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

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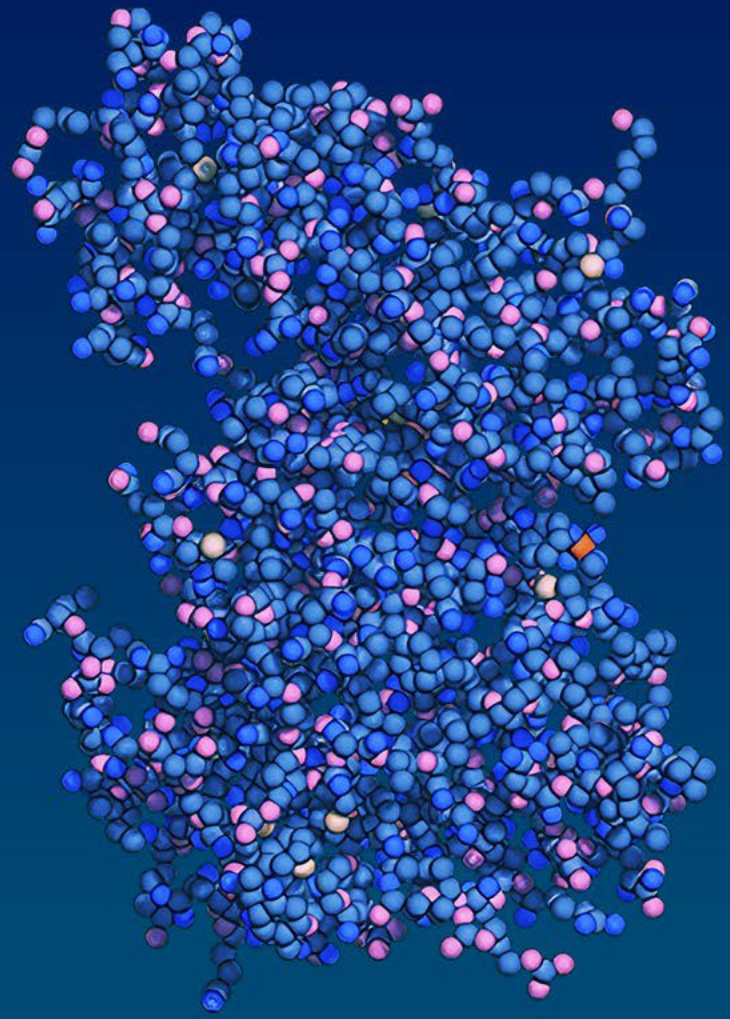
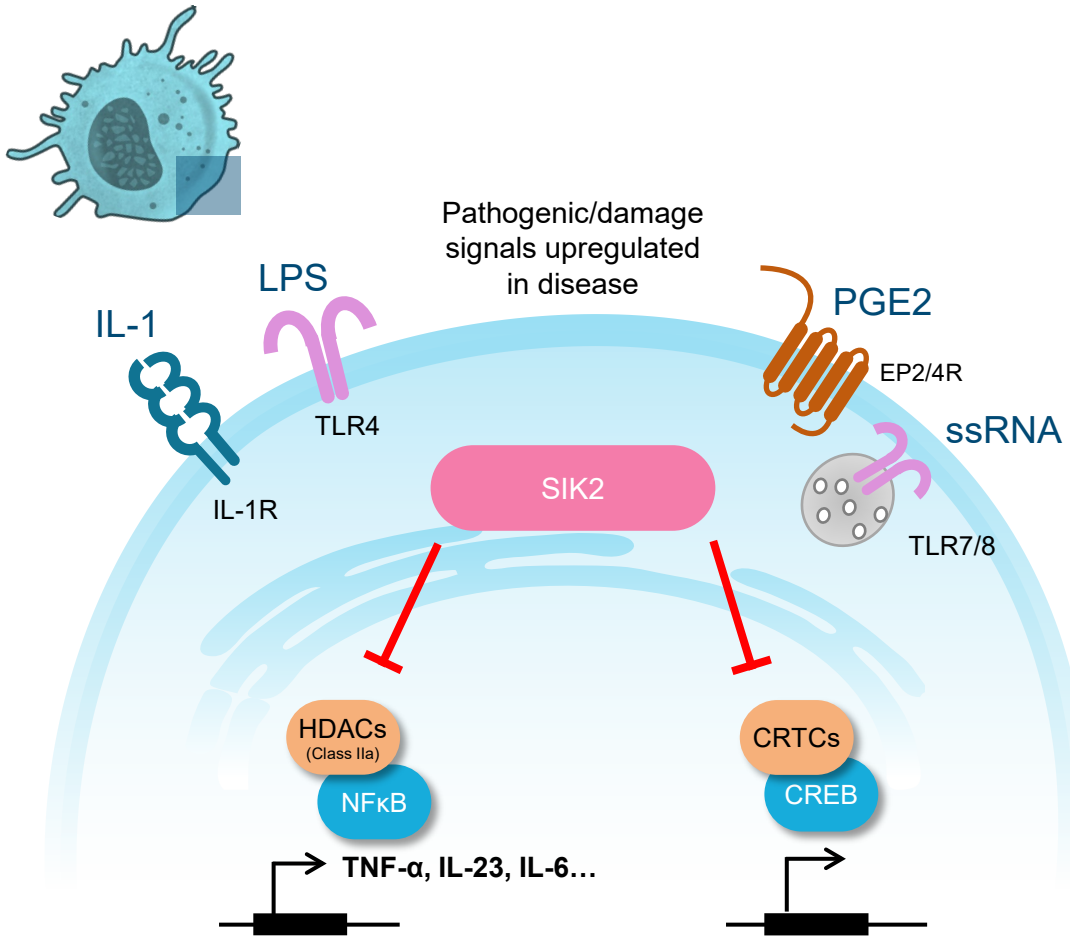
DDW2026
Digestive Disease Week®
MAY 2–5, 2026 | CHICAGO, IL
EXHIBIT DATES: MAY 3–5, 2026



