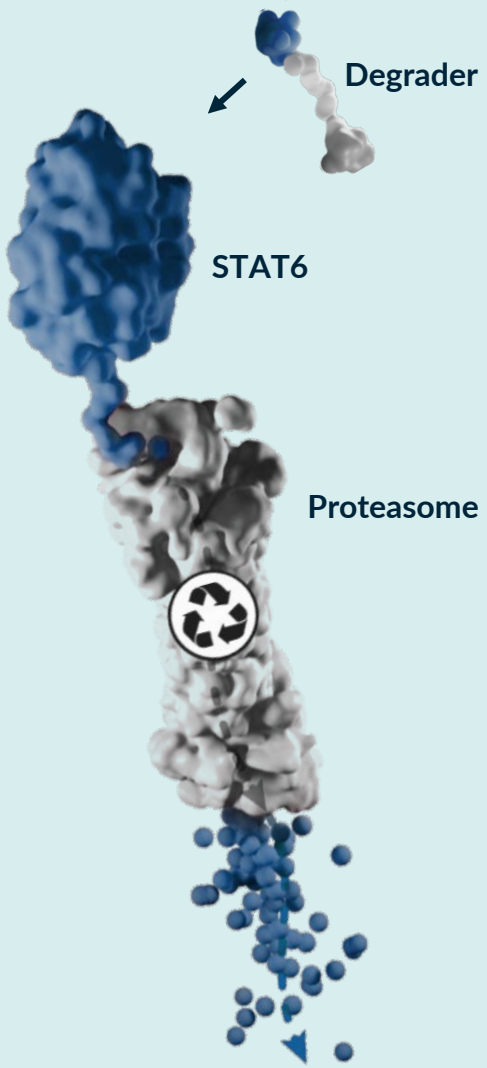

53901. Potent and Selective Oral STAT6 Degraders Inhibit IL-4 and IL-13 Functions in Human Cells and Block TH2 Inflammation in a Mouse Model of Atopic Dermatitis

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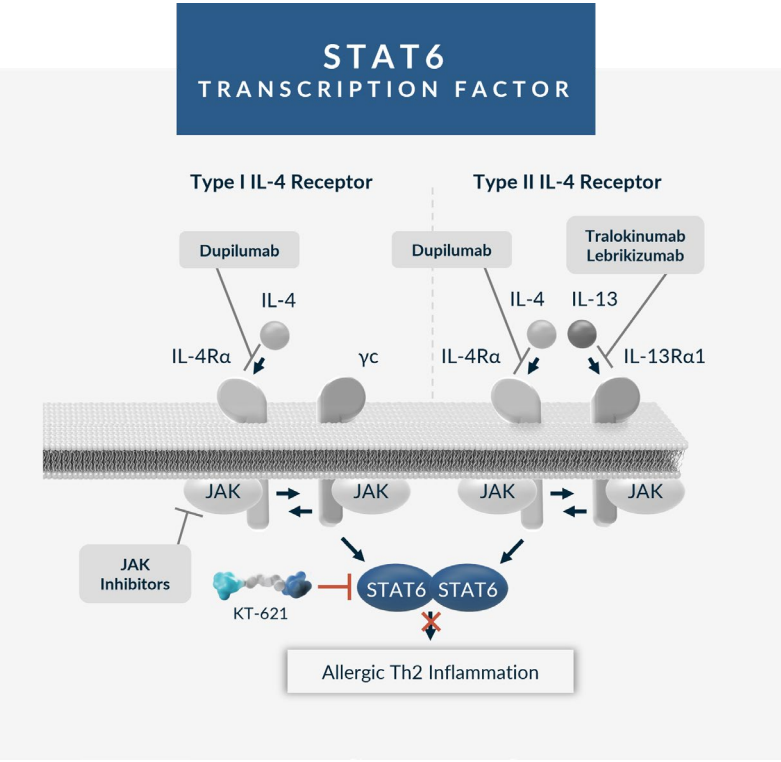
Introduction

STAT6 is an undrugged essential transcription factor in the IL-4 and 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-4/13 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 binding event is sufficient to drive degradation.



Methods and Results

We have developed highly potent STAT6 degraders that can selectively degrade and deplete STAT6 in various disease relevant human immune and tissue cells (shown here within), fully block various IL-4/13 functions in these cells with picomolar IC_{50} lower than the IL-4Rα monoclonal antibody dupilumab, and do not degrade or inhibit any other STAT transcription factors.

