

Inflammatory Bowel Disease

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting inflammatory condition of the gastrointestinal tract that is usually manifest as 1 of 2 distinct, but sometimes overlapping clinical entities; ulcerative colitis (UC) and Crohn's disease (CD). While CD is a multifocal, transmural inflammatory process that can affect any part of the digestive tract, UC is characterized by a superficial, continuous inflammation, which is limited to the large intestine. IBD is most commonly diagnosed between the third and fourth decade of life, with no difference noted between males and females.



Until recently, the clinical treatments for UC and CD were relatively limited, essentially comprising of 5-aminosalicylic acid (ASA) compounds, steroids and azathioprine/ 6-mercaptopurine. In the 1990s, immunoregulatory agents used in IBD were expanded to include methotrexate and cyclosporine in select patient populations. The approval of infliximab (Remicade; Centocor), a chimeric monoclonal antibody directed against tumor-necrosis factor- α (TNF α), for the treatment of CD in 1998 by the FDA launched the era of biologic therapy for IBD.

PharmaLegacy Models and Research Tools

IBD models can be either induced or spontaneously occurring in animals. Induced models include: (i) Animals treated with agents that promote intestinal inflammation, (ii) Rodents that have been genetically manipulated (iii) Immunodeficient animals. As the onset of inflammation is immediate and the procedure is relatively straightforward, chemically induced models of intestinal inflammation have become the most commonly used IBD animal models. At PharmaLegacy we have validated a complete set of IBD models in rodents.

Model	DNBS induced colitis		Oxazolone induced colitis	DSS induced colitis
Animal	SJL/J mice	Wistar rats	SJL/J mice	C57BL/6 mice
Human disease	CD		UC	UC
Pathogenesis	A Th1-polarized type of T-cell response		A Th2-polarized type of response	Th1 and Th2 cells play a pathogenic role in the chronic phase
Clinical symptoms	Weight loss, loose stool/diarrhea, hematochezia (mice), colon shortening			
Pathology change	Leukocyte infiltration associated with deep chronic ulceration; Submucosal edema; Inflammation involving the entire length of the bowel		Prominent mucosal and submucosal leukocyte infiltration associated with ulceration; Severe damage of the epithelial cell layer and crypts; Submucosal edema; Inflammation confined to the distal segment of the colon	
1° Endpoints	Colonic weight, colonic length, colonic damage score, body weight change.			
2° Endpoints	Histopathology; Immunohistochemistry; Cytokines/Chemokine Analysis; T cell proliferation; Infiltration cell types			

DNBS - dinitrobenzene sulfonic acid DSS - dextran-sulfate sodium

Related Capabilities

- * Antigen-specific T-cell responses
- * Detection of tissue cytokine levels (protein, mRNA) by ELISA or real time RT-PCR
- * Histopathology and immunohistochemistry changes in colonic tissues
- * Flow cytometry analysis of cell functions including intracellular staining of cytokines
- * Detection of signal transduction by western blot

Case Study - DNBS Induced IBD in Wistar Rats

Inhibitory effect of sulfasalazine on DNBS induced IBD in Wistar rats

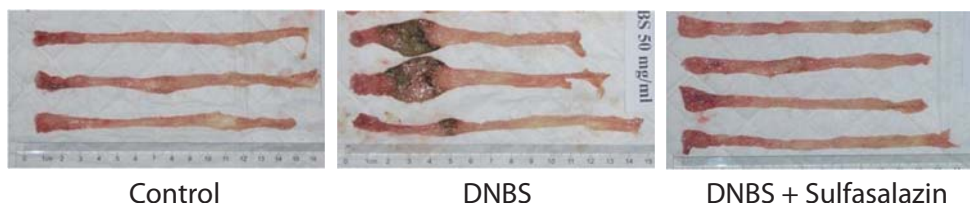
Male Wistar rats (150–160 g) were used in the study. Colitis was induced by intracolonic administration of 0.5 mL DNBS in 30% ethanol. Animals were then treated orally with 300 mg/kg sulfasalazine-1 once daily for 7 days. An equal volume of 30% ethanol was administered as the control. Animals were sacrificed 2 hrs after the last dose.

Group	Ulcer area (cm ²)	Colon weight (g)	Body weight (g)	Colon length (cm)	Ratio		IR (%)	Ration	
					CW/CL/BW x1000			CW/CL/BW x100	IR (%)
Control	0.13±0.13	1.31±0.05	196.02±2.78	16.19±0.44	0.423±0.03		0.67±0.03		
DNBS 50mg/ml	2.36±0.79	0.71±0.13*	182.43±4.30	13.09±0.35	0.73±0.07**		0.95±0.09		
Sulfasalazine -1	0.77±0.48	1.39±0.08	183.05±4.96	13.63±0.69	0.59±0.07	46%	0.77±0.07	65%	

(*p<0.05, **p<0.01 vs Control group by Student's t-test)

DNBS induction resulted in ulcer, length shortening and weight increase of the colon. The Sulfasalazin daily treatment significantly improved these syndromes.

Representative view of the colons on Day 7 after DNBS:



Control

DNBS

DNBS + Sulfasalazin

Exceptional Preclinical Pharmacology Studies -

With a complete set of IBD models, our scientists specialized both in immunology and pharmacology have been helping our clients with exceptional services in various IBD studies:

1. Efficacy studies of drug compounds (clinical symptoms and disease score)

2. Proof of concept studies for early drug development:

- effects of anti-inflammation: T cell and macrophage migration
- effects of anti-autoimmune disorder
- effects of cytokine/chemokine response
- evaluation of therapeutic profile and potentials

3. Demonstration of differential regulation of disease progression

4. Investigation of the mechanisms of immune tolerance induction

About PharmaLegacy Services

- World-class quality with increased speed and output at competitive cost.
- International GLP and QA-based operation.
- Electronic data management system (BioBook) for quality execution and maximum IP protection.
- AAALAC accredited large capacity to house over 10,000 animals under SPF and conventional conditions.
- Availability of 4,000 non-human primates for research use.