Microbiome Modulator Drugs – The New Generation of Therapeutic

Find out more
The discovery and deep investigation of the microbiome has been one of the most cutting-edge advances in biomedical research of recent times. Every human being hosts between 10–100 trillion symbiotic micro-organisms, including bacteria, viruses, and archaea. The collective genomes of these micro-organisms form what is known as the human microbiome.\(^1\) The microbiome impacts human physiological functions in many ways, such as contributing to metabolic functions, protecting against pathogens, and interacting with immune system development.\(^2\) Research is now very much focused upon investigating how exactly its interactions within the body contribute to health and disease. As a deeper understanding of these interactions is gained, the floodgates have opened for drug development companies to investigate the potential of microbiome modulating therapies for the treatment of disease. This white paper provides an overview of the novel microbiome modulator industrial development landscape using Pharmaprojects data, and analyzes the potential for treating multiple diseases.

### Industrial Drug Development Landscape

Pharmaprojects has tracked trends in drug development each year from 1980 until present, which reveal a boom in the development of novel microbiome modulator candidates over the past six years (Figure 1). Industrial interest began in 2011, with two microbiome modulators in active development at that time. As of January 2018, the number of these drugs in development stands at 70. The sudden spark in industrial interest is recent, as seen by the 65% increase in the number of microbiome modulators being developed over the past two years.

The development of microbiome modulators is primarily at the early stages, with most candidates in preclinical development and few reaching clinical trials. The magnitude of growth in this area can be explained mostly by the more than six-fold increase in drugs at preclinical stage (as shown in Figure 2). But, over the past three years more candidates have entered clinical trials, and currently there are three candidates at Phase III status. At this point in time, there are no drugs approved for use as human therapeutics, and therefore, the market is wide open in this space.

### Figure 1: Number of microbiome modulators in active development, by year, 2011–17

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>2</td>
</tr>
<tr>
<td>2012</td>
<td>2</td>
</tr>
<tr>
<td>2013</td>
<td>4</td>
</tr>
<tr>
<td>2014</td>
<td>5</td>
</tr>
<tr>
<td>2015</td>
<td>13</td>
</tr>
<tr>
<td>2016</td>
<td>27</td>
</tr>
<tr>
<td>2017</td>
<td>70</td>
</tr>
</tbody>
</table>

Source: Pharmaprojects®, January 2018

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Which Companies are Investing in this Research Area?

A total of 26 smaller companies are exploring this new area of research. 10 of these companies are developing more than two novel microbiome drugs (Table 1), the majority of which purely focus on products targeting the microbiome. Assembly Biosciences and Enterome are the only companies in this list that also research drug development in other areas. Seres Therapeutics is the clear leader in terms of microbiome research, with 10 drugs currently in development. The company harnesses its propriety discovery and design platform to understand how the microbiome may be involved in specific indications, and is developing Ecobiotic drugs (a collection of specific bacteria), which aim to restore it to a healthy state.
Although no Big Pharma companies have originated any microbiome drug development technologies, a few have shown interest in this area and formed research collaborations with other smaller companies. Janssen (Johnson & Johnson) is pursuing development in this area for the treatment of inflammatory bowel disease (IBD). Janssen in-licensed Vedanta’s preclinical asset, VE-202, in 2015, and took over development and future commercialization of the drug for IBD. Janssen also formed a collaborative research agreement with Enterome in 2016. This collaboration aims to discover bioactive molecules and novel targets of the gut microbiome, and develop them as therapeutics for Crohn’s disease, a subtype of IBD. AbbVie is also interested in the IBD therapeutic area, and formed a licensing agreement with Synlogic in 2016. Under terms of this agreement, the companies will collaborate using Synlogic’s proprietary development platform, to discover novel synthetic biotic medicines which modulate the microbiome. Enterome also entered a research collaboration agreement with Bristol-Myers Squibb in 2016. The companies will work together to discover and develop microbiome-derived biomarkers, drug targets, and bioactive molecules for the treatment of immuno-oncology indications.

