KYMERA 10 EST. 2016



First-in-Class Oral IRF5 Degrader, KT-579, Demonstrates Significant Activity Alone or in the Presence of Background Therapies in Preclinical Lupus Models

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American College of Rheumatology Convergence | November 2026

Forward Looking Statements

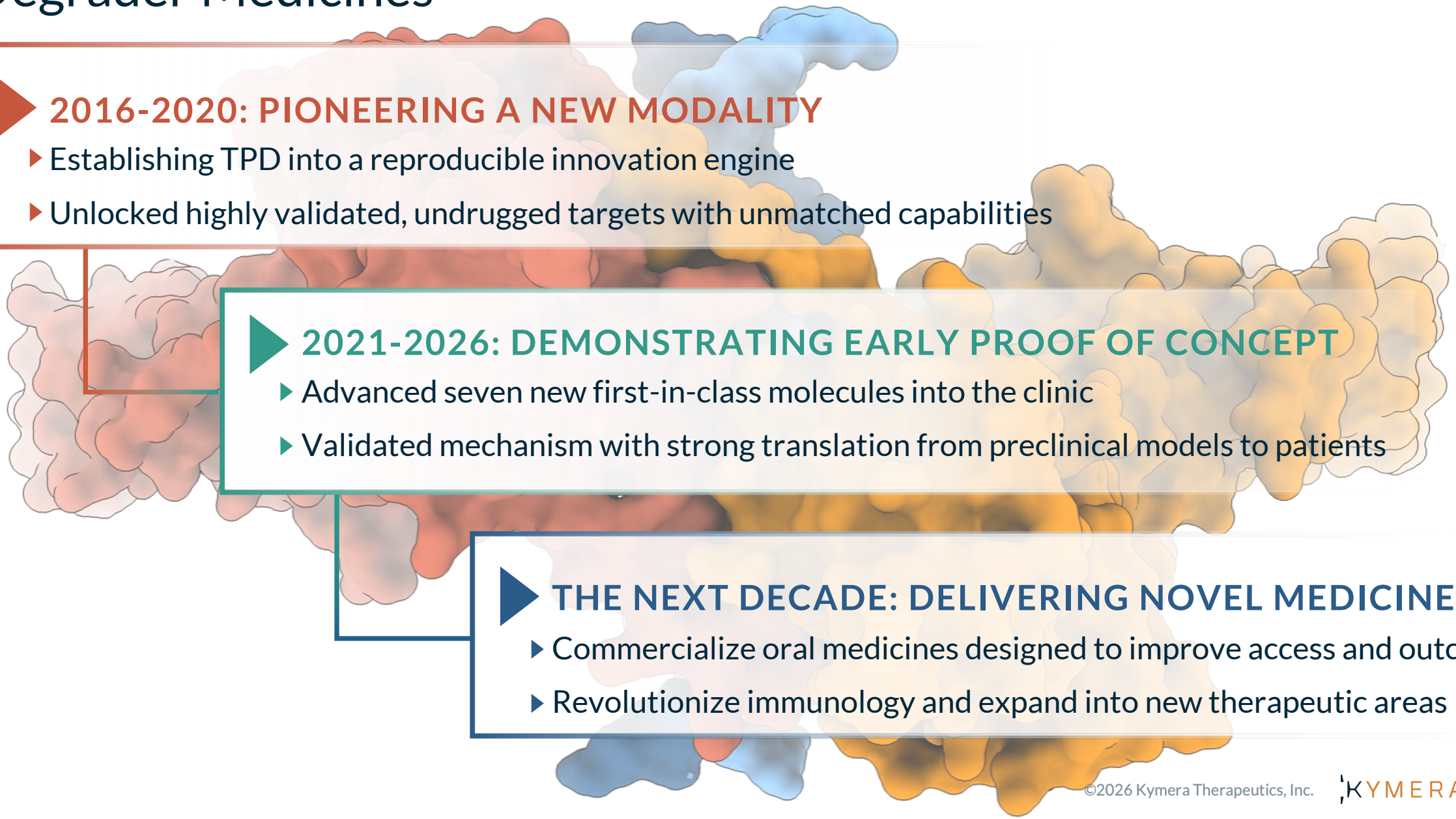
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Kymera: Industry Leader in Developing Oral Small Molecule Degrader Medicines



2016-2020: PIONEERING A NEW MODALITY

- Establishing TPD into a reproducible innovation engine
- Unlocked highly validated, undrugged targets with unmatched capabilities

2021-2026: DEMONSTRATING EARLY PROOF OF CONCEPT

- Advanced seven new first-in-class molecules into the clinic
- Validated mechanism with strong translation from preclinical models to patients

THE NEXT DECADE: DELIVERING NOVEL MEDICINES

- Commercialize oral medicines designed to improve access and outcomes
- Revolutionize immunology and expand into new therapeutic areas

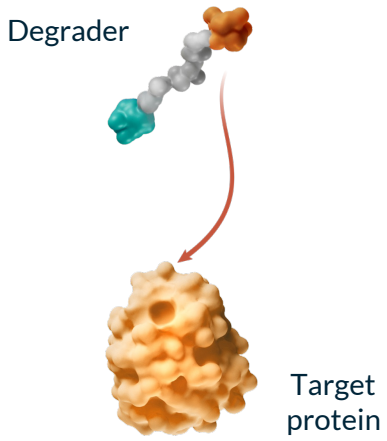
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Targeted Protein Degradation: Achieving Biologics-like Activity with Oral Medicines

Targeted Protein Degradation (TPD) Mechanism of Action

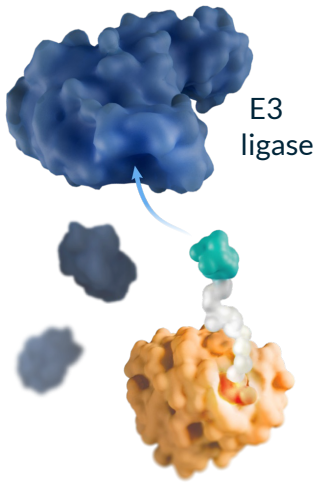
Harnessing the E3 Ubiquitin Proteasome System

1 Catching the Target Protein

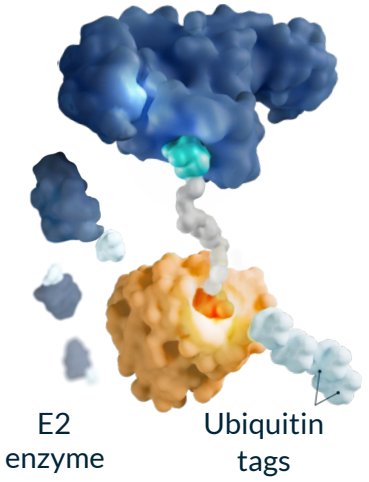


Degrader molecule engages target protein and E3 ubiquitin ligase to bring them in close proximity

