Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Translating Genetic Insights into Improved Clinical Diagnosis and Therapy of Severe Insulin Resistance.

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

Long-standing research led by Prof. O'Rahilly (Department of Clinical Biochemistry) into the genetic and biochemical basis of severe insulin resistance syndromes, has led to improvements in diagnosis and care of patients internationally. These advances have facilitated revision of existing clinical classifications and implementation of novel diagnostic and management algorithms for these conditions. The clinical applicability of this research was recognised in 2011 by the Department of Health-England who have commissioned a national severe insulin resistance service in Cambridge, with support totalling ~£450,000 per annum.

2. Underpinning research (indicative maximum 500 words)

Severe insulin resistance and lipodystrophy are rare but devastating disorders associated with high morbidity and early mortality. Their rarity has denied patients suffering from them widespread access to diagnostic expertise, commonly leaving them subject to suboptimal clinical management and often very poor outcomes, including badly controlled diabetes, with attendant micro- and macrovascular complications, pancreatitis, chronic liver disease and subfertility.

The underpinning research was instigated by Stephen O'Rahilly (Professor of Metabolic Medicine 1996-2001, Professor of Clinical Biochemistry and Medicine 2001-present) at the University of Cambridge, with more recent co-direction by Drs David Savage (Senior Research Associate since 2006) and Robert Semple (Senior Research Associate since 2008), each of whom trained in the O'Rahilly laboratory. The specific findings leading to the described impact arose from genetic, biochemical and physiological studies undertaken between 1996 and 2011.

The guiding strategy was to identify and recruit, through widespread international collaboration, patients with severe forms of insulin resistance but not severe obesity, to a genetic and clinical study. These efforts led to the establishment of a unique collection ('biobank') of DNA and blood samples from patients with severe insulin resistance. Since 1996 the cohort has grown to include samples from over 1000 patients worldwide. The research used the best available genetic techniques to determine the genetic aetiology of the severe metabolic derangement. The precise genetic basis for 10 previously uncharacterised syndromes characterised by impaired or excessive insulin action have been identified to date. The disorders are now primarily classified according to the gene in which pathogenic mutations were identified: 1) PPARG (1999); 2) PPARG/PPP1R3A (2002); 3) AKT2 (2004); 4) TBC1D4 (2009); 5) CIDEC (2009); 6) PLIN (2011); 7) LMNA (2000); 8) BSCL2 (2001); 9) CAV1 (2008); and 10) PCNT (2011) (1-5) (underpinning research summarised in reference 1). These syndromes have been characterised in detail in terms of both the cellular dysfunction and their impact on whole body physiology. This information has aided the identification of similarly affected patients worldwide. The research has also recently identified two genetic syndromes characterised by excessive insulin-like action (4,5)

Using biomarkers not in routine clinical use they were able to establish a novel biochemical fingerprint that reliably identifies certain subgroups and allows targeting of subsequent genetic analyses (6).Highly related research, led by Professor O'Rahilly (1997-present), regarding the effects of recombinant leptin therapy on severely obese children with congenital leptin deficiency also provided underpinning information and experience important in later impact on treating patients with severe insulin resistance.

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

1. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. Endocr Rev. 2011;32:498-514.Citations:19 (Scopus 10/09/13)
2. Gandotra S, Le Dour C, Bottomley W, Cervera P, Giral P, Reznik Y, Charpentier G, Auclair M, Delépine M, Barroso I, Semple RK, Lathrop M, Lascols O, Capeau J, O'Rahilly S, Magré J, Savage DB, Vigouroux C. Perilipin deficiency and autosomal dominant partial lipodystrophy. N Engl J Med. 2011;364:740-8.Citations: 30 (Scopus 10/09/13)
3. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD,

