RETINA REPORTER

RETINA australia

Retina Australia's Bi-Annual Newsletter

DECEMBER 2022

CONTENT:

Welcome to Retina Reporter

Welcome to the first edition of Retina Reporter, Retina Australia's new bi-annual newsletter. We will continue to keep you abreast of the activities of Retina Australia and other related inherited retinal disease information, feature updates of medical and scientific research developments translated for easy understanding, along with highlights of stories of interest.

Between each bi-annual Retina Reporter, the latest news will be delivered to you via our e-newsletter, the newly branded Retina Insider. It will also include invitations to upcoming webinars and information sessions, and provide research and news updates both nationally and internationally.

Report from the Chair

I would like to thank all members and friends of Retina Australia, for their continued support and invaluable contributions, especially during the previous three, COVID-19 affected, years. I hope that 2023 will bring a somewhat normal routine and we can continue to strive towards “a world without inherited blindness”.

As you may be aware, Retina Australia is thrilled to announce that Julia Hall has been appointed as the inaugural Chief Executive Officer to lead Retina Australia through its next phase of development.

Julia commenced with us on Monday 3 October, hitting the ground running by making connections with many stakeholders and philanthropic fundraisers as well as working with the Board to produce and implement a new Strategic Plan for the organisation for the next three years. The Board of Retina Australia is extremely excited about this appointment and believe that Julia will be a huge asset to the organisation.

Retina Australia held its 38th Annual General Meeting via Zoom on 15 October 2022. Members were provided with the Chairman’s Annual Report, as well as the 2021-2022 audited financial statements. The election of Board members was also endorsed. The current members of the Board are: Leighton Boyd AM (Chairman), Peter Maas (Deputy Chairman), Joshua Ginpil (Treasurer), Rosemary Boyd OAM (Company Secretary), Jane Cherry, Jessica Coleman, Lindsay DaCosta, and Dr Heather Mack AM.

I would like to thank retiring directors Mary-Anne Carmody and Julie Demarte for their significant contribution to the work of Retina Australia over many years. Mary-Anne has been a valued volunteer since the mid-80’s undertaking many roles over time and I am very pleased that she has agreed to remain as chair of the Board Governance Committee. Julie joined the Board six years ago and whilst maintaining the role of President of Retina Australia WA, helped steer Retina Australia towards its new beginning as an amalgamated national organisation in October 2018.

With Julia’s assistance, and with the strengthened governance provided by our newly established Board committees, all directors have a new vigour in pursuing our mission “to support people affected by inherited retinal disease”. I look forward to the next years with enthusiasm.

Thank you for your continued membership and support,

Leighton Boyd

Chair
Retina Australia

Chief Executive Officer Introduction

It's been a whirlwind couple of months since joining Retina Australia, during which time we have reconfirmed our organisational statements, developed a new Strategic Plan 2023-2025, redesigned and launched our newsletter - Retina Reporter, and are soon to unveil an upgraded, new look website. Our aim is to build our research commitment and impact, and improve our information and support to our valued community. The Board has also approved our 2023 grants for two new innovative research projects to further medical advancements into inherited retinal diseases.

After only a short time, it has already been such a pleasure to work with our hard working staff and dedicated Board, which is one that also appreciates the importance of establishing good governance as the foundation from which to build success. Our new organisational statements and Strategic Plan 2023-2025 will guide our committed focus toward our Mission.

With values aligned and a unified drive to create positive outcomes for people affected by inherited retinal diseases, I am confident that together we will grow and continue to drive impact. Especially encouraging at this time, are the promising recent medical research developments, particularly in the area of gene therapy. I am incredibly excited to join the Retina Australia team for this next stage of growth and I look forward to connecting with you, our Retina Australia members and supporters.

Julia Hall
Chief Executive Officer
Retina Australia

Summary Strategic Plan 2023-2025

Strategic Pillar	Strategic Goal
Research	To fund the best Australian research into the detection, better treatments, and prevention, with the hope of progression towards cures into inherited retinal diseases
Information	To be the leading source of information on inherited retinal diseases
Support	To facilitate the development of meaningful social connections for people with inherited retinal diseases, and their families and carers
Sustainability	To ensure the ongoing viability of Retina Australia and therefore its ability to continue to support and positively impact the inherited retinal disease community
Governance	To continuously improve and strengthen organisational governance

2023 Retina Australia Research Grants

We are excited to announce the 2023 Retina Australia Research Grant awards:

