Institution: University of Bristol		
Unit of Assessment: 8) Chemistry		
Title of case study: Breakthrough in glucose receptor development leads to a multimillion-dollar deal for a radical new diabetes treatment, and a new science incubator to kick-start Bristol's biotech industry		
Period when the underpinning research was undertaken: 2011-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Anthony P. Davis	**Role(s) (e.g. job title):** Professor of Supramolecular Chemistry	**Period(s) employed by submitting HEI:** 2000-present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Today 442 million people, around 9% of the world's adult population, live with diabetes. Around 10% of these suffer with type 1 diabetes and require regular injections of the glucose-regulating hormone insulin to manage this life-changing disease. Synthetic glucose receptors could dramatically transform the lives of type 1 diabetics by enabling the development of a novel glucose-responsive insulin. New receptors, pioneered and developed in Bristol, have been engineered to bind to glucose with an outstanding affinity and almost perfect chemical selectivity. This breakthrough was commercialised through a spin-out company acquired in 2018 by Novo Nordisk, the world's leading supplier of insulin, in a deal worth up to USD830 million (GBP642M). The research also led directly to the creation of a new incubator facility, Unit DX, to solve the lack of specialist facilities for chemistry and biotech start-ups in the Bristol region. To date, Unit DX has supported over 57 different member companies, generated 125 scientific sector jobs in the West of England, and secured funding approaching GBP40M through grants and equity investments.

2. Underpinning research

Biomimetic glucose receptors

Binding carbohydrates in water is recognised as one of the most challenging aims in supramolecular chemistry. The most common approach is to incorporate boronic acid units in receptors and exploit their reversible reaction with the diol units present in saccharides. However, practical exploitation of boron-based receptors has run into difficulties – good selectivity is difficult to achieve, and the receptors are sensitive to oxidants present in biological media. The alternative is to avoid the use of covalent bonding and rely purely on the non-covalent interactions used by natural proteins. This "biomimetic approach" increases the challenge still further, so that only a handful of groups have made the attempt. The Anthony Davis (APD) group is a pioneer in this area and has assumed a world-leading role [1].

The most important target for carbohydrate receptors is glucose. Glucose receptors could be used in a number of ways to help diabetics (e.g. glucose monitoring devices, insulin delivery systems), and diabetes is one of the world's major health problems. Over 2005-16 the APD group reported a series of biomimetic glucose receptors, exemplified in Fig. 1. The anthracene-based monocycle **1** was especially significant. This molecule was easy to prepare, gave increased fluorescence emission on binding to glucose, and had potential for continuous glucose monitoring in diabetics [2,3].

