

The Potent and Selective Oral STAT6 Degradator, KT-621, Affects Gene Transcripts in Human Keratinocytes as Effectively as Dupilumab, and Blocks Th2 Inflammation in Atopic Dermatitis and Asthma Mouse Models

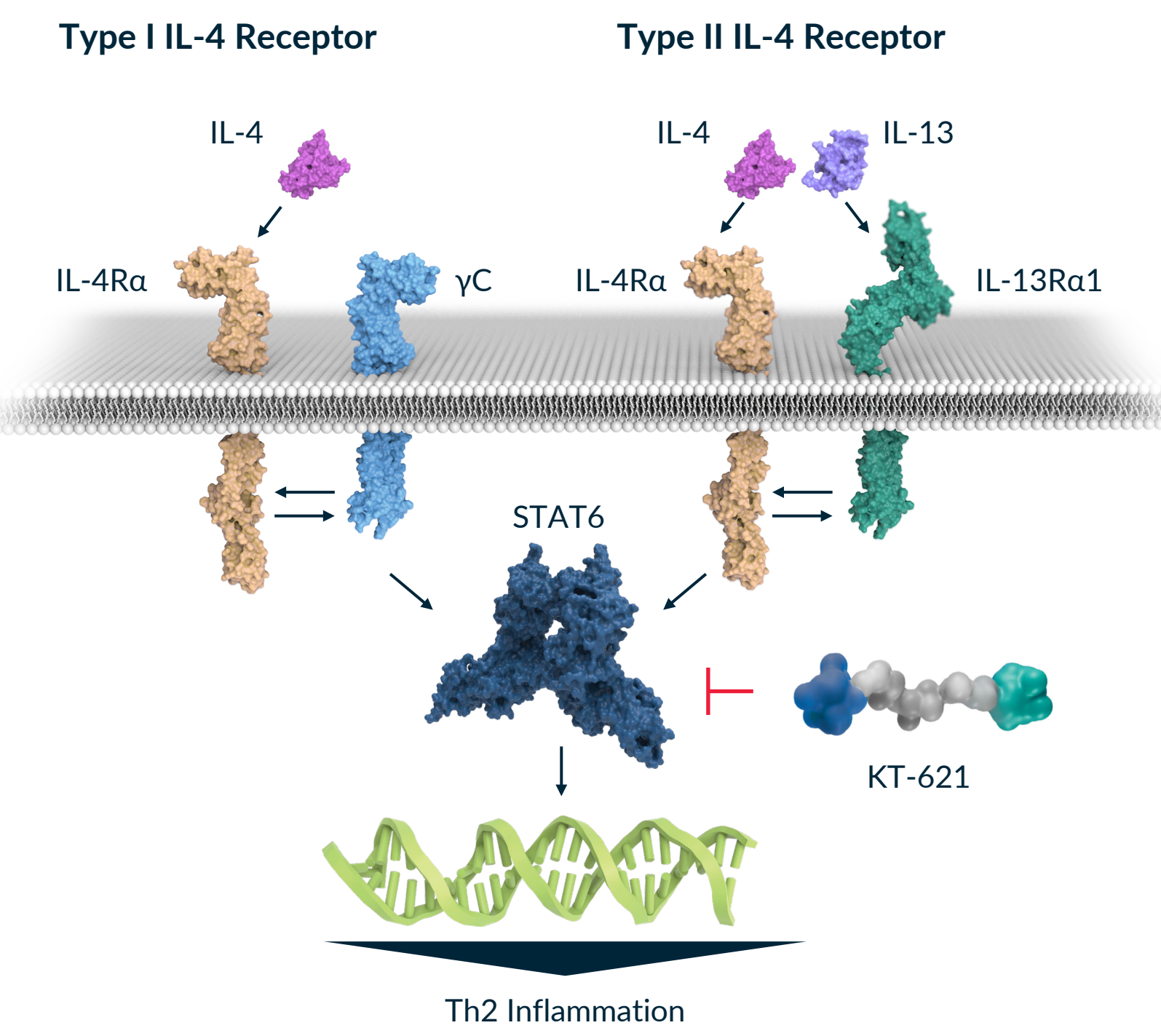
Amy Wang, Bin Yang, Karen Yuan, Alamgir Hossain, Rahul Karnik, James Shaw, Huijun Dong, Bruce Follows, Chris Browne, Ralf Schmidt, Rupa Sawant, Bradley Enerson, Chad Nivens, Nello Mainolfi

