Institution: The University of Reading

Unit of Assessment: 6 (Agriculture, Food and Veterinary Sciences)

Title of case study: Developments in prebiotic research for modulating the human gut microbiome and increasing awareness of potential health benefits.

Period when the underpinning research was undertaken: Between 2000 and 2018

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:
Glenn R Gibson	Professor of Food Microbiology, Head of Food Microbial Sciences Group	April 1999 and present
Gemma E Walton	Lecturer in Metagenomics, Research Fellow	November 2006 and present
Professor Robert A Rastall	Head of Outreach and Enterprise, Head of Department, Director of Research, Head of Food and Bioprocessing Sciences Group	September 1993 and present
Dimitris Charalampopoulos	Professor of Biotechnology, Associate Professor, Senior Lecturer	September 2005 and present

Period when the claimed impact occurred: Between August 2013 and November 2020

Is this case study continued from a case study submitted in 2014?

Yes: The 2014 case study covered the invention, development and commercialisation of a new prebiotic product for improving gut health: Bimuno. The research in the present case study covers ongoing advances in prebiotic science to understand the range of potential health benefits that can be gained from modifying the gut microbiome through the consumption of prebiotic-containing food products and supplements, including Bimuno. The translation of these findings has been realised through engagement with a wider range of stakeholders and beneficiaries.

1. Summary of the impact

Research expertise, developed through extensive investigations conducted at the University of Reading over the past two decades, has shaped a new definition of prebiotics, benefiting researchers, commercial companies and consumers around the world. The work of Gibson and colleagues has broadened and deepened our understanding of the role of prebiotics to health and wellbeing and the importance of gut health, guiding the development of policy and practice, including with the UK parliament through the formation of the new Human Microbiome All Party Parliamentary Group. Evidence of the beneficial health effects of Bimuno – a commercial prebiotic product itself developed from research at Reading – has underpinned the ongoing distribution of the product, including the commercialisation of spin off prebiotic products made by other companies. These prebiotic products have benefited the health and wellbeing of consumers, in particular protecting against travellers' diarrhoea and notably used and endorsed by elite athletes including Team GB in the Rio 2016 Olympics. Furthermore, these prebiotics have been reported by consumers to relieve the symptoms of IBS and symptoms associated with gut pain in children with Autistic Spectrum Disorders (ASD).

2. Underpinning research

Over the past 20 years, the University of Reading has been at the forefront of research into prebiotics – dietary ingredients that selectively encourage the proliferation of microorganisms that are beneficial to health. From early pioneering work, which first instigated the concept of prebiotics as microbiome management tools, the team has explored the mechanisms of action of candidate products using validated laboratory gut models [1]. Gibson *et al.* have also completed over 50 human intervention studies to assess the influence of prebiotic products on gut microbiota and

health, in collaboration with major food manufacturers, including Kellogg's, Nestlé, Tate & Lyle, Proctor & Gamble and GSK [2].

Notably, this body of research has included the synthesis of a novel prebiotic to enhance the growth of beneficial gut bacteria with greater efficacy than has been previously achieved, using reverse enzyme technology in bifidobacteria themselves. This breakthrough underpinned the development of a commercial galactooligosaccharide product, Bimuno.

Bimuno research and development programme

Galactooligosaccharides (GOS) are prebiotics associated with increased populations and fermentation products of the *Bifidobacterium* species, which are known to be beneficial to gut health. Typically, GOS are synthesised from lactose using β-galactosidase enzymes derived from yeasts or bacilli. The University of Reading research improved upon prebiotic selectivity by exploiting a β-galactosidase from *Bifidobacterium bifidum* NCIMB 41171. As such, target bifidobacteria in the gut can metabolise more readily the GOS prebiotics produced from enzymes originating from this specific strain. Following *in vitro* assessments and pig trials, Gibson *et al*. found that the novel product could effectively increase colonic bifidobacteria in people [3]. Subsequently, the Reading team, including Professor Kim Watson from the School of Biological Sciences and in collaboration with Bimuno's manufacturers, Clasado, developed a recombinant galactosidase enzyme which was more selective towards synthesis of GOS from lactose rather than hydrolysis, and thus gave higher GOS production yields [4].

