WVU IACUC Model Guidance Sheet: Inflammatory Bowel Disease (IBD)

Purpose

Inflammatory bowel disease (IBD) models are commonly used to study two main diseases - Crohn's disease and ulcerative colitis. There are several IBD models available including chemical induced, adoptive T-cell transfer, genetically modified animals, and spontaneous models. This document is meant to provide an overview and animal welfare considerations when working with models of IBD in rodents.

Definitions

Dextran Sulfate Sodium (DSS) - water-soluble compound which is toxic to the colonic epithelium and induces ulcerative colitis when administered in drinking water to mice and rats. The colonic toxicity of DSS is dependent on its relative molecular weight, with 36-50 kDa recommended for model induction.

2,4,6-trinitrobenzene sulfonic acid (TNBS) - small haptenizing molecule used to study the immunological aspects of colitis which resembles Crohn's disease. **TNBS** induces a Th1 mediated immune response after intracolonic administration.

Polyinosinic:polycytidylic acid (poly I:C) – synthetic analogue of retroviral genomic double-stranded RNA (dsRNA), which is the molecular pattern associated with viral infection that predominantly induces duodenal inflammation (i.e., duodenitis), a Crohn's disease in mice.

Guidance

1. Chemical Induction- Inbred strains are commonly used but can be applied broadly to different strains.
    a. DSS
        i. Administered in drinking water. The colitogenic potential of DSS can vary between vendors and lots. It is recommended to purchase in bulk and determine the needed concentration for that batch with a pilot. The concentration required will vary with strain and model. Recommend DSS molecular weight 36-50 kDa (MP Biomedicals).
        ii. Describe the model used in the animal use protocol, including: strain, length of treatment, number of treatment periods, molecular weight of compound, and concentration in drinking water.
        iii. Water intake should be monitored daily to ensure animals are not drinking too much or too little water.
        iv. DSS is stable at room temperature and water bottles should be changed every 2 days or if turbidity is noted. It is best practice to use autoclaved water for DSS administration.
        v. Monitoring: Animals should be monitored daily for the following parameters. A scoring system is recommended for consistent humane endpoints.
            – Body weight

- Fecal occult blood: Collect feces by placing single mouse in empty cage without bedding. Collect feces with sterile forceps. Use Occult Blood Tests (e.g., Hemoccult II Dispense Pak Plus test) to evaluate feces for occult blood.
- Evaluate Stool: normal consistency > soft stool > very soft stool > watery stool

b. TNBS
   i. Dose administration fluctuates based on animal model, sex, age, body weight and strain. Typical dosage ranges from 0.3-5 mg/mouse depending on model severity. Doses higher than 3.75 mg may lead to severe colitis and mortality.
   ii. Animals should be anesthetized for administration. Compound is administered rectally and not to exceed a volume of 200 ul. Most studies use a volume around 150 ul. Reflux is high with volumes exceeding 100 ul so consider placing the animals into the Trendeleburg position (head tilted down position) for post administration.
   iii. Ethanol (10-80%, 50% typically used) is commonly used as a vehicle for this compound.
   iv. Monitoring: Animals should be evaluated daily for body weight, stool consistency, anus appearance, overall appearance, clinical signs of illness.

c. Poly I:C
   i. Single dose of poly I:C (15 μg/mouse) induces severe mucosal injury in the duodenal villous cells 6-24 h after injection.
   ii. Phosphate-buffered saline (PBS) is used as vehicle for poly I:C.
   iii. Poly I:C administered via intraperitoneal (IP) injection.
   iv. Animals should be monitored daily for weight loss, stool consistency, overall appearance, and clinical signs of illness.

2. Adoptive Transfer
   a. Induces chronic small bowel and colonic inflammation 5-10 weeks after adoptive transfer of CD4+ T-cells from donor mice to syngeneic SCID or RAG1 mice.
   b. Monitoring
      i. Clinical signs may start to develop around week 4-5, monitoring should increase to daily at this time.
      ii. Weigh mice weekly to start and more frequently once disease progression is noted.
      iii. Fecal consistency
      iv. General appearance

3. IL-10 knockout mouse
   a. Spontaneous inflammation of the colon. This model can take an extended period for disease to develop.
   b. Weight loss is not a common feature. Anus appearance and stool blood should be monitored after 4 – 6 weeks.

4. SAMP2/YitFc mouse strain
    a. Mice develop spontaneous acute ileitis in 5 – 6 weeks, while chronic ileitis is developed in 9 – 16 weeks.
    b. Monitoring: After 6th week, animals should be evaluated daily for body weight, bloody stool, stool consistency, anus appearance, overall appearance, clinical signs of illness.

Scoring system:

Parameter and Score	0	1	2	3	4
Weight Loss	<1%	1-5%	5-10%	10-20%	>20%
Stool Consistency	Normal	Soft	Very Soft		Diarrhea
Fecal Occult Blood	No Blood	Hemoccult Positive	Hemoccult positive, dark	Visible blood	Gross Rectal Bleeding

References

https://currentprotocols.onlinelibrary.wiley.com/doi/10.1002/0471142735.im1525s104
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8687830/
https://www.invivocue.com/services/mouse-models/model-of-inflammatory-bowel-disease-ibd/
file:///C:/Users/tmc00012/Downloads/jcm-08-01574-v2.pdf