Preclinical characterization of IMU-856, an orally available epigenetic modulator of gut barrier function and regeneration

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Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.

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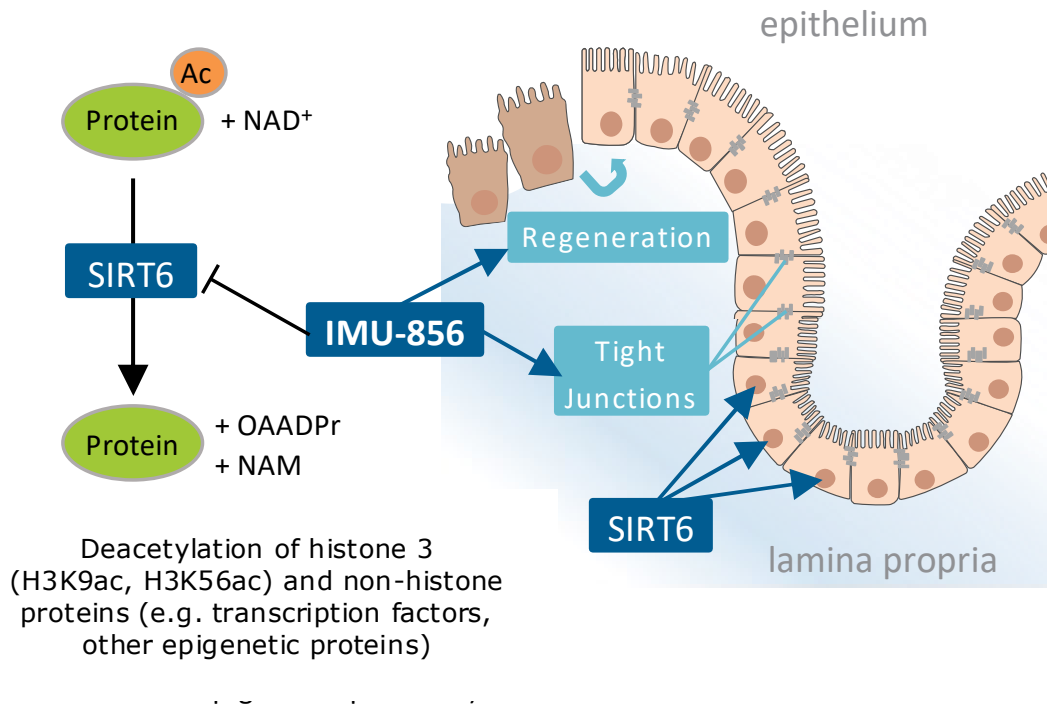
Disclosures

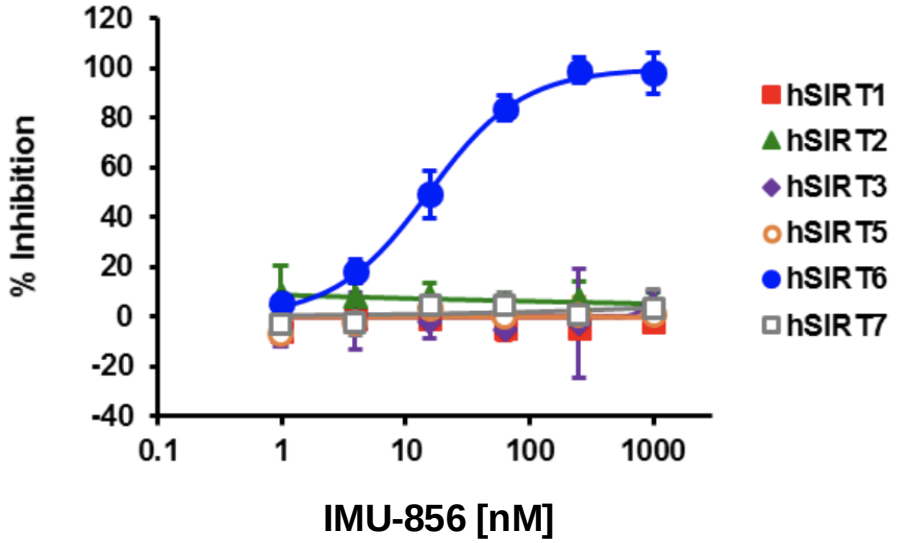
Dr Martina Wirth

- I am an employee of Immunic AG, option and shareholder of Immunic Inc.

