

## More than a Gut feeling....

9 July, 2015

**OptiBiotix' long term aim is to develop 'microbiome modulators' which can influence changes in the make-up of the bacterial populations in the gastrointestinal tract and around the human body. These changes could potentially generate general or specific health benefits and, in time, modulate disease relevant pathways to downgrade and even help prevent a variety of increasingly widespread, lifestyle diseases.**

### Dietary product opportunity in weight management

A 3-component formulation has been selected for its ability to enhance satiety, increased metabolic rate and a reduced calorie 'harvest' from one's gut. A JV with NIZO aims to put the supplement in partner products in 2015.

### Cholesterol reduction clinical trial results due in Q4 2015

Results for a Lactobacillus probiotic should be available in the final quarter of 2015. This product concept is a must-have for functional food segment players. OPTI recently signed a placeholder option agreement with a multinational consumer goods company.

- **OptiBiotics platform:** The main research programme is to develop novel 'oligosaccharides' as 'microbiome modulators'. An OptiBiotic formulation uses the 'oligo' sugar to fuel the growth of a proprietary microbial strain(s) **to help modulate population surges in 'good' gut (or other localised) bacteria and derive well-evidenced health benefits.** The market opportunity for (a range of) disease-specific OptiBiotics is substantial, potentially valued at >\$1bn.
- **Multi-channel distribution model:** OPTI is a virtual company, focusing on its R&D (includes OptiScreen and microbiome modulation for advanced 'oligo' prebiotics) whilst out-sourcing clinical trials, manufacturing and downstream activities. The aim is to license its product and microbial strain IP, or have product supply agreements with appropriate partners, in order to develop a robust royalty income stream.
- **A preliminary sales- and royalty-based model suggests a DCF valuation up to £50m.** Positive news and a future differentiated OptiBiotic portfolio with multiple disease-specific products **could achieve a multiple of this.** Although the latter represents a high-risk programme its success should signal potential market leadership and a premium M&A exit route for investors.

#### Company Data

EPIC	OPTI
Price	34.6p
52 week Hi/Lo	41/8p
Market cap	£25.5m

#### Share Price, p



Source: ADVFN

#### Description

OptiBiotix Health PLC (OPTI) has established a pipeline of microbiome modulators that can impact on lipid and cholesterol management, energy harvest and appetite suppression.

#### Historic metrics

Year end Nov, £m	2013*	2014
Revenues	0.0	0.0
Operating loss	(0.341)	(0.489)
Pretax loss	(2.176)	(0.854)
Loss per share (pence)	(463.82)	(3.03)
Cash & cash equivalents	0.0	2.870

Source: Company \*16 months ended 30 November 2013

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## Introduction

OPTI was established in 2012 **to develop products to modify the human microbiome** (microbial genome), that is the 'collective' genome of the microbes in the gut system and other microbial ecosystems of the human body. For example, some gut bacteria are associated with diarrhoea and other gut disorders whilst others, known as **probiotics**, can have positive effects. Complementary products, known as **prebiotics** are non-digestible food ingredients that stimulate the growth or activity of (specific) bacteria in the digestive system which are beneficial to the host's health (so-called 'functional foods').

**OPTI's research and product development concept is to deliver a significant advance** upon the present limited outcomes knowledge for probiotics and prebiotics in functional foods. **The company aims to deliver product formulations**, its so-called '**microbiome modulators**', that are designed to be able to uniquely address an individual's health deficiencies and **bring well-evidenced and significant health benefits. We expect consumers to pay premium prices for such products - this is the essence of OPTI's business model.**

**OPTI's commercial opportunity** is to develop a range of 'microbiome modulator' formulations, incorporating proprietary microbial strains and/or novel oligosaccharides (simply, sweet sugars but no calories) that can function in helping prevent and manage human diseases. **OPTI's initial targets are in metabolic health**, and include obesity and high cholesterol, characterised as lifestyle diseases (consuming too much processed food, high in sugar, fat and calories whilst taking too little exercise). **Future target areas include central nervous system disorders, immune and skin health (all areas where the research literature has highlighted a potential role for the gut or local microbiome to play a role in disease processes).**

OPTI's technology platforms, **OptiScreen** and **OptiBiotics**, represent an emerging set of scientific disciplines that are focused on identifying microbial strains and (complementary) novel oligosaccharides that can **modulate** and **enhance** the activity of bacteria in the gut system (and elsewhere), potentially amplifying known health benefits and bringing new ones.

**Microbes in medicine** (and particularly bacteria) are often '**bad actors**', responsible for serious diseases in normal people and potential opportunistic diseases in immune-suppressed individuals. **However, in the realm of gut microbiology many** of the trillions of bacteria, in mixed species populations, **are recognised as 'good actors'** - able to co-exist with their human host and secrete bio-active metabolites that can enhance the nutritional and health status of the host (e.g. vitamins, co-factors).

**OPTI is developing a portfolio of products** playing to this microbial theme. They are, initially, focused on two key health areas:

- Weight management (through regulating appetite suppression and microbe 'energy harvesting'), and
- Lipid and cholesterol modulation.

**An important future line of products** is the novel oligosaccharides (which can also be described as prebiotics) acting as 'microbiome modulators', to selectively boost good bacteria and reap their specific or collective health benefits in the target disease areas.

**OPTI products are aimed** at commercially significant lifestyle disease markets (**initially** obesity and high cholesterol, in the metabolic health area). Although marketed pharmaceutical drugs are available for treatment, the complementary nutritional and probiotic/prebiotic formulation options are basic and limited (by their lack of supporting clinical evidence). Nevertheless, the latter markets - and particularly focused efforts directed at influencing gut (and other) bacteria - represent emerging scientific innovation and are growing fast, with estimates of a potential market value approaching >\$1bn.

**In our opinion, bringing through better defined products with well-evidenced clinical data should introduce a step-change in the growth and commercial prospects for this emerging sector.**

**OPTI's Weight management product** has successfully completed feasibility and evaluation studies. The company entered a joint venture (JV) agreement with NIP BV (a subsidiary of NIZO Food Research BV) to establish product distribution channels and partnerships for the final product (yoghurt and other dairy formats). Commercial partnering discussions have started well.

Importantly, and in relation to the weight management product, OPTI has signed a letter of intent (LOI) with Venture Life Group (AIM ticker, VLG) to enter a strategic development and commercial alliance. This would align OPTI's expertise in developing microbiome modulators to improve health with VLG's formulation, manufacturing and international distribution capabilities (possible target markets include developed and emerging markets). A potential first project for the OPTI/VLG alliance could be to investigate the commercial value of translating the weight management product into different formulations/presentations - tailored for regional and cultural preferences.

OPTI's other initial product is a capsular food supplement to reduce cholesterol. **Clinical studies commenced in January at the University of Reading.** This probiotic contains a *Lactobacillus plantarum* strain and the studies are aimed to demonstrate a cholesterol-lowering outcome in patients who have high cholesterol levels. OPTI signed an initial placeholder option agreement with a **multinational consumer food company** in June 2015.

