

# Epithelial Mechanisms in Mucosal Inflammation: From IBD to Chronic Rhinosinusitis

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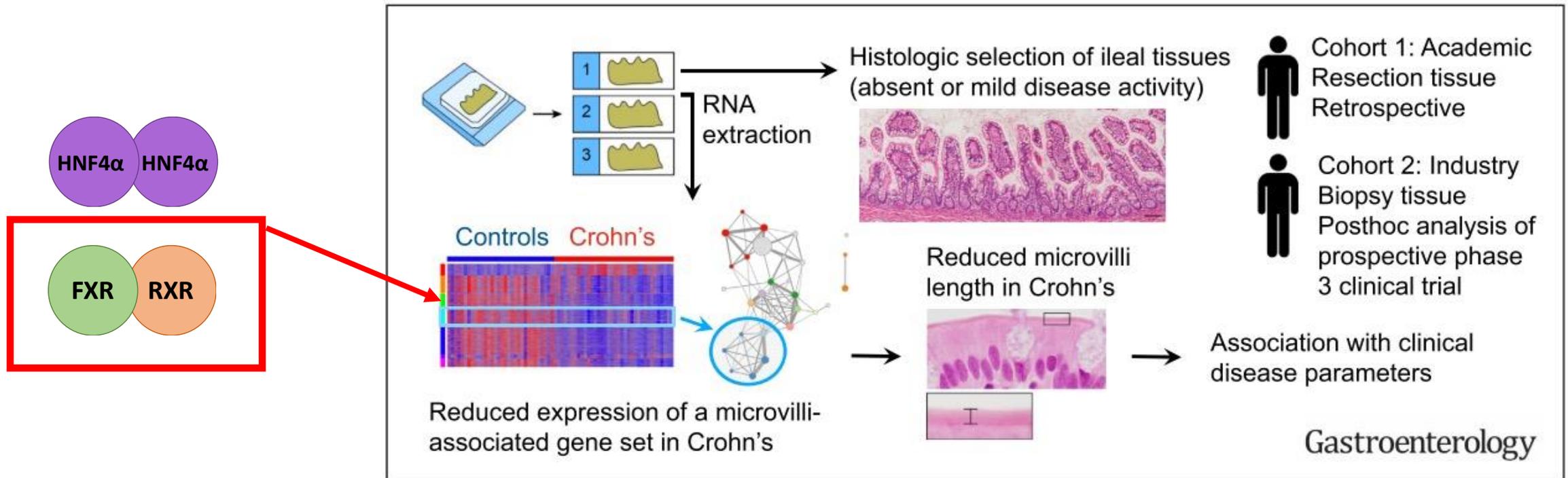
Play Gloria!





# Introduction: Epithelial defects in IBD

- Previous work identified a gene cluster associated with an epithelial defect in biopsy specimens from IBD patients
- Several nuclear receptors deduced bioinformatically as upstream drivers of the down-regulated gene set