Salt-Inducible Kinase 2 (SIK2): A Key Signaling Node Relevant to IBD Pathology



- Salt-inducible kinases modulate cytokine gene expression in myeloid cells through phosphorylation of transcriptional coregulators.[1]
- SIK2 shows the highest kinase activity in myeloid cells.[2]

References: [1.] Lombardi MS, et al. *J Leukoc Biol.* 2016;99(5):711-721; [2.] Darling NJ, et al. *Biochem J.* 2017;474(4):521-537

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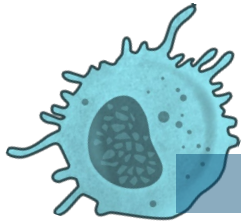
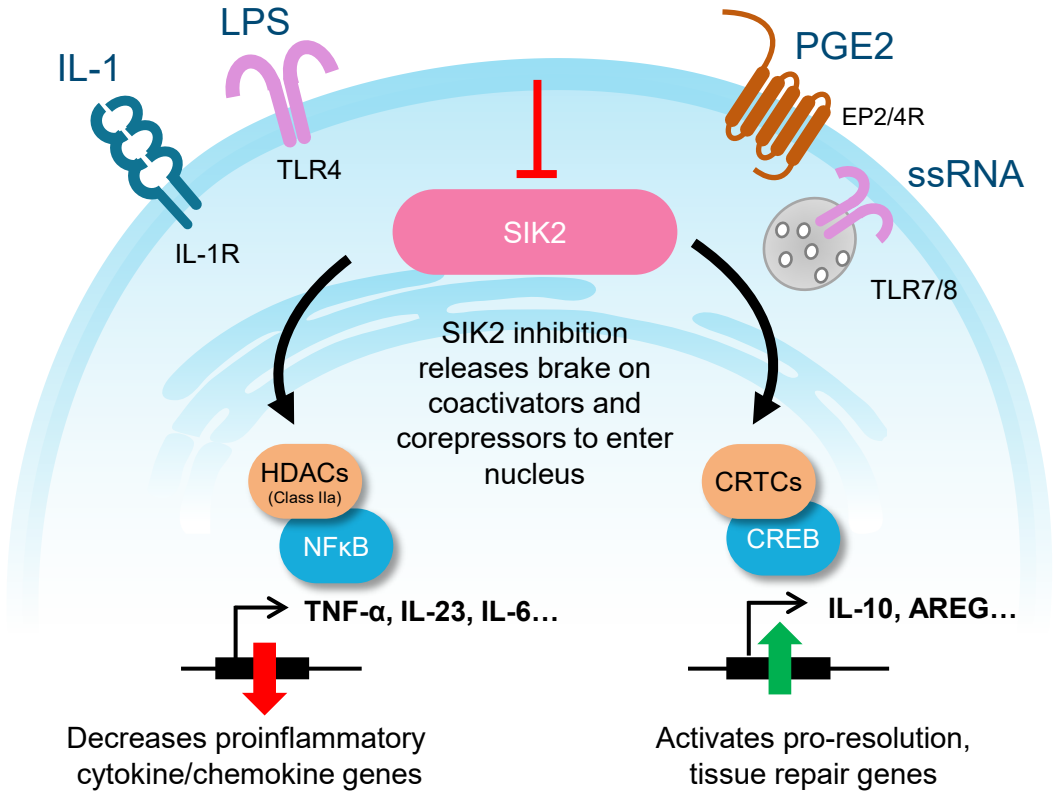
Salt-Inducible Kinase 2 (SIK2): A Key Signaling Node Relevant to IBD Pathology





- Salt-inducible kinases modulate cytokine gene expression in myeloid cells through 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 (TNFα, IL-12/23, IL-6, and IL-1β) induced by Toll-like receptor (TLR) or IL-1 receptor (IL-1R) agonists.[1,2]
- SIK2 LOF also augments production of IL-10, an effect not observed with SIK1 or SIK3 LOF.[2]

References: [1.] Lombardi MS, et al. *J Leukoc Biol.* 2016;99(5):711-721; [2.] Darling NJ, et al. *Biochem J.* 2017;474(4):521-537

