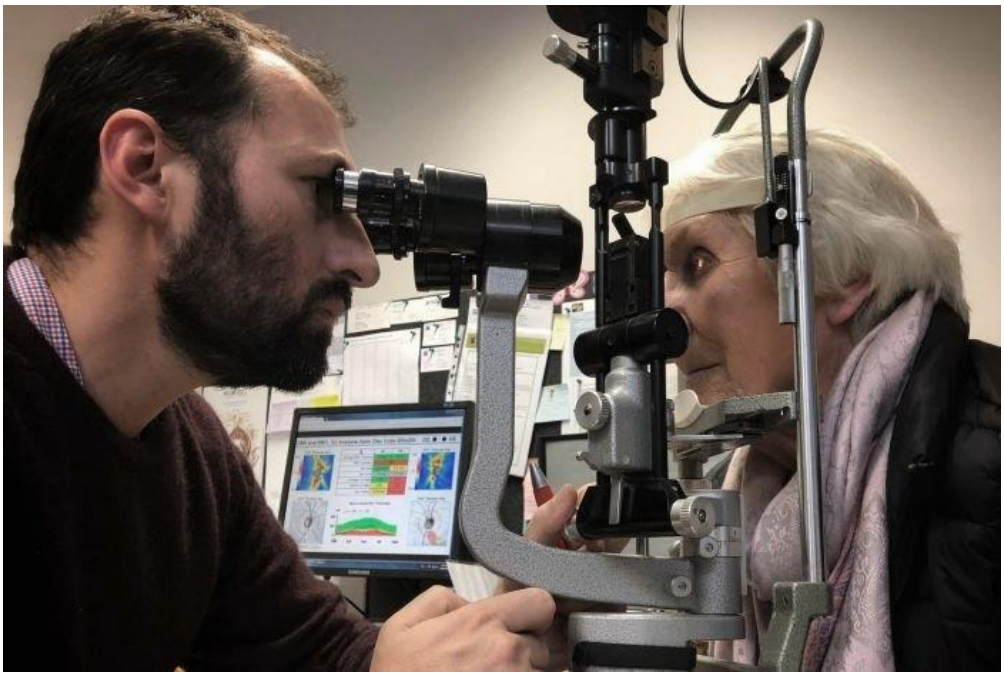


Giant cell arteritis (GCA) is an inflammatory disease causing headaches, joint and facial pain, fever and may cause permanent vision loss. It is the most common form of vasculitis in elderly people, with most patients over the age of 50 and making a timely diagnosis and intervention crucial to prevent vision loss.

“If untreated, GCA can cause catastrophic complications including blindness, strokes, as well as aortic dissection and rupture. GCA represents one of the few true ophthalmic emergencies,” explained Prof Hewitt.

“Even after successful treatment with corticosteroids, GCA relapses in 20-30% of patients. There is a significant need for more effective and safer treatments for GCA.”

In ground-breaking pilot work, Prof Hewitt and his research team have identified a novel locus on chromosome 15 that is associated with GCA. Two implicated genes in this region (milk fat globule-EGF factor 8 MFGE8 and hyaluronan and proteoglycan link protein 3; HAPLN3) will be studied in this project to further elucidate the molecular mechanisms that may be involved.

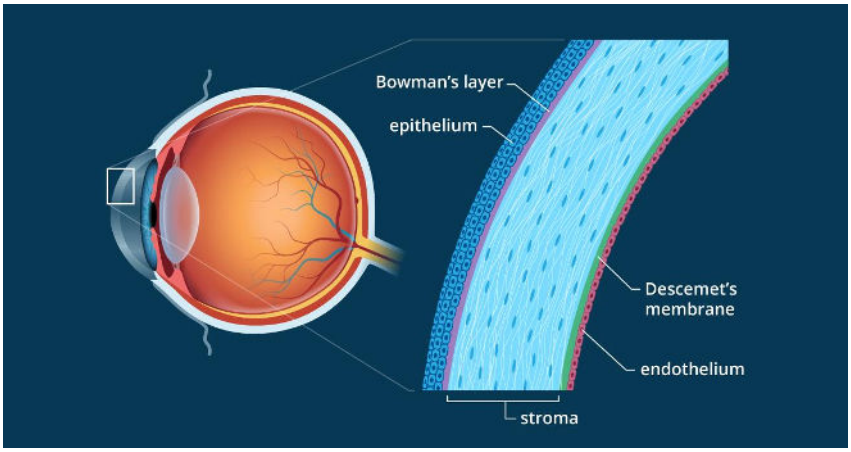


Revolutionising treatment of Fuchs' Endothelial Dystrophy: Can corneal transplant be avoided?