Assessing response to Bimuno in targeted consumer groups

Over the past 12 years, Gibson and colleagues have shown that GOS-mediated microbial changes in the gut are accompanied by a variety of beneficial health effects:

- In a 10-week trial with 40 free-living volunteers (aged 65–80 years) a significant increase in the numbers of bifidobacteria was associated with positive effects on certain markers of the immune response, including anti-inflammatory mediators.
- A 12-week study of 45 overweight adults demonstrated that GOS supplementation improved immune function and aspects of the metabolic syndrome (markers of insulin resistance, inflammatory mediators and blood lipid profiles).
- A four-week trial of 44 patients with IBS demonstrated that bifidobacteria in the colonic microbiota was enhanced in a dose-responsive manner and this was associated with reduced IBS symptoms (significantly improved stool consistency, reduced flatulence and bloating) [5].
- Taking GOS (5.5 g/d) as a preventative measure before travelling significantly reduced the incidence and duration of diarrhoea in a trial of 159 otherwise healthy travellers [6].
- A 10-week trial of 26 children with Autistic Spectrum Disorders (ASDs) found that the GOS could reduce common symptoms of gastrointestinal distress. It also improved faecal bacteriology, metabolite production, reduced antisocial behaviour and improved sleep patterns. [7]

This body of research has significantly increased understanding of the role that prebiotics can play in supporting the gut microbiome to improve host health and reduce the risk of disease.

3. References to the research

This research has been supported by multiple grants from industry partners as well as competitive awards from BBSRC, including BB/HOO4734/1. Human trials were registered at clinicaltrials.gov, for example NCT03168503, NCT01303484, NCT02720900, and the ISRCTN, for example ISRCTN54052375. The findings have been published in highly respected, peer-reviewed journals such as the *American Journal of Clinical Nutrition* (Impact Factor 6.7).

[1] **Costabile, A., Walton, G.E.,** Tzortzis, G., Vulevic, J., **Charalampopoulos, D. and Gibson G.R.** (2015). 'Effects of orange juice formulation on prebiotic functionality using an *in vitro* colonic model system'. *PLoS One*. **10**(3), e0121955. DOI: https://doi.org/10.1371/journal.pone.0121955.

[2] **Costabile, A**., Bergillos-Meca, T., Rasinkangas, P., Korpela, K., de Vos, W.M. and **Gibson, G.R.** (2017). 'Effects of soluble corn fiber alone or in synbiotic combination with *Lactobacillus*

rhamnosus GG and the pilus-deficient derivative GG-PB12 on fecal microbiota, metabolism, and markers of immune function: A randomized, double-blind, placebo-controlled, crossover study in healthy elderly (Saimes Study)'. *Frontiers in Immunology* **12**, 1443. DOI: https://doi.org/10.3389/fimmu.2017.01443.

[3] **Depeint, F., Tzortzis, G., Vulevic, J., I'Anson, K.** and **Gibson G.R**. (2008). 'Prebiotic evaluation of a novel galactooligosaccharide mixture produced by the enzymatic activity of *Bifidobacterium bifidum* NCIMB 41171, in healthy humans: a randomized, double-blind, crossover, placebo-controlled intervention study'. *American Journal of Clinical Nutrition* **87** (3), 785-791. DOI: https://doi.org/10.1093/ajcn/87.3.785

[4] **Osman, A.,** Tzortzis, G., **Rastall, R. and Charalampopoulos, D.** (2013). 'High yield production of a soluble bifidobacterial β-galactosidase (BbgIV) in *E. coli* DH5α with improved catalytic efficiency for the synthesis of prebiotic galactooligosaccharides'. *Journal of Agricultural and Food Chemistry*, **61** (9), 2213-2223. DOI: https://doi.org/10.1021/jf304792g

[5] Silk, D.B., Davis, A., **Vulevic, J**., Tzortzis, G. and **Gibson, G.R**. (2009). 'Clinical trial: the effects of a *trans*-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome'. *Alimentary Pharmacology and Therapy*. **29** (5), 508-518. DOI: https://doi.org/10.1111/j.1365-2036.2008.03911.x

[6] **Drakoularakou, A**., Tzortzis, G., **Rastall, R.A**. and **Gibson, G.R**. (2010). 'A double-blind, placebo-controlled, randomized human study assessing the capacity of a novel galacto-oligosaccharide mixture in reducing travellers' diarrhoea'. *European Journal of Clinical Nutrition* **64** (2), 146-152. DOI: https://doi.org/10.1038/ejcn.2009.120

