



Royal Victoria Eye & Ear Hospital Research Foundation

Progress Report on activities, 2010 -2011





COMMITTEE AND SERVICES

Chairperson	Noel Horgan
Treasurer	Mark Cahill
Lecturer in Ocular Genetics	Paul Kenna
Committee Member	Aoife Doyle
Committee Member	Susan Kennedy
Committee Member	Dara Kilmartin
Committee Member	David Mooney
Committee Member	Con Timon
Committee Member	Tony Healy
Committee Member	Conor Murphy
Research Technician	Hilary Dempsey
Research Nurse	Claire English
Research Photographer	Hugh Nolan
Research Secretary	Cathy King
Research Coordinator	Emma-Jayne Verner

SERVICES AVAILABLE

Clinical Electrophysiology Service – to assess retinal and brain stem function
Colour Vision Testing – Farnsworth Munsell 100 hue
Dark Adaptation
Visual field testing for glaucoma patients (Humphrey Analyser)
A-Scans for assessing power of lens implants for cataract surgery
Assessment of visual function in Medico Legal cases
Full eye examination for patients and their families suffering from Retinitis Pigmentosa and other inherited retinal degenerations
Pattern E.R.G for pre-clinical visual function loss in Glaucoma
Optical Coherence Tomography for Assessment of Macular Disease and Glaucoma
CDX for Retinal Nerve Fibre assessment in Glaucoma

Since its establishment in 1974 the Research Foundation at the Royal Victoria Eye & Ear Hospital, Dublin has had a particular interest in patients with various forms of inherited and metabolic retinal diseases. It was amongst the first centres in the country to develop electrodiagnostics to aid in the diagnosis and assessment of patients with blinding conditions. Today, the Unit possesses state-of-the-art electrodiagnostic equipment and can carry out the full range of electrophysiological tests of retinal and visual function to the highest international standards.

The last year has been a very busy one in the Research Foundation. The annual report highlights the ongoing research being undertaken both in the Research Foundation and the hospital itself. With regards to ocular genetics research the Research Foundation has a long history of collaboration with the Ocular Genetics Unit in Trinity College Dublin where researchers were instrumental in identifying the first disease-causing gene in any form of Retinitis Pigmentosa (RP), rhodopsin, in 1989. The genetics behind inherited retinopathy is on-going. The Research Foundation is also involved in studies to determine the genetic basis for age related macular degeneration as a significant cause of vision loss in patients over the age of 50. The remit of the Research Foundation has expanded over the last number of years and also includes research on all types of eye disease including retinal disease, ocular oncology, ocular inflammation, corneal disease and eye complications of systemic disease. The full details of all ongoing research is outlined in this report.

The Research Foundation is the principal investigating site in Ireland for a number of drug trials involving anti-VEGF medications for the treatment of retinal diseases. This collaboration with pharmaceutical companies is a new avenue for the Research Foundation and we hope to develop this facility in the future.

One of the key innovations since the last report has been the initiation of the Dr Eithne Walls research meeting, which took place at the end of June. This research meeting is for the young doctors in the hospital to present their research and to develop their ability to undertake research and present it to their peers. This is in memory of Dr Eithne Walls, a former Riverdancer and Doctor at the hospital, who was a passenger along with her friends and colleagues Dr Aisling Butler and Dr Jane Deasy on the ill-fated Air France Flight 447 which disappeared over the Atlantic on June 1 2009. Each June Bank Holiday since then her friends, family, and former colleagues in both Riverdance and the hospital have come together to run the Mini Marathon as a way of remembering Eithne.

The Research Foundation has joined the Medical Research Charities Group and we hope that this collaboration will allow us to fund more projects in the hospital. Another new initiative this year was the instigation of a summer student fellowship which was highly successful. This allowed a medical student to spend a short period observing and undertaking research in a centre of excellence. Research undertaken by the Foundation has been presented at a number of national and international meetings in the last year and a number of publications have been produced as a result of the research ongoing in the Foundation.

