INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

IRAK4 Degradation vs. Inhibition

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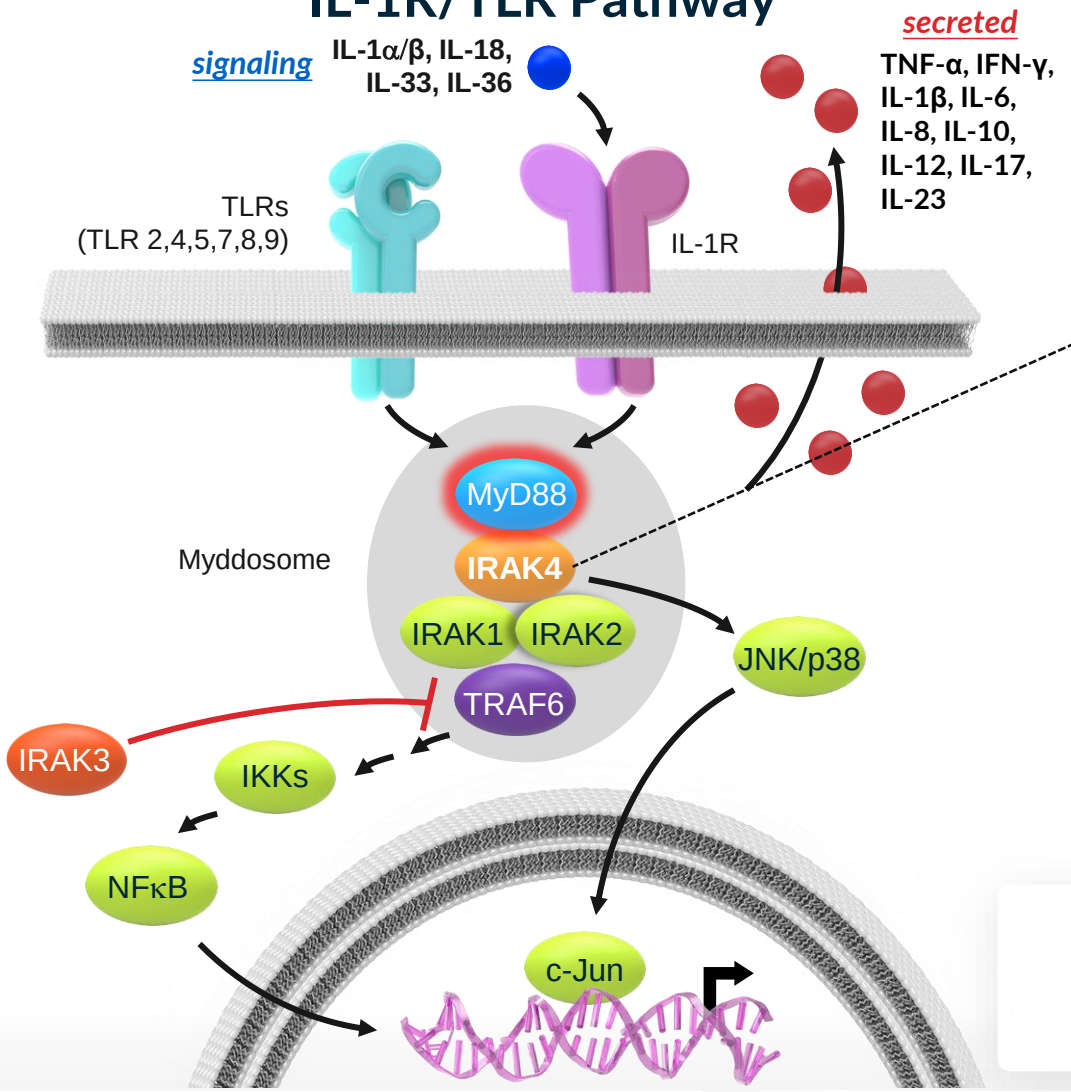
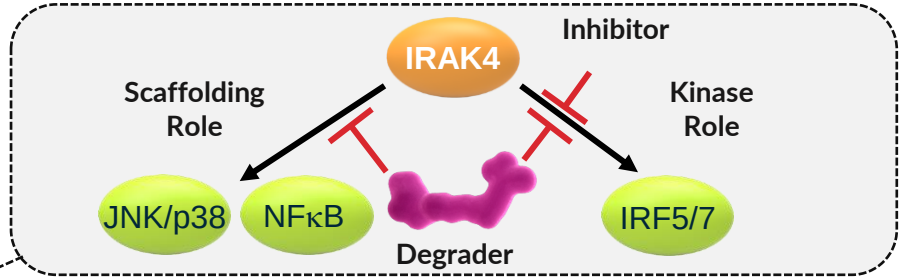
Degrading IRAK4: Best Approach to Block IL-1R/TLR driven Inflammation

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

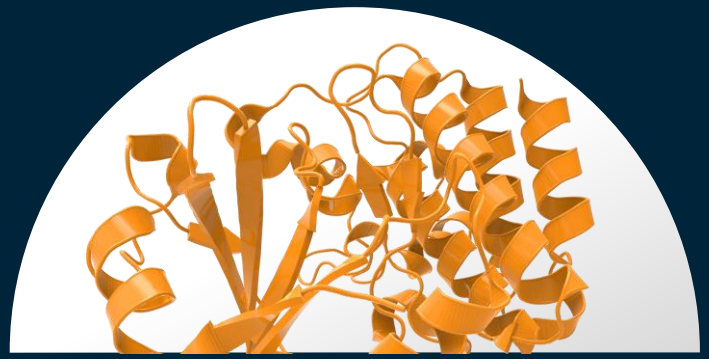
IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa
IL-1α: Atopic Dermatitis
IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis
IRAK4 SMI: Rheumatoid Arthritis

