5th Annual TPD Targeted Protein Degradation

Phase 1 Single and Multiple Ascending Dose Trial of KT-474 in Healthy Volunteers

Jared Gollob, M.D. - Chief Medical Officer

October 2022

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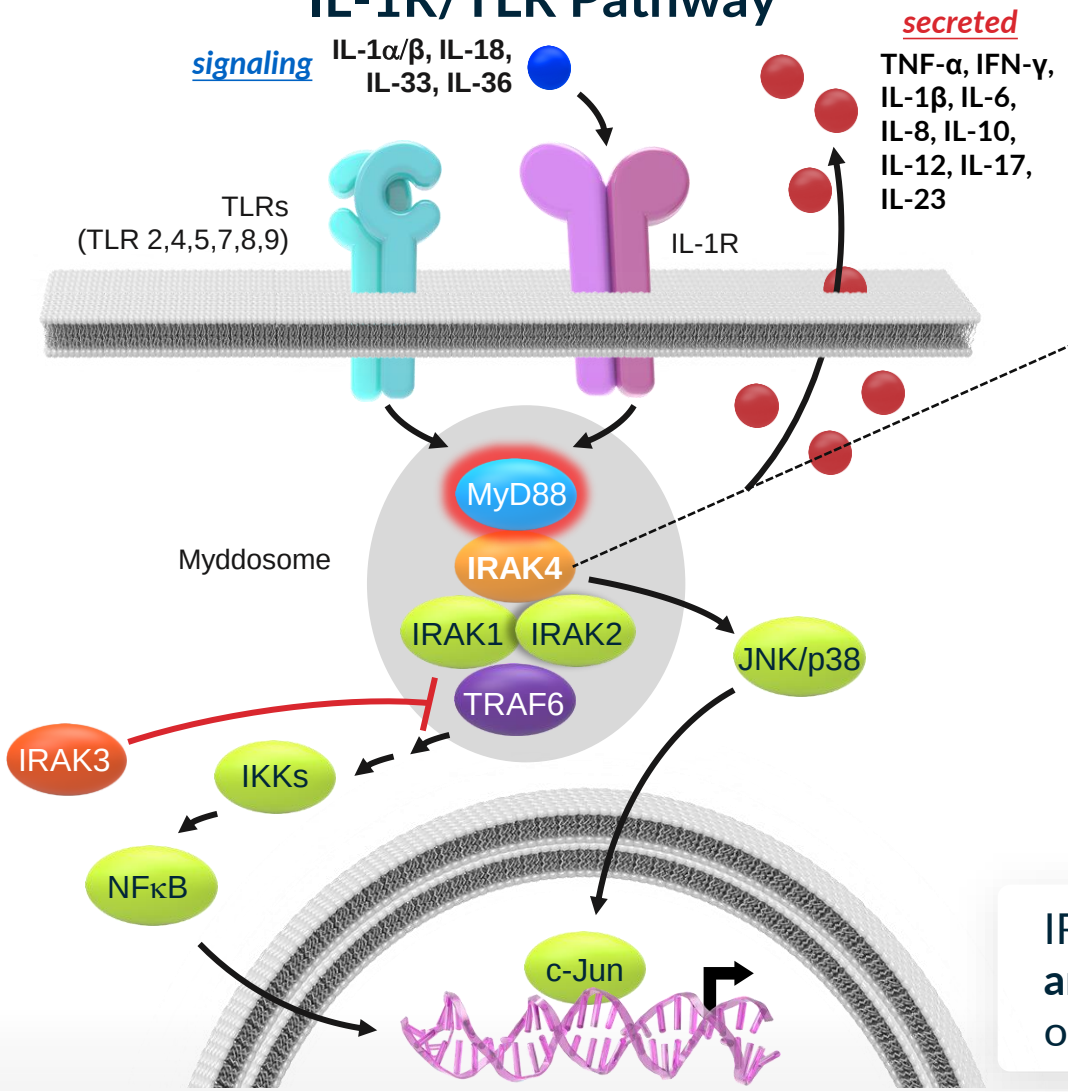
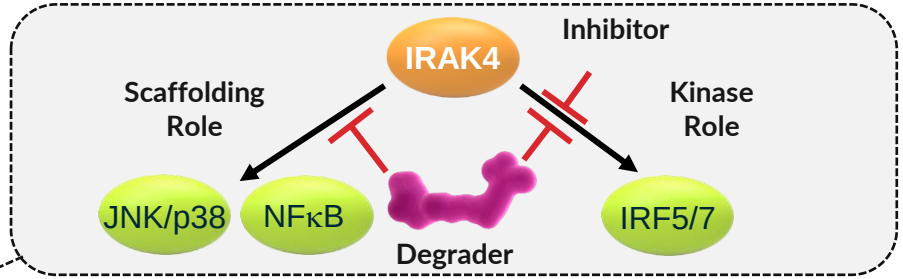
Degrading IRAK4: Best Approach to Block IL-1R/TLR driven Inflammation

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

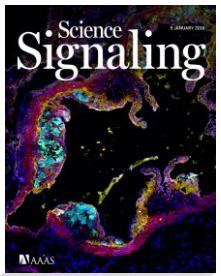
Human Genetics

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 KO/Degradation Differentiated Over Kinase Inhibition in TLR Activation

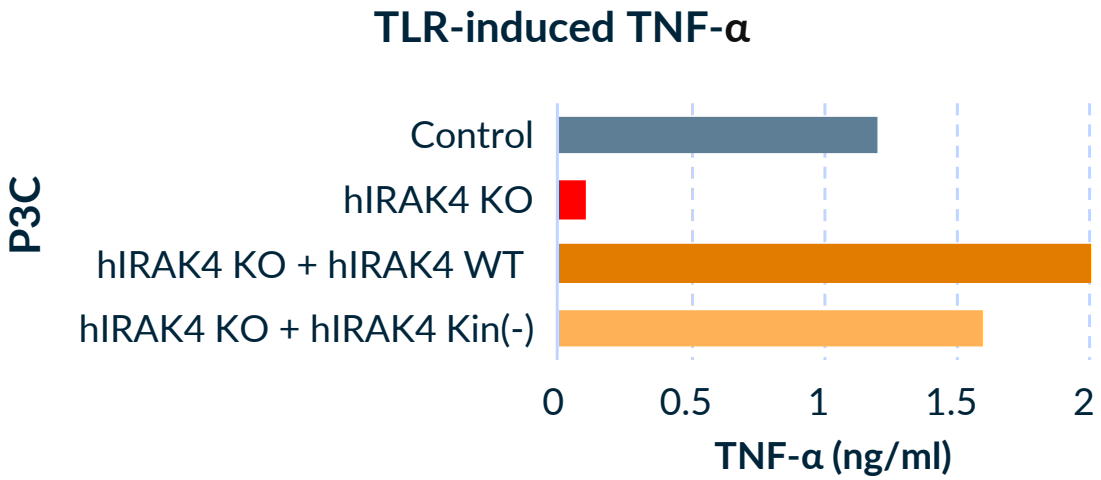
Science Signaling



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
- Kinase dead and a WT IRAK4 rescue behave similarly
- This demonstrates 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

JCB Journal of Cell Biology

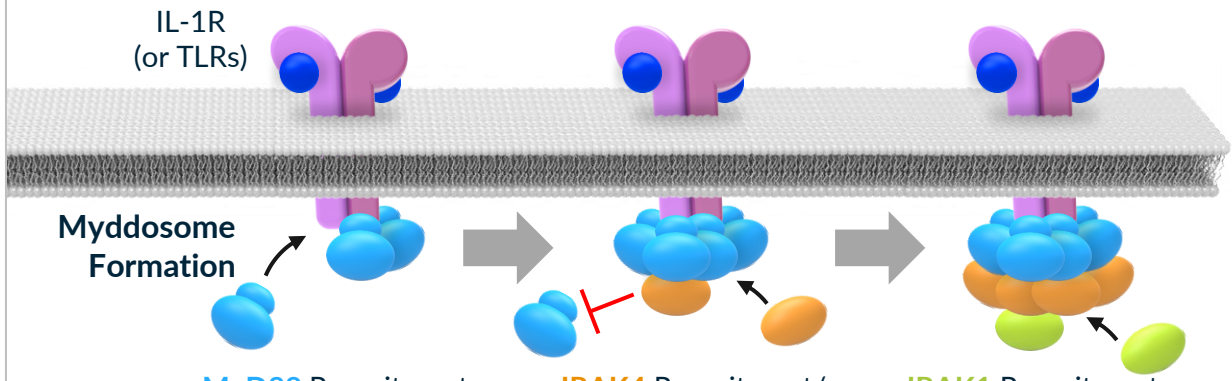
MyD88 oligomer size functions as a physical threshold to trigger IL1R Myddosome signaling

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

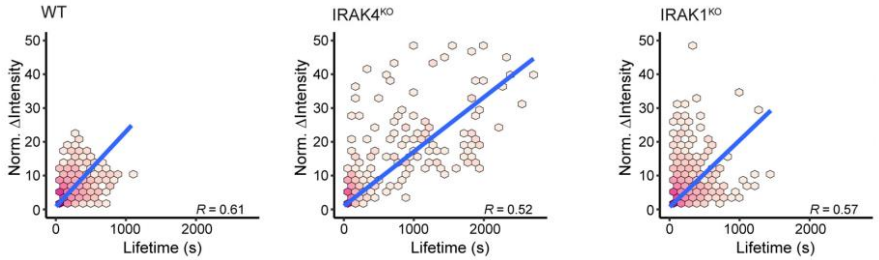
A recurring feature of innate immune receptor signaling is the self-assembly of signaling proteins into oligomeric complexes. The Myddosome is an oligomeric complex that is required to transmit inflammatory signals from TLR/IL1Rs and consists of MyD88 and IRAK family kinases. However, the molecular basis 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



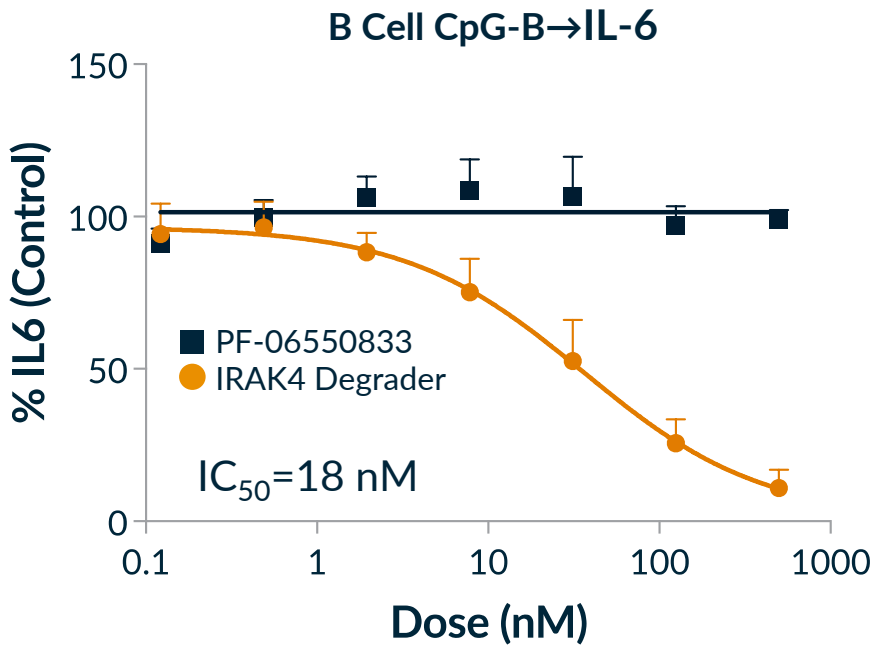
- IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation
- Macromolecular assembly of proteins **in itself** can be considered a signal transduction step

