Institution: University of Oxford

Unit of Assessment: 4 – Psychology, Psychiatry and Neuroscience

Title of case study: Nightstar: Improving vision and creating world's largest retinal gene therapy company

Period when the underpinning research was undertaken: 2009 - 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:
Robert MacLaren	Professor of Ophthalmology	2008-present
Alun Barnard	Postdoctoral Research Scientist	2009-present
Markus Groppe	Academic Clinical Lecturer	2010-2014
Thomas Edwards	Clinical Research Fellow	2014-2017
Kanmin Xue	Academic Clinical Lecturer, Research Fellow	2014-2018, Jan 2020-present
Jasmina Cehajic-Kapetanovic	Clinical Research Fellow	2018-present
Michelle McClements	Postdoctoral Research Scientist	2012-present

Period when the claimed impact occurred: 2014 - December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

At the University of Oxford, Professor Robert MacLaren led the first clinical trials of gene therapy for choroideremia and X-linked retinal pigmentosa, both of which are inherited diseases leading to blindness, following his development of novel gene therapy vectors. This was the first time gene therapy had successfully been able to target the eye's photoreceptor cells and reverse visual field loss in retinitis pigmentosa.

This work led to the formation of a spinout company, Nightstar, in 2014. Licensing of subsequent research at Oxford, extending the approach to other kinds of retinal pigmentosa, created the world's largest retinal gene therapy company and the most comprehensive international gene therapy programme for any genetic disease to date.

Nightstar was listed on NASDAQ in 2017, and in 2019, the company was acquired by the multinational biotechnology company Biogen for USD877,000,000, representing the third most valuable British biotech exit in the last two decades.

2. Underpinning research

Gene therapy for blindness caused by choroideremia

Oxford research in retinal gene therapy initially developed an adeno-associated viral (AAV) vector to treat choroideremia, a rare cause of blindness affecting young men. Professor MacLaren designed the AAV vector and tested it in knockout mice and human cells, in collaboration with Miguel Seabra at Imperial College London. Having verified its effectiveness with the preclinical studies, he led the first-in-man gene therapy clinical trial. The inventiveness of the gene therapy also included developing a new surgical technique to detach the retina safely, in order to administer the gene-carrying viral vector. Both the vector design and surgical method were patented. The initial results of the trial were successful [1], with early improvements in vision sustained over the long term in treated patients [2]. The trial was completed showing a statistically significant improvement in visual acuity in treated eyes compared with controls – the first ocular gene therapy trial to meet this important endpoint [3].

In addition to the trial in Oxford, Professor MacLaren set up academic research collaborations to test the vector in choroideremia patients in Canada (Edmonton), Finland (Helsinki),

Germany (Tübingen) and the USA (Miami), providing these countries with their first ever AAV gene therapy treatments. Subsequently Nightstar led phase III clinical trials using the Oxford vector, by expanding trial sites across the USA. By including the Netherlands, Denmark, France, Brazil and Chile, it became the most global gene therapy trial for any single gene disorder to date.

Gene therapy for X-linked retinitis pigmentosa

X-linked retinitis pigmentosa (RP) is the most prevalent of the severe forms of inherited sight loss in young adults and the most widely recognised cause of RP in children. Although the *RPGR* (retinitis pigmentosa GTPase regulator) cDNA fits into an AAV vector, all the leading gene therapy centres worldwide at the time had failed to make an AAV vector that could express the correct RPGR protein *in vivo*. This is likely to be because compared to other cells, eye photoreceptors have alternate splicing for the *RPGR* gene; the distal part of the retina-specific RPGR splice isoform contains several hundred repetitive sequence repeats, which lead to cloning errors. MacLaren and his team recognised this problem and designed a codon-optimised RPGR sequence that disabled the splice donor site and added cytosine nucleotides in specific locations to overcome these issues. They showed that this codon-optimised RPGR vector was effective in animal models of the disease, representing the first proof of principle that full length RPGR with all functional domains could be delivered to the retina successfully *in vivo* using an AAV [4].

