7 March 2017

The Gut Microbiome

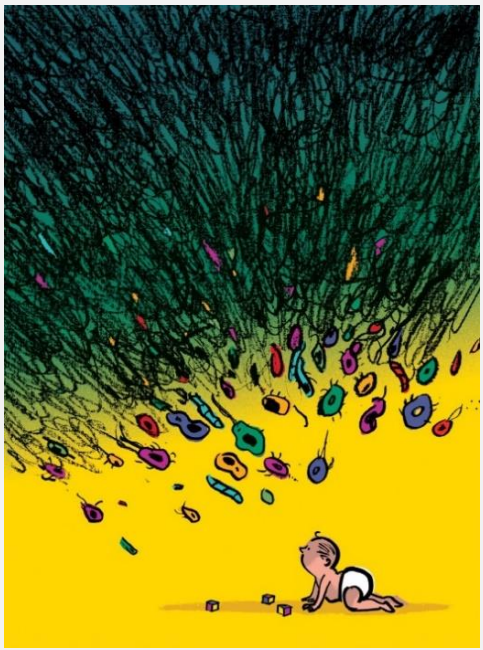
Biotechnology

The new age of live-biotherapeutics

The awareness of the microbiome and its relationship to human health and disease has grown in recent years and now attracts much interest from the global pharmaceutical and biotechnology industry. The human microbiome is comprised of over 100 trillion microbes which live in a number of different niches on or in the body, but mostly in the gut. The realisation that these microbes are more than mere 'passengers' has come about as alterations in the numeric and functional diversity of the microbial community have been characterised in far greater detail than ever before. Driven by technology innovations the growing depth of microbiome knowledge has enabled the dissection of associations between specific microbial communities and certain disease states. In this context, the potential to exploit the microbiome to treat or prevent the development of diseases is now being more fully explored by scientists and clinicians in both academia and industry. Strategies to therapeutically exploit the gut microbiome include standard small-molecule drug approaches, selective dietary supplements and bacteria themselves as therapeutic agents, so called live biotherapeutic products.

Global interest in the microbiome – the microbiome has been the subject of intense interest by both academia and the pharmaceutical industry in recent years. This is evidenced by the rapidly growing number of scientific publications in the field from 247 papers in 2005 to over 5,000 papers in 2015, and almost 400 clinical studies in the USA. Further recognition of the clinical potential of the field has come in the form of government sponsored initiatives such as the Human Microbiome Project launched in 2008 for which the US National Institutes of Health (NIH) invested $115m in 2012. This NIH backing raised the institutional and scientific credibility of the field and triggered greater academic and industry efforts to recruit the best scientific talent and technology development. Significant licensing and co-development deals have followed to secure access and rights to the technologies and products of innovators and developers.

Commercial opportunities – the microbiome could have an impact on diverse diseases ranging from local conditions of the gut (e.g. Crohn's disease, ulcerative colitis) to systemic diseases including autoimmune and neurological disorders (e.g. multiple sclerosis, Parkinson's disease), cancer and respiratory ailments (e.g. asthma, COPD). These therapeutic areas are highly valued as pharmaceutical markets with many products reaching blockbuster sales levels. Targeting the functions of the gut microbiome represents a new strategy for therapeutic intervention and drug development. Indeed, efforts to develop microbiome-targeted drugs include everything from dietary factors and drugs to enhance or limit certain microbial activity to administering specific live bacteria themselves as the active therapeutic agents (live biotherapeutic products or LBPs). LBPs are attractive as product candidates because their derivation from commensal bacteria enables a shortening of development timelines as health regulators believe they are safe.



By the time a child crawls, he is blanketed by an enormous cloud of microorganisms.

Illustration by Nishant Choksi, From The New Yorker (Oct 22 issue, 2012)

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** Zeus Capital acts as NOMAD and Broker to this company*

Analyst:

Dr Gary Waanders +44 20 3829 5617
gary.waanders@zeuscapital.co.uk

Zeus Capital Contacts:

Dominic Wilson	+44 20 3829 5628
Hugh Kingsmill Moore	+44 20 3829 5622
John Goold	+44 20 3829 5601
Dominic King	+44 20 3829 5607
Ben Robertson	+44 20 3829 5625
Mike Cuthbert	+44 20 3829 5621
Victoria Ayton	+44 20 3829 5603
Mike Seabrook	+44 20 3829 5626
Alex Davies	+44 20 3829 5620
Ronayne O'Mahony	+44 20 3829 5624

Email: firstname.surname@zeuscapital.co.uk

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The Microbiome

All plant and animal life on earth evolved in the presence of an environment replete with bacteria and other simple microbial life forms. In this context, it should not be surprising that microbial life co-evolved to become an integral part of larger host organisms, often cooperating with and contributing to the health of the host. The most significant aggregations of microbes occur in areas where the larger hosts have the most intimate interactions with the environment such as on the exterior contact surfaces and in areas where the organisms extract energy and nutrition from the environment (e.g. along the digestive tract of animals or root systems of plants).

In 1988, JM Whipps et al[1] first used the term, microbiome, and described it as:-

A convenient ecological framework in which to examine biocontrol systems is that of the microbiome. … defined as a characteristic microbial community occupying a reasonably well defined habitat which has distinct physio-chemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity. (pg 176).

This broad description covers all microbiomes in all niches. A microbiome can include a range of micro-organisms from the simplest viruses to bacteria and fungi. The ability of scientists to now more fully characterise the diversity within a microbiome is one of the main drivers for the increase in microbiome research now being conducted. Until relatively recently, establishing a picture of the full diversity of the microbes within a community relied primarily on cultivation. However, the limitations of cultivation - less than 10% of microbes within a typical sample being amenable to culture - have been well-known for decades. The limitation of only being able to look at cultivation-amenable microbes meant that the complexity of a microbial community could not be accurately and fully determined.

Against this background, recent technological advances have enabled substantially more detailed knowledge to be obtained about complete microbial communities than was previously possible in a culture-independent manner. In fact, the technological advances driving the increased research effort include both whole genome sequencing approaches (metagenomics popular among clinical microbiologists looking for high-resolution information to improve understanding of bacterial pathogenesis) and methods to analyse the small subunit (16S) ribosomal RNA gene (community-scale approaches favoured by environmental microbiologists). The scientific cornerstones of these technologies combined with other approaches, such as transriptomics and metabolomics which further characterise the function and molecular products of the microbiome and its constituent strains, has seen an explosion of data which has given rise to a new level of understanding about how microbial communities influence the health and disease states of the hosts with which they associate.

In the following discussion, we restrict ourselves to the human microbiome which encompasses all the micro-organisms living in and on us, but more specifically to the gut microbiome, the largest and most diverse community of bacteria associated with humans. Indeed, it has been variously estimated that the bacterial community found within the human intestinal tract includes approximately 100 trillion or so microbes, weighs around 2 kg in adults (some have described it as another ‘organ’), and contains approximately 100 different bacterial genes for every human gene. More than 90% of the human gut microbiome is composed of four major phyla: Firmicutes (49-76%, mostly *Clostridium* XIV and IV groups), Bacteroidetes (16-23%), and to a much lesser extent, the Actinobacteria and Proteobacteria phyla.

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[1] JM Whipps, K Lewis, and RC Cooke. *Mycoparasitism and plant disease control* 161-87. In: Fungi in Biological Control Systems. Edited by NM Burge, Manchester University Press, 1988

There is growing evidence that the composition and function of the gut microbiome can have effects locally and at distant sites in the body elicited through a variety of soluble mediators including metabolites from the bacteria as well as immunological factors (both cellular and soluble). Published research suggests that the human microbiome is a fundamental component of human physiology, with an estimated one-third of circulating metabolites being a product of the gut microbiome. Changes in the microbiome can trigger changes in human cellular activities, resulting in disease or contributing to its progression.

A variety of functions have been attributed to the gut microbiome:

- Promote the development of a functional intestine
- Digest certain foods to provide nutrients necessary for growth and well-being
- Participate in the development and maintenance of a well-balanced immune system
- Modulate the synthesis and secretion of certain hormones, vitamins and others molecules
- Energy extraction from ingested food
- Assist host cells to produce an effective barrier against harmful pathogens in the intestine

Under selective pressures encountered throughout life the gut microbiome evolves in a dynamic process from the initial microbial communities with which the gut was first seeded in infancy. Selection is driven by diet, host genetics, and environmental exposures (including infections and the use of antibiotics). From the age of 3 years the human gut microbiome is largely established and stable, however, some factors can still affect its composition including diet changes and transient use of antibiotics.

After exposure to transient selective pressures the microbiome is often seen to recover its original composition. Nonetheless, lasting changes to the microbiome do occur resulting in dysregulation of the microbiome, ranging from aberrant functionality to reduced microbial diversity. These alterations could either directly or indirectly lead to disease development.

Given the close interactions between the host and the microbiome, alterations in the composition and function of the microbiome are often associated with immune dysregulation and inflammation (e.g. Crohn's disease or allergies), and changes in food metabolism with potential consequences on conditions such as obesity and diabetes. Chronic changes to the gut microbiome barrier function might also be associated with increased susceptibility to hospital acquired infections. It is also possible that long-term changes to the chemistry of the microbiome could lead to certain disturbances in the central nervous system including conditions such as depression and Parkinson's disease.

In the past two decades, the field of microbiome science has emerged following certain key technology developments which have allowed complex microbial communities to be more comprehensively characterised. Clearly, a number of scientific disciplines have had an important role to play in this emerging field including microbiology and immunology most obviously. But as the understanding of the relationship between the human host and the gut microbiome in health and disease states grows, the microbiome is drawing interest from a wider group of scientists and clinicians in fields such as oncology, neurology and psychology, metabolism and endocrinology, respiratory medicine, and others.

In the following text, we aim to provide a glimpse of the accumulating science around the gut microbiome in health and disease, and the opportunities this understanding is creating for the development of new therapeutic interventions in a wide range of diseases.

Gut microbiome in health & disease

The microbes associated with our bodies have long been suspected of conferring important functions to the human body, including playing a major role in our nutrition and susceptibility to disease. The virtual explosion of activity in the study of the human microbiome through high-profile projects such as the US NIH-initiated Human Microbiome Project and the international metaHIT initiatives, increasing the awareness of the microbiome in the biomedical research community. With this increased activity, has come a much more detailed understanding of the microbiome and its relationship to health and disease.

The gut microbiome and health

The commensal bacteria colonising the gut and making up the microbiome perform a number of functions through their normal life cycle which provide benefits to their human hosts and maintaining homeostasis. The relationship works both ways with the human host providing both nutrition and an environment for the bacteria to flourish.

We can think about the gut as a reactor which processes dietary inputs to generate energy and produce and extract nutrients for use around the body. The involvement of the microbiome is critical in this function, as a gut devoid of a viable community of commensal bacteria is not able to metabolise all the components of our diet (e.g. plant fibres) or produce all of the important bioactive molecules which we need to thrive. Metabolically, the microbiome plays a key role in the absorption of important minerals, the best studied example being iron absorption.

The microbiome is responsible for the production of a wide variety of vitamins that are used by other microbes as well as by our bodies. Some of these vitamins include: vitamin B12, vitamin B6, vitamin B5, vitamin B3, biotin, tetrahydrofolate, and vitamin K. Commensal gut bacteria, particularly *Clostridium sporogenes,* have been implicated in the transformation of indole to indole-3-propionic acid, a powerful neuroprotective antioxidant that protects human cell membranes from oxidative damage and, potentially, carcinogenesis.

