

## Therapeutic Efficacy of a Novel Oral NRF2 Activator in a Murine Ulcerative Colitis Model

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## Abstract

Ulcerative colitis (UC) arises from three interconnected pathological processes: persistent mucosal inflammation, impaired epithelial barrier function, and elevated oxidative stress. NRF2 (NF-E2-related factor 2) is a transcription factor that serves as a central coordinator of cellular defense programs, orchestrates antioxidant defenses, inhibits inflammatory pathways, and facilitates epithelial regeneration. Beyond its cytoprotective functions, NRF2 activation regulates intestinal immunity and influences UC development. To address the multifactorial drivers of UC, we have developed MTAI-1025, a novel, potent, and selective oral NRF2 agonist that shows efficacy in a preclinical model of UC.

## Results

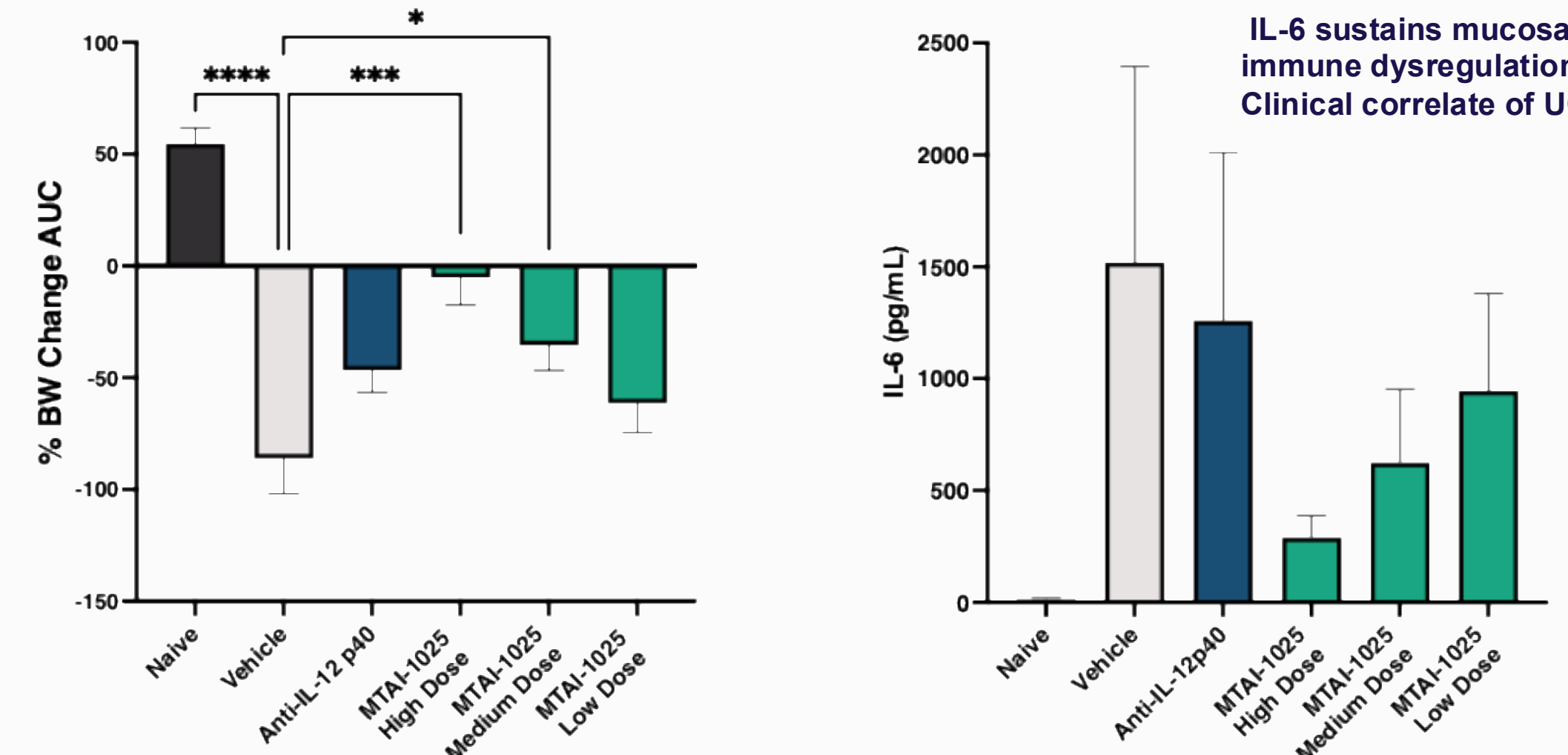
These studies demonstrate that MTAI-1025 reduces disease severity and inflammatory cytokine burden in a DSS mouse model of UC. Induction of the canonical NRF2 transcriptional target *Nqo1* in colon tissue confirms on-target pathway engagement in the inflamed mucosa.

