

# Inflammatory Bowel Disease Models



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2022.10

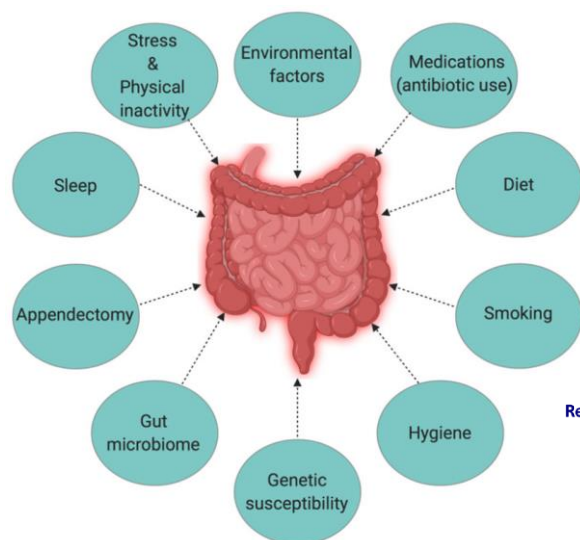
OncoWuXi Newsletter

- Introduction of Inflammatory Bowel Disease
- Animal models for inflammatory bowel disease
  - DSS-induced acute and chronic colitis model in mice
  - Oxazolone induced colitis model in mice and rats
  - TNBS-induced colitis model in Balb/c mice and SD rats
  - Anti-CD40 antibody induced colitis model in SCID mice
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- How to pick up the right model for IBD?
- Inflammatory and auto-immune disease platform

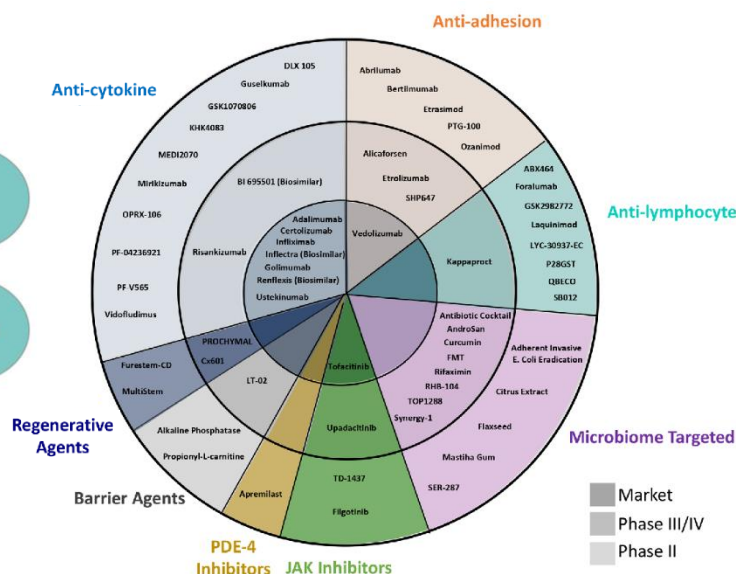
# Inflammatory Bowel Disease (IBD)

Multi-factors triggered inflammatory bowel disease

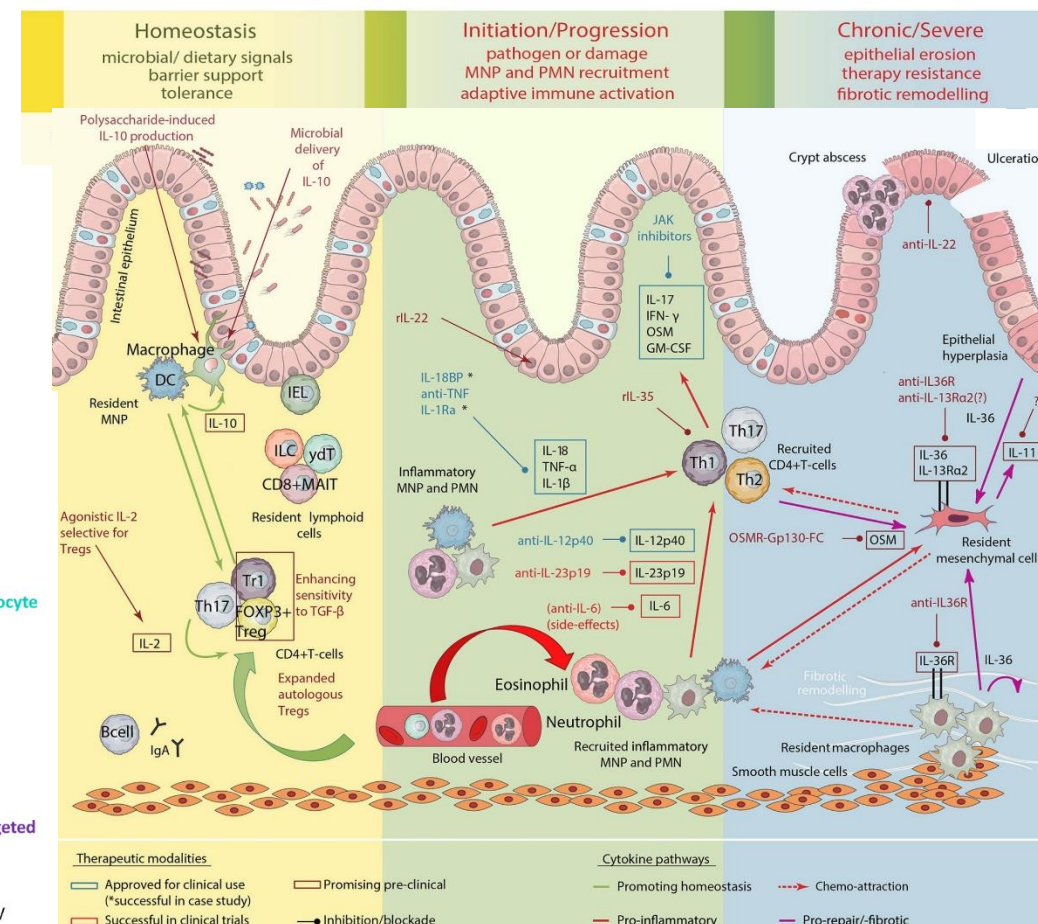
- IBD is defined as a chronic intestinal inflammation with abdominal bloating, abdominal pain, severe pelvic muscle spasms, diarrhea, bloody stools and loss of weight.
- The prevalence of IBD ranges from 0.25% to 0.32% around the world. Crohn's disease and ulcerative colitis are the most common forms of IBD. Crohn's disease is slightly more common in women, while ulcerative colitis is slightly more common in men.



