The Ophthalmic Research Institute of Australia

Annual Report 2020-2021

ORIA

Contents

Thanks to:

Perth Eye Foundation

ANZSRS

RANZCO Australian and New Zealand Eye Foundation

RANZCO The Royal Australian and New Zealand College of Ophthalmologists
THE LEADERS IN COLLABORATIVE EYE CARE
NEW SOUTH WALES BRANCH

ORIA is registered with the Australian Charities and Not-for-profits Commission (ACNC)

ABN: 37008393146

ORIA
ADVANCING EYE RESEARCH

Chair's Report

On behalf of the ORIA board I am pleased to present the Ophthalmic Research Institute of Australia's Annual Report for 2020-21.

Over the last year, the ORIA has continued to grow and excel as a respected Health Promotion Charity (HPC). This has enabled us to continue to support and promote research into the causes of eye disease and the prevention of blindness. We have been gratified in being able to further our vision to alleviate the burden from blindness and vision impairment through research.

Following a rigorous process in September 2020, nine cutting-edge grants totalling $428,822.87 were awarded for ophthalmic research projects across the country in a variety of organisations and institutes. Grant outcomes will save and restore sight leading to improved clinical practice as well as uncovering new knowledge. Artificial intelligence, gene therapy, photobiomodulation, diabetic retinopathy and retinal dystrophy are some of the areas to be investigated. We were very fortunate to have had over 70 excellent reviewers and 11 expert panellists along with Prof Alex Hewitt (RAC Chair) and A/Prof Sam Fraser-Bell (RAC Secretary) working this year to ensure the process went smoothly.

The board recognises the importance of building relationships with our key partners. During the year, members of the ORIA Executive team, the CEO and myself met with the President of Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Prof Nitin Verma and CEO Mr David Andrews. We were grateful to have RANZCO-appointed board members to the ORIA, Dr Bill Glasson and Dr Richard Stawell, present to facilitate engagement between the organisations. The board is pleased that a Memorandum of Understanding between the organisations is under development. The ORIA were also grateful to RANZCO for assistance with a large-scale policy development project undertaken by the CEO with the board members.

The achievements in this report reflect the hard work and dedication of our CEO Diane Harapin and the vision and expertise of our board members, research committee and external grant reviewers. I would like to thank each and every one of our team for their contributions, commitment and passion despite the many challenges of the past year. I am also thankful to Vice Chair Prof Mark Gillies, Treasurer Clin A/Prof Paul Healey, Secretary A/Prof Richard Mills, Chair of the RAC Prof Alex Hewitt and RAC Secretary A/Prof Sam Fraser-Bell who have all worked tirelessly to support the ORIA this year. It has been a privilege to work with so many people who are passionate about the need to support eye research. Our team has led to improvements in the organisation's efficiency, governance, public profile and IT systems. A key initiative was the development and launch of our first online grant portal and a new website to reflect our modern vision.

We are very grateful for support from the following donors, many of whom support ophthalmic research year after year: the Perth Eye Foundation, RANZCO NSW Branch, ANZSRS, the Humbley Foundation, RANZCO's ANZEF, Dr Adam Rudkin, Trew Bequest, and the Stephenson Foundation.

ORIA donors are aligned with our mission to support and promote research that discovers new knowledge and improves patient outcomes and practice by providing access to funding, building relationships with our stakeholders and the community, and advocating for eye research in Australia.

The ORIA recognises the need to engage its members and the community. In 2020, we held our first webinar which highlighted the achievements of ORIA-funded research. Communication has been via a new online members' newsletter the ORIA NEWS and a growing social media presence (Twitter, LinkedIn, Facebook, Instagram). The need to deliver our services to a high standard has been recognised by the board. To support our services we applied for and were given a small administration grant from the NSW government to upgrade our communications, systems and information technology.

ORIA's Investment Advisory Committee have also provided valuable advice throughout the year, and we have been working closely with the team at Escala Partners. In a period of low interest rates and wildly fluctuating stock markets the IAC have worked hard to ensure the safekeeping of ORIA's capital reserves. A restructuring and rebalancing of the portfolio managed by Escala Partners has seen capital growth of over $2M to $14.7M as well as a retained income of $1.4m in the 20/21 financial year. This is an excellent result for a conservative investment approach. Thanks go to Mr Dennis Clarebrough from Lodge Partners, as well as our Treasurer and Chair who sit on the IAC for their ongoing stewardship of our financial resources.

In 2021-22, the ORIA will maintain our focus on further improving our efficiency, governance, social presence and partnerships with our stakeholders to better support Australian ophthalmic research. The board will continue with a review of our strategic directions with the aim of securing a strong future pathway for the ORIA to deliver ophthalmic research that improves patient care and advances knowledge.

Stephanie Watson
Chair, ORIA

Thank You!

ORIA would like to thank the external referees who kindly gave advice that helped with the allocation of the 2020/2021 grants. Their work is invaluable.

Dr Monica Acosta
Dr Lauren Ayton Slater
Dr Radha Ayyagari
A/Prof Chandra Balaratnasingam
A/Prof Nigel Barnett
Dr Karl Brown
Prof Kathryn Burdon
Dr Fred Chen
Dr Leanne Cheung
Dr Glyn Chidlow
A/Prof Elaine Chong
Dr Antony Clark
Dr Georgia Cleary
Dr Oliver Comyn
A/Prof Mark Daniell
Dr Rosie Dawkins
Prof Nick Di Girolamo
A/Prof Lauren Downie
Prof Harminder Dua
Dr Katie Edwards
Dr Samuel Eggenberger
Dr Jesse Gale
Dr Patricia Garcia
Prof Mark Gillies
Prof Stuart Graham
Dr Matt Green
Dr Xavier Hadoux
Dr Stephanie Hagstrom
Prof Ming He
Dr Sheng Chiong Hong
Prof Glen Jeffery
Prof Robin G Jones
Dr Sam Kain
Dr Sanjay Kedhar
Dr Stuart Keel
Dr Jwu Jin Khong
A/Prof Mitchell Lawlor
A/Prof Christopher Layton
Dr Belinda Leong
Dr Grace Lidgerwood
A/Prof Gerald Liew
Dr Gareth Lingham
Prof Keith Martin
Dr Anu Mathew
Prof Helen Danesh Meyer
Dr Emeline Nandrot
Dr Riccardo Natoli
Prof Andrea O'Connor
A/Prof Michael O'Connor
Dr Michael O'Gallagher
Dr Francois Paquet-Durand
Dr Gary Swee Lim Peh
Dr Con Petsoglou
Dr Shiwani Sharma
Dr Michelle T. Sun
Dr Jenifer Thompson
Dr Lay Khoon Too
A/Prof Peter van Wijngaarden
A/Prof Andrew White
Dr Ling Zhu

ORIA would like to offer a special thank you to our generous donors, without whose support we would not have been able to fund such important research projects over the year.

Adam Rudkin	$1,000
ANZSRS	$25,000
Helen Margaret Trew Estate	$4,640
Ivy May Stephenson Trust	$663
Perth Eye Foundation	$50,000
ANZEF	$50,000
RANZCO NSW Branch	$150,000
Richard and Ina Humbley Foundation	$22,617
Other	$22,000
Total	**$325,920**

Grants Awarded 2020 for 2021

Chief Investigator	Other Investigator	Named Grant	Title of Project	Amount
Prof Robert Casson		Esme Anderson Grant	Retinal ganglion cell neuroprotection with photobiomodulation	$47,100.00
Dr Jason Charng	Dr David Alonso-Caneiro, Prof David Mackey	Perth Eye Foundation Grant	Applying machine learning to efficiently analyse fundus autofluorescence images in preparation for gene therapy	$47,800.00
Dr Elisa Cornish	A/Prof Samantha Fraser-Bell	ORIA Priming Grant	Near-infrared Light Photobiomodulation Treatment for Retinal Vein Occlusion Macular Oedema (NIRVO)	$50,000.00
Prof Robyn Jamieson	Prof John Grigg	RANZCO NSW Branch Grant	A new inflammatory pathway for modulation in the retinal dystrophies	$50,000.00
Dr Shweta Kaushik	Prof David Simmons, Dr Chee L. Khoo, Dr Marko Andric (FRANZCO, ORIA), Dr Kate McBride, Dr Jason R. Daley, Ms Xingdi Wang, Dr Vallimayil Velayutham, Dr Uchechukwu Levi Osuagwu	Australia and New Zealand Eye Foundation Grant	South Western Eye and Diabetes Deep Learning Algorithm (SWEDDLA) Study	$49,984.87
Dr Grace Lidgerwood	Dr M Mirazaei, A/Prof Pebay, A/Prof Hewitt	Richard and Ina Humbley Foundation Grant	Proteomics of RPE cells for the study of Geographic Atrophy	$35,000.00
A/Prof Chi Luu	A/Prof Penelope Allen, MBBS (FRANZCO), Dr Mohit Shivdasani, PhD	Hardie Anselmi Bequest Grant	Development of a novel hybrid vision restoration strategy	$48,970.00
Dr Carla Mellough	Prof Piroska Rakoczy, Prof Ian J. Constable (FRANZCO, ORIA)	R and L Lowe Bequest Grant	Investigating human vascular endothelial growth factor physiology	$50,000.00
Dr Ting Zhang	Prof Mark Gillies	RANZCO NSW Branch Grant	Targeting the pentose phosphate pathway in Müller cells to treat photoreceptor degeneration	$49,968.00
Total for 2020-2021				**$428,822.87**

Progress Reports on 2019/2020 Grants

ORIA Grant

Title: A new drug to control scarring after glaucoma surgery

Investigator: Dr Elsa Chan

Co-investigators: Dr Manisha Shah, Dr Jennifer Fan Gaskin

Aim: To evaluate the anti-scarring properties of 3',4'-dihydroxyflavonol (DiOHF) in human tissue cultures termed fibroblasts and a preclinical model of glaucoma surgery (GS).

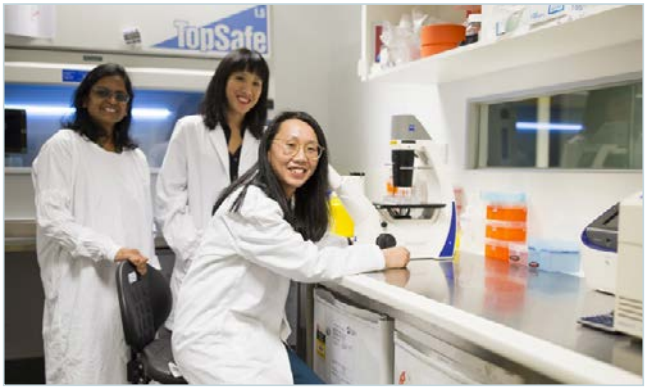
Methods: Fibroblast activities such as migration, growth, contraction and scarring protein synthesis were assessed after DiOHF treatment. Histology evaluation was performed on eyes from GS-operated mice which had treatment of either DiOHF or its control for 14 days.

Key Results: DiOHF reduced fibroblast activities that contribute to scarring. The adjacent diagram shows less deposition of the scarring protein collagen (in red) at the surgical wound from mice treated with DiOHF when compared to the control. The anti-scarring action of DiOHF is comparable to the standard-of-care mitomycin C and is attributable to the antioxidant effect.

Conclusion: DiOHF may be a safer and superior wound-modulating agent compared to the use of the cytotoxic agent mitomycin C in limiting post-surgical scarring.

Implications for Clinical Practice/Science and Future Research: A safer anti-scarring therapy improves the surgical outcomes of glaucoma surgery. DiOHF creates new opportunities for anti-scarring treatment in other eye disorders.

Publications or conference abstracts arising from this work: Fan Gaskin JC, Shah MH, Chan EC. Oxidative Stress and the Role of NADPH Oxidase in Glaucoma. Antioxidants 2021; 10:238.



(Left to right) Dr Manisha Shah, Dr Jennifer Fan Gaskin and Dr Elsa Chan

Australian and New Zealand Society of Retinal Specialists (ANZRS) Grant

Title: Optimising a pipeline for developing treatment for *CRB1*-related inherited retinal diseases

Investigator: A/Prof Fred K. Chen

Co-investigator: Prof Sue Fletcher

Aim: In this project we aimed to: 1) generate personalised retinal cell models for patients with *CRB1* mutations; 2) design and test antisense oligonucleotide drugs for treatment of *CRB1* mutations; and 3) develop a new method for inducing *CRB1* expression in skin cells.

