Kaleido Biosciences
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Small molecules harnessing the gut microbiome

Maximizing the potential of the resident gut microbiome, Kaleido Biosciences is developing novel glycans with the ability to change the metabolic output of the microbiome and have a clinically significant impact across a broad range of diseases.

Science on the human microbiome represents one of the most exciting areas of innovation. A broad and rapidly growing body of research has revealed that humans live in intimate association with the vast and diverse microbial communities of the gut. These microorganisms are not just passengers, but actively take part in a complex network of molecular interactions with the host, which directly impacts the maintenance of health as well as the onset and progression of diseases.

These insights have fueled an increase in investment in microbiome therapeutic development. Most aim at selectively adding or subtracting bacteria to correct microbiomes. These first microbiome therapies have recently seen notable success in *Clostridium difficile* infection; however, challenges remain as to the choice of strains, utility across indications, and product complexity and manufacturing.

Kaleido Biosciences, a clinical-stage health-care company, is taking a differentiated therapeutic approach by developing small molecules that selectively restore the composition and metabolic output of damaged resident microbiomes. This unique modality, consisting of synthetic glycans and a proprietary development platform, enables drug discovery research and clinical translation at unprecedented speed.

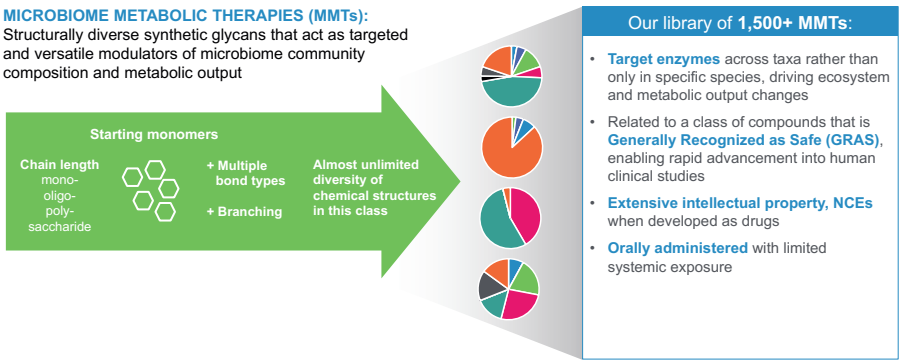

Fig. 1 | Synthetic glycan chemistry enables extensive array of Microbiome Metabolic Therapies (MMTs). Using a chemistry-driven approach to systematically drive functional outputs of the microbiome, Kaleido Biosciences has built a proprietary product platform. NCEs, new chemical entities.

Inspired by nature

Gut microorganisms are genetically and functionally differentiated by their ability to utilize specific structurally distinct glycans (polysaccharides). Kaleido capitalizes on this principle to synthesize novel, structurally diverse glycan ensembles, Microbiome Metabolic Therapies (MMTs) that are selectively utilized by specific microorganisms or by broader microbial populations that have the receptive genetic make-up. The diversity of structure and microbiome-modulating activity of MMTs is achieved by controlling their building block composition, linkage distribution and size (Fig. 1).

"Recent clinical advancements have provided greater confidence that microbiome-based approaches can be translated into clinically validated therapies. Given that our tailored MMTs act on specific metabolic pathways that occur across species, we have demonstrated that we can drive the microbiome towards a desired composition and activity, in a targeted and optimized manner and across diverse diseases," explained Johan van Hylckama Vlieg, Kaleido's CSO.

Platform for rapid advancement

Using its synthetic glycan chemistry, Kaleido has created a library containing more than 1,500 MMTs that have a unique ability to re-engineer the composition of existing microbiomes and promote the production of specific metabolites, making them potent polypharmacological therapeutic candidates. Furthermore, they can be produced on easily scalable small-molecule manufacturing platforms and can move rapidly to clinical studies.

The effect of MMTs is first tested ex vivo using a highly multiplexed advanced screening platform with microbiome communities from both healthy and patient populations. To establish how MMTs impact therapeutically relevant pathways, a broad range of bioanalytical technologies are used to analyze metabolites, effector molecules and host responses, while sequencing determines key microbial population changes.

A candidate MMT may then either undergo further testing in animal models or go straight into clinical evaluation in humans. Abbreviated development may be possible in some cases because MMTs are synthesized from naturally occurring carbohydrate monomers, are orally administered with limited systemic exposure and can be designated as Generally Recognized as Safe (GRAS).

"Our model has the potential to be faster and more cost efficient than traditional discovery and development," according to Katharine Knobil, Kaleido's CMO and head of R&D. It took just two years from conducting the first ex vivo screening of Kaleido's lead candidate for urea cycle disorders (UCD) to starting phase 2 trials, she pointed out.

Broad pipeline

Research initially focused on diseases targeting a single metabolite, such as ammonia reduction in UCD (KB195) and hepatic encephalopathy (KB174). The portfolio has since expanded to encompass multiple mechanisms on which MMTs can act, and Kaleido is now advancing a pipeline of candidates promoting immune homeostasis. Ongoing clinical programs include trials in ulcerative colitis (KB295) and in patients with mild-to-moderate COVID-19 (KB109). Furthermore, expected delivery of multiple clinical-ready candidates in 2021 from preclinical programs include MMTs that reduce trimethylamine and inflammatory markers in metabolic conditions, and immune-potentiating MMTs for use in immuno-oncology.

"There is a strong correlation between microbiome profiles and successful treatment with checkpoint inhibitors," explained Knobil. "We are currently assessing MMTs that can alter the microbiome with the goal of helping more people respond to checkpoint inhibitor therapy and with potentially greater effect."

Future outlook

Kaleido is already collaborating with the Johnson & Johnson subsidiary, Janssen, to explore the potential for MMTs in childhood onset of atopic, immune and metabolic conditions.

"Our MMTs are targeted and have broad applicability across a variety of conditions," said van Hylckama Vlieg. "The gut microbiome is a largely untapped frontier in health care, and we are uniquely positioned to succeed in translating its promise into solutions for patients."

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