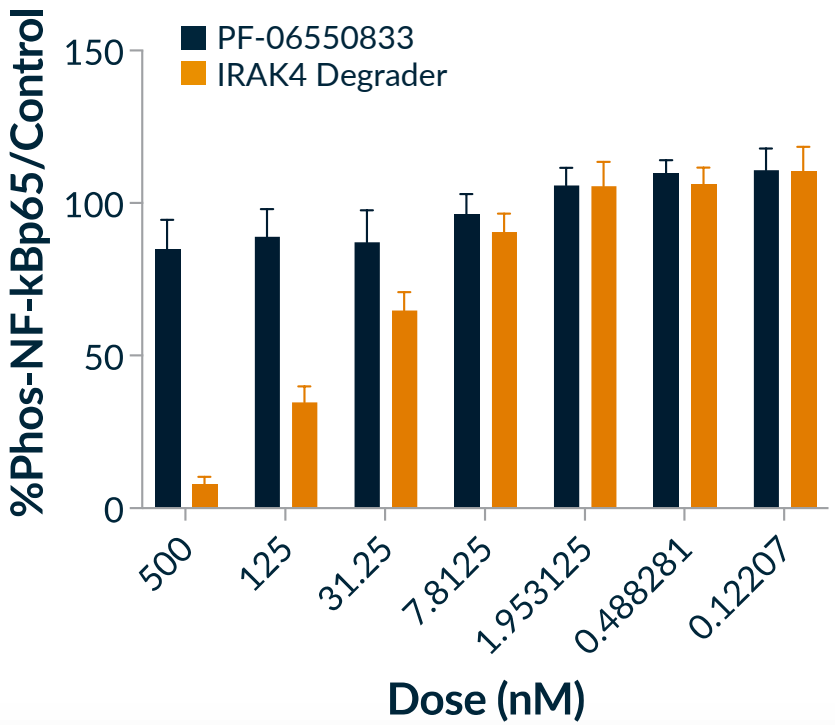


Source: Deliz-Aguirre, et al. *J. Cell Biol.*, 2021

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

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



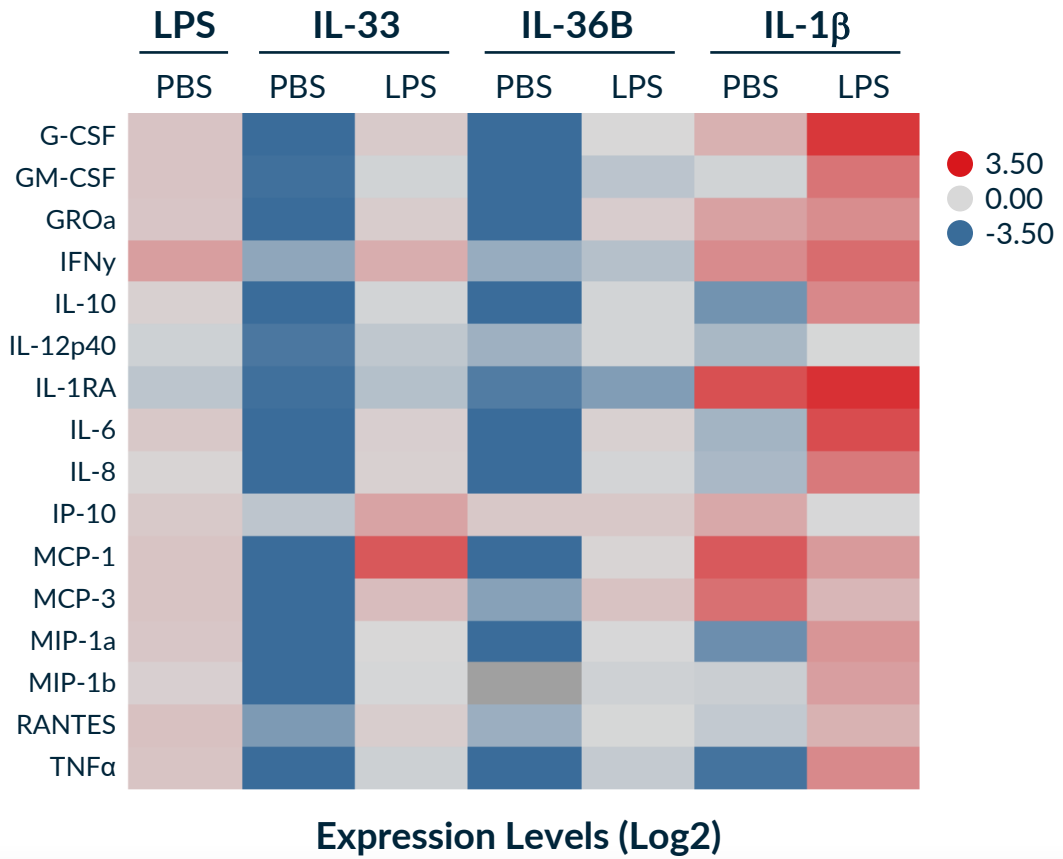


- IRAK4 degradation leads to inhibition of TLR9/ CpG-B induced IL-6

- Pathway engagement results in downstream NF-κB activation which only a degrader can block.

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

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



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

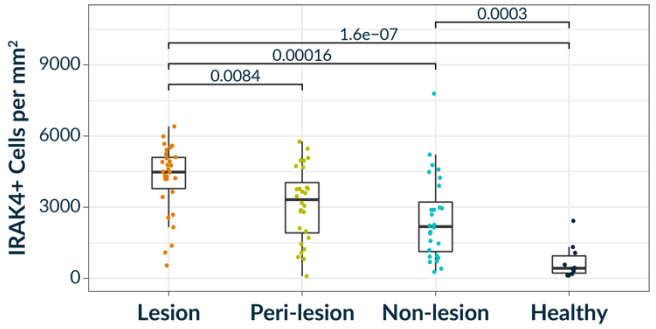
Cytokine/ Chemokine Induced by IL-1β + LPS	IRAK4 Degrader [IC_{50}] nM	E3-ve Control [IC_{50}] nM	PF-06550833 [IC_{50}] nM	BAYER Inh. [IC_{50}] nM
IL-6	**0.8**	427.5	>2000	>2000
IL-8	**0.08**	>2000	1400	>2000
G-CSF	**0.5**	>2000	>2000	>2000
GM-CSF	**2.6**	161.6	8.1	464.9
CXCL1 (GROα)	**76.4**	1100	>2000	>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

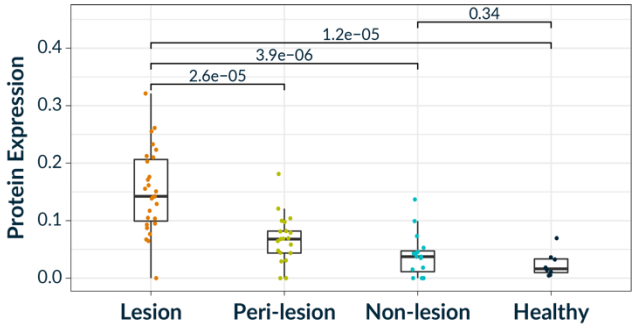
IRAK4 Protein Expression in Autoimmune Diseases: Upregulation in Skin of HS Patients Compared to Healthy Subjects

IRAK4 protein levels overexpressed in HS patient skin lesions

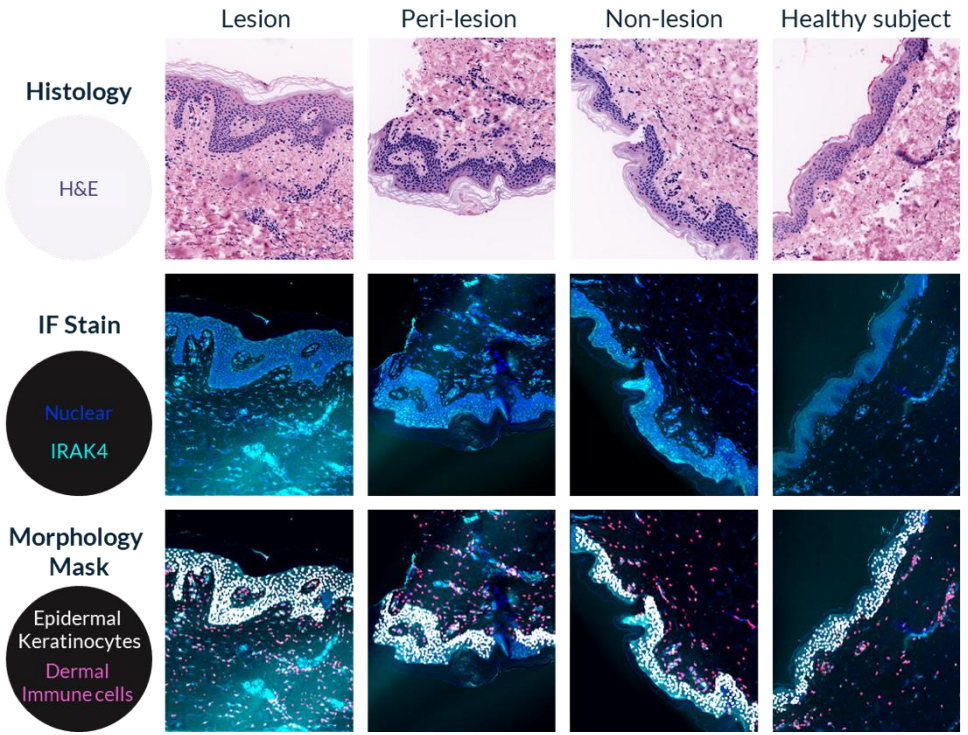
Immunofluorescence (IF)



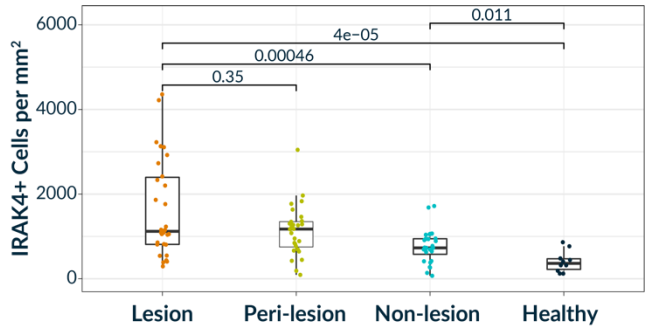
Mass Spectrometry (MS)



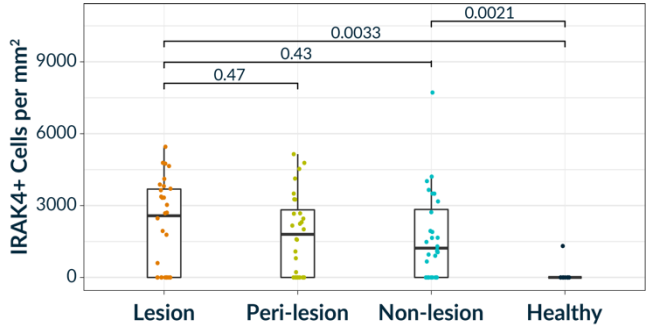
IRAK4 expression is upregulated in dermis and epidermis of HS patients relative to healthy subject skin



