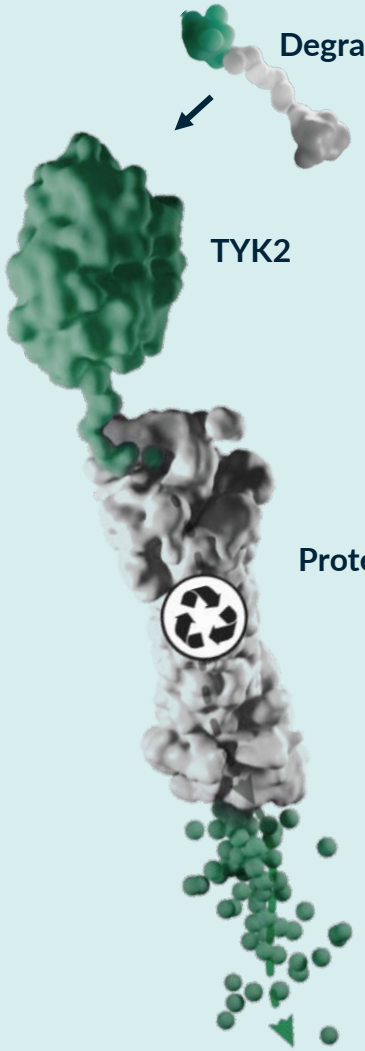

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54020. Potent and Selective TYK2 degraders, Devoid of JAK Activity, Potently and Completely Suppress IL12/23 and Type I IFN Signaling Pathways

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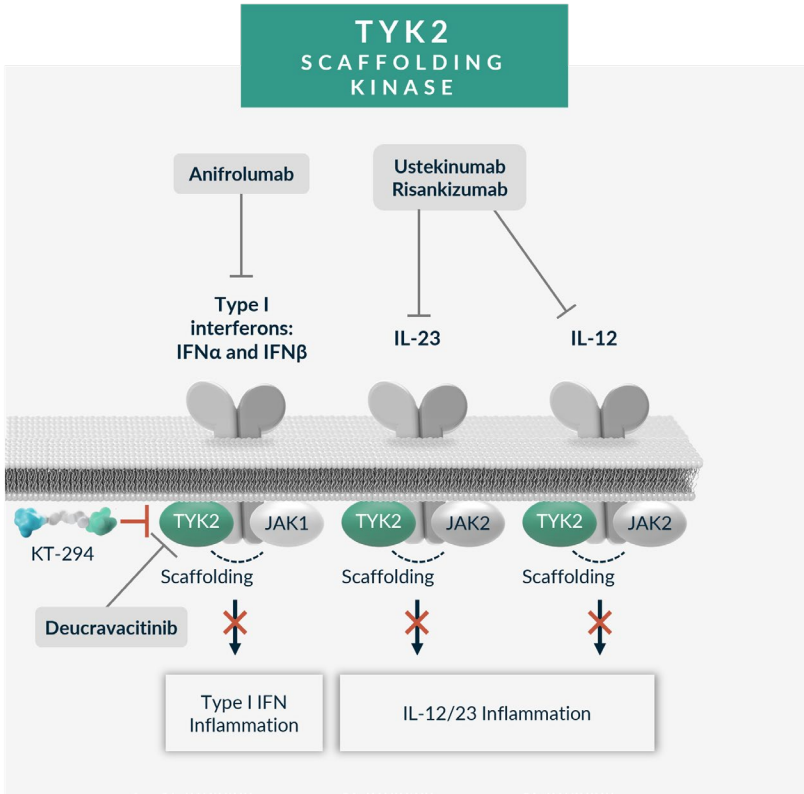
Introduction

TYK2, a member of the JAK family of kinases, binds the IL-12, IL-23 and type I IFN receptors to recruit and phosphorylate signal transducer and activation of transcription (STAT) transcription factors. A loss of function variant is protective in autoimmune diseases and an allosteric inhibitor (deucravacitinib) of TYK2 as well as biological agents targeting IL-12, IL-23 and IFN-α have been approved for the treatment of multiple autoimmune diseases, making TYK2 a highly attractive target. A common missense variant of TYK2, P1104A, rendering the protein catalytically inactive still supports signaling through the Type I IFN pathway, indicating that blocking the scaffolding function is required for inhibition of type I IFN. In addition, TYK2 inhibitors either approved or in clinical development have not demonstrated full target inhibition at clinically relevant doses.