Dr Elaine Chong, Dr Elsie Chan & Dr Gregory Moloney, Centre for Eye Research Australia, Royal Victorian Eye & Ear Hospital, Melbourne, Victoria

Fuchs' Endothelial Dystrophy is a genetic eye condition in which protein accumulates on the back surface of the cornea (known as the endothelium) causing it to break down. This in turn allows more fluid than normal into the cornea and causes swelling. The swelling causes the cornea to become hazy and the vision cloudy, particularly first thing in the morning.

"Currently, the only treatment available is a cornea transplant (graft). However, recent studies have suggested that Descemet's membrane only removal without a corneal graft may produce equally good visual results. The effects may also be augmented by the use of Rho Kinase Inhibitor eye drops," said the researchers.



Descemetorhexis without endothelial keratoplasty (DWEK) involves the removal of Descemet's membrane without a corneal transplant. There is also emerging evidence that Rho-associated kinase inhibitor (ripasudil drops) assist with endothelial healing. In this research a prospective, randomised study will evaluate the efficacy of both of these novel treatments in 60 Fuchs' Endothelial Dystrophy patients.

"DWEK with and/or without ripasudil rescue is a novel treatment with enormous implications to patients and our public health resources. Corneal transplants are generally successful, but have a number of disadvantages," said the researchers.

The shortcomings include the limited supply of donor cornea tissue for transplantation and the need for repeated transplants, as most transplants last for an average of less than 5 years. This study has the potential to not only improve patient care but reduce costs.

Steps towards gene therapy for diabetic retinopathy

Dr Guei-Sheung Liu, Menzies Institute for Medical Research, University of Tasmania, Tasmania

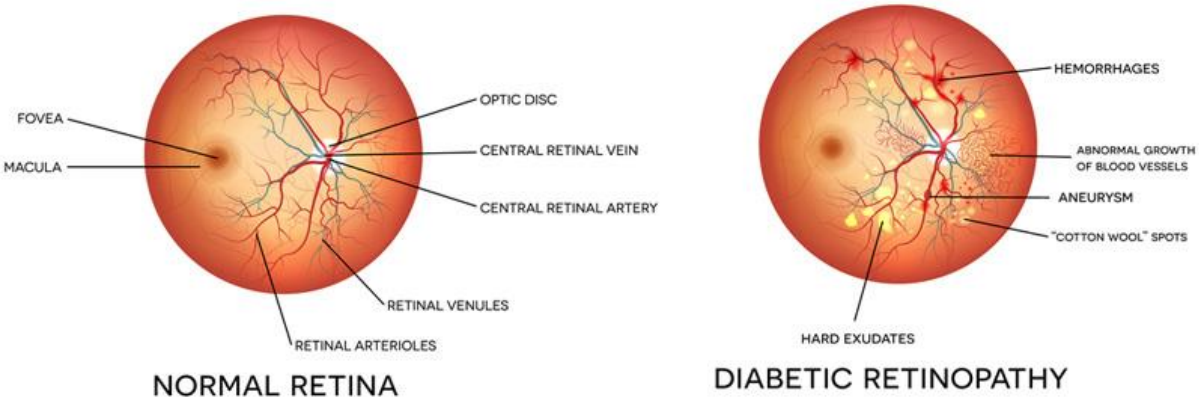
Diabetic retinopathy is a frequent complication of diabetes and is a leading cause of vision loss worldwide. Treatments for diabetic retinopathy include anti-VEGF treatments (such as VEGF (vascular endothelial growth factor) neutralising proteins) however these require ongoing eye injections and carry risks and are expensive.

In this research project a novel approach for delivery of VEGF inhibition into the cells will be investigated.

“We will use an adeno-associated virus (AAV) vector to deliver an intracellular VEGF decoy receptor (Flt23k) that neutralises intracellular VEGF and prevents its secretion,” said Dr Liu.

The therapeutic efficacy and effect of retinal vascular hyper-permeability will be evaluated in a diabetic animal model.

“Vision loss from diabetic retinopathy is a global health concern, significantly impacting the quality of life of patients. Our project will validate a new strategy for blocking VEGF in the eye, with the advantage that it is longer lasting and can be switched on only when needed,” said Dr Liu.