Dermal Immune Cells

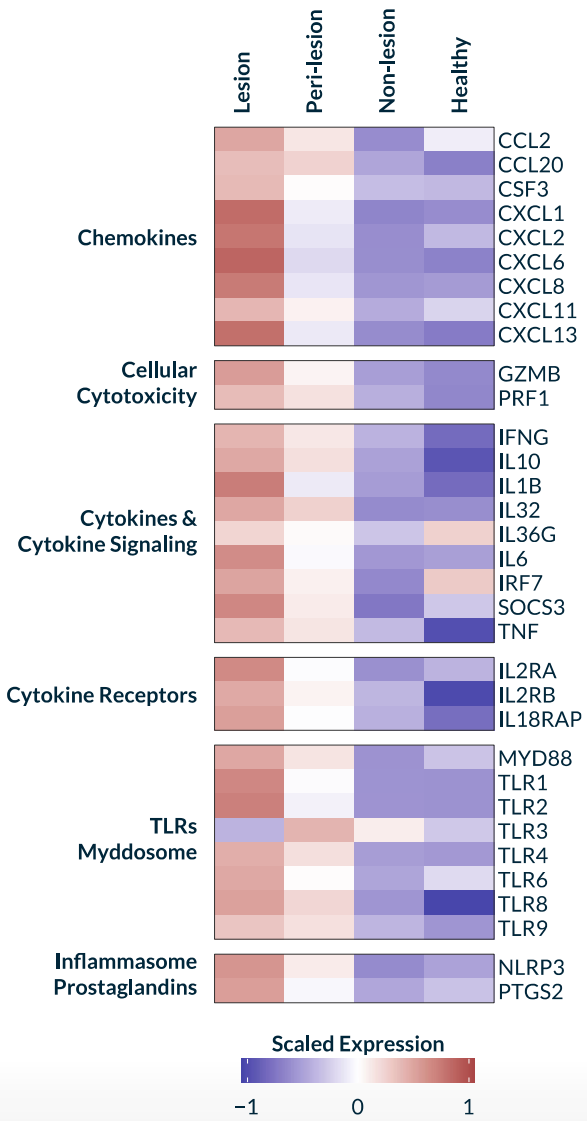


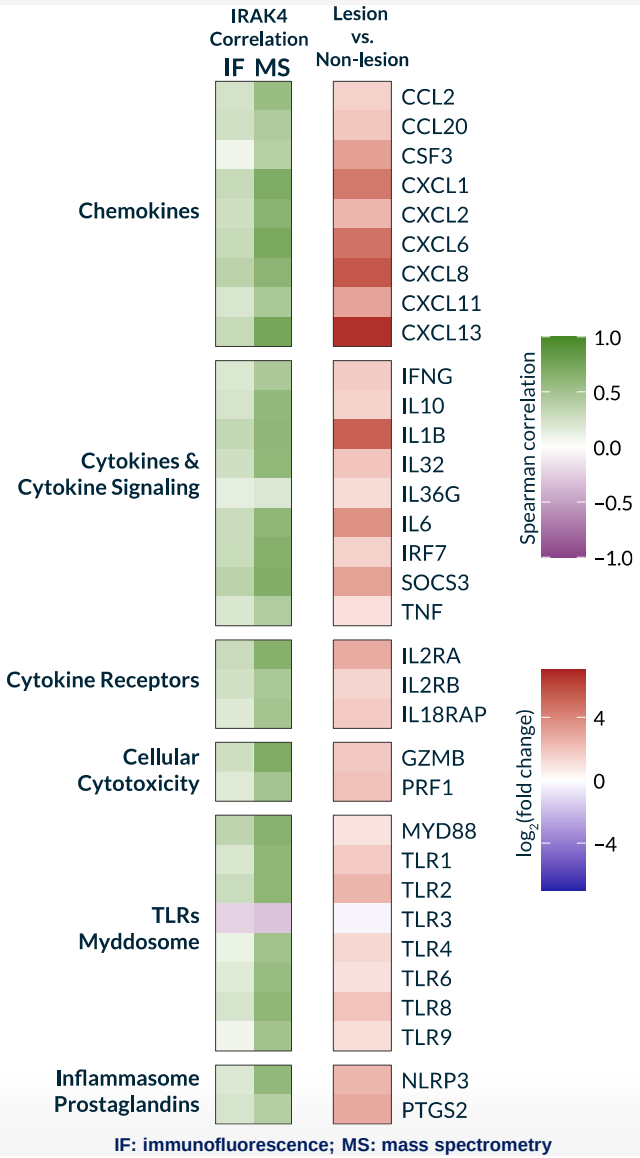
Epidermal Keratinocytes



Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

Multiple Proinflammatory Transcripts Are Upregulated and Correlate with IRAK4 Protein Levels in HS Skin Lesions



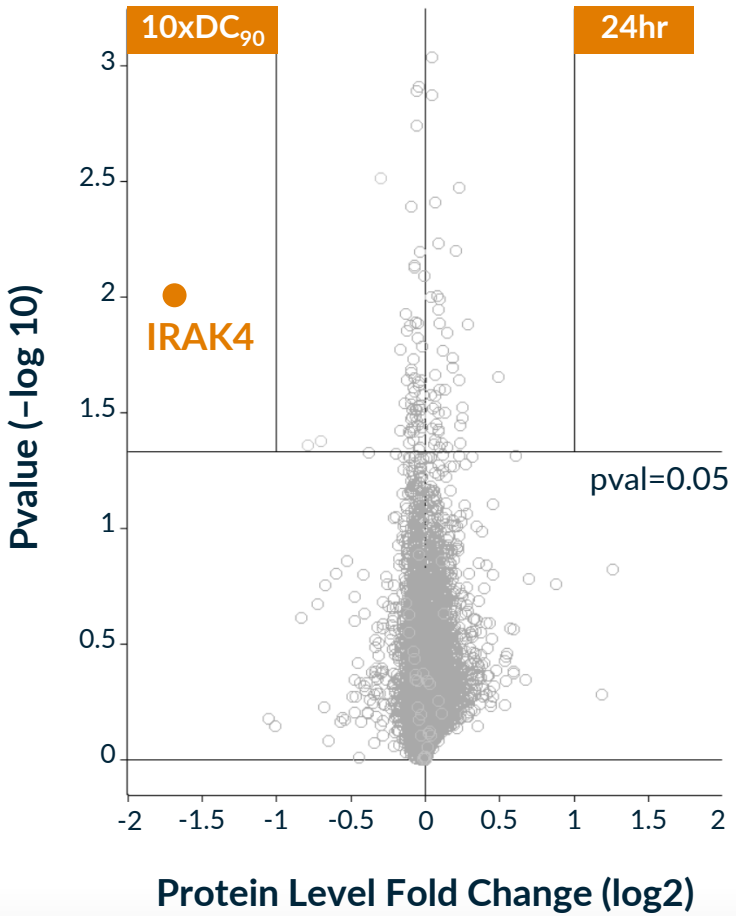


- Upregulation of TLRs, IL-1β/IL-36, MYD88, and multiple additional drivers of inflammation that all correlate with IRAK4 protein expression
- Highlights potential of IRAK4 targeting to treat diseases like HS characterized by marked pleiotropic inflammation

Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

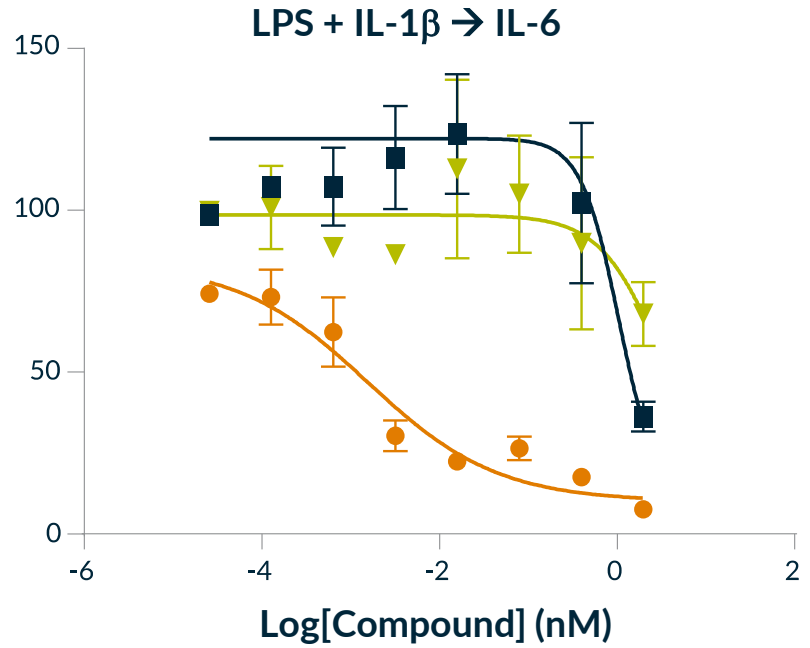
KT-474: Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

Degradation and Selectivity



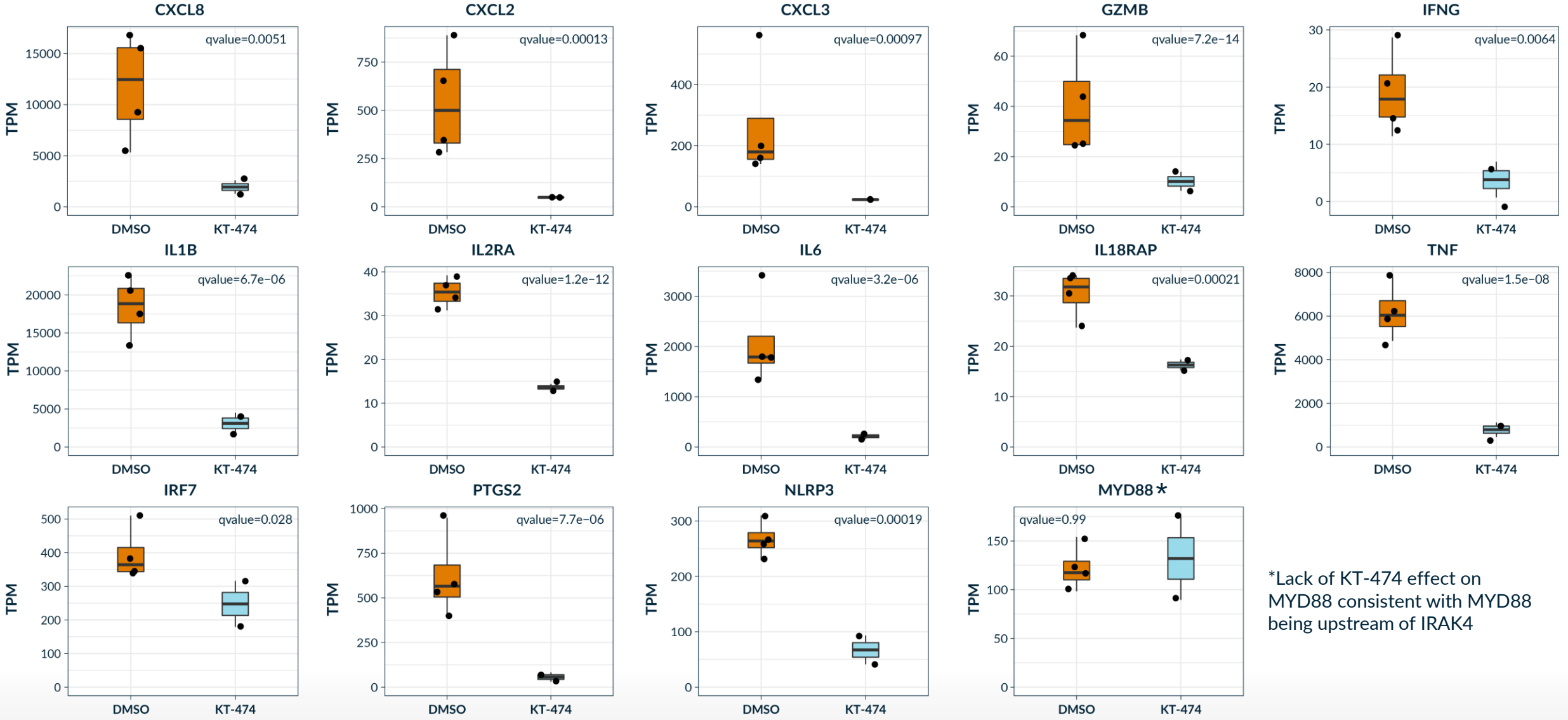
- KT-474 DC_{50} = 2.1 nM in human immune cells
- KT-474 only degraded IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- KT-474 better able to inhibit IL-6 under both LPS and LPS + IL-1β than clinically active IRAK4 SM kinase inhibitor PF-06550833

Superiority over SM kinase Inhibitor



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

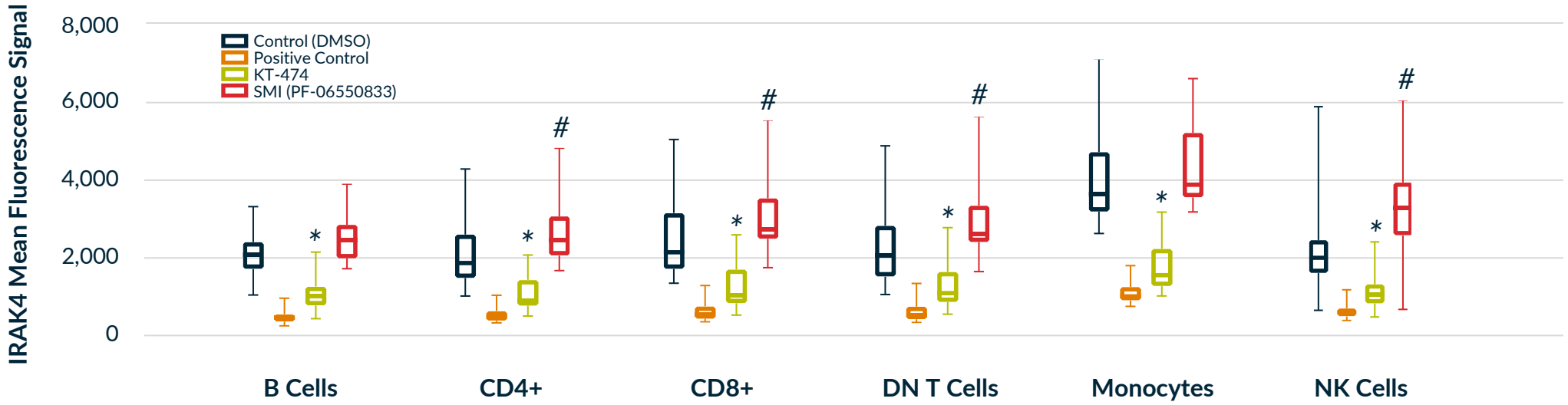
IRAK4 Degrader KT-474 Inhibits TLR-Mediated Induction of HS-Overexpressed Proinflammatory Transcripts in Healthy Monocytes



