4th Annual TPD Targeted Protein Degradation

KYMERA EST. 2016

Safety, PK and PD from Single Ascending Dose Portion of KT-474 Phase 1 Trial in Healthy Volunteers

Jared Gollob, M.D. - Chief Medical Officer

4th Annual TPD Summit, Keynote Plenary Session

October 27, 2021

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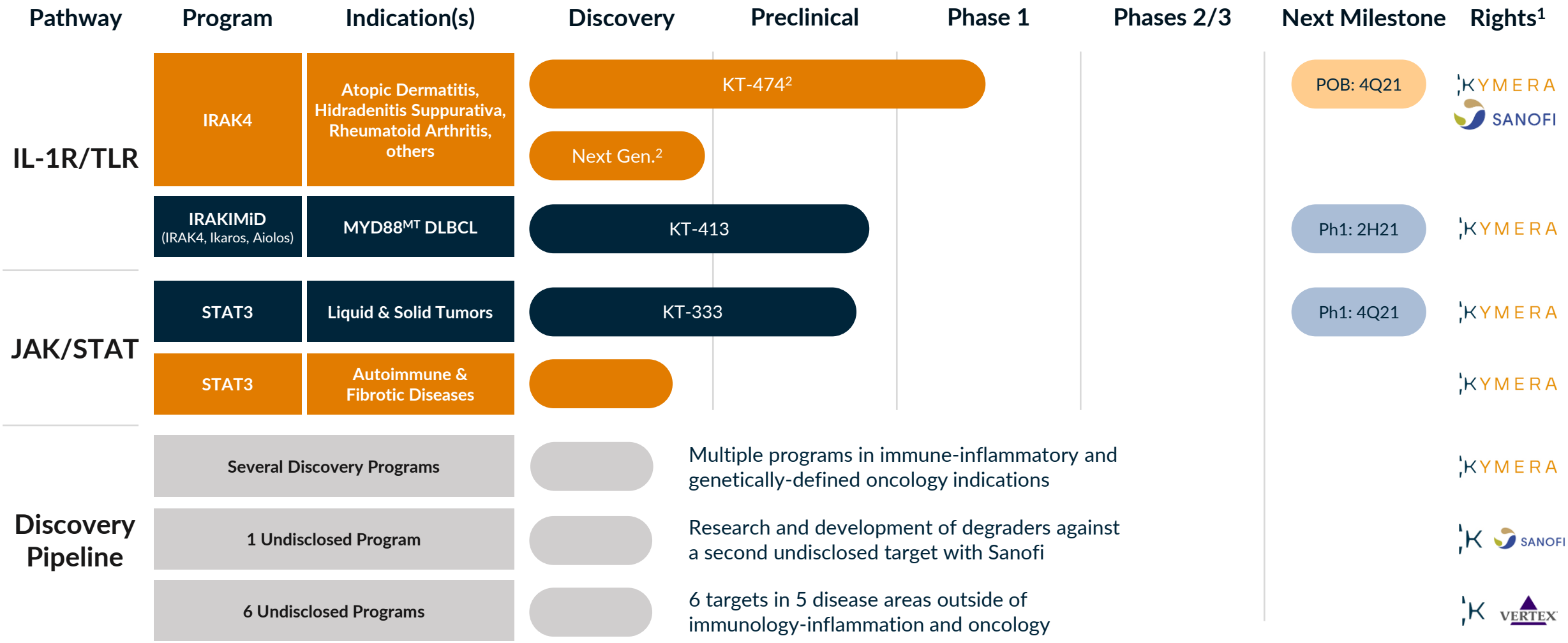
Kymera's Pipeline of Novel Protein Degraders

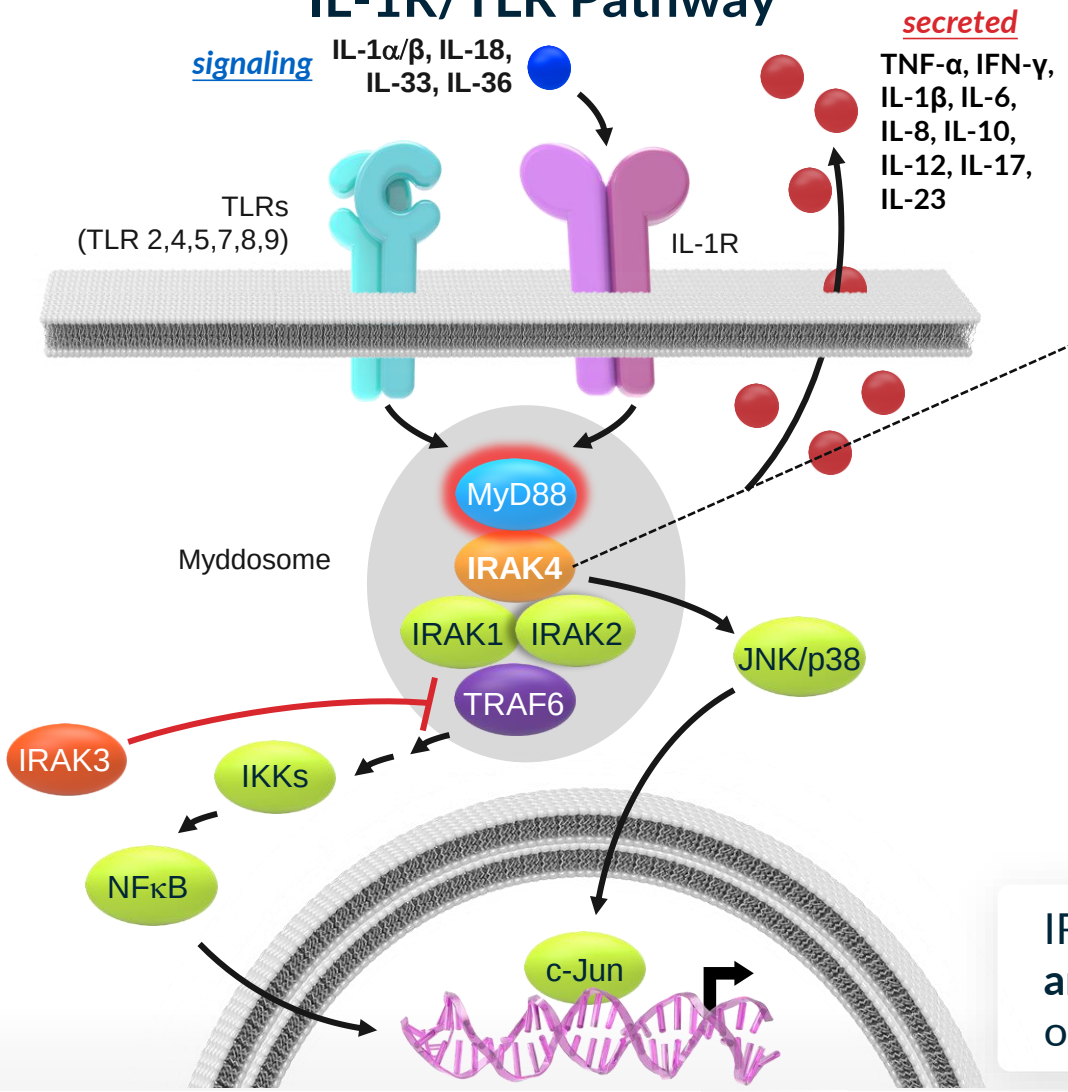


1. Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
2. Sanofi collaboration to develop IRAK4 degrader candidates, including KT-474 (SAR444656), outside of oncology and immuno-oncology fields.