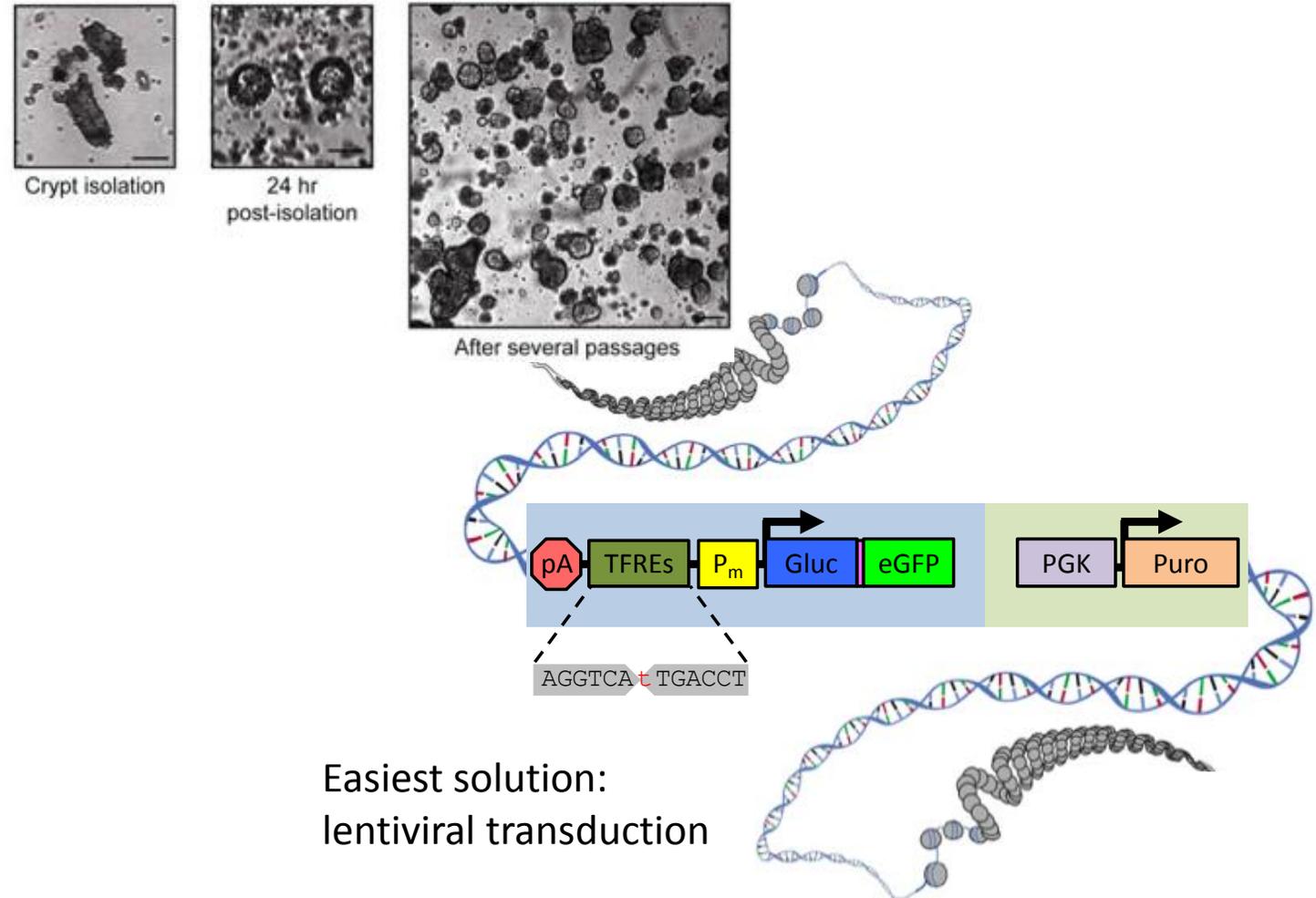


# Methods: find factors driving the defect

- Make reporters for identified nuclear receptors in human intestinal stem cell lines
- Screen libraries of host, microbial and/or environmental factors for effects on activity

- What about FXR?

