

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

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ACR 2019

November 11, 2019

Oral poster presentation

Kymera Therapeutics

Disclosure statement

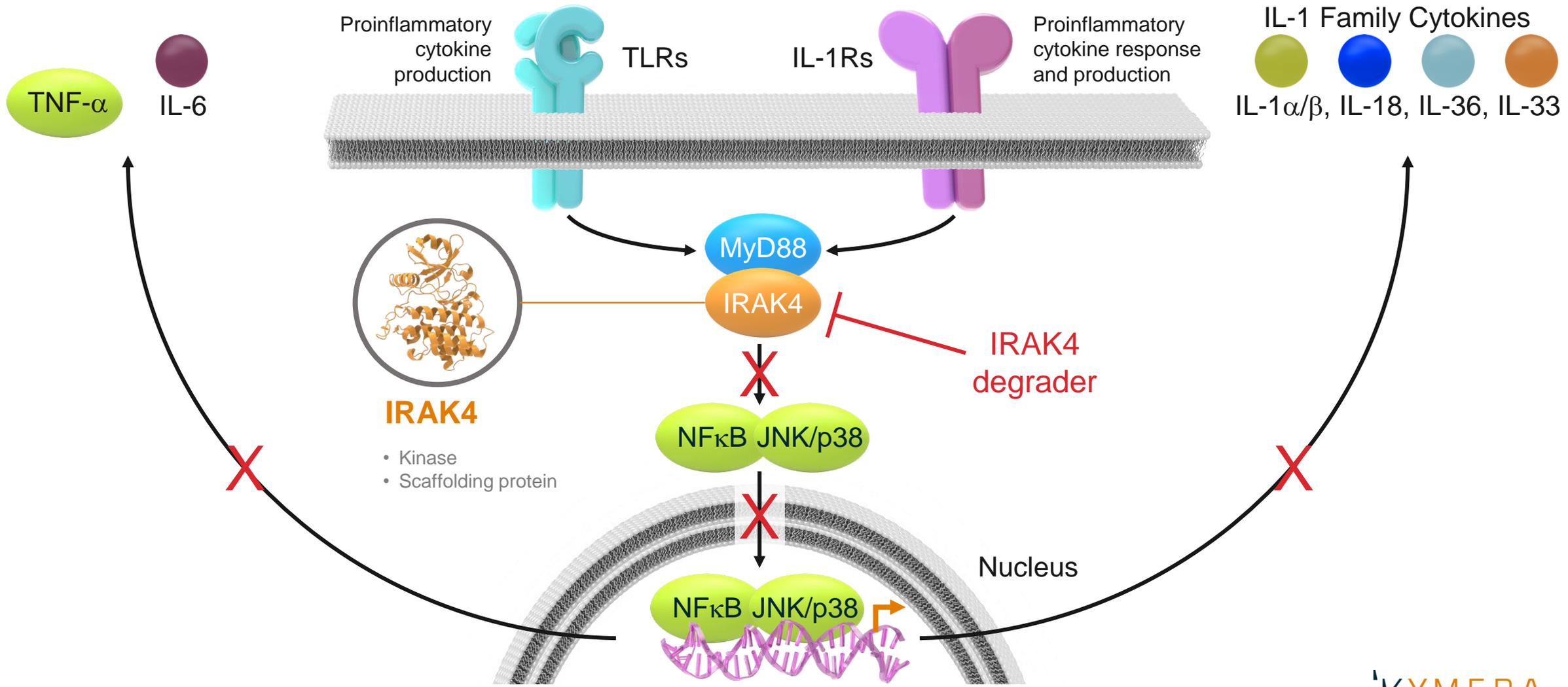
Kymera Therapeutics employee

Overview

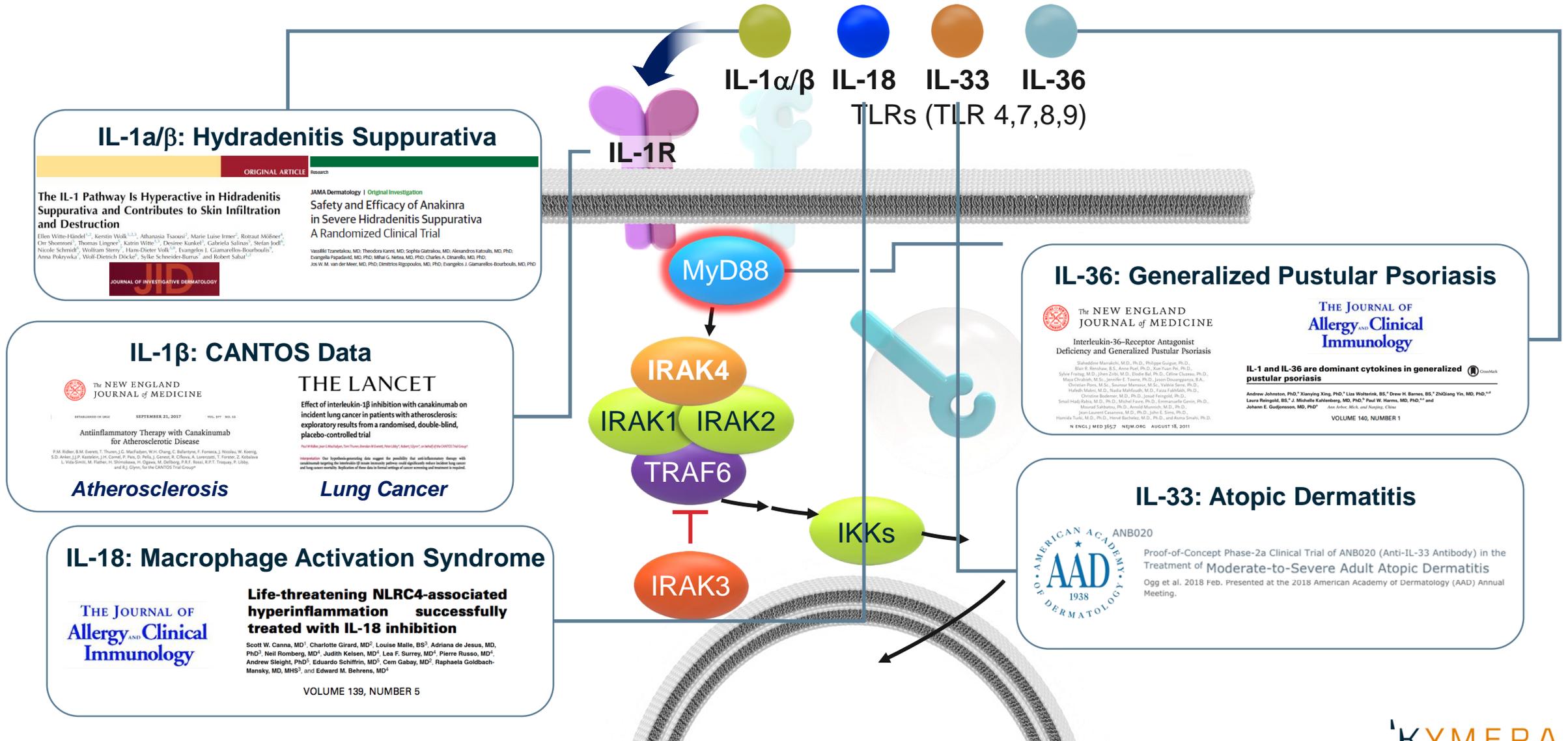
- **IRAK4 as a clinically validated target**
- **Biology of targeted protein degradation**
- **IRAK4 degradation leads to superior activity compared to kinase inhibition**
- ***In vivo* anti-inflammatory activity of oral IRAK4 degrader**