Table 1: Companies developing more than two novel microbiome modulators

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of microbiome modulators in pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seres Therapeutics</td>
<td>10</td>
</tr>
<tr>
<td>Assembly Biosciences</td>
<td>7</td>
</tr>
<tr>
<td>Evelo Bioscience</td>
<td>6</td>
</tr>
<tr>
<td>Vedanta Biosciences</td>
<td>5</td>
</tr>
<tr>
<td>Fimbrion</td>
<td>4</td>
</tr>
<tr>
<td>ImmuneBiotech</td>
<td>3</td>
</tr>
<tr>
<td>MatriSys Bioscience</td>
<td>3</td>
</tr>
<tr>
<td>Second Genome</td>
<td>3</td>
</tr>
<tr>
<td>Caelus Health</td>
<td>3</td>
</tr>
<tr>
<td>Enterome</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: Pharmaprojects®, January 2018
The human microbiome is the aggregate of the genomes of all microbes which reside on or within the body. The microbiota population can become imbalanced when there are more ‘bad’, pathogenic bacteria present than ‘good’ bacteria, which is called dysbiosis. Microbiota inhabit a vast number of human tissues, including the gut, skin, oral cavity, esophagus, oropharynx, vagina, uterus, and ovaries. Due to their presence all over the body, imbalances in the microbiota could cause a range of illnesses, offering immense potential for microbiome therapeutics.

Figure 3 presents the counts of drugs in development for diseases categorized by therapeutic area (TA). Presently, a large proportion of novel microbiome modulators are being investigated for infectious diseases, but gastrointestinal (GI) disorders are also popular. Other TAs under development include metabolic disorders, dermatology, oncology, and neurological disorders.

**Figure 3: Number of novel pipeline microbiome modulators within each therapeutic area**

![Pie chart showing the number of novel pipeline microbiome modulators within each therapeutic area. Neurological disorders have 3 candidates, dermatological indications have 8 candidates, cancers have 8 candidates, metabolic disorders have 10 candidates, gastrointestinal disorders have 24 candidates, infections have 21 candidates.]

Note: some candidates will be in development across multiple TAs and are counted multiple times.

Source: Pharmaprojects®, January 2018

Infectious disease

Infectious disease is the most common area of development, as demonstrated in Figure 3. Antibiotic resistance is a major global health concern, as our ability to treat infectious disease is challenged by multi-drug resistant bacteria, the emergence of which is linked to the excessive use of antibiotics. Thus, developing methods of pathogen control that do not involve antibiotics is important and will be an essential step in the treatment of infectious disease. Additionally, when traditional antibiotics are used to treat infection, they deplete the healthy, protective bacteria, as well as the pathogenic organisms. This disrupts the microbiome and creates an environment in which pathogenic drug-resistant bacteria can colonize and cause disease. Moreover, research suggests that the gut microbiome can act as a reservoir for antibiotic-resistant genes, where they can be transferred to other bacteria between hosts, which would aid transmission through populations. Considering this, it is vital that the microbiome is investigated in infectious disease drug development. Accordingly, industrial research focused on developing targeted antibacterial products which preserve the microbiome, or candidates which act to rebuild the microbiome after infection, is ongoing.

The three main areas being investigated are Clostridium difficile infection (C.difficile), methicillin-resistant Staphylococcus aureus (MRSA), and urinary tract infections (UTIs). As seen in Figure 4, the majority of drugs are being developed for C. difficile, and most function to rebuild the microbiome. Interestingly, those candidates that aim to preserve the microbiome, whilst still targeting pathogenic bacteria, are mostly being investigated for UTIs and MRSA.

Figure 4: Number of pipeline candidates which function to rebuild the microbiome, or preserve the microbiome, for top infectious disease indications

Note: drugs in development for unspecified infectious disease excluded from chart count (n=5). Abbreviations used in Figure: C. diff = Clostridium difficile infection; MRSA = methicillin-resistant Staphylococcus aureus infection; UTIs = urinary tract infections

