Mdr1a Constitutive Knockout Mice

The murine multiple drug resistance (*mdr*) gene, *mdr1a*, encodes a 170-kDa transmembrane protein that is expressed on many tissues including intestinal epithelial cells, $CD8^+$ T cells and $CD4^+$ T cells. *Mdr1a* KO mice obtained from Taconic (model # MDR1A-F) have been shown to be susceptible to developing severe intestinal inflammation when housed in specific-pathogen-free (SPF) animal facility conditions (Panwala et al., 1998). The presentation of disease in these mice closely resembles what occurs in human inflammatory bowel disease (IBD) and is defined by dysregulation of epithelial cell growth and lymphocyte infiltration into the lamina propria of the large intestine (Panwala et al., 1998). These mice develop significant disease with marked epithelial cell hyperplasia, edema, neutrophil and lymphocyte infiltration in the mucosa and significant depletion of mucin-secreting goblet cells.

Primary endpoints include colon weight to length ratio collected at necropsy, as well as, histopathological evaluations of colons. Live phase data include evaluation of disease activity index (DAI) through assessment of stool consistency, presence of occult blood/gross bleeding and incidence of anal prolapse throughout the duration of the study.

Protocol:
Female mice were evenly distributed among groups based on age and then randomized based on body weight. FVB mice were used as non-diseased controls (Group 1). Baseline DAI was scored (*see scoring system below) after randomization and prior to any treatment. Body weight was recorded three times weekly, and DAI was recorded once weekly. Endoscopy (**see scoring system below) was performed once per week on disease control mice (Group 3) to track loss of vascularity and development of mucosal erosion and ulcerations. A cohort of mice (Group 4) were administered i.p. injections of anti-IL-12 on days 0, 7, 14, 21, 28 and 35. On study day 42, the animals were euthanized via CO_2 asphyxiation followed by cervical dislocation. The entire colon was removed, measured, weighed and collected for histopathological evaluation.

***Disease Activity Index (DAI):**
Cumulative score from three different parameters:

Prolapse:
- 0: no protrusion
- 1: mild
- 2: pronounced
- 3: severe

Stool Consistency
- 0: dry, well formed, highly consistent, no visible blood
- 1: moist, formed, less consistent, no visible blood
- 2: very moist, somewhat formed, small dark blood spots
- 3: diarrhea, no form, visible blood in stool or around anus

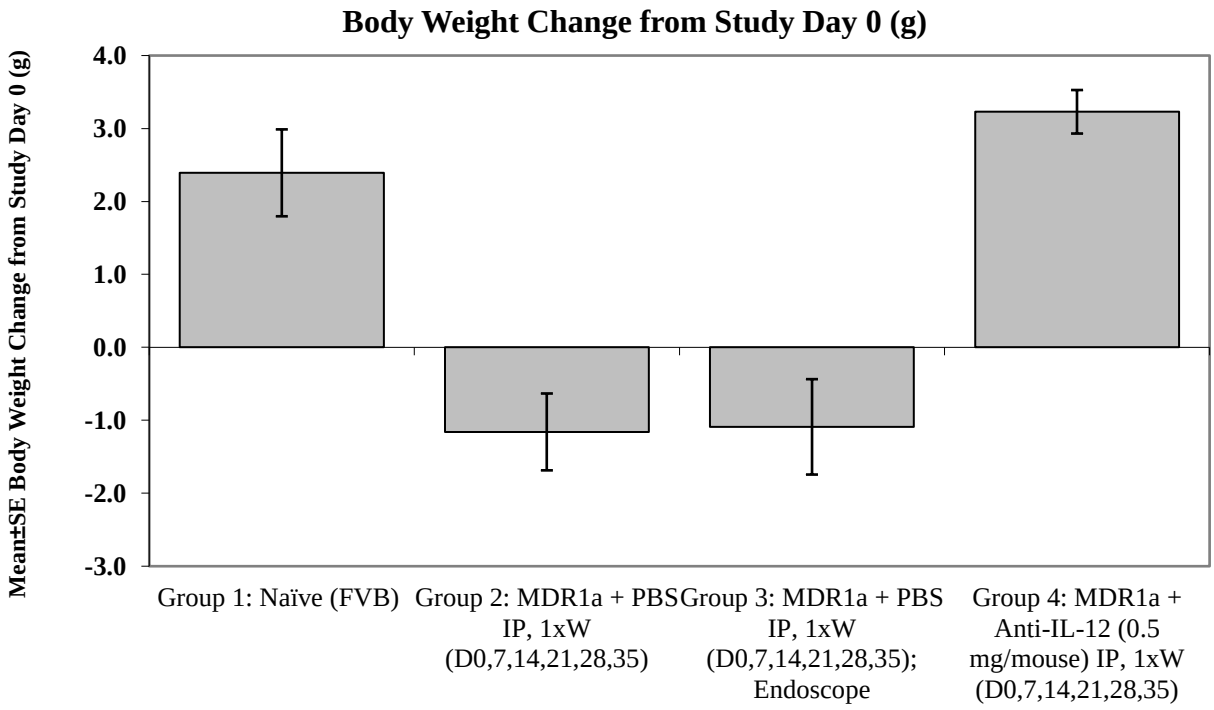
Occult Blood or Gross Bleeding (Hemoccult slides):

