



# SFI-HRB-Wellcome Trust Biomedical Research Partnership Information Day

Dublin, 30<sup>th</sup> April 2012

*On Prevention of Blindness: The Ocular  
Genetics Research Programme at Trinity College*

*From Pete Humphries, The Ocular Genetics Unit, Institute of  
Genetics, Trinity College Dublin*

## *The Problem*

*Almost 200 million people are visually handicapped. Many have degenerative retinal disease (retinopathies). Preventive therapies are limited, and in many cases non-existent*

# *Retinitis pigmentosa*

*An hereditary condition – the most prevalent cause of blindness in people of working age in the developed world. Tunnel vision then usually severe visual handicap.*

*Risk factors: almost totally genetic*





***Age-related macular degeneration (AMD).***  
*The most prevalent cause of visual handicap in older people.*

*You lose central vision.*



*Risk factors: age, smoking, diet and genetics.*

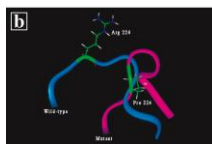
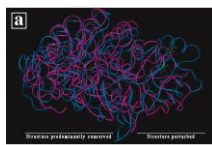
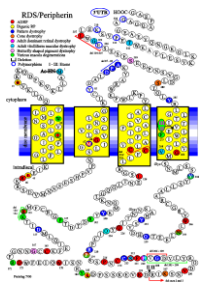
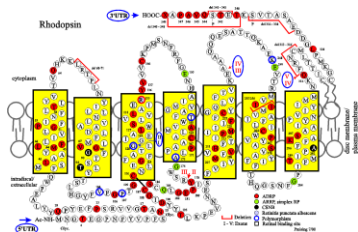
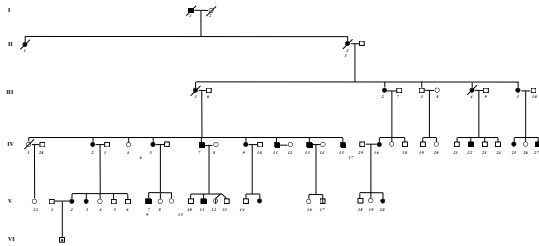
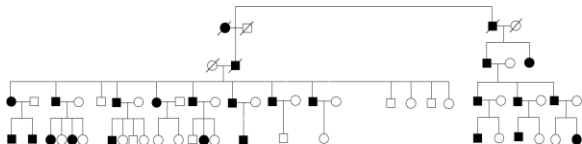
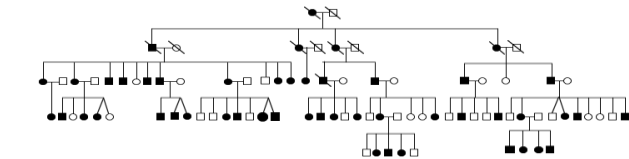


*The key early paper: Shomi Bhattacharya, Alan Wright and colleagues localize the first RP gene in 1984*

*Bhattacharya SS, Wright AF, Clayton JF, Price WH, Phillips CI, McKeown CME, Jay M, Bird A, Pearson PL, Southern EM and Evans HJ, Close genetic linkage between X-linked retinitis pigmentosa and a restriction fragment length polymorphism identified by recombinant DNA probe L1.28, Nature 309 (1984) 253-255.*

*This seminal paper stimulated our own research on the genetics of hereditary retinopathies*

*Our hunt for RP genes was kick-started by FB-Ireland, the US RP Foundation and the HRB in 1985. The Wellcome Trust then funds a series of Project and Programme Grants and provided capital resources for fitting out of the Ocular Genetics Unit laboratories and a state of the art specific pathogen-free animal facility.*



**OCULAR GENETICS TCD**

1989: Rhodopsin, 3q

1991: RDS-peripherin, 6p

1993: IMPDH1, 7q

1997: knockout of Rhodopsin gene, a model of recessive RP



*A slightly mind-boggling problem:*

*Hereditary retinopathies: 202 loci – 161 genes.  
Probably as many more remain to be identified.  
Gene-based medicines can work, but targeting  
up to 400 genes will be a logistical and  
economic nightmare.*

*Are there any alternatives ???*



*2008: Wellcome Trust funds a grant to enable the development of a method of getting drugs safely across the inner blood-retina barrier.*

Inner retinal microvasculature

*Endothelial cells lining the inner retinal vessels are sealed by 'tight junctions' comprising over 30 proteins – the inner blood retina barrier.*

*98% of systemically administrable low molecular weight potentially therapeutic drugs can not cross this barrier or do so only with limited efficiency*

