

Selective SIK2 Inhibition Suppresses Intestinal Inflammation and Promotes Mucosal Healing in Models of Colitis

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THERAPEUTICS



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#P0115

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BACKGROUND

Salt-Inducible Kinase 2 (SIK2) is a Key Signaling Node Relevant to IBD Pathology

- Salt-inducible kinases (SIKs) amplify proinflammatory gene expression in myeloid cells via phosphorylation of transcriptional coregulators.¹
- SIK2 shows the highest kinase activity in myeloid cells.²
- Genetic loss-of-function (LOF) of SIK2 in mice or use of pan-SIK inhibitors decreases proinflammatory cytokines (TNF α , IL-12/23, IL-6, and IL-1 β) induced by Toll-like receptor (TLR) or IL-1 receptor (IL-1R) agonists.^{1,2}
- SIK2 LOF also enhances production of the anti-inflammatory cytokine IL-10, an effect not observed with SIK1 or SIK3 LOF.²
- Inhibition of SIK1 has known cardiotoxicity risk,⁵ while SIK3 KO in mice and LOF mutation in human result in bone defects,⁶ underscoring the potential importance of selective SIK2 inhibition as a therapeutic strategy.
- This profile suggests selective SIK2 inhibition may offer therapeutic benefit for inflammatory bowel disease (IBD) and other chronic inflammatory diseases, yet pharmacological SIK2-selective inhibitors have not been previously characterized.^{3,4}