Kymera Therapeutics, 500 North Beacon Street, 4th Floor, Watertown, MA 02472

INTRODUCTION

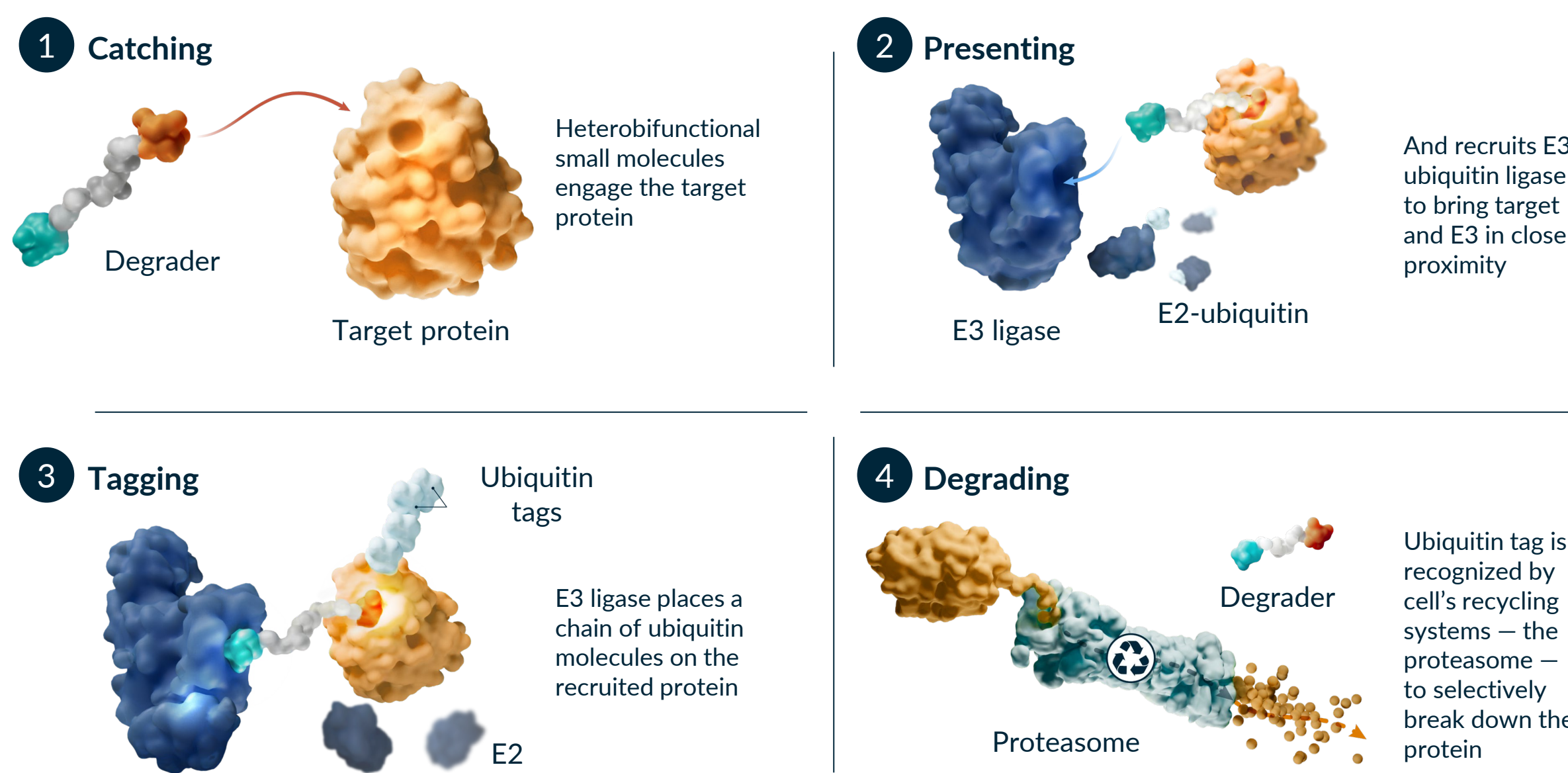
STAT6 is an essential transcription factor in the IL-4/IL-13 signaling pathways and the central driver of Th2 inflammation in allergic/atopic diseases. Multiple gain of function mutations of STAT6 have been identified to cause severe atopic/allergic diseases in humans. Dupilumab, an injectable monoclonal antibody that blocks IL-4/IL-13 signaling, is an approved therapy for multiple atopic/allergic 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. 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 simple 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/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
- Human heterozygous LOF are healthy and protected against Th2 inflammation
- Dupilumab, an IL-4Rα monoclonal Ab has been approved in: Atopic Dermatitis, Asthma, Bullous Pemphigoid, Chronic Rhinosinusitis with Nasal Polyps, COPD, Eosinophilic Esophagitis, Prurigo Nodularis, and is in 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 Degradator of STAT6