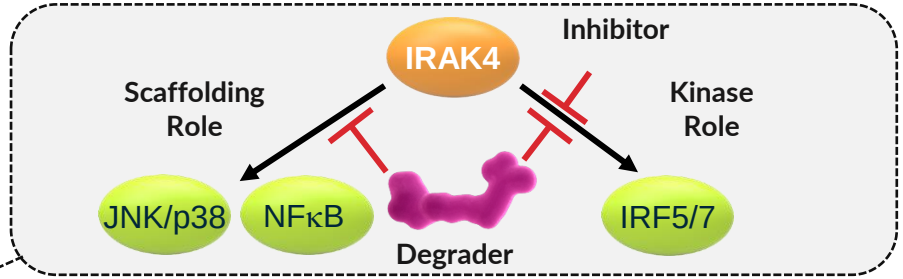
● = Oncology ● = Immunology-Inflammation

IRAK4 Targeting: Degrader Advantage, Clinical Validation, and Human Genetics De-risking

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

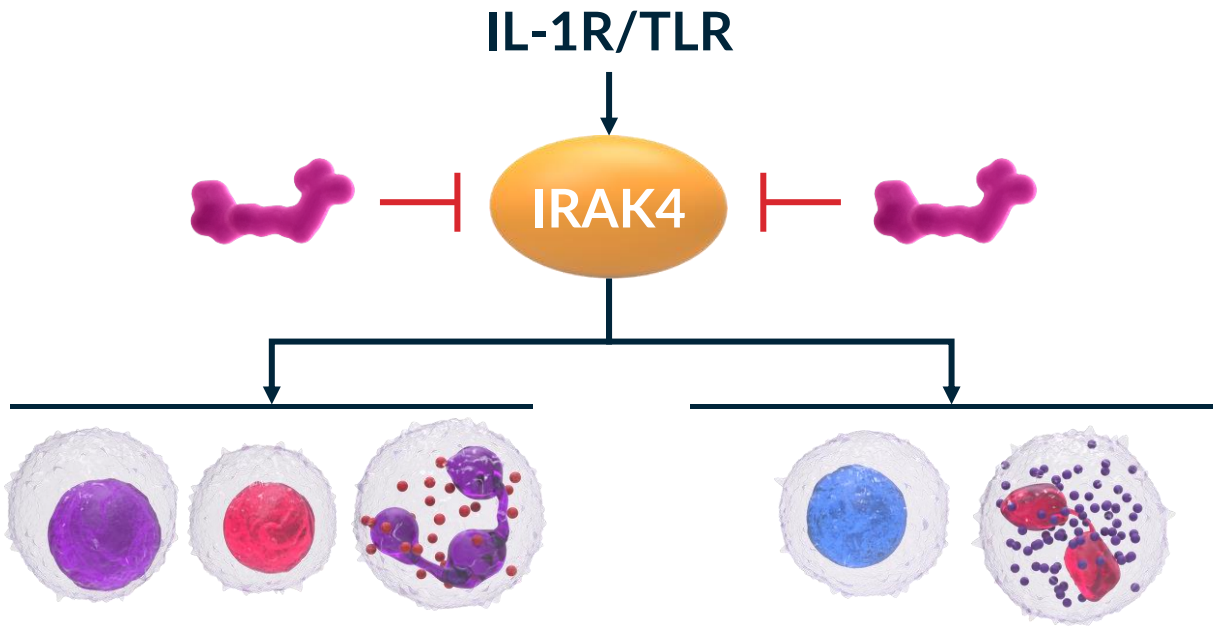
IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa
IL-1α: Atopic Dermatitis
IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis
IRAK4 SMI: Rheumatoid Arthritis

Human Genetics

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

Development Opportunities for IRAK4 Degrader in Inflammation
Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Systemic Lupus Erythematosus
- Inflammatory Bowel Disease
- Gout
- Psoriasis
- Behcet's Disease

Th2/Eosinophils

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

Limitations of Current Therapies

Anti-Cytokine/Cytokine Receptor Antibodies

- Target only 1-2 cytokines
- Require injection

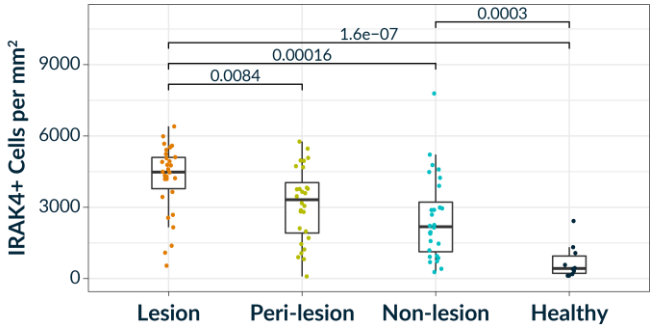
Small Molecule Inhibitors

- Limited pathway blockade (IRAK4 SMI)
- Safety issues (JAK family)

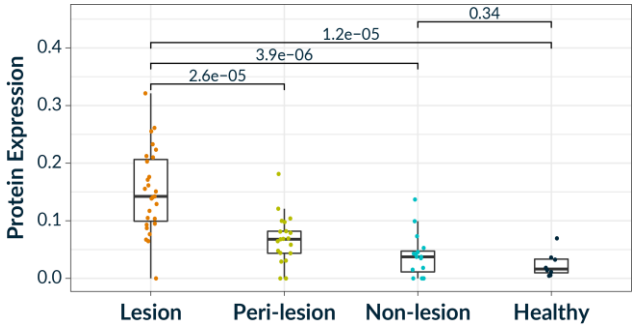
IRAK4 Protein Expression in Autoimmune Diseases: Upregulation in Skin of HS Patients Compared to Healthy Subjects

