Platform for Targeted Genetic Manipulation of Non-Model Gut Microbes

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**Background & Unmet Need**

- Hundreds of microbiota genes are associated with host biology/disease
- However, unraveling the causal contribution of a microbiota gene to host biology remains difficult as many of the genes are encoded by nonmodel gut commensals and are not genetically targetable
- While genetic toolsets are readily available for model bacteria, many nonmodel gut bacteria (e.g., Lachnospiraceae and Prevotella) are not genome sequenced, and it is unknown how to introduce exogenous DNA or which gene manipulation tool to use
- **Unmet Need**: A generalizable approach to identify gene transfer methodology and build gene manipulation tools for nonmodel microbes in the gut

**Technology Overview**

- **The Technology**: Genetic manipulation pipeline to identify gene transfer methodology and build a genetic tool for nonmodel human gut commensals
- The pipeline efficiently identified the gene transfer methods for 88 (mostly nonmodel) gut bacterial isolates and built their tool for targeted gene manipulation
- Via a multifactorial optimization of their conjugation/transformation conditions, gene transfer methods were identified for 38 nonmodel gut Clostridia, with genetic tools successfully implemented in 27 of the Clostridia strains
- **PoC Data**: Using the platform, the team demonstrated that deletion of a commensal gene for bile acid synthesis (bai) in a Clostridia commensal uncovered a role for the bai gene in mediating colon inflammation and host gut microbiome composition

**Inventors**: Chun-Jun Guo

**Patents**: PCT Application Filed


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**Cornell Reference**: D-9388
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Technology Applications

- Enables precise control of microbiome molecular output to interrogate effects on host biology
- Genetic engineering toolkit for therapeutic and synthetic biology applications using nonmodel gut bacteria

Technology Advantages

- Gene manipulation tools were implemented without requiring prior knowledge of genome sequences
- Provides a library of targetable gut isolates and validated genetic tools
- Expands the scope of commensals that may be employed as “live biotherapeutics”

Supporting Data / Figures

1. A genetic manipulation pipeline
2. Modulate microbiota metabolites
3. Disrupt single microbiota gene baIH
4. baIH mediates colon inflammation

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Figure 1: Overview of the platform for genetic manipulation for non-model microbes in the gut.