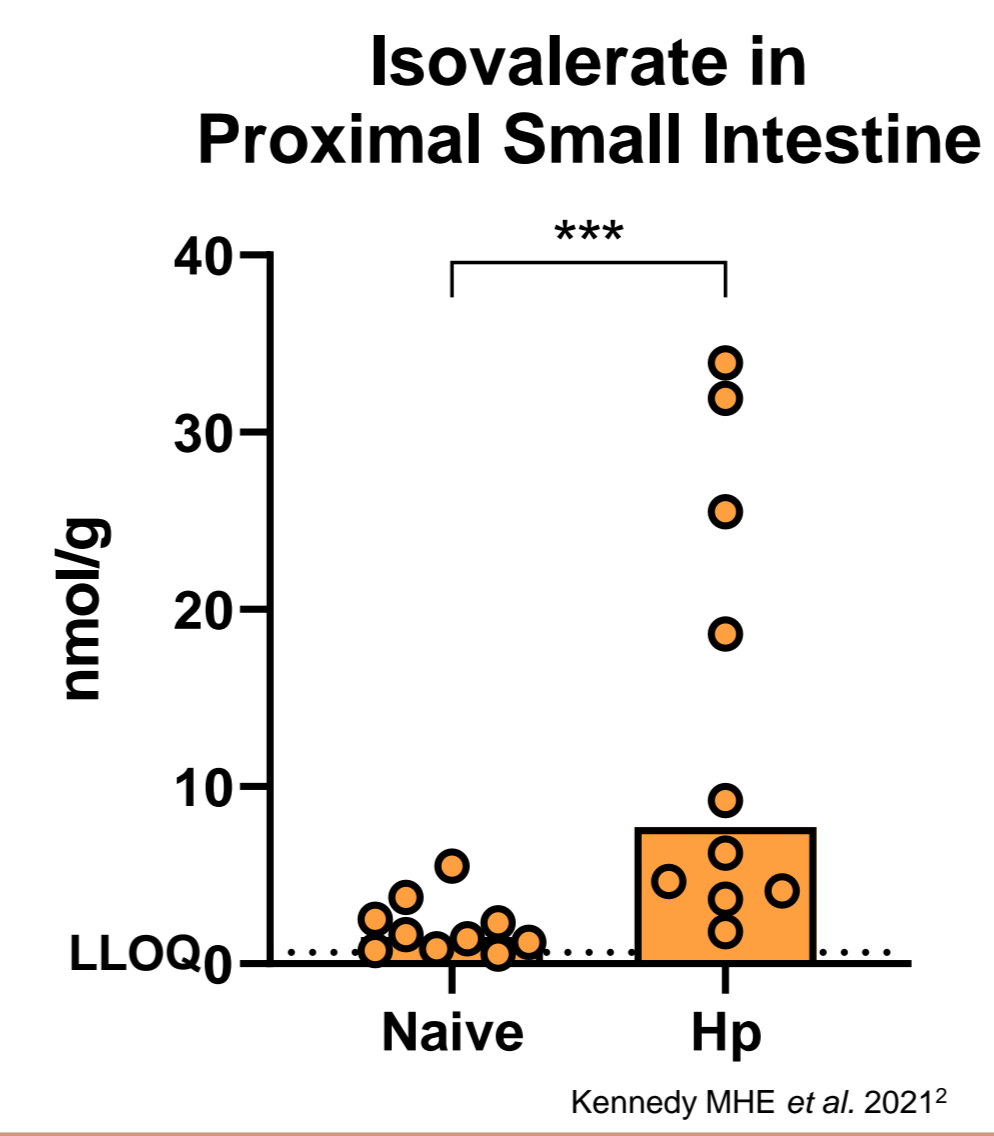
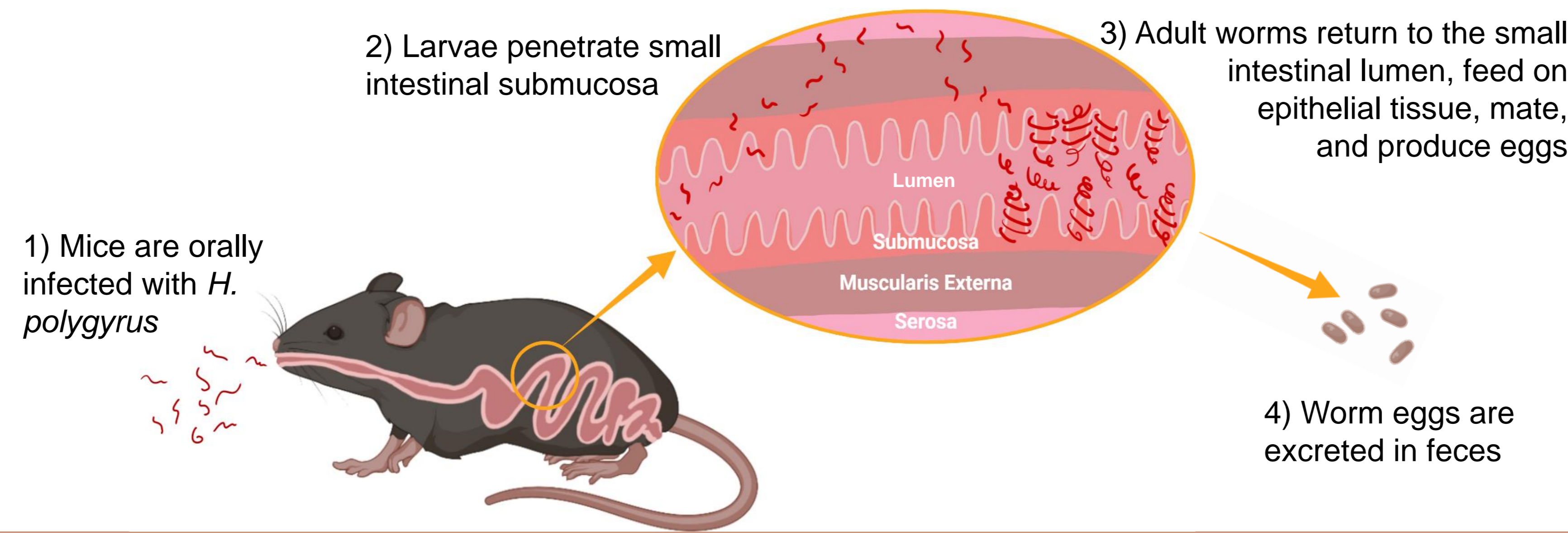


