

## Introduction

- The microbiota-gut-brain (MGB)-axis is an important pathway for maintaining health and well-being.
- Disruptions in the axis have been identified in numerous disease states, including inflammatory bowel disease, diabetes, and autism spectrum disorders.
- Early development is an important life stage for normal establishment of the microbiota, development of the gastrointestinal (GI) tract and neurobiological growth and maturation, which together comprise the MGB-axis.
- Exposure to pathophysiological stimuli, such as neurotoxicants, during this important developmental period can have long-term consequences on overall health and well-being.

**Assessing the physiology of the gastrointestinal tract following neonatal neurotoxicant exposure will help identify the pathway through which exposure may impact the developing host, including the brain, and modulation of behavior.**

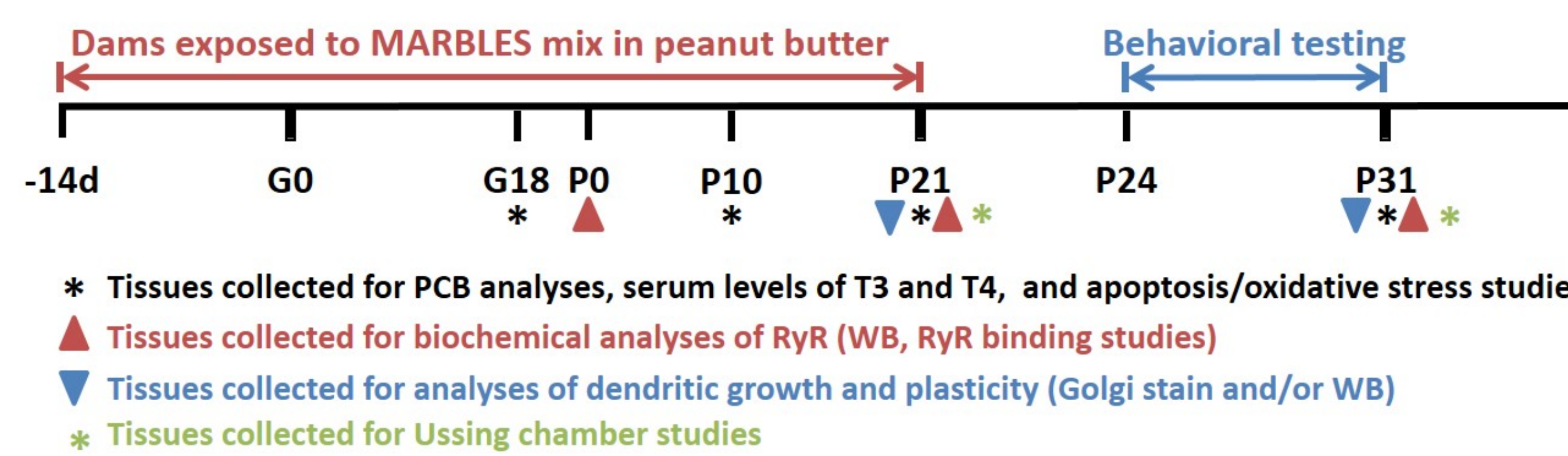
## Methods

- Mice:** C57BL/6 (B6) - WT; *Ryr1* (T48261) gain of function mutation and the X-linked *FMR1* premutation (180-200 CGG repeats)
- Marbles Mix:** The MARBLES PCB mix will be primarily based on the relative concentration profile of the PCB congeners detected in the gestational environment throughout pregnancy in the high-risk MARBLES population: PCB 84, 91, 95, 131, 132, 135, 136, 149, 153, 174, 175, 176, and 196. Three additional PCB congeners will be included in the MARBLES mix: PCB 118, 138, and 180.
- Ussing chambers:** Distal ileum and proximal colon were collected at P28 to assess secretory state (short circuit current [Isc]) and conductance (G).
- Quantitative PCR:** Expression of seven gene targets  $\beta$ -actin, IL-6, IL-10, BDNF, REGIII $\gamma$ , NOD1 and NOD2 was detected in distal ileum and proximal colon following RNA extraction, cDNA synthesis and qPCR.
- Microbiota:** Fecal pellets were collected at P28 for assessment of the composition of the microbiota by qPCR using well-characterized primers for *Bacillus*, *Lactobacillus*, *E. rectale*, *Bacteroides*, *Firmicutes*, *Enterobacteriaceae*, and *SFB* – with results quantified using primers for Eubacteria) as well as for sequencing by Illumina using the V3-V5 region of the 16S gene.

