Developing a Drug Discovery Platform to Target Gut Microbiota-Associated Ammonia Production

Kelsey Miller, Jonathan W. Leff, Nicholas Beauchemin, Christopher M. Liu, Mitchell Antalek, David Belanger, Michael A. Mahowald, Margaret J. Koziel, Madeline Hartman, Maxwell Hecht, Brian Meehan
Kaleido Biosciences, Inc., Lexington, MA; *corresponding author

INTRODUCTION
The gut microbiome plays a significant role in the production and consumption of ammonia, which is central to the pathogenesis of several ammonia-processing related diseases. We sought to develop a drug discovery platform to identify novel targets, Microbiome Metabolic Therapies (MMTs™), that reduce net ammonia production by the gut microbiome with improved tolerability over clinical standards of care. Kaleido’s research accelerates the discovery process by studying chemical matter appropriate for non-IND human clinical studies to demonstrate safety and translational pharmacology.

METHODS FOR SCREENING AND SAR
Ex vivo screening of over 200 MMTs across healthy and patient human microbiome samples identified glycans that altered ammonia production to varying degrees. A computational pipeline fed with chemo- and bio-analytic data was used to derive structure-activity relationships (SAR) to show that medicinal chemistry techniques could be applied to the microbiome. Shown below, one SAR study used multi-dimensional NMR data and ammonia reduction data to reveal 2 structural features strongly correlated to ammonia reduction and 1 feature strongly correlated to ammonia increases across multiple microbiome samples.

IDENTIFICATION OF KB195
KB195 was evaluated in a non-IND human clinical study using regulations supporting research with food. Healthy volunteers were challenged with a high protein diet to artificially increase nitrogen metabolism. After run-in periods on both normal (e.g., ad libitum) and high-protein diets, subjects were randomly assigned to treatment groups: a maltodextrin placebo group, KB195, and a control glycan with reported prebiotic properties. Subjects were dosed with 15N-lactoureide at days 1 and 20; urinary 15N then stood as a surrogate measurement for microbiome-host ammonia exchange.

RESULTS AND CONCLUSIONS

KB195 Observed to Have a Significant Effect on Ammonia Reduction
Fewer Subjects on KB195 Reported Persistent Diarrhea*

*When dosed at 72 grams/day, KB195 reduced urinary 15N by 40.5% (p=0.0126) compared to placebo and was better tolerated than the control glycan.

The reduction in 15N excretion is consistent with the reported effects of lactose – an approved treatment for hyperammonemia – in this model system

• Decrease in urinary 15N excretion observed following KB195 dosing was not associated with microbiome composition at baseline
• Data suggest KB195 may have activity across a range of microbiomes

REFERENCES AND ACKNOWLEDGMENTS

Acknowledgements:
1. Based on our experience with UCD, we believe we may be able to advance other MMT candidates directly into Phase 2.
3. The study also included an additional control glycan arm (N=12), but there were operational challenges that resulted in interruptions in the dosing schedule. As a result, we decided to equlibrately the arm as a control in the study and do not show the results here.
5. Based on Bristol Stool Score

Presented at the Keystone Symposia, Microbiome: Chemical Mechanisms and Biological Consequences, held from March 10-14, 2019, in Montreal, Quebec.