Potent and Selective Oral STAT6 Degrader, KT-621, Inhibits IL-4 and IL-13 Functions in Human Cells and Blocks Th2 Inflammation in House Dust Mite Models of Asthma Prophylactically and Therapeutically

#P1564

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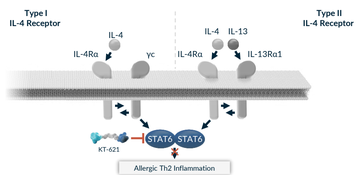
INTRODUCTION

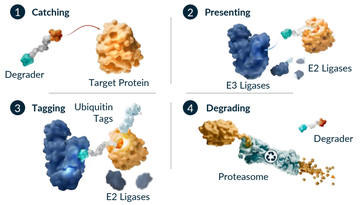
STAT6 is a historically undrugged essential transcription factor in the IL-4/IL-13 signaling pathways and the central driver of Th2 inflammation in allergic and atopic diseases. Multiple gain of function mutations of STAT6 have been identified to cause severe atopic/allergic diseases in humans. Dupilumab, an injectable monoclonal antibody that blocks IL-4/IL-13 signaling, is an approved therapy for multiple allergic/atopic diseases therefore targeting STAT6 in these diseases is supported by both human genetics and dupilumab's clinical activity. STAT6 functions through protein-protein and protein-DNA interactions. For these reasons, it has been challenging to selectively and potently inhibit STAT6 with traditional small molecule inhibitors. However, STAT6 is well suited for a novel targeted protein degradation approach, where a single binding event is sufficient to drive degradation of the protein and fully block its functions.

STAT6 Biology and Target Rationale



- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases
- Gain of function mutations of STAT6 cause severe allergic diseases in human
- Human heterozygous LOF are healthy and protected against Th2 inflammation
- STAT6 KO mice develop normally, are viable and fertile
- Dupilumab, an IL-4Rα monoclonal Ab that blocks IL-4/IL-13 signaling, has been approved in AD, Asthma, COPD, CRSwNP, EoE, PN, CSU, has positive Phase 3 data in BP, and is in late-stage development for multiple additional indications
- STAT6 degradation can achieve dupilumab–like pathway inhibition

Proteome Editing with Targeted Protein Degradation



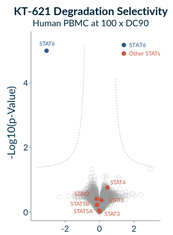
RESULTS

Figure 1. KT-621: A Highly Selective Picomolar Degrader of STAT6

A

	Human Primary Cell Type	KT-621, DC_{50} (pM)
	Hematopoietic cell, all TH2 disease	
Blood	Human PBMC	13
	Human CD3 T cell	36
	Human CD14 monocyte	60
	Human CD19 B cell	86
	Human eosinophil	99
	Epithelial cell, AD, CSU, asthma, COPD	
Skin	Human keratinocyte (adult)	22
	Human keratinocyte (neonatal)	18
Lungs	Human bronchial tracheal epithelial cell	33
	Human small airway epithelial cells	35
	Smooth muscle cell, asthma, COPD, EoE	
Throat/Airway	Human bronchial smooth muscle cell	25
	Human esophageal smooth muscle cell	33
Blood Vessels	**Endothelial cell, all TH2 disease**	
	Human vascular endothelial cell	46
Neurons	**Neuron, AD, PN, CSU**	
	Human iPSC derived sensory neuron	22

B



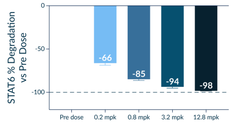
A) Consistent degradation by KT-621 across all disease relevant cell types evaluated. **B**) Exquisite STAT6 degradation selectivity in proteomics experiment and complete functional selectivity of KT-621 against all other STATs.

