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

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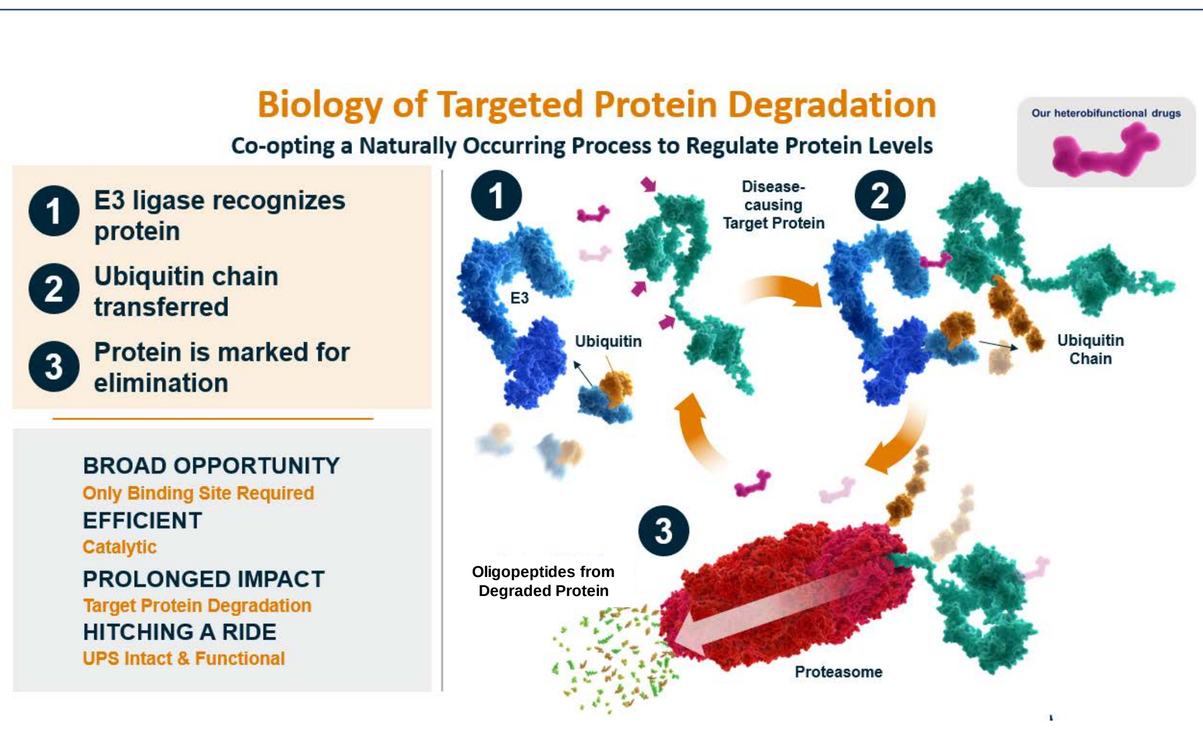
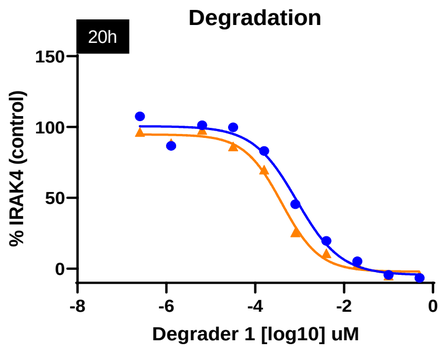
Introduction

- **Interleukin-1 receptor associated kinase 4 (IRAK4) plays a central role in myddosome signaling via kinase and scaffolding functions, making it an attractive target for the treatment of TLR- and IL-1R-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**