## Background

**Intestinal helminth infections** have immunomodulatory effects including the dampening of pro-inflammatory processes and the repair of intestinal epithelial cell damage. Helminth infection-induced alteration to the host's microbiota composition is thought to contribute, likely in part through the actions of microbe-derived metabolites<sup>1</sup>.

We use the murine *Heligmosomoides polygyrus* infection as a model to (1) understand how chronic helminth infection affects the host and (2) identify small molecules that could modulate host immunity.



### Intestinal short-chain fatty acids (SCFAs):

- Bacterial fermentation products/metabolites
- Many induce anti-inflammatory pathways and promote epithelial barrier integrity

### Isovalerate:

- Branched SCFA
- Significantly upregulated in the proximal small intestine of a mouse during *H. polygyrus* infection<sup>2</sup>
- Effects on the intestinal epithelium largely unknown

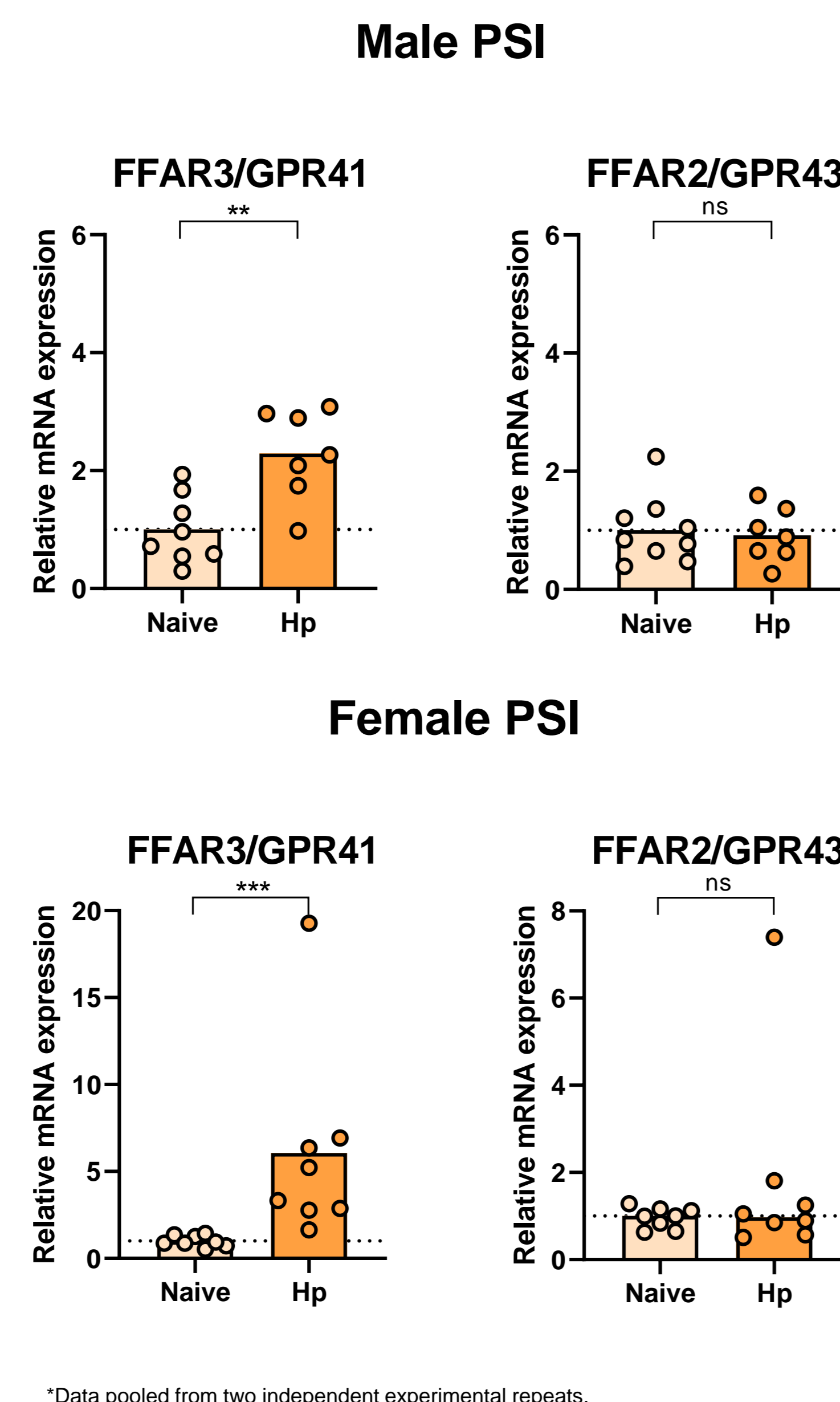
## Hypothesis

I propose that the upregulation of isovalerate in the proximal small intestine during *H. polygyrus* infection helps repair helminth-induced damage to the intestinal epithelium, considering that this is the site where the helminth resides.

**Thus, I hypothesize that isovaleric signalling through SCFA receptors in the proximal small intestine (PSI) can promote intestinal barrier integrity.**

## Results

**Question #1** Can we expect isovaleric signalling through SCFA receptors to be enhanced in the proximal small intestine during *H. polygyrus* infection, or are the receptors down-regulated?

