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Harnessing the gut–immune–brain axis to treat disease

How a 100-year-old study spawned a novel class of multifunctional neurological treatments.

Bloom Science is a rare mix of novel technology and extensive clinical validation. The biotech company is working at a scientific frontier, leveraging microbial genetics, synthetic biology and artificial intelligence (AI) to create multifunctional treatments for multi-pathway-based neurological conditions. Yet, unlike most pioneering developers of new modalities, Bloom's programs are underpinned by a century of clinical evidence of the efficacy of modulating the gut–immune–brain axis to treat disease.

The story of Bloom dates back around 100 years to the discovery that the low-carbohydrate high-fat ketogenic diet alleviates seizures. Elaine Hsiao, Bloom's co-founder and a professor at the University of California, Los Angeles, brought the story into the 21st century by studying the effect of these dietary changes on the microbiome and whether they drive the effectiveness of the diet.

Hsiao and her collaborators showed that the diet changes the microbiome, and that the effectiveness of the diet is contingent on the microbiota. Going a step further, the team showed that the effect of the diet can be replicated using the bacterial strains that increase in abundance after the switch from carbohydrates to fats.

Bloom, building on the mouse data and analyses of clinical responders, worked to refine the approach by building libraries of all the bacterial species of interest. The libraries cover the genetic diversity of the species, enabling the researchers to identify strains with superior profiles for particular uses. Bloom runs in vitro assays specific to particular pathways and phenotypes to screen for high-performing strains. The company then mixes and matches high-performing strains, generating engineered consortia with optimized efficacy.

The research is also supported by knockout libraries, which enable Bloom to see the essential genes for any given phenotype, and human responder and animal data that, when paired with AI methods, reveal the metabolites that are predictive of particular outcomes such as seizure protection. Knowing which gene cassettes are responsible for the production of key metabolites empowers Bloom to engineer bacteria to improve efficacy, either by inserting a gene cassette into a strain or—in the company's preferred method—by enhancing a strain's existing activity.

Bloom has used its synthetic-biology capabilities to select and genetically manipulate anaerobic bacteria to reproduce documented human clinical responses in various animal models of neurological disease. The platform leverages the knowledge base that the biotech has built up from its screening and metabolite profiling to inform the engineering of strains with optimal profiles.

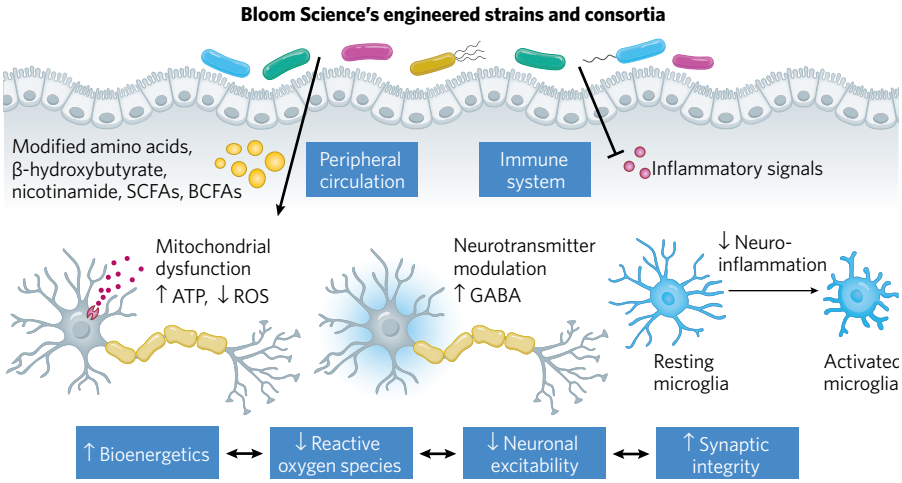

Fig. 1 | Engineering bacterial consortia and strains. The effects of Bloom's live therapeutics alter the metabolic processing of key biochemicals. ATP, adenosine triphosphate; BCFA, bacterial cellular fatty acids; GABA, gamma-aminobutyric acid; ROS, reactive oxygen species; SCFA, short-chain fatty acids

Moving toward the clinic

Bloom has used its capabilities to create two orally administered lead programs.

The first, BL-001, is a live biotherapeutic designed to treat drug-resistant seizures in patients with Dravet syndrome and other developmental and epileptic encephalopathies.

This drug candidate, which is based on Hsiao's work, is designed to replicate the metabolic profile of validated ketogenic diets and thereby alter the metabolic processing of key biochemicals (Fig. 1). In doing so, BL-001 alters the bioenergetic infrastructures in neurons and astrocytes, driving increased biosynthesis of gamma aminobutyric acid (GABA), a neurotransmitter implicated in various seizure disorders including Dravet syndrome.

Preclinical results show that BL-001 restores impaired bioenergetics and mitochondrial function and reduces neuroinflammatory signals. Bloom is now preparing to start a phase 1 clinical trial in early 2023 to gather data that could ultimately lead to pivotal studies in pediatric Dravet and Lennox–Gastaut syndrome.

The second lead program, BL-002, targets motor-neuron cell death in amyotrophic lateral sclerosis (ALS). BL-002 is built on evidence that oxidative stress drives ALS by causing the loss of motor neurons and the dysfunction of mitochondria.

Nicotinamide, an important NAD+ pathway metabolite and a derivative of vitamin B3, can counter the effects of ALS. This vitamin is produced in the gut by *Akkermansia muciniphila*, a bacterium that Bloom has shown attenuates motor-neuron loss, and increases lifespan and motor coordination, in ALS model mice. Nicotinamide, which is found at low levels in ALS patients, acts on energy metabolism and mitochondrial function. Bloom's *Akkermansia* therapy increases nicotinamide levels in mice.

Building on the platform

With two lead programs advancing toward human trials, Bloom is poised to start validating its novel approach to the treatment of neurological conditions in the clinic. The programs have the potential to address major unmet medical needs and lay the groundwork for second-generation candidates that will benefit from Bloom's explorations of how to enhance the functions and properties of bacteria.

As Bloom pursues the opportunities, it continues to show that its focus on engineering commensal bacterial consortia and strains found in the mucosal layer of the gut gives it advantages over other synthetic-biology startups and creates drug candidates with superior efficacy, safety and drug-like properties.

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