0: no blue stain
1: visible light blue stain
2: dark blue stain
3: visible blood, dark blue stain

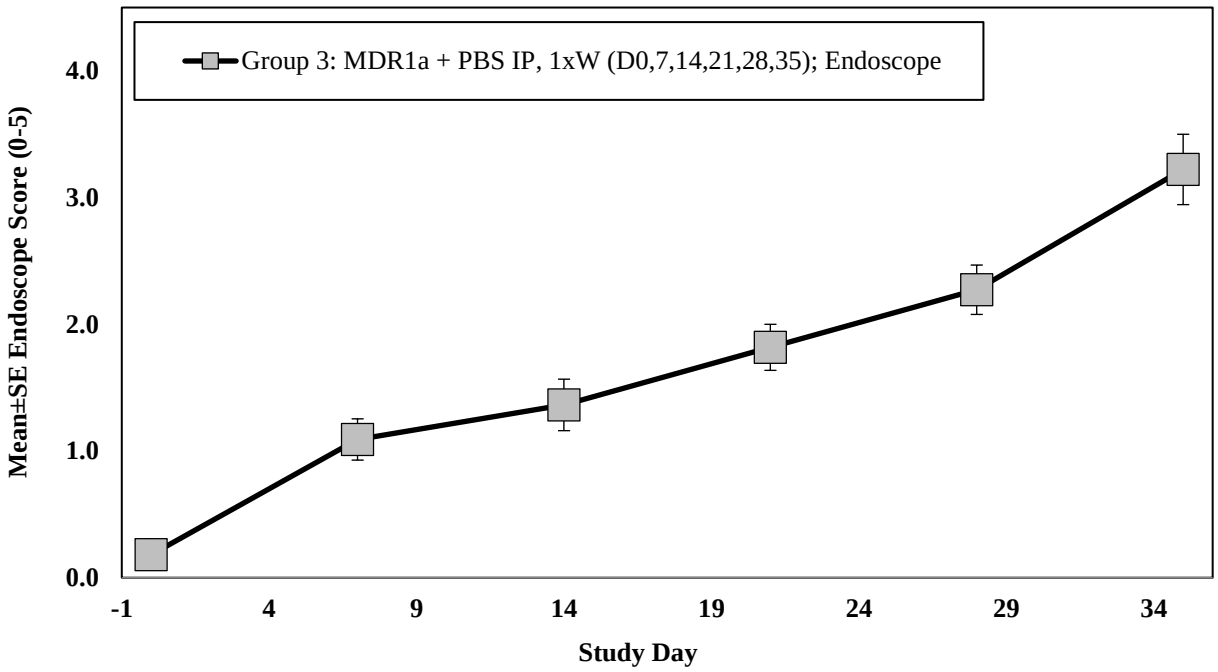
****Endoscopic Scoring System:**

0: Normal
1: Moderate loss of vascularity (small vessels cannot be seen)
2: Severe loss of vascularity (large and small vessels cannot be seen), presence of contact bleeding
3: Presence of mucosal erosions
4: Ulcerations and/or gross bleeding