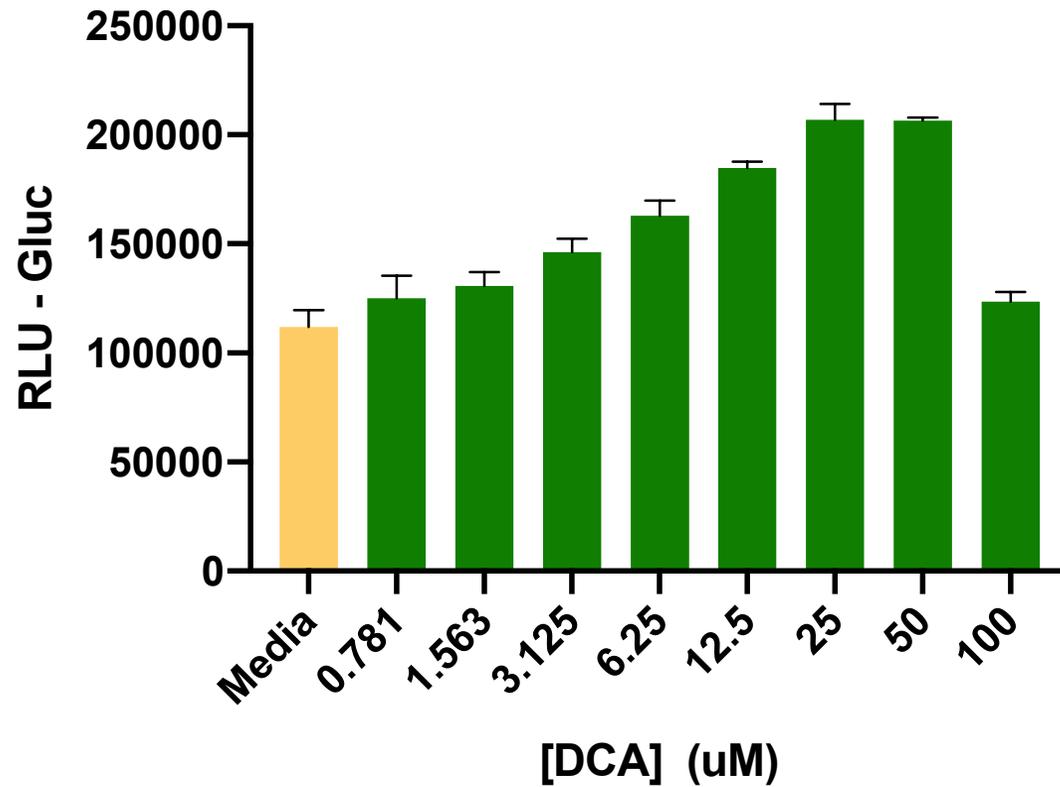
- Bile acid receptor
- Role in bile acid homeostasis
- Also implicated in multiple chronic inflammatory diseases
- One thought is that it links metabolic derangements to inflammation