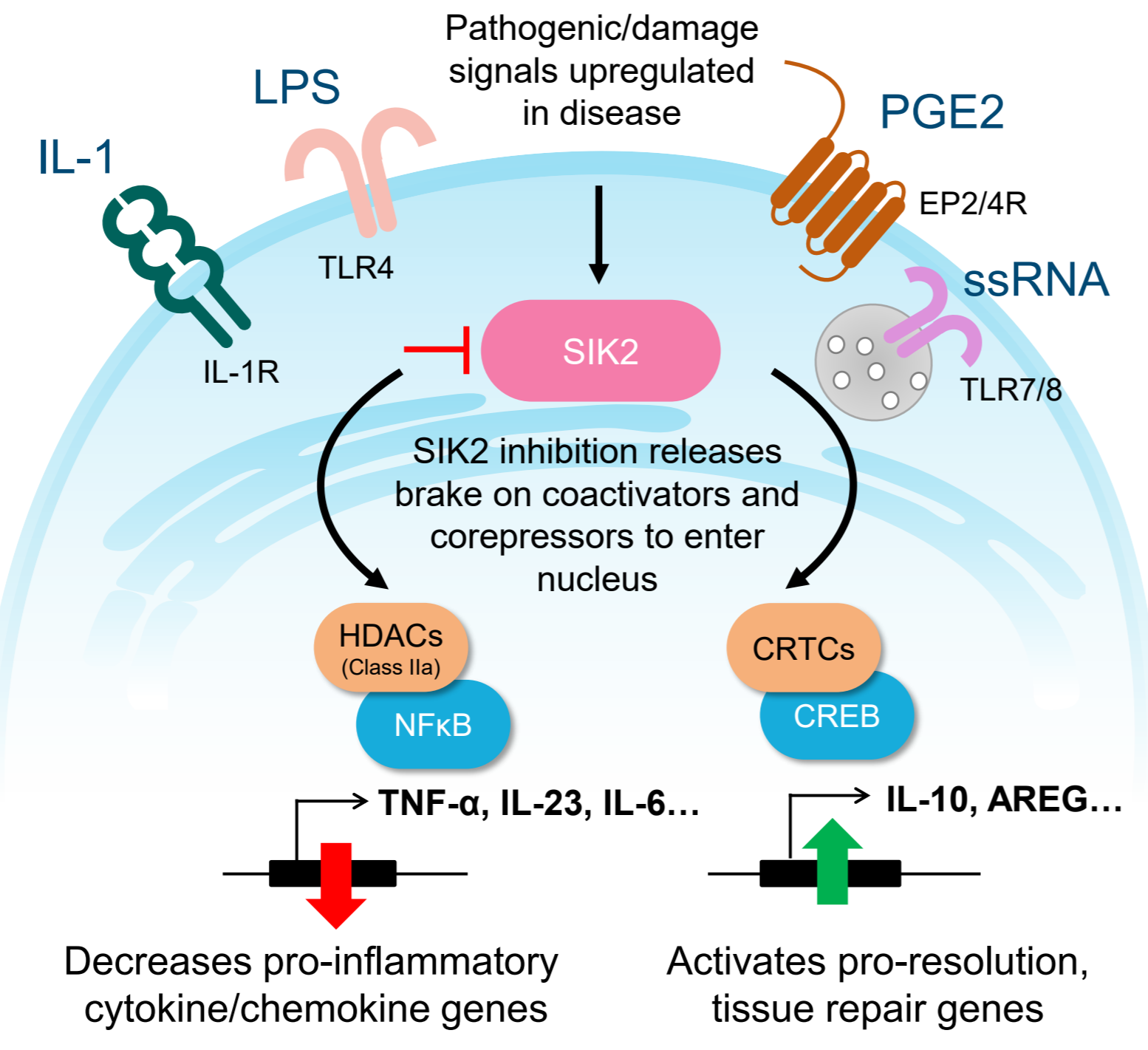
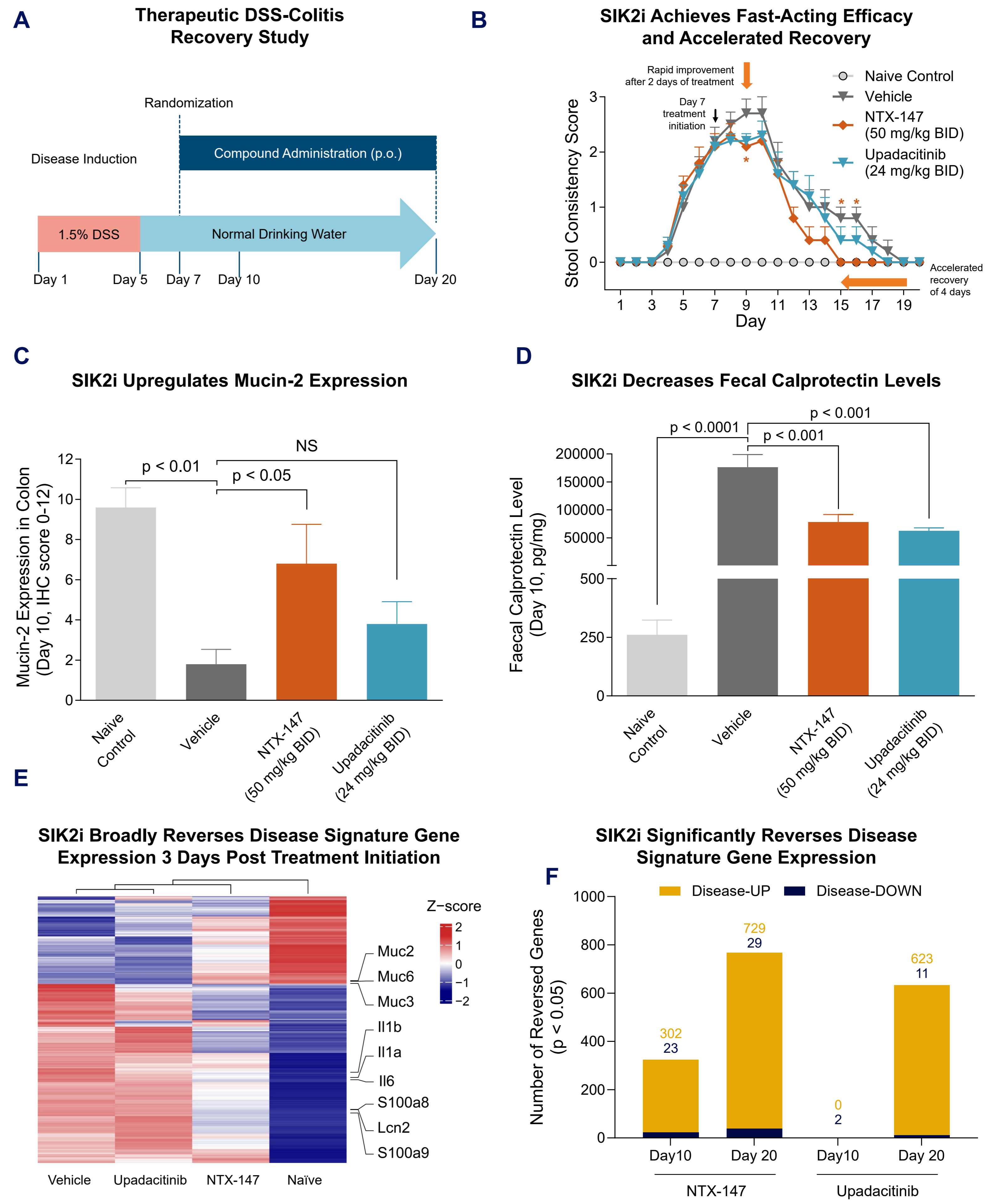