The RPGR vector was patented and the IP licensed to Nightstar. This led to the world's first gene therapy trial for X-linked RP, recruiting the first patient in Oxford in March 2017, with MacLaren as the lead surgeon. The results in the first 18 patients undergoing treatment with the vector showed improvements in visual field at optimal doses and anatomical evidence of regeneration of photoreceptor outer segments as a result of the RPGR gene replacement [6]. The results of this trial have been widely recognised by the international community as representing a key milestone over the 170 years during which RP has been considered to be incurable. The trial represented the first successful targeting of photoreceptor cells and reversal of visual field loss using gene therapy in RP. It is also the only example to date of anatomical reversal of degenerative changes seen in the disease [5].

Gene therapy for Stargardt disease

Stargardt disease is the most common cause of recessively inherited childhood blindness but the relevant ABCA4 coding sequence at 6.7kB is too large to fit into AAV. To overcome this problem, Professor MacLaren and his team devised a 'dual vector' method to split the ABCA4 coding sequence into two overlapping fragments that could be delivered in two separate vectors. The 'plus and minus' strands then recombine through a PCR-like reaction and the overlapping DNA sequence undergo reverse polymerisation into double stranded DNA to yield sustained gene expression. Specifically, MacLaren's team assessed the varying efficacy of different lengths of ABCA4 overlap to show that it was optimal in the 200 base pair range, with minimal expression of incomplete gene fragments [6].

Other retinal gene therapy programmes

Many causes of RP are not suitable for AAV gene replacement, either due to being dominantly inherited, having genes too large for dual vector delivery or even having no genetic diagnosis. MacLaren and his team pursued an alternative neuroprotection strategy and discovered in 2017 that ciliary neurotrophic factor (CNTF) could confer life-long protection of the retina in mice with RP, but only when delivered at the correct dose. The MacLaren team also showed in 2015 that ectopically expressed melanopsin (a light-sensitive retinal protein) could confer light sensitivity to the retina of blind mice with RP, when targeted to specific retinal cells using a modified AAV capsid.

3. References to the research

(all journal articles; authors with University of Oxford affiliation given in bold)

1. **MacLaren RE**, **Groppe M**, **Barnard AR**, Cottriall CL, Tolmachova T, **Seymour L**, Clark KR, During MJ, Cremers FP, Black GC, Lotery AJ, **Downes SM**, Webster AR, Seabra MC. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet* 2014; 383(9923):1129-37. DOI: 10.1016/S0140-6736(13)62117-0
2. **Edwards TL**, **Jolly JK**, **Groppe M**, **Barnard AR**, Cottriall CL, Tolmachova T, Black GC, Webster AR, Lotery AJ, Holder GE, **Xue K**, **Downes SM**, **Simunovic MP**, Seabra MC, **MacLaren RE**. Visual Acuity after Retinal Gene Therapy for Choroideremia. *N Engl J Med*. 2016; 374(20):1996-8. DOI: 10.1056/NEJMc1509501
3. **Xue K**, **Jolly JK**, **Barnard AR**, Rudenko A, **Salvetti AP**, **Patrício MI**, **Edwards TL**, **Groppe M**, **Orlans HO**, Tolmachova T, Black GC, Webster AR, Lotery AJ, Holder GE, **Downes SM**, Seabra MC, **MacLaren RE**. Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia. *Nat Med.* 2018; 24(10):1507-1512. DOI: 10.1038/s41591-018-0185-5
4. **Fischer MD**, **McClements ME**, **Martinez-Fernandez de la Camara C**, **Bellingrath JS**, **Dauletbekov D**, Ramsden SC, **Hickey DG**, **Barnard AR**, **MacLaren RE**. Codon-Optimized RPGR Improves Stability and Efficacy of AAV8 Gene Therapy in Two Mouse Models of X-Linked Retinitis Pigmentosa. *Mol Ther*. 2017; 25(8):1854 - 1865. DOI: 10.1016/j.ymthe.2017.05.005
5. **Cehajic-Kapetanovic J**, **Xue K**, **Martinez-Fernandez de la Camara C**, **Nanda A**, **Davies A**, **Wood LJ**, **Salvetti AP**, **Fischer MD**, **Aylward JW**, **Barnard AR**, **Jolly JK**, Luo E, Lujan BJ, Ong T, Girach A, Black GCM, Gregori NZ, Davis JL, Rosa PR, Lotery AJ, Lam BL, Stanga PE, **MacLaren RE**. Initial results from a first-in-human gene therapy trial on X-linked retinitis pigmentosa caused by mutations in *RPGR*. *Nat Med*. 2020; 26(3):354-359. DOI: 10.1038/s41591-020-0763-1
6. **McClements ME**, **Barnard AR**, Singh MS, **Charbel Issa P**, Jiang Z, Radu RA, **MacLaren RE**. An AAV Dual Vector Strategy Ameliorates the Stargardt Phenotype in Adult Abca4-/- Mice. *Hum Gene Ther.* 2019;30(5):590-600. DOI: 10.1089/hum.2018.156