IRAK4 protein levels overexpressed in HS patient skin lesions

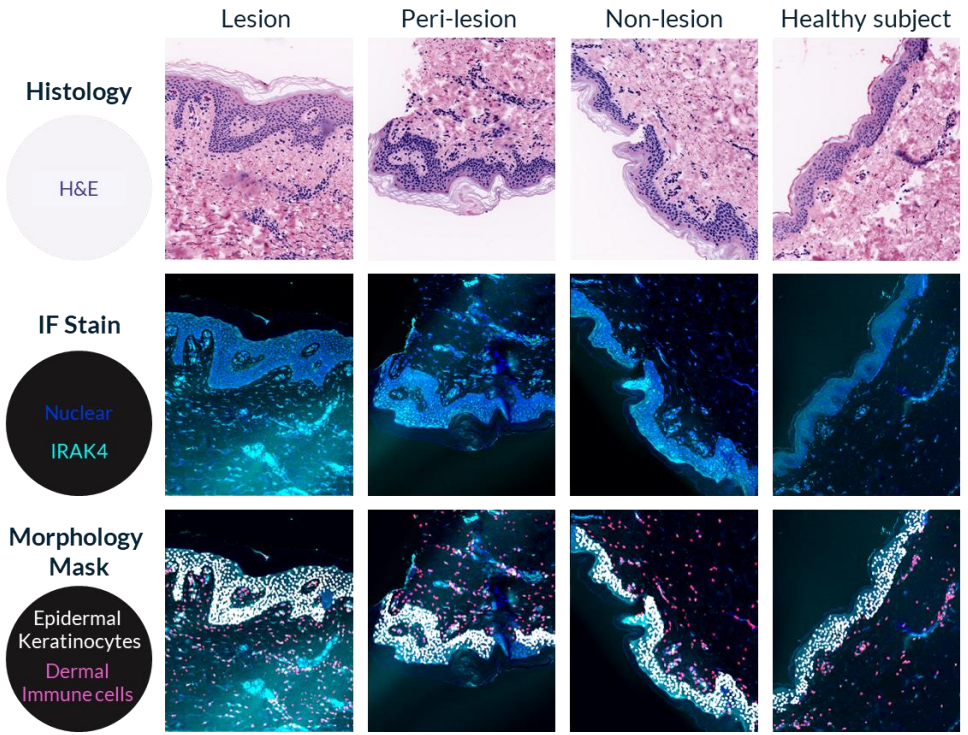
Immunofluorescence (IF)



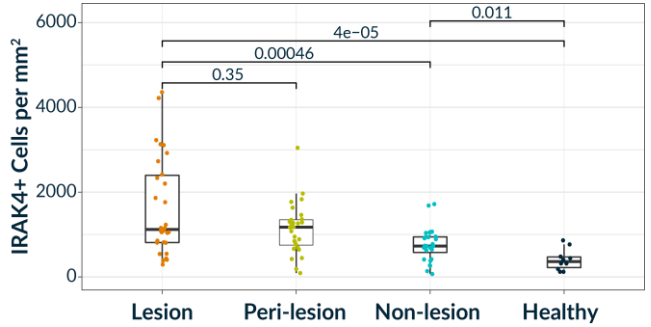
Mass Spectrometry (MS)



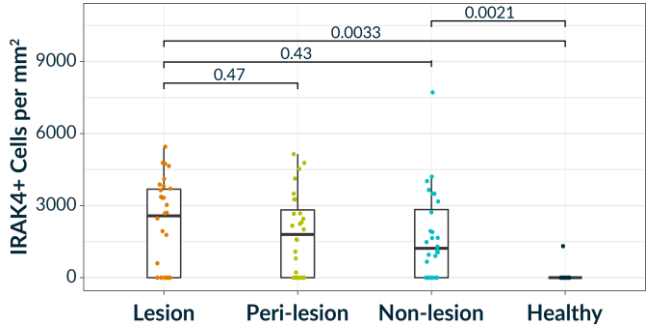
IRAK4 expression is upregulated in dermis and epidermis of HS patients relative to healthy subject skin



