First-in-Class Oral IRF5 Degrader, KT-579, Demonstrates Selective and Potent In Vitro and In Vivo Activity in Human Cellular Assays and Mouse Models of Lupus

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BACKGROUND

IRF5 is a transcription factor and master regulator of pro-inflammatory immune responses activated downstream of specific pattern recognition receptors, like Toll-like receptors (TLRs). Downstream of TLR7, TL8 and TLR9 activation, IRF5 can act as a central node and regulate genes for pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-23), Type I IFN, and cellular functions such as B cell activation and antibody secretion. IRF5 is constitutively expressed and activated in immune cell types such as dendritic cells, monocytes, macrophages, and B cells. Human genetic and functional studies have linked IRF5 dysregulation to the pathogenesis of multiple autoimmune diseases, including SLE and Sjögren's, and Irf5-deficient mice protect from lupus onset and severity. In SLE, endosomal TLRs recognize nuclear self-antigens, and can trigger IRF5 activation to drive the breakdown of immune tolerance via a cascade involving increased Type I IFN and pro-inflammatory cytokine production, and autoantibody production. Despite its strong mechanistic and genetic validation, IRF5 has historically remained undrugged likely due to its lack of catalytic activity, activation complexity and multiple functional isoforms. IRF5 is well suited for targeted protein degradation. KT-579, a potent and selective oral IRF5 degrader, offers a novel approach to modulating immune responses driven by IRF5.

OBJECTIVES

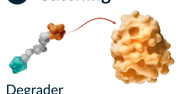
To evaluate the in vitro potency, selectivity, and functional activity of IRF5 degradation by KT-579 in human healthy or patient-derived cells. In addition, to assess the in vivo therapeutic potential of the oral IRF5 degrader, KT-579, by evaluating its dose-dependent activity and immunomodulatory effects in the MRL.lpr and the NZB.W1, mouse models of lupus and compare the activity of an IRF5 degrader with targeted agents in clinical-stage testing or approved in SLE treatment.

Targeted Protein Degradation: Achieving Biologics-like Activity with Oral Medicines

Targeted Protein Degradation (TPD) Mechanism of Action

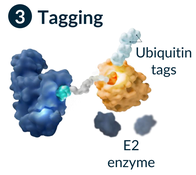
Harnessing the E3 Ubiquitin Proteasome System

1 Catching — Hetero-bifunctional small molecules engage the target protein

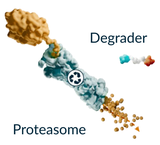


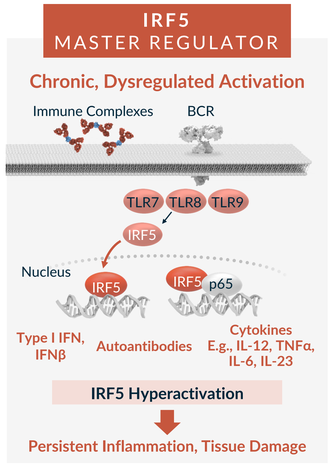
2 Presenting — And recruits E3 ubiquitin ligase to bring target and E3 in close proximity

3 Tagging — E3 ligase places a chain of ubiquitin molecules on the recruited protein



4 Degrading — Ubiquitin tag is recognized by cell's recycling system — the proteasome — to selectively break down the protein





Target Biology and Rationale

- Chronic stimulation or dysregulated endosomal TLR signaling contributes to SLE pathogenesis[1]
- IRF5 is primarily expressed in myeloid and B cells
- Downstream of endosomal TLRs, IRF5 regulates pro-inflammatory cytokines, Type I IFN and autoantibody production in a cell and activation-specific manner

Genetically and Clinically Validated

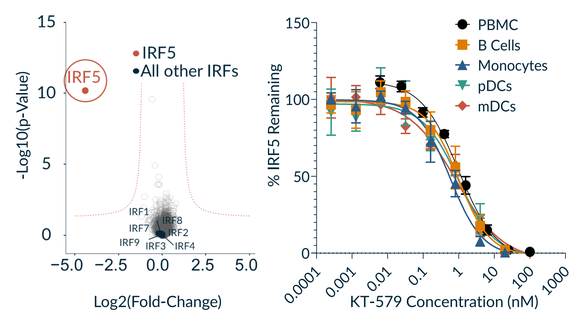
- IRF5 risk variants associate with increased susceptibility to SLE, Sjögren's, RA, SSc, IBD

Degrader Approach: KT-579

- TPD allows for a single and specific binding event to drive depletion of the protein and disrupt all IRF5 signaling