## Hypothesis

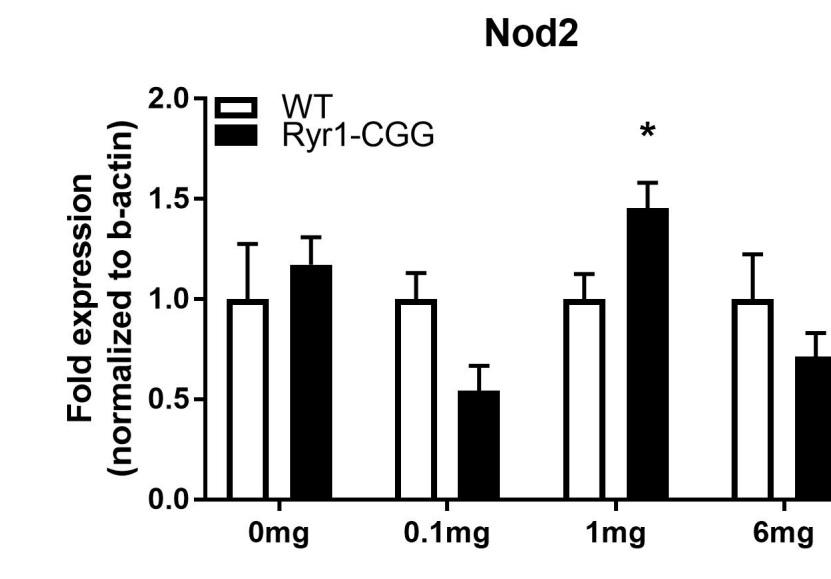
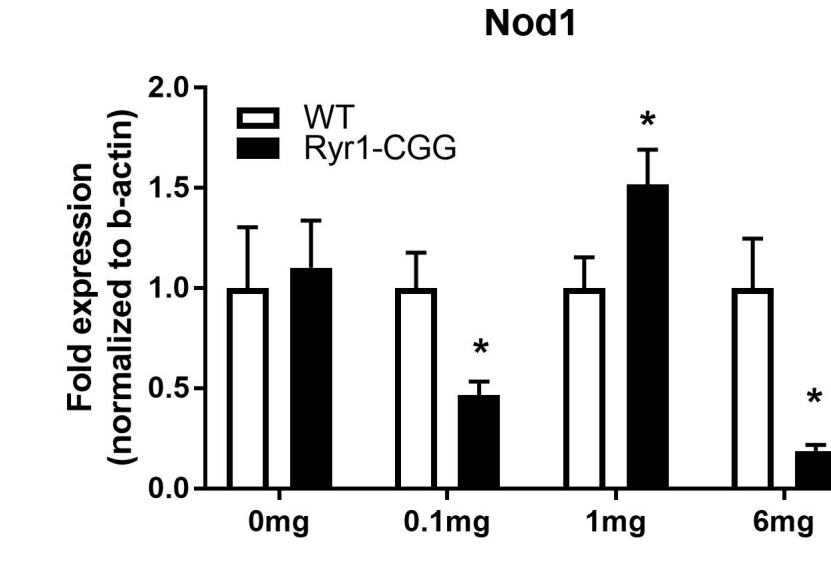
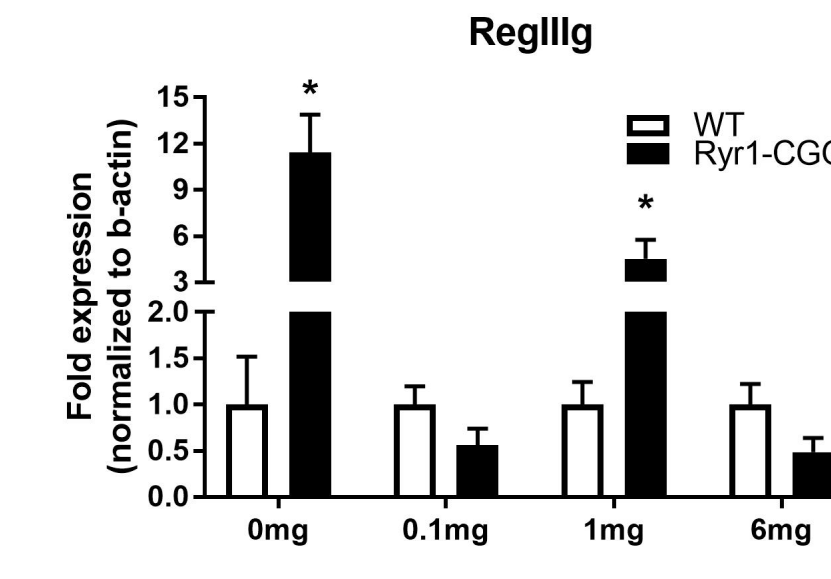
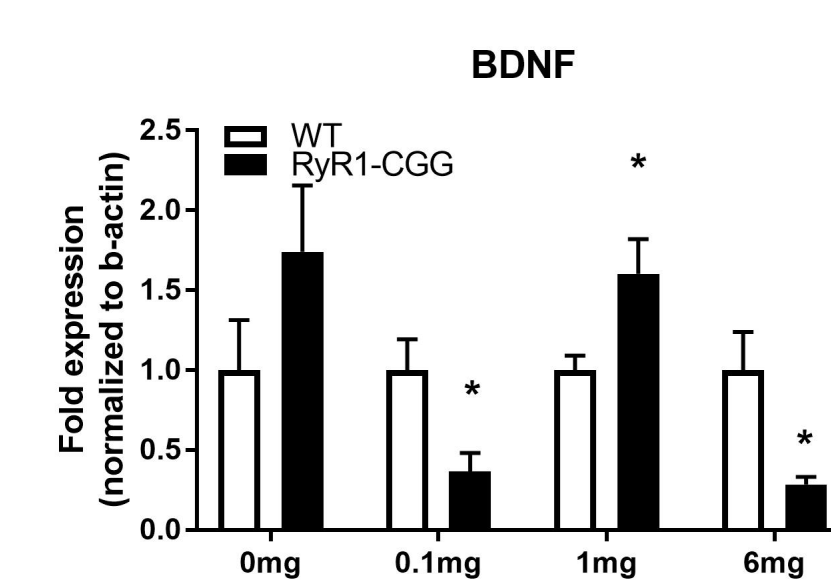
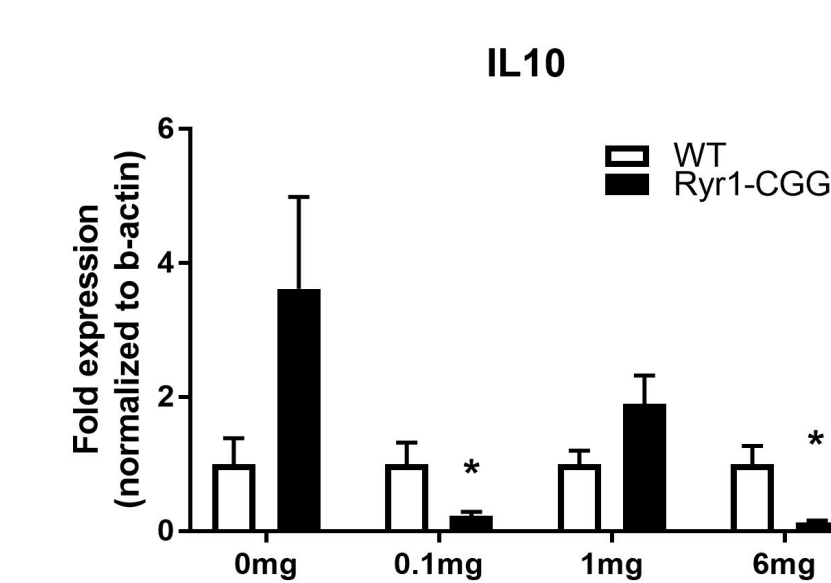
