Institution: The University of Manchester

Unit of Assessment: 1

Title of case study: Improved clinical management of lysosomal disorders

1. Summary of the impact

Researchers at the University of Manchester (UoM) characterised fatal childhood lysosomal storage diseases (LSDs) and developed new treatments. The research has led to the licensing of 6 drugs worldwide (of a total of 9 available) for LSDs including mucopolysaccharide disease I, II, IIIA, IVA, VI, Fabry, Pompe and Niemann Pick C. As a result, longevity and quality of life have improved for more than 800 LSD patients in England and more than 3000 worldwide. Home enzyme treatment has improved quality of life for the majority of LSD patients in the UK (>400). The research has broadened the scope of haematopoietic stem cell transplantation for LSDs and reduced mortality, benefiting more than 100 LSD patients worldwide.

2. Underpinning research

UoM researchers are given in bold.

The aims of the research carried out at UoM were to improve the diagnosis, treatment and management of LSDs. The research was carried out between 1993 and 2013, with the majority of the work taking place 2005-13.

Key UoM researchers:

- **Ed Wraith** (Honorary Senior Lecturer, 1993-2008; Honorary Professor, 2008-2013)
- **Lez Fairbairn** (Professor, 1993-2005)
- **Robert Wynn** (Honorary Lecturer, 1998-2007; Honorary Senior Lecturer, 2007-date)
- **Brian Bigger** (Research Fellow, 2006-2008; Senior Research Fellow, 2008-2013; Reader, 2013-date)
- **Simon Jones** (Honorary Lecturer, 2009-date)

Genetic characterisation of LSDs

- **Wraith** and colleagues have identified several major genetic mutations in LSDs including mucopolysaccharidosis type II, IV, VI, Gaucher and Fabry since 1993.
- **Wraith** recognised a poor genotype-phenotype correlation, but as many patients are from consanguineous backgrounds, **Wraith** identified that common mutations followed similar clinical courses, allowing improved clinical classification of MPS diseases.

Bone marrow transplantation and gene therapy development for MPSI

- **Wraith, Fairbairn** and colleagues characterised outcomes after haematopoietic stem cell transplantation (HSCT) in MPS I, II and III. This is the only treatment for some LSDs and led to adoption of HSCT for MPSI Hurler and discontinuation for MPSII and III.
- A retroviral HSCT gene therapy approach was adopted for MPSI Hurler which resulted in an unsuccessful clinical trial in Manchester in 1997.

Natural history studies on LSDs

- Several natural history studies on MPSI (MPSI Registry), MPSII (Hunter outcome survey), MPSIII, MPSIVA (MOR001), MPSVI (Clinical Surveillance Program), alpha mannosidosis (Alpha-man), were led in Manchester or with significant contributions from **Wraith**, **Jones** and colleagues.
- **Wraith**, **Bigger**, **Jones** and colleagues validated biomarkers of lysosomal diseases including dermatan sulphate chondroitin sulphate ratio and HCIIT against clinical outcomes in mucopolysaccharidosis diseases.

Treatment development for LSDs

- **Wraith** and **Jones** were co-investigators on clinical trials evaluating enzyme replacement

therapy for MPSI, MPSII, MPSVI, Fabry, and Pompe disease, and the substrate reduction therapy drug miglustat for Niemann Pick C.

- **Jones** is co-investigator in ongoing enzyme replacement therapy trials for MPSIIIA, MPSIIIA-C, MPS IVA and Wolman.
- 6 licensed drugs resulted from this work and **Wraith** and colleagues demonstrated that enzyme replacement therapy for MPSII and VI could be given safely at home.
- **Wraith**, **Bigger**, **Jones**, **Wynn** developed the substrate reduction therapy drug genistein for MPSIII (trial starting January 2014) and HSCT gene therapy for MPSIIIA (trial starting 2015).
- **Wraith**, **Wynn**, **Bigger** and colleagues showed HSCT to be more effective than enzyme replacement therapy in MPSI, which has significantly improved transplantation mortality in MPSIH and in a pan-European HSCT policy, and broadened the indication of HSCT to include more LSDs.

