Draft Update for 2019 - 2020

Funding

Novel imaging modalities for clinical trials Drs. MacDonald, Xu, Zhai
4D-Molecular Therapeutics, Nightstar Therapeutics *University of Alberta*

We continue to review the results of natural history studies to evaluate the outcome measures that are chosen to determine safety and efficacy. Novel approaches have been developed to track the changes in retinal pigment epithelium and photoreceptor areas over time.

Retinal imaging data analysis in choroideremia Dr. Fay Yi Zhai, Dr. MacDonald
Choroideremia Research Foundation USA *University of Alberta*

Choroideremia is an X-linked recessive retinal dystrophy caused by loss of function mutations in the *CHM* gene and is presumably amenable to CHM gene replacement therapy. Our research team conducted the first trial of ocular gene therapy in Canada which aimed to treat 6 choroideremia patients. During 5 years of follow-up, we accumulated multimodal clinical data from 6 research subjects. Dr. Zhai has been developing precise quantification methods for choroideremia trials. She successfully used Photoshop-based preserved fundus autofluorescence area and *en face* ellipsoid zone area as measures for the retinal pigmented epithelium and photoreceptors. The methods she developed help us to learn more about the natural history of disease progression, and provide reliable endpoints to evaluate the efficacy of therapeutic agents that aim to treat choroideremia.

Immune responses to viral mediated gene transfer Dr. Ian MacDonald
Fighting Blindness Canada *University of Alberta*

Innate immunity is triggered as a response in the retina to subretinal injection of AAV2 vectors with therapeutic genes. Our team is investigating the mechanisms underlying this response to then define how best to prevent or treat this reaction through re-design of vectors or coincident treatment with immunosuppression.

Retinopathy linked to mutations in CFAP20 Drs. Allison, Arno, AuDoucette, Leroux, MacDonald
Models and Mechanisms, Care4Rare *UC London, Simon Fraser U, UCalgary, UAlberta*

Our joint laboratories work on a rare disorder affecting rod photoreceptors and its relationship to mutations in a gene called *Ciliary Flagellar Associated Protein 20* (*CFAP20*). CFAP20 is a highly conserved protein associated with motile cilia function that has never been associated with human disease. The project uses interrogates the role of CFAP20 in primary cilia of animal models and specific cells (photoreceptors and retinal pigment epithelium) through international collaborations between UofA (Allison, MacDonald) UofC (Billie Au) , Simon Fraser University (Michel LeRoux), and University College London (Gavin Arno)

PEX6 mutations result in an Usher-like syndrome Drs. Benson, MacDonald
Fighting Blindness Canada *University of Alberta*

Peroxisomal biogenesis disorders (PBDs) are a group of recessively-inherited conditions that cause multisystem disease including retinal degeneration, sensorineural hearing loss, neurologic dysfunction, and other anomalies. There are no disease-modifying treatments currently available. Our lab identified a PBD in a young patient with compound heterozygous changes in *PEX6*. To investigate the mechanism of disease, we obtained

patient-derived skin fibroblasts and generated a *PEX6* knockout cell line using CRISPR/Cas9 technology for functional studies. Understanding disease at an individual patient level will inform the development of future therapeutic strategies.

RP1L1 retinopathy: A ciliopathy causing occult macular dystrophy and RP Drs. Allison, MacDonald
Rare Diseases Models and Mechanisms *University of Alberta*

The photoreceptor sensory cilium is the site of light detection; its dysfunction results in photoreceptor degeneration and vision loss. RP1L1 is a photoreceptor cilium component and RP1L1 mutations lead to progressive photoreceptor disease through unknown mechanisms. Our team aims to elucidate underlying causes of rod and cone degeneration when RP1L1 is mutated, determine function of RP1L1 protein, and identify potential therapeutic targets

Publications

Xu M, Zhai Y, MacDonald IM. Visual Field Progression in Retinitis Pigmentosa. *Invest Ophthalmol Vis Sci.* 2020, In press.

Zhai Y, Xu M, Dimopoulos IS, et al. Quantification of RPE Changes in Choroideremia Using a Photoshop-Based Method. *Transl Vis Sci Technol*. 2020, In press.

Noel NCL, MacDonald IM. RP1L1 and Inherited Photoreceptor Disease: A Review [published online ahead of print, 2020 Apr 30]. *Surv Ophthalmol*. 2020;S0039-6257(20)30071-0. doi:10.1016/j.survophthal.2020.04.005

Benson MD, MacDonald IM, Sheehan M, Jain S. Improved electroretinographic responses following dietary intervention in a patient with Refsum disease. *J Inherit Metab Dis Rep.* 2020, In press.

Zhai Y, MacDonald IM. OCT Changes in 4-Year-Old Choroideremia Patient. *Ophthalmology*. 2019;126(10):1357. doi:10.1016/j.ophtha.2019.05.026

Dimopoulos IS, Hoang SC, Radziwon A, et al. Two-Year Results After AAV2-Mediated Gene Therapy for Choroideremia: The Alberta Experience. *Am J Ophthalmol*. 2018;193:130-142. doi:10.1016/j.ajo.2018.06.011

Student and Fellow Accolades

Matthew D Benson - Ivy A Thomson and William A Thomson Graduate Scholarship (2019); Fighting Blindness Canada (FBC) Clinician-Scientist Emerging Leader Award (2018)

Nicole N. L. Noel -- Frederick Banting and Charles Best Canada Graduate Scholarship (CIHR CGS-D) (2018); President's Doctoral Prize of Distinction (2018); Queen Elizabeth II PhD Scholarship (2018); Alberta Innovates Graduate Scholarship (2017); University of Alberta Doctoral Recruitment Scholarship (2017)

Kimberly M Papp - Alberta Innovates Summer Studentship (2019; 2020).

Paul Crichton - University of Alberta Graduate Entrance Scholarship (2020-21)