Institution: University of Ulster

Unit of Assessment: 3B Allied Health Professions, Dentistry, Nursing and Pharmacy – Biomedical Sciences

Title of case study: Generation of innovative approaches and intellectual property on peptide therapeutics for industry development in relation to diabetes

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

Diabetes research at University of Ulster (Ulster) addresses the unmet need of industry for new and more effective commercially applicable approaches for diabetes therapy. We have generated a new class of innovative peptide therapeutics resulting in a strong portfolio of intellectual property, significant international recognition, financial investment and job creation, with commercialisation through Ulster's technology transfer company, Innovation Ulster (IUL), and the Ulster start-up company, Diabetica Ltd. Our substantial interactions with industry have resulted in the licensing and further development of our international patents on stable incretin peptides for diabetes and, through our discovery of their positive effects on cognition, for treatment of Alzheimer's disease. This work has provided industry with new and commercially viable approaches to significantly improve the lives of people with diabetes and related neurodegenerative disease.

2. Underpinning research (indicative maximum 500 words)

The Diabetes Research Group (DRG), located in the purpose built SAAD Centre for Pharmacy & Diabetes at Ulster, has a strong track record of preclinical drug discovery and development, involving basic laboratory work, both *in vitro* and *in vivo*. The key researchers involved in this case study are Professor PR Flatt, Professor FPM O'Harte, Professor VA Gault and Dr N Irwin who were all employed full-time at Ulster at the time that the research was carried out from 1998 onwards. The exploitation of DRG research findings is supported by IUL which, in conjunction with the Ulster start-up company Diabetica Ltd., oversees the management of our IP portfolio, on-going liaison with industry as well as commercialisation of research outputs. The results of this research have also been published in top peer-reviewed journals.

There is a continuing and unmet need for new drugs to counter the epidemic of type 2 diabetes, obesity and related complications. Our research has focused on the development of novel peptide therapeutics based on peptide hormones secreted from the gut in response to nutrient ingestion, most notably glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP) and cholecystokinin (CCK). These hormones play an important physiological role in the regulation of feeding, insulin secretion and blood glucose control. In the late 1990s, we discovered that N-terminal glycation of these hormones prevented their degradation and enhanced bioactivity so that they could be used potentially for treatment of obesity-related type 2 diabetes (for GIP see [1]). We went on to develop a strong series of anti-diabetic N-terminally modified enzyme resistant analogues of GIP, GLP-1 and CCK8 using amino acid substitutions plus possible additional acylation or mini-PEGylation modifications to further extend half-life and therapeutic utility [2-6]. Early IP space for GLP-1 was taken by industry but by 2008 we had secured world-wide patents for analogues of GIP and CCK-8 consisting of 3 patent families covering 14 granted patents in the USA, Canada and Europe. In generating GIP agonists, we developed antagonists such as (Pro^3)GIP which unexpectedly turned out to represent an entirely unexpected and new potential class of anti-diabetic agent, acting through weight loss and the alleviation of obesity-related insulin resistance and beta cell rest [3,4]. Recently, we discovered that these novel GIP and GLP-1 peptides cross the blood-brain barrier, activate hippocampal G-protein coupled receptors and reverse defects of cognition in high fat fed, obese-diabetic mice and in transgenic animal models of Alzheimer's disease, making the above mentioned peptide families strong candidates for the treatment of neurodegenerative disease (for GLP-1 see [5], patents granted and pending).

Key staff at Ulster:

PR Flatt (Head DRG; Prof 1989-present); FPM O'Harte (Research Officer (RO) 1993-, L 1995-; R 2000-, Prof 2005-present); VA Gault (PhD student 1998-, RO 2002-, L 2004-, SL 2009-, Prof 2013–present); N Irwin (PhD student 2001-, RO 2004-, L 2009-present); C Holscher (L 2004-, SL 2006-, Prof 2012-13). All were employed full-time at Ulster throughout period indicated.

3. References to the research *(All papers cited are included in Section 5)*.

[1] O'Harte, F. P. M., Mooney, M. H., Flatt, P. R. (1999). NH_2-terminally modified gastric inhibitory polypeptide exhibits amino-peptidase resistance and enhanced antihyperglycemic activity. *Diabetes*, 48, 758-765.
DOI: 10.2337/diabetes.48.4.758
Times Cited: 50 SJR: 3.810 SNIP: 2.093 Impact Factor: 7.895

