Institution: University of Oxford

Unit of Assessment: 5 – Biological Sciences

Title of case study: Life-changing treatments and clinical tools for lysosomal storage disorders

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:
Frances Platt	Prof of Biochemistry & Pharmacology	1989 onwards
Danielle te Vruchte	Graduate Research Assistant	2001 – 2016, 2020 – present
David Priestman	Postdoctoral researcher	1998 – 2010, 2011 – present
David Smith	Research technician	2002-2012, 2016 – present

Period when the claimed impact occurred: August 2013 – December 2020

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

1. Summary of the impact

Research at the University of Oxford led to the development of treatments for the lysosomal storage disorder Niemann-Pick disease type C (NP-C), a rare but devastating multi-system disorder. The resulting drug, miglustat, is the only drug currently licensed for NP-C. Miglustat significantly slows disease progression, improves quality of life, increases life expectancy, and is used by the majority of NP-C patients worldwide. In the UK, between 70% and 90% of the approximately 100 patients receive the drug. The introduction of miglustat generic drugs in 2019 has reduced costs, leading to healthcare savings. University of Oxford researchers have developed other new drugs for NP-C that are benefiting patients worldwide in clinical trials, and new tools for monitoring disease progression that are being adopted as international standards.

2. Underpinning research

Developing therapies for lysosomal storage disorders

Niemann-Pick disease type C (NP-C) is a lysosomal storage disorder (LSD) in which molecules destined for breakdown and recycling (e.g. glycosphingolipids) accumulate to pathological levels, affecting multiple organs including the central nervous system. In prior research, Platt and colleagues at the University of Oxford had developed a glucose analogue (*N*B-DNJ or miglustat) that inhibits glycosphingolipid biosynthesis, providing the potential for an oral-based treatment for LSDs termed 'substrate reduction therapy' (SRT). The drug was initially approved for the LSD type 1 (Gaucher disease) in 2002/2003 and marketed by Actelion as Zavesca.

Platt and her colleagues then investigated the use of miglustat in NP-C. Although this disease had previously been considered to be a cholesterol storage disorder, in 2004 the group demonstrated that treating a patient with miglustat reduced pathological lipid storage, improved endosomal uptake and normalised lipid trafficking [1]. Since miglustat has no direct effect on cholesterol metabolism, this research indicated that accumulation of glycosphingolipids was the primary pathogenic event in NP-C and so miglustat could be an effective treatment. An international clinical trial followed, and in 2009 miglustat was approved by the European Medicines Agency as the first and only targeted therapy for treating NP-C. In 2009/10, Platt began working with the company Orphazyme to investigate whether therapies targeting the Heat-Shock-Protein-70 (HSP70) family of chaperones might have therapeutic potential. Platt and colleagues showed in mouse models that increasing HSP70 levels by direct administration of recombinant HSP70 or with arimoclomol or a related drug bimoclomol (both small molecule inducers of HSP70) improved neurological function and reduced lipid storage in mouse models of three LSDs: NP-C, Sandhoff disease and Fabry disease. These proof-of-concept studies were published in 2016 [2].

In 2016, Platt started to investigate the potential of acetyl leucine as a treatment for NP-C patients. Building on observational clinical studies that indicated that the racemic compound improved symptoms of ataxia in NP-C patients, Platt and colleagues at the University of Oxford and elsewhere undertook work in mouse models of NP-C. They found that the L-enantiomer (ALL) but not the D-enantiomer delayed disease progression and extended life span in mouse models, and that patients treated in the observational study showed stabilisation or improvement in multiple neurological domains, not just those relating to ataxia, after 12 months [3].

Next, Platt and colleagues developed a second-generation compound for SRT that also inhibits glycosphingolipid biosynthesis - the galactose analogue of miglustat, *N*B-DGJ. They tested this compound, named lucerastat, in a mouse model of the LSD Sandhoff disease where it showed greater therapeutic efficacy than *N*B-DNJ (miglustat) with no detectable side effects [4]. Lucerastat could be tolerated at high dose, leading to extended life expectancy and increased delay in symptom onset. Platt and Priestman subsequently carried out preclinical work with lucerastat in collaboration with Actelion for another LSD, Fabry disease, in which the first-line treatment is not fully effective [5].

Developing tools for monitoring NP-C disease progression

Platt and her collaborator Mario-Cortina Borja, an applied statistician at UCL, developed an annual severity *increment* score (ASIS), that uses several criteria to monitor disease severity and progression. Working with clinical colleagues they demonstrated that ASIS can be used to better stratify patients and measure response to therapy in clinical trials [6]. Platt and Cortina-Borja also showed in this study that a less burdensome 5-domain severity scale, comprising a subset of the full scale of 17 neurological domains with most relevance to quality of life, correlated well with the full scale and could therefore be used more easily and consistently to assess clinical severity in patients.

