A First-in-Class Selective and Potent IRAK4 Degrader Demonstrates Robust *in Vitro* and *in Vivo* Inhibition of TLR/IL-1R Activation and Inflammation

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Oral poster presentation
Kymera Therapeutics

Disclosure statement

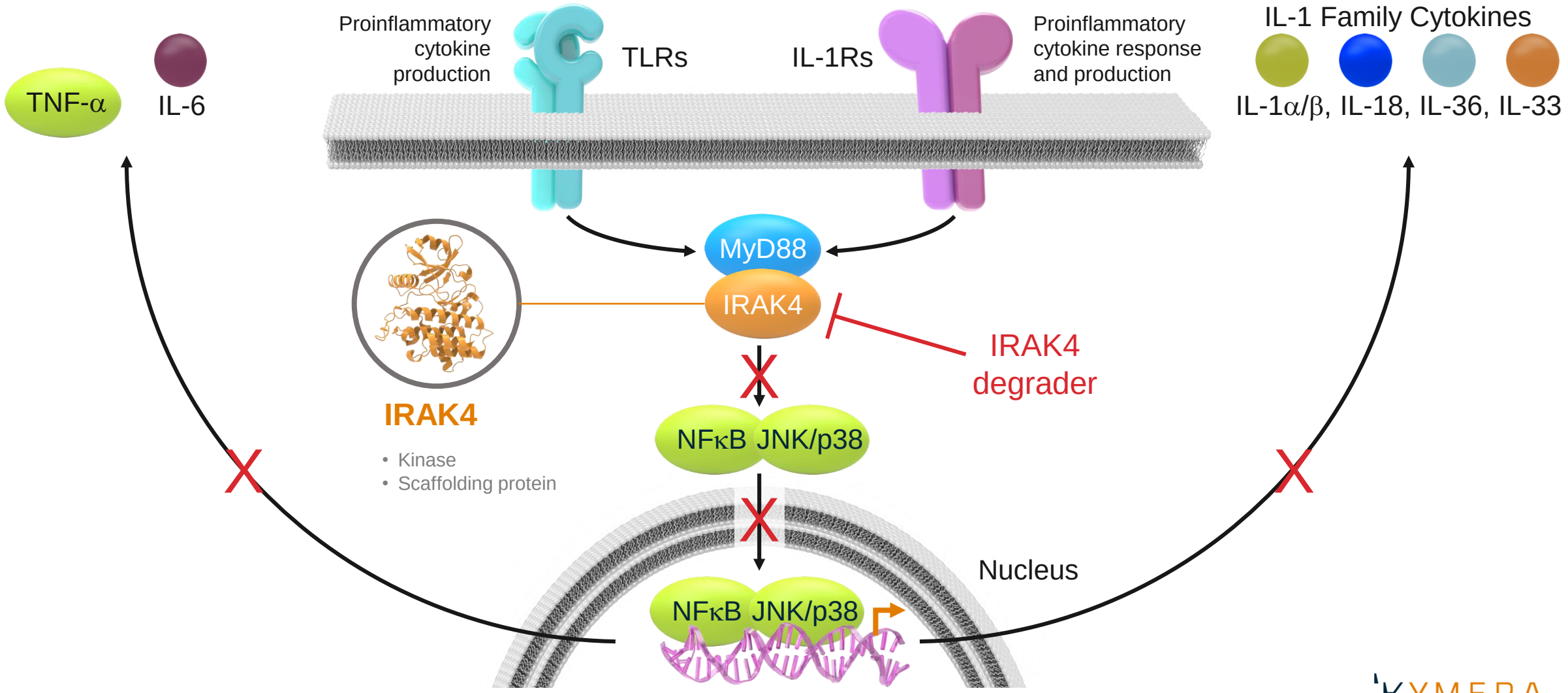
Kymera Therapeutics employee

Overview

- **IRAK4 as a clinically validated target**
- **Biology of targeted protein degradation**
- **IRAK4 degradation leads to superior activity compared to kinase inhibition**
- ***In vivo* anti-inflammatory activity of oral IRAK4 degrader**