Our STAT6 degraders are orally bioavailable in multiple preclinical species and are able to deplete STAT6 *in vivo*. In a MC903-induced atopic dermatitis mouse model, orally administered STAT6 degraders demonstrate complete inhibition on the total serum IgE, a TH2 inflammation biomarker. STAT6 degradation is a potential novel oral approach for blocking the IL-4/13 pathways in development for the treatment of atopic dermatitis and other allergic diseases.

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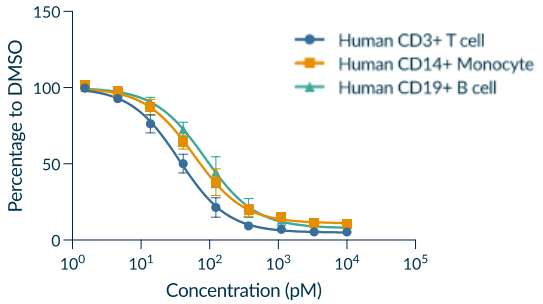
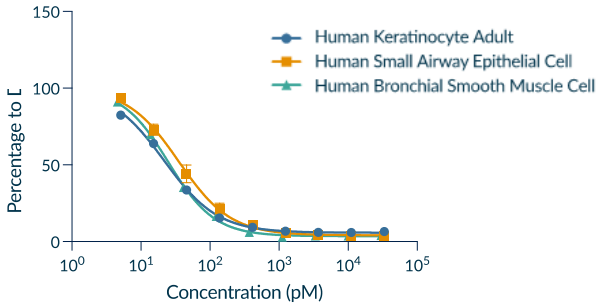
Results

KT-621 shows consistent degradation across all disease relevant human cell types evaluated

STAT6 Degradation in Hematopoietic Cells



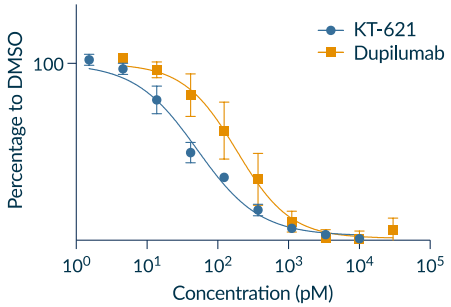
STAT6 Degradation in Tissue Cells



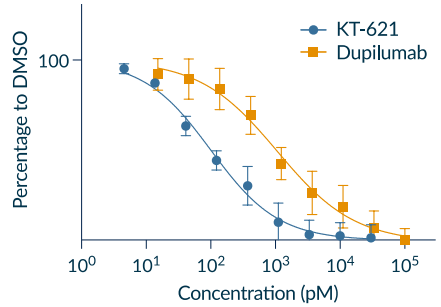
	Human Primary Cell Type	KT-621, DC_{50} (pM)
	Hematopoietic cell (all TH2 diseases)	
Blood	Human PBMC	13
Blood	Human CD3 T cell	36
Blood	Human CD14 monocyte	60
Blood	Human CD19 B cell	86
Blood	Human eosinophil	99
	Epithelial cell (AD, CPG, CU, asthma, COPD)	
Skin	Human keratinocyte (adult)	22
Skin	Human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

KT-621 fully blocks IL-4/13 functions in key human TH2 cellular assays with picomolar IC_{50} lower than the IL-4Rα monoclonal antibody dupilumab

