

Institution: University of Reading
Unit of Assessment: Agriculture, Veterinary & Food Science
Title of case study: Development of a new prebiotic product (Bimuno) - from research to retail.
<p>1. Summary of the impact</p> <p>Prebiotics are dietary ingredients selectively fermented by populations of gut bacteria seen as beneficial to health. Following the development of the concept of prebiotics by Professors Glenn Gibson and Marcel Roberfroid, research at the University of Reading has developed, pilot-manufactured and tested in humans, a novel prebiotic that shows greater selectivity for beneficial gut bacteria. The prebiotic has been commercialised through formation of a new Small Medium Enterprise (SME) company, Clasado. A range of functional food product formulations of the prebiotic is available over the counter at a variety of supermarket and high street outlets in the UK, as well as products containing it as a branded ingredient in North America. Research on Bimuno conducted at Reading has therefore had impact on human health through alleviation, or attenuation, of symptoms of common gut disorders and on the economy through the formation of a new SME company.</p>
<p>2. Underpinning research</p> <p>Background</p> <p>The concept of prebiotics was first described by Glenn Gibson, (then at the Institute of Food Research, Reading) and Marcel Roberfroid (at the University Catholique Louvain, Belgium) in 1995. Prebiotics are non-digestible food components that selectively encourage proliferation of beneficial colonic microflora. Bacteria belonging to the genera <i>Bifidobacterium</i> and <i>Lactobacillus</i> are most commonly targeted by prebiotics. Since his appointment as Professor of Food Microbiology at the University of Reading in 1999, Gibson has continued to develop and extend his work on prebiotics, which has included extensive commercial application and the development of a novel prebiotic for use in humans named Bimuno. The Bimuno development programme brought together Gibson's research on prebiotics with Professor Bob Rastall's (Department of Food and Nutritional Sciences, 1994 – present) research on enzymic development of novel functional food ingredients. Together, they set out to develop a novel prebiotic designed to benefit human health and well-being. Their aim was to improve upon existing products by synthesising a prebiotic that would enhance the growth of beneficial groups of bacteria with greater efficacy than previously achieved.</p> <p>A candidate prebiotic must escape digestion in the upper gut, reach the large intestine, and be utilised selectively by a restricted group of microorganisms that have clearly identified health promoting properties. Among dietary oligosaccharides, galactooligosaccharides (GOS) are the most promising candidates as potential prebiotics, as they have been associated with increased populations and fermentation products of <i>Bifidobacterium</i> spp.</p> <p>Assessing novel GOS mixture synthesised with enzymes from <i>Bifidobacterium bifidum</i></p> <p>GOS are synthesized by enzymatic catalysis of lactose using a β-galactosidase enzyme. The amount and nature of the GOS mixture synthesized is dependent upon the source of the enzyme as well as reaction conditions. Typically, GOS are synthesised through enzymatic catalysis of lactose using β galactosidase enzymes derived from yeasts or bacilli. However, Gibson and Rastall aimed to improve the selectivity of their GOS by sourcing β-galactosidase from a beneficial bacterial (probiotic) strain, <i>Bifidobacterium bifidum</i> NCIMB 41171. Their hypothesis was that the target bacteria will more readily metabolise prebiotics produced from enzymes originating from their conspecifics, resulting in a higher selectivity.</p> <p>Gibson and his colleagues at Reading developed their novel GOS mixture, known as Bimuno, and assessed its prebiotic potential <i>in vitro</i> and in pigs. They monitored changes in the gut bacteria in response to different doses of Bimuno [1]. The prebiotic significantly increased the density of colonic bifidobacteria providing evidence for its potential as a prebiotic [1]. In 2008, the researchers demonstrated that the beneficial effects of Bimuno also extended to humans, but also that GOS mixtures produced with different β galactosidases showed different prebiotic properties [2]. The GOS mixture derived using enzymes from <i>B. bifidum</i>, produced a larger ratio of bifidobacteria in the gut than existing prebiotics [2].</p> <p>Assessing response to Bimuno in targeted groups of people</p>