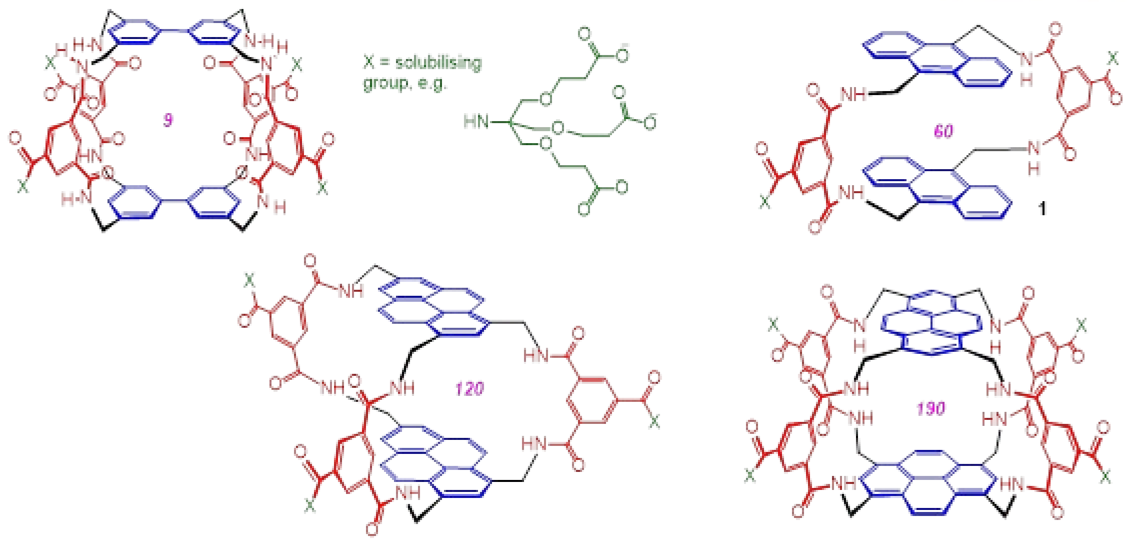

Figure 1: A selection from the first-generation carbohydrate receptors reported by the APD group between 2005 and 2016, including the fluorogenic glucose sensor **1** which was originally chosen for commercialisation. Numbers in magenta are binding constants (K_a) to glucose, units M^{-1}. For comparison, the carbohydrate binding protein (lectin) Concanavalin binds with glucose with K_a = 540 M^{-1}.

A truly effective glucose receptor

While the results had been positive, the APD group realised that higher affinities would be needed for most applications. They also discovered that the receptors (including **1**) bound strongly to polar aromatic molecules such as uric acid, present in biological samples. Glucose binding was thus inhibited in these media, so that sensors based on **1** would have a very restricted scope.

To solve these problems, a new design was proposed in early 2016 using a bis-urea spacer in place of the isophthalamide unit (Fig. 2). This increased the height of the cavity, discouraging binding to aromatics, while providing additional potential hydrogen bonding. When this unit was incorporated in the C3-symmetrical structure **2** (Fig. 2b) the complementarity to glucose was remarkable. Modelling (Fig. 2c) showed that the cavity was almost perfectly sized for the carbohydrate, forming 10 intermolecular hydrogen bonds and excellent apolar interactions.

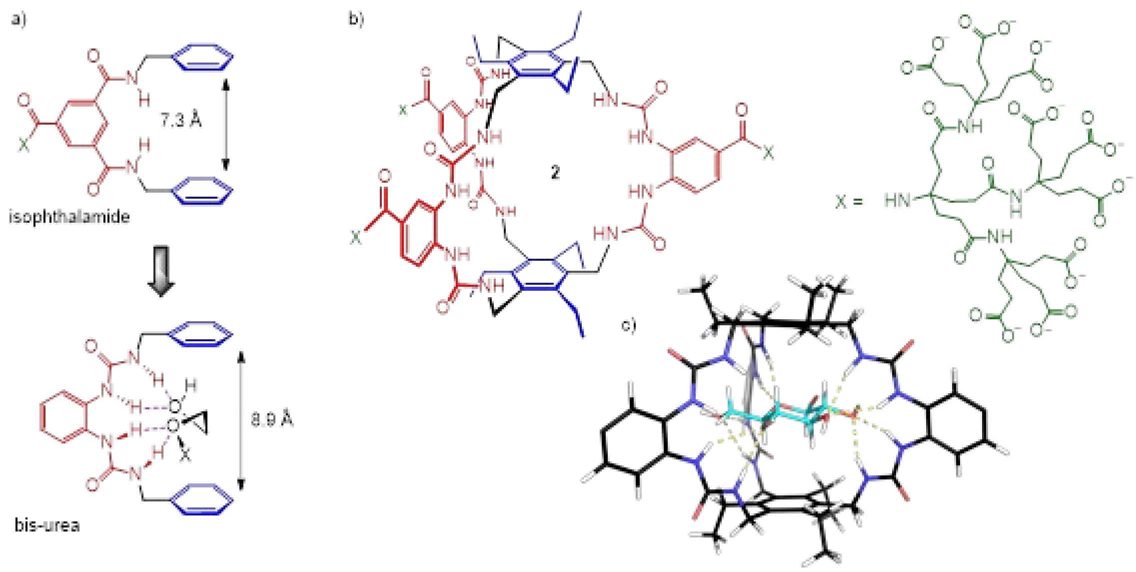

Figure 2: Design of a truly effective glucose receptor. a) The key innovation – replacement of the isophthalamide spacer from earlier receptors with the extended and more polar bis-urea. As shown, the bis-urea is specifically preorganised for hydrogen bonding to the O-C-C-O arrangement common in carbohydrates. b) Three of these bis-ureas are employed in new-generation receptor **2**. c) Model of glucose in the cavity of **2**.

