Institution: King's College London

Unit of Assessment: UoA5

Title of case study: Retinal Rejuvenation Therapy.

1. Summary of the impact

Bruch's membrane is a structure in the retina responsible for "waste disposal." Scientists at KCL have provided evidence that matrix metalloproteinase enzymes clear debris from the membrane and that a loss of this activity contributes to a build-up of debris that causes a decline in visual function with normal aging or a more rapid decline in individuals with retinal disease. This has resulted in the development of a highly innovative Retinal Rejuvenation Therapy based on the use of pain-free nanosecond laser pulses to the eye that stimulate a "cleansing" response to improve nutrient supply across, and waste removal from, Bruch's membrane. Clinical studies suggest that this novel treatment has the potential to significantly improve the quality of life of people suffering from age-related macular degeneration and diabetic retinopathy, diseases that cause vision impairment and blindness in millions of people worldwide.

2. Underpinning research

The light sensing and signalling processes of the human retina require a high level of support in terms of energy supply and waste removal to ensure optimal functionality. A monolayer of epithelial cells – the retinal pigmented epithelium (RPE) – separates the light sensing and signalling processes from the blood supply of the choroid and controls many bi-directional support functions. The RPE cells are attached to a basement membrane – Bruch's membrane – a thin extra-cellular matrix of collagen layers that acts as a semi-permeable barrier between the RPE and choroid blood vessels. The work of Prof John Marshall (1991-2009, Frost Professor of Ophthalmology at the Rayne Institute, Head of the Academic Department of Ophthalmology) and King's College London (KCL) colleagues including Dr Ali Hussain (research fellow with Marshall during this period) has shown that degradation of the transport functions of Bruch's membrane is a major contributor to the decline in visual function with normal aging or a more rapid decline due to diseases such as age-related macular degeneration (AMD).

A healthy Bruch's membrane ensures good nutrient supply to the light sensing photoreceptor cells and, as importantly, the efficient removal of lipid-based debris generated by normal turnover and renewal of the outer segment of the rod cell. KCL researchers extensively characterised age-related decline in the hydrodynamic properties of Bruch's membrane in the human eye (Starita C, et al. 1996). By investigating the diffusional transport of amino acids over mounted human Bruch's membranes they were able to show a significant linear decline with donor age (Hussain AA, et al. 2002). They have also shown how these hydrodynamic properties are correlated with increased lipid accumulation. In a study of Batten disease, where deposition of lipofuscin-like material derived from photoreceptor outer segments is thought to exacerbate degenerative changes in Bruch's membrane, KCL researchers found the maximal capacity for fluid transport was halved for every 17 years of life (Starita C, et al. 1995).

Researchers at KCL have provided evidence that matrix metalloproteinase (MMP) enzymes clear debris from Bruch's membrane and that a loss of this activity contributes to a build-up of debris, leading to a decline in visual function with normal aging or a more rapid decline in individuals with retinal disease. The group characterised the nature of the MMPs expressed by human RPE cells and provided evidence that two of these, MPP-2 and MMP-9, are essential for extracellular remodelling and debris clearance in Bruch's membrane. For instance, using human MMP-2 and -9 expressing RPE primary or cell-line cultures added to a mounted Bruch's membrane, they showed that these MMPs can significantly increase the hydraulic connectivity of Bruch's membrane. They concluded that this "suggests a mechanism that may allow debris removal" (Ahir A, et al. 2002).

KCL researchers have also demonstrated that increasing levels of inactive MMPs and scarcity of active MMPs correlate with aging and proposed this to account for impaired extracellular degradation in both normal aging and macular degeneration (Guo L, et al. 1999). More detailed molecular studies provided evidence that as we age, MMP-2 and -9 are sequestered into high molecular weight complexes composed of inactive enzyme and this is likely to contribute to

reduced matrix degradation and turnover of Bruch's membrane in both normal aging and age-related macular degeneration (Hussain AA, et al. 2010).

This underpinning work led KCL researchers to collaborate with colleagues at the South Australian Institute of Ophthalmology to develop and test a method of retinal regeneration that improves retinal function by reversal of the degradation of the transport properties of Bruch's membrane. The method involves irradiation through the cornea of the eye to the RPE by a laser pulse or sequence of laser pulses. Applied radiant exposure triggers cellular responses that improve the hydraulic conductivity of Bruch's membrane without causing irreversible damage to adjacent retinal structures and layers. This work is described in two patents filed in 2007/8 and published in 2009/10 (see Impact section).