- Establishing novel AAV gene editing for Usher Syndrome - Dr Anai Gonzalez-Cordero, Children's Medical Research Institute, Sydney
- Using RNA-silencing to tackle neuroinflammation in retinal degeneration - Dr Adrian Cioanca, John Curtin School of Medical Research, Canberra

Chief Investigator
Dr Anai Gonzalez-Cordero
Children's Medical Research Institute, Sydney

Co-Investigator
Dr Samantha Ginn,
Children's Medical Research Institute, Sydney

Grant awarded
$55,774

Timing
1 Year 2023

Establishing novel AAV gene editing for Usher syndrome

Project Aim
To establish proof-of-concept for adeno associated viral (AAV) vectors gene editing treatments designed specifically for genetically confirmed Usher Syndrome subtype 1 Australian patients.

Project Summary
In this study, we will evaluate efficacy for Usher 1B and 1F gene therapy using genome editing. We have the ability to generate the light-sensing photoreceptor cells for testing of these therapies in the patients' own cells, by converting their blood or skin cells into induced pluripotent stem cells (iPSC) and then generating mini-retinae, retinal organoids. We have generated retinal organoids from Usher patients and use these to test whether therapies reverse their specific genetic defect. Here, these retinal organoids will be treated using a novel approach which will replace the region of the gene that encompasses the mutation in a permanent manner. This process requires two viral vectors, one to deliver the gene editing machinery and another to deliver the correct region of the genome. The use of two viral vectors entering the cells simultaneously is inefficient and thus we will test the use of lipid nanoparticles (LNPs) to deliver the Cas9 instead of a viral vector. This also avoids long term exposure to Cas9 in the cells, thus reducing unwanted editing of other genome parts.

Expected outcomes
This project is expected to (1) generate pre-clinical data and establish efficacy for AAV gene editing to treat Usher patients and other patients with common IRDs; (2) provide more access to clinical trials by developing gene editing tools that are suitable and efficacious to use in clinical trials; (3) lead to new health technologies embedded in health practice: this study uses stem cells and its derivative organoids which, as new health technologies, will be used for precision medicine functional assays.

Using RNA-silencing to tackle neuroinflammation in retinal degeneration

Chief Investigator
Dr Adrian Cioanca, John Curtin School of Medical Research, Canberra

Co-Investigators
Dr Riccardo Natoli, John Curtin School of Medical Research, Canberra

Dr Michelle Madigan, Save Sight Institute, Sydney

Dr Elisa Cornish, University of Sydney

Grant awarded
$59,869

Timing
1 Year 2023

Project Aim

To unpack the role of CEBPD in neuroinflammation by studying CEBPD expression patterns in human age-related macular degeneration (AMD) donor tissue and by modulating its activity in robust animal models of retinal degeneration. CEBPD (CCAAT Enhancer Binding Protein Delta) is a Protein Coding gene.

Project Summary

This project leverages the power of silencer RNAs (siRNA) to target a novel mediator of retinal neuroinflammation. Neuroinflammation is a well-established central driver of neuronal cell death in retinal degenerations including the highly prevalent AMD. Because neuroinflammation and neuronal cell death are tightly interconnected, therapies targeting retinal neuroinflammation have the potential to slow down neuronal cell loss and therefore preserve vision.

The therapeutic target investigated here is the CEBPD - a transcription factor we have identified as pivotal in retinal neuroinflammation. Transcription factors access a cell's DNA, where a single transcription factor initiates the synthesis of 200-1000 mRNAs that perform similar biological functions. In the case of CEBPD, the mRNA pool synthesised following its activation is strongly associated with neuroinflammation and degeneration, therefore targeting CEBPD is a powerful way for shutting down complex neuroinflammatory pathways.

Our preliminary findings show that CEBPD activation occurs in the early stages of retinal degeneration and importantly, inhibiting CEBPD using siRNA reduces neuroinflammation and preserves retinal function.

Expected outcomes

This project is expected to contribute to the development of successful therapies for atrophic AMD which require supressing neuroinflammation by (1) developing a unique method of tackling neuroinflammation by using CEBPD siRNAs and other pharmacological CEBPD inhibitors; (2) and generating pre-clinical data using a retinal degeneration model developed by Dr Natoli that recapitulates key AMD facets including neuroinflammation and progressive focal photoreceptor cell death.

Retina Australia Research Grant Impact Reports

We are delighted to provide updates on previous grant projects that were awarded by Retina Australia in 2021 and are now completed and reported on.