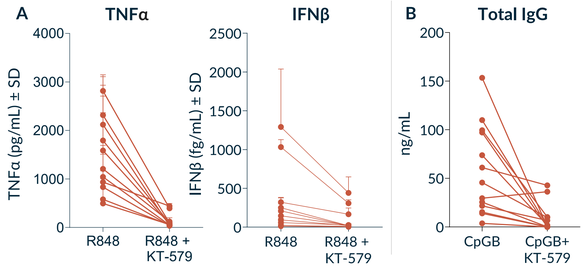
RESULTS

Figure 1. An Exquisitely Selective and Potent Oral IRF5 Degrader



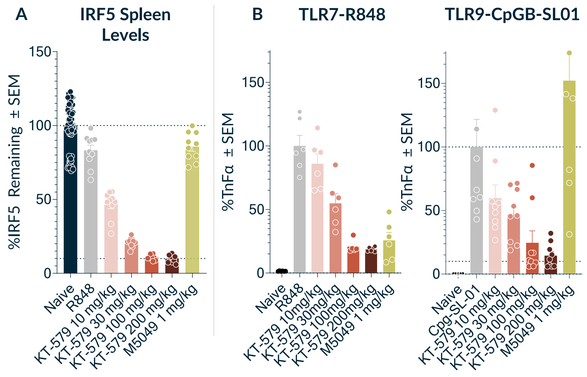
A) KT-579 selectively degrades IRF5 in the detectable proteome (>10,000 proteins) **B)** KT-579 potently degrades IRF5 in key functional cell types.

Figure 2. KT-579 Effectively Blocks TLR induced Pro-inflammatory Cytokines, Type I IFN Induction, and IgG Levels in SLE PBMC Samples



A) KT-579 treatment (100nM) for 24h, followed by 24h of R848 (TLR7/8) stimulation **B)** KT-579 treatment (100nM) and CpG stimulation for 7 days to induced plasmablast differentiation and measure IgG levels.

Figure 3. Orally dosed KT-579 leads to dose-dependent inhibition of TLR7 or TLR9 induced cytokine production

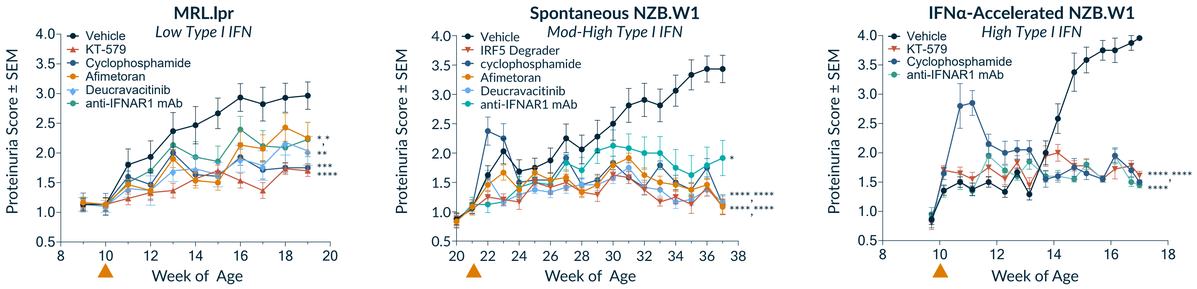


A) IRF5 remaining levels in mouse spleen following 4 days of oral dosing **B)** KT-579 not M5049 (TLR7/8 SMI), blocks both TLR7 and TLR9 induced pro-inflammatory cytokines, including TNFα (shown), IL-6, IL-12p40, IFNβ (not shown).

METHODS

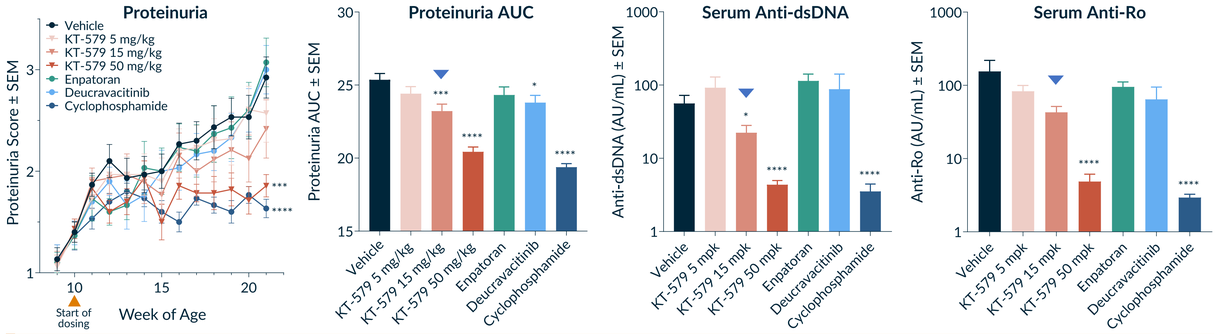
Peripheral blood mononuclear cells (PBMCs) derived from healthy or patient donors were cultured with KT-579 in the presence or absence of TLR7, TLR8 or TLR9 activation to evaluate KT-579 selectivity by global proteomics, potency to degrade IRF5 by flow cytometry or western methods, and functional activity via cytokine release, plasmablast differentiation and IgG release by flow cytometry or ELISA. Following 4x daily oral administration of KT-579, plasma cytokines and IRF5 levels were measured in the spleen in mouse models of acute TLR7 or TLR9 systemic activation. Oral IRF5 degrader or KT-579 doses (100-200mg/kg) achieving maximum IRF5 degradation were tested across the different mouse lupus models. KT-579 or IRF5 degrader, MC049, Deucravacitinib (30mg/kg), Afimetoran (10mg/kg), Enpatoran (1mg/kg) were administered orally via gavage. Cyclophosphamide (50mg/kg) was administered i.p. and anti-IFNAR 20-25mg/kg (5A3) was administered s.c. Comparator doses were selected to cover reported efficacious exposures[2]. Cyclophosphamide was dosed i.p. used as a positive control. KT-579 at doses of 5, 15, and 50mg/kg were orally administered daily in the MRL.lpr lupus mouse model to evaluate dose response effects on relevant lupus disease terminal endpoints subsets. All data are graphed as mean ± error unless otherwise noted.