IMU-856 is a highly selective and potent modulator of the histone/protein deacetylase SIRT6 (sirtuin 6)



Deacetylation of histone 3 (H3K9ac, H3K56ac) and non-histone proteins (e.g. transcription factors, other epigenetic proteins)

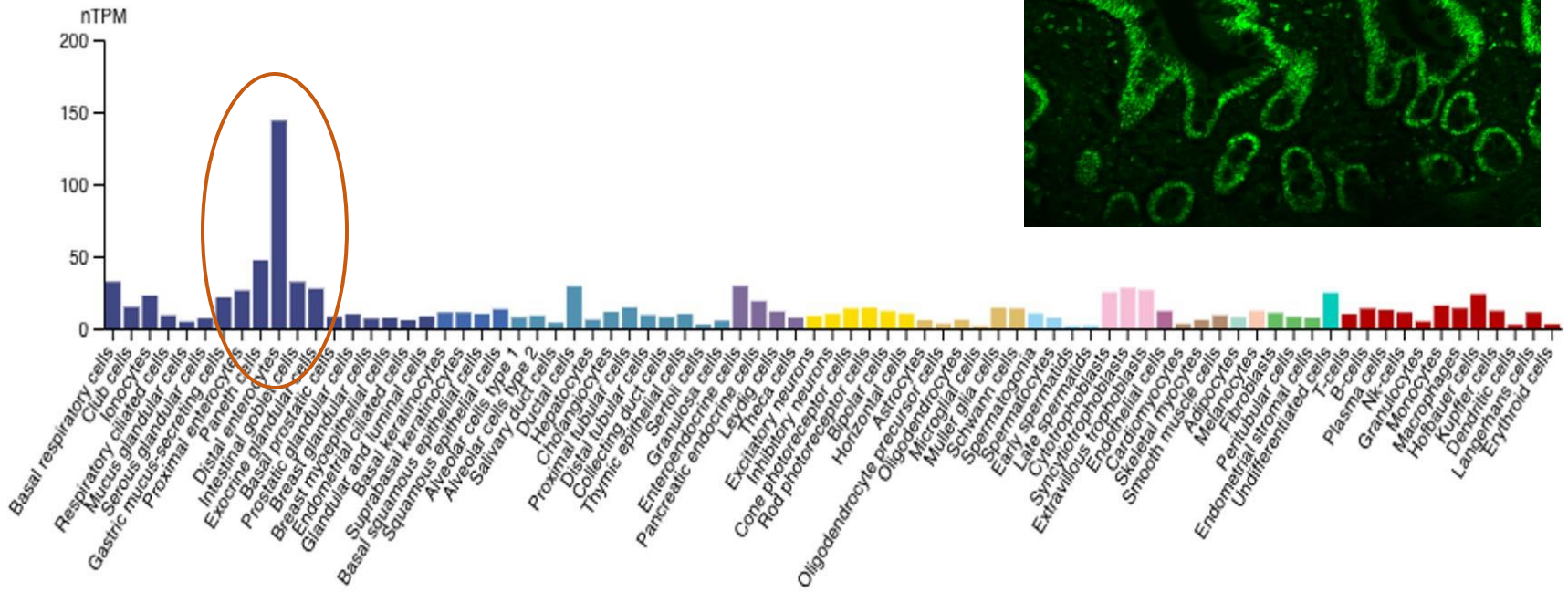


Highly selective and potent inhibition of the histone/protein deacetylase activity of SIRT6 over other sirtuin family members