Lewis H, Schafer AJ, Chatterjee VK, O'Rahilly S. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999;402:880-3.Citations: 30 (Scopus 10/09/13)
4. Hussain K, Challis B, Rocha N, Payne F, Minic M, Thompson A, Daly A, Scott C, Harris J, Smillie BJL, Savage DB, Ramaswami U, De Lonlay P, O'Rahilly S, Barroso I, Semple RK. An Activating Mutation of AKT2 and Human Hypoglycemia. Science 2011;334:474.
Citations: 20 (Scopus 10/09/13)
5. Lindhurst MJ, Parker VER, Payne F, Sapp JC, Rudge S, Harris J, Witkowski AM, Zhang Q, Groeneveld MP, Scott CE, Daly A, Huson SM, Tosi LL, Cunningham ML, Darling TN, Geer J, Gucev Z, Sutton VR, Tziotzios C, Dixon AK, Helliwell T, O'Rahilly S, Savage DB, Wakelam MJO, Barroso I, Biesecker LG, Semple RK. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. Nat Genet 2012;44:928-33.Citations: 12 (Scopus 10/09/13)
6. Semple RK, Halberg NH, Burling K, Soos MA, Schraw T, Luan J, Cochran EK, Dunger DB, Wareham NJ, Scherer PE, Gorden P, O'Rahilly S. Paradoxical elevation of high-molecular weight adiponectin in acquired extreme insulin resistance due to insulin receptor antibodies. Diabetes 2007;56:1712-7. Citations: 39 (Scopus 10/09/13)

Evidence of Quality

In recognition of the importance of this work Prof O'Rahilly has received many national and international honours including the Fellowship of the Royal Society, Foreign Associateship of the National Academy of Sciences of the USA and Hon Membership of the German Society for Internal Medicine. He has received Honorary Doctorates from University College Dublin and the Universities of Warwick and Dundee Among the international prizes he has been awarded are the Heinrich Wieland Prize, the Feldberg Prize, the Clinical Endocrinology Award of the Endocrine Society of North America, the Luft Award and the Inbev Baillet Latour Prize. He was knighted in June 2013 for services to medical research. Drs Semple and Savage have been awarded highly prestigious Wellcome Trust Senior Research Fellowships to purse basic and translational research in this area.

Selected Research Grant Support

Stephen O'Rahilly has held continuous Wellcome Trust Programme Grant/Senior Investigator funding since 1999 Most recent renewal: Title: Insulin Resistance: lessons from extreme phenotypes Period: 2011-2016 Amount: £2,072,000

PI: Stephen O'Rahilly, Wellcome Trust Consortium Grant
Title: Integrative physiology of common metabolic disease Sponsor: Wellcome Trust Period: 2002-2008Amount: £5,000,000 (£3,199,360 for Cambridge)

PI: David Savage, Wellcome Trust Senior Clinical Fellowship
Title: Lipodystrophy- A Paradigm For Elucidating Pathogenic Mechanisms In The Metabolic Syndrome Sponsor: Wellcome Trust Period: 2010-2015Amount: £1,302,000

PI: Robert Semple, Wellcome Trust Senior Clinical Fellowship
Title: Genetic Dissection of Mechanisms Linking Insulin Resistance to Major Human Diseases Sponsor: Wellcome Trust Period: 2012-2017 Amount: £1,609,000

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

The research led by Professor O'Rahilly has had impact on patients, practitioners and the wider public as follows;

Impact on Health

Public health and wellbeing has improved.

Patients who have serious diseases, the cause of which is not known to medical science, suffer not only from the direct adverse effects of their disorders but also from the anxiety and demoralisation that result when they cannot be provided with any meaningful explanation for their disease. O'Rahilly's research has provided patients with meaningful explanations for the causes of their

serious sometimes life-threatening disorders when previously there were none, leading to an immediate and positive impact on patient wellbeing and satisfaction and, in an increasing number of cases, initiation of trials of novel approaches to therapy. Specifically, O'Rahilly, Savage and Semple have discovered or made major contributions to the discovery of 10, previously unrecognised, genetic syndromes of severe insulin resistance / lipodystrophy and two further syndromes of excessive insulin-like action. In several of these disorders understanding the molecular basis has suggested specific new treatment strategies which are currently being explored in pre-clinical models and a subset in the clinic. The publication of these discoveries and their presentation at international meetings has led to the same benefits being conferred on patients world-wide (1).