Human Genetics

Adult humans with **IRAK4 Null Mutation are healthy**

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

IRAK4 Degradation vs Inhibition
Overview

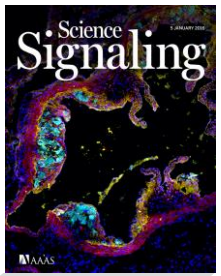


We and others have shown that IRAK4 degradation **is required to block IL1R/TLR pathway activation,** especially in high-inflammatory states where small molecule kinase inhibitors fail

- IRAK4 KO is able **to block TLR activation** unlike the kinase dead rescue
- IRAK4 **scaffolding function** is critical in Myddosome formation and pathway signaling
- IRAK4 degradation, but not kinase inhibition, can **block TLR induced NF-κB translocation**
- IRAK4 degradation, but not kinase inhibition, can **block IL1R+TLR activation**
- IRAK4 degradation is superior to kinase inhibition at **blocking downstream phosphoproteome**
- IRAK4 degradation **is active in all blood cell types** in HS patients while SMI can increase IRAK4 levels
- IRAK4 degradation is superior to inhibition in a **variety of preclinical efficacy models**

IRAK4 KO/Degradation Differentiated Over Kinase Inhibition in TLR Activation – External Data

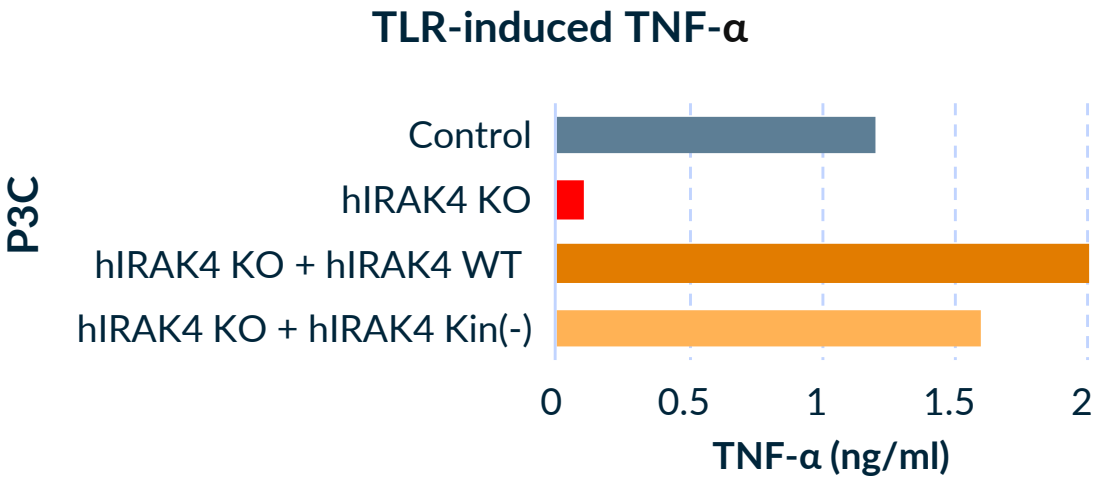
Science Signaling



Comprehensive RNAi-based screening of human and mouse TLR pathways identifies species-specific preferences in signaling protein use

JING SUN, NING LI, KYU-SEON OH, BHASKAR DUTTA, SHARAT J. VAYTTADEN, BIN LIN, THOMAS S. EBERT, DOMINIC DE NARDO, JOIE DAVIS, RUSTAM BAGIRZADEH, NICOLAS W. LOUNSBURY, CHANDRASHEKHAR PASARE, EICKE LATZ, VEIT HORNUNG, AND IAIN D. C. FRASER

Toll-like receptors (TLRs) are a major class of pattern recognition receptors, which mediate the responses of innate immune cells to microbial stimuli. To systematically determine the roles of proteins in canonical TLR signaling pathways, we conducted an RNA interference (RNAi)–based screen in human and mouse macrophages. We observed a pattern of conserved signaling module dependencies across species, but found notable species-specific requirements at the level of individual proteins. Among these, we identified unexpected differences in the involvement of members of the interleukin-1 receptor–associated kinase (IRAK) family between the human and mouse TLR pathways. Whereas TLR signaling in mouse macrophages depended primarily on IRAK4 and IRAK2, with little or no role for IRAK1, TLR signaling and proinflammatory cytokine production in human macrophages depended on IRAK1, with knockdown of IRAK4 or IRAK2 having less of an effect. Consistent with species-specific roles for these kinases, IRAK4 orthologs failed to rescue signaling in IRAK4-deficient macrophages from the other species, and only mouse macrophages required the kinase activity of IRAK4 to mediate TLR responses. The identification of a critical role for IRAK1 in TLR signaling in humans could potentially explain the association of IRAK1 with several autoimmune diseases. Furthermore, this study demonstrated how systematic screening can be used to identify important characteristics of innate immune responses across species, which could optimize therapeutic targeting to manipulate human TLR-dependent outputs.