2 Presenting the Target Protein

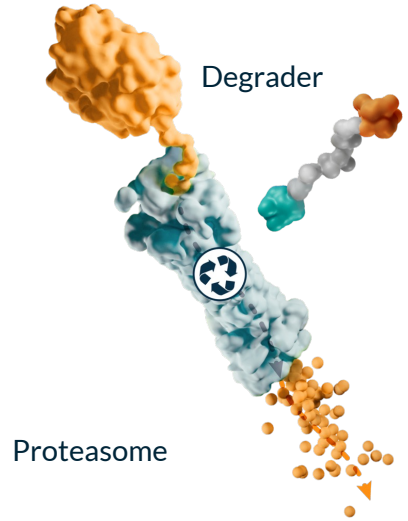


3 Tagging the Target Protein



E3 ligase places a chain of ubiquitin molecules on the target protein

4 Degrading the Target Protein



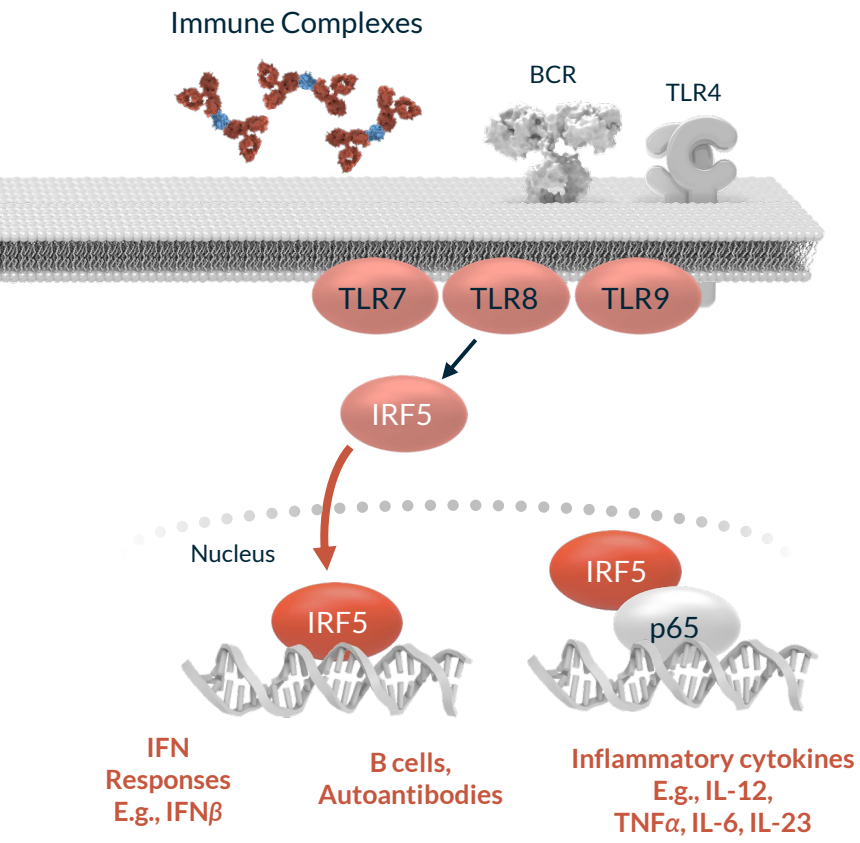
Ubiquitin is recognized by the proteasome to selectively degrade the target protein

Catalytic activity of degraders enables a single molecule to drive degradation of multiple copies of the target protein, delivering deep and continuous pathway blockade with biologics-like activity in a pill

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IRF5 a Central Driver of Immune Dysregulation in Autoimmune Diseases

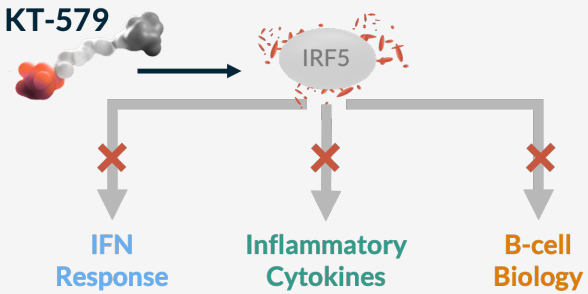
Chronic, Dysregulated Activation



IRF5 Hyperactivation

Persistent Inflammation, Tissue Damage

IRF5 is a transcription factor and central node connecting three clinically validated inflammatory pathways



- IRF5 is a member of the interferon regulatory family (IRF) of proteins and is activated in a context dependent manner (cell and stimulant dependent)
- IRF5 is **predominantly expressed and activated** in immune cell types: Dendritic Cells (DCs), Monocytes, Macrophages, and B cells
- In normal controlled immune responses, IRF5 is transiently activated by pattern recognition receptors (PRRs) with quick inflammation resolution
- In **autoimmune** diseases, like SLE, endosomal TLR **chronic activation** locks IRF5 into a hyperactive state leading to **amplified** upregulation of **pro-inflammatory and disease-defining pathways**
- IRF5 risk variants and functional hyperactivation associate with increased signaling in multiple clinically validated pathways **(Type I IFN, Cytokines, Autoantibodies)**
- KT-579 selectively degrades IRF5 and **enables simultaneous modulation** of multiple dysregulated disease-defining pathways

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IRF5 is a Genetically Validated Target in SLE

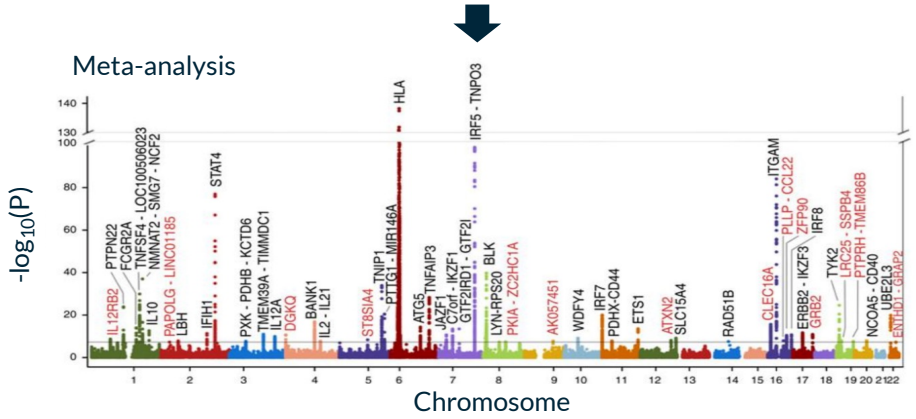
Human Genetics

- Multiple GWAS studies identify IRF5 as an autoimmune susceptibility gene[1]
- IRF5 risk haplotypes and hyperactivated IRF5 levels in SLE patients associated with high serum IFNα levels and autoantibodies

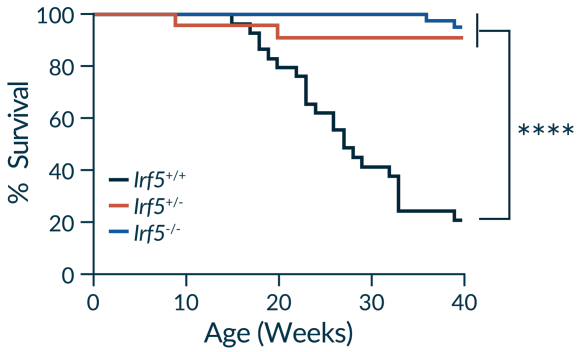
Mouse IRF5 KO Studies

- KO mice are viable and fertile; with normal B cell development
- IRF5 KO mouse can protect or attenuate disease in models of SLE
- In a mouse model of lupus IRF5 plays an essential role in lupus pathogenesis, that is independent of Type I IFN pathways[2]

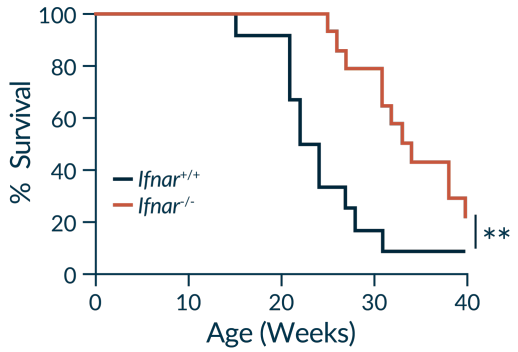
Meta-analyses Identified IRF5 as a Risk Locus for SLE