*Lack of KT-474 effect on MYD88 consistent with MYD88 being upstream of IRAK4

IRAK4 Degrader Downregulates IRAK4; SMI can Increase it in HS Patients Blood

IRAK4 Levels Following Treatment with IRAK4 Degrader or Kinase Inhibitor



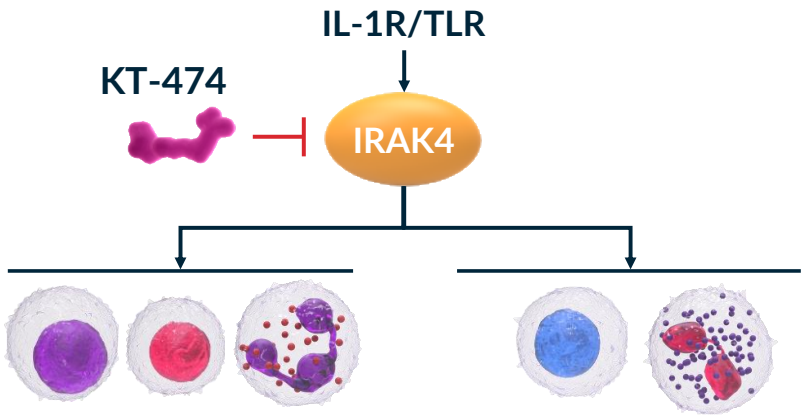
N=30 patients, One-way ANOVA* KT-474 vs DMSO Control p≤0.0001, #SMI (PF-06550833) vs DMSO Control p≤0.02
Positive Control: cells treated with IRAK4 blocking antibody prior to IRAK4 staining

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**

Potential Best-in-class Oral Small Molecule Mechanism in I/I

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Lupus
- IBD
- Gout
- Psoriasis

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

$ 150B Combined global drug sales

Indication	2021 Prevalence US/EU5/JP	2021 Global Sales
AD	~82.5 M	$5,760 M
HS	~785 K	$1,106 M
RA	~4.6 M	$27,634 M
SLE	~580 K	$1,333 M
IBD	~3.2 M	$21,710 M
Gout	~18.2 M	$1,319 M
Psoriasis	~15.8 M	$23,268 M
Asthma	~87.3 M	$15,664 M
COPD	~61.7 M	$9,960 M
CRSwNP	~20.4 M	$2,622 M

Limitations of Current Therapies

- **Anti-Cytokine/Cytokine Receptor Antibodies**
  - Target only 1-2 cytokines
  - Require injection
- **Small Molecule Inhibitors**
  - Limited pathway blockade (IRAK4 SMI)
  - Safety issues (JAK family)

Source: EvaluatePharma; GlobalData; Dash. Allied Market Research. 2021; Koto. Modern Rheumatology. 2021; Ahn. JAMA Otolaryngol Head Neck Surg. 2016; UC: Ulcerative Colitis; CD: Crohn's Disease.

KT-474 Phase 1 Design

Double-blind, Placebo-controlled SAD and MAD in HV; Open Label Patient Cohort in HS & AD Patients

Completed

Parts A & B

Healthy Volunteers SAD and MAD

7 SAD cohorts
- 8 subjects per cohort (6:2 randomization)
- 57 adult healthy subjects dosed

Single dose (25-1600 mg)

4 MAD cohorts
- 12 subjects per cohort (9:3 randomization)
- 48 adult healthy subjects dosed

14x daily doses (25-200 mg)

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin (MAD only)
- *Ex vivo* response of whole blood to TLR agonists (SAD & MAD)

Ongoing

Part C

HS and AD Patients

1 cohort
Up to 30 HS and AD patients

75 mg (fed state)
(~equivalent exposure to 100mg fasted MAD cohort dose level)

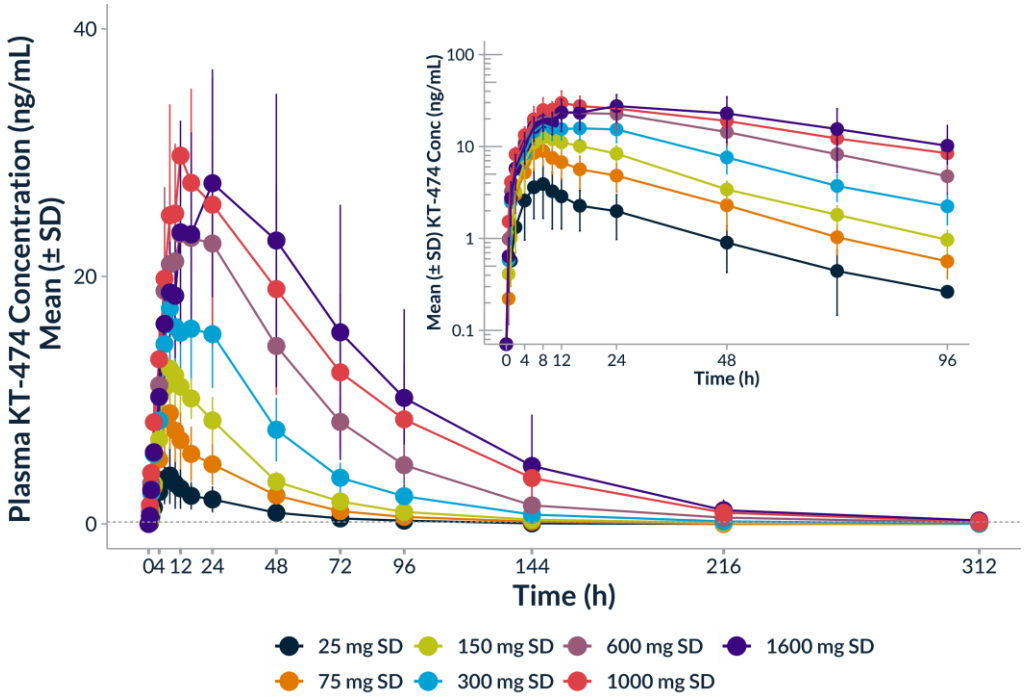
Open-label

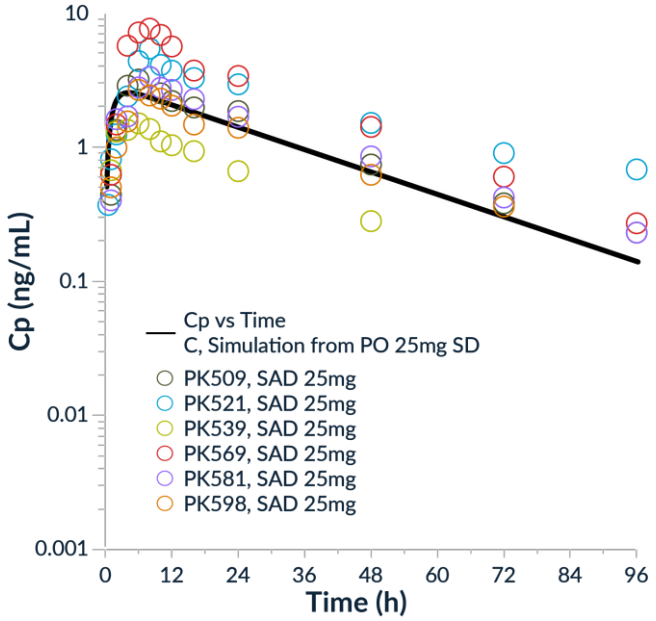
28x daily doses

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin
- Change in systemic inflammatory biomarkers and proinflammatory gene transcripts in skin
- *Ex vivo* response of whole blood to TLR agonists
- Clinical endpoints: EASI (AD), Total AN Count (HS), symptom scores and global assessments

SAD Study: Favorable PK after Single Oral Dosing Predicted by Preclinical ADME/PK



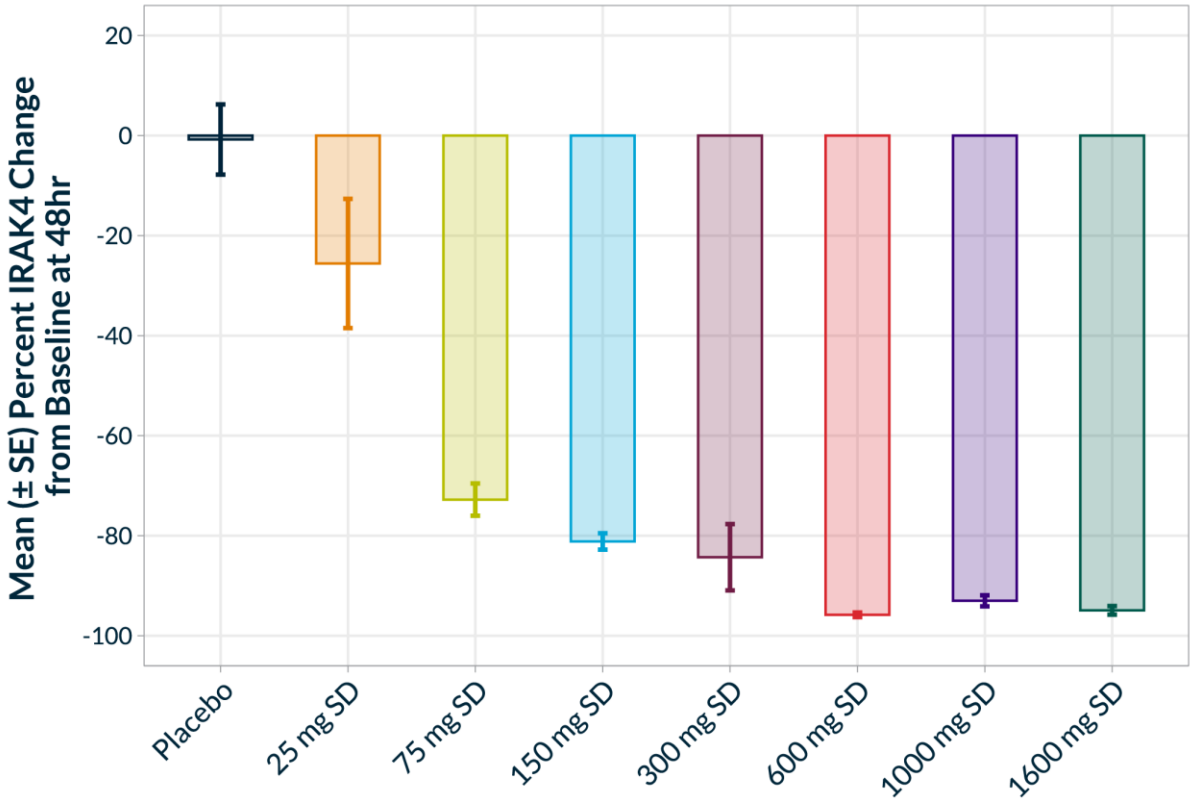


KT-474 25mg, PO	Predicted	Observed
C_{max} (ng/mL)	2.5	3.5
T_{max} (h)	4.1	7.3
AUC∞ (ng/mL*h)	91	112
$T_{1/2}$ (h)	22	25

- Consistent PK after single dosing: C_{max} achieved between 7-24 hours, half-life = 25-40 hours
- Dose dependent exposure increases, plateauing after the 1000 mg dose
- Low to moderate inter-subject variability in exposure
- High fidelity of translation from preclinical to clinical

