NOBLE
LIFE SCIENCES

PRECLINICAL DEVELOPMENT

DSS-Induced Colitis Mouse Models

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Inflammatory bowel disease (IBD) is a chronic, remitting, and relapsing inflammatory disorder encompassing Crohn's disease (CD) and ulcerative colitis (UC). CD is predominantly driven by innate cells with a (Th) 2-mediated immune response. Experimental models of IBD can provide valuable insights into disease pathogenesis, and critically the development of new drugs to treat these debilitating diseases. While a variety of animal models exist that mimic these diseases there are two widely accepted models, trinitrobenzene sulfuric acid (TNBS)-induced colitis, and dextran sulfate sodium (DSS)-induced colitis, that have been very well studied and provide valuable systems for new drug development.

The DSS colitis model is frequently used in IBD research due to its rapidity, simplicity, and reproducibility. This disease model also has many similarities to human UC in anatomical location and clinical and histological features. Administration of DSS in mice causes injury to the colonic epithelium allowing the dissemination of proinflammatory intestinal contents (e.g. bacteria and their products) into the underlying tissue, which results in acute inflammation characterized by ulcers, loss of crypts, infiltration of granulocytes, and macrophages, and activation of lymphocytes.

Induction of either acute or chronic colitis can be achieved by modifying the concentration of DSS and the frequency of administration. Mice exposed to 2.5% DSS in the drinking water for seven days induce the acute DSS model. For the chronic model, mice are exposed to 2.5% DSS in drinking water for seven days, followed by seven days of normal tap water. This process is repeated for 5 weeks.

DSS Colitis Model

A total of fifteen (15) female C57Bl/6 mice were assigned to three (3) groups with six (6) mice in Group 1; 4 (four) mice in Group 2 and 5 (five) mice in Group 3. for the study (Table 1).

Group (n)	Designation	Material	Dosing	Frequency
1 (6)	Control	Naïve mice	Normal water	NA
2 (4)	Acute	2.5% DSS	**In drinking water**	weekly
3 (5)	Chronic	2.5% DSS	**In drinking water**	*bi-weekly
* 2.5% DSS water alternated with normal drinking water bi-weekly for 5 weeks				

On days 1-7, mice in Group 2 (Acute) and Group 3 (Chronic) were provided access to drinking water containing 2.5 % DSS *ad libitum*, while mice in Group 1 received drinking water without DSS. Mice in all groups were weighed and assessed daily for clinical markers of disease to obtain a Disease Activity Index (DAI) score, according to the scoring criteria in Table 2. Three mice in Group 1 and all 4 mice in Group 2 were humanely euthanized on Study Day 8 for analysis of disease biomarkers in an acute colitis model. The remaining three (3) mice in Group 1 and five (5) mice in Group 5 were survived an additional 4 weeks to establish the chronic model of DSS-induced colitis with bi-weekly alternating treatment with 2.5% DSS-drinking water and normal drinking water for the Group 3 mice.

Stool consistency:	
Score	**Description**
0	Separate hard lumps
1	Sausage like with cracks
2	soft blobs
3	watery, no solid pieces
Anal Prolapse:	
Score	**Description**
0	Not visible outside the body
1	Visible outside the body

Fecal blood	
Score	**Description**
0	No Blood in Stool
1	Blood in Stool
Weight loss	
Score	**Description**
0	< 1% body weight loss
1	1 to <5% body weight loss
2	5 to <10% body weight loss
3	10 to <15% body weight loss
4	> 15% body weight loss

Table 2 . Standardized Disease Activity Index Scoring Criteria. Disease Activity Index (DAI) is calculated as the sum of all scores and can be effectively used to standardize disease severity scoring.

