Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Therapeutic Developments for Sphingolipidoses

1. Summary of the impact (indicative maximum 100 words)

Research conducted by Professor TM Cox has led to several advances in the management of lysosomal storage disorders; i) development of miglustat (Zavesca®); now available throughout the world (EMA and FDA approved) for adult patients with Gaucher's disease and throughout the European Union and five other countries worldwide for adult and pediatric patients with Niemann-Pick type C disease, ii) development of the potential successor eliglustat; now in Phase 3 clinical trials, iii) identification of a biomarker for Gaucher's: CCL18/PARC, now incorporated into NHS standard operating procedures for monitoring therapeutic intervention. His pre-clinical research into gene therapy for Tay-Sachs disease also helped establish the NIH-funded Gene Therapy Consortium and gain the FDA's pre-IND approval for clinical trials in 2013, which together have raised public awareness of this disease.

2. Underpinning research (indicative maximum 500 words)

The underpinning research led by Professor Cox (Dept of Medicine, since 1989), sought to develop innovative treatments for glycosphingolipid disorders (sphingolipidoses). These inherited conditions arise from genetic defects in lysosomal proteins; principally acid hydrolases which break down glycolipids. Pathological accumulation of macromolecular substrates and other metabolites in the lysosomal compartment impairs cellular integrity and function and affects many tissues including the bone marrow, liver, spleen, bone, lungs; in neuronopathic Gaucher's and Tay-Sachs diseases, neurodegeneration is relentless and often severe with onset in infancy and childhood.

Potential therapies could act by i) inhibiting the enzyme responsible for glycolipid synthesis or ii) augmenting the enzyme responsible for its degradation, both approaches being dependent on therapeutic delivery to the target tissue; finally iii) gene transfer offers the prospect of definitive therapeutic correction. Cox and colleagues (Mistry, Clinical Lecturer and Wraight, Consultant Radiologist) conducted a definitive proof-of-principle study for enzyme therapy that was specifically aimed at measuring enzyme half-life and exploring targeting in living patients affected by Gaucher's disease. Here, deficient glucocerebrosidase activity causes systemic accumulation of glucocerebroside by pathological macrophages in viscera and bone marrow. Radiolabelled enzymatically active human glucocerebrosidase (modified to increase its affinity for macrophage glycoprotein receptors), was administered intravenously to eight patients with Gaucher disease with scintigraphic monitoring of its distribution, pharmacodynamics and metabolism. It was found that natural and recombinant enzymes were avidly taken up into liver, spleen and bone marrow; that uptake was saturable, indicating targeting of receptors on macrophages, and that enzyme turnover was consistent with therapeutic posology; specific correction of the enzyme defect in Gaucher cells purified from surgically removed fresh spleen tissue was also shown [1].

After scientific discussions with Platt and Butters (University of Oxford), in 1998 Cox chose the target disease, designed and led the pivotal trial (with clinical collaborators, Hollak, The Netherlands; Hrebicek, Czech Republic, and Zimran, Israel) of a multicentre, 1-year open-label study in patients with non-neuronopathic Gaucher's disease. In this study the intervention was the UDP-glucosylceramide synthase inhibitor; N-butyldeoxynojirimycin (miglustat), an approach based on modulating glycosphingolipid synthesis (substrate reduction therapy). This treatment was tolerable and improved several clinical features, including low blood counts and enlargement of the liver and spleen [2]. In an exploratory clinical experiment in 2003-4, with Lachmann (MRC Clinician Scientist and Clinical Lecturer until 2005, now The National Hospital for Neurology and Neurosurgery, London) and the Platt laboratory, it was shown that the same agent had corrective cellular effects on the related disorder, Niemann-Pick disease type C (NPC). Here, treatment with miglustat reduced pathological lipid storage and corrected the defective lysosomal trafficking in NPC readily detected in circulating B lymphocytes [3].