To characterize the immunomodulatory properties of MTAI-1025, we examined its anti-inflammatory activity in primary human immune cells. MTAI-1025 suppressed IL-12 and IL-23 secretion from LPS-stimulated monocyte-derived dendritic cells. These cytokines are implicated in the initiation and perpetuation of mucosal inflammation in UC. MTAI-1025 also attenuated activation of anti-CD3/CD28-stimulated T cells and inhibited the differentiation of naïve T cells into Th1, Th2, and Th17 effector subsets. The aberrant expansion of these effector populations is a hallmark of the dysregulated mucosal immune response that sustains chronic inflammation and tissue damage in UC.

MTAI-1025 protected confluent human colonic epithelial monolayers against loss of viability when challenged with differentiated, activated THP-1 cells which models the epithelial injury driven by infiltrating immune cells at the inflamed mucosa. Preservation of epithelial integrity is critical in UC, where barrier breakdown perpetuates antigen translocation and further amplifies the inflammatory cascade.

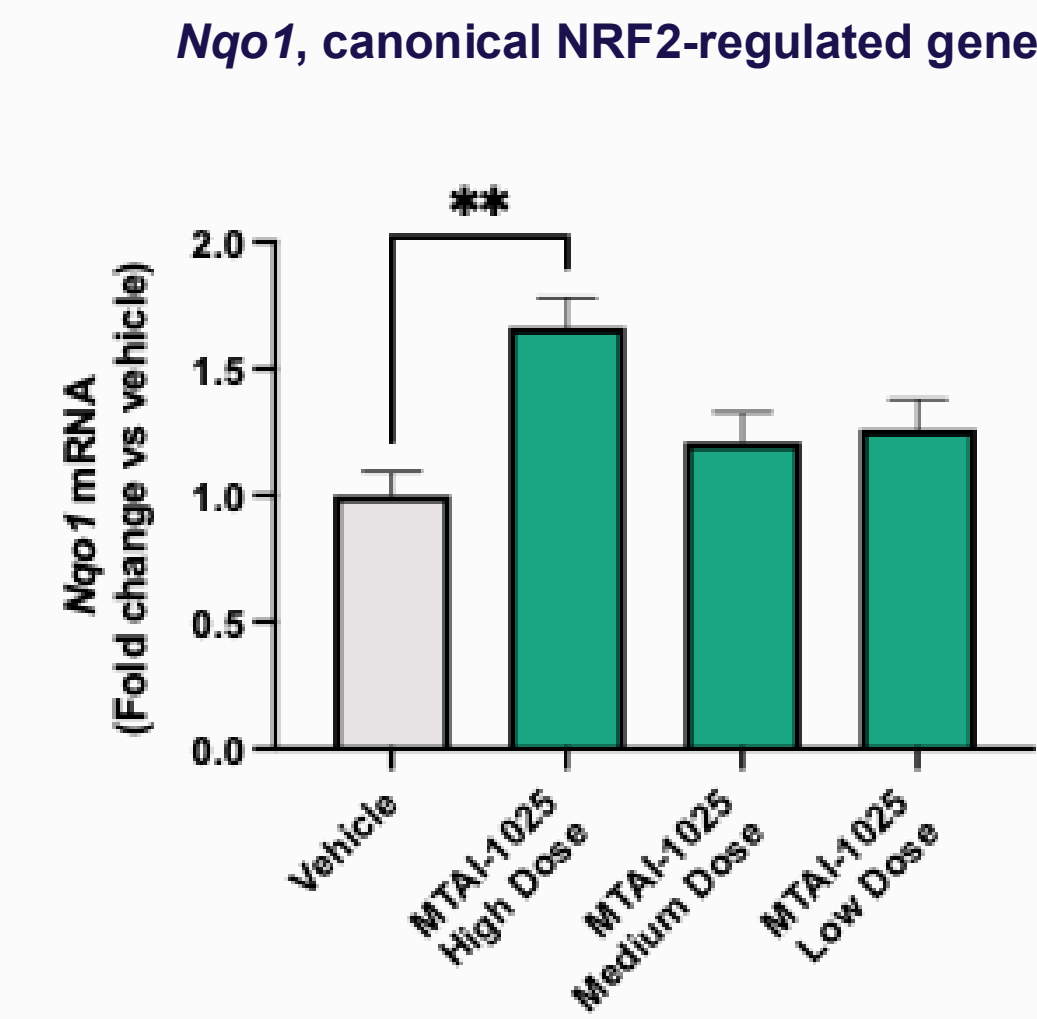
Collectively, these findings demonstrate that MTAI-1025 engages multiple pathological nodes of UC disease progression, supporting its continued development as a therapeutic candidate for UC.