Acute DSS-induced colitis model:

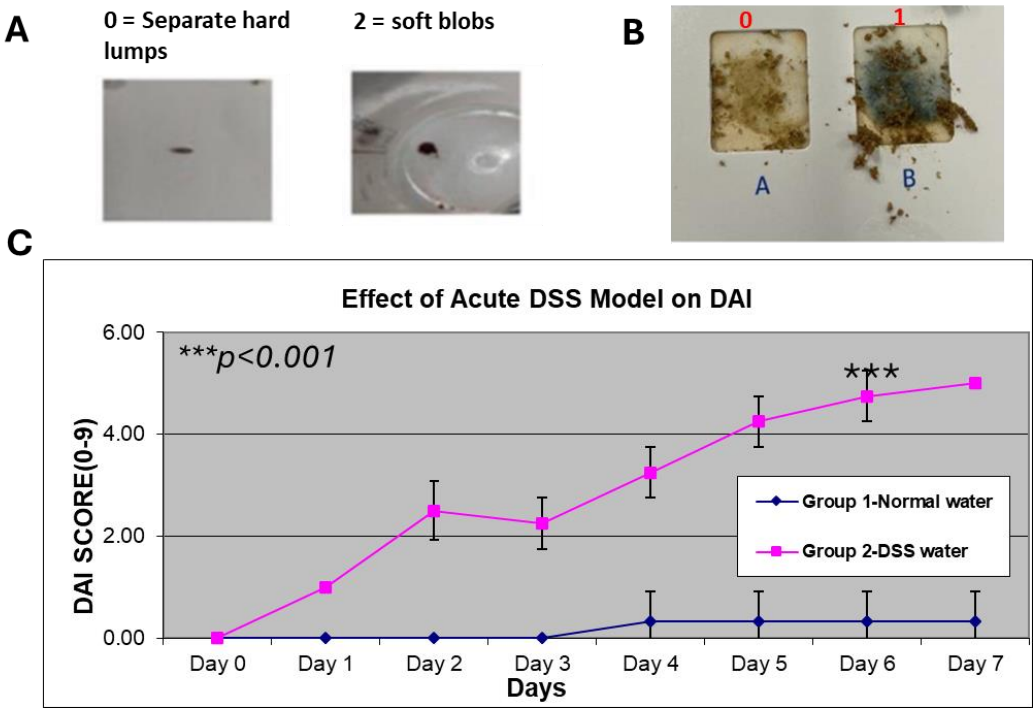


Fig. 1. Clinical symptoms of acute DSS colitis. Experimental colitis was induced by inclusion of 2.5% DSS for 7 days in drinking water. A) typical stool consistency score, B) occult blood in stool score (0 or 1), and C) disease activity index (DAI). ****P<0.001*

2) Colonic Parameters of acute DSS colitis in mice.