Mechanistic Rationale for IRAK4 Degradation in Immunology

Myddosome Targeting Blocks IL-1 Family Cytokine Production and Response



Multiple Validated Clinical Entry Points for IRAK4 Degradator



IL-1α/β: Hidradenitis Suppurativa

ORIGINAL ARTICLE Research

The IL-1 Pathway Is Hyperactive in Hidradenitis Suppurativa and Contributes to Skin Infiltration and Destruction

Ellen Witte-Händel^{1,2}, Kerstin Wolk^{1,2,3}, Athanasia Tsacou², Marie Luise Irmer², Retzaut Mökner², Or Shomroni², Thomas Lingner², Katrin Witte^{1,2}, Désirée Kunkel², Gabriela Salinas², Stefan Jodl², Nicole Schmitt², Wolfram Storz², Hans-Dieter Volk^{1,2}, Evangelos J. Giamarellos-Bourboulis², Anna Pokrywka², Wolf-Dietrich Döcke², Sylke Schneider-Burnus², and Robert Sabat^{1,2}

JAMA Dermatology | Original Investigation
Safety and Efficacy of Anakinra in Severe Hidradenitis Suppurativa: A Randomized Clinical Trial

Vasiliki Tzaniatou, MD; Theodoros Karat, MD; Sophia Gattalou, MD; Alexandros Tsalikis, MD; Ph.D.; Evangelos Papadavid, MD; Ph.D.; Mihai G. Netea, MD; Ph.D.; Charles A. Dinarello, MD; Ph.D.; Jos W. M. van der Meer, MD; Ph.D.; Dimitrios Rigopoulos, MD; Ph.D.; Evangelos J. Giamarellos-Bourboulis, MD; Ph.D.

JOURNAL OF INVESTIGATIVE DERMATOLOGY

IL-1β: CANTOS Data

THE LANCET

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Atherosclerosis Lung Cancer

THE NEW ENGLAND JOURNAL OF MEDICINE

Antinflammatory Therapy with Canakinumab for Atherosclerotic Disease

F.M. Balken, B.M. Everett, T. Thorne, J.G. MacFarland, W.H. Chang, C. Ballantyne, F. Fornara, J. Nicolau, W. Koenig, S.D. Anker, J.P. Kanevski, J.H. Connors, P. Libby, D. Polk, J. Goren, R. Collins, A. Lerman, T. Forster, Z. Kobayashi, L. Vitek, S. Smith, M. Flather, H. Shimokata, H. Ogunba, M. Dahlborg, P.K.T. Ross, B.P.T. Trappay, P. Libby, and K.J. Cyren, for the CANTOS Trial Group

IL-18: Macrophage Activation Syndrome

Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition

Scott W. Canina, MD¹, Charlotte Girard, MD², Louise Matle, BS¹, Adriana de Jesus, MD, PhD³, Neil Romborg, MD⁴, Judith Keenan, MD⁴, Lea F. Surrey, MD⁴, Pierre Russo, MD⁴, Andrew Sleight, PhD⁵, Eduardo Schiffhryn, MD⁵, Cem Gabay, MD⁶, Raphaela Goldbach-Mansky, MD, MHS⁵, and Edward M. Behrens, MD⁴

THE JOURNAL OF Allergy AND Clinical Immunology

VOLUME 139, NUMBER 5

IL-36: Generalized Pustular Psoriasis

THE NEW ENGLAND JOURNAL OF MEDICINE

Interleukin-36-Receptor Antagonist Deficiency and Generalized Pustular Psoriasis

THE JOURNAL OF Allergy AND Clinical Immunology

IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis

Andrew Johnston, PhD¹; Xinying Xing, PhD²; Lisa Walderick, BS²; Drew H. Barnes, BS²; ZhiQiang Yin, MD, PhD^{3,4}; Laura Reingold, BS²; J. Michelle Kahlenberg, MD, PhD⁵; Paul W. Harris, MD, PhD^{6,7}; and Johann E. Gudjonsson, MD, PhD⁸

