Research Excellence Framework: Impact pilot exercise
Example case studies from Clinical Medicine

November 2010

Introduction

1. This document provides some examples of case studies submitted to the impact pilot exercise that the Clinical Medicine panel scored highly, and that indicate good practice in terms of the pilot submissions.

2. They are presented here in a revised format to that in which they were submitted. The original template required the impact arising to be described first, followed by the underpinning research and ending with evidence for both previous sections[1].

3. The expert panels recommended that the sections in the template should be reversed, starting with a clear description of the research and justification that it is of high quality, followed by an explanation of how it led to the impact and what that impact was. It was also recommended that the references to the research should be separated from references to 'user contacts' and external sources of corroboration.

4. For the purposes of publishing these examples, therefore, we invited participating institutions to revise the case studies that had been identified as suitable for publication[2]. A revised template and guidance were provided to ensure clear presentation of the evidence for publication. Further refinements to the template and guidance for the full REF will be made subsequently.

5. The examples published were selected from among the highest-scoring case studies submitted to the pilot, to show a range of types of impacts that were submitted, and to provide examples of good practice from among the pilot submissions.

6. The examples do not represent model case studies that should be replicated in REF submissions. As the range of published examples is intended to show, there are many and diverse ways in which impacts arise and can be described for assessment in the REF.

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[1] This template can be viewed in the 'Guidance on submissions for institutions participating in the pilot' available at www.ref.ac.uk under Impact pilot exercise.

[2] For this we provided further guidance, 'REF impact pilot: revised case study template and guidance' (July 2010), available at www.ref.ac.uk under Impact pilot exercise.

Cardiff University characterisation of genes leads to improved diagnosis, prevention and treatment of inherited diseases (Cardiff University)

1. Short summary of the case study

Research at Cardiff University has transformed healthcare in several important inherited diseases. The identification and characterisation of the genes for autosomal recessive colorectal cancer (MUTYH), Huntington's disease (HTT), myotonic dysytrophy (DMPK), tuberous sclerosis (TSC1/TSC2) and autosomal dominant polycystic kidney disease (PKD1) by researchers at the University lead directly to improved clinical genetic management and treatment of patients and families with these disorders. Cardiff University lead the development of new and highly accurate diagnostic and predictive gene tests and improved genetic counselling. These changes in clinical practice have become embedded not only in the NHS but also in many overseas healthcare systems in the public sector and, through licensing of IP and know-how, to the North American commercial sector. Cardiff University was awarded the Queen's Anniversary Prize in 2007 for its leading role in identifying the causes of inherited diseases, developing new diagnostic tests and translating the findings to the clinic.

2.Underpinning research

The impacts reported here flow from basic medical genetic research undertaken from the 1990s to 2002 that identified and characterised genes for several major mendelian disorders. Associated translational and social science research has also been undertaken during this period and up to the present. This addressed clinical and socio-ethical issues surrounding implementation of genetic testing in healthcare and more recently has exploited knowledge of gene function to devise novel approaches to molecularly targeted therapies for inherited disease.

The positional cloning strategies that were used to identify disease genes prior to significant characterisation of the human genome were major endeavours undertaken by international consortia involving several research groups. Researchers at the Institute of Medical Genetics, Cardiff University (Harper, Shaw for Huntington's disease[1,2] and myotonic dystrophy[3]; Sampson for tuberous sclerosis 2[4], polycystic kidney disease[5]; Sampson and Cheadle tuberous sclerosis 1[6]) either led these consortia or played major roles within them that were critical to success. Later, when disease gene identification became feasible with much smaller teams, Sampson and Cheadle identified MUTYH as the first gene causing autosomal recessive predisposition to colorectal cancer[7,8]. Ethical issues raised by advances in genetics and the social consequences of applications in clinical practice have been extensively explored by PIs from the Institute of Medical Genetics (notably Clarke and Harper) working closely with colleagues from Cardiff University's School of Social Sciences as well as with national and international collaborators including experts in law, governmental policy makers and industry representatives (for example from the insurance sector). This work established current UK clinical practice in relation to predictive genetic testing and genetic testing of children, the moratorium on use of genetic test results by insurance companies in the UK and also influenced the development of European and international policy in this area[9].

Translational research via early phase clinical trials for tuberous sclerosis using mTOR inhibitors has been led in Europe by Sampson[10] and represents one of the earliest examples of a molecularly

targeted approach to treatment of inherited disease. This has led to current phase III international commercial trials by Novartis in which the Institute of Medical Genetics is collaborating. While all impacts described in this report were dependent upon research undertaken at Cardiff University, the development of trials of molecularly targeted therapy in tuberous sclerosis required in addition the identification of Rheb as the substrate for the GAP activity of the TSC1/2 complex, an advance made by Tee (now also at the Institute of Medical Genetics) while he was at Harvard, USA.

Benefits to the University from the commercialisation of DNA diagnostics for these disorders in North America were secured through successful patenting and out-licensing undertaken by the University, in some cases working with the MRC. Seamless working between the University, the NHS and the UK Genetic Testing Network led to rapid implementation of tests through NHS diagnostic laboratories. Public engagement relating to the research and its translation was secured by Cardiff University through funding for the Wales Gene Park from Welsh Assembly Government (see www.wgp.cf.ac.uk).

3. References to the research

Peer-reviewed Journal Publications:

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993;72:971-983.

2. Snell RG. MacMillan JC. Cheadle JP. Fenton I. Lazarou LP. Davies P. MacDonald ME. Gusella JF. Harper PS. Shaw DJ. Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nature Genetics. 4(4):393-7, 1993 Aug.

3. Harley HG, Rundle SA, MacMillan JC, Myring J, Brook JD, Crow S, Reardon W, Fenton I, Shaw DJ, Harper PS. Size of Unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. Am J Hum Genet 1993;52(6):1164-74.

4. The European Chromosome 16 Tuberous Sclerosis Consortium.Identification and characterisation of the tuberous sclerosis gene on chromosome 16. Cell 1993;75:1305-1315 (J Sampson corresponding author)

5. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14kb transcript and lies within a duplicated region on chromosome 16. Cell 1994;77:881-894

6. The TSC1 Consortium. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science 1997;277:805-808

7. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, Hodges AK, Davies DR, David SS, Sampson JR, Cheadle JP. Inherited variants of MYH associated with somatic G:C>T:A mutations in colorectal tumors. Nat Genet. 2002;30:227-232 (J Sampson corresponding author)

8. Sampson JR, Dolwani S, Jones S, Eccles D, Ellis A, Evans DG, Frayling I, Jordan S, Maher ER, Mak T, Maynard J, Pigatto F, Shaw J, Cheadle JP. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet. 2003 Jul 5;362(9377):39-41.

9. Harper PS. Insurance and genetic testing. Lancet 1993;341:224-227.

10. Davies DM, Johnson SR, Tattersfield AE, Kingswood JC, Cox JA, McCartney DL, Doyle T, Elmslie F, Saggar A, deVries PJ, Sampson JR. Sirolimus therapy in tuberous sclerosis or sporadic lymphangioleiomyomatosis. New England Journal of Medicine 2008 Jan, 358(2): 200-203.