Methods: Fibroblasts derived from patients with *CRB1*-associated retinopathy were reprogrammed into induced pluripotent stem cells, differentiated into retinal organoids and screened for splicing defects by RT-PCR. Patient fibroblasts were transfected with Cas9-VPR and guide RNAs targeting the *CRB1* promoter and *CRB1* expression was analysed by quantitative PCR.

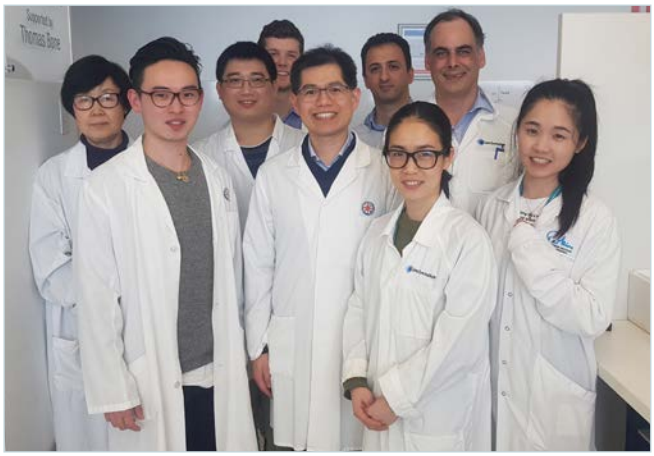
Key Results: Analysis of patient-derived retinal organoids indicated *CRB1* splicing defects occurred in 2/4 patients analysed (Aim 1). Antisense oligonucleotide drugs for treating *CRB1* splice mutations have been designed and are being screened in patient retinal organoids (Aim 2). Furthermore, we demonstrated induction of *CRB1* expression in patient skin fibroblasts by CRISPR activation (Aim 3).

Conclusion: We have identified two Western Australian patients with splice-altering mutations in *CRB1* that may be amenable to treatment with antisense oligonucleotide drugs. Additionally, we demonstrated the feasibility of inducing *CRB1* expression in patient-derived skin cells through CRISPR activation.

Implications for Clinical Practice/Science and Future Research: We have successfully optimised our pipeline for developing treatments for patients with *CRB1*-associated retinopathy. These pilot studies provided preliminary data for a successful application to the NHMRC for funding to continue our work in developing therapies for *CRB1*-associated retinopathy and other inherited retinal diseases.

Publications:

1. Moon SY, *et al*. 'Generation of two induced pluripotent stem cell lines from a retinitis pigmentosa patient with compound heterozygous mutations in *CRB1*.' *Stem Cell Res*. 2021 54:102403.
2. Zhang X, *et al*. 'Characterization of *CRB1* splicing in retinal organoids derived from a patient with adult-onset rod-cone dystrophy caused by the c.1892A>G and c.2548G>A variants.' *Mol Genet Genomic Med*. 2020 8(11):e1489



R and L Lowe Bequest Grant

Title: A novel calpain antagonist for ischemic retinal vein occlusion

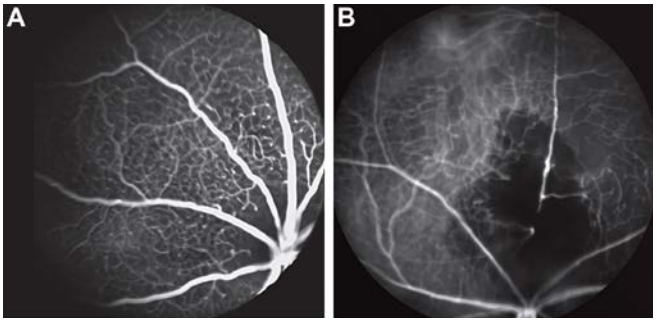
Investigator: Dr Glyn Chidlow

Co-Investigator: Dr Andreas Ebneter

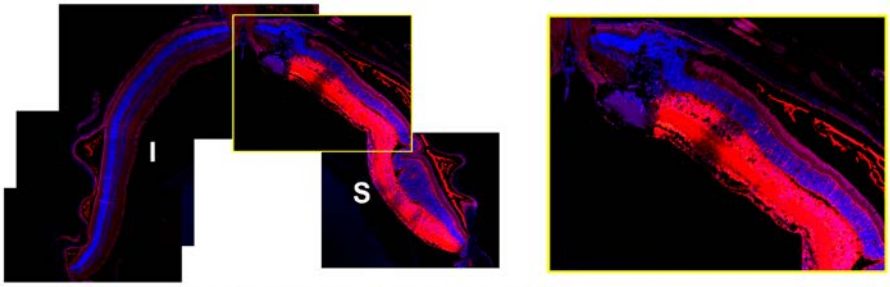
Aim: Retinal vein occlusions are common disorders which occur when blood clots block veins within the retina. The aims of this project are to establish translatable rodent models of ischemic retinal vein occlusion (iRVO) and to assess the therapeutic value of a novel calpain antagonist.

Methods: Venous supply to a proportion of the retina is blocked by targeting two to three major veins via laser treatment. The extent of ischemic injury and nerve cell survival are assessed by functional and histopathological methodologies. Some eyes receive a single injection of the calpain antagonist to assess whether it aids recovery.

Key Results: We have successfully established rat and mouse models of iRVO. Following venous blockage, spatially-defined areas of low oxygen availability (hypoxia) are evident within the retina throughout the first 24 hours, with decreasing hypoxia observed in subsequent days. These hypoxic regions are associated with nerve cell stress and death, together with activation and proliferation of the supporting glial cells. We are presently conducting experiments with the novel drug in order to ascertain its potential clinical effectiveness.



Fluorescein angiographic findings seven days after experimental iRVO. (A) control retina (B) iRVO of a single vessel. Absence of blood flow and drop out of capillaries in the drainage area of the affected vein is observed.



Localisation of hypoxia (red) at 24 hours following induction of BRVO. No hypoxia is evident in the unaffected inferior retina (I); hypoxia is widespread in the affected Superior retina (S).

Dr Chidlow

Dr Ebneter

Conclusion: We have successfully developed rodent models of iRVO that recapitulate the disease pathology that occurs in patients with ischemic vein occlusions. These exciting results have allowed us to commence testing of a novel therapy for the disease.

Implications for Clinical Practice/Science and Future Research: There is currently no effective treatment for individuals with iRVO. The development of valid preclinical models of the disease is a vitally important step for testing new therapeutic strategies. The novel drug being evaluated in this project has the potential for rapid clinical translation at the time of diagnosis.

Publications arising from this work:

Characterisation of a Rat Model of Branch Retinal Vein Occlusion. A thesis submitted in partial fulfilment of the Honours Degree of Bachelor of Health and Medical Sciences, University of Adelaide. Luke Rezk. November 2021.

Poster presentation:
Characterisation of a Rat Model of Branch Retinal Vein Occlusion. Luke Rezk, Robert Casson, Glyn Chidlow. Florey Undergraduate Conference, University of Adelaide. October 2021.

ORIA Grant

Title: Modulating neuroserpin using a gene therapy technique to reduce oxidative damage in glaucoma (Developing a gene therapy for glaucoma)

Investigator: Dr Nitin Chitranshi

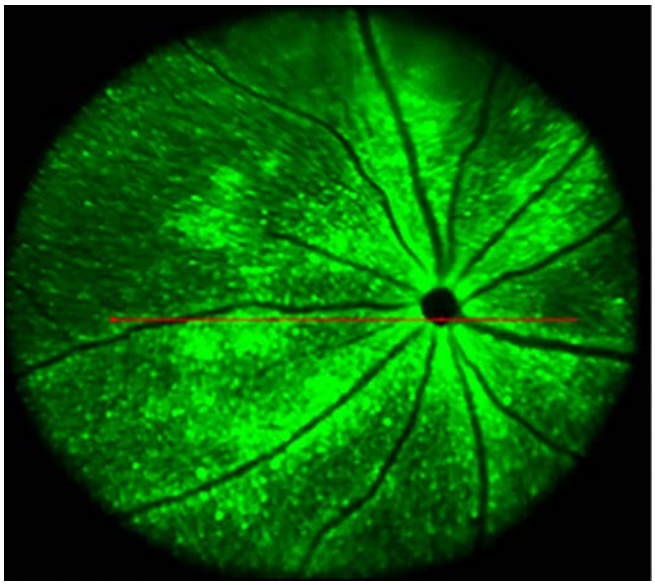
Aim: The aim of the study is to deliver serine protease inhibitor, neuroserpin protein, to prevent vision loss caused by plasmin proteolytic activity in the experimental animal glaucoma model.

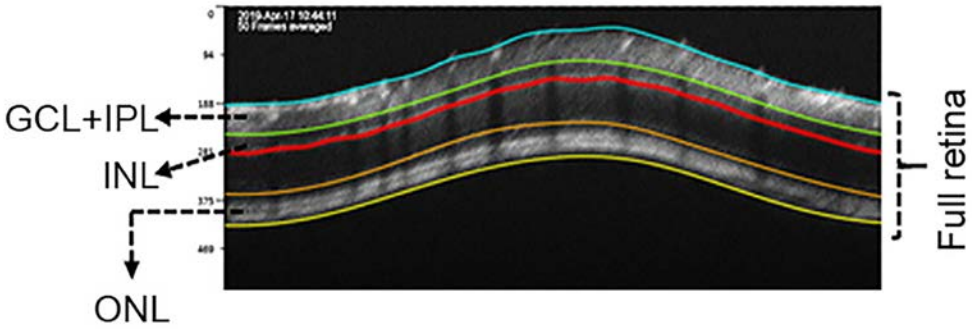
Method: Viral vector mediated overexpression of neuroserpin was achieved by intravitreal injection in animal eyes exposed to microbead induced high intraocular pressure (IOP).

Key Results: Successful transgene (neuroserpin) was overexpressed in the mouse retinal ganglion cells (RGCs) and green florescence protein (GFP) was observed in the mouse fundus imaging. Overexpression of neuroserpin in the high IOP protected the RGC structure and reduced functional damage induced by glaucoma. Neuroserpin overexpression protects against retinal cell apoptosis associated with glaucomatous damage. Overexpressed neuroserpin was shown to elicit stronger plasmin inhibitory activity.

Conclusion: Our retinal gene delivery is the first identification of a serine protease inhibitor that can protect RGCs and can become a potential therapeutic target in both glaucoma and other neurodegenerative disorders.

Implications for Clinical Practice/Science and Future Research: Over 300,000 Australians live with glaucoma and almost 10% of the population over 80 years are affected. The total community cost is expected to increase to $4.3 billion p.a. by 2025. Current management is limited to lowering the IOP which we know is not enough. Therefore, it is extremely important to better understand mechanisms underlying RGC loss and structural damage in glaucoma and to develop therapeutic strategies which can directly protect against this. Now we are interested in preparing the nanoparticle-based delivery system of neuroserpin to the retina to protect RGC damage in glaucoma.





ORIA Grant *continued*

Publications:

Nitin Chitranshi, Ashutosh Kumar, Samran Sheriff, Veer Gupta, Angela Godinez, Danit Saks, Soumalya Sarkar, Ting Shen, Mehdi Mirzaei, Devaraj Basavarajappa, Morteza Abyadeh, Sachin K Singh, Kamal Dua, Kam YJ Zhang, Stuart L Graham, Vivek K Gupta (2021). Identification of Novel Cathepsin B Inhibitors with Implications in Alzheimer's Disease: Computational Refining and Biochemical Evaluation. Cells, 10(8), 1946; https://doi.org/10.3390/cells10081946

Mojdeh Abbasi, Vivek Gupta, Nitin Chitranshi, Veer Gupta, Reza Ranjbaran, Rashi Rajput, Kanishka Pushpitha, Devaraj KB, Yuyi You, Robert G. Parton, Mehdi Mirzaei, Stuart L. Graham (2021). Inner retinal injury in experimental glaucoma is prevented upon AAV mediated Shp2 silencing in a caveolin dependent manner. Theranostics. 11(13):6154-6172. doi:10.7150/thno.55472

Morteza Abyadeh,Vivek Gupta, Nitin Chitranshi, Veer Gupta, Danit Saks, Roshana Vander Wall, Matthew J. Fitzhenry, Angela Godinez, Danit Saks, Devaraj Basavarajappa, Yuyi You, Ghasen H Sakekdeh, Paul A Haynes, Stuart L Graham, Mehdi Mirzaei (2021). Mitochondrial dysfunction in Alzheimer's disease—a proteomics perspective. Expert Rev Proteomics. 18(4):295-304. doi: 10.1080/14789450.2021.1918550.