Karma Yeshe etc., *J. Clin. Med.*, 2020, 9(5), 1273



Calen A. Steiner etc., *Practical Gastro*, April 2019, Volume XLIII, Issue 4

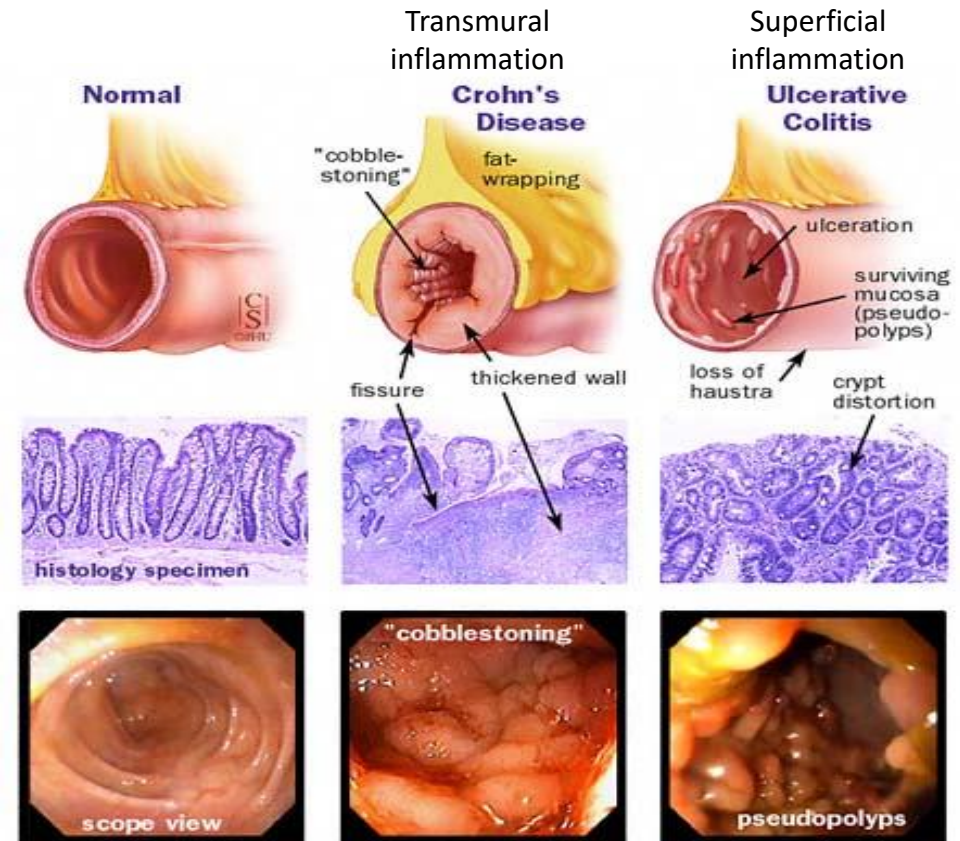


*Immunity* Vol 50(4), April 2019

# Animal models for inflammatory bowel disease

## □ Inflammatory bowel disease models

- DSS induced acute colitis in mice
- DSS induced chronic colitis in mice
- Oxazolone induced acute colitis in mice
- Oxazolone induced acute colitis in rats
- TNBS induced acute colitis in mice
- TNBS induced acute colitis in rats
- Anti-CD40 antibody induced colitis in mice
- T cell transfer induced chronic colitis in mice
- Spontaneous colitis in IL10<sup>-/-</sup> Balb/c mice