Samples of **2** were prepared in October 2016 with spectacular results [4,5]. The new receptor bound glucose with K_a ~20,000 M^{-1}, approximately 200 times more strongly than the anthracene-based system **1**. Selectivity against most other carbohydrates was 100:1 or better, and non-carbohydrates (including aromatics) were not bound at all. This performance is remarkable not just in the context of carbohydrate recognition, but in relation to supramolecular chemistry as a whole. Although receptor **2** was unsuitable for direct use as a glucose monitor (it binds too strongly), it was clear that indirect sensing applications would be feasible (see Fig.3a) and would be operable in biological media. Applications in glucose-sensitive materials (e.g. insulin-containing gels) could also be envisaged (Fig.3b).

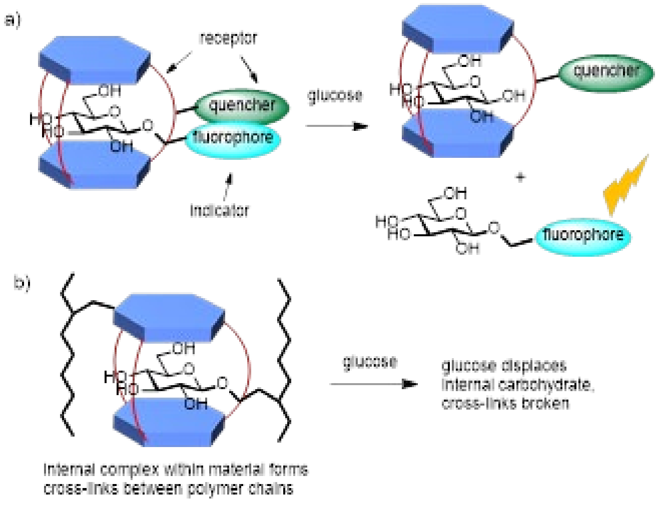

Figure 3: Potential applications of receptor **2**. a) Sensing through displacement of an indicator species. The indicator cannot fluoresce when bound to the receptor, but emits when displaced by glucose. b) Glucose-sensitive materials. External glucose breaks cross-links, changing material properties, e.g. causing release of insulin.

3. References to the research

[1] **Davis AP**. (2020). Biomimetic carbohydrate recognition, *Chemical Society Reviews,* **49**, pp.2531-2545, 10.1039/C9CS00391F

[2] Ke C, Destecroix H, Crump MP, **Davis AP**. (2012). A simple and accessible synthetic lectin for glucose recognition and sensing, *Nature Chemistry*, **4**, pp.718-723, 10.1038/nchem.1409

[3] Ke C and **Davis AP**. (2013). *Anthracenyl-Tetralactam Macrocycles and Their Use in Detecting Target Saccharides*, International Patent Application PCT/GB2013/051079, Publication Number WO 2013/160701 A1

[4] Tromans RA, Carter TS, Chabanne L, Crump MP, Li H, Matlock JV, Orchard MG, **Davis AP** (2019). A biomimetic receptor for glucose, *Nature Chemistry*, **11**, pp.52-56, 10.1038/s41557-018-0155-z

[5] **Davis AP**, Tromans R, Wilson MR, Orchard MG, Chapman AG, Tomsett MR, Matlock JV. (2018). *Macrocyclic Compounds*, GB Patent Application GB1704125.2,PCT/GB2018/050679

Funding information

Davis AP (PI), *From temples to patios for carbohydrate recognition - expanding the scope of synthetic lectins,* EPSRC EP/I028501/1, 2011-2014, GBP329,322

Davis AP (PI), *Synthetic Lectins for Oligosaccharide Binding in Aqueous Media,* EPSRC EP/D060192/1, 2006-2009, GBP231,891

Chenfeng Ke (PI, University of Bristol), *Towards glucose sensing with synthetic lectins*, Royal Society Newton International Fellowship, 2009-2011

Clayden J (PI, University of Bristol), EPSRC Centre for Doctoral Training in Chemical Synthesis, EP/L015366/1, 2014-2022, GBP5.32 million

4. Details of the impact

The exploitation of glucose receptors **1** and **2** led to two main impacts:

- The creation of two successful spin-out companies, one of which was acquired by the world's major supplier of insulin
- The launch of Unit DX, the first incubator facility for chemistry-based start-ups in Bristol.