Mehdi Mirzaei, Vivek Gupta, Nitin Chitranshi, Liting Deng, Kanishka Pushpitha, Mojdeh Abbasi, Joel Chick, Rashi Rajput, Yunqi Wu, Matthew J MacKay, Ghasen H Salekdeh, Veer Gupta, Paul A Haynes, Stuart L Graham (2020). Retinal Proteomics of Experimental Glaucoma Model Reveal Intra-Ocular Pressure Induced Mediators of Neurodegenerative Changes. J. of Cell. Biochem. https://doi.org/10.1002/jcb.29822

Veer Bala Gupta, Nitin Chitranshi, Jurre den Haan, Mehdi Mirzaei, Yuyi You, Devaraj KB, Jeremiah KH Lim, Angela Godinez, Silvia Di Angelantonio, Perminder Sachdev, Ghasem H Salekdeh, Femke Bouwman, Stuart Graham, Vivek Gupta (2020). Retinal changes in Alzheimer's disease-integrated prospects of imaging, functional and molecular advances. Prog Retin Eye Res. Sep 2:100899. doi: 10.1016/j.preteyeres.2020.100899.

Mojdeh Abbasi, Vivek K Gupta, Nitin Chitranshi, Veer Gupta, Mehdi Mirzaei, Yogita Dheer, Linda Garthwaite, Thiri Zaw, Robert G. Parton, Yuyi You, Stuart L Graham (2020). Caveolin-1 Ablation imparts Partial Protection Against Inner Retinal Injury in Experimental Glaucoma and Reduces Apoptotic Activation. Journal of Mol. Neurobiology 57 (9), 3759-3784.

Oral/Poster presentations:

Nitin Chitranshi, Rashi Rajput, Angela Godinez, Devaraj Basarjappa, Veer Gupta, Mehdi Mirzaei, Tim Magnus, Giovanna Galliciotti, Vivek K Gupta, Stuart L Graham (2021). Neuroserpin overexpressing mice are protected against retinal ganglion cells and optic nerve axonal loss in experimental glaucoma. World Glaucoma Congress, Japan, 2021

Rashi Rajput, Nitin Chitranshi, Angela Godinez, Kanishka Pushpitha, Devaraj Basarjappa, Vivek K Gupta, Stuart L Graham (2021). Antibody mediated neutralisation of Neuroserpin exacerbates retinal ganglion cell and optic nerve axonal damage in experimental glaucoma. World Glaucoma Congress, Japan, 2021

Angela Godinez, Rashi Rajput, Nitin Chitranshi, Vivek K Gupta, Stuart L. Graham, (2021). The neuroprotective effects of exogenous SERPINI1 administration on the retina in chronic glaucomatous conditions. Annual Conference of Association for Research in Vision and Ophthalmology (ARVO), Virtual Meeting, USA.

Nitin Chitranshi, Rashi Rajput, Linda Garthwaite, Kanishka Pushpitha, Mehdi Mirzaei, Samran Sheriff, Angela Godinez, Veer Bala Gupta, Stuart L Graham, Vivek K Gupta (2020). Retinal inhibition of glycogen synthase kinase 3 beta protects against tau phosphorylation and stabilises microtubule assembly. The Alzheimer's Association International Conference, Alzheimer's & Dementia, Volume 16, Issue S2, e046558

Vivek K Gupta, Nitin Chitranshi, Kanishka Pushpitha, Rashi Rajput, Veer Bala Gupta, Mehdi Mirzaei, Devaraj Basavarajappa, Stuart L. Graham (2020). Tau hyperphosphorylation in the retinal ganglion cells is attenuated upon silencing of SHP2 phosphatase. The Alzheimer's Association International Conference, Alzheimer's & Dementia, Volume 16, Issue S2, e046753

Kanishka Pushpitha, Mehdi Mirzaei, Nitin Chitranshi, Rashi Rajput, Stuart L Graham, Vivek K Gupta (2020). Alterations of the proteolytic and proteasomal enzymes in the retina in APP/PS1 mouse model of Alzheimer's disease. Annual Conference of Association for Research in Vision and Ophthalmology (ARVO), Virtual Meeting, USA. IOVS 61 (7), 4425

Rashi Rajput, Nitin Chitranshi, Kanishka Pushpitha, Devaraj Basavarajappa, Vivek K Gupta, Stuart L Graham (2020). Design and Evaluation of Novel AAV Viral Constructs with High Transduction Efficiency in Animal RGCs and Neuronal SH-SY5Y Cells. Annual Meeting of American Society of Gene and Cell Therapy 2020, USA. Molecular Therapy 28 (4), 269.

Perth Eye Foundation Grant

Title: Improving the prediction of glaucoma progression to prevent irreversible blindness

Investigator: Prof Jamie Craig

Co-investigator: A/Prof Owen Siggs

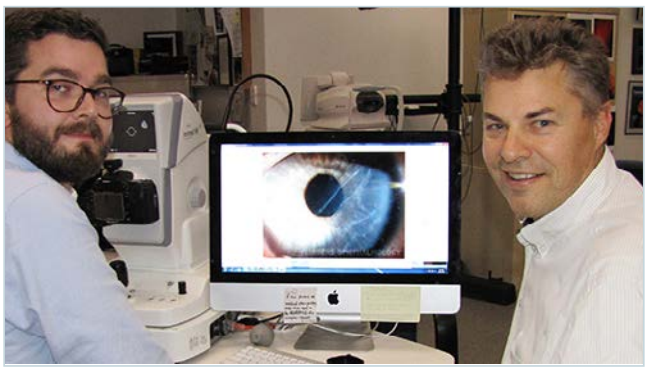
Aim: To apply machine learning approaches to better understand glaucoma risk.

Methods: We assembled >44,000 longitudinal OCT scans from glaucoma suspects (labelled according to visual field outcomes), and >77,000 retinal fundus images from a population cohort (labelled for vertical cup-to-disc ratio (VCDR) and vertical disc diameter (VDD)). Convolutional neural network (CNN) models were developed on both datasets.

Key Results: A preliminary model developed using the glaucoma suspect OCT dataset was non-inferior to clinician prediction of visual field conversion within 5 years. Models developed using the retinal fundus image dataset were used to estimate VCDR and VDD in a large unlabelled dataset, allowing detection of previously unknown genetic loci associated with VCDR and VDD.

Conclusion: Machine learning models can be used to predict future glaucoma risk and reveal new insights into the genetic architecture of optic nerve head parameters.

Implications for Clinical Practice/Science and Future Research: This work demonstrates potential applications of machine learning in understanding glaucoma risk, both as a decision support tool for predicting future conversion risk in glaucoma suspects, as well as a research tool for automated image labelling to empower large genetic association studies. Further work is underway to incorporate clinical, genomic, and imaging data into a multimodal glaucoma suspect prediction model.



Right of photo: Prof Jamie Craig (Chief Investigator), Consultant Ophthalmologist, Matthew Flinders Distinguished Professor of Ophthalmology, Flinders University and NHMRC Senior Practitioner Fellow

Left of photo: A/Prof Owen Siggs (Co-investigator), Head of the Genomic Medicine Lab, Garvan Institute & Snow Fellow

Publications: Han X, Steven K, Qassim A, Marshall HN, Bean C, Tremeer M, An J, Siggs OM, Gharahkhani P, Craig JE, Hewitt AW, Trzaskowski M, MacGregor S. Automated AI labeling of optic nerve head enables insights into cross-ancestry glaucoma risk and genetic discovery in >280,000 images from UKB and CLSA. Am J Hum Genet. 2021 Jul 1;108(7):1204-1216. doi: 10.1016/j.

Hardie-Anselmi Grant

Title: Pre-clinical validation of gene therapy for Bietti crystalline dystrophy

Investigator: Dr Thomas Edwards

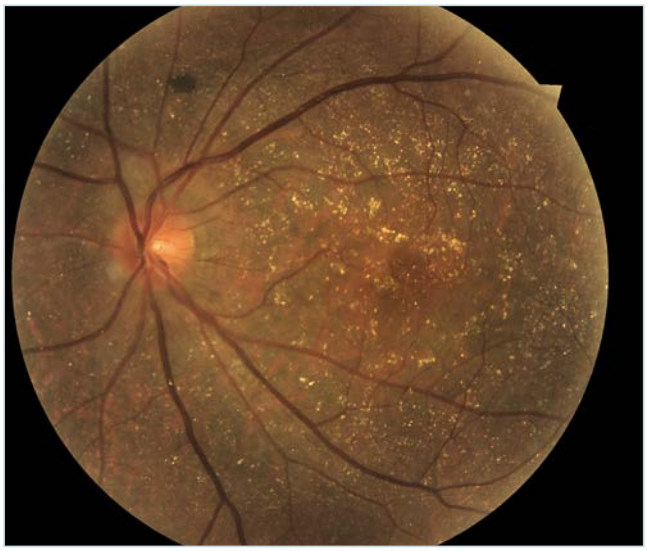
Co-investigators: Dr Doron Hickey, Dr Sloan Wang, A/Prof Alice Pébay

Aim: To induce viral-mediated expression of the Bietti crystalline dystrophy (BCD) gene, CYP4V2 protein, in various cell and animal models.

Methods: We used an AAV2 vector system to deliver CYP4V2 protein cDNA into cultured human cell lines and then examined expression and function of CYP4V2 protein. We then went on to assess in vivo expression in a wild-type mouse model following sub-retinal injection before transducing cultured human retinal explants to further validate our vector.

Key results: We demonstrated robust viral-mediated CYP4V2 expression and functional gains in human cell models, including disease-specific iPSC-derived RPE cells. High levels of CYP4V2 expression were detected by immunocytochemistry in our mouse model following subretinal injection. AAV2-mediated CYP4V2 expression was seen preferentially in the RPE layer of cultured human retinal explants.

Conclusion: Bietti crystalline dystrophy is a blinding inherited retinal degeneration caused by loss of function mutations in CYP4V2. With thanks to the generous support of an ORIA research grant, we have completed promising pre-clinical validation experiments of a gene augmentation strategy for BCD.



Retina of a Bietti crystalline dystrophy patient showing the striking crystalline deposits

Implications for Clinical Practice: These data have provided the foundation for further translational experiments, which we hope will culminate in a phase I clinical trial based at CERA and the Royal Victorian Eye and Ear Hospital.

Richard and Ina Humbley Grant

Title: Target the Notch signalling pathway to prevent retinal fibrosis

Investigator: Prof Mark Gillies

Co-investigators: Dr Yashar Seyed Razavi, Dr Ting Zhang

Aim: We aimed to characterise a mouse model of subretinal fibrosis and explore molecular treatment targets, such as the Notch signalling pathway, that may prevent scarring of the retina.

