Special Report

Emerging Therapy Areas

Microbiome-based Therapeutics
Microbiome-based therapeutics, an emerging field with applications in various therapeutic areas; oncology and immunology are the upcoming segments in microbiome space

**Microbiome-based therapeutics**

- The microbiome involves the natural bacterial colonization of the body, including the skin, gut, and stomach. Research over the past few years has shown there is an interaction between the microbiota and organ systems. Examples include the gut-brain axis and other such interactions that impact the metabolism, neurology, infection, gut health, and other chronic health conditions.

- Microbiome therapeutics received a big boost in August 2020 when Seres Therapeutics’ gut microbiota capsule SER-109 met its primary end point in a Phase III clinical trial. In 2020, over 640 microbiome-related patents were granted and around 575 clinical trials were launched in the microbiome segment.

- The global microbiome therapeutics market is expected to reach approximately USD 150 Mn by 2025, recording a CAGR of 21.9% from 2023. Gastrointestinal (GI) indications, such as ulcerative colitis and irritable bowel syndrome, would be the key segments, accounting for about 36.28% of the market. Upcoming indications being explored in the microbiome space include oncology, metabolic, infectious, and inflammatory diseases.

**Microbiome-based Therapeutic Areas**

- **Gastrointestinal**
  - Crohn’s Disease
  - Hepatic Encephalopathy
  - Irritable Bowel Syndrome
  - Ulcerative Colitis
  - Necrotizing Enterocolitis

- **Immunology**
  - Plaque Psoriasis
  - Graft Versus Host Disease
  - Peanut and Food Allergy

- **Oncology**
  - Bladder Cancer
  - Melanoma
  - Renal Cell Carcinoma
  - Gastric Cancer
  - Colorectal Cancer

- **Infectious Disease**
  - COVID-19
  - Clostridioides Difficile Infections
  - Bacterial Vaginosis

Other therapy areas include drug candidates for metabolic disorders, dermatology, genitourinary disorders and sex hormones, and neurological disorders.

*Source: Industry Reports, News Articles, Company websites, Aranca Analysis*
Innovation in sequencing, increasing potential role of microbiome in immunology and oncology segments prompt companies to invest in development of microbiome-based drugs

Key market drivers and trends

**Entry of Major Pharmaceutical Players**
- A number of big pharmaceutical players such as MSD, Takeda, and AstraZeneca have started investing in the microbiome space.
- Since 2018, pharmaceutical-biotech partnerships and collaborations have been on the rise in the microbiome arena. For example, Takeda has partnered with several companies such as Finch, Enterome, Debiopharm, and Nubiyota in the past six years.
- Clinical trials are ongoing for a wide range of indications such as oncology, immunology (autoimmune diseases and allergies), and infectious diseases.

**Government Initiatives**
- Several government initiatives have supported the microbiome market. The White House Office of Science and Technology Policy, in collaboration with federal agencies and private sector stakeholders, announced the National Microbiome Initiative.
- Large-scale sequence-based microbiome projects, such as the Metagenomics of the Human Intestinal Tract consortium funded by the European Commission, have catalyzed microbiome research.

**Rapid Scientific Innovations and Newer Technologies**
- Research in microbiome in human health has recently gained more traction with the availability of genome sequencing and omics tools (metabolomics, metagenomics, and metatranscriptomics).
- Metagenomic sequencing would further aid the identification of the desired microbial species that can be assayed for pharmacokinetic properties and metabolites using techniques such as mass spectrometry and high-performance liquid chromatography.

**Novel Product Development and Impact of COVID-19**
- Increased funding and investments for research and therapeutic innovation, along with significant focus on human microbiome therapeutics development, are the major factors driving the market.
- Novel products are currently in the late stage of development, with significant Phase III trial results announced in 2020 for Seres Therapeutics, Ferring, and Rebiotix.
- The COVID-19 pandemic has fueled the need to understand and investigate how the microbiome can be utilized for promoting a healthy immune system.

Source: Industry Reports, News Articles, Company websites, Aranca Analysis
Two pipeline candidates in GI therapy are already in Phase III with encouraging results; most research molecules primarily target ulcerative colitis and Crohn’s disease.