3. References to the research (University of Oxford employees in **bold**, students in *italics*)

1. Lachmann RH, **te Vruchte D**, *Lloyd-Evans E*, **Reinkensmeier G**, **Sillence DJ**, **Fernandez-Guillen L**, **Dwek RA**, **Butters TD**, Cox TM, **Platt FM**. (2004) Treatment with miglustat reverses the lipid-trafficking defect in Niemann–Pick disease type C. *Neurobiol Dis.* 16: 654–658. DOI: 10.1016/j.nbd.2004.05.002
2. Kirkegaard T, *Gray J*, **Priestman DA**, **Wallom K-L**, **Atkins J**, Olsen OD, Klein A, Drndarski S, Petersen NHT, Ingemann L, **Smith DA**, **Morris L**, Bornaes C, Jorgensen SH, **Williams I**, Hinsby A, Arenz C, Begley D, Jaattela M and **Platt FM**. (2016) Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses. *Science Translational Medicine* 8;335. DOI: 10.1126/scitranslmed.aad9823
3. *Kaya E*, **Smith DA**, **Smith C**, **Morris L**, Bremova-Ertl, Cortina-Borja M, **Fineran P**, Morten KJ, Poulton J, Boland B, Spencer J, Strupp M and **Platt FM**. (2020) Acetyl-leucine slows disease progression in lysosomal storage disorders. *Brain Communications.* DOI: 10.1093/braincomms/fcaa148
4. *Andersson U*, **Smith D**, *Jeyakumar M*, **Butters TD**, Borja MC, **Dwek RA**, **Platt FM**. (2004) Improved outcome of N-butyldeoxygalactonojirimycin-mediated substrate reduction therapy in a mouse model of Sandhoff disease. *Neurobiology of Disease* 16: 506–515. DOI: 10.1016/j.nbd.2004.04.012
5. Welford R, Mühlemann A, **Priestman D**, Garzotti M, Deymier C, Ertel E, Iglarz M, Baldoni D, **Platt F** & Probst M. (2017) Lucerastat, an iminosugar for substrate reduction therapy in Fabry disease: preclinical evidence. *Molecular Genetics and Metabolism.* 120. S139-S140. DOI: 10.1016/j.ymgme.2016.11.369
6. Cortina-Borja M, **te Vruchte D**, Mengel E, Amraoui Y, Imrie J, Jones SA, i Dali C, **Fineran P**, Kirkegaard T, Runz H, Lachmann R, Bremova-Ertl T, Strupp M and **Platt FM**. (2018) Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. *Orphanet Journal of Rare Diseases* 13;143. DOI: 10.1186/s13023-018-0880-9

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4. Details of the impact

Background and context of impact

NP-C is a rare disease (1 in 100,000 live births) with a highly variable but uniformly fatal clinical spectrum, ranging from a perinatal, rapidly progressive systemic disorder to an adult-onset chronic and life-limiting neurodegenerative form. Platt's research has had an impact on patients with NP-C and other LSDs in three main areas: (a) Miglustat is the only approved targeted therapy for the disease and has had a transformational impact on the treatment of NP-C patients worldwide; (b) Benefits to the companies Orphazyme, IntraBio and Idorsia in reaching clinical trials of efficacy of new treatments, and in one case FDA Breakthrough Therapy status ahead of full approval; (c) development and validation of a simplified clinical severity scale that has been recommended for multiple clinical purposes including in clinical trials.

> ***"****The impact of Professor Platt's work in the area of Lysosomal diseases and in particular NPC, has been truly immense. It has not only led to the only approved therapy for NPC, but has greatly expanded our understanding of the disease, and contributed to the development of other therapeutic targets and new ways to monitor and assess disease progression."*
>
> Niemann-Pick UK [A]

Impact of miglustat and its generics on quality of life

Multiple studies have shown that miglustat substantially slows or stabilises progression of neurological manifestations of the disease and leads to significant improvements in both life expectancy and quality of life. This is affirmed by two long-term follow-up studies of the largest cohort of miglustat-treated NP-C patients from 2009 to 2017 [B]. One of these studies described a range of improved treatment outcomes for 472 patients from 22 countries and reported that 70% of patients on continuous treatment had improved or had stable disease [Bi]. The other study found a significant reduction in the risk of mortality for 789 patients from 21 countries; compared with patients not treated, median survival of treated patients was longer by approximately 10 years from onset of the patients' neurological manifestations [Bii].