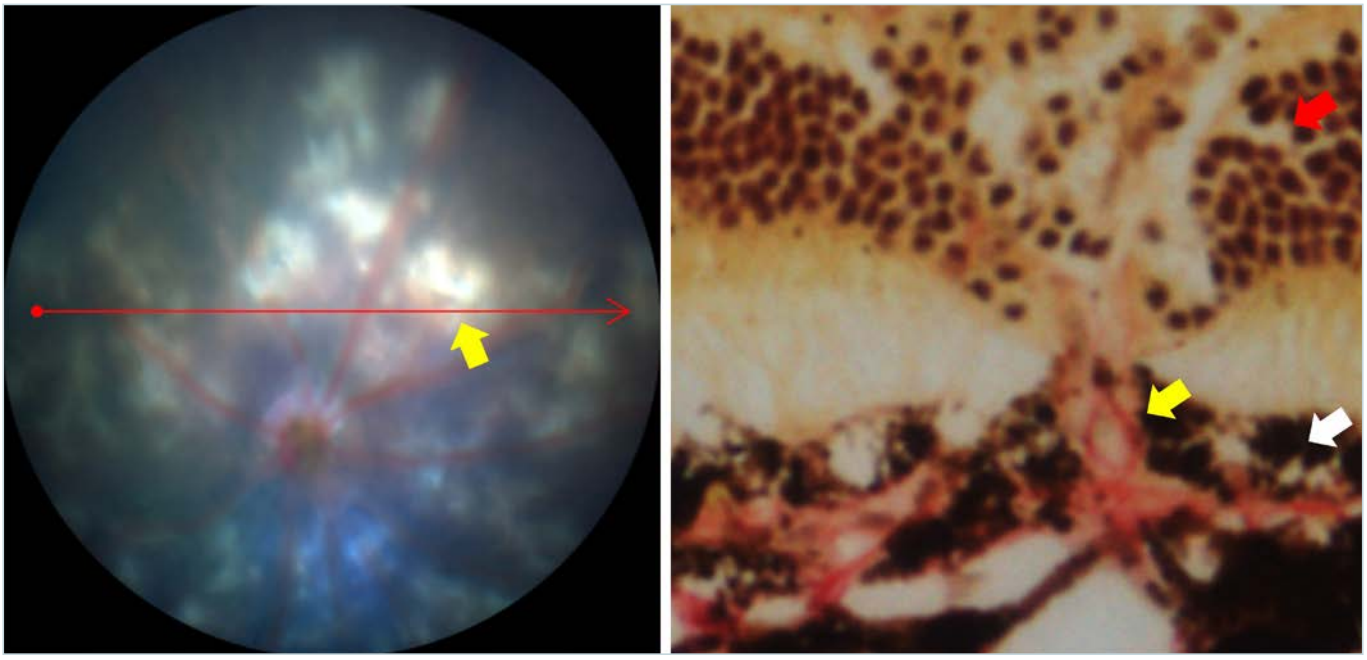
Methods: The development of subretinal fibrosis and the efficacy of treatments with a VEGF inhibitor or a Notch signalling inhibitor in this mouse model were investigated by assessing lesions with colour retinal photographs, optical coherence tomography, immunostaining of retinal sections and analysing the expression of proteins associated with fibrosis by Western blot.

Key Results: We found subretinal lesions in JR5558 mice expand between 4 and 8 weeks of age, becoming established in size and location around 12 weeks. The number of lesions increased between 4-8 weeks and remained static from 12 weeks. The model displayed several key molecular and pathological features of subretinal fibrosis. The VEGF inhibitor aflibercept inhibited the development of retinal fibrosis but the notch inhibitor was ineffective.

Conclusion: We have established that JR5558 mice are a good model of the scarring that may cause blindness in wet macular degeneration. Having demonstrated that the subretinal 'lesions' in these mice do contain a significant fibrotic component, we will now use this model to find ways to prevent retinal scarring.

Implications for Clinical Practice/Science and Future Research: We found that naturally-occurring subretinal lesions in JR5558 mice have a prominent fibrotic component that grows reliably and predictably, making these mice a good model for further screening of anti-fibrosis treatments in vivo.

Publications or conference abstracts arising from this work: Yashar Seyed-Razavi, So-Ra Lee, Jiawen Fan, Weiyong Shen, Mark C Gillies. JR5558 transgenic mice are a reliable model to investigate subretinal fibrosis. ARVO Annual Meeting Abstract, 2021, manuscript in preparation.



The Macula Research Group has characterised a mouse model of subretinal fibrosis which can be used to screen anti-fibrotic drugs.
Yellow arrows: Fibrotic scars (one of the most common causes of poor outcomes for nAMD patients) in a mouse retina are similar to humans.
Red arrow: retina.
White arrow: pigmented cell layer at the base of the retina.

ORIA Grant

Title: Engineering molecular tools to correct Leber's Hereditary Optic Neuropathy mutations in the mitochondria

Investigator: Dr Sandy Hung

Co-investigators: Lisa Kearns, Dr Helena Liang

Aim: To engineer and interrogate the use of programmable base editing tools to correct mitochondrial DNA (mtDNA) mutations that specifically cause Leber's Hereditary Optic Neuropathy (LHON).

Methods: We took on several approaches to develop a tool to edit mtDNA. To use CRISPR gene editing, we investigated ways to deliver the CRISPR protein and RNA into mitochondria. We also developed and tested TALE-mediated gene editing approaches to target the specific mutation in mtDNA which causes LHON.

Key Results: CRISPR gene editing: CRISPR/Cas system is a revolutionary tool which can be easily designed to target various DNA sequences. It is made up of two components—a protein (Cas) and guide RNA component—which need to come together for CRISPR editing to work. Therefore for this aim we developed and tested several approaches to introduce CRISPR machinery into the mitochondria. We successfully generated several cell lines expressing various CRISPR Cas proteins which localised to the mitochondria. However, we were unsuccessful in introducing the guide RNA into the mitochondria with the methods that we have tested in the study (mitochondria targeting RNA aptamer, mitoAAV).

Dr Sandy Hung

TALE-mediated gene editing: We designed and constructed adenine base editor and helicase fused to Transcription Activator-Like Effector (TALE) sequences, which can be programmed to target specific DNA sequences. The TALE-base editor was able to target and edit nucleotides around our target region, however the editing was not specific. Further developments will be necessary to increase the specificity and efficiency of this construct.

Conclusion: Several gene editing approaches to target mtDNA were tested and while we could deliver CRISPR protein into the mitochondria, we could not deliver CRISPR guide RNA into the mitochondria despite trying several approaches. Further engineering will be required to test other methods for RNA delivery as well as to develop effective and specific TALE-base editing approaches.

Implications for Clinical Practice/Science and Future Research: We had tested some approaches for delivery of protein and RNA into the mitochondria. Despite various publications outlining that delivery of RNA into the mitochondria using RNA aptamer or mitoAAV systems were possible, of the methods that we tested we were not able to deliver guide RNA into the mitochondria successfully. The second approach that we conducted using TALE-base editor is exciting because it can make gene editing in specific DNA regions, however more engineering will be required to make this editor more specific and effective.

RANZCO NSW Branch Grant

Title: Steps to therapy in early-onset retinal dystrophies

Investigator: Prof Robyn Jamieson

Co-investigators: Dr Anai Gonzalez Cordero, Prof John Grigg

The work of the Eye Genetics Research Unit in genomics of inherited retinal dystrophies (IRDs), has revealed that approximately two-thirds of the variants we detect in IRD patients are in genes encoding proteins involved in cilia structure or function of the photoreceptors (PRs). The human retina is an inaccessible tissue for functional biological assays, so human induced pluripotent stem cell (iPSC)-derived retinal organoids and retinal pigment epithelium (RPE) provide a powerful resource for development of improved therapies in these conditions.

Aim: To use our expertise in human iPSC-retinal organoid and RPE differentiation, gene editing and ciliary assays, to assess phenotypic impact and gene replacement in early-onset cilia-associated IRDs. Mutations in these early-onset cilia-associated disease genes lead to the severe retinal dystrophy, Leber congenital amaurosis (LCA).

Methods: To test the impact of the ciliopathy gene variant of uncertain significance (VOUS) under investigation and assess a novel gene replacement strategy, we generated iPSCs from control and LCA patient peripheral blood mononuclear cells. Gene expression studies using qRT-PCR and immunohistochemistry were performed to confirm pluripotency of the iPSCs. CRISPR/Cas9 genome editing and homology directed repair was undertaken in our control human iPSC line to generate the novel ciliopathy gene VOUS in homozygous form.

Key Results: The LCA patient line had a homozygous stop mutation in the ciliopathy disease gene. These lines were differentiated to retinal organoids with development of the neuroretinal layer seen at 24-28 weeks (Fig.1A-C) and further to an age of 30 weeks, when the iPSC-derived photoreceptor cells expressed key markers and morphological features including cilia markers and light-sensing outer segments (Fig.1D,E).

Conclusion: The ciliopathy disease gene investigated in this study is critical for transport of proteins such as Rhodopsin from the inner to the outer segment of the photoreceptors. In the mutant iPSCs (VOUS and LCA) we showed abnormal localisation of ciliary transition zone markers (Fig.1D) and Rhodopsin (Fig.1E) compared with control. The cDNA of the ciliopathy disease gene has been cloned into an AAV cassette containing the human rhodopsin kinase promoter. Preliminary results following transduction of the therapeutic product indicate amelioration of phenotypic features in mutant organoids.

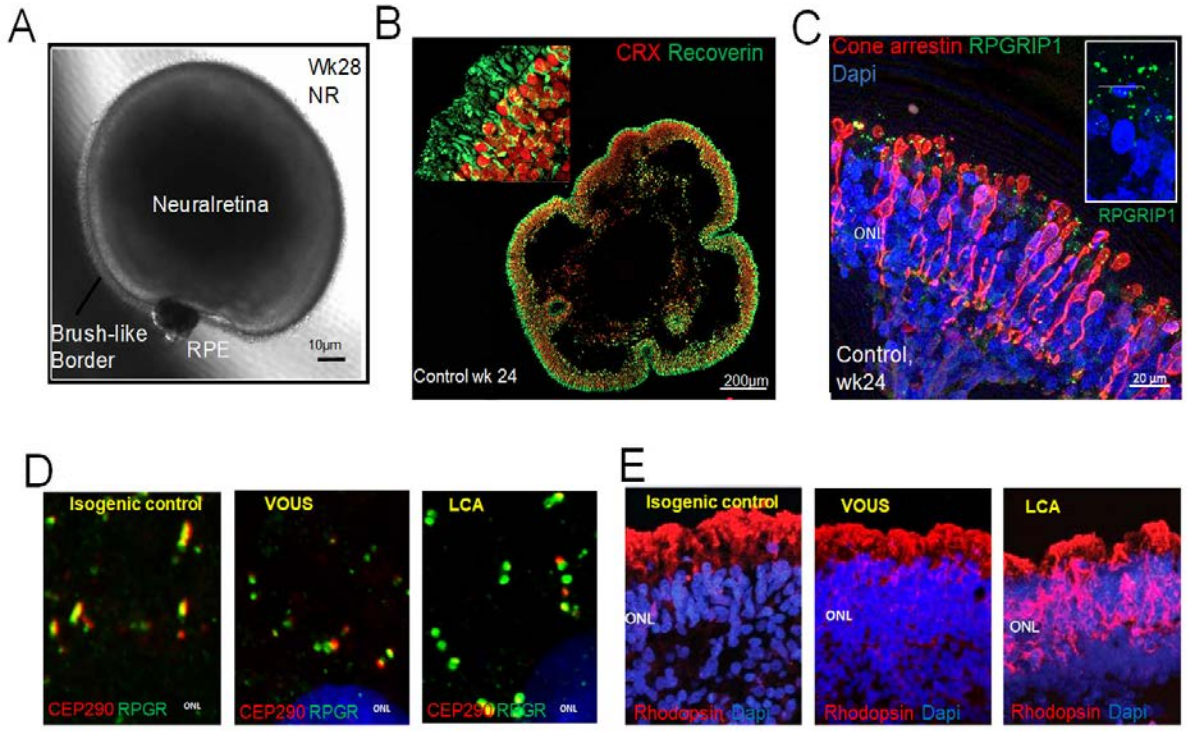


Figure 1. Human iPSC differentiation to retinal organoids, and disease biomarkers in early-onset retinal dystrophies. A. *Retinal organoid, 28 wks.* ***B****. IHC: CRX and recoverin retinal markers—photoreceptors on outer aspects of organoids, 24 wks, along with* ***C****. expression of cone arrestin and ciliary protein, RPGRIP1.* ***D-E.*** *IHC of wk 30 control and ciliopathy disease gene organoids (VOUS and LCA) showing* ***D****. abnormal CEP290 and RPGR co-staining, and* ***E.*** *mislocalised rhodopsin compared with control.*

RANZCO NSW Branch Grant *continued*

Implications for Clinical Practice/Science and Future Research: This work demonstrates the value of human stem cells differentiated to retinal organoids as a model system for genetic variant classification and testing of novel genetic therapies. Results from this project will be used for reclassification of the VOUS to a pathogenic variant, so this will be a clinically actionable result valuable for genetic information for the patient and family and access to future clinical trials and therapies. Results from this project also provide valuable preclinical data for novel gene replacement therapy for this and other early-onset retinal dystrophies.