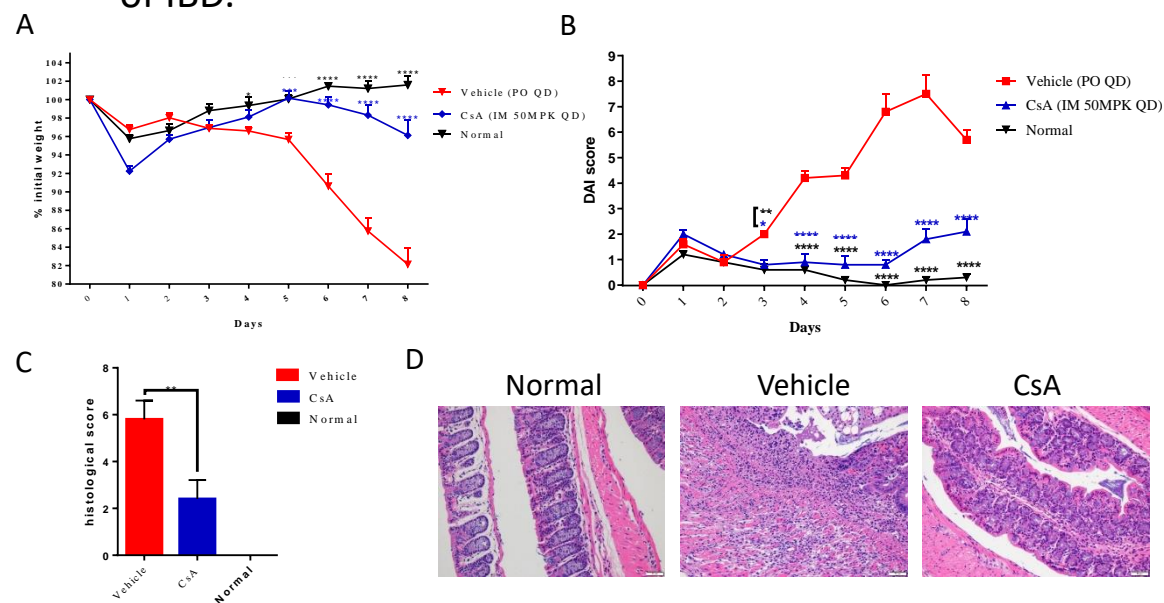
**Figure 4.** Gross (top), histological (center), and endoscopic (bottom) appearance of normal colon, Crohn's disease, and ulcerative colitis.

<http://www.aahclinic.com>



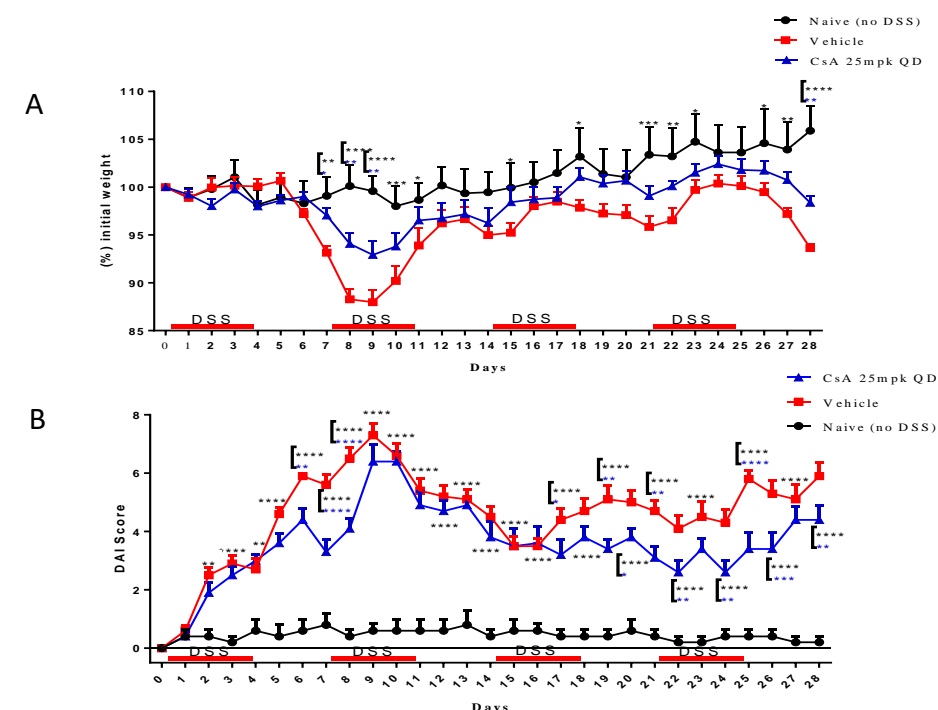
# DSS-induced acute and chronic colitis model in mice

Mice are exposed to Dextran Sulfate Salt (DSS) in water for 7 days to induce inflammation and gland loss with erosion in the colon. Cyclosporine A (CsA) is a reference compound which can be used to relieve their symptoms of IBD.