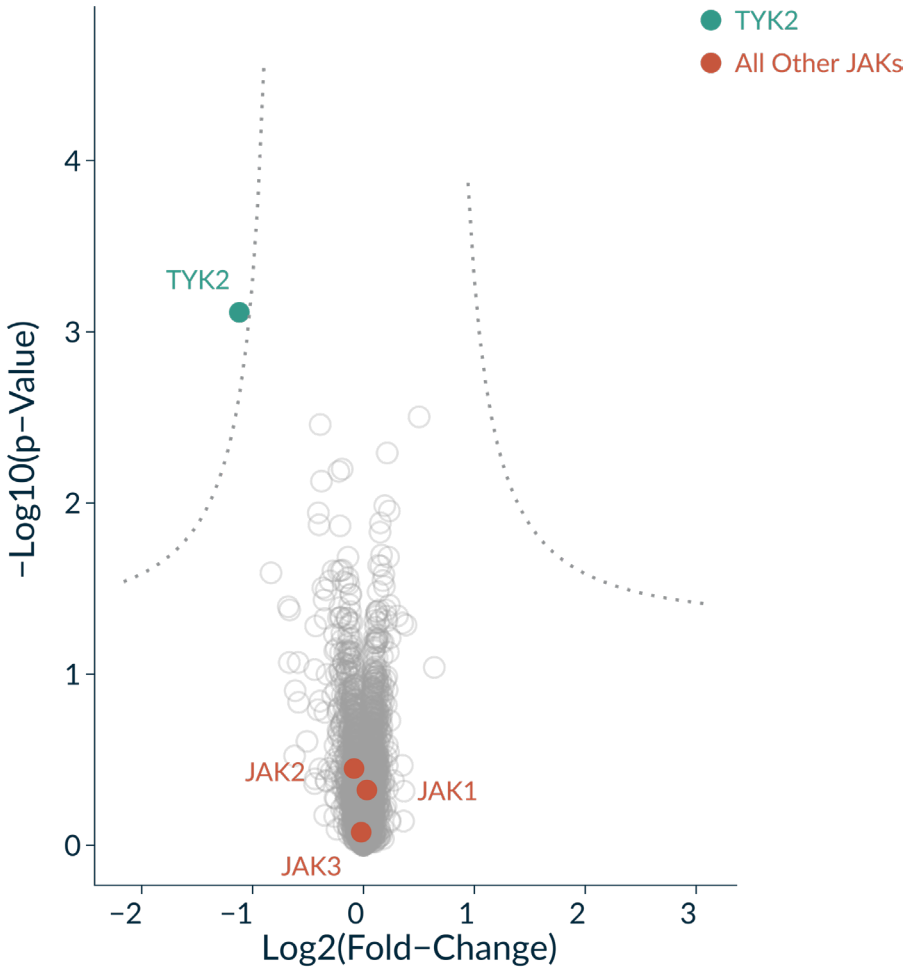
Methods and Results

We have developed a highly potent and exquisitely selective TYK2 degrader KT-294. We tested TYK2 in key cellular assays of the IL-12, IL-23 and IFN-α pathways in human primary cells. We compared the cytokine inhibition profiles of KT-294 with deucravacitinib and TAK-279 which support potential advantage of blocking both catalytic and scaffolding functions by degradation vs. small molecule inhibition. KT-294 is orally bioavailable and achieved full TYK2 degradation *in vivo* with low oral doses.