4. The contribution, impact or benefit

Research at Cardiff University has transformed healthcare in several inherited diseases. The identification and characterisation of a series of genes for major inherited disorders including autosomal recessive colorectal cancer (MUTYH, MAP), Huntington's disease (HTT), myotonic dysytrophy (DMPK), tuberous sclerosis (TSC1 and TSC2) and autosomal dominant polycystic kidney disease (PKD1) has impacted upon the diagnosis, clinical genetic management and treatment of patients and families with these disorders.

The impact of our research into inherited diseases has been global with new genetic tests, policies and practice developed in Cardiff now embedded in the NHS and also in many overseas healthcare systems. Tests which allow earlier and more accurate diagnosis, are now available to UK families through the NHS UK Genetic Testing Network and have also been widely adopted across Europe, North America and Australasia.
We established international patents (US 7,393,940; US 6,232,452; US 6,207,374; US 6,326,483; US 6,548,258; US 5,955,265; US5,977,333) and licensing agreements with medical diagnostic companies that have brought these tests to the North American market, for example MUTYH through the Colaris AP® testing kit (Myriad Genetics) and DMPK, TSC1/2 and PKD1 testing through Athena Diagnostics. This commercialisation established sustained streams of royalty income for Cardiff University and has led to joint research activities and publications with industry (e.g. Azzopardi et al. Cancer Res. 2008 Jan 15;68(2):358-63)

The licence income received from Athena Diagnostics by Cardiff University for the myotonic dystrophy patents in 2007 and 2008 was £17,763. While the TSC and PKD diagnostic tests are also licensed to Athena Diagnostics via the MRC, income received to date has gone into paying the patent prosecution. MUTYH has generated >£100,000 of royalty income to date through a licence to Myriad Genetics. The number of tests carried out by Myriad has increased year on year from 1119 in 2005 to 2775 in 2009.

The diagnostic applications of this work include prenatal and pre-implantation diagnosis for the prevention of some of these disorders (e.g. for tuberous sclerosis), predictive testing either to guide cancer screening surveillance (e.g. for MUTYH-associated polyposis) or for presymptomatic diagnosis (e.g. in Huntington's disease) as well as the definitive diagnosis of symptomatic disease. These practical advances have led to the development of new UK and international policy in relation to the application of genetics in medicine and Cardiff University researchers have played lead roles in this process. Evidence to demonstrate this is provided in section 5.

These advances have also been integrated into UK (and wider) teaching and learning in healthcare as

exemplars of genetics in clinical practice They have also formed the basis for public engagement and debate on translational outcomes of genetics in medicine through the Wales Gene Park (http://www.wgp.cf.ac.uk/) hosted by Cardiff University.

Most recently, in the case of tuberous sclerosis, novel approaches to drug treatment have been developed by Cardiff University based directly upon knowledge of TSC1/2 gene function. Two successful phase II trials, one led from Cardiff (Clinicaltrials.gov NCT00490789) have attracted significant interest from the Pharma sector resulting in the initiation of two commercial international phase III studies (Clinicaltrials.gov NCT00789828 and NCT00790400).

5. References to corroborate the contribution, impact or benefit

Diagnostic tests (UK and European availability of tests):
UKGTN www.ukgtn.nhs.uk
www.eurogentest.org

Organisations who can corroborate claims of contribution, benefit and impact (named contacts can be provided):
Tuberous Sclerosis Association (UK)
Tuberous Sclerosis Alliance (USA)
Polycystic Kidney Disease Foundation
The Huntington Disease Association
The Myotonic Dystrophy Support Group
The Muscular Dystrophy Campaign
Myriad Genetics Inc. (USA)
Athena Diagnostics (USA)
Novartis
United Kingdom Genetics Testing Network
Clinical Genetics Society
British Society for Human Genetics

Prize based upon external assessment of this research and its impact:

Queens Anniversary Prize 2007:
http://www.royalanniversarytrust.org.uk/index.php?article_id=7&FORM[order]=year&FORM[year]=2007

Policy Development:

Clinical Genetics into the 21st Centuary (Royal College of Physicians report, 1996)
Genetic testing for Late Onset Disorders (Dept of Health, 1998)
Genetic Services and Cancer (Dept of Health, 1998)
Genetic Testing of Children (Dept of Health , 2000)
Genetics Servcies for Neurological Disorders (Association of British neurologists and Clinical Genetics Society, 2003)

Public Engagement:

Reports posted at the Wales Gene Park (www.wgp.cf,ac.uk)

Media Coverage:

The Welsh Park at the heart of genetic advances (2005): http://www.walesonline.co.uk/news/health-news/tm_objectid=15108765&method=full&siteid=50082-name_page.html

Fears over fertilization and embryology bill clause (2009). Public debate organised by the Wales Gene Park: http://www.walesonline.co.uk/news/wales-news/2008/04/07/fears-over-fertilisation-and-embryology-bill-clause-91466-20728352/

Education
www.geneticseducation.nhs.uk/teaching-genetics/
www.geneticseducation.nhs.uk/media/16486/Conditions%20-20Huntington%20Disease%20(AD).ppt.

Life-changing therapeutic intervention in patients with neonatal diabetes (Universities of Exeter and Plymouth)

1. Short summary of the case study

The research team led by Prof AT Hattersley has changed dramatically the treatment options for certain patients diagnosed with type 1 diabetes. This has ***improved patient care and quality of life,*** correspondingly ***improved public services***, and ***achieved International impact***. Type 1 diabetes is a life-long illness, most frequently developing in childhood: patients are obliged to receive exogenous insulin (often by multiple daily injections) in perpetuity. This places considerable psychological pressure on the individuals and their families whilst significantly constraining their lifestyle. This research has revealed that in around 50% of cases permanent neonatal diabetes is associated with a particular gene mutation rather than with the autoimmunity that classically causes type 1 diabetes. Accordingly, the research team argued that such patients could be transferred to orally active anti-diabetic drugs (sulphonylureas) instead of insulin injections. This has proved to be the case for a large number of patients with neonatal diabetes.

2.Underpinning research

The underpinning research was carried out under the leadership of Prof AT Hattersley (Professor of Molecular Medicine) at the Peninsula Medical School. Blood cells from patients affected by permanent neonatal diabetes (a group rarely studied previously) were collected and a range of key genes analysed to identify possible mutations. This showed that several different genetic mutations can lead to permanent neonatal diabetes but, most significantly, it became clear that the most common cause was a mutation(s) residing in a region encoding the pore-forming subunit of a type of potassium channel which senses and responds to alterations in the ratio of ATP:ADP in the beta-cells. This protein (Kir6.2) forms a multi-subunit complex with another molecule, the sulphonylurea receptor (SUR1), to generate functionally competent potassium channels that serve as fuel sensors. These channels play a pivotal role in the ability of beta-cells to sense and respond to alterations in blood glucose levels. The team observed that the mutations causing the most severe phenotypes tended to be clustered in a region of the gene that encodes the slide-helix portion of the channel.

Molecular modelling suggested that such mutations would impair the movement of this region of the molecule and thereby prevent closure of the channel in response to a rise in the ATP:ADP ratio. Hence, it was postulated that, in the beta-cells of many patients with neonatal diabetes, increased glucose metabolism is unable to couple effectively with the ion channels that mediate membrane depolarisation (and which ultimately trigger insulin secretion). Importantly, it was also proposed that the binding of sulphonylureas to their receptor should still elicit a depolarising response in these channels, implying that sulphonylureas might also close the channels and facilitate a rise in insulin secretion, when administered to patients *in vivo*.

