Introduction
There is an urgent need to achieve higher rates of clinical response, remission, and mucosal healing in inflammatory bowel disease (IBD). The Janus kinase (JAK)/STAT signaling pathways are important in controlling the aberrant immune response of IBD. Tofacitinib is a potent Janus kinase (JAK) inhibitor with selectivity toward homo- and heterodimers of JAK1 and JAK3, and less potent against JAK2 and JAK1 homodimers in vitro. Inhibition of the JAK2 homodimer has been associated with the risk of anemia, neutropenia, thrombocytopenia, infections, lymphomas, and the inhibition of anti-inflammatory responses in the intestine. Tofacitinib was the first oral JAK inhibitor approved to treat moderate to severe ulcerative colitis (UC). During development, a clear dose-response relationship was observed in terms of efficacy, up to 15 mg twice daily (BID), but only the 5-mg and 10-mg BID doses were approved for clinical use in UC due to observed systemic toxicity. Targeted local delivery of drugs to the colon may increase local tissue concentration to improve efficacy and lower systemic absorption. Pharmacokinetics (PK), pharmacodynamics (PD), and biodistribution of tofacitinib liquid formulation through local administration to the colon were assessed in animal models with surgical implantation of a colonic cancer.

Methods
All animals underwent surgical implantation of a colonic cancer 2 weeks prior dosing. Colitis was induced by exposure to 3% dextran sodium sulfate drinking water from Day 0 to Day 5 in male C57BL/6 mice. Dosing was performed at the peak of disease status (Day 10) via intra-cecal catheter (IC) or oral gavage (PO). Animals received a single dose of control vehicle or tofacitinib citrate (Tofa) suspension in carboxyl methyl cellulose (CMC) via PO (5 and 10 mg/kg) or IC delivery (1, 3, and 10 mg/kg). Direct measurement of total and phosphorylated STAT1, 3, and 5 were quantified through immunohistochemistry in colon tissue to compare the PD effects via IC vs. PO. The biodistribution and coverage of soluble tofacitinib formulation was evaluated in Yorkshire-Cross Swine, because their gastrointestinal physiology is more similar to humans. Animals received 4 IC QD doses of Tofa oral suspension (TOS) or Tofa solubilized formulation (TSF) via an implanted intra-cecal catheter at 0.28 mg/kg/dose or 0.46 mg/kg/dose.

Results
Approximately 10- to 15-fold lower doses of Tofa could be used via intra-cecal delivery to achieve equivalent drug concentrations with minimal systemic drug exposure compared to PO. Mean plasma concentrations of Tofa at 10- to 15-fold lower doses showed a similar dose-level dependency. IC Tofa 10 mg/kg resulted in 20-fold higher tissue/plasma exposure ratio than PO 15 mg/kg.

Intra-cecal delivery of Tofa to the inflamed mucosa can potentiate PD effects in tissue at a lower treatment dose. The levels of pSTAT3 were most significantly induced in the control group, suggesting DSS-colitis may be mediated by the pSTAT3/Akt signaling pathway (Figure 3).

IC CD Tofa at 10- to 15-fold lower dose showed greater efficacy at inhibiting pSTAT3 in the colon over time and compared to higher oral doses (Figure 3).

Conclusion
These results indicate that the targeted delivery of solubilized tofacitinib to the site of inflammation could increase tissue absorption and coverage to achieve maximum efficacy with a lower risk of systemic toxicity.

References

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