Dermal Immune Cells

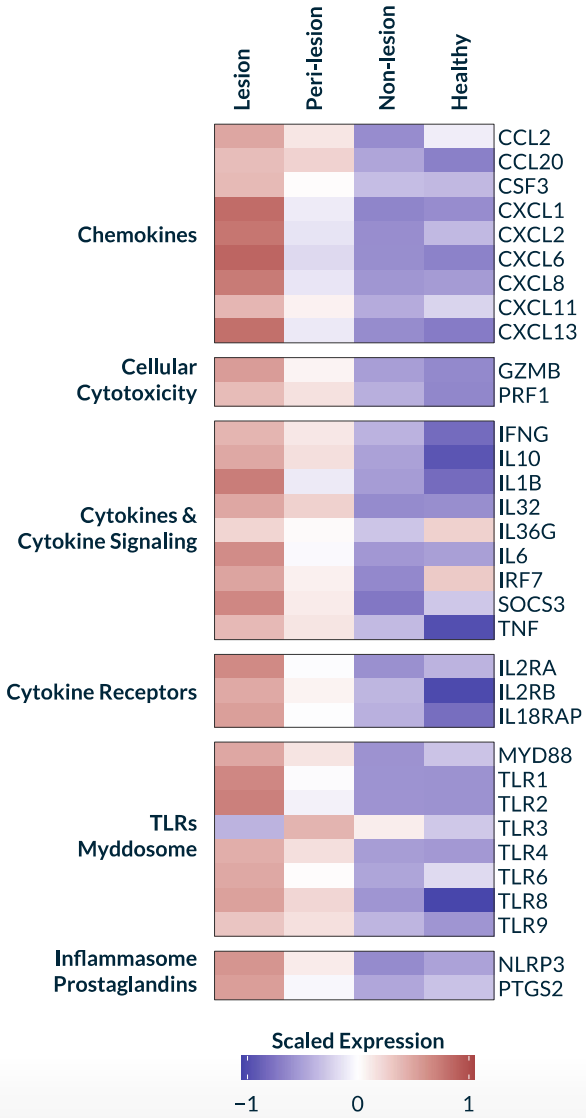


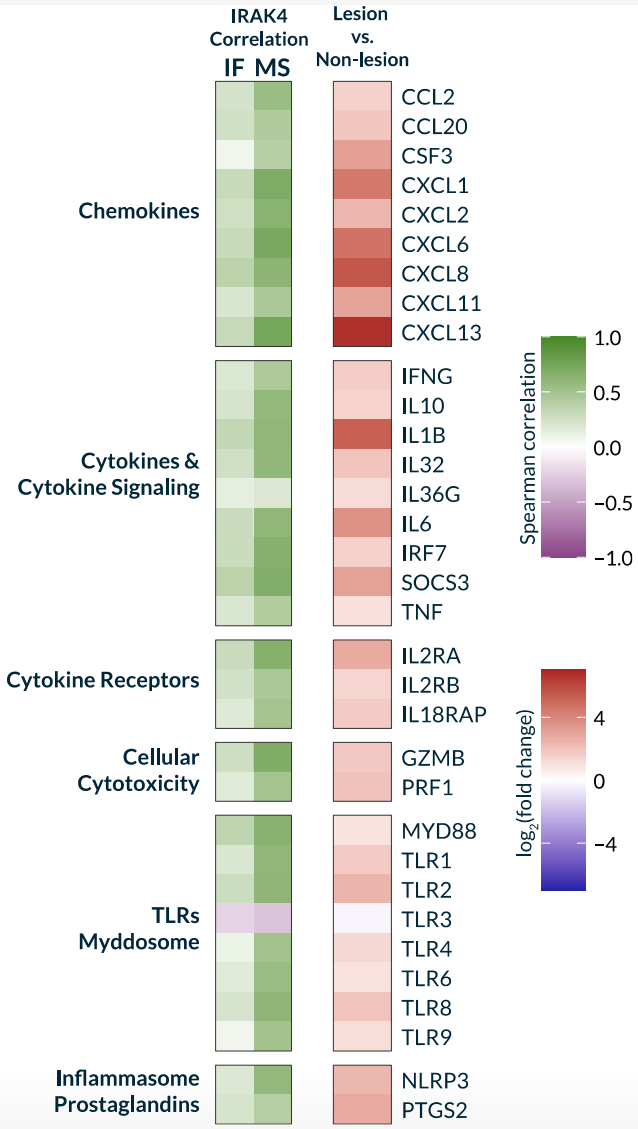
Epidermal Keratinocytes



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





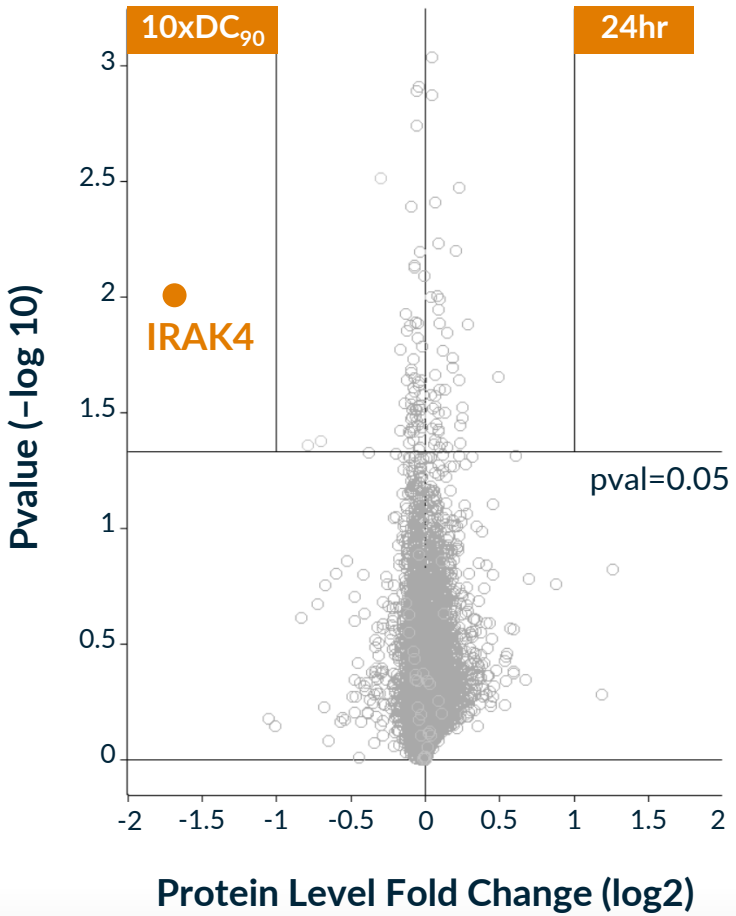
IF: immunofluorescence; MS: mass spectrometry

- 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

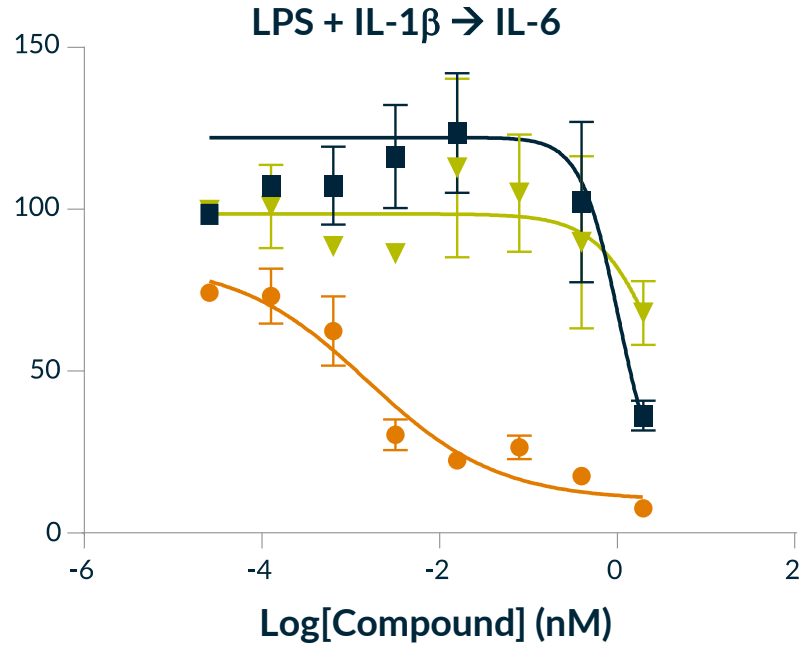
KT-474: Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