Mechanistic Rationale for IRAK4 Degrader in Immunology

Myddosome Targeting Blocks IL-1 Family Cytokine Production and Response



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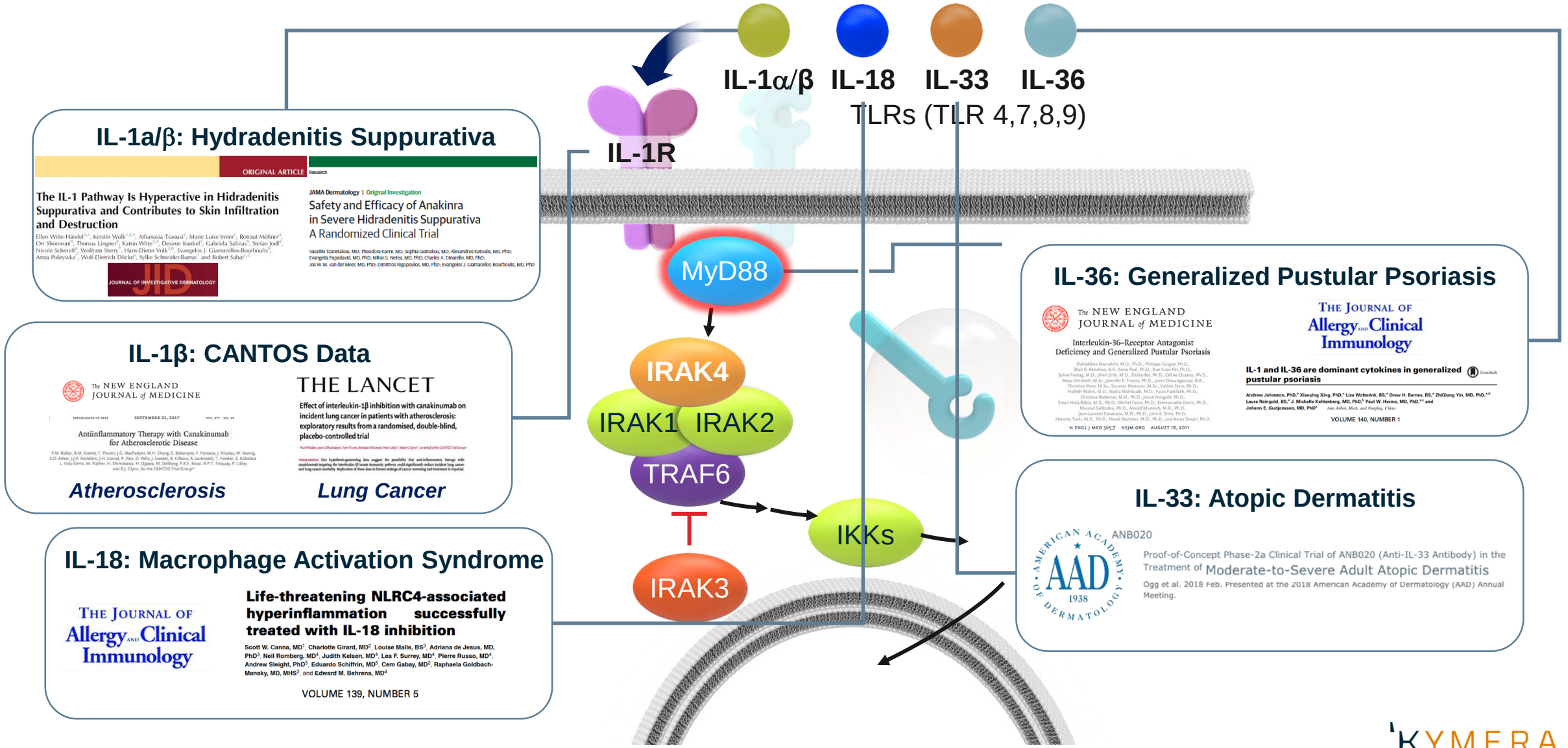
Multiple Validated Clinical Entry Points for IRAK4 Degrader



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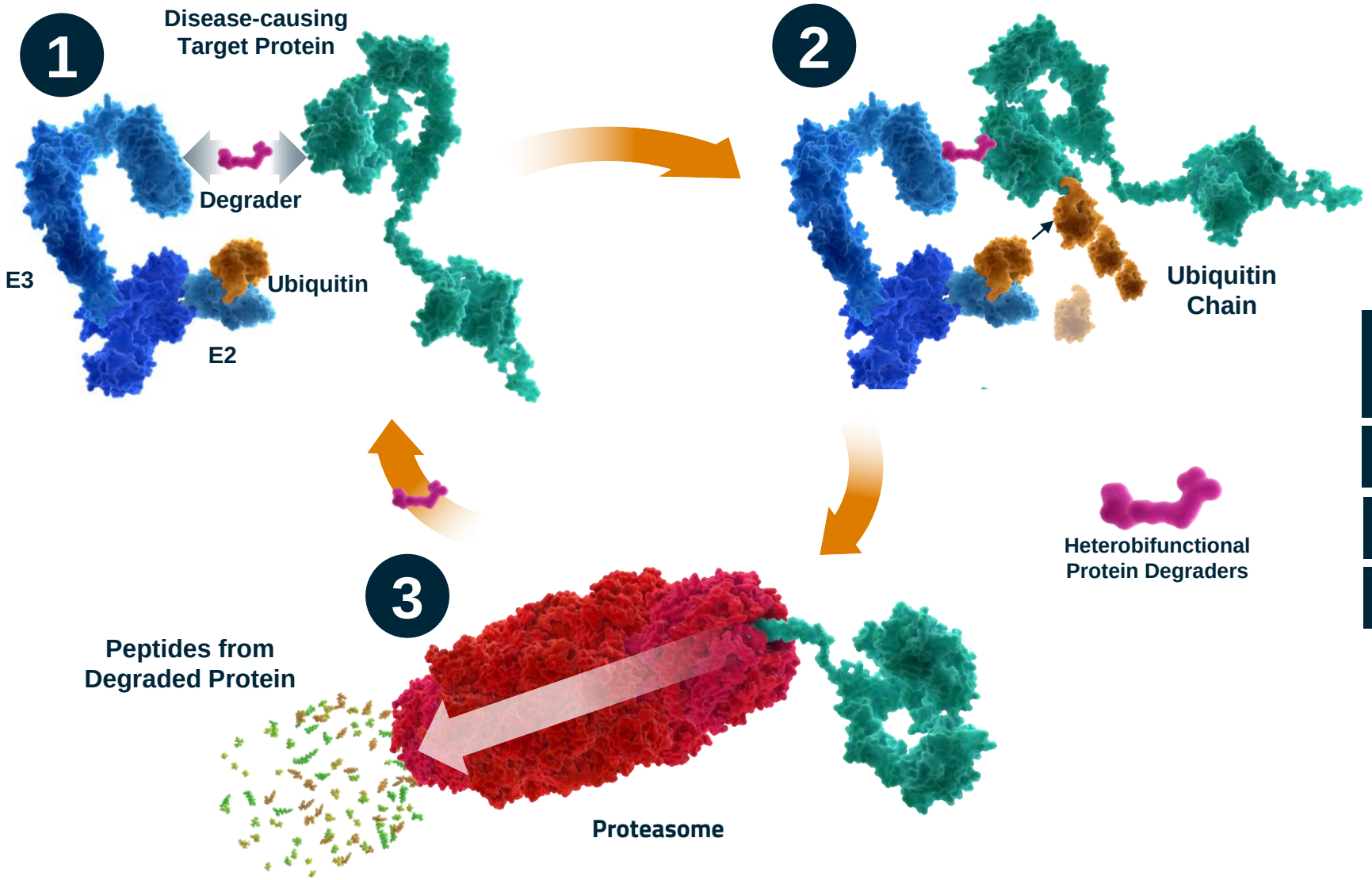
Biology of Targeted Protein Degradation



