RESULTS

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

<table>
<thead>
<tr>
<th>STAT6 Degradation in Human Bronchial Smooth Muscle Cells</th>
<th>Human CD43 - DR</th>
<th>Human CD43 - EC</th>
<th>Human CD43 - Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage Decreased (%)</td>
<td>100</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>

**A** Human Primary Cell Type

- **Hepa shortcut cell line TH2 Disease**
- **Human PBMC**
- **Human GALT**
- **Human CD43 monocyte**
- **Human CD43 cell**
- **Human eosinophil**
- **Endothelial cell and EC complexes**
- **Smooth muscle cell, aorta, COPA Endothelium**
- **CD14 monocyte, CD14 Endothelial cell**
- **Bronchial smooth muscle cell**
- **Endothelial cell, all TH2 disease**

**B** Human vascular endothelial cell

**C** Human eosinophil

**D** Human CD14 monocyte

**E** Human smooth muscle cell

**F** Human smooth muscle cell

**G** Human smooth muscle cell

**H** Human smooth muscle cell

**I** Human smooth muscle cell

**J** Human smooth muscle cell

**K** Human smooth muscle cell

**L** Human smooth muscle cell

**M** Human smooth muscle cell

**N** Human smooth muscle cell

**O** Human smooth muscle cell

**P** Human smooth muscle cell

**Q** Human smooth muscle cell

**R** Human smooth muscle cell

**S** Human smooth muscle cell

**T** Human smooth muscle cell

**U** Human smooth muscle cell

**V** Human smooth muscle cell

**W** Human smooth muscle cell

**X** Human smooth muscle cell

**Y** Human smooth muscle cell

**Z** Human smooth muscle cell

Methods

**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.

CONCLUSIONS

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

**A** 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 pIC50 STAT6 degrader with exquisite selectivity developed with the targeted protein degradation platform at Kymera Therapeutics.**
- **KT-621 degradation by KT-621 fully blocks IL-4/13 in key human TH2 cellular assays with picomolar IC50 lower than dupilumab.**
- **KT-621 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 in low oral doses.**
- **KT-621 is well tolerated in multiple preclinical species.**
- **KT-621 degradation by KT-621 robustly inhibits TH2 inflammation in vivo in the HDM asthma model comparable to the 4E-bla monoclonal antibody dupilumab.**

**REFERENCES**

- **Jung, W et al.** Tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) is a potential mediator of the anti-inflammatory effect of statins. Biochem Pharmacol 2019; 166: 41-48.

**DISCLOSURES**

- The content was drafted by Kymera Therapeutics. Wang, Yang, Ramanathan, Hosain, Dong, Follows, Brown, Harfield, Yim, Sawant, Enerson, Yang, Williams, and Lam are Kymera employees and owns or holds equity interest. Yamamoto is a former Kymera Therapeutics employee and owns equity interest.

**Figure 3:** KT-621 Potently Degraded STAT6 Across Multiple Preclinical Species with Low Oral Doses

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

- **A** IL-4Rα activited dose dependent dose response in dogs with low acid dos. STAT6 levels determined at 24 hours post the Day 7 dosing in BEC induced in HDM sensitized rats with nasal HDM dosing. **B** In NHP: STAT6 levels determined at 24 hours post four daily oral dosing in non human primates. **C** In mice: Dosing for 14 days orally showed that the whole blood and the induced tumor.

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

- **A** Rescue of IL-4/13 Effects in Exposed Smooth Muscle Cells by STAT6 Degrader or Dupilumab

**REFERENCES**

- **Jung, W et al.** Tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) is a potential mediator of the anti-inflammatory effect of statins. Biochem Pharmacol 2019; 166: 41-48.