Creation of spin-out companies, creating jobs and stimulating foreign direct investment
The first spin-out, Ziylo, was founded in 2014 by a group including Anthony Davis and his final-year PhD student Harry Destecroix. The intention was to employ receptor **1** in glucose sensing devices, with continuous glucose monitoring as a longer-term goal. Receptor **1** was patented by the University (UoB) [3], and the IP was licensed to Ziylo in return for a share of the company. By 2017, Ziylo had eight employees and had attracted both investment and grant income from Innovate UK.

When receptor **2** was discovered, Ziylo funded the patenting in return for an exclusive licence and took on some of the developmental work. Based on its outstanding performance, its novelty, and unique mode of operation, receptor **2** was essentially without competition in the pharmaceutical market. The Diabetes Research & Wellness Foundation Research Manager states: *"Research into glucose-responsive, so-called "smart," insulins has been ongoing for some time and there is clearly a lot of commercial interest from the pharmaceutical companies. Although some have made it into clinical trial, the outcomes have not been as positive as many were hoping. This research represents a new chapter in this quest.*" [C]. The outcome was the acquisition of Ziylo by Novo Nordisk, one of the world's major suppliers of insulin, for a sum which ultimately rises to USD830 million depending on research, regulatory and sales milestones [A]. To quote one of the experienced consultants who acted for Ziylo; "*The Ziylo discovery had two key elements of scarcity and potentially ground-breaking technology which drove the price to rarely seen heights for such an early-stage development*" [B]. The sale generated wide publicity, focusing on the role of Destecroix (who was still just 31) and highlighting the potential of a career in scientific entrepreneurship [C]. It later won the prize for "Exit of the Year" at the Global University Venturing Awards, against stiff competition from spinouts from Harvard University, UCL, John Hopkins University and the University of Twente [D]. The judges announcing the award [D] highlighted the global significance of the research, noting that "*there are more than 422 million reasons why the acquisition of Ziylo, a UK-based spinout from University of Bristol working on technology to develop next-generation insulin, by pharmaceutical firm Novo Nordisk for potentially more than USD800 million, emerged as the winner.*" (422 million is the number of people who currently have diabetes according to the World Health Organization (WHO)).

The deal included an up-front payment, which cannot be discussed in quantitative terms (a requirement of Novo Nordisk), but has yielded significant benefits. For example, the portion received by the UoB has been used to help fund three graduate students, two post-doctoral workers, new equipment, a position to support the commercialisation of research in the School of Chemistry, and further commercialisation activities in the wider University community (another two posts). Funds received by other shareholders have entered the local economy in various ways, for example as investments in further start-up companies, especially those hosted by Unit DX (see below).

The agreement with Novo Nordisk involved the creation of a new company, Carbometrics [E] to employ ex-Ziylo personnel and collaborate on the glucose responsive insulin project, funded via a research agreement. The deal also included license-back provisions whereby Carbometrics could exploit the receptor for non-therapeutic applications (e.g. diagnostics). Novo Nordisk has committed substantial resources to the programme and regards it as "*one of (their) most promising lines of research and drug discovery*" [F]. Carbometrics remains based in Bristol and currently employs six full time staff in addition to four directors. Together, Ziylo and Carbometrics have received GBP640,000 grant income (from Innovate UK and the Regional Growth Fund), and GBP1.7M investment [G].