IRF5 KO Increases Survival and has Essential Role in Lupus



Type I IFN Modestly Protects Against Lupus



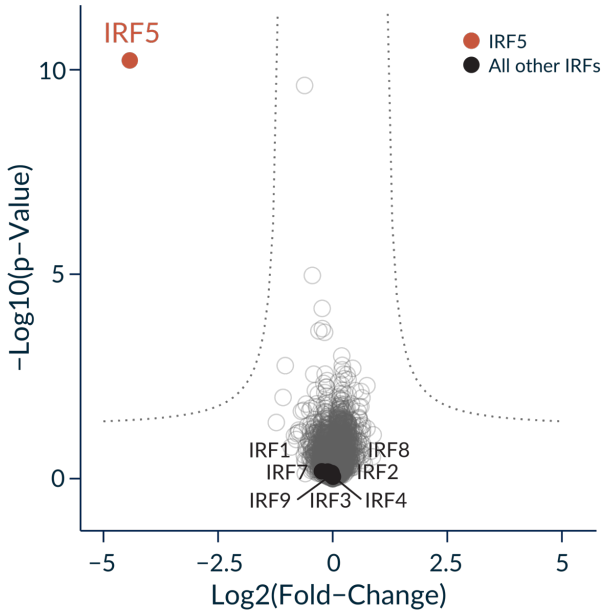
FcyIIB-/-, Yaa lupus mouse model

[1]Santana-de Anda et al. *Autoimmunity Reviews.* 2011; [2]Richez et al. *J Immunol.* 2010.; ****$p < 0.0001$; **$p = 0.0043$.

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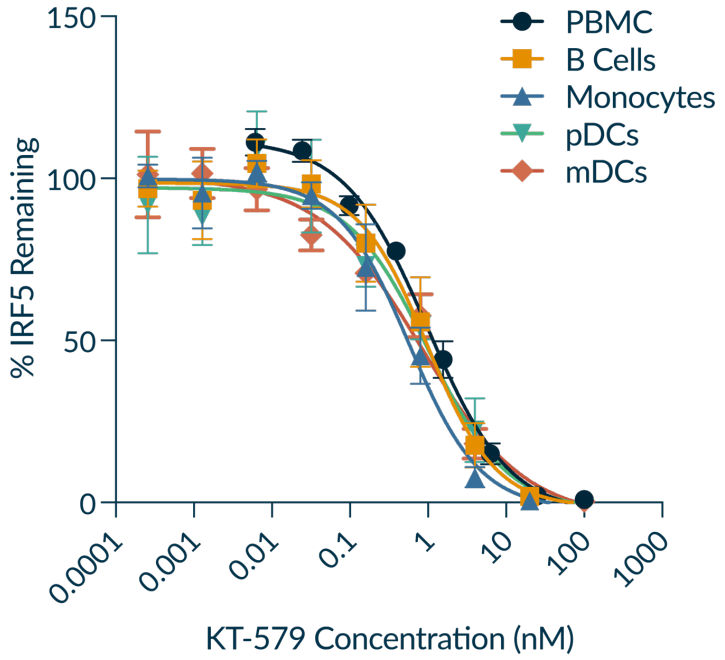
KT-579: An Exquisitely Selective and Potent Oral IRF5 Degrader

KT-579: 10xDC$_{90}$ in hPBMCs @ 24 hrs



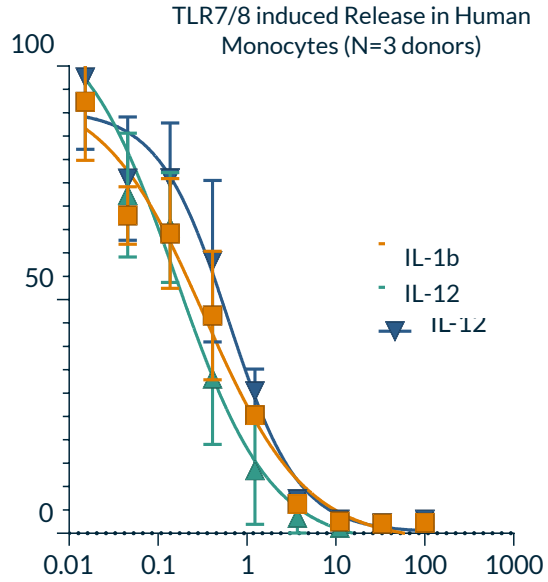
Selectivity Binding and Cellular Assays	KT-579
IRF3, 4, 6, 7, 8 SPR binding, Kd (nM)	>10,000
IRF3 Degradation DC$_{50}$ (nM)	>10,000
IRF7 Degradation DC$_{50}$ (nM)	>10,000

Equipotent Degradation in Relevant hPBMC Subsets @ 24hrs



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

Full Inhibition of IRF5 Regulated Cytokines

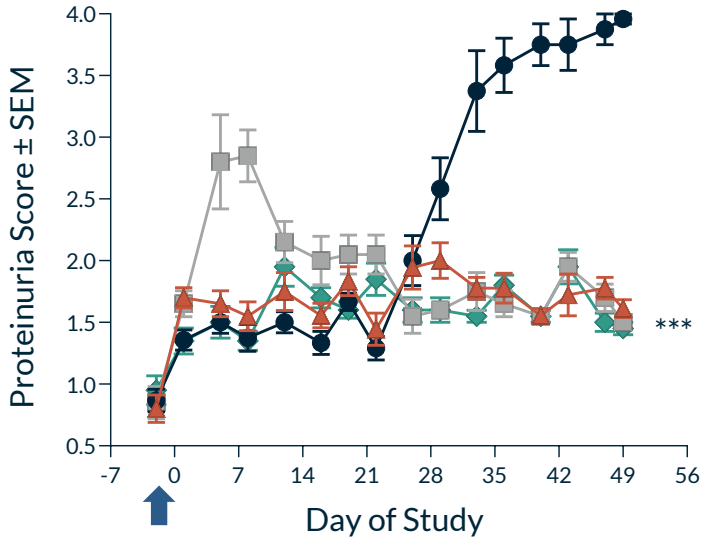


Demonstrated functional inhibition in both healthy and SLE derived PBMCs

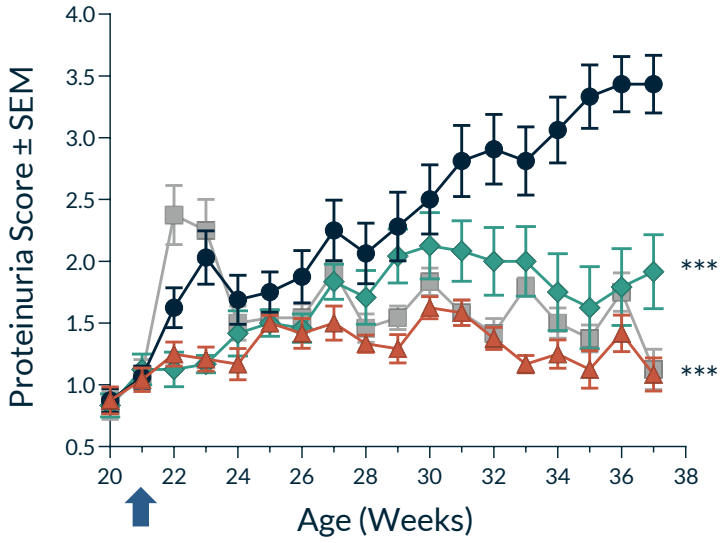
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In vivo Oral IRF5 Degrader Treatment Leads to Significant Single Agent Activity Across Multiple Mouse Models of Lupus