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

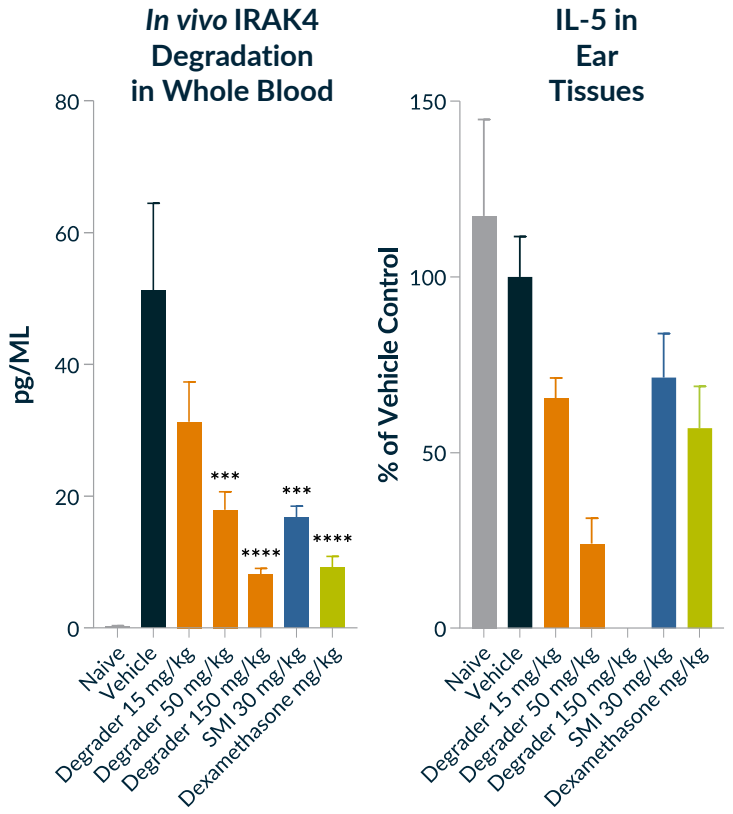
Superiority over SM kinase Inhibitor



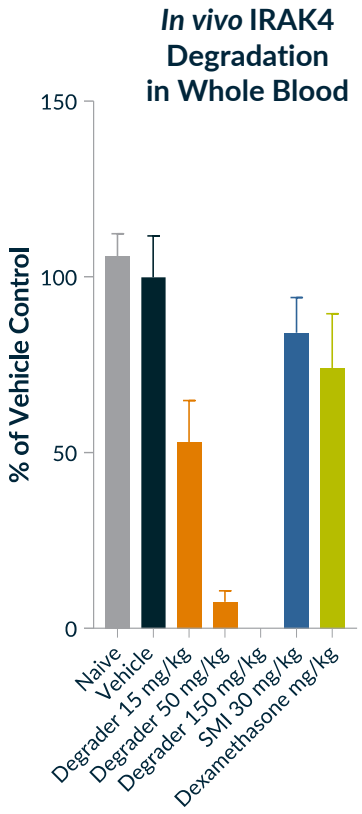
Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

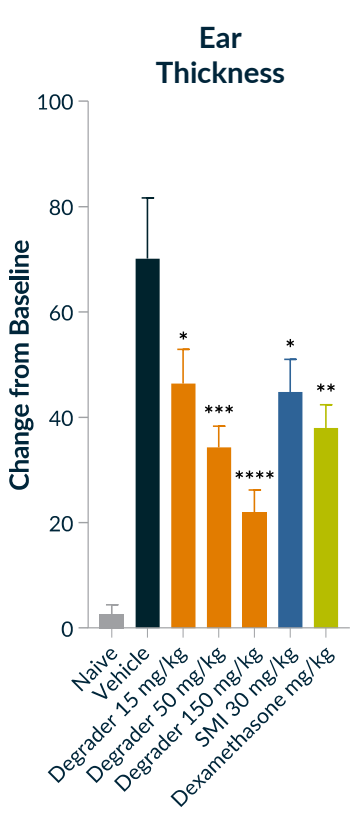
KT-474 is Superior to IRAK4 Small Molecule Inhibitor (SMI) Across Multiple Preclinical Immune-inflammatory *In Vivo* Models

rmIL-33 Intradermal Challenge Model

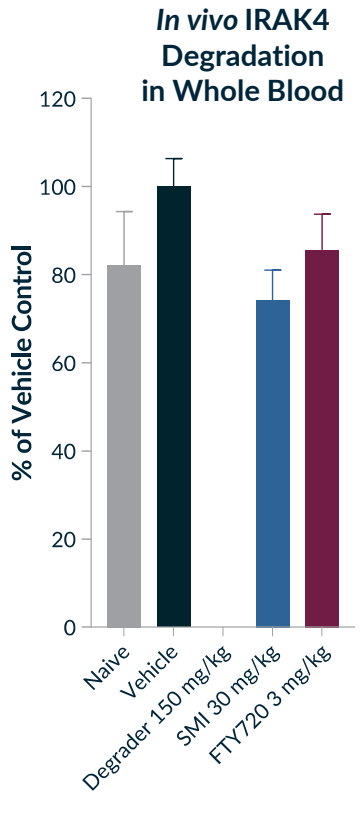


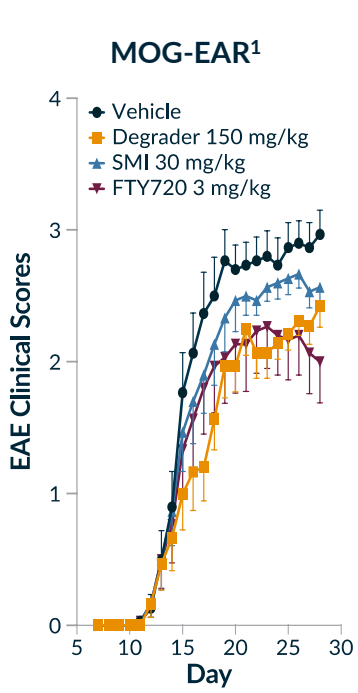
rhIL-36αβγ Intradermal Challenge Model





Th17-mediated Multiple Sclerosis Model





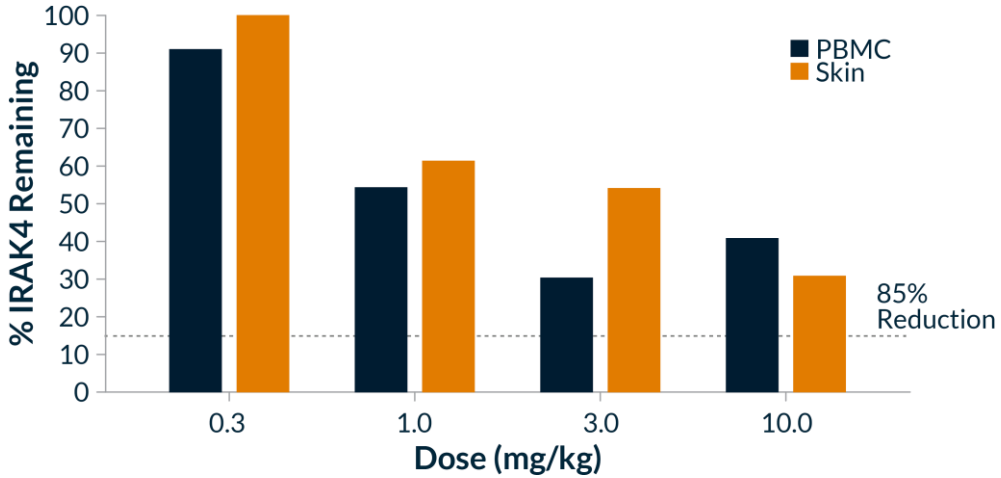
Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