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Gibson and his colleagues then conducted a series of trials to test whether Bimuno had effects in groups of people with compromised colonic microflora. They conducted a trial on elderly people, as aging is associated with a reduction in beneficial bacteria and increased gut inflammation. In 2008, they reported that Bimuno significantly increased numbers of bifidobacteria, at the expense of less beneficial bacteria and that certain markers of the immune response, including anti-inflammatory mediators, were positively affected [3]. A trial in patients with Irritable Bowel Syndrome (IBS) in 2009, provided evidence that Bimuno not only changed the colonic microflora in sufferers by enhancing proportion of bifidobacteria, it alleviated many of their symptoms [4]. In 2010, a trial with otherwise healthy travellers showed that the group taking Bimuno as a preventative measure before travelling, experienced a significantly reduced incidence and duration of traveller's diarrhoea [5]. Most recently, Gibson and his colleagues conducted a trial assessing the effect Bimuno had on overweight adults. Again, Bimuno altered the gut microbiota toward a more beneficial composition and improved immune function, as well as markers of the metabolic syndrome [6]. This series of trials not only established the novel GOS mixture, Bimuno, as an effective prebiotic, but also as a potentially helpful for several conditions.

3. References to the research Research that led to the impact has been published in peer reviewed journals, has been submitted to RAE 2008 or REF2104 and is assessed as of at least 2* quality.

Citation numbers from Web of Science, accessed 4th November 2013

- [1] Tzortzis, G., Goulas, A.K., Gee, J.M. and Gibson, G.R. (2005) A novel galactooligosaccharide mixture increases the bifidobacterial population numbers in a continuous in vitro fermentation system and in the proximal colon of pigs *in vivo*. *Journal of Nutrition* 135 (7): 1726-1731. <<http://jn.nutrition.org/content/135/7/1726.full>> Citations: 80
- [2] 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. <<http://ajcn.nutrition.org/content/87/3/785.full>> Citations: 51
- [3] Vulevic, J., Drakoularakou, A., Yaqoob, P., Tzortzis, G. and Gibson, G.R. (2008) Modulation of the fecal microflora profile and immune function by a novel *trans*-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *American Journal of Clinical Nutrition* 88 (5): 1438-1446. DOI: 10.3945/ajcn.2008.26242 Citations: 60. Submitted under REF2.
- [4] 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: 10.1111/j.1365-2036.2008.03911.x Citations :73. Submitted under REF2.
- [5] 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 galactooligosaccharide mixture in reducing travellers' diarrhoea. *European Journal of Clinical Nutrition* 64 (2): 146-152. DOI: 10.1038/ejcn.2009.120 Citations: 15
- [6] Vulevic, J., Juric, A., Tzortzis, G. and Gibson, G.R. (2013) A mixture of *trans*-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. *Journal of Nutrition* 143 (3):324-31. DOI: 10.3945/jn.112.166132. Submitted under REF2.

Impact factors - *American Journal of Clinical Nutrition*: 6.504, *Journal of Nutrition*: 4.196.

4. Details of the impact

Context

Gastrointestinal dysfunction and disease is the most common cause of hospital admission in the UK, making it a heavy burden for patients, the NHS and the economy. The cost to the NHS is over £2.3bn per annum, with associated non-NHS costs to society in excess of £7bn per annum (Williams *et al* 2007. *Gut* 56, 1-113, doi:10.1136/gut.2006.117598). Incidence of gastrointestinal disease is increasing, which has major implications for healthcare needs. Improving health of the human gut through dietary intervention affords an excellent opportunity for reducing the impact of gastrointestinal disease, yet this approach remains relatively under-explored. The Reading work has contributed to developing dietary interventions for gastrointestinal dysfunction by examining

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the prebiotic effects of a wide array of commercially available foods and food ingredients, including development of the novel prebiotic, Bimuno. Gibson has been instrumental in developing the concept of prebiotics not only through his published output (the original 1995 publication that introduced the concept has received over 2000 citations) but also as a founding member of a dedicated scientific organization with over 700 members (International Scientific Association for Probiotics and Prebiotics (ISAPP)). ISAPP provides a forum for researchers and food and biopharma industry professionals to exchange research findings leading to further opportunities for collaboration and exploitation of the research.

