Utilizing Degraders to Modulate B&T cell Targets for Autoimmune Diseases

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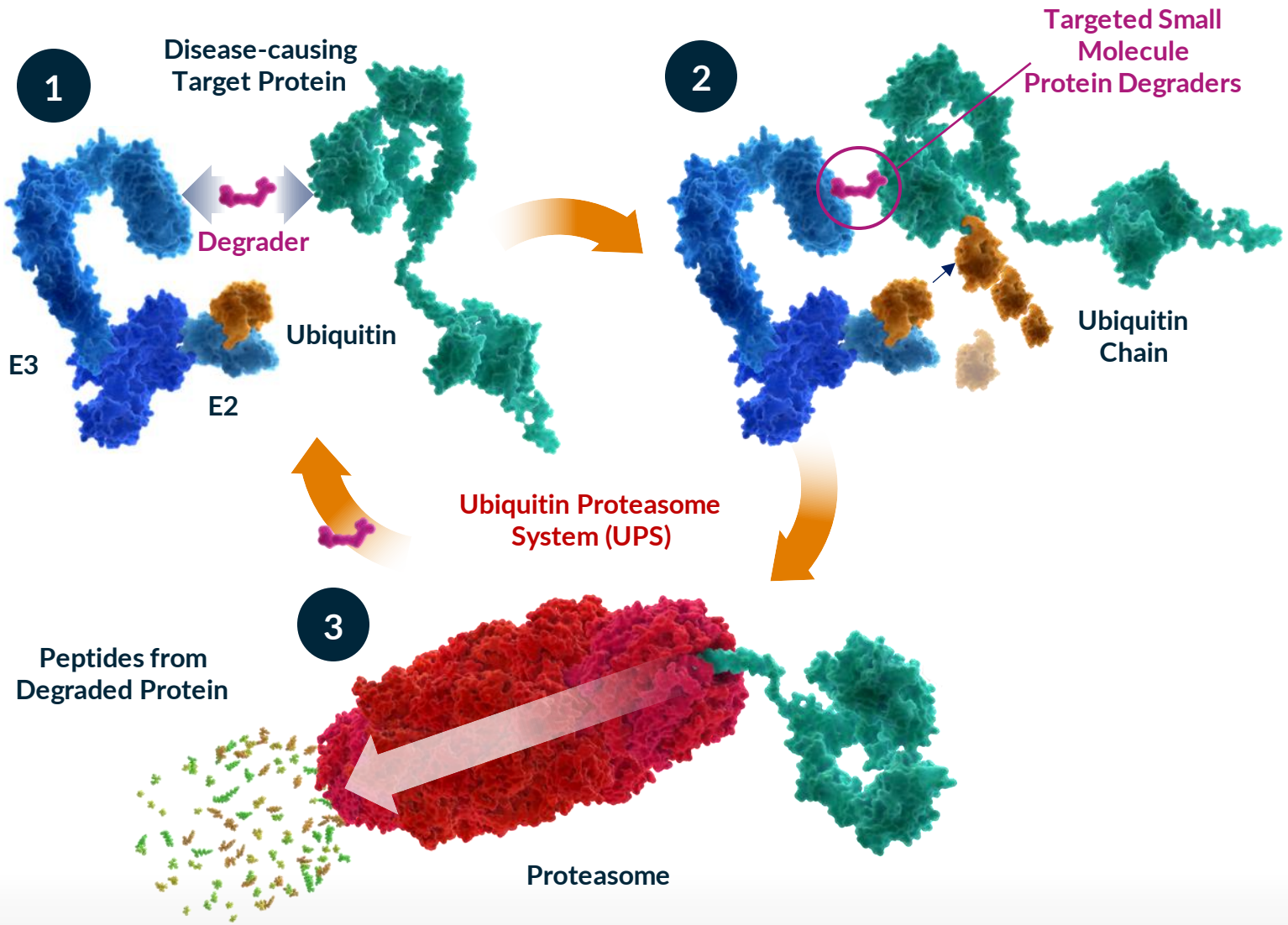
DISCLOSURES

I am a Kymera Therapeutics employee and equity owner.

Proteome Editing with Targeted Protein Degradation

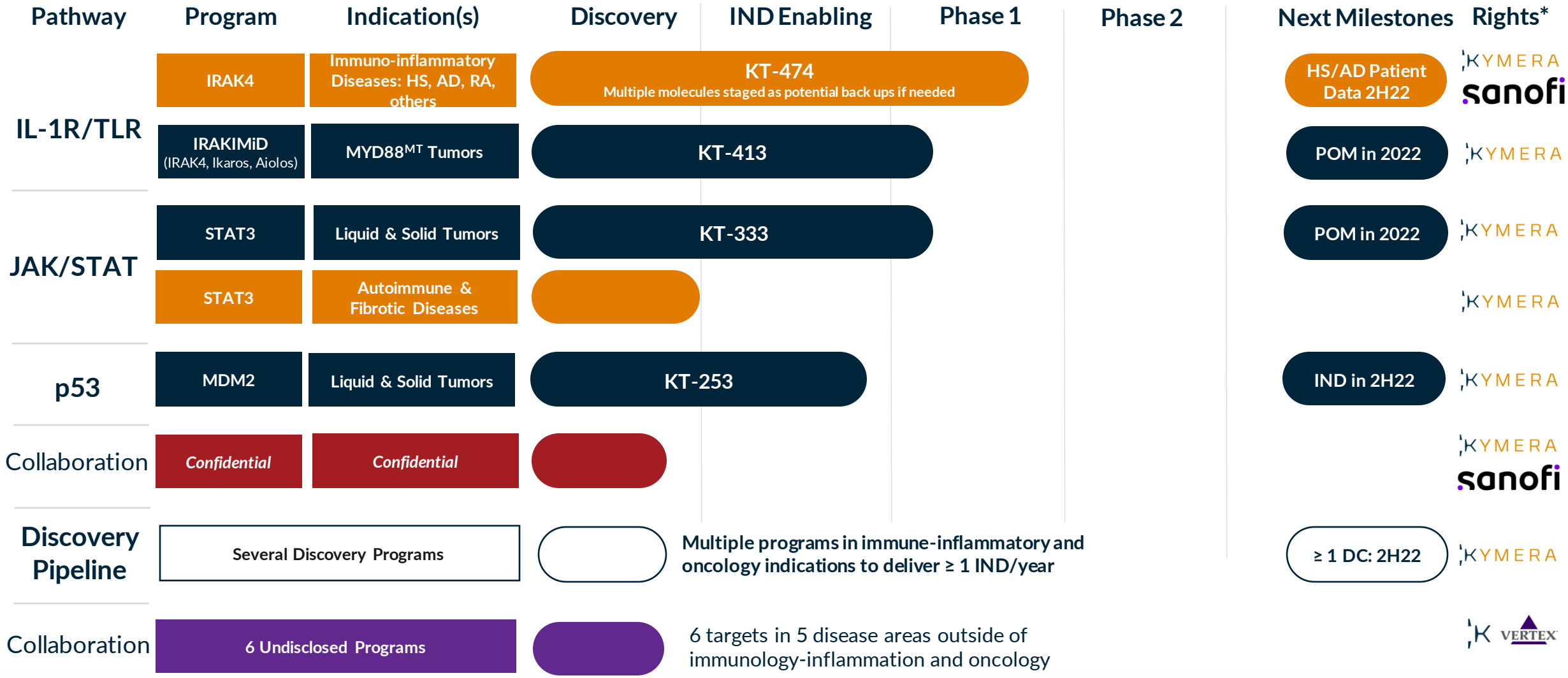
A Nobel Prize (2004) Inspired Technology



Expanded Opportunities

- Small molecule binds to E3 and target protein to affect its degradation
- Small Molecule only needs to "weakly" bind to protein:
  Not inhibit function
- Highly potent/catalytic:
  Small amount of drug needed
- Highly specific
- Genetic–like knock-down effects
- Advantage of small molecule development:
  Route of administration, manufacturing
- Agnostic to protein type and disease

Kymera's Pipeline of Novel Protein Degraders



*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US

How We Select Our Targets

Drug Development Philosophy

Unmet Medical Need

Validated Biology

Undrugged Node

Precision Medicine Approach

Target Types

ID — **Inadequately Drugged Targets with Clear Degrader Advantage**
e.g. IRAK4, MDM2

UD — **Undrugged Targets by any other technology**
e.g. STAT3

TR — **Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression**

Therapeutic Profile

Oncology:
- Clear patient stratification
- Clear single agent activity with potential for expansion with combos
- Multiple addressable unmet needs

Immunology:
- Address key unmet needs providing game changing oral therapies
- Key validated signaling pathways with clear degrader advantage

Other Disease Areas:
- Enabled by E3 ligase differential expression
- Key insights from biology and technology expansion
- Some areas enabled by collaborations

