Institution: University of Brighton		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Targeting life-saving therapies and transforming quality of life for diabetes patients		
Period when the underpinning research was undertaken: 2008 – to date		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Wendy Macfarlane Adrian Bone	Reader in Molecular Biology Professor of Molecular Biology	Oct 2006 – to date Oct 1994 – 2017
Period when the claimed impact occurred: August 2013 – to date		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Brighton (UoB) research on islet transplantation therapy to treat Type 1 Diabetes (T1D) has eradicated hyperglycaemic events in 202 patients. Hyperglycaemic events have reduced from 23 per person per year to less than 1 per person per year and all 202 patients still have a functioning transplant. Additionally, UoB researchers, working in partnership with the UK Islet Transplant Consortium, have developed novel microgravity-based cell enrichment and transportation systems, improving transplant technologies. UoB research has stimulated healthcare industrial innovations and shaped international strategies to fight T1D. Research-led public engagement programmes have enabled more than 80 young adults to reverse their pre-diabetes and restore a normal balanced metabolism.

2. Underpinning research

For over twenty years UoB research has developed life-changing research by improving the understanding of the disease mechanisms in Type 1 and Type 2 diabetes (T1D and T2D). This body of work has led to the development of novel therapeutic approaches to improve the quality of life of patients with these conditions. UoB's clinically reflective research and human tissue studies determined the disease mechanisms underpinning the causes, development and progression of diabetes. This initial work increased the understanding of the complex mechanisms pivotal to the protection of beta cell function and the survival of the beta cells post-transplant, as well as identifying novel key mechanisms contributing to beta cell death in patients with T1D. Findings 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 [references 3.1 and 3.2] was identified as a `Research Highlight' in *Nature* https://www.nature.com/articles/nrendo.2009.84. This research demonstrated for the first time that there is an increased islet cell proliferation in patients with recent-onset T1D [3.2] 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. The translation of beta-cell replacement therapy into clinical application for the treatment of T1D was used to establish the world's first government-funded islet transplant service at six new UK islet-transplant centres (2008) and led to the establishment of the Islet Research European Network (IREN).

This early research went on to underpin the international PEVNET research programme [3.7], with the later research focused on two key priorities:

1. Applying UoB's clinically reflective cellular model systems to improve islet availability, function and survival
2. Prevention and reversal of pre-diabetes and T2D in overweight young individuals

2.1 Improving islet survival and function through technological innovation

Islet transplantation therapy has revolutionised the treatment of T1D, providing proof-of-principle that cell replacement therapy can effectively cure patients and restore normal

regulation of whole-body glucose metabolism [3.1, 3.2]. However, islet transplants are limited by the availability of donor tissue, which also impedes research into new and improved technologies to prolong islet graft survival and function post-transplant. Recent UoB research led to the development of a novel microgravity-based cell clustering technology that generates 3-dimensional cellular aggregates that accurately mimic human islets [3.3, 3.4]. In partnership with Cellon International, research into clinically-reflective cellular model systems was developed to produce bioreactor systems for the growth of cells. Previously, these systems were only used with cells that grow in liquid culture (ie blood cells, lymph etc.); the UoB study was the first to provide proof of principle that 'solid organs' (in this case, the pancreas) could be grown in microgravity 3D conditions [3.3]. Since the initial studies, this work has been expanded to meet the extraordinary challenges of islet transplantation, including overcoming the damaging effects of tissue hypoxia (very low oxygen) in the crucial first 48 hours post-transplant [3.5].

Innovative research into the effects of hypoxia on cell viability and Programmed Cell Death Gene 4 (PDCD4) expression indicated that PDCD4 may be an important factor in regulating beta cell survival during hypoxic stress [3.5]. As part of a European Commission funded project [3.8], UoB researchers combined microgravity 3D culture systems with hypoxic cell culture chambers, to study, for the first time. the detrimental effects of hypoxia on islet graft function in vitro [3.4, 3.5]. This research with Cellon International has seen the design and creation of the first portable microgravity cell enhancement system for the transportation of islets between isolation and transplant centres and the first perfusion microgravity cell culture system allowing real time testing of islet function.

2.2 Prevention and reversal of Type 2 Diabetes

An ongoing research priority is the prevention of T2D through enhanced patient motivation. This empowers patients through the use of innovative technologies and the translation of original basic science into improved clinical practice. UoB's recent work has focused on the long-term detrimental effects of glycaemic variability on beta cell viability and function and the importance of maintaining stable blood glucose concentrations [3.6]. In combination with the latest studies on the use of continuous glucose monitoring system (CGMS) technology, this work has now been translated into tailored diet, exercise and lifestyle programmes for young adults with pre-diabetes and newly diagnosed T2D, in combination with events and workshops designed and run by UoB scientists.

