Institution: University of Brighton
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy
Title of case study: Targeting treatment and improving lives in the diabetes community (ICS [2])

1. Summary of the impact

Research from the University of Brighton's Diabetes Research Group (DRG) has underpinned the translation of beta-cell replacement therapy into clinical application for the treatment of type 1 diabetes (T1D) to establish the world's first government-funded islet transplant service at six new UK islet-transplant centres. As a consequence, the first 65 successful islet transplants were performed, reducing the incidence of hypoglycaemic events by >95% and providing a life-changing therapy for patients. Through a leadership role in Diabetes UK, BONE integrated the interests of stakeholders and professionals to establish a new model for diabetes care. With the Juvenile Diabetes Research Foundation, in 2013 he launched in Parliament the first UK T1D Research Roadmap.

2. Underpinning research

Diabetes research at the University of Brighton has established a progressive research base across 20 years. The DRG applies clinically-reflective model systems and human tissue studies to determine the disease mechanisms underpinning the causes, development and progression of diabetes. Early work [reference 3.1] used biopsies to relate histological change to rodent cell activation during the course of pre-diabetes. This study discovered a significant rise in a coenzyme late in the progression of pre-diabetes that helped to modify knowledge about cell destruction processes. This developmental work documenting the natural history of the disease processes in models of T1D has progressed to studies on newly diagnosed diabetes in humans.

Reported findings [3.2, 3.3], using a unique collection of T1D pancreases, have characterised the inflammatory infiltrate in T1D and provided the first direct evidence that a common enteroviral infection is capable of triggering development of diabetes in genetically susceptible individuals. This work was identified as a 'Research Highlight' in *Nature*. Further research demonstrated for the first time that there is an increased islet cell proliferation in patients with recent-onset T1D [3.4, 3.5] thereby identifying new therapeutic targets and treatments for the cure and prevention of T1D (Juvenile Diabetes Research Federation International–Research Priority Area). These studies were selected by the Editor of *Diabetologia* – the premier European diabetes journal as an 'Editor's choice' article and also triggered a full commentary paper in the same journal. This research was supported by the DRG's participation in an EU programme, the IREN Consortium, which established a European Centre for 'Beta Cell Regenerative Medicine', including central facilities for: (a) human stem cells; (b) human pancreatic islets; (c) viral vector construction and; (d) microarray genetic and proteomic analyses. University of Brighton researchers led the development of cellular/molecular methodologies and model systems for generating, characterising and testing replacement cells and tissues suitable for transplantation.

Research involving model systems expanded previous work started by MACFARLANE and SHAW at Newcastle and went on to develop a glucose-responsive beta-cell line to produce a new and abundant alternative source of insulin producing cells suitable for transplantation and treatment of T1D [3.6]. This work has configured alternative beta-cells as surrogates of native islets and these 3D islet-like clusters have proved an ideal replacement for non-human islets in studies to improve outcomes in human islet transplantation. These research achievements have been driven by EU programmes aimed at improving understanding of T1D and developing better treatments for people living with the disease. The TONECA Co-ordination Action promoted and supported the networking and coordination of research and innovation activities in the field of T1DM by combining expertise and providing open access to new research results throughout the EU. The University of Brighton led one of the four main scientific Work-packages (WP3 – in-vivo model systems) and acted as the UK Regional Coordinating Centre, with responsibility for communication between scientists, physicians and patients and their national organisations (professional and patient). The ongoing PEVNET research programme is detecting the persistent enterovirus infection leading to inflammation and damage of the pancreas and stopping the subsequent development of disease. The work on the detection of viruses (Workpackage 3) is

the responsibility of the collaborative research partnership led by key investigators BONE (Brighton), Morgan (Exeter) and Foulis (Glasgow). The University of Brighton is the co-ordinating centre of the recently awarded NEXT Collaborative Project, which is developing nano-engineered pancreatic islets to investigate adverse immune reactions and develop immune-shielded islets suitable for transplantation into non-systemically immune-suppressed diabetic patients. The tissue engineering of the beta-cells (WP2) and the construction and in-vitro testing of the chimeric islet grafts are the responsibility of University of Brighton researchers MACFARLANE, BONE and SANTIN.

