

BIOBUSINESS BRIEFS

PATENT WATCH

Modulating the human microbiome with live biotherapeutic products: intellectual property landscape

Since the launch of the Human Microbiome Project in 2008, an explosion of research has advanced our understanding of the microbiome's role in various biological processes, such as digestion, the immune response and metabolism (*Nat. Rev. Genet.* 13, 260–270; 2012). The human microbiome has therefore emerged as a new target and treatment modality for a wide range of diseases.

The main strategies to modulate the microbiome include fecal transplantation, small molecules, prebiotics and live microorganisms. In 2012, the FDA

published guidance on developing live biotherapeutic products (LBPs), which paved the road for microbiome-based therapies.

To better understand the intellectual property (IP) surrounding LBP therapy targeting the microbiome, we generated a detailed IP landscape by reviewing and indexing English-language US and Patent Cooperation Treaty (PCT) patents and applications. Documents published by the end of January 2016 and classified in the Cooperative Patent Classification system as A61K 35/74 (which covers medicinal preparations containing live bacteria) were

analysed by indication focus. We identified ~700 documents protecting LBP microbiome therapies. The patent-filing activity has increased dramatically since 2000, with the number of published patent documents per annum doubling from 2002 to 2010. It took only 2 years from 2010 to double again, and the number continues to grow rapidly. Our analysis revealed that the field attracts global interest, as these patent documents were filed in more than 30 countries, on all 6 continents with patent offices.

The LBP IP space is highly fragmented with over 200 different assignees. Only 65% of the documents are assigned to a company and ~20% of the filings are from academia. The top assignees are NESTEC, DuPont, Ganeden and Danone, and they own only 10% of the IP filings. These companies were engaged in the probiotics business long before the emergence of interest in treating diseases by modulating the human microbiome.

FIGURE 1 shows a summary of the indications listed in the LBP IP filings. Unsurprisingly, infectious diseases is the most developed space, as replacing 'bad'

