

Ingenious e-Brain

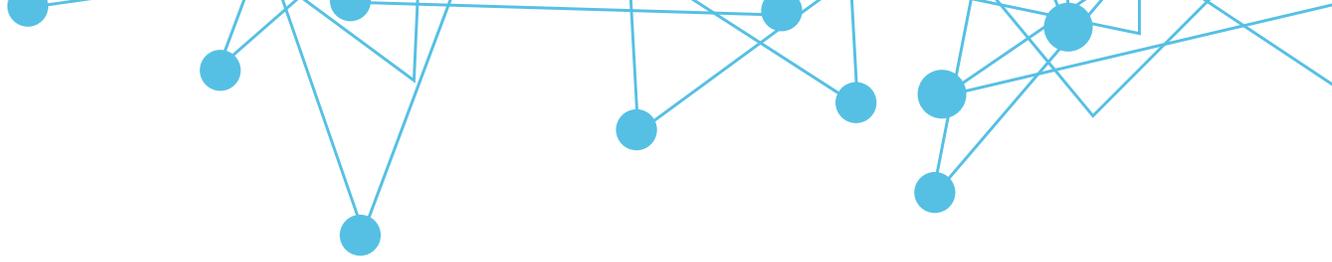
Nurturing Innovations - Fostering Business

Recent Developments in Microbiome Therapeutics

November 2017

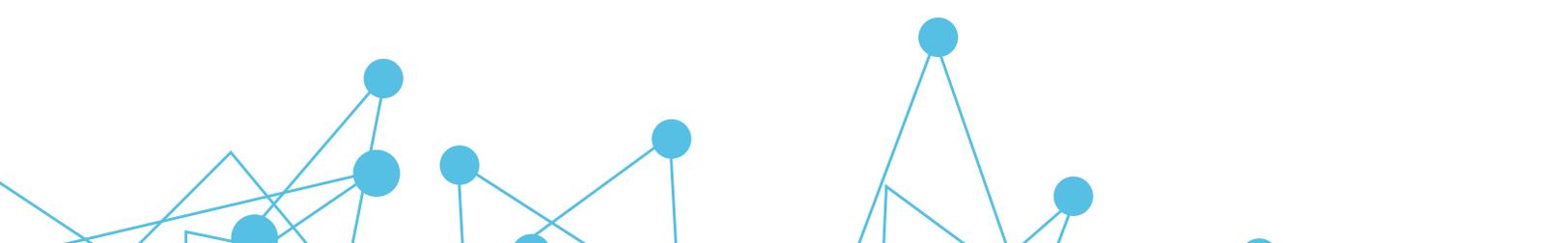


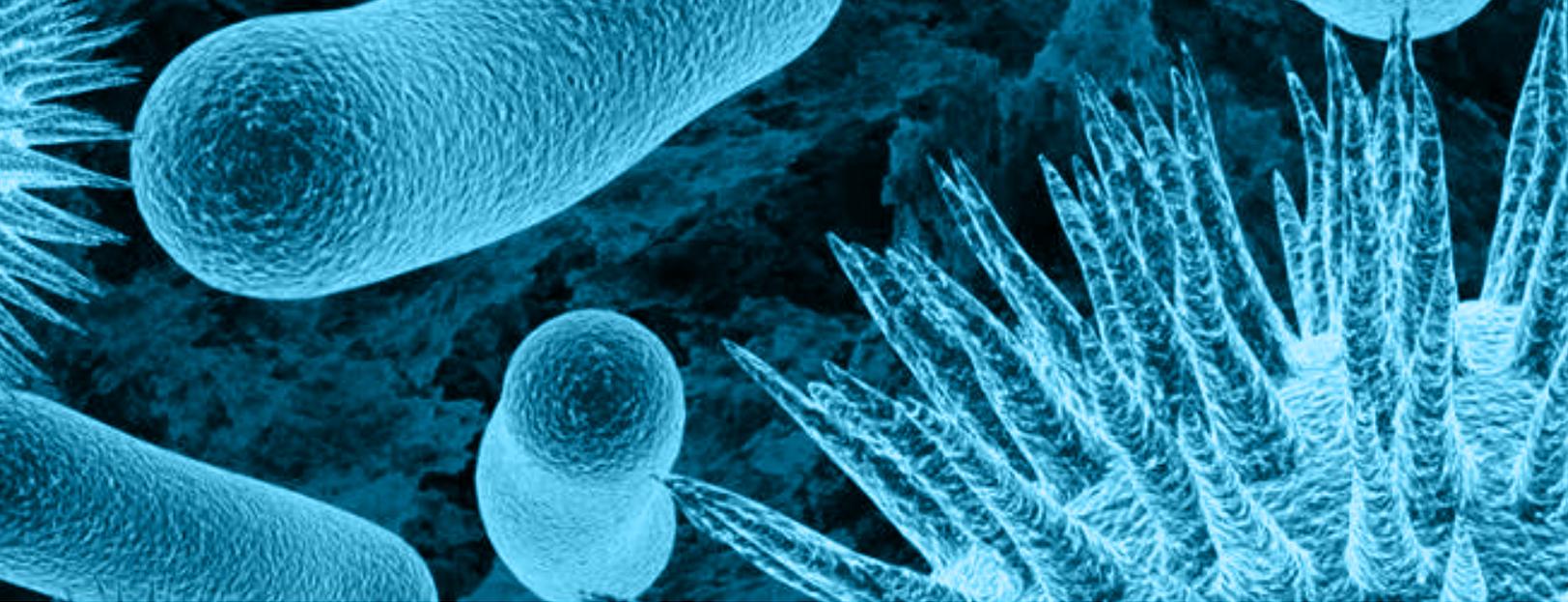
Saumya Garg



Contents

Introduction	3
Cancer	3
Central Nervous System Disorders	4
Oral Care	5
Skin Care	6
Sexually Transmitted Diseases	7
Infant Health	7
Lifestyle Related Diseases	9
Digestive System Diseases	10
Conclusion	14
Disclaimer	19





Introduction

The human microbiome has fascinated scientists for decades. With the advances in sequencing techniques, it has finally become possible for researchers to start putting the pieces of the puzzle together. An entire industry dedicated to Microbiome Therapeutics is slowly taking shape, the sole purpose of which is to identify treatments for ailments such as cancer and autism based on a minor alteration of the body's microbiome. Although the human microbiome consists of bacterial, fungal and viral species, currently the industry is focused on the bacterial part of the microbiome.

In this paper, we will look at some of the recent developments in the field of human microbiome therapeutics. We will also try to understand what some of the companies and research bodies around the world are working on.

Cancer

The International Agency for Research on Cancer (IARC)¹ has designated several microbes as Class 1 (Carcinogens)². These include *Helicobacter pylori*, Hepatitis B virus, Hepatitis C virus, Human Papillomavirus, etc. Further, several metagenomic studies³ have been conducted to identify the presence of commensal bacteria in patients affected by different types of cancer. As a result, several research groups and companies have now turned their attention towards developing therapeutic solutions targeting these bacteria.