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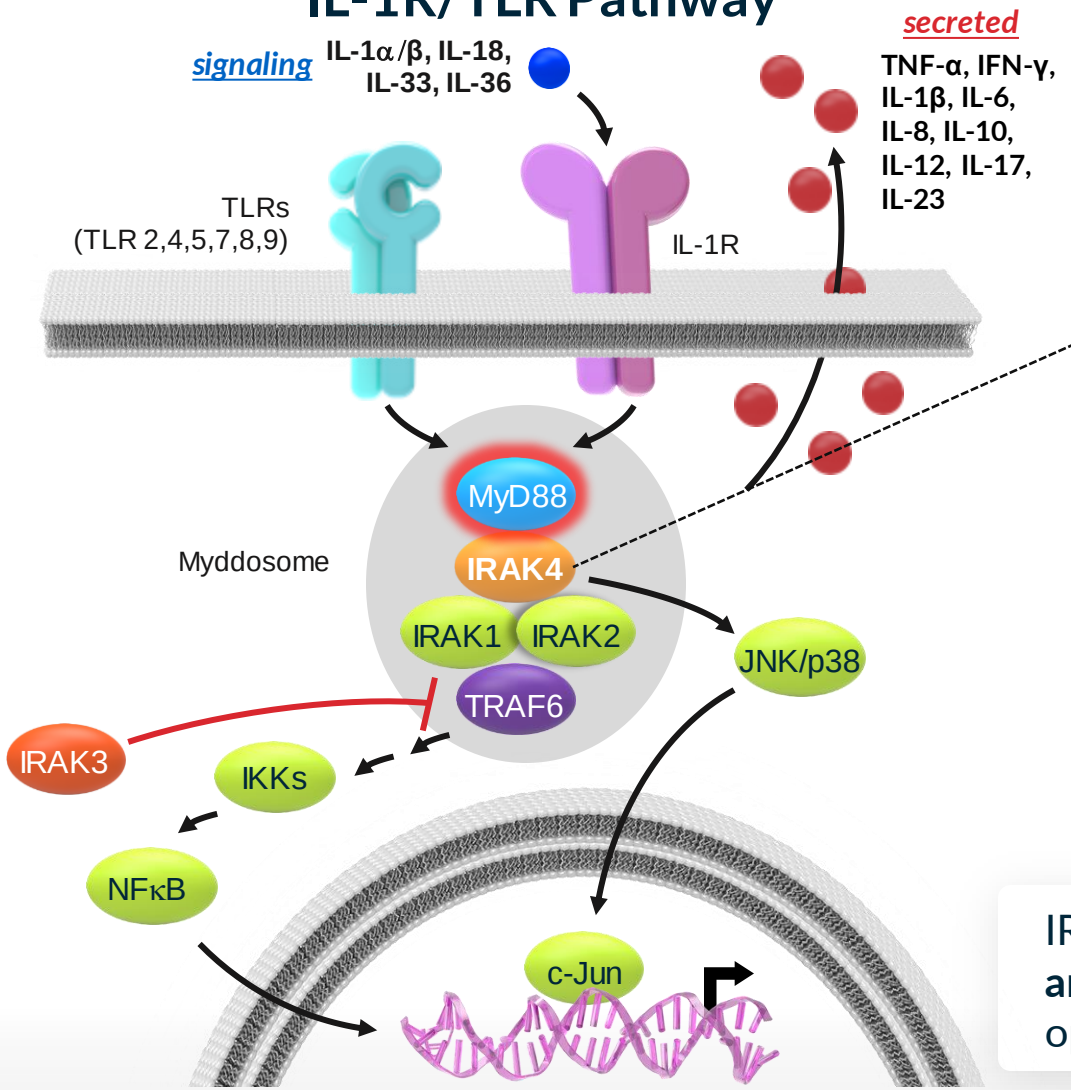
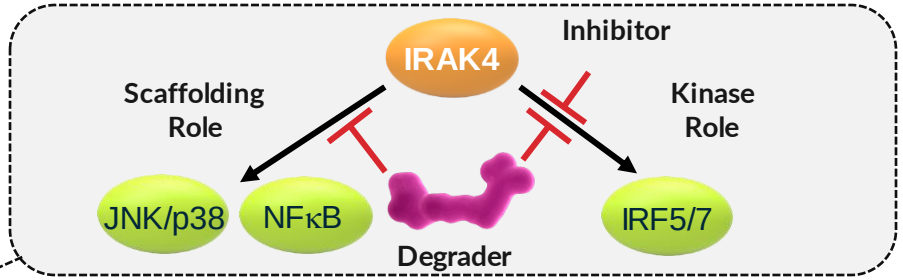
Degrading IRAK4: Best Approach to Block IL-1R/TLR driven Inflammation

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

IL-1α /IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa

IL-1α : Atopic Dermatitis

IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer

IL-18: Macrophage Activation Syndrome

IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis

IRAK4 SMI: Rheumatoid Arthritis

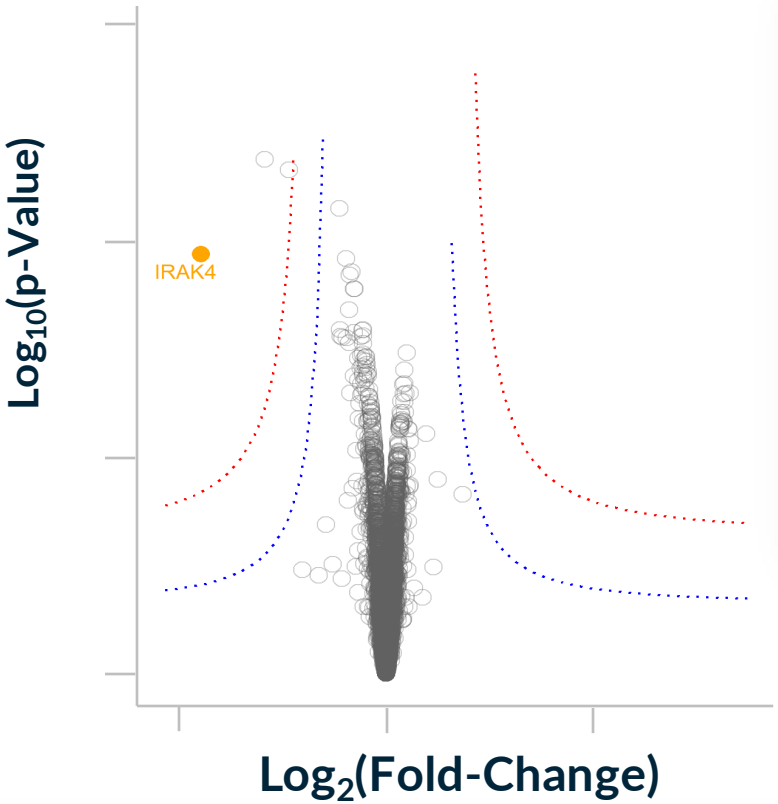
Human Genetics

Adult humans with **IRAK4 Null Mutation are healthy**

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

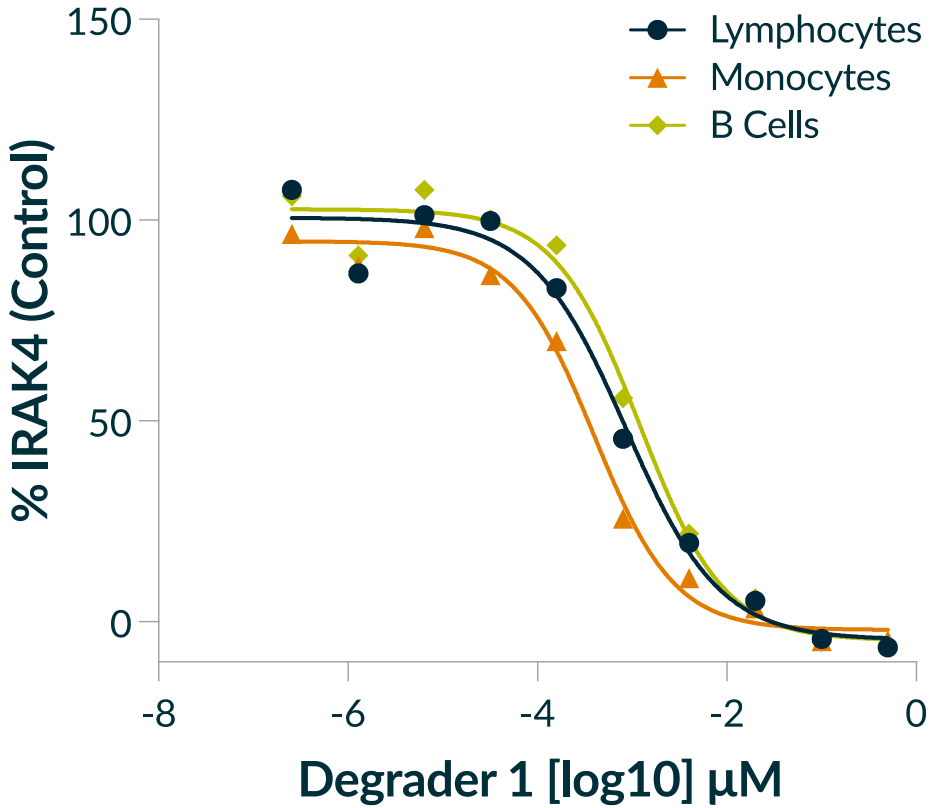
KTX-545 is a Selective and Potent IRAK4 Degrader Across Human Peripheral Mononuclear Subsets

Selectivity in huPBMC (24 h Treatment)

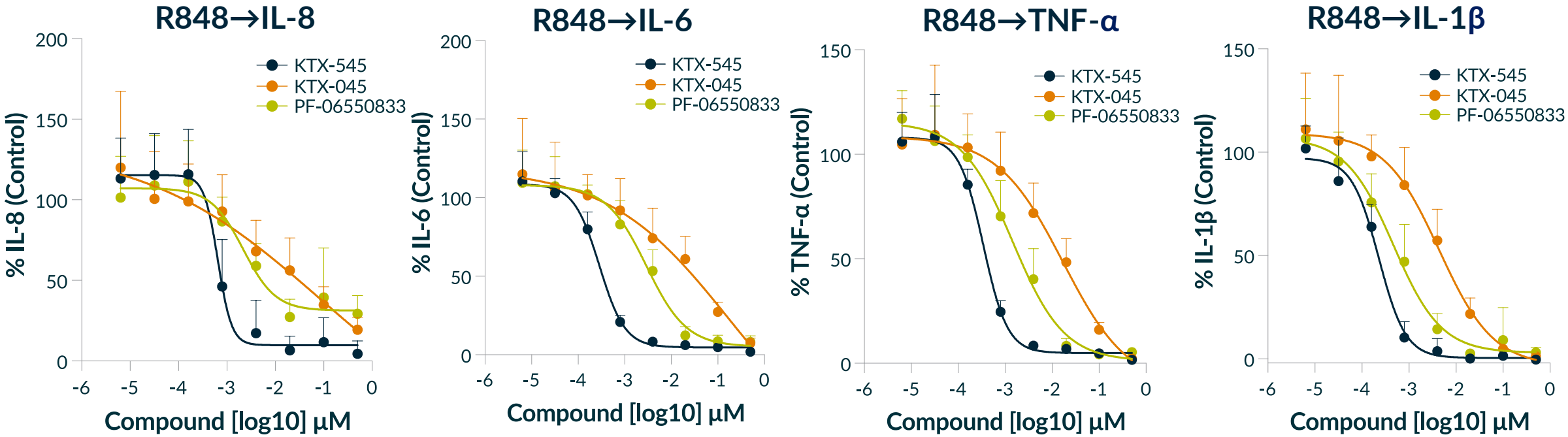


- KTX-545 is a selective and potent tool compound
- KTX-545 only degraded IRAK4 in human immune cells at concentration above the DC_{90}
- KTX-545 degrades PBMC subsets with similar potency (DC50= ~0.5-2nM)