Undruggable Targets

Efficient

Oral

Systemic

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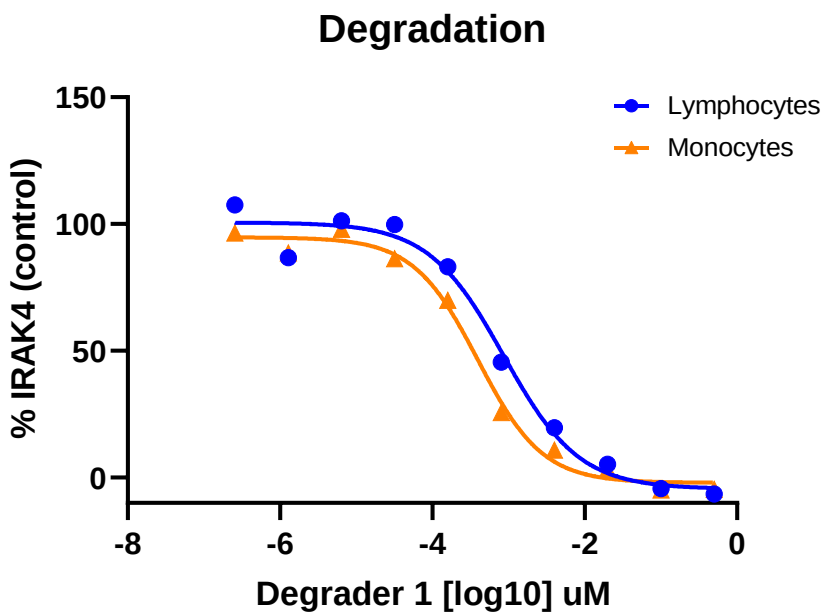
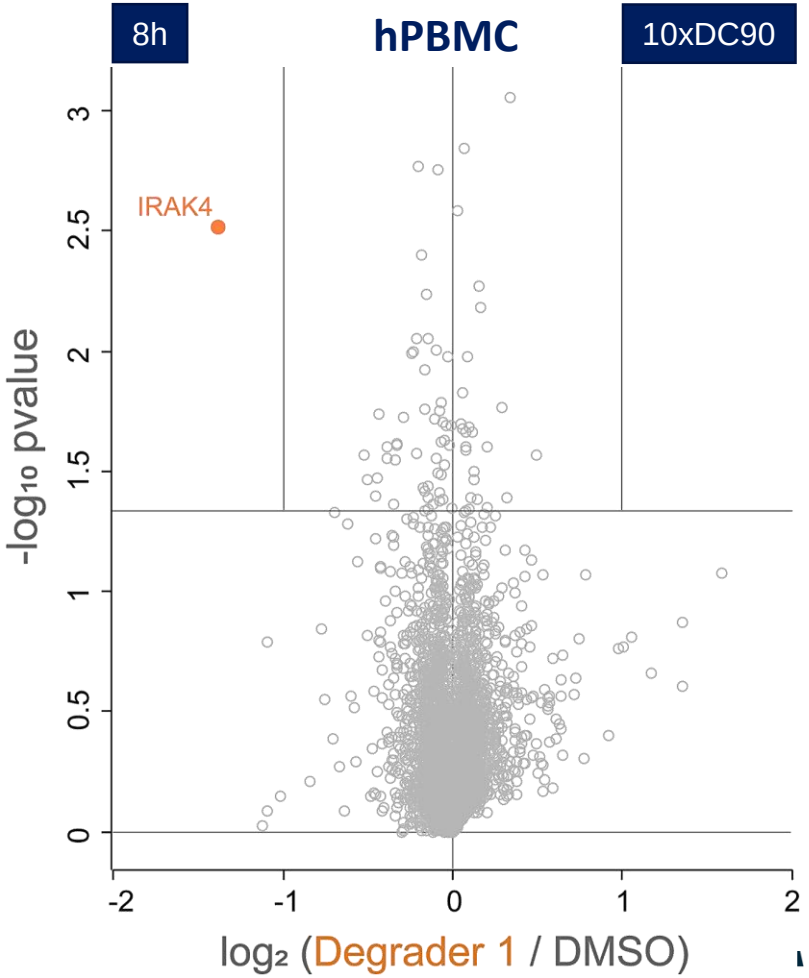
Potent and Selective Degrader of IRAK4