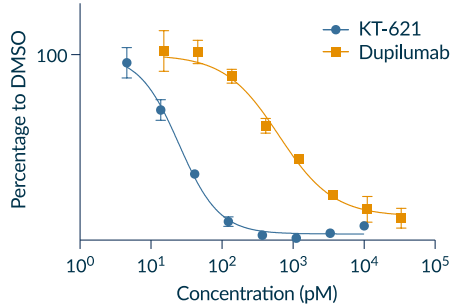
IL-4 Induced TARC Release in Human PBMC



IL-13 Induced CD23 Expression in Human CD19 B Cell



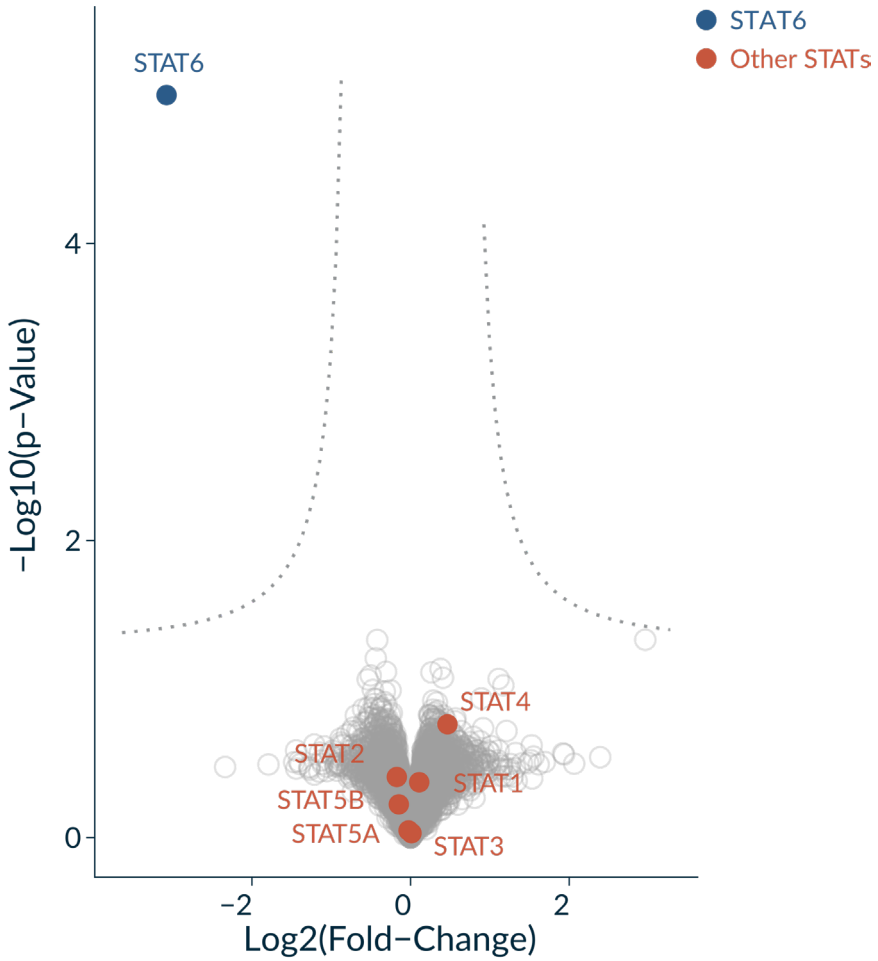
IL-13 Induced Periostin Release in Human Bronchial Smooth Muscle Cell



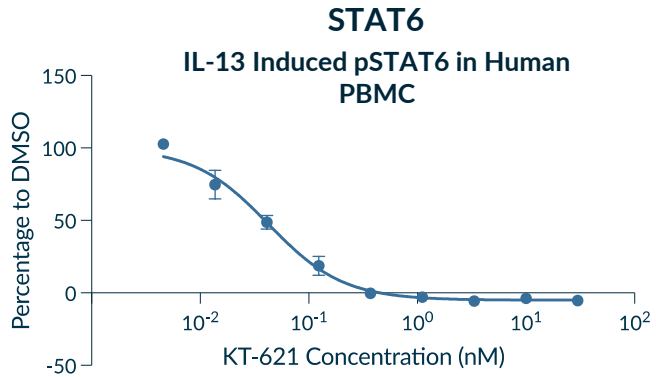
Cellular Functional Assay	KT-621 IC_{50} (pM)	Dupilumab IC_{50} (pM)
IL-4 TARC release in human PBMC	**62**	194
IL-13 TARC release in human PBMC	**43**	113
IL-4 CD23 expression in human CD19 B cell	**125**	354
IL-13 CD23 expression in human CD19 B cell	**98**	1070
IL-13 Periostin release in human bronchial smooth muscle cell	**24**	637
IL-13 Periostin release in human esophageal smooth muscle cell	**39**	431

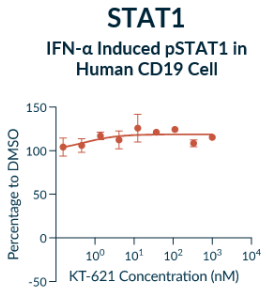
Results

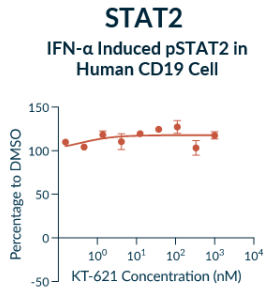
Exquisite STAT6 degradation selectivity of KT-621 in human PBMC proteome at 100 x DC_{90} with no other STATs degraded to any extent

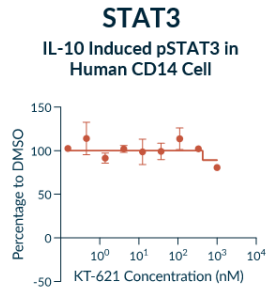


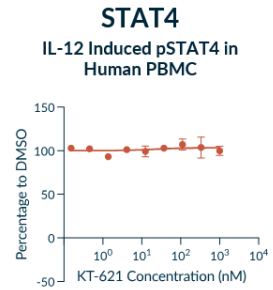
Exquisite pathway selectivity for STAT6 of KT-621 with no observed impact on any other STATs