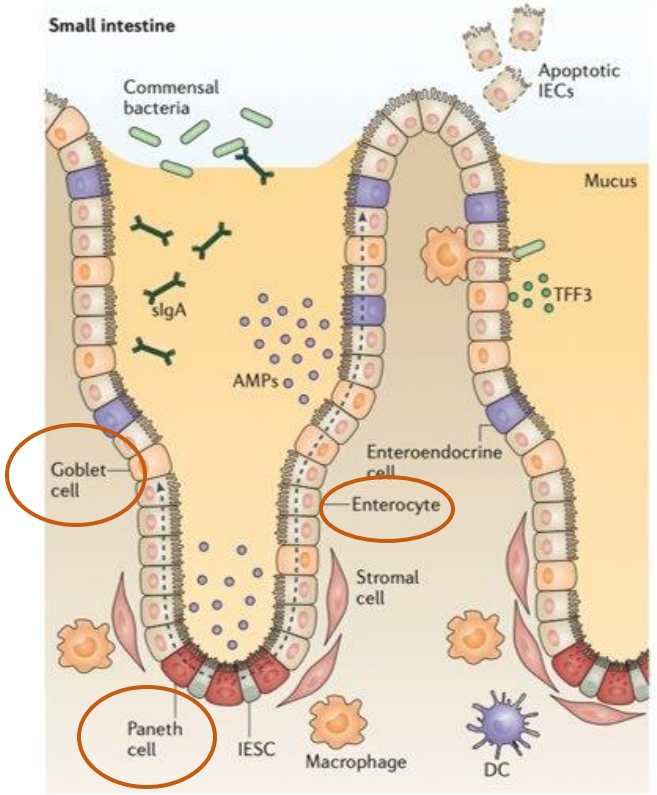
→ IMU-856 is a highly selective modulator of the enzymatic activity and stability of SIRT6

→ IMU-856 improved barrier function and regeneration in human cell and animal models

SIRT6 is highly expressed in intestinal epithelial cells



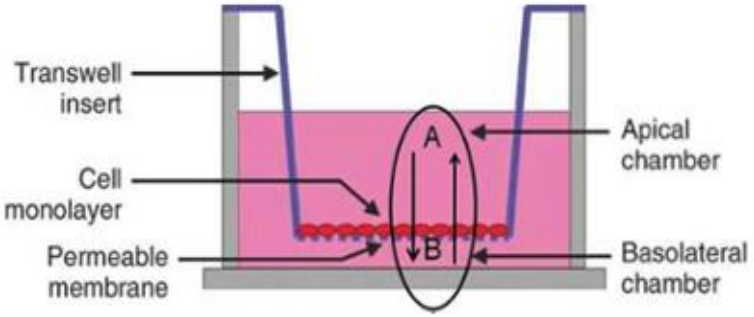
Duodenal biopsy of celiac disease patient



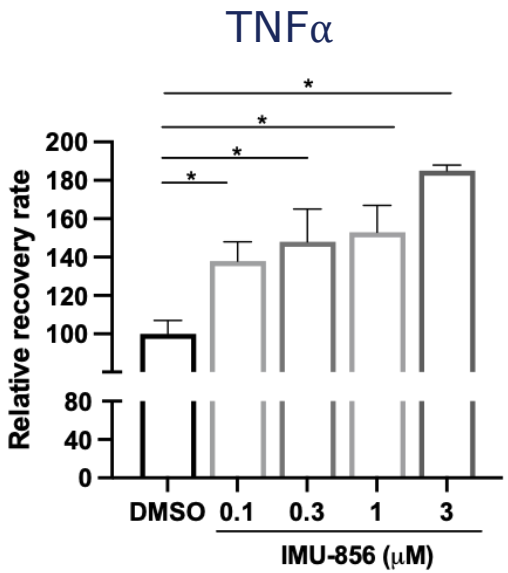
Left graph: https://www.proteinatlas.org/; Right image: Peterson, L., Artis, D. Nat Rev Immunol 14, 141–153. 2014; Duodenal Biopsy: Jilab Inc. / Immunic AG