Potent IRAK4 degradation in immune subsets



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

High Selectivity for IRAK4 over 10,000 Proteins



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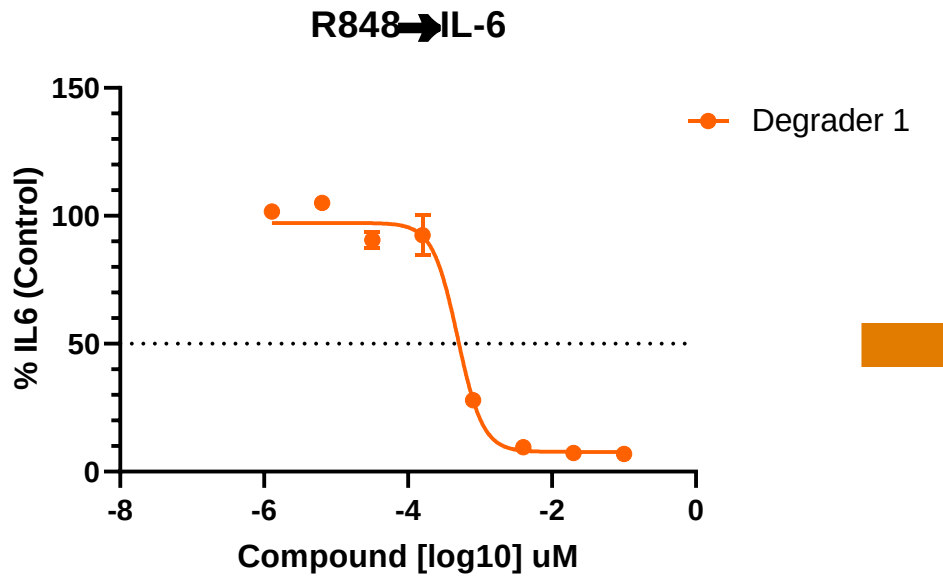
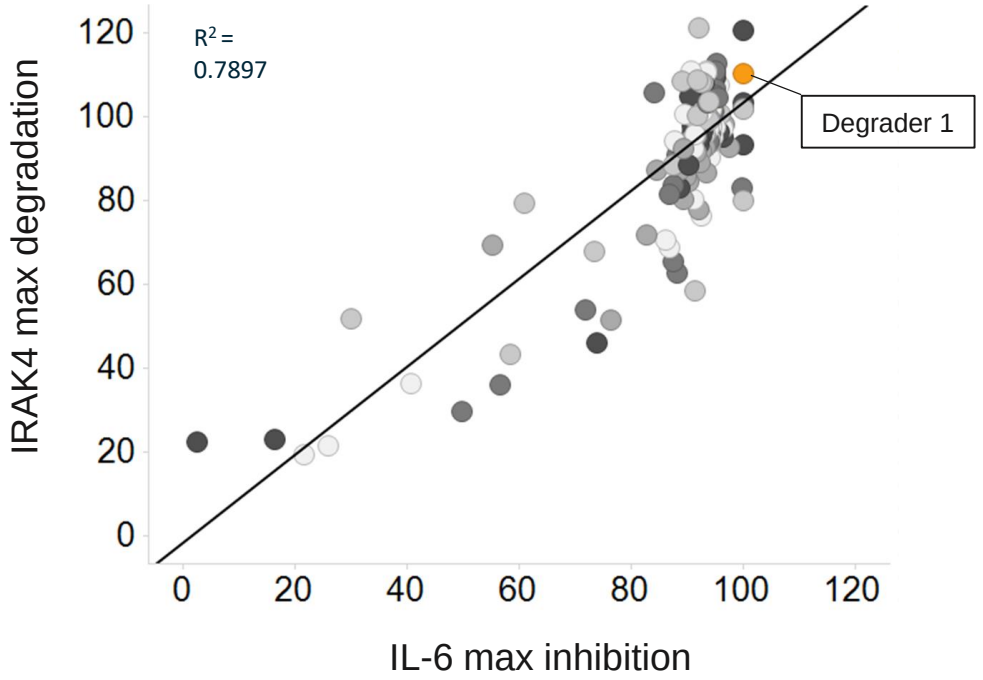
Degrader Inhibition of Cytokine Induction Correlates with IRAK4 Downregulation