Miglustat is authorised for use in most countries except the US and has been recommended as the standard of care for NP-C patients since 2018 [C]. There are approximately 100 NP-C patients currently in the UK, between 70-90% of whom are treated with miglustat. This proportion has increased from an estimated 50% in 2013, and has contributed to a greater proportion of patients diagnosed as children living into their teens/adulthood [A]. The number of patients diagnosed with NP-C, in particular adult-onset patients, has also increased in recent years [A]. A detailed analysis in France showed that during the period 2009-2016, half of new NP-C diagnoses were in adults compared with only one fifth during the period 2000-2008, and suggested this was due to '*improvement in awareness of NP-C among neuropsychiatrists after miglustat therapy became available*' [D].

Although miglustat is not approved by the FDA for treatment of NP-C in the US, it can be prescribed to patients 'off-label' because it is approved for the treatment of Gaucher disease. The Mayo Clinic estimates that there are approximately 500-600 NP-C patients in the US, of whom at least half are treated with miglustat [E].

Economic benefits to pharmaceutical companies and healthcare providers

Sales figures from Actelion, available up to 2016 before the company was taken over by Johnson and Johnson, reflect the increasing use of miglustat (brand name Zavesca) for NP-C [F]. Total sales for miglustat (outside the US) were strong in 2014 (CHF103,000,000), with an increase since 2013 attributed to its indication for NP-C and as a result of "*expanding diagnostic tools and heightened awareness*". Demand against NP-C indication increased in 2015 and gave 'double-digit growth' for 2016. The report for 2016 states that "*Globally, patients receiving*

Zavesca grew by 6% compared to 2015, driven by a 13% increase in the treatment of patients with NP-C".

Following expiry of the patent for use of Zavesca in NP-C in 2019, generics became available that year in many countries. In the UK, all three regional contracts for miglustat use in NP-C patients are currently held by generics companies [G] and in France, most patients are using generics. Generics were introduced at a reduced price compared with Zavesca and the costs of both have fallen over the subsequent 18-month period. The saving varies across European countries from 20% to 50%. In Italy, where contract prices are available, the generic product was first marketed at EUR32 per capsule [text removed for publication] whereas the cost is now EUR15-20 [G]. Given that the daily dose is 6 capsules, the annual saving from using the generic is of order EUR40,000 per patient, per year. The generic is the preferred drug for insurance companies in the US because of its lower cost.

A study published in 2020 showed that miglustat may reduce aspiration risk and improve quality of life, providing further evidence of the benefits of miglustat therapy [H]. This new study, along with supporting evidence from other recent studies, is being used by patient groups and [text removed for publication] [E].

Impact of other, novel treatments for NP-C and related LSDs

As a result of work by Platt and collaborators [2], Orphazyme chose NP-C for its first clinical trial of arimoclomol [I]. The Phase II/III trial in NP-C patients (50 in total, 34 receiving arimoclomol) reported improvement in neurological clinical symptoms and quality of life for patients and slower rates of disease progression (annual progression reduced by more than 60% compared with placebo) following 12 months of treatment [Ji, Jii, Ki]. The best outcomes were seen in patients on miglustat and arimoclomol. Based on these findings and in order to bring the product to patients as soon as possible, the US FDA granted Breakthrough Therapy and Orphan Drug designations to arimoclomol for NP-C in November 2019 [Kii]. A small but increasing number of patients in the US and Europe are being treated via this expanded access programme [I, Ki]. Orphazyme has submitted an application for marketing approval to the FDA in the US (July 2020) [Kiii] and submitted a Marketing Authorisation Application to the European Medicines Agency in November 2020 [Kiv].

There has also been substantial economic impact from the development of arimoclomol with Orphazyme's CSO stating that "*Professor Platt has been instrumental through the development of Orphazyme from being a one-person company [in 2010] to one of Europe's most prolific young biotechs....with >150 employees with offices in Denmark, US, France and Switzerland*" [I].

In October 2020, IntraBio announced results from its trial of ALL in NP-C (NCT03759639, N=32). The compound demonstrated a statistically significant and clinically meaningful improvement in symptoms, functioning, and quality of life for paediatric and adult patients with NP-C [L].

The company Idorsia has invested in the testing of lucerastat, the second generation miglustat analogue developed and tested by Platt and colleagues [4,5], through a randomised, double-blind Phase III trial for Fabry patients across multiple international centres (MODIFY, NCT03425539) [M]. This progressive and potentially life-threatening LSD is more common than NP-C, affecting between 1 in 40,000 and 1 in 60,000 males, and has no fully effective first-line treatment.