Gaining a better understanding of optic nerve damage in MS and neuromyolitis optica (NMO)

Dr Yuyi You, Save Sight Institute, University of Sydney, Sydney, NSW

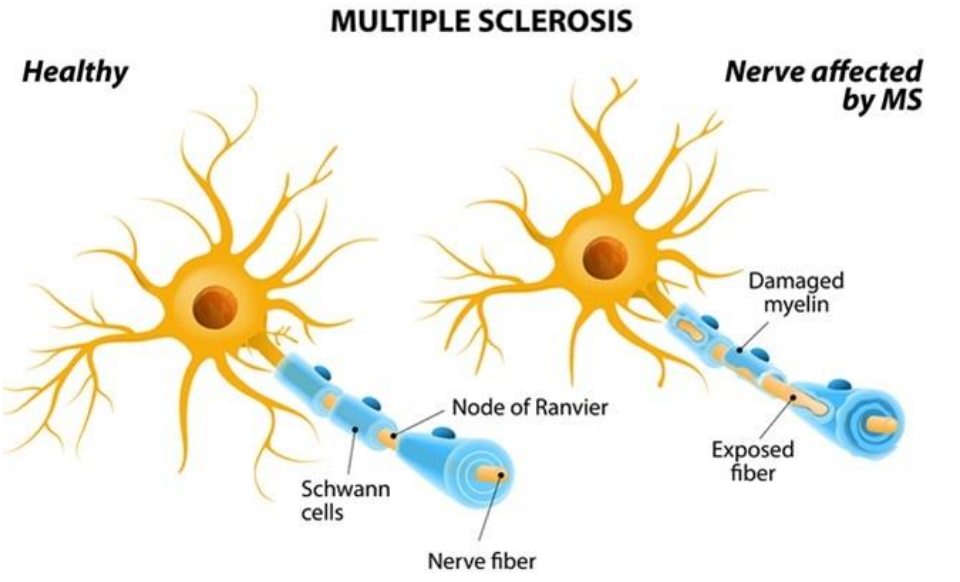
Neuromyelitis optica (NMO) and multiple sclerosis (MS) are autoimmune conditions that cause a loss of myelin, the insulating layer around nerves. In both diseases the visual system and the optic nerve are often affected.

“Differentiating these conditions is critical because prognosis and treatments are very different. There are a considerable number of patients still being misdiagnosed with MS and it is not uncommon that the correct diagnosis of NMO is only made after symptoms worsen with MS disease modifying treatments,” explained Dr You.

Dr You and colleagues will use imaging techniques to work out ways to differentiate between the two conditions by investigating whether they have different patterns of optic nerve damage.

At present the key method of identify which condition patients have is the disease-specific serum immunoglobulin IgG targeting the astrocyte water channel aquaporin-4 (AQP4). The researchers also plan to investigate whether the level of antibodies is linked to the severity of optic nerve damage.

This study will provide clinical guidance for disease differentiation of these two conditions – the leading causes of optic neuritis in neuro-ophthalmology practice. This research will also clarify the mechanisms of optic nerve damage in these neuro-inflammatory disorders.



How does ultraviolet light from the sun damage the eye?

Prof Stephanie Watson, Save Sight Institute, University of Sydney, Sydney, NSW

This study will investigate the cellular mechanisms for ultraviolet radiation damage to the cornea. Ultraviolet radiation from the sun causes common eye disorders, such as pterygium, and serious conditions including ocular surface squamous neoplasia (OSSN) and stem cell damage, but how this happens on a cellular level is poorly understood.

“The epithelium of the eye, along with the skin, is the main tissue exposed to solar ultraviolet radiation. Unlike the skin, diffuse light is a more important source of UVR exposure to the eyes than direct sunlight, and is more difficult to avoid using sunscreens and shade,” explained Prof Watson.

“Little is known of how normal levels of ultraviolet radiation contribute to keratoconus and other forms of corneal blindness,” she said.

Using a laboratory animal model the researchers will investigate cell division in the corneal epithelium cells and whether ultraviolet radiation exposure influences dell division.

“Corneal disease is a leading cause of irreversible blindness, with high costs to the patient and society,” said Prof Watson.

“Understanding the mechanisms that induce common conditions such as pterygia and possibly keratoconus, along with more severe conditions such as OSSN, will allow the development of new therapies to prevent damage and restore tissues, saving sight,” she said.