An improved understanding of the molecular basis of these results was cemented in studies of isolated potassium channels expressed either ectopically in Xenopus oocytes (with Prof FM Ashcroft; University of Oxford) or via transfection technologies in cultured pancreatic beta-cells

(with Prof NG Morgan; Peninsula Medical School). It was confirmed that mutations identified in patients with permanent neonatal diabetes caused defects in channel gating in these model systems such that there was a marked reduction in sensitivity to ATP. As a result, increases in ATP (which accompany enhanced glucose metabolism) did not achieve the appropriate threshold to elicit channel closure. Studies in cultured pancreatic beta-cells confirmed that this led to a failure of nutrient-induced insulin secretion which could be corrected fully by the addition of sulphonylurea. Thus, the phenotype seen in patients was recapitulated *in vitro* and provided full support for the model of neonatal diabetes initially proposed by Prof Hattersley's team.

Clinical evidence derived from early "proof of principle" studies also lent firm support to the proposal that certain patients with neonatal diabetes could be transferred successfully from exogenous insulin therapy to oral sulphonylureas. By monitoring the effects of graded increases in the dose of administered sulphonylurea, a level was achieved at which insulin therapy could be discontinued safely.

3. References to the research

This pioneering research was first reported in a seminal paper published in *New England Journal of Medicine* in 2004 and translation of the findings into altered clinical practice has continued since 2005. A website for patients and healthcare professionals (www.diabetesgenes.org) has been established (73,805 visits to date) and an educational programme introduced. This site is also used across the national network of Genetic Disease Nurses who can update their knowledge and practice from the information provided and by interaction with the research team. The group also advises medical staff internationally on the strategies required for successful transfer from insulin injection to oral therapy in relevant patients.

Key peer-reviewed publications

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.**

310 citations JIF: 50.017

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**.

61 citations JIF: 6.418

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.**

147 citations JIF: 50.017

4. Gloyn AL, Diatloff-Zito C, Edghill EL, Bellanné-Chantelot C, Nivot S, Coutant R, Ellard S, Hattersley AT, Robert JJ. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. **Eur J Hum Genet**. 2006 14 : 824-830.

15 citations JIF: 3.925

5. Tarasov AI, Welters HJ, Senkel S, Ryffel GU, Hattersley AT, Morgan NG, Ashcroft FM. A Kir6.2 mutation causing neonatal diabetes impairs electrical activity and insulin secretion from INS-1 beta-cells. **Diabetes. 2006 55 : 3075-3082.**

14 citations JIF: 8.398

Selected research grant support

1. PI: Professor Andrew Hattersley, with Prof M. McCarthy, Dr M.Walker, Dr J Levy.

Title: Familial resources for mapping susceptibility genes in Type 2 diabetes - funded by
Period: 01/04/01-31/03/04, extended to 30/06/04
Sponsor: MRC
Total awarded: £780K

2. PI: Professor Andrew Hattersley

Title: Monogenic and Polygenic Influences on human fetal growth and development – Wellcome Research Leave Award for Clinical Academics
Period: 2003-2008
Sponsor: The Wellcome Trust
Total Awarded: £1.13M

3. PI: Grant co-ordinated by Medizinische Hochschule Hannover (Prof. Sigurd Lenzen) with co-applicants A Hattersley, M McCarthy, P Froguel, S Lenzen (PI), B Thorens and 11 others.

Title: EURODIA – EU FP6 Integrated Programme
Period: 2006-2010
Sponsor: EU FP6
Total funding of £6M over period 2006-2010

4. PI: Prof T Fraying (PI), Prof Mark McCarthy, Dr Ele Zeggini, Dr Michael Weedon

Title: An investigation of genes in key beta-cell pathways following the type 2 diabetes WTCCC genome wide association study.
Period: 2008-2011
Sponsor: The Wellcome Trust
Total Awarded: £430K

5. PI: Professor Mark McCarthy with Prof. T Fraying
Title: Translating Genome-Wide Association Data from the WTCCC Study into Biological and Clinical Insights in Type 2 Diabetes.;
Period: 2007-2010
Sponsor: MRC
Total Awarded: £ £1,191,684

4. The contribution, impact or benefit

The research described here has impacted dramatically on the lives of patients with certain forms of neonatal diabetes and their families. It has led to a complete change in their treatment such that these individuals no longer rely on daily insulin injections but can have their blood glucose levels controlled adequately with oral sulphonylurea agents. The sulphonylurea treatment is associated with a marked improvement in various measures of blood glucose control and is accompanied by enhanced insulin secretion in response to a meal. This has led to a marked improvement in patient care and their quality of life, it has impacted to improve public services, and the new treatment has been adopted Internationally such that more than 400 patients worldwide have had their diabetes therapy changed since 2005.

The findings of the research team suggested a novel therapeutic approach since it implied that, unlike the situation in autoimmune type 1 diabetes (the “classical” form), patients with permanent neonatal diabetes may still synthesise their own insulin which might then be releasable by appropriately targeted therapeutic intervention. This approach was initially tested by Dr Ewan Pearson (a former PhD student) in a small number of patients who were taken off insulin and placed on oral (sulphonylurea) therapy since it is known that these drugs target the relevant potassium channel and lead to its closure by a mechanism that does not require nutrient metabolism. The initial trials provided proof of principle and were quickly extended to a wider group in several regions across the world. The majority displayed improved control of blood glucose compared to that achieved with exogenous insulin and this was maintained with more prolonged use of sulphonylureas.

The primary indicators of the contribution, impact and benefit from this research are the changes to public service practice and guidelines based on Hattersley’s work being adopted in practice and the fact that this work has been showcased around the globe. Its impact on public services is indicated by changes to the initial screening process demonstrating that, if diagnosed during the first 6 months of life, the majority of cases can be treated by oral means rather than insulin injection, thus leading to changes in how patients administer exogenous insulin themselves.

Evidence of the transformational impact of Hattersley’s work is demonstrated through independent testimony, citations, and measurable changes to drug administration practices.

Many patients have reported transformations in their lifestyles and quality of life. This is attested in video format on the websites of leading research funders (http://www.wellcome.ac.uk/Education-resources/Teaching-and-education/Big-Picture/All-issues/Genes-Genomes-and-Health/WTDV027170.htm); www.diabetes.org.uk/Research/Publications/Research_matters) and global news organisations (http://news.bbc.co.uk/1/hi/health/8176275.stm). 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.

Prof Hattersley has delivered expert advice to bodies including the Department of Health, House of Lords Science and Technology Select Committee (2008) and WHO Expert Committee on Diagnosis and Classification of Diabetes (2009). He receives invitations to speak at conferences worldwide on a regular basis and patients are continuously referred to the team for improved diagnosis of neonatal diabetes from across the globe.

5. References to corroborate the contribution, impact or benefit

Awards and prizes

The research team has received considerable external recognition for its contributions including the award of the Queen's Anniversary Prize for Higher and Further Education (2006). In recognition of this ground-breaking research, Professor Hattersley has received multiple awards over the assessment period, including: Josiah Brown visiting lectureship UCLA USA (2008); NDRI Distinguished Scientist Award for outstanding contributions to the study of diabetes (2008); Dorothy Hodgkin Prize lecture, awarded by Diabetes UK for international achievement in diabetes related science (2007). Most recently, Professor Hattersley was elected to a Fellowship of the Royal Society, in 2010.