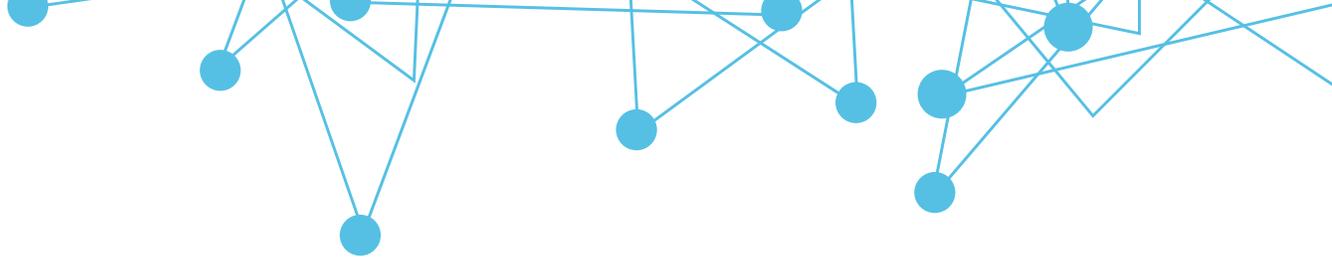
A research collaboration between scientists from The University of Hong Kong and University of East Finland, has led to a significant finding⁴ that liver cancer growth was suppressed in mice that were fed a probiotic mixture,

1 <http://www.iarc.fr/>

2 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum. 2012;100 (p t B):1-441

3 Bhatt, A. P., Redinbo, M. R. and Bultman, S. J. (2017), The role of the microbiome in cancer development and therapy. CA: A Cancer Journal for Clinicians, 67: 326–344. doi:10.3322/caac.21398

4 Li J. et al (2016), Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. PNAS, 113 (9): E1306-E1315. doi: 10.1073/pnas.1518189113



Prohep. Prohep is a novel probiotic mixture composed of equal parts of *Lactobacillus rhamnosus* GG (LGG), viable *Escherichia coli* Nissle 1917 (EcN), and heat-inactivated VSL#3 (Product of VSL Pharmaceuticals, containing *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Lactobacillus delbrueckii* subsp).

One company making strides in cancer immunotherapy is Evelo Biosciences⁵. Evelo is developing monoclonal microbials to target immunomodulatory pathways relevant to cancer, and autoimmune and inflammatory diseases. In April 2016, Evelo entered an exclusive worldwide license with University of Chicago to develop and commercialize the university's microbiome-based cancer immunotherapy solution. Evelo also entered an exclusive collaboration with Mayo Clinic, in August 2016, to isolate and characterize cancer-associated bacteria from stool samples and tumor biopsies of Mayo's patients. With a Series A funding round of \$35 million and a Series B round of \$50 million, Evelo Biosciences is all set to start clinical studies on its anti-cancer microbials in early 2018.

Central Nervous System Disorders

Although the role of the gut microbiome in affecting the neuropathology of an individual is not clear, there exists strong evidence that suggests the presence of a gut-brain axis. Several neural, endocrinal and immune pathways are believed to facilitate communication between the gut and the brain. The two companies that are doing pioneering research in the field of microbiome therapy for mental health disorders are Axial Biotherapeutics and Crestovo (now part of Finch Therapeutics Group⁶).

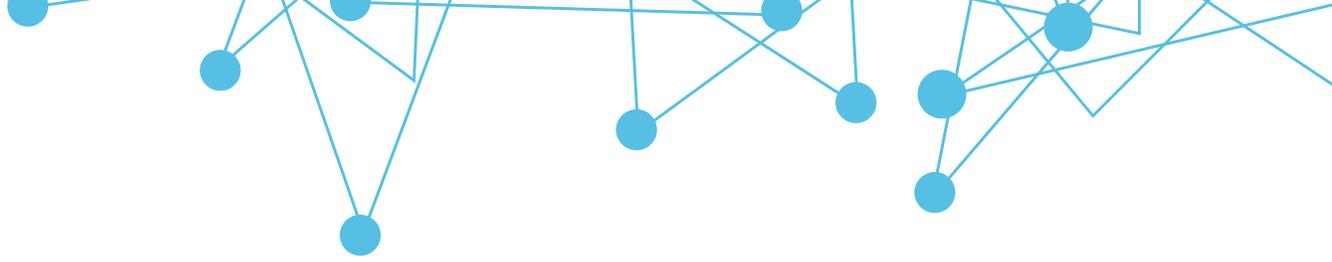
Axial Biotherapeutics⁷ is focused on developing microbial-targeted therapeutics for underserved neurological diseases and disorders, including autism spectrum disorder, Parkinson's and Alzheimer's disease. Launched in November 2016, with Series A funding of \$19.15 million, Axial has an exclusive worldwide license to related intellectual property from Caltech in applications for neurological diseases and disorders. Through a recently validated Parkinson's disease mouse model⁸, researchers at Caltech inferred that targeting the gut microbiome may provide a new approach for diagnosing and treating Parkinson's disease.

⁵ <http://evelobio.com/>

⁶ <http://finchtherapeutics.com/news/2017/10/23/finch-therapeutics-and-crestovo-announce-merger-to-form-finch-therapeutics-group-a-leading-fully-integrated-microbiome-company>

⁷ <https://www.axialbiotherapeutics.com/>

⁸ Sampson T. R. et al (2016), Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell*, 167(6): 1469-1480.e12. doi: 10.1016/j.cell.2016.11.018



Crestovo⁹ aims to use its proprietary Full-Spectrum Microbiota (FSM) platform to develop orally administered bacterial compositions for treating a variety of diseases. Although the company's primary product is targeted against *Clostridium difficile* infections (elaborated in a later section), it is also showing interest in treating mental health diseases. A group of Arizona State University researchers, funded by Crestovo, have recently concluded a small open-label clinical trial¹⁰ evaluating the impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and gastro-intestinal and Autism Spectrum Disorder (ASD) symptoms of 18 ASD-diagnosed children. The results revealed an 80% reduction of gastro-intestinal symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. It was also observed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended.

In a 2016 study¹¹ on mice, conducted by a research group from the Baylor School of Medicine, it was concluded that adding the probiotic *Lactobacillus reuteri* to the diet of patients suffering from neurodevelopmental disorders including ASD, could improve social behavior by enhancing oxytocin levels.

A relatively new company working in the field of microbiome therapy for mental health disorders is HoloBiome¹². It is focused on developing a consortium of neurotransmitter-modulating human gut bacteria, with potential applications beyond mental health. In March 2017, HoloBiome was awarded a Golden Ticket sponsorship by Amgen for using free lab space provided by LabCentral for one year¹³.

Oral Care

One of the most common oral diseases, caused by a dysbiosis between acidogenic pathogens and alkali-generating commensal bacteria colonized in the oral cavity, is dental caries. In a small clinical trial¹⁴ conducted by Sichuan University researchers, it was found that treatment with arginine-containing dentifrice normalized the oral microbiota of patients affected by dental caries.