**A preliminary sales- and royalty-based model suggests a DCF valuation of up to £50m.** However, depending on the model assumptions (licensing deal royalty rates), the fair value range of the company could be a potential £50m-£110m. Positive news on products and a future differentiated OptiBiotic portfolio with multiple disease-specific products **could achieve a multiple of this.** Although the latter represents a high-risk programme its success should signal potential market leadership and a premium M&A exit route for investors.

## Current activities and outlook

### Product development

**OPTI currently has two live product programmes and is developing its OptiBiotics platform** which could develop a range of custom 'microbiome modulator' products.

**The company's long term aim is to bring better science and better health together** - identifying the potential for microbial strain(s) and novel oligosaccharides to modulate the gut microbiome to improve health and, potentially, to prevent disease in target health areas.

### Weight management formulation

The formulation profile is to help support sustained weight management. Obesity is an increasing national and global problem. In the UK obesity-related health problems cost tax payers >£7bn pa. The World Health Organisation has stated that almost 3m people die every year as a result of being overweight.

This product comprises three components, each chosen to help an individual achieve a significant effect in terms of:

- **Satiety** - you feel fuller and are less likely to eat and snack between meals;
- **Metabolic rate enhancement** - you use up more calories; and
- **A 'microbiome modulator'** - which is documented to stimulate the growth of beneficial intestinal bacterial ('stealing' available calories) and the production of appetite regulating metabolites.

An increasing amount of the scientific evidence and potential for constructive intervention in individuals is aimed at modulating the gut microbiome. The first two components have documented claims evidence for satiety and metabolic rate enhancement (in accordance with review by the European Food Standards Agency).

To date the formulation has been added to bread and yoghurts - and mixing, baking and tasting tests have completed successfully. Further work is underway on other potential product lines (cereal bars, fruit and vegetable drinks).

This product is partnered in a JV with NIP BV, a subsidiary of NIZO BV, a leading contract food research company with extensive experience in developing and manufacturing bacterial culture products.

## Probiotic strain(s) for Cholesterol reduction

A high cholesterol level is an established risk factor in cardiovascular disease (CVD). CVD is the world's leading cause of death. In the UK direct and indirect medical spending to treat and help prevent CVD is in the order of £8bn.

Using its OptiScreen platform, OPTI has identified three naturally-occurring Lactobacillus strains which have **been shown to reduce cholesterol (a recognised biomarker for CVD risk) in lab studies by up to 80%**. The bacteria achieve this result through two routes:

- Binding and incorporating cholesterol into their own cells, and
- Increasing the potential for elevated levels of bacterial bile salt hydrolysis (that is, breakdown) to help suppress the bile acid transfer of dietary fat and cholesterol into the host's blood circulation.

Three lactobacilli strains were originally chosen for their activity *in vitro*, and a lead candidate strain subsequently chosen and entered into a clinical trial. The trial commenced in January 2015 at the University of Reading's Food Science Unit. The study design is single-centre, randomised double-blind, placebo-controlled, parallel group. Subjects (50 volunteers) are split between placebo (maltodextrin) or active treatment (with a treatment period of 12 weeks and a wash-out period of 4 weeks).

Primary efficacy outcomes include the important total-, low-density lipoprotein (LDL-) and high-density lipoprotein- (HDL-) cholesterol levels, with a panel of safety tests (full blood count, liver function tests and inflammatory biomarkers). Secondary outcomes include Vitamin D levels and associated changes in the gut microbial flora (obtained through metagenomic and microbial metabolomic profiling).

Full results are expected to be available by September 2015. We understand that there has been significant interest in this product. OPTI announced on 2 June that it has entered an option agreement with a multinational consumer goods company. The terms of the agreement provide this company (for a nominal payment) with an option to enter into a definitive agreement following the results of a trial (presumably the ongoing Reading trial). No other details have been released due to reasons of contractual commercial confidentiality.

## OptiBiotics programme

This is a potential platform for generating a rich variety of novel sugar oligosaccharides from a number of different complex carbohydrate substrates. The project has completed proof of concept and full scale development is ongoing. There are a number of milestones important to the programme's value, including:

1. **Microbial strains are chosen** on the basis of a number of things, including presence in the microbiome, relevant physiological characteristics, intellectual property (IP) freedom and regulatory status.
2. Strain potential to produce, via microbial glycosidases, **novel oligosaccharides of various chain lengths and structures**. Furthermore, microbial strains are rated on yield and against known reference strains (strains can be registered, if novel, whilst new processes and applications can be patented) and **for their health potential**.
3. **Chosen strains and combinations are scaled up** for detailed oligosaccharide production and characterisation studies ahead of clinical trials.
4. **A commercial review** takes account of physical and organoleptic (taste) properties. Furthermore, each novel oligosaccharide is investigated to review its effect on microbiome constituents (individually and collectively). Each 'oligo' is also reviewed in combination with individual microbial strains (or mixtures) to assess the potential for synbiotic activity - either as individual components or in a fixed combination formulation (potential OptiBiotic products).
5. **OptiBiotic product potential** can then be determined through *in vivo* formulation assessments.

This programme could help generate a range of OptiBiotics, that is 'microbiome modulator' formulations, that fall into three separate categories:

- A. Individual **novel 'oligo' formulations** - to increase specific gut bacteria populations;
- B. Combined **synbiotic formulations** - these could offer individual matched combinations of 'oligo' and microbial strain - and could even see the formulations marketed in the same presentation (for example food, capsule, powder); and
- C. Novel oligosaccharides as **alternative sweeteners** - these would be (largely) non-digestible and be used by food manufacturers for low-calorie food and beverage products.

OPTI announced in a 17 April research update that NIZO was carrying out outsourced microbial screening work to look for microbial enzymes that are able to produce novel 'oligo' sugars. The aim is to accelerate OPTI's research working to identify (non-digestible) sugars as described above.

The first phase of this work (originally announced in March) has been completed for 360 strains, demonstrating:

- a) High enzyme activity in a number of Lactobacilli species tested - confirming earlier results.

- b) Very high enzyme activity in a second species (and potential to produce high volumes).
- c) Novel enzyme activity in previously untested strains (OPTI is considering filing additional patents on these findings).

As a result, OPTI is taking 10 enzyme 'high-producer' strains through to additional testing for sugar analysis and pilot scale-up before moving to the next stage (for microbiome modulation potential and 'sweetness' rating).

#### **Recent developments**

Recent developments with its OptiBiotic platform, including identification of new 'oligos' and improvements to the screening process (to predict the utility of microbial strains to produce novel 'oligos'), have allowed a number of additional patent filings to be made, including:

- **A new oligosaccharide** which can increase growth rates in *Propionibacterium* species and enhance the production of propionate, which has been shown to help regulate appetite;
- **A new 'oligo' which enhances the growth rate of *Lactobacillus plantarum*.** This is the species used in OPTI's cholesterol reduction product, providing the project with the potential to increase the microbe's growth rate and, as a result, enhance product performance;
- Improved ability of the OptiBiotic discovery platform to predict the probability of microbial strains to produce **new oligosaccharides** with novel structures, allowing greater screening capacity for species and strains.