Publications or conference abstracts arising from this work: This work has contributed to five invited speaker and other presentations at national and international meetings in 2020/21, including online webinars for the Australasian Society for Stem Cell Research, the Association for Research in Vision and Ophthalmology and the LV Prasad Eye Institute Genetics conference, India (1-5). Work related to this project will be presented at two other meetings in 2021/22 including: the Human Genetics Society of Australasia Annual Scientific Meeting and the Royal Australian and New Zealand College of Ophthalmology Annual Scientific Congress (6,7). Findings from this project have contributed to further funding through the Medical Research Future Fund, Stem Cell Therapies Mission, 'Stem cell derived-retinal organoids to test novel genetic therapies', Gonzalez Cordero, Jamieson, Carvalho, Alexander, Grigg.

Research Dissemination:

1. Jamieson RV. Seeing eye to eye with stem cells: new therapies for retinal diseases. (Retinal organoids and RPE for extending diagnostic yield and testing novel therapies in genetic retinal diseases). Australasian Society for Stem Cell Research (ASSCR), National Stem Cell Conversations Webinar, 3 Mar 2021.
2. Jamieson RV. Stem cells for disease modelling in the retinal dystrophies. Stem Cells in Ophthalmology, Online Education and Webinar, Association for Research in Vision and Ophthalmology, 14 & 21 Jan 2021.
3. Jamieson RV. Ocular gene therapy and editing for precision treatment in retinal diseases. Westmead Hub Precision Medicine Conference, Sydney, 20-21 May 2021.
4. Jamieson RV. Genomics, model systems and gene therapy trials in inherited retinal diseases. LV Prasad Eye Institute Seminar. Hyderabad, India (via webinar) 28 Nov 2020.
5. Loi TH, Fernando M, Cheng A, Kim HJ, Nash B, Yang P, Gonzalez Cordero A, Jamieson RV. Human stem cell derived retinal organoids for modelling inherited retinal dystrophies. Australasian Society for Stem Cell Research (ASSCR) ECR Conference, NSW, 14 May 2021.
6. Nash BM, Loi TH, Sabri A, Eamegdool S, Fernando M, Grigg JR, Gonzalez Cordero A, Jamieson RV. From VOUS to gene therapy: a stem cell-based approach to determining the pathogenicity of novel ocular genomic variants. Human Genetics Society of Australasia Annual Scientific Meeting, Adelaide, South Australia, 14-17 August 2021.
7. Jamieson RV, Nash BM, Loi TH, Sabri A, Fernando M, Grigg JR, Gonzalez Cordero A. Human stem cell-derived retinal organoids for variant classification and genetic therapy testing in the IRDs. Royal Australian and New Zealand College of Ophthalmology Annual Conference, Brisbane, Queensland, 25 February-1 March 2022.

Publications:

1. Nash BM, Watson CJ, Hughes E, Hou AL, Loi TH, Bennetts B, Jelovic D, Polkinghorne PJ, Gorbatov M, Grigg JR, Vincent AL, Jamieson RV. Heterozygous COL9A3 variants cause severe peripheral vitreoretinal degeneration and retinal detachment. European Journal of Human Genetics, 2021. May;29(5):881-886. Epub 2021 Feb 25. PMID: 33633367
2. Ma AS, Yousoof S, Grigg JR, et al. Bennetts B, Jamieson RV. Revealing hidden genetic diagnoses in the ocular anterior segment disorders. Genetics in Medicine, 2020, Oct;22(10):1623-1632. Epub 2020 Jun 5. PMID: 32499604

Ivy May Stephenson Grant

Title: Engineering a synthetic microbial treatment for gyrate atrophy

Investigator: Mr Mohd Khairul Nizam Mohd Khalid

Co-investigator: Prof Alex Hewitt

Aim: To develop live bacterial therapeutics as potential treatment for patients with gyrate atrophy.

Methods: We began with isolating and verifying the probiotic E.coli Nissle 1917 (EcN) strain to be used as chassis for developing the treatment. Next, we transformed the probiotic with our candidate genes and screened for the ability of the transformed bacteria to consume ornithine in vitro. We designed a synthetic circuit containing various combinations of the most effective candidate genes as well as testing for several potential inducible promoters to drive a robust expression of the genetic cassettes. The synthetic circuits were delivered into EcN and we profiled the strain activity using a combination of in vitro ornithine consumption assay, microscopy and flow cytometry. Once we identified the best performing strain, we gavaged them at a concentration of 1010 cfu/ml into our mouse model for gyrate atrophy and measured the serum ornithine levels using UPLC-MS/MS.

Key Results: We identified several candidate genes that were functional when expressed in EcN and showed increased ornithine consumption compared to the wildtype strain. When we tested those functional candidate genes in a synthetic circuit, we found one combination that showed robust expression and high in vitro ornithine consumption activity when induced. When gavaged at 1010 cfu/ml concentration, we found that our engineered strain significantly reduced the systemic ornithine concentration compared to wildtype EcN.

Conclusion: We have successfully developed a probiotic strain with enhanced ability to consume ornithine both in vitro and in vivo.

Implications for Clinical Practice/Science and Future Research: This work offers the prospect of developing a simple, oral therapy, which could reshape the treatment paradigm of this disease and potentially other diseases caused by small-molecule intoxication. The next step is to optimise the strain activity to further enhance its ornithine-consuming/degrading ability before going for full-scale manufacturing for in-human trial.

Publications/conference abstracts:

Delivered a presentation titled 'Steps towards a treatment for gyrate atrophy' during the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Tasmania Branch Meeting 2021 in Hobart from 26-27 June 2021

ORIA Grant

Title: Targeted cancer gene therapy for uveal melanoma

Investigator: Prof Christopher Layton

Co-investigator: Dr Jason Steel

Aim: The goal of this one-year grant was to develop a novel targeted gene therapy system based on Adeno-Associated Virus (AAV) vectors to specifically target and destroy Uveal Melanoma (UM).

Methods: We developed diverse libraries of AAV capsids by genetically cloning the sequence for random peptides into the HI loop of AAV8 and screened the capsids using multiple selection rounds to identify AAV capsids that had high affinity for Uveal Melanoma cell lines. The selected AAV capsids were screened for off target expression in a panel of eye and liver cell lines.

Key Results: We successfully used viral-directed evolution to select an AAV capsid with enhanced transduction and expression in uveal melanoma. The capsid showed a high specificity for UM with little expression detected in non-UM cell lines, including those derived from the eye (primary origin of disease) or the liver (metastatic site). Vectors constructed using the modified capsid resulted in less viral neutralisation when tested against pooled human sera containing AAV directed antibodies. We also developed and evaluated a sophisticated expression cassette to increasing vector specificity. We showed in a panel of liver and UM cell lines that this expression cassette induced high levels of expression in UM but not in liver cell lines.

Conclusion: In this study we have shown, for the first time, that directed evolution of AAV capsids can result in a virus with specificity for uveal melanoma. This, coupled with our novel expression cassette, can allow targeted gene delivery to the cancer.

Implications for Clinical Practice/Science and Future Research: Currently there are no successful treatments for metastatic UM, with these cancers being resistant to standard chemotherapy and radiotherapies. In this study we have thought outside this conventional box to see whether metastatic UM could be targeted by an advanced gene therapy vector, and showed that it could be. This opens up a potential new clinical class of therapeutic with the ability to target UM in the liver. While the study to date has been in cell culture, we will be moving this work into pre-clinical models of UM with the goal of transitioning the science into human clinical trials.

ORIA Grant

Title: Choroidal Melanocytes and Melanocortins: Much More than Melanin

Investigator: A/Prof Michele Madigan

Co-investigators: VA Cioanca, R Natoli, RM Conway and PJ McCluskey

Aim: In the human eye, the vascular, pigmented choroid plays a major role in maintaining normal retinal function. Our study looks at how the melanocortin system (which regulates melanin-making and inflammation) works in choroidal pigmented cells (melanocytes).

Methods: Human donor eyes and primary human choroidal melanocytes are used for gene and protein studies of melanocortin receptors (MCR), and to study α-melanocyte-stimulating hormone (α-MSH)-MCR pathways.

Results and Conclusion: Unstimulated human choroidal melanocytes expressed varying gene levels of MC1R to MC4R, but not MC5R. MC1R protein in melanocytes in human choroid sections and human choroid melanocyte cultures was confirmed. Comparative analysis of transcriptome data for choroid (current study, n=4) *versus* skin (n=4) melanocytes showed both express similar (relatively low) levels of MC1R gene and expressed key downstream melanin-associated genes.

In the next stage we will assess α-MSH-MC1R function and use melanocyte-RPE co-cultures to simulate *in situ* interactions. How α-MSH-MC1R signalling modulates secretion of inflammatory molecules from stimulated melanocytes will be studied. Biological effects of MCR-α-MSH interactions will be analysed with transcriptomics (gene) and protein-based methods.

Clinical implications: Understanding how the melanocortin system can work in human choroidal melanocytes, related to maintaining a 'quiet' choroid immune microenvironment, may potentially generate new sites for treatment for many forms of non-infectious posterior and pan uveitis.

Publications:

Cioanca AV, Wu CS, Natoli R, Conway RM, McCluskey PJ, Jager MJ, Sitiwin EI, Eamegdool SS, Madigan MC (2021). The role of melanocytes in the human choroidal microenvironment and inflammation: Insights from the transcriptome. *Pigment Cell Melanoma Res.* Mar 22. doi: 10.1111/pcmr.12972

Madigan MC, Wu CS, Jager MJ, Conway RM, McCluskey PJ, Natoli R, Cioanca AV. Melanocytes, Inflammation and Responses in the Human Choroid Microenvironment. *Invest. Ophthalmol. Vis. Sci.* 2021; 62(8):2840. (*ARVO Meeting 2021*)

Summary of research findings to date.

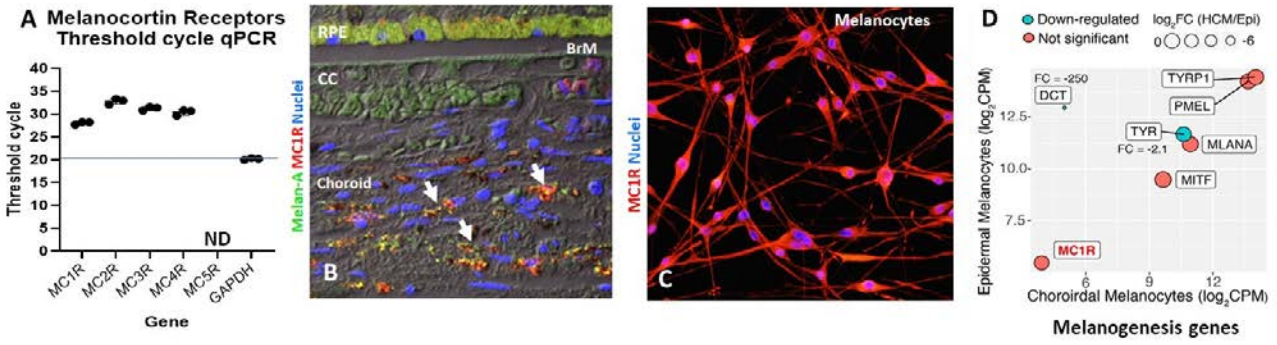


Figure 1. (A) qPCR cycle threshold for melanocortin receptors (*MCR*) and *GAPDH* housekeeping gene in human choroidal melanocytes (n=3). (B) A human choroid cross-section shows MC1R (red) and Melan-A (green, melanocyte marker) protein in melanocytes (arrows). (C) Cultured primary choroidal melanocytes also expressed MC1R protein (red). (D) Scatter plot comparing abundance and expression of melanin-associated genes in choroid (x-axis) *versus* skin (y-axis) melanocytes (from Cioanca *et al.*, 2021). Note similar abundance and expression of *MC1R* gene. [RPE= retinal pigment epithelium; BrM = Bruch's membrane; CC = choriocapillaris].