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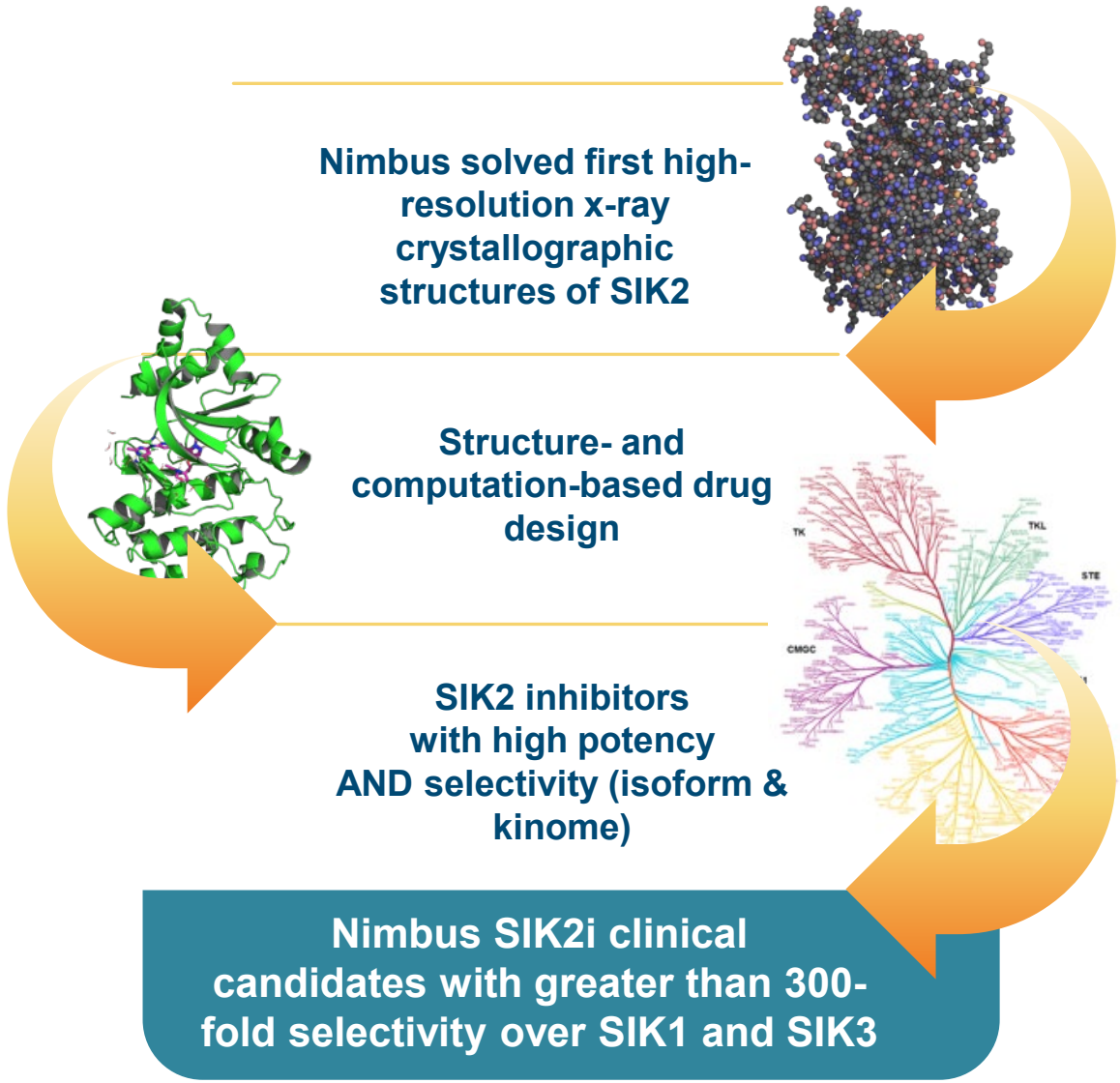
Structure-Guided Drug Discovery Delivers Potent, SIK2-Selective Lead Compounds



SIK2 selectivity is critical for efficacy and safety

- **SIK2:** uniquely delivers dual anti-inflammatory AND pro-resolution effects
- **SIK1:** Known cardiotoxicity risk[3]
- **SIK3:** LOF in mice and humans results in bone defects[4] while knockdown in mice results in fertility defects[5]

Development Candidate Selected

- **Potent**: <20 nM cellular SIK2 IC_{50}
- **Highly selective** against SIK1 & SIK3, minimal hits in kinome
- **Good ADME/PK** supporting QD or BID dosing

References [3.] Clark K, et al. *Proc Natl Acad Sci U S A*. 2012;109(42):16986-16991; [4.] Csukasi F, et al. Sci Transl Med. 2018;10(459): eaat9356; [5.] Hayes, ET, et al. Endocrinology 2024; 165(10):1-10

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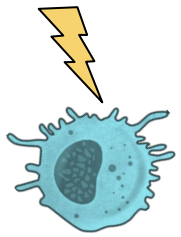
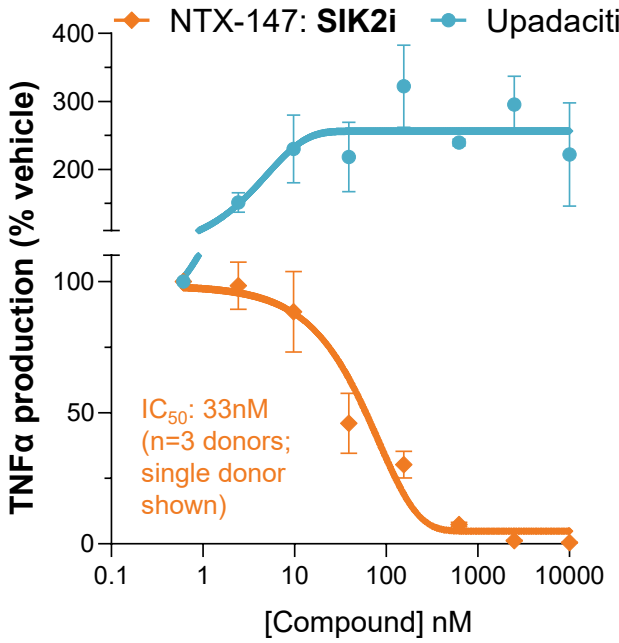
SIK2 Selective Inhibitors Drive Dual Anti-inflammatory and Pro-resolution profiles in Primary Human Macrophages

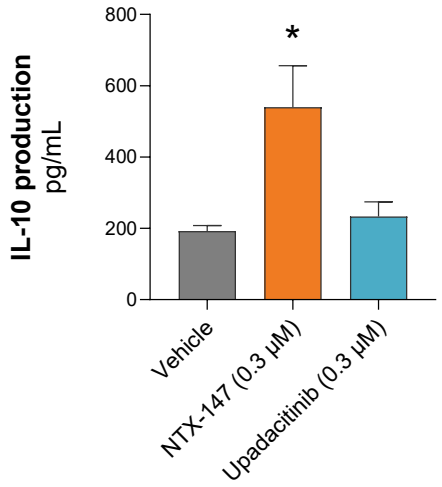
SIK2-Selective Inhibition Exhibits a Differential Cytokine Output vs JAK1i or SIK3i in Human Macrophages