Key Researchers:

Adrian Bone:	Professor of Cell and Molecular Biology (June 1992–to date).
Wendy Macfarlane:	Reader (Oct 2006–to date).
Matteo Santin:	Research Fellow (Oct 1994–Oct 1996), Research Fellow (Nov 1998–Mar 2001), Senior Research Fellow (Apr 2001–Mar 2004) Senior Lecturer (Apr 2004–May 2006), Principal Lecturer and Reader (June 2006–July 2010), Professor of Tissue Regeneration (Aug 2010–to date).

3. References to the research

[3.1] DAVIES, A.J., BONE, A.J., WILKIN, T.J., ROKOS, H. and COLE, D.R. (1994) Serum biopterin – A novel marker for immune activation during prediabetes in the BB rat. *Diabetologia,* 37, pp.466–471. [Quality validation: leading peer-reviewed journal].

[3.2] RICHARDSON. S.J., WILLCOX. A., BONE. A.J., FOULIS, A.K. and MORGAN, N.G. (2009) The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. *Diabetologia,* 52, pp.1143–115. [Quality validation: 105 cites].

[3.3] WILLCOX. A., RICHARDSON, S.J., BONE, A.J., FOULIS, A.K. and MORGAN, N.G. (2009) Analysis of islet inflammation in human type 1 diabetes. *Clinical Experimental Immunology,* 155, pp.173–181. [Quality validation: 108 cites].

[3.4] WILLCOX, A., RICHARDSON, S.J., BONE, A.J., FOULIS, A.K. and MORGAN, N.G. (2010) Evidence of increased islet cell proliferation in patients with recent onset type 1 diabetes. *Diabetologia,* 53, pp.2020–2028. [Quality validation: leading peer-reviewed journal].

[3.5] WILLCOX, A., RICHARDSON, S.J., BONE, A.J., FOULIS, A.K. and MORGAN N.G. (2011) Immunohistochemical analysis of the relationship between islet cell proliferation and the production of the enteroviral capsid protein, vp1, in the islets of patients with recent-onset type 1 diabetes. *Diabetologia: Short Communication,* 54, pp.2417–2420. [Quality validation: leading peer-reviewed journal].

[3.6] ALDIBBIAT, A., MARRIOTT, C.E., SCOUGALL, K.T., CAMPBELL, S.C., HUANG, G.C., MACFARLANE, W.M. and SHAW, J.A.M. (2008) Inability to process and store proinsulin in transdifferentiated pancreatic acinar cells lacking the regulated secretory pathway. *Journal of Endocrinology,* 196, pp.33–43. ISSN 0022-0795. [Quality validation: leading peer-reviewed journal].

Peer-reviewed research grants:

BONE (Steering Committee Member), 'Islet Research European Network [IREN]: Bioengineered cells for gene therapy of diabetes mellitus' EU Commission BIOMED 2 Concerted Action (18 partners). 1998–2002. Total funding: €530k

BONE (Work-package Leader) Coordination Action on the aetiology, pathology and prediction of type 1 diabetes in Europe (Project acronym: TONECA) EU Sixth Framework Programme Priority 1.1.1: Life Sciences, Genomics & Biotechnology for Health. (28 partners). 2004–2008. Total funding: €1.2m

BONE together with Morgan, Foulis and 13 EU partners, 'PEVNET – Persistent virus infection as a cause of pathogenic inflammation in type 1 diabetes – an innovative research programme of biobanks and expertise.' EU 7th FP Collaborative Project. 2011–2016. Total funding: €5.99m.

MACFARLANE, BONE and SANTIN and 4 EU partners – HEI x1, SME x3), 'NEXT – Nano engineering for cross tolerance: a new approach for bioengineered, vascularised, chimeric islet transplantation in non-immunosuppressed hosts.' EU 7th FP Collaborative Project. 2013–2016. Total funding: €4.8m.

