Institution: University of Exeter

Unit of Assessment: Clinical Medicine

Title of case study: Stopping insulin; a life-changing therapeutic intervention for patients with neonatal diabetes

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

The treatment of patients with neonatal diabetes has been transformed by the research of Professors Sian Ellard and Andrew Hattersley at Exeter. Childhood diabetes usually presages a life-long requirement for insulin injections and a reduction in quality of life. This research revealed that ~50% of patients with permanent neonatal diabetes have mutations in a potassium channel regulating insulin secretion. A new diagnostic test was introduced and relevant patients were switched from insulin injections to oral therapy. As a result, patients in 77 countries across 5 continents now benefit from improved care, a better quality of life and reduced healthcare costs.

2. Underpinning research (indicative maximum 500 words)

Before this research, most patients diagnosed with diabetes in the first six months of life faced a lifetime of insulin treatment. In 2002, Prof Hattersley (FRS; appointed to University of Exeter in 1995) initiated an international search for patients with neonatal diabetes and Prof Ellard (appointed in 1997) began the search for disease-causing mutations. As a result, their postdoctoral fellow, Dr Anna Gloyn, found that the most common cause was a mutation in a subunit (Kir6.2) of the pancreatic beta cell ATP-sensitive potassium (K_{ATP}) channel [1,2].

The pancreatic K_{ATP} channel controls electrical activity, linking raised blood glucose levels to insulin secretion. Binding of ATP to the Kir6.2 subunit closes the channel to initiate insulin secretion. Molecular modelling suggested that the patients' mutations would affect ATP binding and hence prevent insulin secretion. This was confirmed by functional studies of isolated potassium channels expressed either in Xenopus oocytes [1] or cultured pancreatic beta-cells (with Prof Noel Morgan in Exeter).

The pivotal stage in the research was recognising the possibility for pharmaceutical intervention. The K_{ATP} channel defect suggested that, in affected patients, the glucose sensing and insulin synthesis/secretion processes are intact, but failure to secrete insulin is due to the channel remaining open in the presence of ATP. Sulphonylurea drugs used to treat type 2 diabetes act by binding to the sulphonylurea receptor (SUR1) subunits of the channel to cause their closure, independently of ATP. Prof Hattersley proposed that sulphonylureas might close the channels and facilitate insulin secretion when administered to patients *in vivo*.

Clinical evidence from "proof of principle" studies supported this possibility and in 2005 Prof Hattersley and PhD student Dr Ewan Pearson led an international clinical trial in which >90% of patients with Kir6.2 mutations were able to stop insulin treatment and achieve better blood glucose control [3]. The improved glycaemic control predicts a lower risk of diabetic complications later in life. In 2006, Prof Ellard found that mutations in the SUR1 subunit also cause neonatal diabetes [4]. Overall, around 50% of patients with permanent neonatal diabetes have a mutation in either the Kir6.2 or SUR1 subunits and most patients respond to sulphonylurea therapy [5].

Approximately 20% of patients with Kir6.2 or SUR1 mutations also have impaired neurological function. A small number have severe developmental delay, epilepsy and neonatal diabetes (named by the

Exeter group as DEND syndrome). Prof FM Ashcroft's group (Oxford) showed that the mutations in these patients have the greatest effect on channel function. A more common intermediate form of DEND syndrome with moderate developmental delay was also recognised and the researchers investigated the responses of these patients to sulphonylurea treatment. Reports have described improved cognitive function (particularly speech and concentration), behaviour, sleeping patterns and motor development [6]. The neurological benefits are likely to be greatest in those children treated with sulphonylureas from diagnosis since brain plasticity is greatest in early childhood.

This research has provided one of the first examples of genomic medicine where detailed knowledge of a patient's genome determines their optimal treatment.

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

Evidence of the quality of the research is provided via a selection of highly-cited, peer reviewed, publications and by the award of external grant support.

1. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JP, Sumnik Z, van Rhijn A, Wales JK, Clark P, Gorman S, Aisenberg J, Ellard S, Njølstad PR, Ashcroft FM, Hattersley AT. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med. 2004 350: 1838-1849. (692 citations to Oct 13)

2. Flanagan SE, Edghill EL, Gloyn AL, Ellard S, Hattersley AT. Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. Diabetologia. 2006 49: 1190-1197. (130 citations to Oct 13)

3. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, Shield J, Robert JJ, Holst JJ, Clark PM, Ellard S, Søvik O, Polak M, Hattersley AT; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006 355: 467-777. (423 citations to Oct 13)

4: Ellard S, Flanagan SE, Girard CA, Patch AM, Harries LW, Parrish A, Edghill EL, Mackay DJ, Proks P, Shimomura K, Haberland H, Carson DJ, Shield JP, Hattersley AT, Ashcroft FM. Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. Am J Hum Genet. 2007 81:375-82. (81 citations to Oct 13)

5: Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT; Neonatal Diabetes International Collaborative Group. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care. 2008 31:204-9. (76 citations to Oct 13)

6: Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the KCNJ11 gene. Diabetologia. 2006 49:2559-63. (57 citations to Oct 13).

Grants:

1) Wellcome Trust 2003-2008 £1.13M (Prof Hattersley)
   Title: Monogenic and Polygenic Influences on human fetal growth and development – Wellcome Research Leave Award for Clinical Academics
2) Wellcome Trust 2008-2011 £430K (Prof Frayling co-PI)
   Title: An investigation of genes in key beta-cell pathways following the type 2 diabetes WTCCC

genome wide association study.