LPS (3-24h)



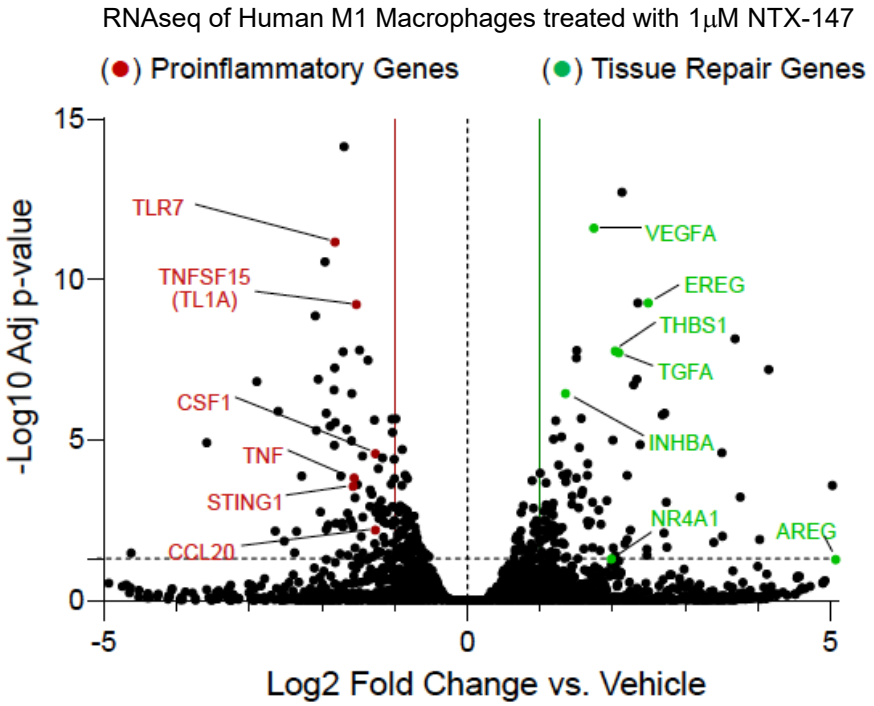
Human M0 / M1 macrophages





Compound	TNFα	IL-23	IL-6	IL-10
SIK2i (NTX-147)	▼	▼	▼	▲
SIK3i (NTX-902)	▼	▲	no effect	no effect
JAK1i (upadacitinib)	▲	▲	no effect	no effect

SIK2 Inhibitor (NTX-147) Downregulates Proinflammatory Genes and Upregulates Tissue Repair Genes



Other key observations in SIK2i treated macrophages:

- ▲ **amphiregulin/thrombospondin** secretion
- Not seen with JAK1 or SIK3 selective inhibitors

* n=2 donors; p<0.05 one-way ANOVA with Dunnett's multiple comparison test

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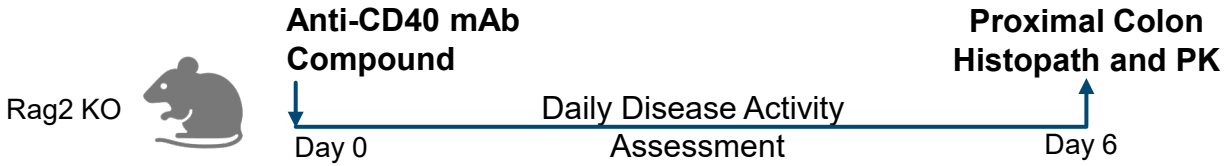
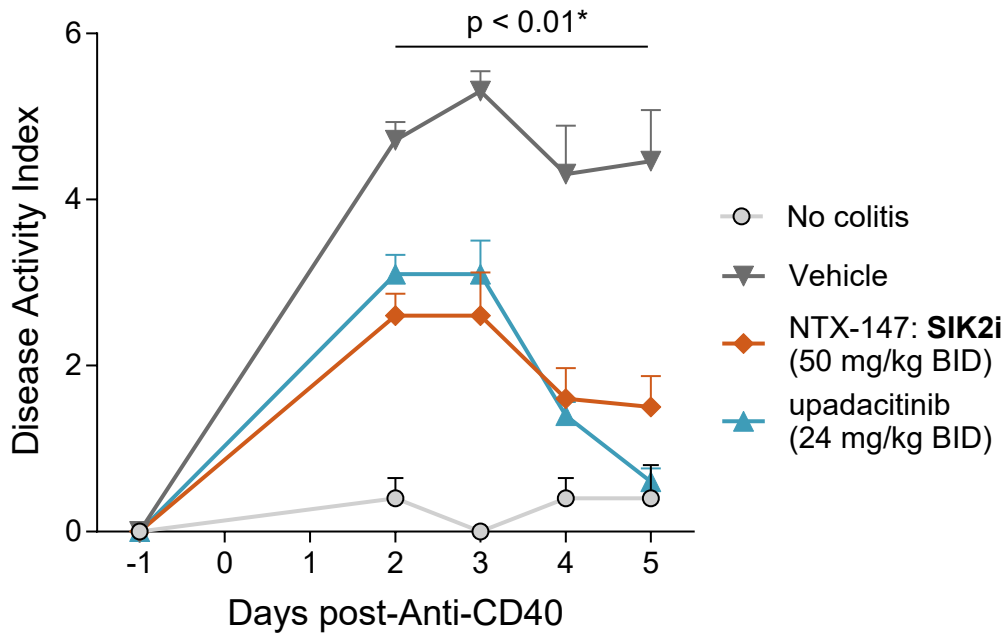
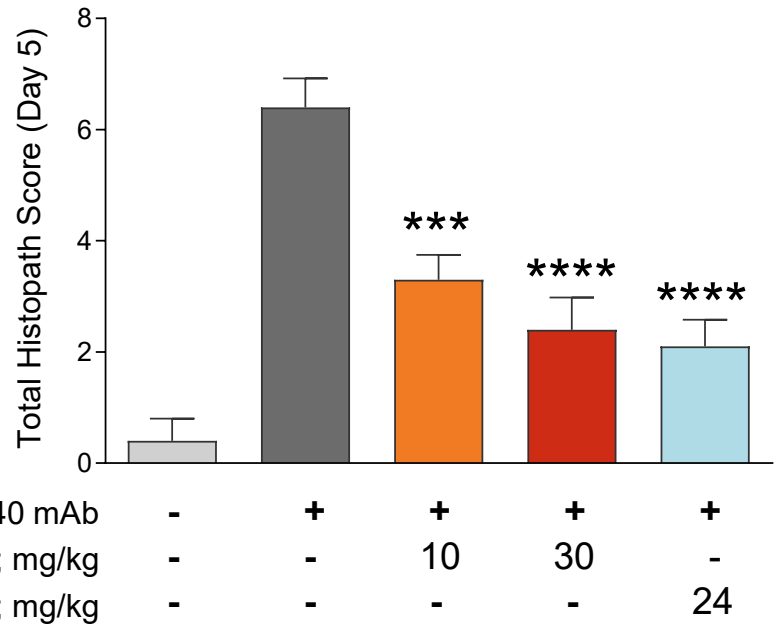
Prophylactic Dosing of a SIK2 Selective Inhibitor Protects Mice from Anti-CD40 mAb Induced Colitis