Fig 3: Therapeutic Dosing of SIK2-selective Inhibitor Accelerates Recovery and Mucosal Healing in DSS Injury-induced Colitis



METHODS

- Using structure-based drug design, we developed highly SIK2-selective small-molecule inhibitors with nanomolar cellular potency, high selectivity over SIK1 and SIK3, and suitable pharmacokinetic (PK) properties to support *in vivo* evaluation.
- The *in vitro* potency of SIK2-selective inhibitors was assessed using biochemical and mouse/human cellular assays.
- The *in vivo* activity, efficacy and mechanism-of-action of SIK2-selective inhibitors were studied in the dextran sodium sulfate (DSS)-induced colitis model and the anti-CD40 colitis mouse models dosed both prophylactically and therapeutically.

RESULTS

Table 1: Highly Potent and Selective Lead Series of SIK2 Inhibitors, Exemplified by NTX-147 and NTX-856

Parameter	<i>In vitro</i> Assay	NTX-147	NTX-856
Potency (K _i ADP, μ M)	Human SIK2 ADP-Glo	0.002	0.003
	Human SIK1 ADP-Glo	1.76	0.32
	Human SIK3 ADP-Glo	0.24	1.59
Cellular Potency (μ M)	HEK-293, SIK2-only, CRTC3 nuclear translocation (EC ₅₀) *	0.0003	0.002
	RAW264.7 SIK2-only, CRTC3 nuclear translocation (EC ₅₀) *	0.005	0.006
	RAW264.7 SIK3-only, CRTC3 nuclear translocation (EC ₅₀) *	5.13	5.68
	Human monocyte-derived macrophage, TNF α by LPS (IC ₅₀)	0.018	ND
SIK Selectivity (Fold)	Selectivity over SIK1 (biochem)	733x	95x
	Selectivity over SIK3 (biochem/cell)	100x / 1115x	468x / 947x
Kinase Selectivity	Kinome Panel (hits >70% inhibition at 1 μ M and 1 mM ATP)	8 of 408 kinases (2%)	2 of 402 kinases (0.5%)

*Cell lines engineered to express only SIK2 or SIK3, with SIK1 and/or SIK2/SIK3 knocked out

Fig 1: SIK2-selective Inhibition Reduces Proinflammatory Cytokine Production and Upregulates Pro-resolution Factors in Macrophages

