Project: Towards a better understanding of Keratoconus - risk factors, clinical features and the genetics

Supervised by: Dr Srujana Sahebjada

Area of Research: Corneal Research

Project Summary: Keratoconus is a common condition that affects the cornea and despite its increasing prevalence, the cause of keratoconus is largely unknown. The aim of the project is to better understand the underlying molecular causes, clinical characteristics and treatment options of keratoconus to develop strategies that can halt the disease progression. The project involves collection of large datasets from the clinical records and images, an exciting opportunity to conduct big data analysis and manuscript writing.

Students with backgrounds in computer science and database software’s, statistics or medical, optometry and visual science are welcome to apply.

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Project: Genes in Keratoconus corneas

Supervised by: Dr Srujana Sahebjada

Area of Research: Corneal Research

Project Summary: Keratoconus affects up to 1 in 500 people and genetics is known to play a major role. The overall goal of this project is to use a novel genetic technique, RNA sequencing (RNA-seq), to identify specific genes in the localised corneal tissue to better understand the pathogenesis of keratoconus. The project involves undertaking bioinformatic and pathway analysis of sequenced data and identifying genes associated with keratoconus in each of the corneal layers. This study will provide crucial insights into keratoconus and reduce the need for corneal transplantation, particularly in children.

Students with backgrounds in bioinformatics and genetics are welcome to apply.
Project: Repair of the cornea to restore vision: Translation to surgical repair device

Supervised by: Prof Greg Dusting and Dr Karl Brown

Area of Research: Corneal Research

Project Summary: Severe burns and corneal disease leads to vascularisation and ulceration of the corneal surface, which is currently treated by corneal transplants and lifelong anti-rejection drugs. Many countries in the world do not have sufficient donors to meet the increasing demand for this procedure. At CERA we work closely with chemical engineers and veterinary scientists at the University of Melbourne to develop engineered constructs to replace the damaged corneal endothelium. Materials and procedures have been patented, and one is under commercial development.

The current project is to develop a source of corneal endothelium from human induced pluripotent stem cells (iPS cells) and grow these on patented hydrogel films to replace damaged endothelium. Alternatively, the reprogramming of appropriate cells from patient donors direct to corneal endothelium will be explored. Mechanisms of adhesion and proliferation of these cells will be examined, and preclinical transplantation studies will be carried out in sheep in the veterinary facility.

This project would be suitable for medical or biomedical science students with an interest in cell biology, pharmacology or ophthalmology to work towards clinical application of this novel technique with an ophthalmologist, stem cell scientist, veterinary scientists and other cell biologists. A short project as part of this program is available for a summer vacation student working alongside scientists and clinicians.
Project: Does high-risk genotype or phenotype drive the loss of rod function in age-related macular degeneration?

Supervised by: A/Prof Chi Luu

Area of Research: Macular Research

Project Summary: Patients with age-related macular degeneration (AMD) often report visual symptoms of difficulties with night vision and a delay in adjusting from bright to dim lighting in the early stages of the disease. This is consistent with the findings of poor rod function in patients with intermediate AMD. Recently, our group and others have shown that intermediate AMD eyes with reticular pseudodrusen (RPD), an AMD phenotype, have a greater impairment in rod function, especially within the central 8° of the retina, compared to AMD eyes without RPD. Early this year, a study by Mullins et al reported a strong association between high-risk ARMS2 genotype and delayed rod-mediated dark adaptation. However, that study did not account for the potential influence of the presence or absence of RPD on rod function. Given that we and other groups have previously shown that ARMS2 A69S variant is associated more closely with RPD, it remains to be determined if the association between ARMS2 genotype and delayed rod-mediated dark adaptation is related to the presence or absence of RPD.

The aim of the proposed project is to investigate whether abnormal rod function in eyes with intermediate AMD is related to the ARMS2 genotype or the RPD phenotype. It is hypothesised that ARMS2 may play a role in the formation of the RPD in the subretinal space, and that the presence of the RPD impairs the visual cycle function of the RPE and leads to the impairment of rod function.

The genotype, phenotype and rod function data have already collected. The student is expected to perform the data analysis and write up the results.
**Project:** Effect of stimulation on retinal structure and function in a retinal degeneration model

**Supervised by:** Dr Carly Abbott and A/Prof Chi Luu

**Area of Research:** Macular Research

**Project Summary:** This project will involve longitudinal analysis of retinal function (electroretinogram) and retinal structure (optical coherence tomography) data from an animal model of retinal degeneration where treatment arms are receiving different dosages of low level electrical stimulation. The stimulation paradigm is designed to prolong retinal cell survival in the degeneration model. Inherited retinal degeneration is the largest cause of blindness in the working age population and currently there are no treatments available.