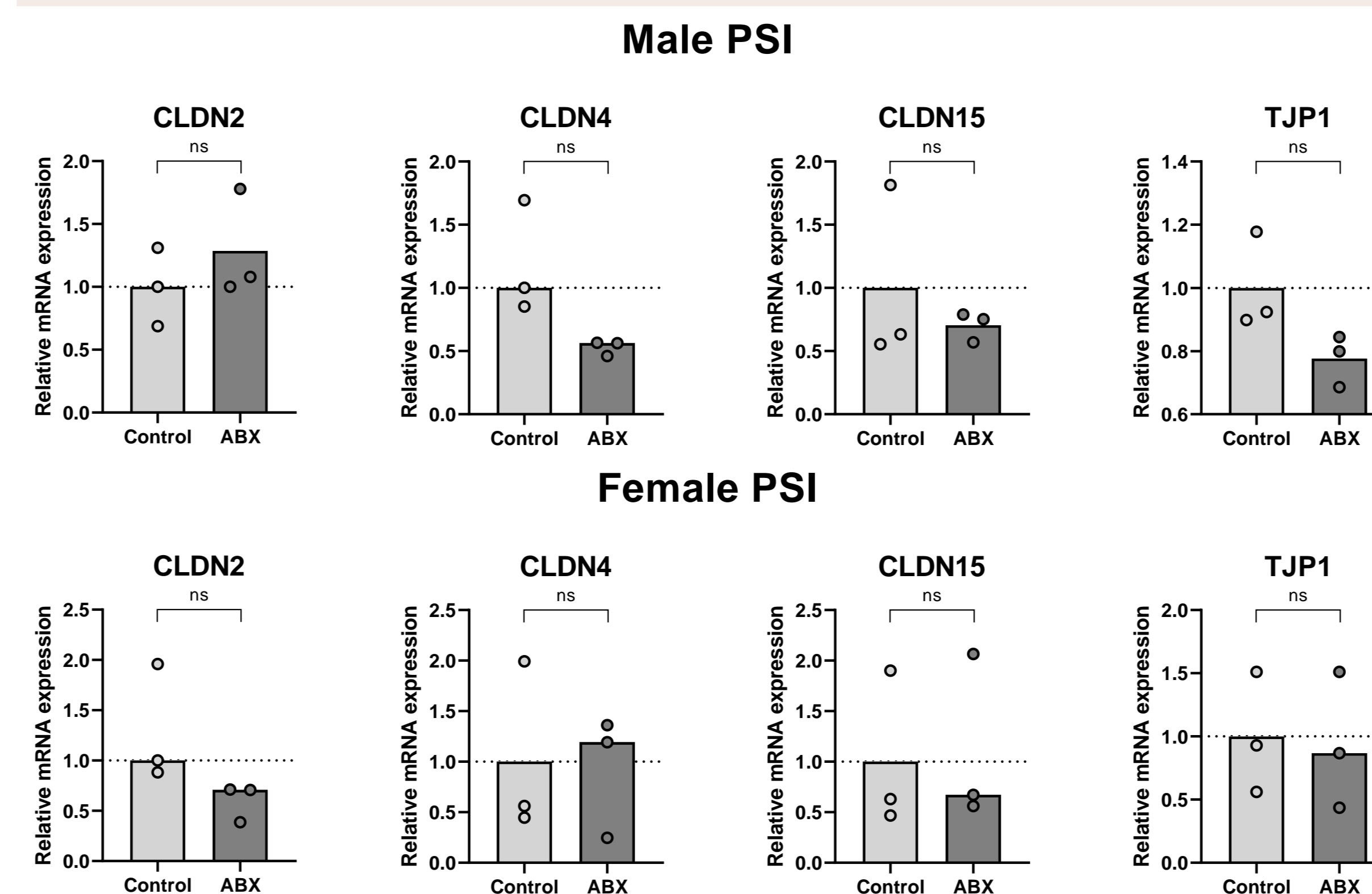


**Results:** The proximal small intestinal expression levels of SCFA receptors FFAR2 and FFAR3 are unchanged and significantly upregulated, respectively, during infection in both male and female mice.