Launch of Bristol's first incubator for chemistry-based start-ups
Ziylo was initially based at the University of Bristol, but the scarcity of fume-hood space prompted a search for alternatives. It became clear that (i) there were none in the Bristol area, and (ii) this lack of facilities could be strangling chemistry-based companies at birth. A facility for Ziylo and other start-up companies was generated, a building near the centre of Bristol acquired and provisioned with 24 fume-hoods, data services and other equipment, and branded Unit DX [H]. Ziylo moved in and within two years of opening, Unit DX was at full capacity. It currently hosts 18 companies in the Chemistry, Materials, Life Sciences, Quantum Technology and Electronic Engineering sectors. At least one company (Inductosense) has outgrown the incubator and moved on into more spacious accommodation. Unit DX supports 11 scientific sector jobs directly and 114 indirectly in its member companies. The combined total of known grants and investment in member companies since the May 2017 opening stands at approximately GBP40M, 25% of the total deep tech capital raised at seed level in the South-West of England since 2017 [H]. The news of Ziylo's success in August 2018 had a clear stimulatory effect on Unit DX activity. Unit DX received a significant increase in inward investment enquiries from scientific SMEs looking to establish or relocate their laboratory operations in the region, and from investors, many based in the Golden Triangle, wanting to invest in 'the next Ziylo' (see, for example, Fig. 4).

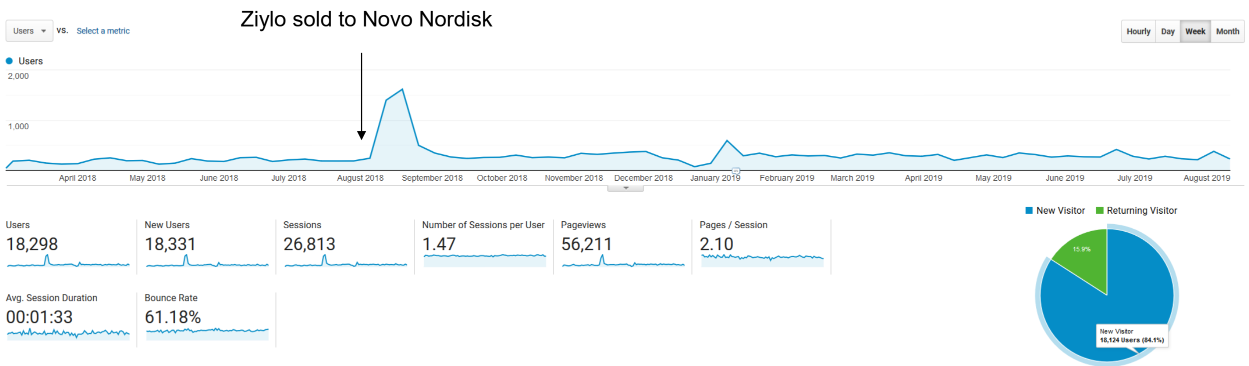

Figure 4: Google analytics data relating to the Unit DX website, April 2018 – August 2019. A surge of activity is observed in August 2018, coincident with the sale of Ziylo. Subsequent activity remains higher than before the Ziylo sale. The success of Ziylo, based on receptor **2**, has thus helped to drive the success of Unit DX.

5. Sources to corroborate the impact

[A] Novo Nordisk – Press release (2018), *Novo Nordisk acquires Ziylo Ltd to accelerate its development of glucose responsive insulins*; University of Bristol – Press release (2018), University spin-out Ziylo acquired by global healthcare company in $800m deal which could transform the treatment of diabetes [Accessed 23/10/20]; Chemistry World Article – Article (2018), Sensing the sweet spot [Accessed 23/10/20]
[B] Plexsus Consulting – Corroborating Letter (2019)
[C] Media coverage of the Ziylo sale (2018): Diabetes Research & Wellness Foundation, Forbes, Financial Times, Sun, Daily Mail
[D] Global University Venturing – Article (2019), *Exit of the Year: Ziylo* [Accessed 23/10/20]
[E] Carbometrics home page https://www.carbometrics.com/ [Accessed 23/10/20]
[F] Novo Nordisk – Corroborating Letter (2020), Senior Alliance Director
[G] Carbometrics Ltd – Corroborating Letter (2020), Director
[H] Chemistry World – Article (2016), *Chemist's struggles spawn Bristol lab incubator* [Accessed 26/10/20]; TechSPARK – Article (2019), *Bristol to add two new science incubators* [Accessed 26/10/20]; Unit DX – Report (2019), prepared by their Centre Director