## MTAI-1025 mediates a dose-dependent reduction in weight loss and IL-6 abundance in a DSS-induced colitis model

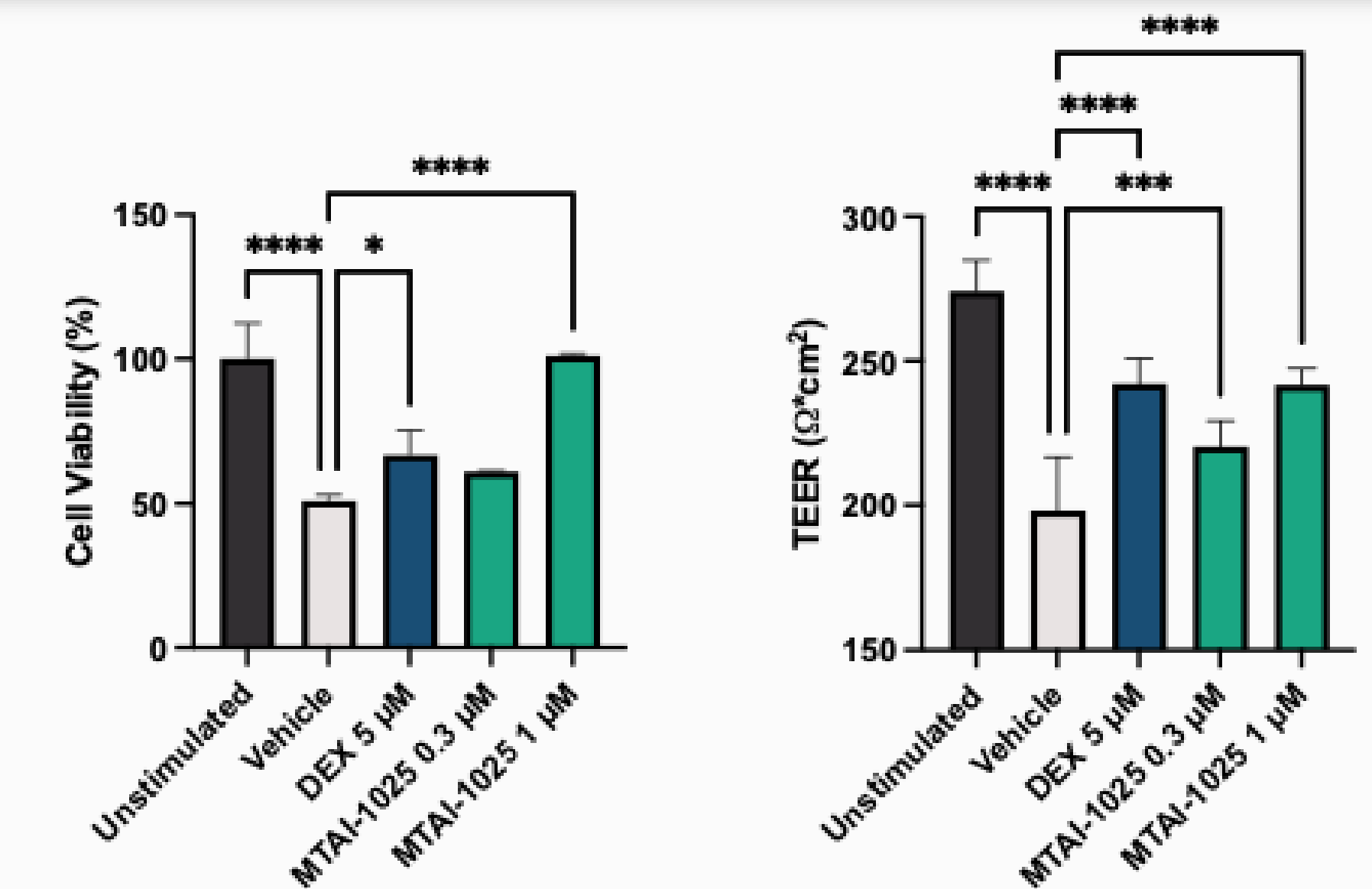


C57BL/6 mice received MTAI-1025 or vehicle PO daily from days -1 to 12. Anti-IL-12p40 monoclonal antibody (10 mg/kg) was administered IP on days 6 and 9. Disease Activity Index (DAI) and body weights (BW) were monitored daily. Colonic tissue was assessed for histopathology, cytokines, and NRF2 target gene induction. Anti-IL-12p40 positive control is the mouse equivalent of the anti-IL12/IL23 biologic Ustekinumab ("Stelara®"). Statistical analyses: one-way ANOVA with Dunnett's Multiple Comparisons Test vs. Vehicle \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, \*\*\*\*P < 0.0001. Data shown are average ± SEM