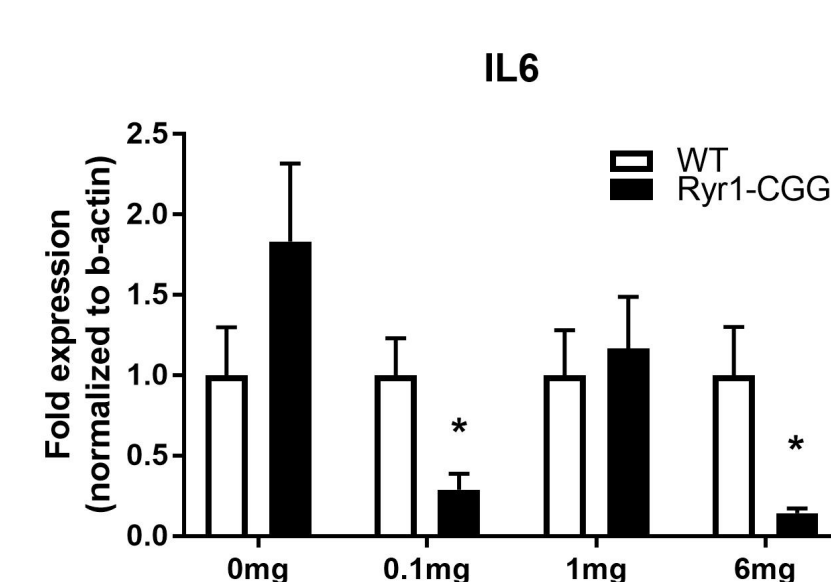
**We hypothesize that exposure to polychlorinated biphenyls (PCBs) during gestation and lactation in mice will result in GI pathophysiology and an altered intestinal microbiota composition.**

