Institution: The University of Manchester		
Unit of Assessment: 1 (Clinical Medicine)		
Title of case study: Advancing treatments for lysosomal storage disorders.		
Period when the underpinning research was undertaken: February 2006 – December 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:**
Brian Bigger	Chair in Cell & Gene Therapy Reader Senior Research Fellow	2016 – present 2008 – 2016 2006 – 2008
Robert Wynn	Honorary Clinical Professor Honorary Senior Lecturer	2013 – present 2008 – 2013
Simon Jones	Honorary Senior Lecturer	2011 – present
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Manchester (UoM) researchers developed new treatments for rare childhood lysosomal storage diseases (LSDs) and built commercial capacity in the sector. Research led to licensing two drugs worldwide for LSDs: Sebelipase Alfa for lysosomal acid lipase deficiency (LAL-D) and Elosulfase Alfa for mucopolysaccharidosis (MPS) IVA (Morquio A syndrome), marketed by Alexion Pharmaceuticals and Biomarin Pharmaceuticals, respectively. As a result, >90 LSD patients in England and >1,000 worldwide have been treated. UoM researchers were scientific co-founders of Orchard Therapeutics Plc, a company specialising in developing gene therapy treatments for rare diseases. UoM research was instrumental in the company securing USD33,000,000 financing, allowing successful launch and growth from 33 to >250 employees across the UK and USA.

2. Underpinning research

Background

Lysosomal storage diseases (LSDs) are multisystem disorders caused by absence of specific lysosomal enzymes that degrade complex macromolecules. They typically affect children and are often severe, with multi-organ dysfunction including the heart, bones and joints, and neurological deficits, often progressing, causing early death. Management of these diseases is typically palliative and lifelong, requiring multiple surgeries and interventions. There is no cure for LSDs but the development of enzyme replacement therapy (ERT) has shifted treatment emphasis from management of symptoms towards disease modification.

Sebelipase Alfa for LAL-D

LAL-D (infant form historically known as Wolman disease) is a rare, chronic progressive disorder affecting around 20 in 1,000,000 people. The body‘s ability to produce lysosomal acid lipase is affected. This enzyme is needed to breakdown lipids (fats) and cholesterol in cells. LAL-D leads to fat accumulating in organs and tissues, causing liver and cardiovascular diseases. It progresses rapidly, with death usually occurring a few weeks after diagnosis (median 3.7 months). The most rapidly progressing presentation is in infants, usually leading to death before 6 months of age.

Jones led two phase II/III multicentre international studies into Sebelipase Alfa (a recombinant human lysosomal acid lipase (LAL) enzyme developed as an ERT for LAL-D), recruiting half of the total patients enrolled. These studies showed that Sebelipase Alfa improved one-year survival from 0% to 67% (equivalent to median survival increase from 3.7

months historically to 'median survival not yet reached' in the treatment cohort), with clinically meaningful improvements in growth and other key disease manifestations [1].

Elosulfase alfa for Morquio A syndrome

Morquio A syndrome (mucopolysaccharidosis IVA, MPS IVA) is a rare lysosomal disease in which mucopolysaccharide keratan sulfate (a type of complex carbohydrate) builds up in the body with skeletal and cardiac manifestations affecting an estimated one in 2-300,000. It is a heterogeneous, progressive disease leading to various complications e.g. heart, lung, muscle and bone problems. These can reduce endurance, make regular activities difficult, limit mobility and reduce quality of life. Prior to this research, there was no approved treatment other than supportive care.

Seven multicentre clinical studies were conducted to licence an ERT with Elosulfase Alfa, and Jones helped design the overall trials and led the Manchester arm of each, including MOR001 Natural History, MOR002/MOR100 phase I/II and extension, MOR004/005 phase II/III plus extension, MOR006 non-ambulatory study, MOR007 <5 years trial, and MOR008 attenuated patient trial [2]. The primary efficacy measure for the treatment was a 6-minute walk test distance (6MWT). Results showed Elosulfase Alfa improved endurance (via improved 6MWT outcomes) and had an acceptable safety profile [2]. A further study of a patient group of <5-year-olds showed early intervention with Elosulfase Alfa was well tolerated, with significant reduction of keratan sulphate storage in this age group (30.2% against baseline at week 2, and 43.5% at week 52) [3].