Figure 2: KT-621 Fully Blocks IL-4/IL-13 Functions in Human Primary Cells, More Potently than Dupilumab

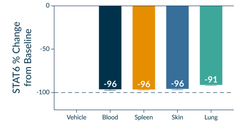
		Cellular Functional Assay	KT-621 IC_{50} (pM)	Dupilumab IC_{50} (pM)
TARC	Serum Th2 biomarker, chemoattractant for Th2 cell	IL-4 TARC release in human PBMC	62	194
		IL-13 TARC release in human PBMC	43	113
CD23	B cell activation marker, correlates with IgE class switch	IL-4 CD23 expression in human CD19 B cell	125	354
		IL-13 CD23 expression in human CD19 B cell	98	1070
PERIOSTIN	Serum Th2 biomarker and ECM protein associated with tissue remodeling in atopic diseases	IL-13 Periostin release in human bronchial smooth muscle cell	24	637
		IL-13 Periostin release in human esophageal smooth muscle cell	39	431

Figure 3: KT-621 Potently Degrades STAT6 Across Preclinical Species with Low Oral Doses

A

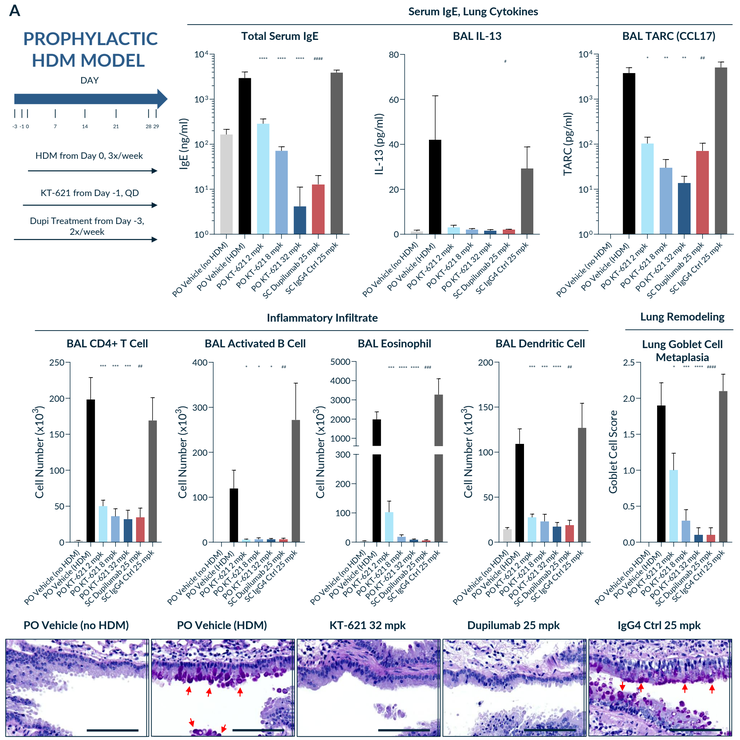


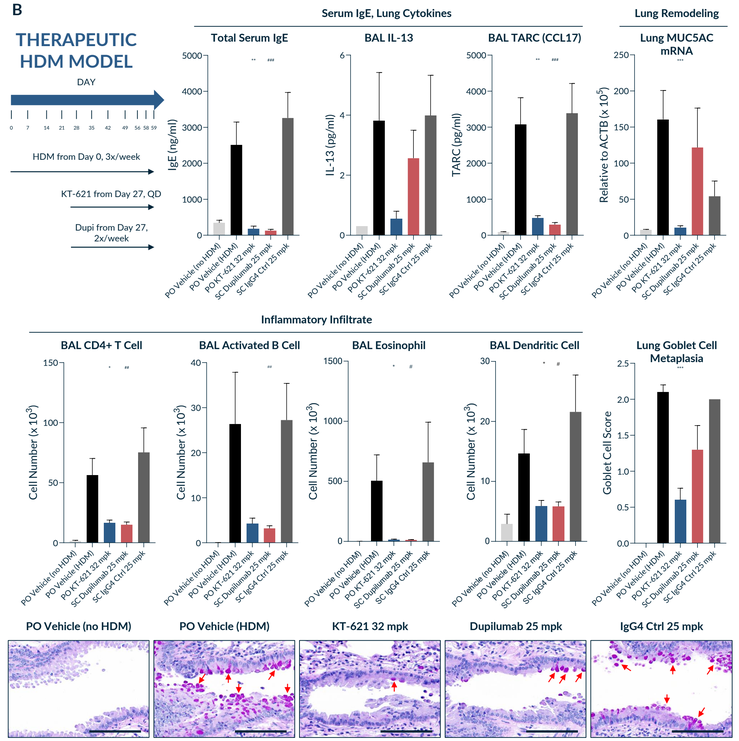
B



A) KT-621 achieves dose dependent deep degradation in dogs with low oral doses. STAT6 levels determined at 24 hours post the Day 7 dosing in PBMC isolated from the whole blood. **B**) KT-621 degrades STAT6 in disease relevant tissues in NHP. STAT6 levels determined at 24 hours post the Day 14 dose in PBMC isolated from the whole blood or the indicated tissues.