- IRAK4 KO has a strong response to TLR activation
- A kinase dead and a WT rescue behave similarly
- This demonstrate that kinase function has no impact on TLR activation response

Source: Sun, et al. *Science Signaling*, 2016

Scaffolding Function of IRAK4 is Critical for Myddosome Formation – External Data

JCB Journal of Cell Biology

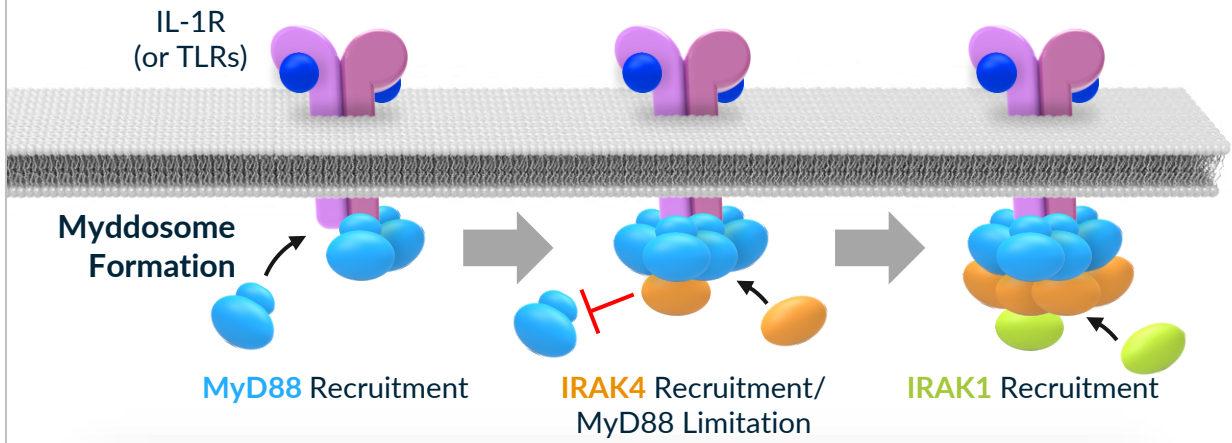
MyD88 oligomer size functions as a physical threshold to trigger IL1R Myddosome signaling

Rafael Deliz-Aguirre*, Fakun Cao*, Fenja H.U. Gerpott, Nichanok Auevechanichkul, Mariam Chupanova, YeVin Mun, Elke Ziska, and Marcus J. Taylor

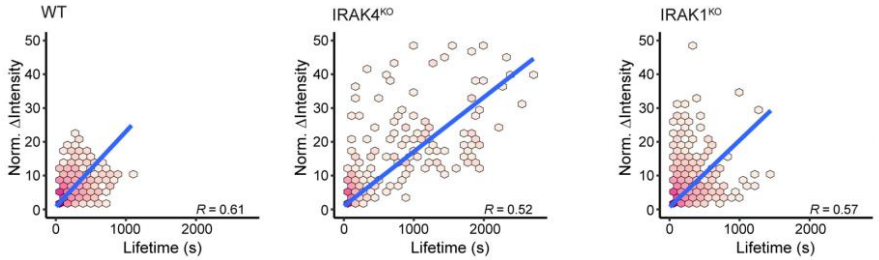
A recurring feature of innate immune receptor signaling is the self-assembly of signaling proteins into oligomeric complexes. The Myddosome is an oligomeric complex that is required to transmit inflammatory signals from TLR/IL1Rs and consists of MyD88 and IRAK family kinases. However, the molecular basis for how Myddosome proteins self-assemble and regulate intracellular signaling remains poorly understood. Here, we developed a novel assay to analyze the spatiotemporal dynamics of IL1R and Myddosome signaling in live cells. We found that MyD88 oligomerization is inducible and initially reversible. Moreover, the formation of larger, stable oligomers consisting of more than four MyD88s triggers the sequential recruitment of IRAK4 and IRAK1. Notably, genetic knockout of IRAK4 enhanced MyD88 oligomerization, indicating that IRAK4 controls MyD88 oligomer size and growth. MyD88 oligomer size thus functions as a physical threshold to trigger downstream signaling. These results provide a mechanistic basis for how protein oligomerization might function in cell signaling pathways.

"…indicating that IRAK4 controls MyD88 oligomer size and growth. MyD88 oligomer size thus functions as a physical threshold to trigger downstream signaling."

IRAK4 Scaffolding Role Functions to Limit MYD88 Oligomer Size and Trigger Myddosome Formation



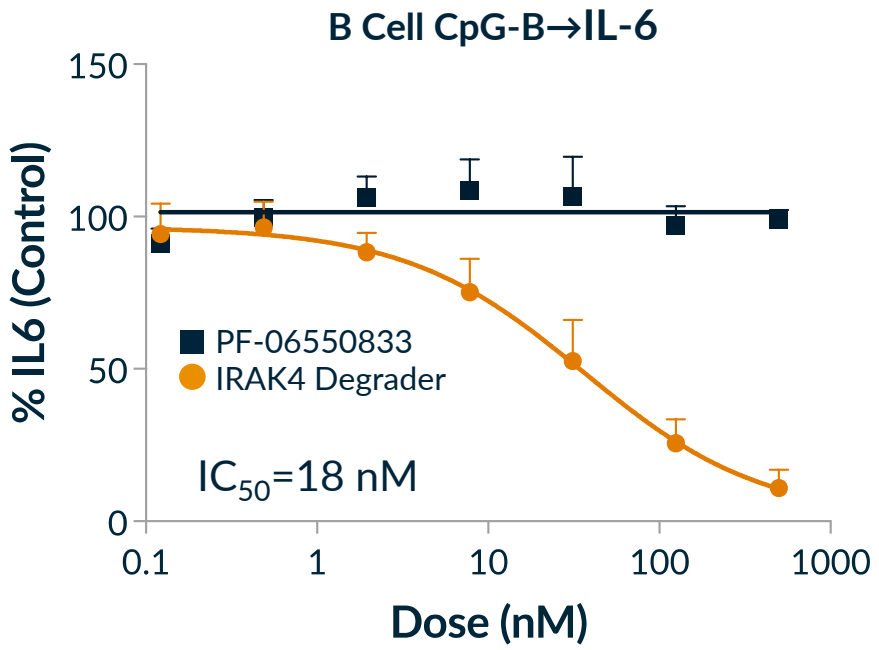
- IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation
- Macromolecular assembly of proteins **in itself** can be considered a signal transduction step

