Potent and Selective Oral IRF5 Degrader, KT-579, Demonstrates *in vitro* and *in vivo* Activity Comparable or Superior to Approved or Clinically Active Agents in Human Cellular Assays and Lupus Efficacy Models

#0913

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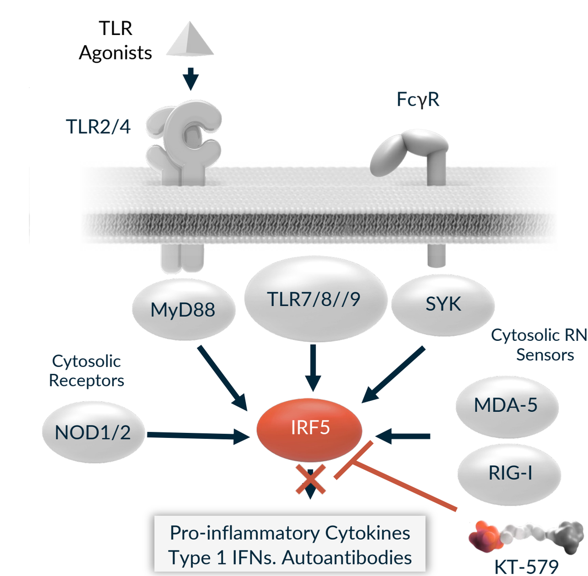
INTRODUCTION

IRF5 is a transcription factor and regulator of immune responses activated downstream of pattern recognition receptors, in particular endosomal toll-like receptors (TLR), TLR7, TLR8 and TLR9. IRF5 regulates pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-23), autoantibody production and Type I IFN, and is selectively expressed and activated in specific cell types such as dendritic cells, monocytes, macrophages, and B cells. Human genetic and functional studies have linked IRF5 in the pathogenesis of multiple autoimmune diseases, including SLE, RA, and Sjögren's, and *Irf5*-deficient mice are protected from lupus onset and severity[1]. In SLE, endosomal TLRs recognize nuclear self-antigens, triggering IRF5 activation and driving the breakdown of immune tolerance via a cascade involving B cell activation, autoantibody and pro-inflammatory cytokine production. 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. KT-579, an oral IRF5 degrader, has demonstrated potent and selective activity in preclinical studies, offering a novel approach to modulating this key driver of immunity.

IRF5 Biology and Target Rationale



Target Biology and Rationale

- Impaired function of endosomal TLR signaling contributes to SLE pathogenesis[2]
- IRF5 regulates pro-inflammatory cytokines, Type I IFN and autoantibody production in a cell and activation-specific manner, including downstream of endosomal TLR7, TLR8 and TLR9 activation