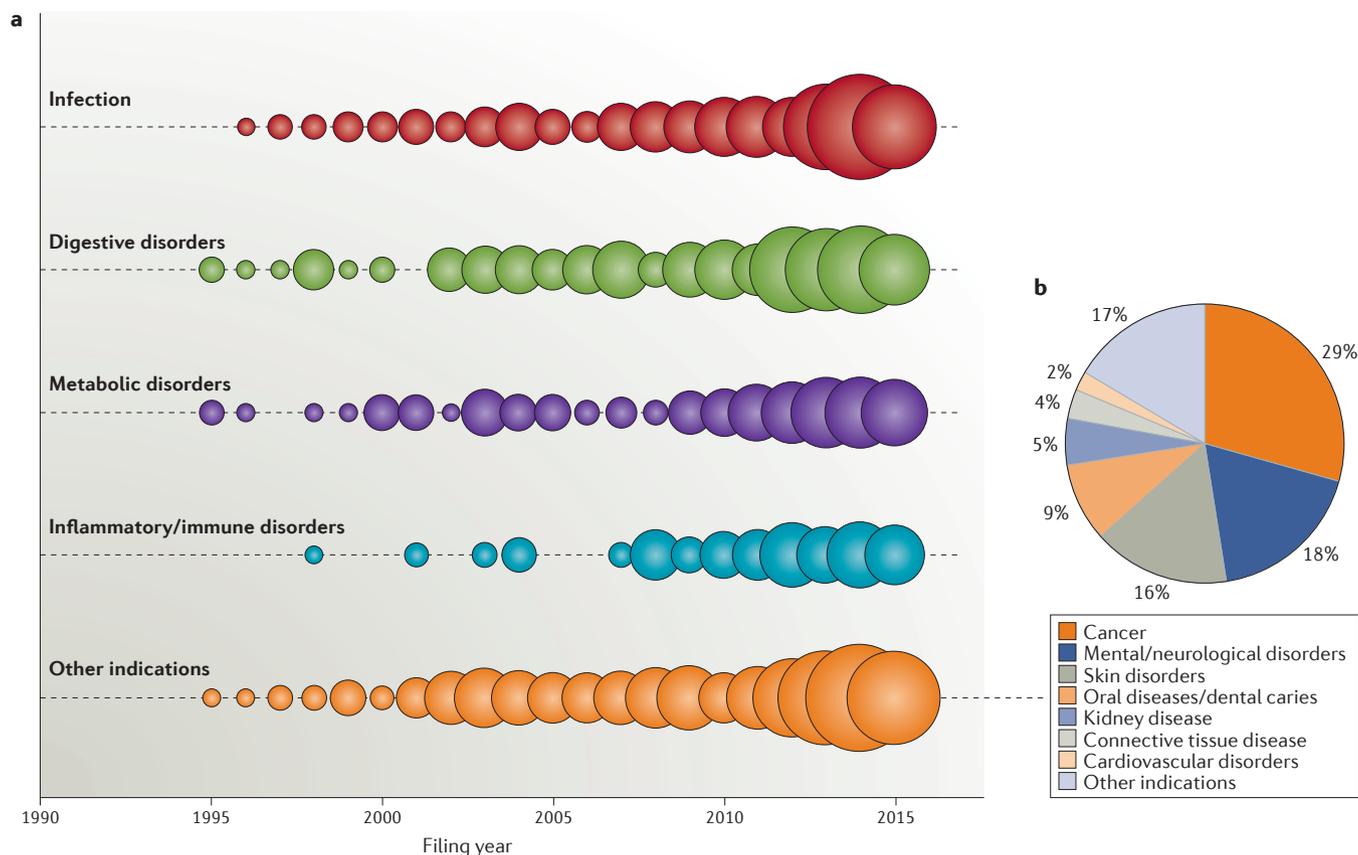


Figure 1 | Intellectual property filing activity for live biotherapeutic products by indication focus. a | Patent documents are plotted by filing year and indication focus (infection, digestive disorders, metabolic disorders, inflammatory/immune disorders and other indications).

Bubbles are coloured according to indication focus and the size of the bubble represents the number of patent documents filed in a given year. **b** | The distribution of indications within the 'other indications' focus is summarized in the pie chart.

bacteria with 'good' bacteria has long been a staple of various probiotics. The treatment of digestive disorders is the second most active space. Recently, other diseases, such as metabolic and inflammatory/immune disorders, have been strongly connected with microbiome imbalances. Filings on these indications also have a strong growth trend. Finally, we observed that innovators are exploring the use of LBPs in diverse therapeutic areas that have less obvious microbiome connections, such as cancer, mental and neurological disorders, oral diseases and tooth decay, as well as disorders of the skin, kidney, connective tissue, cardiovascular system and others.

The LBPs currently in clinical trials are from small biotechnology companies, including Osel, 4D Pharma, Rebiotix and Seres Therapeutics. A more comprehensive analysis of these companies' IP portfolios revealed that they use very different technologies to modulate microbiota. Osel's documents focus solely on lactobacillus to treat vaginal infection. 4D Pharma specializes in identifying single bacterial strains to treat various indications. Rebiotix is the leader in fecal transplantation for the treatment of gut dysbiosis caused by *Clostridium difficile* infection. Rebiotix' filing activities initially covered direct processing of donor

fecal material and evolved to additionally cover pre-screening for desired bacterial diversity in fecal samples. Seres is developing bacterial spore cocktails to repopulate the gastrointestinal tract for the treatment of *C. difficile* infection. Of these companies, Seres has the most US-granted patents in their LBP portfolio.

Pharmaceutical and food companies with long-standing interests in LBPs, small biotechnology companies and academia all share LBP innovation leadership. With new start-ups jumping into the space and big pharmaceutical companies entering the field through partnering and licensing opportunities, we anticipate that the space will remain fragmented for the foreseeable future. There is a large array of indications that may be amenable to LBP treatment according to the IP filings, but very few have been clinically tested. Thus, we are just beginning to see the potential of the LBP therapeutic approach.

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