Ann Arbor, Mich, and Nanjing, China

VOLUME 140, NUMBER 1

IL-33: Atopic Dermatitis

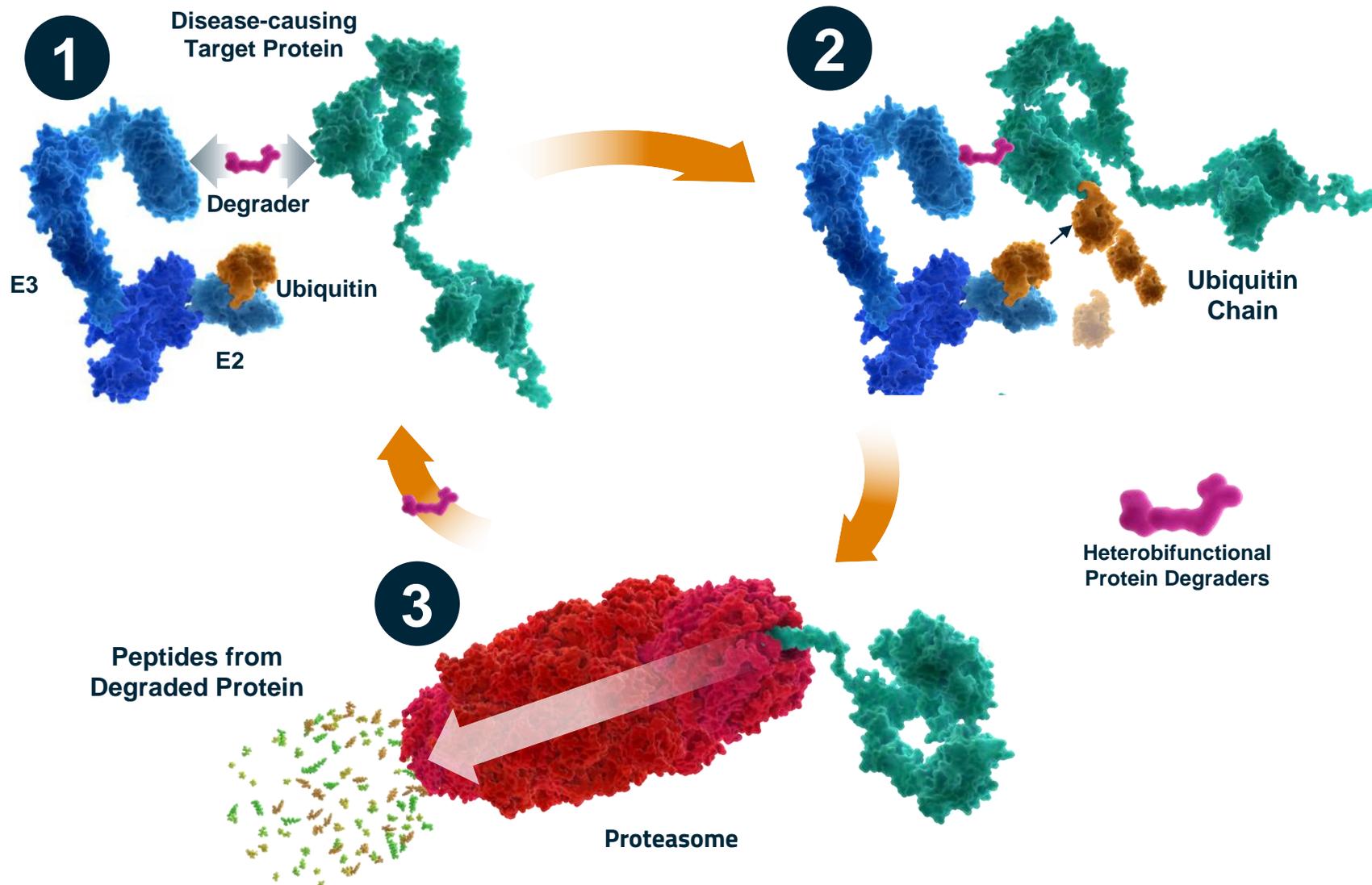
ANB020

Proof-of-Concept Phase-2a Clinical Trial of ANB020 (Anti-IL-33 Antibody) in the Treatment of Moderate-to-Severe Adult Atopic Dermatitis

Ogg et al. 2018 Feb. Presented at the 2018 American Academy of Dermatology (AAD) Annual Meeting.