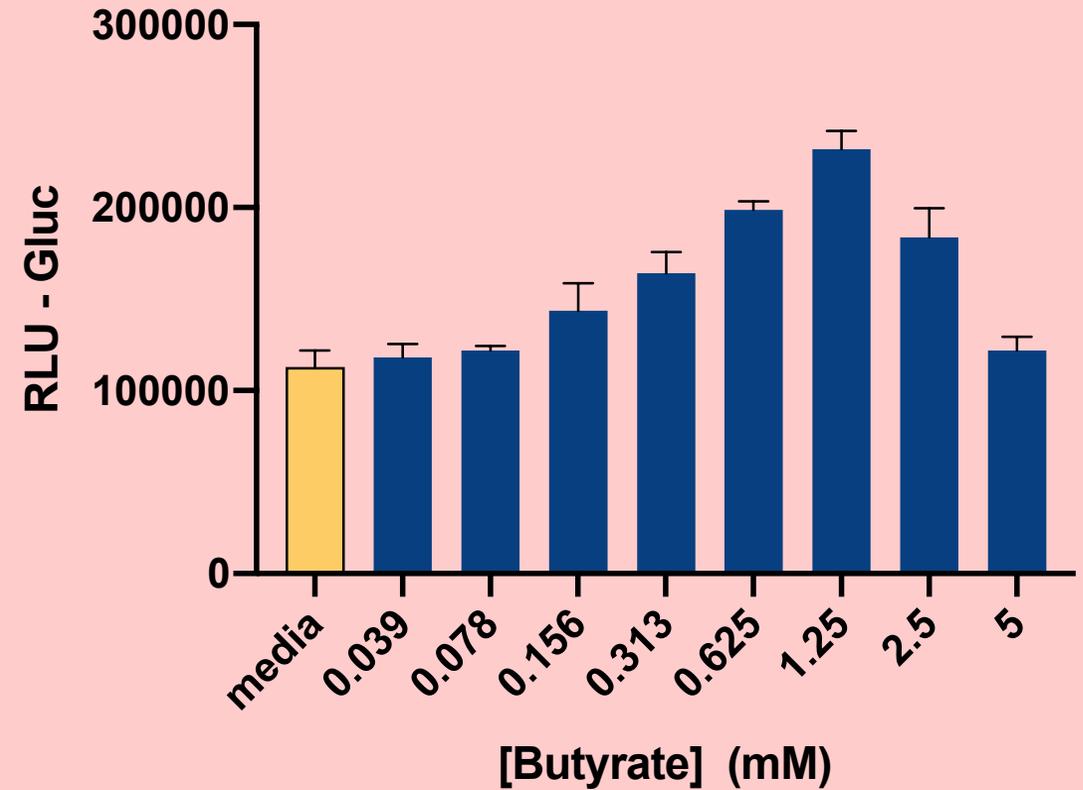


# Results: an interesting finding during validation

## FXR reporter – Human IECs



DCA = deoxycholic acid



The SCFA butyrate appears to activate FXR



# Future directions

- Continue screens as planned
- Pursue butyrate/FXR story
  - Tregs?
    - Lck-Cre x FXR<sup>fl/fl</sup> breeding underway
  - Macrophages?
    - LysM-Cre x FXR<sup>fl/fl</sup> litters almost ready

## The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition

Pamela V. Chang<sup>a</sup>, Liming Hao<sup>b</sup>, Stefan Offermanns<sup>c</sup>, and Ruslan Medzhitov<sup>a,d,1</sup>

Departments of <sup>a</sup>Immunobiology and <sup>b</sup>Pathology, Yale University School of Medicine, New Haven, CT 06520; <sup>c</sup>Department of Pharmacology, Max Planck Institute for Heart and Lung Research, 61231 Bad Nauheim, Germany; and <sup>d</sup>Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06520

## LETTER

doi:10.1038/nature12726

## Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

Nicholas Arpaia<sup>1,2</sup>, Clarissa Campbell<sup>1,2</sup>, Xiyang Fan<sup>1,2</sup>, Stanislav Dikiy<sup>1,2</sup>, Joris van der Veeke<sup>1,2</sup>, Paul deRoos<sup>1,2</sup>, Hui Liu<sup>3</sup>, Justin R. Cross<sup>3</sup>, Klaus Pfeffer<sup>4</sup>, Paul J. Coffer<sup>1,2,5</sup> & Alexander Y. Rudenski<sup>1,2</sup>

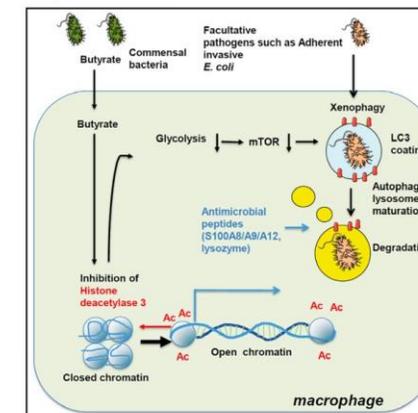
## The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic T<sub>reg</sub> Cell Homeostasis

Patrick M. Smith,<sup>1</sup> Michael R. Howitt,<sup>1</sup> Nicolai Panikov,<sup>1</sup> Monia Michaud,<sup>1</sup> Carey Ann Gallini,<sup>1</sup> Mohammad Bohlooly-Y,<sup>5</sup> Jonathan N. Glickman,<sup>6,7</sup> Wendy S. Garrett<sup>1,2,3,4\*</sup>

## Immunity

### The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages

#### Graphical Abstract



#### Authors

Julie Schulthess, Sumeet Pandey, Melania Capitani, ..., Carolina V. Arancibia-Cárcamo, Holm H. Uhlig, Fiona Powrie