Degradation in huPBMC (24 h Treatment)



IRAK4 Degradation Leads to more Potent Cytokine Inhibition in TLR7/8 activated PBMCs

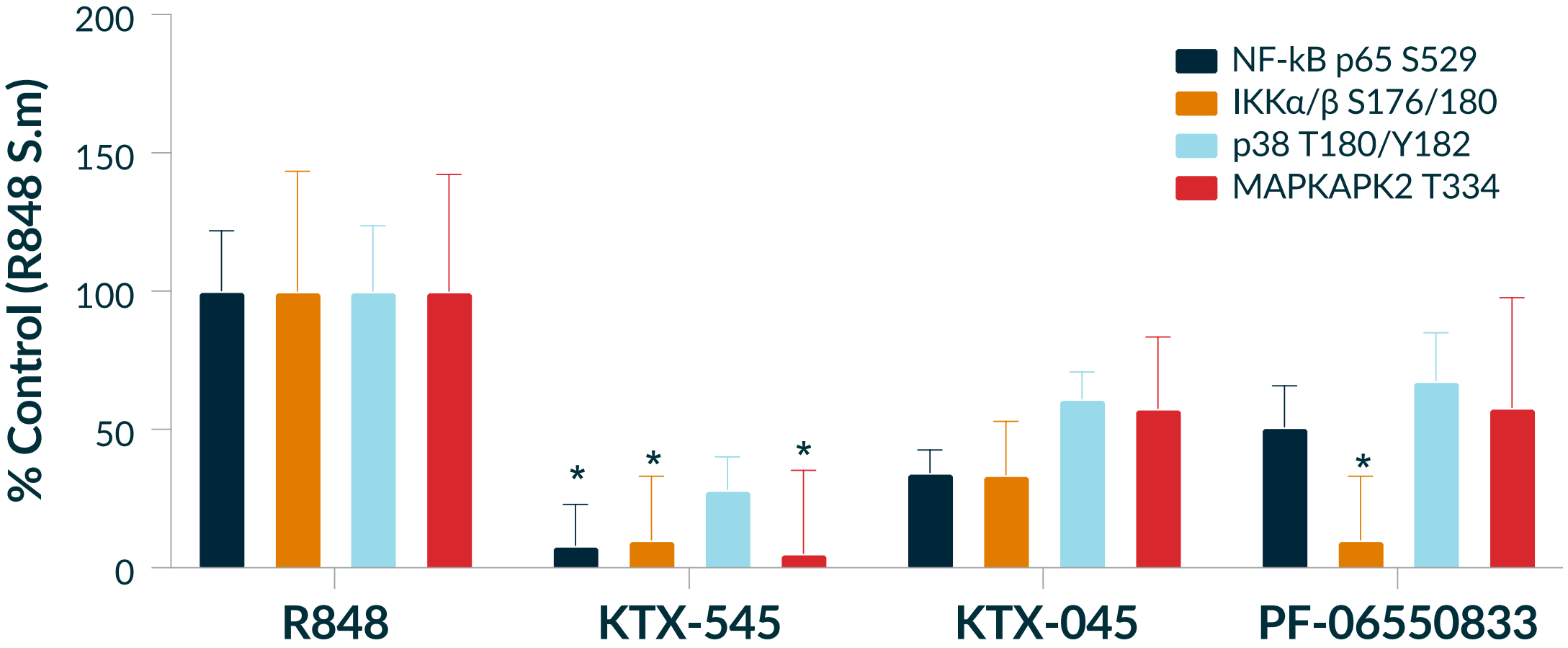


*Cytokine	KTX-545	**KTX-045	PF-06550833
IL-8 IC_{50}, nM	0.9 (0.2)	26.4 (15.1)	6.2 (2.1)
IL-6 IC_{50}, nM	0.3 (0.03)	30.0 (10.9)	3.9 (1.0)
TNF-α IC_{50}, nM	0.4 (0.03)	15.8 (2.8)	2.3 (0.8)
IL-1β IC_{50}, nM	0.2 (0.04)	5.2 (1.4)	0.7 (0.3)

*N=5 donors mean values reported (±SEM)

**KTX-045 is a negative control with no degrader function

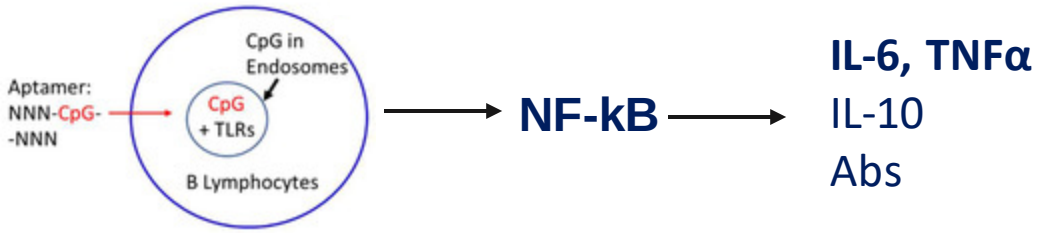
IRAK4 Degradation inhibits TLR Activated NF-kB p65 and MAPK Signaling in Monocytes