We would like to congratulate Sorchá Ni Dhubhghaill for submitting her PhD on work which was carried out here in collaboration with the Ocular Genetics Unit in Trinity College, Dublin. The Royal Victoria Eye & Ear Hospital look forward to having further submissions from the Research Foundation for research undertaken at a higher degree. At the back of the progress report there is a covenant form and we would hope that people would consider donating to the Foundation by using the covenant method.

Current Research

Genetics Research

Working with Irish families with autosomal dominant forms of the inherited retinal degeneration, Retinitis Pigmentosa (RP) and in collaboration with the Ocular Genetics Unit at Trinity College Dublin Foundation researchers were instrumental in identifying the first disease-causing gene in any form of RP, rhodopsin, in 1989. Subsequently other RP causing genes were identified in families who were characterised at the Foundation, namely the Peripherin/RDS and the mitochondrial MTT52 genes.

At present, patients with inherited retinal degenerations face inexorable loss of vision, in many cases resulting in total blindness. However, as a result of the molecular genetic advances with which the Foundation has been intimately involved, realistic prospects now exist to give hope that treatments will become available in the foreseeable future. At the Foundation, we aim to continue to be at the forefront of research which will eventually result in the development of sight-saving treatments for these patients.

In the past year we identified two novel functions within the Rhodopsin gene in patients attending the Unit. The clinical phenotype associated with one of the mutations was reported at ARVO 2010, in Fort Lauderdale, USA.

Projects

1 A) Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is one of the most common causes of visual impairment in the Irish population. Although many risk factors for the condition have been identified, recent research has highlighted the significance of genetic factors in increasing the risk of an individual developing this disease. A large-scale study into the genetics of AMD is presently underway at the Foundation to characterise the importance of genetic risk factors in the Irish AMD population.

2 Retinitis Pigmentosa

A) ADRP with Choroidal Involvement associated with Asp477Gly Mutation within the Rpe65 Gene

In a collaborative research effort between the Research Foundation at the Royal Victoria Eye and Ear Hospital and the Ocular Genetics Unit at Trinity College, Dublin investigators identified a new gene responsible for a form of autosomal dominant Retinitis Pigmentosa. The results were published in October 2011. Linkage testing using Affymetrix 6.0 SNP Arrays mapped the disease locus in TCD-G, an Irish family with autosomal dominant retinitis pigmentosa (adRP) ascertained and clinically characterised at the Foundation to an 8.8 Mb region on 1p31. Candidate gene and exome sequencing resulted in the identification of an Asp477Gly mutation in exon 13 of the RPE65 gene tracking with the disease in TCD-G.

The Asp477Gly mutation was not present in Irish controls, but was found in a second Irish family identified at the Foundation, provisionally diagnosed with Choroideraemia, but in whom no Choroideraemia gene mutation had been found. Mutations in RPE65 are a known cause of recessive Leber congenital amaurosis (LCA) and recessive RP, but no dominant mutations have been reported. This important paper (A dominant mutation in RPE65 identified by whole-exome sequencing causes retinitis pigmentosa with choroidal involvement. Bowne SJ, Humphries MM, Sullivan LS, Kenna PF, et. al. Eur J Hum Genet. 2011 Oct;19(10):1074-81. doi: 10.1038/ejhg.2011.86. Epub 2011 Jun 8) documented for the first time a dominantly acting mutation in this gene in 2 families with a clinical picture somewhat reminiscent of Choroideraemia. Approximately 20% of patients with a diagnosis of Choroideraemia do not have mutations in the X-linked gene for Choroideraemia. It is likely that mutations in RPE65 may be responsible for the disease in these patients.

Gene therapy for LCA patients with RPE65 mutations has shown great promise, raising the possibility of related therapies for dominant-acting mutations in this gene. A second, Canadian human clinical trial, showing promising effects of oral administration of a 9-cis-retinal analogue in patients with LCA due to recessively acting RPE65 mutations, may also hold out the prospect of beneficial effects in patients with Retinitis Pigmentosa due to dominantly acting RPE65 mutations.

