Honours and PostDoctorate Research Projects

Available from 1st Semester, 2018

Lions Eye Institute, Perth

Return to Index

Research Groups	
Genetics and Epidemiology	The Young Adults Myopia Study (YAMS)
Retinal Genomics & Therapy	Cellular and molecular characterisation of cone photoreceptor migration in normal and degenerate retinas
	Voltage-gated potassium channels in inherited retinal dystrophy: disease mechanisms and treatment strategies
	Investigating the correlation of myopia susceptibility with cone opsin gene variants
	Studying primary and secondary cone degeneration and cell death mechanisms in inherited retinal disorders
Experimental Immunology	Improving CMV immune responses in bone-marrow transplant recipients
	Impact of viral infection on autoimmunity
Ocular Tissue Engineering	General Information
	Modelling Inherited Retinal Diseases Using Induced Pluripotent Stem Cells and Disease Progression Analysis
	Project 1: Generation of a patient-derived iPSC model of IRD
	Project 2: Clinical trial in a dish
	Project 3: Monitoring disease progression
	The use of human retinal organoids to study human retinal cell maturation and development
	Project 1: Single cell analysis of stem cell-derived human retinal organoids
	Project 2: Defining the cell surface antigen profile of human retinal cells
	Project 3: Improving the functionality of human retinal organoids in vitro
Outback Medicine	Improving service delivery in eye health in Western Australia
	Telehealth versus Face-to-Face Ophthalmology Consultations: How does the management of patients with cataracts differ?
	Monitoring and evaluating a culturally-appropriate teleophthalmology service in Western Australia.
Pharmacology & Physiology	Modulation of vasoactivity of retinal veins
	Characterisation of Conjunctival Lymphatics
	Developing laser ultrafine microsurgery for intraocular surgery

Return to Index

About the Lions Eye Institute.

The Lions Eye Institute is a not-for-profit centre of excellence that combines world class scientific research into the prevention of blindness with the highest level of eye care delivery. It incorporates one of Australia's largest ophthalmic practices, including a Day Surgery Unit and a Laser Vision Centre. LEI also houses the Lions Eye Bank, Lions Optics, Lions Outback Vision, and the Lions Save-Sight Foundation WA.

Return to Index

Genetics and Epidemiology

Project title: The Young Adults Myopia Study (YAMS)

A project suitable for PhD studies

Supervisor(s)	Laboratory	Email
Dr David Mackey (Primary)	Epidemiology and Genetics	DavidMackey@lei.org.au

Project Synopsis:

Myopia is the most common vision disorder of young adults. Affecting about 23% of the worlds population. Individuals with myopia are at increased risk of irreversible blindness from retinal detachment, myopic macular degeneration, and glaucoma.

In the 20-ear follow-up study of the Western Austrlaia Pregnancy cohort (The Raine Study), several genetic and environmental risk factors for the development of childhood myopia were identified, including higher levels of education and lower time spent outdoors. However, the drivers of myiopis progression and later-onset myopia in early adulthood are yet to be defined.

Role of the Student:

The upcoming 28-year follow-up of the Raine cohort will provide an excellent opportunity to investigate how genetic and environmental factors, such as eduation level, time spent outdoors, and intensity of use of personal electronic devices, are specifically associated with devellpmnt and progression of myopia in young adulthood.

Students will be trained in many critical aspects of research including clinical data collection , statistical analyses, scientific writing, and presentation. At the end of the program, students will obtain valuable clinical and research experience skills, especially in the field of epidemiology, myopia, and/or glaucoma. There is also the opportunity for one half-day per week of employed clinical work. Students interested in research areas such as ophthalmology, optometry, orthoptics, genetics, biostatistics, and other related fields are encouraged to apply. Specific project ideas and aims will be discussed with the supervisors. Please contact Professor David Mackey (DavidMackey@lei.org.au)to register your interest.

For further information and entry requirements, please refer to the following websites:

- UWA: https://study.uwa.edu.au/courses/doctor-of-philosphy
- LEI: https://www.lei.org.au/
- Raine Study: https://www.rainestudy.org.au/

Return to Index

Retinal Genomics and Therapy

Project title: Cellular and molecular characterisation of cone photoreceptor migration in normal and degenerate retinas

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Dr Livia Carvalho (Primary)	Retinal Genomics and Therapy	liviacarvalho@lei.org.au
Prof David Hunt (Co-supervisor)	Retinal Genomics and Therapy	david.hunt@uwa.edu.au

Project Synopsis:

Vision is the most precious of our senses, yet our knowledge of many of the component processes of its development remains incomplete. The mature mammalian retina has a layered structure where different neurons and glia cells are organized into laminated layers. This is achieved because the development of the retina is a highly coordinated event requiring specific timing and spatial arrangements. Within the retina, light detection is mediated via cone and rod photoreceptors, with reading, facial recognition and colour vision dependent on cones. Retinal neuron and glia proliferation and differentiation have been well documented on a morphological and molecular level but very little is known about the molecular mechanisms behind cone migration events during development and it could be affected during disease. The overall objective of this project is to establish the basic cellular and molecular pathways behind cone photoreceptor migration and will include characterisation of cone migration using mouse models; next generation sequencing and proteomics technologies to define the pathways that are activated in normal and degenerate retinas and establish an in vitro modelling system to study and modulate cone migration. This project will use a broad-range of molecular, histological and cell culture techniques and the student can be engaged in all or just some aspects of the proposal. More specifically, the student's role can include all or part of management of mouse line colonies, tissue collections and sample preparation, immunohistochemistry experiments, microscopy imaging, extraction of high quality nucleic acids; preparation of DNA and protein libraries for running of the transcriptome and proteome sequencing experiments and analysis.