Figure 4: KT-621 Prevents Disease Progression and Reverses Disease in Both Prophylactic and Therapeutic HDM Asthma Models Equally or more Effectively than Dupilumab





A) A lung inflammation model induced by intranasal house dust mite (HDM) administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. *Allergy*. 2020). KT-621 dosed once daily (QD) orally for 31 days at 2/8/32 mpk doses showed 72/85/91% STAT6 degradation respectively in mouse spleen. Dupilumab dosed 9 times subcutaneously at 25 mpk BIW (IL-4Rα saturating dose), effect equivalent to 300 mg every other week in human. **B**) HDM-induced asthma model with a therapeutic regimen, KT-621 administered orally for 4 weeks with continuous HDM stimulation after disease establishment at 4 weeks not only fully prevented disease progression but also reversed pre-established disease. BAL, bronchoalveolar lavage. * Significance to PO vehicle (HDM), # Significance to SC IgG4 Ctrl 25 mpk. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, and ****p ≤ 0.0001.

METHODS

We have developed a highly potent, selective, orally administered degrader of STAT6, KT-621, and assessed Th2 functional inhibition in disease-relevant human primary cells *in vitro*. Additionally, KT-621 was assessed *in vivo* across multiple preclinical species for STAT6 degradation. We also compared the efficacy of KT-621 to dupilumab *in vivo* in HDM-induced asthma models in the IL4/IL4RA humanized mice.

KT-621 potently and selectively degraded STAT6 in various disease-relevant human primary cells including lymphocytes, myeloid cells, lung epithelial cells, bronchial smooth muscle cells, and vascular endothelial cells. As a result of STAT6 degradation, KT-621 fully blocked various IL-4/IL-13 functions in these cells with low picomolar potencies superior to dupilumab and did not degrade or inhibit any other STAT transcription factors or other proteins. In addition, KT-621 showed potent STAT6 degradation and IL-4/IL-13 functional inhibition in human whole blood. At low oral doses, KT-621 demonstrated deep *in vivo* STAT6 degradation, suppressed Th2 biomarkers, and was well-tolerated in multiple preclinical studies. In the intranasal HDM-induced asthma model in the hIL4/hIL4RA humanized mice, orally administered KT-621 demonstrated excellent *in vivo* efficacy comparable to that of an IL-4Rα saturating dose of dupilumab included in the same prophylactic study. Furthermore, in the HDM-induced asthma model with a treatment regimen, KT-621 administered orally after disease establishment not only fully prevented disease progression but also reversed pre-established inflammatory response and relevant features of airway remodeling.

CONCLUSIONS

STAT6 degradation is a novel oral approach for blocking the IL-4/IL-13 signaling pathways.

STAT6 degrader KT-621 has best-in-pathway potential for allergic and atopic diseases with a dupilumab-like activity profile and oral dosing

- KT-621 is a pM STAT6 degrader with exquisite selectivity developed with a clinically validated degrader platform at Kymera.
- STAT6 degradation by KT-621 fully blocks IL-4/IL-13 in key human Th2 cellular assays with picomolar IC_{50}s lower than dupilumab.
- KT-621 is orally bioavailable and can fully degrade STAT6 *in vivo* across several preclinical species including NHP with low oral doses.
- KT-621 is well tolerated in multiple preclinical species and in safety studies at concentrations that were 40-fold above efficacious concentrations.
- STAT6 degradation by KT-621 robustly inhibits Th2 inflammation *in vivo* in the mouse HDM asthma model comparable or superior to the IL-4Rα monoclonal antibody dupilumab prophylactically and therapeutically.
- KT-621 is currently in a Phase 1b clinical trial in AD patients (BroADen – NCT#06945458); Phase 2b trials in AD and asthma to be initiated in Q4 2025 and Q1 2026, respectively.

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DISCLOSURES

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