Work on Bimuno has led to the formation of a new SME (Clasado) with significant potential for further growth and contribution to the economy. The wider research on other prebiotics has also had direct commercial impact with the estimated total economic impact of prebiotics to be €300m per annum in Europe with an annual growth rate of 14% (<http://www.food.frost.com>). There has also been significant benefit to the health and welfare of consumers, as well as a wider effect on society through stimulating public debate and awareness of the role of colonic bacteria in human health.

Spin-out company expands with new products commercialised

Between 2003 and 2013, the Reading team led the generation, pilot manufacturing and testing of the Bimuno novel prebiotic food ingredient and supplement. A worldwide patent was granted for Bimuno and the product is available in the UK as a range of retail products and in North America as a branded ingredient in dietary supplements and medical foods.

Since 2003, Clasado has continued to invest in an on-going programme of research and development at the University of Reading. The research that assessed Bimuno's effect on targeted groups of people [3-6], such as sufferers of IBS and traveller's diarrhoea, has led to the development and commercialisation of several new products: Bimuno IMMUNAID, to help maintain immune health, Bimuno TRAVELAID, for gut health maintenance when travelling abroad and Bimuno IBAID to help main digestive function; all launched in 2008.

George Tzortis, first a PhD student, and later a post-doctoral researcher working on Bimuno at Reading (2005-2008), became Clasado's Research & Development Manager, further supporting the extension of the research into the innovation and product development chain. Since Clasado was established, it has "*grown to employ over 20 people with extensive outsourced operations for manufacturing, packaging & regulatory functions*" [a]. In 2009, the company was awarded the Frost & Sullivan 2009 European Food & Beverage New Product Innovation Award for the Bimuno product [b].

The Bimuno brand is now firmly established in the market and Clasado is "*enjoying commercial success through the Bimuno product range*" [a]. The products are sold in retail outlets across the UK, such as Boots, Sainsburys and Tesco. Bimuno products are also sold online globally through the Clasado website. In the USA, Bimuno is included as a branded ingredient in products such as Medtrition National Nutrition's Banatrol plus (diarrhoea treatment) and ArgiMent™ (for dietary management of pressure ulcers and wounds), and GMC's Preventive Nutrition® Healthy Digestion Formula (health supplement). The Company contracts out its manufacturing, packaging and regulatory functions thus allowing focus on its core business of being a technology innovator. Clasado is developing commercial partnerships with a number of worldwide partners capable of delivering a global leadership position in Wellness using Clasado's current and future IP under the Bimuno® brand and other filed Trade Marks.

Public health and well-being improved

The Bimuno product range has beneficial effects on the health and well-being of its consumers. Benefits demonstrated through laboratory and clinical trials at Reading include:

- Reducing the risk of gastrointestinal dysfunction through prophylactic means in persons ostensibly free of disease [2];
- Supporting immune defences in the elderly [3];
- Supporting gut health while abroad, especially in high risk destinations for gastroenteritis [5];
- Reducing symptoms of Irritable Bowel Syndrome [4];
- Positively affecting certain markers of metabolic syndrome in obese individuals [6].

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As the products are over-the-counter dietary supplements for self-selection it is not possible to give specific evidence for the number of consumers that have benefited. However, testimonials from users indicate the Bimuno products have been life-changing, with IBS sufferers claiming that “*it is no exaggeration to say [Bimuno] has turned [their] life around*” [c] and that after years of trying other treatment options “*[Bimuno tablets] are the only things that have worked*” [d].