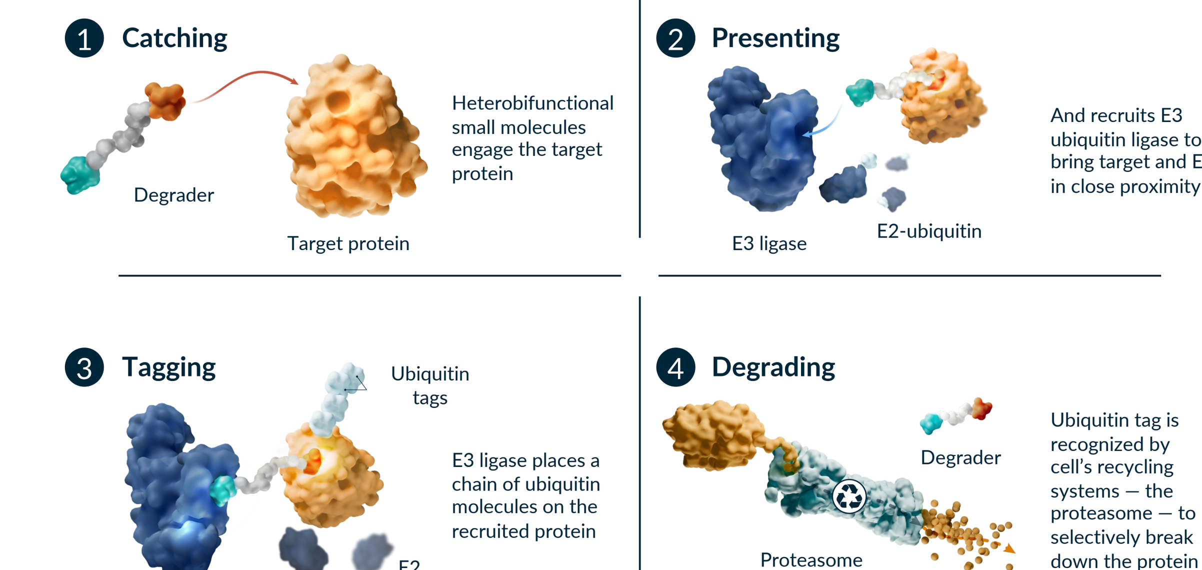
Genetically and Clinically Validated

- IRF5 functional risk variants associate with increased susceptibility to SLE, Sjögren's, RA, IBD, and SSc1, 2
- IRF5 regulated pathways have been clinically validated by multiple drugs (i.e. TLR7/8, anti-IFN, -TNF, IL-6, IL-12, IL-23 Ab, B cell targeting agents)

IRF5 Degrader Advantage

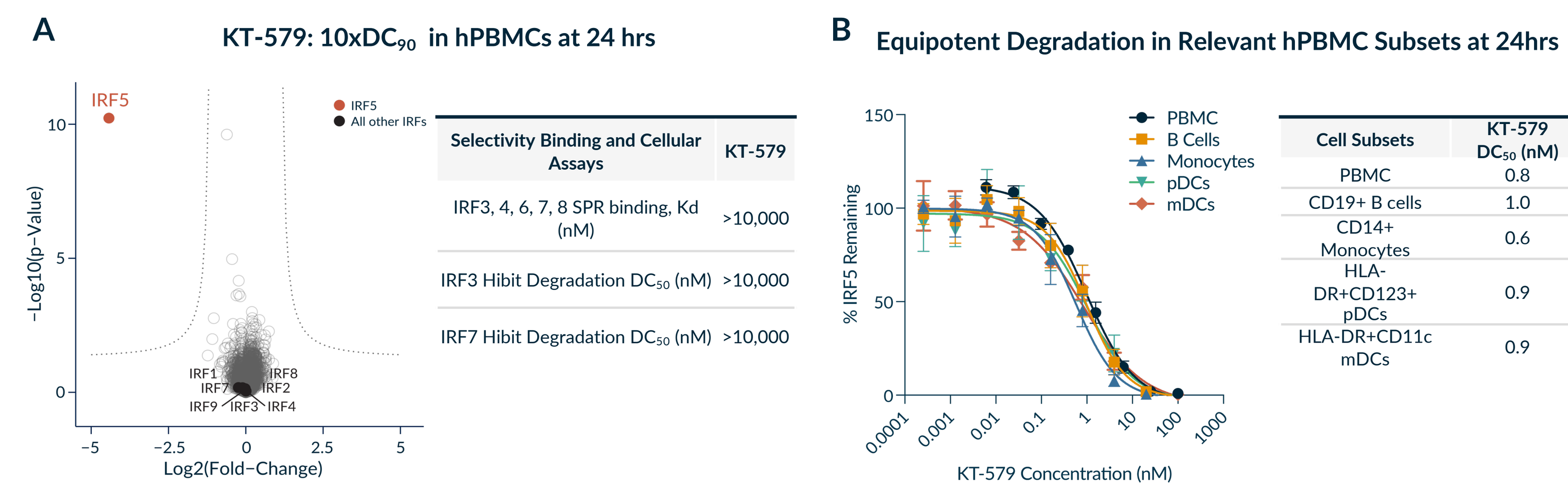
- Conventional approaches have failed to effectively and selectively block IRF5 due to multiple activation steps and IRF family member homology
- TPD allows for a single and specific binding event to drive depletion of the protein and disrupt all IRF5 signaling