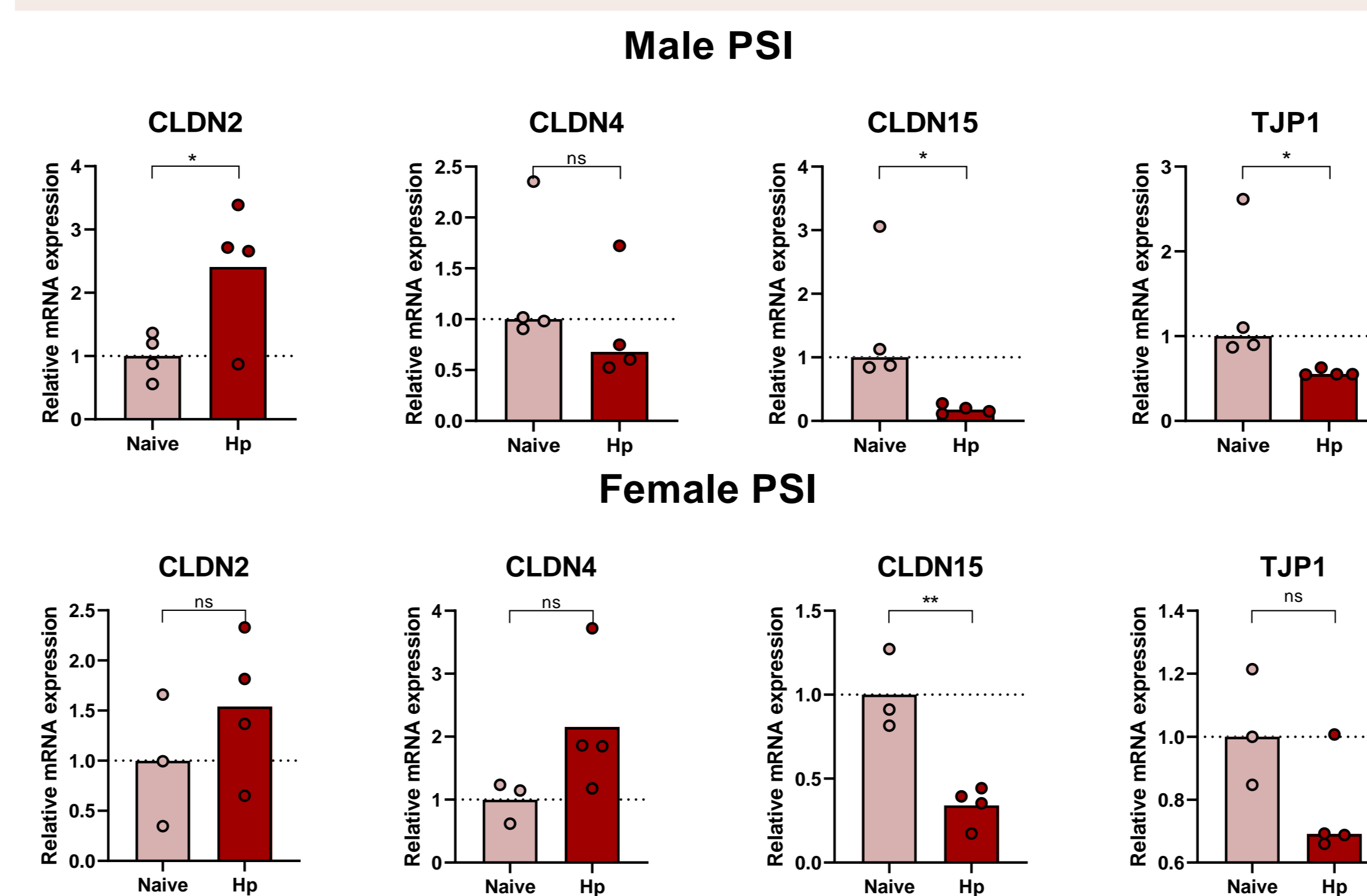
**Receptor-mediated isovaleric signalling is likely increased in the proximal small intestine during *H. polygyrus* infection.**

**Question #2** Can we design a suitable mouse model of a breached small intestinal barrier so we can assess the ability of isovalerate to repair epithelial barrier damage in downstream experiments?

Does microbial depletion via oral antibiotics significantly disrupt tight junction protein expression in the proximal small intestine?



Does *H. polygyrus* infection significantly disrupt tight junction protein expression in the proximal small intestine?