**A further positive development for OPTI's OptiBiotic platform was announced on 9 July.** The company is aiming to accelerate the laboratory development through collaborating with Spain's Instituto de Quimica Organica General (IQOG), part of the Spanish National Research Council based in Madrid. IQOG is an internationally renowned centre for the synthesis, analysis and study of the biological behaviour of organic compounds in humans.

**This agreement aims to progress OPTI's novel 'oligos' (from its OptiBiotic platform) through scale-up and testing ready for human studies** (in 2016). The programme is making good progress and is set to include strains (in addition to those identified by OPTI) from a number of international partners, subject to finalisation of commercial terms.

**The development and scale-up activities are to focus on assessing the functional properties of the novel oligosaccharides** that OPTI has generated, assessing these 'oligos' (sugars of various chain lengths) for their 'sweet but healthy' profile. Apart from necessary analytical (increased purity, to >85%) and characterisation (organoleptic properties, including taste, texture, aftertaste) tests, **IQOG is to assess the 'oligos' for their microbiome modulation effects.**

**The aim is to identify (calorie-reduced) 'oligos' that can act as 'microbiome modulators', with the potential to prevent, manage and treat disease.** The complementary part of this programme aims to identify the microbiome strains (with species and genera affiliations) whose growth rate can be selectively enhanced using the 'oligos' in order to obtain the desired health benefits.

As mentioned above, **the objective of this work is to develop new calorie-low/calorie-free sweeteners that could function as 'microbiome modulators' and potentially also fill a role as replacement 'sweet but healthy' sugars in products across the food industry.**

## Commercial discussions and status

**The weight management formulation evaluation and joint venture agreement happened sooner than expected** (announced 21 January 2015); it has been tested in yoghurt with satisfactory tasting results. OPTI's partner, NIP BV, is a subsidiary of NIZO BV, the well-known contract food research organisation (working across the industry in R&D and manufacturing). A data pack is currently being worked up for potential customer engagement discussions, directed at both developed and emerging market audiences.

**The clinical study phase for the cholesterol-lowering project has started** (19 January), with results expected by September 2015. This probiotic product concept, with a potential disease risk-reduction/prevention claim is a must-have for the big functional food groups. OPTI has seen a substantial interest in the product with a number of discussions on the go.

As mentioned above OPTI announced on 2 June 2015 that it has entered into an option agreement with a multinational consumer products company. Depending on the results of the ongoing trial this could develop into a definitive agreement. No other details have been released due to reasons of contractual commercial confidentiality.

**OPTI have produced a number of oligosaccharides** in the microbiome modulation programme and are in the process of selecting candidates for their ability to demonstrate enhanced overall functionality formulated alone or with specific microbial strain(s) - **as potential OptiBiotic products**. The company aims to complete further development milestones in another 12 months (minimum). This timeline is somewhat fluid and may lengthen, depending on the scope and scale of *in vivo* studies, before OPTI is in a position to file OptiBiotic submissions for health benefit-related claims.



## Valuation

**OPTI currently has no revenues.** However, the company has a number of potential business opportunities and future revenue streams that should, in time, allow us to develop a detailed earnings model.

**The market opportunity is a significant and multi-channel one.**

According to a report published in September by MarketsandMarkets, focused on the **therapeutic and diagnostic** opportunities, **the emerging microbiome market will reach \$658m in size by 2023** (from an estimated \$294m in 2019), expanding at a CAGR of >22% in the forecast period. Europe is expected to have double-digit annual growth and to be the largest-growing region in 2019, followed by Asia, while North America's growth will be slower (due to lack of awareness of the potential benefits of probiotics).

**The impact of microbiome-derived therapies on human health could be huge,** offering pharmaceutical companies and biotech companies strong market entry, growth opportunities - **and premium valuations.** However, there are a number of potential issues to overcome - a major challenge will be to prove that such therapies represent an improvement over current treatments, with well-designed and controlled clinical trials that demonstrate a superior long-term efficacy and safety (to current pharmacotherapy). Currently, scientists are still trying to understand how the microbiome works.

**Other opportunities for microbiome modulation can be found in the functional foods sector.** Functional foods ('foods with an added nutritional value') are an almost \$200bn global market, that includes (amongst other products) probiotics, prebiotics and mixtures. Probiotic products represent a fast-growing segment in the \$32bn Vitamins, mineral & supplements (VMS) market. For example, the US probiotic market is valued at ~\$3bn, with the separate probiotic yoghurt market estimated to be worth ~\$1bn in 2015. The prebiotics market is currently worth an estimated \$3bn, consisting of infant formulae, dietary supplements and animal feed. New functional applications in health foods and beverages are rapidly expanding this segment.

**This is the market landscape that OPTI are targeting** with their initial two products and its OptiBiotics programme. We believe that a significant commercial opportunity is set to open up as the latter microbiome modulation programme gears up and develops a shortlist of potential prebiotic and OptiBiotic product candidates.

**A future opportunity for the OptiBiotics programme is to develop microbiome modulators** (strain or strains, or sugar/s or both) that can deliver proven health benefits. If successful, the commercial value could be significant. For example, consider the therapeutic market for the sale of omega-3 fatty acids (extracted from fish oil) to help lower elevated triglyceride levels to improve cardiovascular health. GSK's Lovaza omega-3 product had sales of >\$1bn in 2013. Two additional brand products compete in this market (Amarin's Vascepa and AstraZeneca's Epanova), although generic entrants are already hurting Lovaza's sales figures.

**The important takeaway** is that this market has been built on scientific expertise, clinical evidence and efficient ingredient manufacture and supply; for example, the active ingredient market for omega-3 is worth **\$1.5bn.**

Similarly, if OPTI can develop a clear scientific rationale for its products, albeit (initially) in the non-pharmaceutical space and secure the appropriate health benefit claims to allow optimal market positioning, then its IP licensing and product formulation supply (separate strains, prebiotics and microbiome modulators) business could develop at a significant scale and pace - and help create matching value.

**Our valuation analysis works through a preliminary sales revenue forecast of OPTI's product portfolio.** A snapshot of potential sales revenues and royalty income at various royalty rates is shown in the table. In approximate figures we have extrapolated this to a cash flow stream going out to 2025, which is the input into our DCF analysis.

**Clearly this is very much a preliminary exercise** and majors on the initial two products and potential other functional food opportunities. **Currently we resist the temptation to include revenues from potential future microbial therapeutics products**, but their addition would likely add significant revenue streams and have a similarly positive effect on the valuation.

Revenue and royalty potential (initial products only)			
Revenues \$m	FY20e	FY23e	FY25e
Probiotic 1	20	100	120
Probiotic 2	5	40	100
Weight management formulation	15	20	20
'Oligo' (Synbiotic)	5	60	120
'Oligo' (Optibiotic)	0	10	60
Novel sweetener (food industry)	2	20	80
<b>Royalty Income, £m (5% rate)</b>	<b>1.5</b>	<b>7.8</b>	<b>15.6</b>
<b>Royalty Income, £m (10% rate)</b>	<b>2.9</b>	<b>15.6</b>	<b>31.3</b>

Source: analyst

So, for the moment, we believe that this exercise suggests a **fair value range for the OPTI business**, based on a 5% royalty rate and a DCF discount rate of 10-14%, of **up to £50m**. Alternatively and more probably, as OPTI is able to connect health benefits to its products through well-evidenced studies, the royalty rate is likely to increase. Therefore, **at the enhanced 10% royalty rate** and a DCF discount rate of 10-14%, **the fair value range of the company is increased to a potential £50m-£110m**.