Patient testimonies:

For the patients who have so far switched from insulin injections to sulphonylurea tablets the change in lifestyle has been major. One family (from North America) describe it as having "changed our life" whilst a patient in Scotland (treated as part of the UK wide trial) now says she "feels a lot better with my diabetes being better controlled" whilst her husband describes her now as "totally different" and for one child's family "Life has completely changed. Before the diagnosis of the disorder we were unable to live the life of a normal family. Since starting his treatment in September family life has completely changed. He's gone from a child who was either completely manic because his sugars were through the roof or lethargic and grumpy because he was having a hypo, to a normal child. He is now able to be more independent; he attends school, is generally well and has not had one hypo. I have even had the courage to let him go to a friend's for tea".

Title of case study: Smoke-free legislation and hospitalisations for Acute Coronary Syndrome (ACS) (University of Glasgow)

1. Short summary of the case study

This University of Glasgow led study provided the most robust evidence that smoke-free legislation has a significant impact on heart disease. Professor Pell's research has raised public awareness of smoke-free legislation and the benefits it brings to smokers and non-smokers.

The research has influenced public policy debate both in the UK and internationally. It provided scientific evidence endorsing Scotland's decision to put the smoking ban in place and it has informed the evaluation of the subsequent English legislation.

2.Underpinning research

Professor Pell's research was a multi-centre study, led by the University of Glasgow and undertaken between 2005 and 2008. It was part of a national evaluation of the impact of Scotland's smoke-free legislation funded by NHS Scotland.

Professor Pell held three positions over the period the study was conducted. Professor Pell started the study as an NHS consultant with an honorary University of Glasgow contract, then continued as Chair in the British Heart Foundation Centre and finished the study and wrote it up as the Henry Mechan Professor of Public Health at the University of Glasgow.

Key academics co-investigators involved in the research include: Professor Stuart Cobbe, University of Glasgow; Professor Dave Newby, University of Edinburgh; and Professor Stuart Pringle, University of Dundee.

Previous studies have suggested a reduction in the total number of hospital admissions for acute coronary syndrome after the enactment of legislation banning smoking in public places. However, it was unknown whether the reduction in admissions involved non-smokers, smokers, or both. This was also the first study to have collected data prospectively using a standardised case definition (see reference 2, section 3).

Since the end of March 2006, smoking has been prohibited by law in all enclosed public places throughout Scotland. Professor Pell's research team collected information prospectively on smoking status and exposure to second-hand smoke based on questionnaires and biochemical findings from all patients admitted with acute coronary syndrome to nine Scottish hospitals during the 10-month period preceding the passage of the legislation and during the same period the next year. These hospitals accounted for 64% of admissions for acute coronary syndrome in Scotland, which has a population of 5.1 million.

Overall, the number of admissions for acute coronary syndrome decreased from 3235 to 2684--a 17% reduction (95% confidence interval, 16 to 18)--as compared with a 4% reduction in England (which has no such legislation) during the same period and a mean annual decrease of 3%

(maximum decrease, 9%) in Scotland during the decade preceding the study. The reduction in the number of admissions was not due to an increase in the number of deaths of patients with acute coronary syndrome who were not admitted to the hospital; this latter number decreased by 6%. There was a 14% reduction in the number of admissions for acute coronary syndrome among smokers, a 19% reduction among former smokers, and a 21% reduction among persons who had never smoked. Persons who had never smoked reported a decrease in the weekly duration of exposure to second-hand smoke ($P<0.001$ by the chi-square test for trend) that was confirmed by a decrease in their geometric mean concentration of serum cotinine from 0.68 to 0.56ng per millilitre ($P<0.001$ by the t-test).

The number of admissions for acute coronary syndrome decreased after the implementation of smoke-free legislation. A total of 67% of the decrease involved non-smokers. However, fewer admissions among smokers also contributed to the overall reduction.

The nine hospitals used in the study account for 63% of all Scottish admissions for heart attack.

3. References to the research

Publications/references:

Professor Pell's work was published in the New England Journal of Medicine (impact factor 50.0) and received 31 citations in the first year since publication.

1. Pell JP, Haw S, Cobbe S, et al. Smoke-free legislation and hospitalizations for acute coronary syndrome. New England Journal of Medicine 2008; 359: 482-91 – ***Peer-reviewed*** **Voted the top paper of 2008 by the American Heart Association**
2. Pell JP, Haw SJ, Cobbe SM, et al. Validity of self-reported smoking status: comparison of patients admitted to hospital with acute coronary syndrome and the general population. Nicotine and Tobacco Research 2008; 10(5): 861-6 – ***Peer-reviewed***
3. Pell JP, Haw S. The triumph of national smoke-free legislation. Heart 2009; 95(17): 1377-9. doi 10.1136/hrt.2009.176230 (Featured Editorial) – ***Peer-reviewed***
4. Pell JP, Haw S, Cobbe S, et al. Secondhand smoke exposure and survival following acute coronary syndrome: prospective cohort study of 1261 consecutive admissions among never-smokers. Heart 2009; 95: 1415-1418; doi 10.1136/hrt.2009.171702 – ***Peer-reviewed***

Other references:

1. Listed in the Faculty of 1000 most important scientific discoveries http://www.f1000medicine.com/article/fc5mj6jdz4wzr8c/id/1119839
2. Voted by the American Heart Association and American Stroke Association to be the most important research advance of 2008 http://www.americanheart.org/downloadable/heart/1237914748043Top10ResearchAdvances-08-1page.pdf

Grant funding:

NHS Health Scotland. Pell JP, Cobbe SM, Fischbacher C, Newby DE, Pell ACH, Dunn F, Murdoch D, MacIntyre P, Oldroyd K, Pringle S, Gilbert T. StOPIT: Study of public place intervention on tobacco exposure. 2005-2008, £545,387

4. The contribution, impact or benefit

This University of Glasgow led study provided the most robust evidence that smoke-free legislation has a significant impact on heart disease. The seminal work by Professor Jill Pell was voted the most important research advance of 2008 by the American Heart Association and is listed in the Faculty of 1000 most important scientific discoveries (ref. 2 and 3).

The pan-Scotland study, led by the University of Glasgow, found a 17% fall in admissions for heart attacks in the first year after the smoking ban came into force in Scotland. This compares with an annual reduction in Scottish admissions for heart attack of 3% per year in the decade before the ban and only a 4% decrease in England, where there was no such legislation. The study was unique in that it was able to demonstrate for the first time that smoke-free legislation was effective in protecting non-smokers specifically from the effects of passive smoking.

One of the primary aims of smoke-free legislation is to protect non-smokers from the effects of passive smoking. This study showed that, amongst non-smokers, there was a 20% reduction in heart attack admissions, confirming that the legislation has been effective in helping non-smokers. The decrease in Scotland was highest in never-smokers, but there was also a smaller decrease in former smokers. Smokers also saw a 14% decline. Of the decrease in hospital admissions, 67% were non-smokers, supporting the argument that protection for these individuals is an important benefit of this legislation, and it should be extended more broadly.

Professor Pell's research has raised public awareness of smoke-free legislation and the benefits it brings to smokers and non-smokers. The results of the research have had extensive International media coverage throughout 2008, appearing in national and international newspapers, radio and the internet. Stand out examples include articles in The Wall Street Journal, Time Magazine and the Today Programme on Radio 4.

