Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Development of novel therapies for inborn errors of immunity in children and adults via a spin-out company and an NHS England commissioning policy

Period when the underpinning research was undertaken: 2008-2020

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:
Bobby Gaspar	**Professor, Paediatrics and Immunology**	**1992 (GOSH) - 2020**
Adrian Thrasher	**Professor, Paediatric Immunology**	**1995 (GOSH) - Present**
Emma Morris	**Professor, Clinical Cell and Gene Therapy**	**2005- present**

Period when the claimed impact occurred: 2013-2020

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

1. Summary of the impact

More than 5000 people each year are diagnosed with one of the rare chronic disorders called primary immunodeficiencies (PID). These individuals have little or no functioning immune system and are at constant risk of life-threatening infection. In severe cases, babies do not survive beyond a year old. UCL investigators have pioneered new gene therapies that allow affected individuals to lead long and healthy lives without further treatment. They created a biotech company Orchard Therapeutics (valued at USD1,200,000,000 at time of NASDAQ listing and employing approximately 250 FTE) to further develop the gene therapy. They have also produced the clinical evidence necessary to ensure adults as well as children can access life-saving allogeneic haematopoietic stem cell transplantation (Allo-HSCT) and gene therapy, resulting in a new NHS England commissioning policy.

2. Underpinning research

Research at UCL has led to the first haematopoietic stem cell (HSC) gene therapy for severe primary immunodeficiencies (PID). PID are a group of rare inherited diseases, characterized by severe dysfunction of adaptive and/or innate immunity that affect more than 5000 people in the UK. Up to six million people worldwide could be living with a PID, but at present only approximately 2% have been diagnosed. Patients with severe PID present with serious or life-threatening infections, autoimmunity, inflammation and complications related to immune dysregulation such as malignancy. Over 430 genetic forms of PID exist, with approximately 20 specific diseases accounting for 90% of cases. Infants with some forms of severe PID do not survive beyond a year without treatment. Where a compatible donor can be identified, transplantation of haematopoietic stem cells (Allo-HSCT) is the standard of care, but this requires a lengthy hospital stay with chemotherapy to remove the patient's existing bone-marrow cells, in preparation for transplantation.

Development of Gene Therapy for PID

Researchers at UCL Great Ormond Street Institute of Child Health (UCL GOS ICH) were amongst the first to identify genes responsible for several primary immunodeficiencies, opening up opportunities to develop new and improved treatments for these life-threatening diseases. One approach, developed at UCL, is to insert a functional copy of the defective gene into the patient's own HSCs thus correcting the disease and preventing complications associated with

using donor immune cells. The team developed viral vectors that could efficiently introduce the gene into HSCs, which led to seminal clinical trials for two of the most common PIDs - X-linked severe combined immunodeficiency (SCID X1) and ADA deficient SCID (**R1, R2**). These trials were amongst the first to demonstrate that gene therapy could correct a genetic disease. Following the realisation that some viral vectors were able to activate oncogenes and cause leukaemia (**R3**), researchers at UCL collaborated with others to engineer and design new, safer vectors that could efficiently transfer the functional gene to the HSCs without activating cancer-causing oncogenes. Subsequently, Thrasher and Gaspar tested the vectors in a series of clinical trials in X-linked SCID (**R4**), Wiskott-Aldrich Syndrome (WAS) (**R5**) and X-linked chronic granulomatous disease (CGD) demonstrating effective long term immune reconstitution and high levels of safety.

Allo-HSCT transplantation and gene therapy for PID in adults

Morris and colleagues at UCL designed and carried out a study of 29 adult patients with PID who underwent Allo-HSCT. The study described the largest series of transplanted adult PID patients in the world at that time and demonstrated 85% survival rates at three years post-transplant, suggesting that all adults with an appropriately matched donor should be considered for these potentially curative transplants (**R6**). This development built on UCL's experience in pioneering reduced intensity conditioning chemotherapy for Allo-HSCT. The conditioning chemotherapy is given prior to infusion of donor HSCs and is required to remove the patient's own abnormal HSCs prior to transplant. The standard conditioning chemotherapy is poorly tolerated in sicker and/or older patients, but the UCL team developed reduced intensity conditioning that was well tolerated in adult patients.