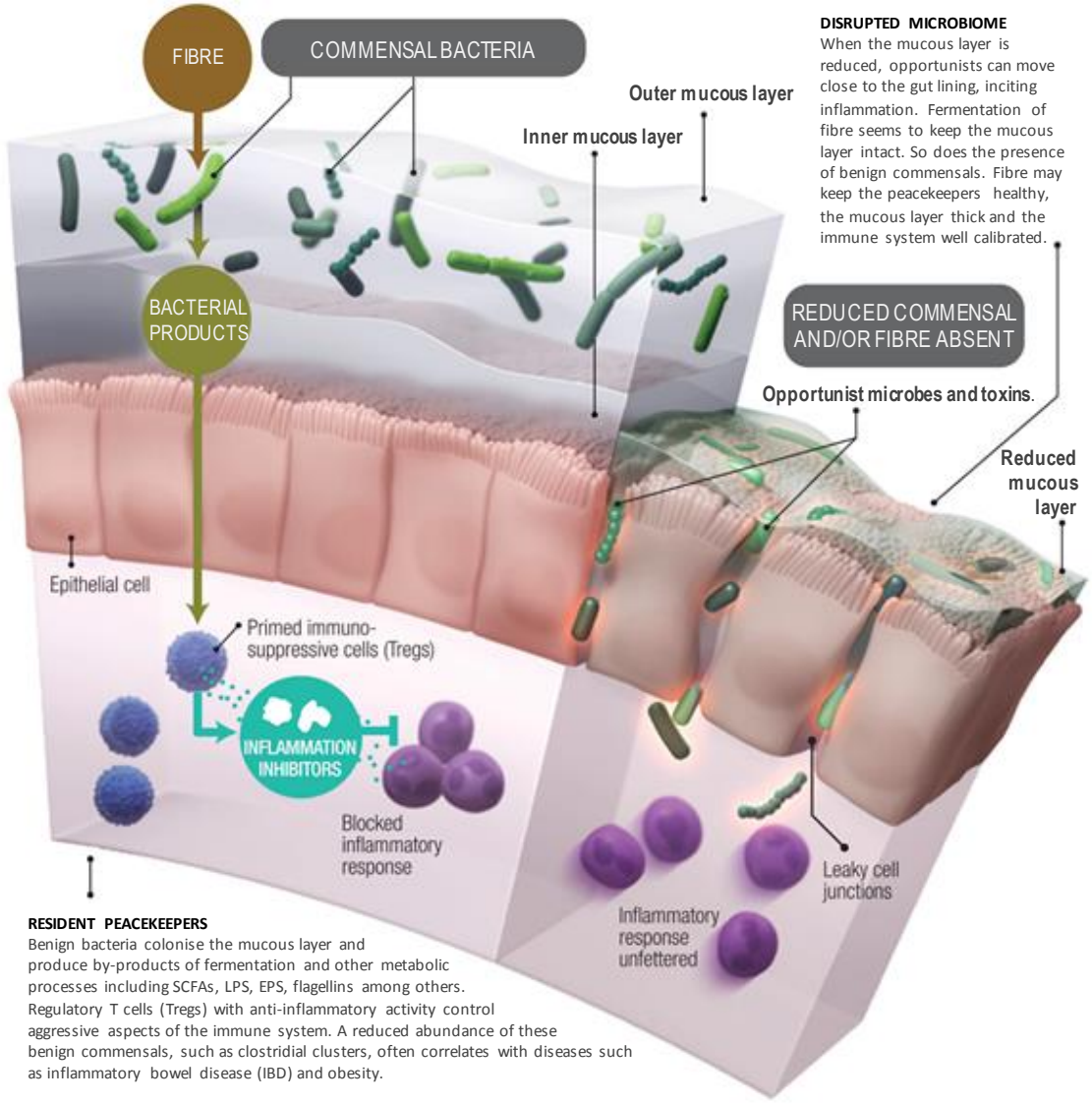
The microbiome is also important for the production of certain essential amino acids and even around 95% of the body's serotonin (a neurotransmitter which plays a central part in gut motor function and digestion, as well as in various cognitive and mood disorders). Additionally, bacteria impact fat and glucose utilisation as well as the lymphocyte response to intestinal injury.

Bacterial processing of dietary macronutrients results in the production of different metabolites, some of which are associated with clear beneficial effects. For example, short chain fatty acids (SCFAs) including acetate, butyrate and propionate are produced through fermentation of soluble fibre by many commensals including clostridial clusters (just one example is *Faecalibacterium prausnitzii*). Fermentable fibre supports the beneficial microbes which in turn promotes the health and barrier function of the mucous layer in the lumen of the gut and this reduces the likelihood of infection and systemic inflammation. Butyrate is also an important energy source for intestinal epithelium and increases production of mucin and antimicrobial peptides such as α-defensin. A model for how the bacterial community might act to help regulate the gut environment in health and inflammation is shown schematically in Exhibit 1.

The SCFAs and other bacterial products such as lipopolysaccharide (LPS, a cell wall component), EPS (exopolysaccharides, a secreted product), flagellins and small molecule metabolites all interact with cells of the immune system. Some induce regulatory T cells (Tregs) which have a predominantly anti-inflammatory activity.

While the SCFAs and other bacterial metabolic products are clearly able to influence the local environment of the gut, particularly around the luminal interface of the mucous layer, these products are also able to influence host physiology at more distant sites of the body, notably the immune system, the central nervous system (CNS) and the brain itself [2]. In addition to the direct actions of microbial metabolites on the CNS and brain, another mechanism through which the microbiome influences CNS and brain physiology is likely to involve immunological mediators including both CNS tissue-resident immune cells and soluble products such as cytokines (interleukins 4, 6, 10, and 17a, type-1 interferon, and others) and possibly (auto)antibodies.

Exhibit 1: Microbiome role in gut health and disease



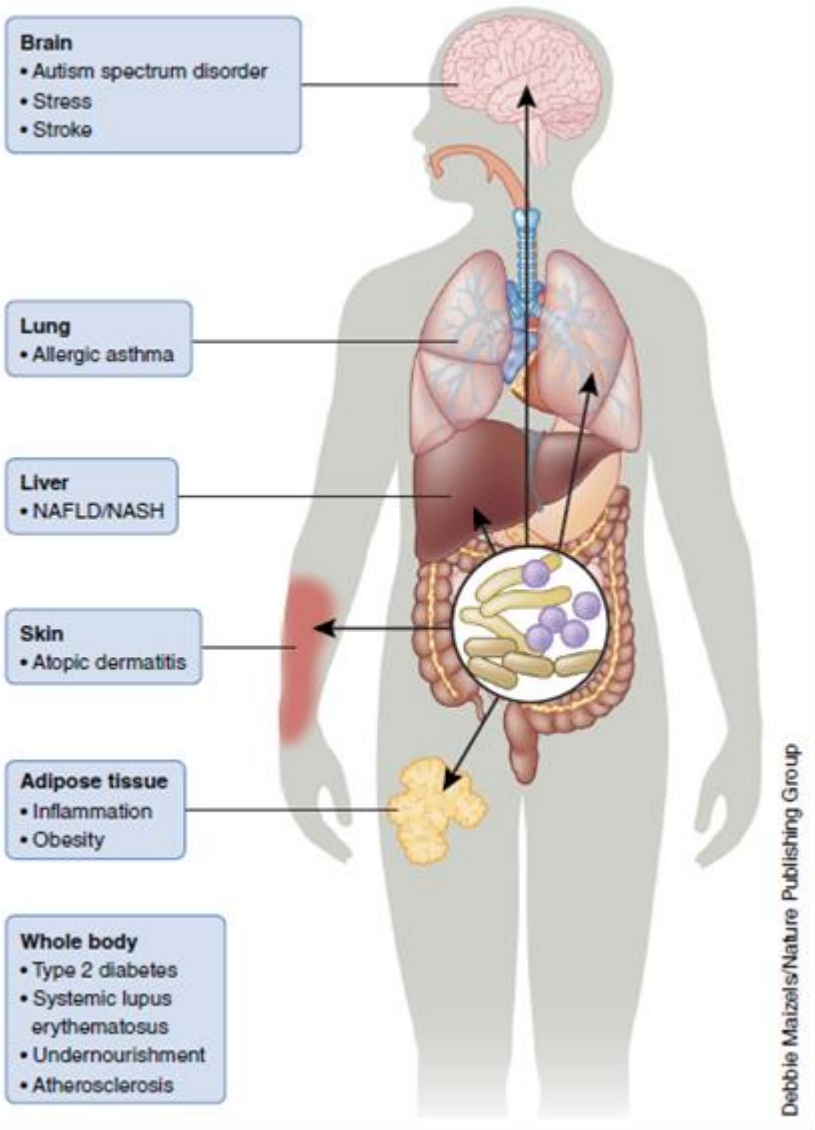
Source: Adapted from Bollrath and Powrie, 2013. Feed your Tregs more fiber. Science. 341; August 2. Illustration by AXS Biomedical Animation Studio.

[2] Fung *et al.*, 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience, 20:145-155,

The gut microbiome and disease

The gut microbiome plays an important role in maintaining homeostasis in the gut and at distant sites but any dysregulation of its functionality risks inducing a variety of acute and/or chronic disease states, depending on the nature and duration of such dysregulation. The microbiome contributes to host susceptibility to a variety of diseases, not only those restricted to the gastro-intestinal tract such as inflammatory bowel disease (IBD), but others including autoimmune, respiratory, cardiovascular, and immunological diseases, and neurological disorders, and cancer, among others[3]. Some of these are depicted schematically in Exhibit 2. Research is also showing that specific bacteria can restore functionality in certain diseases states.

Exhibit 2: Gut microbiome associated with various diseases



Source: Schroeder and Backhed, 2016. Signals from the gut microbiota to distant organs in physiology and disease. Nature Medicine 222:1079-1089 ; NAFLD – non-alcoholic fatty liver disease; NASH – non-alcoholic steatohepatitis..

[3] Robinson, C *et al*., 2010. From structure to function: the ecology of host-associated microbial communities. Microbiology and Molecular Biology Reviews. 74: 453-476.

Gastro-intestinal disease (IBD) and the gut microbiome

Inflammatory bowel disease (IBD) is characterised by chronic and relapsing inflammation of the mucosal surface of the gastrointestinal tract (and gut wall in severe cases) and includes two primary types – Crohn's disease (CD) and ulcerative colitis (UC). Both are considered to be autoimmune diseases with an unknown cause. Crohn's can be diagnosed anywhere along the digestive tract (from mouth to anus) while ulcerative colitis is restricted to the large intestine (colon). While genetic background is considered to be involved in the pathophysiology of IBD, given the identification of multiple susceptibility genes, genetic factors alone cannot explain the rapid increase in the incidence of IBD suggesting environmental factors also play a role. With the growing knowledge of the gut microbiome it has been hypothesised that IBD results from an abnormal interaction between the gut microbiome and the immune system.

This idea is supported by research with germ-free mice which do not develop a gut microbiome (and also have underdeveloped immune systems, brains, shrunken heart and lungs, and abnormalities in the large intestine). Work with these mice has demonstrated the transmission of IBD through the inoculation of the mice with the gut microbiomes of human patients with IBD but not the microbiomes of healthy donors. This research suggests an important role for the gut microbiome in IBD and has since been extended in human studies. From these it is clear that patients with IBD have an altered microbiome in comparison to the healthy population.

Recent work has characterised the alterations to the microbiome of newly diagnosed paediatric CD patients [4]. The study was interesting because microbial alterations in new-onset paediatric patients would more likely be causative and not affected by chronic inflammation or concomitant medications. This research identified different bacterial populations which correlate, either positively or negatively, with disease severity and notably included a relative decrease in butyrate-producing bacteria such as *Blautia*, Lachnospiraceae, *Roseburia, Eubacterium rectale, Ruminococcus, Clostridium* and *Faecalibacterium*.

In contrast, an increase in hydrogen sulphide (H_2S)-producing bacteria was identified including members of the order Bacteriodales, the families Enterobacteriaceae and Veillonellaceae, and the genera *Atopobium, Fusobacterium, Leptotrichia, Sutterella, Vibrio, Parabacteroides, Prevotella, Peptostreptococcus, Peptococcus* and *Streptococcus*. It is noteworthy that many of these (*Atopobium, Fusobacterium, Veillonella, Prevotella, Streptococcus and Leptotrichia*) are known to produce H_2S through the fermentation of sulphur-containing amino-acids.

Butyrate, and other SCFAs, are thought to be protective against inflammation while excess H_2S, which is normally detoxified through mitochondrial oxidation, may damage the intestinal barrier and contribute to T cell activation and inflammation. This work suggested that an imbalance in microbial butyrate/H_2S production might contribute to Crohn's disease pathology. 4D Pharma has seen similar effects in its Blautix programme treating irritable bowel syndrome (IBS).

Correcting the microbiome dysfunction associated with IBD and returning it to a benign (anti-inflammatory) state could be a lucrative opportunity for the right approach. In 2017, the global market for IBD treatments is estimated to be worth between $6.2bn and $9.6bn (BCC Research and Visiongain, respectively), despite many of the products in the space being generic. The majority of products addressing the IBD market focus on directly suppressing immunological activity to dampen inflammation. While many of these treatments are effective for a while, they can also cause significant, therapy-limiting side effects. New efficacious treatments with stronger safety and tolerability profiles should be well received.

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[4] Mottawea *et al*., 2016. Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. Nat. Commun. 7: 13419.

Several attempts have been made to correct the problems of IBD using approaches targeting the microbiome of IBD patients. Indeed, while antibiotics may be among the environmental root causes of the problem which could ultimately lead to the development of IBD, they are also used with limited success in controlling the acute flares of disease. This is mainly through control of bacteria which are associated with the inflammation. However, these treatments are necessarily short-term and potential problems of tolerability and drug resistance limit efficacy.

More direct approaches to rebalancing the microbiome of IBD patients have had mixed results. Faecal microbial transplants (FMT) have been used for the treatment of various conditions including IBD. The first FMT for IBD (UC) was reported in the Lancet in 1989 and resulted in drug-free remission[5]. However, there have been mixed results in subsequent small clinical trials examining FMT in UC which is likely a result of small sample sizes, variation in methodology and selection of donor stool. Inevitably, as a commercially viable product option the FMT approach does not hold much promise, partially because of the mixed results, but more because most patients have high resistance to the concept of stool transplantation.

Gastro-intestinal disease - recurrent *C. difficile* infection

C. difficile infects the colon and produces toxins that cause inflammation and severe diarrhoea. It can also result in serious complications including bowel perforation, toxic megacolon and sepsis, and in the most severe cases it can be fatal. The use of broad spectrum antibiotics that cause widespread damage to the microbiome is thought to be a prime factor in allowing overgrowth of *C. difficile* bacteria.

The current standard treatments for *C. difficile* infection (CDI) are ironically, the antibiotics metronidazole and vancomycin. While effective at reducing levels of *C. difficile*, these antibiotics also cause significant damage to the gut microbiome leaving patients vulnerable to disease recurrence, the primary clinical issue. Each additional episode of the disease is associated with greater disease severity and higher mortality rates. It has been reported that approximately 25% of CDI patients suffer a second episode of the infection, and the risk of further recurrence rises to 65% after a patient suffers a second episode of CDI. Recurrent disease is associated with an increased burden on the healthcare system.

