Potent and Selective Oral IRF5 Degrader, KT-579, Demonstrates Robust Anti-inflammatory Activity and Disease Modulation in Preclinical In Vivo Models of Inflammatory Bowel Disease

#Tu1441

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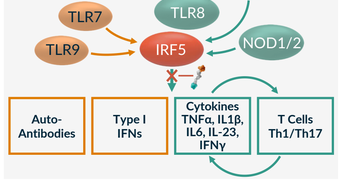
1. INTRODUCTION

IRF5, a historically undrugged transcription factor, is an autoimmune susceptibility gene that has been linked to IBD and other autoimmune diseases including SLE, RA, Sjögren's, and SSc. IRF5 is a regulator of immune responses activated downstream of pattern recognition receptors, like toll-like receptors (TLR). IRF5 regulates pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-23), autoantibody production and Type I IFN. IRF5 is selectively expressed and activated in specific cell types such as dendritic cells, monocytes, M1 macrophages, and B cells[1]. IBD comprises a group of chronic inflammatory conditions that involve the tissues of the gastrointestinal tract, particularly the intestinal mucosal lining and, possibly, deeper underlying tissues. The inflamed colon contains a larger number of infiltrated monocytes, activated macrophages and T cells in addition to neutrophils and dendritic cells. Human genetics and mouse IRF5 KO studies implicate IRF5 in IBD where dysregulated myeloid activity contributes to chronic intestinal inflammation[2-3]. Despite its strong mechanistic and genetic validation, IRF5 has historically remained undrugged likely due to its activation complexity and multiple functional isoforms. IRF5 is well suited for targeted protein degradation, where a single binding event drives activity. KT-579, an oral IRF5 degrader, has demonstrated potent and selective activity in preclinical *in vitro* myeloid assays and *in vivo* IBD models, offering a new approach to modulating this key driver of immunity.

IRF5 Biology and Target Rationale

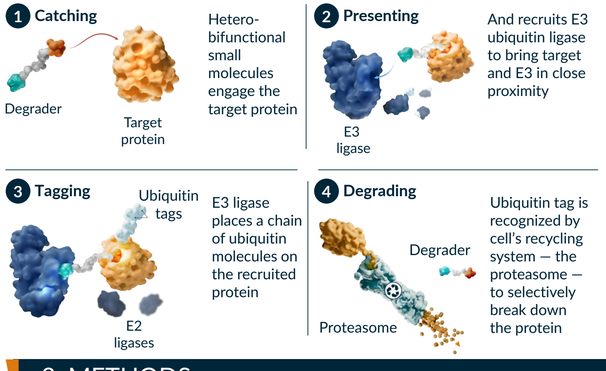
IRF5 Activates Pro-inflammatory Reponses Involved in IBD



Target Biology and Rationale

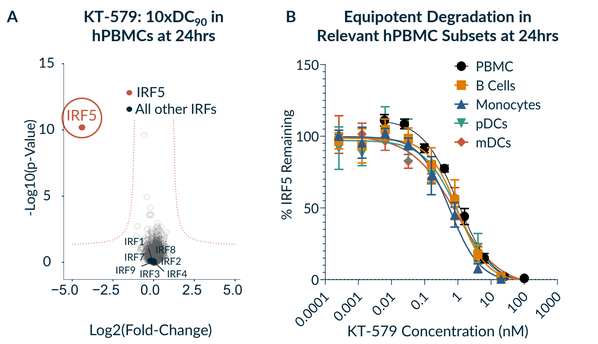
- IRF5 is predominantly expressed and activated in specific cell types: Dendritic Cells (DCs), Monocytes, Macrophages, and B cells
- IRF5 is activated by pattern recognition receptors (PRRs) during immune responses or when dysregulated in autoimmune diseases
- The cell and stim-dependent activation profile has the potential to amplify disease-defining pathways dependent on autoimmune or autoinflammatory disease
- IBD: Chronic activation by intestinal microbiota, danger signals and PRRs can lead to amplification of innate-induced cytokine responses and T cell activation

Proteome Editing with Targeted Protein Degradation



3. RESULTS

Figure 1. An Exquisitely Selective and Picomolar Oral IRF5 Degrader

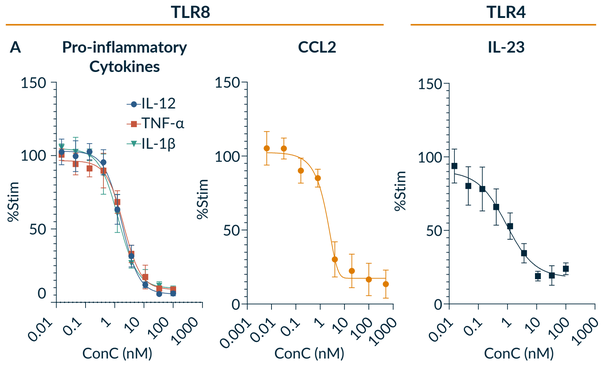


Selectivity Binding and Cellular Assays	KT-579
IRF3, 4, 6, 7, 8 SPR binding, Kd (nM)	>10,000
IRF3 Degradation DC_{50} (nM)	>10,000
IRF7 Degradation DC_{50} (nM)	>10,000