The study demonstrated outstanding outcomes following Allo-HSCT for adults with complex PID and high co-morbidities going into transplant, with more than 80% patients able to come off immunoglobulin replacement therapy or ongoing immune suppression at a median of 3 years post-transplant. There were no cases of early or late graft rejection. Patients can resolve infections and have good functional immune reconstitution (**R6**). In addition to developing Allo-HSCT for adult PID patients, the team has also, for the first time, demonstrated that adults with monogenic PID such as WAS can also benefit from gene therapy (**R7**).

3. References to the research

R1 Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Zhang F, Adams S, Bjorkegren E, Bayford J, Brown L, Davies EG, Veys P, Fairbanks L, Bordon V, Petropolou T, Kinnon C, Thrasher AJ (2011) Hematopoietic stem cell gene therapy for adenosine deaminase-deficient severe combined immunodeficiency leads to long-term immunological recovery and metabolic correction. *Sci Transl Med*. Aug 24;3(97):97ra80 DOI: 10.1126/scitranslmed.3002716

R2 Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Adams S, Howe SJ, Al Ghonaium A, Bayford J, Brown L, Davies EG, Kinnon C, Thrasher AJ (2011) Long-term persistence of a polyclonal T cell repertoire after gene therapy for x-linked severe combined immunodeficiency. *Sci Transl Med.* Aug 24;3(97):97ra79. DOI: 10.1126/scitranslmed.3002715

R3 Howe SJ, Mansour MR, Schwarzwaelder K, Bartholomae C, Hubank M, Kempski H, Brugman MH, Pike-Overzet K, Chatters SJ, de Ridder D, Gilmour KC, Adams S, Thornhill SI, Parsley KL, Staal FJ, Gale RE, Linch DC, Bayford J, Brown L, Quaye M, Kinnon C, Ancliff P, Webb DK, Schmidt M, von Kalle C, Gaspar HB, Thrasher AJ. (2008) Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. *J Clin Invest.* Sep;118(9):3143-50 DOI: 10.1172/JCI35798

R4 Hacein-Bey-Abina S, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, Bleesing J, Blondeau J, de Boer H, Buckland KF, Caccavelli L, Cros G, De Oliveira S, Fernández KS, Guo D, Harris CE, Hopkins G, Lehmann LE, Lim A, London WB, van der Loo JC, Malani N, Male F, Malik P, Marinovic MA, McNicol AM, Moshous D, Neven B, Oleastro M, Picard C, Ritz J, Rivat C, Schambach A, Shaw KL, Sherman EA, Silberstein LE, Six E, Touzot F, Tsytsykova A, Xu-

Bayford J, Baum C, Bushman FD, Fischer A, Kohn DB, Filipovich AH, Notarangelo LD, Cavazzana M, Williams DA, Thrasher AJ. (2014) A modified γ-retrovirus vector for X-linked severe combined immunodeficiency. *N Engl J Med*. Oct 9;371(15):1407-17 DOI: 10.1056/NEJMoa1404588

R5 Hacein-Bey Abina S*, Gaspar HB*, Blondeau J, Caccavelli L, Charrier S, Buckland K, Picard C, Six E, Himoudi N, Gilmour K, McNicol AM, Hara H, Xu-Bayford J, Rivat C, Touzot F, Mavilio F, Lim A, Treluyer JM, Héritier S, Lefrère F, Magalon J, Pengue-Koyi I, Honnet G, Blanche S, Sherman EA, Male F, Berry C, Malani N, Bushman FD, Fischer A, Thrasher AJ, Galy A, Cavazzana M (2015) Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome *JAMA*. Apr 21;313(15):1550-63. DOI: 10.1001/jama.2015.3253

R6 Fox TA, Chakraverty R, Burns S, Carpenter B, Thomson K, Lowe D, Fielding A, Peggs K, Kottaridis P, Uttenthal B, Bigley V, Buckland M, Grandage V, Denovan S, Grace S, Dahlstrom J, Workman S, Symes A, Mackinnon S, Hough R, Morris E. (2018) Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood*. Feb 22;131(8):917-931. DOI: 10.1182/blood-2017-09-807487.