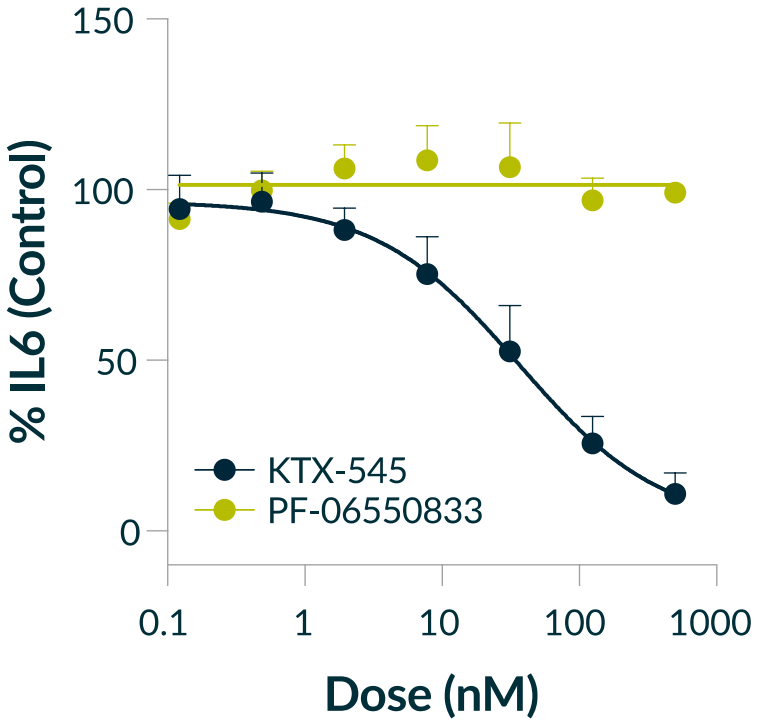
*p<0.05 relative to R848 stim control

B cells as a Cell Model to Investigate NF-kB signaling

TLR9/CpG-B

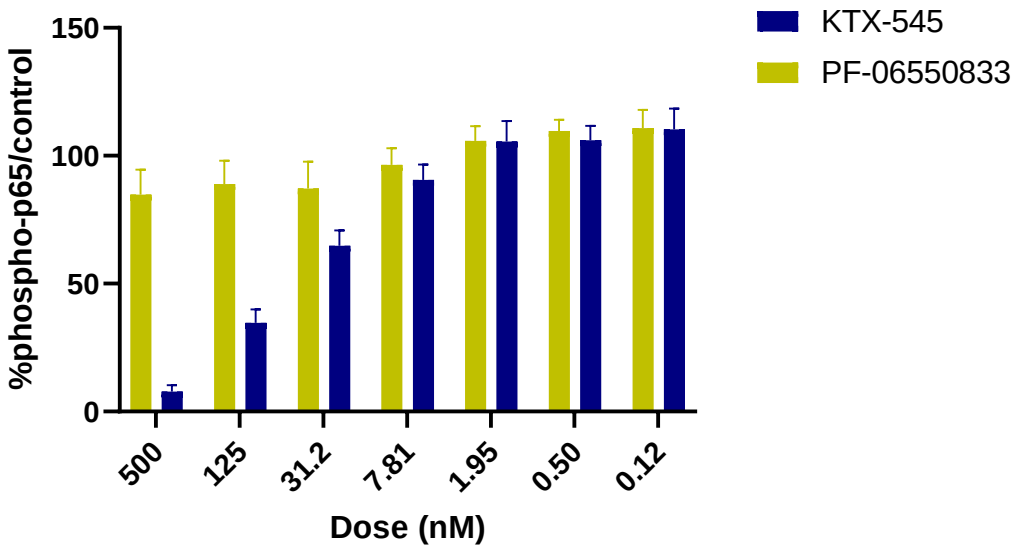


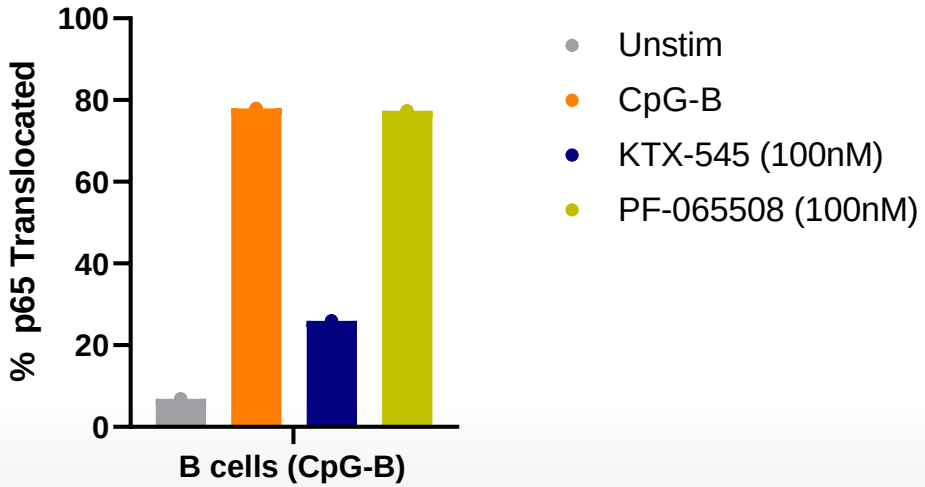
IRAK4 Degradation but Not Kinase Inhibition Blocks CpG-B Induced Pro-inflammatory Cytokines in B cells

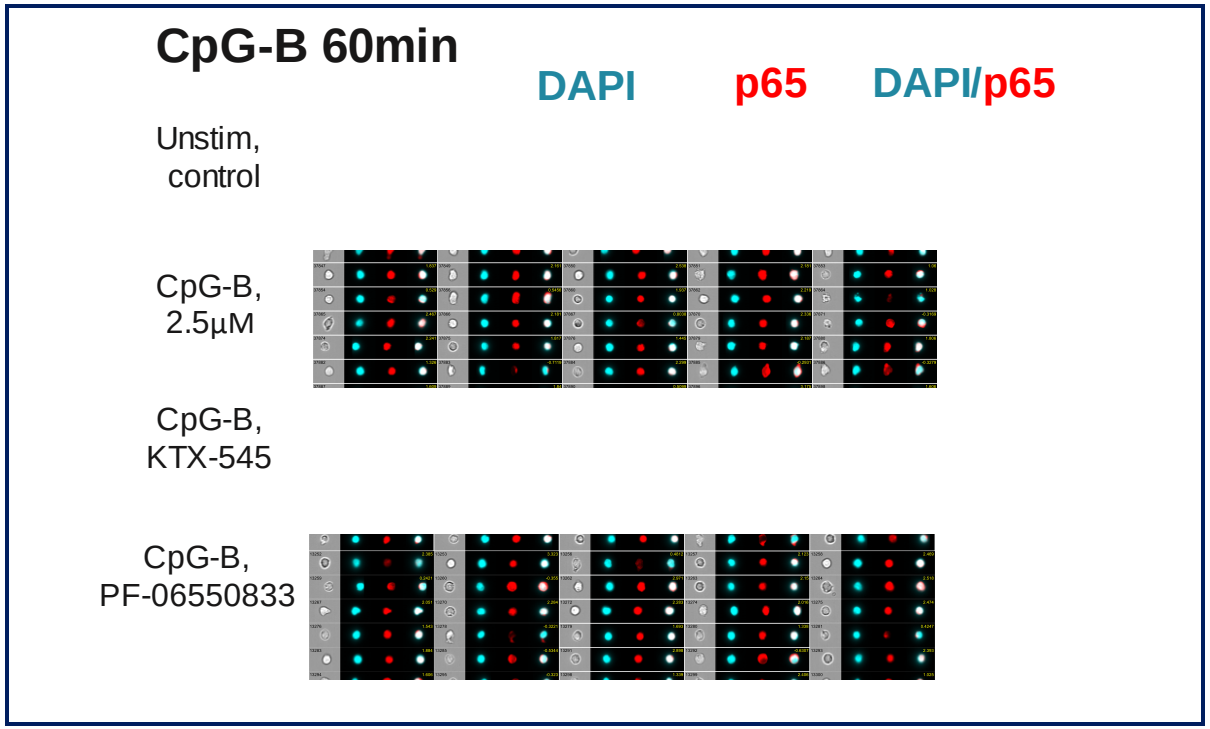


IC_{50} (nM)	KTX-545 (nM)	PF-06550833
IL-6	18	ND
TNFα	17	ND

IRAK4 Degradation but Not Kinase Inhibition Blocks p65 Activation and Nuclear Translocation in B cells