3. References to the research

[3.1] 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*(6), 1143-115. https://doi/10.1007/s00125-009-1276-0 [Quality validation: published in a leading peer-reviewed journal].

[3.2] 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*(9), 2020-2028. https://doi/10.1007/s00125-010-1817-6 [Quality validation: published in a leading peer-reviewed journal].

[3.3] Alhasawi, N., Kumar, S., Bone, A. J. Marriott, C. E. and Macfarlane, W. M. (2015). Optimisation of islet cells for transplantation therapy in Type 1 diabetes. Special Issue. *Diabetic Medicine 32*(S1), 36-38. https://doi.org/10.1111/dme.12668 [Quality validation: published in a leading peer-reviewed journal].

[3.4] Alhasawi, N., Kumar, S., Macfarlane, W. M., Marriott, C. M., and Bone, A. J., (2014). Protection of islet cells for transplantation therapy in Type 1 diabetes. *Diabetic Medicine* 31(SI) 32-33. https://doi.org/10.1111/dme.12378_1 [Quality validation: published in a leading peer-reviewed journal].

[3.5] Kumar, S., Marriott, C. E., Alhasawi, N., Bone, A. J. and Macfarlane, W. M. (2017). The role of tumour suppressor PDCD4 in beta cell death in hypoxia *PLoS ONE*. *12*(7), e0181235. https://doi.org/10.1371/journal.pone.0181235 [Quality validation: published in a leading peer-reviewed journal].

[3.6] Ordor, V., Kumar, S., Marriott, C. E., Bone, A. J. and Macfarlane, W. M. (2018). Glycaemic variability induces beta cell dysfunction: The role of oscillations in glucose concentration. *Diabetic Medicine* 35(S1), 40-51. https://doi.org/10.1111/dme.3_13571

[Quality validation: published in a leading peer-reviewed journal].

Key research grants

[3.7] Adrian Bone [PI], EU 7th Framework Programme Collaborative Project, 2011 – 2016, Persistent virus infection as a cause of pathogenic inflammation in type 1 diabetes [PEVNET], Total EUR5,990,000. UoB sub-contracted as consultant via the University of Exeter.

[3.8] Matteo Santin [PI], FP7-HEALTH-2013- INNOVATION-1, 2014 – 2017, Nano Engineering for Cross Tolerance: new approach for bioengineered, vascularised, chimeric islet transplantation in non-immunosuppressed hosts [NEXT]. Total funding EUR4,741,726. UoB allocation EUR670,581.

4. Details of the impact

There are currently 400,000 patients with T1D in the UK. A typical T1D patient suffers an average of two symptomatic hypoglycaemic episodes a week, hence thousands of episodes across a lifetime. They will suffer at least one episode of severe, disabling hypoglycaemia (often with seizure or coma) every year. This number rises dramatically in patients with poorly controlled diabetes, leading to frequent hospitalisation and life-threatening consequences. Prior to islet transplantation therapy, the gold standard for treatment of T1D was a complex regime of manual, sub-cutaneous insulin injections, in combination with frequent finger prick blood glucose monitoring and carbohydrate counting. Optimising this regime for an individual is extremely challenging and requires immense commitment from patients. UoB's sustained developmental research programme, working collaboratively with clinicians, charities and industry, has produced innovative solutions that have transformed the treatment of T1D. This is partnered with embedded public engagement strategies that have resulted in the reversal of pre-diabetes and greater awareness of life-changing therapies amongst those at greater risk of developing T2D.

4.1 Improving transplant technologies and outcomes

UoB research provided much of the basic science underpinning both the initial establishment and the ongoing activity (2013-onwards) of the UK Islet Transplant Consortium (UKITC). An islet transplant is a low-impact, but life changing therapy as it controls hypoglycaemic events for those patients most severely affected and is offered only when all other treatment options have failed. The clinical translation of beta-cell replacement therapy was used to establish the UKITC. Transplants provided through the consortium have, on average, reduced hypoglycaemic events from 23 per person per year to less than 1 per person per year. These islet transplants lead to improved awareness of hypoglycaemia, less variability in blood glucose levels, improved average blood glucose, improved quality of life and reduced fear of hypoglycaemic events [Sources 5.1, 5.2, 5.3].

