RP Fighting Blindness Gene Therapy Centre

March 2017

Summary of the project

Set up in 2011, the RP Fighting Blindness Gene Team Appeal has raised £750,000 over five years to build a centre of excellence for the development of gene therapies for the treatment of inherited retinal dystrophies. The Centre is led by Professors Robin Ali, James Bainbridge and Michel Michaelides at the UCL Institute of Ophthalmology and Moorfields Eye Hospital. The appeal followed on from the team's success in 2007 when we began the world's first clinical trial to assess the safety and potential benefits of gene therapy for Leber congenital amaurosis type 2 (LCA2), caused by mutations in the gene RPE65. The generous support of Gene Team donors has allowed the team to complete their first gene therapy study and to retain experienced staff so that they could develop a range of other gene therapies. Two of these new gene therapies are now in early phase clinical trials; a third trial will start in June/July 2017 with other trials to follow.

The aim of the project was to develop clinical trials of gene therapy for various forms of retinal dystrophy, with a focus on those disorders where there is the strongest scientific evidence to support this as a suitable approach to treatment. Gene Team Appeal has allowed us to:

- Expand our team of specialist clinicians and researchers, recruiting and retaining individuals with expertise and experience in conducting clinical trials and in developing and manufacturing gene therapy products. This has enabled us to establish a world-leading international clinical centre for ocular gene therapy.
- Complete our first clinical trial of gene therapy for LCA2, and to plan new clinical trials.
- Leverage substantial additional funding from the Medical Research Council, National Institute for Health Research and other sources to support the development of gene therapies for a broad range of inherited retinal conditions.
- Initiate two new gene therapy trials with additional trials to follow shortly.

Background

Inherited retinal dystrophies are disorders of the eye caused by mutations (mistakes) in one of many different genes encoding the proteins required for normal function of the retina - the light-sensitive tissue at the back of the eye. When the cells of the retina become impaired, this can affect aspects of our vision such as sensitivity to light or daylight or colour vision. In many inherited retinal conditions, impairment can become so severe that the cells die. When many retinal cells die, vision is reduced further and in some cases, may be lost completely. Collectively, inherited retinal conditions affect around 1 in every 4,000 people and are a common cause of slight loss among children and the leading cause of certified blindness among working-age adults in the UK. Apart from the Argos retinal prosthetic that restores very basic function in patients with advanced RP, there are no other licensed treatments for any form of inherited retinal dystrophy.

Over the past 25 years, we have been at the international forefront of developing gene therapy for the treatment of inherited retinal dystrophies and have developed the methods to deliver genes efficiently to the retina and demonstrated effective rescue of many different animal models of retinal dystrophy. The technology involves engineering a virus to make it harmless and able to carry a normal copy of the damaged gene. The modified virus is called a gene therapy vector and it is injected into the eye where it delivers the new gene to cells in the retina, thereby restoring the cell's ability to make the normal protein.

The challenge now is to optimise the technology for the treatment of patients rather than animals and to develop a platform that can be used to generate effective gene therapies for people. It is most likely that each type of retinal dystrophy will require its own separate gene therapy to be developed and we, therefore, need to develop a centre of excellence that can develop licenced therapies for a range of conditions.

Support for the RP Fighting Blindness Gene Therapy Centre

Gene Team appeal has provided funding to support seven members of our research team:

- Dr Koji Nishiguchi and Dr Venki Sundaram; specialist ophthalmologists with clinical trials experience who helped conduct our RPE65 clinical trial and design subsequent trials.
- Dr Susanne Barker and Dr Mark Basche; researchers with experience of developing and safety testing of gene therapy vectors.
- Ms Rand Al-Nackkash, Ms Ryea Maswood and Ms Areta Michacz; research technicians with training in the manufacture and purification of gene therapy vectors.

Main clinical achievements:

RPE65 gene therapy trial for LCA2:

- In 2014, we completed our world-first clinical trial of RPE65 gene therapy to treat LCA2 and published the results in the prestigious New England Journal of Medicine (Bainbridge *et al*. 2015).
- Twelve people (6 to 23 years of age) received RPE65 gene therapy and were monitored over three years. Five of the trial participants experienced an increased light sensitivity of the retina that translated to an improved ability to navigate in dim light in the first 6 to 12 months following treatment, which then declined slowly over the three years. For most participants' their vision remained unchanged and there was no evidence of major long-term side effects.
- This trial has shown that gene therapy is safe and that some people with retinal dystrophy can experience improvements in their vision. These results are consistent with those of other research groups conducting similar trials. We have now developed a new, more potent gene therapy vector (Georgiardis et al. 2016) that produces substantially more RPE65 protein and might provide a more effective therapy for patients.
- Based on the success of our first trial, we secured funding from the Medical Research Council to conduct a clinical trial of our new optimised RPE65 vector.
- We have manufactured the new clinical grade vector and tested its safety. The clinical trial started in May 2016 and to date, six participants have received the new vector. We expect to complete this trial in the next 12 months.