**Figure. A.** Body weight change for in-life study **B.** Disease activity index (DAI) score for stool consistency and rectal bleeding **C.** Histopathology score for Swiss-rolled colon **D.** Representative image for HE staining of colon tissue.

Mice are exposed to 4 cycles of DSS and distilled water at 4 day-on-3 day-off interval to induce chronic inflammation in bowel.

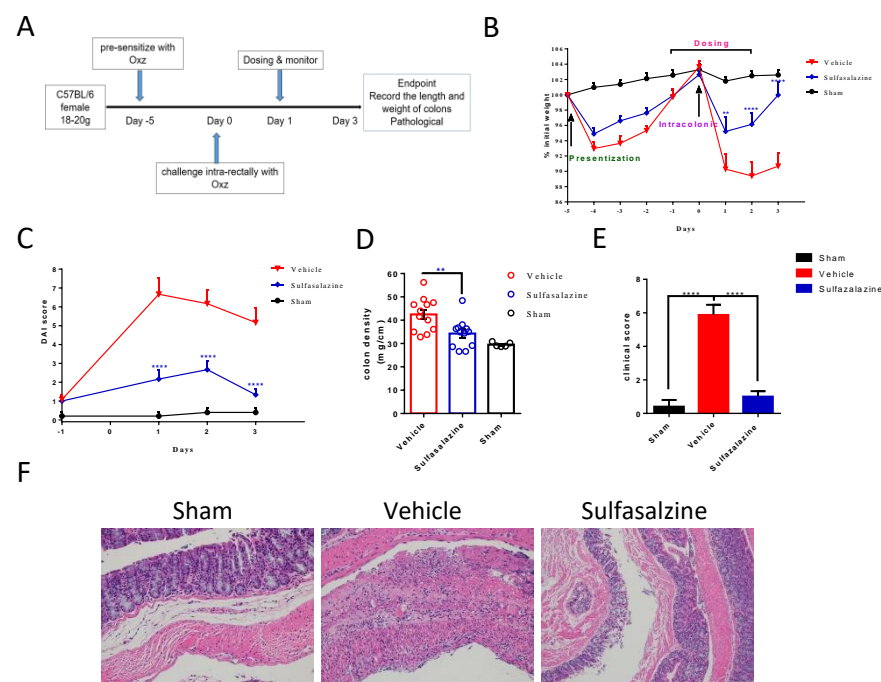


**Figure. A.** Body weight change for in-life study **B.** DAI score for chronic colitis model

# Oxazolone induced colitis model in mice and rats

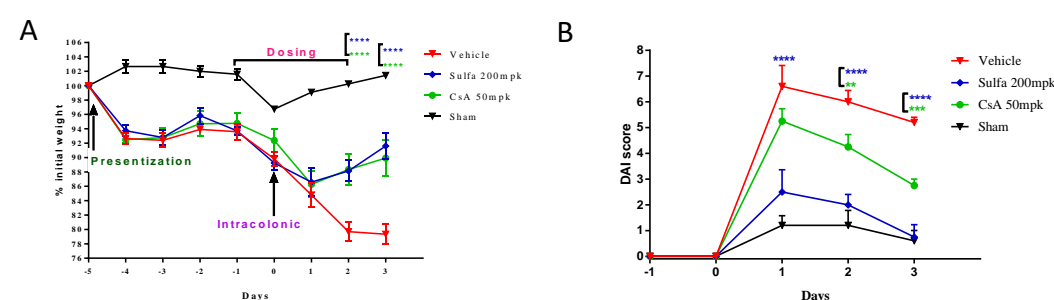
- Ulcerative colitis (UC) is one of the most common forms of IBD in human and Th2 immune responses are always observed in patients. Oxazolone treatment can trigger similar Th2 responses in animals, so Oxazolone induced colitis model can be a better tool to understand human UC mechanism and develop new therapeutic drugs.