Developing a sight-saving drug for retinal detachment

Dr WengOnn Chan, Ophthalmic Research Laboratories, Ophthalmology Network, Royal Adelaide Hospital, University of Adelaide, South Australia

Retinal detachment is a common ophthalmic condition and causes blindness if left untreated. This is because the blood supply is compromised leading to the irreversible death of specialised light-detecting cells call photoreceptors.

In this exciting research project, a new drug will be tested to see if it can rescue the dying photoreceptors. A novel calpain antagonist will be investigated in a laboratory animal model to test its effect on rod and cone survival.

“Although the latest vitreoretinal surgical techniques generally achieve good results augmenting photoreceptor survival in the perioperative period would be a useful adjunct to the surgical armamentarium,” explained Dr Chan.

Glaucoma gene therapy: protecting cells to prevent vision loss

Dr Mark Hassall, Flinders Centre for Ophthalmology, Eye and Vision Research School of Medicine, Flinders University, South Australia

Glaucoma is a leading cause of irreversible blindness and affects an estimated 80 million people worldwide.

Glaucoma affects the ganglion cells of the retina through both increased eye pressure and genetic susceptibility resulting in vision loss.

“Current treatments slow vision loss by lowering eye pressure but cannot protect ganglion cells directly,” explained Dr Hassall.

“This project will use established gene therapy strategies to deliver protective genes to the retina with the aim of protecting retinal ganglion cells and prolonging vision in glaucoma,” he said.

Targeting inflammation to prevent age-related macular degeneration

Dr Nilisha Fernando, The John Curtin School of Medical Research, The Australian National University, Canberra, ACT

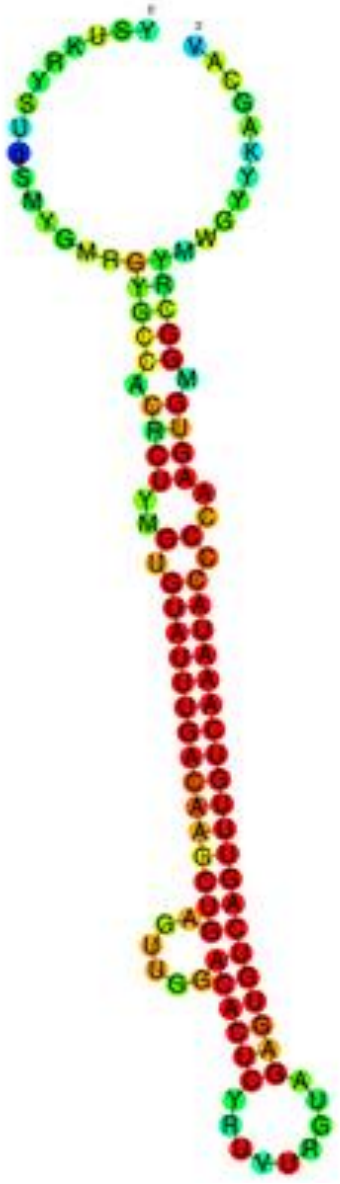
Age-Related Macular Degeneration (AMD) is the leading cause of vision loss in the Western world.

“There are two forms of the disease, 'wet' AMD, characterised by choroidal neovascularisation, and 'dry' AMD, in which an atrophic retinal lesion develops,” explained Dr Fernando.

“There are no treatments for dry AMD, it has been suggested that targeting retinal inflammation, a key feature of disease progression, could lead to the development of novel therapeutics,” she said.

In this study the research team will investigate microRNAs (miRNAs) which are ‘master regulators’ of gene expression. On microRNA in particular, called miR-223, is known to regulate inflammasome - a critical inflammatory pathway that has been strongly linked to the progression of retinal degeneration. Using tissue from people with AMD in combination with an animal model, the therapeutic potential of miR-223 will be investigated.

“These findings could be of major importance in shaping the therapeutic landscape for the treatment of retinal degenerations such as AMD, as well as other neuro-inflammatory diseases where inflammasome activation plays a key role in disease progression,” said Dr Fernando.