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

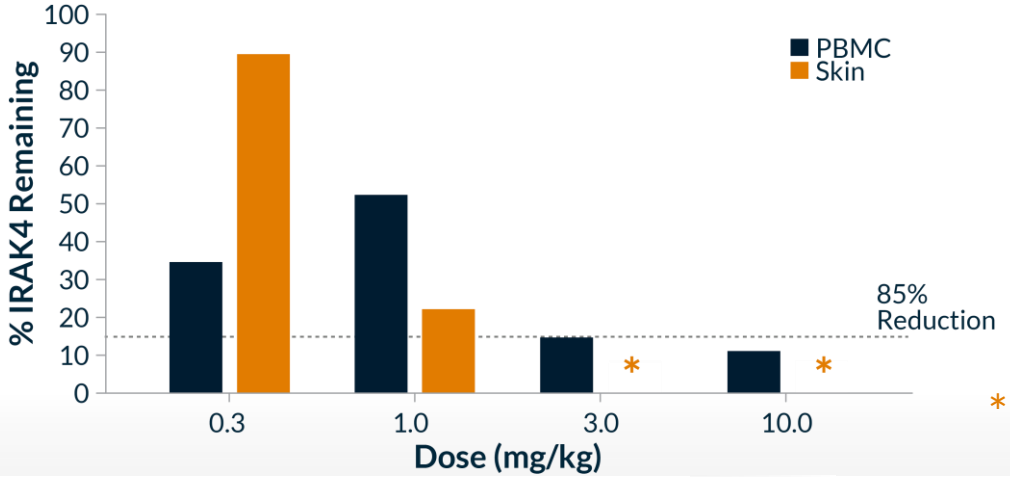
1. Myelin Oligodendrocyte Glycoprotein-induced Experimental Autoimmune Encephalomyelitis (MOG-EAR) Model

KT-474 Multi-dosing (Daily x 7 Days) Maximizes IRAK4 Degradation at Lower Doses in Dogs

