Identification of highly potent and selective Interleukin-1 receptor associated kinase 4 (IRAK4) degraders for the treatment of hidradenitis suppurativa

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Introduction

- Interleukin-1 receptor associated kinase 4 (IRAK4) plays a central role in myeloid signaling via kinase and scaffolding functions, making it an attractive target for the treatment of TLR- and IL-1-driven inflammatory diseases
- IL-1 family cytokines and TLRs, are central to the pathophysiology of hidradenitis suppurativa (HS), a Th1- and Th17-mediated neutrophilic, chronic inflammatory skin disease
- Orally administered hetero-bifunctional molecules have been developed that selectively target IRAK4 for degradation and elimination by the ubiquitin proteasome pathway

Biology of Targeted Protein Degradation

Co-opting a Naturally Occurring Process to Regulate Protein Levels

1. E3 ligase recognizes protein substrate
2. Ubiquitin chain transferred
3. Protein is marked for elimination

PROLONGED IMPACT

IRAK4 degradation blocks IL-1-mediated neutrophilic inflammation

Orally Active IRAK4 Degrader Blocks IL-1 Driven Neutrophilic Infiltration in MSU Air Pouch Model

IRAK4 levels were measured by targeted mass spec. Neutrophil infiltrate counts were recorded, dose of compound was administered, and MSU crystals were injected into the air pouch. On day 4, the last dose of Compound was administered, and MSU crystals were injected into the air pouch. 12 hours later, relevant tissues and exudate from the pouch was collected. IRAK4 levels in exudate were measured by targeted mass spec. Neutrophil infiltrate counts were recorded, and IL-1β levels were measured by ELISA from exudate.

IRAK4 Degraders are highly orally active in the mouse imiquimod psoriasis model, with reduction of skin thickening and both Th1 and Th17 cytokines. In addition, they effectively block 8-1 driven neutrophilic inflammation in the mouse MSU air pouch model.

PMBCs were pre-treated with compounds for 20 hours followed by R848 (TLR7/8) or LPS (TLR4) stimulation. 5 hours post-stimulation, cytokines were measured by MSD. For phosphoprotein profiling, samples were collected 15 min post-stimulation. Flow methods were used to gate monocytes and measure phosphoproteins.

For IMQ treated mice, pmcs were pre-treated with compounds for 20 hours followed by dual activation with LPS at 10ng/mL, and IL-1β at 20ng/mL. 24 hours following stimulation, cytokines were measured by MSD.

Potent and Selective Degraders of IRAK4

IRAK4 Degradation has Broader and more Potent Effect on TIR Activation Compared to Kinase Inhibition

Potent IRAK4 degradation in immune subsets

 Highly selective for IRAK4 over 10,000 proteins

PBMCs were pre-treated with compounds for 20 hours followed by R848 (TLR7/8) or LPS (TLR4) stimulation. 5 hours post-stimulation, cytokines were measured by MSD. For phosphoprotein profiling, samples were collected 15 min post-stimulation. Flow methods were used to gate monocytes and measure phosphoproteins.

Orally Active IRAK4 Degrader Blocks IL-1 Driven Neutrophilic Infiltration in MSU Air Pouch Model

Skin thickness, Day 5

Imiquimod was applied to the ear on Day 0 and ear thickness was measured daily. Degrader 2 was closed only for 3 days, BID following air pouch generation. On day 4, the last dose of compound was administered, and MSU crystals were injected into the air pouch. 12 hours later, relevant tissues and exudate from the pouch was collected. IRAK4 levels in exudate were measured by targeted mass spec. Neutrophil infiltrate counts were recorded, and IL-1β levels were measured by ELISA from exudate.

Reduction in Circulating Pro-Inflammatory Cytokines

Degrader 1 was dosed i.p. for 3 days, BID. At the end of the study (day 5), plasma samples were collected and Pro-inflammatory cytokines were measured by Lumene assay.

Summary

- Kymera has developed first in class selective and potent IRAK4 degraders
- IRAK4 degraders are highly effective and superior to SBI at inhibiting myelodysplasia signaling and blocking cytokine/chemokine induction by TLR agonists and IL-1
- IRAK4 degraders are highly orally active in the mouse imiquimod psoriasis model, with reduction of skin thickening and both Th1 and Th17 cytokines. In addition, they effectively block 8-1 driven neutrophilic inflammation in the mouse MSU air pouch model
- Daily oral dosing of an IRAK4 degrader in dogs for 2 weeks was well-tolerated and led to complete suppression of IRAK4 protein in skin and immune cells
- Collectively, these data show IRAK4 degraders have the potential to treat TLR- and IL-1-driven neutrophilic inflammation and autoimmune diseases such as hidradenitis suppurativa (HS)
- IRAK4 degrader for HS is being advanced into the clinic in 2020