The research has influenced public policy debate both in the UK and internationally. It provided scientific evidence endorsing Scotland's decision to put the smoking ban in place. It has informed the evaluation of the subsequent English legislation. Furthermore, Professor Pell has shared her findings with policy makers in numerous countries in which legislation was being considered or had recently been introduced, including India, Sweden, Spain and Greece.

5. References to corroborate the contribution, impact or benefit

Media coverage:

Professor Pell's research was given extensive international media and press coverage, including Wall Street Journal, Time Magazine, Today Programme (10th September), BBC News Website and British broadsheets including:

The Times

The Guardian

Named contact:

Contact details of the individual who led the study which informed the English legislation were

provided for corroboration purposes.

Resulted in numerous invitations to present the results in other countries including:
Stockholm - Europrevent - 9 May 2009
Barcelona - European Society of Cardiology - 30 August 2009
Athens - 12th International Symposium on Atherosclerosis and Related Risk Factors - 15 November 2008
Mumbai - 14th World Conference on Tobacco and Health - 12 March 2009

More details about the research can be found at:
http://www.healthscotland.com/scotlands-health/evidence/smokefreelegislation/publications.aspx#stopit

The Scottish Government Website:
http://www.scotland.gov.uk/News/Releases/2007/09/10081400

Anti-TNF: a revolution in the treatment of rheumatoid arthritis (Imperial College London)

1. Short summary of the case study

Professor Feldman identified a therapeutic target, TNFα, in the human disease tissue (rheumatoid synovium) and, in collaboration with Professor Sir Ravinder Maini, used monoclonal antibodies to TNFα to effectively treat rheumatoid arthritis. This collaboration of Imperial College London researchers has led to a profound technology change. It is now known that monoclonal antibodies can be used for the long-term treatment of rheumatoid arthritis as well as other chronic diseases.

2.Underpinning research

The identification of tumour necrosis factor (TNF) as a key therapeutic target in the abnormal joint lining in RA, began with observations by Fionula Brennan working under the direction of Professor Marc Feldmann. The first clinical study, performed at Charing Cross Hospital, published in 1993, enrolled 20 patients with disease refractory to all existing treatment who were given a single infusion of infliximab, a monoclonal antibody to TNF (1). Results in the RA study were dramatic and led to a randomised placebo-controlled trial in collaboration with three other European centres (2). Remarkably the response rate with the highest dose of infliximab was 79% at 4 weeks in comparison to 8% with placebo. The success of repeated treatments was first demonstrated in a small study (3); however the degree of response was less, partly due to the monoclonal antibody inducing an immune response to itself which limited its effectiveness. Further studies of the mouse model undertaken by Richard Williams, under the direction of Marc Feldmann, indicated that combining an anti-TNF monoclonal antibody with a therapy targeting the T cells of the immune system might improve response through synergy and a reduction in immunogenicity (4, 5). This finding led to combining methotrexate, already established in the treatment of RA, with infliximab in the next randomised-controlled trial (6). The demonstration of synergy with this combination of therapy, in the absence of increased toxicity, has set the gold standard of pharmacological management. Further clinical studies led by Sir Ravinder Maini and Marc Feldmann demonstrated that biologic TNF inhibition plus methotrexate markedly inhibits the structural joint damage previously thought to be an irreversible feature of RA (7,8). Clinical science studies undertaken by Peter Taylor, working with Profs Maini and Feldmann, used biologic TNF inhibitors to investigate the pathobiology of TNF in RA and demonstrated that this cytokine regulates inflammatory cell migration to joints via modulation of chemokines and adhesion molecules as well as joint vascularity (9,10).

Prof. Feldmann is Head of the Kennedy Institute of Rheumatology at Imperial College London. The Institute's current medical and scientific work is in building on his major discovery, and in helping translate laboratory discoveries into medical advances, especially in novel research areas with big unmet needs. The Institute is the flagship of the Arthritis Research Campaign and central to delivering the Faculty's mission of research excellence.

3. References to the research

Current research funding

- Arthritis Research Campaign. Institute core grant research support. 2007-2012. £22.5m (£4.5m per annum).
- European Union. Mechanisms to attack steering effectors of rheumatoid syndromes with innovated therapy choices. 2008-2013. £833k.
- European Union. Atheroremo (with C. Monaco). 2008-2013. £1m.
- GlaxoSmithKline GMEC. 2008-2010. £38k.
- GlaxoSmithKline. Validation of p55 TNF-R as a therapeutic target to RA. (with R. Williams). 2009-2011. £223k.
- KIR Trust funding totaling £3.284M. A breakdown of funding available on request.
- N.I.H. / Cornell. New strategies to prevent death from influenza (with T. Hussell and B. Foxwell). 2006-2011. £931k.
- National Institute of Health Research. NIHR Senior Investigator Award. 2009-2012. £45k.
- Wyeth. Evaluation of new biomarkers and therapeutic targets in RA (with F. Brennan). 2008-2009. £335k;

Peer reviewed publications

1. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, Brennan FM, Walker J, Bijl H, Ghrayeb J, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis Rheum. 1993;36:1681-90.
2. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, Brennan FM, Walker J, Bijl H, Ghrayeb J, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994;344:1105-10.
3. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, et al. Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet. 1994;344:1125-7.
4. Williams RO, Mason LJ, Feldmann M, Maini RN. Synergy between anti-CD4 and anti-tumor necrosis factor in the amelioration of established collagen-induced arthritis. Proc Natl Acad Sci U S A. 1994;91:2762-6.

5. Williams RO, Ghrayeb J, Feldmann M, Maini RN. Successful therapy of collagen-induced arthritis with TNF receptor-IgG fusion protein and combination with anti-CD4. Immunology. 1995;84:433-9.

6. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41:1552-63.

7. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932-9.

8. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, St Clair EW, Keenan GF, van der Heijde D, Marsters PA, Lipsky PE; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50:1051-65.

9. Taylor PC, Peters AM, Paleolog E, Chapman PT, Elliott MJ, McCloskey R, Feldmann M, Maini RN. Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor α blockade in patients with rheumatoid arthritis. Arthritis Rheum. 2000;43:38-47.

10. Taylor PC, Steuer A, Gruber J, Cosgrove DO, Blomley MJK, Marsters PA, Wagner CL, McClinton C, Maini RN. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiological evaluation in a randomized, placebo-controlled study of infliximab therapy in early Rheumatoid Arthritis. Arthritis Rheum. 2004;50:1107-1116.

4. The contribution, impact or benefit

Rheumatoid arthritis (RA) is a persistent inflammatory arthritis of synovial joints that affects 0.5-1% of the population and can lead to pain, deformity and loss of function, work disability, economic losses and premature death. Prior to the development of anti-TNF therapies, a considerable proportion of patients treated with the available disease modifying therapies still had evidence of persistent disease activity and on-going joint damage. Since the late 1990s however, the introduction of anti-TNF agents has profoundly changed the management of severe rheumatoid arthritis throughout the developed world with well over 1 million patients now having received this treatment (16) and sales of the 3 licensed TNF inhibitors reaching $9 billion in 2006. Guidelines on the use of anti-TNF inhibitors in RA were issued by the British Society of Rheumatology in 2001, and therapy was endorsed by the National Institute of Clinical Excellence in 2002 (16). The combination of an anti-TNF inhibitor with methotrexate remains unsurpassed in reducing the signs and symptoms of disease and amelioration of joint destruction (18). Current NICE (2009) and

British Society of Rheumatology (2005) guidelines address the optimal use of biologics (anti-TNF agents) and disease modifying anti-rheumatic drugs (including methotrexate) for the management of RA (14,15).