Proteome Editing with Targeted Protein Degradation



RESULTS

Figure 1. KT-579: An Exquisitely Selective and Potent Oral IRF5 Degrader

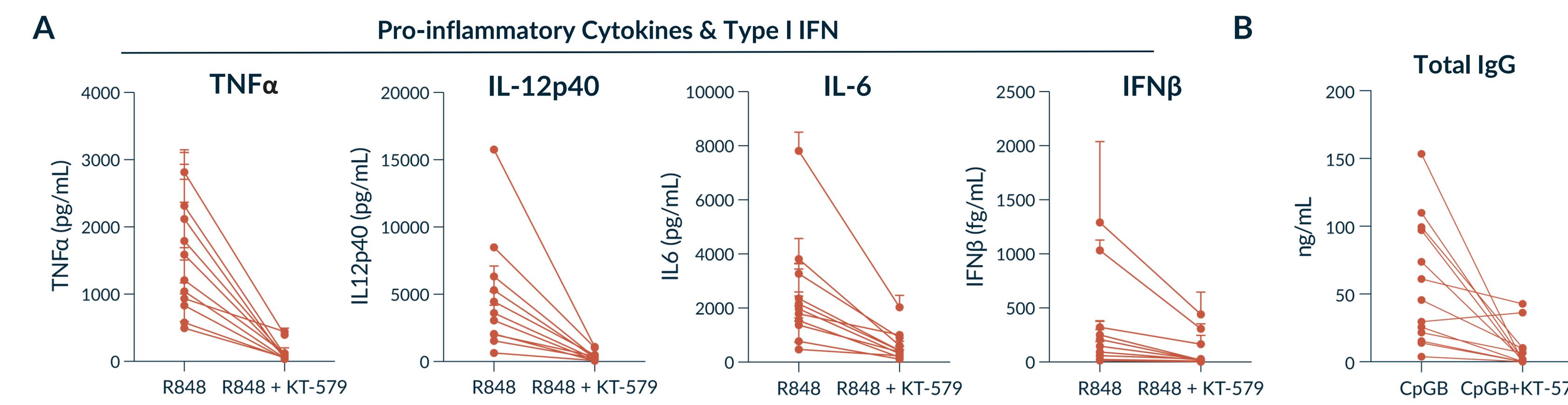


Selectivity Binding and Cellular Assays	KT-579
IRF3, 4, 6, 7, 8 SPR binding, Kd (nM)	>10,000
IRF3 Hibit Degradation DC_{50} (nM)	>10,000
IRF7 Hibit Degradation DC_{50} (nM)	>10,000

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

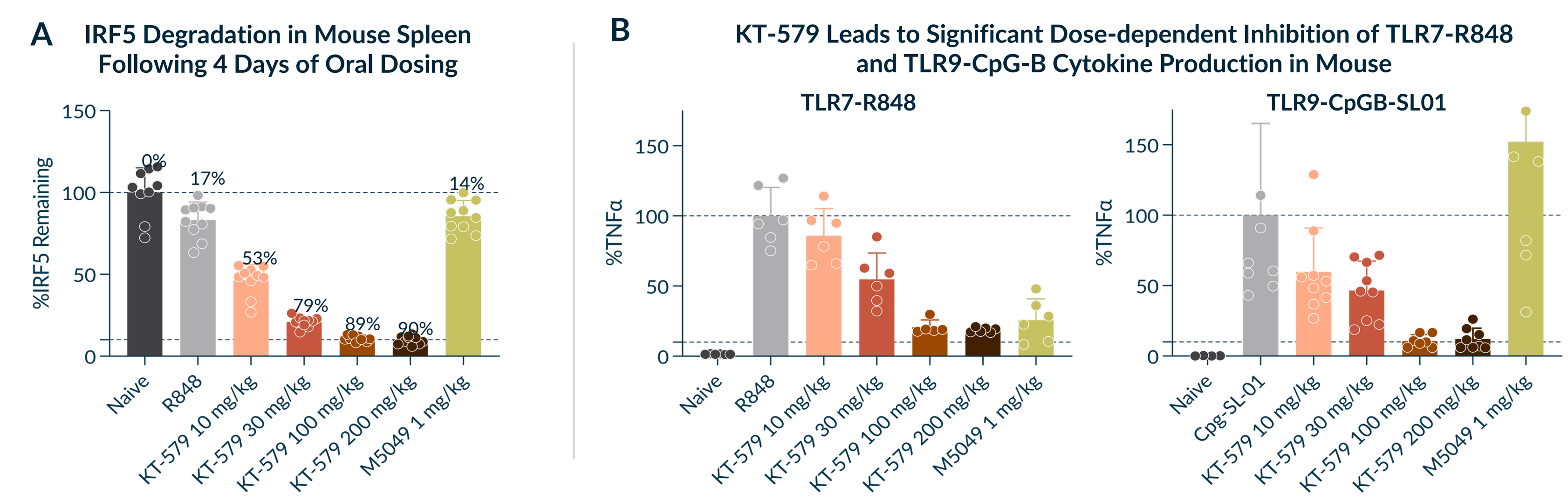
A) KT-579 selectively degrades IRF5 in the detectable proteome (>10,000 proteins) B) KT-579 potently degrades IRF5 in key functional cell types