Return to Index

Retinal Genomics and Therapy

Project title: Voltage-gated potassium channels in inherited retinal dystrophy: disease mechanisms and treatment strategies

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Dr Livia Carvalho (Primary)	Retinal Genomics and Therapy	liviacarvalho@lei.org.au
Prof David Hunt (Co-supervisor)	Retinal Genomics and Therapy	david.hunt@uwa.edu.au

Project Synopsis:

Inherited retinal disease is a major contributor to blindness in the developed world. At the clinical level it is not possible to diagnose the precise genetic lesion without molecular analysis. A major exception to this is a disorder which presents as a cone dystrophy with supernormal rod electroretinogram (CDSRE) and it has now been established that the unusual electroretinogram (ERG) is diagnostic for the disorder. We have previously demonstrated that mutations in the gene KCNV2 which encodes the voltage-gated K+ channel protein subunit Kv8.2 which is expressed in the light-sensing photoreceptor neurons in the retina, are responsible for this disorder. The ERG disease phenotype indicates that mutations in KCNV2 disrupt photoreceptor adaptation, the fundamental physiological process by which light sensitivity is modulated under different levels of illumination. However, the precise mechanism has yet to be defined. Kv8.2 is the first and, as yet, only voltage-gated K+ channel protein where disease-causing mutations affecting vision have been identified. Also, CDSRE is a good candidate for treatment using viral-based gene therapy approaches. Specific project aims include: establish the site of gene expression; determine disease progression in the retina of mutant mice; determine the impact of loss of Kv subunits on gene expression in specific cell types in the retina and examine gene therapy treatment approach for Kv8.2 deficiency using a novel viral vector.

Role of the Student:

This project will uses a broad-range of molecular, histological and electrophysiology techniques and the student will be engaged in all aspects of the proposal. More specifically, the student's role can include all or some aspects of running of the mouse line colonies, tissue collections and sample preparation, immunohistochemistry experiments, *in vivo* and *in vitro* electrophysiology experiments, sample preparation for transcriptome and proteome sequencing experiments and design and cloning of AAV viral vectors. They will also be expected to participate in literature reviews and manuscript preparation.

Return to Index

Retinal Genomics and Therapy

Project title: Investigating the correlation of myopia susceptibility with cone opsin gene variants

A project suitable for Honours

Supervisor(s)	Laboratory	Email
Dr Livia Carvalho (Primary)	Retinal Genomics and Therapy	liviacarvalho@lei.org.au
Prof David Hunt (Co-supervisor)	Retinal Genomics and Therapy	david.hunt@uwa.edu.au

Project Synopsis

Refractive errors are the most common cause of visual impairment in humans, with elongation of the eye - myopia - the most prevalent form. The frequency of myopia is increasing, reaching epidemic proportions in some countries, with a lack of exposure to daylight cited as a major environmental factor. The process of emmetropization, eye lengthening, is regulated by visual experience to match the eye's optics and to compensate for variation in corneal/lens curvature and power. The signals that guide this process are initiated largely by light absorption of the photopigments found in L and M cones. Changes in the pattern of light and dark in the retinal image that characterizes blurred versus sharply focused images are monitored to stop eye growth when the correct length for coordinated plano (neutral) optics is reached. In the absence of sufficient daylight, this process malfunctions, resulting in myopia. This project will examine the link between myopia and changes in the expression of the cone visual pigment (opsin) genes. The approach will be two-fold. Firstly, we will expand our previous study of opsin gene sequences in myopic individuals and secondly, we will use the zebrafish as a model system to study the effect of opsin gene variants on the development of the eye. The first part of this project will use a broad-range of molecular techniques including quantitative and long-range PCRs, cloning, DNA sequencing, site-directed mutagenesis and in vitro expression studies. The second part of this study will use CRISPR-Cas9 technology in the zebrafish to evaluate the effect of sequence variants of the M/L opsin gene on eye development and morphology and its contribution to refractive errors like myopia.

Return to Index

Retinal Genomics and Therapy

Project title: Studying primary and secondary cone degeneration and cell death mechanisms in inherited retinal disorders

A project suitable for Honours

Supervisor(s)	Laboratory	Email
Dr Livia Carvalho (Primary)	Retinal Genomics and Therapy	liviacarvalho@lei.org.au
Prof David Hunt (Co-supervisor)	Retinal Genomics and Therapy	david.hunt@uwa.edu.au

Project Synopsis

Inherited retinal degeneration (IRD) is a major contributor to early onset blindness worldwide. Currently there is no definite treatment to cure or delay disease progression and restore vision, leaving patients with a poor visual prognosis. The retina is quite unique in the number of different mutations that can cause vision loss, with >400 different disease genes now identified. Amongst the different neuronal cell types in the retina, the photoreceptor cells, which are critically important for light detection, are one of the main targets for mutations leading to vision loss. There are two types of photoreceptors, the rods and cones; rods are active in dim light/night vision, whereas cones are critical for some of the most essential aspects of vision like facial recognition, colour, high acuity vision fine processing and contrast detection. Interestingly, cone photoreceptors appear to be remarkably sensitive and will undergo degeneration even when the genetic lesion is present only in rod-specific genes. Thus, cone loss in IRD can be divided into either primary or secondary cone death depending on whether the mutation is present in a cone- or rod-specific gene, respectively. Using different mouse models of a cone-specific disorder as our primary tools, we hypothesize that primary and secondary cone death are driven by separate molecular pathways. The overall goal of this project is to combine gene and protein expression profiles with a method for following cone fate in the retina of mouse models of inherited retinal degeneration. This project will also provide a parallel study of different cone degeneration models of primary and secondary cone death and will thereby enable the exact pathways behind cell death to be identified, together with the identification of the common and differential factors involved in each type of inherited retinal degeneration.