### Pipeline Analysis of Key Players in GI Therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Indication</th>
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<tbody>
<tr>
<td><strong>Phase III</strong></td>
<td><strong>Necrotizing Enterocolitis</strong></td>
</tr>
<tr>
<td>IBP-9414 Infant Bacterial Therapeutics AB</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>RBX-2660 Rebiotix Inc</td>
<td>Hepatic Encephalopathy</td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td><strong>Reflux Esophagitis</strong></td>
</tr>
<tr>
<td>RBX-2660 Rebiotix Inc</td>
<td>Gastroesophageal Reflux Disease</td>
</tr>
<tr>
<td>MBK-002 Mikrobiomik Healthcare Company</td>
<td>Non-Alcoholic Steatohepatitis</td>
</tr>
<tr>
<td><strong>Phase I</strong></td>
<td><strong>Ulcerative Colitis</strong></td>
</tr>
<tr>
<td>RBX-2660 Rebiotix Inc</td>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td>SR-287 Seres Therapeutics Inc</td>
<td>Crohn's Disease (Regional Enteritis)</td>
</tr>
<tr>
<td>**Special Report: Microbiome Based Therapies - Emerging Therapy Area</td>
<td>May 2021**</td>
</tr>
<tr>
<td>MRx-1234 4D Pharma</td>
<td>Colitis</td>
</tr>
<tr>
<td>BX-003 BiomX Inc</td>
<td>Intestinal Infection</td>
</tr>
<tr>
<td><strong>Source:</strong> Aranca Analysis</td>
<td><strong>VE-202A Vedanta Biosciences</strong></td>
</tr>
<tr>
<td>CR-1301 Conaris Research Institute</td>
<td><strong>VE-303 Vedanta Biosciences</strong></td>
</tr>
</tbody>
</table>
More advanced research carried out in immunology, oncology therapy, with several drugs in early stage of development for different indications

**Pipeline Analysis of Key Players in Immunology Therapy**

**Phase I**
- EDP-1815
  - Evelo Biosciences
- CBM-588
  - Miyarisan Pharmaceutical

**Phase II**
- ribaxamase
  - Synthetic Biologics Inc
- MaaT-013
  - MaaT Pharma
- VE-416
  - Vedanta Biosciences
- SFA-002 ER
  - SFA Therapeutics
- STMC-103H
  - Siolta Therapeutics

**Pipeline Analysis of Key Players in Oncology Therapy**

**Phase I**
- EO-2401
  - Enterome Bioscience
- MRx-518
  - 4D Pharma
- SYNB-1891
  - Synlogic

**Phase II**
- MRx-518
  - 4D Pharma
- CNV-NT
  - BioMed Valley Discoveries
- GEN-001
  - Genome & Co
- CBM-588
  - Miyarisan Pharmaceutical
- Biologic Molecule
  - Ella Therapeutics
- MBK-004
  - Mikrobionik Healthcare Company

**Indication**
- Plaque Psoriasis (Psoriasis Vulgaris)
- Graft Versus Host Disease
- Peanut Allergy
- Hematopoietic Stem Cell Transplantation
- Autoimmune Disorders; Psoriasis
- Allergies; Food Allergy
- Adrenocortical Carcinoma; Paraganglioma; Recurrent GBM
- Bladder Cancer; Melanoma; NSCLC; RCC
- Gastric Cancer; Metastatic Colorectal Cancer; Melanoma
- Multiple Cancer Indications
- Head & Neck Cancer; SCC; NSCLC; UCC; Solid Tumor
- Renal Cell Carcinoma
- Lymphoma; Solid Tumor
- Metastatic Melanoma
- Unspecified Cancer

**Abbreviations:**
- NSCLC: Non-small-cell lung carcinoma
- RCC: Renal cell carcinoma
- SCC: Squamous cell carcinoma
- UCC: Urothelial carcinoma

**Source:** Aranca Analysis
Within infectious disease space, over 50% of pipeline molecules involved in treatment of Clostridium difficile associated disease…

<table>
<thead>
<tr>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td><strong>EDP-1815</strong> Evelo Biosciences</td>
<td><strong>SER-109</strong> Seres Therapeutics</td>
</tr>
<tr>
<td><strong>CP-101</strong> Finch Therapeutics</td>
<td><strong>GTX-005</strong> Galenus Therapeutics</td>
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<tr>
<td><strong>KB-109</strong> Kaleido Biosciences</td>
<td><strong>MBK-001</strong> Mikrobiomik Healthcare Company</td>
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<td><strong>MRx-4DP0004</strong> 4D Pharma</td>
<td><strong>GTX-001</strong> Galenus Therapeutics</td>
</tr>
<tr>
<td><strong>ribaxamase</strong> Synthetic Biologics</td>
<td><strong>GTX-002</strong> Galenus Therapeutics</td>
</tr>
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<td><strong>VE-303</strong> Vedanta Biosciences</td>
<td><strong>GTX-008</strong> Galenus Therapeutics</td>
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<td><strong>VP-20621</strong> Destiny Pharma</td>
<td><strong>RBX-2660</strong> Rebiotix Inc</td>
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<td><strong>RBX-7455</strong> Rebiotix Inc</td>
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<td><strong>C-1205</strong> Atterx Biotherapeutics</td>
<td><strong>LACTIN-V</strong> Osel Inc</td>
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<td><strong>FS-0809</strong> FloraSeq</td>
<td><strong>Biologic Molecule</strong> Suzhou Ousai Weike Biomedical Technology</td>
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<tr>
<td><strong>GTX-001</strong> Galenus Therapeutics</td>
<td><strong>BioPlx-01WT</strong> BioPlx Microbiomics</td>
</tr>
<tr>
<td><strong>GTX-008</strong> Galenus Therapeutics</td>
<td><strong>GTX-005</strong> Galenus Therapeutics</td>
</tr>
</tbody>
</table>