From 1997-2000 Cox and colleagues led studies with Aerts and colleagues (The Netherlands) to

identify biomarkers associated with Gaucher disease. By comparing rare gene expression subtractively in spleen tissue and plasma samples from control subjects and patients, and from patients before and after therapeutic intervention, they ascertained that the chemokine CCL18/PARC was elevated in this disease and reduced following therapy [4]. CCL18/PARC met criteria as a novel biomarker to assess disease management [4, 5, 6]. In 2004-6 Cox and colleagues conducted a gene-therapy study using a rodent model for acute Tay-Sachs disease - the Sandhoff mouse also has genetic deficiency of lysosomal beta-hexosaminidase A. Cachón-González et al. used intracranial adeno-associated viral vectors to transduce human beta-hexosaminidase alpha and beta subunits into the brain: while untreated mice died before 18 weeks of age, gene transfer rescued the mice for over a year [7]. Furthermore, disease onset was delayed and neurological function was preserved. Experiments, in collaboration with researchers at Auburn University, Alabama in Sandhoff cats confirmed these findings [8] and validated the principle of gene transfer widely in the neuraxis for these disorders.

3. References to the research (indicative maximum of six references)

1) Mistry PK, Wraight EP, Cox TM (1996).Therapeutic delivery of proteins to macrophages: implications for treatment of Gaucher's disease. Lancet; 348: 1555-9. DOI: 10.1016/S0140-6736(96)04451-0

2) Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebícek M, Platt F, Butters T, Dwek R, Moyses C, Gow I, Elstein D, Zimran A (2000). Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet; 355: 1481-5. DOI: 10.1016/S0140-6736(00)02161-9

3) 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. Neurobiology of Disease 16: 654-658. DOI: 10.1016/j.nbd.2004.05.002

4) Boot R.G., Verhoek M., de Cost M, Hollak CE, Maas M, Bleijtevens B., Van Breemen MJ., van Meurs M., Boven LA., Laman JD., Moran MT, Cox TM., Aerts JM. (2004). Marked elevation of the chemokine CCL18/PARC in Gaucher disease: a novel surrogate marker for assessing therapeutic intervention. Blood 103: 33-39. DOI: 10.1182/blood-2003-05-1612

5) Moran MT, Schofield JP, Hayman AR, Shi GP, Young E, Cox TM (2000) Pathologic gene expression in Gaucher disease: up-regulation of cysteine proteinases including osteoclastic cathepsin K. Blood. Sep 1;96(5):1969-78.PMID: 10961902

6) Deegan, PB., Moran, M-T., McFarlane, I., Schofield, JP., Boot, RG., Aerts, JMFG., and Cox, TM. (2005) Clinical evaluation of chemokine and enzymatic biomarkers of Gaucher disease. Blood Cells, Molecules and Disease 35: 259-267. DOI: 10.1016/j.bcmd.2005.05.005

7) Cachón-González MB, Wang SZ, Lynch A, Ziegler R, Cheng SH, Cox TM (2006). Effective gene therapy in an authentic model of Tay-Sachs-related diseases. Proc Natl Acad Sci (U S A); 103: 10373-8. DOI: 10.1073%2Fpnas.0603765103

8) Bradbury AM , Cochran JN, McCurdy VJ, Johnson AK, Brunson BL , Gray-Edwards H, Leroy SG, Hwang M, Randle AN, Jackson LS, Morrison NE, Baek RC, Seyfried TN, Cheng SH, Cox NR, Baker HJ, Cachón-González MB, Cox TM, Sena-Esteves M, Martin DR.(2013). Therapeutic response in feline Sandhoff disease despite immunity to intracranial gene therapy. Molecular Therapy;21(7):1306-15. doi: 10.1038/mt.2013.86

Peer-reviewed Research Funding:

Charities; Sparks, the children's charity; CLIMB; National Tay-Sachs & Allied Diseases Association (USA); Croucher Foundation Hong Kong, MPS Society, UK Gaucher's Association, Hunter's Hope and Paul Morgan Trust and Niemann-Pick Disease Group totalling £1.32m.

Government sources; MRC and MRC/FEC joint funding (DTI-LINK award 8/CE09147 and Confidence in Concepts award to University) totalling £3.845m over the research period, including on-going funding. NIH totalling £1.741m over the research period, including on-going funding. European Commission FP7-HEALTH-201678; £265,000 over the research period.

Future funding secured; MRC Stratified Medicine Consortium award (1/10/2013-31/12/2017; one of only three UK programmes funded for research into rare disease) GAUCHERITE consortium: http://www.mrc.ac.uk/Newspublications/News/MRC008947 Lead applicant; Cox (FEC £3.728m. MRC contribution (£2.922m) and MRC Biomedical Catalyst MR/K025570/1 (1/10/2013-31/12/2017 £2.804m) Lead applicant; Cox.