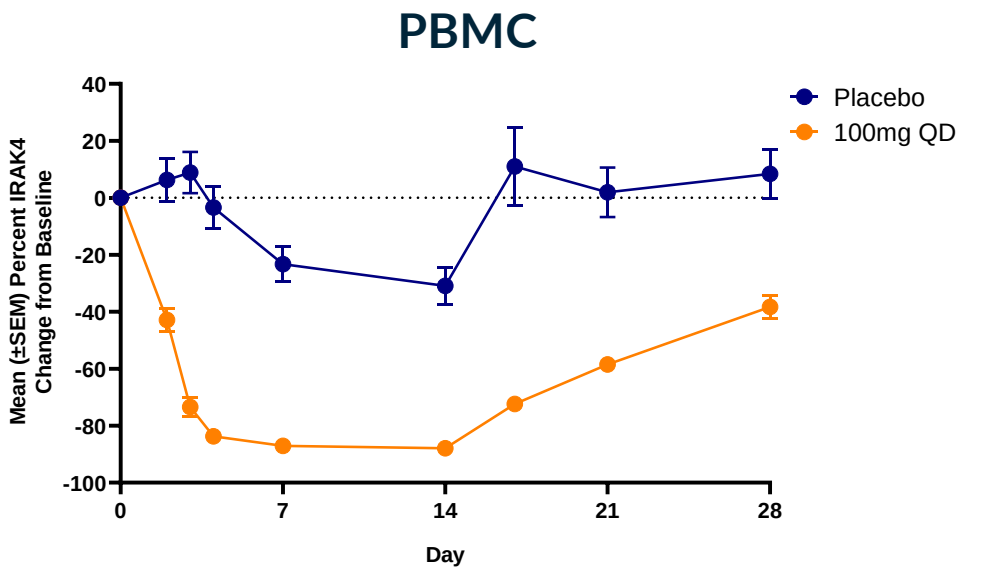


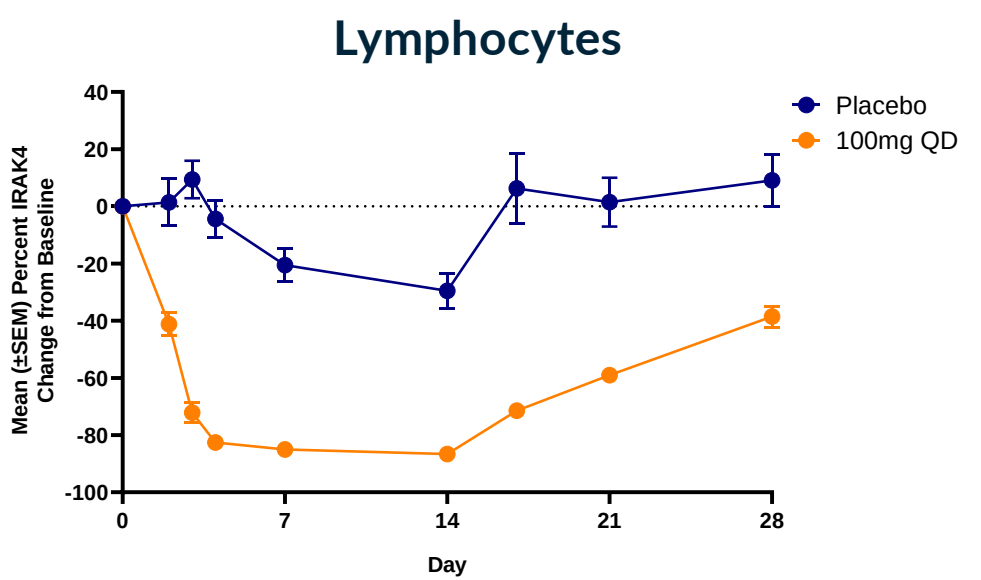


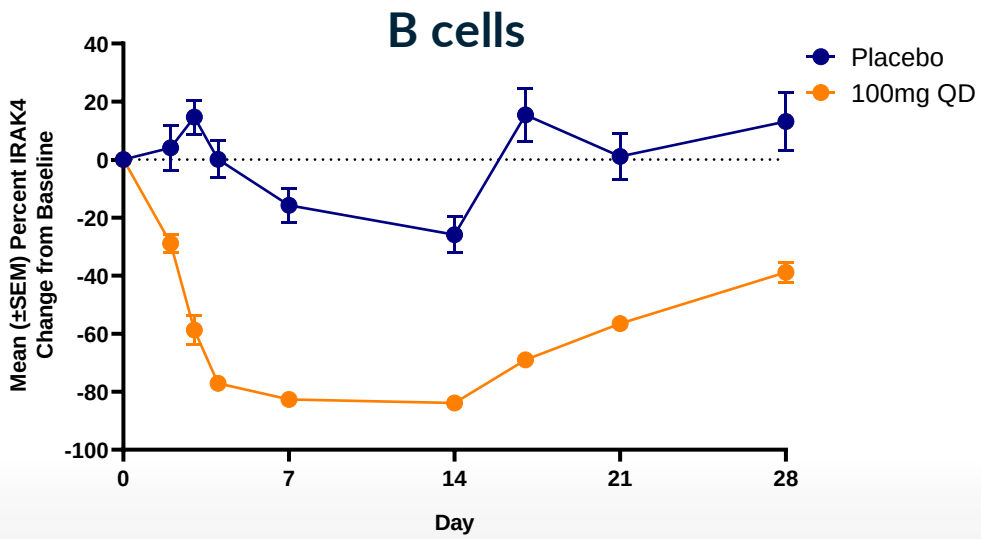


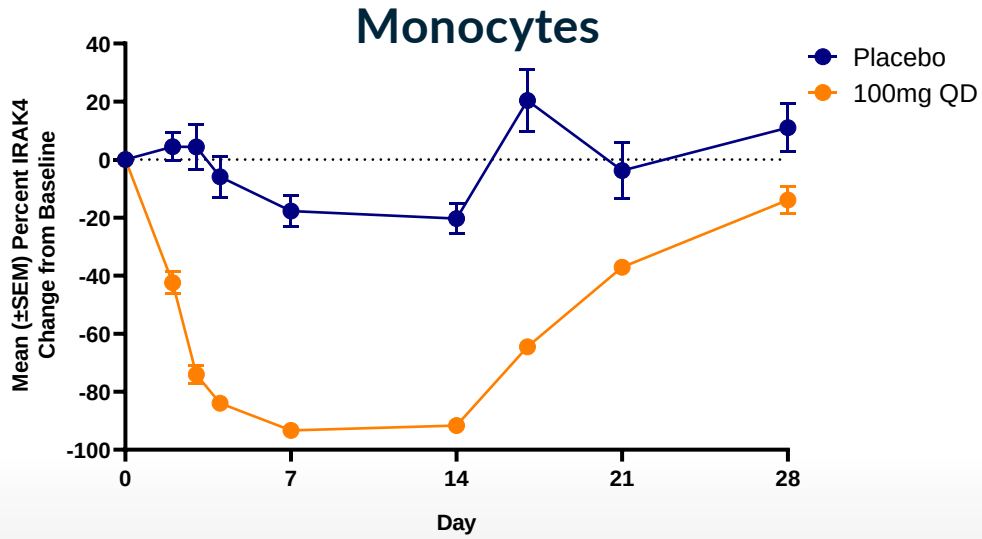
- CD19+ naïve B cells isolated from huPBMC were treated overnight with compounds before activation with CpG-B for 60 minutes
- Phospho-p65 events were measured by flow and Nuclear translocation events were captured with Imagestream X and reported as %p65 translocated

KT-474 Achieved Similar and Sustained IRAK4 Degradation across PBMC Subsets with Multiple Daily Doses (14 Days) in Phase I HV Study









IRAK4 detected using FLOW

IRAK4 Summary

- Both scaffold and kinase activity is critical for IRAK4 function. KTX-545 is a potent and selective IRAK4 degrader and the cellular data generated here demonstrate that IRAK4 degradation is superior to kinase inhibition due to its removal of both scaffolding and kinase functions
- In TLR7/8-R848 activated monocytes, IRAK4 degradation inhibits phosphorylation of NF-kb p65 and MAPK signaling. In TLR9-CpG-B activated B cells, IRAK4 degradation leads to inhibition of nuclear p65 translocation and pro-inflammatory cytokine induction
- These data highlight the potential for IRAK4 degraders to block multiple TLR signaling pathways across different immune cell types in a manner superior to IRAK4 kinase inhibitors and thereby impact TLR/IL-1R-driven inflammatory and autoimmune diseases
- KT-474, our lead IRAK4 degrader molecule is currently in a Phase I trial where safety and activity is being assessed in healthy volunteers and in patients with atopic dermatitis and hidradenitis suppurativa. In healthy volunteers, KT-474 achieved comparable IRAK4 degradation in circulating monocytes and B cells.

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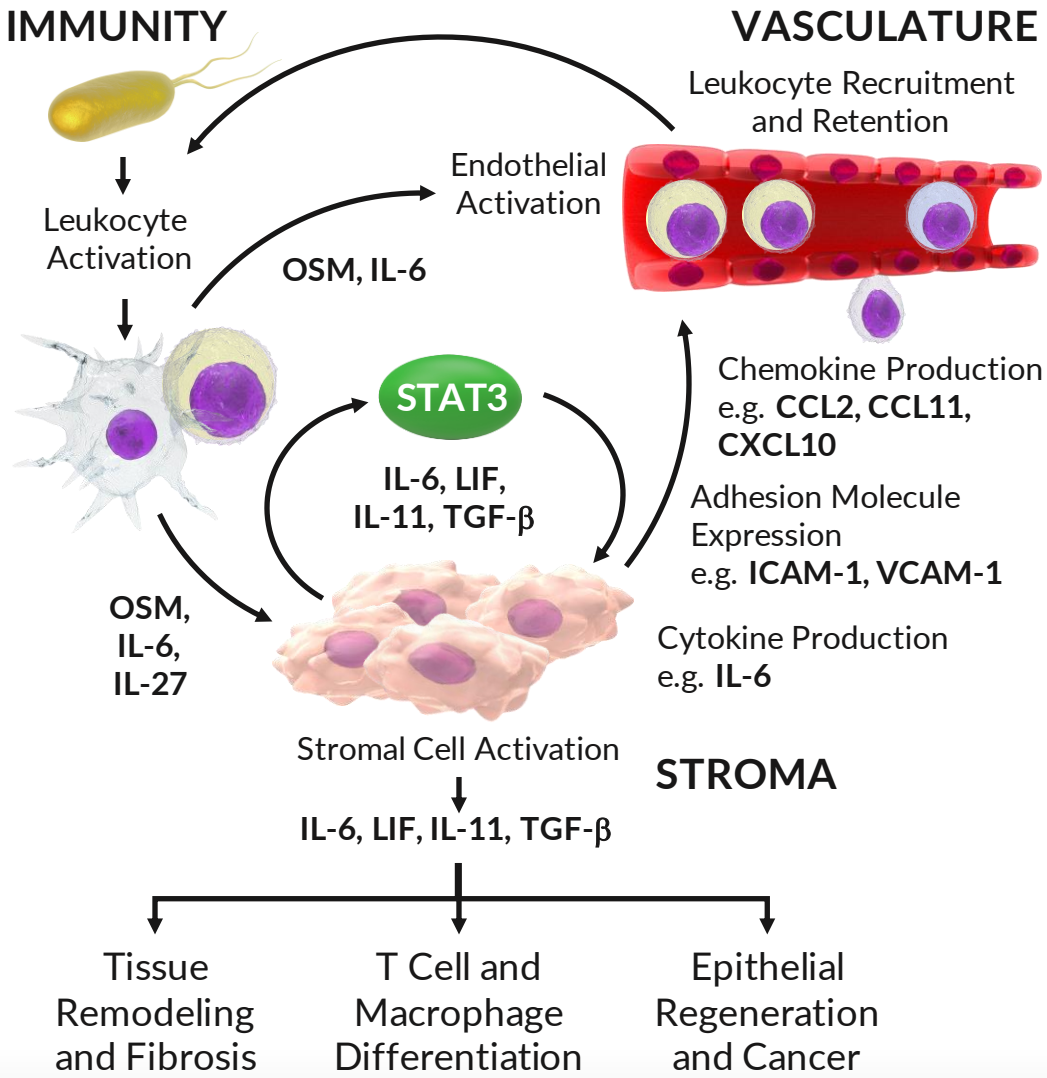
Overview of STAT3 Biology

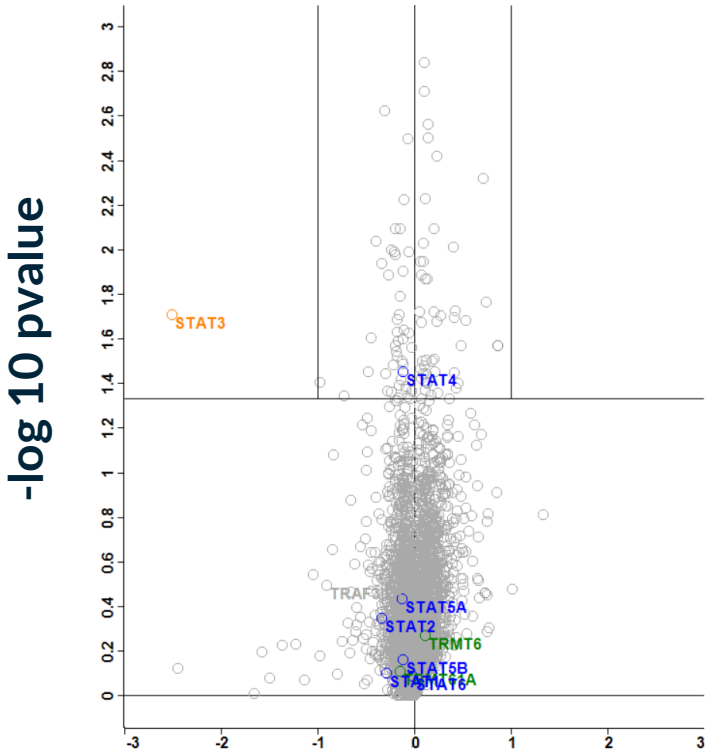
- STAT3 is an undruggable transcription factor
- STAT3 is activated by multiple tyrosine kinases and plays a critical role in the signaling of cytokines, hormones, and growth factors including **IL-6**, **IL-11**, **OSM**, **TGF-β**, **VEGF**
- STAT3 signaling is required for Th17 differentiation in vitro and in vivo
- Increased STAT3 activation is associated with disease severity in chronic inflammation, including **SSc**, **RA**, **AS**, **MS**, **IBD**, **PsO**
- STAT3 gain-of-function (GoF) mutations lead to a poly-autoimmunity reminiscent of conditions such as Systemic Sclerosis (SSc) and interstitial lung disease (ILD)
  - JAK inhibitors have shown activity in patients with STAT3 GoF mutations and multiple different autoimmune manifestation