One company working in the domain of microbiome therapeutics for oral health is C3J Therapeutics¹⁵. C3J's proprietary Specifically Targeted Antimicrobial Peptides (STAMP) Platform technology allows the antimicrobial peptides to selectively kill pathogenic bacteria. The company's C16G2 STAMP program has been developed to

9 <https://www.crestovo.com/>

10 Kang D. W. et al (2017), Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*, 5(1):10. doi: 10.1186/s40168-016-0225-7

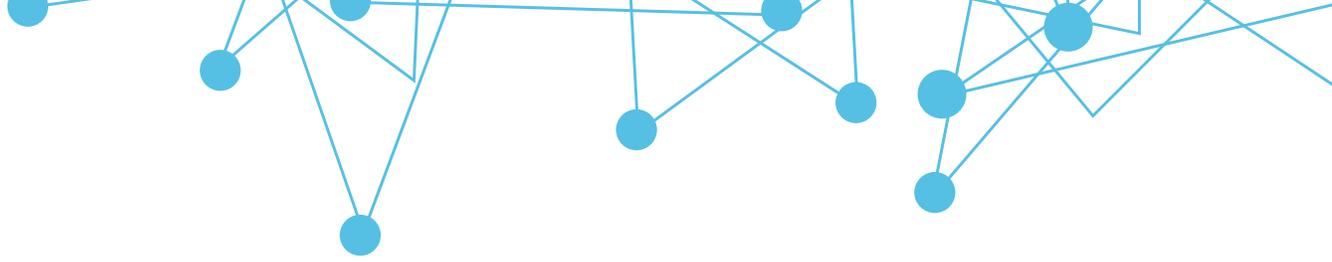
11 Buffington S. A. et al (2016), Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. *Cell*, 165(7): 1762-1775. doi: 10.1016/j.cell.2016.06.001

12 <https://holobiome.org/>

13 <https://www.prnewswire.com/news-releases/amgen-awards-three-golden-tickets-for-labcentral-residency-300430168.html>

14 Zheng X. et al (2017). *Scientific Reports* 7, Article number: 7206. doi: 10.1038/s41598-017-07042-w

15 <http://www.c3jtherapeutics.com/>



target *Streptococcus mutans* for the treatment of oral dysbiosis. The C16G2 peptide is currently undergoing Phase 2 Clinical trials under a US FDA IND application. In December 2016, the company revealed two new formulations, varnish and tooth strip, for the C16G2 product. To date, C3J Therapeutics has raised a total of \$105 million via three rounds of funding.

Skin Care

Several companies are making good progress in providing microbiome based therapeutics for skin diseases. One such company is Azitra Inc¹⁶. Azitra's core technology involves genetically engineering normal skin bacteria to express therapeutic proteins that need to be delivered to the skin. In April 2017, Azitra raised \$2.9 million from a Series A funding round, which will be utilized in testing its lead candidate, AZT-01, across several skin conditions such as eczema, rare genetic skin diseases etc. as well as for cosmetic applications¹⁷.

Naked Biome¹⁸ is working towards developing probiotic treatments for acne, eczema, psoriasis and rosacea. The company is utilizing next generation sequencing techniques for profiling healthy and diseased skin to identify unique microbial signatures that naturally aid against diseases. Although still at the data gathering stage, Naked Biome has been selected for funding by the Illumina Accelerator. The company has raised a total of \$9.4 million¹⁹ since its inception, two years ago. A direct competitor of Naked Biome is SkinomiX²⁰, also working on acne using similar techniques. No further information was available for SkinomiX.

Xycrobe Therapeutics²¹ is an early stage biotech company working towards converting the skin's healthy bacteria into biotherapeutic delivery vehicles for treatment of inflammatory diseases of the skin. Xycrobe's platform utilizes two naturally occurring skin bacteria – *Propionibacterium acnes* and an undisclosed species. In August 2016, Xycrobe entered into a research collaboration with Johnson & Johnson Innovation to develop future therapeutic and commercial applications of the Xycrobe platform²². Xycrobe is actively seeking investors so that it can perform animal and human pilot studies as well as set up a GMP facility for its xycrobes²³.

16 <https://azitrainc.com/>

17 <http://www.fiercebiotech.com/biotech/skin-disease-biotech-azitra-closes-2-9m-series-a-for-microbiome-work>

18 <http://www.nakedbiome.com/>

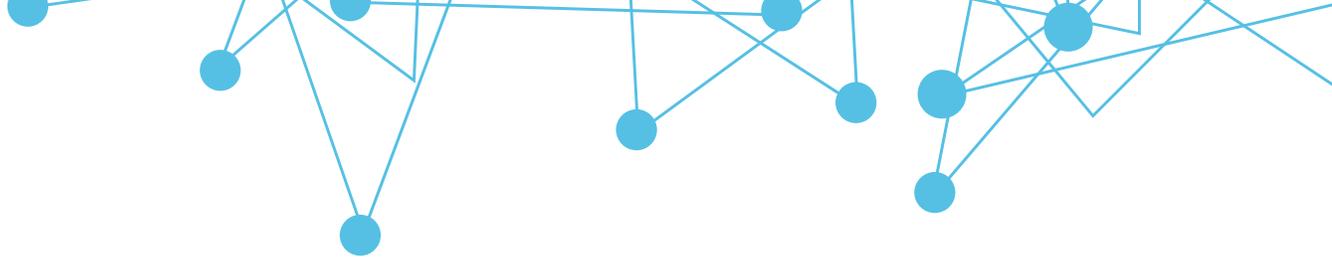
19 <https://pitchbook.com/profiles/naked-biome-profile-investors-funding-valuation-and-analysis>

20 <http://www.skinomix.com/>

21 <http://www.xycrobe.com/home.html>

22 <https://www.prnewswire.com/news-releases/xycrobe-announces-research-collaboration-with-johnson--johnson-innovation-300313494.html>

23 <http://www.medstartr.com/project/detail/1307>



Another company working in the acne domain is AOBiome Therapeutics²⁴, a clinical-stage company that has been developing its patented microbiome-targeted therapies for systemic and local inflammatory conditions of the skin. In October 2017, the company reported positive efficacy results for the Phase 2B clinical trials of its Ammonia Oxidizing Bacteria (AOB) product candidate, *Nitrosomonas eutropha*, for the treatment of acne. The company is conducting clinical trials for its AOB to fight other non-skin related diseases as well (elaborated in later sections). In January 2017, iCarbonX, China's largest health data collection and analysis platform, invested \$30 million in AOBiome, raising its total funding to \$38.7 million.

Sexually Transmitted Diseases

The human urogenital tract's health is largely dependent on its microbial inhabitants. A woman's urogenital bacteria, primarily Lactobacilli, have been known to play protective as well as preventative roles. In February 2016, researchers from the University of Bologna, Italy, published the results from an *in vitro* study²⁵ about the effects of *Lactobacillus crispatus* on *Chlamydia trachomatis*. It was found that high levels of *L. crispatus* inhibited the infectivity of *C. trachomatis*. This finding could be a breakthrough for *Chlamydia* treatments, since it is the leading cause of sexually transmitted bacterial infections with nearly 100 million new cases each year.