Source: Pharmaprojects®, January 2018

More than half (13 out of 24) of all microbiome modulators being developed for infectious disease are specifically indicated for the treatment of C. difficile infection (Figure 4). C. difficile is a common environmental bacterium, which most often resides in the bowel of both children and adults without causing any issues. However, in some cases it can act as an opportunistic pathogen and cause illness, ranging from mild diarrhea to more serious conditions such as pseudomembranous colitis, sepsis, and even death. It is considered to be one of the leading infectious threats to public health. C. difficile infection is commonly seen after antibiotics have been taken for an unrelated issue, as the antibiotics remove both the protective resident bacteria as well as the pathogen targets, which allows for opportunistic infection and can cause so-called antibiotic-associated diarrhea. Currently, six drugs have reached clinical development stages for this public health issue; these are listed in Table 2.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Company</th>
<th>Development phase</th>
<th>Drug description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SER-109</td>
<td>Seres Therapeutics</td>
<td>Phase III</td>
<td>Orally delivered ecology of bacterial spores derived from healthy human donor</td>
</tr>
<tr>
<td>RBX-2660</td>
<td>Rebiotix</td>
<td>Phase III</td>
<td>Live microbes derived from healthy human donors and delivered via enema</td>
</tr>
<tr>
<td>SYN-004</td>
<td>Synthetic Biologics</td>
<td>Phase II</td>
<td>Breaks down intravenous beta-lactam antibiotics in the gut</td>
</tr>
<tr>
<td>SER-262</td>
<td>Seres Therapeutics</td>
<td>Phase I</td>
<td>Synthetically derived microbe ecology</td>
</tr>
<tr>
<td>RBX-7455</td>
<td>Rebiotix</td>
<td>Phase I</td>
<td>Live microbes derived from healthy human donors and delivered orally</td>
</tr>
<tr>
<td>FIN-403</td>
<td>Finch Therapeutics</td>
<td>Phase I</td>
<td>Synthetically derived microbe ecology</td>
</tr>
</tbody>
</table>

All candidates included in Table 2, apart from Synthetic Biologics’ SYN-004, act to rebuild the microbiome following dysbiosis caused by C. difficile infection, by introducing groups of protective microbiota in the gut. The principal behind this is to re-establish the healthy microbiota, which would act to reduce numbers of C. difficile through outcompeting for nutrients or direct bacteriostatic effects.

The most advanced candidates are SER-109 (Seres Therapeutics) and RBX-2660 (Rebiotix), which are both probiotic products. SER-109 is an encapsulated combination of purified probiotic eubacterial spores, which received breakthrough therapy designation and orphan drug designation from the FDA in 2015. A Phase II trial in 30 patients was completed in 2014, and demonstrated no product-related adverse events. It is now currently in a Phase III (ESCOPAR

III) and an extension study (ESCOPAR IV) in a total of 420 adults with C. difficile infection, expected to be completed in 2019. RBX-2660 is a suspension of live bacteria and was investigated in a Phase II trial in 242 subjects with recurrent C. difficile infection, completed in 2017. Treatment with open-label RBX-2660 resulted in a significant reduction in C. difficile reoccurrence when compared with a historical control group. It is currently in Phase III trials in the US and Canada, which are also expected to be completed in 2019.

Conversely SYN-004, which is in Phase II development, works to degrade intravenous beta-lactam antibiotics in the gut, as a preventative measure against dysbiosis and C. difficile infection. Beta-lactam antibiotics are commonly used to treat many different infections in hospitalized patients. This drug acts to preserve the gut microbiome during IV antibiotic treatment for non-GI infections, and therefore prevents dysbiosis. SYN-004 received FDA breakthrough therapy status in May 2017, and initiation of a Phase III trial is expected in early 2018.

MRSA is a multi-drug resistant superbug which can cause difficult-to-treat infections and is prevalent in establishments with high numbers of vulnerable, immunocompromised people, such as hospitals and nursing homes. It has been estimated that MRSA is responsible for 80,500 severe infections and over 11,000 deaths in the US each year.8 One company developing targeted antibacterial products for MRSA is Micreos. Micreos’s Phase II candidate, SA.100, is an endolysin enzyme, which is targeted to specifically destroy the bacterial walls of Staphylococcus aureus (including MRSA), but still preserve the rest of the microbiome. This ability to preserve the microbiome makes the product more suitable for chronic usage than standard antibiotics, and thus it is ideal for use in hospitalized patients and immunocompromised individuals. XZ.700 is a second-generation endolysin enzyme, which is currently in preclinical development, and the company plans to initiate a Phase I/II trial in 2018, initially to treat atopic dermatitis, for which S. aureus has been implicated as a contributing organism.

Fimbrion is another company investigating targeted antibacterial products, with four currently in preclinical development, specifically for the treatment of UTIs. UTIs are very common, and it is estimated that around 50% of women will experience this infection at some point in their lives.9 Around 10% of UTIs are caused by antibiotic-resistant bacteria,10 and therefore it is vital that targeted treatments are developed to prevent the spread of resistant strains. Fimbrion is developing mannoside-based products which block FimH, a bladder epithelial cell surface receptor through which pathogenic bacteria enter the bladder.