Research into MPSIIIA, MPSIIIB, MPSIIIC

Bigger, Jones and Wynn developed haematopoietic stem cell gene therapy for the neurological lysosomal disease MPSIIIA, demonstrating preclinical proof of concept for correction of neurological symptoms where conventional transplant is ineffectual [4], and further provided preclinical bio-distribution and toxicity data on the drug product. Bigger later demonstrated similar correction of neurological symptoms in MPSIIIB [5], MPSII [6], and adeno-associated vector gene therapy, which successfully treated MPSIIIC. Clinical trial design for MPS IIIA, MPS IIIB and MPS IIIC was led by UoM researchers. A clinical trial in Manchester led by Bigger, Wynn, Jones started in December 2019 and is ongoing.

3. References to the research

1. **Jones SA**, Rojas-Caro S, Quinn AG, Friedman M, Marulkar S, Ezgu F, Zaki O, Gargus JJ, Hughes J, Plantaz D, Vara R, Eckert S, Arnoux JB, Brassier A, Le Quan Sang KH, Valayannopoulos V. Survival in infants treated with Sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multicenter, dose-escalation study. *Orphanet Journal of Rare Diseases*. 2017 Feb 8;12(1):25. DOI:10.1186/s13023-017-0587-3.
2. Hendriksz CJ, Burton B, Fleming TR, Harmatz P, Hughes D, **Jones SA**, Lin SP, Mengel E, Scarpa M, Valayannopoulos V, Giugliani R; STRIVE Investigators, Slasor P, Lounsbury D, Dummer W. Efficacy and safety of enzyme replacement therapy with BMN 110 (Elosulfase Alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. *Journal of Inherited Metabolic Disease*. 2014 Nov;37(6):979-90. DOI: 10.1007/s10545-014-9715-6 .
3. **Jones SA**, Bialer M, Parini R, Martin K, Wang H, Yang K, Shaywitz AJ, Harmatz P. Safety and clinical activity of Elosulfase Alfa in pediatric patients with Morquio A syndrome (mucopolysaccharidosis IVA) less than 5 y. *Pediatric Research*. 2015 Dec;78(6):717-22. DOI:10.1038/pr.2015.169.
4. Sergijenko A, Langford-Smith A, Liao AY, Pickford CE, McDermott J, Nowinski G, Langford-Smith KJ, Merry CL, **Jones SA**, Wraith JE, **Wynn RF**, Wilkinson FL, **Bigger BW**. Myeloid/Microglial driven autologous hematopoietic stem cell gene therapy corrects a neuronopathic lysosomal disease. *Molecular Therapy*. 2013 Oct;21(10):1938-49. DOI:10.1038/mt.2013.141.

5. Holley RJ, Ellison SM, Fil D, O'Leary C, McDermott J, Senthivel N, Langford-Smith AWW, Wilkinson FL, D'Souza Z, Parker H, Liao A, Rowlston S, Gleitz HFE, Kan SH, Dickson PI, **Bigger BW**. Macrophage enzyme and reduced inflammation drive brain correction of mucopolysaccharidosis IIIB by stem cell gene therapy. *Brain*. 2018 Jan 1;141(1):99-116. DOI:10.1093/brain/awx311.

6. Gleitz HF, Liao AY, Cook JR, Rowlston SF, Forte GM, D'Souza Z, O'Leary C, Holley RJ, **Bigger BW**. Brain-targeted stem cell gene therapy corrects mucopolysaccharidosis type II via multiple mechanisms. *EMBO Molecular Medicine*. 2018 Jul;10(7):e8730. DOI: 10.15252/emmm.201708730.*Cover featured

Patents

WO 2018/011572 Al , 'Gene therapy' involving compositions and adeno associated viral vectors comprising an optimised HGSNAT nucleic acid sequence, priority date 12 July 2016, naming Brian Bigger and Claire O'Leary as inventors. Relates to treatment of MPS IIIC.

WO2018146473A1, 'Gene therapy' relating to stem cell gene therapies for the treatment of mucopolysaccharidosis (MPS) II. Priority date 7 Feb 2017, naming Brian Bigger as one of the inventors.

4. Details of the impact

Context

UoM researchers led an international work programme delivering treatments for Mucopolysaccharide and related lysosomal diseases. Although rare, one baby born every eight days globally will be diagnosed with an MPS or related disease. These multi-organ storage diseases cause progressive physical disability and, in many cases, severe progressive mental deterioration resulting in childhood death.