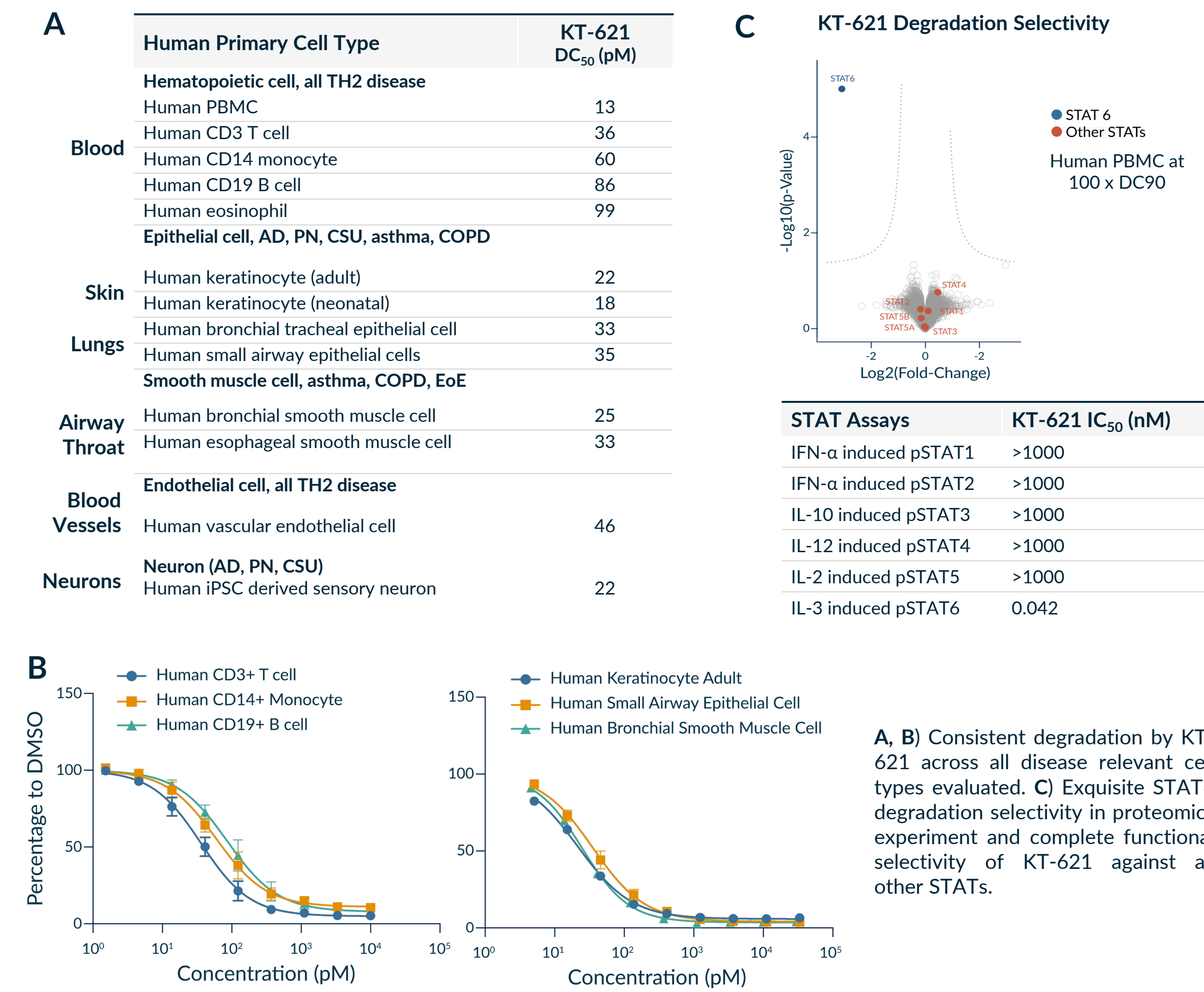


Figure 2: KT-621 Fully Blocks IL-4/13 Functions in Human Primary Cells, More Potently than Dupilumab

