

Potent and Selective Oral STAT6 Degraders Inhibit IL-4 and IL-13 Functions in Human Cells and Block TH2 Inflammation In Vivo in a Mouse Model

#Tu1488

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INTRODUCTION

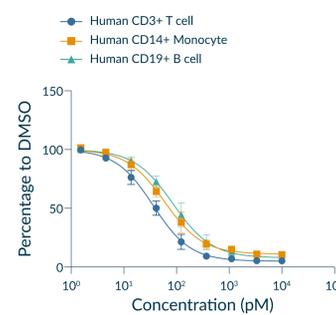
STAT6 is an undrugged essential transcription factor in the IL-4/IL-13 signaling pathways and the central driver of TH2 inflammation in allergic diseases. Multiple gain of function mutations of STAT6 were identified to cause severe allergic diseases in human. Dupilumab, an injectable monoclonal antibody that blocks IL-4/IL-13 signaling, is an approved therapy for multiple allergic diseases. STAT6 targeting is therefore supported by both human genetics and dupilumab's clinical pathway validation. 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. It is, however, well suited for a targeted protein degradation approach, where a simple binding event is sufficient to drive degradation.

RESULTS

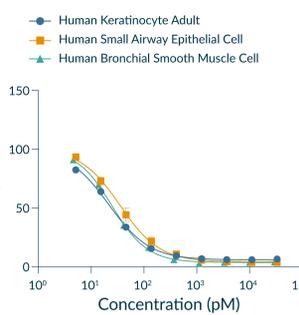
Figure 1. KT-621: A Highly Selective Picomolar Degradator of STAT6

Human Primary Cell Type	KT-621, DC ₅₀ (pM)
Hematopoietic cell, all TH2 disease	
Human PBMC	13
Blood	
Human CD3 T cell	36
Human CD14 monocyte	60
Human CD19 B cell	86
Human eosinophil	99
Epithelial cell, AD, CPG, CU, asthma, COPD	
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	
Human bronchial smooth muscle cell	25
Throat/Airway	
Human esophageal smooth muscle cell	33
Endothelial cell, all TH2 disease	
Blood Vessels	
Human vascular endothelial cell	46

STAT6 Degradation in Hematopoietic Cells

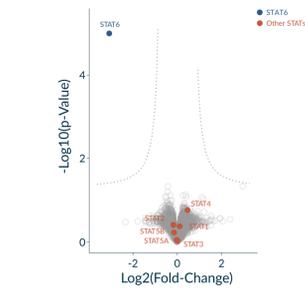


STAT6 Degradation in Tissues Cells



B

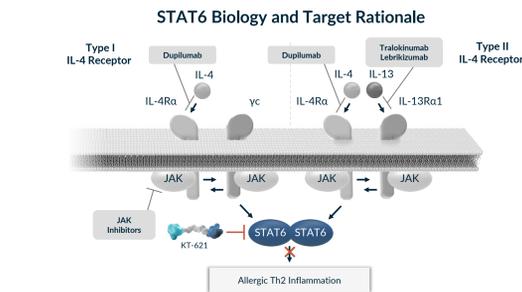
KT-621 Degradation Selectivity



A) Consistent degradation by KT-621 across all disease relevant cell types evaluated. B) Complete STAT6 degradation and function selectivity of KT-621 against all other STATs.

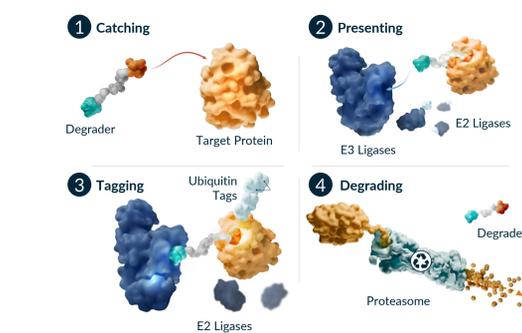
KT-621 Function Selectivity

STAT Assays	KT-621, DC ₅₀ (pM)
IFN-α induced pSTAT1	>1000
IFN-α induced pSTAT2	>1000
IL-10 induced pSTAT3	>1000
IL-12 induced pSTAT4	>1000
IL-2 induced pSTAT5	>1000
IL-3 induced pSTAT6	0.042