The success of anti-TNF therapy also provides proof of principle that blockade of a single cytokine is capable of treating a complex inflammatory disease such as RA. Due to the overlapping functions of many cytokines, such a concept was not previously popular (12). Now it has led to the development of numerous other biological therapies, targeting different cytokines, some of which have also now entered clinical practice. It has led to the use of monoclonal antibodies to TNF for other chronic diseases, namely ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis and juvenile rheumatoid arthritis. Other monoclonal antibodies have subsequently been developed for chronic disease, and the pharmaceutical industry's pipeline is now about 1/3 monoclonal antibodies, essentially all for chronic disease. Whilst initiation of an anti-TNF inhibitor in established disease does not result in cure, evidence is now emerging that commencing this treatment in early disease might result in drug-free remission for some patients (13).

The improvement in the quality of life of patients with rheumatics diseases is considerable. The long term impact of Feldmann and Maini's work is that the interest in the therapeutic use of monoclonal antibodies in the pharmaceutical industry has blossomed and this is the most rapidly growing sector of the pharmaceutical industry. As use of the monoclonal antibodies grows, the cost of making antibodies is dropping. It will eventually benefit the patients also, as new products are launched, especially generic versions of the best selling antibodies, as they lose patent protection. Thus there will be long term impact over the whole pharmaceutical industry.

5. References to corroborate the contribution, impact or benefit

11. Taylor PC, Feldmann M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. Nat Rev Rheumatol. 2009;5:578-82.

12. Feldmann M, Maini Sir R. Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. Immunol Rev. 2008;223:7-19.

13. Van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJ, van der Lubbe PA, de Beus WM, Grillet BA, Ronday HK, Huizinga TW, Breedveld FC, Dijkmans BA, Allaart CF. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009;68:914-21.

Guidelines

14. 2005 British Society for Rheumatology Guidelines: http://bit.ly/cu1j5Q

15. 2009 NICE guidelines: http://bit.ly/ckMWY2

Further references

16. NICE Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis: http://bit.ly/cDP2SM (WAS 3)

Researcher homepages

17. Professor Marc Feldmann: http://www1.imperial.ac.uk/medicine/people/m.feldmann/

18. Professor Sir Ravinder Maini: http://www1.imperial.ac.uk/medicine/people/r.maini/

Patents

- US App 09/285,531. Small molecular weight TNF receptor multimeric molecule. Y Chernajovsky, R Neve, M. Feldmann.

- US App 08/446,674 / 20030064070A1. Multiple administration of anti-TNF antibody. M Feldmann, RN Maini, J Woody.

- US App 08/602,272 / 20020081306A1. Methods of preventing or treating cardiovascular, cerebrovascular and thrombotic disorders with tumor necrosis factor antagonists. MJ Elliott, RN Maini, M Feldmann,

- US App 08/854/881. Suppression of TNF and vascular endothelial growth factor in therapy. M Feldmann, RN Maini, EM Paleolog.

- US App 20020136723A1. Anti-TNF antibodies and methotrexate in the treatment of autoimmune disease. M Feldmann, RN Maini.

- US App 20020068057A1. Treatment of autoimmune and inflammatory disorders. M Feldmann, RN Maini, RO Williams.

- US App 20020039734A1. Composition, kits and methods for identification of modulation of T helper-1 and T helper-2 cells and diseases associated therewith. C Hanrahan, M Feldmann, WL Trepicchio.

- US App 20020010180A1. TNFα antagonists and methotrexate in the treatment of TNF-mediated disease. M Feldmann, RN Maini.

- PCT/GB00/03660. Therapeutic methods and compounds (refers to cytokine activated T cells as a target in rheumatoid arthritic). M Feldmann, BMJ Foxwell, FM Brennan.

- Eur 98942892.5 / PCT/GB98/02753/ US App 20020177572A1. Viral infection of cells (refers to adenoviral system and its uses). M Feldmann, BMJ Foxwell, FM Brennan and J Bondeson.

- Reporter genes (in adenovirus). M Feldmann, BMJ Foxwell.

- US App 20030153518A1. Activation and inhibition of immune system (refers to use of NFκB inhibitors to promote tolerance and NFκB inducers as molecular adjuvants for vaccines). M Feldmann, BMJ Foxwell.

- WOO1/21823 PCT Pending. Adenoviral Vectors. M Feldmann, B Foxwell.

Further information

'European Inventor of the Year' Award in the 'Lifetime Achievement' category from the European Patent Office for work and inventions in developing treatments for autoimmune diseases/anti-TNF therapy.

Development of the Imperial spin-out company Thiakis Ltd to investigate synthetic oxyntomodulin analogues for obesity therapy and subsequent sale of Thiakis to Wyeth Pharmaceuticals (Imperial College London)

1. Short summary of the case study

Imperial College London researchers have developed and sold a spin-out company, Thiakis Ltd, which investigated analogues for obesity therapy. In December 2008, Thiakis Ltd was sold to Wyeth Pharmaceuticals to develop Thiakis' lead product TKS 1225, a synthetic analogue of oxyntomodulin. Wyeth acquired Thiakis for approximately $30 million with additional payments of $120 million conditional on the achievement of set milestones.

2.Underpinning research

One approach to the treatment of obesity is through manipulation of the body's natural regulatory circuits for appetite control. Several gut hormones including peptide YY (PYY), oxyntomodulin (OXM), pancreatic polypeptide (PP) and glucagon-like peptide (GLP-1) are released in response to food intake and act centrally through the hypothalamus to regulate appetite. Research led by Professor Steve Bloom at the Department of Investigative Medicine, Imperial College London, over the last 20 years has focused on the mechanisms of appetite suppression and how these can be exploited to treat obesity. Professor Steve Bloom has pioneered the use of gut hormones as natural appetite regulators. Early work focused on GLP-1; in 1987 the group performed the first human infusions of GLP-1 and its analogue exanatide to show that GLP-1 markedly enhanced insulin secretion in response to a meal and caused an improvement in glycaemic control in diabetics. This led the way for the use of this hormone, related analogues and inhibitors of GLP-1 breakdown in the treatment of diabetes. Several GLP-1 related molecules (e.g. exanatide, liraglutide, vildagliptin) are now either licensed or undergoing clinical trials (e.g. Byetta, NovoNordisk).

Over the following 10 years, the group focused research on the role of gut hormones and demonstrated in a Nature paper (1) that intracerebroventricular (ICV) GLP-1 powerfully inhibits feeding in fasted rats and established GLP-1 as a new physiological mediator of satiety. Another Nature paper in 2002, demonstrated that the gut hormone PYY_{3-36}, a Y2R agonist, inhibits food intake and reduces weight gain in rats (2).

In parallel to this work, research was also focusing on another cleavage product of the proglucagon precursor, oxyntomodulin. When administered to rats oxyntomodulin reduces food intake, increases energy expenditure and reduces the rate of increase in body weight (3-6).

Groundbreaking studies then followed which demonstrated that in humans, i.v. infusion of oxyntomodulin reduces food intake (7). Administration of the gut hormone oxyntomodulin in human volunteers results in weight loss of 0.5kg per week over four weeks, greater than for any other therapy with the advantage of having minimal side effects. The weight loss may be due to oxyntomodulin's dual effect of reducing food intake and increasing energy expenditure, an effect not documented with other therapies. This suggested that oxyntomodulin was a strong candidate for obesity therapy.