Results

KT-294, a highly selective picomolar TYK2 degrader, recapitulates TYK2 human deficiency biology and fully Inhibits IL-12/23 and IFN-α, and spares IL-10/22

Selective TYK2 Degradation by KT-294 in human PBMC Proteome at 10x DC_{90}



Cellular Degradation/Functional Assay	KT-294 DC_{50}/IC_{50} (nM)
Human PBMC degradation	0.08
Human keratinocyte (neonatal and adult)	0.07
IL-23 pathway	
IL-23 pSTAT4 in human PBMC	0.7
IL-23 pSTAT3 in human CD3+CD161high TH17 cell	2.1
IL-23/IL-1β IFN-γ release in human PBMC	2.4
Type I IFN pathway	
IFN-α pSTAT1 in human CD19 B cell	13
IFN-α pSTAT2 in human CD19 B cell	15
IFN-α IP10 release in human PBMC	4.9
IL-12 pathway	
IL-12/IL-18 pSTAT4 in human PBMC	1.3
IL-12/IL-18 IFN-γ release in human PBMC	10
IL-10 and IL-22 pathways	
IL-10 pSTAT3 in human CD14 monocyte	> 1000
IL-22 pSTAT1 in HT29 cell	> 1000
IL-22 pSTAT3 in HT29 cell	> 1000

Results

KT-294, unlike allosteric TYK2 inhibitor deucravacitinib, does not inhibit IL-10

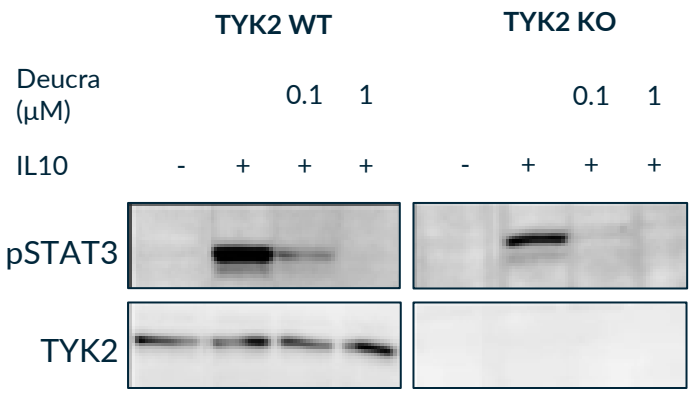
IL-10 has essential roles in intestinal homeostasis

- Loss of function mutations of the IL-10 pathway cause early onset refractory colitis in humans

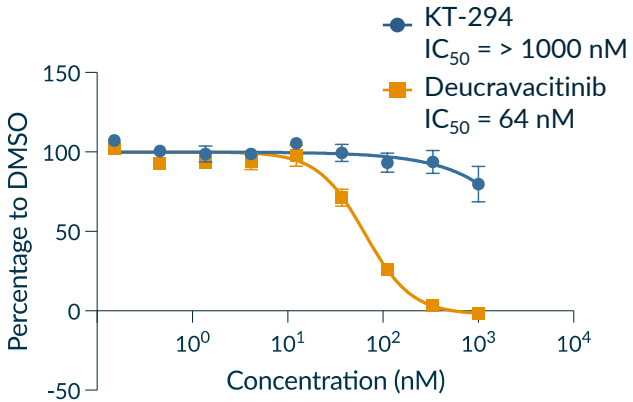
Deucravacitinib inhibits IL-10 through JAK1

- Deucravacitinib JAK1 Ki = 0.33 nM (Burke et al. Sci Transl Med. 2019)
- KT-294 JAK1 Ki = > 1000 nM