3. References to the research

Ahir A, Guo L, Hussain AA, Marshall J.Expression of metalloproteinases from human retinal pigment epithelial cells and their effects on the hydraulic conductivity of Bruch's membrane. Invest Ophthalmol Vis Sci 2002;43(2):458-65. http://www.iovs.org/content/43/2/458.long (29 Scopus citations)

Guo L, Hussain AA, Limb GA, Marshall J. Age-dependent variation in metalloproteinase activity of isolated human Bruch's membrane and choroid. Invest Ophthalmol Vis Sci 1999;40(11):2676-82. Link: http://www.iovs.org/content/40/11/2676.long (55 Scopus citations)

Hussain AA, Rowe L, Marshall J.Age-related alterations in the diffusional transport of amino acids across the human Bruch's-choroid complex. J Opt Soc Am A Opt Image Sci Vis 2002;19(1):166-72. Doi: http://dx.doi.org/10.1364/JOSAA.19.000166 (40 Scopus citations)

Hussain AA, Lee Y, Marshall J. High molecular-weight gelatinase species of human Bruch's membrane: compositional analyses and age-related changes. Invest Ophthalmol Vis Sci 2010;51(5):2363-71. Doi: 10.1167/iovs.09-4259 (2 Scopus citations)

Starita C, Hussain AA, Marshall J.Decreasing hydraulic conductivity of Bruch's membrane: relevance to photoreceptor survival and lipofuscinoses. Am J Med Genet 1995;57(2):235-7. Doi: 10.1002/ajmg.1320570224 (17 Scopus citations)

Starita C, Hussain AA, Pagliarini S, Marshall J. Hydrodynamics of ageing Bruch's membrane: implications for macular disease. Exp Eye Res 1996;62(5):565-72. Doi: http://dx.doi.org/10.1006/exer.1996.0066 (89 Scopus citations)

4. Details of the impact

Research from King's College London (KCL) has highlighted the important role that Bruch's membrane plays in maintaining homeostasis in both normal and diseased eyes. Based on this underpinning research, Prof Marshall entered into an agreement with the Australian-based company Ellex R&D Pty Ltd to develop a highly novel and innovative treatment for retinal disease. This company has a background in designing, manufacturing and marketing lasers and diagnostic ultrasound systems used by ophthalmologists to diagnose and treat eye disease. They have subsidiaries in the United States, Japan, Germany and Australia and a network of distribution partners in more than 100 countries (1a).

The breakthrough with regard to retinal disease was based on the hypothesis developed by KCL and colleagues at the South Australian Institute of Ophthalmology that extremely short pulses of nanosecond laser energy to the retinal pigment epithelium (RPE) would stimulate the releases of enzymes that are usually in place to digest accumulated waste products within Bruch's membrane. This would improve the energy supply to, and waste removal from, the retinal photoreceptors, thus promoting their health and preventing degeneration. As described in two patents filed in 2007/8 and published in 2009/10, which together cite the majority of the KCL-led references discussed above, this sequence of laser pulses improves the hydraulic conductivity of Bruch's membrane without causing irreversible damage to adjacent retinal structures and layers (2b,c).

This procedure is now known as Ellex Retinal Rejuvenation Therapy or Ellex 2RT™. It was proposed that it could halt, or even reverse, the natural age-related decline in the hydrodynamic properties of Bruch's membrane that limit vision impairment in normal aging and in disease states such as Age-Related Macular Degeneration (AMD) and diabetic neuropathy. AMD, which causes irreversible central vision loss, is the leading cause of blindness in those over 50. It affects millions of people worldwide and costs hundreds of millions of pounds in direct health-care costs. The more aggressive 'wet' form can be treated with highly invasive, very expensive, intraocular injections of anti-VEGF molecules that aim to stop growth of abnormal blood vessels. However, as such treatment is only approved for advanced or end-stage disease it only addresses disease complications, not formation. Diabetic retinopathy, caused by blood vessel changes that result in bleeding in the eye or fluid leak, can cause vision impairment and blindness. Laser based thermal retinal photocoagulation is the standard treatment, but the "trade-off" for the prevention of blindness is that this often painful treatment can cause irreversible collateral thermal damage.