## Oxazolone induced colitis model in C57BL/6 mice

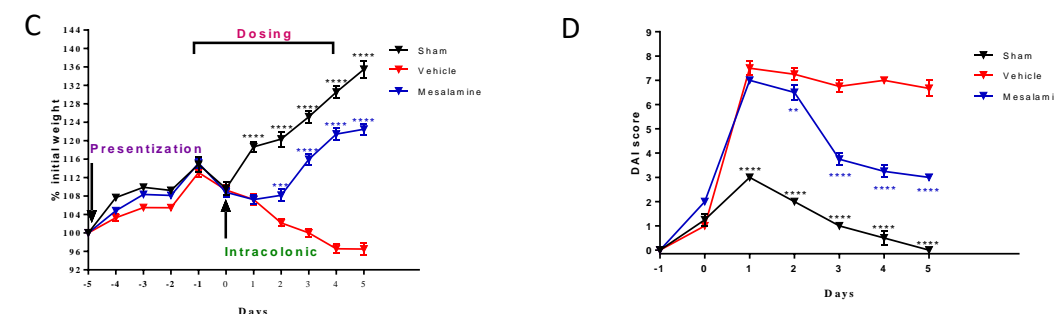


**Figure. A.** Flow chart of Oxazolone induced acute colitis in C57BL/6 mice **B.** Body weight change **C.** DAI score of **D.** Colon density, colon weight per unit of colon length **E.** Histopathological score of colon **F.** Representative image of HE staining for colon tissue

## Oxazolone induced colitis model in Balb/c mice



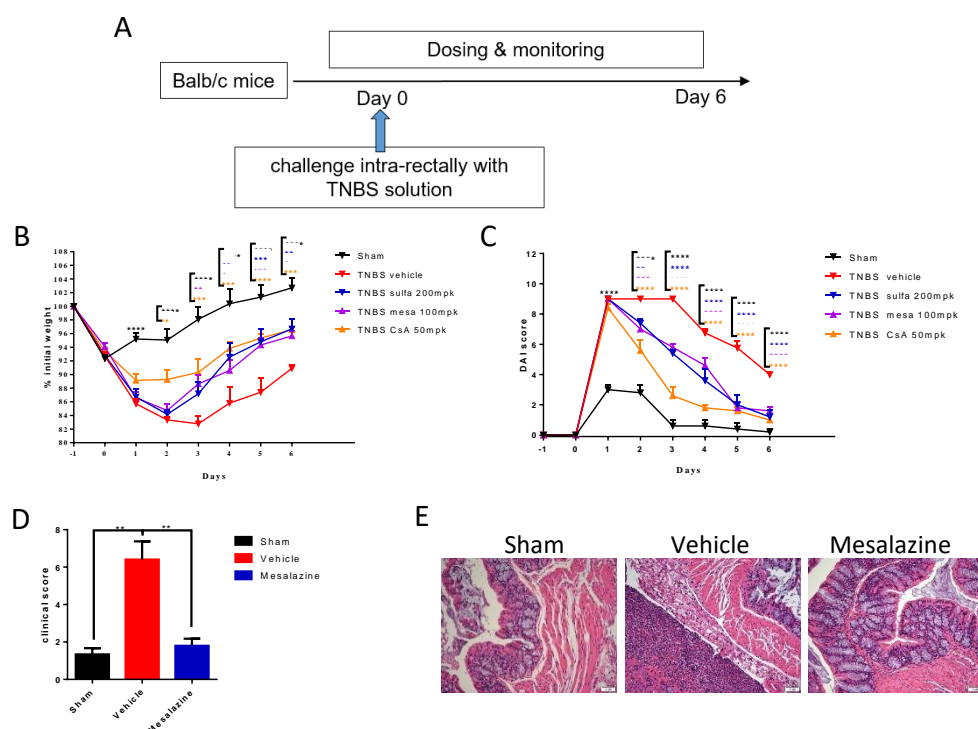
## Oxazolone induced colitis model in SD rats



**Figure. A.** Body weight change of Oxazolone induced colitis model in Balb/c mice **B.** DAI score **C.** Body weight change of Oxazolone induced colitis model in SD rats **D.** DAI score

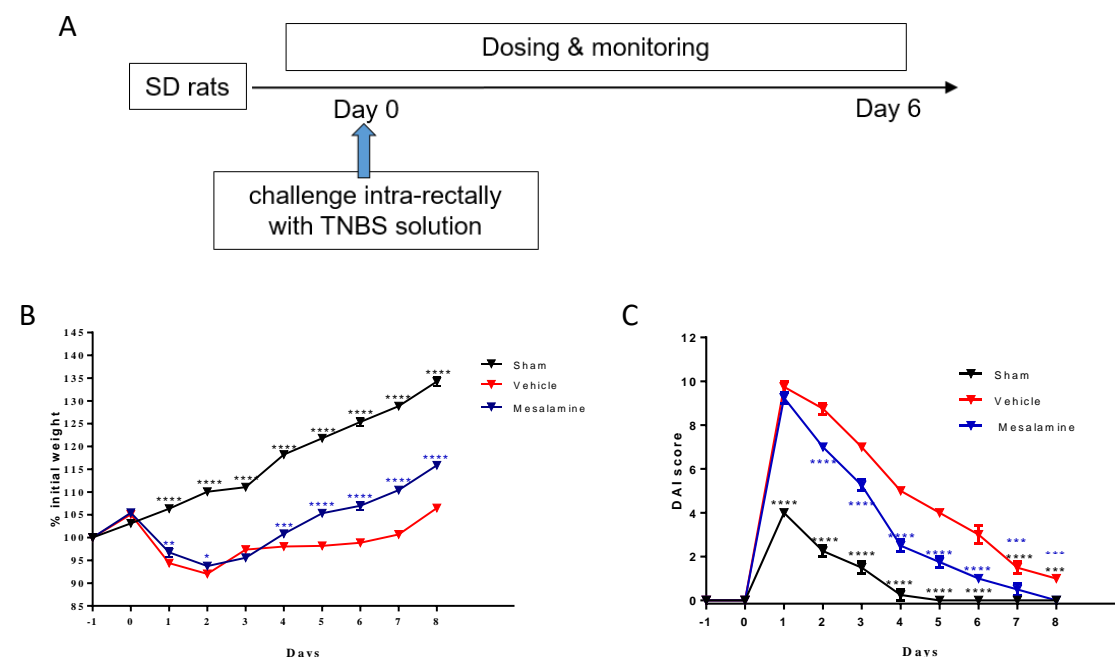
# TNBS-induced colitis model in Balb/c mice and SD rats