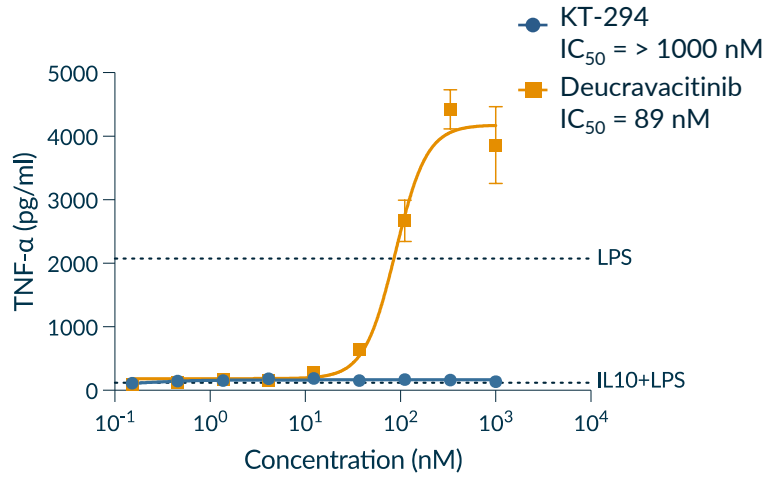
Deucravacitinib Inhibited IL-10 induced pSTAT3 in TYK2 KO EBV B Cell



Deucravacitinib Inhibited IL-10 Induced pSTAT3 in Human CD14 Monocyte



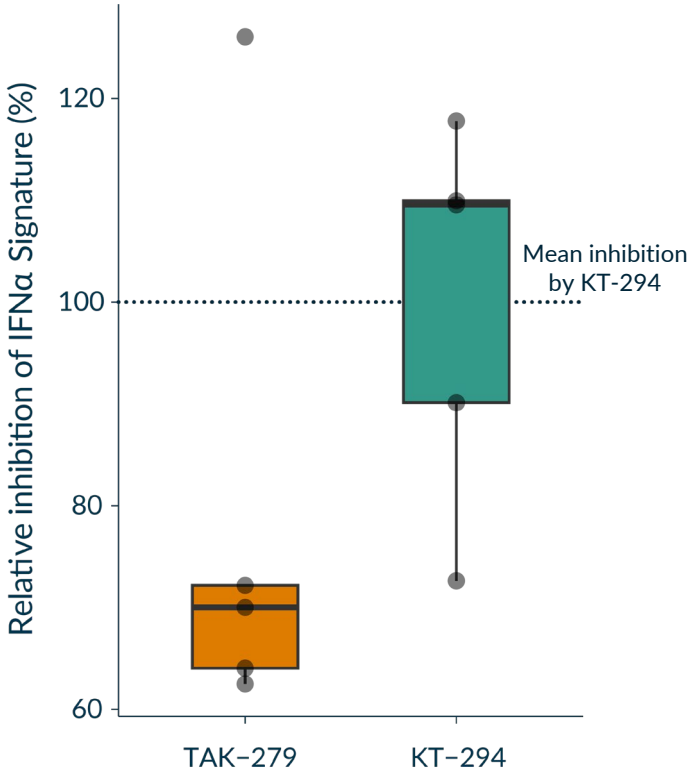
Deucravacitinib inhibited IL-10's function of suppressing LPS induced TNF-α release in human CD14 monocyte



Results

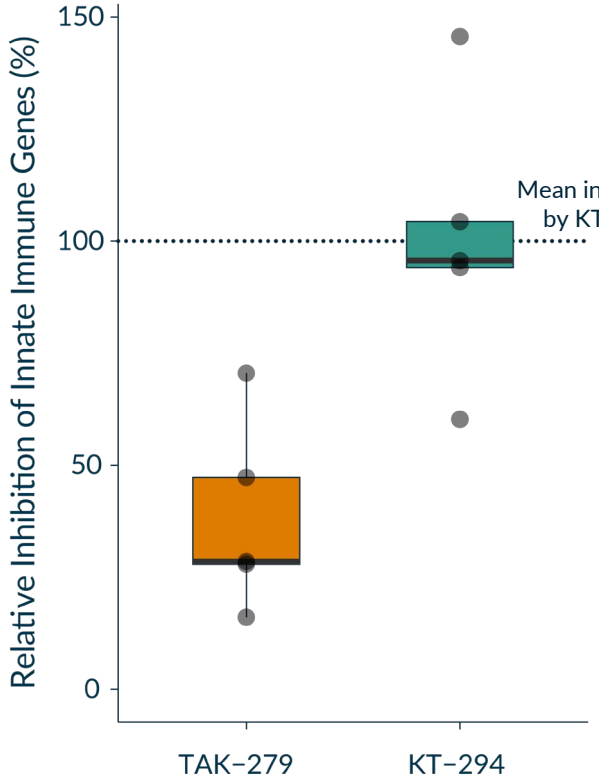
Superior Inhibition of type I IFN pathway and innate immunity by KT-294 vs TAK-279