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



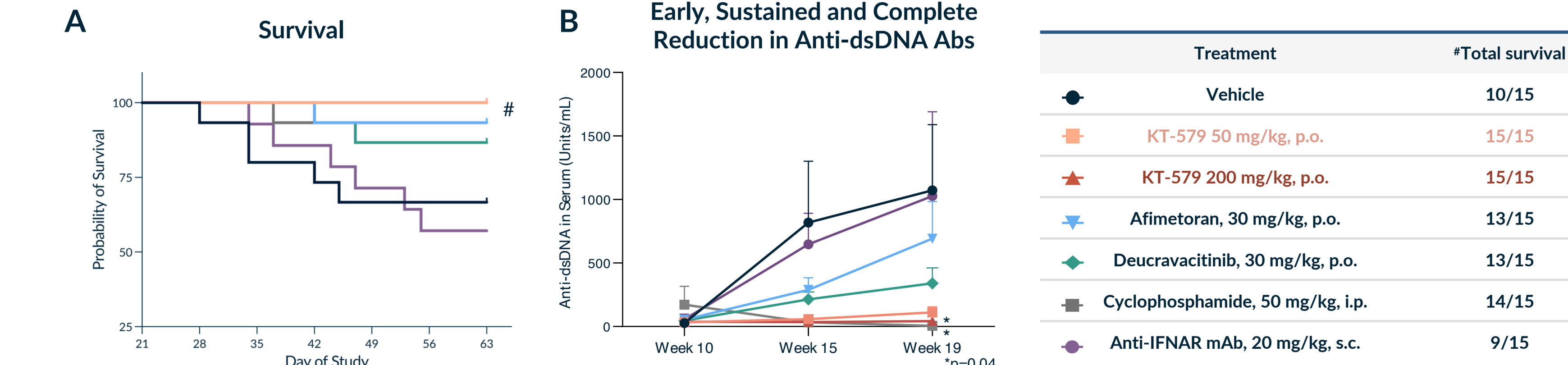
A) KT-579 inhibits pro-inflammatory cytokines and Type I IFN that are commonly elevated in autoimmune diseases. Degrader treatment (100nM) for 24h, followed by 24h of R848 (TLR7/8) stimulation. B) In a 7-day culture, KT-579 inhibits TLR9 (CpG-B) induced plasmablast differentiation (data not shown) and IgG production

Figure 3. Orally dosed KT-579 Effectively Degrades IRF5 and Blocks Circulating Cytokines in Acute Systemic TLR Stimulation Mouse Models



A) KT-579 induced on average a max of 90% IRF5 degradation in mouse spleen tissue. 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)

Figure 4. KT-579 Demonstrates Better Outcomes than Approved or Clinically Active Drugs in the MRL/lpr Spontaneous Mouse Model of Lupus



Treatment	#Total survival
Vehicle	10/15
KT-579 50 mg/kg, p.o.	15/15
KT-579 200 mg/kg, p.o.	15/15
Afimetoran, 30 mg/kg, p.o.	13/15
Deucravacitinib, 30 mg/kg, p.o.	13/15
Cyclophosphamide, 50 mg/kg, i.p.	14/15
Anti-IFNAR mAb, 20 mg/kg, s.c.	9/15

MRL/lpr mice have a susceptible genetic background and single inactivating mutation in Fas gene, quickly developing lupus-like symptoms and manifestations. **A)** KT-579 daily oral dosing was well tolerated, and all mice in both dose groups survived the length of the study, unlike the comparators. #KT-579 50 mg/kg p.o. and 200 mg/kg p.o. lines are overlapping. **B)** Only KT-579 and cyclophosphamide significantly reduced anti-dsDNA through end of the study, better than all other approved or clinically active mechanisms tested.