CNGB3 gene therapy for achromatopsia:

- Achromatopsia affects about 1 in 60,000 people making it about three times more common than LCA. People with achromatopsia experience decreased vision, are colour-blind and extremely sensitive to light. Around half of all cases of achromatopsia in the world are caused by mutations in the CNGB3 gene. We have previously demonstrated very effective rescue of mouse models of the condition using gene therapy.
- In 2013, we secured funding from the Medical Research Council to conduct a clinical trial of a CNGB3 gene therapy.
- We have manufactured a clinical grade vector, tested its safety and designed the clinical trial.
- In 2013-2015, we secured funding from The Wellcome Trust and NIH to set up Europe's first adaptive optics (AO) System – an advanced imaging technology which allows us to examine the health of the individual's cells of the retina. Using the AO system, we have been able to establish that achromatopsia is much slower progressing than LCA, and so we believe that we will be able to treat a greater range of

age of people with achromatopsia (Aboshiha et al. 2014). We have also learned that while two people with achromatopsia may appear to have similar levels of visual decline, the health of their retinal cells may vary greatly. For future clinical trials, the overall health of the retinal cells will be important criteria for enrolment (Sundaram et al. 2014).
- Approval for a clinical trial of CNGB3 gene therapy was obtained in the last quarter of 2016 and the first participant received the vector in February 2017. We expect to complete this trial in the next 24 months.

RPGR gene therapy for X-linked RP3
- X-linked RP3 is one of the most common forms of retinitis pigmentosa. It is very rare in women but affects about 1 in 15,000 men. Although a very challenging gene defect to treat, after 10 years of optimisation, we have now finalised the development of a gene therapy vector and have demonstrated that mice with X-linked RP3 respond well to gene therapy and show long term preservation of the retina.
- We have also carried out extensive studies of patients with X-linked RP3 to determine the most practical trial outcome measures to assess the effectiveness of this gene therapy.
- With financial support from MeiraGTx Ltd, we have manufactured a clinical grade vector, tested its safety and designed the clinical trial.
- We are awaiting approval from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) to begin the trial and anticipate starting the trial in June/July 2017. The trial is being be funded by MeiraGTx.

AIPL1 gene therapy for LCA4:
- We have developed a gene therapy for LCA4, a particularly rare and rapidly progressing form of inherited retinal dystrophy, caused by mutations in the AIPL1 gene.
- Children with LCA4 lose their sight within the first few years after birth. Previously, it was thought that sight-loss occurred too quickly to be able to develop an effective treatment. However, we have shown in mice models of LCA4 that we can restore vision and improve the health of the retina with gene therapy.
- We have carried out a study to identify the group of patients with LCA4 who would be the most promising candidates for treatment with gene therapy. We have now assessed 42 patients (0.5 to 43 years of age) with this condition using our AO system. Results indicate that at a very young age, children with AIPL1 mutations still have some intact retinal tissue that may respond to treatment with gene therapy (Aboshiha et al. 2015).
- During 2015/2016, we worked with Moorfields Eye Charity to raise funds to support the manufacture and testing of a clinical grade AILP1 gene therapy vector. This work is also being supported by MeiraGTx and will begin in March 2017. It expected to take approximately eight months to complete after which we will be in a position to provide, under a Hospitals Exemption Licence, an experimental therapy at Moorfields Eye Hospital to children with LCA4.

Future research plans

A new pipeline of gene therapies to be developed:

- The RP Fighting Blindness Centre will continue to develop new gene therapies for inherited retinal dystrophies and will seek funding from a range of public and private sources to support pre-clinical research and early phase clinical trials.
- In recognition that we are likely only to be able to use government and charitable funding to develop a fraction of our pipeline part way through to licensed products, we developed a commercial strategy to attract private investment. Our aim is to continue to advance the best underpinning science and to

license gene therapy products to a commercial entity that can advance therapies beyond the first-in-man studies that we can carry out with support from MRC and charities, through to licensure. One of our challenges is that gene therapy is a new technology and in general, industry lacks appropriate expertise to take it forward in an effective way. To address this, in 2015, we established a university spin-out company, Athena Vision Ltd (now a subsidiary of Meira GTx Ltd) which will have the option to licence some of the gene therapy products we are developing.