3. References to the research

The research was published in the top metabolic journals of the field. Key references:

1. **Wraith JE**, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Swiedler SJ, Kakkis ED, Braakman T, Chadbourne E, Walton-Bowen K, Cox GF. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α-L-iduronidase (laronidase). *The Journal of Pediatrics*. 2004;144(5):581-8. DOI: 10.1016/j.jpeds.2004.01.046

2. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, Leslie N, Levine J, Spencer C, McDonald M, Li J, Dumontier J, Halberthal M, Chien YH, Hopkin R, Vijayaraghavan S, Gruskin D, Bartholomew D, van der Ploeg A, Clancy JP, Parini R, Morin G, Beck M, De la Gastine GS, Jokic M, Thurberg B, Richards S, Bali D, Davison M, Worden MA, Chen YT, **Wraith JE**. Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology*. 2007;68(2):99-109. DOI: 10.1212/01.wnl.0000251268.41188.04

3. Patterson MC, Vecchio D, Prady H, Abel L, **Wraith JE**. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *The Lancet Neurology*. 2007;6(9):765-72. DOI: 10.1016/S1474-4422(07)70194-1

4. Pastores GM, Arn P, Beck M, Clarke JTR, Guffon N, Kaplan P, Muenzer J, Norato DYJ, Shapiro E, Thomas J, Viskochil D, **Wraith JE**. The MPS I registry: Design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis Type I. *Molecular Genetics and Metabolism*. 2007;91(1):37-47. DOI: 10.1016/j.ymgme.2007.01.011

5. **Wynn RF, Wraith JE**, Mercer J, O'Meara A, Tylee K, Thornley M, Church HJ, **Bigger BW**. Improved Metabolic Correction in Patients with Lysosomal Storage Disease Treated with Hematopoietic Stem Cell Transplant Compared with Enzyme Replacement Therapy. *The Journal of Pediatrics*. 2009;154(4):609-11. DOI: 10.1016/j.jpeds.2008.11.005

6. Malinowska M, Wilkinson FL, Langford-Smith KJ, Langford-Smith A, Brown JR, Crawford BE, Vanier MT, Grynkiewicz G, **Wynn RF, Wraith JE**, Wegrzyn G, **Bigger BW.** Genistein improves neuropathology and corrects behaviour in a mouse model of neurodegenerative metabolic disease. *PLoS One*. 2010;5(12):e14192. DOI: 10.1371/journal.pone.0014192

4. Details of the impact

See section 5 for corroborating sources S1-S9.

Context

Over 70 lysosomal diseases exist with an incidence of 1/7000. They are progressive, multisystem diseases, usually affecting children, with severely shortened life expectancy. In 1993 there was one treatment for LSDs: haematopoietic stem cell transplant. This was only effective in severe

MPSI and had a high procedure-related mortality rate of ~45%. Drug treatments were slow to appear and individually had limited impact; the first drug in 1994 for Gaucher disease was cerezyme (imiglucerase), used for around 80 patients in the UK. In the early 1990s, LSDs were often diagnosed very late or misdiagnosed and palliative management was dispersed throughout the UK.

Reach and significance of the impact

Improved clinical management of LSDs

- Several multinational collaborative natural history studies in Manchester, most of which are still ongoing, resulted in improved/earlier LSD diagnosis and disease management (S1).
- **Wraith** wrote NHS clinical management guidelines for 6 LSDs which helped to reduce age of diagnosis in several LSDs including MPSI, from an average range of 2-10 years of age (2000) to 3 months-4 years of age (2013), depending on severity (S2). This improvement is important as early treatment has increased clinical benefit.
- 2005: Manchester was made one of eight National Specialist Commissioned Centres in England for management and treatment of LSDs with **Wraith** (now **Jones**) as director due to **Wraith's** natural history trial background (S3-S6).
- 2010-11 Manchester's recognition as a worldwide centre for LSDs resulted in Manchester and **Wraith** handling 15,500 diagnoses per annum for paediatric inherited metabolic diseases from over 20 countries, of which ~30% are LSDs.
- 2010-11: 1983 LSD patients were managed at 8 NCG centres – 350 in Manchester (S5).

Enzyme replacement and substrate reduction therapies

Enzyme replacement therapy trials with **Wraith/Jones** as CI in Manchester were conducted for the LSDs MPSI, MPSII, MPSVI, Fabry**,** and Pompe disease, and the substrate reduction therapy drug miglustat for Niemann pick C, in collaboration with Biomarin, Shire, TKT, Genzyme, Actelion and Synageva.