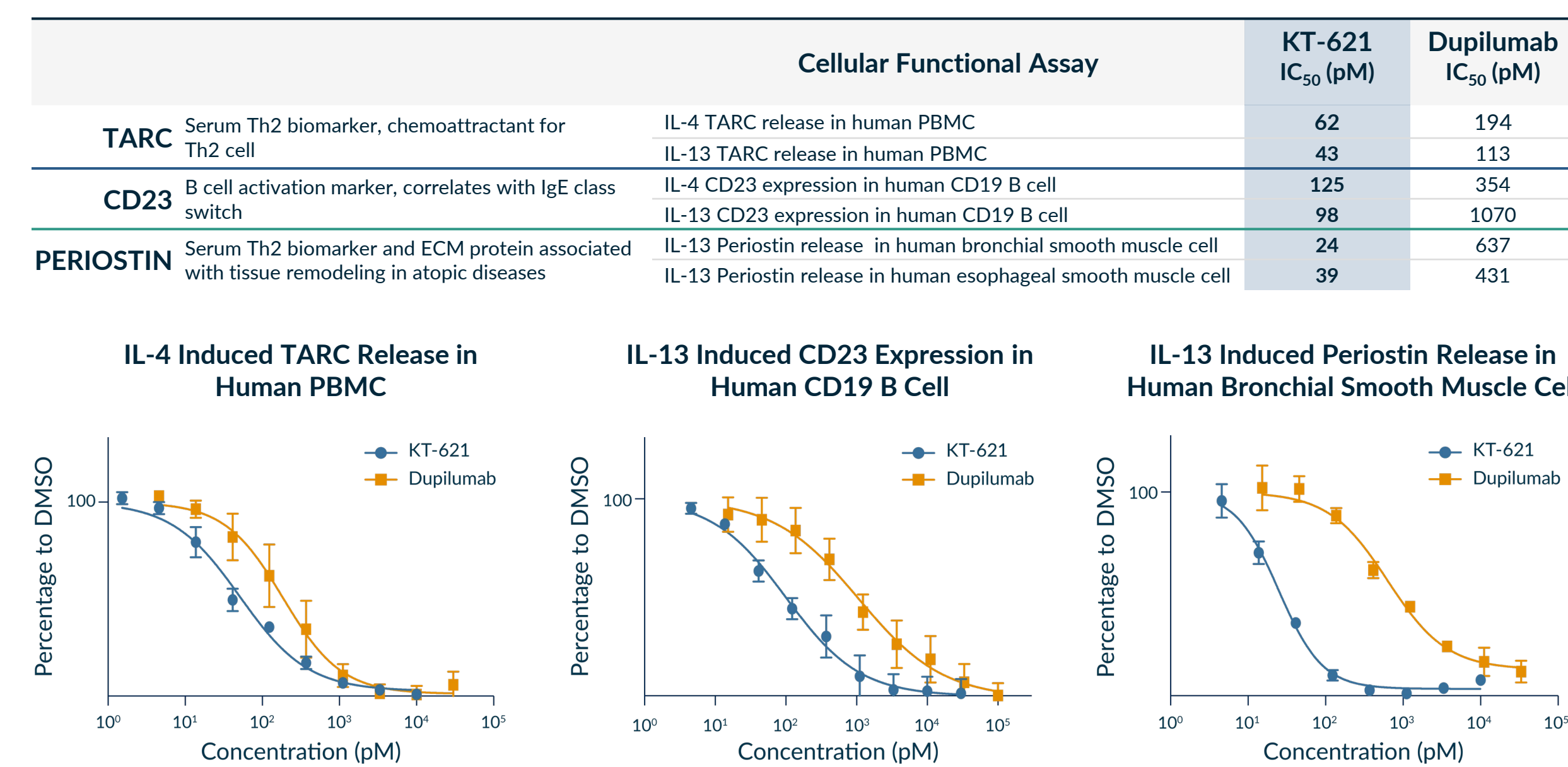
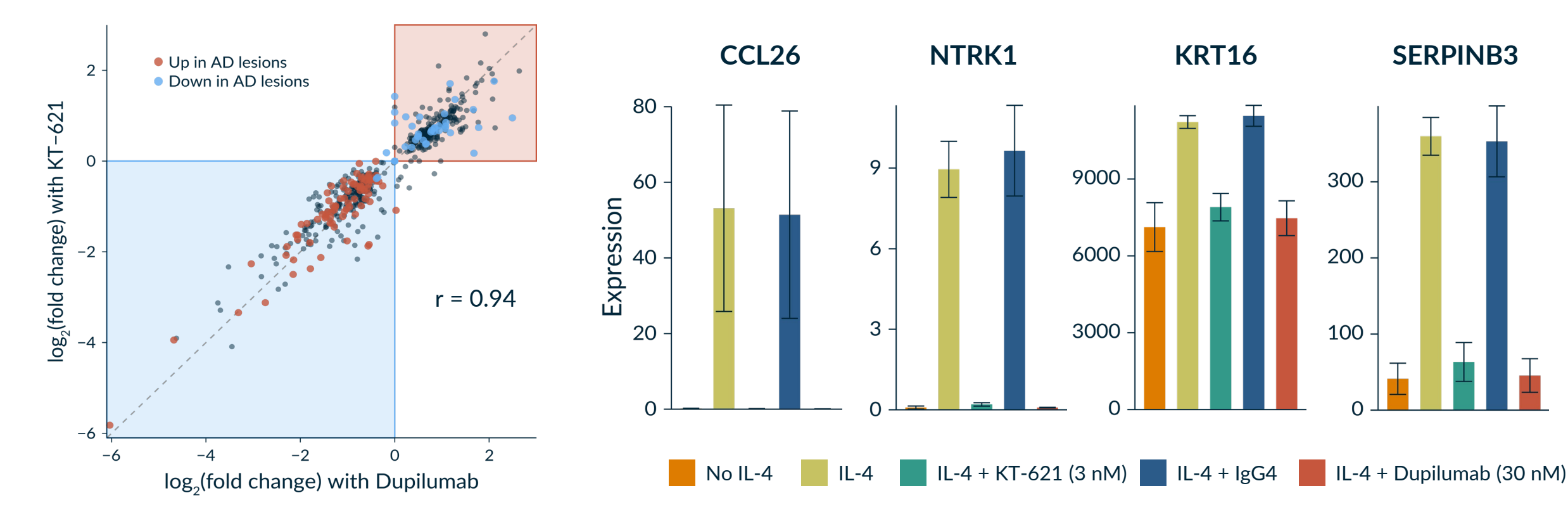