Oxyntomodulin is inactivated by enzyme action and studies therefore focused on developing analogues (6). One particular analogue synthesised as part of this programme, TKS 1225, was developed by the Imperial spin-out company Thiakis Ltd and is now being evaluated by Pfizer Inc. as a potential therapy for obesity. This could clearly have a significant impact on the health of the nation and represent a major cost saving for the NHS.

3. References to the research

Research funding

- Medical Research Council Programme (G7811974) and two Wellcome Trust Programme Grants have supported this work.

Peer reviewed publications

1. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, Bloom SR. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature.* 1996;379:69–72.

2. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY (3-36) physiologically inhibits food intake. Nature. 2002;418:650-4.

3. Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M, Ghatei MA, Bloom SR. Peripheral oxyntomodulin reduces food intake and body weight gain in rats. *Endocrinology*. 2004;145:2687–2695.

4. Dakin CL, Gunn I, Small CJ, Edwards CM, Hay DL, Smith DM, Ghatei MA, Bloom SR. Oxyntomodulin inhibits food intake in the rat. *Endocrinology*. 2001;142:4244–4250.

5. Dakin CL, Small CJ, Park AJ, Seth A, Ghatei MA, Bloom SR. Repeated ICV administration of oxyntomodulin causes a greater reduction in body weight gain than in pair-fed rats. *Am J Physiol Endocrinol Metab.* 2002;283:E1173–E1177.

6. Druce MR, Minion JS, Field BCT, Patel SR, Shillito JC, Tilby M, Beale KE, Murphy KG, Ghatei MA, Bloom SR. Investigation of structure-activity relationships of oxyntomodulin (OXM) using OXM analogues. *Endocrinology*. 2009;150: 1712-22.
7. Cohen MA, Ellis SM, Le Roux CW, Batterham RL, Park A, Patterson M, Frost GS, Ghatei MA, Bloom SR. Oxyntomodulin suppresses appetite and reduces food intake in humans. *J Clin Endocrinol Metab.* 2003;88:4696–4701.

8. Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, Wren AM, Frost GS, Meeran K, Ghatei MA, Bloom SR. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes.* 2005;54:2390–2395.

9. Wynne K, Park AJ, Small CJ, Meeran K, Ghatei MA, Frost GS, Bloom SR. Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. *Int J Obes (Lond)*. 2006;30:1729–1736.

4. The contribution, impact or benefit

Our researchers have developed and sold a spin-out company, Thiakis Ltd, which investigated analogues for obesity therapy.

Obesity represents one of the greatest threats to the health of the developed world. Classified as an epidemic by the WHO, over 1 billion overweight adults worldwide and an estimated 22m children under five are obese, with annual figures rising sharply. Obesity increases the risk of heart disease, type two diabetes, stroke, some forms of cancer, arthritis, and respiratory disease and translates into healthcare costs of more than £0.5 billion every year in the UK. The current crisis has prompted public health initiatives to improve diet and promote exercise; however, these have proved largely ineffective, highlighting the urgent need for improved therapies for the treatment of obesity.

Currently available drug treatments have limited efficacy producing only modest short-term weight loss and are limited by side effects. To date the most successful treatment is major gastrointestinal surgery which leads to weight loss through a permanent loss in appetite. However the morbidity and mortality associated with bypass surgery in addition to practical and financial constraints usually limit this approach to only the severely obese patient.

Thiakis Ltd, an Imperial spin-out company was founded in 2004 by Professor Steve Bloom and Dr John Burt (formerly Head of Medical and Life Sciences at Imperial Innovations), together with Imperial Innovations to develop novel medicines for the treatment of obesity based on the peptide hormones PYY_{3-36} and oxyntomodulin.

Since 2005, human studies in the department had demonstrated that self administered oxyntomodulin both increases energy expenditure and causes significant weight loss with minimal side effects (8, 9) making oxyntomodulin a strong therapeutic target. Further studies (6) developed a number of oxyntomodulin analogues to investigate the contribution of different regions of the molecule to its function and sensitivity to proteolytic degradation. Patents were successfully filed by the department relating to use of oxyntomodulin, oxyntomodulin analogues (10-12) and the methods employed in studies.

In 2006, Thiakis raised £10 million in its first and only funding round from a syndicate of investors led by Advent Venture Partners, Novo A/S and Imperial Innovations to develop oxyntomodulin analogues. In December 2008, Thiakis Ltd was sold to Wyeth Pharmaceuticals to develop Thiakis' lead product TKS 1225, a synthetic analogue of oxyntomodulin. Wyeth acquired Thiakis for approximately $30 million with additional payments of $120 million conditional on the achievement of set milestones (13, 14).

Wyeth Pharmaceuticals was subsequently acquired by Pfizer in 2009 which has continued

development of the analogue.

Impact indicators

Creation of a new business:

- Establishment of a spin-out company securing £10m funding
- Sale of Thiakis to Wyeth Pharmaceuticals for $30 million with additional payments of $120 million
- Three patents awarded
- Milestones and royalties from drug sales due under licence agreement

Improved health outcomes

- Drugs in Phase I/II clinical trials

Delivery of highly skilled people:

- Career development of four scientists and ten trainees have acquired specialist knowledge of drug development

*Advisory roles for the pharmaceutical industry, research funding committees and professional bodies (*http://www1.imperial.ac.uk/medicine/people/s.bloom/*)*

Research income from a government organisation and a medical charity

5. References to corroborate the contribution, impact or benefit

Patents

10. WO2004062685. Modification of feeding behaviour and weight control by oxyntomodulin. Bloom SR, Ghatei MA, Small C, Dakin C. http://bit.ly/diYY5o

11. WO2006134340. Oxyntomodulin analogues and their effects on feeding behaviour. Bloom SR, Ghatei MA. http://bit.ly/cRJADi

12. WO2003057235. Modification of feeding behaviour. Bloom SR, Small C, Batterham R, Ghatei M. http://bit.ly/d6LAvM

Further references

13. Press release: Wyeth Pharmaceuticals Acquires Thiakis Limited. 18/12/2008. http://bit.ly/ce1UFv

14. Press release: Imperial Innovations Portfolio Company Trade Sale for up to £100 million. 18/12/2008. http://bit.ly/biYWS0

Researcher homepage

15. Professor Stephen Bloom: http://www1.imperial.ac.uk/medicine/people/s.bloom/

Reduction of recurrent stroke risk by early intervention (University of Oxford)

1. Short summary of the case study

Results from a series of studies of early prognosis and treatment after a transient ischaemic attack (TIA) and minor stroke have been used to redesign stroke-prevention services in the UK and elsewhere, and informed the Department of Health's National Stroke Strategy. Professor Rothwell and colleagues showed that the early risk of a major stroke in the first few days after these more minor 'warning' events was much higher than had previously been supposed and developed simple clinical risk scores (ABCD system) to identify high-risk patients. They then showed in the EXPRESS study that urgent use of existing treatments (including antiplatelet drugs, blood pressure-lowering and cholesterol-lowering drugs) reduced the 90-day risk of major stroke by about 80% compared with standard care. This strategy is now being rolled out across the UK, with the expectation of preventing about 10,000 strokes per year and saving the NHS up to £200 million in acute care costs alone.