Potent inhibition of IL-6



Compound	IL-6 IC_{50} (nM)
Degrader 1	0.2 ± 0.2

Degradation correlates with cytokine inhibition



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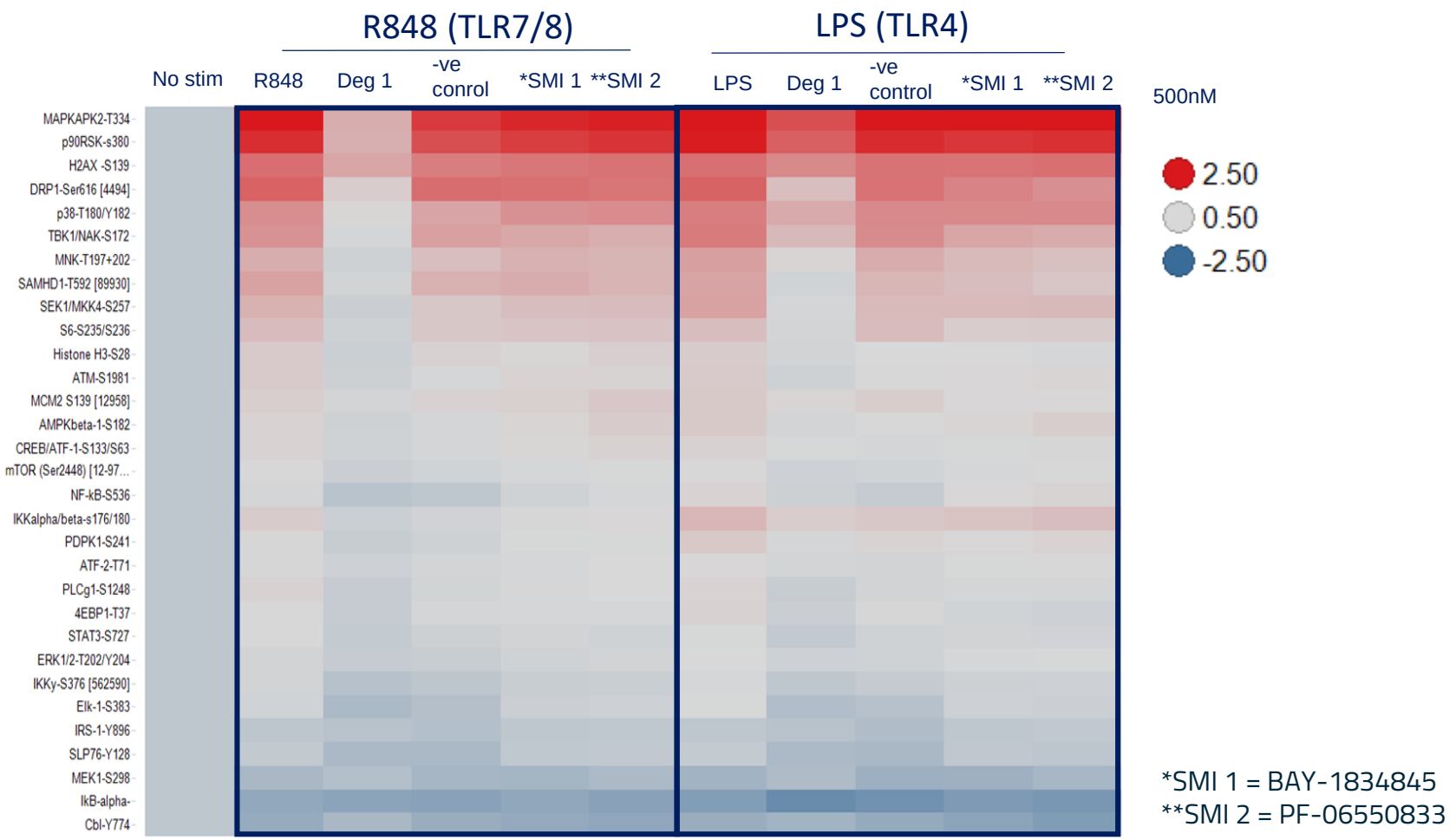
IRAK4 Degradation is Superior to Kinase Inhibition in Blocking TLR Activation



*SMI 1 = BAY-1834845
**SMI 2 = PF-06550833

Degradation inhibits phosphorylation events downstream of TLR activation in human PBMCs

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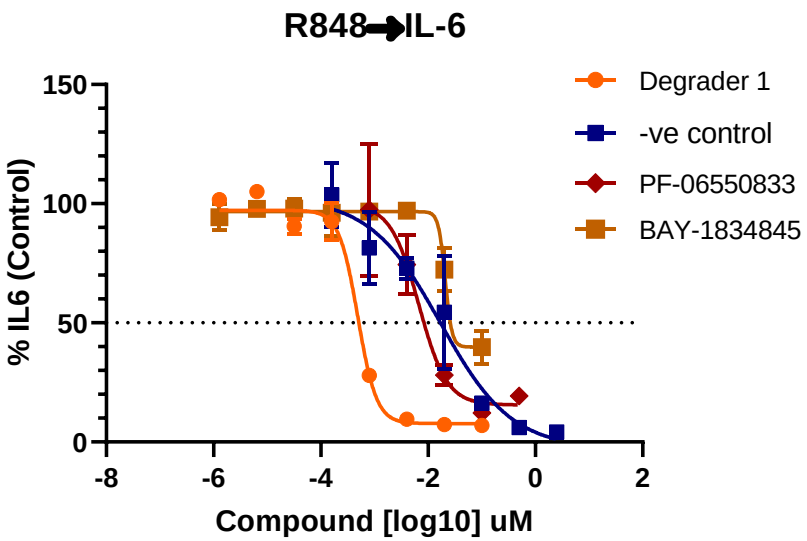
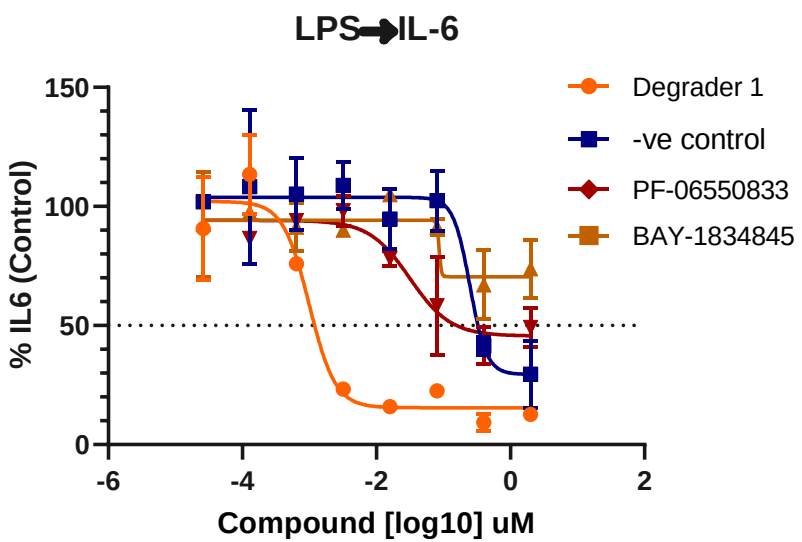
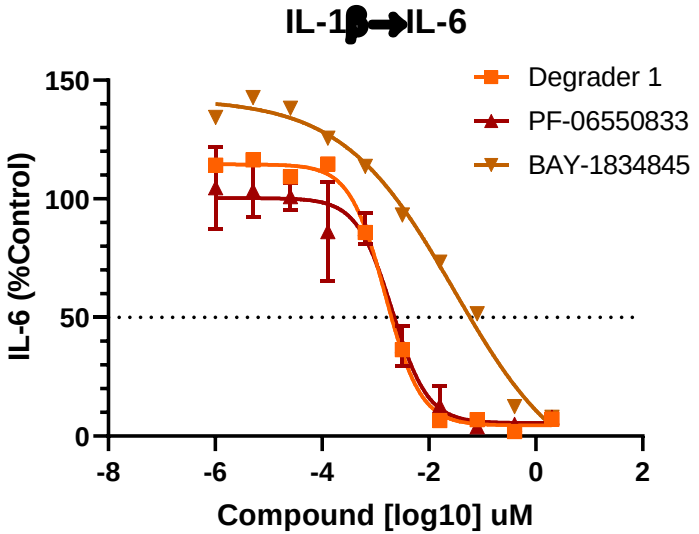
IRAK4 Degradation has Broader and More Potent Effect on TIR-Stimulated Cytokines Compared to Kinase Inhibition