4. Details of the impact (indicative maximum 750 words)

Research by Cox and collaborators has led to i) innovative therapy for glycosphingolipidoses now approved for Gaucher's disease and Niemann-Pick type C disease, UK/worldwide, ii) further adoption of this strategy in Phase 3 clinical trials iii) development of novel monitoring and diagnostic tests for managing Gaucher's disease – adopted by the NHS and international clinical trials.

Impact on health and welfare

New clinical interventions: After Cox's paper in the Lancet (2000) on the efficacy of miglustat in adults with Gaucher's disease, with a 2-year extension phase, Oxford Glycosciences gained approval as (Zavesca®) in 2002 and 2003 from the EMA and FDA for Gaucher Disease; the drug was acquired by Actelion in 2005. The suggestion by Cox (Lancet 2000), that the therapy warranted exploration in other glycosphingolipid disorders, prompted trials by Actelion (2002-2008; NCT00517153) in Niemann Pick type C disease; ultimately leading to approval of miglustat (in the UK/ world) for both conditions [1, 2]. Cox has also led post-marketing studies into the efficacy of miglustat for disease maintenance in Gaucher disease [3]. Cox is currently lead investigator of the multinational Phase 3 "ENCORE" trial (sponsored by Genzyme) for the compound eliglustat with the same therapeutic target in Gaucher disease (NST00943111); early results (9th Annual Lysosomal Disease Network WORLD Symposium in Orlando, Florida February 2013), show that this study has met its primary efficacy endpoint [4].

Novel diagnostics: After showing that high concentrations of CCL18/PARC in Gaucher disease decreased after treatment; this biomarker was incorporated into NHS's Standard Operating Procedures (2007 updated 2012) for determining disease severity and treatment success [5] The chemokine is now in widespread use and is a primary outcome in therapeutic trials where it is used as a response marker and to compare competing preparations e.g. velaglucerase alfa and imiglucerase (for example see ref 6)

Impact on society, culture, creativity

Public understanding and debate: Professor Cox has been actively engaged in raising awareness of lysosomal disorders amongst both the general public and patient groups and their families so that they may better understand the aetiology and management of these disorders. He made a presentation interview with The Naked Scientists (BBC radio programme; 19th April 2011), regarding gene therapy for lysosomal diseases attracted approximately 55,000 downloads worldwide with an equivalent audience estimated for the live radio show (The Naked Scientists, personal communication; Ref 7). Cox frequently communicates with charitable patient organizations to apprise them of advancements in the field. He hosted a WebEx (20th May 2013) for the UK Gaucher Association. On 14th October 2012 delivered the 17th McFadzean Oration at the Hong Kong College of Physicians on the funding of treatment for rare disorders such as Gaucher disease was delivered to a multi-faculty audience of practitioners during the principal training days of the Hong Kong Academy of Medicine. In 2011 he helped start the UK Cure Tay-Sachs Foundation (Patron) and interacts with the National Tay-Sachs and Allied diseases Foundation, Boston USA through the Tay-Sachs Gene Therapy (TSGT) Consortium, which was founded on the discoveries of the Cox group in gene transfer.

Impact on commerce

New product development and business performance: Firstly, publication of the Lancet (2000) article (ref 2, section 3) and marketing of Zavesca® by Oxford Glycosciences reduced the stock value of Genzyme corporation which had the exclusive market for Cerezyme, the enzyme therapy for Gaucher disease [8]. This drove Genzyme to forge an academic partnership to develop other orally active UDP-glucosylceramide synthase inhibitor molecules - thus generating the licensed eligustat tartrate programme with late-phase 3 clinical trials in Gaucher disease. Secondly, approval of the drug miglustat, facilitated for Oxford GlycoSciences by the research of Cox, Lachmann (Clinical Research Fellow) in Cambridge and FM Platt and T Butters (cell biologist and biochemist in Oxford) and colleagues has brought substantial revenue; the Actelion website citing sales figures of approximately CHF20m (Swiss franc) per quarter since 2012 [9]. Thirdly, the assay for CCL18/PARC, mentioned above, based on ELISA, sold by R&D systems (product DY394; £450 per kit) whose website cites Cox TM *et al*. as evidence for use as a biomarker of Gaucher disease.