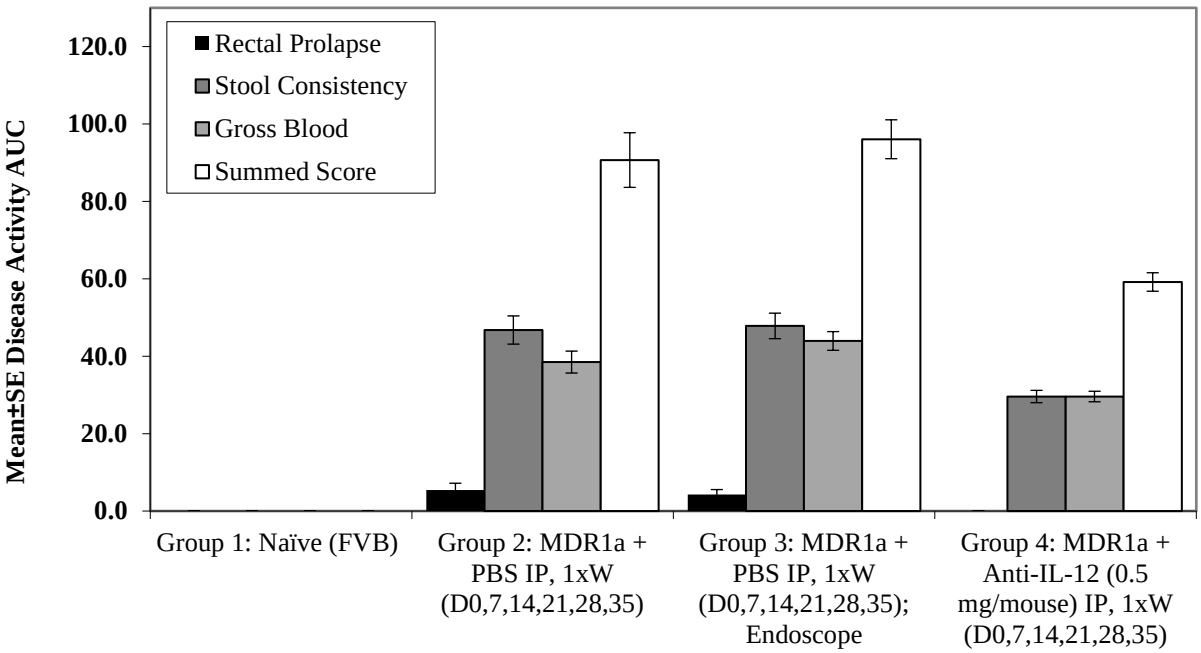
Results:



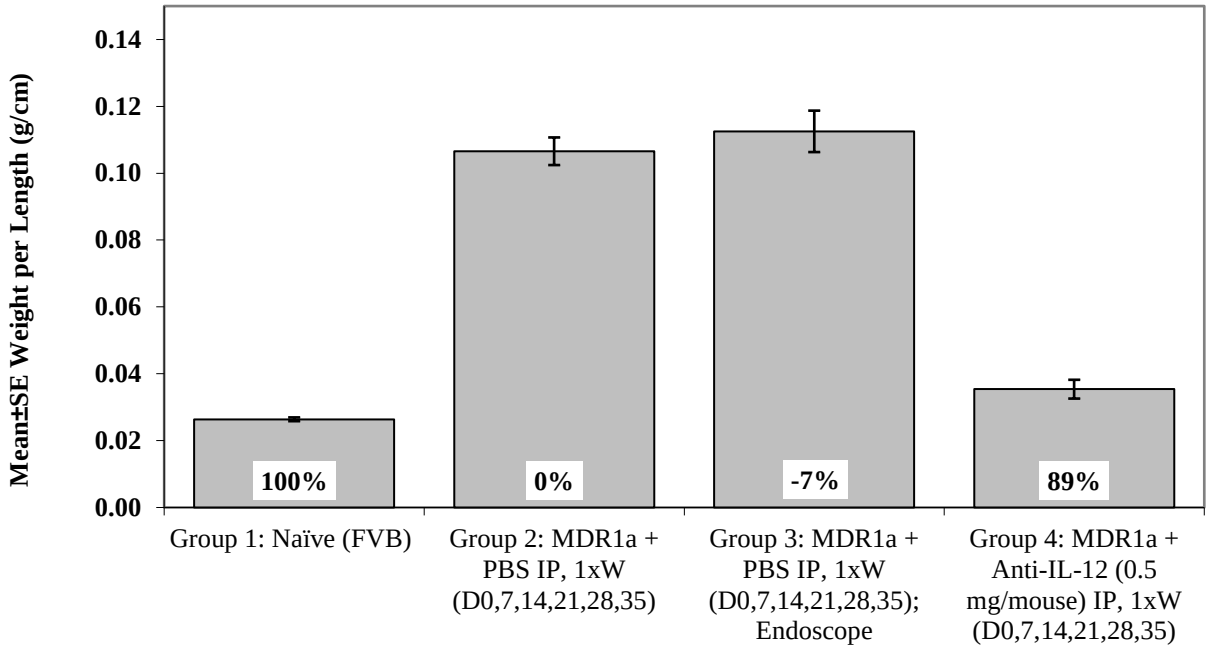
Endoscope Scores Over Time (0-4)