Infant Health

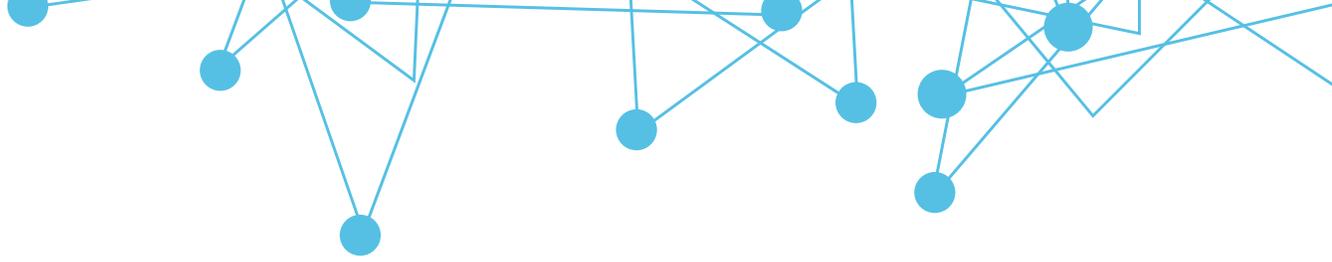
A major domain of focus for microbiome therapeutics is neonatal or infant health. It has been established that several metabolic and immune disorders in adult life arise due to a predisposition to these diseases as a result of dysbiosis in the neonatal intestinal colonization of bacteria. Thus, scientists are now focusing on fixing this dysbiosis early in life.

In February 2017, a group of scientists from the United Kingdom, published the findings from a study²⁶ conducted to identify the effect of *Bifidobacterium lactis* NCC2818 *subsp. lactis* on the intestinal microbiota, metabolism and mucosal immune system of neonatal piglets. It was found that the probiotic supplementation reinforced intestinal barrier integrity and had significant effects on the development of the mucosal immune system and metabolic function. The study was partly funded by Nestlé.

24 <https://aobiome.com/>

25 Nardini, P. et al (2016), *Lactobacillus crispatus* inhibits the infectivity of *Chlamydia trachomatis* elementary bodies, *in vitro* study. Scientific Reports 6, Article Number: 29024. doi: 10.1038/srep29024

26 Lewis M.C. et al (2017), Early intervention with *Bifidobacterium lactis* NCC2818 modulates the host-microbe interface independent of the sustained changes induced by the neonatal environment. Scientific Reports 7, Article Number: 5310. doi:10.1038/s41598-017-05689-z



In another study²⁷, results of which were published in February 2016, it was found that sialylated milk oligosaccharides promoted microbiota-dependent increase of lean body mass gain, change in bone morphology, and an altered liver, muscle, and brain metabolism. The study was conducted in mice as well as piglets and may solve a big challenge of infant undernutrition. Researchers from Washington University, University of California Davis and Duke University collaborated to carry out the various aspects of the study. Co-founders of the company Evolve Biosystems²⁸, were also involved in the design and execution of the pre-clinical studies. Evolve Biosystems is dedicated to developing probiotic products for resolving infant gut dysbiosis. Their product Evivo, is a probiotic powder consisting of activated *Bifidobacterium infantis* EVC001-ActiBif™. To date, the company has raised \$29 million via two rounds of funding. The company also sells GlycoGuard®, another *B. infantis* based product, for nursing foals.

Results of a pilot study²⁹ published in March 2016, showed that vaginal microbes of the mother can be partially restored at birth in C-section delivered babies. This finding is extremely crucial since several epidemiological studies have found a correlation between C-section delivery and increased risk of obesity, asthma, allergies and immune deficiencies. Building on this research is the company, Commense Health³⁰, a subsidiary of PureTech Health³¹. In March 2016, Commense obtained an exclusive, worldwide license from New York University for a technology designed to enable microbial transfer in newborns who may not have been exposed to vaginal microbiome, including those delivered via C-section³². Further, in May 2017, Commense signed a licensing agreement³³ with the University of British Columbia for a microbiome-based therapy for prevention of childhood asthma and other allergic diseases.

Infant Bacterial Therapeutics AB³⁴ is working on developing preventive treatments for infant rare diseases, specifically Necrotizing Enterocolitis (NEC). IBT's lead drug candidate, IBP-9414, has been granted Orphan Drug Designation by the FDA and the European Commission. IBP-9414 has been designed to prevent NEC in premature infants. The initial evaluation of the results from the Phase 2 clinical trial conducted for this drug has demonstrated similar safety and tolerability profile in the active and placebo groups. The company is also pursuing its second rare disease program, IBP-1016, for the treatment of gastroschisis. IBT is a public company listed on the Stockholm Stock Exchange.

27 Charbonneau M.R. et al (2016), Sialylated Milk Oligosaccharides Promote Microbiota-Dependent Growth in Models of Infant Undernutrition. *Cell* 164(5): 859-871. doi: 10.1016/j.cell.2016.01.024

28 <https://www.evolvebiosystems.com/>

29 Dominguez-Bello M.G. (2016), Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nature Medicine* 22: 250-253. doi: 10.1038/nm.4039

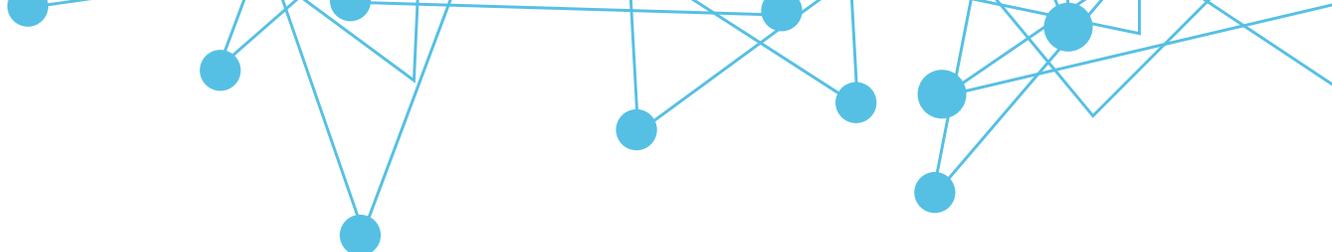
30 <http://www.commensehealth.com/>

31 <http://puretechhealth.com/>

32 <http://www.businesswire.com/news/home/20160331005339/en/Commense-Advances-Microbiome-Platform-Targeting-Early-Childhood>

33 <http://www.gelesis.com/press-releases/05052017.php>

34 <http://ibtherapeutics.com/>



Lifestyle Related Diseases

With the fast paced and hectic lives we spend nowadays, lifestyle related diseases can be found in nearly all homes. These diseases include type 2 diabetes, obesity, hypertension etc. Consumption of high-energy and high-fat foods causes Metabolic Syndrome (MS), which affects nearly 35% of all US adults (as of 2012)³⁵.

In March 2017, Ezaki Glico Co. Ltd.³⁶, in collaboration with several researchers from Tokyo, published results from a study³⁷ investigating the effects of probiotic *Bifidobacterium* treatment on MS. The group found that the probiotic, *Bifidobacterium animalis* ssp. *lactis* GCL2505, improved metabolic disorders by reducing visceral fat accumulation and improving glucose tolerance.

In another 2017 study³⁸, researchers from China found that oral supplementation with the probiotics, *Bifidobacterium pseudocatenulatum* LI09 and *Bifidobacterium catenulatum* LI10, attenuated D-galactosamine (D-GalN) induced liver damage. The probiotics further conferred liver protection, reduced ileal mucosal injury and gut flora dysbiosis, as well as alleviated the increase of cytokines in plasma.