- 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 (GOF) mutations of STAT6 cause severe allergic diseases in human.
- STAT6 KO mice develop normally, are viable and fertile.
- Dupilumab, an IL-4Ra monoclonal Ab has been approved in: Atopic dermatitis, Asthma, CRSwNP, Eosinophilic Esophagitis, Prurigo Nodularis, has positive Phase 3 data in COPD and is in development for multiple additional indications.
- STAT6 degradation can achieve dupilumab-like pathway inhibition.

Proteome Editing with Targeted Protein Degradation

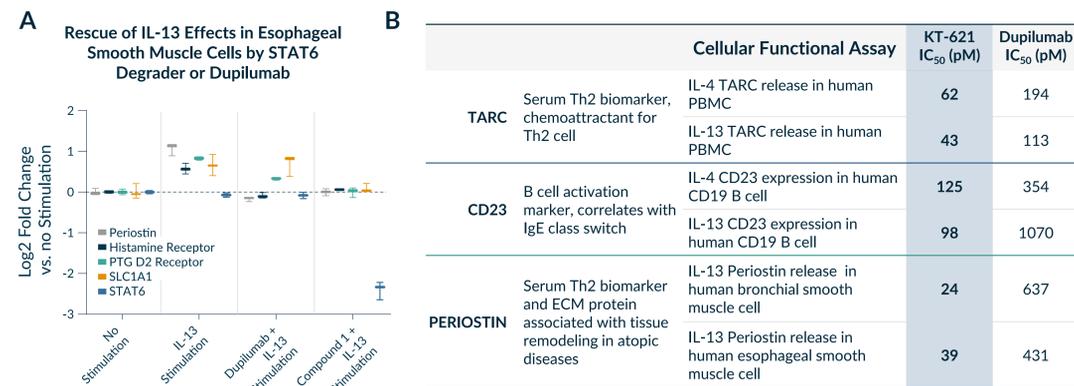


METHODS

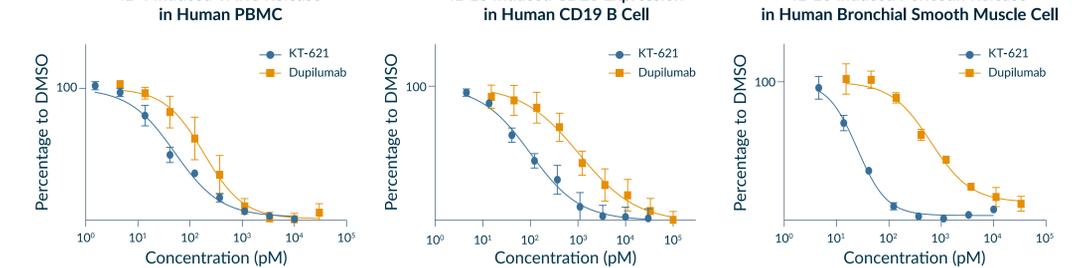
We developed highly potent and selective oral STAT6 degraders and assessed their functions in disease-relevant human primary immune and tissue cells in vitro. We also compared the efficacy of our STAT6 degraders to dupilumab in vivo in an intranasal house dust mite (HDM) induced lung inflammation model in a hIL4/hIL4RA humanized mice.

Our STAT6 degraders potently and selectively degraded and depleted 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, our degraders fully blocked various IL-4/IL-13 functions in these cells with picomolar potencies comparable or superior to dupilumab and did not degrade or inhibit any other STAT transcription factors. Specifically in esophageal smooth muscle cells, global proteomics demonstrated that our STAT6 degraders fully inhibited IL-13 induced expression of effector genes including periostin (POSTN), histamine H1 receptor (HRH1), and prostaglandin D2 receptor 2 (PTGDR2) that contribute to enhanced contractile response of esophageal muscle cells. Our STAT6 degraders showed potent STAT6 degradation and IL-4/IL-13 functional inhibition in human whole blood, were orally bioavailable in multiple preclinical species, and were able to deplete STAT6 in vivo. In an HDM induced asthma mouse model, orally administered STAT6 degrader KT-621 demonstrated robust degradation and reduced TH2 inflammation comparable to an IL-4Ra saturating dose of dupilumab.

