Microbiome therapeutics-Assessing market potential

Over the past decade, significant advancements have been made in the field of medical sciences. Discovery of new therapeutic classes and development of novel technologies have led to better treatment strategies and improved quality of life for the patients. Microbiome therapeutics has emerged as a significant addition to the innovations in medical science.

Source: microbediscovery.org

The term human microbiota is defined as the entire assemblage of micro-organisms which are residing in our body and microbiome consists of all the genes that our microbiota contains. Burgeoning research into how microbiome is associated with the human body has led to fascinating outcomes. Studies show that microbiome can have numerous effects on the human body systems like metabolism, immunity, nervous system and skin.

A deranged microbiome composition (dysbiosis) has been associated with numerous diseases like inflammatory bowel disease (IBD), allergies, multiple sclerosis, diabetes, fatty liver disease, neurological disorders, asthma, cancer, and autism. To better understand these links, many projects launched in the past few years have focused on mapping microbial genes that are associated with the various diseases.

Several projects, like the Human Microbiome Project in the US and the MetaHIT project in Europe, have provided mind-blowing insights into various disease like IBD, diabetes, and obesity. Such advances in deciphering the human microbiome have led to the fabrication of various methods to identify and manipulate it.

Potential for the development in a number of indications

The human microbiome's role as a potential avenue for drug development has led to a heated race to market among many Pharma companies. Novel technologies have being fostered and alliances are being made to succeed in this nascent area of development. Clostridium difficile (C. diff) infection is the leading disease which is targeted but there are also a plethora of other indications in the queue.

Insights into gut-brain interactions can pave the way for treatment of various neurological conditions like depression, anxiety, autism and Parkinson's disease. This would open up more market opportunities for microbiome therapeutics.

Another hot area of microbiome research is in drug response and interaction. The microbiome is known to interact with more than 60 drugs.

Antibiotic overuse resulting in bacterial resistance has been a matter of concern for many decades. Companies like EpiBiom, Eligo Bioscience, and C3J Therapeutics are working in this area with technology platforms designed specifically to target harmful bacteria and protect the useful ones.

Understanding the interactions between human body and microbiome can also open up avenues in precision medicine. Utilization of big data to provide insights into various complex mechanisms involved will definitely prove to be a game changer in this regard. Gusto Global, a UChicago based start-up is actively working in this area. They have come up with, GUST+, a computational modeling platform, which will help analyze the microbiome-human interactions.

Fecal Microbiota Transplant -Clostridium difficile infection:
Microbiome therapeutics are mainly concentrated on C. diff. Infections, IBD, Crohn's disease and diabetes with C. difficile Infections contributing to the largest market share.

Fecal Microbiota Transplant (FMT) works on the principle of revamping the unhealthy microbiome with a healthy one. This technique has demonstrated significant outcomes in gut diseases like C. difficile infection and IBD.

Even though FMT is perceived to be an effective treatment, there are a lot of apprehensions surrounding its usage. The main problem with FMT is the logistics of delivering the stool product. FMT usually involves treatment delivery through colonoscopy and hence fecal capsules are viewed to be advantageous to the patients.

Microbiome related clinical trials

Even though currently there are no approved microbiome therapeutics, the pipeline consists of 120 drugs at various phases of development. Majority of the pipeline candidates are in the preclinical phase and there is a lot of uncertainty regarding their further movement towards the clinical phase. However, a few have managed to reach phase 3 of clinical trials and are on the verge of entering the real market. A large chunk of the drugs in the pipeline are directed towards gastrointestinal disorders.

The frontrunner, Rebiotix has RBX2660 as its drug candidate for the treatment of recurrent Clostridium difficile infection. It is currently in phase 3. Rebiotix's Microbiota Restoration Therapy (MRT) platform works on the principle of introducing healthy, live, human-derived microbes into a patient's intestinal tract to target disease.

Synthetic Biologics has ribaxamase and SYN-010 in its microbiome pipeline. Both candidates are poised to enter Phase 3 clinical trials. SYN-004 (ribaxamase) is being investigated in C. diff. infections, and SYN-010 in the treatment of IBS-C. Not far behind is Seres Therapeutics, with its drug SER-109 for recurrent C. Diff. It is currently in phase 2.

Regulatory aspects related to microbiome therapeutics:

Growing interest in microbiome therapeutics has led to an enormous amount of investments made by various microbiome focussed firms.