- Mice are rectally injected with hapten TNBS (2,4,6-trinitrobenzene sulfonic acid) to induce inflammation and gland loss with erosion in the colon, mimicking human Crohn's disease.



**Figure. A.** Flow chart for TNBS induced colitis model in mice **B-C.** In-life assessments including body weight change and DAI score **D.** Histopathological score **E.** Representative image of HE staining for colon tissue

- Rats are rectally injected with hapten TNBS to induce inflammation and gland loss with erosion in the colon, mimicking human Crohn's disease.



**Figure. A.** Flow chart for TNBS induced colitis model in SD rats **B-C.** In-life assessments including body weight change and DAI score

# Anti-CD40 antibody induced colitis model in SCID mice

- Mice are injected peritoneally with anti-CD40 antibodies to induce colitis through activation of CD40-CD40L signaling pathway. More specifically, anti-CD40 antibody injection activates the housing dendritic cells migrating from LP layer to mLN. And the DCs affect the Treg differentiation, leading to the colitis.

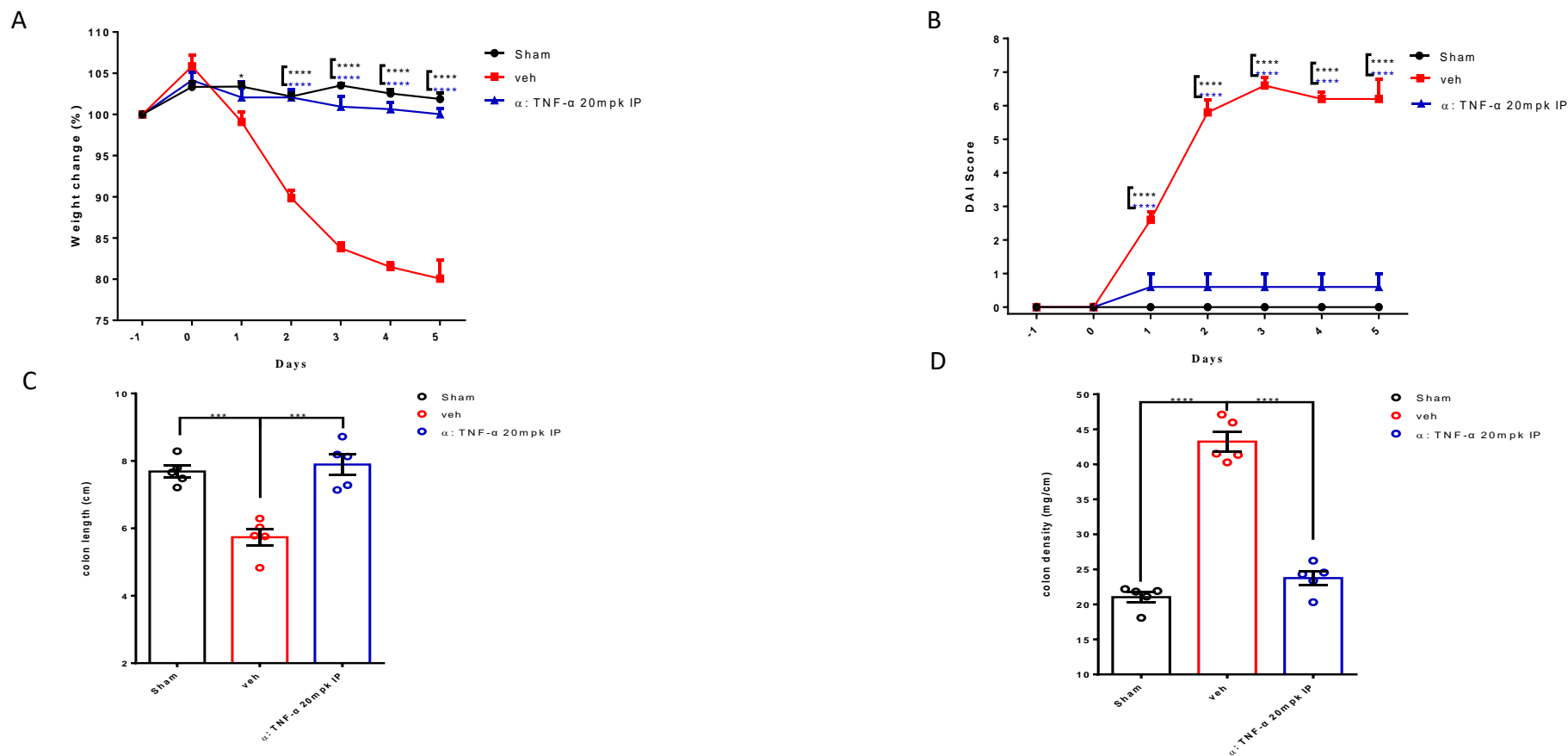
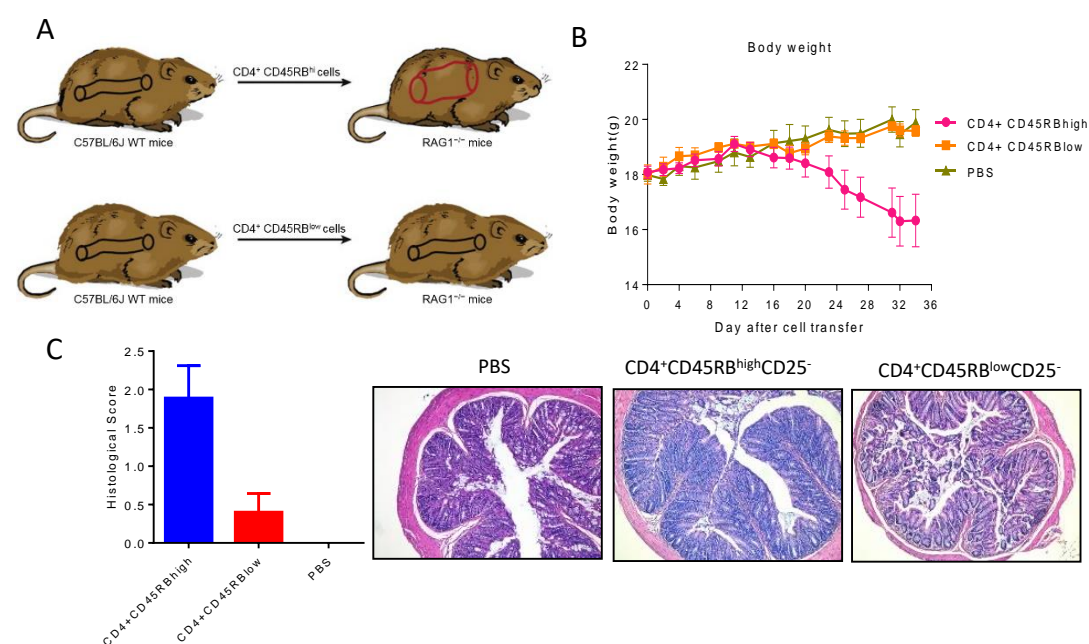


Figure. A. Body weight change B. DAI score C. Colon weight D. Unit of colon weight



1. Enrichment for CD4<sup>+</sup> T cells
2. Cell sorting for purification of CD4<sup>+</sup>CD45RB<sup>high</sup> cells
3. Injection of SCID/RAG1<sup>-/-</sup> mice with purified CD4<sup>+</sup> CD45RB<sup>high</sup> T cells
4. Monitoring disease progression and evaluation of colitis

### T cell transfer induced colitis model in RAG1<sup>-/-</sup> mice



**Figure. A.** Schematic diagram of T cell transfer induced colitis in RAG1<sup>-/-</sup> mice **B.** In-life assessments (Body weight change) in RAG1<sup>-/-</sup> mice **C.** Histology assessments