Return to Index

Experimental Immunology

Project title: Improving CMV immune responses in bone-marrow transplant recipients

A project suitable for Honours

Supervisor(s)	Laboratory	Email
Professor Mariapia Degli-Esposti (Primary)	Experimental Immunology	mariapia@lei.org.au
Dr Christopher Andoniou (Co-supervisor)	Experimental Immunology	candoniou@lei.org.au

Project Synopsis:

Human cytomegalovirus (HCMV) is a common pathogen that causes a subclinical infection in immunocompetent individuals. Following primary infection the host immune system is unable to completely clear the virus leading to a latent infection that lasts for the life of the host and may reactivate at any time. Allogeneic haematopoietic stem cell transplantation (alloHSCT) is used to treat some forms of leukemia however, complications, particularly graft-versus-host disease (GVHD) and opportunistic infections can limit the treatments effectiveness. In particular, HCMV reactivation following alloHSCT remains a significant clinical problem with CMV infection associated with lower overall survival and higher transplant-related mortality. Understanding the factors controlling viral reactivation and how these may contribute to GVHD has been hampered by the lack of an appropriate experimental model. We have established a model of CMV reactivation during alloHSCT that accurately reflects the clinical scenario. This model will be used to define the factors controlling CMV reaction, how CMV reactivation impact on GVHD, and will be used to develop therapies that improve viral control. Techniques such as fluorescence activated cell sorting (FACS) analysis, microscopy, histology, PCR and in vitro tissue culture will be utilized to complete the project. The information generated from this project has the potential to improve clinical outcomes in patients undergoing alloHSCT.

Return to Index

Experimental Immunology

Project title: Impact of viral infection on autoimmunity

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Professor Mariapia Degli-Esposti (Primary)	Experimental Immunology	mariapia@lei.org.au
Dr Iona Schuster (Co-supervisor)	Experimental Immunology	IonaSchuster@lei.org.au

Project Synopsis:

Viral infections have long been suspected to play a role in autoimmunity, with members of the herpes virus family such as cytomegalovirus (CMV) specifically implicated. We use the model of murine CMV, a natural pathogen of the mouse with high similarity to its human counterpart, to investigate the mechanisms underlying the generation of protective antiviral responses and how these correlate with the onset of autoreactive responses. In a recent publication, we have shown that a strong anti-viral T cell response generated in the absence of certain immune regulatory mechanisms improves viral control. However, once the virus is controlled, this strong anti-viral response leads to increased generation of auto-specific immune responses resulting in a loss of tissue function. The autoimmune disease generated represents the best available model of the second most common autoimmune disease of man, Sjogren's Syndrome, a condition that affects vision by severely compromising tears production.

The goal of this project is to further extend our understanding of the processes and mechanisms underlying the generation of autoreactive immune populations in the context of viral infection.

An additional related project studying the impact of CMV in the development and progression of uveitis is also available. Uveitis is the third leading cause of blindness worldwide (What is Uveitis?)

Experimental approaches will include *in vitro* and *in vivo* techniques using a range of wildtype as well as gene-targeted mouse strains and MCMV viruses. Techniques include molecular approaches, such as cloning and PCR, tissue culture work, such as the maintenance of cell lines and cell-based assays, and the preparation of different tissues for histological analysis of tissue pathology, characterization of infiltrating cell types, and assessment of changes in tissue architecture. Furthermore, we use flow cytometry to characterize and quantify immune cell populations isolated from different tissues at various times post infection. Our lab runs one of the few 16-colour flow cytometers in Western Australia, allowing us to perform in depth analysis of multiple cell subsets simultaneously.

Return to Index

HUMAN OCULAR TISSUE ENGINEERING LABORATORY

Research interests

The Ocular Tissue Engineering Laboratory was established by Dr Fred Chen in 2011 with three aims: (i) to develop stem cell therapies for retinal diseases such as age-related macular degeneration (AMD) and inherited retinal diseases (IRDs), (ii) to investigate the use of multimodal retinal imaging in the measurement of disease progression rate in retinal degeneration and (iii) to conduct obsverstaional cohort studies to monitor natural history and test novel therapies for retinal diseases in randomised controlled trials.

Our specific research interests include the culture and differentiation of adult stem cells, induction of pluripotent and retinal cell fate by cellular reprogramming and extracellular matrix production using macromolecular crowding. With a focus on clinical translation, we aim to combine these approaches towards the tissue engineering of an autologous retinal pigment epithelial patch for the treatment of AMD. We also develop novel methods of analysing various types of retinal images such as optical coherence tomography (angiography), fundus autofluorescence, adaptive optics retinal photographs and microperimetry. Our clinical studies examines the effect of macular surgery and hydroxychloroquine toxicity on photogreceptor cells, IRD progression rates, AMD evolution, novel intravitreal therapies for neovascular and atrophic AMD and nanosecond laser for drusen.

Background: Age-related macular degeneration (AMD) is the most common cause of blindness in the Western world. A common final pathway in AMD is the degeneration of specialized layers of support cells and extracellular matrix situated between the retina and the choroid; consisting of the retinal pigment epithelium (RPE), Bruch's membrane (BrM) and capillary network of the choroid. Current surgical approaches to replace RPE in wet and dry AMD include full macular translocation and autologous RPE-choroid patch graft. These techniques have provided the proof of principle that visual function can be rescued by autologous RPE transplantation. However, there are significant limitations in these techniques related to surgical complication rates. A more clinically feasible approach is to create a bioengineered RPE patch ex vivo using cells derived from easily accessible sources.