Recurrent CDI represents a significant problem in North America and Europe with estimates of up to 700,000 cases of CDI per year in the US alone leading to 14,000 deaths per annum. The US Center for Disease Control and Prevention has designated *C. difficile* as one of three pathogens that poses an immediate public health threat and requires urgent and aggressive action. In the US, it is estimated that CDI-related acute care costs total $4.8 billion per year.

Interestingly, the treatment of recurrent CDI using a 'non-standard' approach focusing on the restoration of a healthy microbiome has been particularly successful. In one randomised clinical study, comparing FMT to antibiotics for the treatment of recurrent CDI, the results were strikingly good. Of the 16 patients receiving FMT, 13 (81%) experienced resolution of *C.difficile* associated diarrhoea, whereas only 4 of 13 (31%) patients receiving antibiotics achieved a similar resolution.

However, as with IBD, we believe only a minority of patients i.e. those most severely affected by recurrent CDI, will consent to undergo FMT due to the challenges of the concept. In this regard, FMT is unlikely to ever become a standard therapy for recurrent CDI.

Alternative approaches by a number of companies are looking to develop specific treatments for recurrent CDI, using either small molecule drugs (e.g. Summit Therapeutics is developing

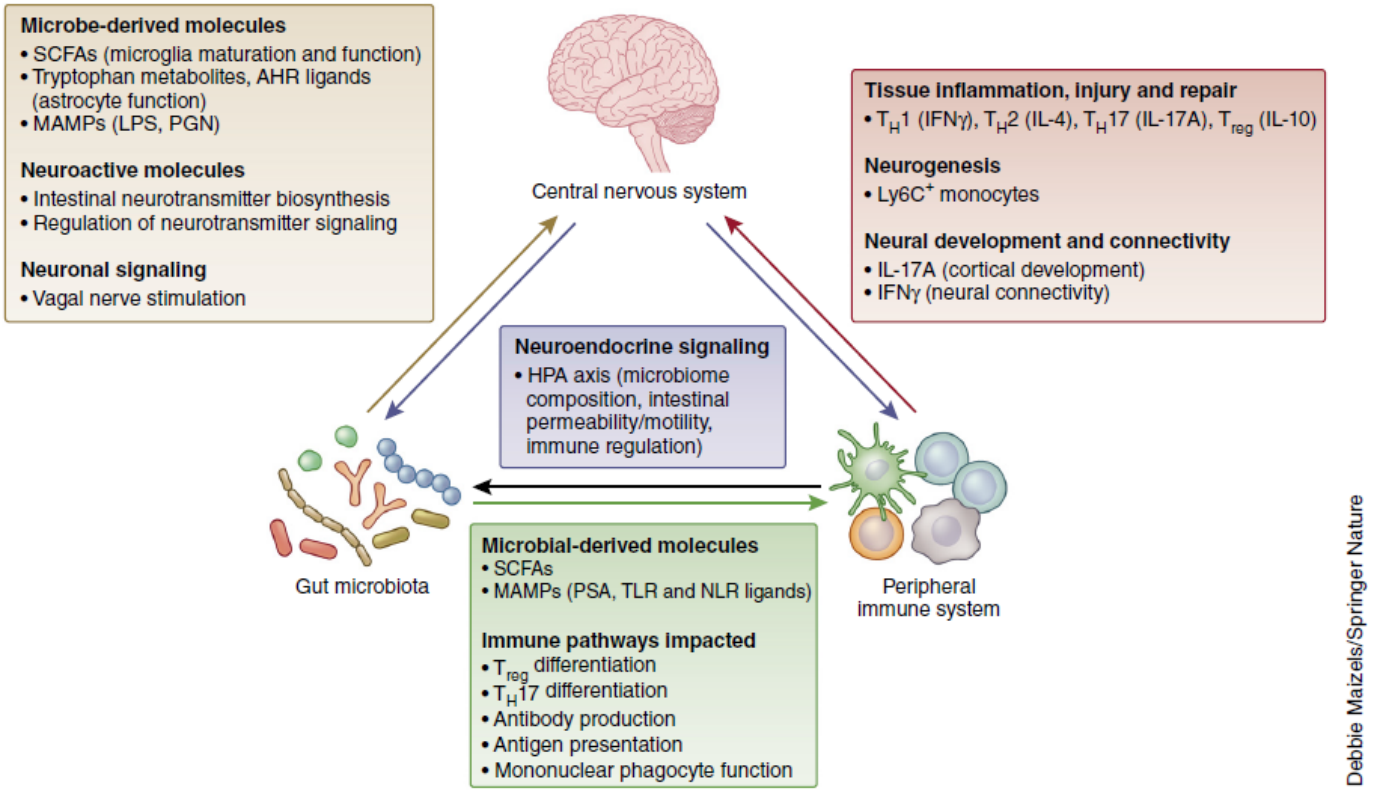
[5] Bennet JD and Brinkman M. 1989. Treatment of ulcerative colitis by implantation of normal colonic flora. Lancet. Jan 21; 1(8630): 164

ridinilazole, an antibiotic with greater selectivity for *C. difficile*) or attempting to restore the balance to the microbiome using commensal clostridial bacterial mixtures (e.g. Seres Therapeutics). Summit's ridinilazole has achieved good results in phase II trials and is now in planning ahead of phase III clinical development. However, unsuccessful phase II results for Seres Therapeutics' SER-109, due apparently to misdiagnosis and suboptimal dosing in some patients, suggest revisions to the product and its development plans before this product moves forward in this indication.

Central nervous system disorders impacted by the gut microbiome

The concept that there is communication between the gut and the brain goes back over 100 years. The neural link between the two, the vagus nerve, helps the brain control the digestive process and signalling feedback from the gut can influence both perception and behaviour, hinting at why CNS disorders are so often accompanied by digestive problems. While the gut microbiome interacts both directly with the CNS and via soluble factors, an additional layer of complexity comes from the crosstalk of both the microbiome and CNS with cells of the immune system and their mediators, as illustrated below (Exhibit 3).

Exhibit 3: The gut-brain-immune axis



Source: from[2] Fung et al., 2017. Nature Neuroscience 20:145-155. Interactions between the intestinal microbiota, peripheral immune system and CNS are essential for the maintenance of host health. Recognition of microbial derived products such as microbe-associated molecular patterns (MAMPs) and metabolic by-products of microbes (short chain fatty acids, SCFAs) activates distinct immune pathways throughout the host. The microbiota and immune system can independently or cooperatively regulate neurophysiology. Therefore, a prevailing theme in studies aimed at understanding the microbiota–gut–brain axis involves the role of intestinal microbes in modulating CNS function through CNS-resident and peripheral immune pathways. Biochemical changes in the CNS can also lead to altered microbial composition and immune cell responses through the HPA axis. Altogether, these findings suggest that the microbiota, immune system and CNS communicate bidirectionally. Future studies investigating the functional outcomes of these bidirectional interactions will inform the development of new therapeutic strategies for the treatment of neurological disorders. IFNg, interferon gamma; LPS, lipopolysaccharide; NLR, Nod-like receptor; PGN, peptidoglycan; TLR, Toll-like receptor.

The microbiome is known to be a key regulator of stress and neuroinflammation and its ability to control brain development, function, and behaviour has been demonstrated in model systems. For example, germ-free mice (absent gut microbiome and having underdeveloped brains and CNS cells) appear to be more hyperactive and 'daring' than normal mice and tend to be much more prone to stress and anxiety. These behavioural traits can be re-normalised by colonising the gut of the germ-free mice with a particular strain of bacteria (*Bifidobacterium infantis*).

It is intriguing that the function and disorders of the CNS can be so affected by the presence or absence of particular bacteria in the gut as described in Exhibit 4. While these studies highlight the changes in the relative abundance of different bacteria, the field has continued to move towards the more interesting molecular mechanisms (biochemical and immunological) which explain the changes in functional capacity of the gut microbiome and its interactions with the immune system and the CNS, thus generating better targets for rational product development.

Exhibit 4: Alterations in the gut microbiota in neurological and psychiatric disorders

Pathology type	Condition	Associated microbial changes
Autoimmune disease	Multiple sclerosis	**Increased:** *Methanobrevibacter*, *Akkermansia,* Desulfovibroneceae, *Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia*, *Dorea, Streptococcus*, *Eggerthella, Ruminococcus* **Decreased:** *Butyricimonas,* Lachnospiraceae, Ruminococcaceae, *Parabacteroides*, *Adlercreutzia*, *Prevotella,* Clostridia clusters XIVa and IV, Bacteroidetes, *Faecalibacterium,* Bacteroidaceae
Neurodegenerative disorders	Parkinson's disease	**Increased:** *Blautia*, *Coprococcus*, *Roseburia*, Proteobacteria, **Decreased:** *Faecalibacterium*, Prevotellaceae
	Alzheimer's disease	Associated with bacterial and viral infection
Injury	Spinal cord injury (SCI)	SCI with motor neuron bowel syndrome: **Decreased:** *Pseudobutyrivibrio, Dialister, Megamonas, Roseburia* SCI with neuropathic bladder: **Increased:** *Klebsiella, Escherichia, Enterococcus* **Decreased:** *Lactobacillus, Corynebacterium, Staphylococcus, Streptococcus, Prevotella, Veillonella*
Neuropsychiatric conditions	Major depressive disorder	**Increased:** Actinomycineae, Coriobacterineae, Lactobacillaceae, Streptococcaceae, Clostridiales, Eubacteriaceae, Lachnospiraceae, Ruminococcaceae, Erysipelotrichaceae Enterobacteriaceae, *Alistipes*, Acidaminococcaceae, Fusobacteriaceae, Porphyromonadaceae, Rikenellaceae **Decreased:** *Bifidobacterium, Lactobacillus*, Bacteroidaceae, Rikenellaceae, Lachnospiraceae, Acidaminococcaceae, Sutterellaceae, Erysipelotrichaceae, Prevotellaceae, Ruminococcaceae and Veillonellaceae *Faecalibacterium* negatively correlated with depressive symptoms
	Anxiety disorder	Probiotic administration of *B. longum* and *Lactobacillus helveticus* **decreased** anxiety Probiotic administration of *Lactobacillus casei, Lactobacillus acidophilus, L. rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, B. longum, Streptococcus thermophilus and Bifidobacterium lactis* **decreased** anxiety
Autism		**Increased:** *Lactobacillus, Desulfovibrio, Clostridium (clusters I and II), Bacteroides, Porphyromonas, Prevotella, Pseudomonas, Aeromonas,* Enterobacteriaceae*, Sutterella, Lachnospiraceae, Ruminococcaceae, Bacteroidetes, Proteobacterium* **Decreased:** *Bacteroides / Firmicutes* (ratio), *Enterococcus, Lactobacillus, Streptococcus, Lactococcus, Staphylococcus,* Bifidobacteria, *Prevotella, Coprococcus, Veillonellaceae, Bifidobacterium, Actinobacterium*

Source: Summarised from[2] Fung et al., 2017. Nature Neuroscience 20:145-155.

Clearly, the size of the commercial opportunities for products addressing some of these conditions will be huge. For example, the global multiple sclerosis market is estimated to reach $20bn by 2020 (GlobalData) while the market for Parkinson's disease drugs could climb to $3.5bn by 2020 (Visiongain), and Alzheimer's disease, based on no new product approvals, might grow to $6.2bn in 2020 (BCC Research). Given the demographics and incidence of Alzheimer's disease, we believe that any successfully developed product would revolutionise the market.

Autoimmune diseases and the role of the gut microbiome

The role of the gut microbiome in autoimmunity has garnered significant attention, and evidence suggests a particular role for intestinal microbiome alterations in autoimmune disease development. If not the cause of these autoimmune diseases, the microbiome might influence their exacerbation or remission. In this respect, the microbiome could represent a new target for therapeutic intervention to control the activity of autoimmune diseases. In fact, certain microbiome by-products, particularly SCFAs, are known to be excellent down-regulators of inflammation involving adaptive immunity. However, SCFAs can potentially also increase inflammation mediated by innate immune cells[6].

We have highlighted above the activity of the gut microbiome in IBD (encompassing both CD and UC) and in Exhibit 4 listed some of the reported perturbations in the gut microbiome in cases of multiple sclerosis. Each of these diseases is considered to be autoimmune given the central involvement of the immune system in disease development and progression.

Other autoimmune diseases where the gut microbiome is implicated with a potential role include type 1 diabetes and rheumatoid arthritis (RA). Type 1 diabetes is a disease involving autoimmune destruction of pancreatic beta cells in genetically predisposed individuals. In type 1 diabetes, the gut microbiome has been characterised with lower overall diversity and the sharp expansion of distinct groups of bacteria including *Ruminococcus gnavus* and *Streptococcus infantarius*, both known 'pathobionts' (commensal bacteria that have the capacity to behave as pathogens). Conversely, a number of species which are commonly depleted in inflammatory states, such as *Coprococcus eutactus* and *Dialister invisus*, were found to be completely absent in cases of type 1 diabetes[7].

The increasing incidence of autoimmune diseases may be explained by changes in early microbial exposure, leading to altered immune maturation. Early-onset autoimmune diseases are common in Finland and Estonia but are less prevalent in Russia. Bacteroides species are found at low abundance in the gut microbiomes of Russian but dominate in Finnish and Estonian infants[8]. The lipopolysaccharide (LPS) exposures in Russian infants is primarily from *Escherichia coli*, which is a potent innate immune activator. Bacteroides LPS is structurally distinct from *E. coli* LPS and inhibits innate immune signalling and endotoxin tolerance. The incidence of autoimmune diabetes in the non-obese diabetic mouse model is reduced by *E. coli* LPS but not *B. dorei* LPS. These results support a role for early colonization of the microbiome by defined bacteria in order to ensure appropriate immune education and avoid downstream development of autoimmune disorders.