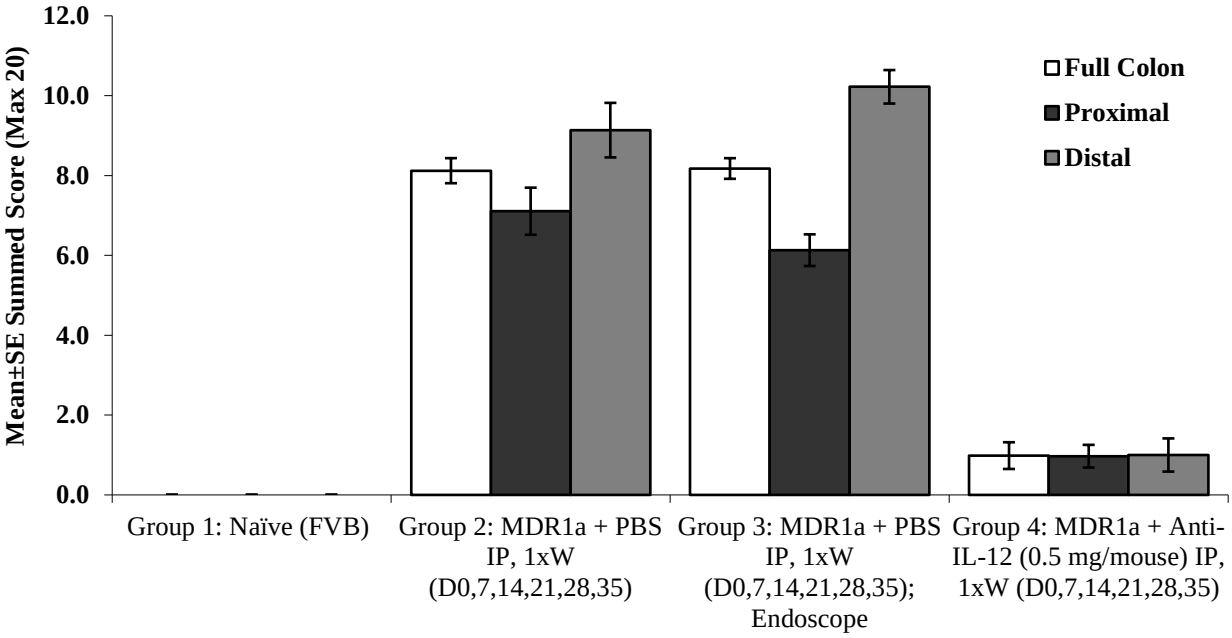
Disease Activity AUC



Colon Weight per Length (g/cm)



Summed Colon Histopathology Score



Representative Endoscope Photos:

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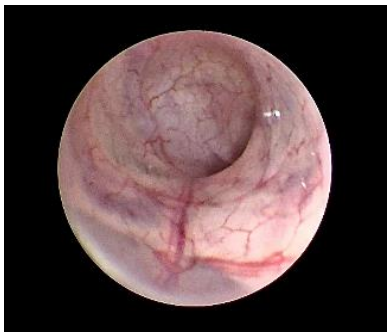
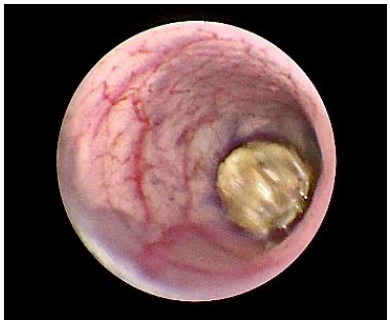
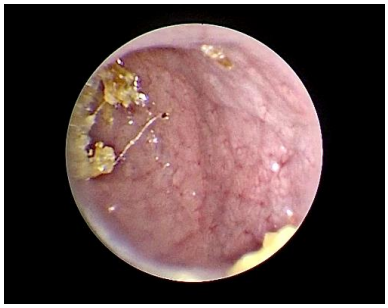


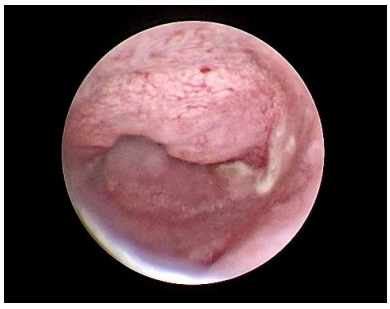
Score = 1



Score = 2



Score = 3



References:

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3. Koboziev I, Karlsson F, Zhang S, Grisham MB. Pharmacological intervention studies using mouse models of the inflammatory bowel diseases: translating preclinical data into new drug therapies. Inflamm Bowel Dis. 2011 May;17(5):1229-1245.
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5. Read S and Powrie F. Induction of inflammatory bowel disease in immunodeficient mice by depletion of regulatory T cells. Curr Protoc Immunol. 2001 May;Chapter 15:Unit 15.13.