Method for Restoration of Paneth Cell Alpha-defensins in Human Intestinal Epithelial Cells

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ABSTRACT

Researchers at the University of California, Davis have discovered FOXO inhibition using compounds such as AS1842856 dramatically enhances alpha-defensin expression in human intestinal organoids, restoring antimicrobial peptide levels comparable to native tissue.

FULL DESCRIPTION

This technology leverages the inhibition of Forkhead box-O transcription factors (FOXO) to induce robust expression of Paneth cell products, particularly antimicrobial alpha-defensins, in human intestinal epithelial cells cultured as organoids. While native small intestinal tissue expresses alpha-defensins abundantly, organoids typically show negligible expression. Treatment with FOXO inhibitors (e.g., AS1842856) increases alpha-defensin gene expression by more than 10,000-fold within days, restoring levels similar to native tissue. This method applies to organoids derived from both small intestine and colon tissues, providing an improved model for Paneth cell research as well as a potential therapeutic strategy for diseases involving Paneth cell dysfunction and reduced defensin expression, including inflammatory bowel diseases (IBD) and other gastrointestinal disorders.

APPLICATIONS

- Development of novel therapeutics for inflammatory bowel disease (IBD) and Crohn's disease targeting Paneth cell function.
- Production of intestinal organoid models for pharmaceutical drug screening and microbiome interaction studies.
- Screening platform to evaluate antibiotics and other therapeutic candidates impacting gut epithelial physiology and microbiota.
- Research tools for studying gut immunity, epithelial barrier integrity, and gastrointestinal diseases associated with dysbiosis.
- Potential cell-based therapies involving transplantation of enhanced intestinal organoids to treat intestinal dysbiosis.
- Applications in gastrointestinal disease modeling including irritable bowel syndrome (IBS), obesity, neurodegenerative diseases, and diabetes.

FEATURES/BENEFITS

- Restores alpha-defensin expression in human intestinal organoids to native tissue levels with >10,000-fold increase.
- Utilizes known, cell-permeable FOXO inhibitors (e.g., AS1842856) with potential for safe in vivo application.
- Applicable to organoids derived from both small intestinal and colon tissues.
- Enhances the physiological relevance of organoid models for gut microbiota and innate immunity research.
- Facilitates screening of candidate agents affecting intestinal epithelial physiology and antimicrobial responses.
- Potential for development of therapeutics targeting Paneth cell dysfunction and gastrointestinal dysbiosis.

PATENT STATUS

Patent Pending

CONTACT

Prabakaran Soundararajan
psoundararajan@ucdavis.edu
tel: .



INVENTORS

- Ashwood, Paul
- Eng, Serena

OTHER INFORMATION

KEYWORDS

alpha-defensins, AS1842856, Crohn's disease, FOXO inhibition, inflammatory bowel disease, intestinal dysbiosis, intestinal organoids, Paneth cells, therapeutics, Wnt3A

CATEGORIZED AS

- **Biotechnology**
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- **Medical**
  - Disease: Digestive System
  - Research Tools
  - Stem Cell
  - Therapeutics

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