## MTAI-1025 engages the NRF2 pathway in colon tissue

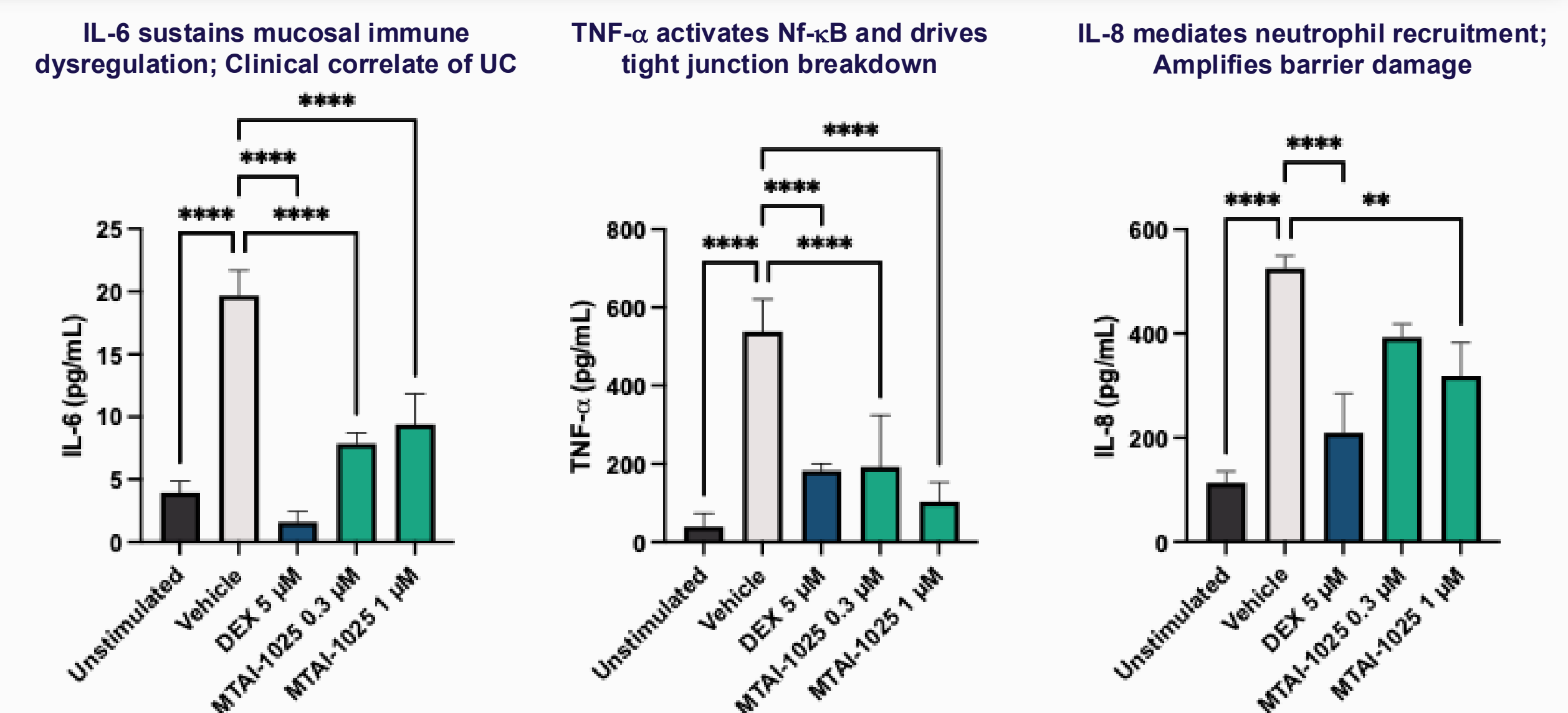


## MTAI-1025 protects against epithelial cell death and barrier disruption mediated by activated THP-1 cells



Human colonic epithelial cell monolayers (NCM460) were co-cultured with differentiated THP-1 cells and pretreated for 24h w/compound. Viability, barrier integrity (TEER), and cytokines measured after 24h