Rheumatoid arthritis (RA), a more common autoimmune disease than type 1 diabetes, has been associated with a relative over-abundance of *Prevotella copri* bacteria and other bacteria such

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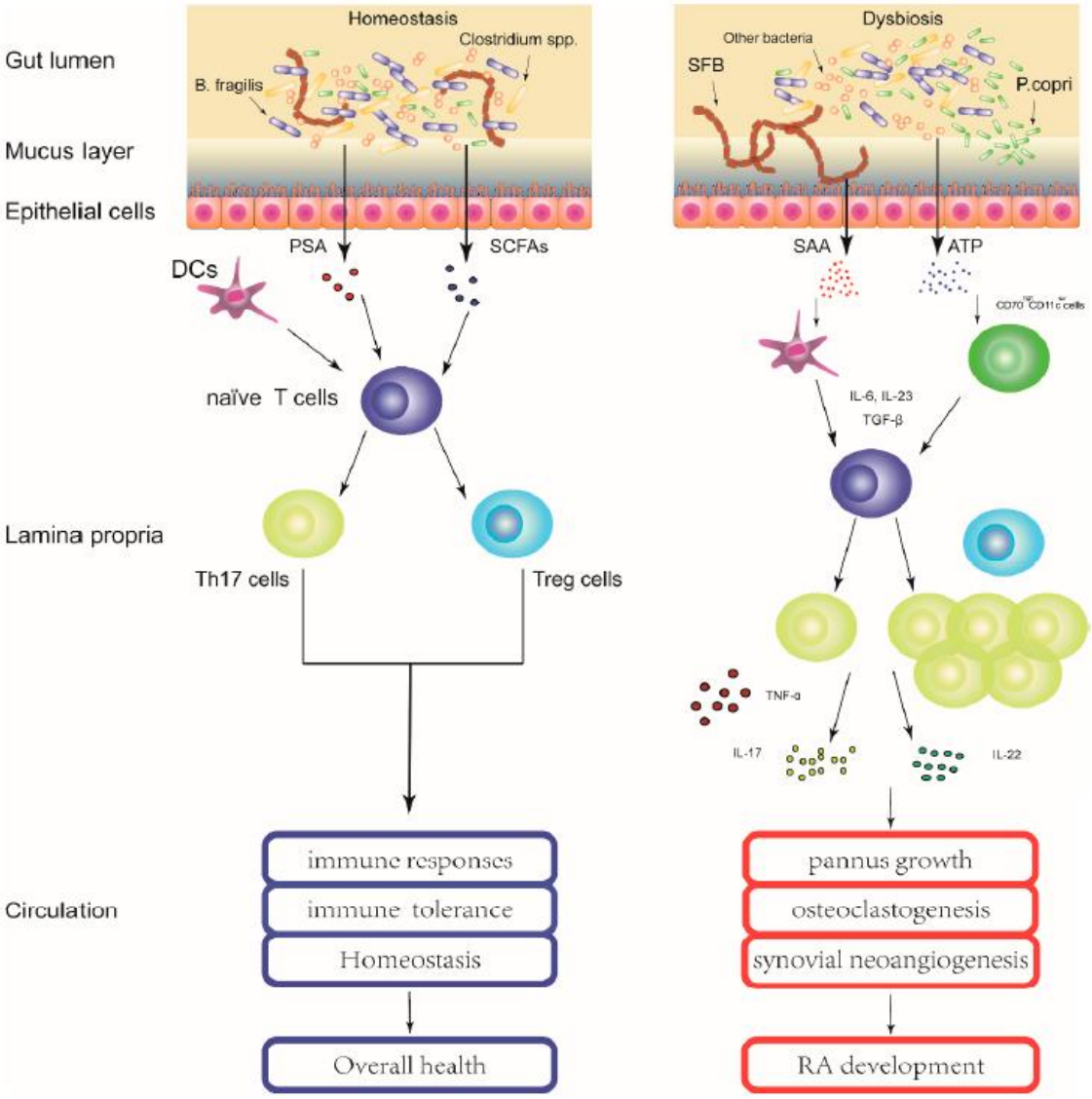
[6] Mizuno M *et al*., 2017. The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. PLoS ONE 12(2): e0173032. doi:10.1371/ journal.pone.0173032.

[7] Kostic AD *et al*., 2015. The Dynamics of the Human Infant Gut Microbiome in Development and in Progression towards Type 1 Diabetes. Cell Host Microbe 17: 260-273.

[8] Vatanen T *et al*., 2016. Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. Cell. 165: 842 – 853.

as *Lactobacillus salivarius* (this being present in even greater amounts in individuals with very active RA) while *Haemophilus spp.* were depleted in RA patients [9]. Abnormalities detected in the gut microbiomes of patients were partially resolved after successful RA treatment. The mechanisms through which these alterations in the microbiome might act include molecular mimicry of human antigens related to RA and functional differences in the redox environment, transport and metabolism of iron, sulphur, zinc and arginine. These results suggest potential pathways for targeting the composition of the microbiome to improve treatment responses. A model for the development of RA in susceptible individuals is illustrated in Exhibit 5.

Exhibit 5: Contribution of gut microbiome to pathogenesis of RA



Source: Wu et al., 2016. Int. J. Mol. Sci., 17, 431; doi:10.3390/ijms17030431; The healthy gut microbiome (in homeostasis) maintains integrity of the intestinal epithelial cell layer with multiple symbiotic microbes. In genetically susceptible individuals, environmental factors can influence the gut microbiome causing changes in the types and abundance of microbiome (dysbiosis). The dysbiosis, in association with genetic factors, may disrupt the innate and adaptive immune system and contribute to the development of RA via multiple molecular mechanisms. PSA, polysaccharide A; SCFAs, short-chain fatty acids; SAA, serum amyloid A; ATP, adenosine-triphosphate; DCs, dendritic cells; IL, Interleukin; TGF-β, Transforming growth factor-beta; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells.

[9] Zhang Z *et al.*, 2015. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nature Med. 21: 895 – 905.

As shown in Exhibit 5, a potentially important mechanism of action of the microbiome relates to the induction and activity of Treg cells. These cells, which play a critical role in the maintenance of immune homeostasis, have been explored by several groups working on the microbiome but were first raised to prominence by Atarashi et al., in 2011[10]. The group demonstrated that certain bacterial clusters from the gut microbiome, particularly Clostridia clusters IV, XIVa and XXVIII, were strongly associated with the abundance and induction of Treg cell activity in the colonic mucosa. These Clostridia clusters lack prominent toxins and virulence factors. Their presence correlates with resistance to inflammation in the gut (colitis) and lower IgE responses (allergy) due to enhanced activity of Tregs.

The global market for RA drugs is forecast to be worth over $21bn in 2020. RA is a chronic, progressive, and currently incurable autoimmune disease primarily of the joints and affects almost 5 million people in the major developed pharmaceutical markets. It is costly to healthcare services with many patients failing to benefit fully from drug-based therapies while experiencing significant side effects of immunosuppressive regimens. This leads to substantial economic and quality of life impairments for patients (BCC Research).

Respiratory diseases affected by the gut microbiome

Aberrant immune system activity in the airways can have dramatic impacts on quality of life as evident in patients suffering from allergic airway disease. Asthma is estimated to affect approximately 300 million people globally and incidence is increasing. The market for drug therapies is estimated to grow to $22bn by 2020 (Technavio).

Consistent with the Hygiene hypothesis (i.e. that modern life has too little environmental bacterial exposure such that our immune systems become hypersensitive), the early life exposures that correlate with lower probabilities of subsequently developing allergic disease and asthma are generally those that increase an individual's exposure to microbes such as living in contact with farm animals or pet dogs, or having multiple older siblings. The suggestion of the existence of a 'gut-lung axis' acknowledges these real-world observations and others in model systems that exposing the gut microbiome to certain environmental influences in early life can affect an individual's likelihood of developing allergic airway disease later in life[11,12]. A key observation is that in the early life exposures the gastrointestinal tract is involved in reducing the risks of allergy sensitisation. This is supported by observed differences in the stool microbiomes from infants who subsequently develop allergies – these microbiomes having relatively fewer Lactobacilli, Bacteroidetes, and Bifidobacteria and more coliform bacteria, Clostridia, and Enterococci.

Interestingly, while direct ingestion of a single bacteria species (*Lactobacillus johnsonii*) is able to subsequently reduce the risks of allergic disease development in later life[11], it is also possible to replicate this effect by consuming a high-fibre diet. In a model system, this improved the ratio of gut Firmicutes to Bacteroidetes and increased circulating SCFA levels which led to reduced airway T helper type 2 (TH2) function and protected against allergic airway disease[13]. Similarly, gastrointestinal exposure to PSA, a capsular polysaccharide derived from a commensal

[10] K Honda group research: Atarashi K *et al*., 2011. Induction of Colonic Regulatory T Cells by Indigenous Clostridium Species. Science. 331: 337-341 and Atarashi K *et al*., 2013. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 232: doi:10.1038/nature12331

[11] Fujimura KE et al., 2014. House dust exposure mediates gut microbiome Lactobacillus enrichment and airway immune defense against allergens and virus infection. PNAS. 111: 805-810

[12] Huang YJ and Boushey HA. 2015. The microbiome in asthma. J. Allergy Clin. Immunol. 135: 25-30.

[13] Trompette A et al., 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nature Med. 20: 159-166

bacterium (*B. fragilis*), reduced asthma susceptibility in different experimental models via the induction in the gut of IL-10 producing, anti-inflammatory T cells [14].

The airways of subjects receiving appropriate gut exposures to certain beneficial bacteria or their products, are protected from the development of allergic asthma. This protection is mediated by the migration of certain T cells from the gut to the lungs where their anti-inflammatory activity can be demonstrated by reductions in inflammatory cell infiltrates (neutrophils and dendritic cells but not eosinophils) and TH2 cytokines (IL-4, IL-5, and IL-13).

Importantly, these beneficial effects at sites in the lungs resulted from gut microbiome exposures suggesting that targeted manipulation of the gut microbiome, either with single bacterial species or bacterial products, represents a viable strategy for the allergen-independent prevention or management of allergic asthma.

The gut microbiome, cancer and immuno-oncology

Accumulating evidence demonstrates that the gut microbiome and abnormal function therein can influence the development and progression of tumours as well as the response of tumours to chemotherapy. It is evident that many factors which damage the microbiome also favour carcinogenesis. For example, intra-abdominal infections and the frequent use of antibiotics have both been linked to an increased incidence of colorectal cancer[15].

Chronic inflammation is strongly associated with carcinogenesis in many tissues including the colon and liver. A number of by-products of the gut microbiome, such as H_2S or the virulence factor FadA (produced by *Fusobacterium nucleatum*) sustain a pro-inflammatory microenvironment around the epithelial cells lining the intestine and thus mediate oncogenic effects. Indeed, *F. nucleatum* appears to play a role in colorectal carcinogenesis through suppression of the hosts' immune response to tumour.

The presence of bacteria at sites of inflammation could promote cancer development through the secretion of substances that cause DNA damage e.g. reactive oxygen species (from *Enterococcus faecalis*), or the enterotoxin of *Bacteroides fragilis* which activates the oncogene *c-MYC*. These microbial by-products, or other as yet unidentified factors, not only act locally but may influence oncogenesis and tumour progression systemically a have been observed for some extra-intestinal cancers including breast and hepatocellular carcinomas.

Microbiome damage caused by a range of different triggers (pathogenic challenge, genetic factors, environmental factors, and others) can potentially promote oncogenesis through multiple mechanisms including chronic inflammation, metabolic alterations, immunological defects, infectious diseases, and haematopoietic dysfunction[16].

Certain bacterial products such as SCFAs have been demonstrated to suppress tumorigenesis. With this in mind targeted microbiome interventions might be used for either cancer prevention or during cancer therapy as an adjuvant regimen to increase the efficacy (and possibly concomitantly reduce toxicity) of existing treatments.

Interestingly, scientists working in the field of immuno-oncology have found that at least one approved checkpoint inhibitor (anti-CTLA4 or Yervoy, ipilimumab) depends on distinct

[14] Johnson JL et al., 2014. Bacterial capsular polysaccharide prevents the onset of asthma through T-cell activation. Glycobiology. 25: 368-375

[15] Wang JL et al., 2014. Infection, antibiotic therapy and risk of colorectal cancer: A nationwide nested case-control study in patients with Type 2 diabetes mellitus. Int. J. Cancer. 135:956-967

[16] Zitvogel et al., 2015. Cancer and the gut microbiota: an unexpected link. Sci. Transl. Med. 7: 271ps1

Bacteroides species for its efficacy[17]. T cell responses specific for *B. thetaiotaomicron* or *B. fragilis* were associated with the efficacy of CTLA-4 blockade. In the absence of these bacteria CTLA-4 blockade did not work. Another study published in the same issue of Science, revealed a similar deficit in the microbiome, this time in *Bifidobacterium*, resulted in suboptimal efficacy of a different checkpoint inhibitor, an anti-PD-L1 monoclonal, in controlling tumour growth[18]. In the latter case, the effect appeared to have been localised to the level of activity of dendritic cells (innate immune cells involved in antigen presentation) being increased in animals in which the gut microbiome contained *Bifidobacterium*.