R7 Morris EC, Fox T, Chakraverty R, Tendeiro R, Snell K, Rivat C, Grace S, Gilmour K, Workman S, Buckland K, Butler K, Chee R, Salama AD, Ibrahim H, Hara H, Duret C, Mavilio F, Male F, Bushman FD, Galy A, Burns SO, Gaspar HB, Thrasher AJ. (2018) Gene therapy for Wiskott-Aldrich syndrome in a severely affected adult. *Blood*. Sep 14;130(11):1327-1335. DOI: 10.1182/blood-2017-04-777136.

4. Details of the impact

Without treatment, infants with the most severe forms of PID – SCID-X1 and ADA SCID -- usually die from infections within the first year of life. Life expectancy can be improved dramatically if the child receives a haematopoietic stem cell transplant (Allo-HSCT) from the bone marrow of a compatible donor. However, Allo-HSCT requires pre-treatment with chemotherapy to remove the patient's own bone marrow cells, a procedure which is associated with long term side-effects such as impaired growth, compromised fertility, secondary malignancy and hearing loss. Another major complication of Allo-HSCT is the development of graft-versus host disease (GVHD), which occurs when the new immune system (derived from *donor* HSCs) inadvertently recognises recipient (patient) cells as 'foreign' triggering immune-mediated tissue damage, which can be fatal.

Effective gene-therapy treatments developed at UCL (**R1, R4**) have transformed the lives of more than 60 patients with these rare genetic conditions, in the UK alone. The treatments result in a reconstituted immune system, allowing patients to successfully fight infections, which previously would have been life-threatening. Correcting the patient's own immune system removes the risk of GVHD, and also prevents the development of autoimmunity and cancers. The treatments are saving the NHS millions of pounds, particularly for patients with ADA-SCID. They have also resulted in a spin-out company, Orchard Therapeutics, which employs over 250 people in the UK and US, and has a current value of GBP950,000,000. UCL-led clinical studies have also driven changes in NHS clinical commissioning that now give adult patients with PID (as well as children) equal access to effective stem cell therapies and gene therapy treatments.

Curative treatments for patients with PIDs

More than 90% of patients treated with gene therapy for PIDs developed by UCL researchers, remain well and no longer require prophylactic therapy. They respond normally to infections and vaccines and can expect to live a relatively normal life. One parent whose child underwent gene therapy said: "Transplant has made a huge difference to Josh's life and to our family life, he is a healthy boy and can do everything a healthy child can do without fear of getting an infection and being admitted to hospital whereas before transplant we were limited to where we could go, avoiding crowds etc" (**S1**).

More than 65 patients with ADA SCID have been treated to date and 94% are making effective immune responses. The cost of enzyme replacement for ADA-SCID is estimated at GBP350,000 per year minimum cost for the life-time of a patient (**S2**)**.** A significant number of patients no longer require enzyme replacement treatment following gene therapy and this equates to a total cost saving to the NHS of more than GBP10,000,000 to date.

Gene therapy spin-out company – Orchard Therapeutics

The strong clinical data for PID gene therapy and pre-clinical developments in other diseases generated by Thrasher, Gaspar and colleagues at UCL have led to multiple commercial opportunities for both licensing and spin-out. With a USD35,000,000 investment from FPRIME, a venture capital firm, and the UCLTech Fund, Orchard Therapeutics was established in 2015. It has since secured series B funding of USD110,000,000 (Dec 2017) and series C funding of USD150,000,000 (July 2018) from a wide consortium of specialist healthcare investors. On 31 October 2018, Orchard listed on the Nasdaq exchange raising almost USD225,000,000 and a follow on offering in June 2019 secured a further USD130,000,000. In a 'Spot light on Spinouts' report published by RAEng, Orchard "took the record for largest known exit" coming top in the UK for Initial Public Offering (IPO) and was valued at exit at GBP950,000,000 (**S3**). The company has headquarters and laboratories in London, UK with 150 staff. It also has an office in Boston US (approximately 50 staff) and offices elsewhere in the US and EU (with a further 50 staff) (**S4**).