3) MRC 2007-2010 £1.19M (Prof Frayling co-PI)
   Title: Translating Genome-Wide Association Data from the WTCCC Study into Biological and Clinical Insights in Type 2 Diabetes.
4) European Commission FP7 Initial Training Networks (Marie Curie) 2009-2013 €400K (PI Prof Hatterley and 12 others)
   Title: BOLD – Biology of Liver and Pancreatic Development and Disease
5) Wellcome Trust 2012-2019 £2.9M (Joint PIs Prof Ellard and Hattersley) Title: New insights from neonatal diabetes

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

1) **Diagnostic genetic testing is now available for all patients diagnosed with neonatal diabetes**. Multiple laboratories in Europe and the USA have set up testing for neonatal diabetes. However, for those patients in countries without genetic testing laboratories or for whom the cost of testing is prohibitive, the Exeter laboratory provides rapid testing at no cost to the patient or their parents (funded by the Wellcome Trust). Patients continue to be referred for testing from across the world and, to October 2013, 1169 referrals had been received from 77 countries across 5 continents. The number of patients diagnosed with a K_{ATP} channel mutation causing neonatal diabetes had increased from 10 reported in the first publication (2004) to 454 in October 2013.
2) **Public awareness of neonatal diabetes and the need for genetic testing has been raised**. In July 2009, the Royal Society hosted the first Neonatal Diabetes Open Day for families whose lives have been changed by this research. 45 families came from across the world to celebrate the life-changing transformations they have experienced. Colleagues in Chicago (USA) were inspired to create a US registry and held their first Neonatal Diabetes Family Meeting in June 2010. Facebook groups have been created by parents and parent-led meetings have followed.
3) **Most patients found to have a K_{ATP} channel mutation can stop insulin treatment and achieve better glucose control with sulphonylurea tablets**. For most patients their glucose control on insulin was outside treatment targets but on sulphonylureas glucose levels are maintained within treatment targets and often close to the levels in people without diabetes. More than 500 patients worldwide have now had their diabetes therapy changed and many more newly diagnosed individuals who would otherwise have been prescribed insulin therapy, are being treated with tablets.
4) **Changing from insulin injections to sulphonylurea tablets improves quality of life** by stopping pain at injection sites and removing the many restrictions on life that are imposed by multi-injection or insulin pump therapy. The regulation of insulin secretion in response to ingestion of food means that the patients' diet is no longer tightly restricted. They also experience fewer hypoglycaemic episodes.

5) **The better glycaemic control achieved with sulphonylureas will reduce the future risk of diabetic complications** including heart attack, stroke, kidney failure, blindness and neuropathy.
6) Many of the 20% of **patients with neurological impairment have seen an improvement in their motor skills, cognitive function, speech, concentration, sleep and behaviour**. Reports from parents have been substantiated by teachers and healthcare professionals. The early diagnosis made possible by clinical diagnostic genetic testing means that the maximum number of patients can benefit from improved neurological outcome as well as better diabetes

control and lifestyle gains.

7) **Reduced healthcare costs** due to the cheaper treatment (sulphonylurea tablets vs insulin), reduction in blood glucose monitoring and reduced risk of diabetic complications later in life. For example, colleagues in the USA (g; below) estimate that genetic testing followed by transfer to sulphonylureas and consequent improved glycaemic control saves $12,528 per patient at 10 years and $30,437 at 30 years.
8) This work has **informed public debate on genomic medicine.**

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

Diagnostic genetic testing for all patients diagnosed with neonatal diabetes.

a) The Exeter website www.diabetesgenes.org provides information on genetic testing for neonatal diabetes and has received >115000 hits (at Sept 2013).

Raised public awareness of neonatal diabetes and the need for genetic testing.

b) The Wellcome Trust made a video which is available on their website http://www.wellcome.ac.uk/Education-resources/Teaching-and-education/Big-Picture/All-issues/Genes-Genomes-and-Health/WTDV027170.htm
c) Diabetes UK includes neonatal diabetes within its website "Guide to diabetes" http://www.diabetes.org.uk/Guide-to-diabetes/Introduction-to-diabetes/What_is_diabetes/Neonatal-diabetes/
d) A documentary entitled "Journey to a Miracle: Freedom from Insulin" is in production. A pilot is available at http://www.tmktv.com/result.php?title=Journey-to-a-Miracle:-Freedom-from-Insulin---Pilot

Improved quality of life for patients with a K_{ATP} channel mutation who stop insulin treatment

Transfer from insulin to sulphonylurea tablets has transformed patient lives. Patients and parents describe the effect this has had on their lives in the video filmed by the Wellcome Trust and TMKTV Documentary (see b and d).

e) The Exeter team were awarded the ISPAD (International Society for Paediatric and Adolescent Diabetes) Prize for Innovation in Pediatric Diabetes Care in 2012 see http://www.ispad.org/
f) There have been numerous reports on the TV news and in newspapers about the improved quality of life for patients. One example can be seen on the BBC website http://news.bbc.co.uk/1/hi/health/8176275.stm (August 2009)

Reduced healthcare costs due to the cheaper treatment (sulphonylurea tablets vs insulin), reduction in blood glucose monitoring and reduced risk of diabetic complications later in life.

g) Colleagues in Chicago (USA) demonstrated by modelling that genetic testing for neonatal diabetes is cost-effective with savings achieved within 10 years from testing (Greeley et al 2011 Diabetes Care 34, 622-627).

Informed public debate on genomic medicine

h) The House of Lords Select Committee on Science and Technology conducted an enquiry into genomic medicine. Their report was published in 2009 and includes the example of neonatal diabetes (see page 18 http://www.parliament.uk/business/committees/committees-archive/lords-s-t-select/genomic/).