With a focus on clinical translation, we are examining potential sources of autologous RPE cells, such as induced pluripotent stem cells (iPSC) and human limbal stem cells for RPE patch engineering. In addition, we are developing methods for direct reprogramming of RPE cells from patient cells using retinal transcription factors. Finally, we are developing novel carrier substrates for RPE patch engineering, including bioengineered Bruch's-like membrane and a primitive microvasculature capable of integrating with the host choroid.

Inherited retinal diseases (IRDs) is the most common cause of blindness in the working age population. It is caused by more than 500 genes. There is currently no treatment for these conditions although several gene therapy trials are underway for a handful of genes, including *ABCA4* (Stargardt disease), *CHM* (choroideremia) and *RPGR* (x-linked retinits pigmentosa). Our research focus in IRDs is to identify

Return to Index

disease causing mutation, measure disease progression rate and create a model of the disease in the dish for understanding mechanism and testing new drugs.

Scientific discipline

- Stem Cell Biology
- Cell transplantation
- Tissue Engineering
- Image analysis
- Clinical trials
- Disease modelling

Keywords

- Pluripotency
- Induced pluripotent stem cells
- Limbal stem cells
- Transplantation
- Animal models
- Retinal pigment epithelium
- Macular degeneration
- Retinitis pigmentosa
- Stargardt disease
- Genetic eye disease
- Optical coherence tomography
- Fundus autofluorescence
- Microperimetry

References (including student publications)

1. Huang D, Fletcher S, Wilton SD, Palmer N, **McLenachan S**, Mackey DA, **Chen FK**. Inherited retinal disease therapies targeting precursor messenger ribonucleic acid. Vision 2017, (1(3), 22.
2. Huynh E, Chandrasekera E, **Bukowska D**, **McLenachan S**, Mackey DA, **Chen FK**. Past, present and future concepts of the choroidal scleral interface morphology on optical coherence tomography. Asia-Pacific Journal of Ophthalmology 2017;6(1):94-103.
3. Wong EN, Chew AL, Morgan WH, Patel PJ, **Chen FK**. The use of microperimetry to detect functional progression in non-neovascular age-related macular degeneration: A systematic review. Asia-Pacific Journal of Ophthalmology 2017;6(1):70-79.
4. **Chen FK**, Menghini M, Hansen A, Mackey DA, Constable IJ, **Sampson DM**. Intra-session repeatability and inter-ocular symmetry of foveal avascular zone and retinal vessel density in optical coherence tomography angiography. Trans Vis Sci Tech accepted 2017 November 5th .

Return to Index

5. Wong EN, de Soyza J, Mackey DM, Constable IJ, **Chen FK**. Inter-session test-retest variability of microperimetry in type 2 macular telangiectasia. Trans Vis Sci Tech accepted 2017 October 30th .
6. Chew A, **Sampson D**, Kashani I, **Chen FK**. Agreement in cone density derived from gaze-directed single images versus wide-field montage using adaptive optics flood illumination ophthalmoscopy. Trans Vis Sci Tech accepted 2017 October 26th .
7. Australian cohort. Molecular Genetics and Genomic Medicine accepted 2017 June 29th.
8. Cunningham WJ, Balaratnasingam C, Chen Y, **Chen FK.** Cuticular drusen in an indigenous Australia. Retinal Cases & Brief Reports 2017 October 20th.
9. Chew AL, **Sampson DM**, Chelva E, Khan JC, **Chen FK**. Perifoveal interdigitation zone loss in hydroxychloroquine toxicity leads to subclinical bull's eye lesion appearance on near infrared reflectance imaging. Documenta Ophthalmologica accepted 2017 September 28th.
10. Chen Y, Chen SDM, **Chen FK**. Branch retinal vein occlusion secondary to a retinal arteriolar macroaneurysm: a novel mechanism supported by multimodal imaging. Retinal Cases & Brief Reports 2017 Jan 10th.
11. **McLenachan S**, **Zhang D**, Hao E, Zhang L, **Chen S-C**, **Chen FK**. Human limbal neurospheres prevent photoreceptor cell death in a rat model of retinal degeneration. Clin Experiment Ophthalmol 2017;45(6):613-624.
12. **Sampson DM**, Gon P, An D, Menghini M, Hansen A, Mackey DA, Sampson DD, **Chen FK**. Axial length variation impacts on superficial retinal vessel density and foveal avascular zone area measurements using optical coherence tomography angiography. IOVS 2017;58(7):3065-3072.
13. **Chen FK**, Chew AL, **Zhang D**, **Chen S-C**, Chelva E, Chandrasekera E, Koay EMH, Forrester J, **McLenachan S**. Acute progressive paravascular placoid neuroretinopathy with negative type electroretinopathy in paraneoplastic retinopathy. Documenta Ophthalmologica 2017 134(3):227-235. [Case Report]
14. **McLenachan S**, Hao E, **Zhang D**, Zhang L, Edel M, **Chen FK**. Bioengineered Bruch's-like extracellular matrix promotes retinal pigment epithelium differentiation. Biochemistry and Biophysics Reports 2017;10:178-185.
15. **Chen FK**, **McLenachan S**, Edel M, Da Cruz L, Coffey PJ, Mackey DA. iPS cells for modelling and treatment of retinal diseases. J. Clin Med 2014;3(4):1511-1541.
16. **McLenachan S**, Magno AL, Ramos R, Catita J, McMenamin PG; **Chen FK**, Rakoczy EP, Ruberte J Angiography Reveals Novel Features of the Retinal Vasculature in Healthy and Diabetic Mice. Exp Eye Research 2015;138:6-21
17. Alvarez-Palomo AB, Lucas M, Dilley RJ, **McLenachan S**, **Chen FK**, Requena J, Sal MF, Lucas A, Alvarez I, Jaraquemada D, Edel MJ. The Power and the Promise of Cell Reprogramming: Personalized Autologous Body Organ and Cell Transplantation. J. Clin Med 2014; 3(2):373-387
18. Alvarez-Palomo AB, **McLenachan S**, Requena J, Menchon C, Barrot C, **Chen FK**, Munne-Bosch S, Edel MJ. Plant hormones increase efficiency of reprogramming mouse somatic cells to induced pluripotent stem cells and reduces tumorigenicity. Stem Cells Dev 2014;23(6):586-93.
19. **McLenachan S**, **Zhang D**, Alvarez-Palomo AB, Edel MJ, **Chen FK**. mRNA transfection of mouse and human neural stem cell cultures. PLoS One. 2013;8:e83596.