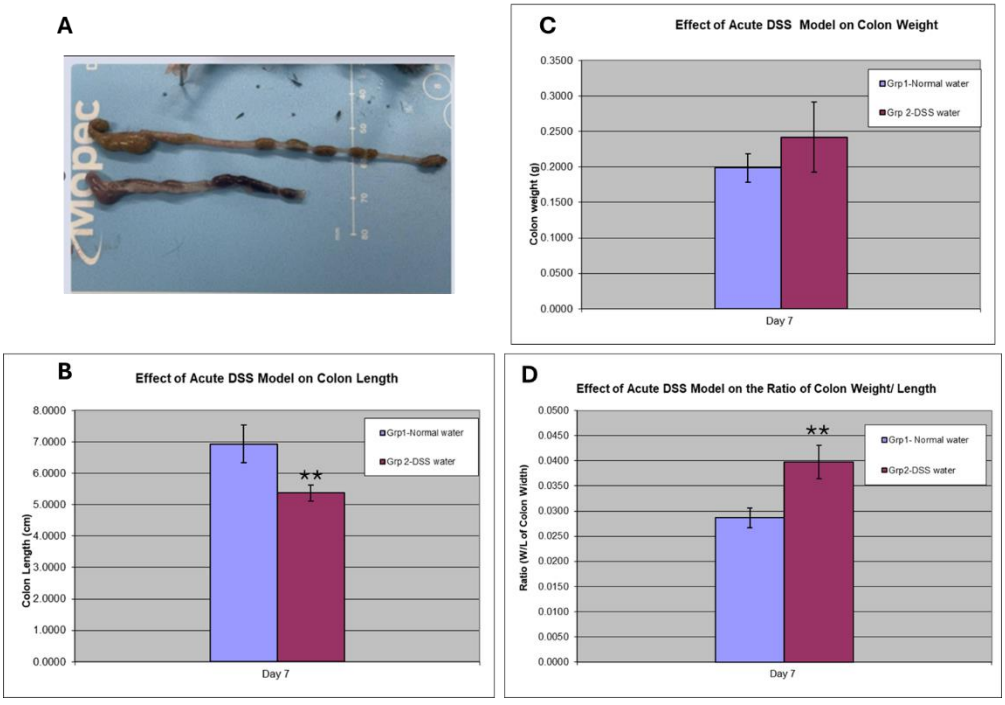


Fig. 2. Colonic Parameters of acute DSS colitis. Experimental colitis was induced by DSS for 7 days in drinking water. A) Representative colon images in DSS mice and normal mice, B) colonic length, C) colonic weight, and D) Ratio of colonic weight to length. **p <0.01*

3) Ratio of Spleen weight to Body weight of DSS mice (acute)

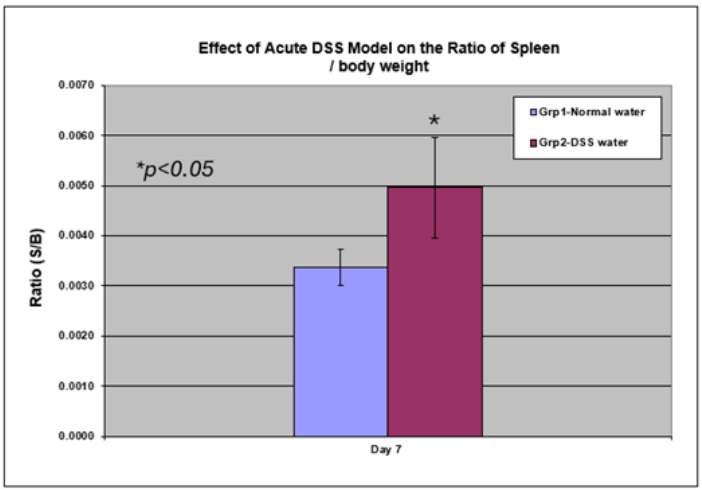
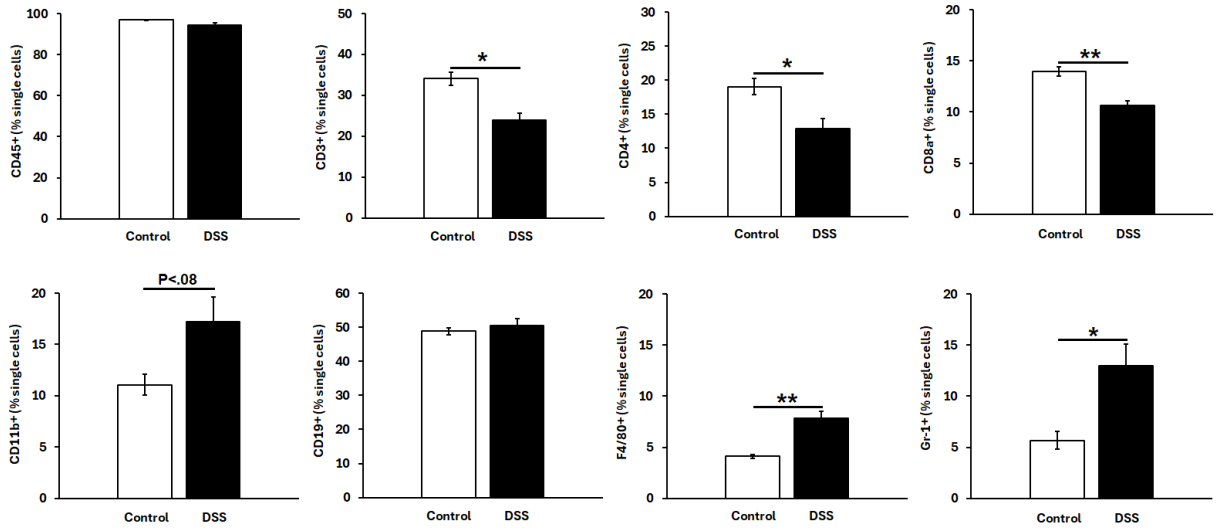