Outputs from UoM programme have led to:

1. Clinical impact from trials run in Manchester including market authorisation of new treatments.
2. Economic impact through establishing a company (Orchard Therapeutics) to test new gene therapies, and licencing of two Manchester gene therapies to US companies (AvroBio, Phoenix Nest) (MPSII, MPSIIIC), with the advantage of increased enzyme expression from a single treatment.

Reach and significance of the impact

Enabling new treatments for lysosomal storage disorders

Over the past six years, Manchester recruited five global first patients and the majority of patients onto 13 multicentre lysosomal storage disease studies. Two treatments gained market authorisation as a direct result of UoM work in these trials, leading to >90 LSD patients in England and >1,000 worldwide being treated [A].

Example 1: LAL-D

Prior to Sebelipase Alfa availability (marketed as Kanuma, Alexion Pharmaceuticals, Inc.), treatment options centred upon supportive interventions, including blood transfusions and nutritional supplementation, but average infant life expectancy was less than four months from diagnosis. Through UoM's research, in collaboration with other centres [1], ERT Sebelipase Alfa for LAL-D has been approved worldwide: European Medicines Agency (EMA) September 2015) [Bi]; US Food and Drug Administration (FDA) December 2015 [Bii]; Japan's Ministry of Health, Labour and Welfare (MHLW) March 2016 [Biii]; and Health Canada December 2017 [Biv].

Albie, diagnosed with LAL-D at two months, took part in the Kanuma trial, commencing in 2011. His mother Charlotte stated, "*After several weeks of treatment, Albie gradually began to put on weight and improve*" [C]. Prior to this treatment, most infants with LAL-D died before reaching six months of age. Albie is now eight years old.

Sebelipase Alfa was initially rejected by the National Institute for Health and Care Excellence (NICE) in 2017 for financial reasons although NICE committee "*recognised that sebelipase alfa is a potentially life-saving treatment in this population, and there is a compelling clinical need*" [Di]. The decision is under appeal but the schedule has been affected by Covid-19 and does not currently have a timeline for restarting [Dii].

Alexion reported Kanuma net product sales of USD112,200,000 in 2019, compared to USD92,000,000 in 2018 and USD65,600,000 in 2017, representing a 22% and 40% increase respectively [E].

Example 2: Morquio syndrome/MPS IVA

Resulting from UoM research [2,3], ERT for Morquio syndrome involving Elosulfase Alpha (marketed as Vimizim, Biomarin Pharmaceuticals) has been approved worldwide: US FDA February 2014 [Fi]; EMA April 2014 [Fii]; Health Canada July 2014 [Fiii]; National Health Surveillance Agency Brazil , MHLW Japan, Australian Therapeutic Goods Administration December 2014 [Fiv] and National Medical Products Administration, China June 2019 [Fv]. In all these countries, Vimizim was the first treatment approved for Morquio A syndrome. At the time of EU approval, Chief Executive of the MPS Society, (UK) said, "*For patients with Morquio A disease now having a specific drug treatment option provides real hope after decades of sadness and loss for so many families"* [Fii].

In December 2015, NICE recommended funding Elosulfase Alfa treatment for Morquio A syndrome [G]. At the time of NICE evaluation (2015), there were 88 people living with MPS IVA in England, with ~3 new diagnoses per year. The company and patient group noted that 74–77 of these were anticipated to be eligible for ERT with Elosulfase Alfa [G].

Biomarin annual reports record Vimizim sales of USD544,300,000 in 2019, up from USD482,000,000 (2018) and USD413,300,000 (2017), a 13% and 17% increase respectively year on year. Vimizim is only used to treat Morquio A [H].