▶ FIGURE microRNA miR-223

Leverage of ORIA Funding

► 13 projects funded for 2019, with a total investment of $641,739

► In 2018/2019 **12 peer-reviewed publications** acknowledged ORIA funding

► Demonstrated funding leverage of 10 times for 2009[1] ORIA funding – in 2009 13 grants (totalling $557,051) were awarded. This 'seeding' or 'incubator' funding led to:

- 7 NHMRC Project Grants
- 1 NHMRC Research Fellowship
- 1 NHMRC Career Development Fellowship
- Total follow-on NHMRC funding $6.4million equivalent to more than **10 times amplification of funds**

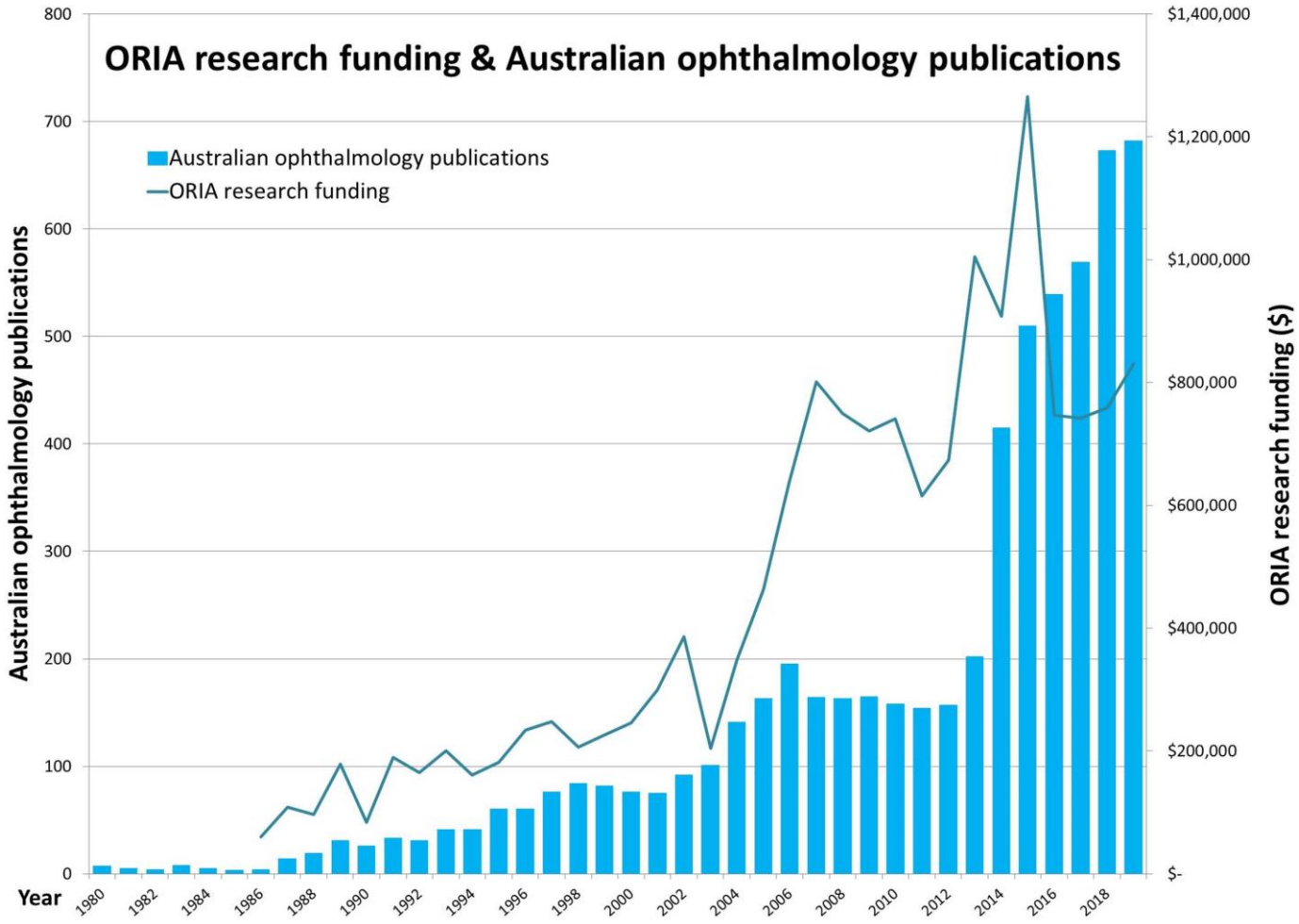
► Demonstrated funding leverage of 36 times for 2010 ORIA funding – in 2010 12 grants were awarded. In total 7 ORIA grant recipients went on to gain further NHMRC funding in the following years. The incubator funding led to 18 further grants from the NHMRC alone:

- 1 NHMRC Program Grant
- 7 NHMRC Project Grants
- 3 NHMRC Research Fellowships
- 3 NHMRC Practitioner Fellowships
- 2 NHMRC Early Career Fellowships
- 1 NHMRC Career Development Fellowship
- 1 NHMRC Development Grant
- Total follow-on NHMRC funding $18.2million equivalent to more than **36 times amplification of funds**

[1] Note that there is a lag time from award of funding to full fruition of research outputs, including publications and leverage of the research to gain additional funds from other sources.