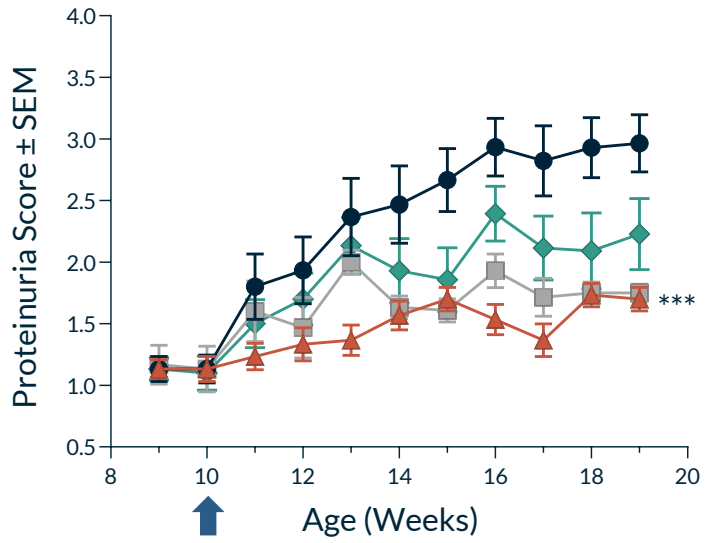
IFN-α Accelerated NZBWF1
High Blood IFN



Spontaneous NZBWF1
Moderate Blood IFN



MRL.lpr
Low Blood IFN



Treatment initiated

Vehicle | IRF5 Degrader | anti-IFNARI 5A3 mAb | Cyclophosphamide

Activity achieved at >80% IRF5 degradation

- The robust *in vivo* preclinical activity of IRF5 degradation highlights the potential for this differentiated mechanism and multifaceted approach to address the heterogeneity and complexity of lupus disease
- KT-579 consistently demonstrated significant decrease of human disease relevant blood and tissue biomarkers (e.g., circulating autoantibodies, ISGs, IgG/C3, PB/ABCs)

One-way AOVA , multiple comparisons vs Vehicle control *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001.

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KT-579 Preclinical Characterization in Presence of Common Background Therapies

1. **How does KT-579 compare with prednisolone and HCQ activity?**

2. **Does HCQ interfere with KT-579 B cell activity?**
   HCQ modifies lysosomal function

3. **Does KT-579 have steroid sparing activity?**
   In vivo low-dose vs high-dose prednisolone

Human Primary Cells



- ✓ Degradation potency
- ✓ TLR induced cytokine inhibition
- ✓ B cell functional assays

NZBW1 Lupus Model

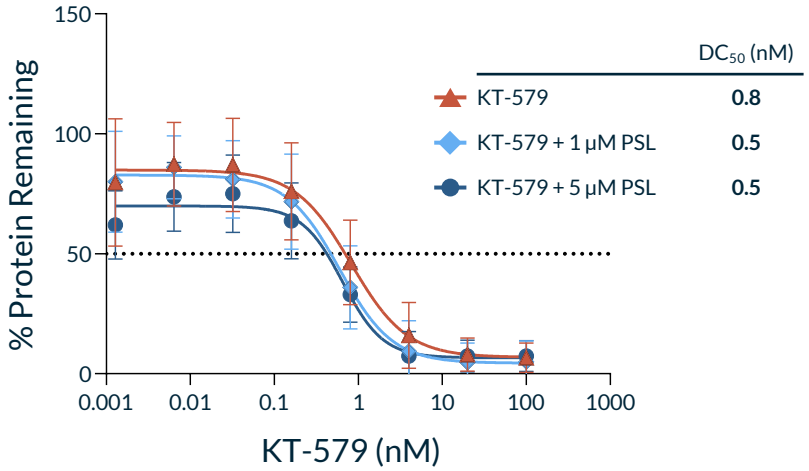
- ✓ Low and high dose of PSL (equivalent ~5 vs 50mg human dose exposure)
- ✓ Included HCQ (equivalent to ~400mg human total exposure)

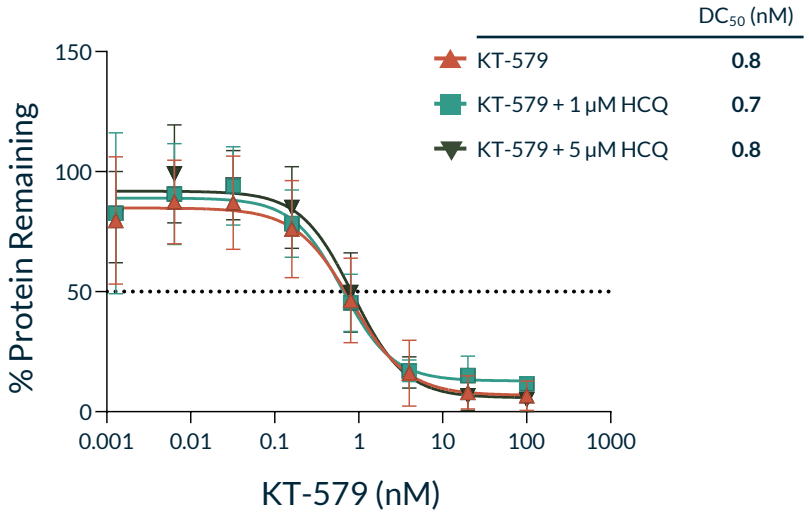
PSL= prednisolone
HCQ=Hydroxychloroquine