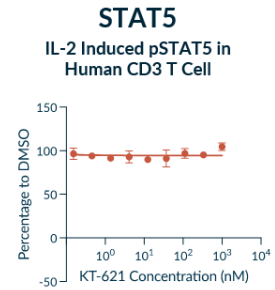








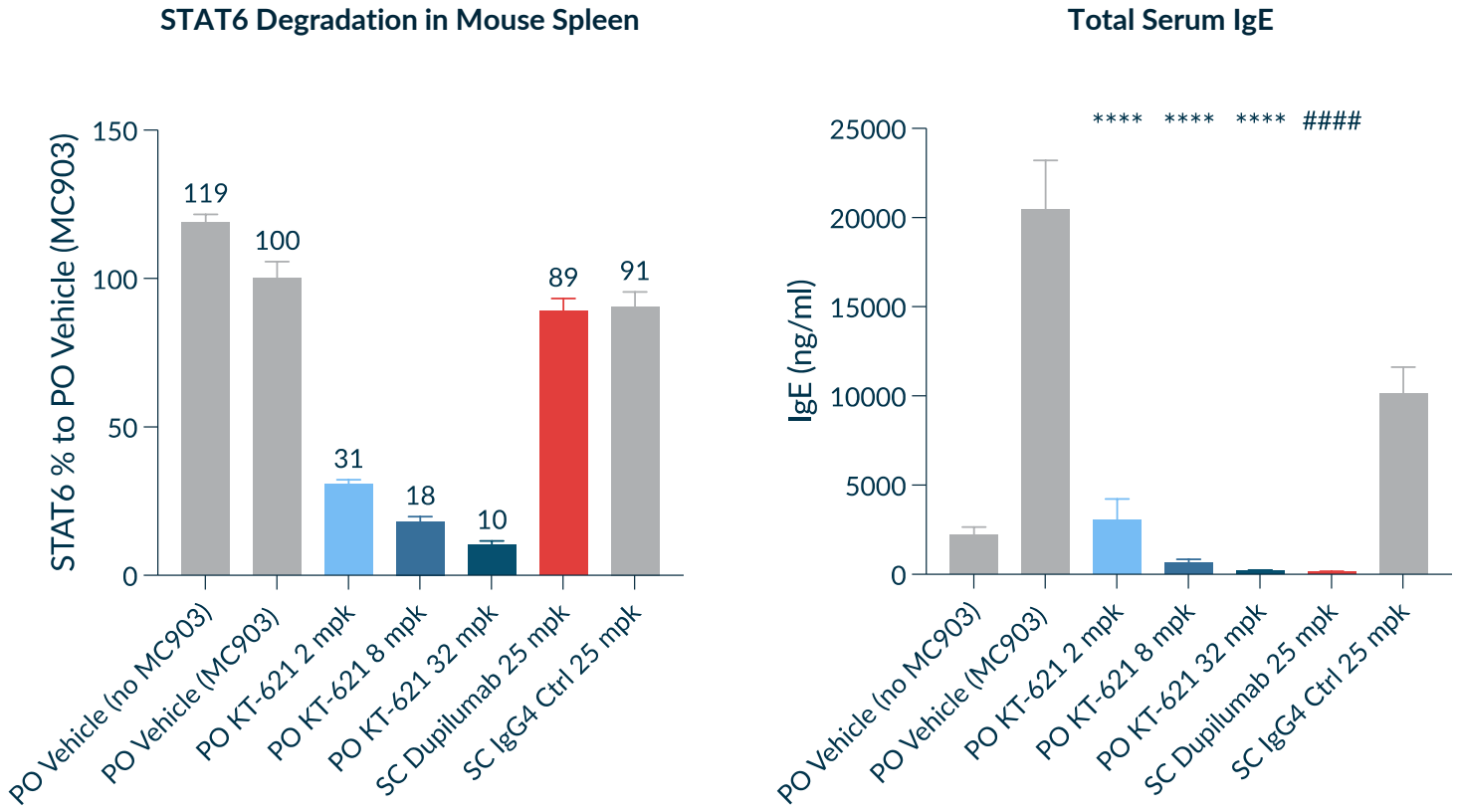




STAT assays	KT-621, IC_{50} (nM)
IFN-α induced pSTAT1	> 1000
IFN-α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042

Results

KT-621 has comparable *in vivo* activity to IL-4Rα saturating dose of the IL-4Rα monoclonal antibody dupilumab on a biomarker of TH2 inflammation in the MC903 atopic dermatitis model