IRAK4 Knockdown 24h after Day 1 Dose



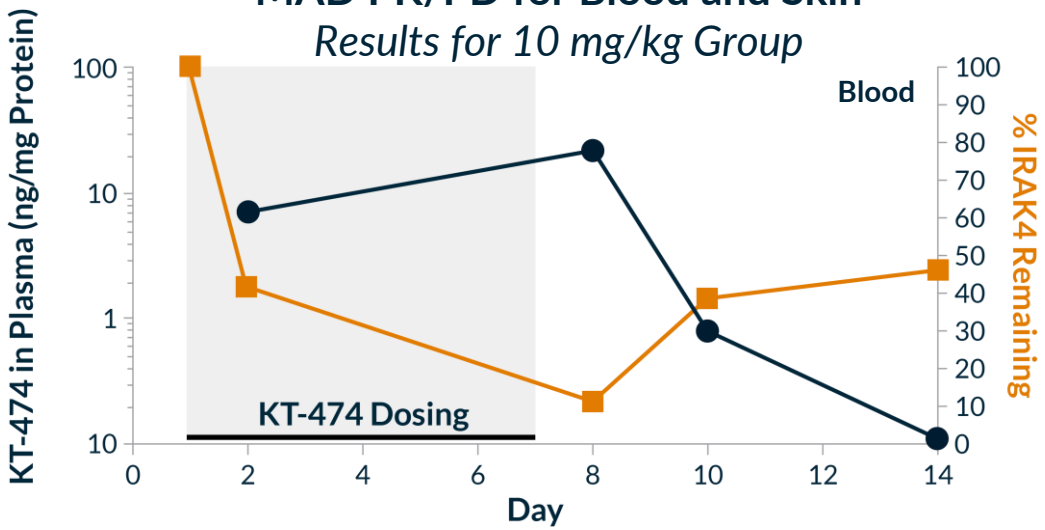
IRAK4 Knockdown 24h after Day 7 Dose

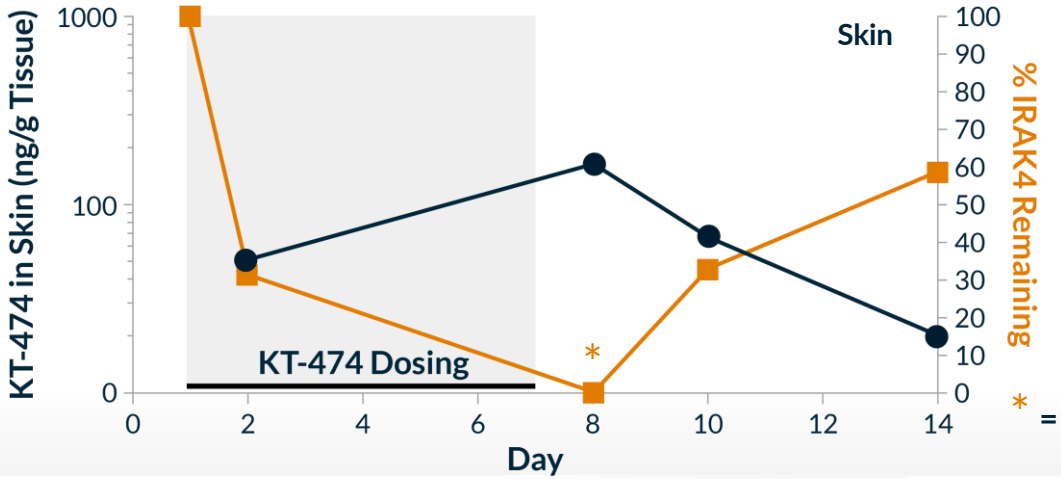


* = BLQ

MAD PK/PD for Blood and Skin

Results for 10 mg/kg Group

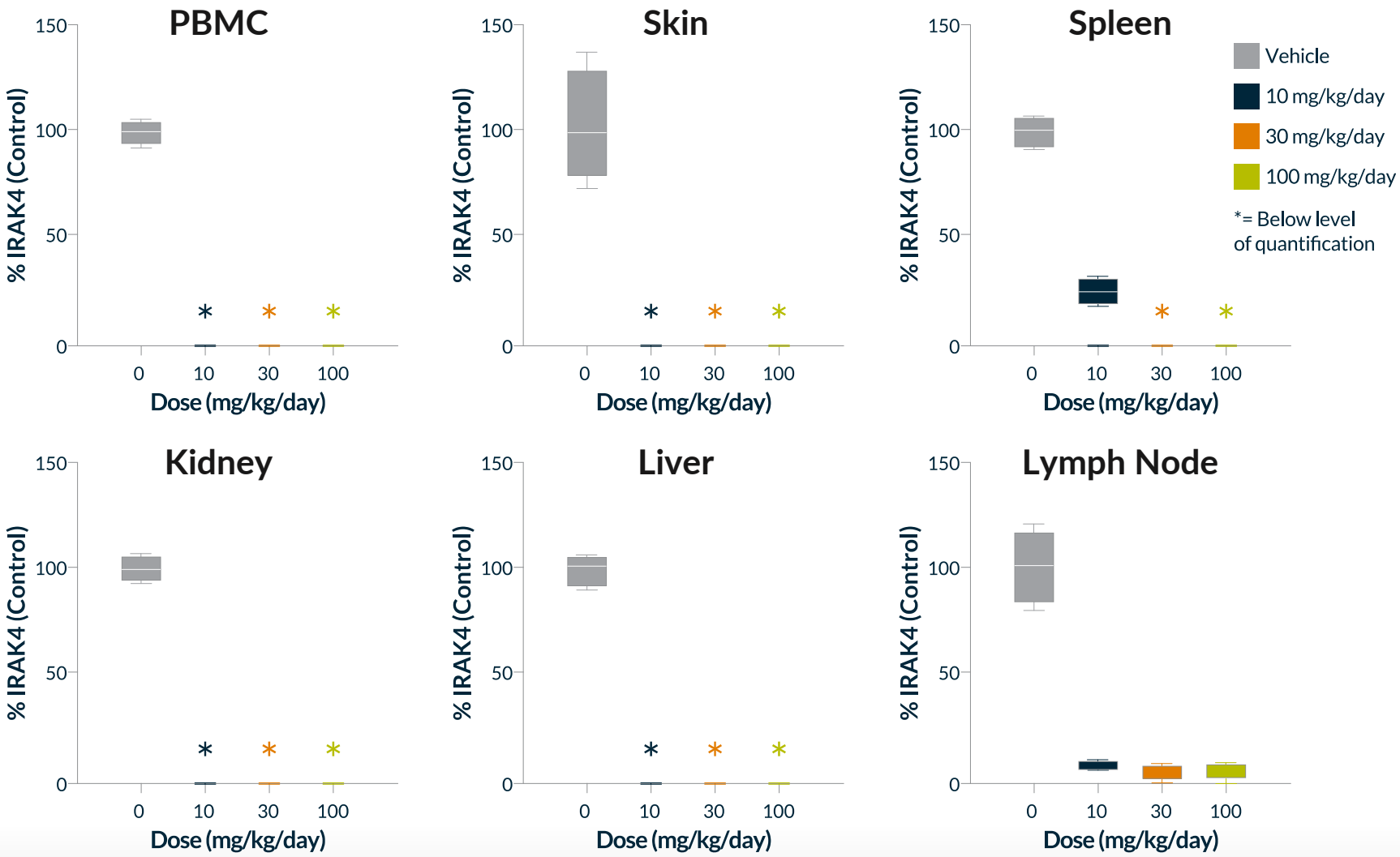




* = BLQ

KT-474: Near Complete Systemic IRAK4 Degradation is Well Tolerated in Preclinical Non-rodent Model

- Orally-administered KT-474 evaluated in a 14-day non-GLP tox and PKPD study in rodent and non-rodents (shown).
- Almost complete knockdown demonstrated across multiple tissues at multiple doses
- Compound well-tolerated at all doses up to 600 mg/kg for rodents and 100 mg/kg for non-rodents



KT-474 Phase 1 Trial Design

Double-blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) trial

Three-part Phase 1 Design

1 SAD Portion
Healthy Volunteers

- **7** cohorts (up to 56 adult healthy subjects)
- **8** per cohort (6:2 randomization)
- **Single** dosing (starting dose 25 mg)

2 MAD Portion
Healthy Volunteers

- **5** cohorts (up to 60 adult healthy subjects)
- **12** per cohort (9:3 randomization)
- **14x** daily doses (starting dose 25 mg)

3 MAD Portion
Patient Cohort

- **1** cohort (up to 20 AD and HS patients)
- Open-label
- **14x** daily doses

Endpoints

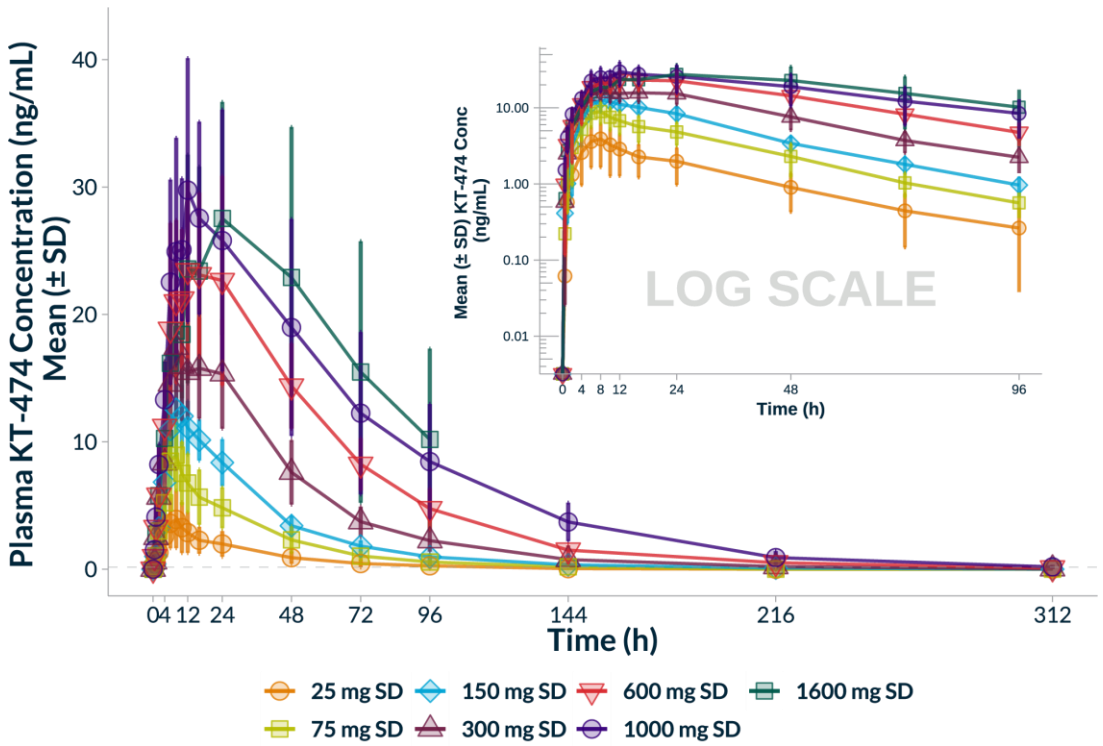
Primary
- Safety & tolerability

Secondary/ Exploratory
SAD & MAD
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC

Exploratory
SAD & MAD
- *Ex vivo* response of whole blood to TLR agonists (SAD & MAD) and IL-1β (MAD only)

Exploratory
MAD Only
- IRAK4 knockdown in skin biopsies
- Proinflammatory cytokine and chemokine levels in skin biopsies (Patients only)
- Plasma C-reactive protein (HV and Patients) and cytokine levels (Patients only)