DCF valuation		Discount Rate				
		10.0%	12.0%	14.0%	16.0%	20.0%
<b>Terminal</b>	<b>1.5%</b>	94.5	65.4	47.1	34.8	20.1
<b>Growth</b>	<b>2.0%</b>	99.7	68.3	48.8	25.8	20.5
<b>Rate</b>	<b>2.5%</b>	105.7	71.4	50.6	36.9	21.0
	<b>3.0%</b>	112.5	74.9	52.5	38.1	21.5

Source: analyst; Assumptions - see text, plus 10% royalty rate (2015-2025)

**Reviewing the corporate landscape we can find some pointers that support this forecasting and valuation perspective.**

Furthermore, we also believe that a future exit could be achieved through a trade sale at a significant premium to our estimated valuation range. The M&A market for specialty food ingredients continues to rise on increased customer awareness and buying decisions for products with health-related claims.

**The addition of potential microbial therapeutics products to the pipeline would be likely to add significant valuation uplift.**

We identify below some of the deals that we have integrated into our due diligence and analysis. In addition, we also include some details, for comparison purposes, of some of the companies currently active in the premium microbial therapeutics space.

**Food products and supplements/microbial formulations - Probiotics**

**BioGaia (BG) and Nestlé have collaborated since 2008 in the infant nutrition area**, and in 2012 formed a strategic partnership to allow Nestlé a perpetual licence to access BG's probiotic *Lactobacillus reuteri* 'Protectis' strain (for infant nutrition products). **In return BG was to be paid €50.8m over 5 years** (initial payment of €40m in 2012 plus the balance in additional payments on achieving certain milestones). The agreement was extended in 2013 to a new category of probiotic products, destined for international marketing and especially in emerging markets. Most recently (**February 2015**), Nestlé launched a powder formula for children over the age of one year, with a scientific publication (2014) demonstrating the prevention of infections in children (>1 year old).

More recently the company's subsidiary, Infant Bacterial Therapeutics, received Orphan Drug designation status from the FDA for an *L.reuteri* formulation for the prevention of necrotising enterocolitis, a leading cause of death in premature babies. BG is quoted on Nasdaq OMX (Ticker BIOG\_B) with a market cap of over £300m.

**AB-Biotics signed a global collaboration and licensing agreement in May 2014** with DuPont Nutrition & Health on **AB-Life**, AB-Biotics' probiotic, which is claimed to maintain healthy levels of cholesterol in at-risk individuals (AB-Biotics was granted a European patent for its AB-Life probiotic in September 2014). AB-Life is a formulation of three *Lactobacillus plantarum* strains. DuPont has exclusive rights for the production, marketing and global sales of AB-Life (to add to its HOWARU portfolio), whilst AB-Biotics is to continue clinical development on the product to support additional health benefits. Financial details were not disclosed.

AB-Life was able to reduce total cholesterol levels in a clinical trial between 14%-18%, through acting in a couple of ways: by capturing and immobilising dietary cholesterol in its membrane and, secondly, by activating the metabolism of bile salts which means that the liver is forced to process blood cholesterol in order to synthesise more bile salts. This is particularly important, since it is known that 60%-70% of blood cholesterol is not diet-related.

**AB-Biotics agreed with Sanofi in October 2014** to launch a probiotic into the paediatric gastric health market in Spain. Sanogermina, a live culture probiotic, has been specifically designed with children in mind. A clinical study has shown that 14 days of Sanogermina supplements can help reduce daily crying time by >60% (in infant with a daily average crying time between 60-240 minutes). Financial details were not disclosed. AB-Biotics, with a market cap of €20m, is quoted on the Spanish Ibex exchange (Ticker ABB).

**Ganeden Biotech sold two established and marketed probiotic brands**, Sustenex and Digestive Advantage, in 2011 to Schiff Nutrition International (now part of Reckitt Benckiser) **for \$40m in cash and a royalty income on future sales**. The deal also included a licence to use Ganeden's probiotic technology (strain), GanedenBC, in the OTC and dietary supplement space and future collaborative research activities. GanedenBC is a *Bacillus coagulans* strain that clinical trials have suggested may be effective in irritable bowel syndrome, flatulence and in support of the immune system.

Since it started producing the BC probiotic strain in 2008 it has been able to strike deals to get the strain into >100 products. The two proprietary products that it sold had become too large and overly needy for advertising and marketing spend, making it an easy decision to cash in. Although Ganeden doesn't publish financials we believe that combined sales for Sustenex and Digestive Advantage were in the \$20m range (suggesting a sales figure of ~2x sales).

### Food products and supplements - Prebiotics

**Clasado's Bimuno** emerged from its prebiotic research programmes (including work at Reading University). Clasado (based in UK and Malta) develops products directed towards 'healthy eating for all'. The company works on the proven concept of general health being linked to the digestive system and diet. In addition, Clasado has research and development activities investigating areas including food supplements, infant nutrition, livestock feed and pet nutrition.

Bimuno GOS is a blend of beta-galacto-oligosaccharides derived from lactose conversion using *Bifidobacterium bifidum* NCIMB 41171 enzymes (see the OptiBiotics programme section for the scientific rationale). Clasado found that its use in humans produced a larger ratio of bifidobacteria in the gut than other (existing) prebiotics. A range of functional food product formulations of Bimuno is available over the counter at a variety of supermarket and high street outlets in the UK, as well as products containing Bimuno as a branded ingredient in North America.

### Biotherapeutics

**4D Pharma** (quoted on AIM, ticker DDDD, market cap over £500m) exploits its 'live biotherapeutics', a new class of medicine, to manipulate the population of gut bacteria to influence the function of human physiological systems, like the immune and nervous systems. The company raised £17m (gross) going public in February 2014, a further £22m in June 2014 and a further £35m in January 2015. 4D has two products commencing clinical trials in H1 2015 - Blautix for the treatment of Irritable Bowel Syndrome and Thetanix for paediatric Crohn's Disease. A third product, Rosburix, received Orphan Drug designation from the FDA in August 2014 for paediatric ulcerative colitis.

With its proprietary MicroRx discovery platform the company has identified a number of bacteria that have demonstrated encouraging effects in preclinical models of rheumatoid arthritis, allergic asthma and severe steroid-resistant asthma.

**Seres Therapeutics** (quoted on NASDAQ, ticker MCRB, market cap of \$1.5bn - **IPO 25 June 2015 raised net proceeds of \$140m**) aims to identify functional differences between healthy and dysbiotic ('imbalanced') microbiomes, and rationally design its potential 'Ecobiotic' drugs.

These therapeutics are 'ecological compositions' made up of beneficial organisms that are designed to target functional deficiencies and re-establish the cornerstone features of a healthy microbiome. MCRB's pipeline is targeting recurrent C diff infections (in Phase 2 studies) and Inflammatory Bowel Disease (Phase 1), with a preclinical programme into C diff infections. Seres' discovery efforts are currently focused on metabolic, inflammatory, and infectious diseases. Nestlé's Health Sciences unit invested \$65m in Seres earlier this year.