## Timeline



## Results

### Colon Expression



### Ileum Expression

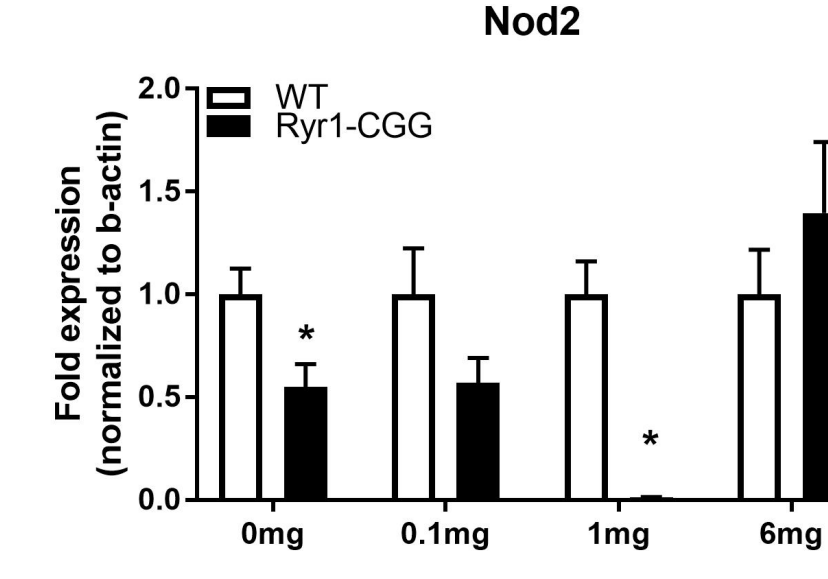