**Indication**
- Coronavirus Disease 2019
- Clostridium difficile Associated Disease
- Unknown
- Bacterial Vaginosis
- Methicillin-Resistant Staphylococcus aureus (MRSA) Infections
- Urinary Tract Infections Due To Catheter Encrustation

**Source:** Aranca Analysis
…several molecules also targeting COVID-19 infection; recent activity seen in metabolic therapy, with many molecules in early stage of development.

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Indication</th>
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<tbody>
<tr>
<td><strong>Pipeline Analysis of Key Players in Infectious Disease Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBX-2660</td>
<td>Biologic Molecule</td>
<td>Biologic molecule</td>
</tr>
<tr>
<td>Rebiotix Inc</td>
<td>Guangdong Longchuangji</td>
<td>Persephone Biosciences</td>
</tr>
<tr>
<td>MET-2</td>
<td>SER-262</td>
<td>SFA-006</td>
</tr>
<tr>
<td>Nubiyota</td>
<td>Seres Therapeutics</td>
<td>SFA Therapeutics</td>
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</tbody>
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<tr>
<th>Phase I</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td><strong>Pipeline Analysis of Key Players in Metabolic Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNB-1618</td>
<td>CP-001</td>
<td>MET-2</td>
<td>MET-5</td>
</tr>
<tr>
<td>Synlogic Inc</td>
<td>Caelus Health</td>
<td>Nubiyota</td>
<td>Nubiyota</td>
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**Source:** Aranca Analysis
Rise in collaborations in microbiome space witnessed over past five years; Takeda partners with several developers for a strong foothold in microbiome domain

<table>
<thead>
<tr>
<th>Developer</th>
<th>Partnering Company</th>
<th>Deal Value</th>
<th>Date</th>
<th>Key Takeaways</th>
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</thead>
<tbody>
<tr>
<td>Debiopharm</td>
<td>Takeda</td>
<td>-</td>
<td>June 2020</td>
<td>▪ Development of microbiome therapeutics for treatment of IBD and other GI disorders</td>
</tr>
<tr>
<td>Second Genome</td>
<td>Gilead</td>
<td>USD 38 Mn upfront</td>
<td>April 2020</td>
<td>▪ Identification of biomarkers for five of Gilead’s clinical candidates and drug targets of IBD</td>
</tr>
<tr>
<td>Holobiome</td>
<td>Johnson &amp; Johnson</td>
<td>-</td>
<td>December 2019</td>
<td>▪ Development of proprietary bacterial consortia for treatment of digestive diseases</td>
</tr>
</tbody>
</table>
| Finch Therapeutics | Takeda             | -                        | November 2019 | ▪ Development of microbiome-based therapeutics using Finch’s Human-First Discovery platform  
                                                                        ▪ Evaluation of preclinical candidate FIN-524 for treatment of ulcerative colitis |
| 4D Pharma        | Merck & Co. Inc (MSD) | Up to USD 347.5 Mn in milestone payment | October 2019 | ▪ Development of live biotherapeutics for vaccines  
                                                                        ▪ Clinical trial conducted for evaluating combination of Keytruda (pembrolizumab) by MSD and 4D's live biotherapeutic candidate MRx0518 in patients with solid tumors |
| Seres Therapeutics | AstraZeneca        | USD 20 Mn in three equal installments over 2 years | March 2019 | ▪ Evaluation of microbiome-based therapies on their capacity to augment cancer immunotherapy  
                                                                        ▪ SER-401 may be studied in combination with checkpoint inhibitors from AstraZeneca’s cancer pipeline such as Imfinzi (durvalumab) |
| Vedanta Biosciences | BMS                | -                        | December 2018 | ▪ Evaluation of BMS’s Opdivo (nivolumab) in combination with Vedanta Biosciences’ VE800 in patients with metastatic or advanced cancers |