B) Registry of Irish Patients with Leber Congenital Amaurosis and Early Onset Severe Retinal Dystrophy

Welcome Trust – HRB Centre for Clinical Research, Molecular Medicine Ireland, P. Kenna (RVEEH), M. Cahill (RVEEH), D. Keegan (MMH), I. Flitcroft (MMH).

This collaborative research co-ordinated by Mr. P. Kenna of the Research Foundation at the Eye and Ear Hospital and Mr. David Keegan of the Mater Misericordiae Hospital aims to identify Irish patients with Leber Congenital Amaurosis or Early Onset Severe Retinal Dystrophy (EOSRD), conditions in which gene mutations in the RPE65 gene have been identified. The aim is to document the incidence of these rare inherited disorders in the Irish population and to identify those individuals who might benefit from the encouraging results of the on-going clinical trials of gene therapy in these conditions.

C) Genetic Characterisation of a population of Irish Retinal degeneration patients

The study, funded by the Health Research Board of Ireland aims to analyse the DNA of a cohort of Irish patients with a variety of inherited retinal degenerations using next generation gene sequencing technology. This is a collaborative effort between Mr. P. Kenna of the Research Foundation, The Royal Victoria Eye and Ear Hospital and Prof. G. Jane Farrar at the Genetics Department, Trinity College Dublin.

- (Paul Kenna)

Retinal disease

The Research Foundation has funded a trial project to improve the diabetic retinopathy screening service in the hospital. The Research Foundation is the principal investigating site in Ireland for a number of drug trials involving anti-VEGF medications for the treatment of retinal diseases. This collaboration with pharmaceutical companies is a new avenue for the Research Foundation and we hope to develop this facility in the future.

Projects

1 Objective three-steps grading of digital fundus photographs of diabetic retinopathy.

This project is using objective three-step grading of fundus photographs of patients with diabetic retinopathy. 450 hospital-based patients have been screened to date. The three step process increases the quality of the grading of the screening programme. A quality component has been the use of OCT to detect diabetic macular oedema. This project will be expanded in 2012 to include 2 primary care practices located in Ranelagh and Churchtown. It is hoped that some of the lessons learned from this programme would be adapted by the proposed National Screening Programme which is scheduled to start by the HSE towards the end of 2012.

2 RETAIN Study

This is a phase 3 clinical trial investigating the use of Ranibizumab (anti-VEGF medication) for the treatment of macular oedema. The Research Foundation is the principal investigating site for the study. The project started in January 2011 and will continue until January 2013. 5 patients have enrolled in the study which requires monthly visits and extensive investigation of each patient.

3 BRIGHTER Study

This is a phase 3 clinical trial examining the use of Ranibizumab in the treatment of macular oedema secondary to branch retinal vein occlusion. The Research Foundation will be the principal investigator on site for this trial in Ireland. It is proposed that recruitment for the study will commence in March 2012.

4 CRYSTAL Study

This is a phase 3 trial examining the use of Ranibizumab in the treatment of macular oedema secondary to central retinal vein occlusion. The Research Foundation will be the principal investigator on site for this trial in Ireland. It is proposed that recruitment for the study will start in March 2012.

- (Mark Cahill)

Ocular Pathology

This is a collaboration between the oncology and pathology services at Royal Victoria Eye & Ear Hospital and Dublin City University looking at potential prognostic biomarkers in eye cancer. The pathology and ocular oncology unit at Royal Victoria Eye & Ear Hospital are also working closely with the NICBI on a Research Foundation supported research programme in identifying specific proteins in patients with eye melanoma that helps to predict the spread of cancer outside the eye, with the aim of improving long term patient survival.