Return to Index

Ocular Tissue Engineering

Project title: Modelling Inherited Retinal Diseases Using Induced Pluripotent Stem Cells and Disease Progression Analysis

Projects suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Dr Samuel McLenachan (Co-supervisor)	Ocular Tissue Engineering	smclenachan@lei.org.au
Dr Carla Mellough (Co-supervisor)	Ocular Tissue Engineering	CarlaMellough@lei.org.au
Dr Fred Chen (Primary)	Ocular Tissue Engineering	fredchen@lei.org.au

Project Synopsis:

Inherited retinal disorders (IRDs), such as retinitis pigmentosa (RP), are a major cause of blindness in Australian children. The Ocular Tissue Engineering Laboratory is developing patient cell derived models of IRDs for the elucidation of disease mechanisms and evaluation of therapeutic approaches. Our lab has established a cell bank containing dermal fibroblasts from patients with a wide range of IRDs. Our patients receive comprehensive clinical examinations and genetic screening. To generate personalized models of IRDs, skin cells harvested from patients with retinal disease-causing mutations are reprogrammed to produce induced pluripotent stem cells (iPSC). These iPSCs can be differentiated to produce many different cell types in the laboratory, enabling the reproduction of a patient's retinal, neural and cardiac tissues in a cell culture dish. Patient-iPSC provide an ideal platform for characterizing the molecular pathophysiology of novel or poorly understood gene mutations. Moreover these lines can be used to screen for agents that can correct the molecular defect. To date, several iPSC disease models have been generated in our laboratory from patients with mutations in genes including CLN3, RP1, CRB1, USH2A, PRPF31, OTX2 and SNRNP200. Available projects for honours students are listed below.

Whilst disease is modelling using iPSC, patients with these conditions are being monitored using optical coherence tomography, fundus autofluorescence, adaptive optic retinal imaging and microperimetry. This data is collected at 6 monthly intervals for analysis of diasese progression rate.

Return to Index

Available projects:

Project 1: Generation of a patient-derived iPSC model of IRD

In this project, the student will reprogram patient fibroblasts to pluripotency to produce a personalized iPSC model of the selected IRD. The disease causing mutation will be corrected by CRISPR/Cas gene editing to generate isogenic control iPSC lines. Patient- and repaired-iPSC lines will be differentiated into retinal and cardiac tissues. Mutant and repaired transcripts of the selected genes will be characterized in iPSC as well as retinal and cardiac tissues.

Project 2: Clinical trial in a dish

In this project, the student will utilise an established iPSC model of retinitis pigmentosa to characterize molecular pathophysiology and evaluate treatment strategies. iPSC carrying a dominant, nonsense mutation in the RP1 gene and control-iPSC will be differentiated into retinal organoids and RP1 expression characterized using RT-PCR, transcript sequencing and western blot. To restore translation of full length RP1 protein from the mutant transcript, retinal organoids will be treated with Ataluren, a translational read through inducing drug.

Project 3: Monitoring disease progression rate

In this project, the student will collect and analyse retinal images to determine the rate of disease progression. Patients have undergone 6 monthly imaging sessions and retinal scans will need to be segmented prior to analysis. Students with programming experience and statistical skills can analyse this unique dataset to discover new patterns of disease progression and correlate this with genetic analysis results and serum biomarker profiles such as anti-retinal antibody specificity.

Return to Index

Ocular Tissue Engineering

Project title: The use of human retinal organoids to study human retinal cell maturation and development

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Dr Carla Mellough (Primary)	Ocular Tissue Engineering	CarlaMellough@lei.org.au
Dr Livia Carvalho (co-supervisor)	Retinal Genomics and Therapy	liviacarvalho@lei.org.au
Dr Sam McLenachan (co-supervisor)	Ocular Tissue Engineering	smclenachan@lei.org.au
Dr Fred Chen (co-supervisor)	Ocular Tissue Engineering	fredchen@lei.org.au

Project Synopsis:

The developing human eye has been a particularly difficult organ for researchers to study due to the scarcity and minute volume of available tissue. To model and study retinal development, the investigation of a single retinal cell type may not be sufficient, as retinal cells do not work in isolation, but are interdependent upon each other to develop and function normally. Retinal progenitors interact with a variety of neighbouring cell types during their development, migration, specification and maturation. Therefore, to ascertain the basis of more complex interactive and expression dynamics, the study of laminated human neural retinal tissue containing multiple retinal cell types is extremely valuable.

Pioneering breakthroughs in ophthalmic and stem cell research over the last 5 years has allowed us to generate 3-dimensional (3D) miniorgans in the laboratory from human pluripotent stem cells, including laminated neural retina containing multiple retinal cell types. Since these 'retinal organoids' closely resemble the developing human retina that arises in utero, the advent of this technology has enabled the previously impossible study of the developing human retina, entirely in the laboratory, in a human biological setting.