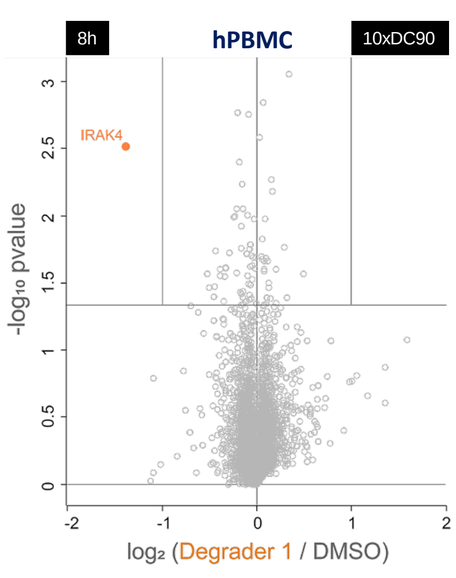
Potent and Selective Degraders of IRAK4

Potent IRAK4 degradation in immune subsets



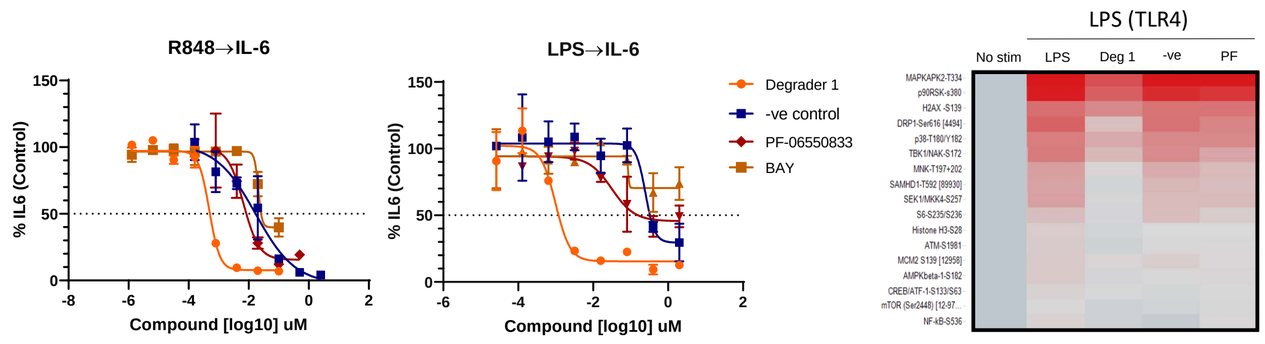
Cell type	IRAK4 DC_{50} (nM)
Monocytes	0.86 ± 0.68
Lymphocytes	1.1 ± 0.53

Highly selective for IRAK4 over 10,000 proteins



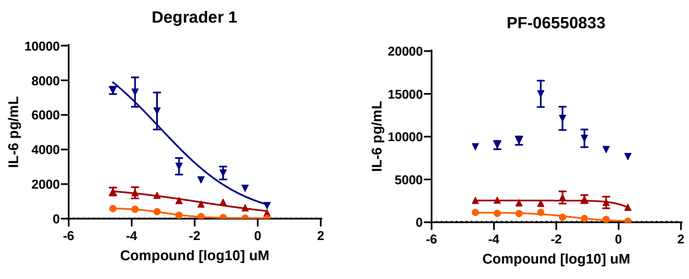
PBMC cells were treated with Degrader 1 at indicated times (20 hours or 8 hours). IRAK4 degradation was detected by flow cytometry methods and concentration where 50% degradation is achieved is reported as DC_{50}. Selectivity was assessed by Mass tandem deep proteomics with a depth of over 10,000 proteins.

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



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.