Compound	IL-6 IC_{50} (nM)	Max inhibition
Degrader 1	0.2 ± 0.2	97 ± 4
-ve control	13.8 ± 0.4	95 ± 1
PF-06550833	5.2 ± 3.5	92 ± 5
BAY-1834845	48.9 ± 13.5	91 ± 13

Compound	IL-6 IC_{50} (nM)	Max inhibition
Degrader 1	4.4 ± 3.2	84 ± 6
-ve control	335.5 ± 81	77 ± 6
PF-06550833	111.3 ± 43.7	47 ± 23
BAY-1834845	220.5 ± 83.4	50 ± 22

Compound	IL-6 IC_{50} (nM)	Max inhibition
Degrader 1	1.46 ± 9.72	95 ± 1
PF-06550833	1.9 ± 0.4	92 ± 1
BAY-1834845	39.2 ± 19.5	91 ± 1

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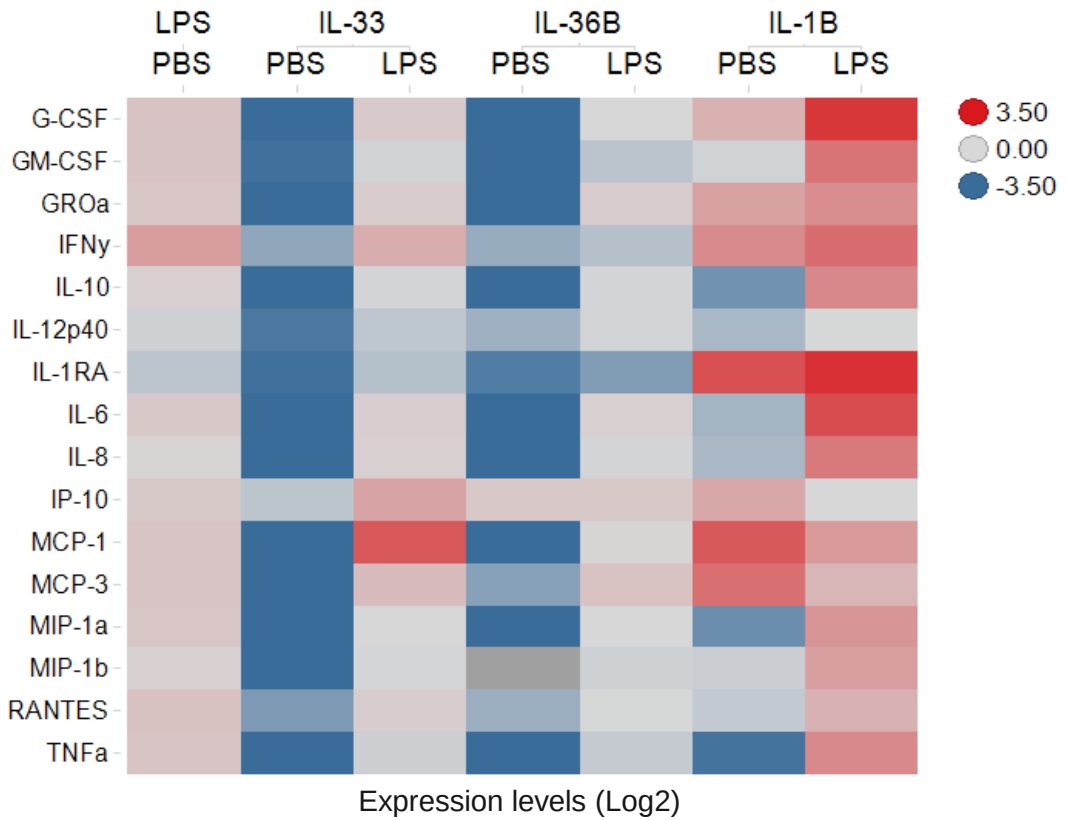
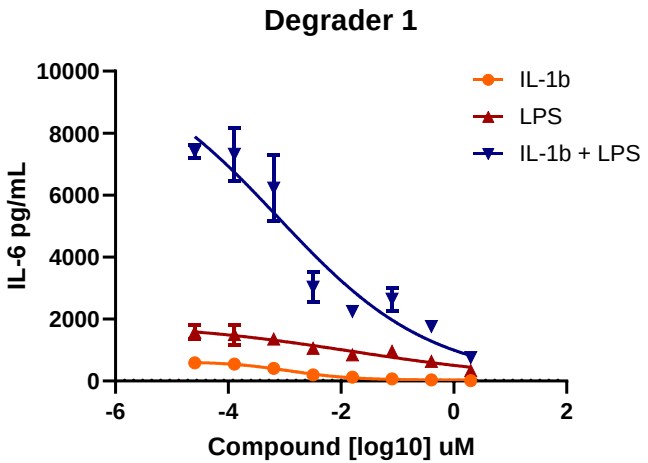
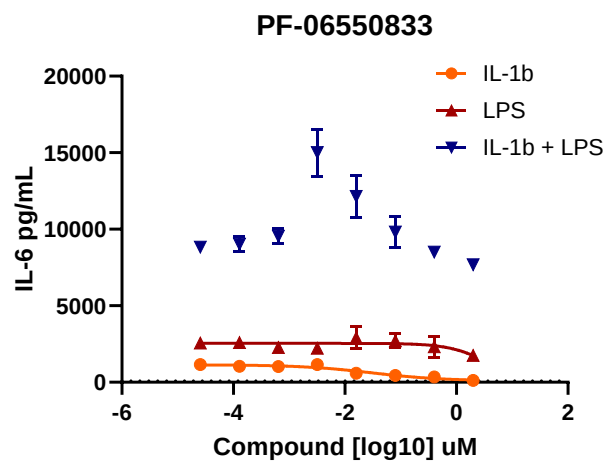