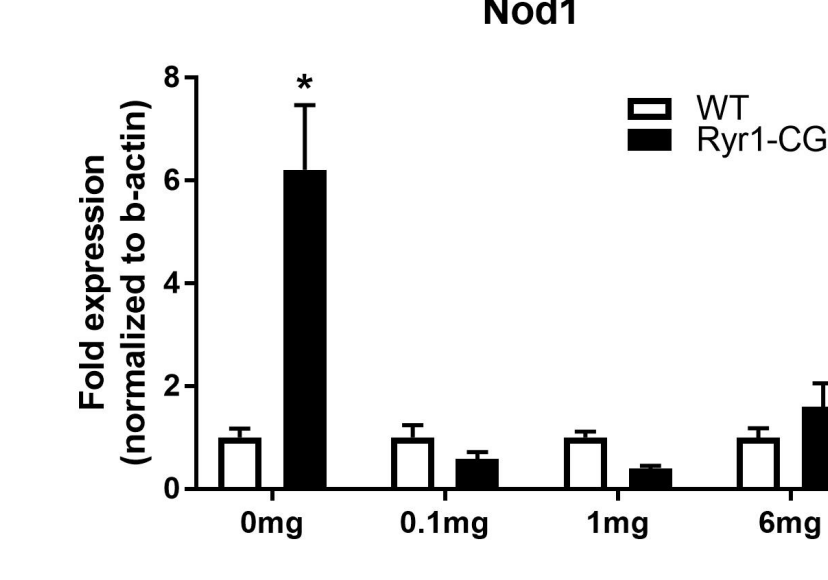
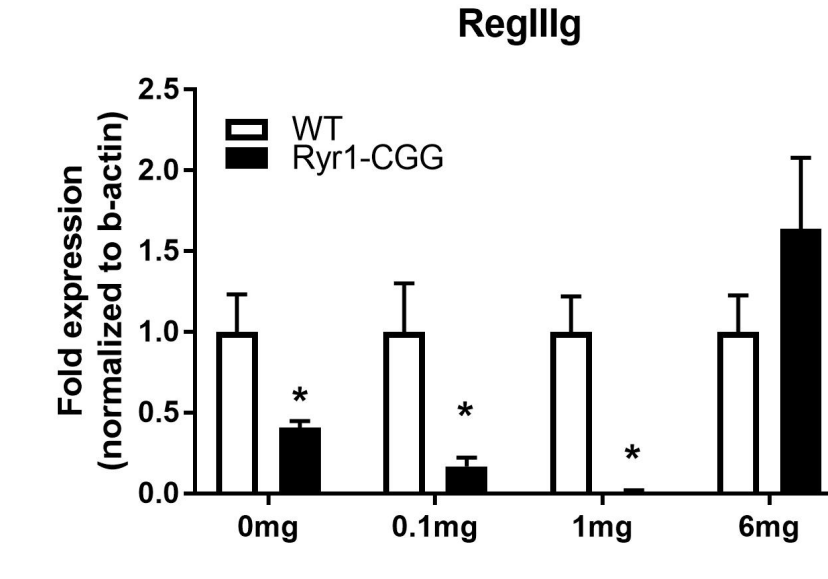
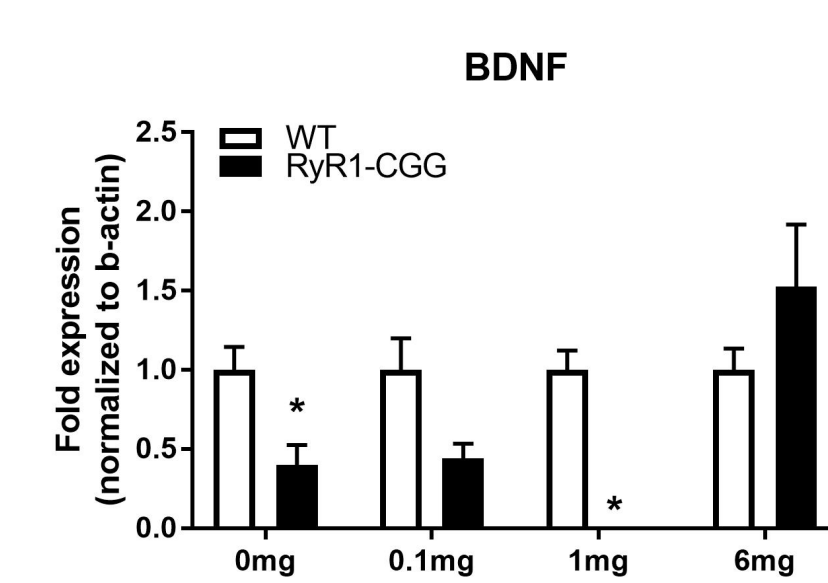