**Second Genome** (private) aims to develop a proprietary, first-in-class microbiome drug discovery platform developing novel therapeutics across a range of diseases. Second Genome has R&D collaborations with Pfizer and Janssen Biotech (Johnson & Johnson), and a partnership with the Mayo Clinic's 'Centre for Individualized Medicine' to support the development of therapeutic products for multiple disease indications. Second Genome's lead candidate, SGM-1019, is a small molecule inhibitor of a key microbiome-mediated target to address inflammation and pain in inflammatory bowel disease (IBD). SGM-1019 has completed a Phase I double blind, placebo controlled, single ascending oral dose trial in healthy subjects. It achieved targeted exposure levels and was well tolerated with no significant adverse events. The company has additional preclinical programs under development in a range of chronic disease indications and a separate microbiome CRO capability (Second Genome Solutions).

**Vedanta Biosciences** (private) is developing therapies that potentially modulate the interactions between the human microbiome and the host immune system. Vedanta's approach uses findings in the field of mucosal immunology to generate safe and potent treatments that induce tolerance and restore intestinal homeostasis (equilibrium). Furthermore, Janssen (J&J) and Vedanta announced in January 2015 that the pharma company would pay an undisclosed initial fee and up to \$241m if Vedanta's mix of clostridial bacteria became a successful treatment for Crohn's disease and ulcerative colitis.

**MicroBiome Therapeutics** (MBT, private, raised >\$2m and Series B financing underway) is developing drug therapies that aim to improve an individual's health status by interacting with the human microbiome in specific ways. MBT develops 'microbiome modulators', to alter bacterial populations and their environment in the gut, to prevent or treat serious health conditions. MBT's initial research and products are focused on metabolic conditions including pre-diabetes, diabetes and obesity.

Prebiotics are a key component of MBT's products. These are non-digestible growth substrates, co-factors and metabolic agents that are preferentially used by beneficial bacteria already resident in the digestive system but in less than desired numbers. Prebiotics can thereby increase the population of health-promoting bacteria at the expense of harmful bacteria.

MBT's lead microbiome modulator, NM505, is in clinical development to assess its efficacy and safety as a reformulation of metformin (the most widely prescribed drug therapy, worldwide, for the management of type 2 diabetes). NM505 may be able to decrease the incidence of the dose-limiting gastrointestinal (GI) side effects associated with metformin, whilst further lowering elevated blood glucose levels.

Another product, NM504, is currently in clinical development as a prescription product for treatment of pre-diabetes and diabetes. It recently completed a trial to assess its ability to improve glycaemic control and enhance insulin sensitivity in pre-diabetic and diabetic patients. In addition, the trial measured other biomarkers of the human microbiome that are associated with GI and metabolic health, as well as safety.

**ViThera Pharmaceuticals'** (private) innovative EnLac technology platform delivers drugs directly to diseased epithelial sites (intestinal wall, vaginal wall, skin) so the drugs are available in high local concentrations. Its probiotic (bacteria)-based products are evolved to associate closely with epithelial cells. ViThera has developed these probiotics to produce and release drugs right against their target tissue where they are needed. The company has in vitro and in vivo proof-of-concept data, with plans to take products into human trials next. Its lead product, VT301, is a treatment that should benefit patients with all stages of Crohn's Disease and Ulcerative Colitis and should also be useful in keeping patients in remission.

**Enterome** (private) is focused on developing diagnostics and therapies for Crohn's disease, using profiling technology for gut bacteria. The firm maps the total faecal bacterial gene content and functions, leading to a 'personal metagenome' (calling it a metagenotype) for each person. This metagenotype can indicate certain disease states, or be measured in one patient over time, for example to monitor changes that may lead to flare-ups or relapse in Crohn's disease.

Enterome is also developing its own drug-companion diagnostic combination in Crohn's. The preclinical drug, EP-8018, is a small molecule inhibitor to limit binding of a type of bacteria called AIEC (adherent-invasive *E. coli*) to a particular cell adhesion receptor. AIEC takes advantage of a temporary inflammatory state following a microbiome imbalance.

The microbiome does not normally allow AIEC to adhere to the gut wall, but a disequilibrium can allow AIEC colonisation and production of TNF (tumor necrosis factor), leading to further inflammation. Whilst approved TNF-blockers, such as Humira, only treat the symptoms, Enterome's drug candidate could target the underlying cause of the disease.

Longer term, Enterome's technology has potential application in other diseases, for example obesity - a weakened/imbanced microbiome, in combination with bad food habits, could be instrumental in obesity. Future novel obesity treatments could target defects in the microbiome.

## Catalysts

We have identified some near-term potential events that could lead to share price moves:

Potential 'trigger' events		
Calendar		Event
2015	Q3	Results expected from cholesterol-lowering clinical study
2015	Q4	Announcement of a manufacturing agreement for its cholesterol reducing microbial strain
2015	Q4	Initial partnering deal for weight management formulation
2016	Q2	Announcement of in licensing/acquisition in new application area
2016	Q2	Announcement of a corporate deal to carry out global studies, incorporate the microbial strain in food ingredients, and distribute the cholesterol reducing strain as a supplement
2016	Q2	Initial partnership deal for OptiBiotic programme
2016	Q3	Microbiome modulators to commence human trials (OptiBiotic programme)

Source: analyst

## Investment Risks

We believe the main uncertainties in OPTI's commercial ambitions and our forecasts relate to:

- Material delays in establishing licences with commercial partners and/or offtake agreements for the products/formulations;
- Lack of efficacy with its current projects - the weight management product and the cholesterol-reducing microbial formulation;
- Delays and difficulties in assessing results and strategic direction for the novel oligosaccharides project and the OptiBiotics programme;
- Failure to gain 'hard' health claims for its formulations from the European Food Safety Authority (and comparable international organisations) - through documented scientific evidence - to allow consumer advertising; and
- Potential product competition, new technology entrants.