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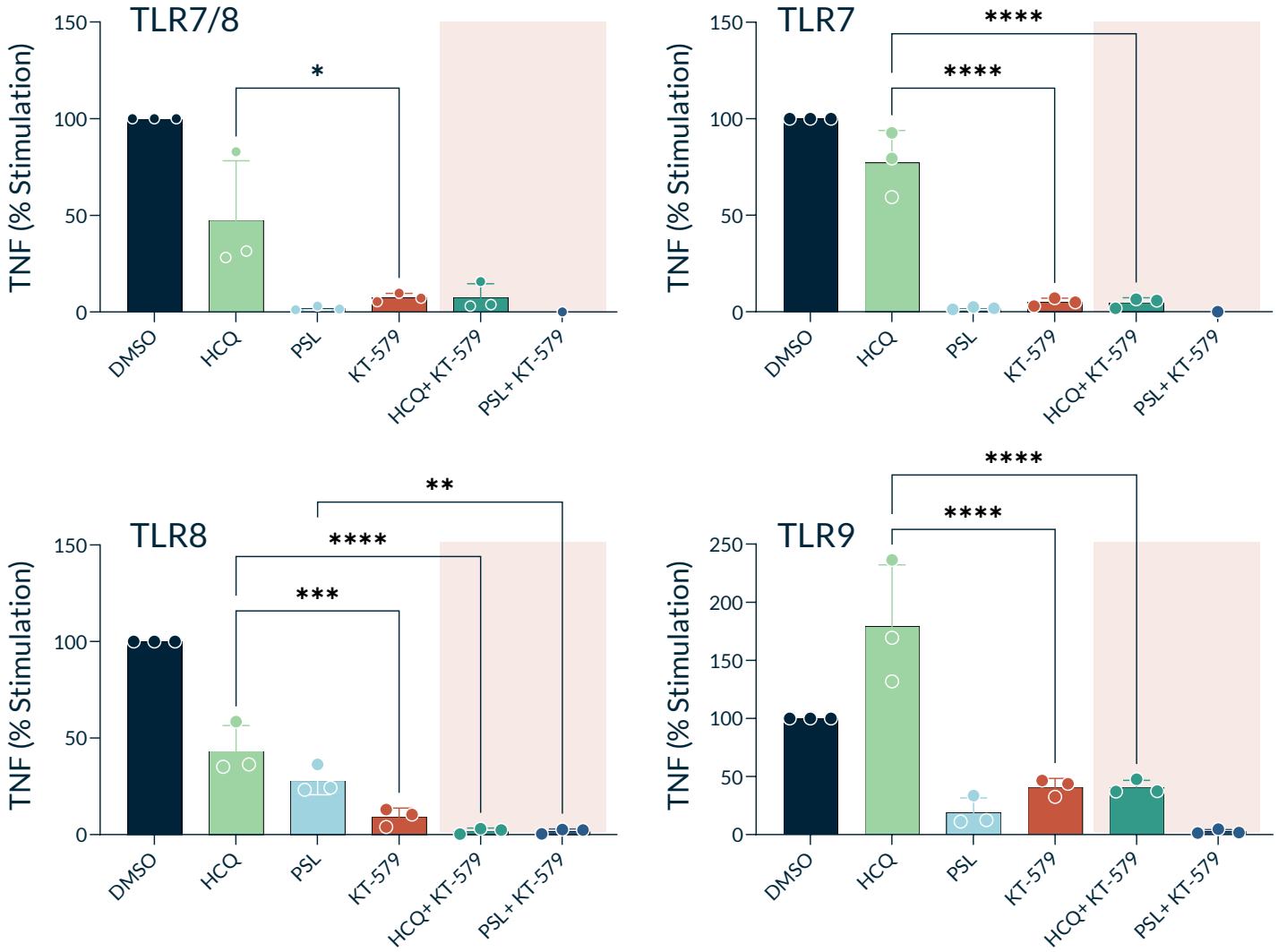
KT-579 Potent PBMC Activity in the Presence of Prednisolone or Hydroxychloroquine

IRF5 Degradation





TLR Induced Cytokine Inhibition

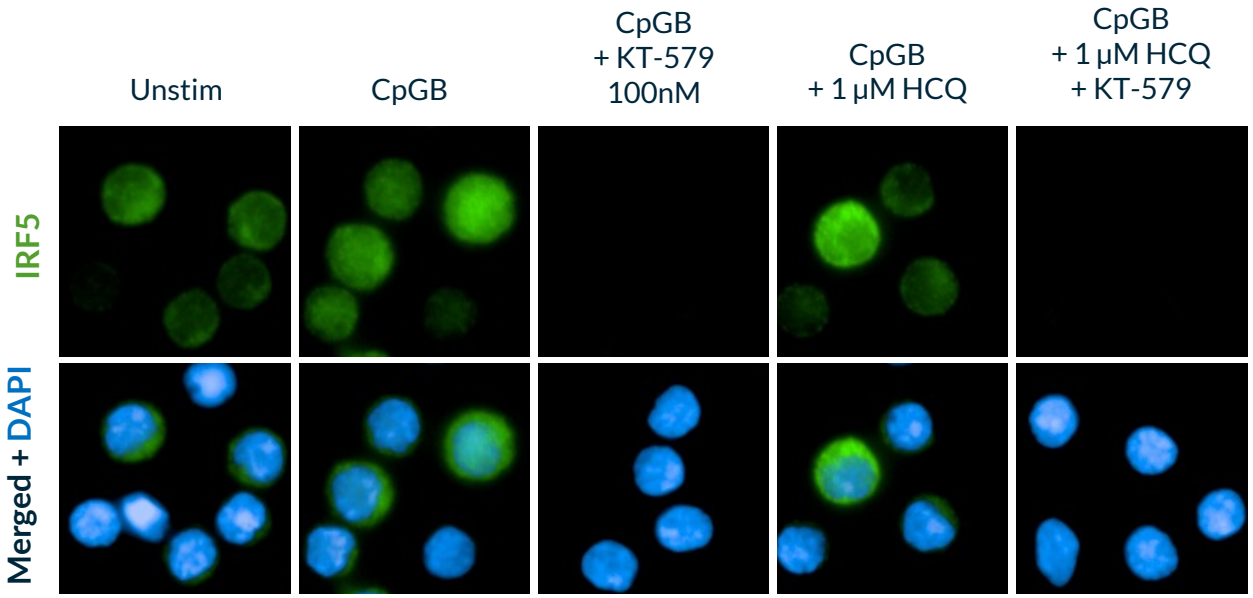


One-way AOVA , multiple comparisons *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001.

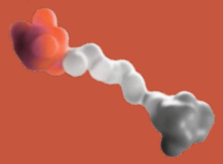
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KT-579, Not Hydroxychloroquine, Inhibits TLR9 Induced Plasmablast Differentiation and IgG Production

KT-579 Blocks TLR9 Induced IRF5 Nuclear Translocation

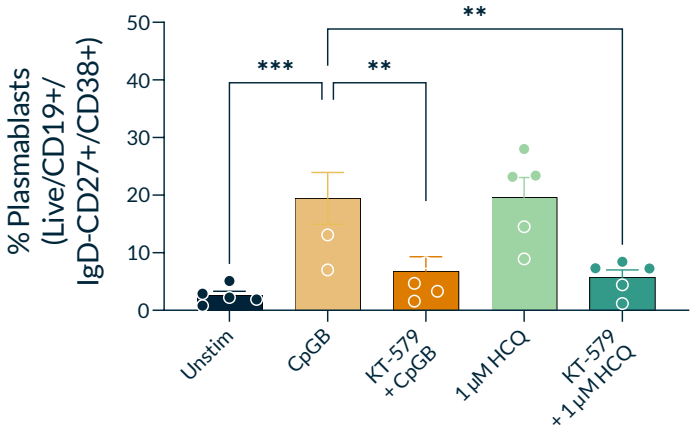


Isolated B cells are pretreated with compounds for 24hrs and then stimulated with TLR9 agonist

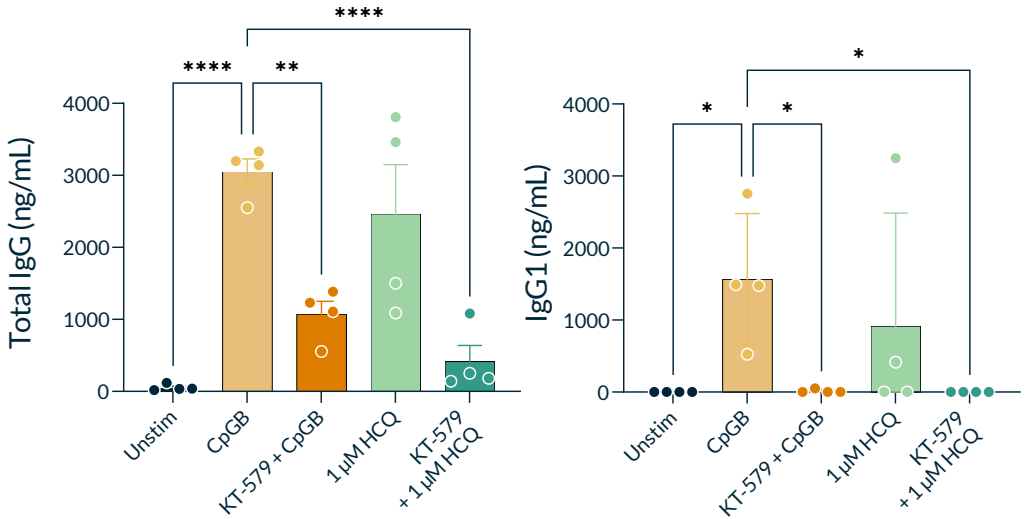


KT-579 demonstrates B-cell activity in the presence of HCQ

KT-579 Inhibits Human Plasmablast Differentiation in Short-term Culture



KT-579 Reduces IgG Production



One-way AOVA , multiple comparisons vs CpGB control *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001.