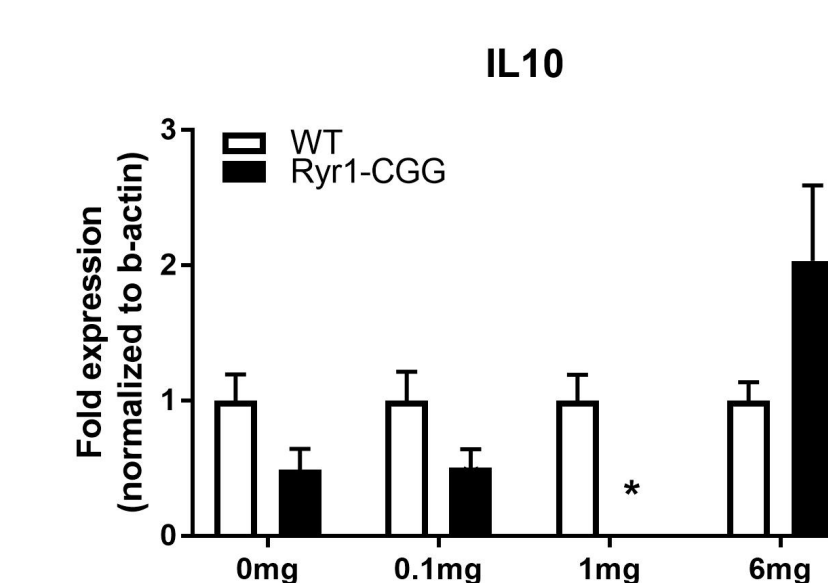
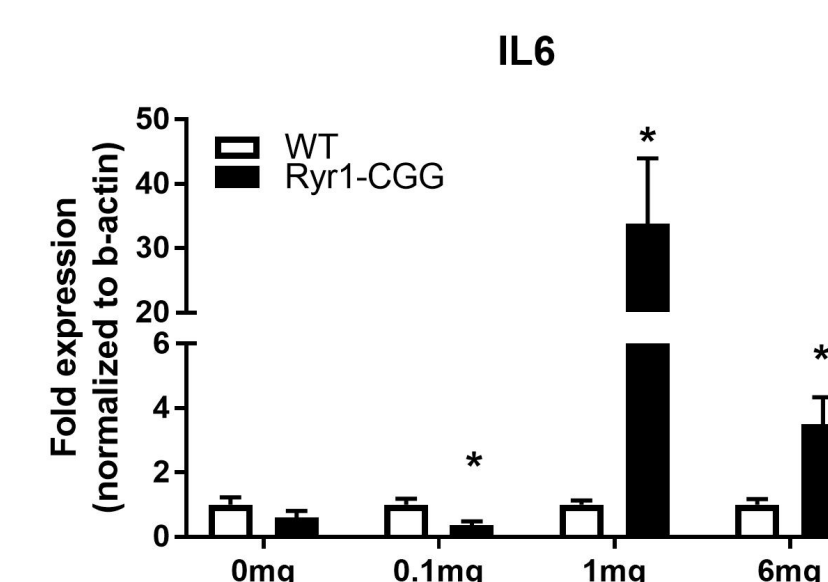
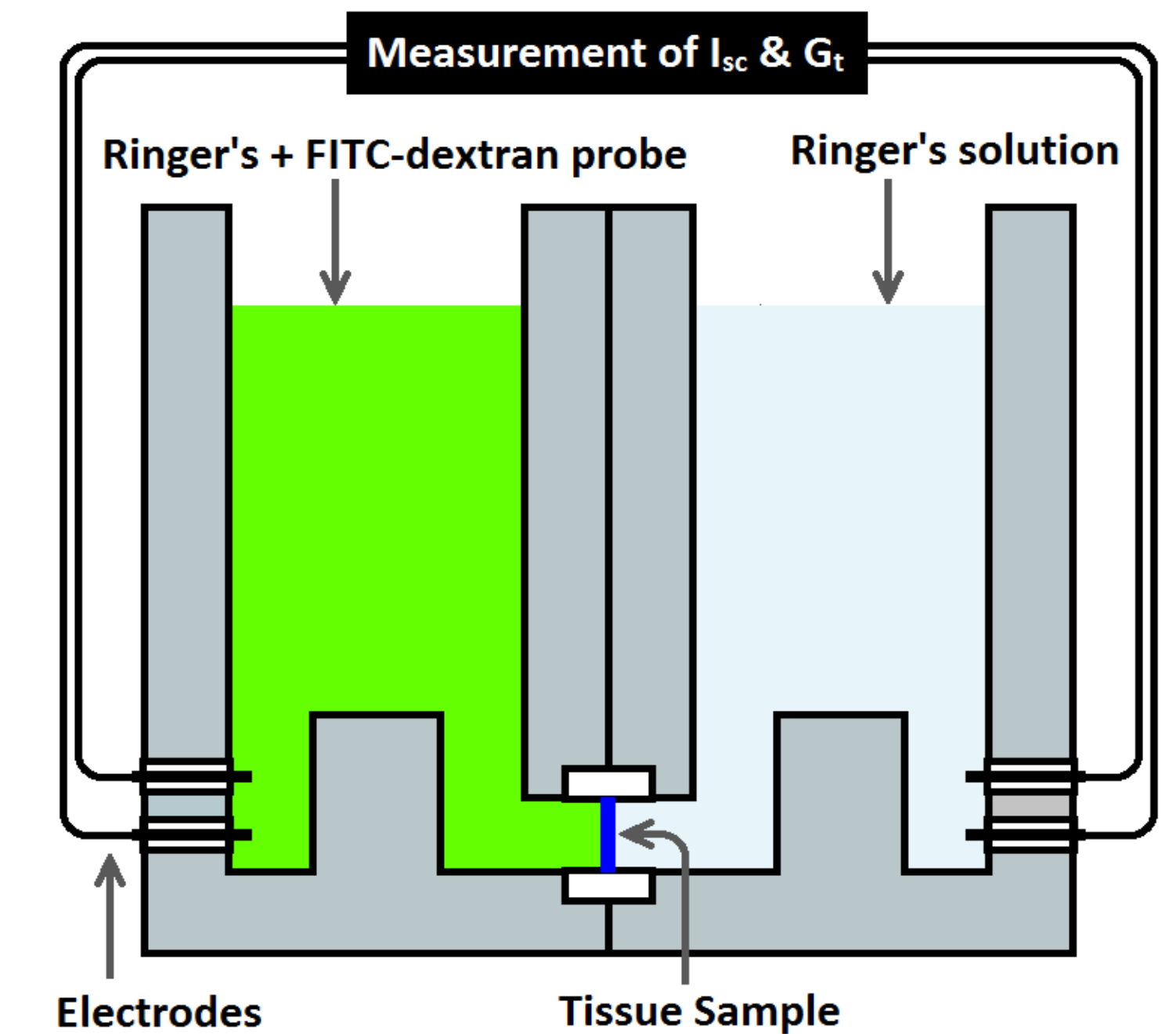