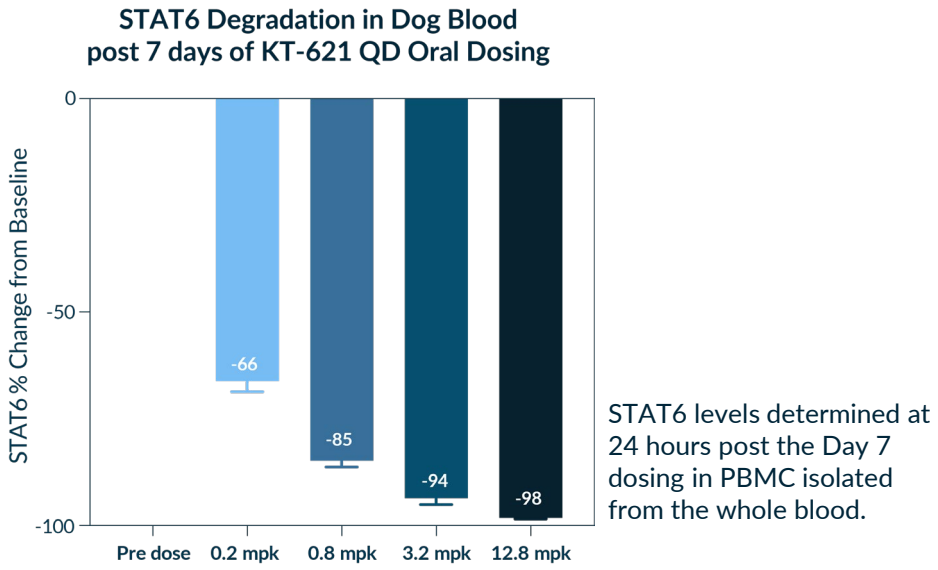
An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

- KT-621 dosed QD orally for 11 days
- Dupilumab dosed 4 times subcutaneously, 25 mpk twice a week (IL-4Rα saturating dose); effect equivalent to 300 mg every other week in human

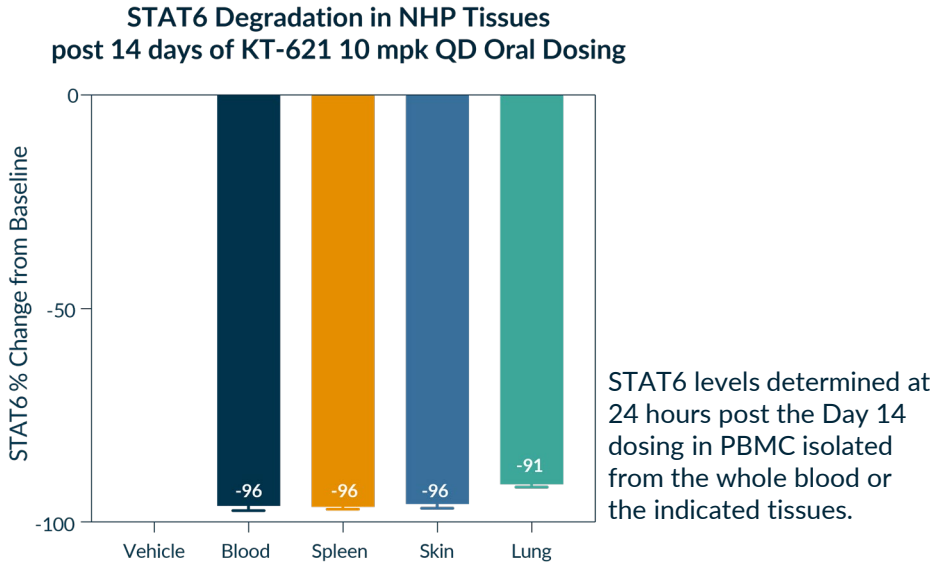
*Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk

Results

KT-621 achieves dose dependent deep degradation of STAT6 *in vivo* with low oral doses and in disease relevant tissues



STAT6 levels determined at 24 hours post the Day 7 dosing in PBMC isolated from the whole blood.



STAT6 levels determined at 24 hours post the Day 14 dosing in PBMC isolated from the whole blood or the indicated tissues.

Conclusion

- 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 by KT-621 robustly inhibits biomarker of TH2 inflammation *in vivo* in the MC903 atopic dermatitis model comparable to the IL-4Rα monoclonal antibody dupilumab.
- 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 is a potential novel oral approach for blocking the IL-4/13 pathways in development for the treatment of atopic dermatitis and other allergic diseases.

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