A Rationally Selected, Orally Administered, Live Biotherapeutic Consortium of Commensal Bacteria for the Treatment of Ulcerative Colitis

Jun Ma [1], Jason Hudak [1], Peyman Akbari [1], Jackie Papkoff [1]

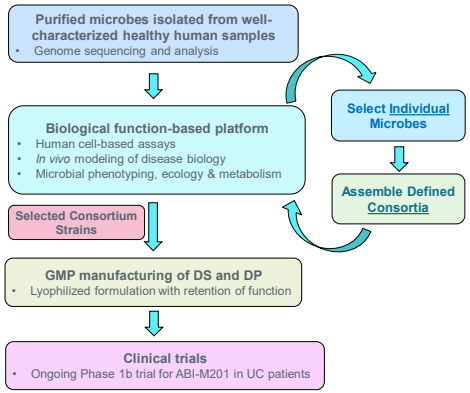
[1] Assembly Biosciences, Inc., South San Francisco, CA

Introduction

Ulcerative colitis (UC) manifests as relapsing-remitting inflammation and ulceration of the colon and rectum. The disease is characterized by innate and adaptive immune inflammation and a damaged gut mucosal barrier. Fecal microbiota transplants have shown limited efficacy in a subset of UC patients, suggesting that a well-defined consortium of bacteria, rationally selected based on disease-relevant mechanisms, could provide meaningful clinical benefit. To this end, we present preclinical results for ABI-M201, a defined, live biotherapeutic consortium currently under evaluation in a Phase 1b clinical trial.

Methods

Rationally Selecting Consortia of Live Microbes with Pharmacological and Biological Functions

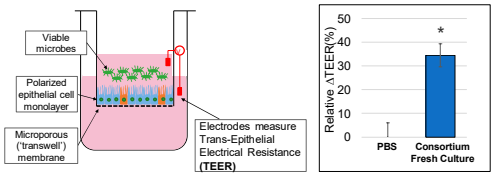


Summary of ABI-M201 Consortium

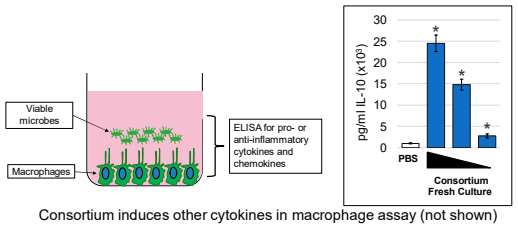
- Commensal microbes isolated and purified from well-curated healthy human samples were extensively characterized and three consortium bacteria were selected using a biological function-based platform
- The ABI-M201 consortium has reproducible activities in validated human cell-based assays reflecting priority mechanisms of action for ulcerative colitis, including
  - Increased barrier function
  - Induction of anti-inflammatory cytokines
- Consortium strains produce beneficial short chain fatty acids (SCFA) and exhibit cross-feeding
- The ABI-M201 consortium shows efficacy in a mouse DSS colitis model
- Well-defined CMC processes were established and GMP manufacturing of ABI-M201 Drug Substance & Drug Product was completed
  - Lyophilized formulation retains functional activities
  - Targeted gastrointestinal tract delivery
- Enrollment ongoing in US & Canada for Phase 1b clinical trial in UC patients

Results

ABI-M201 Consortium Increases Barrier Function in Human Colon Epithelial Cell Assay

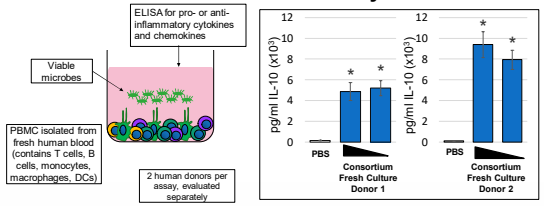


ABI-M201 Consortium Induces Dose-Dependent Increase of the Anti-Inflammatory Cytokine IL-10 in Human Macrophage Cell Line Assay



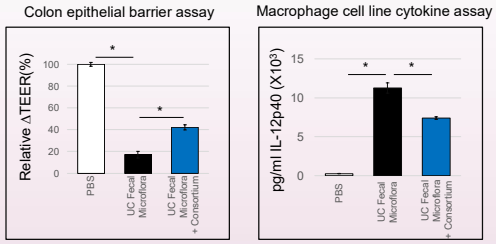
Consortium induces other cytokines in macrophage assay (not shown)