## MTAI-1025 reduces inflammatory cytokines in a human colonic epithelial cell monolayer co-culture

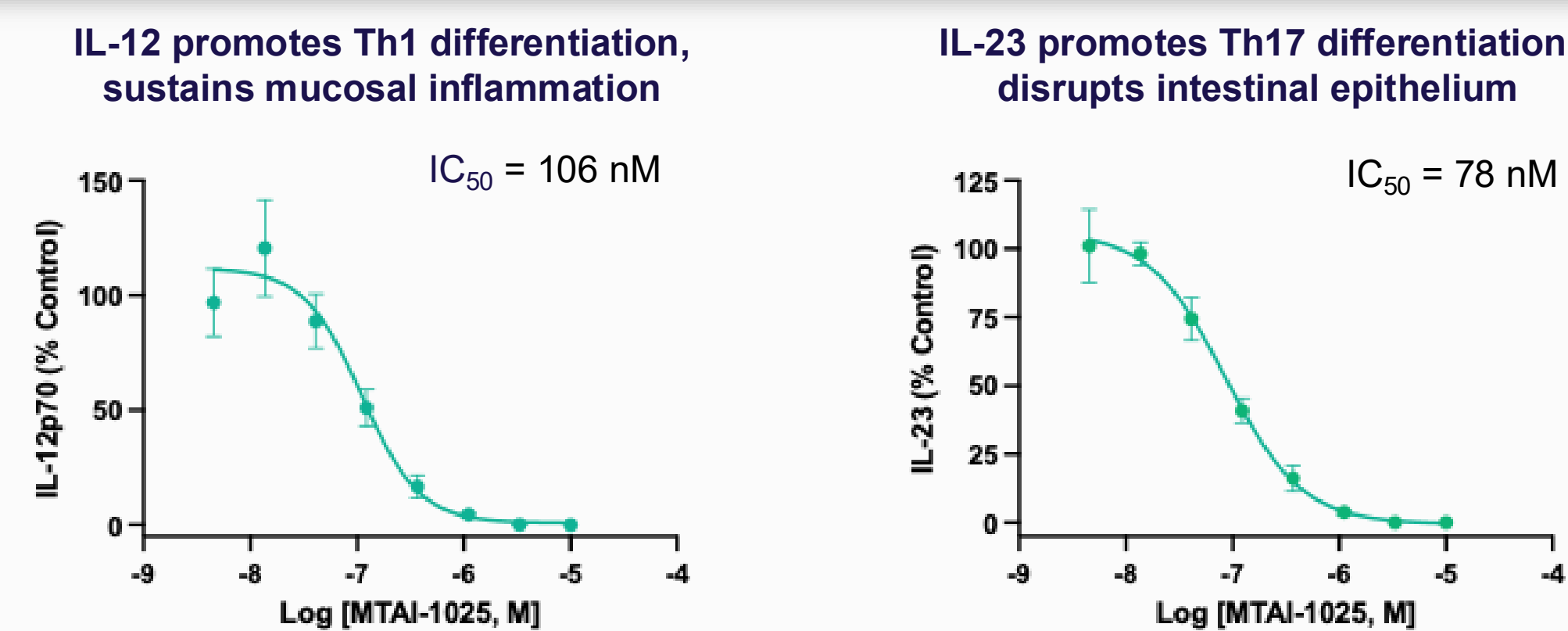


## Conclusion

Montai's first-in-class, oral NRF2 agonist MTAI-1025 addresses underlying drivers of UC