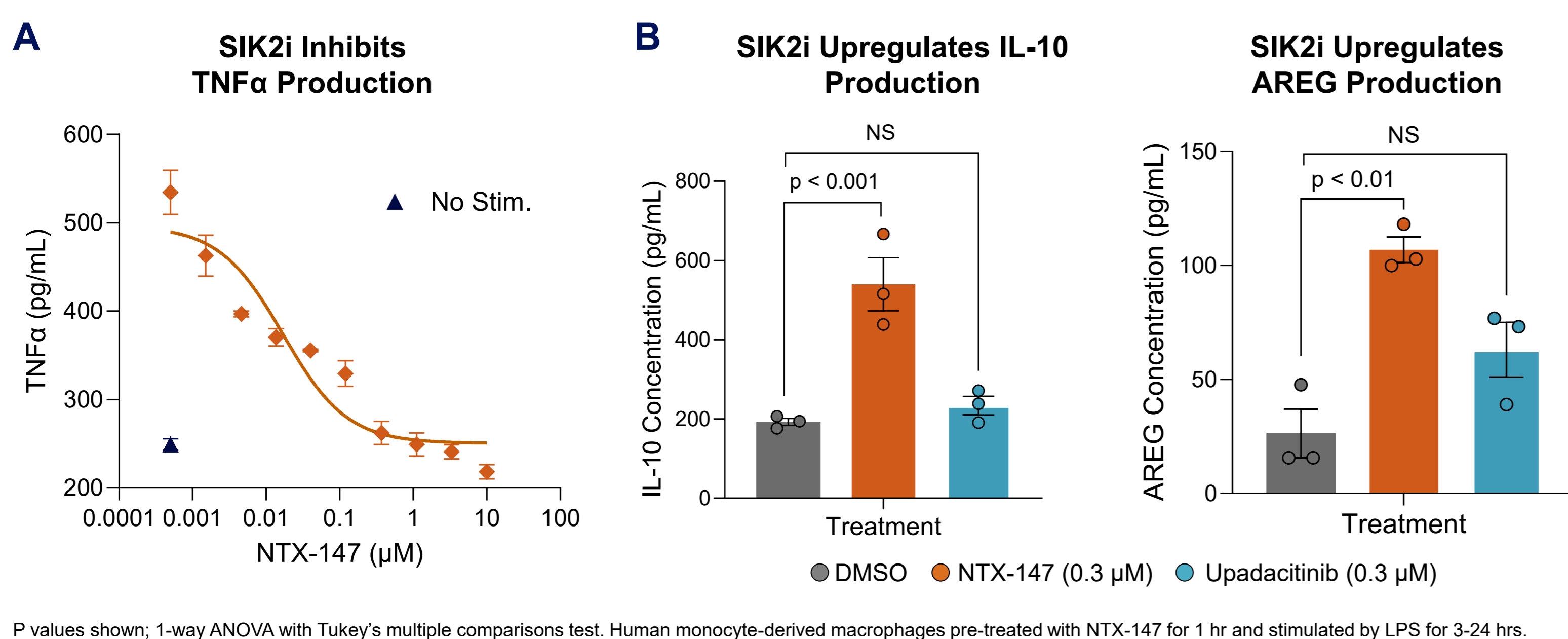
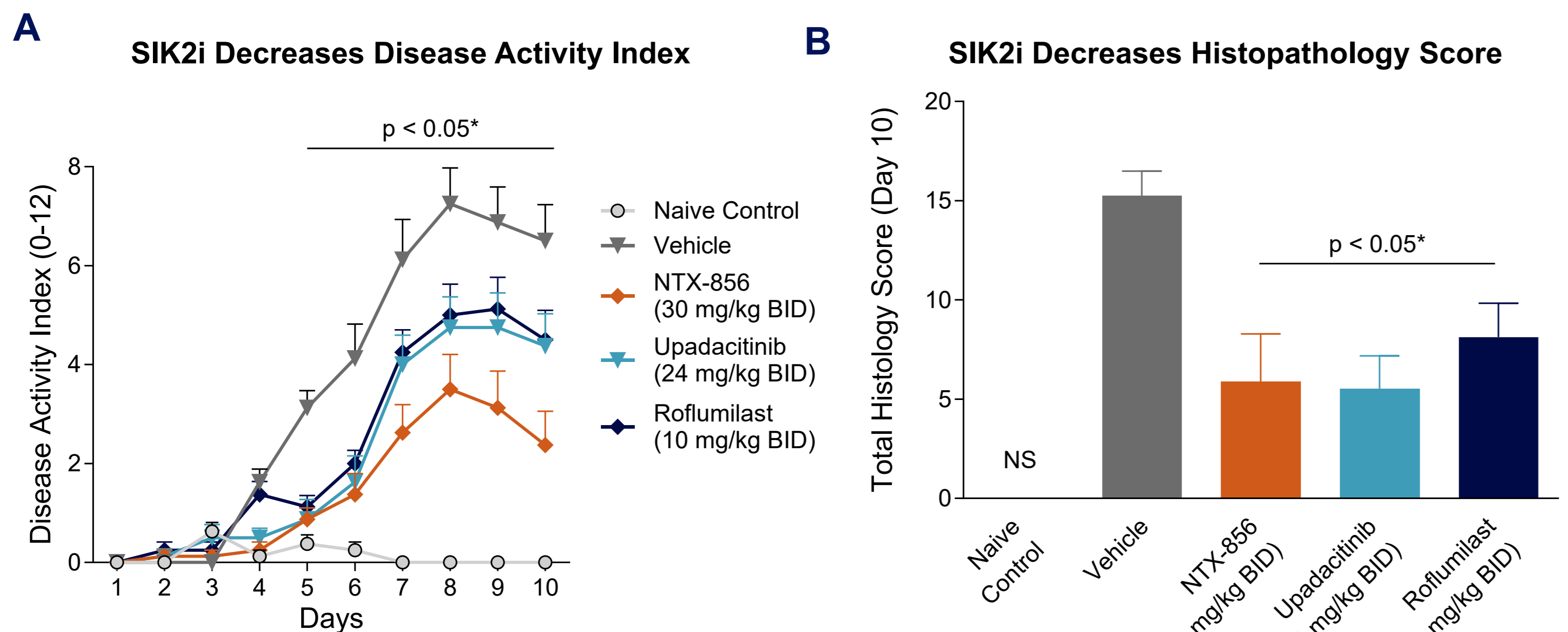