The student will be trained in data analysis, statistics and report writing.

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**Project:** Characterisation of retinal crystals in Bietti crystalline dystrophy

**Supervised by:** Dr Thomas Edwards

**Area of Research:** Retinal Gene Therapy

**Project Summary:** Bietti crystalline dystrophy (BCD) is a progressive inherited retinal disease (IRD) that leads to blindness by middle age and is currently incurable. Crystalline deposits throughout the degenerating retina and retinal pigment epithelium are a unique feature of this disease. This project seeks to develop novel imaging and quantification methods to count and characterise the crystals, with the goal of establishing new outcome measures by which to assess future therapies for BCD.
Project: A non-cytotoxic approach to reduce ocular fibrosis

Supervised by: Dr Manisha Shah and Elsa Chan

Area of Research: Oxidant Signalling Research

Project Summary: Wound healing is a classical response to any tissue injury repair and this process often leads to scar-forming fibrotic lesions. Scarring response is a major problem that influences surgical outcomes in patients with eye disease. The post-surgical scarring in the eye causes vision impairment and blindness. There are some non-selective cytotoxic drugs currently being used in the clinic that exerts serious side-effects and leads to high recurrence rates of fibrosis and surgical failure. Hence there is an immediate need to investigate safer and more effective therapeutic alternatives.

The unit focuses on investigating post-operative ocular scar formation. By understanding the involvement of NADPH oxidase-associated pathways in ROS production in post-surgical ocular fibrosis, we aim to investigate how to improve long-term success of ocular surgery and prevent/treat post-operative ocular scar formation and vision loss in patients.

We use various molecular and cell culture techniques, cell signalling pathway analysis, histological and immunohistochemical analysis and preclinical mouse models of ocular fibrosis to study the various aspects of this project. Students will have an opportunity to learn some of these techniques such as Western blotting, histology and immunohistochemical analysis, microscopy and imaging. The student will be trained and expected to perform respective techniques and data analysis.
Project: Development of retinal regenerative therapy using stem cells and cell reprogramming

Supervised by: Dr Raymond Wong

Area of Research: Cellular Reprogramming

Project Summary: Photoreceptors are light-sensing cells that form the basis of our vision by converting light into electrical signals that can be decoded by the brain. The loss of photoreceptors is a key hallmark of many blinding diseases, such as retinitis pigmentosa, age-related macular degeneration and diabetic retinopathy. These diseases affect millions of patients and cause a significant socio-economic burden on our healthcare system. Currently, there are no effective means to cure blindness once photoreceptors are lost. We must therefore find a new approach to help restore vision to these patients. Regenerative therapy to replace photoreceptors has the very real prospect of helping patients to restore vision.

Cell reprogramming could be the key to this critical issue. This innovative technology relies on converting one cell type into another by rewriting the transcriptome to alter the cell’s identity. One of the most famous examples is the Nobel prize-winning discovery of induced pluripotent stem (iPS) cells, in which the altered expression of four transcription factors converted adult fibroblasts into stem cells. Beyond iPS cells, direct reprogramming is now possible by converting one somatic cell type directly to another, such as fibroblasts to neurons, without passing through an intermediate stem cell state.

This project aims to develop stem cell and cell reprogramming technologies to generate retinal neurons, providing novel regenerative therapy approaches to treat vision impaired patients. Techniques involved in this project include iPS cells, cell reprogramming, CRISPR/Cas9, molecular cloning, fluorescent microscopy and virus generation.
Project: Using CRISPR technology to interrogate the genetic cause of age-related macular degeneration

Supervised by: Dr Raymond Wong

Area of Research: Cellular Reprogramming

Project Summary: Age-related macular degeneration (AMD) is one of the leading causes of blindness in the developed world. Despite intense research efforts, the genetic cause of AMD and the precise pathological mechanism remains unclear. For instance, genome-wide association studies have identified a number of genes associated with AMD. Our group has also recently used single cell transcriptomics to profile gene expression in the human retina, which allowed us to determine the expression of several AMD genes in major retinal cell types. However, the function of these AMD genes in human retina is not well studied.

This project aims to interrogate the functions of these AMD genes in human retinal cells in vitro, using the latest CRISPR technology to perform gain-of-function and loss-of-function studies. Techniques involved in this project include CRISPRa, CRISPRi, transfection, tissue culture, virus generation, fluorescent microscopy and quantitative PCR.