AMERICAN ACADEMY OF DERMATOLOGY 1938

Biology of Targeted Protein Degradation



Undruggable
Targets

Efficient

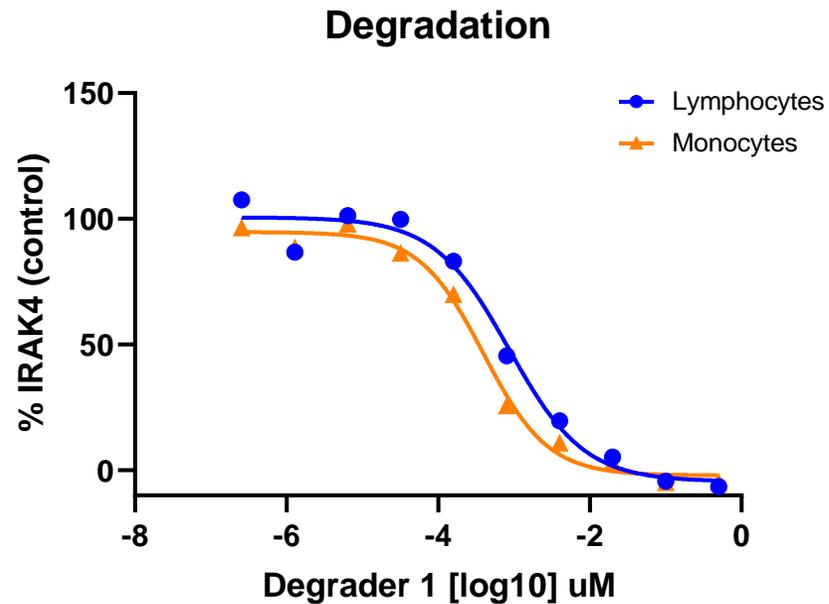
Oral

Systemic

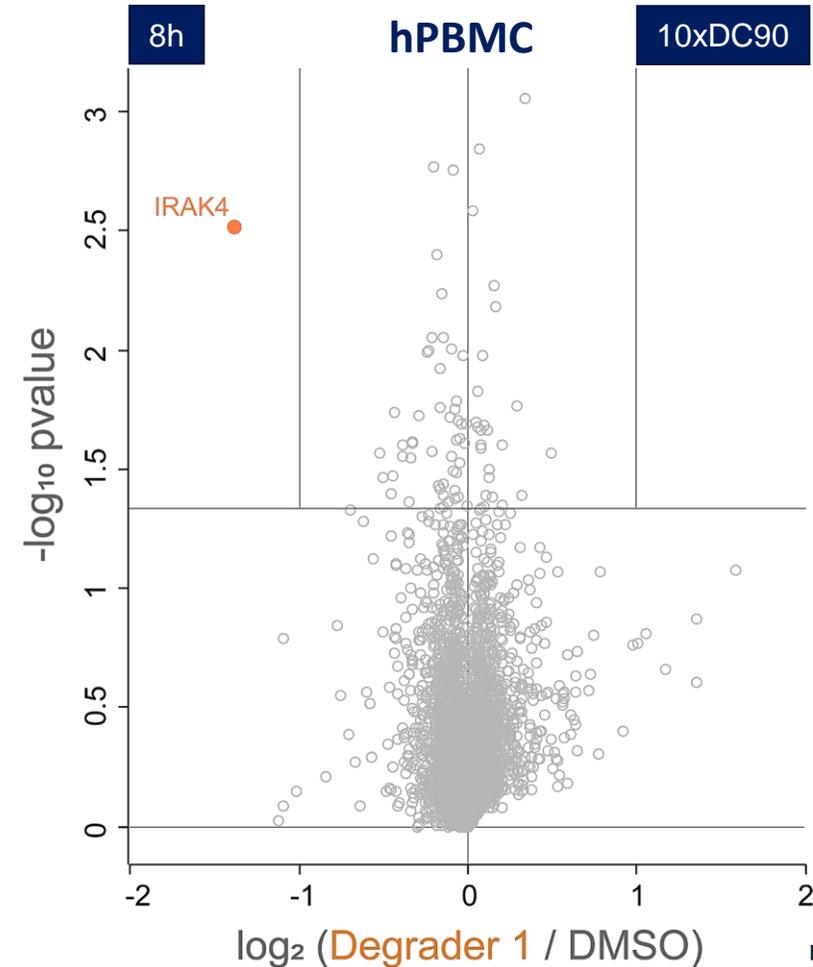
Potent and Selective Degradator of IRAK4