Degrader More Effective than Kinase Inhibitors Against Cytokine/Chemokine Induction by IL-1b + LPS

IL-1β+LPS combination induces enhanced levels of cytokines/CC





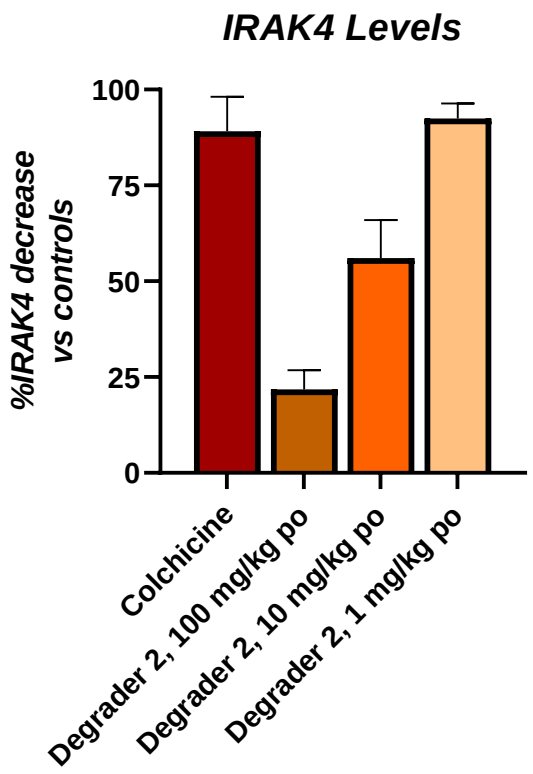


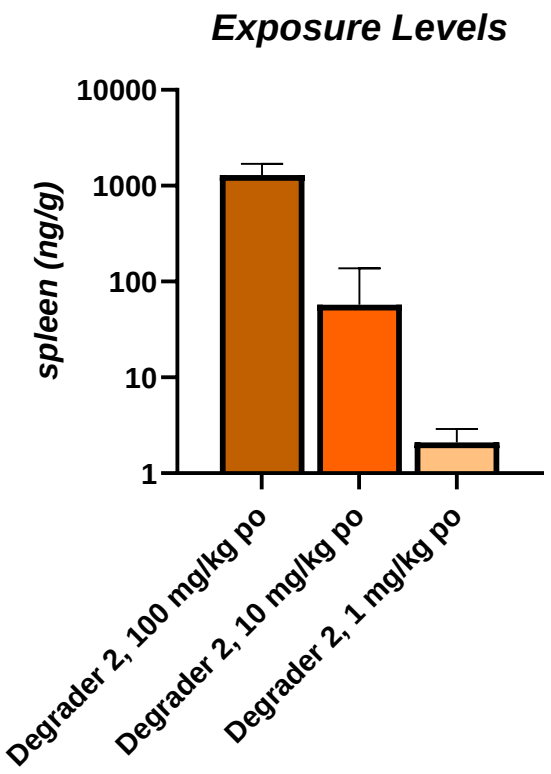
Cytokine/ Chemokine Induced by IL-1b + LPS	Degrader 1 relative [IC50] nM	-ve control relative [IC50] nM	PF-06550833 Relative [IC50] nM	BAY-1834845 Relative [IC50] nM
IL-6	0.8	427.5	>2000	>2000
IL-8	0.08	>2000	1400	>2000
G-CSF	0.5	>2000	>2000	>2000
GM-CSF	2.6	161.6	8.1	464.9
CXCL1 (GROα)	76.4	1100	>2000	>2000
CCL3 (MIP-1α)	42.3	1977	>2000	>2000