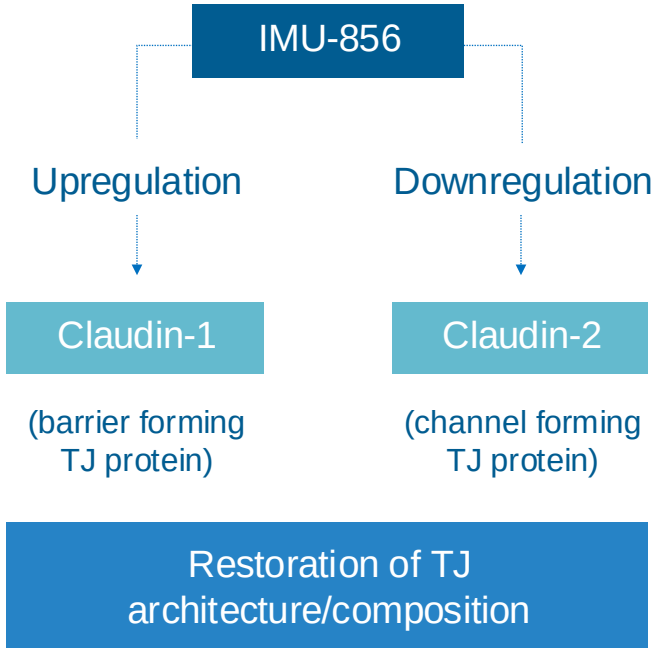
IMU-856 enhances intestinal barrier function by modulation of tight junction (TJ) proteins

Intestinal permeability was measured as TEER (transepithelial electrical resistance) after barrier-disrupting cytokine challenge in Caco-2 cells



48 hours of TNFα challenge followed by 144 hours of IMU-856 treatment





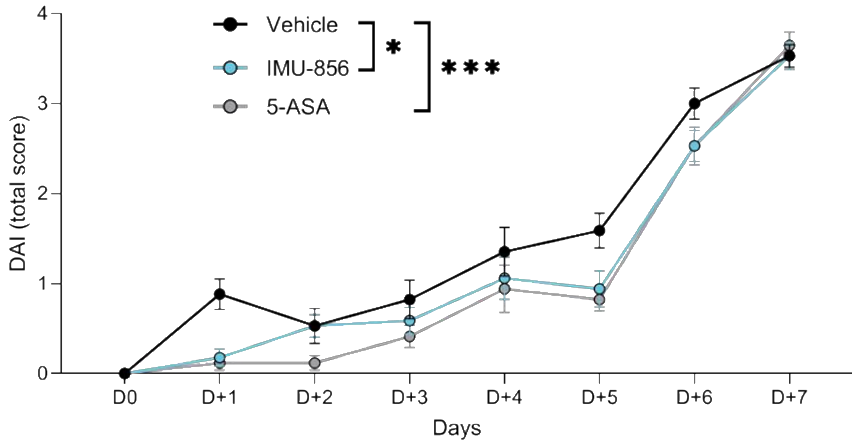
IMU-856 treatment:

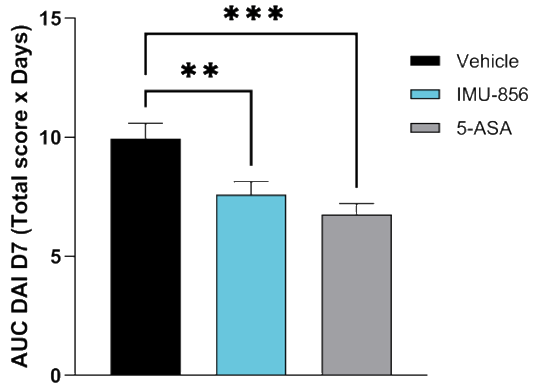
- dose-dependent increase in TEER recovery
- Modulation of tight junction (TJ) composition (protein levels)

TEER: transepithelial electrical resistance; Caco-2 cells: human intestinal epithelial cell line; TNF: tumor necrosis factor; DMSO: dimethyl sulfoxide

IMU-856 is active in acute DSS-induced colitis in mice

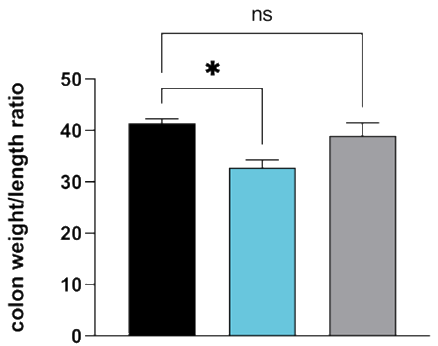
- 2% DSS ad libitum from day 0 to 7
- IMU-856 (p.o. at 3 mg/kg),
  5-ASA (p.o. at 60 mg/kg), or
  vehicle (0.5% MC)
  daily from day 0 to day 7