Funding to R. MacLaren (principal investigator) included:
Wellcome Trust 'Gene therapy for blindness caused by choroideremia: a Phase I clinical trial', total GBP1,096,295 (091984/Z/10/Z, /A and /B, 2011-2015) from the joint Wellcome / NIHR Health Innovation Challenge Fund;
NIHR 'Gene therapy for choroideremia - a Phase II clinical trial', GBP1,566,459 (12/66/35, 2015-2022);
Medical Research Council (MRC), 'Developing gene therapy to treat blindness caused by Stargardt Disease', GBP514,963 (MR/K007629/1, 2013-2017).

4. Details of the impact

Saving eyesight in patients with degenerative retinal disorders

> *For over 30 years I've been living with the awful inevitability that I was going blind but now, as a result of the operation, there's a real prospect that I will continue to be able to see and that's just absolutely fantastic.'* Trial participant [A]

The advance in gene therapy technology developed at the University of Oxford is transforming the treatment of two degenerative retinal disorders. *Choroideremia* is a degenerative retinal disorder affecting one in every 50,000 people. In Phase 1/2 [1, 2], the Oxford researchers conducted a retinal gene therapy clinical trial in 14 patients with choroideremia, treating one eye in each patient (ClinicalTrials.gov reference NCT01461213, 2011-2017). Visual acuity in treated eyes improved relative to untreated eyes over the two-year trial period, commencing October 2012. Furthermore, testing the single treated eye 12 months after gene therapy showed that three patients could read three further lines on a standard optometric eye test. Longer term follow-up with a mean of 3.6 years for 12 participants confirmed that visual acuity gains were sustained, indicating that retinal gene therapy can improve and sustain visual

acuity in a cohort of late-stage choroideremia patients in whom rapid visual acuity loss would ordinarily be expected [3].

One patient in the clinical trial found the improvement very noticeable, reporting:

> *"Immediately afterwards the visual acuity in my left eye was improved enough to see another couple of lines on the sight screen."*

Another patient's testimonial described their expectations being exceeded:

> "*I have had a substantial improvement in the treated eye. This was more than I expected and a better result than the Professor [MacLaren] had contemplated. I have little doubt that without the benefit of this trial my left eye would now be useless*." [A]

X-linked Retinitis Pigmentosa is an inherited disease affecting one in 40,000 people. In the Phase 1 clinical trial in 18 patients with x-linked retinitis pigmentosa, visual field improvements began at one month and were maintained to the last point of follow-up (six months) in six patients. All patients described subjective improvement in visual clarity and increase in field of vision in the treated eye by one month of follow-up [5].

These remarkable outcomes attracted national media coverage in the UK [B, C].

Increased emphasis on prevention of sight loss

The charity Fight for Sight referred to the capabilities of gene therapy in their 2020 report, 'Time to Focus' [D], examining the personal and economic cost of sight loss. The report draws the conclusion that "*sight loss is not inevitable*" and highlights the choroideremia trial [1] as an example of success. Its recommendations include a focus on prevention, not only care; and greater investment in sight loss research, including investment "*to harness the potential of new approaches*". It also reports that the World Health Organisation and the United Nations highlighted in 2019 that more investment was needed in sight loss research globally.

Creation of spin-out: capacity to advance therapies

Following positive outcomes in patients participating in the original Phase 1/2 study, it was clear that there was a need to expedite clinical evaluation of the gene therapy for choroideremia, and to advance the gene therapies (all developed at Oxford) for X-linked retinitis pigmentosa and other inherited retinal disorders in to human clinical trials.