The direct study of retinal cells within a microenvironment and cytoarchitecture akin to the native retina is an incredible opportunity to gain novel insights into the dynamics underlying the histogenesis and maturation of the human retina. Using this retinal organoid platform,

Return to Index

students will have the opportunity to develop skills in human embryonic stem cell culture, cellular differentiation, organoid characterisation and multiple analytical research techniques, in order to gain novel insights into human retinal development, phenotypic specification and maturation.

Available projects:

Project 1: Single cell analysis of stem cell-derived human retinal organoids

The differentiation of stem cells into complex tissues requires coordination between numerous molecular pathways with both temporal and spatial precision. In this project, the student will generate human retinal organoids from human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSC) and process these for single cell RNA-Seq analysis, in order to study the expression dynamics that occur as the early human retina is forming. Synchronised organoid samples will be analysed by immunofluorescent histochemistry, qRT-PCR and flow cytometry for comparative characterisation. The results generated here will provide key insights into the biological instructions and population dynamics governing developing human retinal cells during the organisation of the retina and development of the various retinal phenotypes. The outcome of this project will be the study of the transcriptional dynamics of human retinal cell populations during human retinal organoid development.

Project 2: Defining the cell surface antigen profile of human retinal cells

The pure isolation of stem cell-derived photoreceptor cells from the heterogeneous population of cells found within retinal organoids is essential for the directed study of human photoreceptors and the enrichment of this population for cell replacement therapy. In this project, the student will generate human retinal organoids from hESCs and investigate the surface antigen profile of this tissue using a BD lyoplate screening panel, which allows the profiling of hundreds of human cell surface markers. The student will validate the identified cell surface profiles using immunohistochemical and flow cytometric analysis of surface antigen expression alongside defined retinal phenotype markers, and qRT-PCR. The outcome of this research project will be the identification of a biomarker panel identifying human retinal cells with a particular interest in photoreceptor progenitors.

Return to Index

Project 3: Improving the maturity and functionality of human retinal organoids in vitro

Generating stem cell-derived photoreceptor cells in vitro which not only share a similar expression profile, but can demonstrate the capacity to develop outer segments and elicit a similar electrophysiological profile to native photoreceptors, has been a particularly difficult challenge. Whilst we are now able to generate populations of photoreceptor cells with ease, the low frequency of functional outer segment formation remains limiting. In this project, the student will culture retinal organoids from hESCs and hiPSCs and supplement differentiating cultures with organic compounds known to comprise and support the outer segment, to determine whether this will facilitate enhanced photoreceptor yield, morphology and maturation. The outcome of this research project will be the determination of the role of key outer segment components in human photoreceptor outer segment formation in vitro.

Return to Index

Lions Outback Vision

Project title: Improving service delivery in eye health in Western Australia

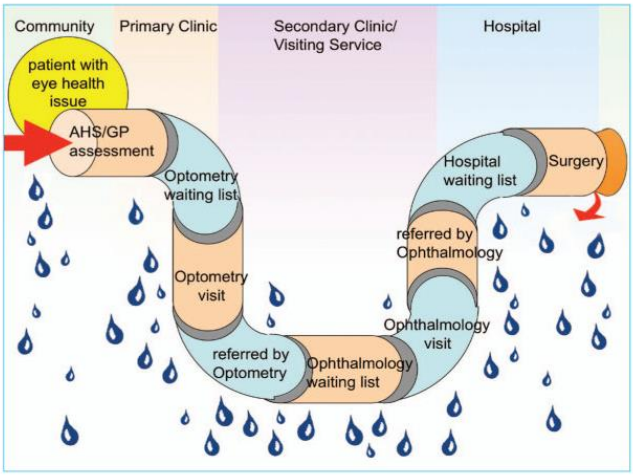
A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
A/Prof Angus Turner (Primary)	Outback Vision	angusturner@lei.org.au
Dr Josephine Muir (co-supervisor)	Outback Vision	JosephineMuir@lei.org.au

Background

Lions Outback Vision is the outreach service arm of the Lions Eye Institute. Established in 2010, Lions Outback Vision provides comprehensive eye health services in rural and remote Western Australia. Lions Outback Vision aims to address the unique challenges of delivering quality specialist eye health care to regional, remote and Indigenous communities across our State with the development and implementation of innovative and sustainable models of service delivery. We currently provide a range of eye health care services throughout the Pilbara, Kimberley, Goldfields, Midwest and Great Southern regions of Western Australia.

Inefficiencies in the eye care system have lead policy makers to describe the patient pathway as a 'leaky pipe' (Anjou, et al. 2013). The 'leaky pipe' maps the many steps, providers and locations for an eye care patient and the potential of drop out from the system. To increase efficiency, the elements of the system need to work closely together and fit into each subsequent element to avoid leakage from the pipe. In an effort to fix the leakages, has the system created more inefficiency through duplication?



This project will analyse the patient pathway of eye health patients accessing Lions Outback Vison's Diabetic Screening Program and the Visiting Optometry Scheme to determine the extent of leakage and/or duplication, and develop potential solutions.

Return to Index

Lions Outback Vision

Project title: Telehealth versus Face-to-Face Ophthalmology Consultations: How does the management of patients with cataracts differ?