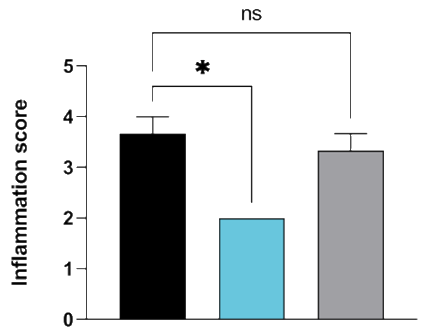




IMU-856 significantly reduced the severity of colitis in mice:

- disease activity index (DAI)
- colon weight/length ratio
- colon inflammation score



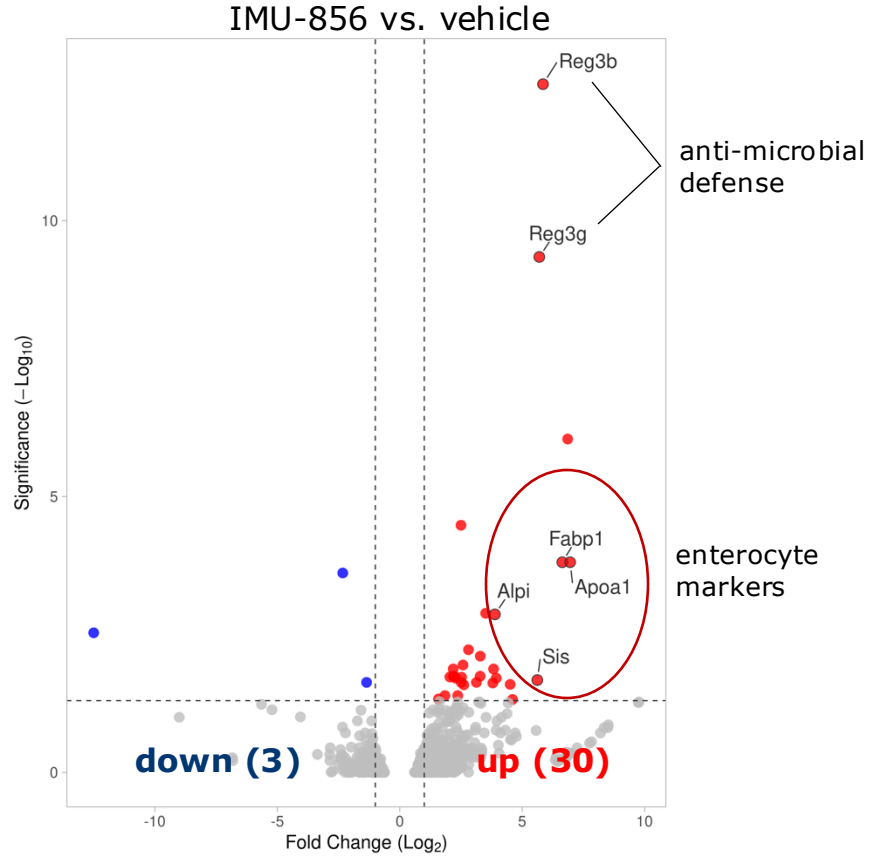


* P < 0.05, ** P < 0.01, *** P < 0.001 compared to vehicle group (Kruskal Wallis, One-way or Two-way ANOVA followed by multiple comparisons test)

Prophylactic DSS-induced colitis mouse model, Urosphere SAS / Immunic AG; DSS: dextran sodium sulfate, 5-ASA: 5-aminosalicylic acid, MC: methylcellulose

IMU-856 preserves functional enterocytes measured by bulk RNA sequencing and plasma citrulline levels

IMU-856 significantly upregulated enterocyte marker genes in colon

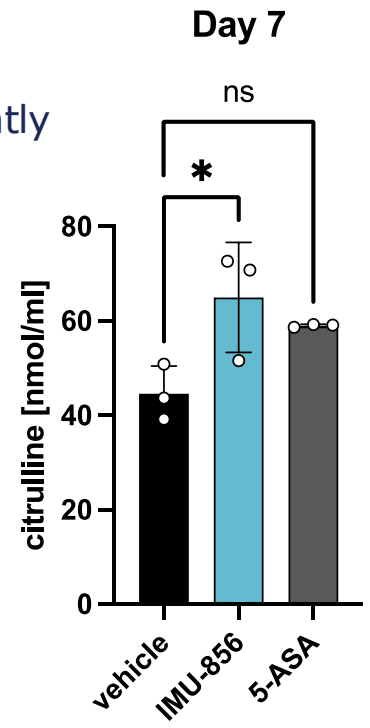


Significant DEGs (FDR p-value < 0.05 and |FoldChange| > 2); up (red): 30 genes; down (blue): 3 genes); colon tissue RNA of acute DSS-induced mice