ORIA People

ORIA Board

Dr Jennifer Fan Gaskin
A/Prof Sam Fraser-Bell
Prof Mark Gillies (Vice Chair)
Dr William Glasson*
Prof Stuart Graham
A/Prof Paul Healey (Treasurer)
A/Prof Alex Hewitt
Dr George Kong
Prof David Mackey
Dr John Males (until March 2021)
Prof Richard Mills (Secretary)
Dr Chameen Samarawickrama
Dr Richard Stawell
A/Prof Andrea Vincent*
Prof Stephanie Watson (Chair)
A/Prof Peter van Wijngaarden

* RANZCO Nominee

2020-2021 RAC Panellists

Prof Alex Hewitt (Chair)
Dr Jennifer Fan Gaskin
A/Prof Samantha Fraser-Bell (Secretary)
A/Prof Adrian Fung
Prof Damien Harkin
A/Prof Michele Madigan
Prof Alice Pébay
A/Prof Chameen Samarawickrama
Dr Isabel Lopez Sanchez
Prof Andrea Vincent
Prof Stephanie Watson
Dr Graham Wilson (New Zealand Save Sight Representative)
Dr John Wood

Macular Research Group Save Sight Institute

Financial Statements

In accordance with a resolution of the directors, the directors submit herewith the financial statements of The Ophthalmic Research Institute of Australia for the year ended on 30 June 2021 and report as follows:

1. Meetings of Directors

During the financial year three meetings of directors were held. Attendances were:

Board Members	Number Eligible to Attend	Number Attended
Prof Stephanie Watson, NSW – Chair	2	2
Prof Mark Gillies, NSW – Vice Chair	2	2
Prof Richard Mills, SA – Honorary Secretary	2	2
A/Prof Paul Healey, NSW – Honorary Treasurer	2	2
Dr Jennifer Fan Gaskin, VIC	2	2
A/Prof Clare Fraser, NSW	2	2
A/Prof Sam Fraser-Bell, NSW	2	2
Prof Stuart Graham, NSW	2	2
A/Prof Alex Hewitt, TAS	2	2
Dr George Kong, VIC	2	2
Prof David Mackey, WA	2	2
Prof Peter J McCluskey, NSW	2	2
Dr John Males, NSW	2	2
Dr Chameen Samarawickrama, NSW	2	2
A/Prof Andrea Vincent, New Zealand	2	2
A/Prof Peter van Wijngaarden, VIC	2	2

2. Indemnifying Officer or Auditor

The company has not during or since the financial year in respect of any person who is or has been an officer or auditor of the company or a related body corporate indemnified or made any relevant agreement for indemnifying against a liability incurred as an officer including costs and expenses in successfully defending legal proceedings or paid or agreed to pay a premium in respect of a contract of insurance against a liability incurred as an officer for the costs or expenses to defend legal proceedings.

3. Principal Activities

The principal activity of the company in the course of the financial period was to provide funds for ophthalmic research. There has been no significant change in the nature of this activity during that period.

4. Operating Results

(1) Operating Revenue

Revenue is mainly derived from investing in shares and interest bearing securities.

	2020/21	2019/20
	$	$
Net dividend, interest and trust distribution income	522,741	547,929
Less Expenses	74,285	76,030
	448,456	**471,899**

(2) Operating Surplus

The surplus of the company before other comprehensive income for the year ended 30 June 2021 was $771,941 (2020: $806,896). This amount is comprised of the following:

	2020/21	2019/20
	$	$
Trust Fund	765,276	739,096
Administration	6,665	67,800
	771,941	**806,896**

Other comprehensive income before grants and Director of Research allocation amounted to a profit of $1,913,699 (2020: loss of $1,099,402) and included a gain on rearrangement of investments of $113,018 (2020: loss of $131,137) and valuation gain on available-for-sale financial assets of $1,800,680 (2020: loss of $968,265).

5. Review of Operations

The surplus for the year was $771,941 compared to $806,896 in 2020.
The administrative operations of the institute for the year resulted in a profit of $6,665 compared with a profit of $67,800 in 2020.

6. Dividends

The company's Articles of Association preclude the payment of dividends to any of its members.

7. State of Affairs

There has been no significant change in the state of affairs of the company occurring during the year.

8. Impact of COVID-19

The pandemic has resulted in a reduction in investment income and the carrying value of investments assets this year.

9. Events Subsequent to the end of the Reporting Period

Other than the ongoing, currently unknown effect of COVID-19, there have been no matters or circumstances arisen since the end of the financial year which significantly affected or may significantly affect the operations of the company, the results of those operations, or the state of affairs of the company in future financial years.

10. Likely Developments

At the date of this report, there are no known unusual developments that will affect the results of the company's operations in subsequent financial years.

11. Share Options

No share options were issued during the year.

12. Directors' Benefits

No director of the company has since the end of the previous financial year received or become entitled to receive a benefit not disclosed in the accounts as directors' emoluments by reason of a contract made by the company or a related corporation with the directors, or with a firm in which he or she has a substantial financial interest.

Some board members were associate investigators on some grants for 2020/2021. The ORIA has stringent governance processes for managing conflicts of interest during the allocation of grants. All grants are evaluated by ORIA's Research Advisory Committee (RAC). The RAC consists of leading research ophthalmologists and vision scientists from Australia and New Zealand. The RAC members are selected annually by the executive. They are joined by reviewers from around the world to conduct the annual grant application review.

Statement of Financial Position

For The Year Ended 30 June 2021

	Note	2020/21 $	2019/20 $
Current Assets			
Cash and Cash Equivalents	3	1,802,329	2,482,450
Receivables	4	398,279	196,460
Investments	5	12,509,613	9,900,007
		14,710,221	**12,578,917**
Non-Current Assets			
Plant & Equipment	6	-	835
Total Assets		**14,710,221**	**12,579,752**
Current Liabilities			
Payables	7	897,638	893,956
Provisions	8	-	-
Total Liabilities		**897,638**	**893,956**
Net Assets		**13,812,583**	**11,685,796**
Equity			
General Fund	13 (a)	-	-
Capital Funds			
Research Fund	9	2,638,254	2,588,305
Settled Funds	10	472,556	472,556
Financial Assets Reserve	11	1,868,374	67,694
Capitalised Profit on Re-arrangement of Investments, Capital Distributions & Transfers	12	7,426,621	7,313,599
		12,405,805	10,442,154
Retained Income - Available for grants	13 (b)	1,406,778	1,243,642
Total Equity		**13,812,583**	**11,685,796**

The accompanying Notes form part of these financial statements.

Trust Fund Statement of Comprehensive Income

For The Year Ended 30 June 2021

	Note	2020/21 $	2019/20 $
Income			
Dividends received from:			
Other Corporations		295,918	454,062
Total Dividends		**295,918**	**454,062**
Interest received from:			
Other Entities		7,891	17,390
Trust distributions received from:			
Other Entities		218,932	76,477
The Richard and Ina Humbley Foundation		22,617	39,177
Donations		294,203	228,020
Total Income for the Year		**839,561**	**815,126**
Expenses			
Commission Paid		74,285	76,030
		74,285	76,030
Surplus For The Year		**765,276**	**739,096**
Other Comprehensive Income			
Valuation Gains/(Losses) on available-for-sale financial assets		1,800,680	(968,265)
Profit/(Loss) on Re-arrangement of Investments		113,019	(131,137)
Total other comprehensive income		1,913,699	(1,099,402)
Surplus for the year before allocation		2,678,975	(360,306)
Grants Allocated/made during the year	14	428,853	591,930
Allocation to Director of Research - Victoria	15	130,000	126,000
		558,853	717,930
Total Comprehensive Income/(Loss)		**2,120,122**	**(1,078,238)**
Profit/(Loss) Attributable to Members of the Entity		206,423	21,164
Total Other Comprehensive Income/(Loss) Attributable to Members of the Entity		1,913,699	(1,099,402)

The accompanying Notes form part of these financial statements.

Statement of Changes in Equity

For The Year Ended 30 June 2021

	GENERAL FUND		CAPITAL FUNDS				TOTAL
	Accumulated Surplus/Deficit	Research Fund	Settled Funds	Realised Profits on Re-arrangement of Investments & Capital Distributions & Transfers	Financial Assets Reserve	Retained Income	
	$	$	$	$	$	$	$
Balance at 1 July 2019	**-**	**2,546,180**	**472,556**	**7,444,740**	**1,035,960**	**1,281,924**	**12,781,499**
Profit / (Loss) for Year	67,800	-	-	-	-	21,164	88,964
Total Other Comprehensive Income	-	-	-	(131,137)	(968,265)	-	(1,099,402)
Capitalised Bequests	-	-	-	-	-	-	-
Transfer from Capital	-	-	-	-	-	-	-
Transfers to/(from) Reserves	(67,800)	41,984	-	-	-	(59,449)	(85,265)
Balance at 30 June 2020	**-**	**2,588,303**	**472,556**	**7,313,603**	**67,694**	**1,243,639**	**11,685,796**
Balance at 1 July 2020	**-**	**2,588,303**	**472,556**	**7,313,603**	**67,694**	**1,243,639**	**11,685,796**
Profit / (Loss) for Year	6,665	-	-	-	-	196,666	203,331
Total Other Comprehensive Income	-	-	-	113,019	1,800,680	-	1,913,699
Capitalised Bequests	-	-	-	-	-	-	-
Transfer from Capital	-	-	-	-	-	-	-
Transfers to/(from) Reserves	(6,665)	49,949	-	-	-	(43,284)	-
Balance at 30 June 2021	**-**	**2,638,254**	**472,556**	**7,426,621**	**1,868,374**	**1,406,778**	**13,812,583**

The accompanying Notes form part of these financial statements.

Administration Statement of Comprehensive Income

For The Year Ended 30 June 2021

	Note	2020/21 $	2019/20 $
Income			
Membership Subscriptions		172,965	187,980
Interest			540
Total Income		**172,965**	**188,521**
Expenses			
Accountancy Fees		24,900	7,900
Sundry Expenses		5,468	10,902
Auditors' Remuneration	16	8,250	8,000
Admin Expenses		-	81,639
Bank Charges		120	120
Depreciation		835	477
IT & Webpage Expenses		14,205	-
Insurance		2,033	1,855
Legal Fees		5,617	-
Superannuation Contribution		10,816	1,014
Salary and Wages		94,056	8,814
Total Expenses		**166,300**	**120,721**
Surplus/(Deficit) For The Year	13(a)	**6,665**	**67,800**
Other Comprehensive Income		**-**	**-**
Total Comprehensive Income		**6,665**	**67,800**

The accompanying Notes form part of these financial statements.

Statement of Cash Flows

For The Year Ended 30 June 2021

	Note	2020/21 $	2019/20 $
Cash Flows From Operating Activities			
Receipts			
Dividends Received		203,138	334,431
Interest Received		7,650	17,931
Trust Distributions		218,932	76,477
Legacies		-	-
Other Revenue		180,084	631,322
RANZCO - Reimbursement of membership fees		172,965	187,980
Payments			
Commissions		(74,285)	(76,030)
Research Grants Paid		(525,233)	(551,185)
Payments to Director of Research - Victoria		-	-
Other		(58,519)	(110,416)
Net Cash (Used in)/Provided by Operating Activities	17	**124,732**	**510,510**
Cash Flows From Investing Activities			
Proceeds from Re-arrangement of Investments		22,477,782	7,055,139
Payments for Property, Plant & Equipment		-	-
Payments for Investments		(23,389,878)	(6,508,227)
Net Cash Used in Investing Activities		(912,096)	546,912
Net(Decrease)/Increase in Cash and Cash Equivalents		(680,121)	1,057,422
Cash and Cash Equivalents at 1 July 2019		2,482,450	1,425,028
Cash and cash equivalents at 30 June 2020	3	**1,802,329**	**2,482,450**

The accompanying Notes form part of these financial statements.

Notes to the Financial Statements

1. Statement Of Accounting Policies

The financial statements are for the Ophthalmic Research Institute of Australia, incorporated and domiciled in Australia. The Ophthalmic Research Institute of Australia is a company limited by guarantee.

(A) BASIS OF PREPARATION

The financial statements are general purpose financial statements that have been prepared in accordance with Australian Accounting Standards (including Australian Accounting Interpretations) and the Australian Charities and Not-for-profits Commission Act 2012.

The accounting policies set out below have been consistently applied to all years presented, unless otherwise stated. The financial report has been prepared on an accruals basis and is based on historical costs and does not take into account changing money values or, except where stated, current valuations of non-current assets. Cost is based on the fair values of the consideration given in exchange for assets.

The following is a summary of the significant accounting policies adopted by the company in the preparation of the financial report.

(B) INCOME TAX

The company is an approved research institute and is exempt from income tax.

(C) TRANSFERS TO CAPITAL FUNDS

(i) Capital profits and losses on disposal of investments & capital distributions.

Realised capital profits and losses on disposal of investments are brought to account in the trust fund as profit/(loss) on rearrangement of investments, however, these amounts are transferred to capital funds and do not form part of retained income available for grants.