In a study³⁹ of high-fat fed mice, a group of Finnish researchers from University of Turku found that oral supplementation with *Faecalibacterium prausnitzii* improved hepatic health, decreased adipose tissue inflammation, and increased muscle mass.

Besides the acne treatment mentioned earlier, AOBiome Therapeutics is also working towards developing treatments for hypertension. Its lead product candidate, B244, a first-in-class, topical formulation of *Nitrosomonas eutropha* D23, is currently undergoing Phase 2 Clinical Trial for testing safety and efficacy in individuals with either systolic prehypertension or systolic Stage 1 hypertension⁴⁰.

35 Moore J.X. et al (2017), Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Prev Chronic Dis* 14:160287. doi: 10.5888/pcd14.160287

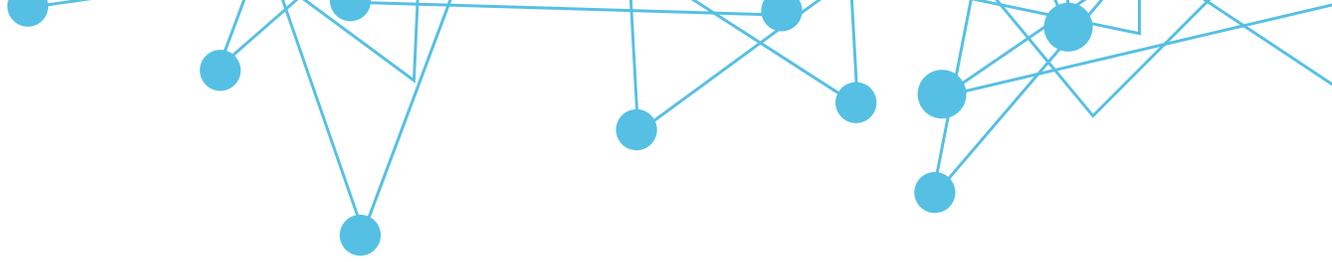
36 <https://www.glico.com/global/>

37 Aoki, R. et al (2017), A proliferative probiotic *Bifidobacterium* strain in the gut ameliorates progression of metabolic disorders via microbiota modulation and acetate elevation. *Scientific Reports* 7, Article Number: 43522. doi: 10.1038/srep43522

38 Fang D. et al (2017), *Bifidobacterium pseudocatenulatum* LI09 and *Bifidobacterium catenulatum* LI10 attenuate D-galactosamine-induced liver injury by modifying the gut microbiota. *Scientific Reports* 7, Article Number: 8770. doi: 10.1038/s41598-017-09395-8

39 Munukka E. (2017), *Faecalibacterium prausnitzii* treatment improves hepatic health and reduces adipose tissue inflammation in high-fat fed mice. *The ISME Journal* 11: 1667-1679. doi: 10.1038/ismej.2017.24

40 https://aobiome.com/news_item&item=140&title=AOBiome-Completes-Patient-Enrollment-In-Phase-2-Clinical-Trial-Of-Lead-Candidate-B244-To-Treat-Elevated-Blood-Pressure



LNC therapeutics⁴¹ is a microbiota-centric R&D products, developing therapies for obesity and related cardiometabolic diseases. The company's Temys project aims to restore the intestinal microbiota of patients with a BMI higher than 25, waist circumference more than 94 cm (men) or 80 cm (women) and who are suffering from more than two cardiometabolic diseases. The company raised \$6.5 million in September 2017, through a Series C round, raising its total funding to \$10 million.

Another company working in the weight management space is the start-up, TargEDys⁴². The company is currently working towards launching its two nutritional products – ProbioSatys™ for overweight people and ProbioNutrys™ for frail people. The company has already tested the proof of concept for ProbioSatys™ in several animal models and is aiming to get it to the market by 2019. Their technology is based on the finding that certain gut bacteria from the enterobacteriaceae family produce a protein (ClpB), that mimics the human satiety hormone (α -MSH), and which directly acts on the satiety regulation center in the brain. After two rounds of funding, TargEDys has a total funding of \$10.3 million⁴³.

Currently focusing on prediabetes and newly diagnosed diabetes type 2, MicroBiome Therapeutics'⁴⁴ lead product, NM504, is a GI microbiome modulator to help prevent diabetes progression and to lessen the limiting GI side-effects of the drug, metformin. In October 2016, USPTO issued a notice of allowance for NM504's patent application⁴⁵. The patent application covers the use of a unique composition of NM504 in diabetic patients and prediabetics at risk of developing diabetes, and delivered via formulations such as capsules, tablets, smoothies and nutrition bars.

Digestive System Diseases

While most of the previously mentioned research groups and companies are working on the indirect effects of the microbiome, a large body of research is still focused on the direct impact of microbiome modulation on the human digestive system, more specifically on treating diarrhea. The newly formed Finch Therapeutics Group⁴⁶, a merger of Finch Therapeutics and Crestovo, is one such company. Finch is a microbiome engineering company that utilizes machine learning algorithms and human-first discovery approach to develop microbial therapies. In collaboration with Takeda, Finch is developing its lead candidate, FIN-524, based on its Rationally-Selected Microbiota™ platform for treating ulcerative colitis. With the October 2017 acquisition, Finch has added Crestovo's lead candidate, CP101,

41 <http://lnctherapeutics.com/>

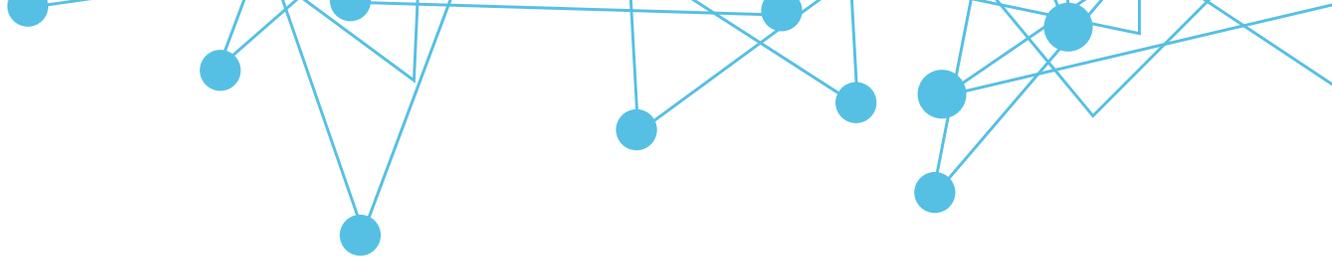
42 <http://www.targedys.com/>

43 <https://www.crunchbase.com/organization/targedys>

44 <http://www.mbiome.com/>

45 U.S. Patent Application No.: 14/238,980, A Human Gastrointestinal Microbiome Modulating Food Supplement for Improving Blood Glucose Regulation

46 <http://finchtherapeutics.com/>



for treating *Clostridium difficile* infections to its product portfolio. CP101 is currently undergoing a multicenter, double-blind, placebo-controlled Phase 2 clinical trial⁴⁷.