UoM research helped build commercial capacity in the UK and overseas

Gene therapy for MPS IIIA (Manchester preclinical programme) [4] was one of three critical founding programmes for UK-based Orchard Therapeutics, founded in 2015 to improve the lives of patients suffering from rare genetic diseases by designing autologous ex vivo gene therapies. Bigger, Jones and Wynn are members of Orchard's Scientific Advisory Board and UoM remains a critical collaborator. The MPS IIIA programme (led by Bigger), was critical in the start-up of the company. Orchard CEO stated, "*The University's research expertise and development work was integral to our success in securing $33 million* [USD33,000,000] *Series A financing, led by F-Prime Capital, which allowed us to successfully launch the company in May 2016"* [Ii]. MPS IIIB [5] was licenced to Orchard Therapeutics in November 2017. Orchard CEO further confirmed, "*The University continues to contribute to the success and growth of our company including our collaboration on a clinical trial for MPSIIIA. The number of people employed by Orchard has risen from 33 in 2017 to over 250 (of which around 85 based are* (sic) *in the UK) by December 2019"* [Ii]. Orchard offered initial shares to the public on the US stock exchange in October 2018 with a market value of USD1,180,000,000 [Iii]. In January 2019 a patient was treated on a compassionate basis with the MPSIIIA genetic therapy and three patients have since been treated on a UoM-sponsored trial. Ten months on from compassionate treatment, Royal Manchester Children's hospital reported the patient was 'doing well' [Ji]. Preliminary clinical trial data showing treatment is safe and well-tolerated was presented in December 2020 at American Society of Hematology Annual meeting [Jii].

5. Sources to corroborate the impact

A. Email from Head of Advocacy and Patient Services, Society of Mucopolysaccharide Diseases (MPS Society), 12 November 2020 - ***confirming estimated numbers of patients treated in England and worldwide with two new drugs for LAL-D and Morquio A developed from UoM research.***

B. Approvals for Sebelipase Alfa (Kanuma) as a treatment for LAL-D:
   i. Alexion press release 1 September 2015 – ***confirms European (EMA) approval.***
   ii. Drugs.com article 8 December 2015 - ***confirms US (FDA) approval.***
   iii. Alexion Press release 28 March 2016 – ***confirms Japanese (MHLW) approval.***
   iv. Health Canada regulatory decision summary -15 December 2017- ***confirms Canadian (Health Canada) approval.***

C. Alexion website featuring Albie's story- ***details of infant patient treated in the first Sebelipase Alfa clinical trials.*** https://alexion.com/our-inspiration/real-stories/lal-d/albies-story

D. NICE guidance. Lysosomal acid lipase deficiency - Sebelipase Alfa:
   i. Final Evaluation Determination Document 15 February 2017- ***confirms clinical need for Sebelipase Alfa as a potentially life-saving treatment***.
   ii. Guidance In Development - Expected publication date TBC –***appeal schedule affected by COVID-19.***

E. Alexion Annual Reports 2018 & 2019 - ***showing sales figures for Kanuma.***

F. Approvals for Elosulphase Alfa (Vimizim) as a treatment for Morquio A Syndrome:
   i. Drugs.com article 14 February 2014 - ***confirms US (FDA) approval.***
   ii. Biomarin press release 28 April 2014 – ***confirms European (EMA) approval and includes statement from Chief Executive of the MPS Society.***
   iii. Biomarin press release 7 July 2014 – confirms ***Canadian (Health Canada) approval.***
   iv. Biomarin press releases December 2014 – ***confirm Brazilian (National Health Surveillance Agency), Japanese (MHLW) and Australian (Therapeutic Goods Administration) approvals.***
   v. Biomarin press release 4 Jun 2019 – ***confirms Chinese (National Medical Products Administration) approval.***

G. NICE Highly specialised technologies guidance 16 December 2015. Elosulfase Alfa for treating mucopolysaccharidosis type IVa. https://www.nice.org.uk/guidance/hst2 ***NICE recommend Elosulfase Alfa for treatment of Morquio A.***

H. Biomarin Annual Reports 2018 and 2019 - ***showing sales figures for Vimizim***.

I. Orchard Therapeutics:
   i. Statement from Chief Executive Officer, 23 September 2020 - ***confirming significance of UoM research in founding the company.***
   ii. *Globalgenes.org article* **'**Gene Therapy Developer Orchard Therapeutics raises $200 million in IPO', 31 October 2018 – ***Orchard becomes public limited company.***

J. MPSIIIA treatments:
   i. Central Manchester Foundation Trust News report 5 November 2019 - ***on progress of MPSIIIA patient treated on a compassionate basis at Royal Manchester Children's Hospital.***
   ii. Abstract of oral presentation on early trial results presented at American Society of Hematology, 7 December 2020 and Orchard Therapeutics press release 8 December 2020 ***– showing positive results for patients treated to date.***