Looking for disease causing mutations in families with dominant RP pedigrees

Chief Investigator
Associate Professor Fred K Chen, Centre for Ophthalmology and Visual Sciences, The University of Western Australia

Co-investigators
Professor Sue Fletcher, Harry Perkins Institute of Medical Research, Perth
Dr Tina Lamey, Sir Charles Gairdner Hospital, Perth
Laura Florez, PYC Therapeutics

Grant awarded - $40,000 (2021)

Project Aim

Retinitis pigmentosa (RP) is a debilitating eye disease that affects 1 in 3,000 people in Australia. RP11 is a type of RP most commonly caused by a mutation in the PRPF31 gene. RP11 is dominantly inherited, meaning that only one copy of the gene with a mutation is required to cause disease and it is estimated to account for 250 cases in Australia. There is no treatment available to patients burdened with this condition. Given the recent development of gene-based therapy to treat PRPF31 disease, we sought to find families with PRPF31-associated RP by performing a gene panel testing on 40 families presenting with a dominant pedigree.

Project Results and Impact

A total of 40 dominant RP families were analysed and 23 (58%) returned a positive or likely positive result. Amongst the remaining 17 (42%) families with inconclusive results, further analysis was undertaken to resolve 9 of these families, identifying PRPF31 (n=3), PRPF6, SAG, RPE65, IMPG1, IMPDH1, and BEST1 as causative genes. This left 8 (20%) dominant RP pedigrees unresolved. Additional analysis is now underway in these 8 unresolved families to find new mutations and new genes causing dominant RP.

Overall we found that the PRPF31 and RHO genes are the most common causes of dominant RP in Australia. PRPF31 mutations can be missed without specific analysis for large deletions in the gene. In total, 13 different genetic diseases were found in 40 families with dominant RP. Many of these genes can manifest in other forms of inherited retinal disease aside from RP and may also have recessive inheritance.
In conclusion, the success rate of gene panel testing can be improved from 58% to 80% with the independent variant curation, additional testing for large deletions and familial phase testing.

Potential participant perspectives in ocular gene therapy in Australia

Chief Investigator
Associate Professor Heather Mack AM, Centre for Eye Research Australia/University of Melbourne

Co-investigators
Professor John Grigg, Save Sight Institute, University of Sydney
Associate Professor Fred Chen, Centre for Ophthalmology and Visual Sciences, Perth
Associate Professor Lauren Ayton, University of Melbourne / Centre for Eye Research Australia

Grant awarded - $20,000 (2021)

Project Aim

Through surveys of Australians living with inherited retinal diseases (IRDs) our aim was to analyse the perspectives of patients regarding their understanding of and interest in both currently approved and future hypothetical gene therapy for retinal dystrophy, and a comparison between how approved and hypothetical gene therapies are viewed. This information would shed light on patient understanding, guide future gene therapy trials and treatments in Australia, and may be used by health economists to apply for government funding for gene therapy for IRD in the future.

Project Results and Impact

This study was the first comprehensive analysis of the perspectives of Australian people with IRD regarding understanding of and interest in gene therapy for retinal disease. Most of the survey respondents (92%) said that they would try gene therapy if it was available now to them or their family members for IRD. However, only 28.3% agreed that they had good knowledge of gene therapy and almost 60% of respondents did report at least one barrier to their future uptake of the treatment. Most obtained information about gene therapy from the internet (49.3%). Knowledge gaps were present regarding methods and outcomes of gene therapy. Most respondents saw economic value in treatment, with 79% agreeing that government subsidy would be an effective use of taxpayer money. This survey has shown high level of interest in the IRD community for gene therapies and highlights the importance of continued research and development into new therapies for people with IRDs.

Published peer-reviewed journal articles

1. Mack HG, Chen FK, Grigg J, Jamieson R, de Roach J, O'Hare F, Britten-Jones AC, McGuinness MB, Tindill N, Ayton LN, for the Australian Ocular Gene Therapy consortium. Perspectives of people with inherited retinal diseases on ocular gene therapy in Australia: protocol for a national survey. British Medical Journal Open2021;11(6):e048361.
2. McGuinness MB, Britten-Jones AC, Ayton LN, Finger RP, Chen FK, Grigg J, Mack HG. Measurement Properties of the Attitudes to Gene Therapy for the Eye (AGT-Eye) Instrument for People with Inherited Retinal Diseases. Translational Vision and Science Technology2022;11(2):14

Strong, fast, then none: development of novel promoters for gene-editing therapies

Chief Investigator
Professor Alex Hewitt, Menzies Institute for Medical Research, Tasmania

Co-investigator
Peter Tran, Menzies Institute for Medical Research, Tasmania

Grant awarded - $40,643 (2021)

Project Aims

Gene editing is a frontier technology that enables the permanent correction of various inherited conditions. The infancy of this technology is not without its limitations, and concerns remain regarding their effectiveness, feasibility, and side-effects.