Figure 5. KT-579 Significantly Reduces Pathogenic Autoantibody Producing B Cell Subsets in the Spleen of of MRL/lpr Mice (week 19)

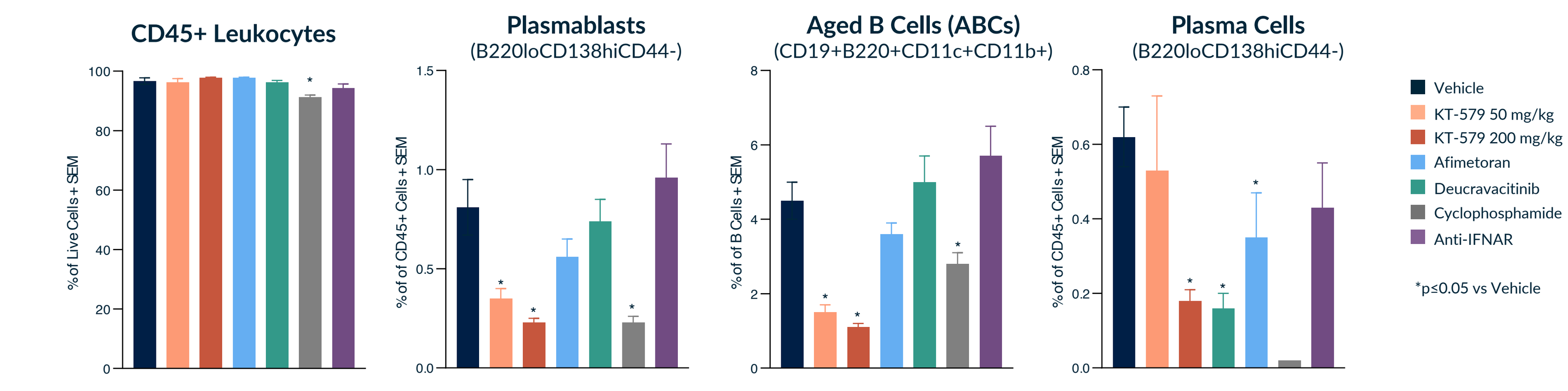
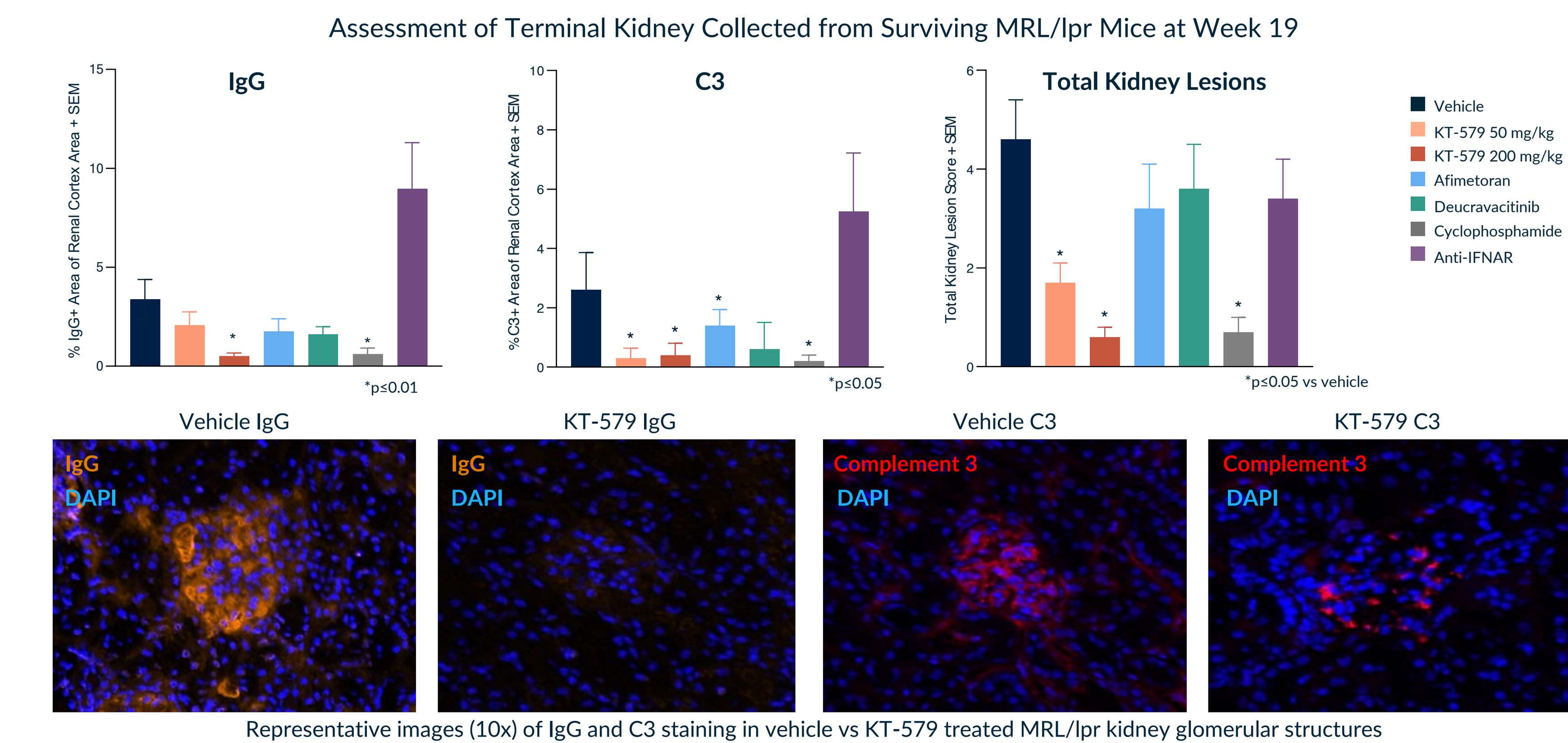


