Immune Checkpoint Blockade and Autoimmune Diseases
Development of a mouse model of colitis induced by anti-CTLA4

#3228

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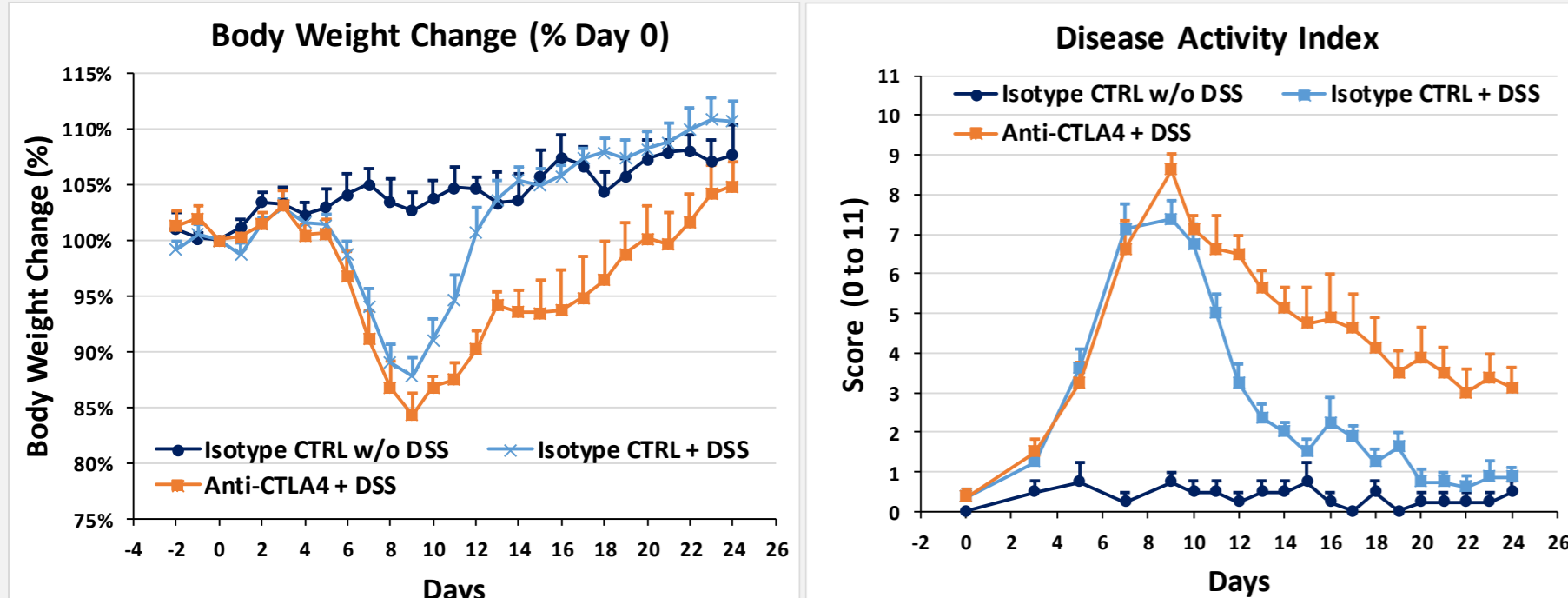
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1 CONTEXT & OBJECTIVES

✓ Immunotherapies, by priming or activating patient's immune system, are promising new cancer treatments with major beneficial clinical outcomes

✓ However, by increasing the activity of the immune system, therapies targeting the immune checkpoint blockade such as anti-CTLA4 can induce profound inflammatory side effects, termed immune-related adverse events, with particular organs affected such as gastrointestinal tract, endocrine glands, skin and liver

✓ In patients treated with the anti-CTLA4 antibody Ipilimumab, the overall incidence of diarrhea and colitis has been reported as 37% *(Bertrand et al. BMC Medicine (2015) 13:211)*