21-gene IFNα Signature Score was Measured by RNAseq



SG15
IFI6
IFI27
SPATS2L
LY6E
IFI44L
OAS3
OAS1
USP18
SIGLEC1
IFIT1
IFI44
HERC5
RTP4
OAS2
MX1
EPSTI1
RSAD2
IFIT3
LAMP3
PLSCR1

12-gene Innate Signature Score was Measured by RNAseq



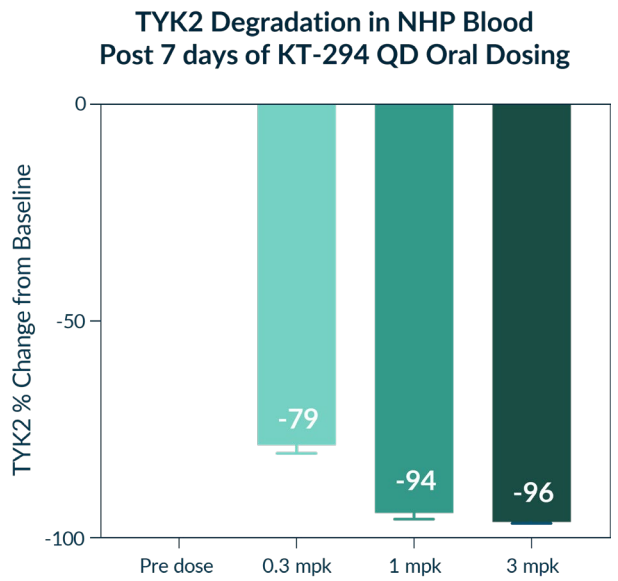
DEFB1
ISG15
DSP
HPSE
ZBP1
HMOX1
HSPA1A
BST2
CYSTM1
DHX58
PSMD9
ARL8A

Doses Used:

- TAK-279 = 422nM (IFN-α stimulated pSTAT2 IC_{95}). Clinical exposure Cmax (free) at 35mg = ~ 77 nM
- KT-294 = 56nM (IFN-α stimulated pSTAT2 IC_{95})

Results

KT-294 achieves dose dependent deep TYK2 degradation *in vivo* with low oral doses



Biological and clinical differentiation

TYK2 Clinical Opportunities	Deucravacitinib IL12/23, IFN, IL10	TAK-279 IL12/23, ~IFN	KT-294 IL12/23, IFN	*KT-294, unlike TYK2 SMI, can replicate the TYK2 deficient phenotype and result: potent Type I IFN, IL-12/23 inhibition fully while sparing IL-10* WITH FOLLOWING EXPECTED CLINICAL DIFFERENTIATION:
Psoriasis	++	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)
Psoriatic Arthritis	++	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)
IBD	-	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile), + sparing IL-10
Lupus & interferonopathies	++	+	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile) + best anti-IFN profile

Conclusion

- KT-294 is a highly potent and selective TYK2 degrader developed with the targeted protein degradation platform at Kymera.
- TYK2 degradation by KT-294 recapitulates human TYK2 deficiency biology with potent IL-12/23 and type I IFN inhibition and sparing of IL-10/22.
- By blocking both the catalytic and scaffolding functions of TYK2, KT-294 achieves a differentiated cytokine inhibition profile supporting potential advantage over small molecules. Unlike deucravacitinib, which inhibits IL-10 through JAK1, KT-294 does not inhibit IL-10, which is important in IBD. Compared to TAK-279, KT-294 fully inhibits Type I IFN which is important in interferonopathies.
- KT-294 demonstrates deep and sustained knock down *in vivo* with low oral doses.

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