[7] **Grimaldi, R**., **Gibson, G. R.**, Vulevic, J., Giallourou, N., Castro-Mejía, J. L., Hansen, L. H., Leigh Gibson, E., Nielsen, D. S. and Costabile, A. (2018). 'A prebiotic intervention study in children with autism spectrum disorders (ASDs)'. *Microbiome*, **6** (1), 133. ISSN 2049-2618 DOI: https://doi.org/10.1186/s40168-018-0523-3

4. Details of the impact

Redefining the prebiotics concept

Advances made as part of an extensive body of research on prebiotics cultivated over the past 20 years at the University of Reading have had a major international influence on how prebiotics are studied and understood, building on the original concept of prebiotics first introduced by Gibson and Marcel Roberfroid. In 2016, Gibson's research expertise was called upon when he chaired an International Scientific Association for Probiotics and Prebiotics (ISAPP) review that led to a consensus statement on the definition and scope of prebiotics. The new definition takes into account new knowledge on the microbiome, health benefits and products that act 'beyond the gut' [E1]. The ISAPP definition is cited by companies, including Yakult and Kellogg's, in their consumer literature, both to raise awareness of prebiotics and to illustrate recommended daily intake. It is also cited in patent applications for prospective prebiotic ingredients. ISAPP itself, which Gibson co-founded and still serves as a board member, is a global forum for prebiotic scientists (including food and pharma industry members) with a central remit to provide consumers and healthcare providers with clear, reliable information on prebiotics.

Informing Parliamentary debate on prebiotics and the role of the microbiome on health

Gibson's body of research and expertise played a key role in making the scientific case for an All-Party Parliamentary Group (APPG) on the Human Microbiome to Julie Elliott MP [page 2, E2]. As a direct result Elliott agreed to Chair the APPG, which was established in February 2019. Gibson is one of three scientific advisors to the APPG, together with Dr Gemma Walton, also from Reading, and Dr Kirsty Hunter (Nottingham Trent University). Since the State Opening of Parliament in December 2019, the group has attracted considerable interest and sign up from over 80 MPs and Peers. University of Reading research findings and expertise has guided the development of briefing documents for APPG meetings (for example on *Clostridium difficile* infections; IBS; and gut-brain interactions including autism) as well as contributed to questions and speeches for members of both Houses, for example as part of the House of Lords wellbeing debate in March 2020. Furthermore, with advice from Gibson, the APPG is developing an inquiry

to look at regulations on foods that benefit the gut microbiome. In May 2020, the APPG also led a 125-signature letter to Secretary of State for Health and Social Care on the use of pro/prebiotics in helping to combat COVID-19. As a result of this, and subsequent parliamentary questions from Elliott, in October 2020 the COVID-19 Therapeutic Taskforce's expert group on prophylaxis were invited by the Department to consider the evidence of the benefits and risks of probiotic supplementation to COVID-19 patients [E3].

Ongoing investment in Bimuno development and generation of sales

Bimuno has been available to consumers since 2008. Since then, the new β-galactosidase, developed by the Reading team in collaboration with Clasado, has led to an improved enzymatic manufacturing process for the commercial production of Bimuno, which increased product yield (from 40% w/w to up to 80%) thereby reducing waste and purification costs. The enzyme manufacturer Biocatalysts Ltd produces this recombinant enzyme exclusively for Clasado and it was certified by the US Food and Drug Administration as 'generally safe for use' in April 2014. During the current REF period, the distribution of Bimuno has continued to expand across the UK retail market (e.g. Tesco, Boots, Sainsburys, Ocado, Holland & Barrett, Amazon) and beyond, with new non-exclusive distribution licences granted to leading suppliers Ashland (October 2019) and Strauber (April 2020) in the USA [E4]. Clasado Ltd's annual accounts have recorded total net sales (across the Bimuno product range) of GBP 6,300,000 between 1 January 2014 and December 2019 [E5]. Furthermore, Bimuno is now listed as an ingredient in a number of other commercially available prebiotic formulations (e.g. PreB2 and Banatrol Plus from Medtrition, Megaprebiotic from Microbiome Labs, and MentaBiotics from Amare Global), thereby generating additional revenue for other companies [E4].