Fig. 3. Ratio of spleen weight of acute DSS colitis. **p <0.05*

4) Flow cytometry of splenic immune cell populations in the acute model identifies specific immune cell populations in disease tissue and quantitative response to treatment.

A) the composition of immune cell populations in the spleen.



B) Representative scatter plots of CD11 b+F4/80+cells and CD11b+Gr-1+cells in the spleen.

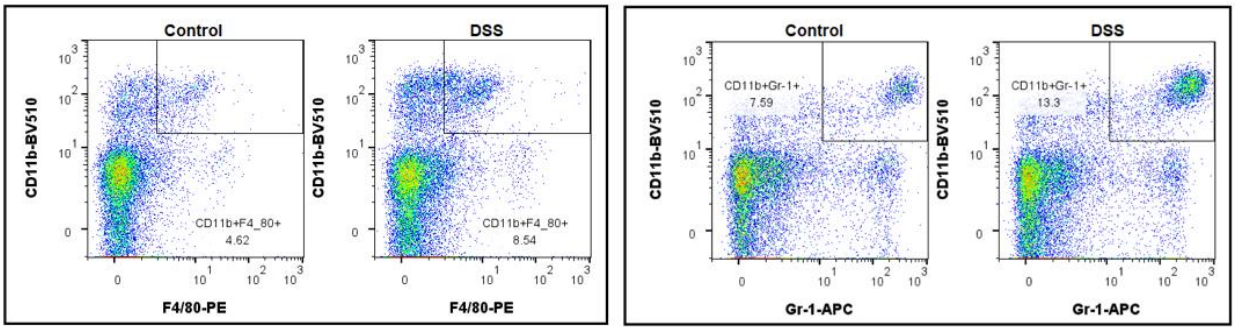


Fig. 4. DSS administration alters A) the composition of immune cell populations of the spleen (Granulocytes, neutrophils, and macrophages increased significantly in DSS mice), and B) the presentative scatter plots of CD11 b+F4/80+cells and CD11b+Gr-1+cells.
Granulocytes are expressed as a percentage of CD45+CD11b+cells, neutrophils are expressed as a percentage of CD11b+Gr-1+cells, and macrophages are expressed as a percentage of CD11 b+F4/80+cells. There is a significant increase in CD11 b+F4/80+cells (*p*<0.01*), CD11b+Gr-1+cells (*P*<0.05*), and a decrease in T cell lineages (CD3+CD4+ cells, *p*<0.05*; CD3+CD8+, *p**<0.01*) in the spleens from DSS treated-mice, *n*=3.

Chronic DSS-induced colitis model:

1) Disease Activity Index in Chronic Model of DSS-induced colitis in mice.