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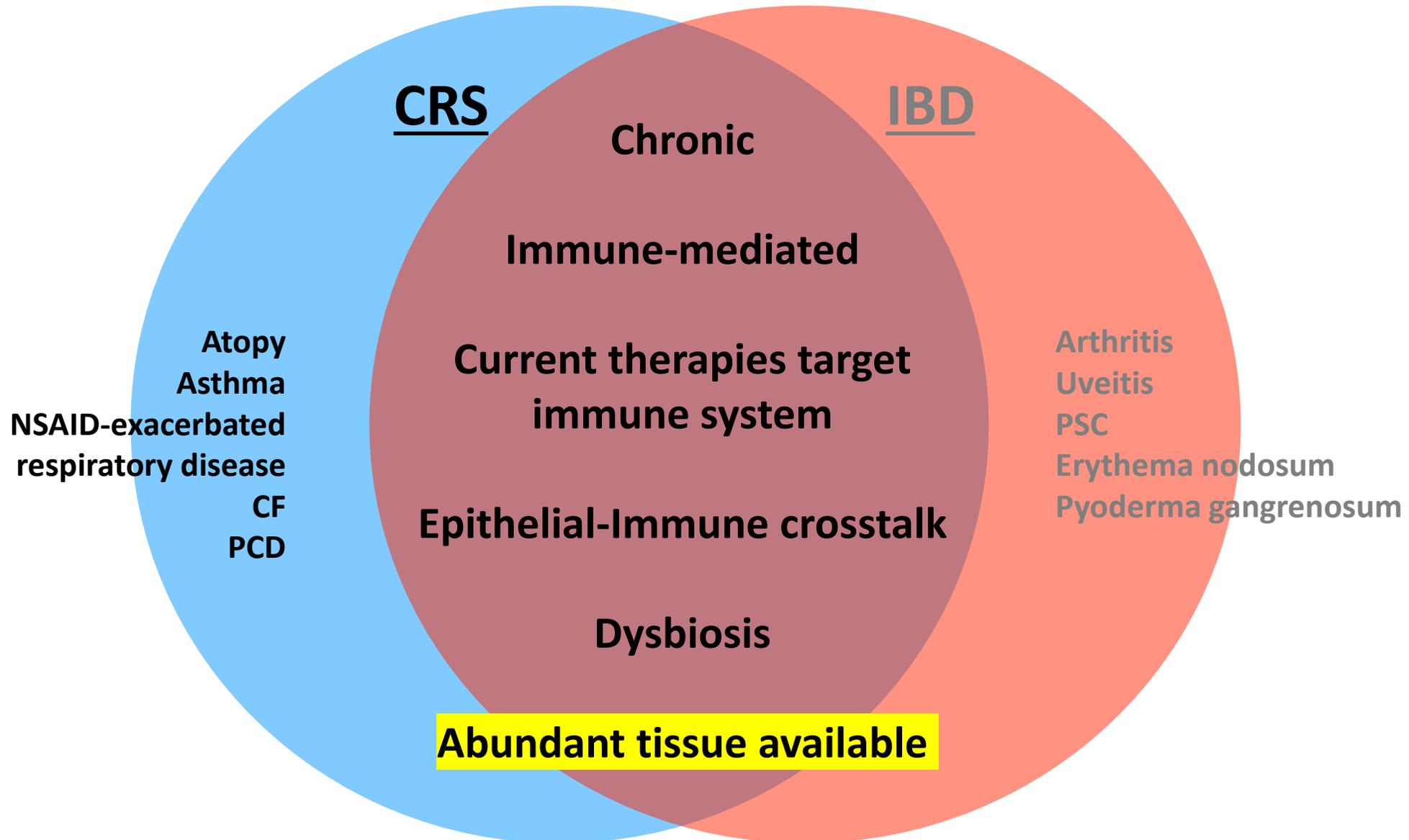
#### In Brief

Macrophages maintain gut homeostasis by eliminating invasive pathogens and regulating inflammatory responses. Schulthess et al. demonstrate that butyrate, a bacterial fermentation product, imprints potent antimicrobial activity during macrophage differentiation through HDAC3i function.