Our aim was to use our novel variant of this technology, which was improved for effectiveness and biosafety, to evaluate its feasibility in correcting various pathogenic conditions as a clinic-ready solution.

Project Results and Impact

With support from Retina Australia we conducted a large-scale study to identify specific patterns in “prime editing” construct design. Specifically, we investigated the generalisable characteristics of non-engineered prime editing design for efficient proof-in-principle gene correction of disease causing variants in 21 genes implicated in inherited retinal diseases, and associated syndromes (such as Usher, and Bardet Biedl syndrome).

We used an “oligopool” approach comprising approximately 12,000 uniquely-barcoded RNA constructs to target a synthetically integrated, mutation-specific sequence, which faithfully recapitulates the disease context. To dissect cell-specific variation we characterised the efficiency of genetic correction across eye cells (photoreceptor and RPE-derived cells).

We found that non-engineered extensions should mediate substitution-type edits as compared to indel-type corrections, and that importantly, the desired edit should be placed close to the target site.

This work has helped establish a set of recommendations for the generalisable design of the prime editors for the correction of inherited retinal disease-causing variants. This will facilitate the ongoing clinical translation of gene editing technologies for the potential correction of inherited retinal disease caused by small genetic changes.

Provision of genetic research reports to research participants via their nominated ophthalmologists or clinical geneticists

Chief Investigator
Jennifer Thompson, Sir Charles Gairdner Hospital, Perth

Co-Investigators
Dr John DeRoach, Sir Charles Gairdner Hospital, Perth
Dr Tina Lamey, Sir Charles Gairdner Hospital, Perth
Ms Terri McLaren, Sir Charles Gairdner Hospital, Perth

Grant awarded - $20,000 (2021)

Project Aims
The major aims of this project were to provide more than 200 genetic research reports to participants via their nominated ophthalmologists or clinical geneticists, and to enhance the knowledge of the genetic spectrum of inherited retinal disease (IRD) in Australia via publications.

Project Results and Impact
363 genetic research reports related to 323 participants were provided to nominated clinicians and genetic counsellors to assist with patient management, and to facilitate genetic counselling and family planning. This cohort included 185 IRD-affected participants, 6 asymptomatic individuals with familial mutations, and 132 unaffected family members (carriers and non-carriers of familial mutations).

These reports detailed the likely genetic cause of disease in participants with a diverse range of clinical diagnoses, caused by pathogenic DNA changes in 37 different genes, and were issued on behalf of The Australian Inherited Retinal Disease Registry and DNA Bank (AIRDR) participants to 29 different ophthalmologists throughout Australia. Of the 185 participants affected with an IRD, 133 participants had the likely cause of disease reported, and 52 participants were unresolved. Of the 52 unresolved participants, 10 are possibly resolved and awaiting further familial analysis.

The genetic results identified in these reports have contributed to various publications enhancing knowledge of the genetic spectrum of IRDs in the Australian population, including the following genes: ABCA4(1-5), PRPF31(6-7) and PRPH2(8). The results of this project have also contributed to the identification of potential candidates for clinical trials or future therapies arising from these trials (subject to specific exclusion/inclusion criteria imposed in the trials/treatments).

The provision of the genetic research reports undertaken in this project have contributed to patient management, including for genetic counselling (6 participants) and family planning (4 participants) purposes. These findings further informed scientific research into the genetic spectrum of IRD in Australia, facilitated investigation into personalised medicine therapies, and identified potential candidates for clinical trials or future therapies arising from these trials.

Improving sensory substitution low vision devices through novel software adaptations

Chief Investigator
Associate Professor Lauren Ayton, University of Melbourne

Co-investigators
Dr Matthew Petoe, Bionics Institute, Melbourne
Dr Chris McCarthy, Swinburne University, Melbourne
Associate Professor Jennifer McGinley, University of Melbourne

Grant awarded - $40,643 (2021)

Project Aims

To investigate the efficacy of sensory substitution devices (SSDs), and then to improve their function using novel software adaptations.