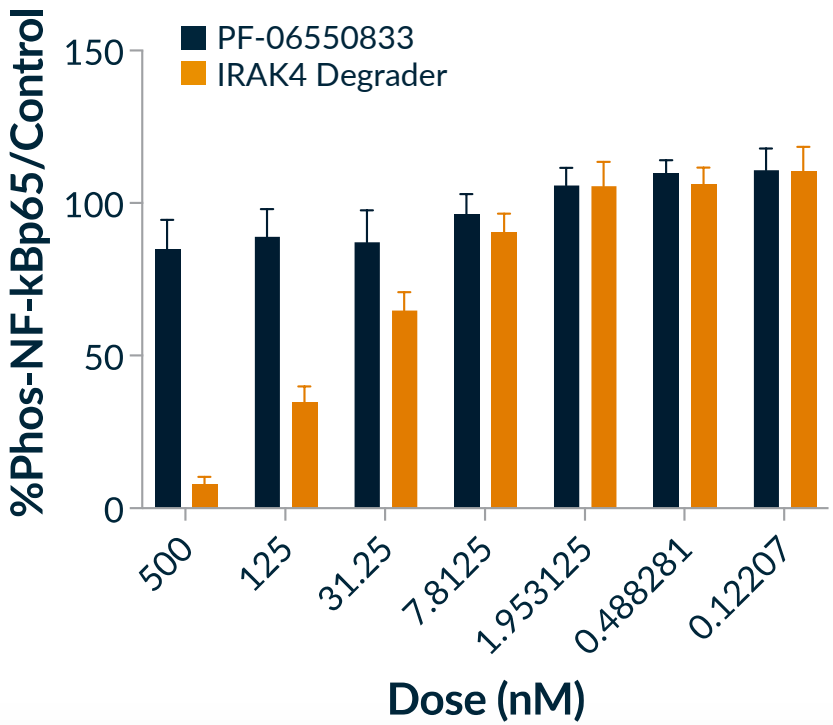


Source: Deliz-Aguirre, et al. *J. Cell Biol.*, 2021

Scaffolding Function of IRAK4 is Critical for Pathway Signaling Through NF-κB – Kymera Data

IRAK4 Scaffolding Function, Not Kinase Activity, is Required for TLR9-mediated Activation of NF-κB in Human B cells

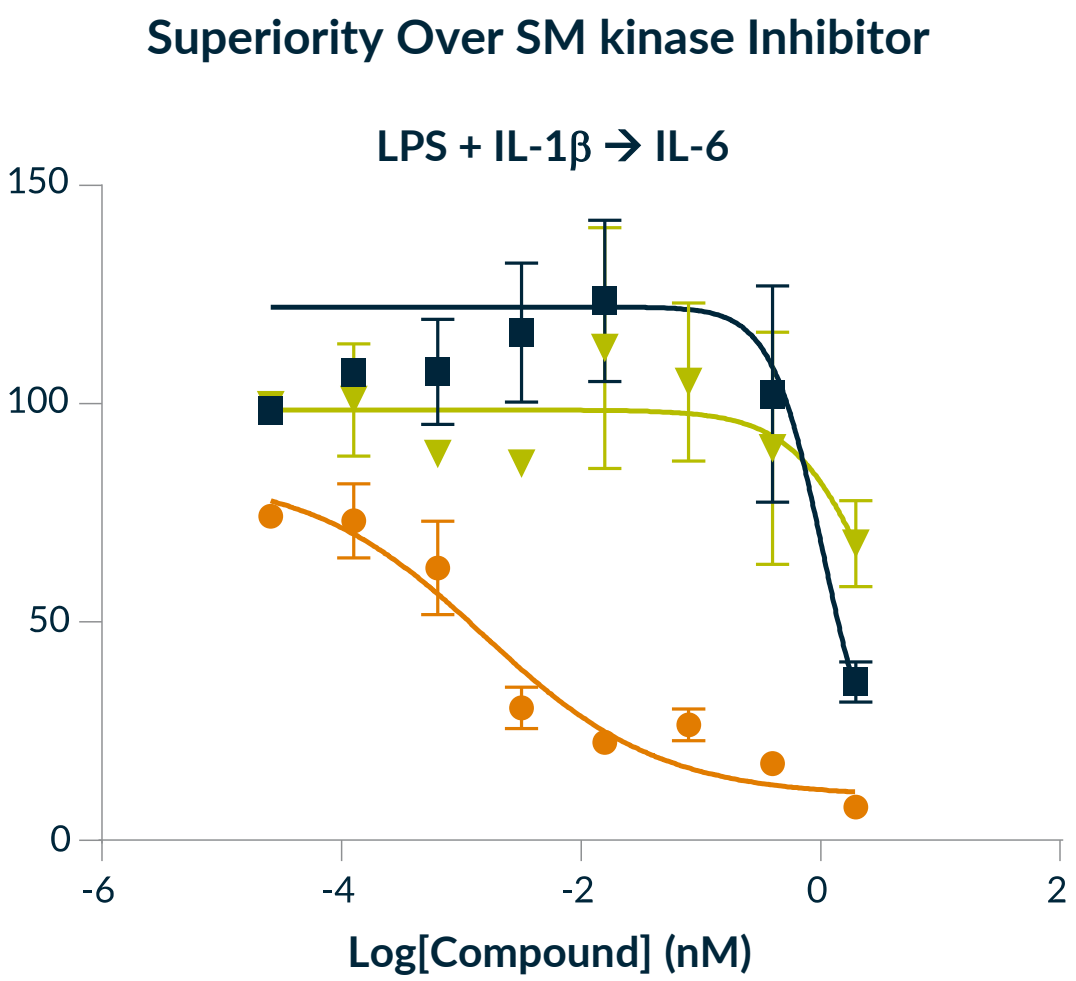




- IRAK4 degradation leads to inhibition of TLR9/ CpG-B induced phos-p65 and IL-6

- Pathway engagement result in downstream signaling that include NF-κB which only a degrader can block.

Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition – Kymera Data

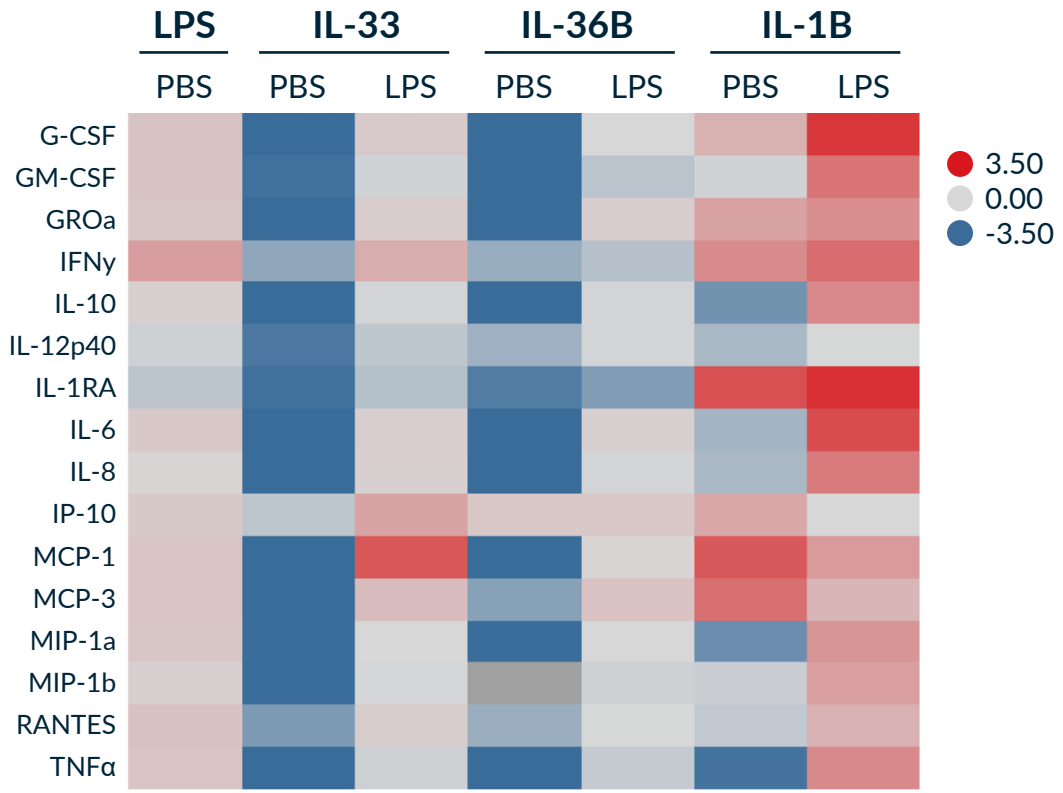


Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

- KT-474 DC_{50} = 2.1 nM in human immune cells
- KT-474 only degraded IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- KT-474 better able to inhibit IL-6 under both LPS and LPS + IL-1β than clinically active IRAK4 SM kinase inhibitor PF-06550833
- In high inflammatory state conditions, degradation is the only mean to pathway blockade

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

IL-1β+LPS Combination Induces Enhanced Levels of Inflammation



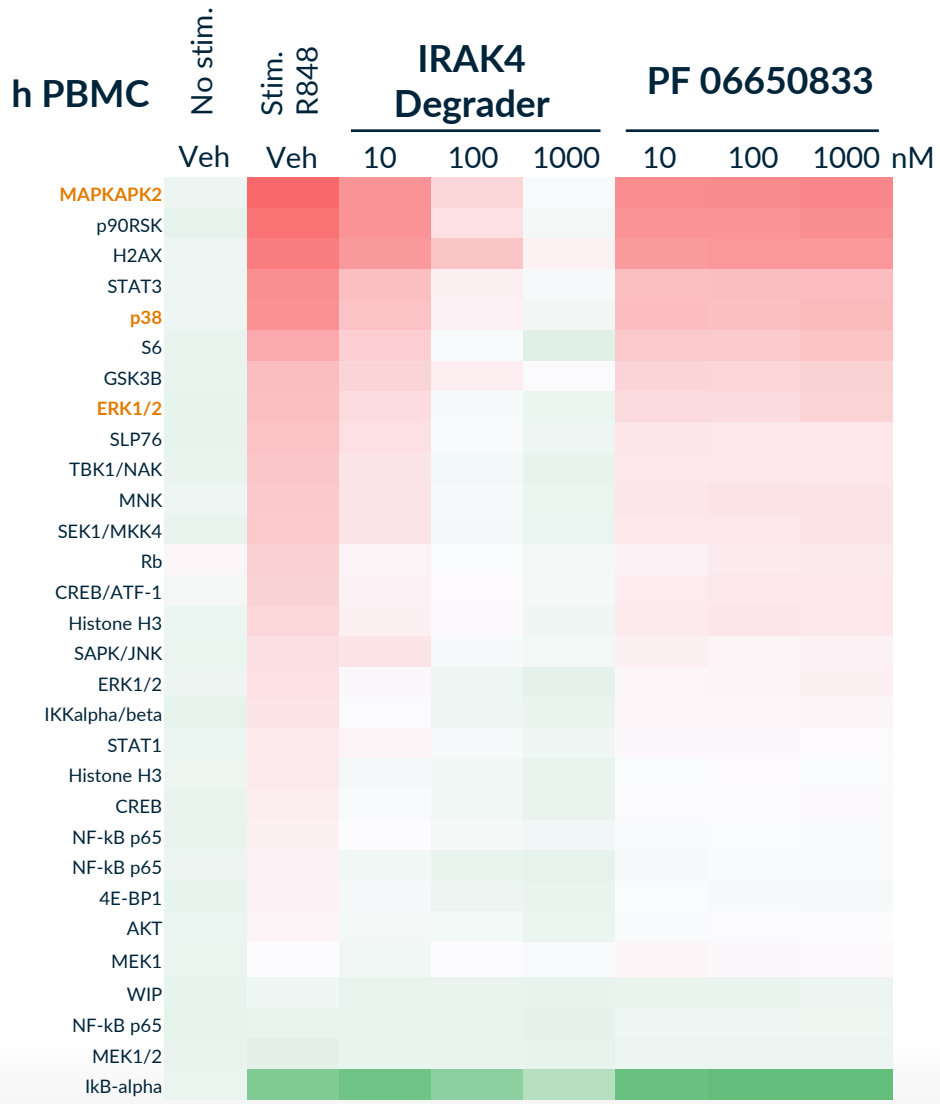
Expression Levels (Log2)