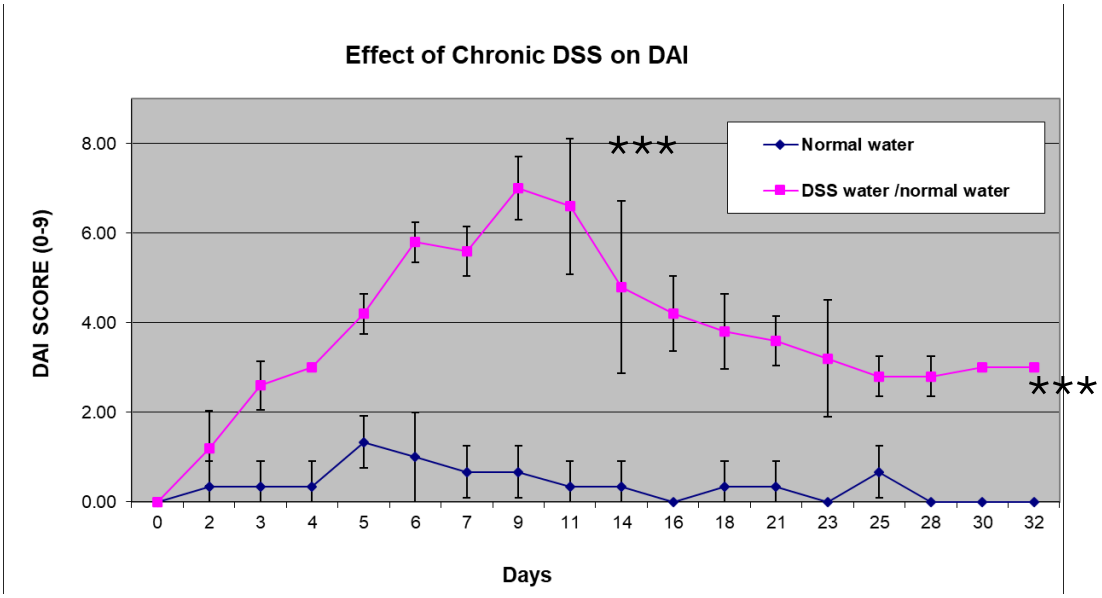


Fig. 1. Disease Activity Index (DAI) of Chronic DSS colitis. Experimental colitis was induced by DSS for 7 days in drinking water, followed by seven days of normal tap water. This process was repeated for 5 weeks. ****P<0.001*

2) Colonic Parameters of Chronic DSS Colitis in Mice.

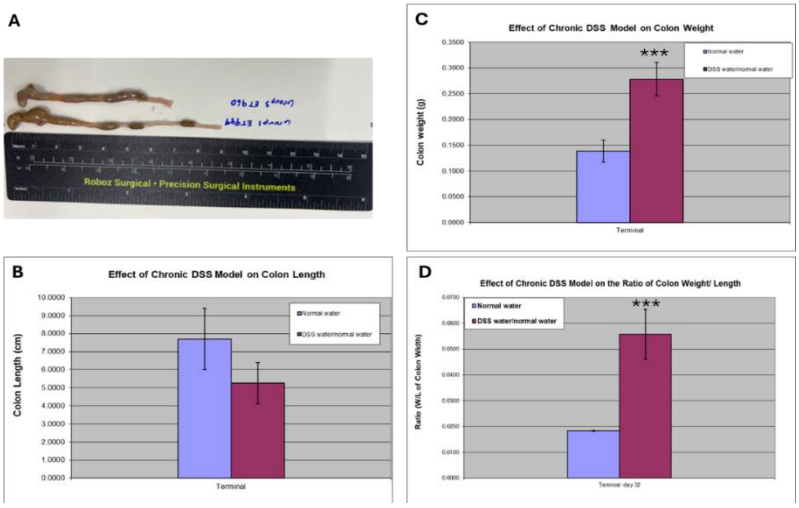


Fig. 2. Colonic Parameters of chronic DSS colitis. A) Representative colon images in DSS mice and normal mice, B) colonic length, C) colonic weight, and D) Ratio of colonic weight to length. ****p <0.001*

3) Ratio of Spleen weight to Body weight of DSS mice (Chronic)