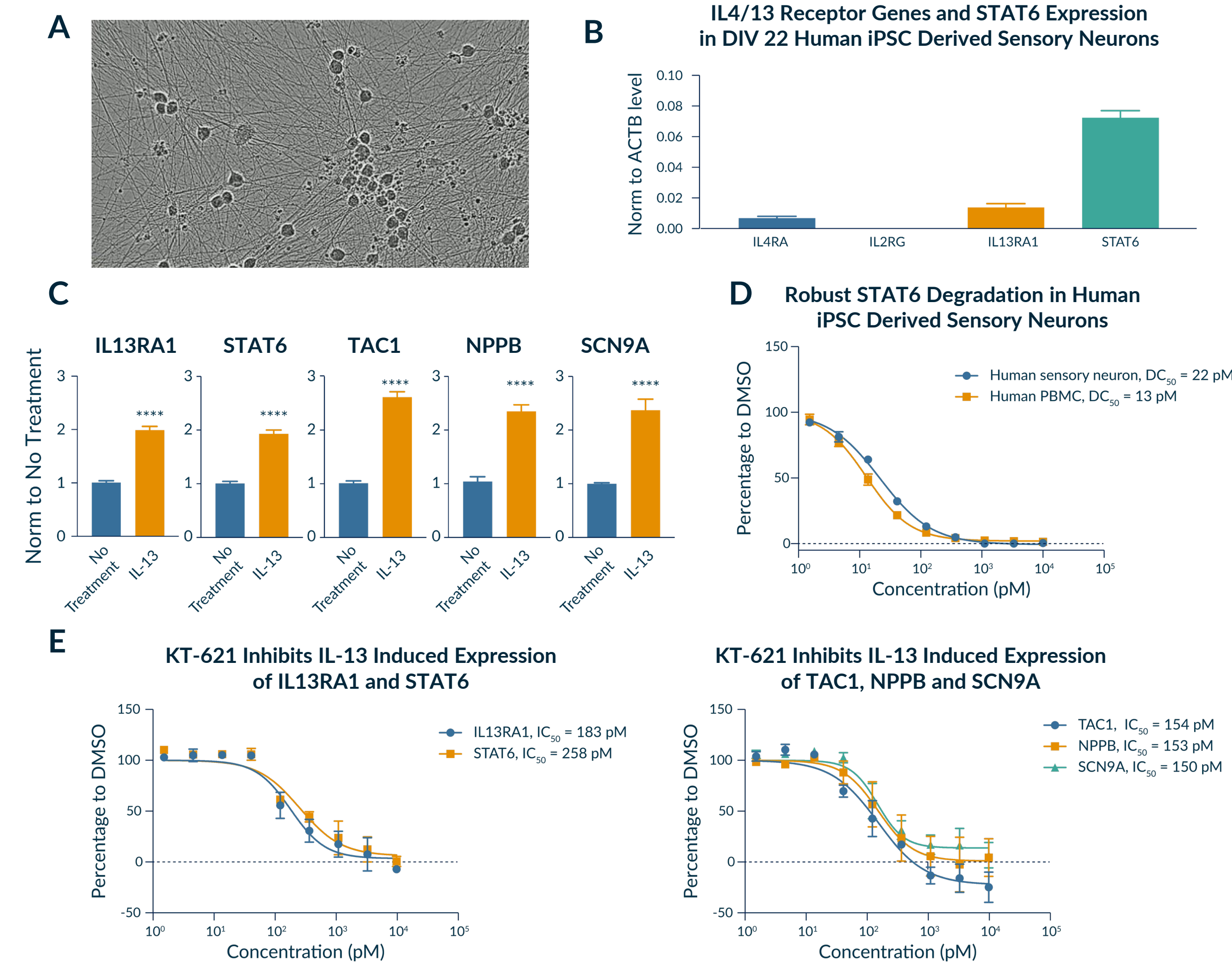