Article

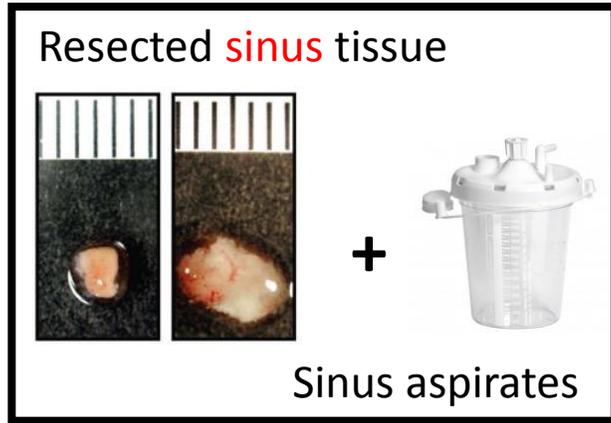


# Longer-term goal: investigate epithelial defects in CRS





# Future: sinonasal epithelial tissue and cell line biobank

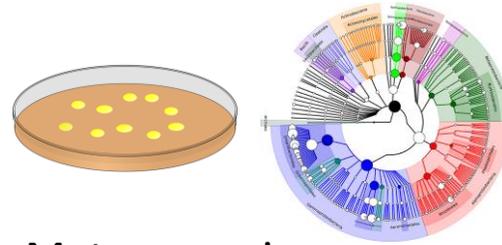


Cell lines/organoids

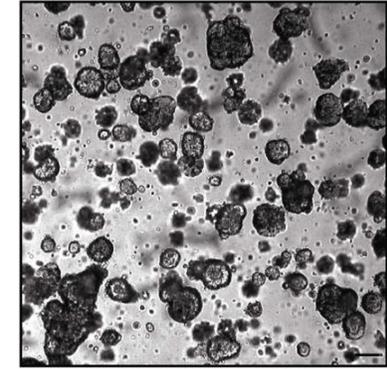


Culture

Shotgun sequencing



Metagenomics



Tissue Blocks



1 2 3 RNA extraction

Histologic selection of ileal tissues (absent or mild disease activity)

Controls Crohn's

Reduced expression of a microvilli-associated gene set in Crohn's

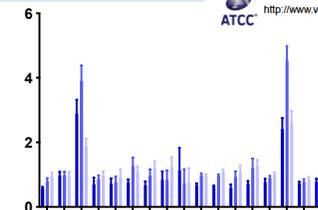
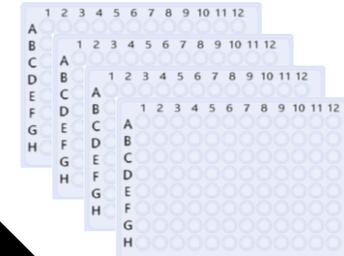
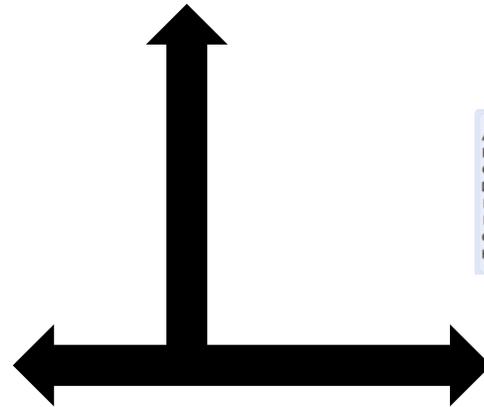
Reduced microvilli length in Crohn's

Association with clinical disease parameters

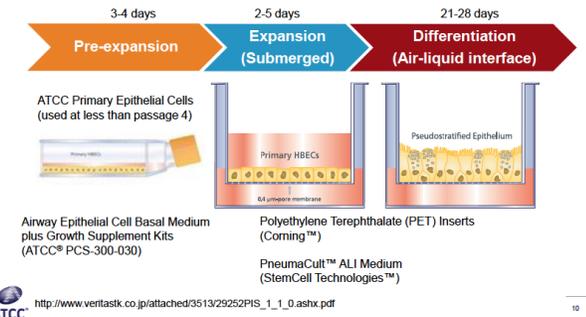
Gastroenterology

Cohort 1: Academic Resection tissue Retrospective

Cohort 2: Industry Biopsy tissue Posthoc analysis of prospective phase 3 clinical trial