## Business backgrounder

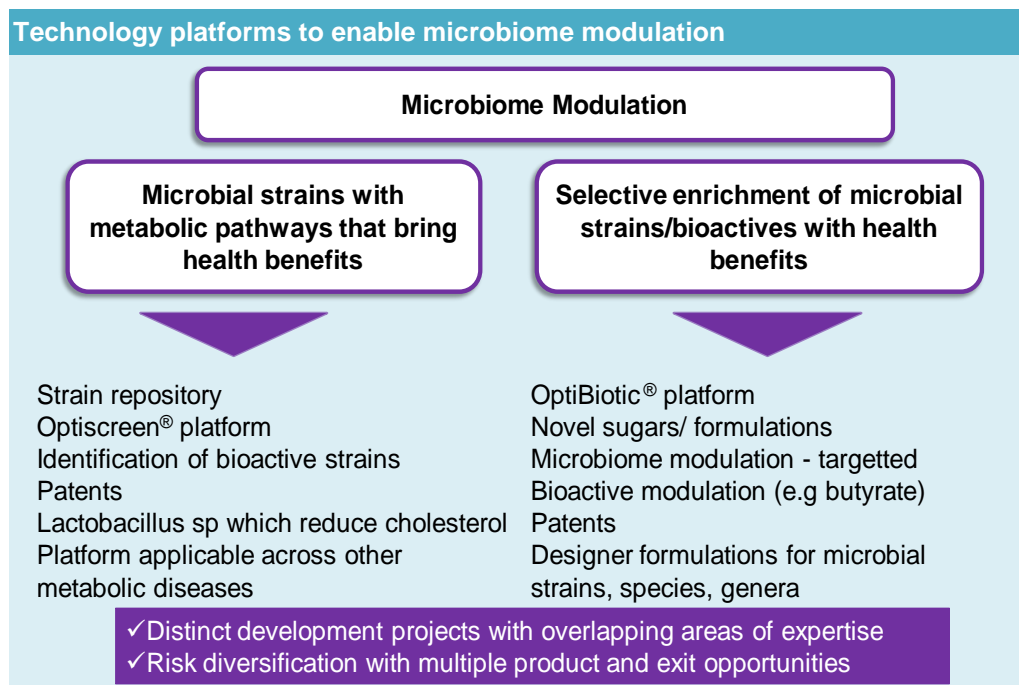
OPTI listed on AIM in August 2014, raising £3.3m (gross) at 8p/share in the process and is currently capitalised at over £25m.

OPTI's strategy is to **bring better science and better health together in a successful commercial package**. That means harnessing the latest understanding on probiotic and prebiotic effects - separately or combined - and 'microbiome modulators' on the human gut. Furthermore, this requires building an evidence base to relate an individual's microbiome (and its modulation) to its potential to positively affect human physiology and, significantly, disease states. **This evidence would differentiate OPTI from the mass marketers** of flavoured yoghurt and dairy-based drinks that are unable to make such a valuable connection.

## Science and technology platforms

OPTI is a virtual company, with 4 employees, some contracted advisors, one Ph.D student, an international scientific advisory committee and a number of academic alliances which provide staff capabilities and facilities. Its offices are based in York, with in-house laboratory facilities at the Science and Technology centre in Reading.

Research comprises the **high-throughput selection of novel microbial strains** (in the gut microbiome) that can bring about reproducible health benefits (**OptiScreen**). This platform has already delivered a patented microbial strain that is incorporated into a probiotic that aims to reduce a person's cholesterol level.



Source: Company

Its proprietary **OptiBiotic platform is a complementary tool**. This method uses a bacteria's own enzymes to generate novel sugars (oligosaccharides) from complex sugar polymers (very long chain carbohydrate molecules).



The shorter, or clipped-chain, 'oligos' are suitable for fuelling the growth of the gut's mixed bacterial populations, and most specifically the strain whose enzymes produced the 'oligo' in the first place (because it is an intermediate in that bacteria's metabolic pathway).

**The aim is to modulate and enhance 'good' bacteria**, helping influence the host (human) metabolism and physiology to down-regulate or even prevent a disease and improve a person's health status. OptiScreen and OptiBiotics are distinct research platforms but overlap in terms of their microbial physiology knowledge base and the potential synergies between end-products ('microbiome modulators').

### The market opportunity

As we have detailed elsewhere, **the aim is to, initially, enter the significant functional foods market** with products that can promote a health benefit as well as the obvious nutritional one.

**OPTI's future commercial opportunity** is to develop a range of 'microbiome modulators', incorporating proprietary microbial strain(s) and novel oligosaccharides (or combinations of both) that can help prevent and manage human diseases. OPTI is aiming to do this via the non-pharmaceutical route, avoiding lengthy and expensive clinical trials and the associated regulatory burden.

**However, it is critical that OPTI is able to establish, through the technology and (required) clinical studies that the health benefits are tangible ones**, since much stricter rules on promotion and advertising are blunting food manufacturer campaigns to derive product differentiation. Proving the health claims puts a company in a position to underpin its advertising - and put some sizzle into the marketing sausage. Without this evidence the regulators can effectively reduce one's advertising to generic words and heavily discount any product ROI.

It is important to understand the recent regulatory changes in this market segment. Since 2012 food companies in the EU have had to comply with a list of approved (and rejected) claims for foods and supplements. All claims require evidence, which has to be independently reviewed by the European Food Safety Authority (EFSA) and approved by the EU.

This has meant that many foods, beverages and supplements actually ended up losing their ability to be marketed for specific nutritional uses and their associated health benefits (a long list includes cranberry juice for urinary infections, glucosamine for joint mobility, taurine for athletic performance).

To date, all claims for probiotics have been rejected by EFSA. More specifically, we understand that the UK's Advertising Standards Authority is not allowing products to be described as 'probiotics' any longer (to earn the label, which implies an automatic health benefit, controlled randomised clinical trials will be necessary). Prebiotics are in a similar position. We understand that all dossier submissions for health claims allied to probiotic/prebiotic/synbiotic products have (so far) drawn a blank with the EFSA's health claims panel (its so-called NDA panel).

Further changes to the EU regulations are in the works, but encouragingly the NDA appear more willing to work with companies to help design appropriate studies to get potential health claims approved.

**In summary**, this means that to create the best possible sales environment for these types of products and for future 'microbiome modulator' products, the 'hard' (specific) claims for health benefits require suitably well-planned research studies that provide a body of evidence in favour of the claim (for example, a probiotic that is claimed to reduce cholesterol levels).

## Board, Senior Management and SAB

**Chairman** - David Evans. David has a significant track record in taking companies through the IPO process, achieving successful investor exits by trade sales and creating shareholder value (including BBI, sold to Inverness Medical and Sirigen Group, sold to Becton Dickinson). David is currently Chairman of Epistem, EKF Diagnostics, Scancell, Omega Diagnostics, Premaitha Health and Venn Life Sciences.

**CEO** - Stephen O'Hara. Founder of OPTI, with a track record of identifying product opportunities and building growth companies. Led the sale of Acolyte Biomedica to 3M. Previous experience at 3M (Director of Microbiology).

**Commercial Director** - James Laird. Previous experience working in commercial and corporate roles for some of the world's leading food companies including Birds Eye (Unilever), Walkers Snacks (Pepsico), and Premier Foods.

**NED** - Dr Mark Wyatt. Extensive experience in developing new product concepts/spin-out companies based on novel science and emerging trends for investment opportunities.

**NED** - Adam Reynolds. Background in corporate finance and boardmember and shareholder of a number of AIM companies (EKF Diagnostics, Orogen Gold, ViaLogy). Current Chairman of Autoclenz.

**NED** - Dr Gareth Barker. VP EMEA, Human Nutrition & Health for DSM Nutritional Products. Extensive experience and knowledge of global markets within the health and nutrition sector.

**Director, R&D** - Dr Sofia Kolida. Previous experience at Reading University in the Dept of Food and Nutritional Sciences. Dr Kolida is widely published in the microbiome field, and her key area of expertise is using novel sugars to modulate the human microbiome to prevent, manage, and treat disease, and their application as food ingredients.