- MeiraGTx, has attracted substantial private investment and is building a major gene therapy manufacturing centre and regulatory capacity in London. This has provided us with additional support for our gene therapy programme and the capability to progress therapies beyond early phase trials through to confirmatory studies and to licenced products.
- Building on our experience and expertise, we have now identified a range of other inherited retinal conditions we believe will respond well to gene therapy and are now developing therapies for many of these including: Usher syndrome, Stargardt disease, LCA Type 13, Batten disease and Bardet-Biedl syndrome.

List of key scientific publications arising from the award

1. Photoreceptor rescue by an abbreviated human RPGR gene in a murine model of X-linked retinitis pigmentosa. Pawlyk BS, Bulgakov OV, Sun X, Adamian M, Shu X, Smith AJ, Berson EL, Ali RR, Khani S, Wright AF, Sandberg MA, Li T. ***Gene Ther.*** 2016 Feb **23**(2):196-204.

2. Development of an optimized AAV2/5 gene therapy vector for Leber congenital amaurosis owing to defects in RPE65. Georgiadis A, Duran Y, Ribeiro J, Abelleira-Hervas L, Robbie SJ, Sünkel-Laing B, Fourali S, Gonzalez-Cordero A, Cristante E, Michaelides M, Bainbridge JW, Smith AJ, Ali RR. ***Gene Ther.*** 2016 **23**(12):857-862.

3. Reliability and Repeatability of Cone Density Measurements in Patients with Congenital Achromatopsia. Abozaid MA, Langlo CS, Dubis AM, Michaelides M, Tarima S, Carroll J. ***Adv Exp Med Biol.*** 2016 **854**:277-83.

4. Gene therapy restores vision in rd1 mice after removal of a confounding mutation in Gpr179. Nishiguchi KM, Carvalho LS, Rizzi M, Powell K, Holthaus SM, Azam SA, Duran Y, Ribeiro J, Luhmann UF, Bainbridge JW, Smith AJ, Ali RR. ***Nat Commun.*** 2015 **23**:6:6006.

5. Investigation of Aberrant Splicing Induced by AIPL1 Variations as a Cause of Leber Congenital Amaurosis. Bellingham J, Davidson AE, Aboshiha J, Simonelli F, Bainbridge JW, Michaelides M, van der Spuy J. ***Invest Ophthalmol Vis Sci.*** 2015 **56**(13):7784-7793.

6. Spectral sensitivity measurements reveal partial success in restoring missing rod function with gene therapy. Ripamonti C, Henning GB, Robbie SJ, Sundaram V, van den Born LI, Casteels I, de Ravel TJ, Moore AT, Smith AJ, Bainbridge JW, Ali RR, Stockman ***A. J Vis.*** 2015 **15**(15):20.

7. Retinal Development in Infants and Young Children with Achromatopsia. Lee H, Purohit R, Sheth V, McLean RJ, Kohl S, Leroy BP, Sundaram V, Michaelides M, Proudlock FA, Gottlob I. ***Ophthalmology.*** 2015 **S0161-6420**(15):00317-6.

8. Long-term effect of gene therapy on Leber's congenital amaurosis. Bainbridge JW, Mehat MS, Sundaram V, Robbie SJ, Barker SE, Ripamonti C, Georgiadis A, Mowat FM, Beattie SG, Gardner PJ, Feathers KL, Luong VA, Yzer S, Balaggan K, Viswanathan A, de Ravel TJ, Casteels I, Holder GE, Tyler N,

Fitzke FW, Weleber RG, Nardini M, Moore AT, Thompson DA, Petersen-Jones SM, Michaelides M, van den Born LI, Stockman A, Smith AJ, Rubin G, Ali RR. ***N Engl J Med.*** 2015 **372**(20):1887-97.

9. Preserved outer retina in AIPL1 Leber's congenital amaurosis: implications for gene therapy. Aboshiha J, Dubis AM, van der Spuy J, Nishiguchi KM, Cheeseman EW, Ayuso C, Ehrenberg M, Simonelli F, Bainbridge JW, Michaelides M. ***Ophthalmology***. 2015 **122**(4):862-4.

10. Advancing therapeutic strategies for inherited retinal degeneration: recommendations from the Monaciano Symposium. Thompson DA, Ali RR, Banin E, Branham KE, Flannery JG, Gamm DM, Hauswirth WW, Heckenlively JR, Iannaccone A, Jayasundera KT, Khan NW, Molday RS, Pennesi ME, Reh TA, Weleber RG, Zacks DN; Monaciano Consortium. ***Invest Ophthalmol Vis Sci***. 2015 **56**(2):918-31.