Analysts have estimated the human microbiome market to reach 3.2 billion USD by 2024. But the uncertainties surrounding the regulatory aspects have been a matter of huge concern for the frontiers of this industry.

A major concern is whether a post-approval monitoring would be demanded by the regulators, which would add further to the cost.

One of the first companies to file an IND was Rebiotix, with its C. diff. infection candidate RBX2660, which is on the verge of entering phase 3.

Booming partnerships

Looking at the business side of microbiome therapeutics, many alliances have been made between Big Pharmas and microbiome companies. Most of the microbiome centered companies are start-ups and are relying heavily on venture capital by Big Pharmas.

Second genome and Pfizer have come together to get insights into the role microbiome plays in obesity and metabolic disorders.

Vedanta has out-licensed VE202, a potential treatment for IBD, to Janssen. Seres Therapeutics has entered into partnerships with Nestle; this will give Nestle the authority to 4 programs related to C. diff. Infections and IBD outside the US and Canada.

Bristol Myers-Squibb has entered into an alliance with Enterome to harness the potential of the microbiome in the immunotherapy space. The partnership will open up novel therapeutic options in immune-oncology. Microbiome-derived drug targets and biomarkers focused to be used in cancer therapeutics and as a diagnostic tool will definitely increase the market prospects of microbiobe therapeutics. Enterome has also entered into a partnership with Takeda and Johnson & Johnson.

Merck is seeking collaborators for its systems biology approach involving omics. Through this, they want to investigate how the integration of the human-microbe pathway will lead to the development of possible biomarkers for their therapeutics. They are also looking to develop vaccines and other novel therapeutics by targeting the microbiome itself. They are currently tracking the microbiota profile of the patients taking the cancer drug, Keytruda and analyzing the individual's response to the drug.

Takeda is all set to target the nonalcoholic steatohepatitis (NASH) market and has collaborated with Finch Therapeutics, a microbiome therapeutics company.

Novel targeting approaches

While the majority of companies follow the approach of adding beneficial bacteria to the gut to combat disease, many are harnessing drugs to selectively target the disease-causing bacteria while keeping the healthy ones intact. Companies following such inverse approach to microbiome therapeutics are Enterome, Second Genome, C3J Therapeutics and Infant Bacterial Therapeutics. EpiBiome and BiomX are also following this "selective" approach by using bacteriophages instead of drug products. Eligo Bioscience is a further ahead from all in this approach and is aiming to deliver the gene editing tool CRISPR/Cas9 into the bacteria via bacteriophages. With this concept, only those bacteria carrying the diseased gene will be destroyed. The Japanese company, Anaero Pharma and Blue Turtle Bio and Synlogic in the US are working to engineer bacteria such that they can produce drug directly within the human gut.

Some of the market drivers for microbiome therapeutics

- Need for personalized medicines for certain diseases.
- Promising data gathered from human microbiome project.
- Government funds and research grants backing microbiome research.
- A plethora of novel microbiome focused drugs and strategies in the pipeline.

A look into the challenges which microbiome based therapy faces

- Various inter-subject and intra-subject variability. It is difficult to predict whether a given microbiome therapy will produce the same response in different patients. Various external factors like diet, medication usage, socioeconomic status, can also change the response among patients.

- Selecting appropriate subjects for trials is also challenging as there is lack of clarity regarding a healthy or dysbiotic microbiome. Other problems will be regarding methods of sample collection and non-availability of a defined clinical end-point.

- There are also some uncertainties surrounding the manufacturing of microbiome. As the starter culture will ultimately decide on the biological activity of bacteria, the whole process of identifying the bacterial strain to delivering it to a patient will be critical.

- Developing oral dosage forms of these drugs would mean making a formulation which will protect the drug from the acidic pH of the stomach plus deliver it to its designated site of absorbtion

- As far as regulatory challenges as concerned, lack of clear regulatory pathways which will ultimately lead to delays in the launch of microbiome therapeutics is a major factor expected to hamper the growth of microbiome therapeutics market.

Future prospects

As numerous companies are exploiting the role of the microbiome in the human body for the development of various treatment options, next step will definitely be exploring biomarkers and diagnostic tools for the same. Even though the microbiome market is witnessing a number of pitfalls, venture capital, and Big Pharma partnerships will aid the researchers to tackle the various obstacles. Eventually, this new chapter in innovations in therapy will provide significant opportunities to overcome a number of challenging health problems.

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