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Discovery and characterization of SIM0711, a potent and selective IRAK4 PROTAC with Enhanced Efficacy and Safety

Peng Gu*[1], Mengyu Wang[2], Minyun Zhou[2], Yuxi Yan[1], Li Sun[2], Yiling Chen[2], Xin Wang[2], Feng Tang[2], Xiaofeng Zhao[2], Shunwei Zhu[1]

[1]Simcere Pharmaceutical Group Limited, Shanghai, China
[2]Simcere Pharmaceutical Group Limited, Nanjing, China

Introduction & Objectives:

IRAK4 plays a pivotal role in the innate immune response, acting downstream of TLRs and IL-1R It exhibits both kinase activity and scaffolding functions, making it a critical target for modulating inflammatory signaling pathways. Traditional IRAK4 kinase inhibitors have shown limited efficacy due to their inability to fully inhibit the scaffolding function of IRAK4. IRAK4 PROTAC offers a novel approach by selectively degrading the entire protein, thereby achieving broader pathway inhibition.

This study aimed to discover and characterize a potent and selective oral IRAK4 PROTAC, and evaluate its therapeutic potential for treating autoimmune and inflammatory diseases.

Materials & Methods:

We developed and extensively characterized SIM0711, an oral IRAK4 PROTAC, *in vitro* and *in vivo*. Its activity was compared with either the benchmark IRAK4 PROTAC (KT-474) or the benchmark IRAK4 inhibitor (PF-06650833). Key assays included:

\1. IRAK4 degradation in human PBMCs and fibroblast/keratinocyte cell lines.

\2. IRAK4 degradation kinetics in THP-1 cells or primary monocytes.

\3. Inhibition of pro-inflammatory cytokines (IL-6 and IL-8) in human PBMCs stimulated by LPS or IL-33.

\4. Efficacy in a mouse model of IL-33-induced skin inflammation.

\5. PK/PD, bioavailability, and safety profiles across multiple species.

Results:

In comparison to benchmark PROTAC KT-474, SIM0711 induced near-complete IRAK4 degradation in diverse primary human immune cells and stromal cell lines, demonstrating faster degradation kinetics in THP-1 cells and primary human monocytes *in vitro*. In the meantime, SIM0711 also led to deeper inhibition of the pro-inflammatory cytokines IL-6 and IL-8 following the stimulation of LPS, or IL-33 compared to either PF-06650833 or KT-474. *In vivo*, in a mouse model of IL-33-induced skin inflammation, SIM0711 dose-dependently reduced skin inflammation, nearly abolishing downstream IL-5 secretion at the inflammation site. Furthermore, SIM0711 demonstrated improved bioavailability, favorable PK/PD characteristics, and good safety profiles across multiple species.

Conclusion:

These findings establish SIM0711 as a best-in-class IRAK4 PROTAC with the potential to treat a wide range of

autoimmune and inflammatory diseases. Its robust IRAK4 degradation, superior anti-inflammatory efficacy, and favorable drug properties support its further development, with an IND submission anticipated in H2 2025.