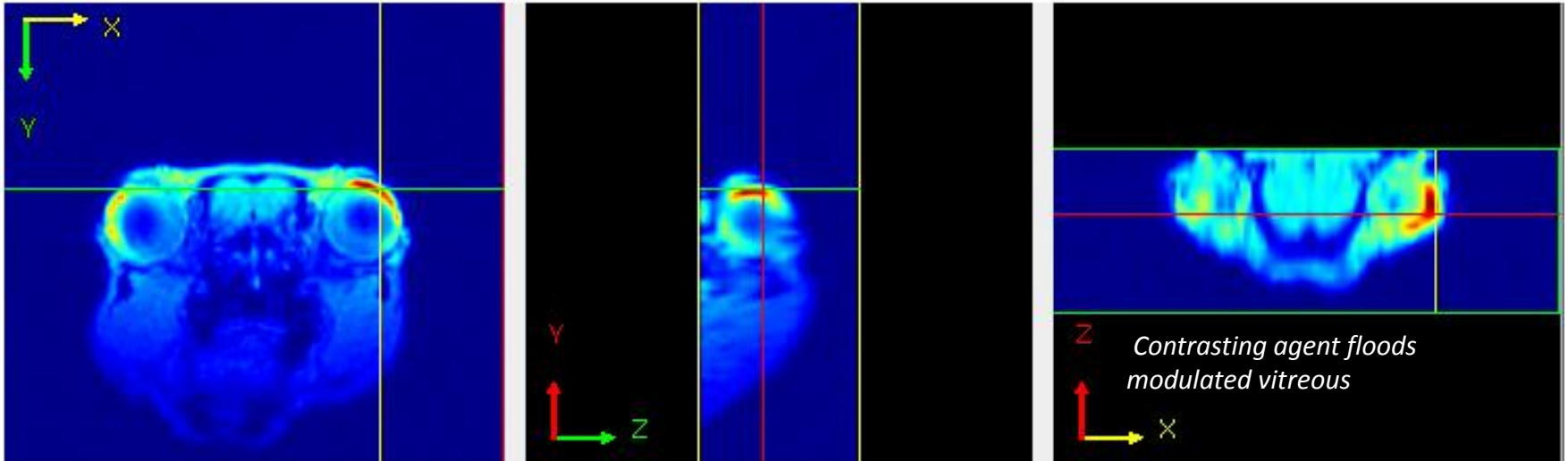
*It turned out that the same technology was highly efficient as a method of removing fluid from the brain (neuronal edema)*



# *Neuronal Barrier Modulation: Systemically administered drugs can now safely flood the retina, exclusive of the brain (or vice-versa)*

*The animal's head is toward you: right eye modulated*

*A genetically-driven virally-mediated barrier modulation system is introduced into the retina and remains dormant until activated by a harmless antibiotic. During the activated phase, the retina is permeable to systemically administered low molecular weight drugs up to 1kD. A given neuroprotective drug can be used to target disease pathologies common to multiple genetic sub-types of disease*



# Translation to clinic



## An experimental platform for systemic drug delivery to the retina

Matthew Campbell<sup>1\*</sup>, Anh T. H. Nguyen<sup>2</sup>, Anna-Sophia Kiang<sup>3</sup>, Lawrence C. S. Tam<sup>2</sup>, Oliviero L. Gobbo<sup>2</sup>, Christian Kerskens<sup>2</sup>, Siorcha Ni Dhubhghaill<sup>2</sup>, Marian M. Humphries<sup>3</sup>, G.-Jane Farrar<sup>2</sup>, Paul F. Kenna<sup>2</sup>, and Peter Humphries<sup>3</sup>

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Edited by John E. Dowling, Harvard University, Cambridge, MA, and approved September 2, 2009 (received for review July 29, 2009)

Degenerative retinopathies, including age-related macular degeneration, diabetic retinopathy, and hereditary retinal disorders—major causes of world blindness—are potentially treatable by using low

barriers (6), in part because of the highly evolved “tight junctions” (TJs) formed between adjacent endothelial cells or RPE cells.

TJs are formed at the apical margin of endothelial cells of the

Research Article

RNA-mediated blood–brain and blood–retina barrier modulation

EMBO  
Molecular Medicine

## Systemic low-molecular weight drug delivery to pre-selected neuronal regions

Matthew Campbell<sup>1\*</sup>, Marian M. Humphries<sup>1</sup>, Anh T. H. Nguyen<sup>1</sup>, Oliviero L. Gobbo<sup>2</sup>, Lawrence C. S. Tam<sup>1</sup>, Mayu Suzuki<sup>1</sup>, Finnian Hanrahan<sup>1</sup>, Ema Ozaki<sup>1</sup>, G.-Jane Farrar<sup>1</sup>, Anna-Sophia Kiang<sup>1</sup>, Paul F. Kenna<sup>1</sup>, Peter Humphries<sup>1</sup>

*Neuronal Barrier Modulation: will require detailed safety and toxicology studies in non-human primates as required for regulatory body approval. Such studies have commenced. Target of initial phase 1 trials: treatment of neuronal edema induced by out-of-hospital cardiac arrest and traumatic brain injury. Technology also validated for low molecular weight drug treatment of retinitis pigmentosa and age-related macular degeneration.*

## *Translation to clinic*

### *Wellcome Trust-HRB Dublin Centre for Clinical Research (DCCR)*

*Initial target: Neuronal edema  
induced by out-of-hospital cardiac  
arrest/traumatic brain injury*

*GMP-grade facility essential for compounding  
Cl5siRNA-In vivo-JetPEI medication*





# *DCCR Translation to clinic:*

*Targeting a newly discovered molecular pathology in age-related macular degeneration may pre-emptively stop or slow progression of the 'dry' into the 'wet' (very much more severe) form of disease*

nature  
medicine

[e-publication ahead of print, April 2012]

NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components

Sarah L Doyle<sup>1,6</sup>, Matthew Campbell<sup>2,6</sup>, Ema Ozaki<sup>2</sup>, Robert G Salomon<sup>3</sup>, Andres Mori<sup>1</sup>, Paul F Kenna<sup>2,4</sup>, Gwyneth Jane Farrar<sup>2</sup>, Anna-Sophia Kiang<sup>2</sup>, Marian M Humphries<sup>2</sup>, Ed C Lavelle<sup>1</sup>, Luke A J O'Neill<sup>1</sup>, Joe G Hollyfield<sup>5</sup> & Peter Humphries<sup>2</sup>





*The Ocular Genetics Unit at Trinity College currently receives the generous support of Science Foundation Ireland (SFI), the Health Research Board of Ireland, Fighting Blindness Ireland, Enterprise Ireland and the American Health Assistance Foundation (AHAF). Development of Neuronal Barrier Modulation technologies for treatment of visual dysfunction following traumatic brain injury is being supported by the US Department of Defense (TATRC).*