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KT-579 Preclinical Characterization in Presence of Common Background Therapies

1. **How does KT-579 compare with prednisolone and HCQ activity?**

2. **Does HCQ interfere with KT-579 B cell activity?**
   HCQ modifies lysosomal function

3. **Does KT-579 have steroid sparing activity?**
   low-dose vs high-dose prednisolone

Human Primary Cells

- ✓ Degradation potency
- ✓ TLR induced cytokine inhibition
- ✓ B cell functional assays

NZBW1 Lupus Model



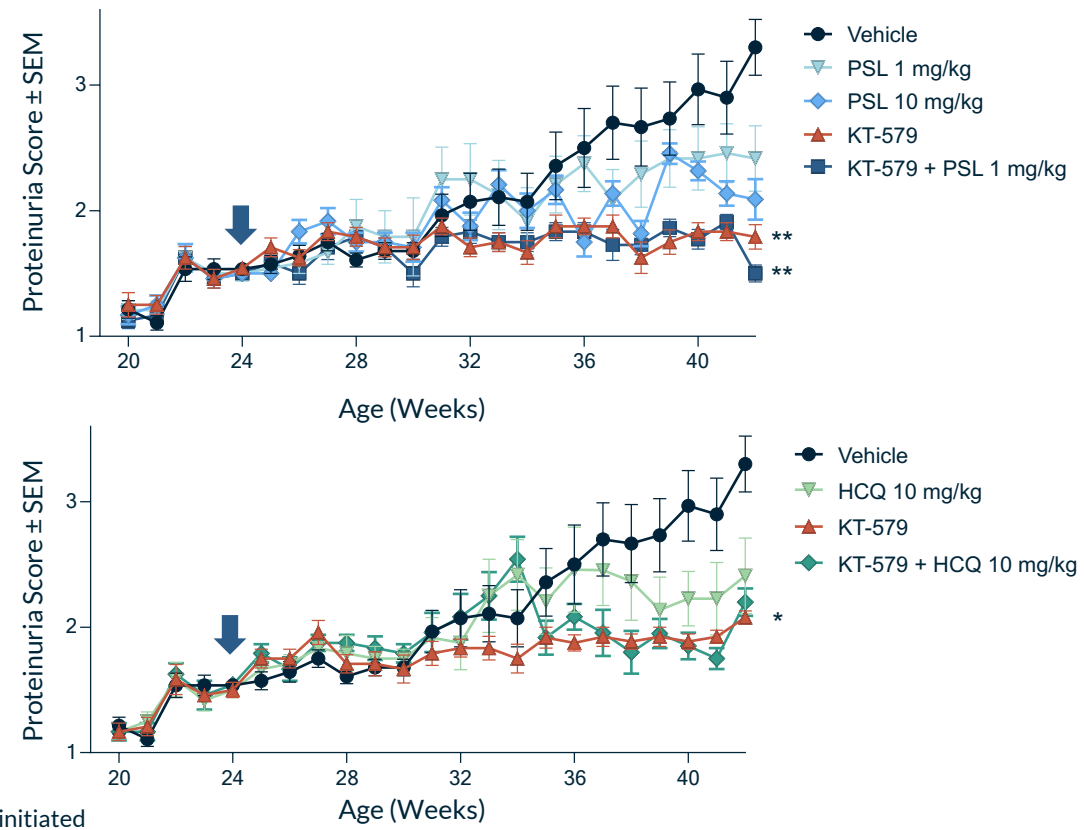
- ✓ Low and high dose of PSL (equivalent ~5 vs 50mg human dose exposure)
- ✓ Included HCQ (equivalent to ~400mg human total exposure)

PSL= prednisolone
HCQ=Hydroxychloroquine

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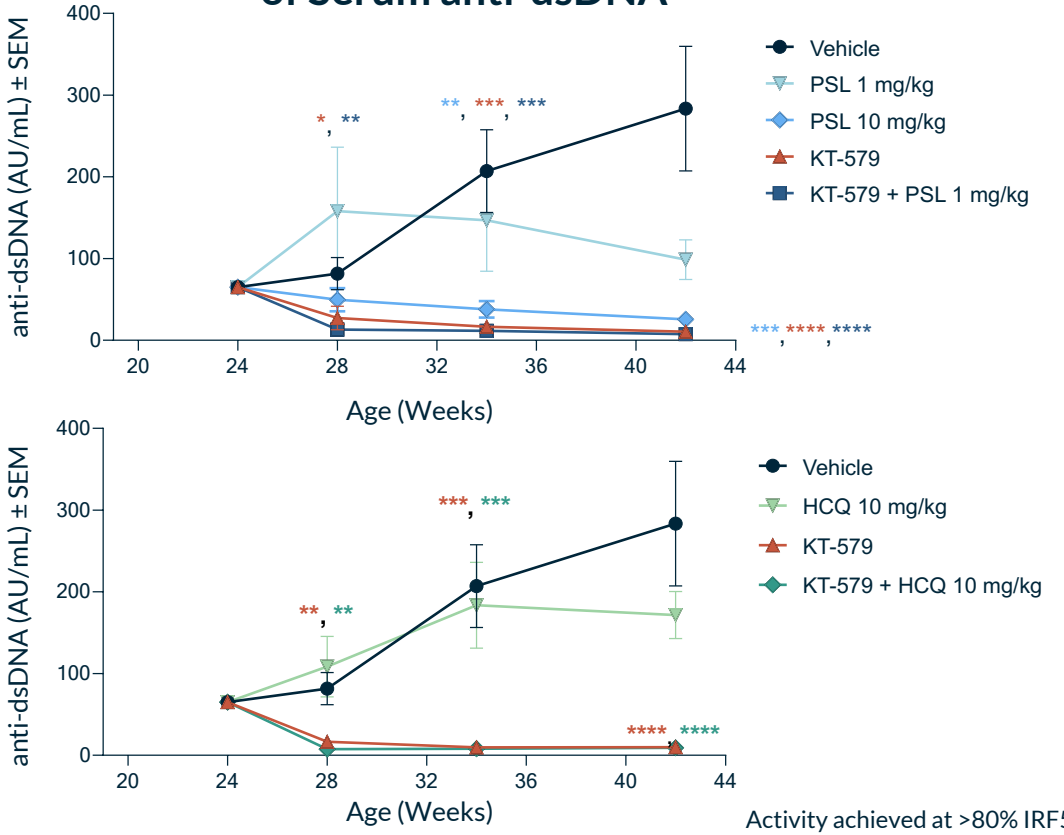
Therapeutic Dosing of KT-579 in NZBW1 Lupus Mouse Model Leads to Significant Activity Alone or in Combination with Background Therapy