SIK2i Reduces Disease Activity



SIK2i Reduces Colitis and Gut Damage



n=5-14 per group; mean ± SEM; * DAI: SIK2i vs Vehicle; p-value shown two-way ANOVA with Bonferroni's multiple comparison test;
Histopath: *** p<0.001, **** p<0.0001 one-way ANOVA with Dunnett's multiple comparison test;
Histopath is combined score of inflammatory infiltrates, edema, goblet cell loss and epithelial damage

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Prophylactic Dosing of a SIK2 Selective Inhibitor Protects Mice from DSS-Induced Colitis

1.5% DSS for 5 days
Compound

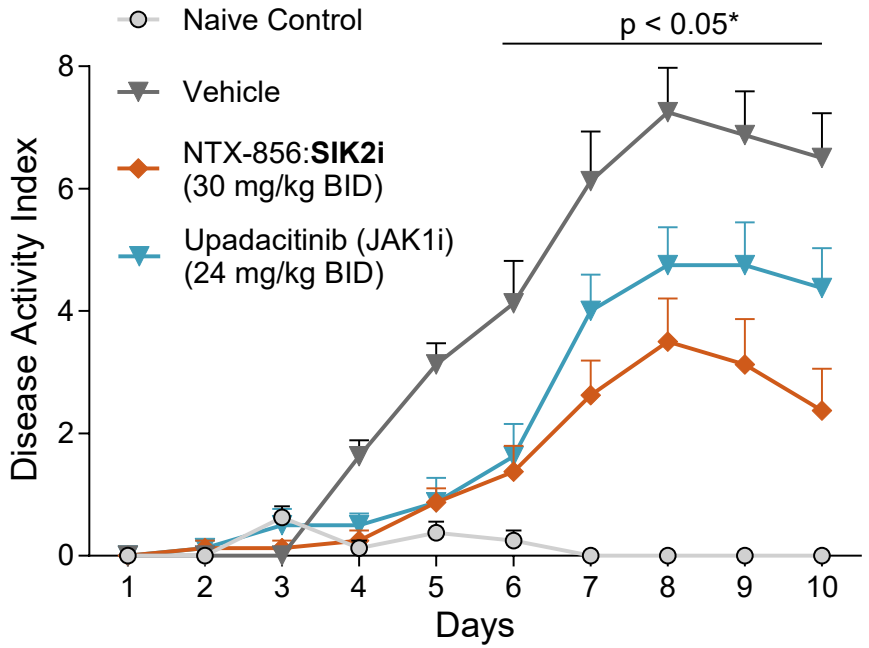
Daily Disease Activity Assessment

Day 0

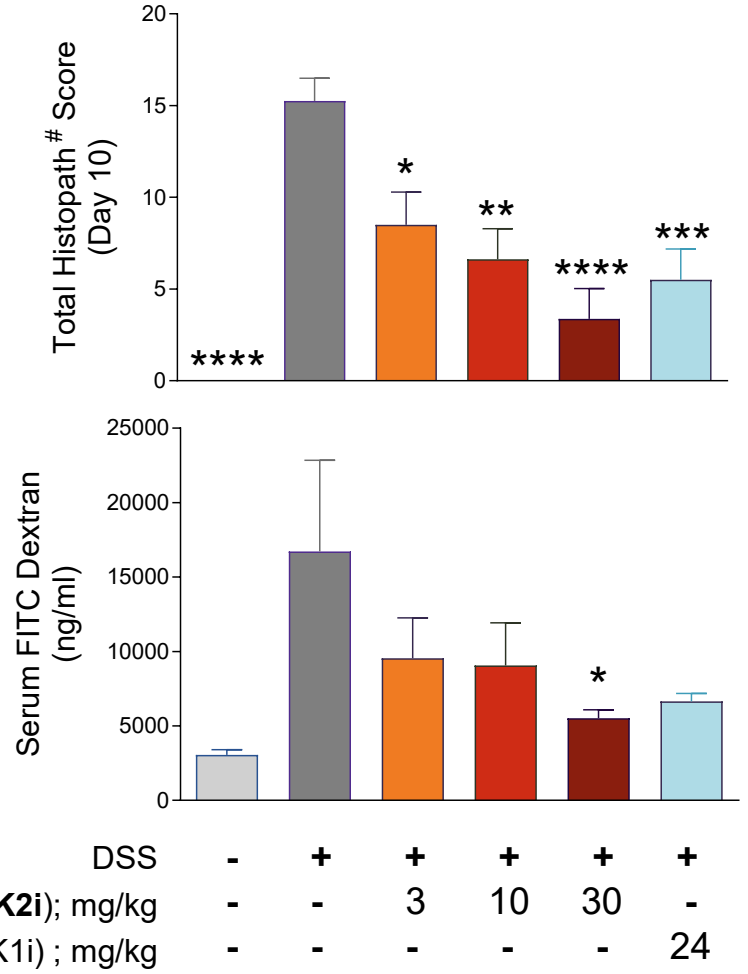
Distal Colon
Histopath, FITC dextran, PK