4. Details of the impact

The World Health Organisation predicts that more than 30 million people will be diagnosed with the T1D disease by 2030, classifying it as a global epidemic. University of Brighton researchers provide the expertise to target treatment and improve lives in the diabetes community through:

Establishing the world's first government-funded islet transplant service: The University of DRG's work on the isolation and functional characterisation of pancreatic beta and surrogate insulin-producing cells provided the basic research underpinning the establishment of the UK Islet Transplant Consortium. The Consortium, chaired by Professor James Shaw (Newcastle), prepared a successful bid to the National Commissioning Group for NHS funding and NICE approval of an integrated UK NHS Islet Transplant Programme. The Programme, launched nationally in 2008, is the world's first government-funded islet transplant service dedicated to patients with type 1 diabetes. This programme saw the establishment of six transplant centres that provide a cost-effective national programme for islet transplantation. These centres were commissioned to deliver a cure for recurrent life-threatening hypoglycaemia (sources 5.1, 5.2, 5.3).

About one third of people with type 1 diabetes will experience a severe hypoglycaemic event each year, requiring intervention and treatment from others. For people who experience multiple severe events, an islet transplant is life-changing therapy. Islet transplantation involves separating out insulin-producing islet tissue from a donor pancreas and transplanting the islets by simple injection into the liver of the patient. These islets develop their own blood supply and produce insulin as required. Islet transplants have been successfully performed on 65 patients between April 2008 and March 2013, with a reduction in severe hypoglycaemic events (>95%) and improved glycaemic control (5.2, 5.4). The frequency of severe hypos was, on average, reduced from 23 per person per year to less than 1 per person per year and overall insulin requirement was halved in these patients. This simple procedure makes the most unmanageable form of this condition manageable. These low-impact transplants are performed under local anaesthetic, taking less than 30 minutes, with patients returning home on the same day free from the burden of insulin injections, finger-prick blood glucose testing and the fear of night-time hypoglycaemic episodes. Patient, family and carer education is an essential aspect of the service delivery to ensure long-term and sustained improvement. MACFARLANE and BONE continue to provide advice to the Consortium as members of the Scientific Advisory Board.

Promoting a wider understanding of the lifestyle issues associated with living with diabetes: BONE's earlier work with the British Diabetic Association (subsequently Diabetes UK) as a member of the UK Advisory Council and Professional Advisory Council Executive, helped the Organisation move from a predominantly clinician-led professional association to the largest organisation in the UK working for people with diabetes. This has helped break down barriers between clinicians and patients through the empowerment of a range of stakeholders. Currently Diabetes UK has a nationwide network of >300 voluntary groups with 300,000 supporters and 6,000 healthcare professional members. BONE'S involvement in this transition was as a member of the Executive Group (Hon. Secretary), which developed the current Diabetes UK Governance Structure. The Expert Group (Science and Research) he chaired was the first to directly engage patients and lay members in priority setting, which has changed the nature of care in the diabetes community. This is a practice subsequently adopted by the other Expert Groups that feed into the UK Advisory Council. This increased leadership role for the lay membership of Diabetes UK required a significant culture change from both healthcare professionals and lay persons alike. The major impacts have been a wider understanding of the lifestyle issues associated with living with diabetes from the healthcare professionals and a heightened sense of engagement of patients and their carers with the work of Diabetes UK. In recognition of this, BONE won an Excellence Award for Outstanding Services to the Advisory Council of Diabetes UK in 2008.

Raising awareness with key policy makers: Brighton DRG works closely, in an advisory capacity, with the major national (Diabetes UK) and international (Juvenile Diabetes Research Foundation – JDRF) diabetes charities and professional bodies (International Diabetes Federation – IDF) (5.5). This work has raised awareness of what living with diabetes involves and the impact it has on the UK. The University of Brighton DRG, along with Brighton MP Caroline Lucas, led the JDRF call for the government to provide additional investment in type 1 diabetes research at the first-ever 'Type 1 Parliament' lobbying event at the Houses of Parliament – 25

April, 2012. Delegates included 60 patients with T1D and over 70 MPs, and the audience was made up of 300 people from key groups including healthcare professionals, corporate supporters and journalists. This lobbying event led to the launch, in June 2013, of the 'Type 1 Diabetes Research Agenda Roadmap for the UK' with the Brighton DRG selected to lead the beta cell research priority area (5.6). This roadmap highlights gaps in resources, has helped to dovetail internationally relevant research priorities, evidenced issues in career structures, grant types and funding stability across the community, thus providing relevant information to government, and enabling them to leverage more funding into T1D research.