Potent IRAK4 degradation in immune subsets

High Selectivity for IRAK4 over 10,000 Proteins



Cell type	IRAK4 DC ₅₀ (nM)
Monocytes	0.86 ± 0.68
Lymphocytes	1.1 ± 0.53

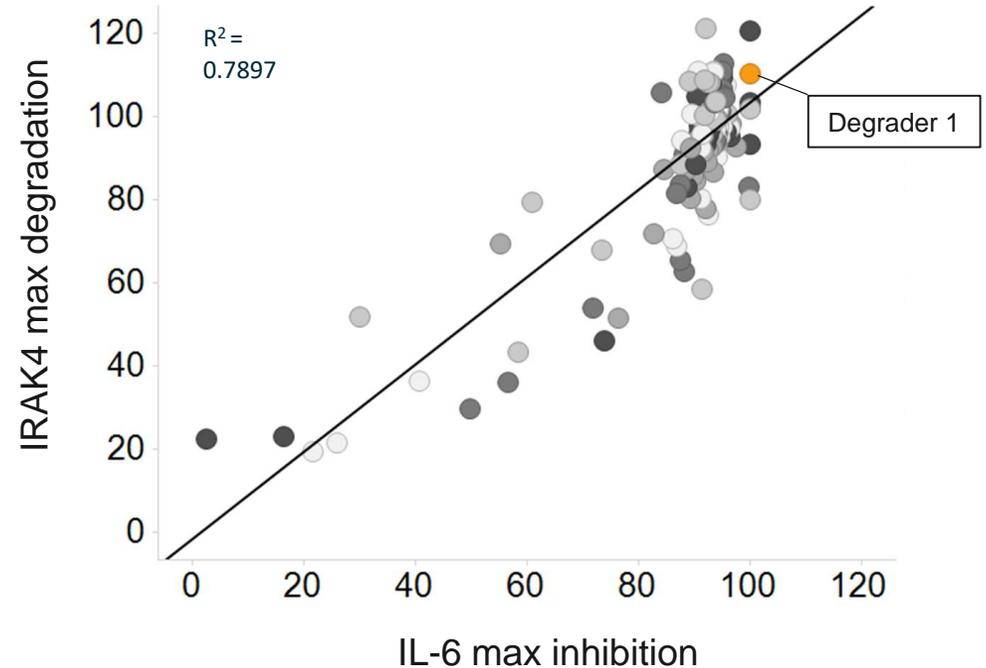
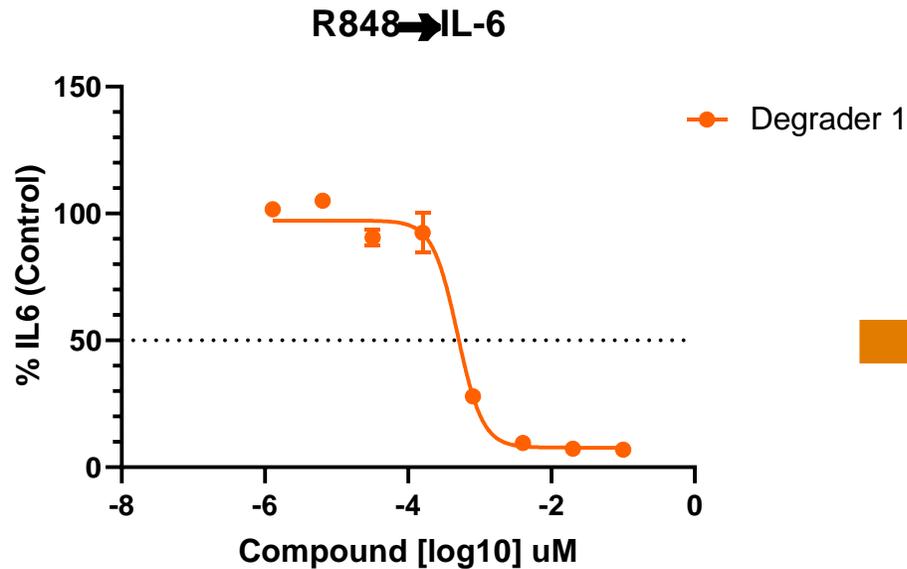