Figure 3. KT-621 Shows Dupilumab-like Activity in IL-4-stimulated Keratinocytes



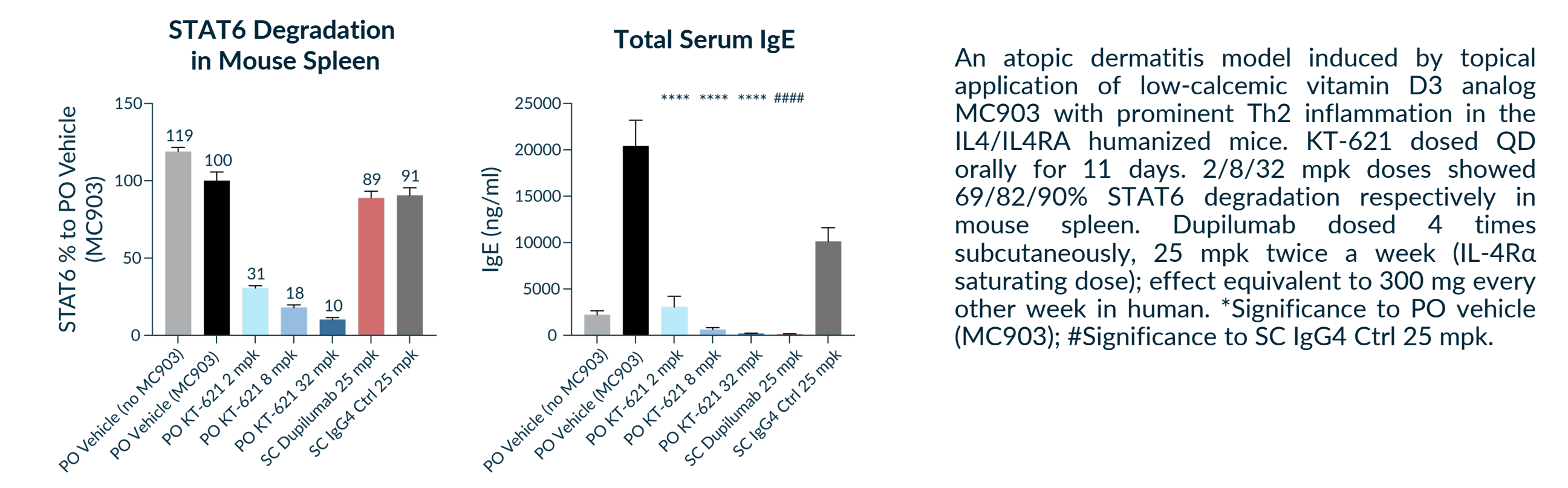
Keratinocytes were pretreated with dupilumab (30 nM) or KT-621 (3 nM), stimulated with IL-4, and profiled with RNAseq. 286 genes modulated by IL-4 stimulation were almost identically affected by dupilumab and KT-621 (Pearson correlation 0.94). Genes that were upregulated (red) or downregulated (blue) in atopic dermatitis lesional skin vs non-lesional skin (Mobus et al. JACI. 2021) were modulated in the opposite direction by KT-621 and dupilumab to similar extents. A few representative genes are shown on the right.