Project Results and Impact

Study 1: Identification of Mobility Goals Using the Canadian Occupational Performance Measure (COPM)

We found that the most common goal in indoor mobility was to feel safe, whereas outdoor goals were more often about feeling confident and independent (with safety also scoring high).

Study 2: Online Survey of Mobility Use and Knowledge and Interest in SSDs

- Around half used a long cane as their primary mobility aid.
- The most problematic situations with mobility aids were crowded places, when stepping down steps and curbs, and when doing exercise.
- Around one-third of participants had used an SSD before, one-third had heard of them, and one-third had never heard of them.
- In general, people were more keen to try audio-based SSDs than body-worn tactile devices, but were also interested in smaller tactile devices, such as a vibrating wristband.

Study 3: Laboratory-Based Study of a tactile SSD which causes vibrations on the back to allow people to sense obstacles and visual targets

Key aims of this study were to investigate whether the SSD and our software, enabled safer and more effective mobility and improved functional vision.

Results demonstrated that the SSD improved detection of obstacles, improved ability to detect faces at a distance of 1.5 to 1.8m away, and enabled augmentation of other senses (hearing, proprioception) to assist in everyday living tasks. Users reported enjoyment in using the device, including a sense of adventure and curiosity about their environment, a belief that the device could be used as a secondary aid for mobility (but unlikely to replace their long cane or guide dog). They also felt this device would be particularly useful in new and unfamiliar environments. We will now also use the software adaptations to assess other types of SSD.

Our PhD student, Rui Jin, will start a study in 2023 testing improved function with similar software, with an auditory and a tactile SSD, investigating preferred modality. If Retina Australia members would like to be involved, please contact Rui Jin directly at: jin.r@unimelb.edu.au.

The Role of Genetic Testing and Future Treatments for Inherited Retinal Diseases

In October, Retina Australia hosted an enlightening webinar on "The Role of Genetic Testing and Future Treatments for Inherited Retinal Diseases", presented by the Janssen Pharmaceutical Companies of Johnson & Johnson.

For those who were able to join us for the webinar, of particular interest was Senior Medical Advisor, Dr Marija McGeachie's (as pictured above right) presentation which highlighted the role of genetic testing and detailed the process of gene therapy.

As a practical example, Dr McGeachie took us through the very promising primary results from a Phase 1/2 clinical study evaluating the AAV5-RPGR gene therapy in patients with RPGR-associated X-linked retinitis pigmentosa (XLRP). This treatment was designed to deliver functional copies of the RPGR gene to counteract the loss of RPGR protein in retinal cells due to anomalies in the RPGR gene, with the goal of preserving and potentially restoring vision for those living with XLRP. There are currently no approved treatments for XLRP. As part of the study, a functional visual assessment was demonstrated, using a mobility maze to evaluate a patient's ability to navigate through real-life simulated obstacles. This was performed before gene therapy treatment and after treatment at nine months. Both improvement in walk time and accuracy was observed in the low and intermediate dose treated cohorts.

Overall, through a one-time administration, treatment was found to have an acceptable safety profile and there were statistically significant improvements in retinal sensitivity in the low and intermediate dose treated eyes compared to untreated eyes in the randomised concurrent control. The Phase 1/2 trial is now closed for recruitment and is not being conducted in Australia. These preliminary results are very encouraging and we look forward to updates on this and the Phase 3 clinical trial, which is currently being conducted in the USA and UK.

Retina Australia would like to thank Janssen for being a valued supporter in 2022.

Friends of Retina Australia

by Angela Boothroyd

Despite COVID-19, the Friends of Retina Australia Perth group have managed to meet up on several occasions this past year. A coffee morning in July was well attended and there were five bushwalks (of between 7-10 km) which are always popular. These would not be possible without the help from our wonderful "Bushies" from the Perth Bushwalkers Club who find suitable trails in the Perth hills and then expertly guide us. Along the way we stop to see, smell and feel the different flowers and other vegetation and listen to the various bird calls. As promised, the spring bushland and flowing creeks always lift our spirits. After the walks we always stop for a delicious brunch kindly sponsored by PYC Therapeutics. This gives us a chance for more chatting and is a great end to a long walk.

We hope that the bushwalks will continue next year in the cooler months and that coffee mornings will happen more regularly. We all find that meeting with others with vision impairment is both inspiring and fulfilling.

Friends of Retina Australia is a peer support group. If you would like to find out more information or join the Friends of Retina Australia Perth group, please contact Angela Boothroyd at friendsofra.perth@retinaaustralia.com.au.