Marshall and his team have led on extensive laboratory investigations to establish the therapeutic effect and safety profile of Ellex 2RT™ and to determine its mechanism of action. Research conducted at St Thomas' Hospital, London (a King's Health partner and part of KCL) and the South Australian Institute of Ophthalmology demonstrated that Ellex 2RT™ does indeed influence the transport properties of Bruch's membrane, most probably via an MMP dependent mechanism (1b, c). Ellex has also undertaken a series of randomised control trials to validate the safety and efficacy of Ellex 2RT™. These suggest that this novel treatment has the potential to significantly improve the quality of life of people suffering from AMD and diabetic retinopathy. For instance, in 2008, Prof Marshal carried out a study of 17 patients (28 eyes) with diabetic macula oedema at St Thomas' Hospital treated with Ellex 2RT™. At 6-month follow-up they demonstrated signs of an improvement in retinal function and a partial reversal of disease progression. In 71% of patients there was an improvement in vision of at least one line, and sometimes two or more lines of visual acuity, changes significantly different from baseline. They also showed a reduction in central macular thickness (an occurrence associated with retinal disease) of more than 5% in 46% of patients (3a, b). In 2010, results of a clinical trial of 48 patients with diabetic retinopathy treated at the Royal Adelaide Hospital, Australia found that at 6-months follow-up, Ellex 2RT™ treatment produced similar reductions in macular oedema as conventional retinal photocoagulation, while using approximately 500 times less laser energy and with no collateral damage. In 2011, interim results of 24 patients with bilateral high-risk early AMD treated by a team at the Victorian Eye and Ear Hospital in Australia show that by 12 months, central visual function improved in 64% of treated eyes, predominantly in the regions of greatest dysfunction that have the highest likelihood of progressing to wet AMD. Retinal imaging confirmed that there was no evidence of laser damage to photoreceptor cells. In many cases the yellow deposits known as drusen, which are present in the retinal tissue of people with AMD, were eliminated (3a).

The demonstrated safety and efficacy of retinal rejuvenation therapy, along with the non-invasive, pain-free nature of the procedure, has given ophthalmologists the potential to treat a wide range of retinal diseases much earlier, halting disease progression and preserving functional vision before irreversible physical damage and vision loss occurs. These positive results have led to Ellex securing FDA approval for 2RT in the treatment of 'clinically significant macular edema' in July 2013 (4). Ellex 2RT™ has featured in news articles, such as a TV report from ABC News Australia in 2010 (5a) and patient-focused websites such as Diabetic Retinopathy.org (5b). Prof Marshall was also featured in the trade-focused magazine Retinal Physician in 2008 following the initial results of the KCL-led trial (5c).

5. Sources to corroborate the impact

1. Ellex R&D Pty Ltd
   a) Website: http://ellex.com/corp
   b) Retinal Rejuvenation Therapy: http://ellex.com/corp/products/retinal-rejuvenation-therapy/2RT
   c) Ellex Media Kit (pgs 11-13): http://www.ellex.com/assets/files/2rt/Ellex2RT_mediakit_iss3.pdf

2. Patents
   a) Retinal Regeneration. US2010049173 (A1). Publication date: 5.Aug.2009. Inventors: Hussain A, Marshall J, Plunkett M. Applicant: Ellex R&D Pty Ltd: http://www.google.com/patents/US20100049173?cl=en
   b) Retinal Rejuvenation laser. US2010152716 (A1). Publication date: 17.Jun.2010. Inventors: Plunkett M, Previn V. Applicant: Ellex R&D Pty Ltd: https://www.google.com/patents/US20100152716?dq=US2010152716+(A1)&ei=D4QtUrKLJMKrhQfTg4CACw

3. Clinical Study Results
   a) Clinical Abstracts: http://www.ellex.de/fileadmin/user_upload/pdf/2rt/Ellex2RT_2011-clinical-abstracts.pdf
   b) Pelosini L, Hamilton R, Mohamed M, Hamilton AM, Marshall J. Retina rejuvenation therapy for diabetic macular edema: a pilot study. Retina 2013;33(3):548-58. Doi: 10.1097/IAE.0b013e3182670fea.

4. FDA approval for Ellex 2RT™: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K122202.pdf

5. Media Reports
   a) ABC News Australia report: http://www.youtube.com/watch?v=67xkfgZQ2o8
   b) Diabetic Retinopathy.org. Pain-Free Laser Therapy Given European Regulatory Approval. 18.7.2012: http://www.diabetic-retinopathy.org/2012/07/pain-free-laser-therapy-given-european.html
   c) Retinal Physician. Retinal Regeneration Study Shows Encouraging Early Results. Published 1.1.2008: http://www.retinalphysician.com/articleviewer.aspx?articleid=101334