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
A/Prof Angus Turner (Primary)	Outback Vision	angusturner@lei.org.au
Dr Josephine Muir (co-supervisor)	Outback Vision	JosephineMuir@lei.org.au

Background and description of project

With the development of technology, teleophthalmology has changed from a novel experiment into a validated clinical tool that is used to provide ophthalmology services to underserviced populations (Bahaadinbeigy, 2012). Previous work has validated teleophthalmology in specialist clinics (Bremer, et al, 2002; Dawson, et al, 2002; Tan, et al, 2013; Marcus, 1998), rural outreach clinics (Cheung, et al 2000), and the emergency department (Bar-Sela and Glovinsky, 2007).

In Western Australia, a teleophthalmology service has been established by Lions Outback Vision (LOV) as a way of reducing the inequity of access to ophthalmologists for those not living in the capital city Perth (Bossuyt, et al, 2015). The teleophthalmology service has significantly reduced the time to review by an ophthalmologist and has also reduced the number of patients requiring transfer to a tertiary centre, resulting in savings to the health system.

To date there has been no assessment of how management outcomes differ between patients seen face-to-face in rural outreach clinics and patients seen by teleophthalmology consultation. Further to this, there has been no assessment of the efficacy of asynchronous teleophthalmology review in this population. This project aims to answer these questions in order to build the evidence base around teleophthalmology, focusing specifically on patients presenting with cataracts.

Return to Index

Lions Outback Vision

Project title: Monitoring and evaluating a culturally-appropriate teleophthalmology service in Western Australia.

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
A/Prof Angus Turner (Primary)	Outback Vision	angusturner@lei.org.au
Dr Josephine Muir (co-supervisor)	Outback Vision	JosephineMuir@lei.org.au

Background and description of project

Teleophthalmology is the delivery of specialist ophthalmic services to patients in a different geographical location, using telecommunications technology. In 2011 a teleophthalmology service commenced in Western Australia. This real-time service operates between a general ophthalmologist based at the Lions Eye Institute, and several general practitioners, optometrists and hospitals in rural and remote Western Australia.

At present, there is a paucity of data on the efficacy of real-time teleophthalmology services, especially relating to patient satisfaction, barriers to utilisation, clinical efficacy and cost-effectiveness. This project proposes to address this gap in evidence by evaluating the teleophthalmology service in Western Australia, identify its utility and limitations, and provide recommendations for future. It is envisaged that the results will be significant and worthy of publication in a medical journal, given the novel nature of the project, potential benefit to patients and relevance to eye care programs in Australia and overseas. While telemedicine has been generally well received by patients and providers, Indigenous Australians' perceptions of telemedicine are unknown. As many patients managed by video-consultation will be Indigenous, an assessment of whether telemedicine provides a culturally-appropriate model of providing healthcare may also be included. Hence, the findings of this project may have broader relevance to any program that includes telemedicine as a means of healthcare delivery to this population.

Return to Index

Pharmacology and Physiology

Project title:
Modulation of vasoactivity of retinal veins

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Associate Prof Er-Ning Su (Co-supervisor)	Physiology & Pharmacology	erning@lei.org.au
Prof Dao-Yi Yu (Primary supervisor)	Physiology & Pharmacology	dyyu@lei.org.au

Project Synopsis:

Recently we demonstrated that retinal vein diameter can be modulated by vasoactive agents that are known to be locally generated such as endothelin-1 and adenosine, using our recently developed isolated perfused porcine retinal vein preparation. Although the retinal circulation is responsible for supplying a high metabolic rate tissue, it must be anatomically sparse to minimize optical interference with the light path to the photoreceptors. These requirements result in a limited flow circulation, with a very high arterio-venous oxygen tension difference. A further unusual feature of the retinal circulation is that it has no autonomic innervation, so total reliance must be placed on local vascular control mechanisms to regulate retinal blood flow. The importance of retinal arteries in blood flow regulation is well recognized. The retinal arteries have a continuous layer of smooth muscle cells that generate the vasoactive response to local stimuli. In contrast, the wall of the retinal veins are very thin and consists of a single layer of endothelial cells and only a few smooth muscle cells. The retinal vein had previously been considered to be incapable of regulating vascular tone, and there has been little attention paid to possible effects of vasoactivity of retinal veins. The retinal veins are the only drainage pathways for blood flowing in the retinal circulation. Retinal vein resistance and diameter changes could potentially affect vein drainage resistance and therefore upstream pressure in the retinal capillaries. It would therefore be interesting to determine whether retinal vein vasoactivity can be modulated locally as a means of influencing retinal blood flow and retinal capillary pressure. Furthermore, retinal vein occlusion is the second most common retinal vascular disorder, often leading to severe loss of visual function. It would be interesting to investigate whether a local venous constriction induced by vasoconstrictive molecules is involved in addition to other pathogenic factors in retinal vein occlusion.

Role of the Student:

This project will use an established isolated perfused retinal vein preparation and test possible modulations of the vasoactivity by some potential vasoactive agents including agonists and antagonists. The student will study direct responses in the isolated retinal vein preparation with potential extension to in vivo experimental studies. Students will be expected to understand previous works in the field and learn the specific hands-on skills required to perform such a study. The student will also participate in manuscript preparation.

Return to Index

References

Yu DY, Su EN, Cringle SJ, Morgan WH, McAllister IL, Yu PK. Local Modulation of Retinal Vein Tone. *Invest Ophthalmol Vis Sci*. 2016;57:412-419.

Yu DY, Yu PK, Cringle SJ, Kang MH, Su EN. Functional and morphological characteristics of the retinal and choroidal vasculature. *Prog Retin Eye Res*. 2014;40:53-93.

Su EN, Kelly ME, Cringle SJ, Yu DY. Role of Endothelium in Abnormal Cannabidiol-Induced Vasoactivity in Retinal Arterioles. *Invest Ophthalmol Vis Sci*. 2015;56:4029-4037.