Adapted from West NT. *Front Immunol* 2019

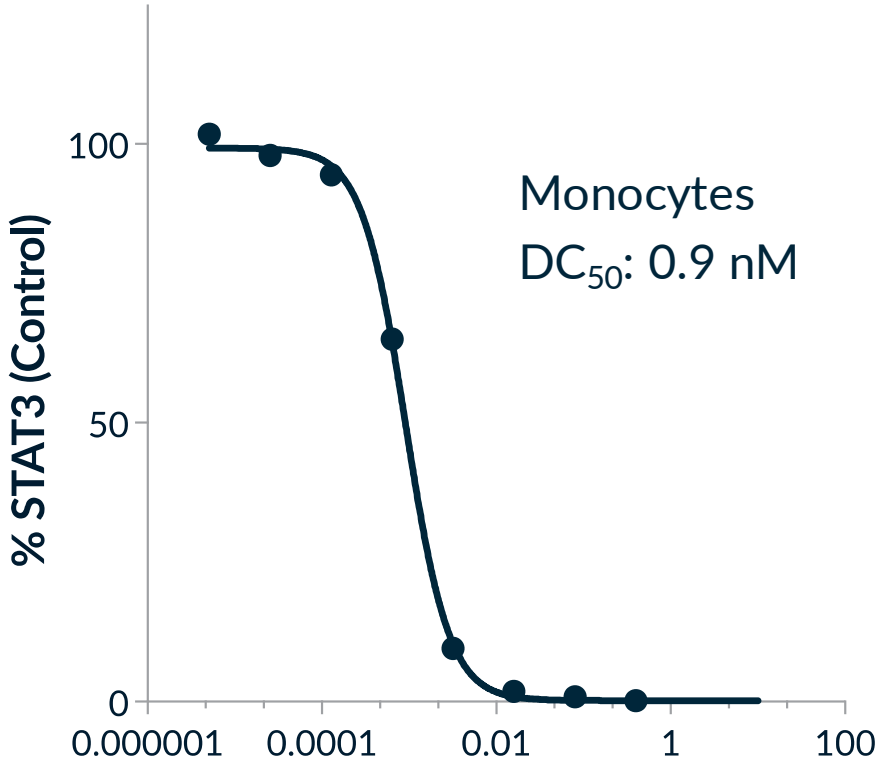
KTX-115 Selectively and Potently Degrades STAT3 in Human PBMC and Whole Blood

KTX-115 Selectively Degrades STAT3 in huPBMC (24 h Treatment)



KTX-115 25 nM (~DC_{95}) / DMSO Average

KTX-115 Potently Degrades STAT3 Human Whole Blood (24 h Treatment)

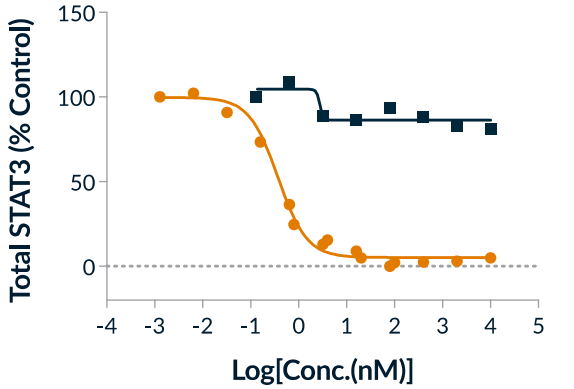


KTX-115 Concentration (FACS)

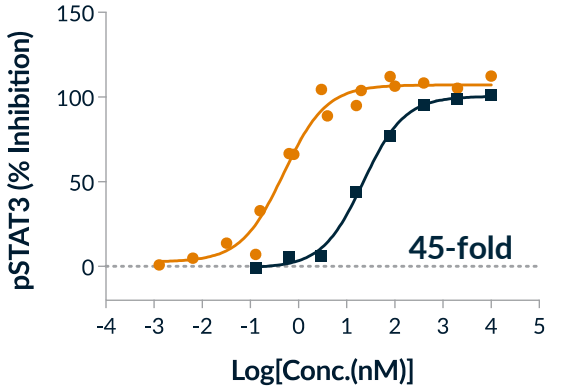
STAT3 Degradation Abrogates STAT3 Phosphorylation and MCP-1/CCL2 Release by Human Monocytes More Potently than JAK Inhibition

- Primary human monocytes or THP-1 monocytes were pre-treated with KTX-115 (20h) or Ruxolitinib (30 min) and then stimulated with rhIL-6 or LPS for 24h before collecting supernatants for MCP-1/CCL2 detection
- For STAT3/pSTAT3 evaluation, cell lysates were collected 30 min. post-stimulation

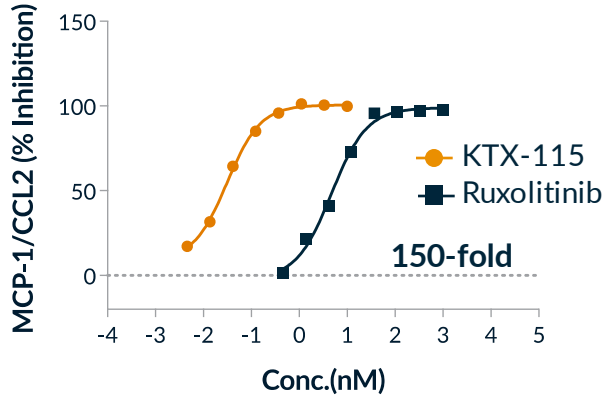
IL-6 stim (CD14+ Monocytes)



HTRF	Ruxolitinib	KTX-115
DC_{50} (nM)	n/a	0.37

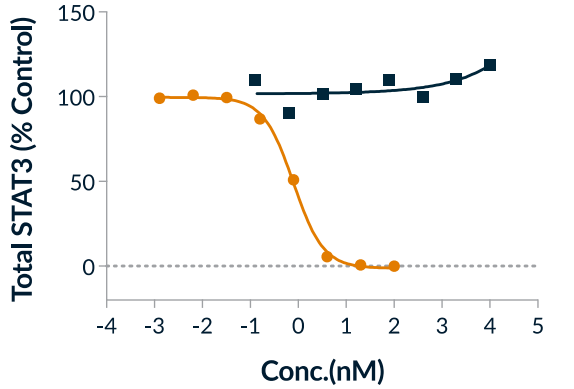


HTRF	Ruxolitinib	KTX-115
IC_{50} (nM)	22.22	0.49

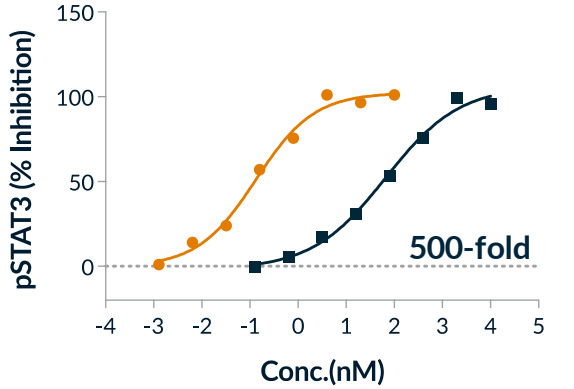


ELISA	Ruxolitinib	KTX-115
IC_{50} (nM)	4.70	0.03

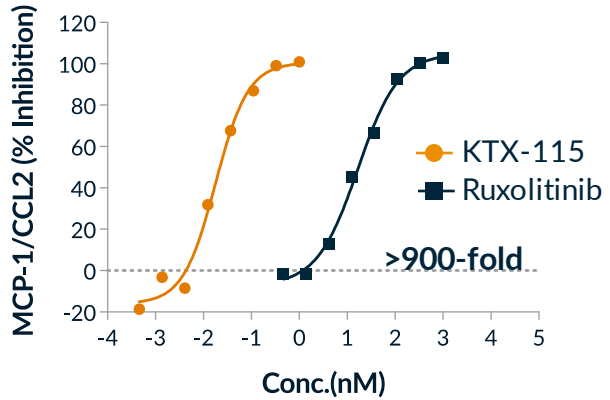
LPS stim (THP-1 Cells)



