Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

Oral drug therapy transforms life for neonatal diabetes sufferers

1. Summary of the impact

Research undertaken by Professor Frances Ashcroft at the University of Oxford and her collaborators at the University of Exeter has led to several hundred neonatal diabetes (ND) patients worldwide being able to switch from daily insulin injections to oral sulphonylurea tablet therapy since 2008. ND is a rare but potentially devastating monogenic form of diabetes affecting about 1 in 150,000 live births. Sufferers were previously assumed to have type 1 diabetes and thus were treated with insulin injections; sulphonylurea treatment has transformed their quality of life and led to marked health improvements. It has also ameliorated the mental and motor developmental delay that affects about a fifth of ND patients.

2. Underpinning research

Early research carried out by Professor Frances Ashcroft and colleagues at the University of Oxford's Department of Physiology, Anatomy and Genetics established the mechanism by which an increase in blood glucose concentration triggers insulin secretion from the beta cells of the pancreas. They identified the key event in this process: the closure of ATP-sensitive potassium (K_{ATP}) channels by glucose metabolism. They discovered that the K_{ATP} channel functions as a gated pore and that when the pore is open insulin secretion is inhibited, and when it is closed insulin release is stimulated.

In 1995, Ashcroft's team cloned and sequenced a key subunit of the channel (Kir6.2) and showed the channel is made up of pore-forming Kir6.2 and regulatory SUR subunits[1]. This work was essential preliminary research that enabled subsequent screening of patients' DNA for mutations causing insulin secretory disorders. In 1997, the team showed that ATP (produced by glucose metabolism) binds to Kir6.2 to cause channel inhibition[2] and identified mutations that impair ATP binding. In 2003, Professor Ashcroft and Dr Declan Doyle (formerly from the University of Oxford's Department of Biochemistry) determined the first atomic structure of a Kir channel[3]. Subsequently, Professor Ashcroft and Professor Mark Sansom, also from the Department of Biochemistry, used this structure to produce a molecular model of Kir6.2 that enabled them to identify the ATP-binding site[4]. This model explained how Kir6.2 mutations impair channel inhibition by ATP.

In 2004, Professor Andrew Hattersley of the University of Exeter found the first mutation in Kir6.2 associated with neonatal diabetes (ND) - a rare genetic disease that affects about 1 in 150,000 live births worldwide, and has a serious impact on health and quality of life. Newborns affected are smaller than those of the same gestational age, due to lack of insulin (a growth factor) in the womb, and can fail to gain weight normally. Diabetes develops within the first six months of life and can be severe; some infants are admitted to hospital with diabetic ketosis. Ashcroft's team showed that the mutation in ND impairs the ability of ATP to shut the K_{ATP} channel[5]; because channel closure is required for insulin secretion, this leads to impaired insulin release and thus to ND. Professors Ashcroft and Hattersley then suggested that it should be possible to treat ND patients with oral sulphonylureas (already in routine clinical use for type 2 diabetes) rather than injections of insulin. Clinical studies showed that sulphonylureas can indeed be successfully used to treat the diabetes of patients with this and many other different K_{ATP} channel mutations.

Recently, Ashcroft's team made a mouse model of human ND and used this to show that the muscle hypotonia and other motor problems of patients with severe ND mutations originate in the brain, not the muscle. This has implications for therapy, as drugs must cross the blood-brain

barrier[6]. Ongoing studies of mice models reveal that sulphonylurea therapy preserves beta cell function and mass better than insulin, and start to explain some of the differences in phenotype between ND and type 2 diabetes.

3. References to the research

1. Sakura H, Ämmälä C, Smith PA, Gribble FM, Ashcroft FM. (1995) Cloning and functional expression of the cDNA encoding a novel ATP-sensitive potassium channel subunit expressed in pancreatic β-cells, brain, heart and skeletal muscle. FEBS Letters 377: 338–344. doi: 10.1016/0014-5793(95)01369-5 ***Paper describing the cloning of Kir6.2. The research also established that the Kir6.2 and SUR subunits compose the K_{ATP} channel.***

2. Tucker SJ, Gribble FM, Zhao C, Trapp S, Ashcroft FM. (1997) Truncation of Kir6.2 produces ATP-sensitive K^+ channels in the absence of the sulphonylurea receptor. Nature 387: 179–183. doi: 10.1038/387179a0 ***Paper reporting that the site at which ATP acts to inhibit the K_{ATP} channel is located on Kir6.2, and that SUR1 is required for sensitivity to sulphonylureas.***

3. Kuo A, Gulbis JM, Antcliff JF, Rahman T, Lowe ED, Zimmer J, Cuthbertson J, Ashcroft FM, Ezaki T, Doyle DA. (2003) Crystal structure of the potassium channel KirBac1.1 in the closed state. Science 300: 1922–1926. doi: 10.1126/science.1085028 ***Paper reporting the structure of a Kir potassium channel, including identification of structural elements involved in gating.***

4. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining J, Slingerland AS, Howard N, Srinivasan S, Silva JMCL, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JPH, Sumnik Z, van Rhijn A, Wales JKH, Clark P, Gorman S, Aisenberg J, Ellard S, Njølstad PR, Ashcroft FM, Hattersley AT. (2004) Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. New England Journal Medicine 350: 1838–1849. doi: 10.1056/NEJMoa032922 ***First report of activating Kir6.2 mutations that cause neonatal diabetes. All functional studies and molecular modelling were done by the Ashcroft team, and the genetic studies were done by the Hattersley team.***

5. Proks P, Antcliff JF, Lippiat J, Gloyn AL, Hattersley AT, Ashcroft FM. (2004) Molecular basis of Kir6.2 mutations associated with neonatal diabetes or neonatal diabetes plus neurological features. Proc Natl Acad Sci U S A. 101: 17539–17544. doi: 10.1073/pnas.0404756101 ***Paper elucidating the molecular mechanism of action of Kir6.2 mutations causing ND. Ashcroft designed and conducted the experiments and wrote the paper; the Hattersley team identified the mutations.***

6. Clark RH, McTaggart JS, Webster R, Mannikko R, Iberl M, Sim XL, Rorsman P, Glitsch M, Beeson D, Ashcroft FM. (2010) Muscle dysfunction caused by a K_{ATP} channel mutation in neonatal diabetes is neuronal in origin. Science 329: 458–461. doi: 10.1126/science.1186146 ***Paper reporting that the motor impairments of ND originate in the central nervous system rather than in muscle or peripheral nerves.***

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4. Details of the impact

The work of Ashcroft at Oxford, with Hattersley's team at Exeter, has transformed therapy for people born with ND. Until 2006, ND patients were treated with insulin because their clinical characteristics suggested an unusually early onset form of type 1 diabetes (in which insulin-secreting beta cells are destroyed and exogenous insulin is essential). As a direct result of the research described above, the first patient was switched to oral sulphonylurea treatment in August 2006, and since then at least 500 patients have transferred from insulin injections to the oral drugs,

the bulk of them from 2008 onwards. Clinicians worldwide now routinely screen infants presenting with ND, as well as adult patients who developed diabetes at a young age, for K_{ATP} channel mutations.

Transfer to oral drugs has not only transformed the quality of life for those with ND (and that of their families), it has also had marked clinical benefits. Fluctuations in blood glucose, a common problem in ND patients, are substantially reduced, and potentially dangerous hypoglycaemic episodes are less common. Blood glucose control is substantially improved, lowering the risk of diabetic complications, such as blindness, kidney disease, heart disease and limb amputations. Such complications account for the majority of the morbidity and mortality burden of diabetes, so this reduction results in life-time cost savings of eventual healthcare needs. Furthermore, daily insulin injections are inconvenient, unpleasant, restrictive in terms of lifestyle, and relatively expensive. By contrast, sulphonylureas are cheap, off-patent, drugs that have been in routine clinical use for treating type 2 diabetes for more than 30 years. In the first study into the use of sulphonylureas to treat ND, 90% of the trial group successfully discontinued insulin after receiving sulphonylureas[7].

About 20% of ND patients with K_{ATP} channel mutations also have neurological symptoms[8, 9]. Some have severe mental and motor developmental delay and (in approximately 3% of cases) epilepsy in addition to ND (named DEND syndrome by Ashcroft and Hattersley)[8]. Most also have muscle hypotonia accompanied by delayed speech and walking. These symptoms arise because K_{ATP} channels are found in brain and muscle, as well as in pancreatic beta cells. Sulphonylurea drugs ameliorate the neurological problems in some of these patients[8]. Importantly, some children who were started on sulphonylureas at diagnosis have not yet developed obvious neurological complications, although it is too early to be certain if this will be true for all patients.

Since 2008, sulphonylurea therapy has become the therapy of choice for patients with K_{ATP} channel mutations. Guidelines from the International Society for Pediatric and Adolescent Diabetes state that ND patients should be treated with sulphonylurea drugs[10]. The NHS has also approved research showing that genetic testing for ND is cost effective, since transfer to sulphonylurea drugs leads to significant cost savings in the long term[11]. Ashcroft and Hattersley have disseminated the results of their research in seminars, lectures, media interviews and other venues, which has been vital in reaching the greatest number of clinicians and new families who might benefit from the drug treatment; as a direct result there are now clinics worldwide offering genetic testing for ND.