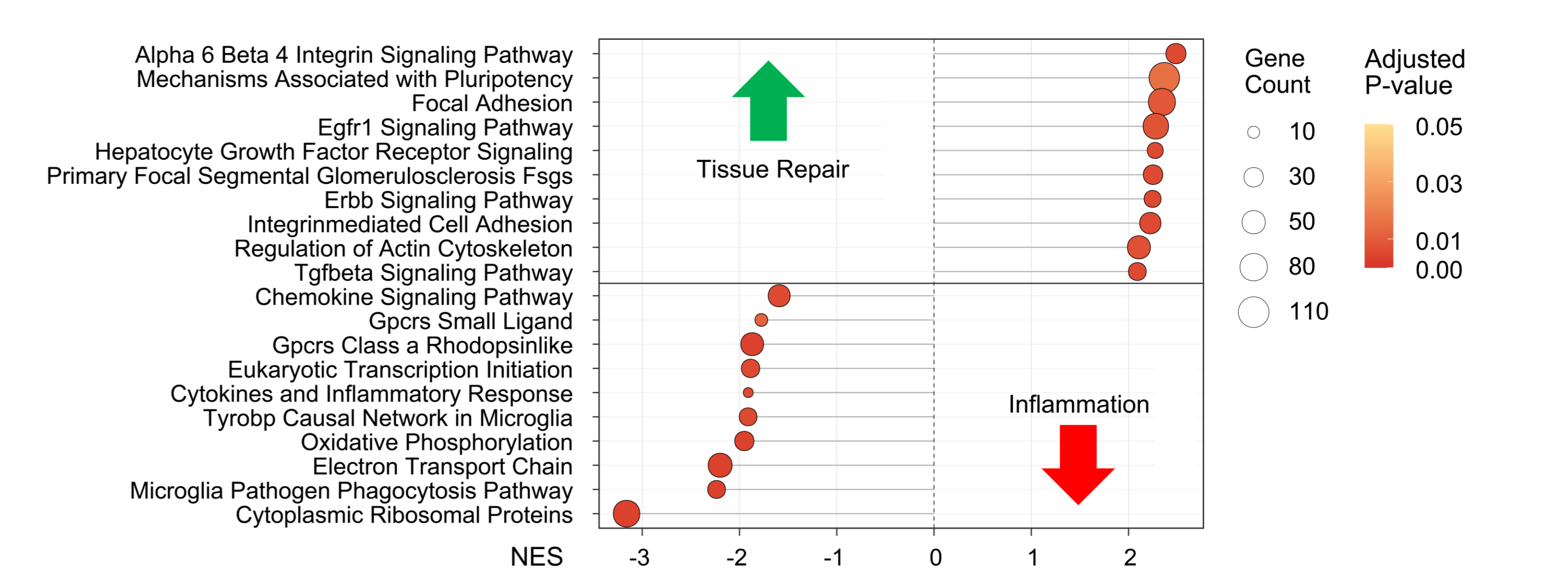