Bimuno users report health benefits across a range of conditions

Consumers rate Bimuno very highly, with 94% positive reviews (n=3,129) recorded on the Trustpilot website between July 2014 and November 2020. Positive testimonials from this site serve to highlight the diverse benefits observed by users to their health and wellbeing [E6]. A notable recommendation for the product came from the health journalist Dr Michael Mosley who tested Bimuno for a BBC documentary 'The Truth About Sleep' (which first aired in May 2017). Of all the strategies Mosley tested to treat his insomnia, he found prebiotics to be the most effective. Bimuno promptly sold out, according to a subsequent report in the Guardian newspaper [E7]. Details of the reported benefits of Bimuno for specific health conditions and user groups are provided below:

i. Endorsement by an IBS support group

The IBS Network, a national charity, has referred to Bimuno as 'the only commercially available prebiotic that has shown benefits for patients with IBS'. The Network's factsheet on pro- and prebiotics also cited the Reading team's 2009 clinical trial on the effects of prebiotic on faecal microflora and IBS symptoms [E8]. In 2019, the Network further endorsed Bimuno by linking up with Clasado to provide new and re-joining Network members with a two-week supply of the product [E8]. The following testimonial is typical of the positive feedback received for Bimuno in relation to IBS: (July 2020) "*My 19-year-old son has been suffering from IBS for about 18 months now, unable to hold down a job due to his stomach problems and very embarrassing for a young man his age… with the help of Bimuno his stomach is far more settled*." [E6]

ii. Influence of the University of Reading study of Bimuno in ASD children

Reports of the 2018 Reading study [7], as well as more general news articles on the link between poor gut microbiome diversity and autism (and the role that Bimuno can potentially play to overcome this), have featured in national news articles (e.g. in the Daily Mail, Independent and Metro) as well as articles written by healthcare professionals working with autistic children [E7].

iii. Advocacy by sports nutritionists for improved international performance

Bimuno has long been recommended to prevent travellers' diarrhoea by travel companies and industry bodies such as the British Global Travel Health Association and Association of British Travel Agents. More recently, this benefit has been recognized by sports nutritionists working with international athletes. For example, Bimuno is on Team GB's approved

suppliers list and it is used routinely by athletes in preparation for and during major international events. This arose from a workshop given by Gibson to the GB cycling team doctors and nutritionists in February 2016 at the Manchester Velodrome. Bimuno was subsequently taken by the whole of Team GB at the Rio 2016 Olympics [*text removed for publication*] [E9].

Bimuno is certified with Informed Sport – a global quality assurance testing programme for sports supplements, part of the LGC Group. Since September 2019, Informed Sport-certified batches of Bimuno have been available to athletes, and the Informed Sport logo features on Bimuno products that are available in retail stores. Bimuno continues to be recommended as a routine supplement by sports nutritionists such as those working with the England Rugby Squad, England Cricket, Chelsea Football Club and Welsh Rugby union squad. Interest in the product from elite sports teams continues to grow, for example Premiership rugby union squad London Irish assessed the performance effects of Bimuno in a season-long study (between 2019 and 2020).

Summary: Research at the University of Reading has increased both the recognition and understanding of the role of prebiotics in human health and wellbeing. From providing the evidence for informed scientific and policy debate, as well as the underpinning science for the health and wellbeing benefits of commercial products, this body of research has stimulated demand from consumers to manage a growing range of conditions, from traveller's diarrhoea to ASD. This in turn is driving significant investment across the food industry, exemplified by cereals company Kellogg's decision to double investment in products promoting good gut health, according to a March 2020 news article [E7]. Kellogg's Wellbeing Category Lead has stated that collaborative research with the Reading team had 'developed our interest in prebiotics' and was a factor in the company's decision to launch new cereal products in 2019 [E10].

5. Sources to corroborate the impact

[E1] Gibson, G., Hutkins, R., Sanders, M. *et al*. (2017). 'Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics'. *Nature Reviews Gastroenterology & Hepatology* **14**, 491–502. DOI: https://doi.org/10.1038/nrgastro.2017.75.

[E2] Testimonial from the APPG Secretariat.

[E3] Question for the Department of Health and Social Care on coronavirus research. UIN 96067, tabled 28 September 2020.

[E4] Examples of Bimuno distribution: license agreements and as an ingredient in other prebiotic products.

[E5] Profit and loss statements extracted from Clasado Ltd full accounts made up between 1 January 2014 and 31 December 2019.

[E6] Screenshots taken from Trustpilot.com on 18 December 2020.

[E7] Selected news articles on the benefits of Bimuno and prebiotics; and development of cereal products containing prebiotic ingredients, published between 2016 and 2020.

[E8] IBS Network Probiotics, Prebiotics and Symbiotics factsheet, published 2016, and Bimuno offer April 2019

[E9] Testimonial from Head of Performance Nutrition, English Institute of Sport.

[E10] Testimonial from Wellbeing Category Lead, Kellogg's.