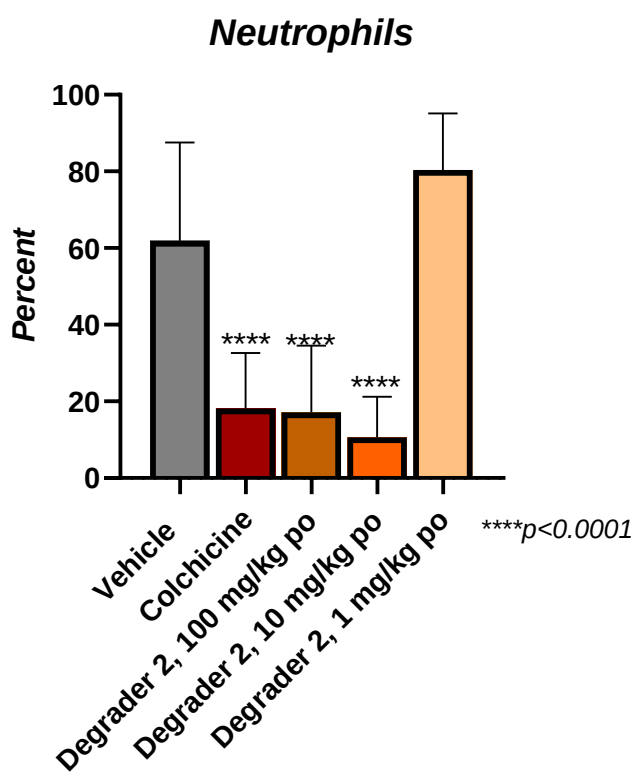
Orally Active IRAK4 Degrader Blocks IL-1-Driven Neutrophilic Inflammation in MSU Air Pouch Model

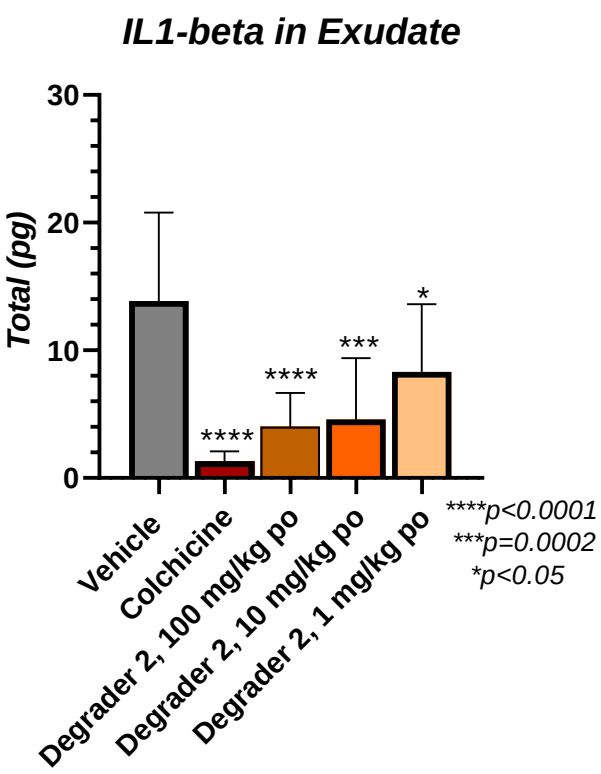
Dose proportional PD and exposure levels in spleen

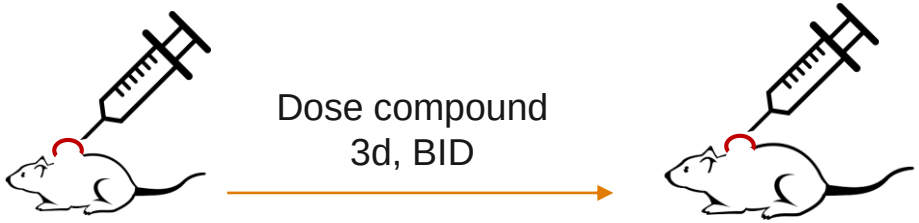
Inhibition of neutrophil infiltration and IL-1β levels











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Summary

- **Kymera has developed first in class potent and selective IRAK4 degraders**
- **These IRAK4 degraders are highly effective at inhibiting myddosome signaling and blocking cytokine/chemokine induction by TLR agonists and IL-1**
- **IRAK4 degraders have superior activity compared to small molecule IRAK4 kinase inhibitors leading to maximal efficacy against multiple proinflammatory stimuli**
- **Orally bioavailable IRAK4 degraders have been developed and are effective at blocking IL-1-driven neutrophilic inflammation in the mouse MSU air pouch model**
- **IRAK4 degraders have the potential to treat TLR/IL-1R-driven inflammation and autoimmune diseases and are being advanced into the clinic in 2020**

Thank you!

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