KT-579 Significantly Reduces Proteinuria



Treatment initiated

KT-579 Leads to Rapid and Sustained Reduction of Serum anti-dsDNA



Activity achieved at >80% IRF5 degradation

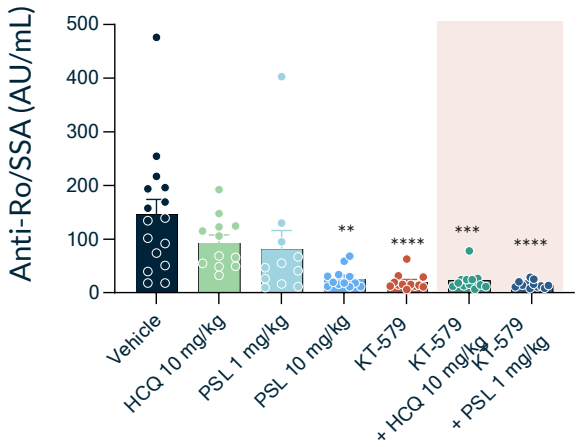
- KT-579 alone or in combination with low dose steroid is as effective as high dose steroid, highlights potential to be steroid-sparing
- KT-579 alone or in combination with HCQ is more effective than HCQ alone
- Combination with background therapy does not impact KT-579 *in vivo* activity on human disease-relevant biomarkers

Left: Mixed effect model vs Vehicle control *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001; Right: Repeat Measure AOVA at each endpoint vs Vehicle control *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001.

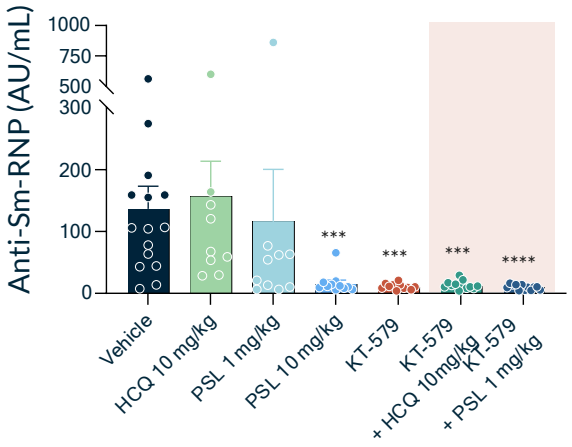
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KT-579 Alone or in Combination with Background Therapy Significantly Decreases Autoantibody B cells and Biomarkers

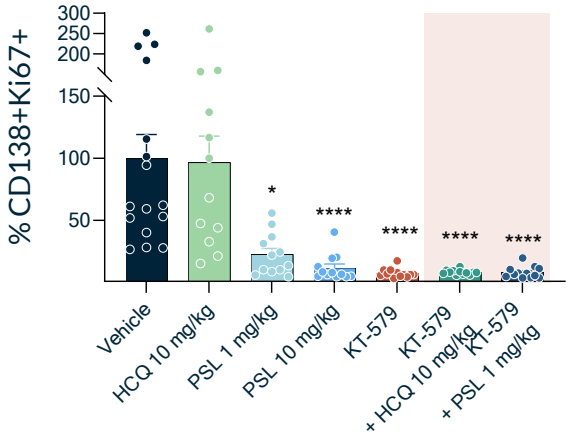
Serum Anti-Ro/SSA



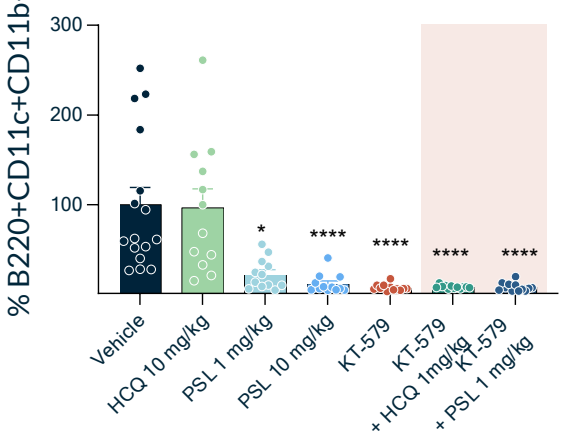
Serum Anti-Sm-RNP



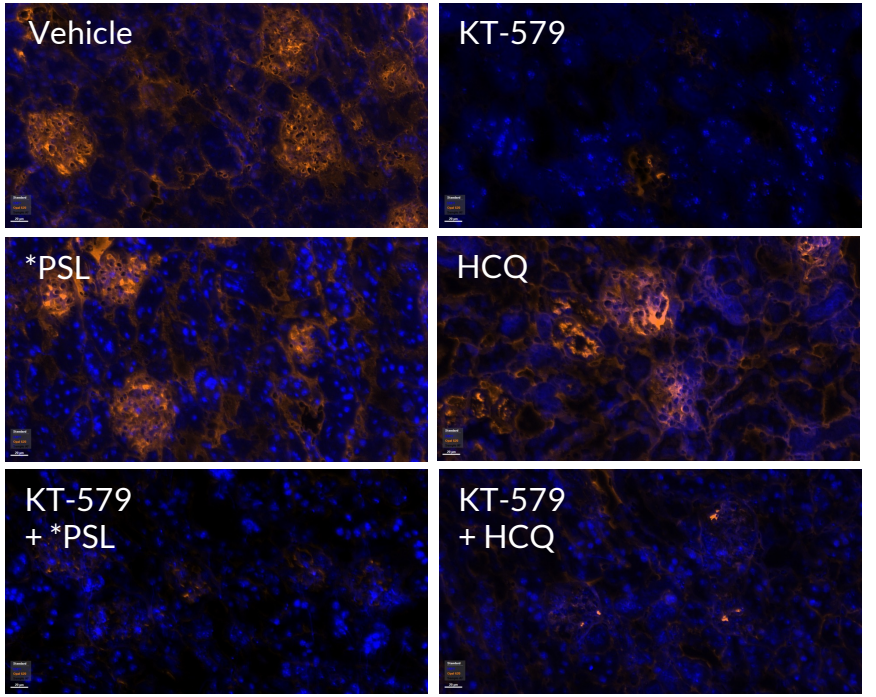
Spleen Plasmablasts



Spleen ABCs



KT-579 Clears IgG Deposition from Kidney



IgG DAPI

Representative images (40x) of IgG staining glomerular structures; *Prednisolone (PSL) 1mg/kg group