Fig 2: Prophylactic Dosing of SIK2-selective Inhibitor Protects Mice from DSS Chemical Injury-induced Colitis



C57BL/6 mice (male, 8-10 weeks old, n = 8 per group). On Day 1, the disease was induced by 1.5% DSS in water daily for 5 days. On day 6 to day 10, all groups were administered with normal facility water and maintained till sacrifice. Compound treatment (p.o.) started on Day 1. (A) *p value shown vs. vehicle; 2-way ANOVA with Bonferroni's multiple comparisons test. (B) *p value shown vs. vehicle; 1-way ANOVA with Dunnett's multiple comparisons test. NTX-856 also reduces Inflammatory cytokine production in colon. Mouse PK of NTX-856 confirmed coverage of SIK2 inhibition, but not SIK1 or SIK3. Comparators are upadacitinib, JAK1 inhibitor and roflumilast, PDE4 inhibitor.

Fig 4: Prophylactic Dosing of SIK2-selective Inhibitor Protected Mice from Anti-CD40 Myeloid Cell-driven Colitis



Rag2 KO mice (female, 8 weeks old, n = 5-14 per group) were randomized on Day -1. On Day 0, colitis was induced by i.v. injection of anti-CD40 antibodies. Compound treatment (p.o.) started on Day 0. (A) *p value shown vs. vehicle; 2-way ANOVA with Bonferroni's multiple comparisons test. (B) *p values shown vs. vehicle; 1-way ANOVA with Dunnett's multiple comparisons test. Mouse PK of NTX-147 confirmed coverage of SIK2 inhibition, but not SIK1 or SIK3.

CONCLUSION

- We identified highly potent and selective SIK2 inhibitors with favorable drug-like properties suitable for once- or twice-daily dosing.
- SIK2 inhibitors demonstrate a distinctive dual mechanism of downregulating intestinal inflammation and upregulating mucosal healing in injury-induced and myeloid cell-driven preclinical colitis models, offering a novel oral therapeutic approach for IBD and other chronic inflammatory diseases.
- Additional translational data demonstrating SIK2 inhibitor anti-inflammatory and mucosal repair activity in human *ex vivo* models of ulcerative colitis are being presented separately (ECCO 2026, Poster #P0156, Daigle SR, et al.).

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