Non Confidential

Degrader Inhibition of Cytokine Induction Correlates with IRAK4 Downregulation

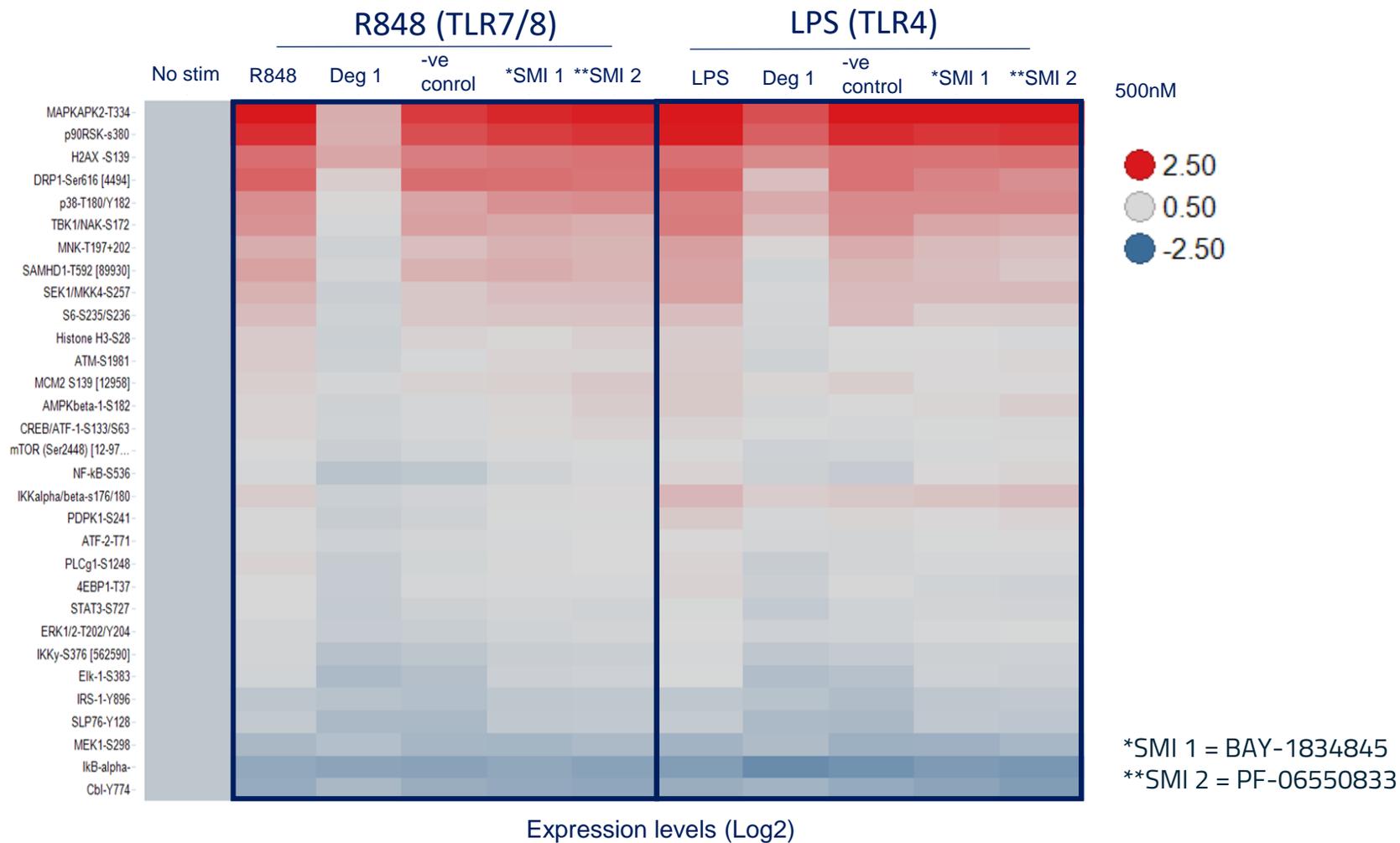
Potent inhibition of IL-6

Degradation correlates with cytokine inhibition



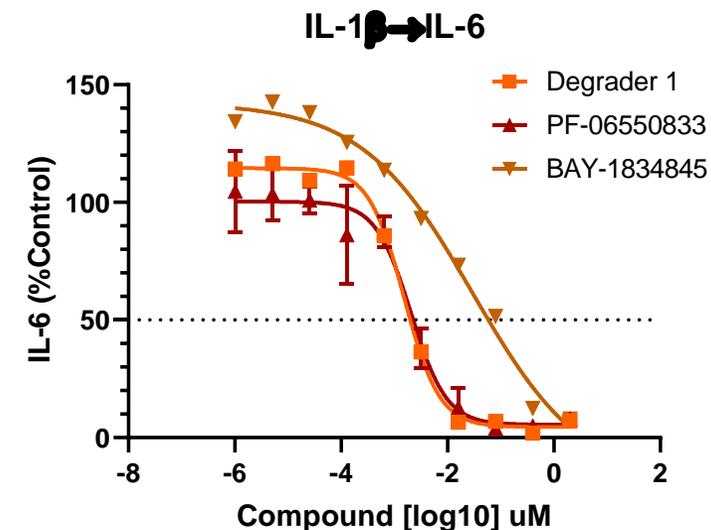
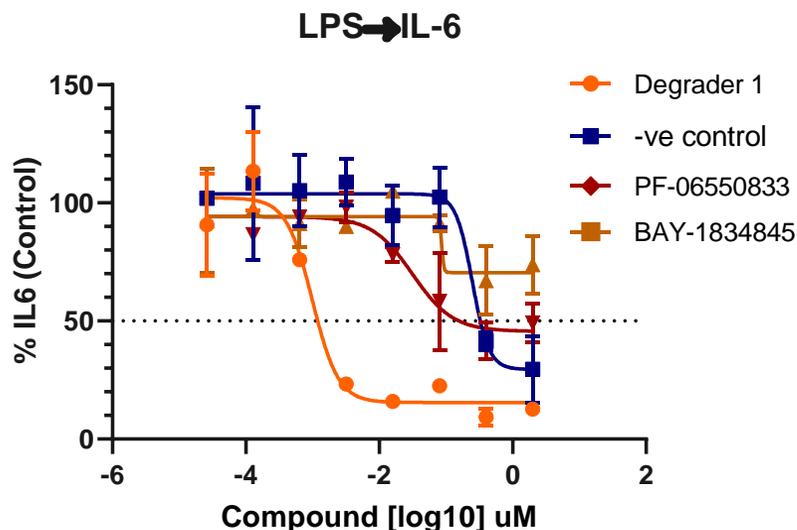
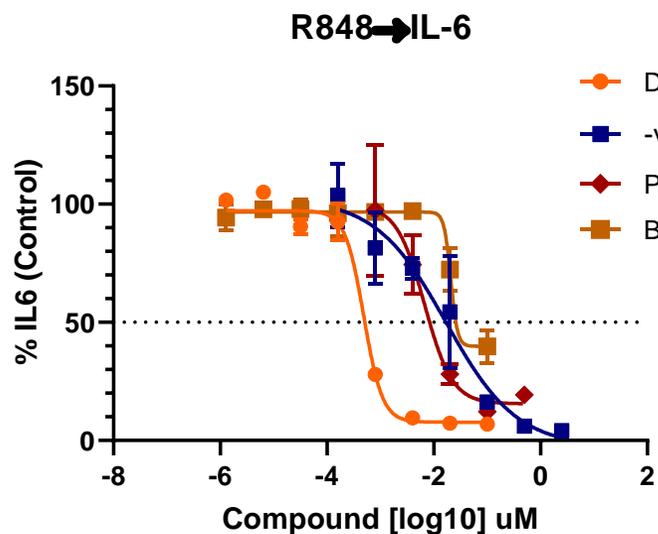
Compound	IL-6 IC ₅₀ (nM)
Degrader 1	0.2 ± 0.2

IRAK4 Degradation is Superior to Kinase Inhibition in Blocking TLR Activation



Degradation inhibits phosphorylation events downstream of TLR activation in human PBMCs