Second Genome⁴⁸ is a clinical stage company, currently focusing on developing its lead candidate SGM-1019, for the treatment of Inflammatory Bowel Disease (IBD). SG-1019 is a small molecule inhibitor of a key microbiome-mediated target that addresses pain and inflammation in IBD. It has successfully completed Phase 1 clinical trials. In April 2016, Second Genome received \$42.6 million in Series B financing from Roche Venture Fund and Pfizer Venture Investments, raising its total funding to nearly \$63 million.

A low-profile company in this domain is NuBiyota⁴⁹. In April 2017, Takeda struck a deal⁵⁰ to access NuBiyota's microbiome platform based on a cocktail of bacteria for gastro-intestinal infections. With this strategic collaboration, NuBiyota received an upfront payment of an undisclosed amount and will receive success-based payments based on development, regulatory and commercial milestones, as well as royalties based on net sales.

In September 2017, a group of Ghent University researchers published results from an *in vitro* study⁵¹ on the effects of butyrate-producing bacteria on patients affected by Crohn's Disease. The study showed that supplementing with butyrate-producing bacteria strengthened the epithelial barrier function and increased butyrate production.

The French company, Enterome Bioscience⁵², is one of the bigger players in the domain. The company has a diverse microbiome therapeutics portfolio including Crohn's Disease, IBD, Immuno-oncology and Autoimmune diseases. The company also develops diagnostic tools for IBD and immuno-oncology. In January 2016, Enterome announced a strategic drug discovery collaboration with Takeda, and a collaborative research agreement with INRA⁵³ and Janssen Biotech (a Johnson & Johnson company), to develop new therapeutics for IBD and Crohn's Disease. In October 2017, the company completed Phase 1 clinical trials for its lead candidate, EB8018, a molecule designed to block FimH, a bacterial adhesin, for the treatment of Crohn's disease. Phase 2 for the drug is expected to start in 2018. EB8018 was in-licensed from Vertex Pharmaceuticals in April 2016. Enterome has raised a total of approx. \$34 million via three rounds of funding.

47 <https://clinicaltrials.gov/ct2/show/NCT03110133>

48 <http://www.secondgenome.com/>

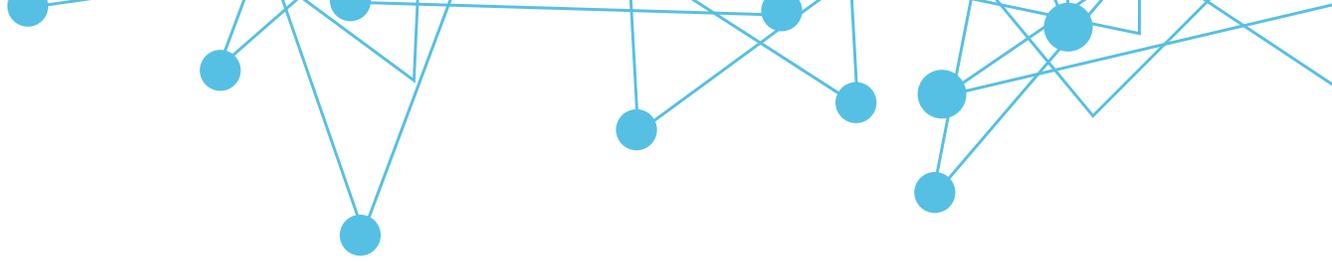
49 <https://www.nubiyota.com/>

50 <https://www.takeda.com/newsroom/newsreleases/2017/takeda-enters-into-strategic-collaboration-with-nubiyota-for-microbiome-therapeutics/>

51 Geirnaert, A. et al (2017), Butyrate-producing bacteria supplemented in vitro to Crohn's disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity. Scientific Reports 7, Article Number: 11450. doi: 10.1038/s41598-017-11734-8

52 <http://www.enterome.fr/site/>

53 INRA: French National Institute for Agriculture Research



Another company with a big focus on Crohn's Disease is 4D Pharma⁵⁴. The company has built a proprietary platform, MicroRx, for rapid discovery of bacteria with therapeutic effects. The company has successfully completed a Phase 1B clinical trial for its lead candidate, Blautix, for treating Irritable Bowel Syndrome. In 2016⁵⁵, the company started Phase 1 clinical trials for another product, Thetanix, to treat Pediatric Crohn's Disease. Thetanix has been assigned Orphan Drug status by the FDA. Further, the company is also developing Rosburix, a product for treating Pediatric Ulcerative Colitis.

Some of the bigger companies in the field of microbiome therapeutics are primarily focused on developing treatments for *Clostridium difficile* infections. Vedanta Biosciences⁵⁶, another PureTech Health subsidiary, primed with a recent funding of \$50 million, is getting its lead candidate, VE 303, ready for Phase 1 clinical trial. Its other lead candidate, VE 202 for Inflammatory Bowel Disease, is expected to enter Phase 1 clinical trial in 2018⁵⁷. The company has been granted several patents covering compositions of microbial consortia for treatment of diseases.

Synthetic Biologics⁵⁸ is a late-stage clinical company with two lead candidates focused on gut disorders. SYN-004 (ribaxamase), an oral tablet, has been designed to protect the gut microbiome from the effects of intravenous beta-lactam antibiotics for the prevention of *Clostridium difficile* infection, pathogenic overgrowth and the emergence of antimicrobial resistance. SYN-010, a proprietary, modified-release formulation of lovastatin lactone, has been designed to reduce the impact of methane producing organisms in the gut microbiome to treat Irritable Bowel Syndrome with Constipation (IBS-C). The company completed Phase 2 clinical trials for both SYN-004 and SYN-010 in 2017, and is now preparing for Phase 3 trials. In May 2017, the US FDA granted SYN-004, a Breakthrough Therapy Designation. The company is listed on the New York Stock Exchange and trades under the ticker SYN⁵⁹.

The most talked about platform in the industry nowadays, Microbiota Restoration Therapy™, belongs to Rebiotix⁶⁰, a clinical stage biotechnology firm. Its lead candidate, RBX2660, an Enema Formulation for prevention of recurrent *Clostridium difficile* is currently undergoing a Phase 3 clinical trial. Another product, RBX7455, a lyophilized non-frozen oral capsule formulation for prevention of recurrent *Clostridium difficile*, is undergoing Phase 1 clinical trial. In September 2017, the company raised \$8.5 million in convertible note, raising its total funding to \$36.3 million to date.