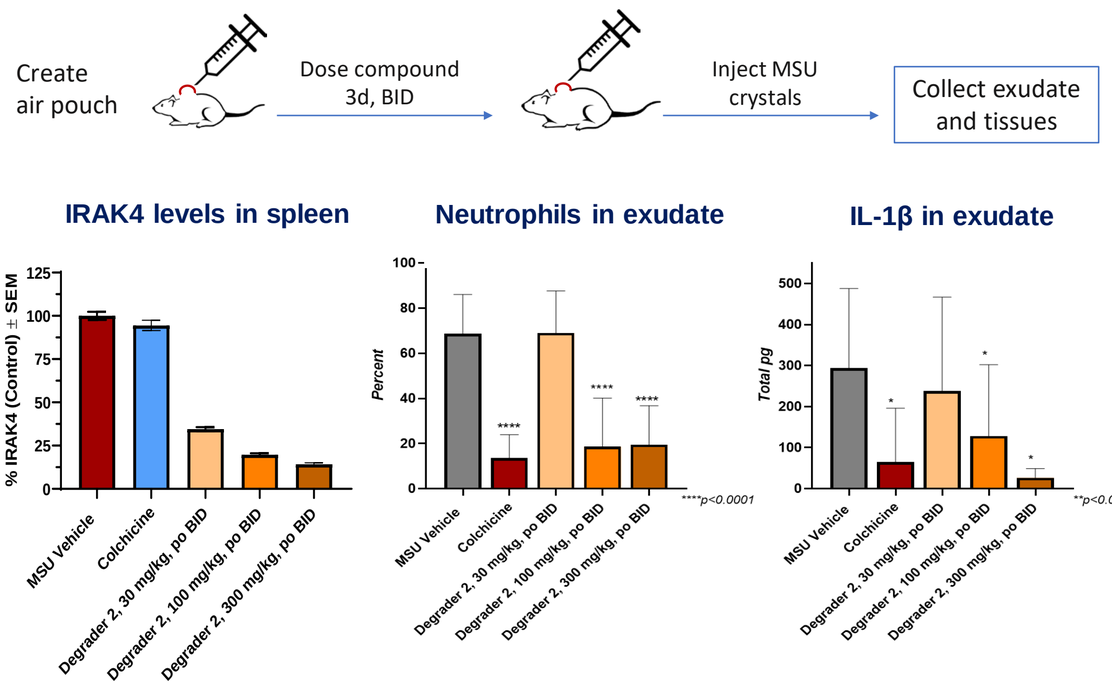
IRAK4 degradation inhibits LPS + IL-1β enhanced cytokine and chemokine production



Cytokine/ Chemokine Induced by IL-1b + LPS	Degrader 1 relative [IC50] nM	PF-06550833 Relative [IC50] nM
IL-6	0.8	>2000
IL-8	0.08	1400
G-CSF	0.5	>2000
GM-CSF	2.6	8.1
CXCL1 (GROα)	76.4	>2000
CCL3 (MIP-1α)	42.3	>2000

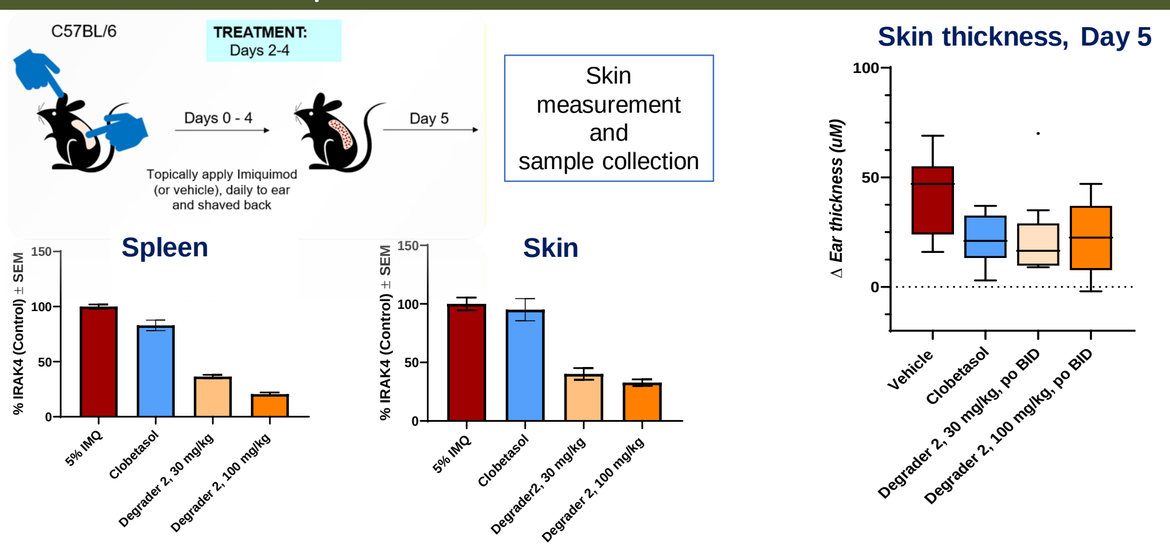
PBMCs were pre- treated with compounds for 20 hours followed by dual activation with LPS at 10ng/mL and IL-1b at 20ng/mL. 24 hours following stimulation, cytokines were measured by MSD.

