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Retina Australia 2021 Grant Recipients Announced

We are pleased to announce that the 2021 recipients of the Retina Australia medical research grants are Dr Lauren Ayton (The University of Melbourne), Professor Alex Hewitt (The University of Tasmania), Dr Fred Chen (The University of Western Australia), Associate Professor Heather Mack (CERA/The University of Melbourne), and Dr Jennifer Thompson (Sir Charles Gairdner Hospital). These grants have a total value of $160,000.

Improving Sensory Substitution Low Vision Devices Through Novel Software Adaptations, Dr Lauren Ayton.

This project aims to use the team's expertise using both invasive (bionic eye & gene therapy) and non-invasive (low vision aid & sensory substitution) technologies to improve new sensory substitution devices for people with low vision. Data will be obtained on the efficacy of two commercially available sensory substitution devices: the BrainPort tactile sensory substitution device and the vOICe vision-to-audio device. Collaboration with the developers of the technologies as well as feedback from participants will lead to both academic outcomes as well as, more importantly, real-world improvements in the usability of these new technologies for people with low vision.

Strong, fast, then none: development of novel promoters for gene-editing therapies, Professor Alex Hewitt.

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. Herein, we use our novel variant of this technology, which has been improved for effectiveness and biosafety, to evaluate its feasibility in correcting various pathogenic conditions as a clinic-ready solution. This work lays the foundation for the clinical translation of our novel gene editor.

Looking for disease-causing mutations in families with dominant RP pedigrees, Dr Fred Chen

RPI I is a type of RP caused by mutations in the PRPF3/ gene and it is estimated to account for 250 cases in Australia. RPI I is dominantly inherited, meaning that only one copy of the gene with a mutation is required to cause disease. There is no treatment available to patients burdened with this condition. Our group is currently developing a novel therapeutic to treat PRPF3 /-associated RP. In laboratory studies using engineered cells from patients, the molecule has rescued some of the functions missing in RP 1 1. The molecule has an excellent safety profile, and it is on track to reach phase 1/2 clinical trials at the end of 2021.

The Australian Inherited Retinal Disease Registry and DNA Bank (AIRDR), and the Lions Eye Institute (LEI) are currently monitoring the disease progression rate in a cohort of 20 patients in Western Australia with disease-causing mutations in PRPF3 l. However, a larger pool of patients fulfilling the eligibility criteria is required for an Australia-wide phase 1/2 clinical trial. We will use specialized gene analysis techniques to rapidly identify PRPF3 I disease causing mutations in autosomal dominant RP families who have provided samples to the AIRDR and DNA bank and select potential participants for future clinical studies. Analysis of these samples will also provide a genetic diagnosis to many of these families, presenting opportunities for them to make informed decisions regarding disease management and family planning.

Through this study, we will also gain greater understanding of the factors contributing to disease penetrance, age of onset and severity in RP 1 1 , through analysis of known modifying factors, such as the number of copies of a repeated sequence the 'MSRI' (upstream of PRPF3 I), and a 'Single Nucleotide Polymorphism' rs48067 I 8 in a modifier gene.

Both these elements are known to be predictors of RPI I disease severity, and it is important that we understand the interaction between with these modifiers, disease progression and response to treatment.

Potential participant perspectives on ocular gene therapy in Australia, Associate Professor Heather Mack.

Previous studies have shown that individuals who might participate in gene therapy clinical trials overestimate clinical effect, and underestimate risks. This study will survey Australian persons with IRD regarding their knowledge of clinical trials and also develop a novel survey instrument to assess understanding of approved ocular gene therapy (AGT-Eye). Results from these surveys will be

correlated with self-reported clinical status, information about quality of life and information about health status.

The findings of the study will provide the first comprehensive analysis of the perspectives of Australian people with IRD regarding 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 will 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.

Provision of genetic research reports to research participants via their nominated ophthalmologists or clinical geneticists, Dr Jennifer Thompson

An important outcome from inherited retinal disease (IRD) registries is the identification of the likely genetic cause of IRD in research participants. This information allows for the identification of cohorts of relevant individuals for research into personalized medicine or for future clinical trials and treatments, and the provision of that information to participants' clinicians may significantly improve patient management.

Improved outcomes for participants resulting from these reports may include:

- informed genetic counselling for genetic risk and family planning purposes;
- investigation, identification and management of undiagnosed syndromic disease;
- initiation of routine retinal monitoring in anticipation of clinical trials or treatments;
- admission of patients into personalised (gene- or variant-specific) medicine research;
- closure for patients having their cause of disease (and inheritance mode) identified, possibly informing their prognosis.

To-date, the Australian Inherited Retinal Disease Registry and DNA Bank has provided 1059 genetic research reports to clinicians and geneticists. To create an informative and robust report, the many suspect DNA sequence changes (variants) identified in a participant via genetic analysis must be assessed to determine the likely cause of the IRD. Meticulous variant pathogenicity assessment according to published guidelines must be carried out by a genetics expert experienced in the field. The data resulting from this project will be published with other established data, extending our knowledge of the causes of IRD in Australia.

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