Amplifying Australian Ophthalmology Research Worldwide

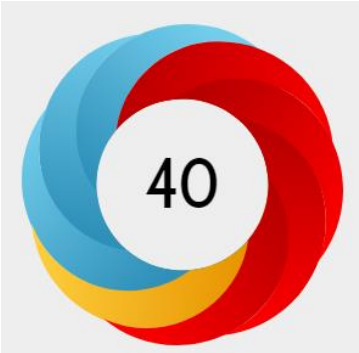
► ORIA funding has increased over time with a corresponding increase in the number of Australian ophthalmology peer-reviewed research publications (see graph below).



ORIA Research Impact Highlights

Publications from ORIA funding – examples of **early and rapid impact** from 2018 funding

► ORIA/RANZCO NSW BRANCH GRANT

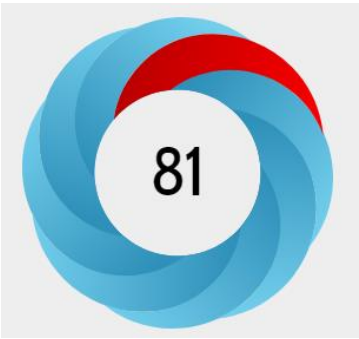


Project Title: Consequences of genetically disrupting serine/glycine metabolism in the retina

Investigator: Dr Weiyong Shen and Prof Mark Gillies, Save Sight Institute, the University of Sydney

Impact: Three publications[1,2] (plus one in press), 6 citations, altimetric score of 40 (high attention score 93rd percentile; top 5% of all research outputs). Mentioned by 4 news outlets.

► RICHARD AND INA HUMBLEY FOUNDATION GRANT



Project Title: Building a reference transcriptome atlas for human retina at a single cell level

Chief Investigator: Dr Raymond Wong and Dr Samuel Lukowski

Impact: One publication[3] with an altimetric score of 81 (high attention score 97th percentile; top 5% of all research outputs). Mentioned by 7 news outlets.

► ORIA GRANT

Project Title: Retinal gene therapy delivery: best route, right place

Investigators: Professor Robyn Jamieson, Dr Leszek Lisowski, Professor John Grigg, Associate Professor Ulrike Grunert, Associate Professor Michele Madigan

Impact: Two publications[4,5]

► ORIA NEW INVESTIGATOR GRANT

Project Title: Monitoring of Visual Fields at Home using a Portable Tablet Device

Chief Investigator: Yu Xiang George, Kong (New Investigator); Supervisor: Professor Mingguang He

Impact: Three presentations and one manuscript in preparation; funding leverage 3 grants totalling >$100,000

► ORIA GRANT

Project title: Developing a blood test for identification of aggressive ocular melanoma

Chief Investigator: A/Prof Elin Gray; Co-Investigators: Dr Tim Isaacs and Prof Mel Ziman

Impact: Three publications[6] (one in press and one in preparation) and three conference presentations

References

1. Zhang T, Gillies MC, Madigan MC, et al. Disruption of De Novo Serine Synthesis in Muller Cells Induced Mitochondrial Dysfunction and Aggravated Oxidative Damage. *Mol Neurobiol* 2018; **55**(8): 7025-37.
2. Zhang T, Zhu L, Madigan MC, et al. Human macular Muller cells rely more on serine biosynthesis to combat oxidative stress than those from the periphery. *Elife* 2019; **8**.
3. Lukowski SW, Lo CY, Sharov AA, et al. A single-cell transcriptome atlas of the adult human retina. *Embo j* 2019; **38**(18): e100811.
4. Ma AS, Grigg JR, Jamieson RV. Phenotype-genotype correlations and emerging pathways in ocular anterior segment dysgenesis. *Hum Genet* 2019; **138**(8-9): 899-915.
5. Ma AS, Grigg JR, Prokudin I, Flaherty M, Bennetts B, Jamieson RV. New mutations in GJA8 expand the phenotype to include total sclerocornea. *Clin Genet* 2018; **93**(1): 155-9.
6. Beasley A, Isaacs T, Khattak MA, et al. Clinical Application of Circulating Tumor Cells and Circulating Tumor DNA in Uveal Melanoma. *JCO Precision Oncology* 2018; (2): 1-12.