KT-474 Achieved >95% IRAK4 Degradation After Single Dose

Percent IRAK4 Reduction in PBMC at 48 Hours Post-Dose Using Mass Spectrometry

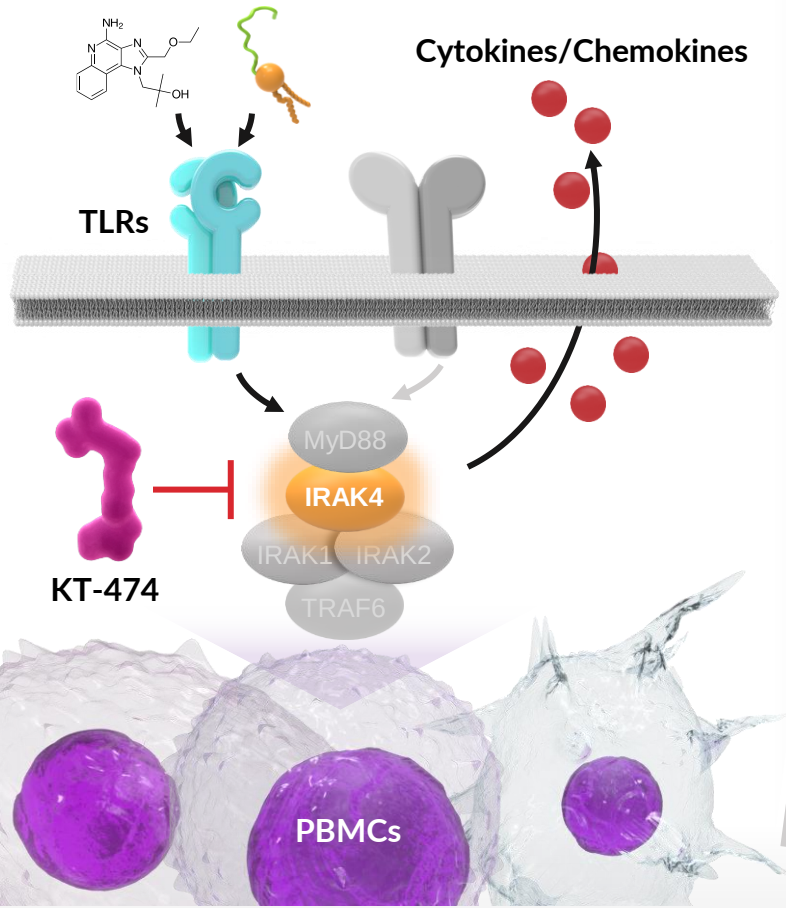


	N	Mean IRAK4 Change	Median IRAK4 Change	p value
Placebo	13	-1%	-2%	--
25 mg	6	-26%	-39%	0.1
75 mg	6	-73%	-75%	<0.0001
150 mg	6	-81%	-82%	<0.0001
300 mg	6	-84%	-89%	<0.0001
600 mg	7	-96%	-96%	<0.0001
1000 mg	5	-93%	-94%	<0.0001
1600 mg	6	-95%	-95%	<0.0001

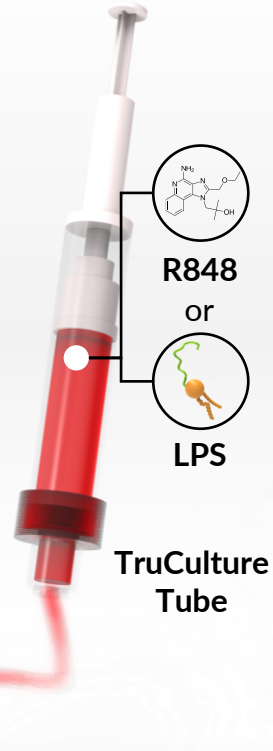
* p-values relative to placebo

Ex Vivo Cytokine Stimulation: Methodology in KT-474 Phase 1 Trial

Impact of KT-474 on TLR-stimulated Cytokine/Chemokine Production



1 Blood Draw Pre-/Post-Dose

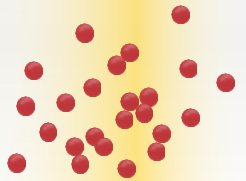


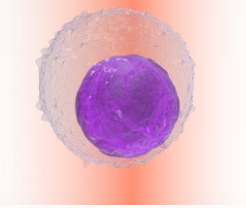
2 Overnight Incubation (37°)

3 Plasma Isolation

4 Cytokine/Chemokine Measurement

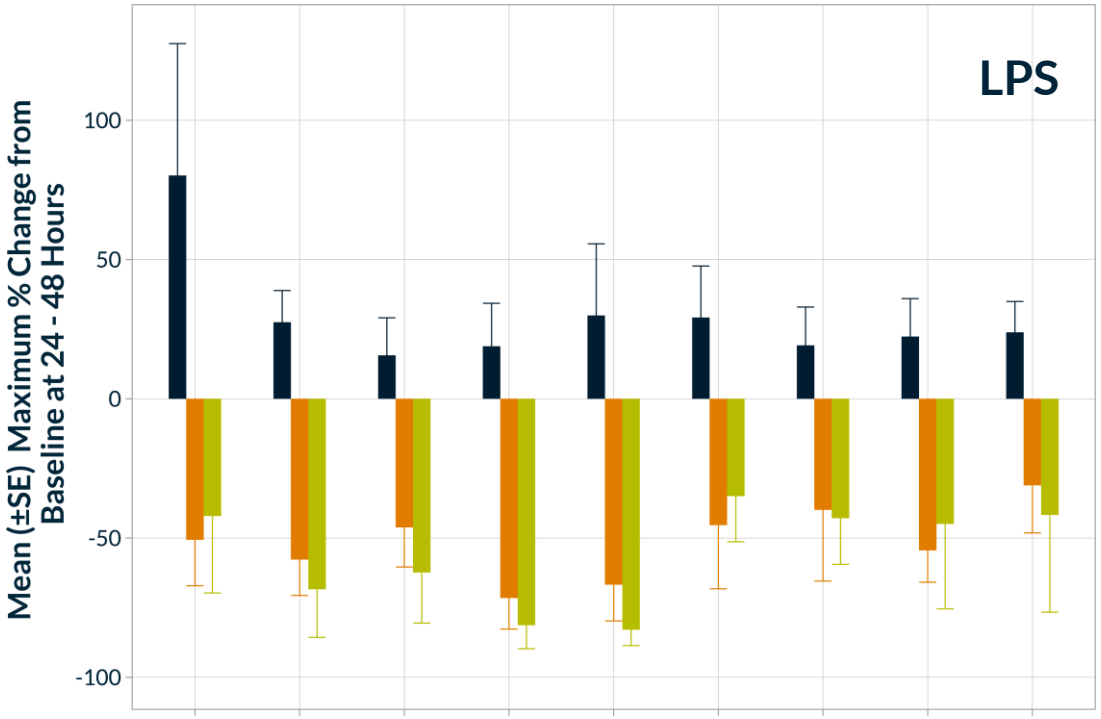
TNF-α, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23

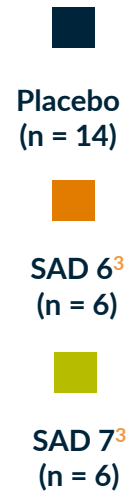


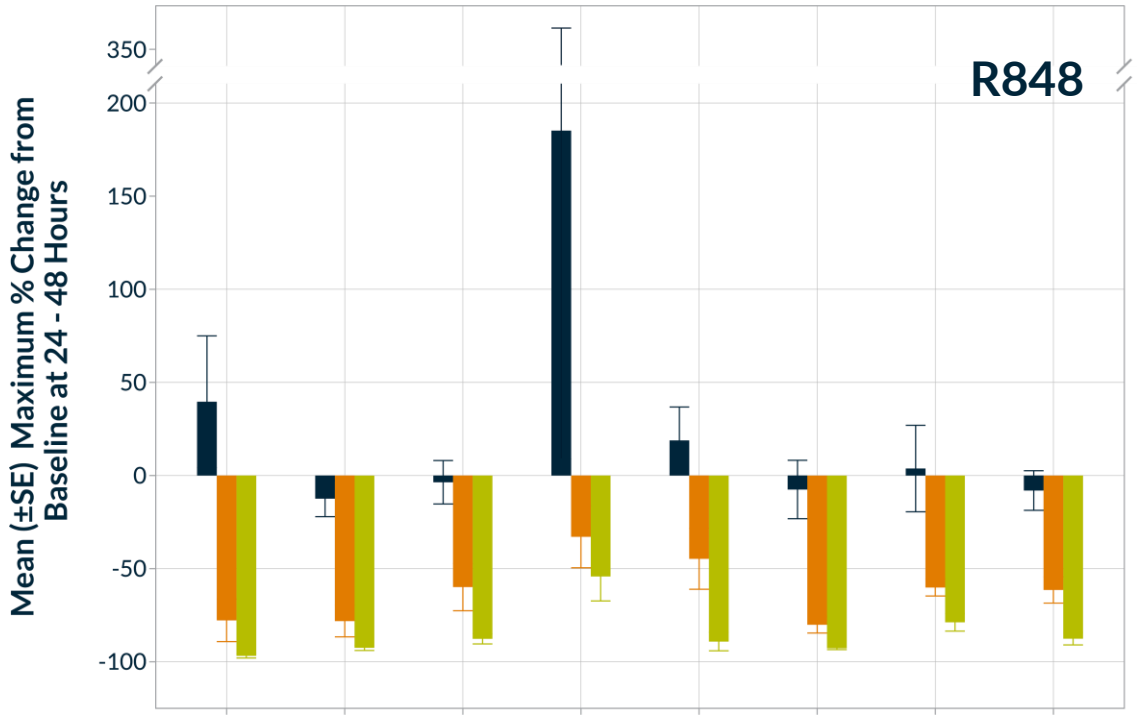


Broad and Deep Inhibition of Disease Relevant Cytokines

Effect Against LPS (TLR4)- or R848 (TLR7/8)-Stimulated Cytokine Induction in Whole Blood







	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	80%	27%	16%	19%	30%	29%	19%	22%	24%
SAD 6 85-93% Degr*	-51%	-58%[1]	-46%[2]	-72%[1]	-67%[2]	-45%[2]	-40%[2]	-54%[2]	-31%
SAD 7 89-95% Degr*	-42%	-68%[1]	-62%[1]	-81%[1]	-83%[1]	-35%[2]	-43%[2]	-45%[2]	-42%[2]

	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	40%	-12%	-4%	185%	19%	-7%	4%	-8%
SAD 6	-78%	-78%[1]	-60%[1]	-33%	-45%	-80%[1]	-60%[1]	-61%
SAD 7	-97%[2]	-92%[1]	-88%[1]	-54%	-89%[1]	-93%[1]	-79%[1]	-88%[2]

[1] = p value < 0.01; [2] = p value < 0.05

*Mean IRAK4 degradation in PBMC at 24-48h

[3]*Ex vivo* cytokine assay was performed at 48h nadir (maximal degradation) only in cohorts 6-7

KT-474 Demonstrates Broadest Anti-inflammatory Effect Compared to Other Clinical Agents