- 2003-13: 6 drugs licensed from these trials in >20 countries including US, Europe, Canada, Latin America, Japan and Australia (S7).
- 2011-12: 9 licensed drugs for 7 LSDs provided in 8 English NCG centres for 801 patients with a drug budget of £124 million, 6 of which (~2/3 of worldwide LSD drug market) were trialled in Manchester by **Wraith/Jones** (S3).
- 2013 >3000 LSD patients in >20 countries worldwide benefited from drug treatment, ~2/3 from the 6 drugs trialled by **Wraith/Jones** (S7, S8).
- 2013 GALNS for MPSIVA trialled in Manchester (**Jones**) awaiting FDA and EMA approval (S7).
- **Wraith** and colleagues have delivered significant quality of life improvements in patients with these 7 LSDs as a result of their research, with improvements in cognitive function, muscular, and skeletal function as well as significantly improved life expectancy of on average around 10 years or more depending on disease severity.
- Previous life expectancies of a few months in MPSI Hurler disease, is now considerably extended lifespans of decades, as well as improved cognitive and/or skeletal outcomes.

Improved haematopoietic stem cell transplantation outcomes

To improve HSCT outcomes, **Fairbairn** and **Wraith** developed retroviral gene therapy in HSCT as a safer and more efficacious alternative with the world's first LSD gene therapy clinical trial for MPSIH in Manchester in 1997.

- This trial allowed a more efficacious approach developed by **Bigger** and colleagues using a lentiviral vector for MPSIIIA between 2007-13, expected in clinical trial in 2015.
- **Wynn** and colleagues developed safer HSCT for LSDs. Prior to 1995, 1-2 patients pa were transplanted for MPSIH in Manchester. By 2010, this rose to 7 pa and transplant expanded to other LSDs, including Niemann Pick CII, resulting in ~10-15 patients transplanted pa (S8, S9).
- Engrafted survival improved from 57% in 1994-2007 to 94% post-2007 and a demonstration by

Wynn, Bigger that HSCT is more effective than ERT in MPSI disease, with some patients' cognitive development in the normal range.

- **Wynn** and colleagues wrote metabolic transplant guidelines for The European Group for Blood and Marrow Transplantation haematopoietic stem cell transplant handbook 2008 which include expansion to other lysosomal diseases (S9).
- Novel biomarkers for LSDs were developed or validated in Manchester including heparan cofactor II thrombin complex and dermatan sulphate chondroitin sulphate ratio, both of which correlate with clinical outcomes in treated patients with MPSI, II and VI.
- Dermatan sulphate chondroitin sulphate ratio has been adopted into standard clinical disease management in Manchester.
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5. Sources to corroborate the impact

S1. Natural history studies: The MPSI registry (Natural history registry) https://www.lsdregistry.net/mpsiregistry/ ; The MPSII Hunter outcome survey (Natural history registry) http://www.globaloutcomesurveys.com/overview.aspx; Alpha mannosidosis FP7 natural history study http://www.alpha-man.eu/index.htm

S2. Department of Health, National Guidelines for treatment of lysosomal diseases: http://www.specialisedservices.nhs.uk/documents/index/document_category_id:23

S3. Advisory Group for National Specialised Services Annual Report, 2011-12 (LSD statistics, p. 82; ERT drug budget, table 10, p. 104; ERT by disease and drug with patient numbers, England, table 11, p. 105).

S4. Advisory Group for National Specialised Services Annual Report 2010-11 (ERT by disease and drug with patient numbers, England, p. 62; p. 79).

S5. National Specialised Commissioning Priorities 2011-12 (Total LSD patient numbers in England, p. 45). http://www.specialisedservices.nhs.uk/library/21/National_Specialised_Commissioning_Priorities_201112.pdf

S6. Changes to National Commissioning Group services and NCG Commissioning intentions 2008-9 (p. 7). http://www.specialisedservices.nhs.uk/library/24/Changes_to_Nationally_Commissioned_Services_from_April_2008_and_the_National_Commissioning_Group_Commissioning_Intentions_for_200809.pdf

S7. Companies benefiting directly from the research: Genzyme http://www.genzyme.co.uk/products.aspx; Shire Human Genetic Therapies www.shire.com/shireplc/en/products/list; Actelion http://www.actelion.co.uk/uk/healthcare-professionals/products/index.page; Biomarin http://www.bmrn.com/products/aldurazyme.php

S8. Organisations directly benefiting from the research: UK MPS society research page http://www.mpssociety.org.uk/research/ ; National MPS Society USA http://www.mpssociety.org/clinical-trials/ ; Canadian MPS society: http://www.mpssociety.ca/page/announcements.aspx

S9. Boelens JJ, Wynn RF, Bierings M. HSCT for inborn errors of metabolism. In: Apperley J et al., editors. *The EBMT-ESH Handbook.* 2008. pp. 544-553. http://www.ebmt.org/Contents/Resources/Library/EBMTESHhandbook/Pages/EBMT-ESH-handbook.aspx