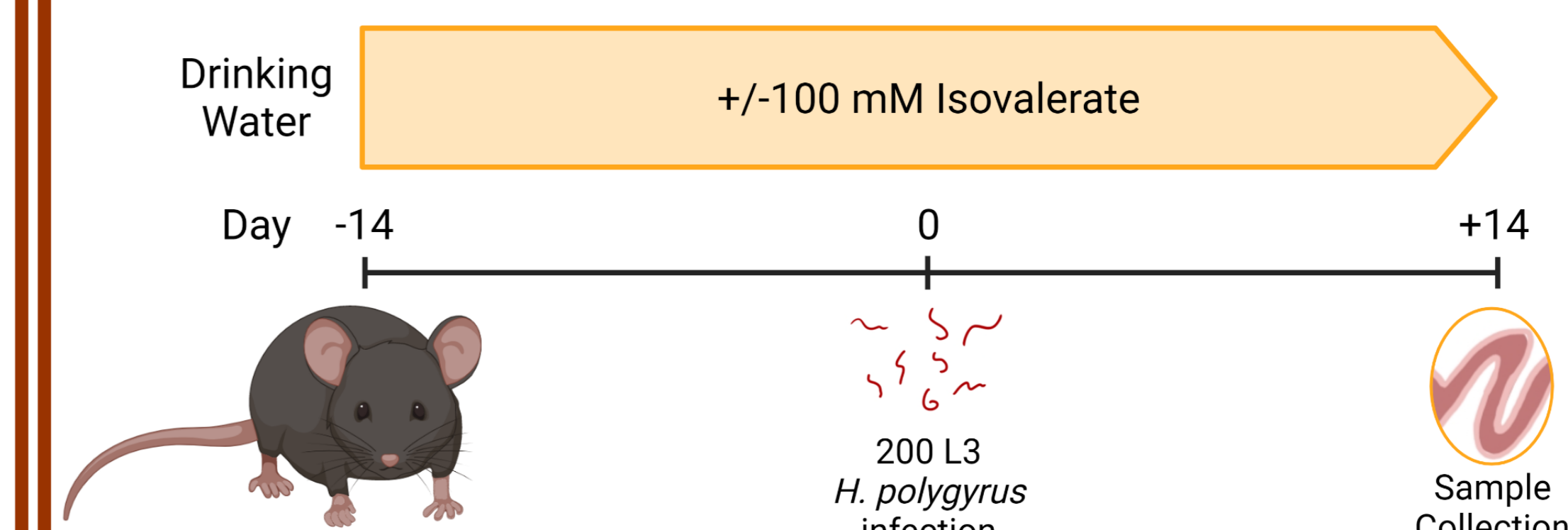
**While microbial depletion does not disrupt small intestinal tight junctions, *H. polygyrus* infection induces significant tight junction disruption in the proximal small intestine and thus can serve as a model of a damaged small intestinal barrier.**

## Conclusions and Future Directions

The significant increase and no change in expression levels of SCFA receptors FFAR3 and FFAR2, respectively, during *H. polygyrus* infection suggest that the observed upregulation of isovalerate in the proximal small intestine enhances the SCFA's