[2] O'Harte, F. P. M., Gault, V. A., Parker, J. C., Harriott, P., Mooney, M. H., Bailey, C. J., Flatt, P. R. (2002). Improved stability, insulin-releasing activity and antidiabetic potential of two novel N-terminal analogues of gastric inhibitory polypeptide: N-acetyl-GIP and pGlu-GIP. *Diabetologia*, 45, 1281-1291.
DOI: 10.1007/s00125-002-0894-6
Times Cited: 45 SJR: 2.596 SNIP: 1.876 Impact Factor: 6.487

[3] Gault, V. A., Irwin, N., Green, B. D., McCluskey, J. T., Greer, B., Bailey, C. J., Harriott, P., O'Harte, F. P. M., Flatt, P. R. (2005). Chemical ablation of gastric inhibitory polypeptide receptor action by daily (Pro^3)GIP administration improves glucose tolerance and ameliorates insulin resistance and abnormalities of islet structure in obesity-diabetes. *Diabetes*, 54, 2436-2446.
DOI: 10.2337/diabetes.54.8.2436
Times Cited: 90 SJR: 3.810 SNIP: 2.093 Impact Factor: 7.895

[4] McClean, P.L., Irwin, N., Cassidy, R.S., Holst, J.J., Gault, V.A., Flatt, P.R. (2007). GIP receptor antagonism reverses obesity, insulin resistance and associated metabolic disturbances in mice induced by prolonged consumption of high fat diet. *Am. J. Physiol.* 293, E1746-E1755.
DOI: 10.1152/ajpendo.00460.2007
Times Cited: 76 SJR: 2.005 SNIP: 1.418 Impact Factor: 4.514

[5] Gengler, S., McClean, P. L., McCurtin, R., Gault, V. A., Holscher, C. (2012). (Val^8)GLP-1 rescues synaptic plasticity and reduces dense core amyloid plaque load in APP/PS1 mice. *Neurobiology of Aging*, 33, 265-76.
DOI: 10.1016/j.neurobiolaging.2010.02.014
Times Cited: 22 SJR: 2.104 SNIP: 1.334 Impact Factor: 6.166

[6] Irwin, N., Frizelle, P., Montgomery, I. A., Moffett, R. C., O'Harte, F. P. M., Flatt, P. R. (2012) Beneficial effects of the novel cholecystokinin agonist (pGlu-Gln)-CCK-8 in mouse models of obesity/diabetes. *Diabetologia*, 55, 2747-58.
DOI: 10.1007/s00125-012-2654-6
Times Cited: 8 SJR: 2.506 SNIP: 1.876 Impact Factor: 6.487

Selected grants awarded *(Full grant details, see Section 5)*:

O'Harte FPM, Gault VA, Harriott P, Flatt PR. Development and evaluation of potent long-acting fatty acid linked analogues of GIP for type 2 diabetes therapy. Diabetes UK, 2004-2007, £149,924.

Irwin N, Gault V, Flatt PR. Actions and mechanisms underlying novel therapeutic actions of GIP receptor antagonists. Diabetes UK, 2006-2009, £148,000.

Flatt PR. Evaluation of novel GLP-1 antidiabetic agent.[text removed for publication], 2007-2010, £456,843.

Flatt PR. Pharmacology feasibility study of incretin receptor antagonists.[text removed for publication], 2013, £98,598.

Holscher C, Gault VA. New strategies to prevent neurodegeneration in Alzheimer's disease using insulin-like drugs Alzheimer's Research Society, 2008-2011, £163,334.

Holscher C. Analysis of novel GLP-1 agonists on neurodegenerative processes in a mouse model of Alzheimer's Disease Alzheimer Society, 2008-2012, £165,000.

Holscher C. Investigation of a novel GLP-1 receptor agonist in several models of neurodegeneration. [text removed for publication], 2012-2013, £180,000.

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

Innovative research described in this Case Study has led to generation of a strong portfolio of IP including the granting of 12 patents since 2008, which themselves demonstrate that our scientific discoveries have hit the impact target of fulfilling the minimum legislative criteria of being non-obvious, novel and capable of being applied in trade/industry. Outcomes of our scientific discoveries also include the attraction of venture capital funding and other investment, formation of the start-up company Diabetica Ltd and creation of 3 jobs together with substantial productive and on-going interactions with industry (see Section 5). Our activities have influenced drug discovery programmes and development of clinical product pipelines in major pharmaceutical companies worldwide (see Section 5 for Testimonials). We have also undertaken significant contract research with [text removed for publication] on incretin mimetics and GIP antagonists, employing 2 other post-doctoral scientists.