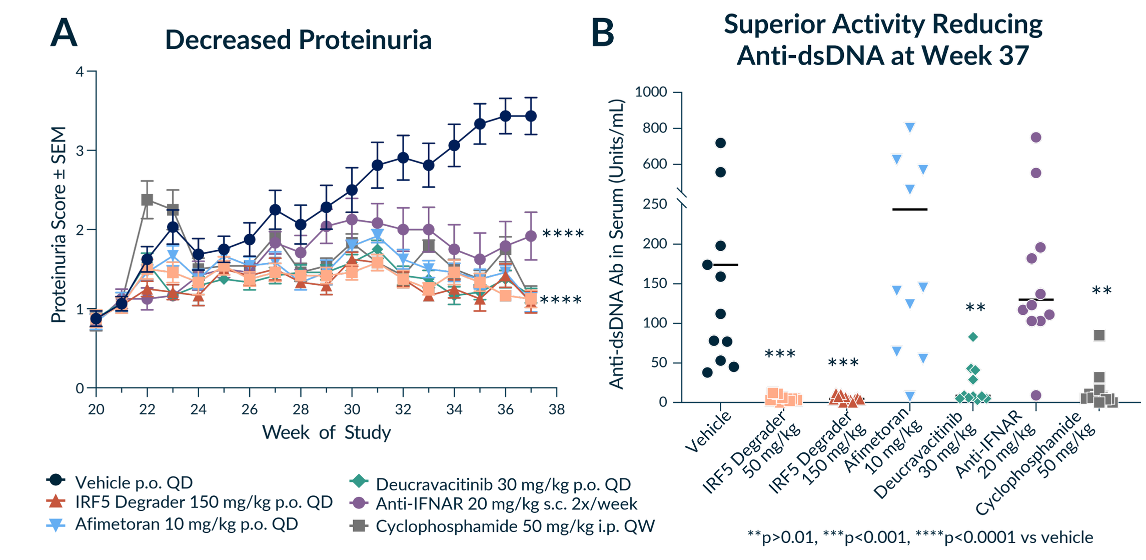
Figure 6. KT-579 Significantly Decreases IgG, Complement 3 (C3) and Renal Disease Progression

