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

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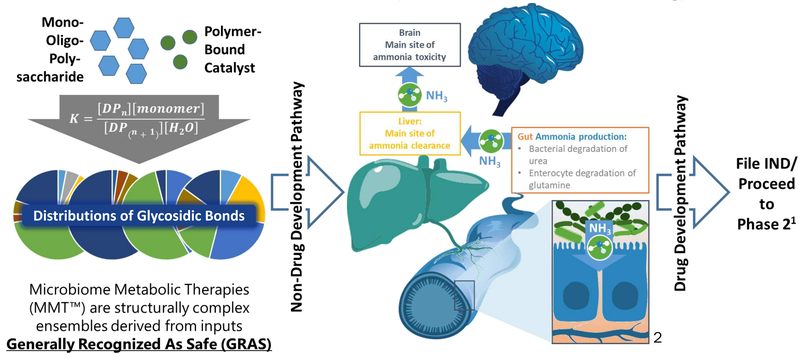
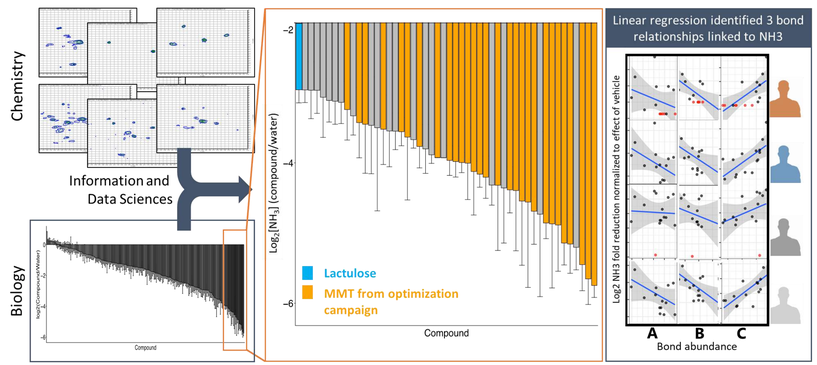
INTRODUCTION

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 glycans, Microbiome Metabolic Therapies (MMT™), 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.



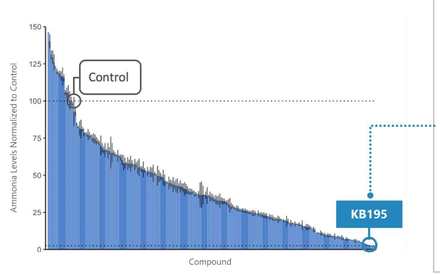
METHODS FOR SCREENING AND SAR

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.

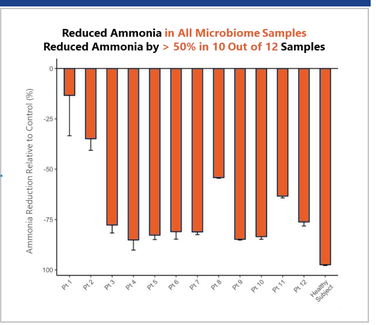


IDENTIFICATION OF KB195

Ability to Screen Many MMTs Across Our Compound Library for Ammonia Reduction



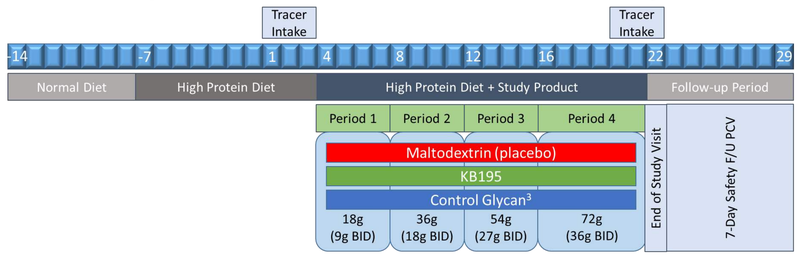
Reduced Ammonia in All Microbiome Samples
Reduced Ammonia by > 50% in 10 Out of 12 Samples