The advantage of products which act to rebuild the microbiome is that they potentially could be used in a multitude of conditions involving dysbiosis. However, due to the variation seen in the microbiome between individuals, these drugs may not be the “one size fits all” remedy that companies are hoping for. Whilst drugs which act to prevent microbiome damage may be more targeted, this means that they may only be useful for certain conditions and in patients with a specific treatment regime. For example, SYN-004 is intended to prevent C. difficile infection in hospitalized patients who are receiving IV beta-lactam antibiotic treatment. But, it will not be possible to use this drug to prevent C. difficile in other vulnerable patients, such as those undergoing chemotherapy. Nevertheless, it is evident that emerging microbiome therapies may be the future of treating threatening infectious diseases, especially C. difficile, in the midst of antibiotic resistance.

Gastrointestinal disorders
Within the second most common area – gastrointestinal disorders – 21 microbiome modulators are currently being developed for the treatment of subtypes of inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), with numerous candidates being developed for more than one subtype (Figure 5). IBD consists of two chronic and currently incurable diseases of inflammation involving the GI tract: ulcerative colitis (UC) and Crohn’s disease. UC is inflammation of the colon and is considered the less severe subset of IBD, whereas Crohn’s disease can cause inflammation anywhere along the GI tract, and results in substantial distress to sufferers. Current treatment options are focused on the use of anti-inflammatory agents (eg aminosalicylates), and biologic therapies such as anti-tumor necrosis factor drugs, including Remicade (infliximab; Johnson and Johnson/Merck & Co/ Mitsubishi Tanabe) and Humira (adalimumab; AbbVie/Eisai). Despite the prevalence of drugs that can result in remission of symptoms of both UC and Crohn’s, there is still an unmet need for well-tolerated treatment that can bring about remission of symptoms quickly.

IBD and its subtypes are characterized by specific microbial signatures, and the deviation from the so-called “healthy plane” has been hypothesized as a potential non-invasive diagnostic method.11 The microbiomes of patients suffering with IBD and its subtypes are thought to fluctuate more so than in healthy patients, and this fluctuation or potential dysbiosis is believed to contribute to the inflammation characteristic of IBD.

IBS, unlike IBD, has no associated inflammation of the gut or clear cause, and is instead better described as a collection of symptoms. IBS is divided into three subtypes: IBS with constipation, with diarrhea, or mixed IBS. The specific cause of IBS is still unknown, but the gut-brain axis has been implicated, with stress and changes in gut bacteria thought to result in alterations in both the nerves controlling bowel movement and fermentation within the intestines.12 Treatment for IBS is focused on symptomatic relief based on the patient’s presenting symptoms at the time, and includes antispasmodics and dietary changes.13

Of the 21 candidates currently under development for gastrointestinal indications, four are in Phase I, with the remaining being preclinical. Figure 5 presents the number of drugs in development for each disease in Phase I or preclinical stages. Microbiome modulators are largely being investigated for the treatment of IBD, with some candidates specifically intended for Crohn’s (3/21) or UC treatment alone (1/21).

13. For more information, please see Datamonitor Healthcare’s coverage of Ulcerative Colitis, Crohn’s Disease, and Irritable Bowel Syndrome. To access, visit: https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/datamonitor-healthcare
Three of the four Phase I candidates are Blautix (Blautia hydrogenotrophica; 4D Pharma), Thetanix (Bacteroides thetaiotaomicron, 4D Pharma), and SER-287 (Seres Therapeutics), which are bacterial cultures designed to modify a patient’s gastrointestinal profile, to help with the symptoms of IBS in the case of Blautix and IBD in the case of Thetanix and SER-287. The fourth Phase I candidate is EB8018 (Enterome), which is a small molecule designed to block adherence of pro-inflammatory bacteria to the gut wall in the treatment of IBD.

Blautix is a single-strain probiotic product consisting of Blautia hydrogenotrophica. As an acetate producing bacteria, Blautix acts to reduce the levels of carbon dioxide and hydrogen in the gut, which are produced by fermentation by other bacteria. This correspondingly reduces the gas and bloating
associated with IBS. Blautix has been tested in a Phase Ib study and met the trial’s primary endpoints of tolerability and safety. Additionally, IBS patients saw a reduction in symptoms and also a reduction in hydrogen breath test, which as Blautix is a hydrogen-consuming bacteria, is a marker of the product’s efficacy.