Screens



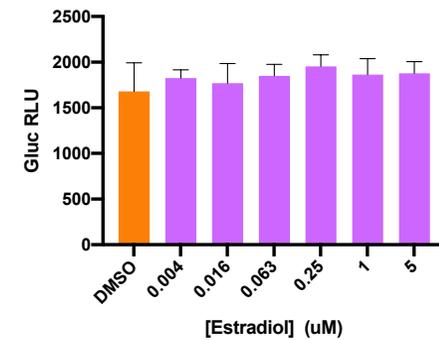
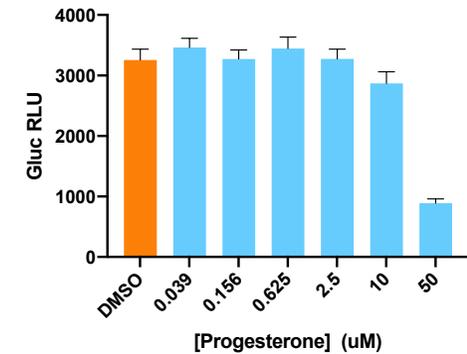
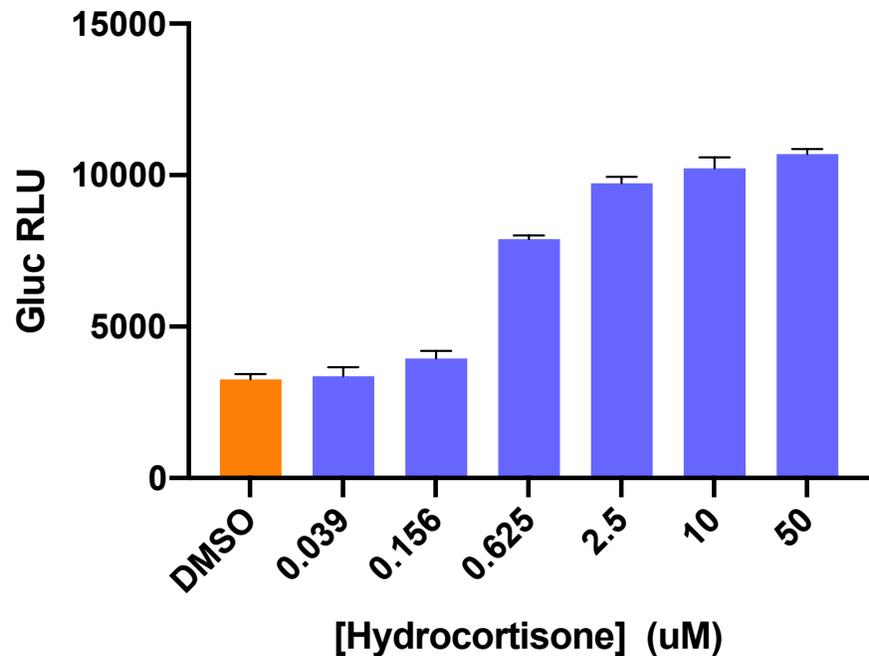
Other *in vitro* assays, e.g. ALI

Phenotypic description/classification  
Bioinformatic target discovery



# Possible directions to take...

- Steroid resistance is a common feature in CRS requiring surgery
  - Utilizing the previously described techniques, I can transduce sinus-derived cell lines into glucocorticoid reporters
  - Screen for factors, such as microbial metabolites, that reduce steroid responsiveness in cultured airway epithelial cells



No activation of this reporter with other steroid hormones



# Possible directions to take...

- If validated initially *in vivo*, translate butyrate/FXR finding to asthma model

Microbiome-driven allergic lung inflammation is ameliorated by short-chain fatty acids

