

Exeliom Biosciences

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# How gut bacteria could transform immunotherapy

With Exeliom Biosciences's drug candidate, EXL01, the long-touted immune-modulation potential of a key gut bacterial species is finally reaching patients in the clinic.

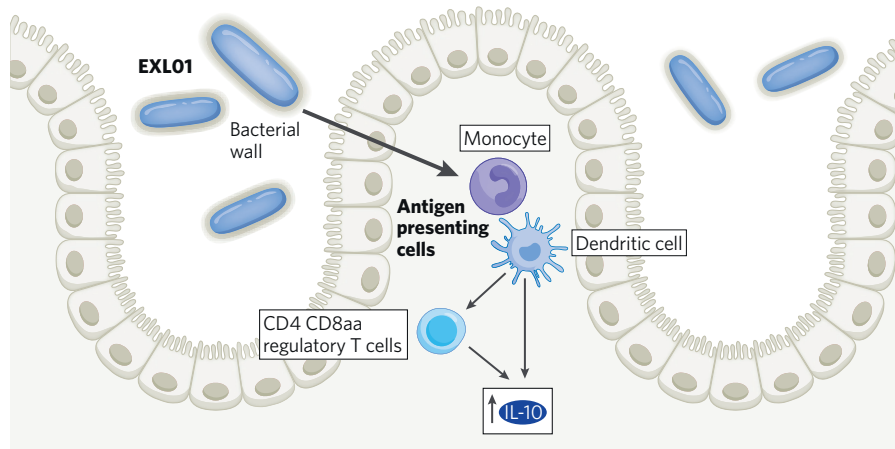
Translating the ever-increasing understanding of the microbiome's role in health and disease into clinical applications has typically meant modifying the gut's fauna with prebiotics, probiotics and faecal matter transplants (FMTs) to correct dysbiosis and re-establish healthy intestinal functioning. Yet this approach to changing the composition of the gut's microbiota is appropriate for only a few medical situations. Although FMT has demonstrated astonishing efficacy against recurrent infections by *Clostridioides difficile*, it has not achieved similar successes in more long-term immune-mediated diseases, such as chronic inflammatory diseases. These conditions remain an unmet medical need that calls for treatments that are more defined and reproducible than FMT, and appropriate for long-term administration.

Exeliom Biosciences is pioneering a new approach of using rationally selected single bacterial species derived from the microbiome as an effective immunotherapy. Exeliom, with offices in Dijon, Paris and Jouy-en-Josas, France, has recently begun a phase 1 trial of EXL01, its *Faecalibacterium prausnitzii*-derived drug candidate, as a maintenance treatment for Crohn's disease (CD). "This is not only the first ever clinical trial of a microbiome-based product in adult CD," said Benjamin Hadida, Exeliom's CEO, "but also something patients have been waiting for since the importance of *F. prausnitzii* in intestinal disorders was established 15 years ago. This phase 1 aims at demonstrating the safety and tolerability of EXL01 in CD patients with corticosteroid-induced remission, while identifying target engagement signals."

## Driving the science

Exeliom is built on a scientific foundation laid down by two of the company's co-founders, Harry Sokol, professor of gastroenterology at Saint Antoine Hospital in Paris, and Philippe Langella, research director at the French National Institute of Agricultural Research. Their research in CD patients revealed that low levels of *F. prausnitzii* at the time of ileal resection are associated with a higher rate of relapse 6 months post-surgery, and also demonstrated that *F. prausnitzii* has anti-inflammatory effects in vitro and in vivo driven by the induction of interleukin-10 (IL-10) expression, as well as other anti-inflammatory processes.

The relative abundance of *F. prausnitzii* serves as a biomarker of intestinal health and can be used to differentiate patients with inflammatory bowel disease (IBD) from healthy subjects. *F. prausnitzii* is a rare bacterial species found in the healthy human gut where it usually accounts for 5-15% of all species in the microbiome. Since Sokol and Langella's seminal work 15 years ago, numerous studies from around the world have confirmed and extended their



**Fig. 1 | How EXL01 works.** EXL01 interacts with immune cells and shifts the immunoregulatory profile from inflammatory to tolerant by restoring a healthy balance of cytokines.

findings, and shown a reduced relative abundance of *F. prausnitzii* in many intestinal disorders and especially IBD, which includes CD and ulcerative colitis.

A deep understanding of how *F. prausnitzii* modulates the immune system has been gained over recent years, and the therapeutic potential of these crucial bacteria has been demonstrated in several colitis models and in vitro systems. The mechanisms of action underlying the anti-inflammatory effects of *F. prausnitzii* have been largely discovered by Sokol and Langella's teams, and rely on the induction of the anti-inflammatory cytokine IL-10 in different immune-cell types, through the effect of molecules present on the bacterial wall.

Despite the widely recognized importance of *F. prausnitzii* for human health, no therapy has been developed based on this insight. A major barrier in this area is the difficulty of working with *F. prausnitzii*, which is one of the most oxygen-sensitive species in the gut. The technical challenge of growing and purifying *F. prausnitzii* at scale and in pharma-compliant conditions has been an obstacle for many teams. Exeliom, however, has conquered the problem, notably through the expertise of the company's third co-founder, Patrick Gervais, emeritus professor of process engineering at l'Institut Agro Dijon formerly known as AgroSup Dijon.

There are numerous strains of *F. prausnitzii*, not all of which show the same beneficial effects on health. Exeliom's lead candidate entering clinical trials, EXL01, is based on a unique strain of *F. prausnitzii*, selected for its superior immune-modulation and biological properties, and the company's intellectual property (IP) coverage protects the use of *F. prausnitzii* in human indications. This, combined with the IP-protected manufacturing process,

puts Exeliom in a strong position as a leader in microbiome-based therapeutics.

## Competitive edge

Exeliom also stands apart from many other companies working in the microbiome space because, rather than developing products within a probiotics regulatory framework, it is following a small-molecule regulatory approach, which means defining pipeline candidates and their associated mechanisms of action. Although EXL01 comprises an unmodified single strain of *F. prausnitzii*, a bacterium is much more complex and has many more effects than a small molecule. Exeliom's data suggest that while the induction of IL-10 is a key element in *F. prausnitzii*'s beneficial effects, it also exhibits other mechanisms of action to produce an immunoregulatory profile favouring immune tolerance (Fig. 1).

Exeliom's clinical trial of EXL01 in CD is the first step to exploring the power of *F. prausnitzii* in a range of indications. The company plans to follow this CD trial with a phase 2 trial in ulcerative colitis, and to pursue more indications in the future, as *F. prausnitzii* has been linked to diseases outside of gastroenterology, including cancer. Exeliom welcomes discussions with investors and other potential partners as the company enters an exciting new chapter in microbiome-based immunotherapy.

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