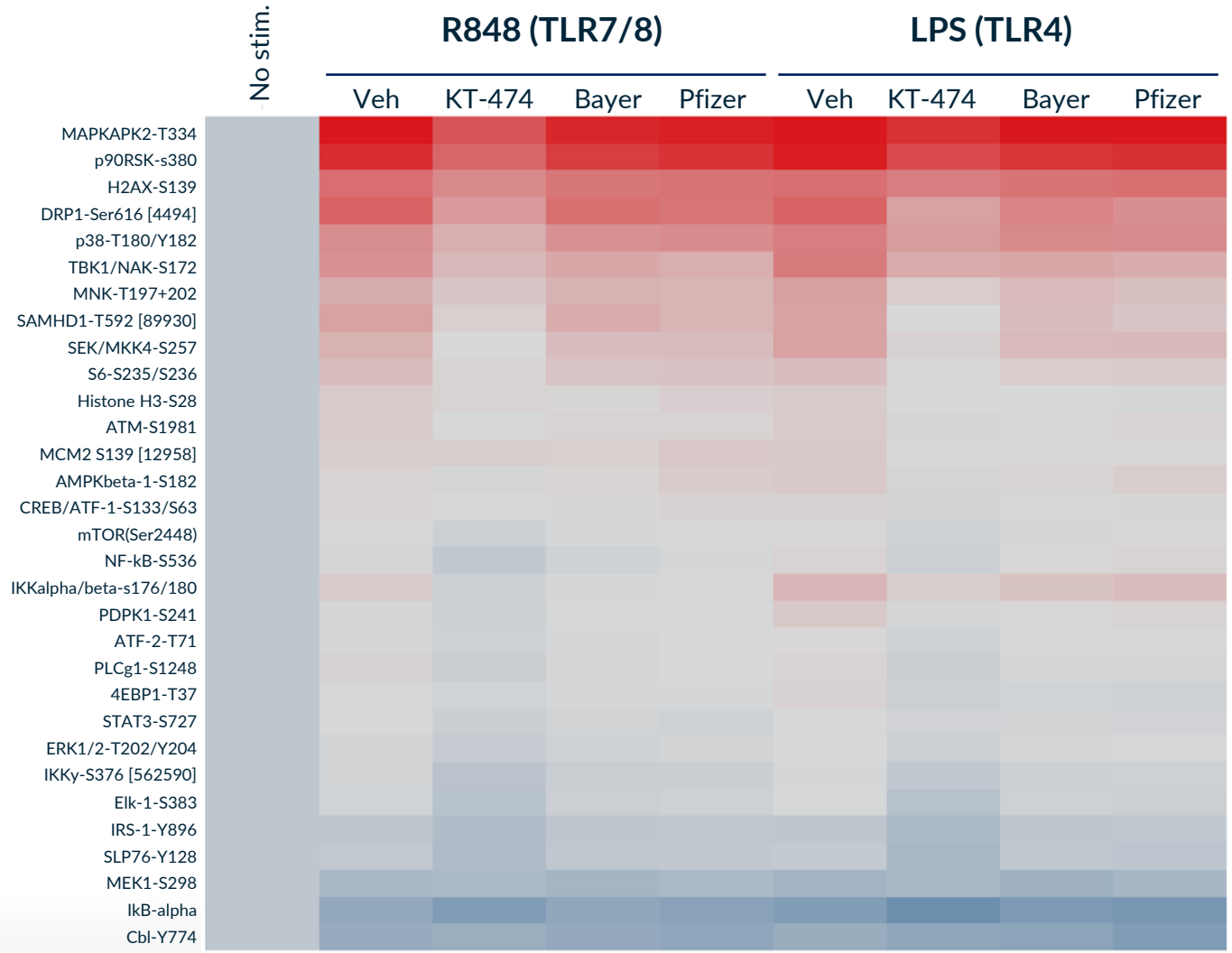
Only IRAK4 Degrader Can Block Pathway Stimulated by IL-1B + LPS

