Personal information on Prof Timothy Barrett and UK research team

I am Professor of Paediatrics at University of Birmingham and Honorary NHS consultant in paediatric endocrinology and diabetes. I divide my time between my laboratory research group in Section of Medical Genetics, The Medical School, Birmingham and my clinical practice at Birmingham Children's Hospital. I currently look after children with hormone disorders such as growth, puberty, thyroid and adrenal problems; and children with diabetes. I run specialist multidisciplinary clinics for children with rare diseases (Alstrom syndrome, Bardet Biedl syndrome, Prader Willi Syndrome). I have applied to The NHS National Commissioning Group to establish a national specialist clinical service for Wolfram syndrome.

My research team comprises Dr Malgosia Zatyka (senior postdoctoral scientist); Ms Samantha Prince (PhD student) and Ms Seley Gharanei (PhD student). Our investigations currently cover three main areas:

1. How the absence of a functional Wolframin protein causes failure of insulin secretion in pancreatic beta cells
2. How individual mutations in the *wfs1* gene result in different severities of symptoms
3. Can we use a cell model of the brain to test possible treatments to delay the progress of the neurodegeneration?

We are very grateful for the support of WellChild who have funded much of our research over many years.

Information on international research efforts

Professors Guy Linnears and Christian Hamel in Montpellier, France, are going to attempt gene therapy in mice with Wolfram syndrome, to try to treat the eye disease.

Professor Alan Permutt in Washington University, St Louis, USA, identified the gene for Wolfram syndrome, WFS1, and is the leading researcher in Wolfram syndrome. His team have a collaboration with Dr Fumi Urano at The University of Massachusetts. They are developing a system for mass testing of potential drug therapies to treat the underlying metabolic disorder in Wolfram syndrome.

Professor Yukio Tanizawa in Japan has identified several defects in insulin secretion that may cause the diabetes in Wolfram syndrome. He worked with Professor Alan Permutt and was also involved in discovery of the causative gene.

Dr Veronique Paquis in University of Nice, France, leads a team that has recently described the neurological abnormalities in Wolfram syndrome in great detail.
Professor Virginia Nunes in University of Barcelona has led a team for many years describing the genetic abnormalities in Spanish families with Wolfram syndrome.

Information on current European Grant
EURO-RARE DIABETES: An EU rare diabetes registry for Wolfram syndrome, Alstrom syndrome and Bardet Biedl syndrome.

I was contacted by Virginie Picard from the Association Francais Myopathie (National French Charity for rare diseases particularly muscle diseases). She had been approached by parents of children with Wolfram syndrome in France who felt that their doctors knew very little about Wolfram syndrome; they had to see many specialists who did not have the complete picture of the syndrome; and they felt that not enough research was being undertaken into the causes and treatment of Wolfram syndrome. These parents formed themselves into the French Wolfram Association, led by Mrs Nolwenn Jaffre, and asked Virginie Picard for help with organising an international conference.

This conference was held in October 2009 and attracted researchers from France, Spain, Japan, USA, and myself from Birmingham *[I can mail you the minutes of this meeting and subsequent meetings for you to add to your website]*. We discussed why it was so difficult to undertake research in this rare disease. One reason was that you need lots of patients and families to understand how the syndrome develops, what complications can result, and how the clinical patterns relate to mistakes in the gene. In addition, it is not possible to test a new treatment without undertaking in contolled clinical trial. This is where one half of people receive a new treatment, the other half receive a dummy treatment, and you follow them up to see if the treated half show improvements compared to the half that had the dummy treatment. We also discussed the need to look for new treatments for Wolfram syndrome. We agreed to put together grant applications to secure some funding for research. I agreed to put together an application to the EU (Executive Agency for Health and Consumers) to develop an EU-wide registry. This is a collaboration between colleagues in England, Scotland, Spain, France, Italy, Poland, and Estonia, with other contributions from Germany, Prof Tanizawa in Japan and Prof

EXECUTIVE SUMMARY OF EURO-RARE DIABETES REGISTRY

• The general objective of this project is to support efficient diagnosis, treatment, and research for the overlapping rare genetic diseases Wolfram, Alstrom and Bardet Biedl (WABB) syndromes in Europe. We will achieve this by implementing an EU registry for WABB, containing clinical, genetic diagnostic and outcome data. The purpose of the registry is: a) to establish the natural history of the 3 diseases (their characteristics, management and outcomes); b) to assess clinical effectiveness of management and quality of care; c) to provide an inventory of patients for recruitment to intervention studies; d) to establish genotype-phenotype correlations. We will achieve high usage of the registry by linking it to rapid genetic testing; and to up to date, accurate information, FAQS, and education material.

• The strategic relevance is its support for equal access to genetic testing, education of health professionals, and empowerment of patients. (Council Recommendation on action in the field of rare diseases); adequate inventorying of WABB diseases (Section II); supporting research (Section III); development of centres of expertise (Section IV); gathering expertise at European level (section V); empowering patient organizations as partners (Section VI); developing sustainability by underpinning a future European Reference Network for WABB diseases (Section VII); supporting the High Level Pharmaceutical Forum Recommendations (2008) to mobilise resources to generate shared information; and supporting an improvement in health outcomes, and therefore Healthy Life Years, a key Lisbon Strategy indicator.

• The contribution to The Second Health Programme is through: a) increased knowledge on these 3 rare diseases by pooling together data on larger number of patients; b) support for research by allowing access to investigators for epidemiological, clinical, genetic and interventional studies; c) effective dissemination of results via the Orphanet network, subject to security for the registry; d) advocacy for improved quality of services via EURORDIS at the European level, and member state specific Orphanet groups at the national level; e) balanced participation. Our project group includes researchers, clinicians, stakeholders, and policy makers from 7 EU member states.

• Methods and means. We will use validated, quantitative questionnaires and focus groups of health professionals, to scope the support requirements of centres for submitting data to the Registry. We will develop a consensus on a core dataset for the Registry, then develop a multifunctional web based Registry with user friendly browser-based access. We will create a WABB microarray capable of identifying up to 600 different mutations. We will undertake quantitative questionnaires and focus groups for patients and health professionals to compile their learning and information needs; write education material and patient information on WABB diseases, and use it to support 'meet the expert' platforms, and fora for client groups.

• Expected outcomes. There will be a step change in volume and quality of clinical research in WABB diseases. The registry will be also be transferable to scientists exploring the mechanisms underlying common diabetes and obesity. This will change our understanding of these rare diseases through increased knowledge of the natural history and genotype phenotype relations informing prognosis. WABB diseases will have increased visibility to the research and health provider communities through Orphanet and EURORDIS. There will be a change in clinical effectiveness of services for WABB patients. The registry will provide data for assessing the clinical effectiveness and cost-effectiveness of standard care and new interventions in a real-world setting. This will lead to improvements in quality of care. The Registry will identify disparities between health care outcomes and provide evidence for health service providers for improvements.