Broad screening of Kaleido's collection identified several MMTs with ammonia reduction greater than lactulose, a carbohydrate dimer that is the first-line treatment for elevated ammonia in patients with hepatic encephalopathy. Follow-up SAR studies on a handful of the most promising MMT resulted in the identification of **KB195, which reduced ammonia in 10/12 UCD patient samples. KB195 also reduced ammonia in 18 of 19 microbiome samples of hepatically impaired patients and outperformed lactulose in reducing ammonia levels in 14 of 19 samples.**

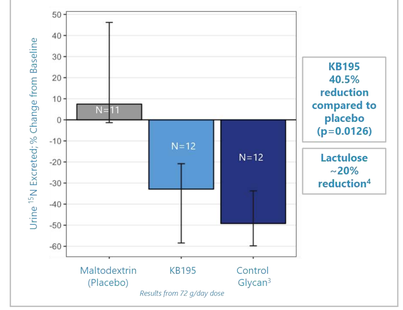
NON-IND HEALTHY VOLUNTEER STUDY

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 ^{15}N-lactoureide at days 1 and 20; urinary ^{15}N then stood as a surrogate measurement for microbiome-host ammonia exchange.

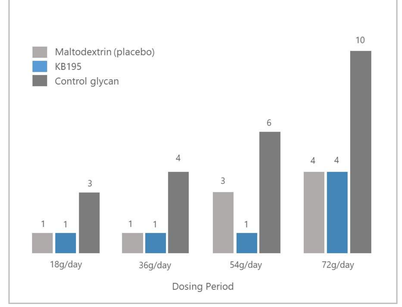


RESULTS AND CONCLUSIONS

KB195 Observed to Have a Significant Effect on Ammonia Reduction

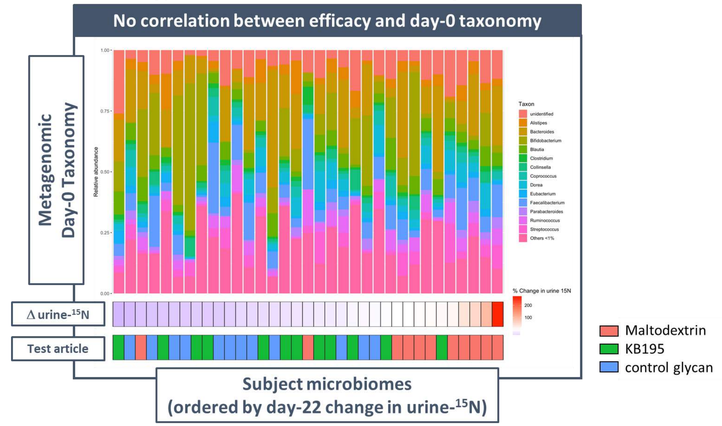


Fewer Subjects on KB195 Reported Persistent Diarrhea[5]



- **When dosed at 72 grams/day, KB195 reduced urinary ^{15}N by 40.5% (p=0.0126) compared to placebo and was better tolerated than the control glycan.**
- The reduction in ^{15}N excretion is consistent with the reported effects of lactulose – an approved treatment for hyperammonemia – in this model system

No correlation between efficacy and day-0 taxonomy



- **Decrease in urinary ^{15}N 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 ACKNOWLEDMENTS

Acknowledgements: Dr. Ruth Thieroff-Ekerdt; Anastasia Murphy; Prof. Dr. Johannes Haberle, University Children's Hospital, Zurich; Flagship Pioneering

References and notes:

1. Based on our experience with UCD, we believe we may be able to advance other MMT candidates directly into Phase 2.
2. Hyperammonemia figure adapted from: Tremaroli et al, Nature Reviews, 2012 & Rao and Gershon, Nature Reviews, 2016.
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 disqualify the arm as a control in the study and do not show the results here.
4. De Preter V. et al., Alimentary Pharmacology & Therapeutics 23, 963-974 (2006)
5. Based on Bristol Stool Score

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