Figure 4. KT-621 Potently Degrades STAT6 and Inhibits IL-13 Induced Expression of Genes Involved in Itch and Pain



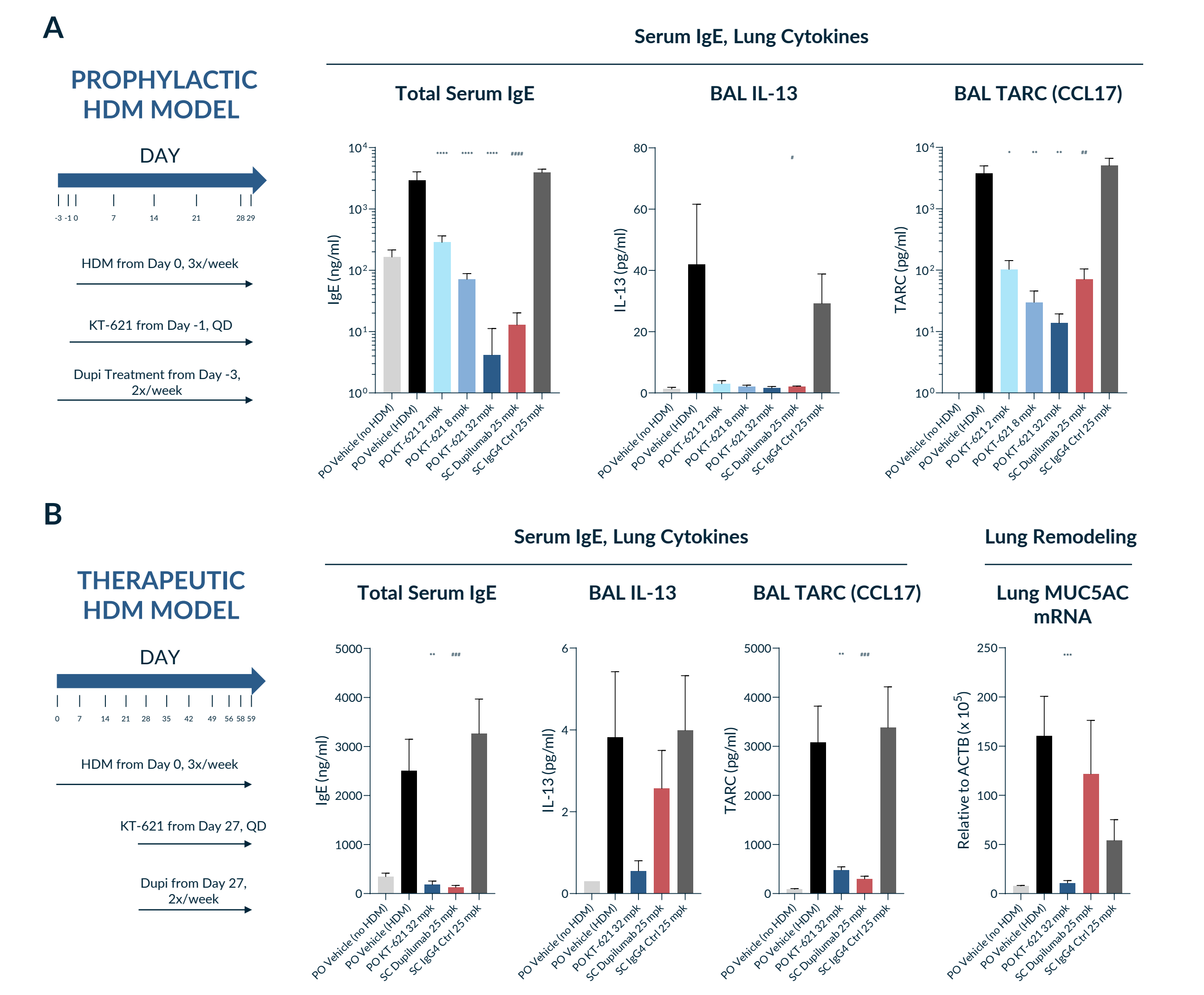
A) human iPSC derived sensory neurons at day in vitro (DIV) 21 of differentiation from sensory neuron progenitors showing typical neuronal morphology with dense neurites. B) IL-4/13 pathway genes IL4RA, IL13RA1 and STAT6 are expressed in human iPSC derived sensory neurons. C) 24 hours of IL-13 (20 ng/ml) stimulation increased the expression of IL-4/13 pathway genes (IL13RA1 and STAT6) and genes involved in itch and pain (TAC1, NPPB, and SCN9A). D) KT-621 potently degrades STAT6 in human iPSC derived sensory neurons with a potency similar to that in human PBMC. E) KT-621 potently inhibits IL-13 induced expression of IL13RA1 and STAT6 which may enhance the neuronal response to IL-4 and IL-13. KT-621 also potently inhibits IL-13 induced expression of TAC1, NPPB, and SCN9A which may enhance neuronal transmission in itch and pain.