Day 10

SIK2i Reduces Disease Activity



SIK2i Reduces Colitis & Gut Permeability



n=8 per group; mean ± SEM; * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 one-way ANOVA with Dunnett's multiple comparison test;
# Histopath is combined score of inflammatory infiltrates, edema, goblet cell loss and epithelial damage

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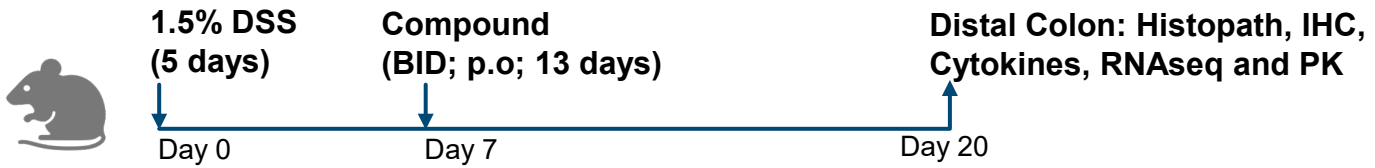
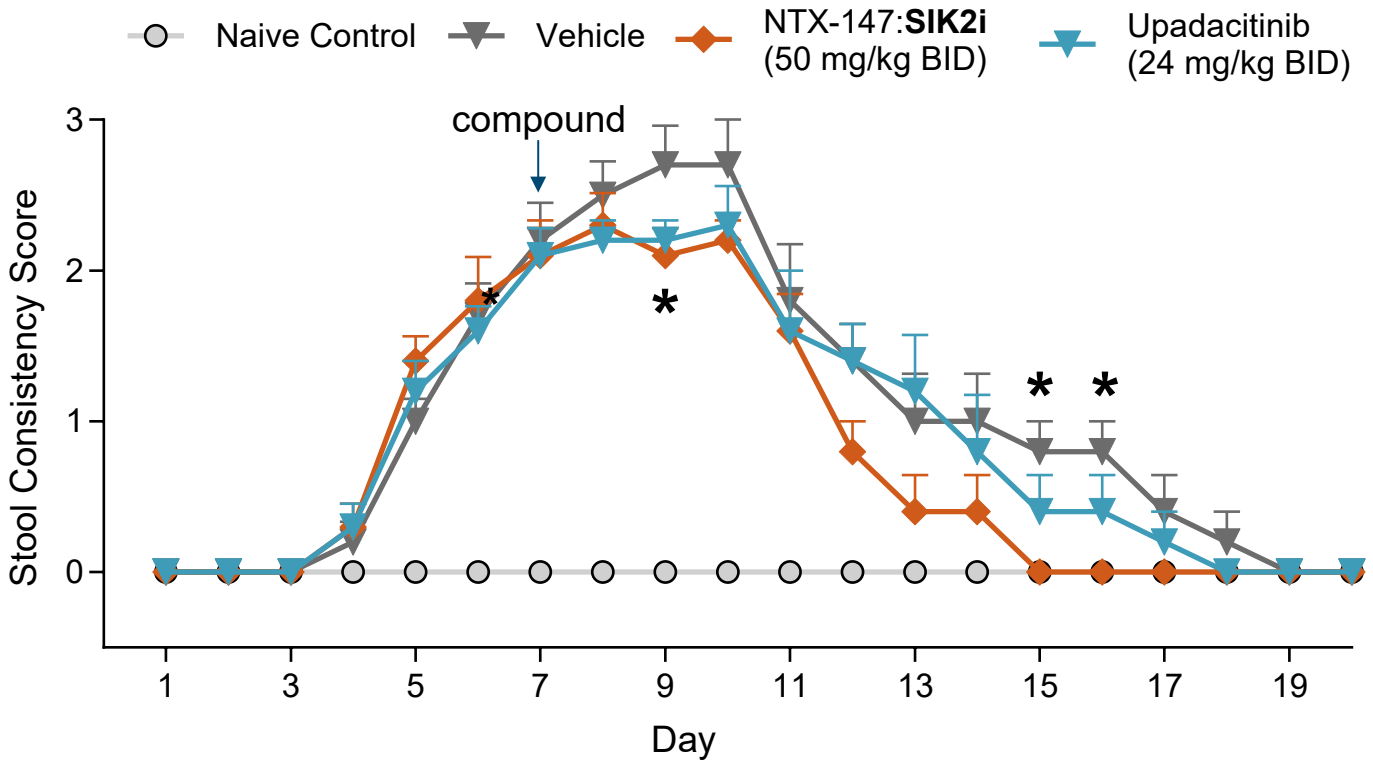
Therapeutic Dosing of a SIK2 Selective Inhibitor Accelerates Recovery in DSS-Induced Colitis