OBJECTIVE

✓ Set up a chronic mouse model of colitis induced by anti-CTLA4 treatment together with dextran sulfate sodium (DSS), a well-known chemical with toxic effects on colonic epithelial cells
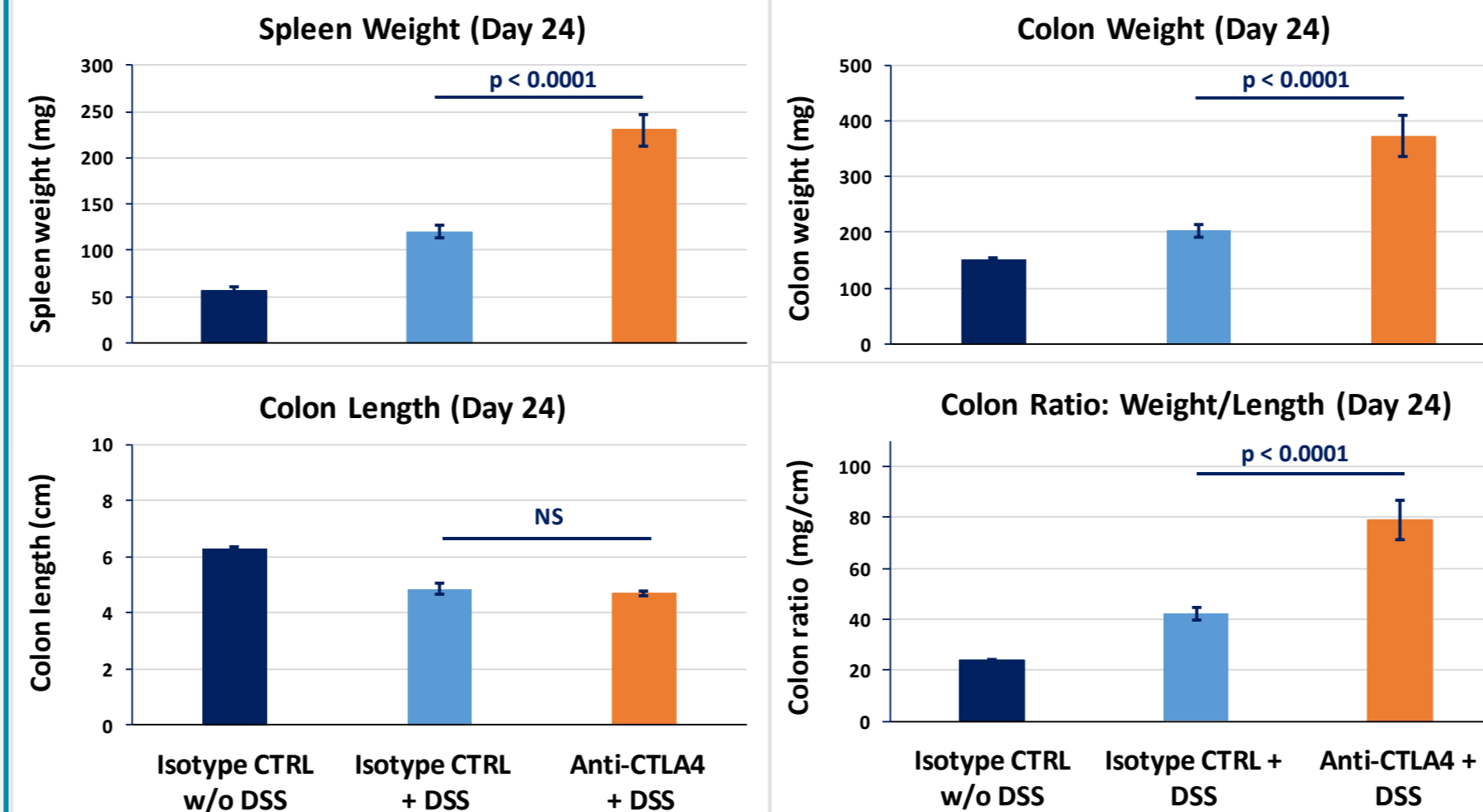
2 RESULTS
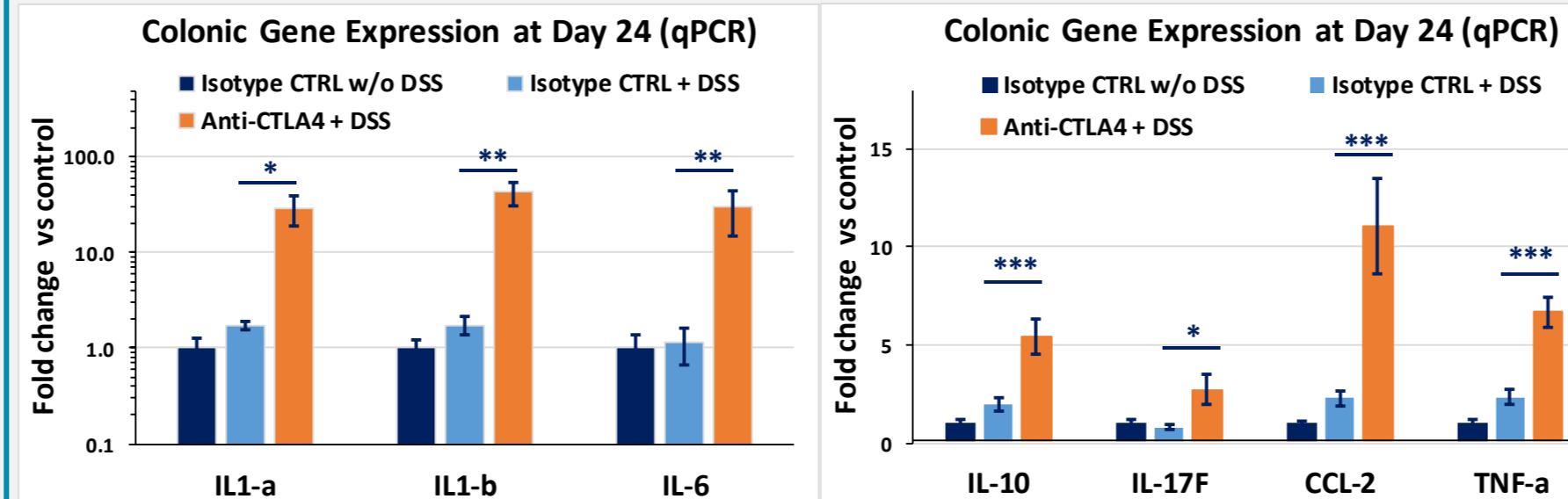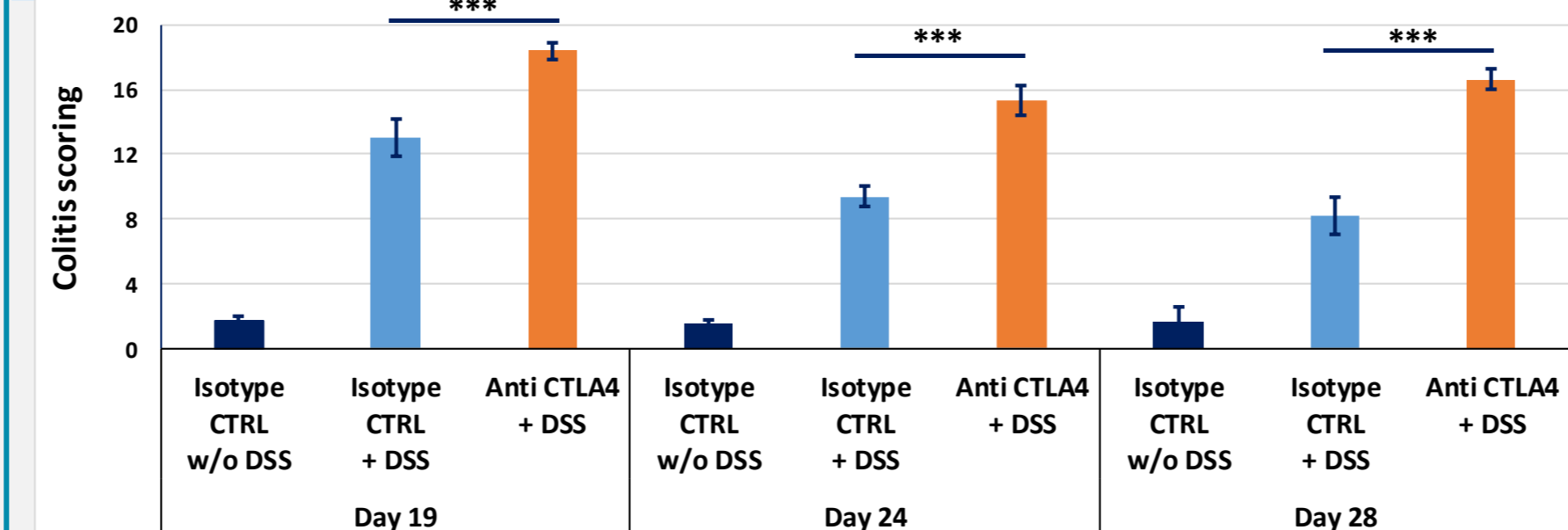
Delayed recovery upon anti-CTLA4 treatment