Figure 5: KT-621 Has Robust in vivo Activity Comparable to IL-4Rα Saturating Dose of Dupilumab 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. 2/8/32 mpk doses showed 69/82/90% STAT6 degradation respectively in mouse spleen. 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 (MC903); #Significance to SC IgG4 Ctrl 25 mpk.

Figure 6: KT-621 Prevents Disease Progression and Reverses Disease in Both Prophylactic and Therapeutic HDM Asthma Models Equally or More Effectively than Dupilumab



A lung inflammation model induced by intranasal house dust mite (HDM) administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floch 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 heterobifunctional degrader of STAT6, KT-621, and assessed functions in disease-relevant human primary immune and tissue cells *in vitro*, including Th2 functional assays. 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 an MC903 induced atopic dermatitis model and a house dust mite (HDM) induced asthma model in the IL4/IL4RA humanized mice. Additionally, we tested KT-621 in an HDM-induced asthma model with a treatment regimen where the disease was established prior to KT-621 treatment.

KT-621 potently and selectively degraded STAT6 in various disease relevant human primary cells including lymphocytes, myeloid cells, epithelial cells, smooth muscle cells, vascular endothelial cells and neurons. As a result of STAT6 degradation, KT-621 fully blocked various IL-4/IL-13 functions in these cells with low picomolar potencies comparable or numerically superior to dupilumab and did not degrade or inhibit any other STAT transcription factors or other proteins. 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 MC903-induced atopic dermatitis mouse model, orally administered KT-621 demonstrated robust degradation of STAT6 *in vivo* and marked reduction of total serum IgE comparable to the activity of an IL-4Rα saturating dose of dupilumab. In the HDM induced asthma model, orally administered KT-621 demonstrated similar robust degradation and reduced all cytokine, cell infiltration, and disease severity readouts in the lung and bronchoalveolar lavage fluid comparable or superior to the IL-4Rα saturating dose of dupilumab. 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 disease.

CONCLUSIONS

STAT6 degradation is a novel oral approach for blocking the IL-4/IL-13 signaling pathways. KT-621, an oral STAT6 degrader, has best-in-pathway potential for allergic and atopic diseases with a dupilumab-like activity profile and oral dosing.

- KT-621 is a picomolar STAT6 degrader with exquisite selectivity developed with a clinically validated degrader platform.
- STAT6 degradation by KT-621 fully blocks IL-4/13 in key human Th2 cellular assays with picomolar IC₅₀s more potent than dupilumab.
- KT-621 shows dupilumab-like activity in IL-4-stimulated keratinocytes.
- KT-621 demonstrates downregulation of itch and pain related gene transcripts induced by IL-13 in human sensory neurons.
- STAT6 degradation by KT-621 robustly inhibits TH2 inflammation *in vivo* in the mouse MC903 atopic dermatitis and HDM asthma model comparable to the IL-4Rα monoclonal antibody dupilumab.
- KT-621 is well tolerated in multiple preclinical species and safety studies with no adverse safety findings at any doses of 4-week and 4-month GLP tox studies in NHP and rodents.
- In the Phase 1 healthy volunteer clinical trial, KT-621 demonstrated complete STAT6 degradation in blood and skin following low daily oral doses, reductions of multiple disease relevant Th2 biomarkers, and a safety profile undifferentiated from placebo.
- KT-621 is in Phase 1 clinical testing in Atopic Dermatitis (AD), with parallel Phase 2b studies in AD and asthma planned for 4Q25 and 1Q26, respectively.

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DISCLOSURES

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