2.Underpinning research

1. The risk of stroke after a TIA had been underestimated previously. Rothwell and colleagues studied the natural history of TIA and minor stroke in the Oxford Vascular Study and demonstrated that the early risk of stroke was much higher than had previously been thought (BMJ 2004; 328: 326-328 – and several other papers).

2. In order to triage patients with TIA who are at highest early risk of major stroke, Rothwell and colleagues developed the ABCD risk score (Lancet 2005;366: 29-36), which they further refined and validated in 2007 (Lancet 2007;369:283-92) and 2010 (Lancet Neurology *in press*).

3. Rothwell and colleagues performed the EXPRESS Study (Lancet 2007; 370: 1432-42) to determine the risks and benefits of acute treatment of TIA and minor stroke. EXPRESS was very novel – a population-based sequential comparison study – one of the most rigorous non-randomised studies of a treatment intervention ever performed. Randomisation to early vs delayed treatment after TIA and minor stroke wasn't feasible (patients would not consent even if ethics approval could be obtained from the relevant committees) – a "catch-22" – treatment very likely to be effective, but not allowed to change clinical services because of lack of evidence. However, by nesting a prospective "before versus after" study within a rigorous population-based disease incidence study (Oxford Vascular Study), with complete ascertainment and follow-up of all patients with TIA and minor stroke in both phases, Rothwell and colleagues obtained a reliable estimate of the effect of the intervention, with the additional major advantage that the estimate was derived from the whole population irrespective of age (30% of patients were aged over 80 years, for example) or mode of presentation – setting a new standard in external validity without undermining internal validity (NICE graded it as Level 2A evidence). As predicted by previous modelling, urgent investigation and treatment reduced the 90-day risk of major recurrent stroke by 80%.

4. Subsequent health-economic analyses of the EXPRESS study by Rothwell and colleagues (Lancet Neurol. 2009; 8:235-43) showed that urgent intervention reduced the risk of disabling stroke and risk of hospitalisation, reducing overall hospital bed-days by over two thirds, generating

savings of £624 per patient treated.

Details of colleagues involved in Professor Rothwell's work:
Drs Coull, Schulz, Flossmann, Lovelock, Chandratheva, Geraghty and Marquardt were all Clinical Research Fellows on the Stroke Prevention Research Unit (SPRU) during this period of research.
Dr Luengo-Fernandez is Senior Researcher and Associate Research Fellow at Oxford University's Health Economics Research Centre, and since 2004 has worked very closely with SPRU.
Dr Matthew Giles is a consultant physician and geriatrician at the John Radcliffe Hospital, and a Biomedical Research Centre Senior Research Fellow on the SPRU.
Mrs Louise Silver is the Study Coordinator of the Oxford Vascular Study and Dr Ziyah Mehta is the Database Manager and statistician.

3. References to the research

The following six key references were all published in peer reviewed journals:

Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. **Lancet Neurol**. 2009; 8:235-43.

Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JNE, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJV, Bosch S, Carasco-Alexander F, Silver LE, Gutnikov SA, Mehta Z, on behalf of the Early use of Existing Preventive Strategies for Stroke (EXPRESS) Study. Major reduction in risk of early recurrent stroke by urgent treatment of TIA and minor stroke: EXPRESS Study. **Lancet** 2007; 370: 1432-42.

Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. **Lancet** 2007;369:283-92.

Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. **Lancet Neurol** 2007; 6:1063-72.

Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JNE, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after a transient ischaemic attack. **Lancet** 2005; 366: 29-36.

Coull A, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after a transient ischaemic attack or minor stroke: implications for public education and organisation of services. **BMJ** 2004; 328: 326-328.

Details of peer reviewed grants and fellowships that supported this work:

Peter Rothwell (PI) "Development of simple prognostic tools to improve the effectiveness of stoke prevention" MRC 01/03/06 - 01/03/09 £546,303
Peter Rothwell (PI) "Oxford Vascular Study" Dunhill Medical Trust 2006-2012 £565,000

Peter Rothwell (PI) “Oxford Vascular Study: Phase 2” NIHR 2006-2011 £837,873
Peter Rothwell (PI) “Oxford Vascular Study” Oxford NIHR Biomedical Research Centre; 2008 – 2011 £250,000
Peter Rothwell (PI) NIHR Senior Investigator Award (fellowship award from NIHR 01/04/09 - 01/04/12

4. The contribution, impact or benefit

The initial research on prognosis demonstrated that the early risk of stroke following a TIA or minor stroke had been substantially underestimated and that all major clinical guidelines were too lax in their recommendations on the speed with which patients should be assessed and treated. Publication of the results lead to most national and international clinical guidelines increasing the urgency with which investigation and treatment was recommended.

However, in order to manage the considerable clinical workload (nearly 100,000 referrals per year in the UK alone), particularly in cash-strapped healthcare systems such as the NHS, it was clear that some method of triage and risk stratification would be very helpful in routine clinical practice, such that patients at highest early risk of stroke could be prioritised for most urgent assessment and treatment. In response to this need, Rothwell and colleagues developed the ABCD risk score (Lancet 2005;366: 29-36), which they further refined and validated (ABCD2 score) in 2007 (Lancet 2007;369:283-92). Use of the ABCD system is now recommended in all major national and international clinical guidelines on TIA and stroke and the system continues to be refined.

Yet, despite the better understanding of prognosis and the “re-branding” of TIA and minor stroke patients as medical emergencies, there was no hard evidence at this stage that urgent assessment and treatment would actually reduce the high early risk of major stroke – and so it was difficult to persuade healthcare systems to act upon the research findings in the face of other priorities with a better evidence base. In 2007, Rothwell and colleagues published the EXPRESS study – showing for the first time that emergency treatment of patients with TIA and minor stroke did reduce the risk of early major recurrent stroke - by about 80%. Subsequent studies showed that the intervention was cost-effective (Lancet Neurol. 2009; 8:235-43) and that, if rolled-out across the UK, it would prevent about 10,000 strokes per year, saving the NHS up to £200M in acute care costs alone.

In response to this evidence, UK and international clinical guidelines changed rapidly. Revised NICE guidelines were published in 2008, following publication of the Department of Health’s National Stroke Strategy the previous year, both of which fully endorsed the “medical emergency” status of TIA and minor stroke, the use of the ABCD2 score and the results of the EXPRESS study.

The implementation of the guidelines that resulted from the work of Rothwell and his team has benefitted groups along the entire healthcare supply chain: individual patients, changes to GPs’ practice through adoption of the NICE guidelines, reduced burden on the NHS for acute care, and reduced costs to wider society for long term care of a patient after a major stroke.

5. References to corroborate the contribution, impact or benefit

Department of Health. National stroke strategy. In: dh.gov.uk/stroke; 2007. [http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_081059.pdf]

European Stroke Organisation. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25:457-507. [http://www.eso-stroke.org/pdf/ESO%20Guidelines_update_Jan_2009.pdf]

National Institute for Health and Clinical Excellence TIA and Stroke Guidelines. www.nice.org.uk; 2008. [http://www.nice.org.uk/nicemedia/pdf/CG68FullGuideline.pdf]

Royal College of Physicians Intercollegiate Stroke Working Party. National clinical guideline for stroke, third edition; 2008.

Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al. National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol. 2006;60:301-313.