54 <https://www.4dpharmapl.com/>

55 <http://globalpharmaupdate.com/4d-pharma-starts-dosing-in-phase-1-trial-with-thetanix-to-treat-paediatric-crohns-disease/>

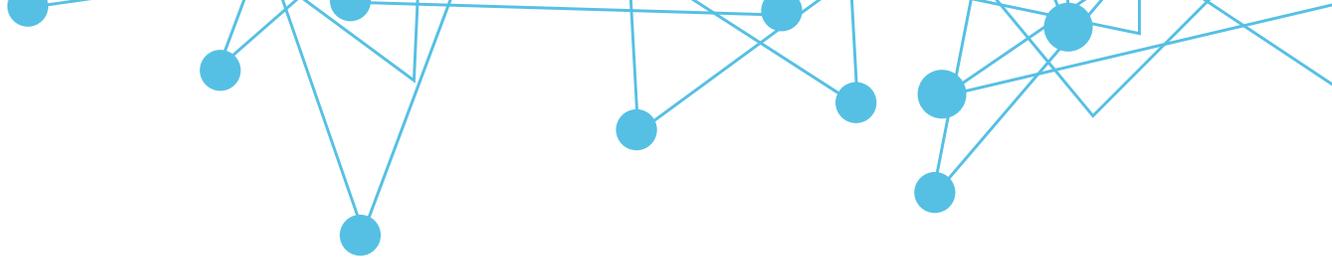
56 <https://www.vedantabio.com/>

57 <http://puretechhealth.com/our-pipeline/microbiome-derived-immune-modulators-ve303-ve202-ve505>

58 <https://www.syntheticbiologics.com/>

59 <https://finance.google.com/finance?q=NYSEMKT:SYN>

60 <http://www.rebiotix.com/>

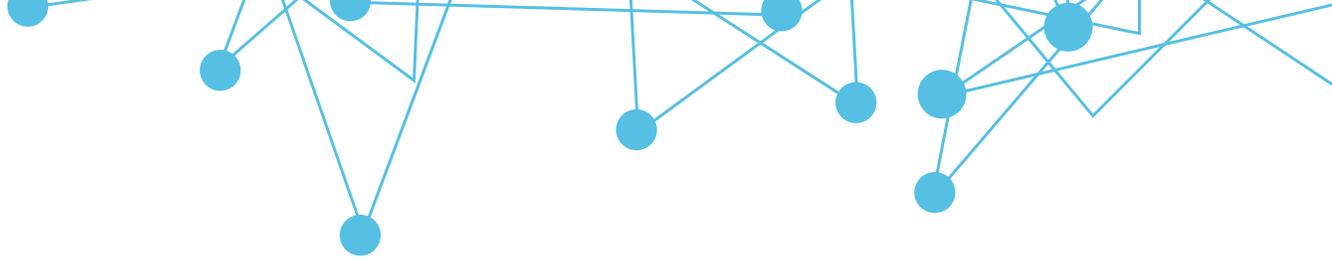


Finally, the largest company in the field is Seres Therapeutics⁶¹. Seres' lead candidate, SER-109, is an oral microbiome therapeutic for the prevention of *Clostridium difficile* infection (CDI) in adults with recurrent CDI. The drug has been designated Breakthrough Therapy and an Orphan Drug by the US FDA and is currently undergoing Phase 3 clinical trial. The company's other candidate, SER-262 for primary CDI, is undergoing Phase 1b clinical trials. Seres' candidate for Ulcerative colitis, SER-287, finished its Phase 1b trial in October 2017, with positive topline results. In January 2016, Seres entered a commercialization agreement with Nestlé for the development and commercialization, outside of the United States and Canada, for its product candidates SER-109 and SER-262 for CDI, and SER-287 and SER-301 for IBD. In exchange for commercial rights, Seres will be provided an upfront payment of \$120 million in cash, followed by a series of milestone payments and tiered royalties on sales. In 2016, Seres also participated in several other industry and academic collaborations to further their work:

- Collaboration with Emulate⁶², a company that develops micro-engineered, living-tissue-based systems called Organs-on-Chips. Seres will use Emulate's intestine-chip platform to identify novel bacteria compositions with therapeutic potential.
- Collaboration with Massachusetts General Hospital. Seres will sponsor a placebo-controlled, proof-of-concept clinical study at the hospital to evaluate the impact of Fecal Microbiota Transplantation (FMT) on adults suffering from obesity and other metabolic disorders.
- Collaboration with Mayo Clinic. Scientists from the two organizations will collaborate on several preclinical and clinical studies to identify novel therapeutics for Primary Sclerosing Cholangitis, Non-Alcoholic Steatohepatitis (NASH) and other liver diseases.
- Collaboration with University of Pennsylvania. Researchers from the two organizations will collaborate on a clinical study to evaluate the role of the microbiome in certain rare genetic metabolic diseases.
- Multi-year research collaboration with Memorial Sloan Kettering Cancer Center, for the discovery and development of microbiome therapeutics in the field of immuno-oncology.
- Academic collaborations with researchers at the Research Institute of St. Joseph's Hamilton and the Medical University of Graz, for therapeutics for Inflammatory Bowel Disease.

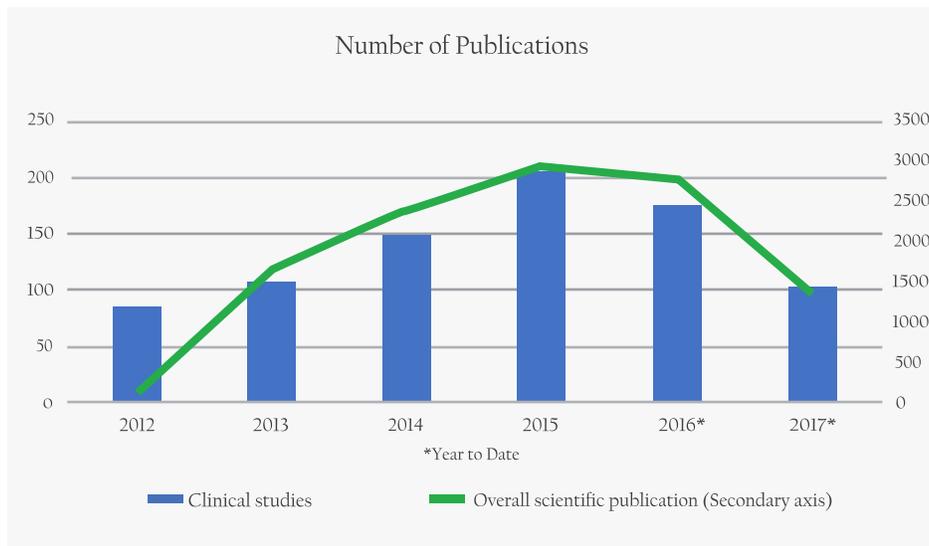
⁶¹ <http://www.serestherapeutics.com/>

⁶² <https://emulatebio.com/>



Conclusion

The past few years have been abuzz with activity in the Microbiome Therapeutics domain. The amount of research being conducted in the domain is increasing steadily⁶³. Several companies have completed preclinical studies for



their lead candidates and the stage is set for human trials. The first drugs targeting the gut microbiome could hit the market as early as 2020. However, failures such as the one faced by Seres in 2016 with the Phase 2 trial of SER-109, as well as regulatory hurdles could delay the launch of commercial drugs in the space. The US FDA and European Medicines Agency have very little experience in evaluating

live bacteria as therapeutics causing another level of regulatory challenge. Also, not all big pharma giants are joining the microbiome therapeutics bandwagon, making it more of a wait and watch game.

⁶³ Data based on search conducted on the PubMed database.