Assessment of Terminal Kidney Collected from Surviving MRL/lpr Mice at Week 19



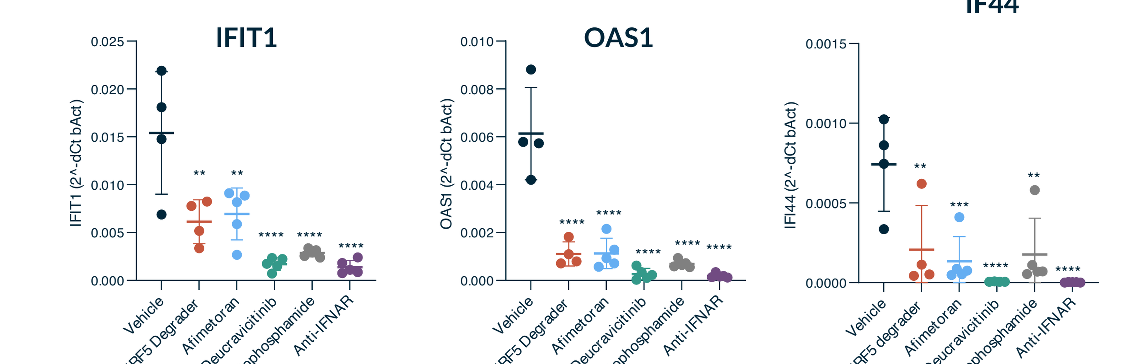
Representative images (10x) of IgG and C3 staining in vehicle vs KT-579 treated MRL/lpr kidney glomerular structures

Figure 7. IRF5 Degradation Demonstrates Generally Better Outcomes than Approved or Clinically Active Drugs in NZB.W1 Spontaneous Mouse Lupus Model



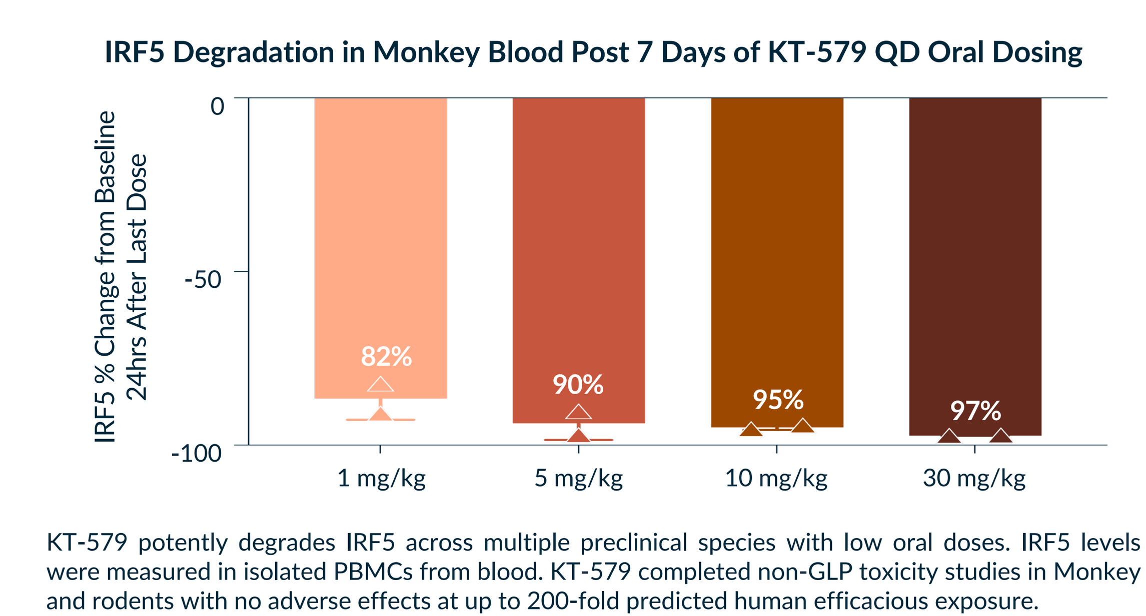
IRF5 degrader, dosed once a day for 107 days, resulted in ~80% and ~90% IRF5 degradation in spleen, and led to **A)** decreased proteinuria and **B)** sustained reduction of serum anti-dsDNA Abs superior or similar to standard of care, approved and clinically active mechanisms tested.