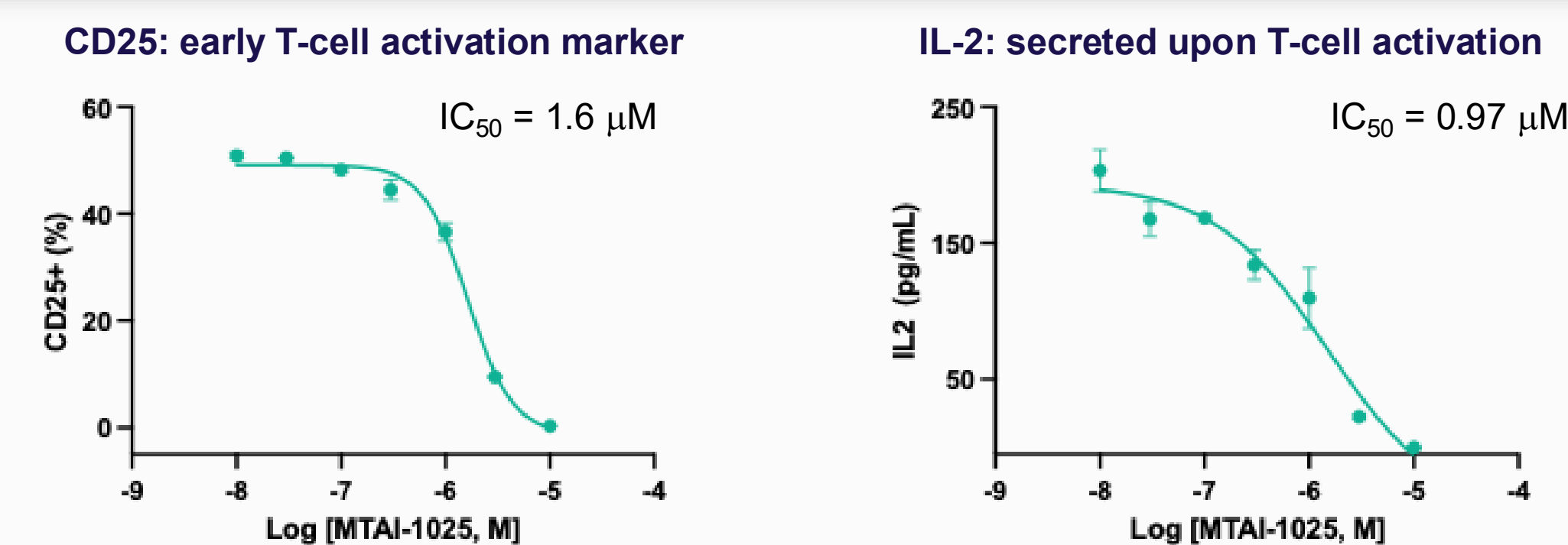
MTAI-1025 attenuates inflammation and epithelial cell damage, with demonstrated efficacy in a UC disease model, supporting its potential as a first-in-class oral NRF2-targeted therapy for UC.