Thetanix is a probiotic product being developed by 4D Pharma for the treatment of pediatric Crohn’s disease. Thetanix is thought to improve mucosal barrier function, resulting in a reduction in pathogens breaching the mucosal barrier, which could lead to reduced inflammation and increased immunity to pathogens. Thetanix is currently in a Phase I study, and 4D Pharma hopes to commence a Phase II study in 2018. Thetanix received orphan drug status from the FDA in 2013, which is an indication of the unmet need for this indication.

SER-287 is an oral formulation of bacterial spores, being developed by Seres Therapeutics for the treatment of ulcerative colitis. It has recently completed a Phase Ib study, which showed a dose-dependent improvement in clinical remission rates in patients unresponsive to current therapies. This means that it was able to produce a better clinical benefit in patients than currently available therapies, and indicates SER-287 to be a very promising candidate for the future treatment of ulcerative colitis. The exact combination of bacteria that is used in SER-287 has not been disclosed, but Seres has indicated that by increasing the integrity of the mucosal barrier in the colon, SER-287 acts to reduce pro-inflammatory signaling from bacteria.

EB8018 is a small molecule, designed to block bacteria that express type 1 fimbrial adhesion FimH from adhering to the gut wall, for the treatment of Crohn’s disease. Bacteria that express FimH are thought to be overabundant in patients suffering from Crohn’s, and are believed to act to increase inflammation and therefore disease severity. By blocking the attachment of these bacteria, it is hypothesized that EB8018 will act to reduce inflammation in the gut and improve patient symptoms, which could have benefits over currently available pharmacological anti-inflammatory agents, as these come with side effects such as a weakened immune system. EB8018 is currently in a Phase I trial to test safety and pharmacokinetics, in preparation for a Phase II proof-of-concept trial expected to be initiated in 2018.

Metabolic diseases
There are currently 10 microbiome modulators in development for metabolic disorders. As seen in Figure 6, the majority of drugs are in preclinical development, and just two drugs are being investigated in clinical trials. They are being developed for a broad range of conditions, including lactose intolerance, liver diseases, insulin-related syndromes, and even the rare maple syrup urine disease.

Figure 6: Number of microbiome modulators in development for metabolic indications, by phase

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase</th>
<th>Number of Microbiome Modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose intolerance</td>
<td>Phase III</td>
<td>3</td>
</tr>
<tr>
<td>Insulin related syndrome</td>
<td>Phase I</td>
<td>1</td>
</tr>
<tr>
<td>Insulin related syndrome</td>
<td>Phase I</td>
<td>1</td>
</tr>
<tr>
<td>Liver disorder</td>
<td>Preclinical</td>
<td>3</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Unspecified</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

People with lactose intolerance have an impaired ability to digest lactose, a carbohydrate found in dairy products. This occurs when the enzyme which breaks down lactose – lactase – does not function properly or production is reduced. Patients with this condition experience very uncomfortable symptoms after consuming dairy, such as abdominal pain, gas, bloating, cramps, and diarrhea.\(^{16}\) There are no treatments for this disease available for patients at this point in time, and currently only two novel drug candidates in development.

Ritter Pharmaceuticals’ RP-G28 is the most advanced candidate, which is currently in Phase III trials. This orally administered, small molecule drug stimulates the growth of lactose-metabolizing bacteria in the gut, and adapts the microbiome to reduce populations of gas-producing bacteria. A multi-center Phase IIb/III trial in 377 patients was completed in 2016. It demonstrated that RP-G28 significantly improved symptoms of lactose intolerance and also allowed patients to consume a greater volume of milk without experiencing discomfort.

Source: Pharmaprojects®, January 2018

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symptoms. Therefore, this drug shows promise in allowing these patients to increase their calcium intake without experiencing uncomfortable side-effects. A further Phase III trial is planned for the first half of 2018, and filings for market authorization in both Europe and the US are expected in 2019. If approved, this will be the first drug ever marketed for this disorder. There is huge market potential, as lactose intolerance is a very common disorder, with approximately 65% of the global population experiencing reduced ability to digest lactose.16

