Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Development of gene therapies for inherited retinal diseases (IRDs)

Period when the underpinning research was undertaken: 2000 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Robin Ali	Professor of Human Molecular Genetics	1994 - 2020
Prof James Bainbridge	Chair of Retinal Studies	2005 - Present
Prof Michel Michaelides	Professor of Ophthalmology	2004 - Present

Period when the claimed impact occurred: 2015 - 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Research at UCL's Institute of Ophthalmology to develop gene therapies for inherited retinal diseases (IRDs) has led to a 2015 spin-out company Athena Vision Ltd. and partnership with gene therapy company MeiraGTx, creating 85 jobs and generating significant initial investment of GDP20,000,000. MeiraGTx has built a MHRA-registered current Good Manufacturing Practice (cGMP) facility for manufacturing of ocular gene therapies, and has a portfolio of products in clinical trials in Europe and the US for diseases including achromatopsia and retinitis pigmentosa. In 2019, MeiraGTx entered into a broad strategic collaboration with Janssen Pharmaceuticals Inc, worth an initial USD100,000,000 to develop and commercialize its ocular products.

2. Underpinning research

Inherited retinal diseases (IRDs) are collectively the commonest cause of sight impairment affecting children and young adults, with a global prevalence of 1 in 3,000 individuals. Gene defects are responsible for dysfunction and/or degeneration of retinal cells, causing severe impairment of sight from birth or during childhood. Sight impairment has a profound impact on affected individuals' quality of life and independence, with significant financial cost to their families and to society.

UCL's Institute of Ophthalmology has established an extensive programme of retinal gene therapy. In 2000, it demonstrated for the first time that recombinant adeno-associated virus (rAAV) vectors can mediate efficient sustained delivery of genes to the retina, and provided the first robust proof-of-concept for gene therapy of retinal disease, using a rAAV vector to improve photoreceptor cell structure and function in a mouse model of IRD **[R1].** The group went on to build an expanding pipeline of candidate gene therapies for IRDs, publishing evidence of benefit in laboratory models of more than 15 different forms of the condition **[R1-R4].**

In 2007 they launched the world's first clinical trial of gene therapy for IRD, including 15 adults and children (6 to 23 years of age) with an early-onset severe retinal dystrophy caused by defects in the gene encoding RPE65 (retinal pigment epithelium–specific protein 65 kDa). In 2008 they published the early results on the first 3 subjects, showing that the gene therapy improved retinal sensitivity and night vision **[R5]**. In 2015, they published the longer-term results, showing that the benefits lasted at least 3 years for some patients after a single

administration of the product **[R6]**. This work, along with trials for RPE65 gene therapy by two other groups, established a proof-of-principle for retinal gene therapy in humans with IRD and was recognised in 2018 by the award of the Champalimaud Vision Prize (EUR1,000,000) jointly to Robin Ali and James Bainbridge and teams from Florida, Pennsylvania and the NIH. Bethesda.

The group has embarked on an accelerated clinical development programme and begun early phase trials for IRDs under their partnership with MeiraGTx as follows:

- 2016 - LCA2 (RPE65 deficiency): 15 participants, complete, showed benefit and is now supporting proposals for a pivotal trial.
- 2017 - congenital achromatopsia (CNGB3 deficiency): 21 participants, fully recruited and in follow-up.
- 2017 - x-linked retinitis pigmentosa (RPGR deficiency): 27 participants, ongoing, early results showing benefit supporting plans for a pivotal trial.
- 2019 - congenital achromatopsia (CNGA3 deficiency): 7 participants, recruitment ongoing.

In 2017, the group manufactured a clinical grade gene therapy vector for AIPL1 deficiency under a hospital exemption "Specials" licence and in 2019 provided experimental treatment for 4 affected infants (outcome to be determined).

3. References to the research

[R1] Restoration of photoreceptor ultrastructure and function in retinal degeneration slow mice by gene therapy. RR Ali, G Sarra, C Stephens, M de Alwis, JWB Bainbridge, PM Munro, S Fauser, MB Reichel, C Kinnon, DM Hunt, SS Bhattacharya and AJ Thrasher ***Nature Genetics*** 2000; **25** (3): 306-310. doi: 10.1038/77068

[R2] Gene therapy for retinitis pigmentosa and Leber congenital amaurosis caused by defects in AIPL1: effective rescue of mouse models of partial and complete Aipl1 deficiency using AAV2/8 vectors. MH Tan, AJ Smith, B Pawlyk, X Xu, X Liu, JW Bainbridge, M Basche, J McIntosh, HV Tran, A Nathanwi, T Li and RR Ali ***Human Molecular Genetics*** 2009; **18** (12): 2099-114. doi: 10.1093/hmg/ddp133

[R3] Long-term and age-dependent restoration of visual function in a mouse model of CNGB3-associated achromatopsia following gene therapy. LS Carvalho, J Xu, RA Pearson, AJ Smith, JW Bainbridge, LM Morries, SJ Fliesler, XQ Ding and RR Ali. ***Human Molecular Genetics*** 2011; **20** (16): 3161-75. doi: 10.1093/hmg/ddr218