Projects

- 1 Proteomic analysis of tumours and vitreous fluid from uveal melanoma**
P.Ramasamy (MD Study), C.Murphy, N.Horgan, P.Meleady, M.Clynes, S.Kennedy
- (Noel Horgan)
- (Susan Kennedy)

Ocular inflammation

The Research Foundation is supporting a novel long term collaboration between the ocular inflammation/cornea service of the Royal Victoria Eye & Ear Hospital under the direction of Professor Conor Murphy and Mr William Power, the National Institute for Cellular Biotechnology (NICBI) at Dublin City University, the department of immunology at the Royal College of Surgeons Ireland and the department of Rheumatology in St.Vincent's University Hospital. This collaboration brings together clinical and scientific skills from a range of disciplines which we hope will improve our understanding of a number of inflammatory eye conditions and corneal diseases and benefit patients through the development of new treatments.

Projects

- 1 Improving outcomes in giant cell arteritis through clinical collaboration**
Clinician Investigators: Prof C.Murphy, Professor of Ophthalmology, Royal Victoria Eye and Ear Hospital and Royal College of Surgeons in Ireland; Dr E.Molloy, Consultant Rheumatologist, St. Vincent's University Hospital.
Scientist Investigator: Dr U.Fearon, Senior Lecturer in Immunology, Department of Rheumatology, Education and Research Centre, St. Vincent's University hospital.
Co-investigator: Prof J.Meaney, Consultant Radiologist, St James' Hospital.
- 2 Acute anterior uveitis and spondylarthropathy research project**
Clinician Investigators: Prof C.Murphy, Consultant Ophthalmic Surgeon and Professor of Ophthalmology, Royal Victoria Eye and Ear Hospital and Royal College of Surgeons in Ireland; Prof O.Fitzgerald, Consultant Rheumatologist, St. Vincent's University Hospital.
Scientist Investigator: Dr U.Fearon, Senior Lecturer in Immunology, Department of Rheumatology, Education and Research Centre, St. Vincent's University hospital.

Clinician Research Scientist: Dr P.Ramasamy, Royal Victoria Eye and Ear Hospital and Royal College of Surgeons in Ireland.

- 3 Evasion of the innate immune response by herpes simplex virus in the cornea: molecular mechanisms mediating interferon down regulation and virus survival**
Clinician Principle investigator: Prof C.Murphy, Consultant Ophthalmic Surgeon, Royal Victoria Eye and Ear Hospital and Professor of Ophthalmology, Royal College of Surgeons in Ireland.
Scientist Principle investigator: Dr C.Jefferies, Senior Lecturer in Immunology, Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland.
Clinician Research Scientist: Dr D.Shahnazaryan, Royal Victoria Eye and Ear Hospital and Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland.
- 4 Innate immunity in HSV-1 keratitis and the role of Toll-like receptor mediated immunomodulation for treatment and prophylaxis**
Clinician Principle investigator: Prof C.Murphy, Consultant Ophthalmic Surgeon, Royal Victoria Eye and Ear Hospital and Professor of Ophthalmology, Royal College of Surgeons in Ireland.
Scientist Principle investigator: Dr C.Jefferies, Senior Lecturer in Immunology, Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland.
Clinician Research Scientist: Dr C.Malone, Royal Victoria Eye and Ear Hospital and Department of Molecular and Cellular Therapeutics, RCSI.
- 5 Corneal Stem Cell Research Project**
W.Power, C.Murphy, F.O'Sullivan, A.Bobart-Hone, M.Clynes & W.Murphy
The Royal Victoria Eye & Ear Hospital, the National Institute for Cellular Biotechnology at Dublin City University and the Irish Blood Transfusion Service (IBTS) are involved in a study harvesting and then growing sheets of stem cells to produce corneal epithelium which can be used to repair diseased or damaged superficial corneal tissue surgically. The group hope to be in a position to bring this new therapy into clinical use in late 2012.
- 6 Investigation of miRNA expression in Fuchs Dystrophy**
W.Power, P.Lee, F.O'Sullivan and M.Clynes
Fuchs' endothelial cell dystrophy (FED) is a chronic, progressive corneal condition. It is characterized by the presence of central corneal guttae in the early stage and may take up to a decade from the onset before it causes debilitating symptoms due to corneal oedema. The aim of this study is to delineate the role of microRNA (miRNA) in the pathogenesis of FED. This project is a collaboration between clinicians at Royal Victoria Eye & Ear Hospital (RVEEH) and molecular scientists at Dublin City University (DCU) to further our understanding of this common condition.
- (Conor Murphy)