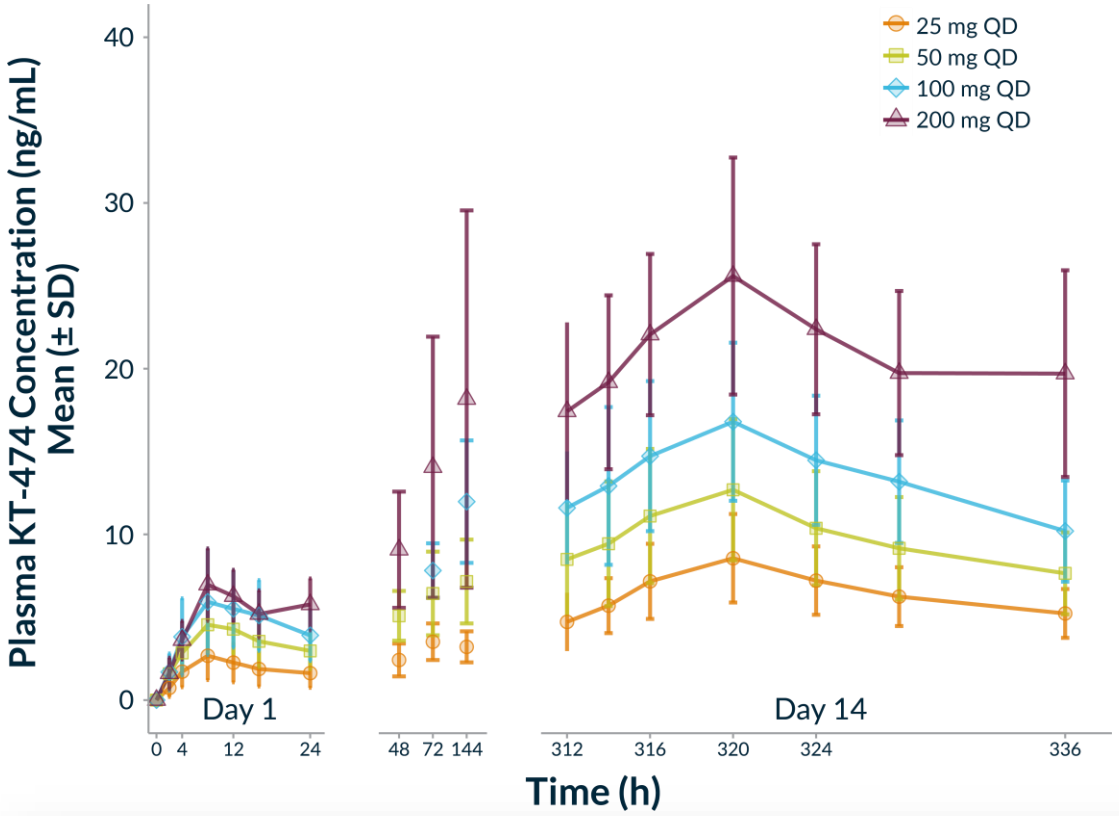
Inhibition of *Ex Vivo* Disease Relevant Cytokine/Chemokine Stimulation by Anti-Inflammatory Agents in Ph1 Studies

Agent/Stimulus	Target	IFNγ	TNFα	IL-1β	IL-6	IL-8	IL-17	IL-12	IL-23	IL-10
KT-474/LPS	**IRAK4 (degrader)**	✓	✓	✓	✓	✓	✓	✓	✓	✓
KT-474/R848	**IRAK4 (degrader)**	✓	✓	✓	✓	✓	✓	✓		✓
CA-4948/R848	IRAK4* (inhibitor)				✓					
GS-5718/R848	IRAK4 (inhibitor)		✓							
ATI-450/LPS	MK2		✓	✓	✓	✓				
ATI-450/IL-1β	MK2		✓		✓	✓				
LY2775240/LPS	PDE4		✓							
Iberdomide/LPS	Ikaros/ Aiolos			✓						
JNJ-61803534/ T cell activation	RORγ						✓			

* Non-selective

Iberdomide: Schafer PH, et al. *Ann Rheum Dis* 2018;77:1516–1523; **LY2775240**: Patel DR, et al. *Clin Transl Sci.* 2021;14:1037–1048; **JNJ61803534**: Xue X, et al. Sci Rep 2021;11:11066-80; **MK2**: Aclaris 2021 Company Overview; **CA-4948**: Booher RN, et al. ASH Annual Meeting 2018, Poster #4168; **GS-5718**: Roedder S, et al. ACR Convergence 2021, Poster #0185

MAD Study: Once Daily Dosing Resulted in High Steady-State Exposures



Steady-State (Day 14) PK Parameters

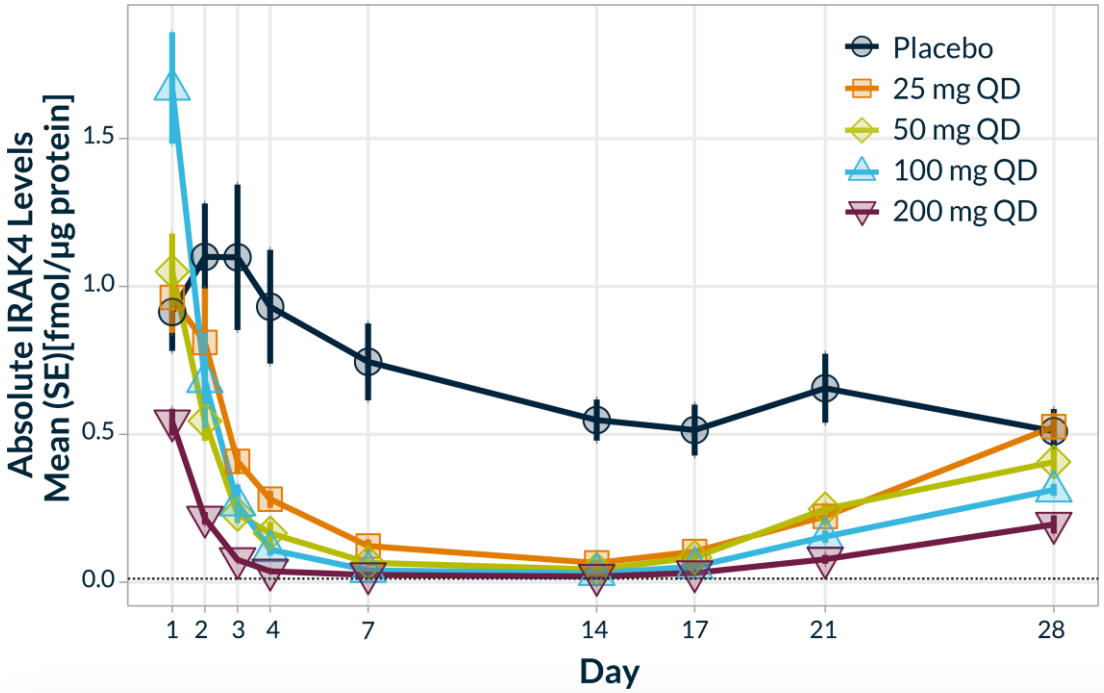
PK Parameter	25 mg QD (n = 9)	50 mg QD (n = 9)	100 mg QD (n = 9)	200 mg QD (n = 9)
C_{max} (ng/mL)	8.20 (34.5)	12.0 (39.1)	16.1 (32.0)	25.2 (26.7)
t_{max} (h)[a]	8.00 (4.0 – 8.0)	8.00 (8.0 – 8.0)	8.00 (8.0 – 12)	8.00 (8.0 – 12)
AUC_{24} (ng*h/mL)	153 (30.8)	224 (39.4)	314 (29.9)	498 (24.0)
C_{trough} (ng/mL)	5.03 (30.3)	7.28 (35.1)	9.81 (30.1)	18.8 (32.6)
Day 14/1 $Ratio_{Cmax}$	3.73 (47.1)	2.64 (26.3)	2.92 (37.7)	3.51 (34.7)
Day 14/1 $Ratio_{AUC}$	4.01 (41.2)	2.97 (23.2)	3.29 (38.9)	4.22 (28.8)

Geometric Mean (%CV) reported for all parameters, except t_{max} where median(range) are presented
Accumulation Ratio represents fold change in exposure from Day 1 to Day 14

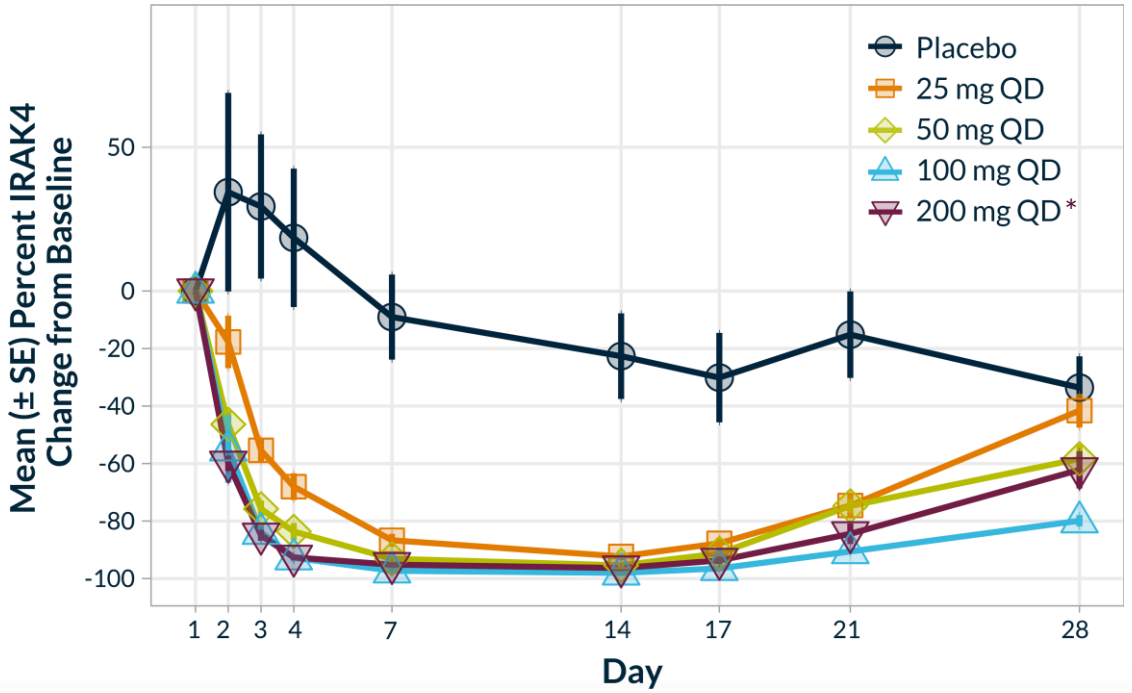
- High steady-state exposures with QD dosing, 3- to 4-fold increase in exposure on Day 14
  - Day 14 Ctrough in range where >90% IRAK4 degradation is expected
- Steady-state reached by Day 7 of dosing

KT-474 Achieved Robust and Sustained IRAK4 Degradation with Multiple Daily Oral Doses (14 Days)

Absolute IRAK4 Levels



Mean % Reduction of IRAK4

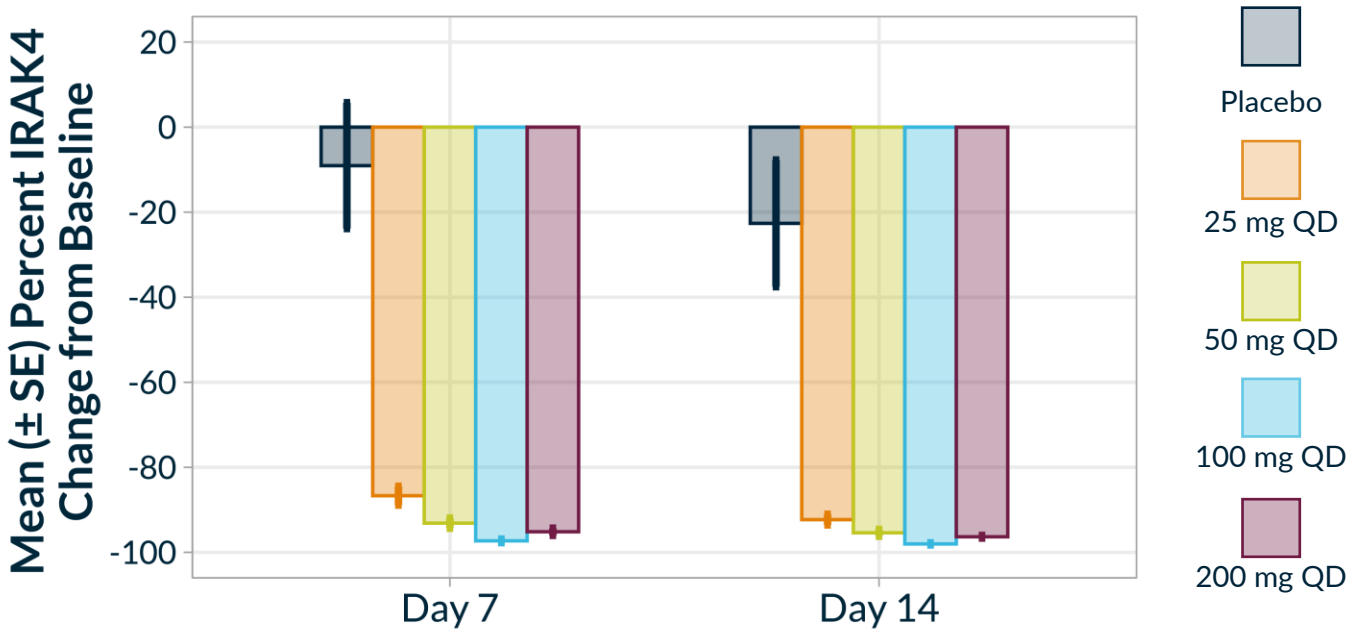


- Detected by mass spectrometry in circulating PBMC
- Steady state IRAK4 reduction achieved between Days 7 and 14
- Recovery towards baseline by Day 28 (2 weeks after last dose)
- MAD 2 through 4 approached Lower Limit of Quantitation (LLOQ)