Capital Distributions and special dividends together with associated imputation credits recognised in the statement of comprehensive income are also transferred to the capital fund and do not form part of retained income available for grants.

(ii) General Research Capital Fund

Ten percent of the net surplus of the General Fund including imputation credits are transferred to the General Research Capital Fund this financial year.

(iii) Allocation of Income to Each Fund

During the year ended 30 June 1993, the investments of the company were separated into the D.W. Research Fund and the General Fund in the ratio of 72% and 28% respectively. As the flow of investment and donation income to and from the two funds does not occur in the same proportion, the ratio of the D.W. Research Fund and the General Fund is no longer at 72% and 28%.

Income from the General Fund which comprises all funds except the D.W. Research Fund, is allocated as follows:

Research Fund	10.0%
Esme Anderson	51.4%
G.J.Williams	8.9%
B. Mitchell	8.9%
Dame Ida Mann	12.5%
R. & L. Lowe Research	8.3%

If and when further donations are received by specific fund(s) the allocation of future income will be distributed to each fund in accordance with its revised proportion to the General Fund. Fifty percent of the income derived from the D.W. Research Fund and its investments is allocated to the Director of Research Victoria.

(D) CASH AND CASH EQUIVALENTS

For the purpose of the statement of cash flows, cash and cash equivalents include cash on hand and at call deposits with banks.

(E) INVESTMENTS

Investments are carried at fair value. Changes in fair value will be held in an equity reserve until the asset is disposed, at which time the changes in fair value will be brought to account through the statement of comprehensive income.

(F) REVENUE

Interest and dividends are recognised when received.

Grants, donations and distributions income are recognised when received.

(G) GOODS AND SERVICES TAX (GST)

All revenue, expenses and assets are recognised net of the amount of goods and services tax (GST), except where the amount of GST incurred is not recoverable from the Australian Tax Office. In these circumstances the GST is recognised as part of the cost of acquisition of the asset or as part of an item of the expense.

Receivables and payables in the statement of financial position are shown inclusive of GST.

(H) FINANCIAL INSTRUMENTS

Recognition and Initial Measurement

Investments and other financial assets are initially measured at fair value. Transaction costs are included as part of the initial measurement, except for financial assets at fair value through profit or loss. Such assets are subsequently measured at either amortised cost or fair value depending on their classification. Classification is determined based on both the business model within which such assets are held and the contractual cash flow characteristics of the financial asset unless an accounting mismatch is being avoided.

Financial assets are derecognised when the rights to receive cash flows have expired or have been transferred and the consolidated entity has transferred substantially all the risks and rewards of ownership. When there is no reasonable expectation of recovering part or all of a financial asset, its carrying value is written off.

Financial assets at fair value through other comprehensive income include equity investments which the company intends to hold for the foreseeable future and has irrevocably elected to classify them as such upon initial recognition.

(I) IMPAIRMENT OF ASSETS

The company recognises a loss allowance for expected credit losses on financial assets which are either measured at amortised cost or fair value through other comprehensive income.

The measurement of the loss allowance depends upon the company's assessment at the end of each reporting period as to whether the financial instrument's credit risk has increased significantly since initial recognition, based on reasonable and supportable information that is available, without undue cost or effort to obtain.

Where there has not been a significant increase in exposure to credit risk since initial recognition, a 12-month expected credit loss allowance is estimated. This represents a portion of the asset's lifetime expected credit losses that is attributable to a default event that is possible within the next 12 months. Where a financial asset has become credit impaired or where it is determined that credit risk has increased significantly, the loss allowance is based on the asset's lifetime expected credit losses. The amount of expected credit loss recognised is measured on the basis of the probability weighted present value of anticipated cash shortfalls over the life of the instrument discounted at the original effective interest rate.

For financial assets measured at fair value through other comprehensive income, the loss allowance is recognised within other comprehensive income. In all other cases, the loss allowance is recognised in profit or loss.

2. Members' Guarantee

If the company is wound up the Memorandum of Association states that each member is required to contribute a maximum of $10.00 each towards meeting any outstanding obligations of the company.

	2020/21	2019/20
	$	$
3. Cash and Cash Equivalents		
General Account	1,032,933	1,457,007
D.W. Research Fund Account	769,396	1,025,443
	1,802,329	**2,482,450**
4. Receivables		
Sundry Debtors	398,279	196,460
	398,279	**196,460**
5. Investments		
Shares in Listed Corporations & Other Securities	12,509,613	9,900,007
Total Available-for-sale Financial Assets	12,509,613	9,900,007
Total Investments	**12,509,613**	**9,900,007**
6. Plant and Equipment		
Office Equipment - at cost	13,151	13,151
Less: Accumulated Depreciation	(13,151)	(12,315)
	-	**835**
Reconciliation		
Reconciliation of the carrying amount of plant and equipment at the beginning and end of the current & previous financial year:		
Carrying amount at beginning of year	835	1312
Additions	-	-
Disposal of Equipment	-	-
Less: Depreciation expense	(835)	(477)
Carrying amount at end of year	**-**	**835**
7. Payables		
Creditors and Accruals	13,402	43,340
Grants Payable	264,236	360,616
Director of Research - Victoria (refer note 15)	620,000	490,000
	897,638	**893,956**
8. Provisions		
Employee Benefits	**-**	**-**

	2020/21 $	2019/20 $
9. Research Capital Fund		
General		
Balance 1 July 2020	2,266,948	2,224,964
Allocation to Capital:		
- 10% Surplus & Imputation Credits & Other Legacies	49,949	41,984
- Capitalised Bequests	-	-
Transfer from Capital:		
- Amount transferred to Income	-	-
Balance 30 June 2021	**2,316,897**	**2,266,948**
Anselmi Estate		
Balance 1 July 2020	290,979	290,979
Allocation during year	-	-
Transfer during year	-	-
Balance 30 June 2021	**290,979**	**290,979**
Ivy May Stephenson Estate		
Balance 1 July 2020	30,376	30,376
Allocation during year	-	-
Transfer during year	-	-
Balance 30 June 2021	**30,376**	**30,376**
TOTAL	**2,638,254**	**2,588,303**

10. Settled Funds		
D.W. Research Funds	200,000	200,000
Esme Anderson	124,326	124,326
G.J. Williams	25,500	25,500
B. Mitchell	26,023	26,023
Dame Ida Mann (Est. 31/03/84)	56,707	56,707
Ronald & Lois Lowe	40,000	40,000
	472,556	**472,556**

11. Financial Assets Reserve		
Balance 1 July 2020	67,694	1,035,960
Revaluation increment/(decrement)	1,800,680	(968,265)
Balance 30 June 2021	**1,868,374**	**67,694**

Financial assets reserve records unrealised gains on revaluation of financial assets to fair value.

12. Capitalised Profit on Re-Arrangement of Investments, Capital Distributions & Transfers

	Balance 30/06/20	Allocation of Realised Profit/ (Loss) on Rearrangement of Investments & Capital Distributions & Transfer	Balance 30/06/21
	$	$	$
Research Fund			
General	153,429	4	153,433
Anselmi Estate	54,955	2	54,957
Ivy May Stephenson	140	-	140
D.W. Research Funds	5,232,009	112,960	5,344,969
Esme Anderson	1,079,815	30	1,079,845
G.J. Williams	185,684	5	185,689
B. Mitchell	183,747	5	183,752
Dame Ida Mann	259,316	7	259,323
Ronald & Lois Lowe	164,509	5	164,514
	7,313,599	**113,018**	**7,426,621**

13. Accumulated Funds

	Note	2020/21	2019/20
		$	$
(a) Administration			
Accumulated Deficits			-
Total Comprehensive Income		6,665	67,800
Total available for appropriation		6,665	67,800
Aggregate of amounts transferred from Administration	13 (a)	(6,665)	(67,800)
Accumulated Deficits - 30 June 2021		-	-
Capital Funds			
(b) Trust Fund			
Retained income		1,243,642	1,281,924
Total Comprehensive Income		206,423	21,166
Total available for appropriation		**1,450,065**	**1,303,090**
Aggregate of amounts transferred to General/Capital Funds			
Adjustment on investment value		-	(82,265)
Administration	13 (b)	6,665	67,800
Research Trust		(49,949)	(41,984)
Retained income - 30 June 2021		**1,406,778**	**1,243,642**

	2020/21	2019/20
	$	$
14. Grants Allocated / Made During the Year		
Dr Fred Chen		50,000
Dr Elsa Ching Chan		49,377
Dr Glyn Chidlow		49,446
Dr Nitin Chitranshi		49,440
Prof Jamie Craig		49,061
Dr Thomas Edwards		49,679
Prof Mark Gillies		50,000
Dr Sandy Hung		50,000
Prof Robyn Jamieson	50,000	50,000
Dr Mohd Khairui Nizam Khalid		50,000
A/Prof Chris Layton		49,997
Dr Michele Madigan		49,825
Prof Robert Casson	47,100	
Dr Jason Charng	47,800	
Dr Elisa Cornish	50,000	
Dr Shweta Kaushik	49,985	
Dr Grace Lidgerwood	35,000	
A/Prof Chi Luu	48,970	
Dr Carla Mellough	50,000	
Dr Tina Zhang	49,968	
Adjustments	(30)	(4,895)
Sub total	**428,853**	**591,930**
Deduct contributions from:		
Other Grants Received	-	-
Perth Eye Foundation	50,000	50,000
ANZSRS	25,000	50,000
RANZCO Eye Foundation	50,000	50,000
RANZCO NSW Branch	150,000	-
Other	22,000	-
Sub total	297,000	150,000
Net	**131,853**	**441,930**

* Grant received by director

	2020/21	2019/20
	$	$
15. Funds Allocated to Director of Ophthalmic Research - Victoria		
Balance as at 1 July 2020	490,000	364,000
Interest for the year	-	-
Allocation for year	130,000	126,000
	620,000	490,000
Payment made to Director of Research	-	
Balance as at 30 June 2021	**620,000**	**490,000**

16. Auditors Remuneration		
Financial Statements - Audit Service Other services	8,250	8,000
	8,250	**8,000**

17. Reconciliation of Net Cash Provided by Operating Activities to Results for Year		
Net Surplus/(Deficit)		
- Trust Fund	2,120,122	(1,078,236)
- Administration	6,665	67,800
	2,126,787	**(1,010,436)**
Depreciation	835	477
Disposal of Equipment	-	-
Provision for Employee Benefits	-	-
Transfer from Capital to Contribute Towards Grants	-	-
(Increase)/Decrease in Receivables	(201,819)	206,262
Increase/(Decrease) in Creditors and Accrued Expenses	(30,029)	48,060
Increase/(Decrease) in Grants Payable	(96,380)	40,745
Increase/(Decrease) in allocation to Director of Research - Victoria	130,000	126,000
Valuation (Gains)/Losses on available-for-sale financial assets	(1,800,680)	968,265
(Profit)/Loss on Rearrangement of Investments	113,018	131,137
Net Cash Provided by /(used in) Operating Activities	**124,732**	**510,510**

18. Disclosures on Directors and Other Key Management Personnel

DIRECTORS

No directors received grants during the year. Refer to Director Benefits on Page 23 for further information.

The names of the directors who have held office during the financial year are:

Prof Stephanie Watson, NSW – Chair
Prof Mark Gillies, NSW – Vice Chair
Prof Richard Mills, SA – Honorary Secretary
A/Prof Paul Healey, NSW – Honorary Treasurer
Dr Jennifer Fan Gaskin, VIC
A/Prof Clare Fraser, NSW
A/Prof Sam Fraser-Bell, NSW
Prof Stuart Graham, NSW
A/Prof Alex Hewitt, TAS
Dr George Kong, VIC
Prof David Mackey, WA
Prof Peter J McCluskey, NSW
Dr John Males, NSW
Dr Chameen Samarawickrama, NSW
A/Prof Andrea Vincent, New Zealand
A/Prof Peter van Wijngaarden, VIC

KEY MANAGEMENT PERSONNEL

Key management personnel are those persons having authority and responsibility for planning, directing and controlling the activities of the entity, directly or indirectly, including any director (whether executive or otherwise) of that entity. Control is the power to govern the financial and operating policies of an entity so as to obtain benefits from its activities.

KEY MANAGEMENT PERSONNEL COMPENSATION

Key Management Personnel has been taken to comprise the directors and one member of the executive management responsible for the day to day financial and operational management of the entity.