Professor Robert MacLaren first met with representatives of Syncona (then the investment arm of the Wellcome Trust) to discuss this in November 2012. They had already identified retinal gene therapy as a key area in which a company could be built, and begun sector-wide research, meeting with leaders across the field. The University of Oxford and Syncona founded spin-out company NightstaRx Ltd, trading as Nightstar, in early 2014. [E]

The ABCA4 [6], AAV-CNTF and the AAV-melanopsin programmes were subsequently licenced to Nightstar, thereby adding considerable value by diversifying the retinal gene therapy portfolio to include many causes of inherited sight loss.

Economic impacts

Over 2014-2019, Syncona invested funds to develop the company, and licensed further programmes from MacLaren's research from the University of Oxford. Nightstar developed two key products: NSR-REP1, potentially the first treatment for choroideremia; and NSR-RPGR which is seeking to treat retinitis pigmentosa. By December 2018, Nightstar had grown to comprise 47 employees based in London and Boston offices. [F]

Nightstar was one of Syncona's first gene therapy companies, and helped establish their portfolio in this area. **Nightstar was acquired by Biogen for USD877,000,000** in early 2019. The deal ranks as the third most valuable British biotech exit in the last two decades [G], and, delivering for Syncona a 4.5x return on their original investment of GBP56,400,000. [E]

This was the first time Syncona had sold a portfolio company.
The Chief Executive of Syncona stated at the time:

> *"In the six years since Syncona founded Nightstar, the company has established itself as one of the global leaders in retinal gene therapies. It is a strong example of our differentiated approach of founding, building and funding global leaders in life science.'* [H]

The acquisition of Nightstar expanded Biogen's focus in ophthalmology, one of its core growth areas, as well as strengthening Biogen's foothold in gene therapy. [I] At the announcement of completion of the sale in June 2019, Biogen's Chief Executive Officer, said

> "*Today marks a significant achievement for Biogen… The acquisition of Nightstar further bolsters our pipeline and is an important step forward toward our goal of a multi-franchise portfolio across complementary modalities."* [J]

Biogen have made substantial investments in Nightstar, demonstrating that gene therapy is a very active workstream in its portfolio. In December 2020 they completed the Phase 3 STAR study (NCT03496012, 170 participants) for the potential treatment of choroideremia [K]. The study was designed to investigate the safety and efficacy of a single subretinal injection of the gene therapy. Nightstar has also commenced a preclinical development programme for the dual vector technology for Stargardt Disease, based on [6].

5. Sources to corroborate the impact

A. Patient testimonials on Syncona website, verifying improvements for patients: https://www.synconaltd.com/news-and-insights/nightstar-testimonials/

B. Article confirming impact for late-stage choroideremia patients, 'They said I'd go blind. Now gene therapy has changed that', *The Guardian* (19 January 2019): www.theguardian.com/science/2019/jan/19/they-said-i-would-go-blind-gene-therapy-has-changed-that

C. BBC News programme exploring impact on *X-linked Retinitis Pigmentosa* patients, Hereditary blindness cure tested, BBC World Service (20 March 2017), transcript provided: www.bbc.co.uk/programmes/p04xd9hl

D. 'Time to Focus' report from by the charity Fight for Sight (September 2020), making recommendations for governments, funding bodies, charities and the research sector: https://www.fightforsight.org.uk/media/3302/time-to-focus-report.pdf

E. Timeline for creation of Nightstar on Syncona website, verifying company development: https://www.synconaltd.com/media/1379/nightstar-timeline-2019-08-15.pdf.

F. Accounts for the company group in the year to December 2018, available at https://find-and-update.company-information.service.gov.uk/company/10852952/filing-history

G. Syncona finds Americans' offer for Nightstar too good to refuse, *The Times* (5 March 2019): https://www.thetimes.co.uk/article/syncona-finds-americans-offer-for-nightstar-too-good-to-refuse-bfdz0gk9s

H. Syncona Press release (4 March 2019), verifying benefits of the sale to Syncona and Biogen: https://www.investegate.co.uk/syncona-limited/sync/nightstar-agreement-to-be-acquired-by-biogen/20190304071151717 6R/

I. Biogen 2019 Year in Review (page 28): https://www.biogen.com/content/dam/corporate/en_us/yir/PDFs/biogen_2019_yearinreview.pdf

J. Biogen Press Release, verifying the details of the purchase of Nightstar: https://investors.biogen.com/news-releases/news-release-details/biogen-completes-acquisition-nightstar-therapeutics

K. Clinical trial record: https://clinicaltrials.gov/ct2/show/NCT03496012