A Cait<sup>1</sup>, MR Hughes<sup>2</sup>, F Antignano<sup>2</sup>, J Cait<sup>2</sup>, PA Dimitriu<sup>1</sup>, KR Maas<sup>1</sup>, LA Reynolds<sup>3</sup>, L Hacker<sup>2</sup>, J Mohr<sup>2</sup>, BB Finlay<sup>1,3,4</sup>, C Zaph<sup>5,6</sup>, KM McNagny<sup>2,7</sup> and WW Mohn<sup>1</sup>

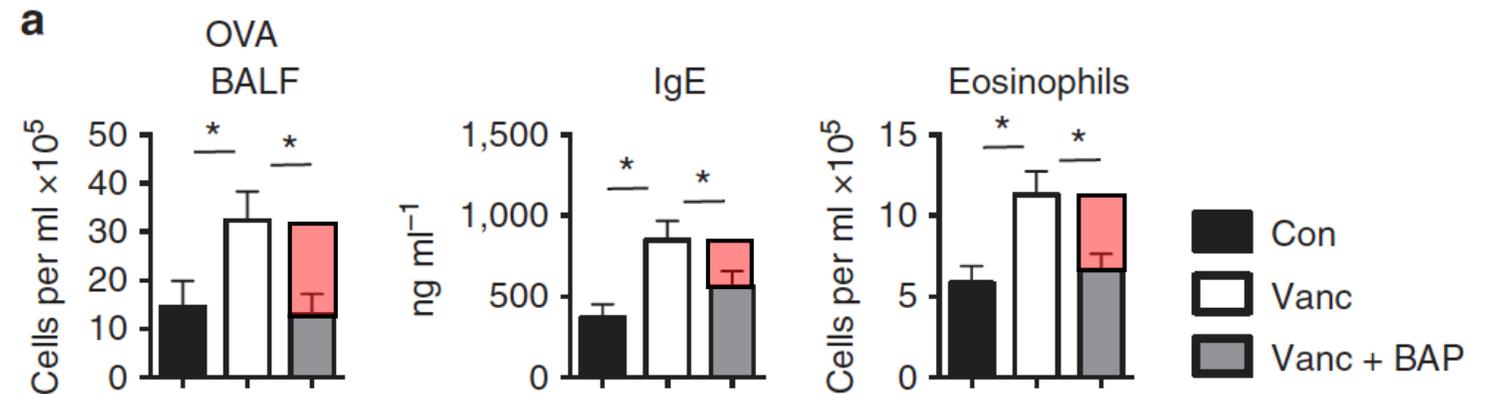
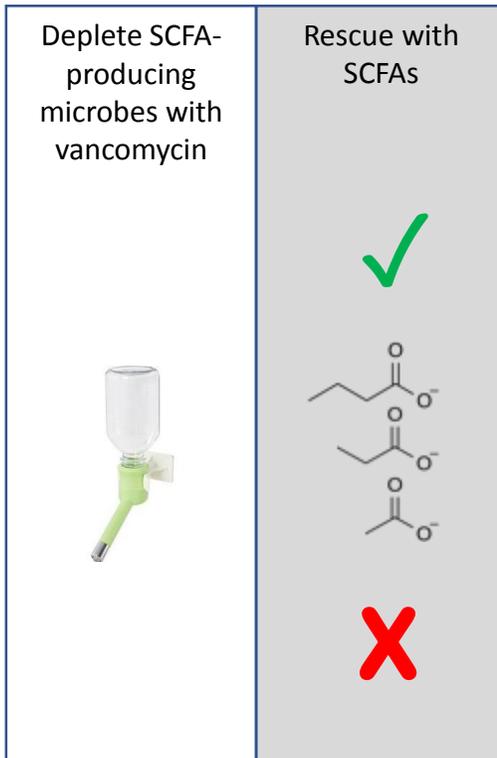
Ovalbumin-sensitized mice



WT



FXR KO





# Summary

- Showed data on the use of biobanked tissue to discover and validate new pathways and potential targets in chronic inflammatory conditions (IBD)
  - Intestinal stem cell lines are amenable to efficient transduction into reporter lines
  - Butyrate activates FXR *in vitro*
- Plan to pursue similar studies in chronic inflammatory diseases of the airways



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SCHOOL OF MEDICINE



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