	2020/21	2019/20
	$	$
(a) Short-term employee benefits	94,056	8,814
(b) Post-employment benefits	10,816	1,104
(c) Other long-term benefits	-	-
(d) Termination benefits	-	-
(e) Share-based payment	-	-

19. Financial Instruments

(A) FINANCIAL RISK MANAGEMENT POLICIES

The entity's financial instruments consist mainly of deposits with banks, local money market instruments, short-term investments, accounts receivable and payable.

The entity does not have any derivative instruments at 30 June 2021.

(i) Treasury Risk Management

An investment committee consisting of Board members of the entity meet on a regular basis to analyse financial risk exposure and to evaluate treasury management strategies in the context of the most recent economic conditions and forecasts.

The committee's overall risk management strategy seeks to assist the entity in meeting its financial targets, whilst minimizing potential adverse effects on financial performance.

Risk management policies are approved and reviewed by the Board on a regular basis. These include credit risk policies and future cash flow requirements.

(ii) Financial Exposures and Management Risk

The main risks the entity is exposed to through its financial instruments are interest rate risk, liquidity risk and credit risk.

Interest rate risk
Interest rate risk is managed with a mixture of fixed and floating rates on investments.

Foreign currency risk
The entity is not exposed to fluctuations in foreign currencies.

Liquidity risk
The entity manages liquidity risk by monitoring forecast cash flows.

Credit risk
The maximum exposure to credit risk, excluding the value of any collateral or other security, at balance date to recognised financial assets, is the carrying amount, net of any provisions for impairment of those assets, as disclosed in the statement of financial position and notes to the financial statements.

The entity does not have any material credit risk exposure to any single receivable or group of receivables under financial instruments entered into by the entity.

Price risk
The group is not exposed to any material commodity price risk.

(B) FINANCIAL INSTRUMENT COMPOSITION AND MATURITY ANALYSIS

The entity's exposure to interest rate risk, which is the risk that a financial instrument's value will fluctuate as a result of changes in market interest rates and the effective weighted average interest rates on those financial assets and financial liabilities, is as follows:

	Weighted Average Effective Interest Rate		Floating Interest		Fixed Interest Rate Maturing				Non Interest Bearing		Total Carrying Amount Per Statement of Financial Position	
	2021	2020	2021	2020	2021	2020	2019	2018	2021	2020	2021	2020
	%	%	$	$	%	%	%	%	$	$	$	$
Financial Assets												
Cash and Cash	0.00	0 .40		2,482,450	-	-	-	-	1,802,329	-	1,802,329	2,482,450
Equivalents												
Listed Investments												
Shares	N/A	N/A	-	-	-	-	-	-	12,509,613	9,900,007	12,509,613	9,900,007
Bank Bills	N/A	N/A	-	-	-	-	-	-	-	-	-	-
Receivables			-	-	-	-	-	-	398,279	196,460	398,279	196,460
Total Financial Assets			**-**	**2,482,450**	**-**	**-**	**-**	**-**	**14,710,221**	**10,096,467**	**14,710,221**	**12,578,917**
Financial Liabilities												
Payables			-	-	-	-	-	-	897,637	893,956	897,637	893,956
Total Financial Liabilities			-	-	-	-	-	-	897,637	893,956	897,637	893,956
Net Financial Assets			**-**	**2,482,450**					**13,812,583**	**9,202,511**	**13,812,583**	**11,684,961**

(C) NET FAIR VALUES

The net fair values of listed investments have been valued at the quoted market bid price at balance date. For other assets and other liabilities the net fair value approximates their carrying value. No financial assets and financial liabilities are readily traded on organised markets in standardised form other than listed investments.

The aggregate net fair values and carrying amounts of financial assets and financial liabilities are disclosed in the statement of financial position and in the notes to and forming part of the financial statements.

(D) SENSITIVITY ANALYSIS

Interest Rate Risk

The entity has performed a sensitivity analysis relating to its exposure to interest rate risk at balance date. This sensitivity analysis demonstrates the effect on the current year results and equity which could result from a change in this risk.

Interest Rate Sensitivity Analysis:

At 30 June 2021, the effect on profit and equity as a result of changes in the interest rate, with all other variables remaining constant, would be as follows:

	Carrying Amount	Interest Rate Risk			
	$	-1% Profit	+1% Profit	-1% Equity	+1% Equity
2020/21					
Financial Assets					
Cash and Cash Equivalents	1,802,329	(18,023)	18,023	(18,023)	18,023
2019/20					
Financial Assets					
Cash and Cash Equivalents	2,482,450	(24,825)	24,825	(24,825)	24,825

20. FAIR VALUE MEASUREMENTS

Financial assets and financial liabilities measured at fair value in the statement of financial position are grouped into three levels of a fair value hierarchy. The three levels are defined based on the observability of significant inputs to the measurement, as follows:

Level 1: quoted prices (unadjusted) in active markets for identical assets or liabilities;

Level 2: inputs other than quoted prices included within level 1 that are observable for the asset or liability, either directly or indirectly;

Level 3: unobservable inputs for the asset or liability.

The following table shows the levels within the hierarchy of financial assets and liabilities measured at fair value on a recurring basis at 30 June 2021 and 30 June 2020:

	Note	Level 1	Level 2	Level 3	Total
		$	$	$	$
30 June 2021					
Assets					
Listed securities	5	12,509,613	-	-	12,509,613
Net fair value		**12,509,613**	**-**	**-**	**12,509,613**
30 June 2020					
Assets					
Listed securities	5	9,900,007	-	-	9,900,007
Net fair value		**9,900,007**	**-**	**-**	**9,900,007**

There were no transfers between Level 1 and Level 2 for assets measured at fair value during 2020 or 2019.

Listed Securities

Fair values have been determined by reference to their quoted bid prices at the reporting date.

21. BENEFICIARY ENTITLEMENT

The company is a beneficiary of The Richard & Ina Humbley Foundation and has an entitlement to income from the foundation to be used for grants in support of research conducted into macular degeneration.

The company accounts for this income on a cash basis.

The income received for the year ended 30 June 2021 from the foundation was **$22,617**.

22. IMPACT OF COVID-19

The spread of novel coronavirus (COVID-19) was declared a public health emergency by the World Health Organisation on 31 January 2020 and upgraded to a global pandemic on 11 March 2020. The rapid spread of the virus has seen an unprecedented global response by governments, regulators and numerous industry sectors. The Australian Federal Government enacted its emergency plan on 29 February 2020.

ORIA's assets are principally represented by investments in public listed entities. The COVID-19 pandemic resulted in a major correction in the Australian Stock Market and this has affected the assets base of ORIA. Additionally, companies have reduced the amount of dividends declared and the attached franking credits which have impacted the financial result.

Timing of the lifting of remaining restrictions remain uncertain at the date of this report, and overall financial impact cannot yet be reliably estimated. At the date of this report the company has sufficient cash reserves to continue operations, at a minimum, for the next 12 months.

23. SUBSEQUENT EVENTS

Other than as noted at note 22 Impact of COVID-19, there have been no significant events occurring after balance date, which may affect either the company's operations, or results of those operations, or the company's state of affairs.

Directors' Declaration

1. The financial statements and notes as set out on pages 22-38:

   (a) comply with Accounting Standards and Australian Charities and Not-for-profits Commission Act 2012; and

   (b) give a true and fair view of the financial position as at 30 June 2021 and performance for the year ended on that date of the company.

2. In the director's opinion there are reasonable grounds to believe that the company will be able to pay its debts as and when they become due and payable.

The declaration is made in accordance with a resolution of the Board of Directors.

On behalf of the Board.

Professor Stephanie Watson
Director

Associate Professor Paul Healey
Director

Sydney, this 6th day of Dec 2021

Auditor's Report

CHARTERED ACCOUNTANTS

Street Address:
461 Whitehorse Road
Balwyn Vic 3103

Postal Address:
PO Box 307
Balwyn Vic 3103

ABN 38 643 502 827

Tel: 9836 8222
Fax: 9836 8331

INDEPENDENT AUDITOR'S REPORT TO THE MEMBERS OF THE OPHTHALMIC RESEARCH INSTITUTE OF AUSTRALIA

Report on the Audit of the Financial Report

Opinion

We have audited the financial report of The Ophthalmic Research Institute of Australia (the registered entity), which comprises the statement of financial position as at 30 June 2021, the statement of profit or loss and other comprehensive income, statement of changes in equity and statement of cash flows for the year then ended, and notes to the financial statements, including a summary of significant accounting policies, and the directors' declaration.

In our opinion, the accompanying financial report of The Ophthalmic Research Institute of Australia has been prepared in accordance with Div 60 of the *Australian Charities and Not-for-profits Commission Act 2012,* including:

(i) giving a true and fair view of the registered entity's financial position as at 30 June 2021 and of its financial performance for the year then ended; and

(ii) complying with Australian Accounting Standards and Div 60 of the *Australian Charities and Not-for-profits Commission Regulation 2013*.

Basis for Opinion

We conducted our audit in accordance with Australian Auditing Standards. Our responsibilities under those standards are further described in the *Auditor's Responsibilities for the Audit of the Financial Report* section of our report. We are independent of the registered entity in accordance with the ethical requirements of the Accounting Professional and Ethical Standards Board's APES 110: *Code of Ethics for Professional Accountants* (the Code) that are relevant to our audit of the financial report in Australia. We have also fulfilled our other ethical responsibilities in accordance with the Code.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Information Other than the Financial Report and Auditor's Report Thereon

The directors are responsible for the other information. The other information comprises the information included in the registered entity's annual report for the year ended 30 June 2021, but does not include the financial report and our auditor's report thereon. Our opinion on the financial report does not cover the other information and accordingly we do not express any form of assurance conclusion thereon. In connection with our audit of the financial report, our responsibility is to read the other information and, in doing so, consider whether the other information is materially inconsistent with the financial report or our knowledge obtained in the audit or otherwise appears to be materially misstated. If, based on the work we have performed, we conclude that there is a material misstatement of this other information, we are required to report that fact. We have nothing to report in this regard.

Responsibilities of the Directors for the Financial Report

The directors of the registered entity are responsible for the preparation of the financial report that gives a true and fair view in accordance with Australian Accounting Standards and the *Australian Charities and Not-for-profits Commission Act 2012* and for such internal control as the directors determine is necessary to enable the preparation of the financial report that gives a true and fair view and is free from material misstatement, whether due to fraud or error.

In preparing the financial report, the directors are responsible for assessing the registered entity's ability to continue as a going concern, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless the directors either intend to liquidate the registered entity or to cease operations, or have no realistic alternative but to do so.

Auditor's Report

INDEPENDENT AUDITOR'S REPORT TO THE MEMBERS OF THE OPHTHALMIC RESEARCH INSTITUTE OF AUSTRALIA

Auditor's Responsibilities for the Audit of the Financial Report

Our objectives are to obtain reasonable assurance about whether the financial report as a whole is free from material misstatement, whether due to fraud or error, and to issue an auditor's report that includes our opinion. Reasonable assurance is a high level of assurance, but is not a guarantee that an audit conducted in accordance with the Australian Auditing Standards will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of this financial report.

As part of an audit in accordance with the Australian Auditing Standards, we exercise professional judgement and maintain professional scepticism throughout the audit. We also:

- Identify and assess the risks of material misstatement of the financial report, whether due to fraud or error, design and perform audit procedures responsive to those risks, and obtain audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control.
- Obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the registered entity's internal control.
- Evaluate the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by the directors.
- Conclude on the appropriateness of the directors' use of the going concern basis of accounting and, based on the audit evidence obtained, whether a material uncertainty exists related to events or conditions that may cast significant doubt on the registered entity's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the financial report or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report. However, future events or conditions may cause the registered entity to cease to continue as a going concern.
- Evaluate the overall presentation, structure and content of the financial report, including the disclosures, and whether the financial report represents the underlying transactions and events in a manner that achieves fair presentation.

We communicate with the directors regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that we identify during our audit.

ORR MARTIN & WATERS

ORR MARTIN & WATERS
Chartered Accountants

L R Gilmour

L R Gilmour

461 Whitehorse Road Balwyn Vic 3103

Dated this 7th day of December 2021

Liability limited by a scheme approved under Professional Standards Legislation

ORIA

Publisher: Diane Harapin Editor: Cindy Larson Grophic Design: Apple Tree Design