receptor-mediated signalling. Such signalling may promote the maintenance of epithelial barrier integrity.

*H. polygyrus*-induced tight junction disruption can serve as a model for a damaged small intestinal barrier. Currently, we are investigating whether the supplementation of mouse drinking water with isovalerate can alleviate such intestinal barrier disruption. In the case of significant results, FFAR3-mediated isovaleric effects can be confirmed by conducting a similar experiment in FFAR3-deficient mice.

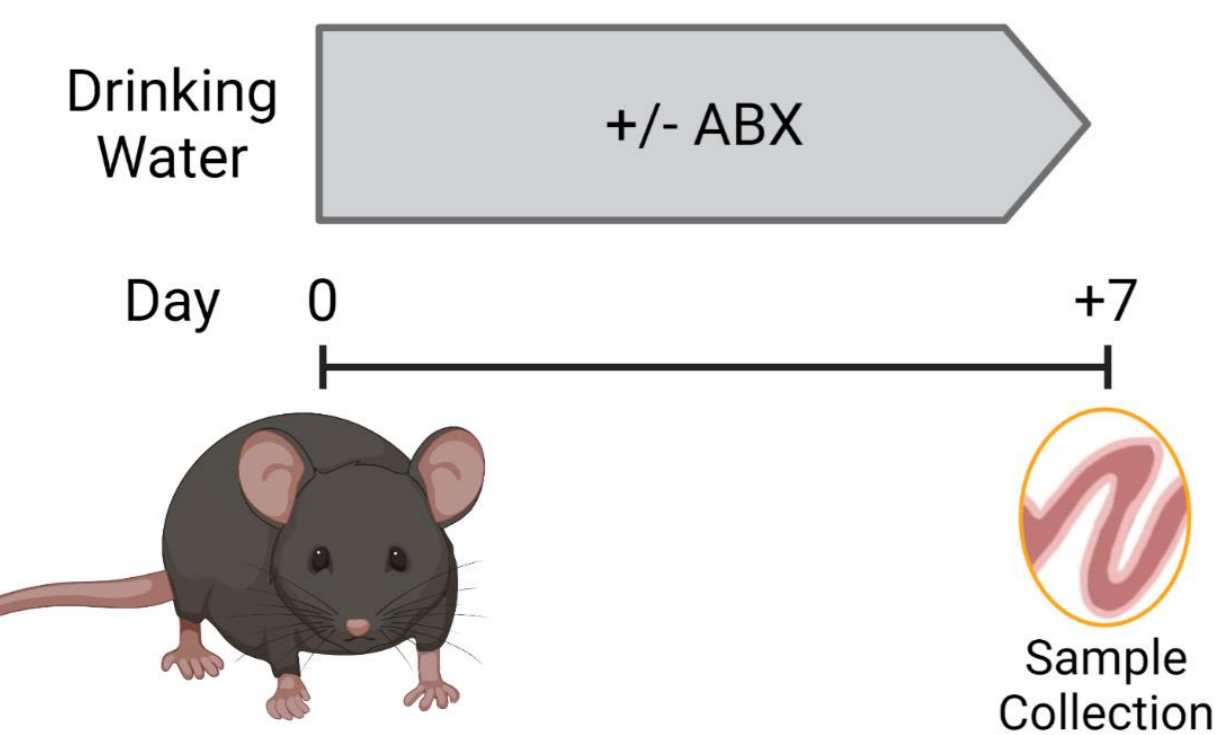
### Current experimental model:



## Methods

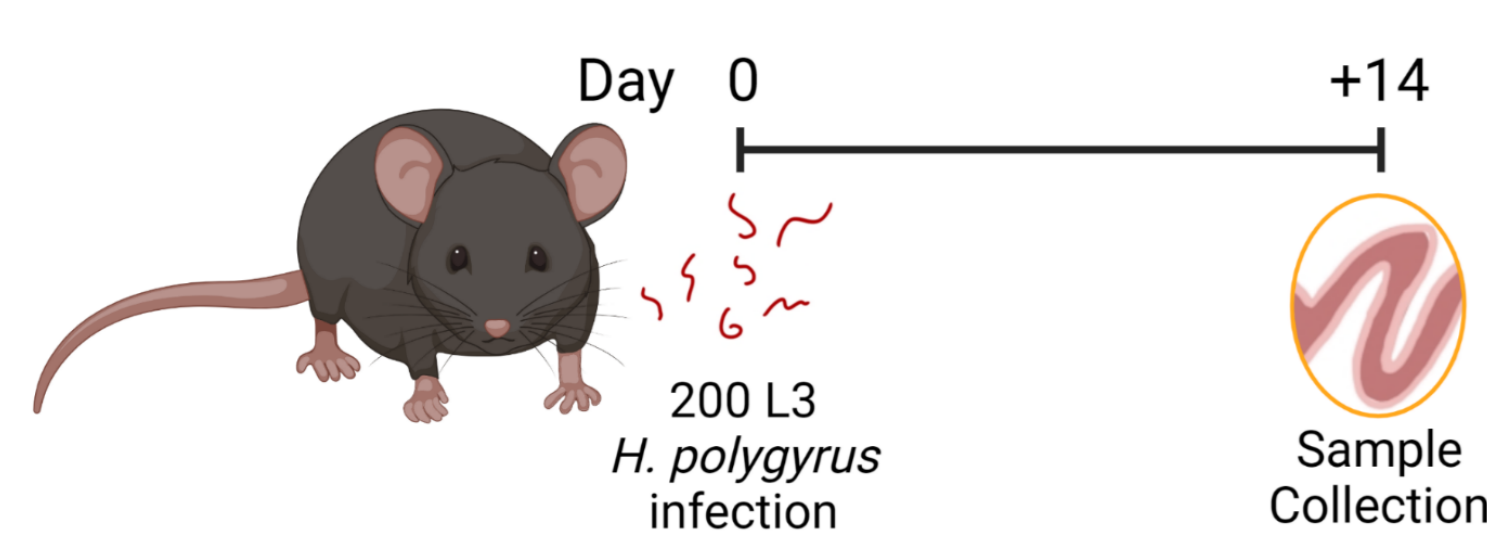
### In vivo experimental models:

#### 1) Microbial depletion via oral antibiotics



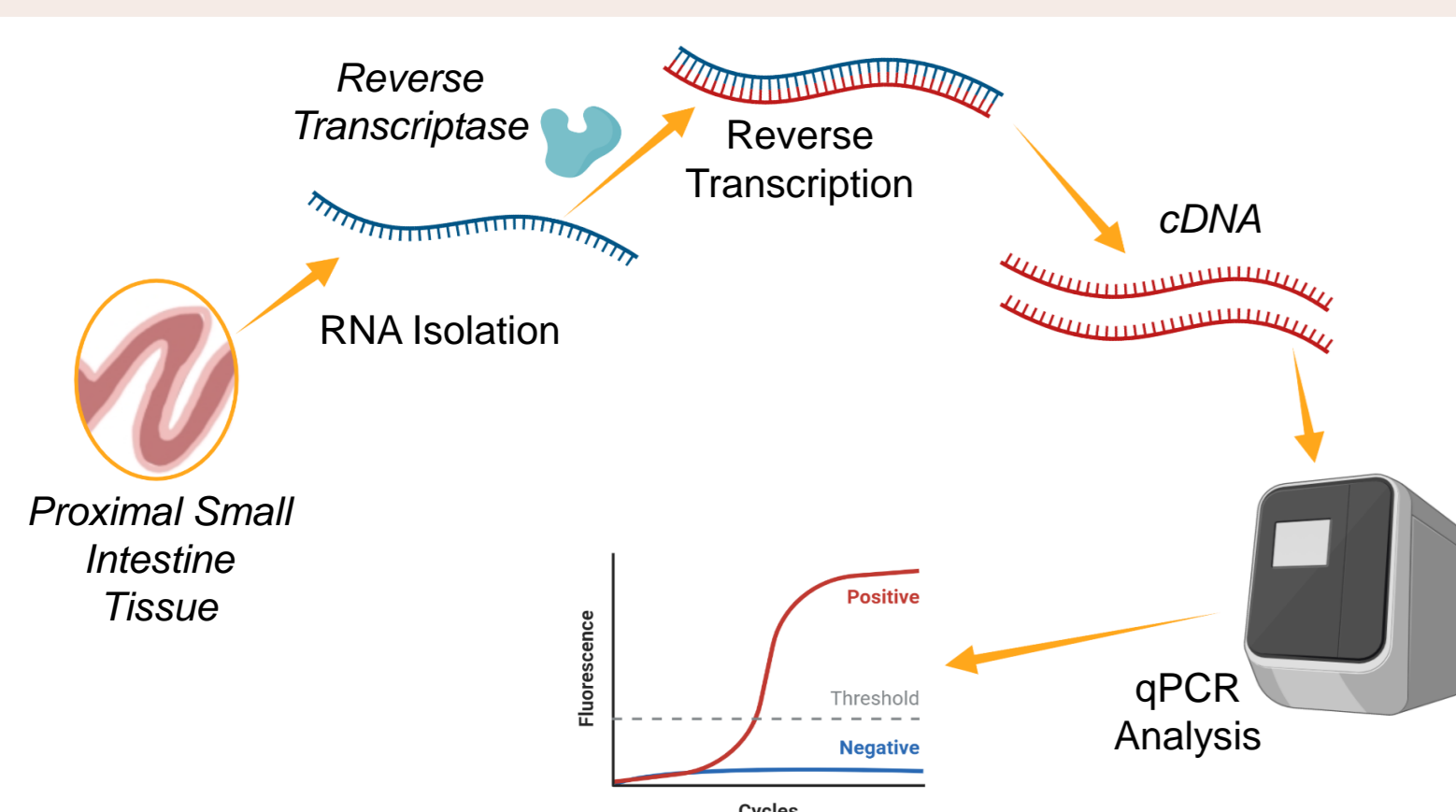
\*Depletion confirmed via fecal DNA extractions from Day 0, 3, and 7 of treatment (data not shown).

#### 2) *H. polygyrus* infection



\*Infection status confirmed with fecal *H. polygyrus* egg counts (data not shown).

### Assessing mammalian gene expression:



## References and Contributions

- Brosschot, T. P. & Reynolds, L. A. The impact of a helminth-modified microbiome on host immunity. *Mucosal Immunol.* 11, 1039–1046 (2018).
- Kennedy, M. H. E. *et al.* Small Intestinal Levels of the Branched Short-Chain Fatty Acid Isovalerate Are Elevated during Infection with *Heligmosomoides polygyrus* and Can Promote Helminth Fecundity. *Infect. Immun.* 89, (2021).

Schematics made using BioRender.



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