These studies demonstrate a key role for the gut microbiome in the immunostimulatory effects of checkpoint blockade and raise the possibility that other members of the microbiome could have similar effects in other cancer therapeutic settings. Manipulating the microbiome of cancer patients being treated with checkpoint inhibitors could strongly enhance the efficacy of these agents, particularly in patients where key microbiome functionality has been destroyed.

Indeed, through pharmacodynamic mechanisms the efficacy and tolerability of some conventional chemotherapeutic drugs can be directly modulated by the gut microbiome[16]. As an example, the orally administered drug, irinotecan, often associated with dose-limiting diarrhoea due to local gut bacteria reactivating the drug. This problem can be controlled by a Chinese herbal medicine (PHY906). Through the action of a local gut bacterial enzyme (β-glucuronidase), PHY906 is processed to become stimulatory for intestinal progenitor cells which promotes the rapid repair of the irinotecan-damage to the gut wall, thus limiting diarrhoea. This treatment promises to enable greater doses of irinotecan to be used thus widening the therapeutic window of the drug and potentially improving cancer responses.

According to Quintiles IMS, the oncology drug market is estimated to grow to $150bn in 2020 from $107bn in 2015 with growth driven primarily by innovation. In cancer treatment, it is clear that there is still substantial unmet medical need for more effective and well tolerated products. As evidenced by the clinical interest in and commercial successes of recent breakthrough products in the Checkpoint Inhibitor class of biologic products, there is significant appetite in the world of oncology for safer, more efficacious products.

[17] Vetizou M *et al*., 2015. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 350: 1079-1084.

[18] Sivan A *et al*., 2015. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy. Science. 350: 1084-1089

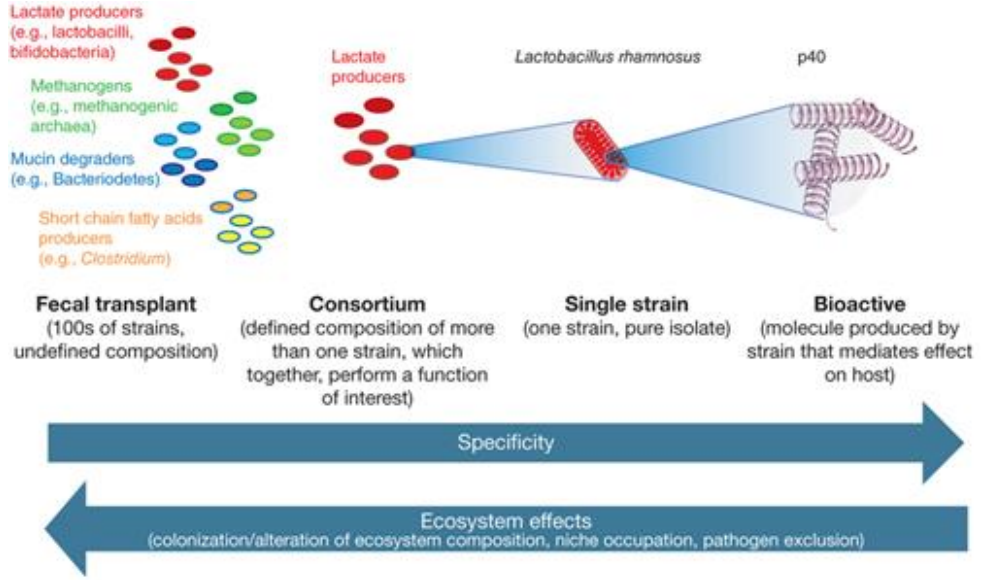
Development of LBPs

The ultimate progression into medical practice of the use of live biotherapeutic products (LBPs) based on the rapidly expanding knowledge of the gut microbiome in health and disease represents a novel route to product development for the biopharmaceutical industry. As with all new drug development, the drivers of drug candidate selection, choice of therapeutic indication, and therapeutic modality include both rational scientific and clinical foundations and the promise of improving upon current standards of care on efficacy and/or safety grounds.

As discussed above, the gut microbiome science base has grown dramatically in recent years thanks to innovations in research technologies allowing for well-informed drug development.

As shown in Exhibit 6, there are many microbiome-derived product categories being pursued by biotech companies, ranging from ecosystem-level interventions on the left to single-target approaches on the right (single target being either single strain LBPs or a single molecule drugs).

Exhibit 6: Medicines from the microbiome



Source: from Olle, B. 2013 Nature Biotechnology 31: 309-315; 'Lactate producer' is used here as a functional attribute descriptive of a community. Species belonging to the 'lactate producers' community (e.g., L. rhamnosus) may also belong to other communities. A community may be described by a metabolic function (e.g., lactate production) or by any other functional attribute (e.g., regulatory T-cell induction or vitamin K production). p40 is a bioactive, soluble protein expressed by L. rhamnosus, which mediates intestinal epithelial homeostasis

For LBPs based on the gut microbiome, the scientific rationale for choosing to target a particular therapeutic indication and product candidate can now be more rigorously tested against an established knowledge base. A good starting point for these new product development programmes is evidence of microbiome dysfunction. Additionally, it is critical to show credible evidence that the bacteria underlying the LBP elicits a measurable and desired functional response in the host. A vital component of any LBP development program should be a robust R&D platform, such as 4D Pharma's MicroRx platform, to functionally identify and test clinically important bacterial strains with the ability to induce desired therapeutic responses.

The development of products derived from the human gut microbiome poses some unique scientific, translational and regulatory challenges relative to standard molecular drugs. Indeed, LBP's form a regulated new class of medicines and in the USA these would be regulated by the FDA's Center for Biologics Evaluation and Research (CBER) division. In June 2016 the FDA

released an updated Guidance for Industry document entitled: Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. Like other therapeutic classes, there are well defined guidelines on how live biotherapeutics should be characterised prior to beginning testing in clinical trials. This includes definitions and examples of accepted assays for identity, purity, potency and stability.

The FDA guidance defines an LBP as:

"*…a biological product that:*

1) contains live organisms, such as bacteria;

2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and

3) is not a vaccine.

For the purposes of this document, LBPs are not filterable viruses, oncolytic bacteria, or products intended as gene therapy agents and, as a general matter, are not administered by injection. An example of an LBP, for the purposes of this document, would be one or more strains of lactobacilli administered orally to treat patients with ulcerative colitis, or administered vaginally to prevent bacterial vaginosis.

A recombinant LBP is a live biotherapeutic product composed of microorganisms that have been genetically modified through the purposeful addition, deletion, or modification of genetic material. A recombinant LBP which is subject to this guidance is likely to raise additional considerations and thus would require additional information to be submitted in an IND. Potential sponsors of an IND for a recombinant LBP are encouraged to contact FDA to obtain additional guidance prior to submission of their IND."

A key feature for all the non-genetically modified LBPs being developed is that their ultimate origin as commensals from the gut of healthy donors potentially enables a more rapid entry into clinical trials on the basis that drug regulatory authorities are prepared to assume the products will be safe. This would minimise the need for extensive preclinical toxicity testing which is both time consuming and costly. Nonetheless, according to the FDA Guidelines (June 2016), the agency still requires the submission of "*…adequate information about pharmacological and toxicological studies of the LBP in laboratory animals, or in vitro, to support a proposed clinical trial evaluating the investigational LBP (21 CFR 312.23(a)(8)).*" It goes on to add: "*…we encourage you to consult the applicable CBER review division, preferably in a pre-IND meeting, regarding the extent and type of non-clinical data necessary to support the proposed clinical investigation…*".

We expect that for LBP's to obtain regulatory approvals, sponsors will still need to satisfy the regulators that individual products meet the prevailing regulatory standards for clinical safety and efficacy as agreed with the authority and as demonstrated through pre-defined, appropriately controlled clinical trials. Depending on the product and indication (Orphan or not), LBP's may need to be tested across all phases of clinical development (from phase I to III) and could also be subject to requirements for post-approval studies. Sponsors will also need to satisfy the regulators that the individual product is reproducibly and reliably manufactured according to the appropriate CMC standards.

We expect significant advantages in manufacturing due to the greater control over processes where LBPs are based on only single commensal strains (e.g. 4D Pharma). In such cases, manufacturing reproducibly and consistently at scale must, logically, be less complicated compared to products where multiple strains are combined for the finished product. We believe that meeting CMC standards for regulatory reviews for single strain LBPs will be much easier to demonstrate.

Biopharma industry interest

As with most fields, academic microbiome research preceded interest in the field from small biotech companies which in turn came before the larger players in the global pharmaceutical industry. While Nestlé and other food and nutrition companies have been collaborating in the field and independently exploring the science for many years, the global biopharmaceutical industry only began to show significant appetite for the field in 2010.

To date, the most significant deals in the gut microbiome LBP space have been struck between J&J and Vedanta, Nestlé Health and Seres Therapeutics, Allergan and Assembly Biosciences, and AbbVie and Synlogic (although no financials were disclosed for this deal).

- J&J and Vedanta Biosciences – in January 2015, J&J in-licensed rights to develop VE202 for up to $339m (including an upfront payment of $98m with development and commercial milestones totalling $241m) plus tiered royalties. VE202 is being developed for the treatment of IBD including both Crohn's disease and ulcerative colitis.
- Nestlé Health and Seres Therapeutics – In January 2015, Nestlé Health Science invested $65m in the Series D financing round for Seres Therapeutics. One year later in January 2016, Nestlé Health signed a licensing deal for the worldwide rights (excluding the USA and Canada) to four Seres LBP candidates (SER-109, SER-262, SER-287, SER-301). The deal included a $120m upfront payment to Seres who will also be eligible to receive development and approval milestone payments totalling up to $660 million, and tiered single to double-digit royalties. The full potential value of the up-front payment, milestones and royalties payable by Nestlé Health Science is over $1.9 billion, assuming all products receive regulatory approval and significant revenue targets are met. Seres Therapeutics will be responsible for all development costs associated with Phase I and Phase II for all four candidates as well as for Phase III for SER-109. Nestlé Health Science will participate with 33% in the development costs associated with Phase III for three candidates (SER-262; SER-287, SER-301).
- Allergan and Assembly Biosciences – in January 2017, Allergan paid an upfront fee of $50m to enter into a research, development, collaboration and license agreement for the exclusive worldwide rights to Assembly's microbiome gastrointestinal (GI) development programs including preclinical compounds ABI-M201 (UC) and ABI-M301 (CD), as well as two additional programmes to be identified by Assembly for IBS; with Diarrhoea (IBS-d), with Constipation (IBS-c) or Mixed (IBS-m). Additionally, Assembly will be entitled to receive undisclosed success-based development and commercial milestone payments, and will be eligible to receive tiered royalties based on net sales. The partners will generally share development costs through proof-of-concept (POC) studies, and Allergan will assume all post-POC development costs.
- AbbVie and Synlogic – In February 2016, AbbVie signed a multi-year global R&D collaboration focused on developing novel synthetic biotic medicines (recombinant LBPs) for the treatment of IBD, with special emphasis on CD and UC. No financial details were disclosed

LBP corporate landscape

The demonstrations in academic reports many years ago, showing that faecal microbial transplantation (FMT) from healthy donors could address certain diseases of the gastrointestinal tract inspired a recent rush of new companies developing LBPs. In this section, we look at a number of companies following on from the observations made in the earlier FMT work and developing LBPs focusing on the gut microbiome.

We have not included a number of other companies which are also addressing the gut microbiome as they are using conventional small-molecule drug approaches (e.g. Enterome in France and Second Genome in the USA). Similarly, a few other companies are developing LBPs but these are addressing the skin microbiome and a variety of topical applications of their LBPs (e.g. AOBiome and Xycrobe Therapeutics).

Exhibit 7: 4D Pharma

4D Pharma	Description
Year established	2013; LSE: DDDD - IPO in 2014, current mkt cap £400m, cash and equivalents estimated £70m 31/12/2016
Location	Leeds, UK
Investors	Institutional investors (Woodford Investment Management, Invesco Asset management, Lansdowne Partners, and others) and management
Funds invested	Since IPO £102.75m.
Science base	MicroRx for rationally selecting specific and desired functional traits of bacteria from proprietary library of over 4,000 individual strains; MicroDx for stratifying and monitoring patient microbiomes; Process development and GMP manufacturing
Area of focus	Gastrointestinal (Irritable Bowel Syndrome IBS, paediatric Crohn's disease pCD and ulcerative colitis pUC), immune-oncology, respiratory (severe neutrophilic asthma, allergic asthma), autoimmune (multiple sclerosis MS, rheumatoid arthritis RA and others) and central nervous system (autism, anxiety/depression)
Key LBP differentiation	All single strain, orally delivered proprietary LBPs with profound functional effects in diseases identified using MicroRx
Lead Product	Blautix for the treatment of IBS, completed phase I with demonstration of safety and tolerability, signals of efficacy (IBS symptom reduction) and mechanism of action (reduction in H_2S gas, increase and stabilise microbiome diversity)
Pipeline	Currently 15 LBP development programmes including 8 with named candidates (Blautix in IBS phase I clinical, Thetanix in pCD phase I clinical, Rosburix in pUC, MRx518 in solid tumours, MRx0004 in severe neutrophilic asthma, MRx0001 in allergic asthma, MRx0002 in MS, and MRx0006 in RA
Facilities	5 sites: Corporate HQ – Leeds (UK); R&D Laboratories – Aberdeen (UK), Cork (Ireland), INRA (France); Development and Manufacturing – Leon (Spain)

Source: publicly disclosed data, 4D Pharma.