Figure 4. Orally Administered IRF5 Degrader Leads to Significant Activity across Multiple Lupus Models



All data analyzed using Kruskall-Wallis at Final Time Point: *, p<0.05, ** p<0.005, *** p<0.0005, **** p<0.0001, reporting data from final measurement ▲ = Start of Dosing

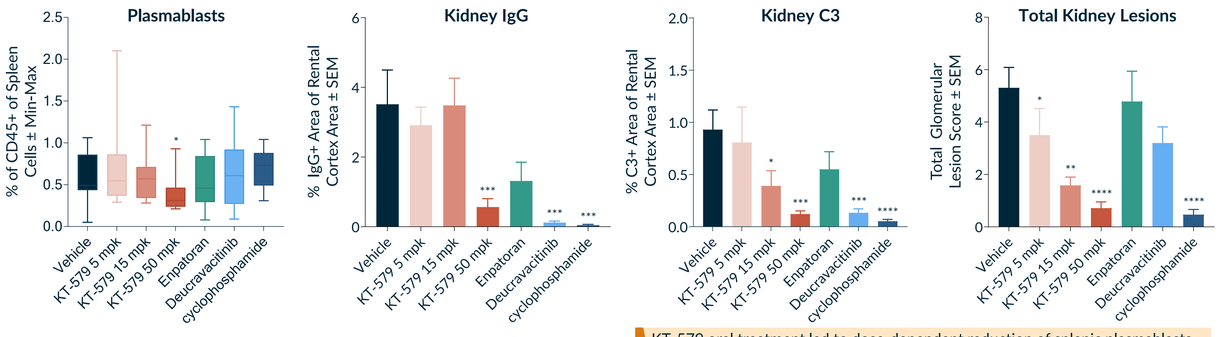
Figure 5. KT-579 Dose-dependent Reduction of Systemic Disease Biomarkers in the MRL.lpr Lupus Model

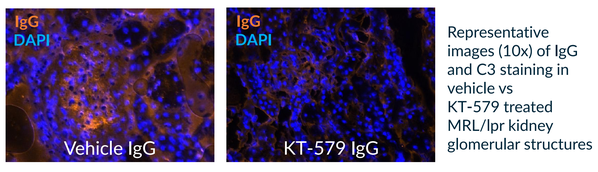


KT-579 daily oral treatment led to dose-dependent reduction of proteinuria and serum autoantibodies measured at terminal collection better than targeted comparators tested. Doses achieving 50% (▼) or greater IRF5 degradation in the spleen demonstrated activity, with consistent and significant activity achieved at KT-579 highest dose.

Proteinuria: Mixed-Effects Model with Geisser-Greenhouse: *** p<0.0005, **** p<0.0001 ; Proteinuria AUC: One Way ANOVA: * p<0.05, *** p<0.005, ****p<0.0001; Anti-dsDNA, Anti-Ro: Kruskal Wallace: * p,0.05, *** p<0.005, **** p<0.0001

Figure 6. KT-579 significantly reduces plasmablasts, kidney IgG deposition and C3, and inhibits kidney disease progression in the MRL.lpr Lupus Model





Representative images (10x) of IgG and C3 staining in vehicle vs KT-579 treated MRL/lpr kidney glomerular structures

KT-579 oral treatment led to dose-dependent reduction of splenic plasmablasts, kidney disease biomarkers, and total kidney lesions assessed at terminal collection

Plasmablast: Welch ANOVA: *- p<0.05, ** p<0.01, *** p<0.005; Kidney IgG, Kidney C3, Total Kidney Lesions: Kruskal-Wallis test: ** p<0.01, ***p<0.001, **** p<0.0001

CONCLUSIONS

- KT-579 is an oral, selective and potent IRF5 degrader that demonstrates significant activity across multiple lupus models with low to high Type I IFN signaling, including a dose-dependent reduction of human disease-relevant lupus biomarkers
- These findings position KT-579 as a potential first-in-class oral approach capable of broadly modulating pathogenic pathways in lupus and other autoimmune diseases The Phase 1 healthy volunteer clinical trial is ongoing, with data expected 2H 2026

REFERENCES & DISCLOSURES

1.Wen, L., et al. Toll-like receptors 7 and 9 regulate the proliferation and differentiation of B cells in systemic lupus erythematosus. Frontiers 2023. (PMID: 36875095)
2. Burke, J.R., et al. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 psuedokinase domain. Science Transl. Medicine 2019 (PMID: 31341059)

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