HTRF	Ruxolitinib	KTX-115
DC_{50} (nM)	n/a	0.80

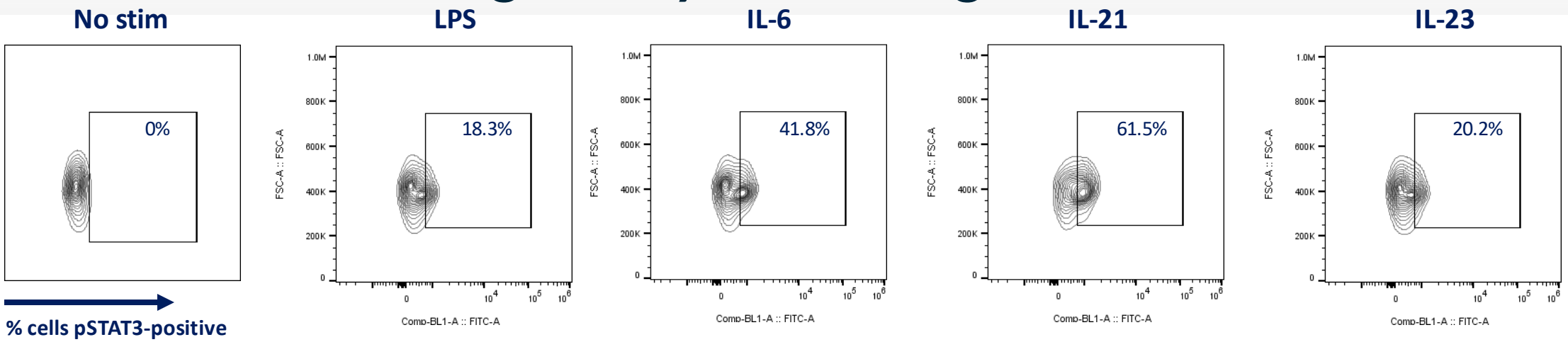


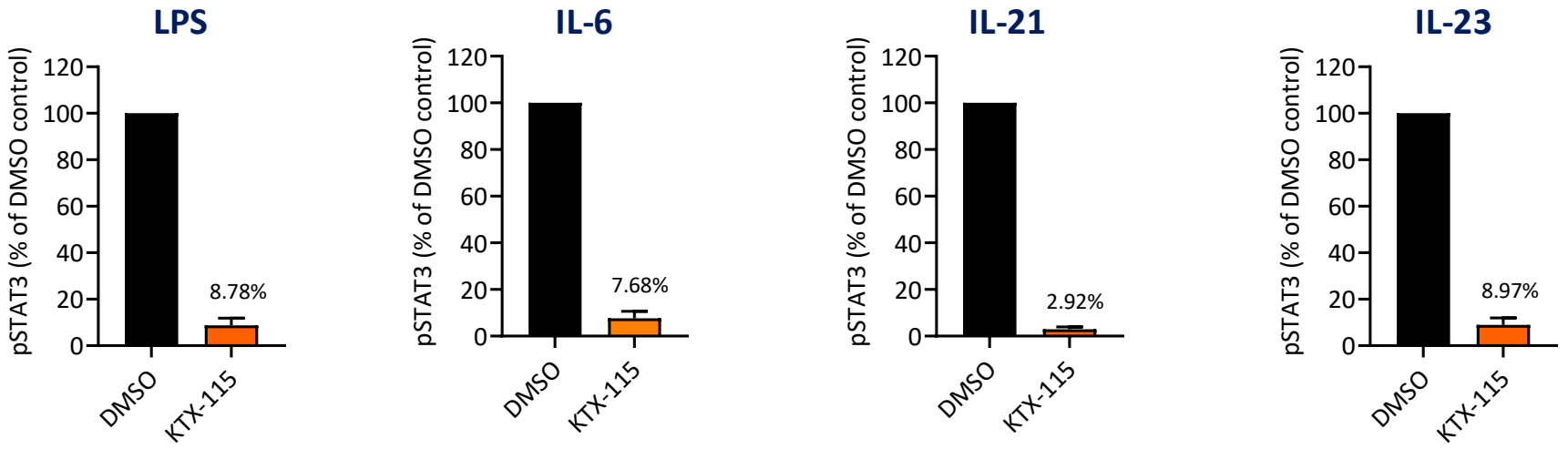
HTRF	Ruxolitinib	KTX-115
IC_{50} (nM)	66.33	0.13



ELISA	Ruxolitinib	KTX-115
IC_{50} (nM)	16.63	0.018

PBMC STAT3 Phosphorylation via Multiple Inflammatory Stimuli is Abrogated by STAT3 degradation

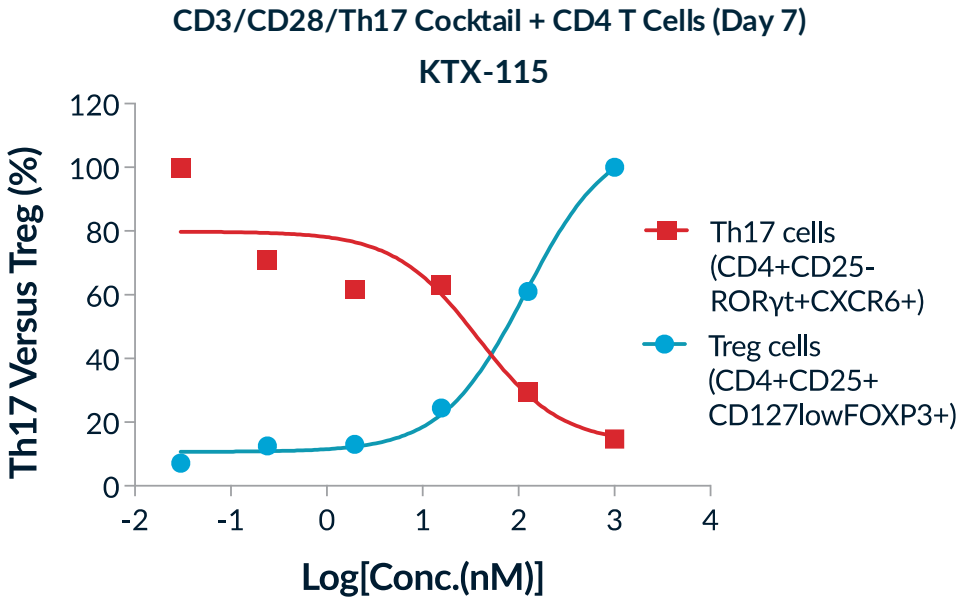


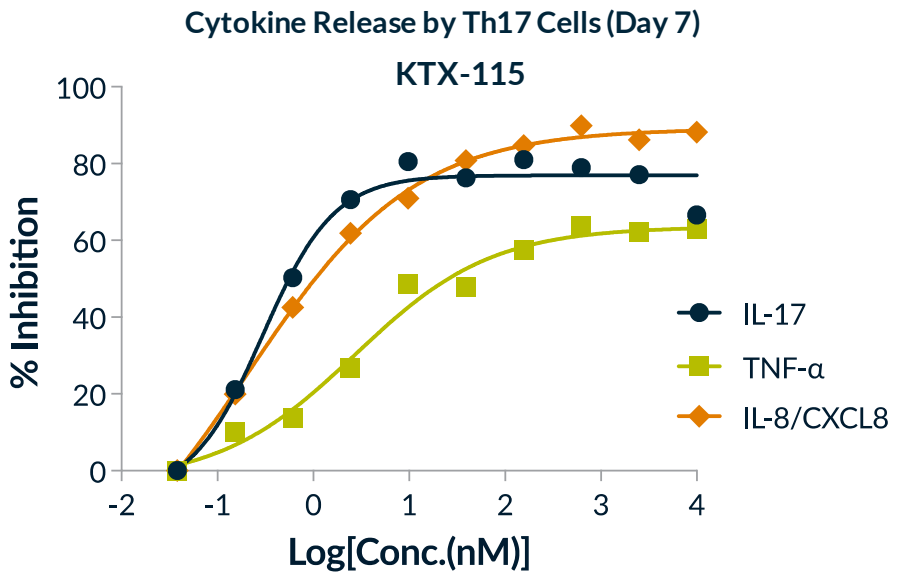


- huPBMC were treated overnight with KTX-115 before stimulation for 30 min. with various stimuli
- Percentages of pSTAT3 positive cells as well as pSTAT3 inhibition (IC_{50}) were estimated for each stimuli

Stimulus	No stim	LPS	IL-6	IL-21	IL-23
pSTAT3 IC_{50}, nM [Flow]	-	6.91	11.27	4.37	9.52
STAT3 DC_{50}, nM [Flow]	n/a	19.79	29.26	16.62	23.02

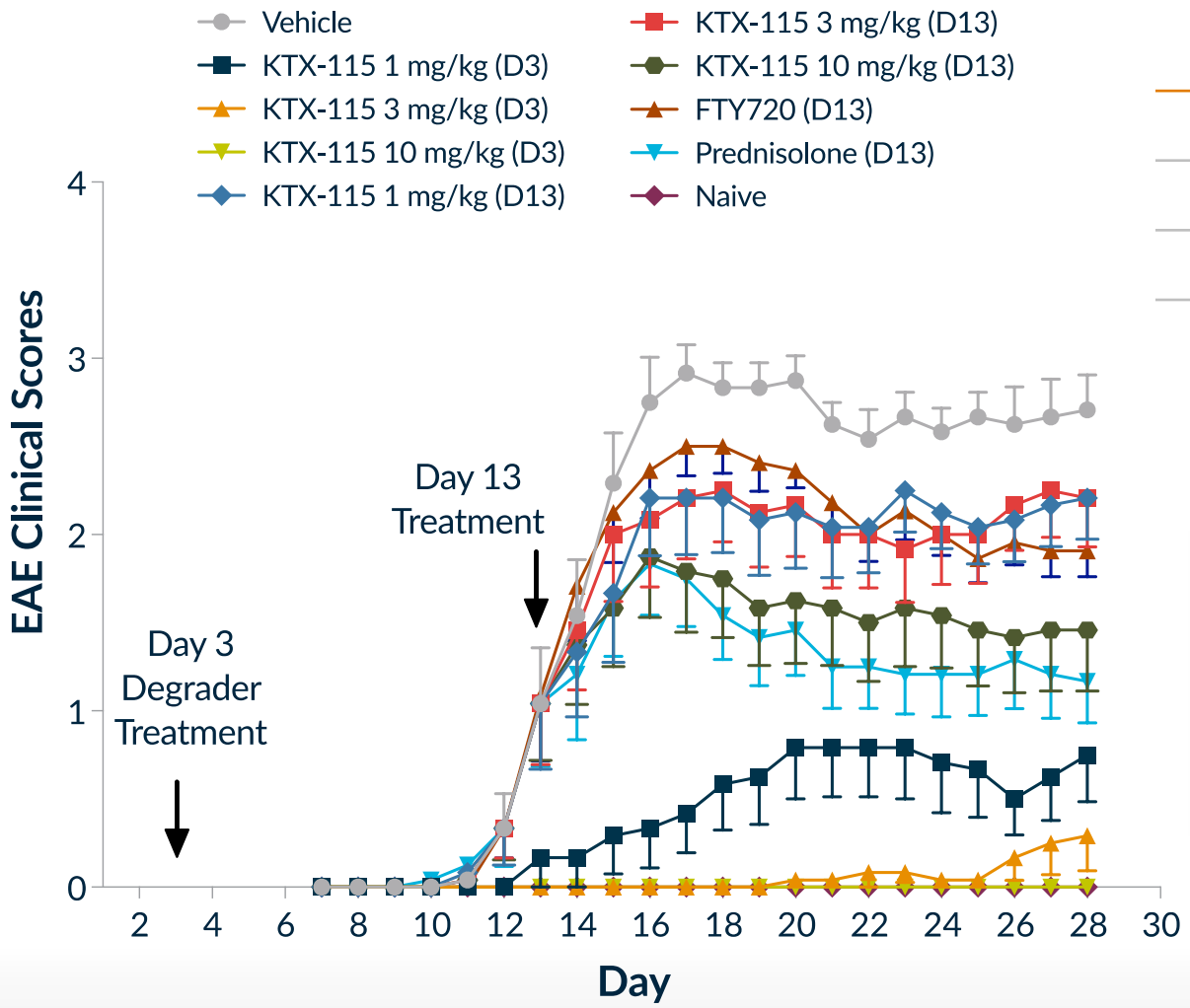
STAT3 Degradation Inhibits CD4+ Th17 Development and Related Cytokine Production