[R4] 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. ***Nature Communications*** 2015; **6** (6006). doi: 10.1038/ncomms7006

[R5] Effect of gene therapy on visual function in Leber Congenital Amaurosis. JWB Bainbridge, AJ Smith, SE Barker, S Robbie, R Henderson, KS Balaggan, A Viswanathan, GE Holder, A Stockman, N Tyler, SS Bhattacharya, AJ Thrasher, FW Fitzke, GS Rubin, AT Moore and RR Ali ***The New England Journal of Medicine*** 2008; **358** (21): 2231. doi: 10.1056/NEJMoa0802268

[R6] 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, Gardner PJ, Feathers KL, Luong VA, Balaggan K,Tyler N, Fitzke FW, Weleber RG, Moore AT, Thompson DA, Petersen-Jones SM, Michaelides M, Smith AJ, Rubin G, Ali RR. ***The New England Journal of Medicine*** 2015; **372**(20):1887-97. doi: 10.1056/NEJMoa1414221

4. Details of the impact

In 2015, UCL supported the formation of biopharmaceutical spin out company Athena Vision Ltd and licences to intellectual property for a pipeline of four programmes of gene therapy for eye disease, with the sole purpose of accelerating the development of new products based

on this body of research. Athena Vision Ltd attracted an initial investment of USD20,000,000 from MeiraGTx to develop and commercialise Athena's ocular gene therapy programme. Athena Vision Ltd. was subsequently acquired by the company in 2016 to complement their gene therapy technology portfolio.

In 2018, MeiraGTx floated on NASDAQ with a market capitalisation of USD425,000,000, raising USD75,000,000 at the close of its initial public offering. In January 2019, the company concluded a licensing deal for its four UCL-led IRD programmes with Janssen Pharmaceuticals Inc. Janssen was drawn to collaborate with MeiraGTx because of their novel gene technology, internal manufacturing capabilities and IRD pipeline, based on UCL's four early-stage trials **[S1]**. These two companies agreed to collaborate in the clinical development of MeiraGTx's leading IRD pipeline, including product candidates for achromatopsia (ACHM, caused by mutations in either CNGB3 or CNGA3) and X-linked retinitis pigmentosa (XLRP). In addition, MeiraGTx and Janssen entered into a research collaboration covering MeiraGTx's pipeline of pre-clinical programs for IRDs, the development of AAV manufacturing technology, and supply agreements. Janssen is funding all clinical development and commercialization costs. The agreement gave MeiraGTx USD100,000,000 in up-front costs, with a further USD390m in milestone payments to come, and stands to benefit from untiered royalty on annual net sales of commercialized products.

Through the continued collaboration between the Institute and MeiraGTx and its partnership with Janssen Pharmaceuticals Inc, the group has been able to accelerate its clinical programme and early phase trials. Impact from these trials so far include improved vision for 15 participants in completed trial testing of an optimised RPE65 vector **[S2, S3].** [TEXT REDACTED FOR PUBLICATION] **[S1, S5].**

To drive these four therapies towards commercialisation and patient delivery, MeiraGTx has brought considerable financial investment into the UK. In London, the company has established a presence in close proximity to UCL's Institute of Ophthalmology, created 150 new jobs to date and established a Good Manufacturing Practice (cGMP) gene therapy production facility that meets MHRA, EMA and FDA regulatory standards to support plans for global commercialisation. This state-of-the-art 29,000-square foot manufacturing facility, completed in 2018, has the flexibility and capacity to produce sufficient product for all of the group's clinical trials and can then scale to commercial capacity**.** More recently further investment was raised on the back of the London facility to extend MeiraGTx's manufacturing capability with the construction of a USD70,000,000 manufacturing complex based in Shannon, Ireland to produce MeiraGTx's gene therapy portfolio **[S5,S6].** [TEXT REDACTED FOR PUBLICATION] **[S1].**

5. Sources to corroborate the impact

[S1] Supporting statement from Janssen Pharmaceuticals Inc.

[S2] ClinicalTrials.gov. Safety Study of RPE65 Gene Therapy to Treat Leber Congenital Amaurosis. Bethesda: U.S. National Library of Medicine; 2000. https://clinicaltrials.gov/ct2/show/NCT00643747

[S3] ClinicalTrials.gov. Clinical Trial of Gene Therapy for the Treatment of Leber Congenital Amaurosis (LCA) (OPTIRPE65). Bethesda: U.S. National Library of Medicine; 2000. https://clinicaltrials.gov/ct2/show/NCT02781480

[S4] ClinicalTrials.gov. Gene Therapy for X-linked Retinitis Pigmentosa (XLRP) Retinitis Pigmentosa GTPase Regulator (RPGR). Bethesda: U.S. National Library of Medicine; 2000. https://clinicaltrials.gov/ct2/show/NCT03252847

[S5] Supporting statement from Chief Development Officer of MeiraGTx

[S6] MeiraGTx website describing manufacturing facilities. https://meiragtx.com/our-strategy/manufacturing/