# How to pick up the right model for IBD?

Multiple models, multiple mechanisms for multiple TAs

Type	Model	Duration	Common positive treatment	Clinically relevant	Mechanism
Genetically-modified	IL-10 <sup>-/-</sup> mice	3-4 Months	Ciprofloxacin, anti-IFN $\gamma$ , anti-IL12p40	Crohn's Disease	IL-10 deficiency loses the suppression on the innate immune response (DCs & Macrophages ) and the adaptive immune response (Th1 & Th17 cells) leading to an excessive secretion of proinflammatory cytokines.
	Foxp3 <sup>-/-</sup> mice		Cyclosporine A, FK506	IPEX	Loss of CD4 <sup>+</sup> CD25 <sup>+</sup> T regulatory cells
Chemically-induced	DSS	7 or 21Days	Cyclosporine A	Ulcerative Colitis	Luminal toxin of DSS leads to loss of epithelial barrier function and entry of luminal organisms or their products into the lamina propria.
	TNBS	7 Days	Cyclosporine A	Crohn's Disease	Hapten TNBS binding to self proteins are captured by APC, and then presented to T cells. Colitis develop when sensitized T cells produce Th1 cytokines such as IL-2, IFN- $\gamma$ and TNF- $\alpha$ .
	OXZ	7 Days	Cyclosporine A	Ulcerative Colitis	Hapten OXZ activates NKT cells which are cytotoxic to epithelial cells.
Adoptive transfer	CD4 <sup>+</sup> CD45RB <sup>high</sup> T cell transfer	5-8 Weeks	anti-TNF $\alpha$ , anti-IL12p40	Ulcerative Colitis & Crohn's Disease	Naïve T cells react in a severe fashion to the gut antigens, become activated forming colitogenic T cells (Th1 & Th17 cells) secreting cytokines that causing severe gut inflammation involving both small and large intestines without suppression from Treg cells. It usually takes around 6–8 weeks, depending on the microbial populations present in the animal facility.

# Inflammatory and auto-immune disease platform

List of available inflammatory and auto-immune disease models

## ☐ Rheumatoid Arthritis

- Collagen induced arthritis (CIA) in DBA/1 mice or Lewis rats
- Collagen induced arthritis (CIA) in rabbits
- Collagen induced arthritis (CIA) in NHP
- Adjuvant induced arthritis (AIA) in Lewis rats
- hTNF $\alpha$  transgenic mice – a spontaneous model
- Anti-collagen antibody induced arthritis in mice

## ☐ Experimental Autoimmune Encephalomyelitis

- MOG-induced EAE in C57BL/6 mice
- MBP68-86-induced EAE model

## ☐ Psoriasis

- Imiquimod-induced psoriasis-like skin inflammation in mice and NHP
- IL-23 induced psoriasis in mice

## ☐ Systemic Lupus Erythematosus(SLE)

- SLE in MRL/MpJ-Fas/J mice

## ☐ Gout

- MSU induced air pouch inflammation in rats

## ☐ GvHD model

- Allogeneic bone marrow transplant induced-GvHD

## ☐ Atopic Dermatitis

- DNCB-induced AD model
- MC903-induced AD model

## ☐ Delayed Type Hypersensitivity (DTH) --Allergy

- mBSA-induced DTH in mice
- DNFB-induced DTH in mice
- Oxazolone-induced DTH in mice

## ☐ Acute Inflammation models

- PMA-induced ear edema model
- LPS - induced cytokine production in mice and rats
- LPS - induced airway inflammation in mice and rats
- Anti-CD3 antibody induced inflammation in mice
- CLP induced sepsis model in mice
- TNF- $\alpha$  shock model
- ConA- induced cytokine production in mice
- KLH-induced T cell dependent antibody response in mice
- Carrageenan-induced paw edema model

# Inflammatory and auto-immune disease platform

List of available inflammatory and auto-immune disease models

## ☐ Inflammatory Bowel diseases model

- DSS induced acute colitis in mice
- DSS induced chronic colitis in mice
- Oxazolone induced colitis in mice
- Oxazolone induced colitis in rats
- TNBS induced colitis in mice
- TNBS induced colitis in rats
- CD40 antibodies induced colitis in mice
- T cell transfer induced chronic colitis in mice
- Spontaneous colitis in IL10<sup>-/-</sup> mice with Balb/c mice

## ☐ Acute pancreatitis model

- Caerulein induced acute pancreatitis in mice
- L-Arg induced acute pancreatitis in mice
- L-Arg induced acute pancreatitis in rats

## ☐ Experimental Sjogren's Syndrome (ESS) model

- Salivary glands protein induced ESS in mice
- Radiation induced ESS in mice

## ☐ Systemic sclerosis model

- Bleomycin induced systemic sclerosis in mice
- HOCL induced systemic sclerosis in mice

## ☐ Asthma model

- OVA induced asthma model in mice
- HDM/ house dust mites induced asthma model in mice

## ☐ Acute Inflammation models

- Zymosan-induced peritonitis model
- Thioglycollate-induced peritonitis model

## ☐ Interstitial cystitis models and bladder pain estimation

- CYP induced acute interstitial cystitis in mice and rats
- CYP induced chronic interstitial cystitis in mice and rats

## ☐ Pulmonary fibrosis model

- Bleomycin induced lung fibrosis in mice

## ☐ Alopecia areata model

- Skin grafted induced AA in mice
- CD8+ T cell transfer induced AA in mice

## ☐ Gastric/ Liver damage model

## ☐ Cancer therapy induced gut syndrome model

- Radiation induced gut syndrome/colitis model in mice
- Chemotherapy induced gut syndrome/colitis model in mice



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