APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

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1. Title.
Investigation of molecular biomarkers for paediatric vitreo-retinal disease and developing novel interventions

2. Portfolio summary.

Aims:
1. To improve the understanding of the molecular aetiology of blinding retinovascular disorders by investigating the RNA & DNA profiles of normal and disease state vitreous.

2. To identify whether modulation of signalling molecules attenuates aberrant angiogenesis and retinopathy in retinovascular disease models.

Background:
Paediatric retinovascular conditions include a range of blinding diseases caused by aberrant retinal vascular development and maintenance. These include relatively common conditions such as Retinopathy of Prematurity (ROP), and rare diseases including Coats disease, Familial Exudative Vitreo-Retinopathy (FEVR), and Persistent Foetal Vasculature (PFV). FEVR is a monogenic disease caused by mutation in several genes (NDP, FZD4, LRP5, TSAPN12) involved in WNT signalling; ROP, Coats disease and PFV, by contrast, are poorly understood, though mounting evidence indicates similar signalling pathways are important. Treatment for all these conditions involves surgical interventions aiming to prevent or repair retinal detachment, remove aberrantly proliferating tissue and or block growth and/or seal leaking blood vessels. These procedures are currently not based on molecular knowledge of the disease and outcomes are variable to poor, often resulting in severe visual impairment in childhood. Around 50 such cases are treated with differing surgical procedures at GOSH each year.

This project will investigate the hypothesis that molecular analysis of the vitreous will reveal abnormal signalling pathways in the diseased retina that will guide development of new molecular based treatments for these vitreo-retinopathies. It will then test the effect of selected biologics after their delivery by intravitreal injection into the murine eyes of wild type and a genetic model of retinovascular disease.

Proposed methodology to be adopted:
It has been recently demonstrated that retinal mRNA, miRNA and DNA can be recovered from the vitreous, the collagenous matrix that fills the posterior volume of the eye. Vitreous sampling provides a unique opportunity to assay the pathological state of the retina as it acts a reservoir of retinal metabolites and signalling molecules. In this project vitreous/tissue and blood samples will be recovered from individuals with retinovascular conditions during normal vitrectomy surgery and age-matched individuals with normal retina undergoing surgery.
proteome analysis will be performed on the control and diseased samples using standard procedures established at ICH and in the host laboratories to identify dysregulated pathways and associated somatic and germ line genetic events occurring in disease. The Ndp-/- mouse line displays several features of paediatric retinovitreal disease including malformed retinal vasculature, persistence of hyaloid vessels and degeneration. This model will be used to test the effect of novel and existing biologics (blocking antibodies, antisense oligos or viral vectors) delivered postnatally by intra-vitreal injection and whether phenotypic amelioration can be achieved. In addition to targets selected from the novel analysis of patient samples conducted in year 1, biologics selected from current knowledge of relevant (VEGF and Wnt) pathways will be tested. For example, in collaboration with Prof John Greenwood at the UCL Institute of Ophthalmology, LRG1 levels (linked to retinal angiogenesis) will be evaluated via an existing ELISA, in blood and vitreous samples and we will assess whether a commercially available humanised antibody to LRG1 modifies the outcome in the disease model.

**Skills to be achieved by the PhD trainee:**
The Vitreo-retinal Surgical Scientist trainee will assist and/or perform vitrectomy surgery in children at GOSH to collect samples for analysis and potentially as part of a multicentre study. Paediatric Vitreo-Retinal surgery is a sub-speciality area that is performed in very few centres in the world. The trainee will be trained in standard vitreoretinal techniques but would subsequently learn endoscopic vitrectomy for retinopathy of prematurity, a technique only done at one other hospital worldwide. S/he will be trained in genetic diagnosis and deep phenotyping of the vitreo-retinal cohort including imaging using the OPTOS wide field scanning laser ophthalmoscope. S/he will be trained in state-of-the-art molecular genetic and cell biology techniques and animal models of eye disease in the laboratory studies, employing a wide range of techniques.

**Relevance to the area of paediatric surgery:**
The sequence of genetic events that encodes abnormal ocular and retinal vascular development and disease is still partially understood. It is important to gain further insights into these processes in order to conceive of novel treatment modalities for these blinding conditions.

**References:**