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



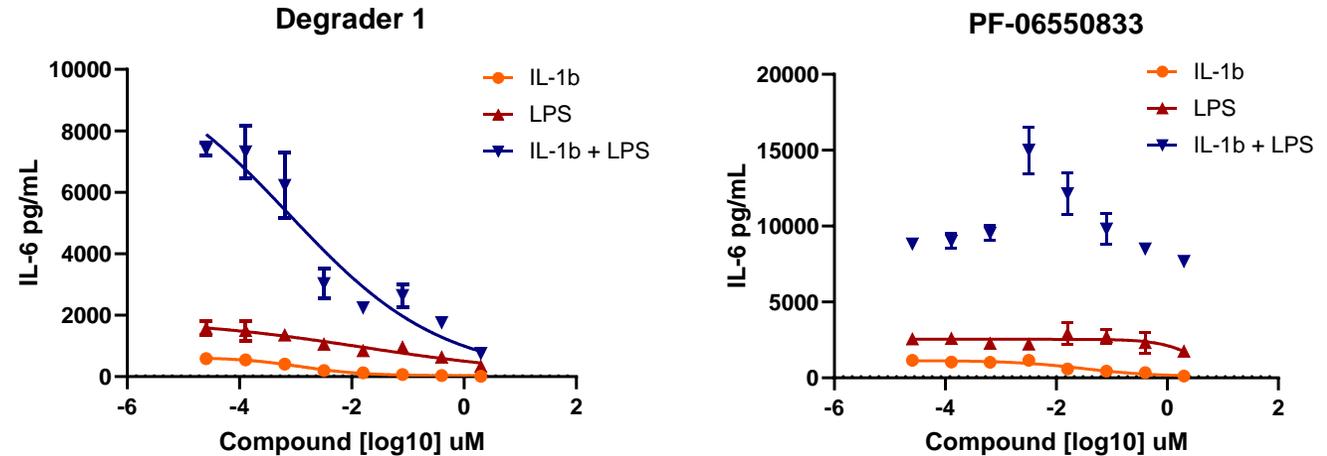
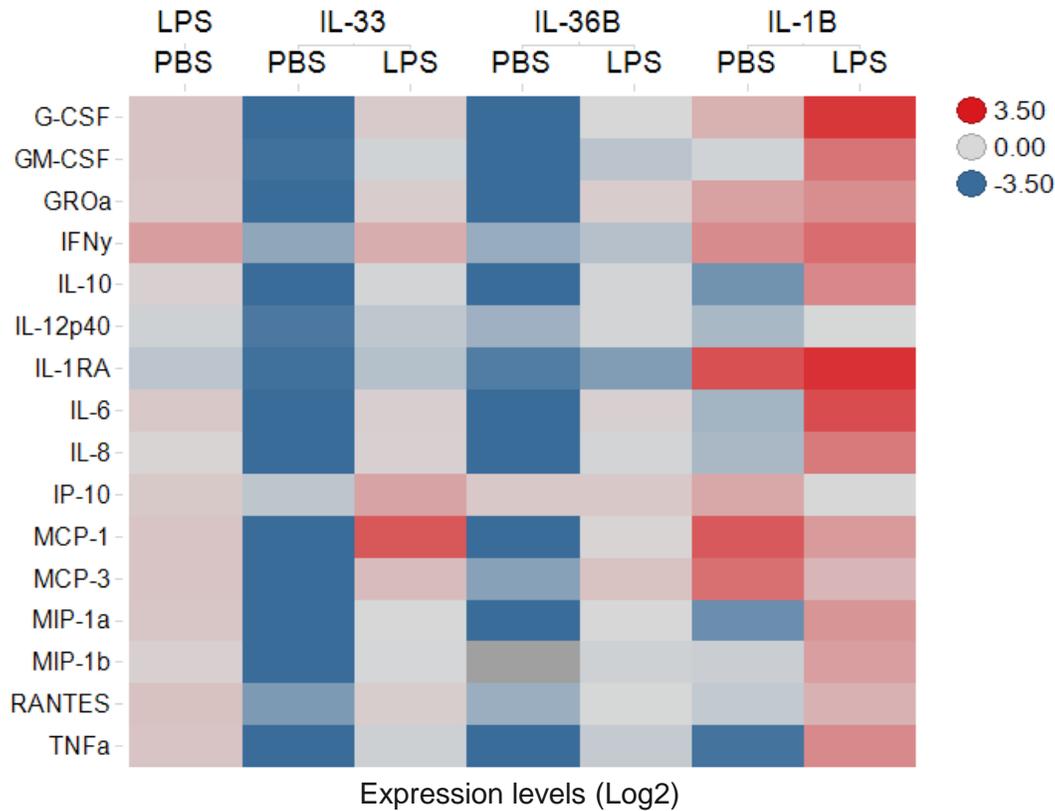
Compound	IL-6 IC ₅₀ (nM)	Max inhibition
Degrader 1	0.2 ± 0.2	97 ± 4
-ve control	13.8 ± 0.4	95 ± 1
PF-06550833	5.2 ± 3.5	92 ± 5
BAY-1834845	48.9 ± 13.5	91 ± 13