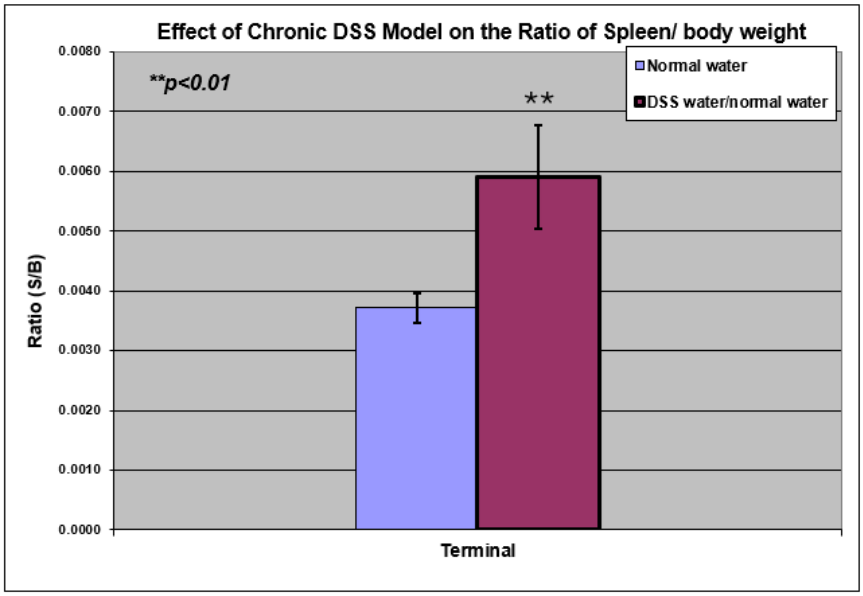
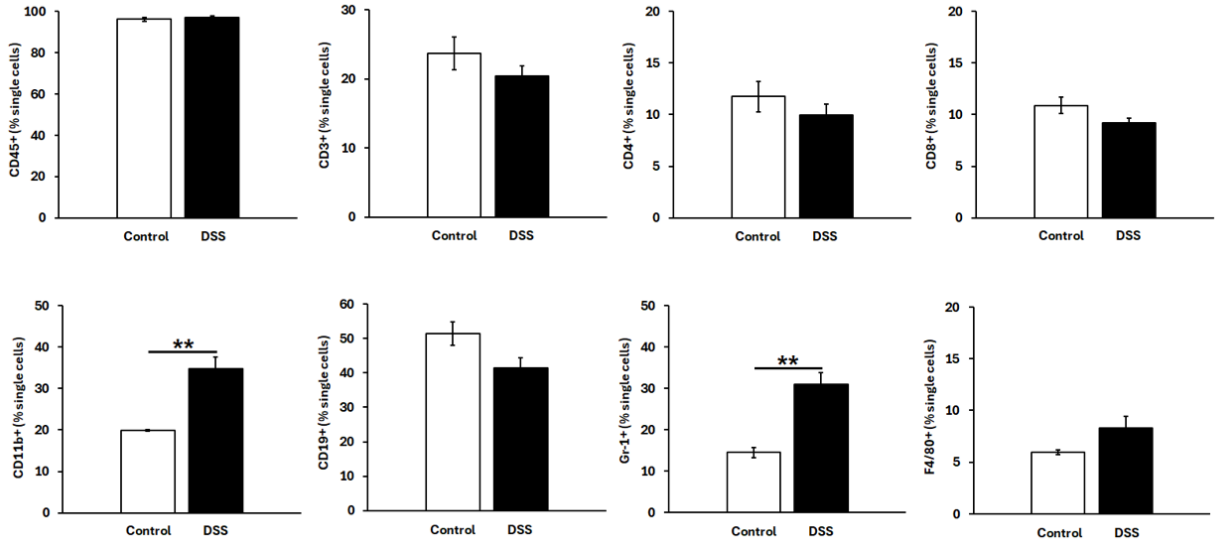


Fig. 3. Ratio of spleen weight of chronic DSS colitis. ***p <0.01*

4) Flow cytometry of immune cell populations of whole blood (Chronic model)

A) the composition of immune cell populations in the blood.