Exhibit 8: Assembly Biosciences

Assembly Biosciences	Description
Year established	2014 through M&A between Ventrus Biosciences and Assembly Pharmaceuticals; NASDAQ: ASMB - current mkt cap $378m, cash and equivalents $55m as at 31/12/2016
Location	Carmel, IN, USA
Investors	Public markets
Funds invested	From 2014 (post M&A) total of $98m raised through public offerings
Science base	A GMP bacteria strain inventory (dozens of strains, vegetative and spore formers) isolated from highly screened source donors and identified by sequencing. A subset of these strains selected based on demonstrated correlations with health outcomes in individuals who have recovered from specific diseases, such as *C. difficile* infection. Process development and GMP manufacturing.
Area of focus	Infectious diseases: HBV (non-microbiome programmes) and recurrent *C. difficile* (microbiome programme). Inflammatory diseases – IBD (UC and CD) and IBS (IBS-c and IBS-d)
Key LBP differentiation	Gemicel® targeted delivery of LBPs to defined regions of gut based on pH
Lead Product	Assembly's first microbiome therapeutic, AB-M101, is designed to cure recurrent CDI using its orally-administered Gemicel® capsule to deliver systematically-selected cGMP-manufactured live bacteria strains to the regions of the lower GI tract where CDI pathogens reside.
Pipeline	Microbiome: ABI-M101 for recurrent *C. difficile* (entering clinical phase I), ABI-M201 and ABI-M301 for UC and CD (pre-clin), IBS programmes in discovery phase; HBV: ABI-H0731 in phase I clinical, 3 other earlier stage HBV programmes.
Facilities	3 sites: Corporate HQ – Carmel, IN (USA); R&D Labs – Bloomington, IN (USA), San Francisco, CA (USA)
Commercial partners	In January 2017, Allergan paid an upfront $50m to enter into a research, development, collaboration and license agreement for the worldwide rights to Assembly's microbiome gastrointestinal (GI) development programs including preclinical compounds ABI-M201 (UC) and ABI-M301 (CD), as well as two additional programmes to be identified by Assembly for IBS; with Diarrhoea (IBS-d), with Constipation (IBS-c) or Mixed (IBS-m)

Source: publicly disclosed data, Assembly Biosciences.

Exhibit 9: Evelo Biosciences

Evelo Biosciences	Description
Year established	2014
Location	Cambridge, MA, USA
Investors	Flagship Ventures
Funds invested	Total equity funding of $42m
Science base	Broad discovery, development and manufacturing platform with expertise in microbiology, immunology, pharmacology and computational biology. Focusing on immune system and microbiome interactions.
Area of focus	Cancer, autoimmune and inflammatory diseases
Key LBP differentiation	Specific bacterial strains to potently activate the immune system against tumours and down-regulate the immune system to treat autoimmune and inflammatory diseases. Identified several drug candidates for oral delivery.
Lead Product	Undisclosed
Pipeline	Aiming to get two programmes into phase I clinical trials in 2017; one each in immune-oncology and autoimmune/inflammatory field
Facilities	Corporate HQ and R&D Labs – Cambridge, MA, USA

Source: publicly disclosed data, Evelo Biosciences.

Exhibit 10: OxThera AB

OxThera AB	Description
Year established	2005
Location	Stockholm, Sweden
Investors	Life Science Partners (Netherlands), Ysios Capital (Spain), Sunstone Capital (Denmark), Kurma Partners and Idinvest Partners (France), Flerie Invest, Stiftelsen Industrifonden and Broduvudet (Sweden)
Funds invested	Total equity estimated at €82m including latest investment round of €32m (Nov 29, 2016)
Science base	Expertise in the field of oxalate metabolism
Area of focus	Treatment of Primary and Secondary hyperoxaluria (PH and SH)
Key LBP differentiation	Single bacterial strain; exclusively relies on oxalate as energy source; extremely efficacious oxalate metabolism
Lead Product	Oxabact®
Pipeline	Oxabact® entering phase III clinical development for PH (Orphan Drug designation in the USA and EU). Oxabact® is an orally delivered LBP comprised of capsules containing freeze-dried *Oxalobacter formigenes* targeted to be released in the lower part of the small intestine. Oxazyme® - oral recombinant oxalate decarboxylase to treat dietary hyperoxaluria and prevent calcium-oxalate kidney stones
Facilities	Stockholm, (Sweden)

Source: publicly disclosed data, OxThera AB.

Exhibit 11: Seres Therapeutics

Seres Therapeutics	Description
Year established	2010; NASDAQ: MCRB - IPO in 2015, current mkt cap $380m, cash and equivalents estimated $230m 31/12/2016
Location	Cambridge, MA, USA
Investors	Flagship VentureLabs®, Enso Ventures, Mayo Clinic, Alexandria Venture Investments, and several private investors
Funds invested	Series A-D totalled $133.5m; IPO raised $140m net.
Science base	Seres Microbiome Therapeutics™ platform - provides insight into the ecologies of disease and then identifies microbial compositions that can catalyse a shift to health; Ecobiotic® microbiome therapeutics – designed combinations of strains in spore form;
Area of focus	Infectious disease, inflammatory/immunology, and metabolic diseases
Key LBP differentiation	Combination of multiple bacterial strains in spore form
Lead Product	SER-109 for the prevention of recurrent Clostridium difficile infection. SER-109 is an investigational, Ecobiotic® drug, which contains a purified ecology of approximately 50 unique bacterial spore-forming anaerobic Firmicutes fractionated from rigorously screened stool donors. In phase II development, recently failed to meet predetermined endpoints; designated Breakthrough Therapy by FDA
Pipeline	SER-109 – a natural combination of spores from multiple Firmicutes in phase II for recurrent *C. difficile* infection; SER-262 – spores from a 'synthetic' (designed) Ecobiotic® combination of bacterial strains in phase I; SER-287 – a natural spore combination in phase I for the treatment of mild-to-moderate UC; SER-155 – in pre-clinical (for HSCT-GvHD + bactermia); SER-301 – designed Ecobiotic® in pre-clinical (for IBD)
Facilities	R&D laboratories (manufacturing?)
Commercial partners	Nestlé Health Science – invested $65m in Series D (Jan 6 2015); licensing deal for ex-USA/Canada rights to SER-109, SER-262, SER-287, SER-301 included $120m upfront payment (Jan 11, 2016).
Other	We understand a class action lawsuit has been filed focused on insider dealing in the months leading up to release of SER-109 phase II failure

Source: publicly disclosed data, Seres Therapeutics.

Exhibit 12: Synlogic

Synlogic	Description
Year established	2013
Location	Cambridge, MA, USA
Investors	Atlas Venture, NEA, Bill & Melinda Gates Foundation, Deerfield Management, OrbiMed
Funds invested	Total equity funding of $74m
Science base	Proprietary synthetic biology and microbiome platform
Area of focus	Rare metabolism deficiencies (Orphan indications) and IBD
Key LBP differentiation	Novel recombinant LBPs designed with synthetic programmable genetic circuits.
Lead Product	SYNB1020, a synthetic biotic (LBP), operating from the gut microbiome, designed to remove excess ammonia from the blood to treat urea cycle disorders (UCD).
Pipeline	Targeting getting SYNB1020 for UCD into phase I clinical development in H1 2017; unnamed programme targeting entry into phase I clinical development within 12 months for phenylketonuria; several earlier stage discovery programmes.
Facilities	Corporate HQ and R&D Labs – Cambridge, MA, USA
Commercial partners	AbbVie a multi-year global R&D collaboration focused on developing novel synthetic biotic medicines for the treatment of IBD, with special emphasis on CD and UC.

Source: publicly disclosed data, Synlogic.

Exhibit 13: Vedanta Biosciences

Vedanta Biosciences	Description
Year established	2010, by Puretech Health plc majority owner (LSE: PRTC - current PRTC mkt cap £283m)
Location	Cambridge, MA, USA
Investors	Puretech Health plc held 83.8% on fully diluted basis Dec 31, 2015. Subsequently, Rock Springs Capital, Invesco Asset Management and Health For Life Capital (Seventure) also invested in June 2016 in $50m round.
Funds invested	We believe Vedanta has received at least $150m through both equity investments and upfront licence fees
Science base	A collection of human-associated bacterial strains characterised according to immune system recognition and responses.
Area of focus	Inflammatory, autoimmune and infectious diseases
Key LBP differentiation	Bacterial consortia of defined strain combinations (cocktail of 17 strains in VE202)
Lead Product	VE202 for the treatment of IBD, pre-clinical, expected to enter phase I in H1 2017
Pipeline	VE202 – for IBD in late pre-clinical; VE303 – for an undisclosed infectious disease in late pre-clinical; VE404 and VE505 in preclinical development for undisclosed indications (possibly autoimmune and inflammatory diseases).
Facilities	Corporate HQ and R&D Labs – Cambridge, MA, (USA)
Commercial partners	In Jan 2015, J&J in-licensed rights to develop VE202 for up to $339m ($98m upfront payment with development and commercial milestones up to $241m) plus tiered royalties

Source: publicly disclosed data, Vedanta Biosciences and Puretech Health plc.

4D Pharma – functionality is key

Key milestones

Technology

Functional screening platform
MicroRx *identifies candidate LBPs by function and mechanism for diseases in & outside the gut such as cancer, multiple sclerosis, severe asthma, rheumatoid arthritis etc*

Functional monitoring platform
MicroDx *enables more precise assessments of the status of the functionality of the gut microbiome.*

Pipeline

Orphan product designations*:*
Thetanix *paediatric Crohn's disease*
Rosburix *paediatric ulcerative colitis*

Clinical pipeline growing

Positive results from phase I trial of ***Blautix*** *in irritable bowel syndrome*

Thetanix *in phase I clinical trial in paediatric Crohn's disease*

Two new candidates to enter clinical development this year:

MRx518 *– immune-oncology*

MRx0004 *– severe neutrophilic asthma*

Corporate

2014 – 4D Pharma IPO on AIM

Capital raised since IPO for investment in platform and products £100+m

Acquired The Microbiota Company (France)

Completed acquisition of GT Biologics

Acquired production assets of Instituto Biomar SA

4D Pharma (LSE: DDDD) is pioneering the development of LBP medicines based on its expert knowledge of the mechanisms through which the microbiome functions in health and disease. 4D Pharma's overriding emphasis for the candidate LBPs it selects using its MicroRx platform is on defining functional traits and mechanisms of action relevant to the diseases being addressed. This emphasis on function and mechanism differentiates the company and its products from all the other companies with interests in the microbiome. The company's microbiome platforms, MicroRx and MicroDx, have been built on robust science and have the potential to generate many novel products for the treatment of a wide variety of diseases (not just diseases of the gut). A number of its LBPs have been taken into clinical trials and demonstrated safety and early signs of efficacy. We believe 4D provides a scientifically credible opportunity for investors to gain exposure to the new wave of medicines based on live-biotherapeutics derived from the microbiome of healthy individuals.

4D Pharma, based in Leeds, UK, was established late in 2013 to focus on developing novel medicines based on and derived from the microbiome of healthy humans. The company's technology, initially developed at the University of Aberdeen, has subsequently been significantly extended and advanced. Today the company directly employs more than 70 people, over 60 of whom are scientists, working in several different sites around Europe (UK, Ireland, France and Spain). 4D has built a library of over 4,000 proprietary bacterial strains from which 15 LBP development programmes have been initiated. Another measure of the progress being made by the company is also evident in the growing intellectual property estate covering the company's lead products and pioneering technologies. The IP estate now comprises 16 patent families with 80 patents granted and another 72 applications.

Importantly, 4D Pharma has incorporated GMP manufacturing within its in-house operational capabilities such that it will not be delayed by third party suppliers in progressing its candidate LBPs into and through clinical development. It has 5-litre up to 3,000-litre fermentation at its site in Leon, Spain, and has the capacity to annually produce over 20 million capsules of its LBPs. For these bacterial strains, the majority of which are anaerobic (exposure to oxygen can be problematic for such organisms), manufacturing at scale is not trivial, requiring significant fermentation know-how and expertise. The manufacturing and development facility offers pilot-to-commercial scale production from a fully equipped plant with development optimisation capabilities (pilot scale), cell banking, QC & QA, and GMP materials warehousing.

4D Pharma Platforms - MicroRx & MicroDx

4D Pharma's proprietary microbiome technology platform, MicroRx, was developed by its scientists to enable the company to rapidly identify commensal bacterial strains exhibiting functional traits chosen for their ability to induce host responses relevant to specific diseases. Using MicroRx, 4D is able to efficiently interrogate its proprietary library of over 4,000 bacterial isolates to rapidly select the most appropriate candidates for target diseases.

Through different rounds of selection using both industry standard and proprietary disease models, 4D can confidently make decisions about the most efficacious candidates to progress into further development. During all the stages of selection, the MicroRx platform focuses on providing the best information about functional biological responses and mechanism of action to drive the greatest potential efficacy of candidates in the targeted disease. Importantly, the unerring focus on biological function and efficacy in disease is only possible if one presumes that each bacterial candidate entering the screening programme will ultimately be safe in man

i.e. safety screens do not need to be performed because all the strains in the library are commensals isolated from healthy individuals.