Figure 8. Significant Inhibition of ISGs in Blood from NZB.W1 Mice at Terminal Collection (week 37)



KT-579 (150mg/kg shown) significantly reduces key interferon genes in the blood from NZB.W1 mice comparable to other test agents. **p≤0.01, **** p≤0.0001 vs vehicle.

Figure 9. KT-579 Potently Degrades at Low Oral Doses in NHP with an Excellent Safety Profile



KT-579 potently degrades IRF5 across multiple preclinical species with low oral doses. IRF5 levels were measured in isolated PBMCs from blood. KT-579 completed non-GLP toxicity studies in Monkey and rodents with no adverse effects at up to 200-fold predicted human efficacious exposure.

METHODS

- *In vitro* cell cultures 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.
- Peripheral blood mononuclear cells (PBMCs) derived from healthy or SLE donors were cultured with KT-579 and stimulated with TLR7/8 (R848) to assess impact on cytokine release or TLR9 (CpG-B) to assess impact on IgG secretion.
- *In vivo* studies: KT-579 or IRF5 degrader, MC049, Deucravacitinib or Afimetoran were administered orally via gavage. Cyclophosphamide was administered i.p. and anti-IFNAR (5A3) was administered s.c. Comparator doses selected based on reported preclinical *in vivo* studies[3]. KT-579 induced IRF5 degradation was assessed by western in spleen following 4 daily doses. In the acute TLR studies, R848 or CpG-B-ODN2006 were injected and blood samples collected 4 or 6 hours post stimulation, respectively. Cytokines were assessed by multiplex MSD assays.
- In the MRL/lpr lupus mouse model, treatment for all compounds was initiated at week 10 and the study was terminated at week 19. Serum anti-dsDNA was assessed by ELISA at week 10, 15 and 19. All other endpoints were assessed at terminal collection. Anti-dsDNA serum levels were assessed by ELISA, and splenocyte suspensions were evaluated by flow. IgG and complement (C3) were assessed by IF staining. Periodic Acid-Schiff staining (PAS) was performed to determine total kidney lesions. Total kidney lesions was a composite score of glomerular, tubular and interstitial lesions.
- In the NZB.W1 lupus mouse model, treatment was initiated at week 21 and the study was terminated at week 37. Proteinuria was assessed weekly. RNA was extracted from blood at week 37 for q-RT-PCR assessment of interferon stimulated genes (ISGs).
- 2-tailed Student t test, or One-Way ANOVA was used for statistical analysis.

CONCLUSIONS

We report here the first potent, selective, oral IRF5 degrader development candidate, KT-579, which depletes IRF5 in human primary cells, SLE patient derived cells, and lupus disease models, demonstrating superior activity to existing comparators tested. *In vivo*, KT-579 demonstrated promising preclinical safety profile in rodents and monkeys achieving >90% degradation. These findings position KT-579 as a novel, first-in-class, oral therapeutic agent with the potential to transform the treatment landscape of lupus and multiple autoimmune diseases driven by IRF5 dysregulation. Phase I clinical testing expected in early 2026.

REFERENCES

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DISCLOSURES

This study was funded by Kymera Therapeutics. Campbell, Zhang, Massa, Leedberg, Corcoran, Lurier, Camire, Carroll, Ho, Chen, Enerson, Mehovic, Zhao, Howarth, Breitkopf, Martinez, Ford, Fei, Sathappa, Williams, Weiss, Shabbir, Mainolfi are Kymera Therapeutics employees and equity owners.