Novome Biotechnologies
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Creating GEMMs for chronic disease

Novome's novel platform develops genetically engineered microbial medicines (GEMMs) for chronic disease, offering the potential to act as a delivery system for novel therapeutic functionality, including proteins and peptides, into the gut microenvironment.

Novome was founded to combine expertise in gut microflora and synthetic biology to create Genetically Engineered Microbial Medicines, or GEMMs—living medicines that deliver safe, oral, 'tunable' therapies through controlled integration of bacteria into the gut microbiome. Series A funding (led by DCVC Bio, 5AM Ventures and Alta Partners) raised $33 million in 2020, and is supporting the continued progress and development of Novome's platform and lead clinical program.

Novome's unique platform technology centers on a ubiquitous gut bacterial species that has been engineered to express a therapeutic product and robustly colonize the gut when administered alongside porphyran, a rare polysaccharide derived from red algae. Because native gut bacteria cannot use porphyran as a carbon source, the therapeutic GEMM has a growth advantage when porphyran is available, allowing it to colonize the gut (Fig. 1).

A first-in-class GEMM for hyperoxaluria is moving into phase 1, based on compelling preclinical data. The underlying cause of secondary hyperoxaluria, excess absorption of oxalate, if left unchecked, can lead to kidney stones and renal failure. Novome's candidate GEMM degrades oxalate in the gut before it can be absorbed. Reduction in urinary oxalate offers a robust surrogate marker for reduced oxalate absorption and an early predictor of clinical efficacy. Beyond hyperoxaluria, Novome's platform has potential to deliver therapies in a wide range of diseases, not only those based in the gut, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), but also chronic conditions involving remote organs that are influenced by the gut microbiome, including cardiovascular, metabolic, and neurologic diseases.

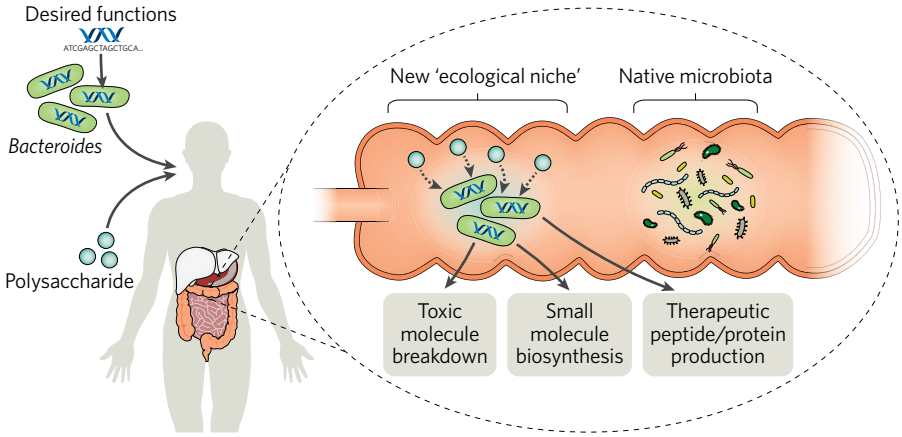

Fig. 1 | Novome GEMM platform overview.

GEMM platform technology

Novome's GEMM platform provides robust and durable colonization of the gut microbiome and high-level therapeutic protein expression, both of which have proved challenging to achieve with other microbe-based therapeutic approaches. Rather than selecting a bacterial species that is easily grown and manipulated in the laboratory, such as *E. coli*, Novome scientists focused on developing genetic tools in the most common of gut flora, *Bacteroides* anaerobes. Because *Bacteroides* are the natural occupants of the gut, they are not expected to be immunogenic. In contrast to engineered *E. coli* or probiotic *Lactobacilli*, the *Bacteroides* GEMMs have been shown to effectively compete with resident microbes to durably colonize the gut. To do so, they rely on a large gene cassette introduced into the *Bacteroides* genome by Novome scientists that allows the GEMM to metabolize porphyran and create a new ecological niche. Daily oral feeding of encapsulated porphyran maintains both GEMM colonization and expression of therapeutic protein(s). Further, preclinical studies show that porphyran feeding allows 'tuning' of GEMM colony level in the gut, increasing or decreasing the number of colony-forming units as a function of porphyran concentrations.

In addition to these advantages, a potent set of proprietary expression tools has been developed at Novome that drives high-level therapeutic protein expression in vivo. Should the GEMM no longer be needed, it can be eliminated by discontinuing porphyran.

Novome's GEMM technology addresses potential shortcomings of first-generation microbiome approaches by enabling and combining:

- High-abundance, highly-reliable colonization of the gastrointestinal tract
- Distinct and novel microbial functionality, through the development of a proprietary genetic toolkit

Lead indication

Secondary hyperoxaluria, Novome's lead target indication, affects ~200k people in the US alone and is linked to overabsorption of oxalate from food. Risk factors notably include underlying gastrointestinal disorders such as gastric bypass surgery or IBD. Novome has completed a pre-IND meeting with the US Food and Drug Administration and a phase 1 trial is expected to begin in early 2021 with a candidate porphyran-regulated GEMM that efficiently degrades oxalate in the gut. Preclinical data obtained with the clinical candidate in several animal models, including a rat model of hyperoxaluria secondary to gastric bypass surgery, demonstrate up to 50% reduction in urinary oxalate. For context, a reduction of 20% in this biomarker is anticipated to be clinically relevant and may provide an early efficacy signal and potential for rapid regulatory approval.

Future development

The Novome GEMM platform technology has broad applications beyond hyperoxaluria, as a system to deliver therapeutic proteins and peptides directly into the gut microenvironment. Not only is there potential to use GEMMs to generate enzymes that catabolize unwanted gut-derived molecules, such as oxalate, but they can also be engineered to generate molecules absent or needed in disease. For example, in IBD and IBS, GEMMs could be engineered to produce anti-inflammatory proteins, peptides or nanobodies to alleviate symptoms, while avoiding systemic immune suppression.

Beyond the gut, there is also growing evidence of the major impact the gut microbiome can have on remote organ systems. GEMM-based treatments could be used to produce signals in the gut that affect these remote systems or to generate metabolites small enough to traverse the gut mucosal barrier to circulate in the blood. Novome's long-term vision includes expansion of its GEMM pipeline into multiple new indications, both independently and with partners.

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