Return to Index

Pharmacology and Physiology

Project title:
Characterisation of Conjunctival Lymphatics

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Associate Professor Paula Yu (Co-supervisor)	Physiology & Pharmacology	PaulaYu@lei.org.au
Prof Dao-Yi Yu (Primary supervisor)	Physiology & Pharmacology	dyyu@lei.org.au

Project Synopsis:

The success of glaucoma surgeries is often dependent on the presence of optimal drainage pathway. It has been suggested in recent years that the rate of fluid drainage from the subconjunctival space is the determining factor in the resultant IOP reduction. The formation of a filtering bleb has been considered a cornerstone of IOP control after glaucoma filtration surgery, and that the tissue resistance around the implant is the dominant regulator of fluid outflow. Subsequent successful removal of the drained aqueous from the bleb is also essential for the success of the surgery and the presence of functional conjunctival lymphatics is believed to play a critical role. To date we have limited knowledge of the conjunctival lymphatics in terms of its three dimensional distribution, structure, function and regulation. This project will study these aspects of the conjunctival lymphatics using pig eye which is readily accessible from local abattoir. It will involve characterisation of the regional and three dimensional distribution patterns of porcine conjunctival lymphatics using well established histological techniques including 5'Nase labelling and immunohistochemistry for specific endothelial and contractile protein markers. Dependent on the timeframe of the student, this project may extend to include functional studies of normal and treated conjunctiva.

Role of the Student:

We are looking for a student to join in this project by doing histological studies (including dissection, specimen preparation, staining, imaging, analysis) on porcine conjunctival lymphatics. The results will be analysed and interpreted with help from supervisors. The student will also participate in manuscript preparation.

Return to Index

References

D-Y. Yu, W.H. Morgan, X. Sun, E-N. Su, S.J. Cringle, P.K.Yu, P. House, W. Guo and X. Yu. The critical role of the conjunctiva in glaucoma filtration surgery. Progress in Retinal and Eye Research 2009; 28:303-328.

W. Guo, Y. Zhu, P.K. Yu, X. Yu, X. Sun, S.J. Cringle, E-N. Su, D-Y. Yu. Quantitative study of the topographic distribution of conjunctival lymphatic vessels in the monkey. Experimental Eye Research 2012; 94:90-97

Return to Index

Pharmacology and Physiology

Project title:
Developing laser ultrafine microsurgery for intraocular surgery

A project suitable for Honours, Masters or PhD studies

Supervisor(s)	Laboratory	Email
Prof Stephen Cringle (Co-supervisor)	Physiology & Pharmacology	steve@lei.org.au
Prof Dao-Yi Yu (Primary supervisor)	Physiology & Pharmacology	dyyu@lei.org.au

Project Synopsis:

The purpose of this project is to develop laser ultrafine microsurgery for intraocular surgery. Intraocular surgical procedures require an advanced level of microsurgical precision and control to avoid complications such as unwanted retinal damage and hemorrhage, a common problem with current mechanical surgical procedures in which scissors, blades, or forceps are used. Laser technology has the potential to provide the required precision and control to transect and remove tissue, with minimal unwanted damage to surrounding tissue. The laser has been widely accepted for corneal refractive surgery, providing exceptional control of ablation depth and minimal damage to surrounding tissue and there have been over millions laser procedures performed worldwide. However, to be used in the intraocular environment, the laser must be equipped with a specially designed delivery system and the laser–tissue interaction is different from that in a gaseous environment. In our previous studies we have demonstrated the potential of 266 nm and 213 nm UV laser wavelengths to accurately cut ocular tissues.[1-4] Advantages of these wavelengths are that they can be produced by a solid state laser source and that it can be delivered through a relatively low-loss fiber-optic probe that can be readily manipulated in the intraocular environment. Successful ablation of retinal tissue would indicate future applications in the cutting of retinal membranes or vascular sheaths in a range of retinal diseases.

Role of the Student:

The student will assist with improvements to the fiberoptic delivery systems and perform studies of tissue ablation rate with a variety of different laser parameters. The suitable candidate should have experience or a keen interest in the biological application of laser technology. All of the required equipment is already in place and a dedicated laser laboratory and optical components are available. There will be ample opportunities to publish research findings and contribute to the development of this exciting new technology to create new treatment possibilities in ophthalmology.

Return to Index

References

Gorbatov, M., Miller, J., Yu, P. K., Cringle, S. J., Yu, D. Y. (2010) Ablation of subretinal tissue with optical fiber delivered 266 nm laser pulses. Exp. Eye Res. 91: 257-263.

Miller, J., Yu, P. K., Cringle, S. J., Yu, D. Y. (2007) Laser-fiber system for ablation of intraocular tissue using the fourth harmonic of a pulsed Nd:YAG laser. Appl. Opt. 46: 413-420.

Miller, J., Yu, X., Yu, P. K., Cringle, S. J., Yu, D.-Y. (2008) Tissue ablation via optical fibre delivery of UV laser radiation. Proc SPIE.

Yu, P. K., Miller, J., Cringle, S. J., Yu, D. Y. (2006) Experimental retinal ablation using a fourth-harmonic 266 nm laser coupled with an optical fiber probe. Invest. Ophthalmol. Vis. Sci. 47: 1587-1593.

Yu, X. B., Miller, J., Yu, P. K., Cringle, S. J., Balaratnasingam, C., Morgan, W. H., Yu, D. Y. (2009) Ablation of intraocular tissue with fiber-optic probe-delivered 266-nm and 213-nm laser energy. Invest. Ophthalmol. Vis. Sci. 50: 3729-3736.

Return to Index