Synlogic, Inc.
www.synlogictx.com

Synlogic probiotics turn up the heat on cancer and metabolic disease

Synlogic is manufacturing synthetic biotic medicines engineered to deliver multimodal therapeutic activities locally.

Newfound appreciation for the role of probiotics in human health has opened up a rich area for discovery. The platform technology of Synlogic, Inc., uses synthetic biology to genetically engineer commensal bacteria (*Escherichia coli* Nissle) to generate synthetic biotic medicines designed to metabolize or synthesize products in the body. These synthetic biotic therapeutics act as 'living medicines' to execute genetically programmed biological functions. The company pipeline includes programs targeting metabolic diseases, inflammatory disorders and immuno-oncology. The company's most advanced candidate therapy, SYNB1020, targets hyperammonemia in individuals born with urea cycle disorders (UCDs). It has been given both Orphan Drug and Fast Track designations and is currently being evaluated in a phase 1 clinical study.

Synlogic probiotics act directly at the site of disease, either through oral delivery to the gut or via intratumoral injection (**Fig. 1a**). This scheme minimizes systemic exposure and related toxicity and safety concerns. In addition, the genetic circuits engineered into the probiotics allow gene expression to switch genes on and off in response to environmental cues. Unique biomarkers can be incorporated into the genetic circuit or may result from exogenous enzymatic activity, facilitating development. In addition, Synlogic probiotic leads can be rapidly generated and optimized to produce one or several active therapeutic functions in a single treatment. Once a successful candidate is identified, it can follow a time-tested path to commercial-scale production. Synlogic's intellectual property includes 14 issued or allowed patents and over 160 pending applications.

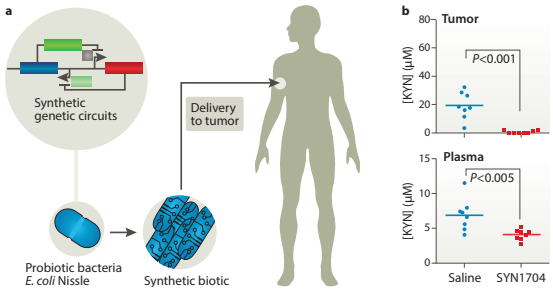

Figure 1: Modifying the tumor microenvironment with Synlogic's synthetic biotic medicines. (a) Synthetic biotic medicines combine a harmless bacteria and synthetic biology to create novel therapies for cancer, as well as inflammatory and metabolic diseases. (b) SYN1704 lowered levels of an immunosuppressive metabolite, kynurenine (Kyn), in tumors and peripheral blood.

Pipeline programs

Synlogic's most advanced pipeline programs target inborn errors of metabolism (IEMs). Individuals with UCD are unable to efficiently convert ammonia, a product of protein breakdown, to urea. The result is hyperammonemia, which can lead to encephalopathy, coma and death. Severe restriction of dietary protein and liver transplant are the current treatment options. SYNB1020 carries a synthetic genetic circuit that converts ammonia to arginine and has been shown to eliminate increases in serum ammonia levels resulting from a high-protein diet in a mouse model of UCD. Beyond UCD, the company plans to initiate a phase 1b trial in patients with cirrhosis and hyperammonemia.

In addition to SYNB1020, SYNB1618, a candidate probiotic to treat phenylketonuria (PKU), is advancing toward the clinic. In PKU, an inborn genetic defect in phenylalanine hydrolase causes the accumulation of phenylalanine, a toxic metabolite. Preclinical data demonstrate that SYNB1618 reduces phenylalanine levels in a mouse model by converting phenylalanine to hippurate, a useful biomarker that can be tracked in the urine.

Modifying the tumor microenviroment

Synlogic's immuno-oncology therapeutic strategies center on altering the tumor microenvironment (TME), and the company is in the process of identifying leads that target multiple immune pathways. Jose Lora, VP of research at Synlogic, noted that many tumors are unresponsive to immune-checkpoint inhibitors, and they typically lack infiltrating lymphocytes owing to a suppressive TME. "The ability to target multiple pathways with a single therapy is a key differentiator for our synthetic biotics platform," said Lora. "We are taking a rational, mechanistic approach to developing immuno-oncology therapeutics, engineering bacteria to execute a combination of functions to modify the tumor microenvironment, turning it from 'cold' to 'hot.'" Gene circuits have been developed and are being screened preclinically for their impact on key immune parameters, including T cell priming and expansion, consumption of immunosuppressive metabolites and changes in extracellular matrix composition. Strategies for immune modulation include the following:

- using the synthetic biotic bacterial chassis itself to directly stimulate innate immune cells to increase antigen presentation and T cell priming;
- engineering bacteria to produce cytokines and mediators that further support T cell activation, survival and expansion;
- programming bacteria to remove immunosuppressive metabolites;
- modifying the tumor stroma by altering the extracellular matrix; and
- creating bacteria that secrete single-chain antibodies (scFvs) or display them on the bacterial cell surface.

Early success in this area includes results with Synlogic probiotics that target kynurenine and adenosine, both known to be associated with immune tolerance. Bacteria engineered to reduce levels of these metabolites have demonstrated activity against their respective targets. In mice, SYN1704, which consumes exogenous kynurenine, was shown to eliminate kynurenine in tumors and reduce it in peripheral blood (**Fig. 1b**).

Synlogic's experienced management team is charting an ambitious path forward, building on foundational science from MIT, the company's patent estate and investments from reputable partners to extend the reach of probiotic therapies.

Further programs to treat metabolic disorders, including acidemias and branched amino acid disorders, are in progress. Immunotherapies are also being developed in partnership with AbbVie for inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, which affect large numbers of people and are in need of innovative, safe and efficacious treatments. The partnership recently achieved its first milestone: delivery of a set of synthetic biotic leads for inflammatory bowel disease.

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