Bimuno incorporated into health advice from medical and other health professionals

In 2010, medical staff for the Welsh athletics team (175 athletes) and the England bowls team (12 athletes) advised athletes to use Bimuno in preparation for and during the 2010 Commonwealth Games in Dehli [e]. Bimuno also supported Team GB in the 2011 World University Games in Shenzhen, China [f]. A sports nutritionist who has worked with the England Rugby Squad, England Cricket, Chelsea Football Club and Welsh Rugby union also recommends Bimuno Travelaid in his work [g]. Bimuno is further validated and distributed through partnerships with a range of organisations, including the IBS network, British Global Travel Health Association, British Dietetic Association’s specialist interest groups, Association of British Travel Agents (ABTA) and Eurochange. Travel Health clinics have also partnered with Bimuno and have incorporated it into part of their regular advice to travellers: “*Taking Bimuno is part of the comprehensive advice we offer our customers who are concerned about tummy trouble spoiling their holiday abroad*” [h]. Moreover, Oxfam, a leading charity offers Bimuno to its volunteers involved with developing world humanitarian assignments [a].

Impacts on public understanding:

The positive effects of Bimuno have been widely reported in the media, including newspaper and magazine articles as well as TV (e.g. Horizon, Don’t Die Young) and radio (e.g. BBC Radio 4 and 5 Live) coverage. High profile written coverage included the Sunday Express (9th October 2012, average circulation 578,774), Full House magazine (9th November 2012, average circulation 150,168) and the Telegraph (21st January 2011, 651,184). Media coverage has contributed to the public awareness and understanding of the concept of bacteria in gut health and overall well-being, as well as the role of prebiotics in improving intestinal health. Gibson and Rastall also presented their prebiotic research at the prestigious Royal Society summer show in 2007 (<http://royalsociety.org/summer-science/2007/digestion-journey/>). The Exhibition is the Society’s main public event of the year open to member of the general public, students, teachers, scientists, policymakers and the media, typically attended by over 12,000 visitors with coverage on TV, in the print media and online.

5. Sources to corroborate the impact

- [a] CEO, Clasado – Testimonial available upon request.
- [b] ‘Excellence in Best Practices Awards Banquet’, *Frost & Sullivan* [website] <<http://www.frost.com/prod/servlet/meawardsevent.pag?id=171353456>> accessed 27 Sept 2013. Industry recognition of the innovation of the Bimuno product.
- [c] ‘Customer Gut Health Testimonials’, *Bimuno* [website] <<http://www.Bimuno.com/testimonials/digestive-health-testimonials/>> accessed 30 Sept 2013. Customer testimonials as to the health benefits of the product.
- [d] Whitehouse, M. (30 Sept 2012) ‘Food for thought’, *Sunday Express Magazine* <http://www.Bimuno.com/wp-content/uploads/2012/10/SundayExpress_011012_F.jpg>. An independent story of an IBS sufferer whos life was improved by Bimuno products.
- [e] ‘Bimuno avoids ‘DelhiBelly’ at the Commonwealth Games’, *Bimuno* [website] <<http://www.Bimuno.com/Bimuno-avoids-%E2%80%98dehli-belly%E2%80%99-at-the-commonwealth-games/>> accessed 30 Sept 2013.
- [f] ‘Bimuno supports world university games 2011 in Shenzhen, China’, *Bimuno* [website] <<http://www.Bimuno.com/blog/2011/08/03/Bimuno-supports-world-university-games-2011-in-shenzhen-china/>> accessed 30 Sept 2013.
- [g] ‘Special Guest Interview: The Food and Travel Secrets of Olympians’, *Starry-Eyed Travels* [website] <bit.ly/QGrZq4> accessed 30 Sept 2013,
- [h] ‘Professional Testimonials’, *Bimuno* [website] <bit.ly/1ap3JIN> accessed 30 Sept 2013. Provides testimonials from industry professionals who are now incorporating Bimuno into the advice they provide customers and patients.