Cytokine/ Chemokine Induced by IL-1b + LPS	IRAK4 Degrader [IC_{50}] nM	E3-ve Control [IC_{50}] nM	PF-06550833 [IC_{50}] nM	BAYER Inh. [IC_{50}] 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

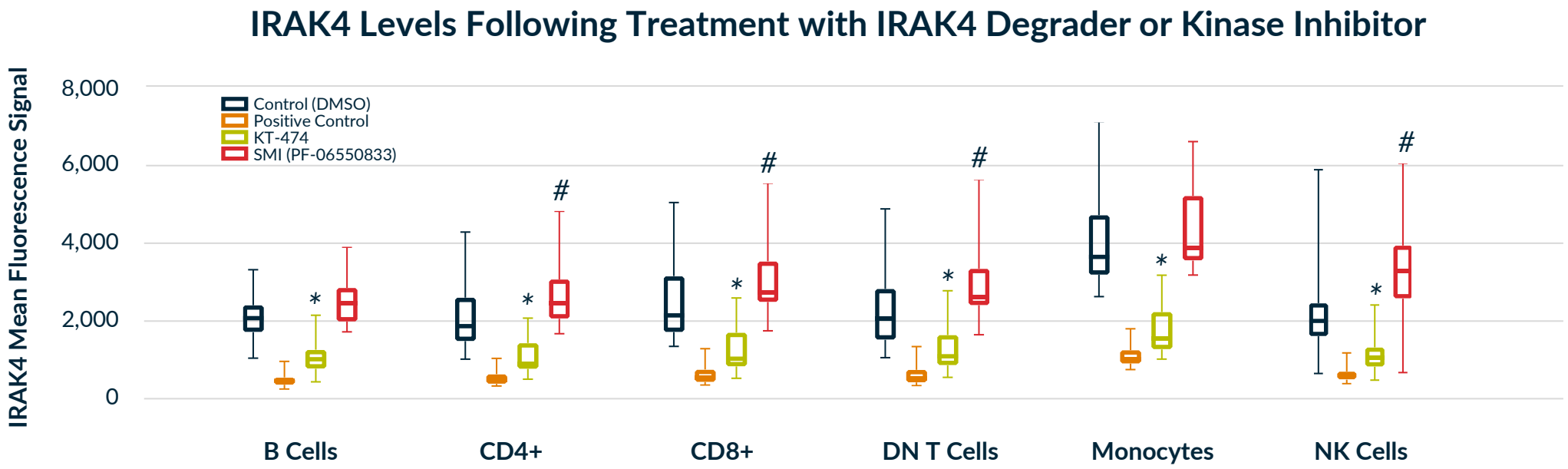
E3-ve Control = an IRAK4 degrader molecule that is not enabled to degrade IRAK4 and functions as an inhibitor

IRAK4 Degradation Reverses Phosphoproteomic Response to Pathway Action Unlike SMI





IRAK4 Degrader Downregulates IRAK4; SMI can Increase it in HS Patients Blood – Non-Interventional Study Data Kymera



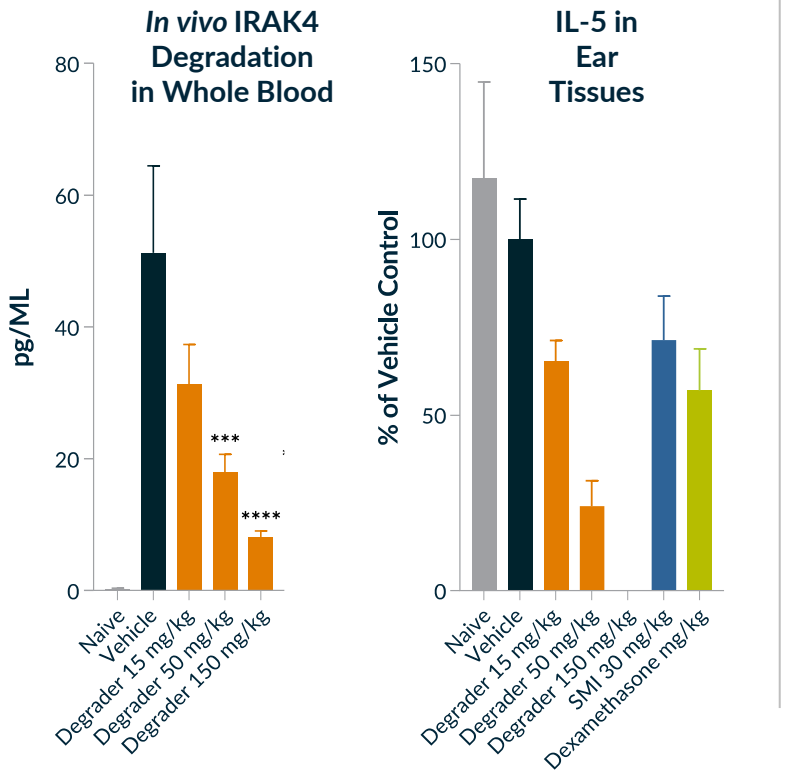
N=30 patients, One-way ANOVA* KT-474 vs DMSO Control p≤0.0001, #SMI (PF-06550833) vs DMSO Control p≤0.02
Positive Control: cells treated with IRAK4 blocking antibody prior to IRAK4 staining