Impact of tools for monitoring NP-C disease progression

The work carried out by Platt and colleagues on developing tools for monitoring NP-C disease progression [6] has had improved the ability to monitor treatment responses in clinical trials. Orphazyme already commenced its trial of arimoclomol before validation of the ASIS metric, but applied the metric to their initial cohort and as a result were able to recruit a larger cohort in order to be more confident of having meaningful outcomes from the study [A]. The company also used the 5-domain clinical severity scale validated by Platt and Cortina-Borja [6] as the primary outcome measure in its trial of arimoclomol [I,J] and used the ASIS metric to examine the rate of disease progression at the start and end of the trial.

5. Sources to corroborate the impact

A. Letter from Chair and Chief Executive, Niemann-Pick UK confirming details of UK NP-C patient numbers and miglustat use and corroborating Platt's contribution to therapies and monitoring tools for NP-C.

B. Journal articles reporting treatment outcomes and survival of NP-C patients on miglustat:
(i) Patterson MC et al (2020), Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: a final report of the NPC Registry. *Orphanet J Rare Dis* 15, 104. DOI: 10.1186/s13023-020-01363-2
(ii) Patterson, MC et al (2020) Long-term survival outcomes of patients with Niemann-Pick disease type C receiving miglustat treatment: A large retrospective observational study. *J. Inherit Metab* Dis. 43:1060–1069. DOI: 10.1002/jimd.12245

C. Journal article: Geberhiwot T et al. (2018) Consensus clinical management guidelines for NP-C. *Orphanet J Rare Dis*. 13:50. DOI: 10.1186/s13023-018-0785-7

D. Journal article: Nadjar et al. (2018) Adult Niemann-Pick disease type C in France. *Orphanet J Rare Dis.* 13:175. DOI: 10.1186/s13023-018-0913-4

E. Corroborator 1: Professor of Neurology, Pediatrics and Medical Genetics at the Mayo Clinic Children's Centre, Rochester, MN, US, who may be contacted to corroborate the use of miglustat in the US

F. Actelion media releases of their full year reports for (i) 2014 (p10, p12), (ii) 2015 (p4, p7) and (iii) 2016 (p3, p6), downloaded from www.actelion.com but no longer available publicly due to acquisition by Johnson and Johnson. 2015 media release available (March 2021) at https://studylib.net/doc/9930950/media-release

G. Corroborator 2: General Manager, Commercial Operations (Europe), Piramal Critical Care, who may be contacted to corroborate use and costs of generics in Europe and UK

H. Journal article: Solomon BI et al. (2020) Association of miglustat with swallowing outcomes in Niemann-Pick Disease, Type C1. *JAMA Neurol*. DOI: 10.1001/jamaneurol.2020.3241

I. Letter from Chief Scientific Officer of Orphazyme, corroborating Professor Platt's contribution to the development of arimoclomol as a treatment for NP-C

J. Report of results from phase II/II trial of arimoclomol (i) from Orphazyme (January 2019): https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3561743&lang=en-GB&companycode=dk-orpha&v= and (ii) poster from the 16th Annual WORLDSymposium™ for lysosomal diseases, February 2020

K. Announcements concerning arimoclomol status from Orphazyme:
i) Company update including summary of phase II/III trial on p.16 (April 2020) https://orphazyme.gcs-web.com/static-files/027b124d-5137-45a5-aa2c-a7ec5235a060
ii) Announcement of Breakthrough Therapy designation for arimoclomol (November 2019): https://www.orphazyme.com/news-feed/2019/11/19/orphazyme-receives-breakthrough-therapy-designation-for-arimoclomol-in-niemann-pick-disease-type-c-npc
iii) Announcement of submission of new drug application to US FDA for arimoclomol for NP-C (July 2020): https://www.orphazyme.com/news-feed/2020/7/20/orphazyme-completes-rolling-submission-of-new-drug-application-to-us-fda-for-arimoclomol-for-niemann-pick-disease-type-c
iv) Announcement of extension of the review period by the FDA to allow completion of the review (December 2020) https://www.orphazyme.com/news-feed/2020/12/27/orphazyme-provides-regulatory-update-on-arimoclomol-for-npc

L. Announcement by IntraBio of trial outcomes 19 October 2020: https://intrabio.com/2020/10/19/intrabio-reports-further-detail-on-positive-data-from-ib1001-multinational-clinical-trial-for-the-treatment-of-niemann-pick-disease-type-c/

M. Fabry Disease News article about the lucerastat trial (February 2020): https://fabrydiseasenews.com/lucerastat/