**SAB - Prof Glenn Gibson** is a Professor of Food Microbial Sciences at the University of Reading. He leads a multi-disciplinary research programme on the human microbiome and its impact on human health and disease. He was responsible for the initiation of the prebiotic concept for gut flora management through diet. Prof Gibson is a former President and a founder member of the International Scientific Association for Probiotics and Prebiotics (ISAPP).

**SAB - Prof Bob Rastall** is a Professor of Biotechnology and Head of Department of Food & Nutritional Sciences at the University of Reading. His research focuses on functional food ingredients, in particular the understanding of how the structure of non-digestible sugars affects their function, and in using this knowledge to generate novel therapeutic candidates. One of his main research activities is the development of biotechnological manufacturing methods for novel oligosaccharides for application as functional food ingredients and as potential pharmaceutical agents.

**SAB - Professor Jason Halford** is head of the Department of Experimental Psychology at Liverpool University and Chair of the UK Association for the Study of Obesity. He is a chartered Health Psychologist and currently the Convenor of the Liverpool Obesity Research Network. His early research focused on the role of serotonin in satiety and the use of feeding behaviour to screen anti-obesity drugs, but more recently has moved into the areas of drug-induced weight gain, the effects of nutrients and fibre on appetite and hormone release, the effects of stress on eating behaviour and on lean/obese differences in the expression of appetite. Prof Halford is the co-ordinator of the 8 million Euro EU Framework seven Satiety Innovation SATIN project ([www.satin-satiety.eu](http://www.satin-satiety.eu)).

**SAB - Professor Patrice Cani** is a research associate at the FRS-FNRS (Fonds de la Recherche Scientifique) in Belgium. He is also group leader in the Metabolism & Nutrition research group (MNUT) at UCL (Université Catholique de Louvain) in Brussels and co-director of the European Associated Laboratory "NeuroMicrobiota" Lab (INSERM/UCL) in Toulouse, France. Since 2010, he has been a regular visiting Professor at Imperial College London in bio molecular medicine. Professor Cani's main interests lie in the investigation of the role of the gut microbiome in the development of metabolic disorders such as obesity, type 2 diabetes and low grade inflammation.

**SAB - Professor Jens Walter** is an Associate Professor at the Campus Alberta Innovation Programme (CAIP) and Chair for Nutrition, Microbes and Gastrointestinal Health at the University of Alberta in Canada. Professor Walter's research is primarily concerned with the microbial ecology of the human and animal gastrointestinal tract and the metabolic and immunological interactions between the microbiome and its host in relation to health.

**SAB - Steven Morrison** has over 23 years' experience in small, medium and large companies directing global drug development programmes and as part of international project teams. Most recently, Steven was Chief Operating Officer (COO) of Provexis which develops and licences foods for specific medical purposes as well as, functional foods & dietary supplements. While there he was responsible for research & development, regulatory affairs, intellectual property and manufacturing. Previous roles include Global Project Leader at Ipsen Ltd., Director at Shire Pharmaceutical Development and Research Associate at American Cyanamid (Lederle Laboratories).

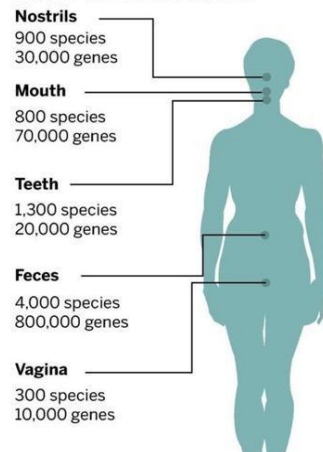
## Glossary

(adapted from *The American College of Gastroenterology*)

**Microbiota (or microbiome)** is the community of micro-organisms that typically inhabits a body organ or part. The human body contains more than 10 times as many microbial cells as human cells. These microorganisms may be commensals (different species living together, in which one derives some benefit while the other is unaffected), symbiotic (having an interdependent relationship), and pathogenic (disease-producing). **Human beings have clusters of bacteria in different parts of the body, such as the skin, the mouth, the vagina, and the intestine.**

Organisms typically found in the human microbiome may generally be categorized as bacteria (the majority), members of domain Archaea, yeasts, single-celled eukaryotes, and various helminth parasites and viruses (including bacteriophages - depend on bacterial hosts).

### MICROBIAL SPECIES AND GENES IN BODILY AREAS



Source: *Human Microbiome Project*

**Gut microbiota** (term nowadays preferred to 'flora' or microflora) refers to the community of micro-organisms that live in the gastrointestinal (gut) tract. Gut microbiota consists of tens of trillions of microorganisms, including at least 1,000 different species of known bacteria with millions of genes. Microbiota can, in total, weigh up to 4.5 pounds. The relationship between gut microbiota and humans is believed to be a mutualistic relationship (the metabolic activities performed by these bacteria resemble those of an organ). Gut microbiota **perform a host of useful functions**, such as fermenting unused energy substrates, helping train the immune system, preventing growth of harmful (pathogenic) bacteria, regulating the development of the gut, producing vitamins for the host (such as biotin and vitamin K), amongst others. However, in certain conditions, **some species are thought to be capable of causing disease** by producing infection or increasing cancer risk for the host.

**Bacteria** constitute a large domain of (prokaryotic) microorganisms. Bacteria are present in most of the Earth's habitats. Bacteria also live in symbiotic and parasitic relationships with plants and animals. The majority of bacteria in the human body are harmless or beneficial, the largest number being in the gut microbiota. However, some species of bacteria are pathogenic and cause infectious diseases.

**Archaea** are a kingdom of single-celled (prokaryotic) microorganisms that are often mutualists (two different species that exist in a mutually beneficial relationship ) or commensals (a species that benefits from other organisms without affecting them). Archaea can be found in extreme habitats - an example is the methanogens that inhabit the human gut and the ruminant gut, where their vast numbers aid digestion.

**Bacterial classification.** All organisms are classified in a hierarchical manner. For bacteria, we begin with the broadest division, the phylum, and work all the way down through sub-phylum, class, order, family, **genus, and species, to strain (most common categories)**. The bacteria included in the phylum **Firmicutes** make up the largest portion of the gut microbiome, and are involved in energy resorption and obesity. **Bacteroides** are a phylum of bacteria commonly found in the human intestine, where they have a symbiotic host-bacterial relationship with humans, helping break down food and producing valuable nutrients and energy (for the host). Bacteroides are increasingly regarded as specialists for the degradation of proteins and carbohydrates. Bacteroides can, however, be pathogenic when introduced to parts of the body other than the gastrointestinal area. They can cause or exacerbate abscesses and other infections.

**Bifidobacterium** is a genus of Gram-positive bacteria that are **a type of lactic acid bacteria**. They are widespread inhabitants of the gastrointestinal tract, vagina, and mouth of mammals, including humans. Bifidobacteria are one of the major genera of bacteria that make up the bacterial population in the colon. **Bifidobacteria can also be used as probiotics.**

**Dysbiosis** (also called dysbacteriosis) refers to 'microbial imbalance' resulting from a change in the number or types of bacteria on or inside the body. This imbalance is most noticeable in the digestive tract or on the skin, but can also occur on any exposed surface or mucous membrane. Researchers speculate that it may play a role in illnesses such as inflammatory bowel disease, chronic fatigue syndrome, obesity, or certain cancers (see Figure - *Diseases influenced by gut microbial metabolism*). One cause of dysbiosis is antibiotic exposure.