KEY TAKEAWAYS

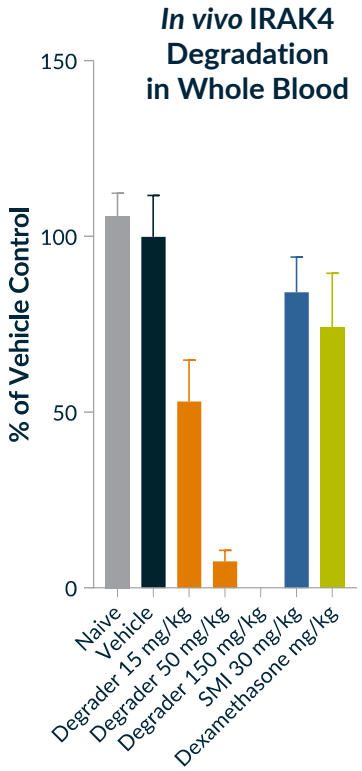
- *Ex vivo* incubation of HS blood with KT-474 reduced IRAK4 to a level approaching the lower limits of detection across all PBMC subsets, irrespective of baseline expression intensity, whereas an IRAK4 kinase inhibitor increased IRAK4 levels in T and NK cells
- **Treatment with an IRAK4 kinase inhibitor led to an increase in IRAK4 levels of up to 2.6-fold in T and NK cells**

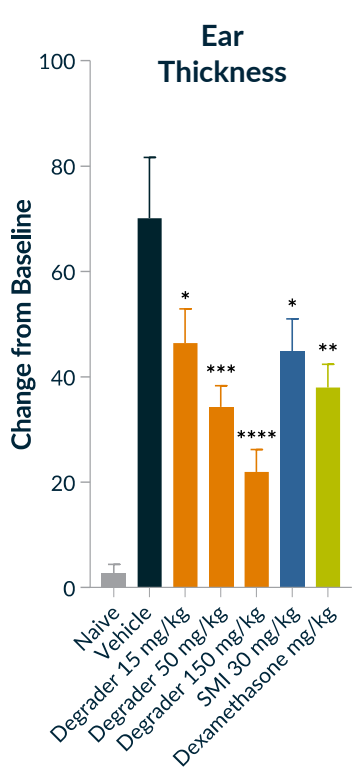
KT-474 is Superior to IRAK4 Small Molecule Inhibitor (SMI) Across Multiple Preclinical Immune-inflammatory *in vivo* Models

rmIL-33 Intradermal Challenge Model

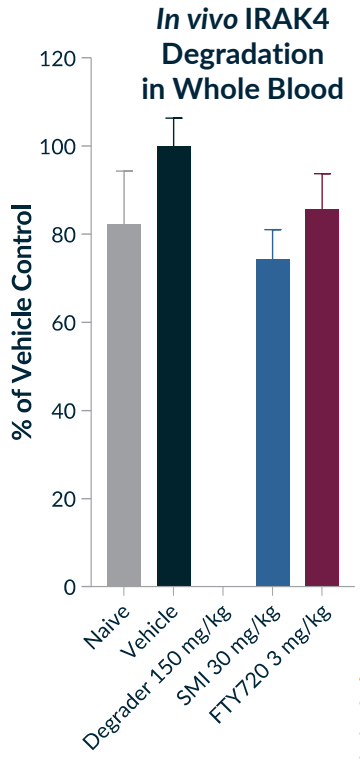


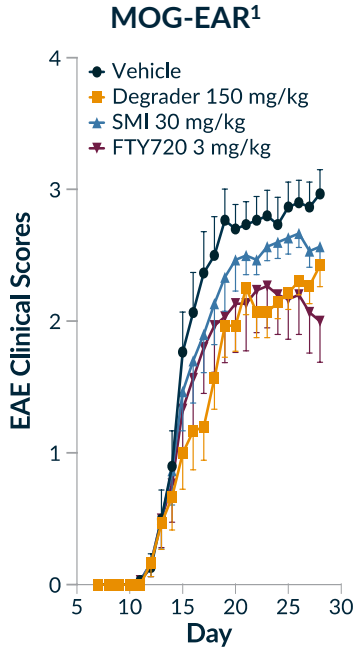
rhIL-36αβγ Intradermal Challenge Model





Th17-mediated Multiple Sclerosis Model





Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

IRAK4 knockdown of ≥85% in whole blood achieved anti-inflammatory effect comparable to potent corticosteroids or approved standard of care drugs in these models as well as in models of TLR4 (MSU-Gout) or TLR7/8 (Imiquimod-Psoriasis) activation that was superior to IRAK4 small molecule inhibitor

1. Myelin Oligodendrocyte Glycoprotein-induced Experimental Autoimmune Encephalomyelitis (MOG-EAR) Model

KT-474: Oral IRAK4 Degrader with Potential to Achieve Broad, Well-Tolerated Anti-Inflammatory Effect in Multiple Diseases

- Healthy volunteer SAD and MAD cohorts demonstrated:
  - Robust and **sustained IRAK4 degradation in blood and skin** with single and multiple daily doses
  - Broad **inhibition of *ex vivo* TLR-mediated cytokine induction**
  - **Generally well tolerated**
- Patient cohort demonstrated:
  - **PK, PD and safety comparable** to healthy volunteers
  - Modest, non-adverse **QTcF prolongation spontaneously resolved back to baseline** during dosing
  - Robust IRAK4 degradation in blood and skin associated with **systemic anti-inflammatory effect** in HS and AD patients, validating pathway and target relevance in HS and AD
  - **Promising clinical activity** exceeding benchmark placebo rates and comparing favorably to SOC biologics **in both HS and AD**
- Phase 1 results in healthy volunteers and patients support Phase 2 advancement in HS and AD
- Sanofi responsible for program development costs
  - Kymera retains option (before Phase 3) for cost and profit sharing
- Topline data from two ongoing trials expected 1H 2025
- Kymera and Sanofi evaluating opportunities to expand indications beyond HS and AD

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