Cell Subsets	KT-579 DC_{50} (nM)
PBMC	0.8
CD19+ B cells	1.0
CD14+ Monocytes	0.6
HLA-DR+CD123+ pDCs	0.9
HLA-DR+CD11c+ mDCs	0.9

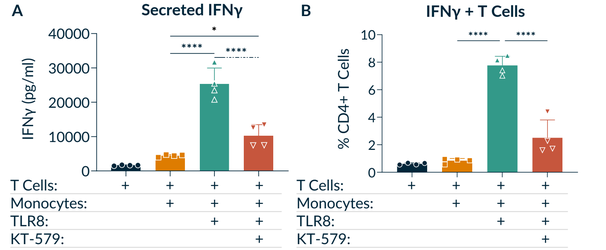
A) KT-579 selectively degrades IRF5 in the detectable proteome (>10,000 proteins). **B)** KT-579 potently degrades IRF5 in key functional cell types.

Figure 2. KT-579 Activity in Monocytes Inhibits IBD-Relevant Pro-Inflammatory Cytokines & Chemokines



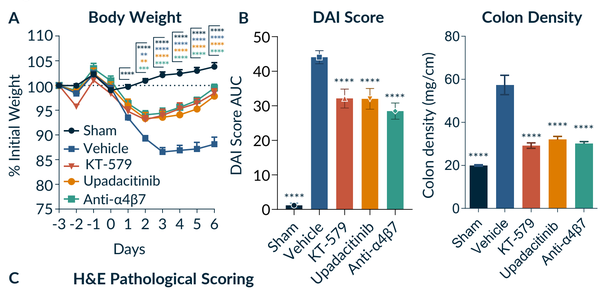
A) IRF5 degradation potently inhibits IBD-relevant proinflammatory cytokines (TNFα, IL-1b, IL-12 and IL-23) and chemokines (CCL2) downstream of TLR4 and TLR8 activation. Primary human monocytes were incubated with compound for 24hr prior to TLR stimulation.

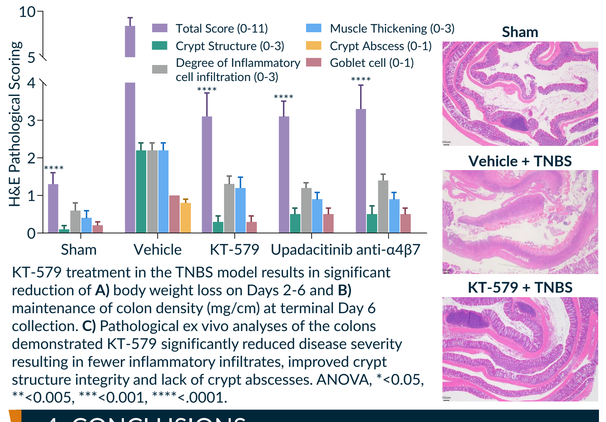
Figure 3. IRF5 Degradation in Monocytes Leads to Significant Reduction in Th1 Polarization *in vitro*



KT-579 leads to significantly decreased Th1 polarization in monocyte-T cell co-culture experiments. Pre-treated monocytes were co-cultured with CD4+ T cells to induce polarization. Significant decrease of Th1 polarization as measured by **A)** soluble IFN-γ and **B)** immunophenotyping of IFN-γ+ T cells post co-culturing. ANOVA, *<0.05, ****<.0001.

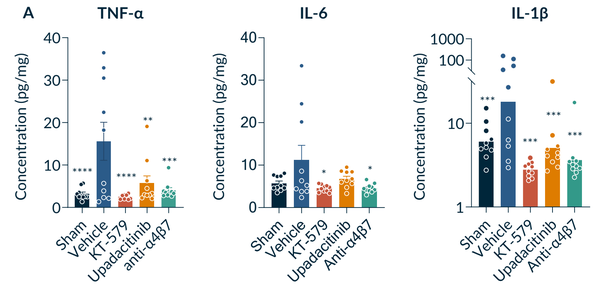
Figure 4. KT-579 Reduces Disease Activity in the TNBS Mouse Model





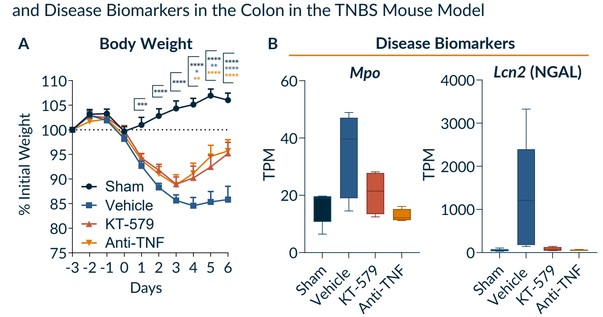
KT-579 treatment in the TNBS model results in significant reduction of **A)** body weight loss on Days 2-6 and **B)** maintenance of colon density (mg/cm) at terminal Day 6 collection. **C)** Pathological ex vivo analyses of the colons demonstrated KT-579 significantly reduced disease severity resulting in fewer inflammatory infiltrates, improved crypt structure integrity and lack of crypt abscesses. ANOVA, *<0.05, **<0.005, ***<0.001, ****<.0001.