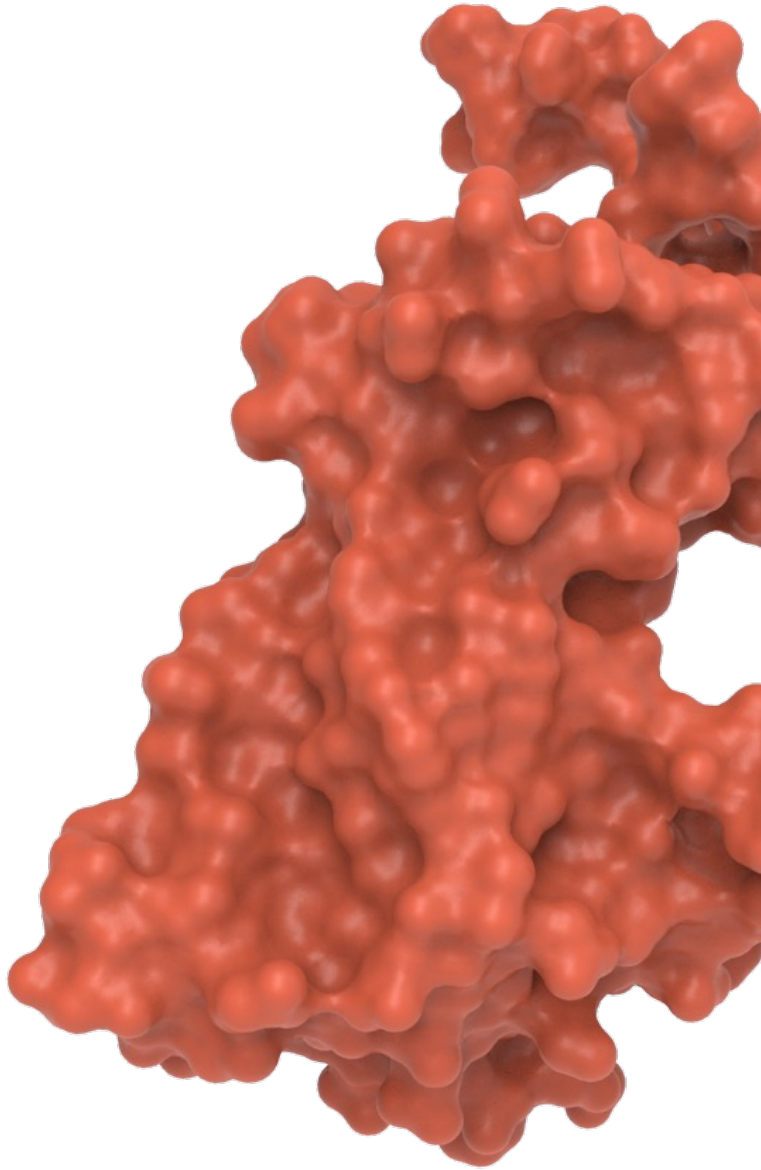
KT-579 reduces circulating autoantibodies, tissue pathogenic autoantibody producing subsets and kidney IgG deposition

Kruskall-wallis with uncorrected Dunn's vs Vehicle control *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001.

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Summary

- **KT-579 is a first-in-class, oral, potent and selective IRF5 degrader that demonstrated significant and consistent activity** across multiple preclinical models of lupus and reproduced IRF5 genetic mouse lupus findings
- **KT-579 activity alone or in the presence of background therapy leads to rapid and meaningful reductions** of human disease-relevant blood and tissue biomarkers, including pathogenic B-cells, with the potential to be steroid sparing
- **Phase 1 HV trial has been successfully completed** with a favorable safety and tolerability profile in healthy volunteers
    - KT-579 demonstrated deep, sustained IRF5 degradation in blood, with ≥90% median IRF5 degradation across multiple dose levels in MAD
    - Robust suppression of disease-relevant blood biomarkers for inflammatory cytokines, interferon response, and B-cell biology



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KT-579: LUMORA Phase 1b Trial

Biomarker Study for First-in-Class Mechanism in Lupus Patients

lumora TRIAL

Adult Patients with Systemic Lupus Erythematosus

Baseline entry criteria:

- ANA ≥1:80
- BILAG-2004 score A or B[1]
- Oral corticosteroid background therapy permitted

Design

- Randomized, double-blind, placebo-controlled
- ~30 patients

Dosing

- KT-579 or placebo (2:1)
- Dosing for 16-weeks

Endpoints

- Safety and tolerability
- Pharmacokinetics
- IRF5 protein levels in blood
- Biomarkers
  - Inflammatory cytokines
  - IFN response
  - B-cell biology
- Exploratory disease endpoints

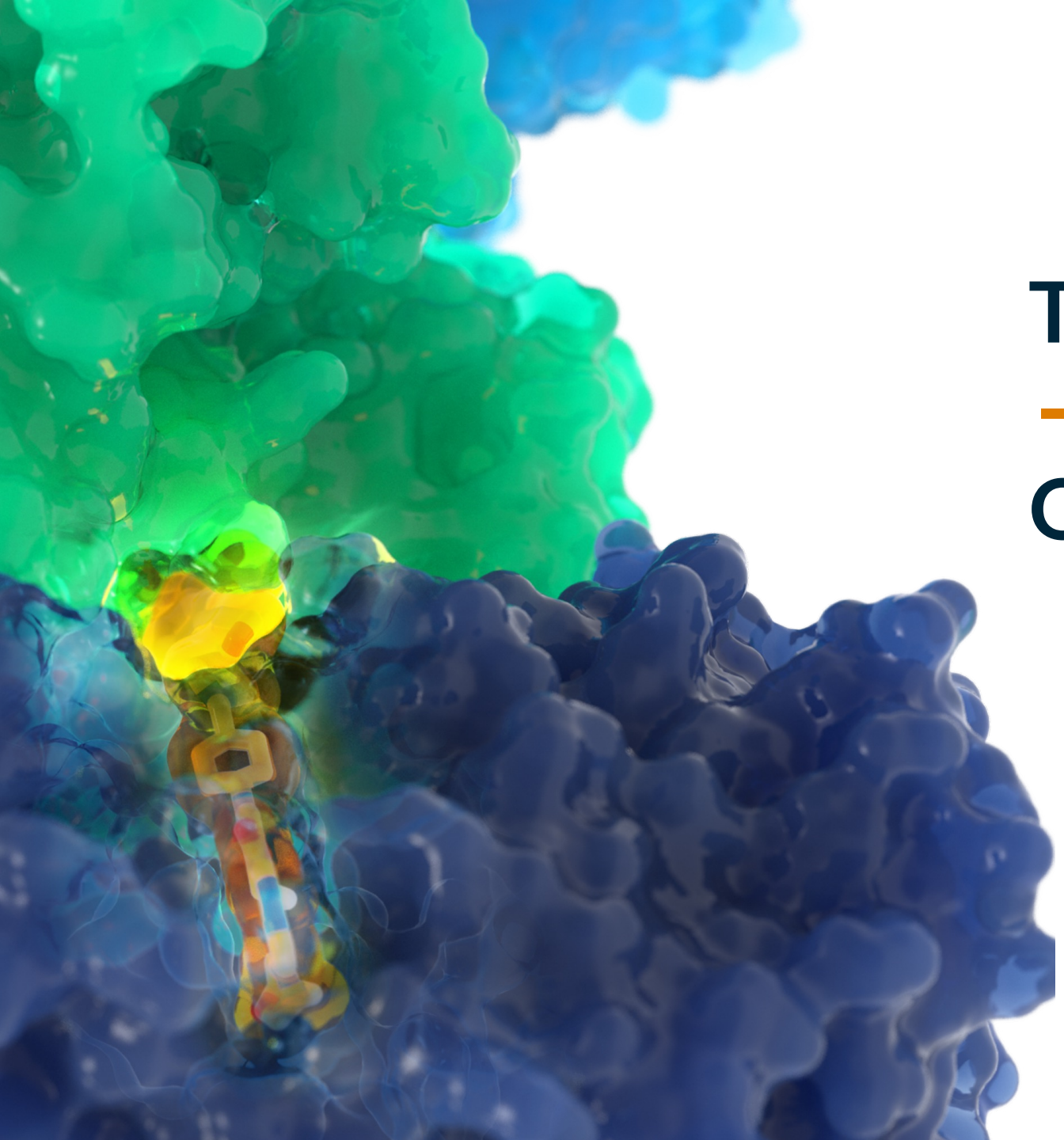
Key Trial Aim

Biomarker study to demonstrate that **KT-579 can modulate underlying disease biology** with a favorable safety and tolerability profile

Status update:
Trial start by early 2027

[1]In mucocutaneous and/or musculoskeletal domains.

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Thank You

Q&A

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