Ashcroft and Hattersley organised and ran the first 'Families Day' meeting for patients with ND and their families in July 2009 in London. Several families remain in regular contact with one or both of the Oxford and Exeter teams. Through such contacts it has become apparent that apart from the clinical benefits associated with sulphonylurea therapy, the impact upon an individual's quality of life, and that of their family, has been considerable. One patient described switching from insulin therapy to sulphonylureas as 'like night and day'[12], and another said the new treatment had 'given him his life back'[13]. Numerous other patient stories describe ways that sulphonylurea treatment has revolutionised their lives with diabetes[14-16]; one mother reports that thanks to sulphonylurea treatment her daughter 'has now been completely off insulin for seven years with the blood sugar control of a non-diabetic. A truly life-changing miracle'[17]. The impact of this research has resulted from an extremely effective collaborative interaction between the researchers at Oxford and Exeter, clinicians, patients, and their families.

5. Sources to corroborate the impact

7. 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 J, Holst JJ, Clark PM, Ellard S, Søvik O, Polak M, Hattersley AT. (2006) Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New England Journal Medicine 355: 467–477. doi: 10.1056/NEJMoa061759 ***Paper reporting the successful transfer of ND patients from insulin to sulphonylureas, and also showing that improved glycaemic control was sustained.***

8. Mlynarski W, Tarasov T, Gach A, Girard CA, Pietrzak I, Zubcevic L, Kusmierek J, Klupa T, Malecki MT, Ashcroft FM. (2007) Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. Nature Clinical Practice Neurology 3: 640–645. doi: 10.1038/ncpneuro0640 ***Paper reporting improved glucose homeostasis and mental and motor function in a patient with both ND and neurological symptoms.***

9. Shimomura K, Hörster F, de Wet H, Flanagan SE, Ellard S, Hattersley AT, Wolf NI, Ashcroft FM, Ebinger F. (2007) A novel mutation causing DEND syndrome – a treatable channelopathy of pancreas and brain. Neurology 69: 1342–1349. doi: 10.1212/01.wnl.0000268488.51776.53 ***Paper reporting that sulphonylurea treatment improved both psychomotor abilities and epilepsy in a child with ND.***

10. Hattersley A, Bruining J, Shield J, Njølstad P, Donaghue KC. (2009) The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric Diabetes 10(S12): 33–42. doi: 10.1111/j.1399-5448.2009.00571.x ***Guidelines from the International Society for Pediatric and Adolescent Diabetes for the treatment of ND, recommending sulphonylurea.***

11. Greeley SAW, John PM, Winn AN, Ornelas J, Lipton RB, Philipson LH, Bell GI, Huang ES. (2011) The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. Diabetes Care 34: 622–627. doi: 10.2337/dc10-1616 ***NHS Economic Evaluation database entry giving an objective evaluation of a study showing that genetic testing of patients with ND leads to significant cost savings.***

12. Wellcome Trust. Breaking Through Neonatal Diabetes (HD) [online video]. London: Wellcome Trust; 23 Jul 2009. Available from: http://www.youtube.com/watch?v=pjvgOTMiAXg ***Building on the ND 'Families Day' in July 2009, a video was produced by the Wellcome Trust that features ND patients discussing the way sulphonylurea treatment has changed their lives.***

13. Elliott J. 'They have given me my life back'. BBC News. 31 Aug 2009 Health. Available from: http://news.bbc.co.uk/1/hi/health/8176275.stm ***BBC report on the major positive impact sulphonylurea treatment has had on a patient, together with an account of 'ND Families Day'.***

14. BBC Radio 4. Frances Ashcroft: The Life Scientific, London; 15 May 2012. Available from: http://www.bbc.co.uk/iplayer/episode/b01hjqhr/The_Life_Scientific_Frances_Ashcroft/ ***Parent's testimony on 'The Life Scientific', a BBC Radio interview with Professor Ashcroft, confirming the benefits of sulphonylurea treatment (at 20 minutes 27 seconds).***

15. University of Chicago Gleacher Center. Celebrating the Miracles [online video]. Chicago: 4 Oct 2010. Available from: http://youtu.be/OglCARmrAPE ***A film made by a parent, featuring many others, discussing how medical breakthroughs such as sulphonylurea treatments have changed their lives and their families' lives for the better.***

16. Journey to a Miracle: Freedom from Insulin - Pilot for USA television documentary in production 2013. Available from: http://tmktv.com/result.php?title=Journey-to-a-Miracle:-Freedom-from-Insulin---Pilot ***A PBS documentary outlining the impact of switching patients from insulin injections to oral therapies for neonatal diabetes with patient and family testimonials.***

17. Email letter from the mother of a patient (held on file) ***outlining the impact of the oral therapy on the health and wellbeing of her daughter.***