Seven designated centres within the consortium, based in Bristol, Edinburgh, North and South London, Manchester, Newcastle and Oxford, provide a cost-effective national programme for islet transplantation, which helps to reduce the GBP1,170,000,000 per year that is spent on hospitalisation of poorly controlled T1D patients. Diabetes UK have invested over GBP2,300,000 into the research and development of this treatment option including the ongoing work of the UKITC [5.2]. Since August 2013, the number of successful islet transplants delivered through the consortium has risen from 65 to 202 across the UK. These numbers are limited by the availability of donor tissue and because donor pancreases are shared equitably between islet and solid organ recipients. There are approximately 40 people on the islet transplantation waiting list each year. All patients who have undergone a transplant experience a long-term reduction in severe hypoglycaemic events [5.1, 5.2, 5.3]. Since 2013 the improved avoidance of hypoglycaemic episodes in these patients has increased from ≥95% to >98% and the longevity of transplant function has improved, with many patients now entering their second decade of clinical benefit. Results are continuing to improve all the time with clear effects on quality of life as a result of these transplants [5.1, 5.3]. Patient stories, reported as part of Diabetes UK's highlight notices, tell of sustained reduction in HbA1c, or glycated haemoglobin, a key measure in the reduction of risk of severe complications with eyes and feet [5.3]. For those suffering with T1D an ideal HbA1c level is 48mmol/mol. Figures in the islet transplant annual report 2018-2019 show that median HbA1c dropped from 62mmol/mol prior to transplant to 48mmol/mol at one-year

post-transplant [5.3, 5.4]. The success of this transplant programme has *'provided a sustainable platform for ongoing service provision and further innovation*' [5.5]. The UoB has also played a key role in improving patient acceptance of the technology behind islet transplantation. Local and national coverage of this research led to a BBC *Inside Out* documentary (2017), helping patients and the public understand both the science and the benefits of the islet transplant technology. Patient testimonials included within this documentary evidence the profound impact of this life-changing therapy. In particular this documentary covers the story of one patient severely affected by unpredictable blackouts who is now able to engage with everyday activities post-transplant: '*I can now live and do whatever I want to do whenever I want to do it without having any worries*' [5.6].

4.2 Building healthcare and industrial strategies to fight Type 1 diabetes

Collaborative research with industrial partners has helped build capacity for technological development and to ensure success of the experimental technologies. Challenges in the expansion of islet transplantation therapy are based on the difficulty in transporting living cells to transplant centres. A partnership with Cellon International (Luxembourg) used UoB research into clinically-reflective cellular model systems to develop a novel microgravity-based cell clustering technology. This technology helps overcome the damaging effects of tissue hypoxia (very low oxygen) in the crucial first 48 hours post-transplant. This led to the creation of the first portable microgravity cell enhancement system for the transportation of islets to transplant centres and the first culture system allowing real time testing of islet function. This is the first direct clinical application of Cellon microgravity technology, helping to drive forward the company's work in this sector by opening technology routes. This is the first step forward in the strategy around the engineering of islet cells for different clinical applications to improve the efficacy of transplant technologies in the long-term fight against the condition [5.2, 5.7]. As confirmed by the Cell Therapy Advanced Specialist to the Northern Alliance Advanced Therapy Treatment Centre '*3D microgravity culture had previously only been used on solid organs, but is now widely utilised in both islet and stem cell biology practice. Pioneering work from the Brighton team in the original development of 3D polymer scaffolds for the growth and differentiation of stem cells also resonates now across a massive expansion in scaffold technologies in this field'* [5.2].

UoB helped to drive the establishment of the Islet Research European Network (IREN), which led to the creation of INNODIA (2015-2022), a global partnership between 31 academic institutions, 6 industrial partners, 1 SME and 2 patient organisations [5.1]. The establishment of this private-public partnership has built capacity by uniting a broad range of knowledge and experience in a unique network now delivering work supporting the long-term strategy to slow down or prevent the onset of T1D. INNODIA is purposefully closely guided by the patients themselves through its Patient Advisory Committee which informs the concept and work of INNODIA, including the development of protocols and the dissemination of this work to the wider public. This ensures that INNODIA helps retain focus on the central voice of those living with T1D and how it affects every day life [5.8]. In September 2020, INNODIA received approval from the regulatory authorities to start MELD-ATG, a study for newly diagnosed T1D patients between the ages of 5 and 25 to slow down the onset of T1D. This is building towards the overarching goal of INNODIA to predict more effectively the risk of developing T1D and the development of novel treatment strategies to delay and ultimately prevent T1D development [5.1, 5.8].