11. A prospective longitudinal study of retinal structure and function in achromatopsia. Aboshiha J, Dubis AM, Cowing J, Fahy RT, Sundaram V, Bainbridge JW, Ali RR, Dubra A, Nardini M, Webster AR, Moore AT, Rubin G, Carroll J, Michaelides M. ***Invest Ophthalmol Vis Sci.*** 2014 **55**(9):5733-43.

12. Dark-adaptation functions in molecularly confirmed achromatopsia and the implications for assessment in retinal therapy trials. Aboshiha J, Luong V, Cowing J, Dubis AM, Bainbridge JW, Ali RR, Webster AR, Moore AT, Fitzke FW, Michaelides M. ***Invest Ophthalmol Vis Sci***. 2014 **55**(10):6340-9.

13. Genotype-dependent variability in residual cone structure in achromatopsia: toward developing metrics for assessing cone health. Dubis AM, Cooper RF, Aboshiha J, Langlo CS, Sundaram V, Liu B, Collison F, Fishman GA, Moore AT, Webster AR, Dubra A, Carroll J, Michaelides M. ***Invest Ophthalmol Vis Sci.*** 2014 **55**(11):7303-11.

14. Severe retinal degeneration in women with a c.2543del mutation in ORF15 of the RPGR gene. Kousal B, Skalicka P, Valesova L, Fletcher T, Hart-Holden N, O'Grady A, Chakarova CF, Michaelides M, Hardcastle AJ, Liskova P. ***Mol Vis***. 2014 **20**:1307-17.

15. Nature of the visual loss in observers with Leber's congenital amaurosis caused by specific mutations in RPE65. Ripamonti C, Henning GB, Ali RR, Bainbridge JW, Robbie SJ, Sundaram V, Luong VA, van den Born LI, Casteels I, de Ravel TJ, Moore AT, Stockman A. ***Invest Ophthalmol Vis Sci***. 2014 **55**(10):6817-28.

16. Retinal structure and function in achromatopsia: implications for gene therapy. Sundaram V, Wilde C, Aboshiha J, Cowing J, Han C, Langlo CS, Chana R, Davidson AE, Sergouniotis PI, Bainbridge JW, Ali RR, Dubra A, Rubin G, Webster AR, Moore AT, Nardini M, Carroll J, Michaelides M. ***Ophthalmology*** 2014 **121**(1): 234-45.

17. Successful gene therapy in older RPE65-deficient dogs following subretinal injection of an adeno-associated vector expressing RPE65. MJ Annear, JT Bartoe, PG Curran, AJ Smith, JW Bainbridge, RR Ali, SM Petersen-Jones. ***Hum Gene Ther.*** 2013 **24**(10):883-93.

18. RPE65 gene therapy slows cone loss in Rpe65-deficient dogs. Mowat FM, Breuwer AR, Bartoe JT, Annear MJ, Zhang Z, Smith AJ, Bainbridge JW, Petersen-Jones SM, Ali RR. ***Gene Ther***. 2013 **20**(5):545-55.

19. Absence of ocular malignant transformation after sub-retinal delivery of rAAV2/2 or integrating lentiviral vectors in p53-deficient mice. Balaggan KS, Duran Y, Georgiadis A, Thaung C, Barker SE, Buch PK, MacNeil A, Robbie S, Bainbridge JW, Smith AJ, Ali RR. ***Gene Ther.*** 2012 **19**(2):182-8.

20. Leber congenital amaurosis associated with AIPL1: challenges in ascribing disease causation, clinical findings, and implications for gene therapy. Tan MH, Mackay DS, Cowing J, Tran HV, Smith AJ, Wright GA, Dev-Borman A, Henderson RH, Moradi P, Russell-Eggitt I, MacLaren RE, Robson AG, Cheetham ME, Thompson DA, Webster AR, Michaelides M, Ali RR, Moore AT. ***PLoS One.*** 2012 **7**(3):e32330.

21. Long-Term Preservation of Cones and Improvement in Visual Function Following Gene Therapy in a Mouse Model of Leber Congenital Amaurosis Caused by Guanylate Cyclase-1 Deficiency Marija Mihelec, Rachael A. Pearson, Scott J. Robbie, Prateek K. Buch, Selina A. Azam, James W.B. Bainbridge, Alexander J. Smith, and Robin R. Ali ***Hum Gene Ther.*** 2011 **22**:1179–1190.

22. Long-term and age-dependent restoration of visual function in a mouse model of CNGB3-associated achromatopsia following gene therapy. Carvalho LS, Xu J, Pearson RA, et al. ***Hum Mol Genet***. 2011 **20**:3161-3175.