Table 1: Average secretory state (ISC) and conductance (G) values for WT and Ryr1-CGG mice at 0mg, 0.1mg, 1mg and 6mg exposure to PCB.

Dose	Average Colon Values				Average Ileum Values			
	WT (ISC)	Ryr1-CGG (ISC)	WT (G)	Ryr1-CGG (G)	WT (ISC)	Ryr1-CGG (ISC)	WT (G)	Ryr1-CGG (G)
0 mg	37.6	37.2	28.6	26.6	40.8	40.8	43.5	38.4
0.1 mg	33.4	20.8	26.7	28.3	45.9	42.8	46.4	42.5
1 mg	39.2	62.8	24.9	28.4	43.7	39.2	40.7	47
6 mg	40	51.1	25.6	26.8	60.9	46.4	47.3	46.6

## Ussing Chamber Principles



## Summary

- Colon expression of IL6, IL10, BDNF, REGIII $\gamma$ , NOD1 and NOD2 was greater in Ryr1-CGG mice compared to WT controls at 0mg and 1mg PCB doses. Higher secretory state (Isc) values were observed in colon tissue from Ryr1-CGG mice compared to WT controls at 1mg and 6mg PCB doses.

## Future Directions

- Physiology of both the ileum and colon, including secretory state (Isc) and conductance (G) data will continue to be collected for *Ryr1* (T48261) and the X-linked *FMR1* premutation (180-200 CGG repeats) mice compared to WT controls following developmental administration of MARBLES mix.
- FIT-C permeability will be quantified to assess macromolecular permeability.
- Microbiota will be analyzed by 16S Illumina sequencing.

## Speculations

- We speculate that developmental PCB exposure will impact the developing gastrointestinal tract and the composition of the microbiota more strongly in mice that contain a genetic predisposition, compared to WT controls.

## Acknowledgements

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