Lower Daily Doses of KT-474 Achieved >98% IRAK4 Degradation (MS)

Plateau in IRAK4 Reduction after 14 days in PBMC after 100 mg

Percent IRAK4 Reduction in PBMC by Mass Spectrometry

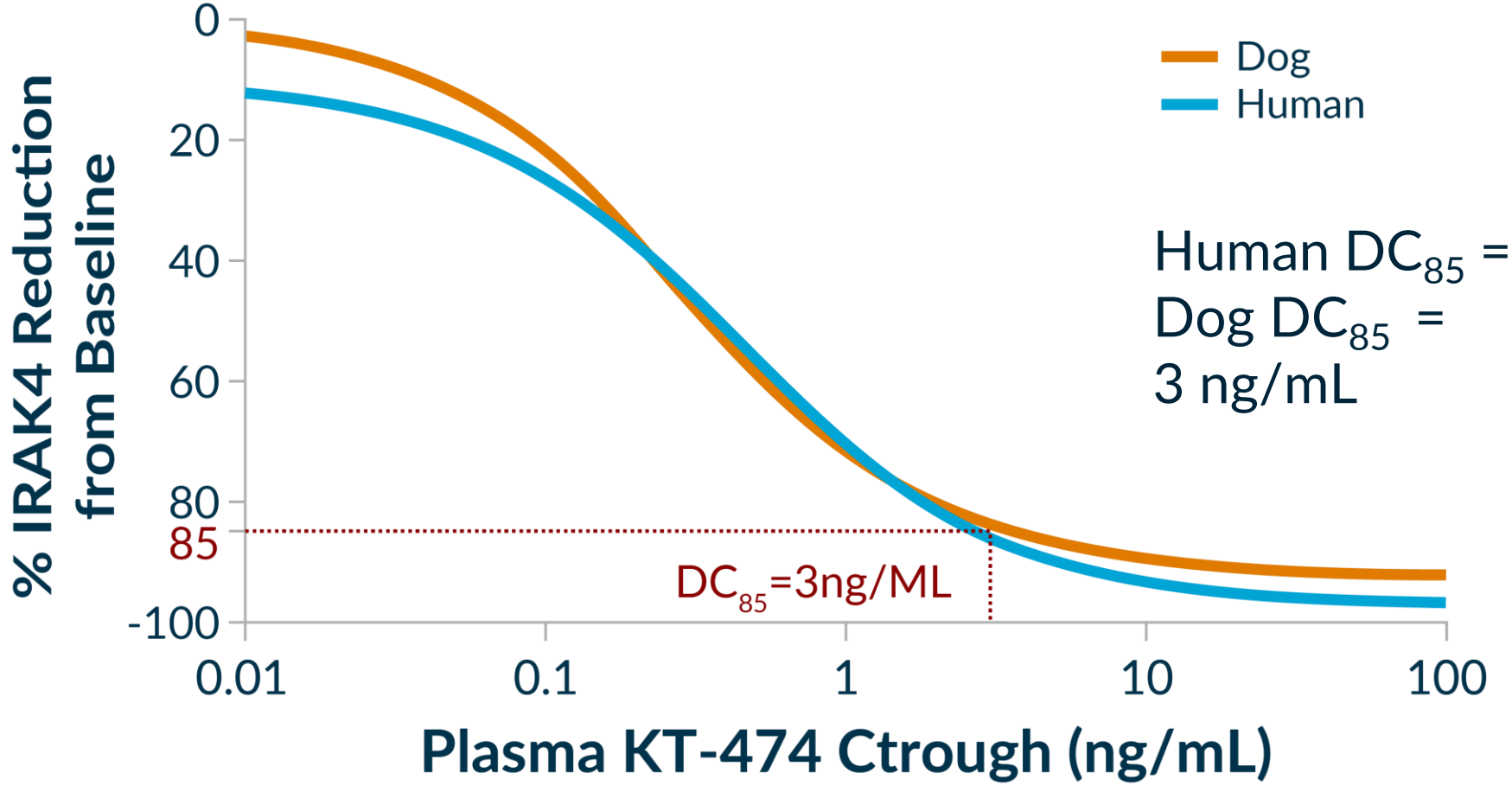


	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
*p value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

* p-values relative to placebo

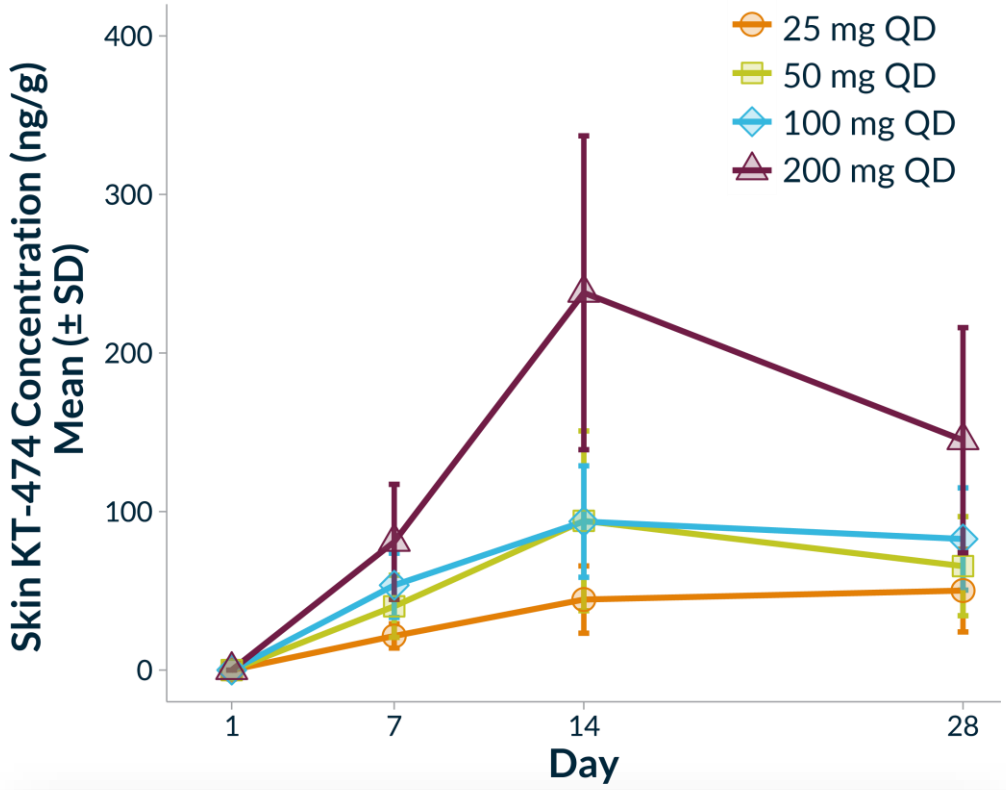
KT-474 PK/PD Translates Well from Dog to Humans

PBMC



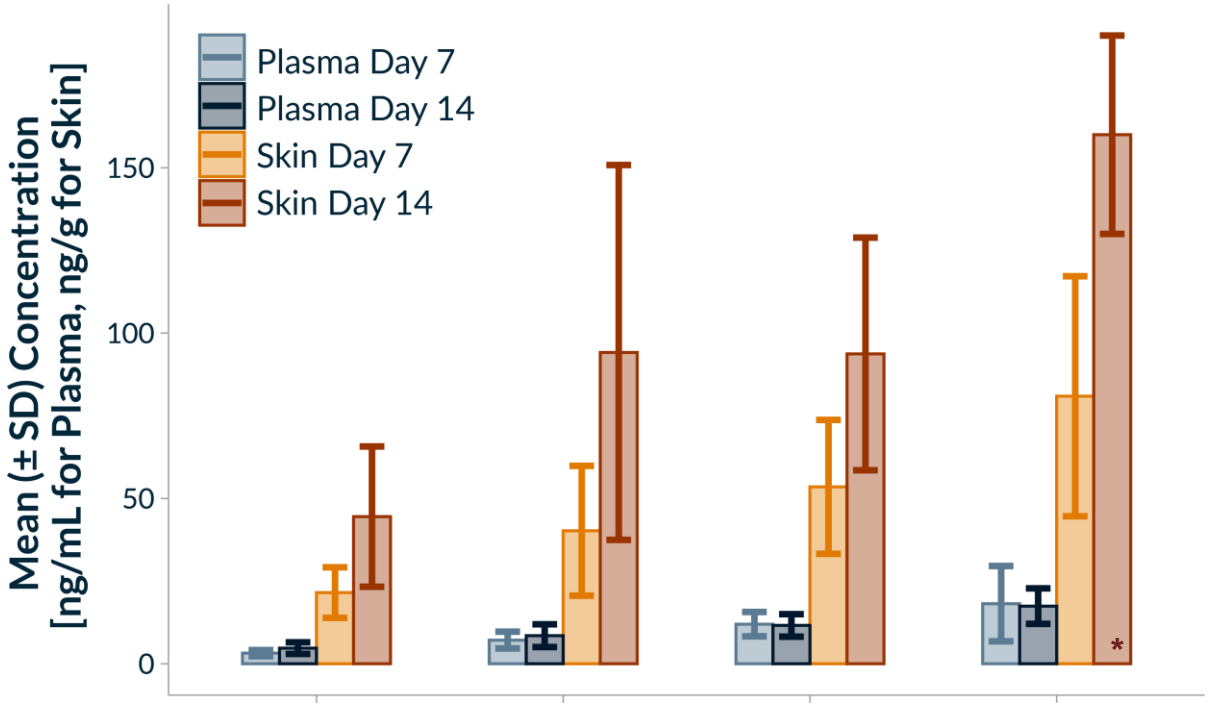
Once Daily Dosing Resulted in High Skin Exposures Exceeding Plasma

KT-474 Levels in Skin



- Increasing exposures through Day 14
- C_{trough} levels in skin ~10-14 fold higher than plasma on Day 14

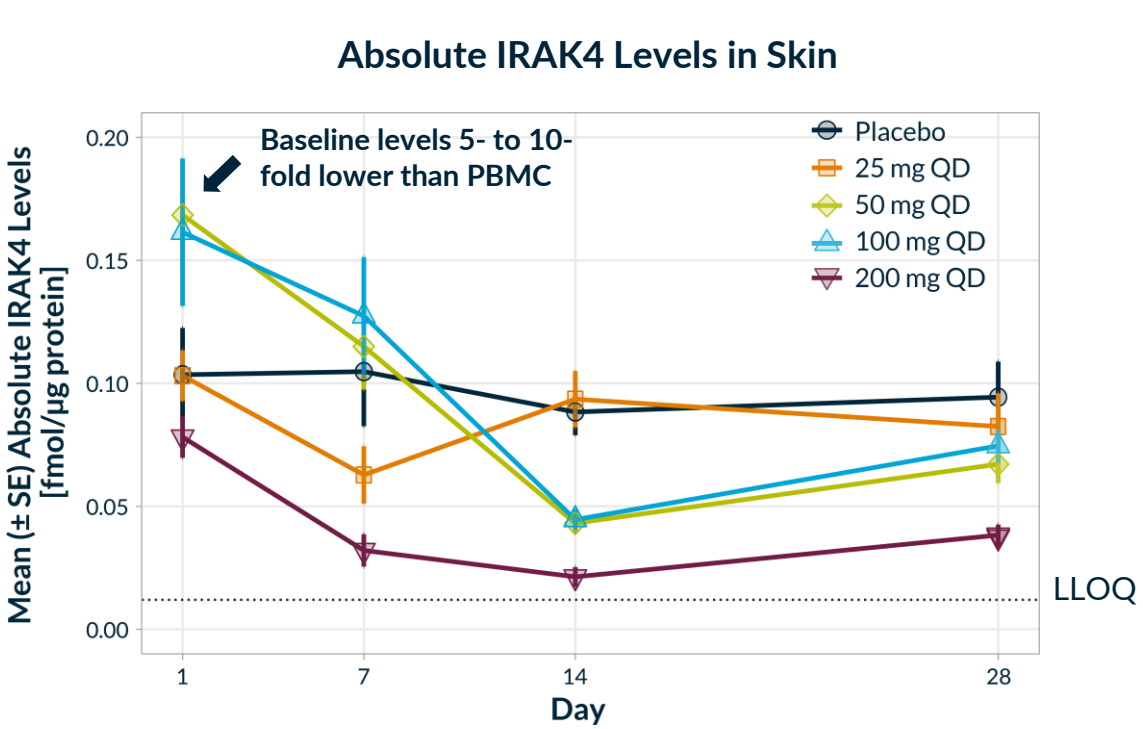
Substantially Larger Skin vs Plasma Exposures at C_{trough}