Figure 2: KT-621 Fully Blocks IL-4/13 Pathways, More Potently than Dupilumab

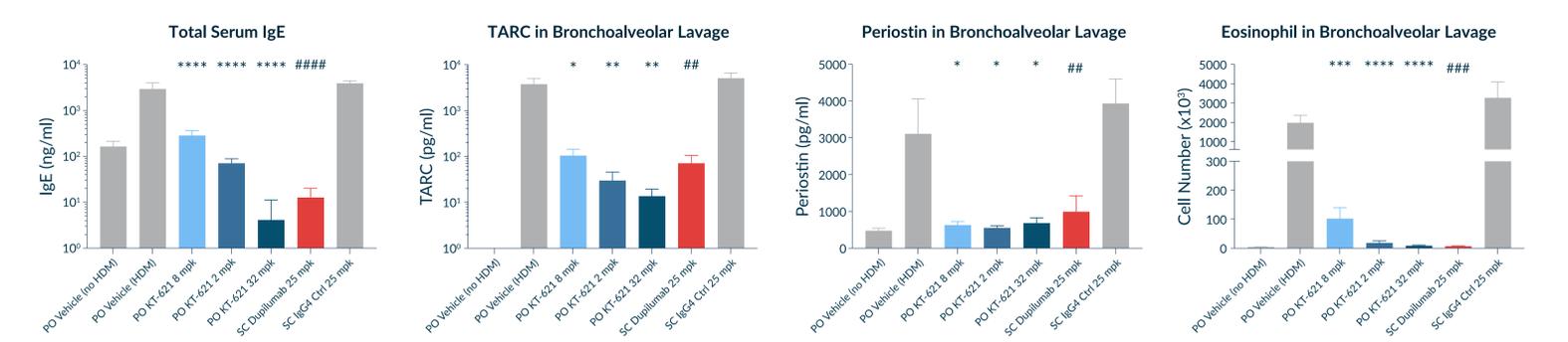


C



A) STAT6 tool degrader Compound 1 (100 nM) fully blocks IL-13 induced gene expression in esophageal smooth muscle cells vs partial inhibition by dupilumab (300 nM). B, C) KT-621 fully blocks key IL-4/13 functional readouts in human cells with lower IC₅₀s vs. dupilumab.

Figure 4: KT-621 Has Comparable in vivo Efficacy to IL-4Ra Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model



A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. Allergy. 2020). KT-621 dosed QD orally for 31 days. 2/8/32 mpk doses showed 72/85/91% STAT6 degradation respectively in mouse spleen. Dupilumab dosed 9 times subcutaneously, 25 mpk BIW (IL-4Ra saturating dose), effect equivalent to 300 mg every other week in human.

CONCLUSIONS

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

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

- KT-621 is a pM STAT6 degrader with exquisite selectivity developed with the targeted protein degradation platform at Kymera.
- STAT6 degradation by KT-621 fully blocks IL-4/13 in key human TH2 cellular assays with picomolar IC₅₀s lower than dupilumab.
- STAT6 degradation fully blocks IL-13 induced gene transcription in human primary esophageal smooth muscle cells, a key cell type in the pathophysiology of eosinophilic esophagitis.
- KT-621 is orally bioavailable and can fully degrade STAT6 in vivo with low oral doses.
- KT-621 is well tolerated in multiple preclinical species.
- STAT6 degradation by KT-621 robustly inhibits TH2 inflammation in vivo in the HDM asthma model comparable to the IL-4Ra monoclonal antibody dupilumab.

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DISCLOSURES

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