## MTAI-1025 reduces IL-12 and IL-23 secretion in LPS-stimulated human monocyte-derived dendritic cells



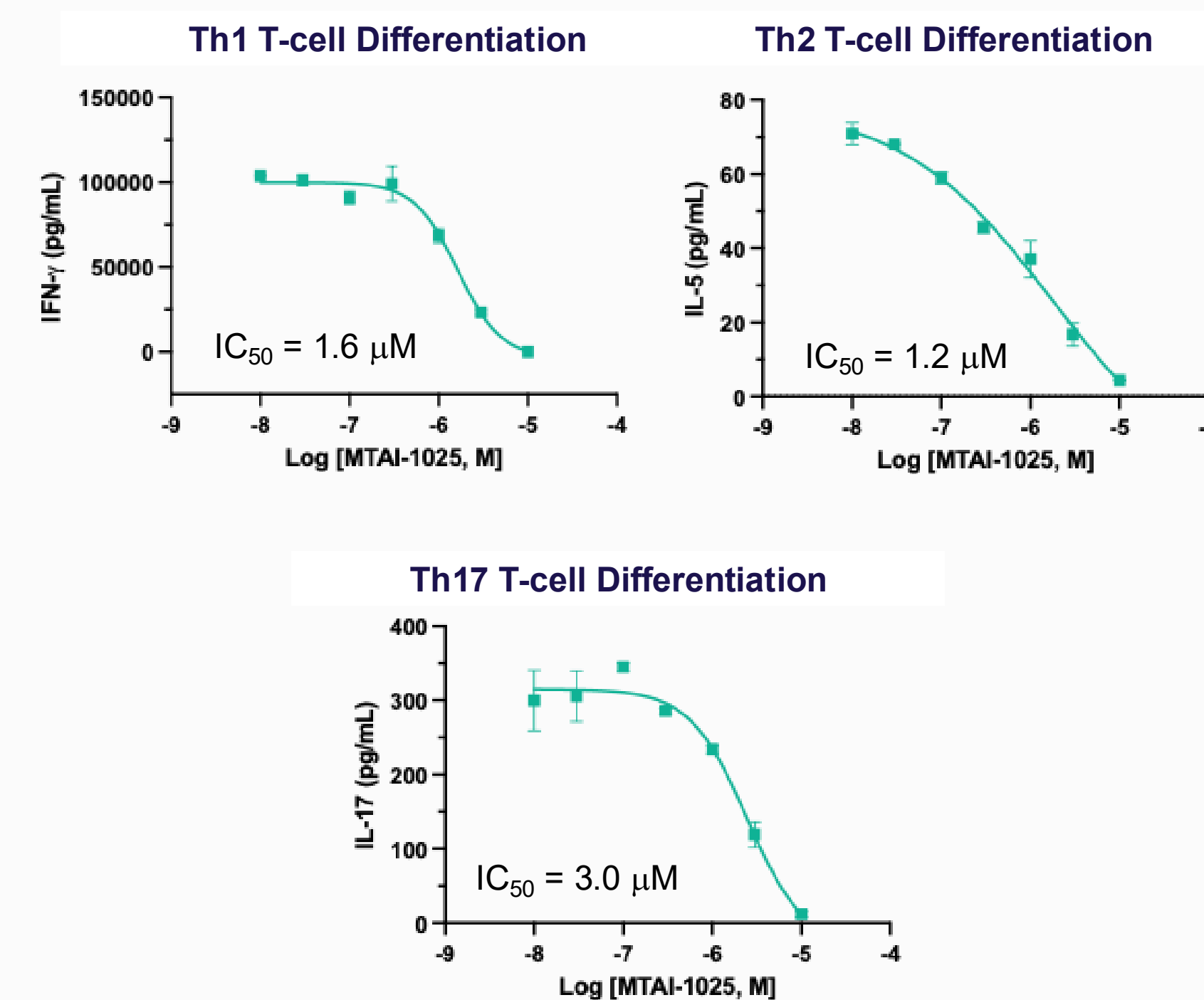
Human peripheral blood monocytes were differentiated into dendritic cells over five days using GM-CSF and IL-4. moDCs were treated with compound for 1h prior to stimulation with LPS

## MTAI-1025 inhibits primary T-cell activation



Purified human T-cells treated with compound for 24h prior to activation with anti-CD3/CD28

## MTAI-1025 inhibits differentiation of Naïve T-cells to effector T-cells



Purified naïve human T-cells treated with compound for 24h prior to activation with anti-CD3/CD28 Dynabeads in the presence of Th1/Th2/Th17 polarizing cytokines for 3d.