Body Weight Change (% Day 0)

Disease Activity Index

RESULTS

Increased spleen & colon weight with anti-CTLA4 treatment

Spleen Weight (Day 24) — p < 0.0001
Colon Weight (Day 24) — p < 0.0001
Colon Length (Day 24) — NS
Colon Ratio: Weight/Length (Day 24) — p < 0.0001

Sustained colon inflammation after anti-CTLA4 treatment

Colonic Gene Expression at Day 24 (qPCR)
Colonic Gene Expression at Day 24 (qPCR)

Histomorphometric analysis of colon - Colitis scoring

Exacerbated colitis after anti-CTLA4 treatment

AB-PAS staining - Day 24

Isotype CTRL w/o DSS   Isotype CTRL + DSS   Anti-CTLA4 + DSS

Phospho-STAT3 detection by IHC – Day 24

Edema
Epithelial cell erosion
Depletion of goblet cells
Leukocyte infiltration

Isotype CTRL + DSS   Anti-CTLA4 + DSS

3 CONCLUSION

✓ The combination of DSS and anti-CTLA4 administration induces a chronic immunotherapy-induced colitis in mice, measurable by different parameters during the in vivo phase and at sacrifice

✓ This model is suitable for evaluating novel immuno-modulatory agents alone, or combination therapies with different immune checkpoint inhibition. Novel chemical entities could also be tested in such a model.

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