SIK2i Achieves Fast-Acting Efficacy and Accelerated Recovery



n=5-10 per treatment group; mean ± SEM; * p<0.05 NTX-147 vs. Vehicle; one-way ANOVA with Dunnett's multiple comparison test

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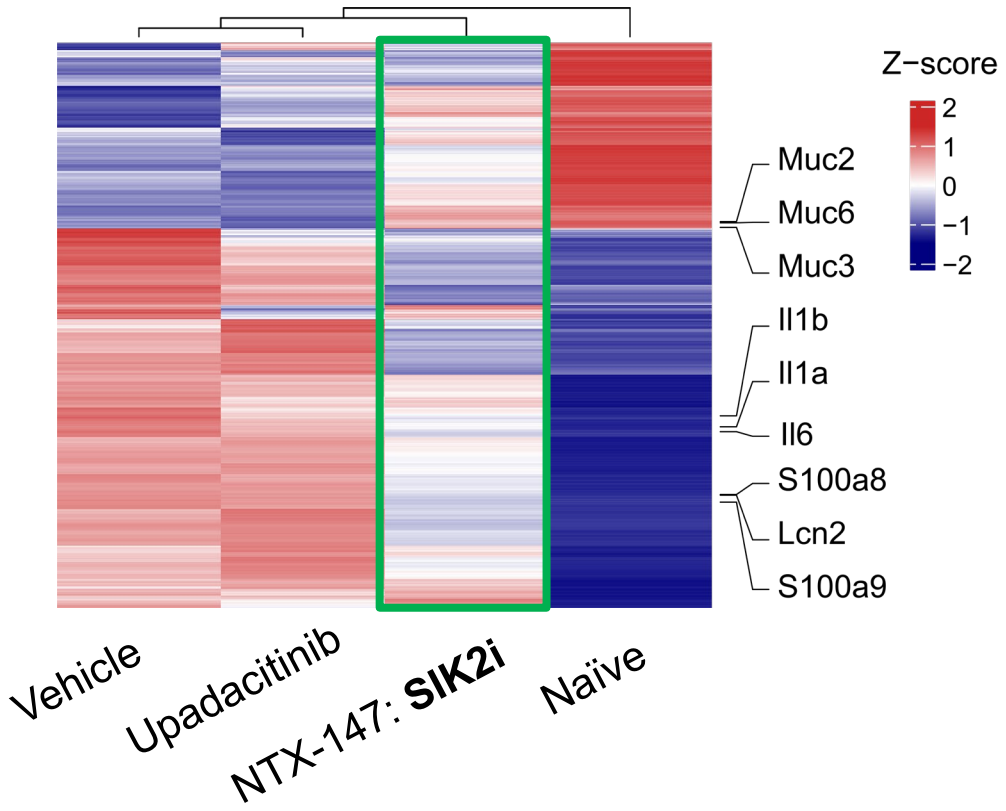
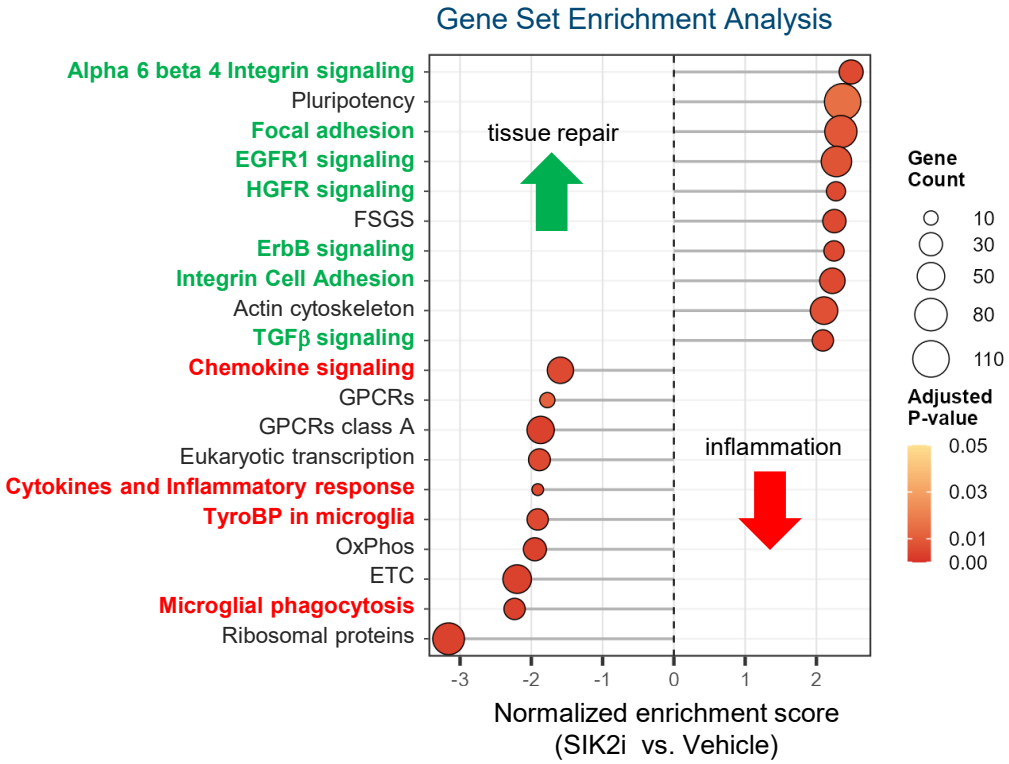
SIK2i Acutely Reverses Colitis Gene Expression in DSS model in 3 days

Acute effects not observed with upadacitinib

SIK2i Broadly Reverses Disease Signature Gene Expression after 3 Days Post-Treatment