APPENDIX

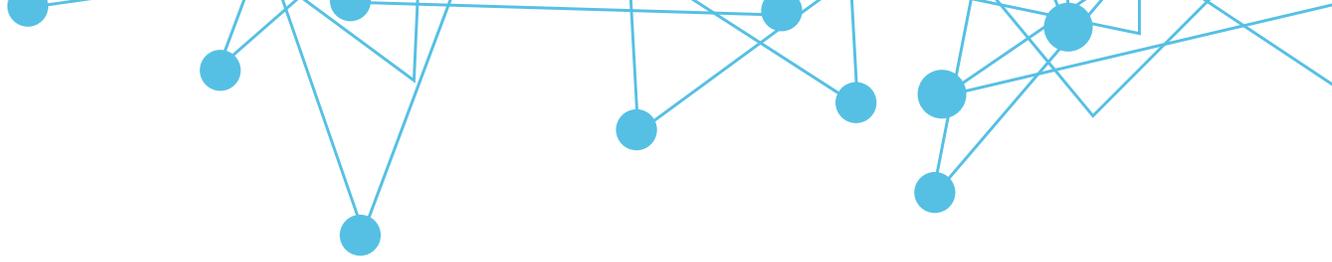
Table 1: Overview of start-ups

Company	Location	Funding to date	Disease Indications	Lead Candidate	Stage of Development					
					Discovery	Preclinical	Clinical			
							Phase 1	Phase 2	Phase 3	
C3J Therapeutics	USA	\$105,000,000	Prevention of Dental Caries	C16G2	█	█	█	█		
			<i>C. difficile</i> Infection	CD17	█	█				
			Obesity, IBD, Autoimmune disease	–	█					
Evelo Biosciences	USA	\$85,000,000	Cancer, Immuno-inflammatory diseases	–	█	█				
Second Genome	USA	\$62,900,000	Inflammatory Bowel Disease	SGM-1019	█	█	█			
Vedanta Biosciences	USA	\$55,400,000	<i>C. difficile</i> Infection	VE 303	█	█	█			
			Inflammatory Bowel Disease	VE 202	█	█				
			Immuno-oncology	VE 505	█	█				
AOBiome Therapeutics	USA	\$38,706,513	Mild to moderate acne	B244	█	█	█	█		
			Hypertension	B244	█	█	█	█		
			Allergic rhinitis	B244	█	█	█			
			Pruritis/Eczema	–	█	█	█			
			Wound healing	–	█	█				
			Thermoregulation	–	█	█				
Rebiotix	USA	\$36,295,000	Recurrent <i>C. difficile</i> Infection	RBX2660 (Enema Formulation)	█	█	█	█	█	
			VRE Elimination		█	█	█			
			Pediatric Ulcerative Colitis		█	█	█			
			Multi-Drug Resistant UTI		█	█	█			
			Hepatic Encephalopathy		█	█	█			
			Recurrent <i>C. difficile</i> Infection	RBX7455 (Oral Formulation)	█	█	█			
Enterome Bioscience	France	\$34,270,000	Crohn's Disease	EB8018	█	█	█			
			Crohn's Disease	EB110, EB220	█	█				
			Ulcerative colitis, Irritable Bowel Syndrome	EB410, EB420	█					
			Glioblastoma	EO2315	█	█				
			Unknown	EO510, EO520	█					
Evolve Biosystems	USA	\$29,000,000	Infant gut dysbiosis	Evivo (commercially available)						

Company	Location	Funding to date	Disease Indications	Lead Candidate	Stage of Development				
					Discovery	Preclinical	Clinical		
							Phase 1	Phase 2	Phase 3
Axial Biotherapeutics	USA	\$19,500,000	CNS Disorders	–					
LNC Therapeutics	France	\$11,610,000	Obesity and associated cardiometabolic diseases	Temys					
TargEDys	France	\$10,264,560	Obesity	ProbioSatys™					
			Underweight	ProbioNutrys™					
Naked Biome	USA	\$9,400,000	Skin diseases	–					
Azitra Inc.	USA	\$3,250,000	Skin diseases	AZT-01					
MicroBiome Therapeutics	USA	\$3,043,445	Prediabetes, Diabetes type 2	NM504					
Xyrobe Therapeutics Inc.	USA	\$199,000	Skin diseases	–					
Finch Therapeutics Group	USA	Unknown	<i>C. difficile</i> Infection	CP101					
			Ulcerative colitis	FIN-524					
			Mental Health	–					
HoloBiome	USA	Unknown	Mental Health	–					
Commense Health	USA	Unknown	Asthma, Allergy and other Pediatric Autoimmune Disorders	COM101					
NUBiyota	Unknown	Unknown	<i>C. difficile</i> Infection	MET-2					

Table 2: Overview of Publicly listed companies

Company	Location	Market Cap	Disease Indications	Lead Candidate	Stage of Development					
					Discovery	Preclinical	Clinical			
							Phase 1	Phase 2	Phase 3	
Seres Therapeutics	USA	\$403,910,000	Recurrent <i>C. difficile</i> Infection	SER-109	█	█	█	█	█	█
			Primary <i>C. difficile</i> Infection	SER-262	█	█	█			
			Ulcerative Colitis	SER-287	█	█	█			
			Inflammatory Bowel Disease	SER-301	█	█				
			Prevention of infection and GVHD following hematopoietic stem cell or organ transplant	SER-155	█	█				
			Immuno-oncology and hematopoietic stem cell transplant	–	█					
			Inflammatory Bowel Disease	–	█					
			Primary sclerosing cholangitis, NASH and other liver diseases	–	█					
			Obesity/Metabolic syndrome	–	█					
			Genetic metabolic diseases	–	█					
4D Pharma PLC	UK	\$252,910,000	Irritable Bowel Syndrome	Blautix	█	█	█			
			Paediatric Crohn’s disease	Thetanix	█	█	█			
			Paediatric Ulcerative Colitis	Rosburix	█	█	█			
			Cancer	MRx518	█	█	█			
			Severe neutrophilic asthma	MRx0004	█	█	█			
			Eosinophilic asthma	MRx0001	█	█	█			
			Rheumatoid arthritis	MRx0006	█	█	█			
			Multiple sclerosis	MRx0002	█	█	█			
			Autism	–	█	█				
			Anxiety/depression	–	█	█				
Synthetic Biologics	USA	\$100,930,000	Primary <i>C. difficile</i> Infection, Pathogenic overgrowth, Antimicrobial Resistance	SYN-004 (Ribaxamase)	█	█	█	█		
			Irritable Bowel Syndrome with constipation	SYN-010	█	█	█	█		
			Pertussis (Whooping Cough)	SYN-005	█	█	█			
			Phenylketonuria (PKU)	SYN-200	█					
Infant Bacterial Therapeutics AB	Sweden	\$88,000,000	Necrotizing Enterocolitis (NEC)	IBP-9414	█	█	█	█		
			Gastroschisis	IBP-1016	█	█				



Disclaimer

The information provided in this document covers a period of two years, 2016 and 2017 (till October). The scope of this document does not include microbiome based devices and diagnostic methods.



Ingenious e-Brain

Nurturing Innovations - Fostering Business

For more details contact us:

services@iebrain.com

Ingenious e-Brain Solutions Pvt. Ltd.

4 Heinrick Way Bridgewater

NJ 08807, New Jersey, USA

Phone: +1 347 480 2054, +1 408 7017314

© Copyright 2017 Ingenious e-Brain Solutions | All Rights Reserved