Insulin-related syndromes include a broad spectrum of diseases such as diabetes, obesity, and glucose intolerance.17 There is currently a global obesity epidemic, with the numbers of people suffering from obesity and associated complications, including diabetes and cardiovascular disease, rising.18 Research suggests that the microbiome plays a role in the development of obesity and insulin resistance. An obesity-associated microbiome has been identified, with a greater capacity for energy harvest than that of lean people, through the breakdown of components of the diet usually resistant to digestion.19 This ability to extract more energy from a diet can result in an excess of energy over physiological requirements, and thus produce an obese phenotype. Additionally, it has been suggested that microbiota consortia of obese people interfere with intestinal permeability and increase the absorption of inflammation-inducing lipopolysaccharides, resulting in impaired insulin signaling.20

Therefore, microbiome modulators have great potential in treating these diseases and slowing the obesity epidemic. There are four microbiome modulator candidates in the pipeline for these disorders. The most advanced, Caelus Health’s CP-001, has reached Phase I trials, and is an oral formulation of Eubacterium hallii. Research has demonstrated that this bacterium is abundant in the gut of lean human individuals, and studies in obese and diabetic mice models suggest that oral administration improves energy metabolism and insulin sensitivity.21

The microbiome is also a potential target for the treatment of the rare metabolic disorder, maple syrup urine disease (MSUD). MSUD is a genetic disorder in which an affected individual is unable to process certain amino acids, which results in sweet smelling urine; giving the condition its name. Symptoms include an inability to eat, vomiting, lethargy, and delayed development. Without treatment, this serious condition can lead to seizures, coma, and death.22 Synlogic is engineering probiotic bacteria to ameliorate errors of metabolism in a patient and reduce pathogenesis by either performing critical functions or delivering the genes to do so. Preclinical studies have demonstrated that the engineered bacteria successfully break down both dietary and systematic sources of metabolites which build to toxic levels in patients with MSUD.

The liver is in close contact with the GI tract, and as such, has the potential to be influenced by the gut microbiome. Emerging evidence suggests that dysbiosis in the gut microbiome is associated with primary sclerosing cholangitis and alcoholic and non-alcoholic liver diseases. Moreover, research has demonstrated that prebiotics and probiotics have been efficacious in treating various complications of liver disease.23 Four companies are currently investigating this type of therapy in the treatment of various liver diseases in preclinical studies.

17. For more information, please see Datamonitor Healthcare’s coverage of Diabetes type 2. To access, visit: https://pharmaitelligence.informa.com/products-and-services/data-and-analysis/datamonitor-healthcare
Dermatological conditions
Eight products are under development for the treatment of dermatological conditions: one in Phase II, one in Phase I, and the rest in preclinical. The most advanced candidate is MSB-01 (MatriSys Bio), a freeze-dried formulation of Staphylococcus hominis Sh-A9 aiming to treat atopic dermatitis by altering the balance of so-called ‘good and bad bacteria’ on the skin. Atopic dermatitis, also known as eczema, is characterized by dry skin and itchiness, and is most commonly seen in children. Treatment is currently focused on over-the-counter and prescription topical agents, with use of system immunosuppressants in more severe cases.24

MSB-01 contains S. hominis Sh-A9, and it is thought that this so-called ‘good bacteria’ can act to reduce levels of the harmful Staphylococcus aureus by producing bacteriocins specific to S. aureus.25 As mentioned previously, higher levels of S. aureus are associated with increased disease severity, and the use of antibiotics is recommended.26 MSB-01’s ability, however, to have an anti-microbial effect specific to S. aureus is more beneficial than the use of broad spectrum antibiotics, as it leaves the rest of the microbiome intact, which reduces the risk of opportunistic pathogens colonizing; a known side-effect of antibiotic usage. This also makes the product more suitable for long-term usage, which is a useful attribute when treating a chronic condition such as atopic dermatitis.

MSB-01 is currently in a Phase II trial in adults with moderate to severe atopic dermatitis and a positive S. aureus lesion. An earlier form of MSB-01 used a collection of bacteria sourced from each patient that exhibited antimicrobial activity, and resulted in dramatic reductions in S. aureus while leaving the rest of the microbiome intact.25 MatriSys Bio also has a candidate in Phase I – MSB-03 – for the treatment of rosacea, which it intends to submit via the 505(b)(2) regulatory pathway (a hybrid between a standard NDA application and a generics application).