Increasing public engagement and promoting understanding of diabetes: The University of Brighton DRG recently made a short film with the organiser of the Sussex Diabetes Gateway, a peer support group for young people with diabetes (5.7). This powerful film describes the impact that involvement with members of the DRG is having in helping youngsters improve their quality of life and their diabetes control. The SD Gateway is one of many local diabetes voluntary groups that have enthusiastically attended the 'Open Lab' sessions run by the DRG at the University of Brighton, promoting public and patient awareness of diabetes research. Other local community groups that visit the University of Brighton DRG and which the DRG visit regularly to give presentations include the Redhill Obesity Community Engagement Group, the Brighton Voluntary group and diabetes patient support groups from Burgess Hill and Hayling Island.

MACFARLANE and BONE are regular invited speakers at JDRF public awareness events throughout the UK, which provide research updates and opportunities for families affected by diabetes to talk with researchers and understand how research teams like the University of Brighton DRG are working together to achieve JDRF's mission to cure, treat and prevent type 1 diabetes. Recent events that have led directly to increased donations to JDRF include – 'The artificial pancreas' – Newcastle, November 2011; 'Discovery Day' – Brighton, November 2011; JDRF Patrons' Club 'Paths to the perfect pancreas' – London, October 2012.

5. Sources to corroborate the impact

5.1 Information on the UK NHS Islet Transplant Programme. Available at: www.nhsbt.nhs.uk/triennial-report/organ-donation-and-transplantation/allocation-of-organs/ [Accessed: 2 November 2013].

5.2 Diabetes UK, 'Diabetes treatments' [online]. Available at: http://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Islet-transplants/?print=2 [Accessed: 2 November 2013]. Guide to treatments that confirms the role of the first government-funded transplant centre and that 95 islet transplants had been performed in 65 people in the UK.

5.3 National Specialised Commissioning Team, Service Specification. Available at: http://www.specialisedservices.nhs.uk/library/36/Service_Specification_and_Standards___Islet_transplantation_and_islet_isolation_1.pdf http://www.specialisedservices.nhs.uk/service/islet-transplant/search:true [Accessed: 2 November 2013]. This document describes the effects of islet transplantation including proven benefits for those who suffer from recurrent episodes of severe hypoglycaemia.

5.4 Young Diabetologists & Endocrinologists (2012), 'Referral criteria for islet transplantation.' Available at: http://www.youngdiabetologists.org.uk/etools/guidelines/islet [Accessed: 2 November 2013]. Confirmation that 96% of all transplants were functioning at one month, and have been maintained long-term Severe hypoglycaemia was reduced by >95% and the UK clinical islet transplant programme has attained its goals of preventing recurrent severe hypoglycaemia, improving glycaemic control and maintaining satisfactory graft function.

5.5 Testimonial available from Head of Research Communication at JDRF, confirming how the Brighton DRG work is contributing to JDRF's mission to finding the cure and the impact of the diabetes research agenda roadmap.

5.6 JDRF (2013) Type 1 Diabetes Research Agenda Roadmap Report. Available at: www.jdrf.org.uk/research/type-1-diabetes-research-roadmap [Accessed: 2 November 2013]. Roadmap Delivered to Parliament 12 June 2013 Brighton's research appears on pages 20-21.

5.7 The Sussex Diabetes Gateway. Available at: http://www.sussexdiabetes.org.uk/ and http://www.sussexdiabetes.org.uk/?p=240 [Accessed: 2 November 2013].