**Fungus** refers to any member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds, as well as mushrooms. These organisms are classified as a kingdom, Fungi, which are separate from plants, animals, protists and bacteria.

**Lactobacillus** is a genus of Gram-positive facultative anaerobic or microaerophilic (require low levels of oxygen to grow, but are poisoned by high levels of oxygen) rod-shaped bacteria. A member of the lactic acid bacteria group, which converts lactose and other sugars to lactic acid. In humans, they are present in the vagina and the gastrointestinal tract, where they make up a small portion of the gut microbiota.

Lactobacilli are also in some fermented foods like yogurt and in dietary supplements. Lactobacilli are used for treating and preventing diarrhoea, including infectious types such as rotaviral diarrhoea in children and traveler's diarrhoea. They are also used to prevent and treat diarrhoea associated with using antibiotics.

**Probiotics** are live micro-organisms similar to those found naturally in the human body. They may be beneficial to health when administered in sufficient quantities. Probiotics help maintain the balance of microbiota in the intestines. They are commonly consumed as part of fermented food (e.g. yogurt, dietary supplements). The largest group of probiotic bacteria in the intestine is made up of lactic acid bacteria, of which *Lactobacillus acidophilus* (found in live culture yoghurt) is the best known. Some yeasts may also act as probiotics.

**Prebiotics** are non-digestible food components that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth and/or activity of advantageous bacteria (e.g., Bifidobacteria and Lactobacilli) that colonize the large intestine. **As a functional food component, prebiotics, like probiotics, are conceptually intermediate between foods and drugs.**

'**Microbiome modulators**' are compounds which can selectively enhance the growth of specific microbial species in the human microbiome. Selectively enhancing specific microbial species creates the capability to modify the human microbiome specific to health needs (See also - *Probiotics, Prebiotics*).

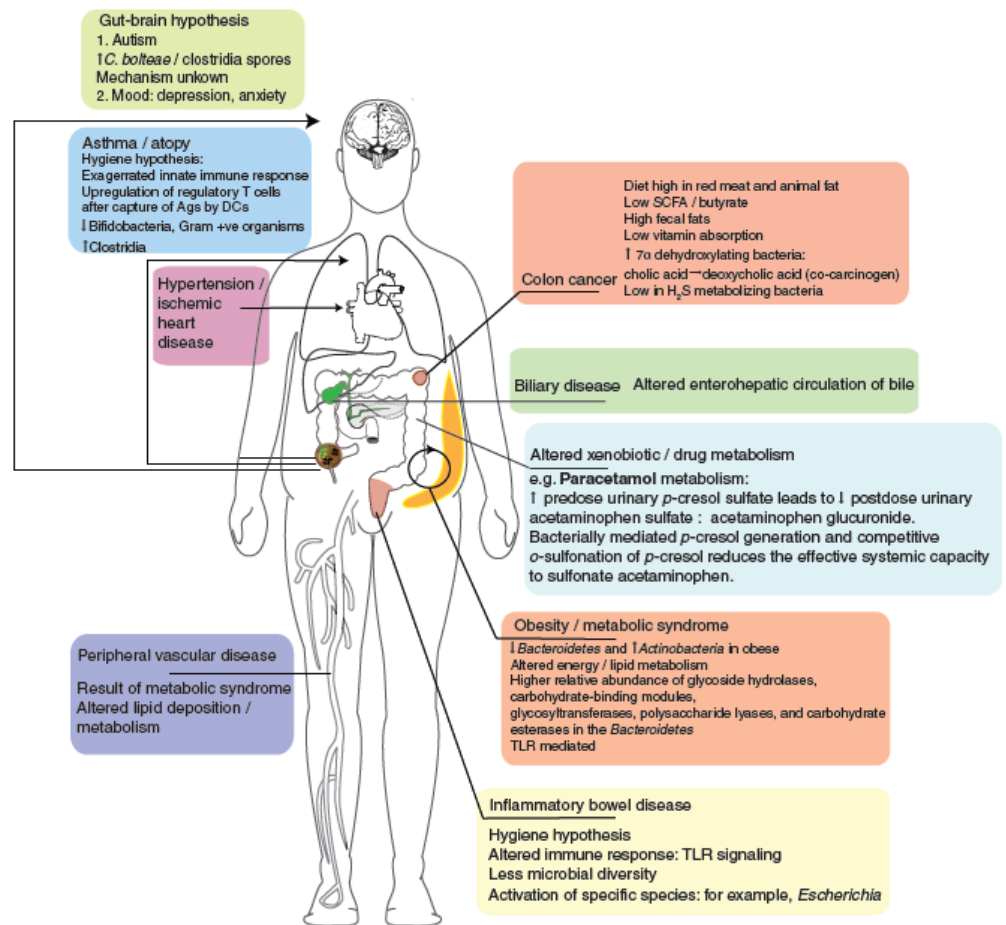
**Clostridium difficile** (or *C. difficile*, aka 'C diff') is a bacterium that can cause symptoms ranging from diarrhoea to life-threatening inflammation of the colon. *Clostridium difficile* most commonly affects older adults in hospitals or in long-term care facilities and typically occurs after use of antibiotic medications. Antibiotic treatment often suppresses and can destroy the normal gut microbiota (particularly broad-spectrum antibiotics) - as a result the gut can be colonised by *C. difficile*. These bacteria release toxins, causing bloating and diarrhoea with abdominal pain, which may become severe (*C diff* infections are becoming more common and difficult to treat).

**Faecal transplant**, also known as "faecal microbiota transplant" or "stool transplant," is the process of transplantation of faecal bacteria from a healthy individual into a recipient. The aim is to re-establish healthy microbiota in the gut of the recipient. It has been proven to be a highly effective treatment for patients suffering from *C. difficile*. It involves restoration of the intestinal microbiome by introducing healthy bacterial flora through infusion of stool obtained from a healthy human donor.

**Human Microbiome Project (HMP)** (<https://commonfund.nih.gov/hmp/index>) The first phase of HMP characterized the composition and diversity of microbial communities, which inhabit major mucosal surfaces of the human body, including nasal passages, oral cavities, skin, gastrointestinal tract, and urogenital tract, and evaluated the genetic metabolic potential of these communities.

More recently, HMP is focused on creating the first integrated dataset of biological properties from both the microbiome and host from studies of microbiome-associated diseases, utilising metagenomic techniques (culture-independent genome sequencing and other related techniques).

### Diseases influenced by gut microbial metabolism



**Source:** Kinross et al. *Genome Medicine* 2011 **3**:14 (The variety of systemic diseases that are directly influenced by gut microbial metabolism and its influence on other mammalian pathways, such as the innate immune system, are shown. Specifically highlighted are the metabolic pathways involved in drug metabolism and obesity that are directly influenced by the gut microbial content. Ags, antigens; *C. boyleae*, *Clostridium boyleae*; DCs; dendritic cells; SCFA, short-chain fatty acid; TLR, Toll-like receptor).



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