IRAK4 Degradation Abrogates Cytokine Release and Improves Disease Endpoints in Murine Models of IL-33/36 as well as Th17-driven Inflammation


INTRODUCTION

Interleukin-1 receptor associated kinase 4 (IRAK4) plays a central role in multiple immune responses by kinases and scaffolding functions, making it an attractive target for the treatment of TLR- and IL-1-driven inflammatory diseases. IL-1 family cytokines, Th17 cells and Th1s, are central to the pathophysiology of several chronic inflammatory diseases. IRAK4 inhibits both linear and independent activities, making degradation a more attractive modality than kinase inhibition alone. Kymera has developed orally administered heterobifunctional molecules that selectively target IRAK4 for degradation and elimination by the ubiquitin proteasome pathway. These degraders have broad and potent activity in vitro against IL-1α, IL-1β, and other proinflammatory cytokines and chemokines induced by TLR agonists and IL-1 family cytokines that is superior to IRAK kinase inhibitors. Kymera’s most advanced IRAK4 degrader is in a Phase 1 trial in healthy volunteers with hidradenitis suppurativa (HS) or atopic dermatitis (AD).

RESULTS

AIM

We sought to evaluate the efficacy of oral IRAK4 degraders in vivo compared to IRAK4 kinase small molecule inhibitors (SMIs), in mechanistic and disease models of IL-33-, IL-36-, and IL-17-driven inflammation. We explored skin and CNS-focused murine models, where these pathways function as key drivers of disease, and we established parallels with human in vitro systems involving the IL-33-, IL-36-, and IL-17 signaling cascades as well.

Figure 1: IL-33 in vitro Assay

- IL-33 and IRAK4 are critical to IL-17-driven inflammation in autoimmune responses. We evaluated the effects of IRAK4 degraders vs. IRAK4 SMIs on the reconstitution of established IL-17-driven inflammation.

CONCLUSIONS

- The data presented here highlight the anti-inflammatory effects of IRAK4 degraders on IRAK4 kinase inhibition.
- In vitro assays with human leukocytes and keratinocytes show that IRAK4 degraders reduced the release of cytokines more efficiently than IRAK4 SMIs.
- Data from in vivo mechanistic assays were confirmed by in vivo mechanistic and disease-like models.
- In these studies, IRAK4 degraders inhibited cytokine production and inflammation upon IL-33 or IL-17 injection more potently than IRAK4 SMIs.
- In fact, IRAK4 degraders provided anti-inflammatory effects comparable or better than dosimetric changes in human in vitro models.

- Moreover, in a classic model of antigen-induced, Th17-driven neuroinflammation (HOG-CX3), IRAK4 degraders reduced clinical scores similarly to FYT225 (a standard of care for MS), and more robustly than IRAK4 SMIs.
- In conclusion, we showed that targeted IRAK4 degradation is an effective approach to decreasing inflammatory cytokine production that is superior to IRAK4 SMIs, with relevance to treatment of inflammatory skin diseases as well as other IL-1, IL-17-driven autoimmune indications.

- Kymera’s most advanced IRAK4 degrader is in Phase 1 trial in healthy volunteers and patients with hidradenitis suppurativa (HS) or atopic dermatitis (AD).

REFERENCES


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