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



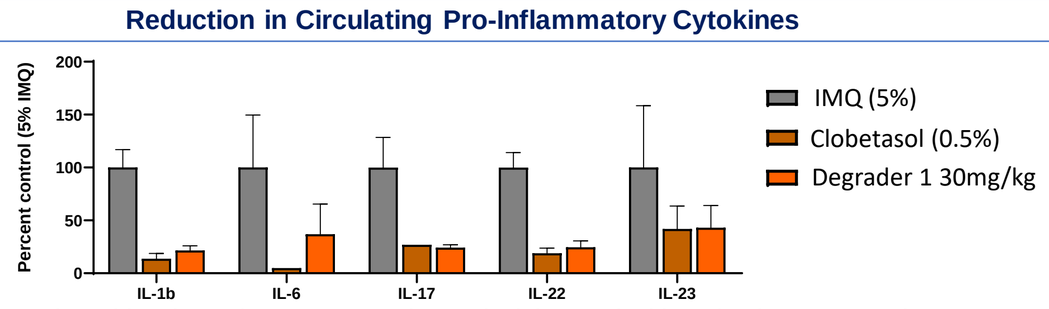
Degrader 2 was dosed orally for 3 days, BID following air pouch generation. On day 4, the last dose of compound was administered, and MSU crystals were injected into the air pouch. 12 hours later, relevant tissues and exudate from the pouch was collected. IRAK4 levels in spleen were measured by targeted mass spec. Neutrophil infiltrate counts were recorded, and IL-1β levels were measured by ELISA from exudate.

IRAK4 Degradation Reduces Skin Thickening and Inhibits Cytokine Signaling in Imiquimod induced Psoriasis Mouse Model



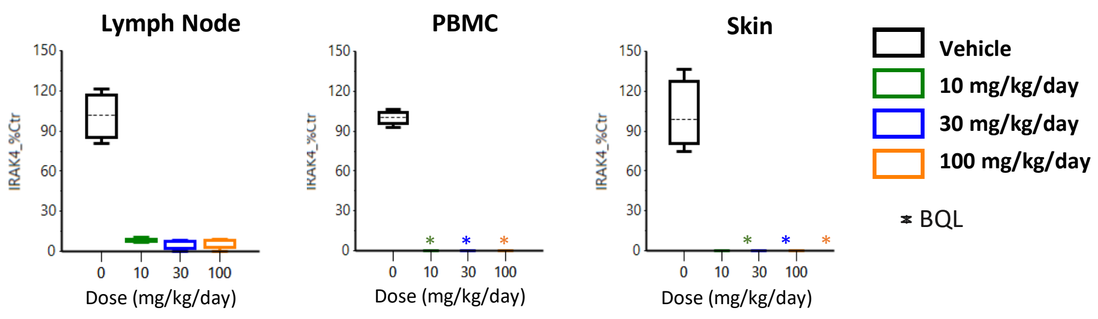
Imiquimod was applied to the ear on Day 0 and ear thickness was measured daily. Degrader 2 was dosed orally for 3 days, BID. At the end of the study (day 5) spleen and skin were collected and IRAK4 levels were measured by targeted mass spec.

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 Luminex assays.

Full degradation of IRAK4 in Skin and Lymphoid tissues in Higher Species



Degrader 2 was dosed orally, QD for 14 days in dog. 24 hours following last dose tissues were collected and IRAK4 levels were measured by targeted mass spec.

Summary

- **Kymera has developed first in class selective and potent IRAK4 degraders**
- **IRAK4 degraders are highly effective and superior to SMI at inhibiting myddosome 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 bock Il-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/IL-1R-driven neutrophilic inflammation and autoimmune diseases such as hidradenitis suppurativa (HS)**
- **IRAK4 degrader for HS is being advanced into the clinic in 2020**