B) Representative scatter plots of CD45+ CD11b+cells and CD11b+Gr-1+cells in the blood.

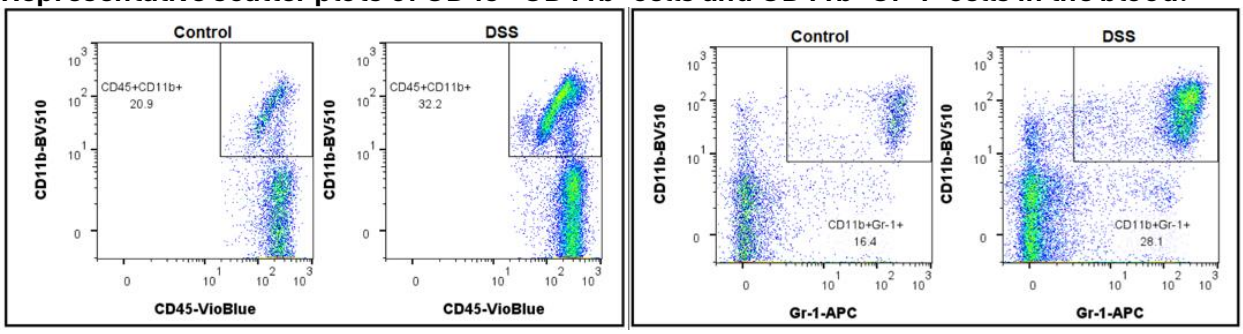
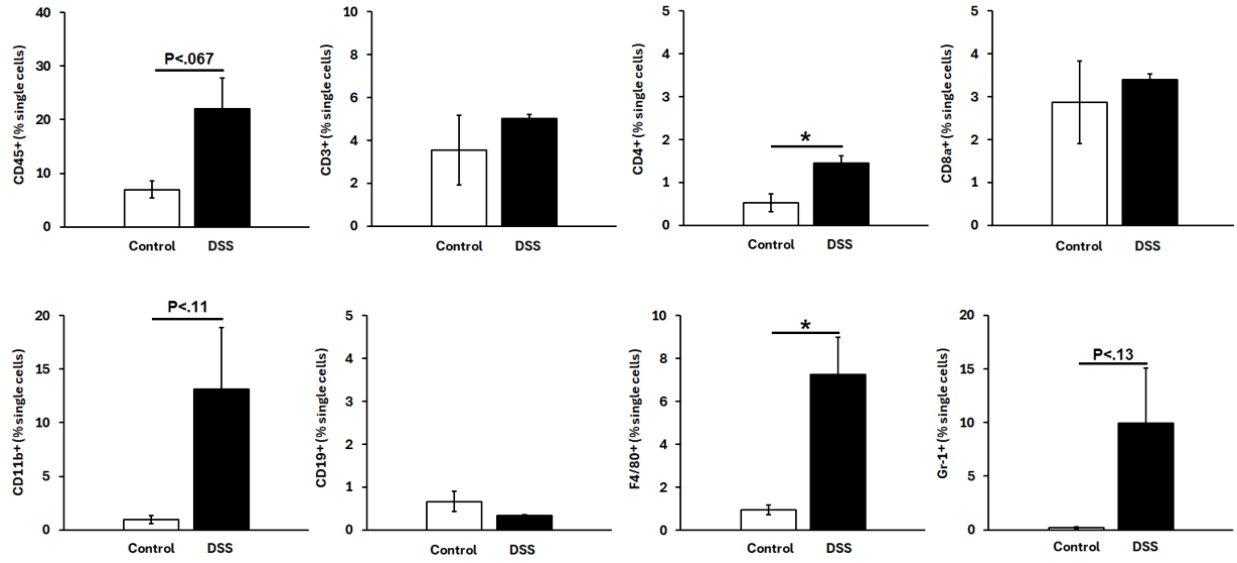


Fig. 4. DSS administration alters A) the composition of immune cell populations in the whole blood, and B) the representative scatter plots of CD45+ CD11b+cells (p*<0.01), and CD11b+Gr-1+cells. There is a significant increase in CD45+ CD11b+cells (p*<0.01), and CD11b+Gr-1+cells (P*<0.05), in the blood from the DSS-treated mice, n=3.