Staphefekt (SA.100; Micreos), mentioned previously, also treats skin infections by reducing levels of S. aureus, but through the action of an endolysin originally isolated from bacteriophages. Staphefekt is the active ingredient in the Gladskin range of creams and lotions, currently available without prescription for patients with skin conditions with an infectious component, such as acne, eczema, and rosacea. Staphefekt specifically targets regions that are highly conserved in S. aureus so that it is less likely that resistance will develop.27 Given the growing danger and awareness of antibiotic resistance, this endolysin-based product could be an attractive alternative. Staphefekt is currently in Phase I for the treatment of atopic dermatitis, rosacea, and acne, whereas a second-generation product – XZ.700 (also mentioned previously) – is being developed for atopic dermatitis. Moreover, further development of XZ.700 in the treatment of acne, rosacea, diabetic wounds, and superficial wound infections has been suggested.

Early research in cancers and neurological indications
There are currently 10 microbiome modulator programs investigating microbiome therapeutics in early preclinical studies for the treatment of a range of cancers. Microbial pathogens play a role in the pathogenesis of some cancer cases, and dysbiosis of the microbiome is associated with malignancy.28 Moreover, research suggests that the microbiome plays a role in determining an individual’s response to cancer medication, as well as susceptibility to toxic side-effects.29

E02315 is Enterome’s lead immuno-oncology candidate, in preclinical development for the treatment of glioblastoma multiforme (GBM), and is a microbiome-derived cancer vaccine. By exposing a patient’s immune system to antigens specific to GBM via the gut, it is thought to boost the immune response and allow cancer cells to be more visible to T cells. Current treatment options for

24. For more information on currently available treatments please see Datamonitor Healthcare’s Atopic Dermatitis treatment module. To access, visit: https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/datamonitor-healthcare
GBM are limited, and it is considered to be the most lethal type of brain cancer, which makes E02315 a potential game changer.30 Another example is the collaboration between Second Genome and the Mayo Clinic, in which they are working to characterize the bacteria present in stools of individuals with different types of cancer. They plan to use these cancer-associated bacteria libraries to identify targets and develop a microbiome-based cancer immunotherapy.

Seres Therapeutics is collaborating with research centers to develop SER-401, an oral therapy consisting of a specialized consortium of live bacteria to be delivered alongside immunotherapy medication (anti-PD-1), to improve its efficacy and safety. This is based on a study showing the impact of microbial profile on the efficacy of anti-PD-1 treatment in patients suffering from melanoma. This study showed that patients who exhibited a greater response to treatment had higher microbial diversity, and a greater proportion of Ruminococcaceae bacteria.31 Seres has used this information to produce SER-401, with the hypothesis that the combination of these specially selected bacteria and PD-1 inhibitors would allow for greater treatment efficacy.

The gut-brain axis links the central and enteric nervous systems and allows them to communicate with each other. Currently, there are three active preclinical drug programs investigating the gut-brain axis and potential applications of microbiome therapeutics in treating neurological disorders. Recent discoveries suggest that the gut microbiome may play a pivotal role in influencing this bi-directional communication through multiple pathophysiological mechanisms. Clinical evidence has demonstrated that there is an association between psychological disorders (eg autism, anxiety, and depression) and dysbiosis in the gut.32 Evelo Biosciences is focused on developing monoclonal microbials, which are specific strains of microbe orally delivered in order to interact with the cells of the gut. They have therapeutic potential through their immunomodulatory functions in the gut. Evelo intends to investigate their ability to treat a range of neuro-inflammatory (ie multiple sclerosis, Alzheimer’s, and Parkinson’s disease) and psychological (ie autism, anxiety, and depression) disorders.

Conclusions

As a result of groundbreaking advances in microbiome research, industrial interest in this area has boomed. Considering the broad spectrum of therapeutic areas impacted by the microbiome, emerging microbiome therapies could make a tremendous difference for many patients worldwide and may be the key to treating currently incurable diseases. The therapeutic potential is huge and could impact a wide range of patients, ranging from those suffering from common disorders such as atopic dermatitis and lactose intolerance, to rare and life-threatening conditions such as brain cancers and MSUD. Moreover, microbiome therapeutics may play a pivotal role in battling looming global health threats such as the obesity epidemic, and antibiotic resistance. Considering this, it is fair to conclude that microbiome modulators are the new generation of therapeutic and there may be many exciting new treatments on the horizon.

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Accurate and timely intelligence about the drug development pipeline is vital to understanding the opportunities and risks in today’s biopharmaceutical marketplace – whether you are targeting an unmet medical need, investigating promising new therapies or researching drug development historical trends and treatment patterns. If you are providing contract research or other services in the pharma industry, you need to stand out. A solid understanding of your potential clients’ pipelines and competition will help you leave a lasting impression.