Exhibit 14 shows the focus of the MicroRx platform is to deliver candidates with excellent knowledge of their function and mechanism of action against targeted diseases. The ability of the company to test candidates for their efficacy and mechanisms of action in disease models has been further expanded recently with the addition of 'germ-free' animal colonies and the flexibility this provides for building new models with tailored gut microbiomes. We believe this capability gives the company a competitive advantage.

Live Biotherapeutic Products LBPs

Bacteria is the 'API'

Regulated as a biologic

Attractive safety profiles (commensals)

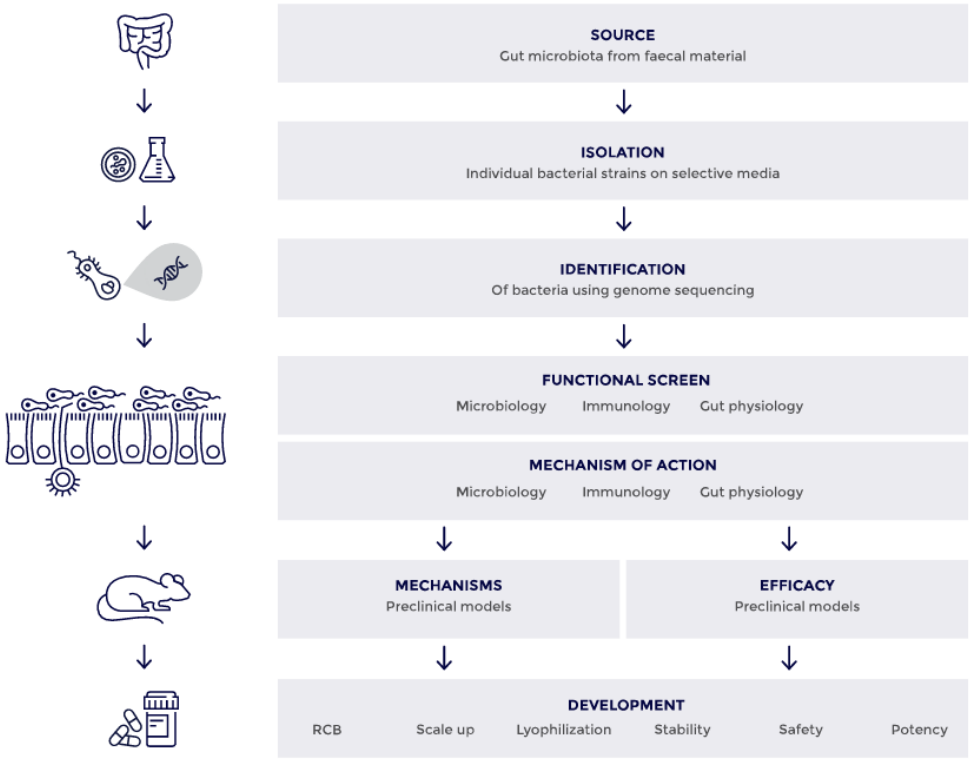
4D Pharma's LBPs

Single strain

Functionality is the key

Rapid, cost-effective development

Exhibit 14: Overview of MicroRx



Source: 4D Pharma

4D Pharma is able to execute this phase of development in as little as 24 months from the initiation of a product development programme to being ready to enter clinical trials. With this level of R&D efficiency it is no surprise that the company is moving so many programmes forward into clinical development (see Exhibit 8).

To be able to deliver on the 24-month time lines for the programmes, 4D Pharma has ensured it can have appropriately manufactured GMP material available from its own facilities.

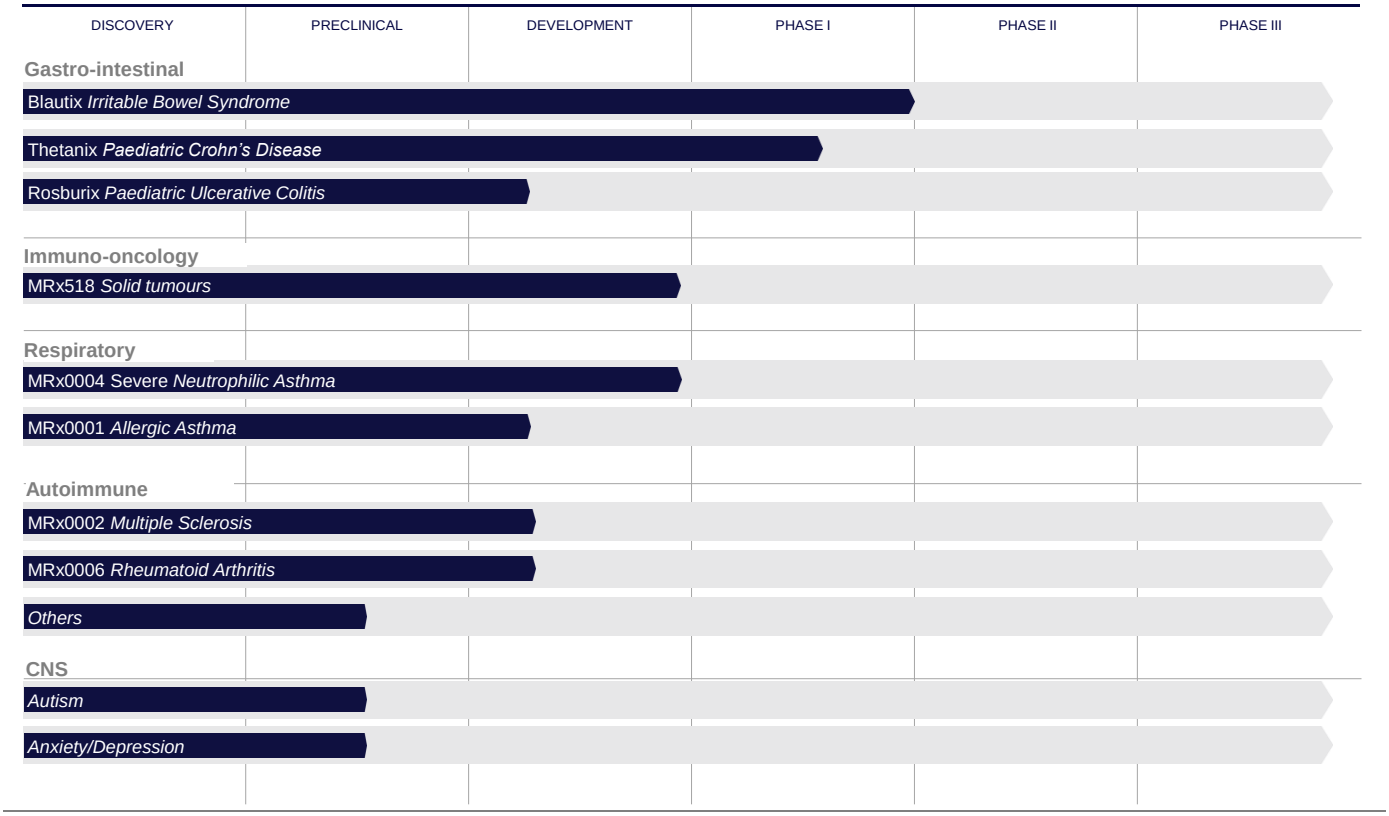
MicroDx characterises the microbiome functionality of patients and will allow the effects of its LBPs to be measured

MicroDx is a platform that can diagnose, stratify and monitor the gut microbiome. It is able to identify 'signatures' of gut microbiome function including metabolite profiles. MicroDx is being tested in IBS in parallel with 4D's Blautix programme and has successfully revealed: - significant differences in the microbiomes of IBS patients and healthy subjects; that IBS subtypes (c, d, & m) are not significantly different from each other; and that MicroDx can differentiate IBS patients from healthy subjects based on metabolite profiles. 4D will incorporate MicroDx into its LBP clinical trials in cancer and severe asthma planned for later this year.

4D Pharma product pipeline

4D Pharma has identified some 15 LBP's as potential products of which it has currently taken 11 into development as shown below in Exhibit 15. This existing pipeline is funded through proof-of-concept. As opposed to conventional biologic therapies, most of which need to be injected, 4D's LBPs are all orally delivered, thus minimising the costs and time involved with administering its products. The programmes all seek to treat the underlying disease as opposed to simply ameliorating symptoms. The company strives for solid evidence for the mechanism of action of each product in the targeted indication as we will describe in more detail below.

Exhibit 15: Current 4D Pharma development pipeline



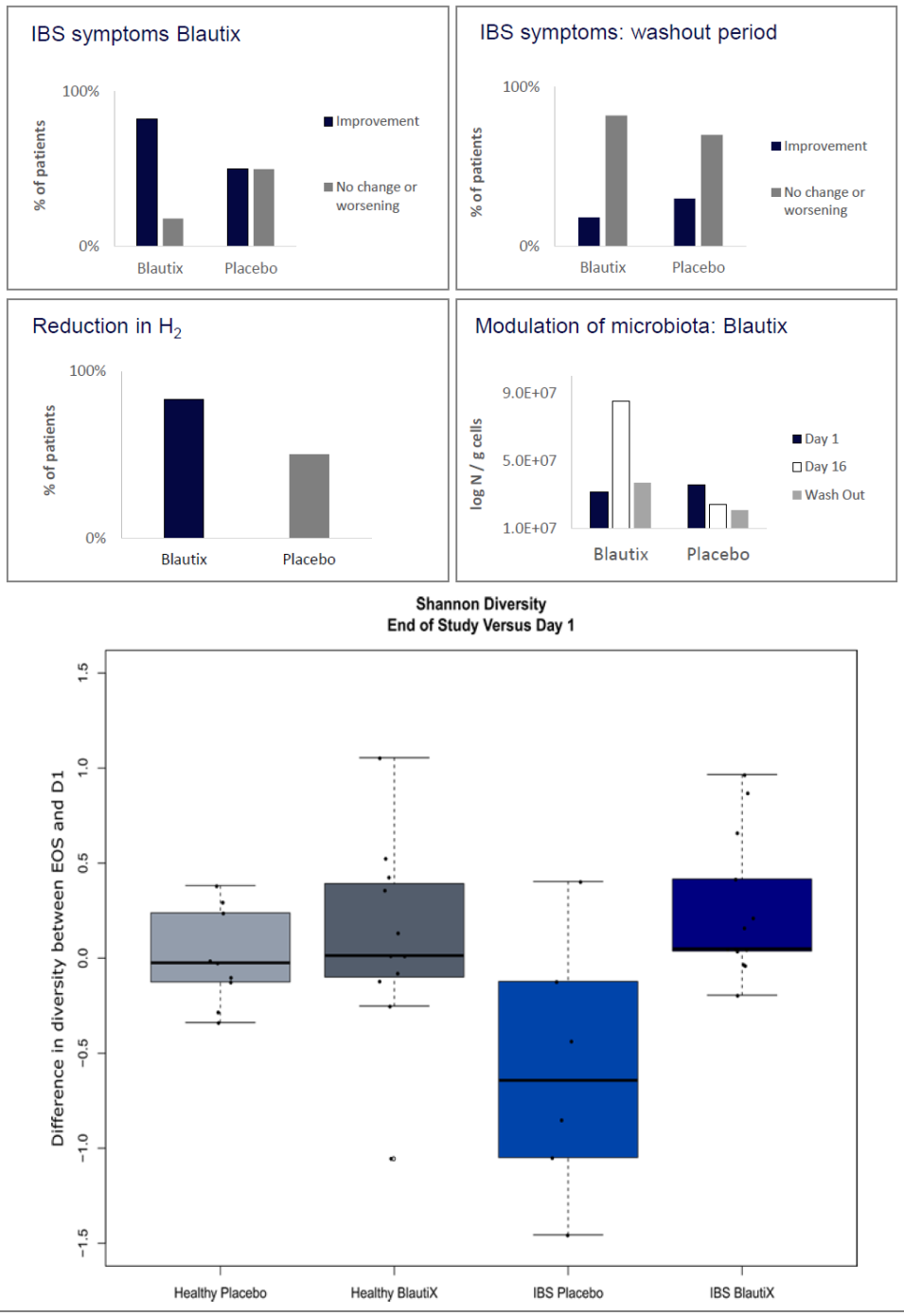
Source: 4D Pharma

Blautix – IBS

Irritable bowel syndrome (IBS) is a condition characterised by abdominal pain, bloating and changes in bowel frequency ranging from diarrhoea to constipation. It is a common condition affecting approximately10-15% of the population. While no single cause has been identified there is increasing evidence that dysfunction of the gut microbiome plays a key role. Current therapies are not particularly effective even though they address symptoms only, not the underlying cause of disease.

4D's Blautix, a single-strain orally delivered LBP, has a distinctive metabolism which uses H_2 as an energy source and consequently reduces levels of H_2S, which is associated with symptoms of IBS. Key findings from a recently completed successful Phase I/Ib clinical study of Blautix in healthy subjects and IBS patients are shown below in Exhibit 16.

Exhibit 16: Blautix phase 1b results trend positively



Source: 4D Pharma

The trial enrolled 2 populations of subjects: 24 healthy volunteers and 24 IBS patients, and these were treated in the ratio of 16 on Blautix and 8 on placebo in each of the two populations. The primary reason for the study was to demonstrate safety and tolerability of the product which was successfully achieved. While the patient numbers were small, the trial generated signals of

Blautix efficacy which were consistent with results obtained in pre-clinical models of its functionality and the proposed mechanism of action:

- a reduction in IBS symptoms
- a reduction in IBS related gas, H_2
- a reduction in the loss of microbiome diversity which was stabilised by Blautix.

On the basis of these results, the company is expected to progress the product into more advanced clinical trials.