Source: Industry Reports, News Articles, Company websites, Aranca Analysis
Market landscape for microbiome-based therapeutics to emerge with increased focus in applications for oncology, adoption of new technological platforms, and collaborations with big pharma

Opportunities in microbiome domain

- The role of the microbiome in cancer treatment is gaining prominence and evidence suggests it plays an important part in the way patients respond to cancer therapies. The gut microbiome influences the response to checkpoint inhibitor immunotherapies. For example, improved efficacy of anti-PD1 treatment, along with increased antitumor T cell responses, is seen in mice transplanted with fecal microbiota from responding patients.
- Several companies are working on enhancing cancer immunity and therapy efficiency. For instance, AstraZeneca collaborated with Seres Therapeutics to explore the use of microbiome therapy (Ser-401) in boosting the efficacy of cancer immunotherapy.

- Companies are exploring different platform technologies to target a wide range of indications.
- For example, Seres Therapeutics follows rigorous purification processes for isolating the desired subset of species and removing pathogens and contaminants.
- Other companies such as Finch, Vedanta, and Microbiotica are focusing more on live therapeutics assembled from experimentally defined consortia of the cultured microorganisms.
- 4D Pharma is using a monoclonal preparation of bacteria to achieve immunomodulation.

- Big pharmaceutical players are slowly gaining a strong foothold in the microbiome field through collaborations, agreements, and partnerships with biotechnology companies.
- Synergistic activities in this space have consistently increased and grew two-fold between 2017 and 2019. Most of the deals revolve around upfront payments and milestones, positively impacting the developer’s revenues. For example, 4D Pharma is set to receive up to USD 347.5 Mn in milestone payments from MSD.
- The presence of big pharmaceutical companies, coupled with a drastic increase in clinical activities in the microbiome space, would be instrumental in the development of microbiome therapeutics.
For more information on this space or any other research needs, Aranca can prove to be a suitable partner

Investing in emerging areas in healthcare – How can Aranca help?

*Research, consolidation, and insightful analysis to aid in-depth understanding of therapy and effective decision-making*

**Therapy Landscape**
In-depth understanding of various fundamental therapy parameters

**Market Analysis**
Assessment of current competitive landscape and available treatment options

**Pricing and Access**
Evaluation of various competitor pricing and market access models

**Epidemiology**
Identification of patient opportunity in key markets across the globe

**Pipeline Analysis**
Competitor asset evaluation across various clinical trial phases

**Disease Burden and Unmet Need**
Evaluation of economic and humanistic burden of disease and key unmet needs

**COMMERCIAL OPPORTUNITY**
Mapping key differentiators | Identifying key market unmet needs | Framing a strong value proposition
Healthcare companies leverage our services for various business needs

**How can Aranca help?**

Our point solutions across the product lifecycle:

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<th>Research and Innovation</th>
<th>Manufacturing/Operations</th>
<th>Lifecycle Management</th>
<th>Corporate Development</th>
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<tr>
<td>▪ Market Opportunity Assessment</td>
<td>▪ Long-term Demand Capacity Planning</td>
<td>▪ Product Launch Support</td>
<td>▪ Licensing &amp; Acquisition Support</td>
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<tr>
<td>▪ Indication Prioritization</td>
<td>▪ Product Portfolio Optimization</td>
<td>▪ Brand Strategy &amp; Communication</td>
<td>▪ Partner Identification</td>
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<tr>
<td>▪ Product Value Proposition Development</td>
<td>▪ Inventory Planning</td>
<td>▪ New Indication/New Market Assessments</td>
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<tr>
<td>▪ Competitor Analysis</td>
<td>▪ Value Chain Analysis</td>
<td>▪ Loss of Exclusivity Planning</td>
<td>▪ Due Diligence</td>
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<tr>
<td>▪ Clinical Trial Analysis</td>
<td>▪ Supplier Identification &amp; Deep Dives</td>
<td>▪ In-/Out-Licensing a Product</td>
<td>▪ Evaluation of Collaboration Options</td>
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<tr>
<td>▪ Pricing and Market Access</td>
<td>▪ Best Cost Sourcing Analysis</td>
<td></td>
<td>▪ Revenue Forecast Models</td>
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</tbody>
</table>

Enabling clients to explore market opportunity for novel drugs, formulations and indications  
Supporting clients on queries regarding running their business operations efficiently  
Managing the product through different stages of its lifecycle by deploying specific strategies that ensure maximum ROI and profitability  
Identifying collaboration opportunities that enable clients to enter new therapy areas or markets through successful partnerships
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