Systemic Disease

The Research Foundation was chosen by Servier, a leading French pharmaceutical company, to do a Phase III multi-centre clinical trial to analyse the retinal effects of Ivabradine, an IF inhibitor used as cardiac rate limiter in heart disease. This trial commenced in October 2009 and will be ongoing for the next three years.

Projects

- 1 Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of Ivabradine administered orally. P.Kenna, L.Cassidy and H.Dempsey.

- (Lorraine Cassidy)

Dublin Mini-Marathon

On 1 June 2009 Dr Eithne Walls, along with her two friends and colleagues Dr Aisling Butler and Dr Jane Deasy, was a passenger on the ill-fated flight AF447 which disappeared over the Atlantic as it travelled from Rio de Janeiro to Paris.

Eithne was a doctor at the Royal Victoria Eye and Ear Hospital and just starting out on her exciting journey to fulfilling a lifelong ambition of becoming an eye surgeon. She was a gifted, vibrant and special person and her loss has had a profound impact on all who were privileged to know her.

Eithne brought something extra to the hospital with her extraordinary good nature, her smile, her enthusiasm and her endless good humour. She threw herself heart and soul into the study of Ophthalmology. She was a delight to work with, an excellent trainee and a compassionate doctor.

Following this tragic accident Eithne's family established a research fund at the Research Foundation in her memory. This fund helps to support the vital research work of the Research Foundation into eye disease.

The Eithne Walls fund provides particular support to young doctors at the hospital engaging in research and wishing to travel abroad to present at international meetings. In 2010 we awarded the first Eithne Walls Medal to Sorchá Ní Dhubhghaill who travelled to a major scientific meeting in the USA to present her work, the subject of her PhD thesis "The effects of acute cigarette smoke exposure on retinal pigment epithelial cells (ARPE-19)".

In 2011 the winner was Mei Chuen Tay for her work entitled "Audit of Uveal Melanoma in Royal Victoria Eye & Ear Hospital". Dr Tay was presented with her medal by the Taoiseach Enda Kenny during the opening ceremony of the Conference and Learning Centre of the Royal Victoria Eye and Ear Hospital.

Last year members of the Riverdance cast along with Eithne's family joined together to run the women's mini-marathon, raising €7,500 for the fund. In 2011 a team of 40 runners joined by staff from the hospital participated again raising €7300 for the Research Foundation.

- (Aoife Doyle)