Improving access to gene therapy treatments for PIDs

The ADA SCID programme and other pre-clinical developments in PID therapies made at UCL have been in-licenced by Orchard Therapeutics, with Gaspar as CEO. The company has also supported development of cryopreserved gene therapy products, which will ultimately allow patients to remain at their local treating centre while cells are shipped to central manufacturing sites for the transduction procedure. This will make the treatment accessible to people living anywhere in the world. To prepare for a commercial product, Orchard is producing a suitable vector with Oxford Biomedica and is performing cell transduction at a commercial manufacturing facility. In April 2018, Orchard secured the rights from GSK to four other HSC gene therapy programmes for other PID (**S3**). In 2020, Orchard is taking forward one approved treatment and six clinical programmes, which have already treated over 170 patients with a combined dataset of over 750 patient years. The gene therapy programme for metachromatic leukodystrophy (MLD) received a positive opinion from the EMA Committee for Medicinal Products for Human Use (CMHP) and received full marketing authorization in the EU for eligible patients in October 2020 (**S5**).

National commissioning policy to ensure equal access to Allo-HSCT and gene therapy for adult PID patients

Many patients with less severe PID remain undiagnosed into early adulthood and present in various specialist clinics with symptoms that can range from lung scarring to inflammatory bowel disease. With the advent of rapid whole genome sequencing, their underlying PIDs can now be identified and treated. However, until January 2018, adult patients with PID did not have access to NHS funding for Allo-HSCT and in many cases could not access the potentially curative therapy. Morris' research demonstrating the effectiveness of Allo-HSCT in adult patients with PID has paved the way for equal access to Allo-HSCT for patients regardless of age. She was the National Clinical Lead working with NHS England (NHSE) to develop and gain approval for the new Clinical Commissioning Policy that was published in July 2019 (**S6**). An NHS financial impact assessment confirmed that Allo-HSCT provided a cost saving to the NHS compared to continued conservative management of adult patients with complex/severe PID. The team at UCL has now transplanted 56 adolescents and adults with PID (with 13 awaiting admission), the largest number of any global centre. It receives at least 2 new referrals per month.

Morris also co-chairs the National Adult PID Bone Marrow Transplant Multidisciplinary Team Meeting, which NHSE requires to meet fortnightly to discuss all adult PID patients being considered for Allo-HSCT. The NHSE commissioning policy on treatments for adult PIDs was also the first to include a *Current Lived Experience/Patient Impact Report* for the Clinical

Priorities Advisory Group, which demonstrates the significant impact the change of policy has on patients and their families.

One transplant recipient said: ”My bone marrow transplant (BMT) has been life changing as I am now pain free, I can eat what I like, I have put on weight and only have to take one medication each day. The first couple of years following BMT I was making up for lost time and enjoying life and all the things I was unable to do when I had Chronic Granulomatous Disease. For the first time in my life I can make plans for the future, as now I have one” (**S1**).

5. Sources to corroborate the impact

S1 NHS England Lived Experience Report for Clinical Priorities Advisory Group. Patient Impact Report for Clinical Priorities Advisory Group Allogeneic Haematopoietic Stem Cell Transplant for Primary Immunodeficiencies (all ages) 11/03/2019.

S2 Ding Y, Thompson JD, Kobrynski L, Ojodu J, Zarbalian G,Grosse SD (2016) Cost-Effectiveness/Cost-Benefit Analysis of Newborn Screening for Severe Combined Immune Deficiency in Washington State J Pediatr.May; 172: 127–135. doi: 10.1016/j.jpeds.2016.01.029

S3 Spotlight on Spinouts. UK Academic Spinout Trends. Royal Academy of Engineering. Jan 2021: https://www.beauhurst.com/wp-content/uploads/2021/01/Spotlight-on-Spinouts.

S4 ORCHARD Therapeutics website: ***https://www.orchard-tx.com/***

S5 Press release 16 October 2020: Orchard Therapeutics receives positive CHMP opinion for Libelmy for the treatment of early onset MLD https://www.globenewswire.com/news-release/2020/10/16/2109748/0/en/Orchard-Therapeutics-Receives-Positive-CHMP-Opinion-for-Libmeldy-for-the-Treatment-of-Early-Onset-Metachromatic-Leukodystrophy-MLD.html

S6 Allogeneic Haematopoietic Stem Cell Transplant for Primary Immunodeficiencies (all ages); NHS England Reference: 170129P.