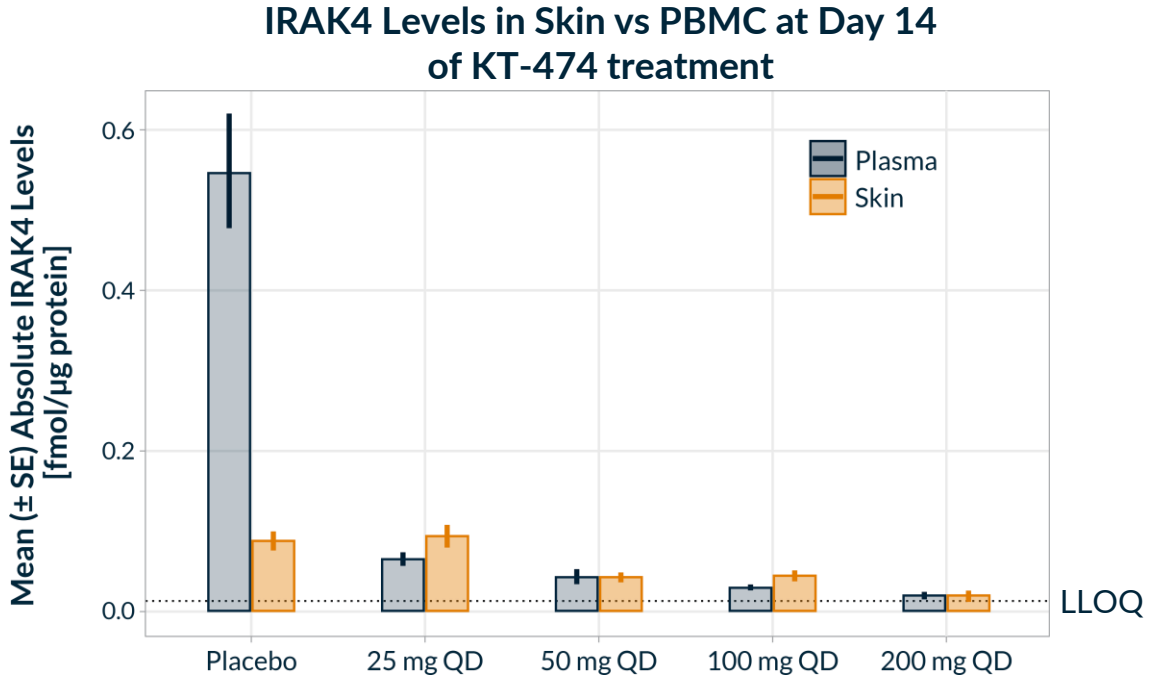


ng/mL (plasma) ng/g (skin)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Plasma Day 7	3.21	7.15	11.9	18.2
Plasma Day 14	4.72	8.49	11.6	17.4
Skin Day 7	21.5	40.2	53.5	80.9
Skin Day 14	44.5	94.2	93.7	238

C_{trough} concentrations shown for Days 1, 7 and 14.

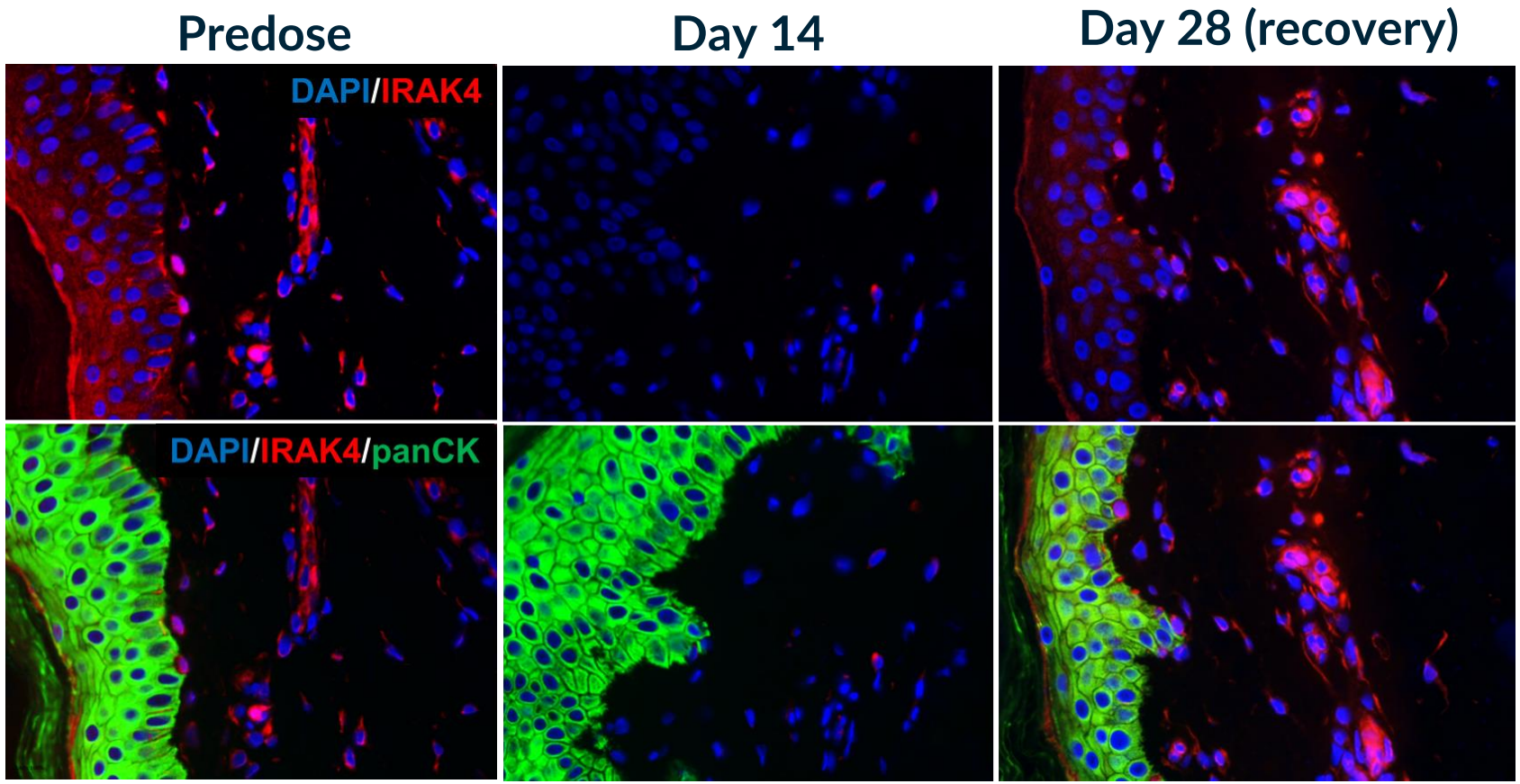
KT-474 Reduced IRAK4 to Near LLOQ in the Skin (MS)





- Baseline IRAK4 levels in skin substantially lower compared to PBMC
- Dose-dependent IRAK4 degradation in skin by mass spectrometry
- Steady-state not yet reached at day 14
- Mean IRAK4 levels at 200 mg dose nearing LLOQ by Day 14, with knockdown up to 90% at 200 mg
- Comparable degradation in PBMC shows that effect of KT-474 is independent of baseline expression level

Substantial IRAK4 Degradation in Skin Observed in Dermis and Epidermis (IRAK4 = Red)

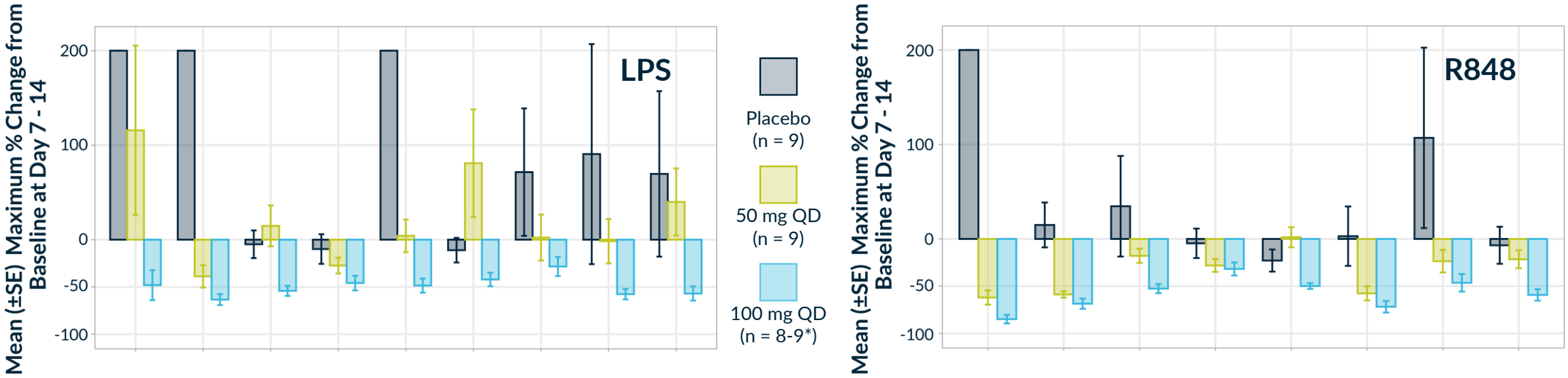


Pan cytokeratin (panCK) is used as the epidermal marker

Representative images from subject in 50 mg cohort

Ex Vivo Inhibition of 9 Disease-Relevant Cytokines, Day 7-14

Results through MAD3 Showed Dose-Dependent Effect Tracking with Extent of Monocyte IRAK4 Degradation



	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	357%	292%	-5%	-10%	880%	-11%	72%	91%	70%
50 mg QD	116%	-39%	15%	-27%	4%	81%	2%	-2%	40%
100 mg QD	-48%	-63%	-54%	-46%	-49%	-42%	-28%	-58%	-57%

	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	>500%	15%	35%	-5%	-23%	3%	107%	-7%
50 mg QD	-62%	-59%	-18%	-28%	2%	-58%	-24%	-21%
100 mg QD	-85%	-68%	-53%	-32%	-50%	-72%	-46%	-59%

50 mg QD: 93-95% PBMC degradation at Day 7-10; **87-90% Monocyte degradation at Day 7-14**
100 mg QD: 97-98% PBMC degradation at Day 7-10; **92-93% Monocyte degradation at Day 7-14**

*n=8 for LPS, n=9 for R848

Mean values > 200% have been replaced by 200 for visualization purposes

KT-474 Phase 1 HV Summary

Phase 1 Summary

- Dose escalation completed; 105 healthy volunteers enrolled in SAD and MAD portions of trial
- **POM**: IRAK4 degradation in blood and skin to near LLOQ; 95-98% mean IRAK4 reduction in blood at top 3 MAD doses (50, 100 and 200 mg)
  - Robust translation of PK/PD from preclinical species to humans
- **POB**: Over 50% inhibition of up to 9 cytokines with up to 85% inhibition at 100 mg MAD dose
- Enrollment and dosing completed in open-label cohort of HS and AD patients treated for 28 days with 14 days of follow-up
  - Results to be presented in December, including PD in skin and blood and exploratory clinical endpoints

Safety Summary

- KT-474 was generally well tolerated, with no SAEs
- MAD TEAEs in 2 or more subjects possibly/probably drug related included Headache (5), Palpitations (3) and Nausea (2)
- A *non-adverse*, non-dose-dependent, self-limiting mean 10-20 msec prolongation of QTc was identified after multi-dosing in MAD, with QTc remaining within normal range (<450 msec).
  - Subsequent analysis suggests weak ion channel binding, not IRAK4 degradation, as likely cause
  - Longer duration dosing in patient cohort will enable further characterization of QTc effect

KYMERA

Thank You!

*This work was done under collaboration agreement with Sanofi