The team have, together with several remarkable patients, also established a patient support group for lipodystrophy, one of the more common causes of severe insulin resistance, with a website that commenced in August 2006 (2). The support group now comprises >150 members and the website is visited ~500-1000 times per month on average by people in the UK and internationally. The patient support group is autonomous but the Cambridge team (led by Dr Savage) provide medical advice where requested and host annual meetings for the patient group, the most recent of which took place in March 2013. Feedback collected at this meeting shows support group members greatly value the clinical and research insights into the condition that it provides, as well as the opportunity to meet others with similar conditions (3).

New diagnostics have been adopted

The success of this research programme has played an important role in driving clinical diagnostic innovations. This has permitted the use of a simple, cheap, biochemical screen that involves measurement of serum adiponectin (4) for these patients, allowing highly efficient (by limiting inappropriate and expensive genetic analysis of large genes (INSR gene has >20 exons)), targeted genetic testing of the gene encoding the insulin receptor and greatly accelerating molecular diagnosis (5). This work culminated in publication of a proposed revised classification of severe insulin resistance syndromes which facilitates both accelerated diagnosis and optimises intervention strategies (reference 1; Section 3).

The development in Cambridge of novel diagnostic algorithms (first implemented in 2008) to expedite molecular diagnosis in insulin resistance has resulted in rapidly increasing rates of genetic diagnosis among patients with severe insulin resistance and lead to increasing numbers of patients receiving a specific molecular diagnosis (~42% of new referrals to the service). The diagnostic improvements made by the Cambridge team have been complemented by access to and clinical use of new peptide-based treatments with rarely available therapeutic agents including recombinant human leptin (made available by Amylin Inc. solely to Cambridge within the UK for named patient use since 2008) and recombinant human IGF-1.

Impact on commerce and economy

Amylin was recently acquired by Bristol Myers Squibb Ltd who are currently pursuing the licensing of leptin as a therapy for orphan diseases of metabolism in the USA and Europe. This work culminated in a successful application to the (now) NHS England National Specialist Commissioning Team for national commissioning of a multidisciplinary clinical service for patients with severe insulin resistance (6,7). This was commissioned in April 2011, with support totalling £450,000 per annum, funding a full-time NHS consultant and specialist nurse, part-time dietician and administrative support, a full range of diagnostic testing, and clinical use of leptin and IGF1. This service, which opened in July 2011, provides clinical, biochemical and genetic assessment for patients with severe insulin resistance (7).

Impact on practitioners and services

The multi-disciplinary team also provides management advice to referring physicians and, in a subset of patients, they initiate and supervise either leptin or IGF-1 therapy. To date 88 patients have been seen in this specialist clinic and rates of referral are increasing rapidly. Diabetic patients with suboptimal glucose (glycaemic) control who have attended our service have already, since July 2011, achieved an average reduction in HBA1c (standard index for diabetes control) of 1.1%.

This level of reduction exceeds the goal of a 1% reduction in HBA1c for novel treatments for type 2 diabetes and is expected to significantly delay micro- and macrovascular complications. Results from a patient feedback survey of the service are included in (8).

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

1. Letter from Director Emeritus National Institute of Diabetes Digestive and Kidney Disorders, Bethesda MD USA (held in University repository)

2. Lipodystrophy support group
http://www.lipodystrophy.co.uk

3. Feedback from attendees of the Lipodystrophy Support Group Meeting hosted in Cambridge 2013 (held in University repository)

4. Supraregional Assay Service (SAS)
http://www.sas-centre.org/centres/hormones/cambridge.html

5. Registered Genetic Tests
UK Genetic Testing Network: http://www.ukgtn.nhs.uk/gtn
Orphanet: http://www.orpha.net/consor/cgi-bin/index.php

6. National Commissioning
http://www.specialisedservices.nhs.uk/service/insulin-resistant-diabetes-service
National Specialised Commissioning Team; 2nd Floor, Southside; 105 Victoria Street; London SW1E 6QT; Direct Line: 020 7932 2601; Email: Commissioners@nsct.nhs.uk

7. National Severe Insulin Resistance Service
http://www.cuh.org.uk/addenbrookes/services/clinical/severe_insulin_resistance_service/severe_insulin_resistance_service_index.html

8. Results of a Patient Satisfaction Questionnaire for the National Severe Insulin Resistance Service (February 2013) (held in University repository)