Presentations & Publications

- 1 Systemic low-molecular weight drug delivery to pre-selected neuronal regions**
M.Campbell, M.M. Humphries, A.T.Nguyen, O.L.Gobbo, L.C.S. Tam, M.Suzuki, F.Hanrahan, E.Ozaki, G.J.Farrar, A.S Kiang, P.F.Kenna, P.Humphries. EMBO Mol Med. 2011 Apr;3(4):235-45.
- 2 A Distinctive Phenotype in Autosomal Dominant Retinitis Pigmentosa due to a Gln184Pro Rhodopsin Mutation**
P.F Kenna, V.Collins, P.Humphries, G.J. Farrar and S.Millington-Ward
ARVO 2010, Monday, May 3, 8:30-10.15am; 1378-A391; Poster
- 3 ADRP with Choroidal Involvement associated with Asp477gly Mutation within the Rpe65 Gene**
P.Humphries, P.F.Kenna, L.C.Tam, S.J Browne, L.S.Sullivan, G.Weinstock, S.H.Blanton, G.J Farrar, S.P.Daiger and M.M.Humphries
ARVO 2011, Thursday, May, 5, 8:30-10:15am; 5408-A73; Poster
- 4 Detection of a Dominant-acting Mutation in RPE65 using Whole-genome Linkage Mapping and Whole-exome Sequencing**
L.S. Sullivan, S.J. Browne, M.M. Humphries, P.F.Kenna, G.M. Weinstock, D.C.Koboldt, S.H.Blanton, P.Humphries and S.P. Daiger
ARVO 2011, Thursday, 5, 8:30-10.15am; 5403-A68; Poster
- 5 A Dominant Mutation in RPE65 identified by whole-exome sequencing causes retinitis pigmentosa with choroidal involvement**
S.J Bowne, MM Humphries, L.S Sullivan, P.F. Kenna, et. al. Eur J Hum Genet. 2011 Oct;19(10):1074-81.
- 6 The frequency of genetic polymorphisms in an Irish Age-related Macular Degeneration population**
S.S Ni Dhubhghaill, M.T Cahill, M.Campbell, L.Cassidy, M.M Humphries and P Humphries. Section of Ophthalmology RAMI Dublin November 2010
- 7 The effects of acute cigarette smoke exposure on retinal pigment epithelial cells (ARPE-19)**
S.S Ni Dhubhghaill, M.T Cahill, M.Campbell, L.Cassidy, M.M Humphries and P Humphries. New England Ophthalmological Society, Back Bay Event Centre, Boston Sept 2010
- 8 Cigarette smoking and Age-related Macular Degeneration**
S.S Ni Dhubhghaill, M.T Cahill, M.Campbell, L.Cassidy, M.M Humphries and P Humphries. Royal Victoria Eye & Ear Hospital BST Research Presentation Dublin 2010. Awarded the Eithne Walls memorial medal for Best Research Presentation.
- 9 Alcon/AAO glaucoma competition: Management of Uveitic glaucoma**
Aifric Martin, Royal Victoria Eye & Ear Hospital, Dr Eithne Walls Memorial Medal Presentation, Dublin, presented June 2010

Medical Research Charities Group

The Medical Research Charities Group is a collaboration of medical research and patient support charities similar to the Research Foundation. It is the aim of this organization to support, promote, and fund medical research for improved Health outcomes. The Medical Research Charities Group and the Health Research Board has approved Joint Funding Schemes for financing a number of research studies. Going forward the Research Foundation will be submitting a number of projects for funding in 2012. The Research Foundation is delighted that this scheme will supplement the research work in the diagnosis, treatment and prevention of ocular disease.

PhD Submission

Sorcha Ni Dhubhghaill recently submitted her thesis for her PhD degree in Trinity College Dublin. This work was performed under the supervision of Mr Mark Cahill. Sorcha's research examines the effect of both environmental and genetic risk factors in age-related macular degeneration in a number of different models including a cellular model and an animal model. Sorcha's study also examined genetic and environmental risk factors in a cohort of patients attending the Royal Victoria Eye & Ear Hospital in the development of macular degeneration.



Student Summer Fellowship

Melissa Murphy's report following her €2,000 travelling Fellowship to WILLS Eye Hospital Philadelphia, From July 19th to August 27th 2010.

"I spent 6 weeks working in WILLS Eye Hospital Philadelphia on a project involving the use of triamcinolone acetonide post radiation therapy for choroidal melanoma. I was involved in data collection and consolidation for 170 patients included in a trial monitoring the use of triamcinolone acetonide to decrease macular oedema post plaque radiotherapy for uveal melanoma. This data has been analysed and submitted for publication. I will also present my findings at the Eithne Walls conference in 2012".



How Can You Help?

1. You can send us a donation. Donations in the excess of €250 per annum qualify for tax relief under charity reference number CHY no: 1604. CHY2 cert is enclosed for tax relief purposes. Self-employed donors should retain this form for tax claim purposes; PAYE donors should return CHY2 to the Research Foundation.
2. Remember us in your will.
3. Your company could help sponsor a project or a piece of equipment at our Research Unit.



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Royal Victoria Eye & Ear Hospital Research Foundation

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