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

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

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

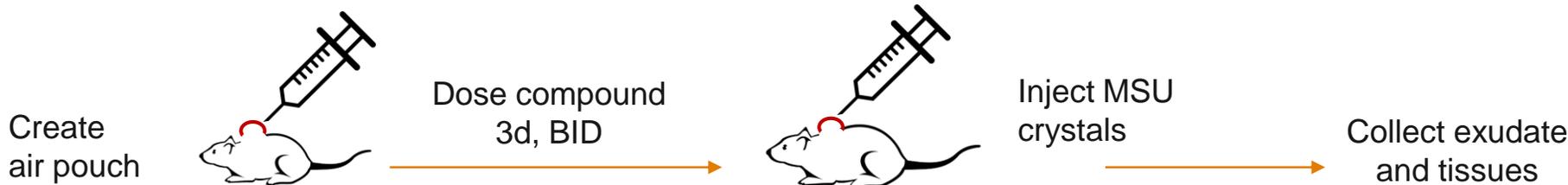
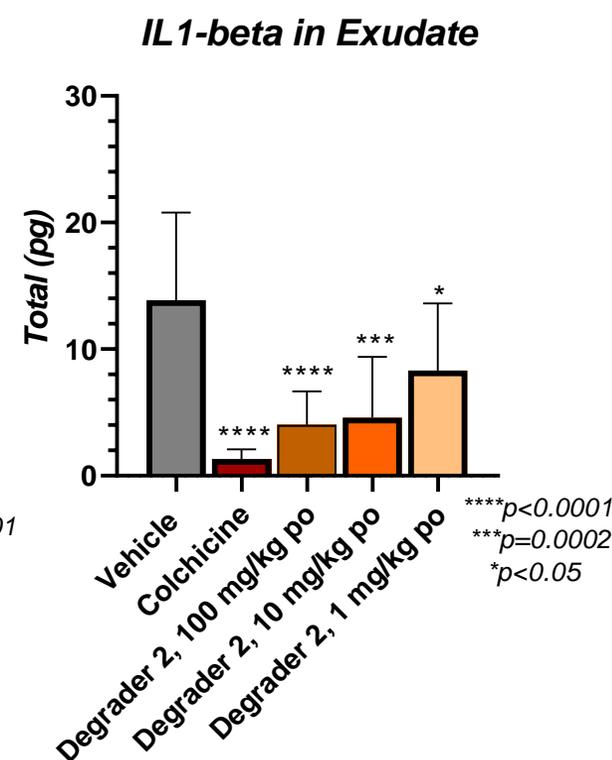
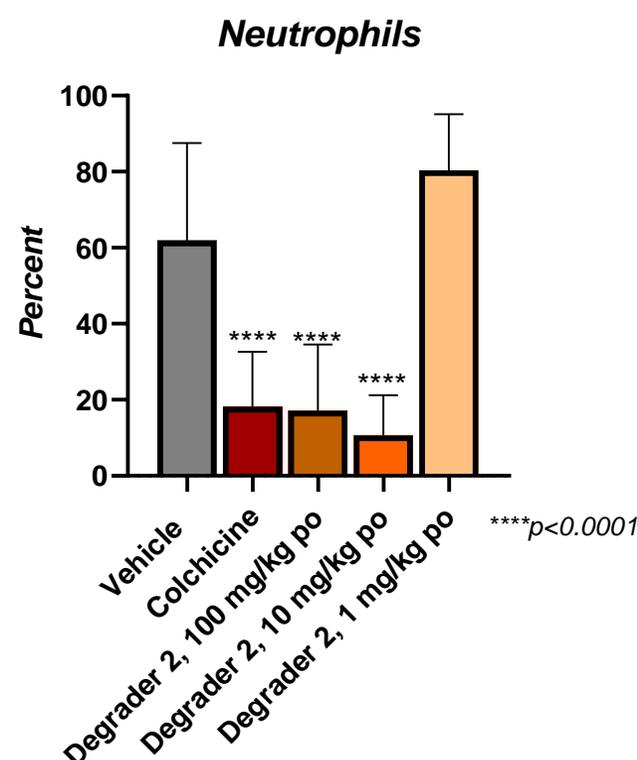
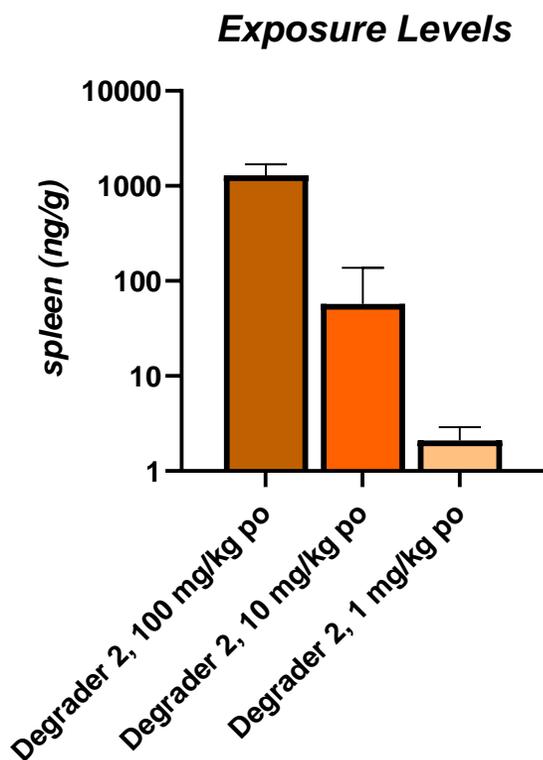
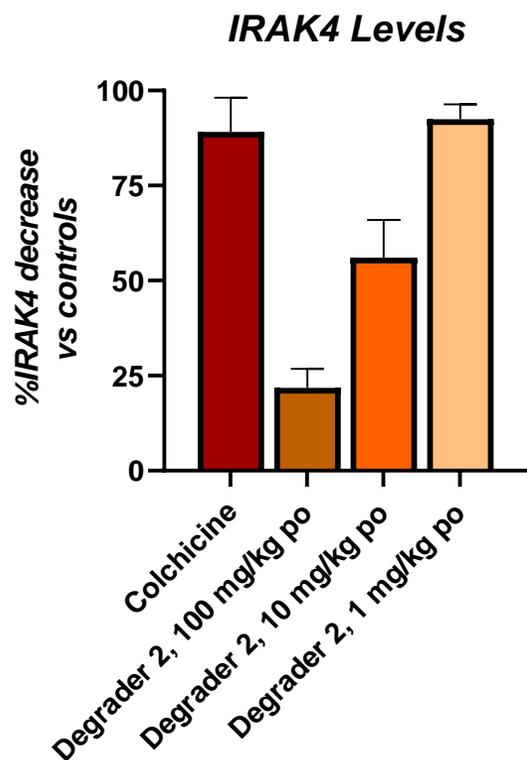


Cytokine/Chemokine Induced by IL-1b + LPS	Degrader 1 relative [IC50] nM	-ve control relative [IC50] nM	PF-06550833 Relative [IC50] nM	BAY-1834845 Relative [IC50] nM
IL-6	0.8	427.5	>2000	>2000
IL-8	0.08	>2000	1400	>2000
G-CSF	0.5	>2000	>2000	>2000
GM-CSF	2.6	161.6	8.1	464.9
CXCL1 (GRO α)	76.4	1100	>2000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

Orally Active IRAK4 Degradator 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-1 β levels



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!