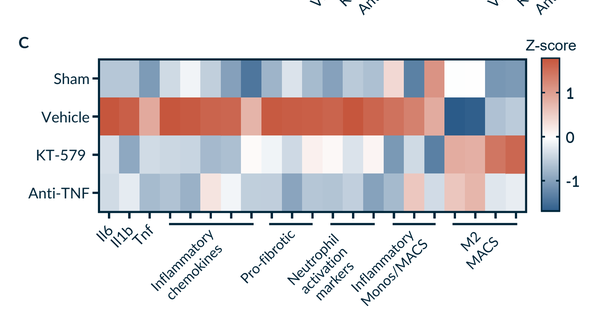
Figure 5. KT-579 Reduces Inflammatory Cytokines in the Colon in the Mouse TNBS Model of IBD



A) KT-579 results in significant reduction of pro-inflammatory cytokine (TNF-α, IL-6, IL-1β) levels in the colon comparable to naïve at terminal day 6 collection. ANOVA, *<0.05, **<0.005, ***<.001, ****<.0001.

Figure 6. KT-579 Reduces Innate Myeloid-induced Inflammatory Environment and Disease Biomarkers in the Colon in the TNBS Mouse Model





KT-579 treatment in the TNBS model results in significant reduction of **A)** body weight loss and **B)** results in reduced levels of colon *Mpo* and *Lcn2*, key IBD biomarkers. **C)** Transcriptomic analysis of colon demonstrates activity of KT-579 across multiple inflammatory cytokines and chemokines, neutrophil activation markers, and markers of fibrosis and inflammatory myeloid cells, with a corresponding increase of M2 markers. ANOVA, *<0.05, **<0.005, ***<0.001, ****<.0001.

2. METHODS

- *In vitro* cell cultures for PBMCs, monocytes, B cells, and dendritic cells were performed by treating cells with compound for 24 hours prior to collection for selectivity and potency assessment or stimulation with TLR agonists for functional studies.
- Monocyte: CD4+ co-culture systems were established with paired donor (autologous) CD14+ monocytes and naïve CD4+ T cells. KT-579 was first added to monocytes 24 hours prior to TLR8 stimulation for an additional 24 hours. Monocytes then underwent a washout before being co-cultured with CD4+ T cells in the presence of bound anti-CD3 and soluble anti-CD28. Co-cultures were assessed for T cell polarization after 48 hours for cytokine production and immunophenotyping of CD4+ T cells.

In vivo studies: TNBS mouse model of IBD was established in BALB/c mice by intracolonic administration of 2% trinitrobenzene sulfonic acid (TNBS) or 50% 0.1mL ethanol for control animals on Day 0 of the study. Prophylactic dosing of KT-579, Vehicle and all comparators was initiated on Day -3 and continued through Day 5. Sham group served as negative disease control (No TNBS). Animals were monitored for signs of disease induction and disease activity score (DAI), body weight loss, stool consistency and blood in the stool daily. On Day 6, colon tissue was collected for colon weight and colon length measurement (reported as colon density). A portion of colon was preserved for cytokine analysis, H&E pathological assessment, and RNA processing for downstream transcriptomics. For transcriptomics sampling, colons were collected on Day 0 or Day 6 post TNBS, and data is a representative profile of selected genes and pathways from both timepoints. One- and Two-Way ANOVA used for statistical analysis.

4. CONCLUSIONS

- KT-579 is an oral, selective and potent IRF5 degrader that sufficiently depletes IRF5 in key immune subsets.
- KT-579 impacts myeloid function by inhibiting pro-inflammatory mediators, including T-cell skewing cytokines that promote Th1 and Th17 T cell responses.
- *In vivo*, KT-579-induced depletion of IRF5 in the mouse TNBS IBD model led to significant reduction of disease activity score, including protection from body weight loss, improvement of crypt structure integrity and complete inhibition of TNFα, IL-1b and IL-6 with similar activity to clinically validated targets.
- Initial transcriptomics analyses supports myeloid and anti-inflammatory activity of KT-579.
- These findings position KT-579 as a potential first-in-class novel oral approach capable of broadly modulating pathogenic pathways in IBD and other autoimmune diseases.
- Phase 1 healthy volunteer clinical trial initiated in early 2026, with data expected 2H 2026.

5. REFERENCES

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6. DISCLOSURES

This study was funded by Kymera Therapeutics. Camire, Corcoran, Lurier, Leedberg, Massa, Zhang, Carroll, Ho, Chen, Lalonde, Mehovic, Karnik, Zhao, Howarth, Breitkopf, Martinez, Kuhn, Kamerkar, Sathappa, Williams, Mainolfi, Campbell are Kymera Therapeutics employees and equity owners.