Our IP on GIP agonists was licensed by IUL/Diabetica Ltd. to Amylin Pharmaceuticals Ltd (now BMS) in March 2006, [text removed for publication]. This includes 2 patent families covering GIP analogues as treatments of diabetes, obesity and related metabolic disease, with 11 granted patents, including 4 in USA and Canada since 2008. As testimony to our impact in this field, GIP agonists are now pipeline products of Ipsen, Eli Lilly, and Amylin (now BMS) targeted for full clinical development as evidenced by their more recent IP filings. Highly positive results of late preclinical work on N- terminally modified GIP agonists have been published recently by Amylin (BMS) scientists (Tatarkiewicz et al, Diabetes Obes Metab. 2013 Jul 16, doi: 10.1111/dom.12181; see Section 5).

We have executed separate evaluation licenses for our IP on GIP antagonists for the treatment of obesity-insulin resistance, to [text removed for publication]. Our ground-breaking research has also driven industry to make their own IP filings and undertake related drug development on GIP receptor antagonists, including Ipsen, Amylin, Sanofi Aventis and Zealand Pharma. Further, Zealand has recently announced a partnership with Lilly to optimise new peptide candidates for diabetes. As clear evidence of impact, our IP has been cited against their patent filings, being included in numerous International search reports as 'prior art'. Further, we have now partnered with the field leader, [text removed for publication], to develop receptor-specific peptidergic therapeutic GIP antagonists through a Research Collaboration Agreement executed on 21/09/12.

We were also early leaders in the development of GLP-1 therapeutics, where our innovative approach and published work informed the field of the significant potential of the GLP-1 receptor as an important drug target. Indeed, GLP-1 mimetics now represent a major success story in diabetes therapy. Furthermore, our subsequent discovery and patent filing of stable GLP-1 and GIP therapeutics for neurodegenerative disease has resulted in 6 granted EU patents since 2012 with a further 7 pending in Europe, USA, Canada and Japan. This IP is being further co-developed under a Research Collaboration and License agreement with [text removed for publication] executed on 8/3/12. In addition, [text removed for publication] has also contributed [text removed for publication] awarded by Alzheimer Society for a clinical trial of liraglutide (stable GLP-1 mimetic) in patients with Alzheimer's disease, which is currently recruiting for patients. As a result of our research, other pharmaceutical companies with

GLP-1 agonists in their pipeline, [text removed for publication] are also now exploring stable GLP-1 for treatment of neurodegenerative disease.

Inherently drug development is a lengthy and perilous process, with low success rate. In this context, the achievements described above plus our significant contract research with industry on the development of GLP-1 and GIP mimetics are significant indicators of impact. More recently, we have focussed attention on preclinical development of stable CCK-8 therapeutics for obesity and associated metabolic disease [6], with 7 granted EU patents, plus 2 further patents granted in USA and Canada since 2008. Our data have been replicated independently by a commercial CRO and we have engaged with more than 30 potential industry partners and executed 2 contractual agreements ([text removed for publication]) to progress commercial development.

A significant contribution to this case study stems from the formation and subsequent commercialisation efforts of Diabetica Ltd. which was founded in September 2004 as University start-up Company. This Company was registered in Northern Ireland under number NI051793, as a vehicle to work alongside IUL to help commercialise technology generated by DRG. Initial investment of near £1m was from IUL and the venture capital company Seroba Bioventures, with subsequent employment of 3 personnel and turnover of over £600,000 from 2004 to 2011. Academic founder members of Diabetica Ltd (Professors PR Flatt, FPM O'Harte and NH McClenaghan (employed at Ulster since 1998)) were winners of the prestigious inaugural Academic Enterprise Awards (ACES) Europe for Life Sciences presented in Stockholm, December 2008. Diabetica Ltd. and IUL continue to work together in exploitation of research conducted and interactions with industry.

Our work in the area of novel peptide therapeutics for diabetes and interactions with industry has been recognised internationally also by prestigious personal awards. Professor PR Flatt was elected Member Royal Irish Academy (2006) and awarded Dorothy Hodgkin Lecture of Diabetes UK (2007). Other prizes include Biochemistry Society Medal (Professor PR Flatt, 2005), Endocrine Society Nordisk Medal (Professor FPM O'Harte, 2006) and European Association for the Study of Diabetes (EASD) Rising Star (Professor VA Gault, 2009). Professor PR Flatt was also member of the influential international working group of Juvenile Diabetes Research Foundation Ltd (JDRF) formulating the 2013 roadmap for the direction of future UK research funding in type 1 diabetes.

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

Sources available from
http://biomed.science.ulster.ac.uk/drgpeptidesimpactcasestudy/indexpage.htm

Ulster patents.
Ulster Agreements with Diabetica.
Peptides - Agreements with third parties.
Industry Collaboration and Agreements
Patents and scientific papers subsequently submitted by industry.
Scientific publications [1-6].
Grants awarded.
Publicity and press releases.
Supporting statements/testimonials.