Academic consultancy: Beyond senior academic and clinical roles Cox is specialist advisor to

several organisations (including: charities (Gaucher Association. Cure Tay-Sachs, Tay-Sachs Gene Therapy Consortium and pharmaceutical companies (trial design, regulatory issues). He is a member of the Scientific (Rare diseases) Board of Genzyme-Sanofi (2013-) and has advised EMA (marketing approval and trial design for aldurazyme (for MPS1), Replagal (for Fabry disease), miglustat and velaglucerase alpha (Gaucher disease) - and on Clinical use of Biomarkers workshop of the Food & Drug administration, Washington DC (2011) Through membership of the TSGT consortium he advised the US Food and Drug Administration on the design of a Clinical trial of Gene Therapy. Cox is chairman of the Scientific Advisory board of the Niemann-Pick Research Foundation.

Impact on practitioners and services

Professional standards and guidelines: Cox's research has directly introduced miglustat as second-line therapy in adults with Type 1 Gaucher disease, for whom enzyme replacement therapy is not suitable. His research into biomarkers has directly led to the incorporation of the CCL18/PARC diagnostic test into the NHS SOP for management of this disorder, as above [5]. Miglustat is the first and only licensed therapy for children and adults with Niemann-Pick disease type C [1].

Professional training: Cox's paper entitled "Gaucher disease: clinical features and natural history" (1997) continues to have impact on healthcare practitioners in their understanding of the disease. The paper is currently cited on the Gaucher Care website as a source of information to aid healthcare professionals in making a diagnosis [10].Professor Cox has frequently lectured at training courses for metabolic clinicians in the University of Mainz from 2006, and from 1996 the biennial European Working Group for the Study of Lysosomal diseases (ESGLD) as well as the Gaucher leadership forum (2008-) – all targeted to healthcare professionals looking to develop improved management protocols and innovative therapies. Professor Cox is joint Editor (2003-) of the three-volume Oxford Textbook of Medicine, 5th edition OUP (2010) – the most comprehensive work of its kind with international sales ~10,000.

Professional Services; In 1997 Professor Cox founded the first National Gaucher service at Addenbrooke's Hospital, Cambridge (now the Lysosomal Disorders Unit [11]), paving the way for a further seven National Centres by 2005. The Unit continues to provide a unique service of clinical management and support that is essential for patients with these disorders, and for their families.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. http://www.medicinescomplete.com/mc/bnf/current/PHP6351-miglustat.htm BNF entry for miglustat being indicated in Gaucher's disease and Niemann Pick type C disease.

2. http://www1.actelion.com/documents/corporate/fact_sheets/FS_MarketedProduct.pdf Actelion's information on product development (miglustat/Zavesca®) citing Elstein et al 2004 (Cox is co-author) and dates for EU approval in Type 1 Gaucher (date) and Niemann Pick Type C (2009)

3. Cox TM, Amato D, Hollak CEM, Luzy C, Silkey M, Giorgino R and Steiner RD. (2013). Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study. Orphanet Journal of Rare Diseases MS: 2012714044731433 (published 7 December 2012).

4. http://news.genzyme.com/press-release/genzyme-announces-positive-new-data-two-phase-3-studies-oral-eliglustat-tartrate-gauch Study sponsor's website confirming primary endpoint of Phase 3 trial has been met.

5. http://www.specialisedservices.nhs.uk/library/23/SOP_for_adult_Gauchers_disease.pdf

6. http://apps.who.int/trialsearch/trial.aspx?trialid=EUCTR2007-002840-21-ES CCL18/PARC as biomarker in primary outcome of a trial on WHO clinical trials register EUCTR2007-002840-21-ES

7. Personal communication from the founder of The Naked Scientists

8. www.secinfo.com/dVut2.2AXk.3.htm *Market response to Actelion developing Zavesca®.*

9. Company website for sales of (Zavesca®) of approximately CHF 20m per quarter since 2012. http://www.actelion.com/en/investors/financial-information/marketed-products/zavesca-sales.page

10. http://www.gauchercare.com/en/healthcare/diagnosing.aspx

11. Lysosomal Disorders Unit: Box 135, Cambridge University Hospitals NHS Foundation Trust: http://www.cuh.org.uk/addenbrookes/services/clinical/lysosomal/lysosomal_index.html