4.3 Delivering effective public engagement programmes that increase patient awareness and acceptance of new technologies

Promoting patient understanding and acceptance of new technologies is a fundamental part of UoB work with the UKITC, Diabetes UK and the Juvenile Diabetes Research Foundation International. UoB have a long and established track record in increasing public awareness through events run for patients and the parents of those with diabetes [5.1, 5.2, 5.9]. This is becoming increasingly important as the NHS now faces a dual challenge of rising numbers of obese and diabetic patients. Treatment costs for complications relating to the disease account for 10% of the NHS budget and in the South East 1% of the regional budget is spent on amputations due to uncontrolled diabetes [5.10]. This is the driver behind a sustained programme of patient and public engagement to deliver early interventions with at-risk

groups. Since August 2013, focused engagement with voluntary support groups has expanded to engage with a further eight new diabetes support groups nationally, three new obesity support groups for young patients nationally (<18 years old); eleven new schools and community colleges locally; and three new local hospitals (Royal Sussex County Hospital, the Royal Alexandra Children's Hospital and the Princess Royal Hospital in Haywards Heath). The focus of this programme is on individual patients and personal management of the condition. Events have increased patient knowledge and understanding of how best to manage the disease, and how to understand the emerging treatment options now available. Evaluation data shows that out of 168 diabetes patients participating in these events 78% felt more positive and confident about managing their diabetes and 83% strongly agreed that they had more knowledge of all the possible treatment options available to them after attending these events [5.9, 5.10]. UoB work with at-risk teenagers has seen the research on glycaemic variability translated into tailored diet and exercise programmes, specific to each patient's own metabolism. A new research-based motivational tool based on stabilising glycaemic profiles, developed as part of this programme, has also had an impact through the reversal of T2D in older patients [5.9, 5.10, 5.11]. The research-led engagement programme allows young patients to understand the effects of food, beverages and exercise on their blood glucose and has helped them to reverse their pre-diabetes and restore a normal balanced metabolism. Since 2013, over 80 young adults have graduated from the Redhill support group and no longer have pre-diabetes or T2D [5.10]. A specialist nurse working closely with the UoB team has confirmed that these successful interventions continue to be '*transformative*' and have built '*a platform for ongoing work in this area*' [5.10].

5. Sources to corroborate the impact

[5.1] Letter of endorsement and research update from Professor James Shaw, Head of the UK Islet Transplant Consortium. This confirms data and outcomes relating to the UKITC.
[5.2] Letter of endorsement and research update from Dr Sandeep Kumar, Cell Therapy Advanced Specialist to the Northern Alliance Advanced Therapy Treatment Centre, NHS Blood and Transplant. This confirms significance of data and outcomes relating to the UKITC, the international networks and public outreach programmes.
[5.3] Public data and information on NHS website/Consortium website. Islet cell transplants for Type 1 diabetes | Diabetes UK My experience receiving an islet transplant | Diabetes UK. [Accessed 18th January 2021].
[5.4] NHS Blood and Transport. Annual report on pancreas and islet transplantation. Report for 2018-2019. nhsbt-pancreas-and-islet-transplantation-annual-report-2018-2019.pdf (windows.net) [Accessed on 18th January 2021]. This provides further evidence and data relating to patient waiting lists and outcomes.
[5.5] Flatt, A., et al. (2020). Chapter 49 - UK's nationally funded integrated islet transplant program: UK's nationally funded integrated islet transplant program - ScienceDirect [Accessed on 18th January 2021].
[5.6] BBC Inside Out Programme (2017). https://research.brighton.ac.uk/en/activities/drg-bbc-inside-out-programme-on-type-1-diabetes [Accessed on 18th January 2021].
[5.7] Letter of endorsement from Dr Richard Fry at Cellon Intl (Luxembourg) that confirms the outcomes relating to the industrial innovations.
[5.8] INNODIA Mission Statement and Research Progress Update: https://www.innodia.eu/about-innodia/ https://www.innodia.eu/pac/ [Accessed on 18th January 2021].
[5.9] Internally produced public engagement and outcomes report. This summarises data from events and interviews including school and patient impact statements with supporting links and references. This demonstrates the promotion and outcomes of public awareness of diabetes research and new and emerging technologies.
[5.10] Impact statement on UOB work with obese individuals in the community and prevention and reversal of Type 2 Diabetes, provided by specialist nurse Michelle Dennis.
[5.11] Collection of local, national and international print and online news articles on the impact of UoB research including reports through leading charities and patient organisations. [Available as a PDF].