5) Flow cytometry of immune cell populations of single cells isolated from the colon (Chronic model)

A) the composition of immune cell populations in the colon.



B) Representative scatter plots of CD45+ CD11b+cells and CD11b+Gr-1+cells in the colon.

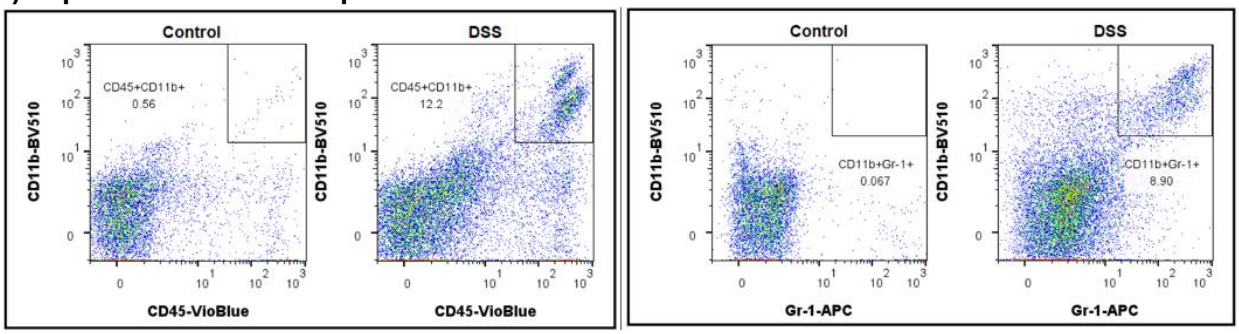


Fig. 5. Leukocytes, Macrophage, neutrophil, and CD4 T helper infiltration in the colon from DSS-induced colitis mice. Leukocytes are expressed as a percentage of CD45 +cells (*p<0.067*); Granulocytes are expressed as a percentage of CD45+CD11b+cells (*p<0.11*), neutrophils are expressed as a percentage of CD11b+Gr-1+cells (*p<0.13*), and macrophages are expressed as a percentage of CD11 b+F4/80+cells (*P*<0.05*) and CD4 helper are expressed as a percentage of CD3+CD4+cells (P*<0.05). *n*=3.

The repose in animals has a high degree of variation and we work with clients to design experiments to correctly power every study appropriately.

In summary, Noble Life Sciences has established models of inflammatory bowel disease including the DSS-induced acute and chronic colitis models in mice for use in preclinical studies. The severity of the disease and activity of new treatments can be characterized and quantified by: Disease activity index (DAI)-total score (stool consistency, fecal blood, anal prolapse, and body weight loss), terminal colon length, weight or ratio of weight/length, cytokines in sera or homogenized tissues, histopathology of colon sections, and flow cytometry analysis (whole blood, LNs, Spleens, and diseased tissues).

About us

Noble Life Sciences has established experience in preclinical testing for multiple therapeutic and prophylactic treatments. We offer a broad spectrum of *in vitro* and *in vivo* services, including cell-based and animal disease model development and experiment design, efficacy, toxicity, PK/PD, and product release studies in both small and large animals.

We are a full-service preclinical contract research organization offering standard GLP study and non-GLP study services. From proof-of-concept studies to preclinical safety and efficacy studies, Noble Life Sciences has a wide range of services to meet your pre-clinical development needs, for more information about Noble Life Sciences, please visit, www.noblelifesci.com