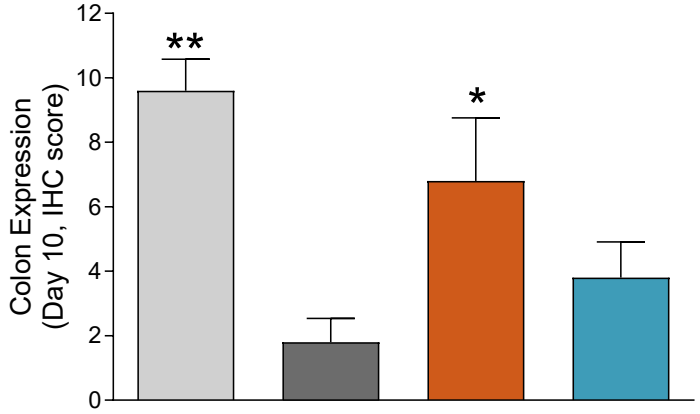
SIK2i Promotes Tissue Repairing and Inhibits Pro-inflammatory Pathways in 3 days

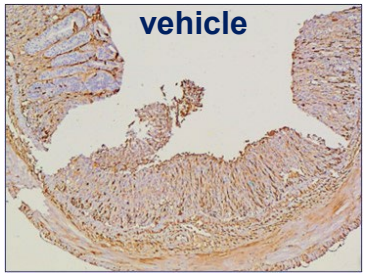


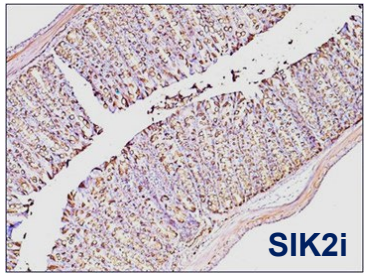
SIK2i Improves Gut Barrier Markers and Correlates of Disease Activity

Acute barrier effects were more robust than with upadacitinib treatment

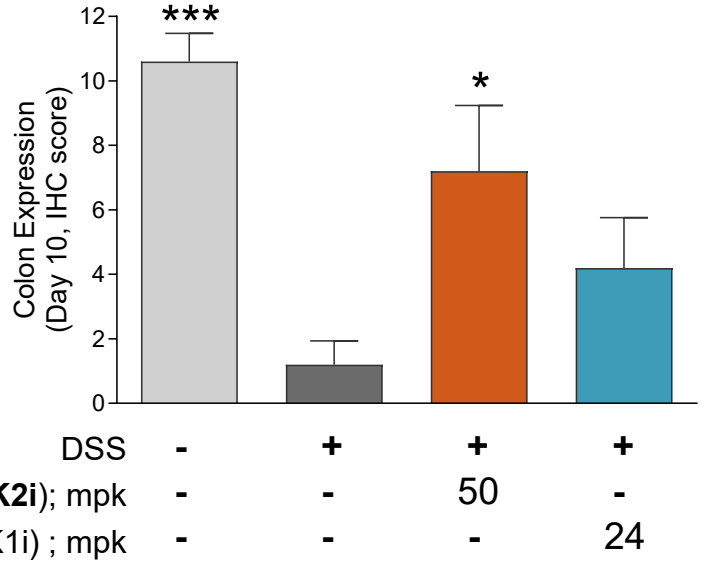
Mucin-2
(barrier integrity)

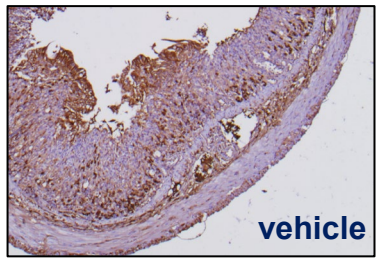






Occludin-1
(tight junctions, barrier function)





Other key observations in SIK2i treated mice

- ▼ **fecal calprotectin/lipocalin-2** at Day 10 & 20
- ▲ **ZO-1** IHC at Day 10
- ▼ **TNFα / IL-6** in colon at Day 10

n=5-10 per treatment group; mean ± SEM; * p<0.05, one-way ANOVA with Dunnett's multiple comparison test

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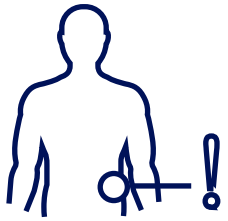
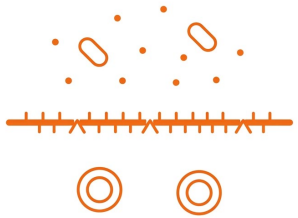
Selective Profile of Nimbus SIK2 Inhibitors Supports Both Anti-inflammatory and Pro-resolving / Tissue Repair



Unmet Need

Despite all advanced treatments, less than 1 in 3 patients suffering with inflammatory bowel disease (IBD) achieve histological remission after 1 year

Potential for first-in-class therapy

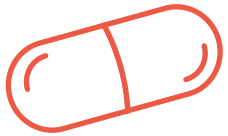


Preclinical Evidence

In preclinical colitis models SIK2 inhibitors demonstrate a unique dual MoA:

- Suppression of intestinal inflammation
- Upregulation of tissue repair pathways in gut

Potential to restore tissue homeostasis in the inflamed gut



Patient Benefit

SIK2 inhibitors may offer a differentiated, oral therapeutic approach to potentially improve long-term clinical remission goals

Potential to be a novel oral therapeutic to treat IBD

Nimbus Progress

Development Candidate selected

IND enabling studies underway

Driving towards First-in-Human

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Please visit our Translational Poster tomorrow!

Tu1466: SIK2 SELECTIVE INHIBITORS DEMONSTRATE DUAL ANTI-INFLAMMATORY AND MUCOSAL REPAIR PROFILES IN HUMAN EX VIVO MODELS OF ULCERATIVE COLITIS

Tuesday 1230-130pm Session# 0034 Mechanisms of IBD Therapeutics