Thetanix – Paediatric Crohn's Disease (pCD)

Crohn's disease (CD) is one of the two main types of IBD, ulcerative colitis (UC) being the other. It occurs throughout the digestive tract but appears more frequently in the small intestine. Paediatric CD (pCD) is relatively rare but in addition to suffering from typical CD symptoms (diarrhoea, rectal bleeding and abdominal pain), pCD patients also experience growth failure through malnutrition, pubertal delay and bone demineralisation. There is a strong need for safer, more tolerable and more effective products to treat this disease because current approaches (adapted from adult treatment regimens) can be problematic for children exacerbating growth retardation.

Thetanix, a single-strain LBP, has an anti-inflammatory mechanism of action achieved through the inhibition of activation of NF-κB, a key intracellular mediator of inflammation. A phase I/Ib trial was initiated in August 2016 in pCD patients 12-18 years of age. This study is a single (Part A) and multiple (Part B) dose study. For part A, following informed consent and screening, 10 eligible subjects with pCD will receive a single dose of Thetanix or placebo in the clinic. A Safety Review Committee will review the safety data up to Day 7 from these first 10 subjects and determine if it is appropriate to continue into Part B in which 10 subjects will receive 15 doses of Thetanix or placebo in a twice daily dosing regimen over 7.5 days. In both parts of the study, 8 of the 10 subjects will randomly receive Thetanix and 2 subjects will randomly receive placebo.

The study will focus primarily on the safety and tolerability of Thetanix. Activity of the product against pCD will nonetheless be assessed against the Paediatric Crohn's Disease Activity Index and by analysing the microbiome and inflammatory markers of patients.

Immuno-oncology

- **MRx518** for the treatment of solid tumours. This orally delivered, single strain LBP has an immune-stimulatory function and has delayed tumour growth and extended survival in preclinical models. In head-to-head comparisons in the preclinical model, these effects have been shown to be comparable in magnitude to responses seen with checkpoint inhibitors. This function has been seen in model systems of lung, liver and breast cancer.

The company is planning an **H2 2017 initiation** of a large, first-in-man study with up to 200 treatment-naïve patients with various solid tumour types. We believe this trial will be the first of its kind an LBP for the treatment of cancer. While safety and tolerability are the primary outcome measures, responses to the product will be determined using a suite of immunological biomarkers.

Respiratory

- **MRx0004** for the treatment of severe neutrophilic asthma. An orally delivered LBP which modulates the innate immune system (involved with antigen non-specific cellular interactions) to reduce the number of neutrophils in the lung without inducing eosinophil infiltration. Severe neutrophilic asthma accounts for 5-10% of all asthma patients and is largely unresponsive to existing asthma medications (inhalers, bronchodilators). Further studies underway to determine additional mechanism of action.

4D Pharma is preparing to initiate a first-in-man study in 50 patients across 5 sites in **H2 2017**. Patients will have either neutrophilic or eosinophilic asthma. While safety and tolerability are the primary outcome measures, responses to the product will be determined using sputum cell counts and lung function as measured by Forced Expiratory Volume in 1 second (FEV1).

Other Pipeline Candidates

- **Rosburix** Addressing UC in paediatric patients (pUC). UC is the subset of IBD where inflammation restricted to the colon and rectum. The disease is more aggressive in pUC compared to adult UC and children are more susceptible to complications (either steroid dependency or colectomy). A better approach is needed.

Rosburix, a single-strain orally delivered LBP, has an anti-inflammatory mechanism of action achieved through the induction of Treg cells, well known to reduce the inflammatory environment in the gut.

- **MRx0006** for the treatment of rheumatoid arthritis (RA). RA is an autoimmune disease of the joints which affects more than 3 million people in the major pharmaceutical markets in North America and Europe. While many patients achieve good results with a range of drug therapies (DMARDS, NSAIDS, and biologics such as anti-TNF monoclonal antibodies), many patients do not obtain relief. Toxicities for thse treatments can become dose-limiting and responders can also become refractory. Clearly, there is room for new safe and effective treatment options.

MRx0006 is an orally delivered single strain LBP which has been shown to reduce clinical scores of joint inflammation as well as protecting from joint damage in an experimental model of arthritis. The mechanism by which it achieves these favourable outcomes appears to be the suppression of systemic inflammatory cascades – particularly levels of IL-10 and interferon-γ. Further work to explore its mechanism of action on the immune system is underway.

- **MRX0002** for the treatment of multiple sclerosis (MS). MS is a relapsing-remitting, progressive neurodegenerative autoimmune disease in which the immune system attacks the myelin sheath surround nerves. Once diagnosed patients usually require medications chronically throughout their lives. The side effects of existing and new medications for MS can be significant and there remains a strong opportunity for safer better medicines.

MRx0002 is an orally delivered single strain LBP which has been shown in models to increase Tregs and protect the spinal cord such that some animals do not show evidence of disease.

Key People

Exhibit 17: Board of Directors & Senior Management

Name	Profile
David Norwood – Non-Executive Chairman	David has had a long career building a number of science, technology and investment companies. He is the founder of IP Group plc, one of the UK's leading technology commercialisation businesses and a shareholder in the Company. Previously, he was Chief Executive of stockbroker Beeson Gregory (acquired by Evolution Group plc) after it acquired IndexIT Partnership, a technology advisory boutique he had founded in 1999. He was a founding shareholder of Evolution Group plc (recently acquired by Investec), and also co-founder of Ora Capital plc. He has been a founder and director of many UK technology companies including Oxford Nanopore Technologies Ltd, Proximagen Ltd, Synairgen plc, Ilika Technologies Ltd, Oxford Catalysts and Plectrum Petroleum (acquired by Cairn Energy plc). He has also acted as seed investor and/or advisor to Wolfson Microelectronics Ltd, Nanoco Technologies Ltd, Tissue Regenix Group plc and Arc International (now part of Synopsys). He is also Non-Executive Chairman of Oxford Pharmascience Group plc.
Duncan Peyton - Chief Executive Officer	Duncan has a proven track record in identifying, investing and growing business within the pharmaceutical sector. He was the founder of Aquarius Equity, a specialist investor in businesses within the life science sector, which provided investors' access to innovative, high growth potential companies that delivered significant capital growth. Duncan started his career in a bio-science start-up business, which ultimately went on to list on the London Stock Exchange, subsequently qualified as a corporate finance lawyer with Addleshaw Goddard, then Addleshaw Booth & Co, and later joined 3i plc as an investment manager. Duncan founded Aquarius in 2005, which made founding investments into Nanoco Technologies Ltd, Auralis Limited (subsequently sold to ViroPharma) and Tissue Regenix Group plc.
Alex Stevenson – Chief Scientific Officer	Alex began his career as a scientist, working in research and for a NYSE quoted drug development company, before moving into early-stage pharmaceutical and healthcare investments. He has fulfilled board level investment and operational management roles. He was a director and shareholder in Aquarius Equity from 2008, where he was responsible for identifying new investments and developing and implementing scientific strategies both pre and post-investment. Prior to joining Aquarius Equity, Alex worked for IP Group plc where he specialised in life science investments, identifying, developing and advising a number of companies in its portfolio, some of which went on to list on AIM. He joined IP Group following its acquisition of Techtran Group Ltd in 2005.
Thomas Engelen – Non-Executive Director	Thomas is also non-executive chairman at Akcros Holdings Ltd, Penlan Healthcare and Quantum Pharmaceutical. Thomas has been a founder and/or non-executive director of a number of UK life sciences companies including Colonis Pharma Ltd, Warneford Partners Ltd and Martindale Pharma Ltd. Thomas has supported private equity and other investors in over 50 potential deal transactions, on targets in Europe and the USA, from cash constrained/chapter 11 to cash-rich with EV of up to $1 billion. Before this Thomas worked in life sciences for over 20 years in senior executive roles. Starting in 1987 at Akzo Nobel Pharma he worked with hospital products, diagnostics and medical equipment as General Manager for Middle East & Africa. After this he led Rosemont Pharmaceuticals in Leeds in niche oral liquid medicines, followed by being President of Organon in Brazil. He was promoted to VP The Americas, and lastly to CMO at Organon, in charge of the global product portfolio, based in the USA. Returning to Europe he led Novartis Consumer Health in the UK.
Senior Management	
Stephen Dunbar – Finance Director	With over 20 years of experience working with both private and listed business, Stephen has provided key financial and strategic advice since inception. Prior to joining 4D pharma plc, Stephen was Group Finance Director of Aquarius Equity Partners, a European healthcare fund. Stephen's role was key in not only the development of the funds, but also the financial stability of the group. At Aquarius, Stephen also played a key role in the development of the portfolio, working with management teams across companies such Nanoco Technologies, Tissue Regenix and Auralis, as well playing a more formal role as interim FD at Brabant Pharma. After qualifying as a Chartered Accountant with Tenon (now RSM), and working as Group FD for a local engineering company, Stephen founded an accountancy practice, Summ.it Assist LLP, which delivers outsourced tailor-made solutions covering financial, HR and IT solutions to SMEs and, since inception, has grown to over 30 staff across offices in Manchester and Mauritius. During this time Stephen has also acted as non-executive director for various SMEs and spent 18 months as interim FD for Touchstar Technologies during the successful reverse takeover of that business by Belgravium Technologies plc.
Christophe Carite – Development Director	Christophe graduated in industrial pharmacy, and he started his industrial career as plant manager for Lallemand Bacteria Division, then occupied various positions in R&D and Marketing in B2B of Pharmaceuticals Ingredients. When presented with the challenge of producing Blautix™ he succeeded where others had previously failed and immediately understood the potential of this microorganism. Now, he is in charge of the pharmaceutical industrial development of all the 4D pipeline with the responsibility of all manufacturing sites.

Laurie Dale – General Counsel and Company Scretary	Laurie is General Counsel and Company Secretary of 4D pharma plc. In his role, he works closely with the Board and senior team, and supports all those within 4D in legal and regulatory compliance. He also co-ordinates the Group's external legal requirements. Prior to joining 4D pharma, Laurie was a corporate lawyer in private practice for over 20 years, holding senior positions with Addleshaw Goddard LLP and Schofield Sweeney LLP. He specialised in mergers and acquisitions and private and public fundraisings (advising corporates, funders and managers alike), and advised both private and quoted businesses generally on all aspects of corporate law. His clients were predominantly technology focussed and included Aquarius Equity Partners, Nanoco Technologies plc, Sanderson Group plc and C4X Discovery Holdings plc. He was also previously external counsel to 4D pharma, and advised it in relation to its IPO and initial fundraisings. He remains a qualified solicitor.
Imke Mulder – Research Director	Imke Mulder is the Research Director at 4D pharma Research Ltd in Aberdeen, Scotland, where she leads a multidisciplinary research group of 30 scientists. After completing her BSc and MSc in Biology at Wageningen University in the Netherlands, she moved to Aberdeen in 2001 to pursue her PhD studies at the Department of Zoology, working on the effects of dietary components on the gut immune system. Imke then carried out 8 years of post-doctoral work as a Research Fellow in the Gut Immunology Group at the Rowett Institute of Nutrition and Health (RINH) in Aberdeen. This work primarily focussed on interactions between the gut microbiota and the host immune system in different model organisms. Specific projects investigated how microbial composition and diversity influences early-life development of the mucosal immune system, and the cell-specific signalling pathways and effector molecules involved in driving health-promoting interactions of the gut microbiota. Imke moved to 4D pharma Research Ltd in 2014 where she leads the development of the MicroRx platform for the discovery of new live biotherapeutics.
Antonio Fernández – General Manager	Antonio was the Chief Executive Officer at Instituto Biomar from 2002, leading a group of fermentation specialist and research scientists in microbiology and natural products chemistry. He received his PhD at Houston's M.D. Anderson Cancer Centre, conducting post-doctoral work in the Departments of Cell Biology and Molecular Pathology from the same institution. After this, Antonio worked in the Departments of Tumour Immunology, at the Dana-Farber Cancer Institute and then Surgical Research at the Children's Hospital, both associated with Harvard Medical School in Boston. He moved back to Spain in 2001, and worked at the research unit in Hospital de Leon from 2001 to 2002, when he joined Instituto Biomar. After the acquisition of Biomar´s production unit by 4D pharma in April 2016, Antonio took up the position of director at 4D pharma Leon.
Eileen O'Herlihy – Project Manager	Eileen has a BSc in Plant Science and aPhD in Plant Biotechnology from University College Cork (UCC). She has worked as a post-doctoral researcher and as a manager on a range of projects both at national and EU level spanning plant and human health. In 2013, Eileen was project manager of ELDERMET, a nationally funded project that established diet-microbiota health interactions in over 500 elderly people. Following this post, she managed the Centre for Gerontology & Rehabilitation, UC,C where she was involved in initiatives focused on the elderly which also supported the European Innovation Partnership on Active and Healthy Ageing. She joined the APC Microbiome Institute (APC) in 2014 as EU Grants Manager where she engaged with stakeholders, built collaborations, inputted into draft work programmes and policy documents, and identified opportunities for microbiome research at national, EU and international level. She has over a decade of experience of working with industry partners in the capacity of research project manager and as a consultant. Eileen is very active in communicating science and creating an awareness through education and public engagement. She is also a member of the APC Microbiome Institute faculty. As Site Manager of 4D pharma Cork Limited, Eileen is responsible for the day-to-day running of the site including: management of clinical trials, administration, HR and liaising with other 4D sites and central management.

Source: 4D Pharma

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