IMU-856 significantly increased plasma citrulline levels

Citrulline is a biomarker for the integrity and functionality of intestinal enterocytes

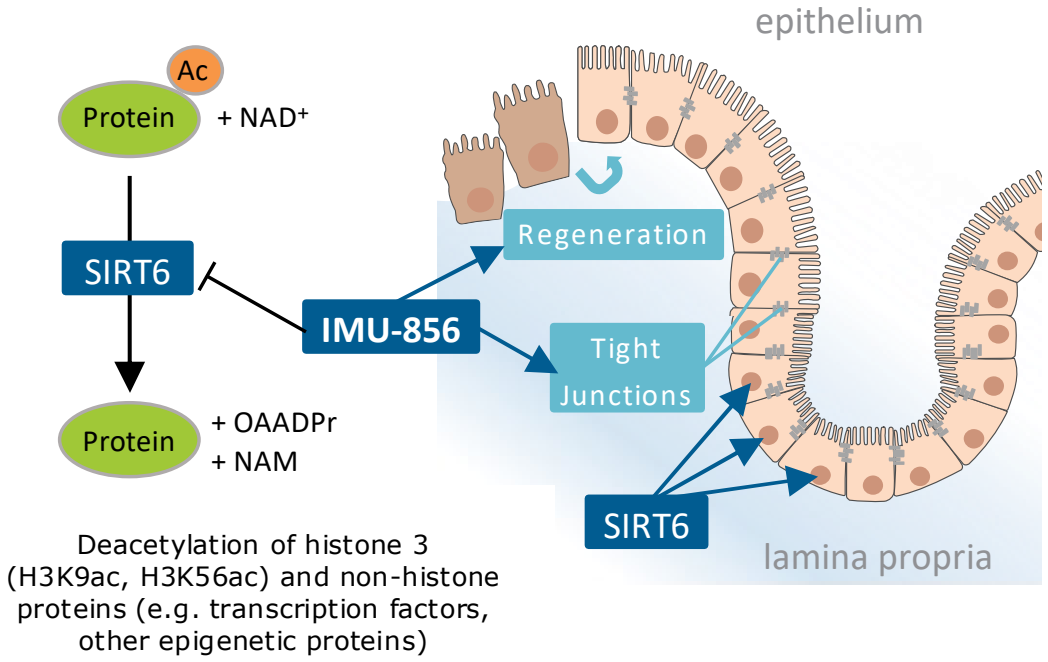
- Impaired intestinal function results in reduced plasma levels of citrulline
- Citrulline plasma levels were significantly higher in IMU-856 treated animals in this DSS colitis model
- Higher citrulline levels seen in celiac disease patients in a phase 1b trial in the active treatment group
  (Daveson et al. (2025) Lancet Gastroenterol Hepatol.)



* P < 0.05 compared to vehicle group (One-way ANOVA followed by Dunnett's multiple comparisons test)

Phase 1 clinical data
Dr. Amelie Schreieck
Abstract: EC25-1515
DOP012, 20th Feb 5:57-6:03 pm

Summary and conclusion



Deacetylation of histone 3 (H3K9ac, H3K56ac) and non-histone proteins (e.g. transcription factors, other epigenetic proteins)

- SIRT6 is highly expressed in intestinal epithelial cells
- IMU-856 is a highly selective and potent modulator of the enzymatic activity and stability of SIRT6
- IMU-856 aims to:
  - regenerate the barrier by supporting renewal and differentiation processes
  - drive tightness of the barrier by regulation of tight junction proteins

  with no signs of immunosuppression seen so far

→ IMU-856 may offer potential for the treatment of IBD and other gastrointestinal diseases with compromised barrier function

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Thank you very much for your attention!

Phase 1 clinical data
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