ABI-M201 Consortium Increases IL-10 in Human PBMC Assay



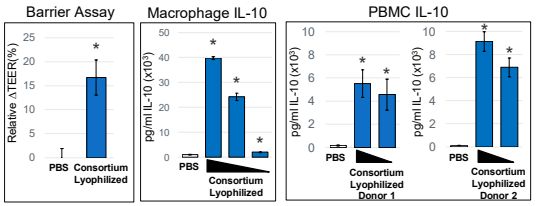
Consortium modulates other cytokines in primary PBMC assay (not shown)

ABI-M201 Consortium Enhances Epithelial Barrier Function and Modulates Macrophage Cytokines in Context of Human UC Fecal Microflora

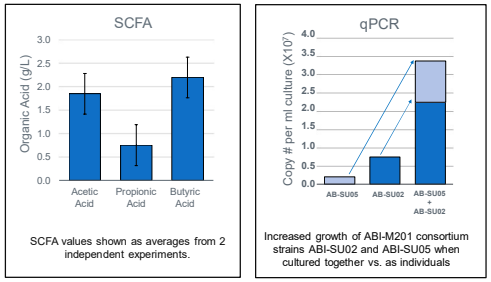


- ABI-M201 protects from UC fecal microflora-induced barrier damage of colon epithelial cells and from microflora-induced inflammatory cytokine production, IL-12p40, by macrophages

Lyophilized Formulation of ABI-M201 Consortium Retains *In Vitro* Activities Demonstrated with Freshly Grown Microbes



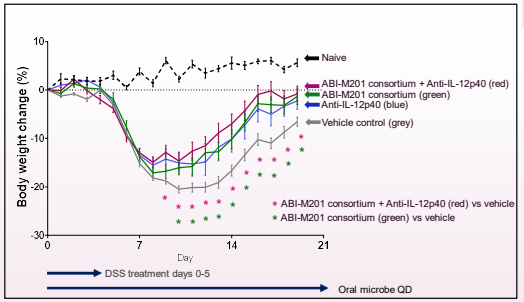
ABI-M201 Consortium Produces Beneficial SCFA and Individual Strains Exhibit Cross-Feeding *In Vitro*



SCFA values shown as averages from 2 independent experiments.

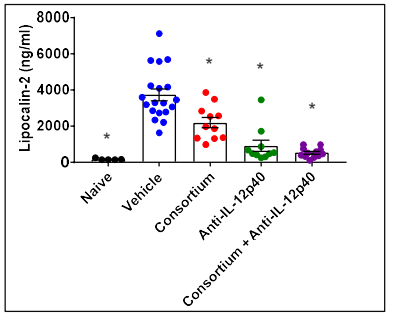
Increased growth of ABI-M201 consortium strains ABI-SU02 and ABI-SU05 when cultured together vs. as individuals

Oral Lyophilized Formulation of ABI-M201 Consortium Has Efficacy in Mouse DSS Colitis Model



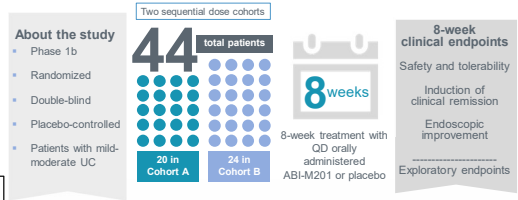
- Efficacy demonstrated in context of native mouse microbiota, no antibiotics or gnotobiotic mice used
- ABI-M201 consortium plus Anti-IL-12p40 shows trend towards better efficacy than either single agent alone
- Consortium, Anti-IL-12p40 & combo improve colitis severity score & stool consistency (not shown)

ABI-M201 Consortium Decreases a Potentially Clinically Relevant Plasma Inflammatory Protein Lipocalin-2 (LCN2), in the DSS Colitis Model



- DSS treatment elevates plasma LCN2
- ABI-M201, Anti-IL-12p40, and their combination, respectively, decrease LCN2
- LCN2 levels directly correlate with efficacy measured by body weight

Ongoing Phase 1b Clinical Trial in Ulcerative Colitis Patients



Statistics

- * p<0.05, Two-stage method of Benjamini, Krieger and Yekutieli for multiple comparison correction by controlling False Discovery Rate
- Student t-test for 2 sample comparison, one-way ANOVA for ≥3 sample comparison, two-way ANOVA for comparison across multiple time points
- Results reproducible across multiple independent experiments

Disclosures

- This work was performed under a partnership with Allergan plc
- JM, JH, and JP are employees, and PA is a former employee, of Assembly Biosciences