- CD4+ naïve T cells isolated from huPBMC were treated overnight with KTX-115 before activation with aCD3/CD28 coated beads and cultured with a pro-Th17 cocktail of cytokines and antibodies
- Ratios of Th17 cells vs. Treg cells as well as cytokines in supernatants were estimated after 7 days of cell culture

STAT3 Degradation Blocks Disease Induction and Diminishes Established Disease in Murine EAE Model

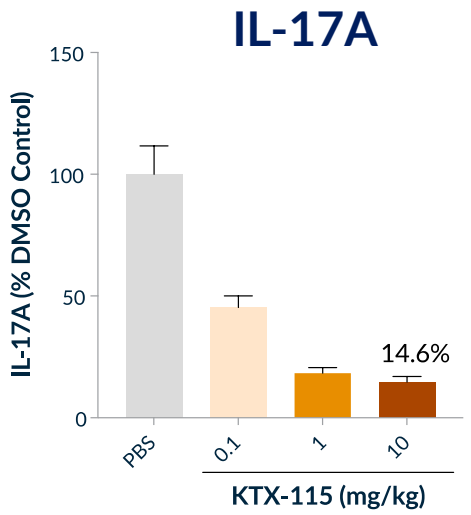


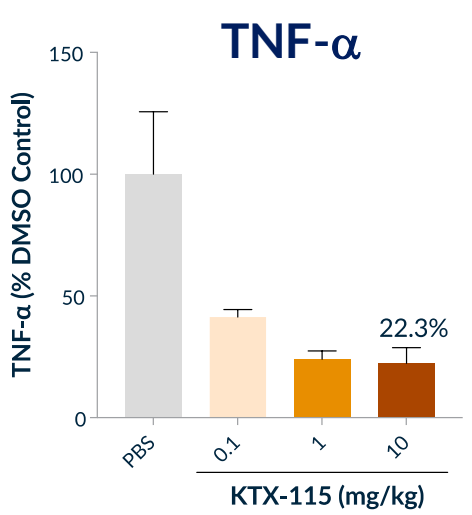
Treatment	EAE Incidence (%)	Median Day of Onset	End Score (+/-SD)
Vehicle	100.0%	13.0	2.71 +/- 0.69
1mg/kg KTX-115	66.7%	23.0	0.75 +/- 0.92
3mg/kg KTX-115	16.7%	>28.0*	0.29 +/- 0.69
10mg/kg KTX-115	0.0%	>28.0*	0.00 +/- 0.00

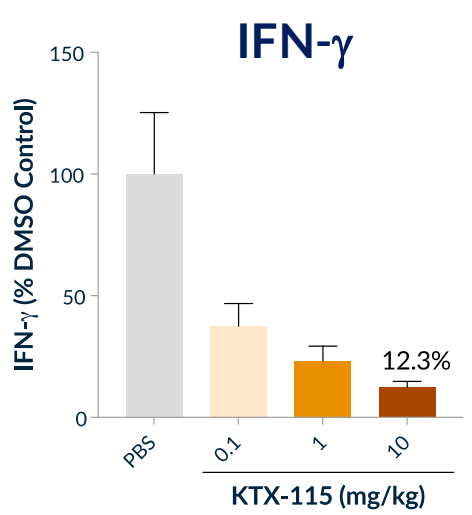
- STAT3 degraders dose-dependently inhibit MOG-EAE induction, preventively. They can also outperform a S1P receptor agonist in therapeutic mode
- They can also outperform a S1P receptor agonist in therapeutic mode

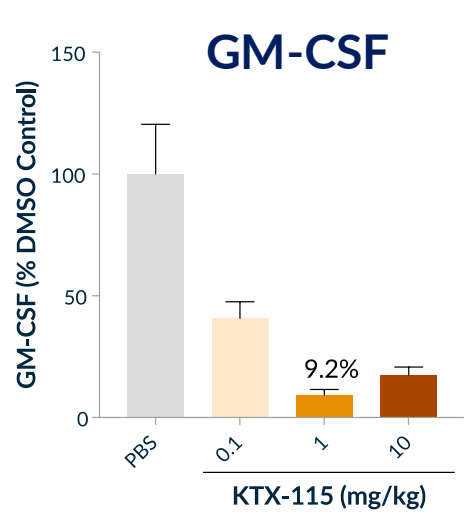
STAT3 Degradation Inhibits TH17 Cytokine Release by DLN Cells even when Restimulated by their Cognate Antigen (MOG)

No MOG Restimulation

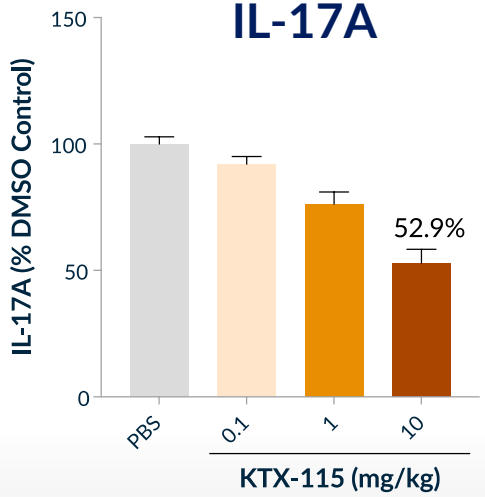


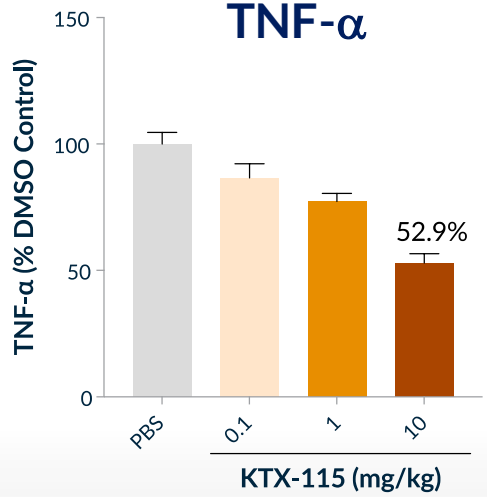


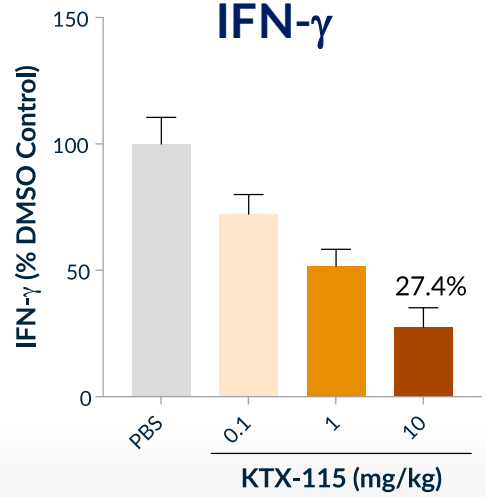


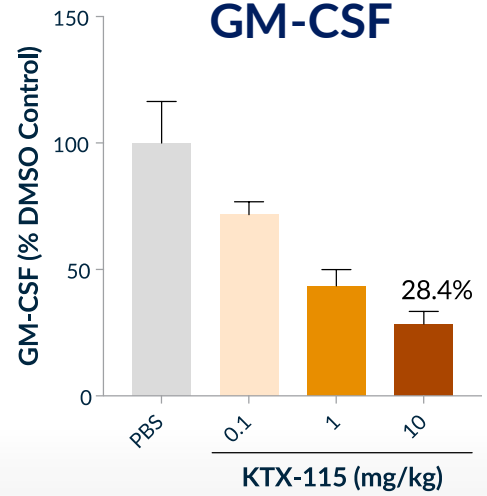


20µg/mL MOG Restimulation









STAT3 Summary

- Kymera has developed highly potent and selective degraders of STAT3, widely considered an “undruggable” target
- STAT3 degradation abrogates activation by multiple inflammatory stimuli in PBMC, monocytes, and CD4+ T cells
- Even limited degradation of STAT3 results in significant inhibition of cytokines involved in inflammation in several cell types (PBMC, monocytes, and T cells)
- Treatment with STAT3 degraders effectively inhibited TH17 differentiation and rebalances T reg ratios
- Robust, dose-dependent reduction of EAE clinical scores in a preclinical mouse model as well as reduction of cellular inflammatory response post restimulation

Thank you

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