SAD Study: Favorable PK after Single Oral Dosing



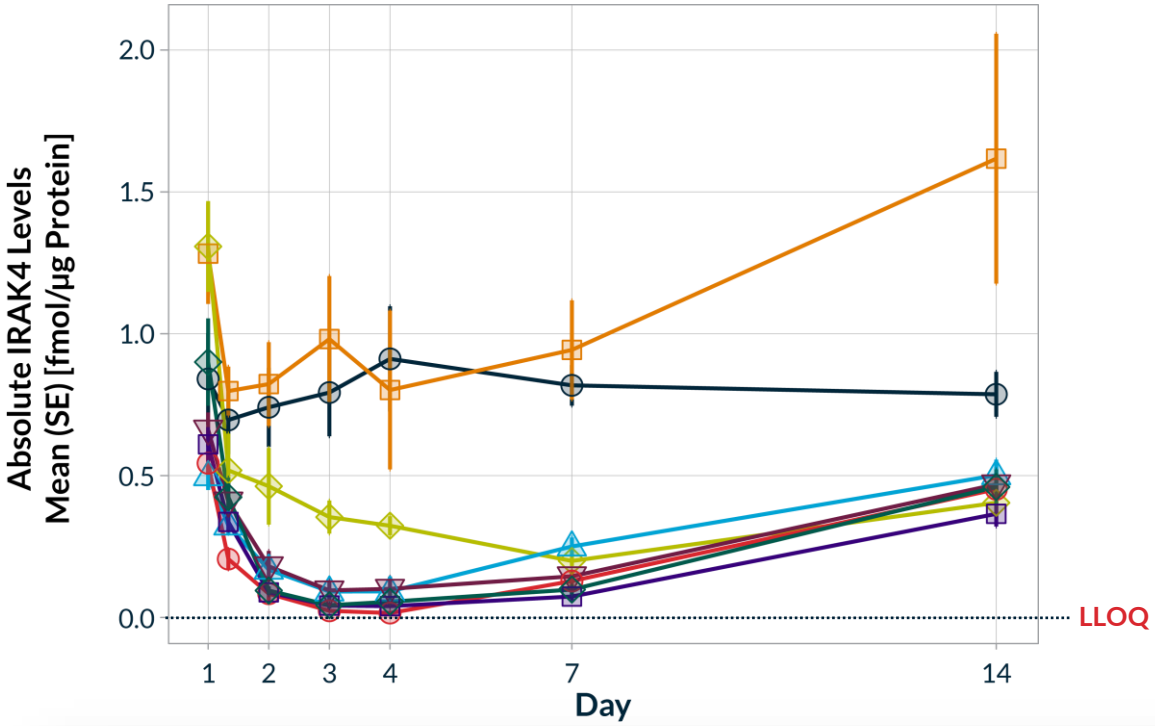
SAD #	Dose	Cmax (ng/mL)	t_{max} (h)	AUC (ng.h/mL)	$t_{1/2}$ (h)
1	25 mg	3.49 (61.2)	8.0 (6.0-8.0)	112 (65.4)	25.2 (27.0)
2	75 mg	9.08 (36.6)	7.0 (6.0-8.0)	288 (36.7)	28.7 (10.1)
3	150 mg	12.7 (25.7)	9.0 (8.0 - 10.0)	483 (21.9)	31.6 (22.1)
4	300 mg	17.4 (29.6)	8.0 (8.0 – 24.0)	869 (31.4)	36.4 (13.1)
5	600 mg	24.2 (27.5)	12.0 (6.00 – 24.0)	1530 (18.6)	40.9 (18.2)
6	1000 mg	27.8 (34.4)	20.0 (6.0 – 24.0)	1890 (60.8)	38.8 (7.0)
7	1600 mg	27.3 (36.2)	24.0 (12.0 – 48.0)	1920 (43.0)	36.4 (46.9)

Geometric Mean (%CV) reported for all parameters, except t_{max} where median (range) are presented

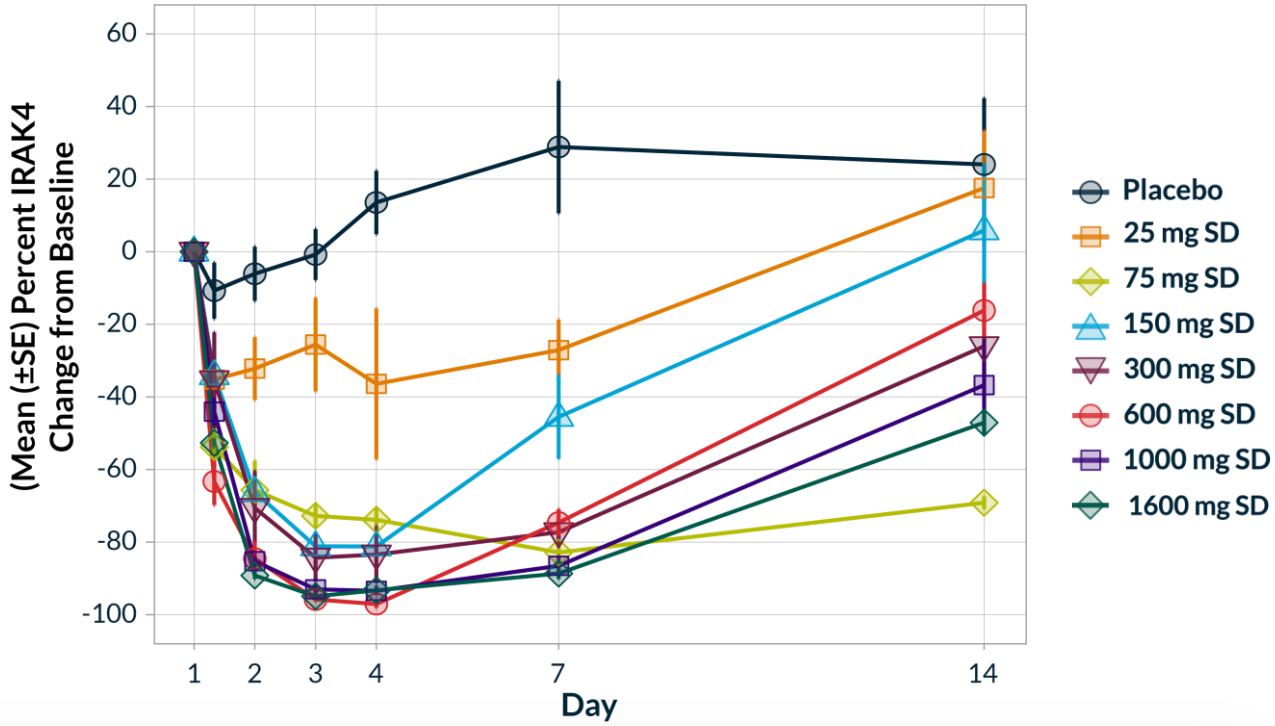
- Consistent PK after single dosing: Cmax achieved between 7-24 hours, half-life = 25-40 hours
- Dose dependent exposure increases, plateauing after the 1000 mg dose
- Low to moderate inter-subject variability in exposure

KT-474 Achieved Deep and Dose-Dependent IRAK4 Degradation after Single Oral Doses that Lasted for at Least 6 Days

Absolute IRAK4 Levels

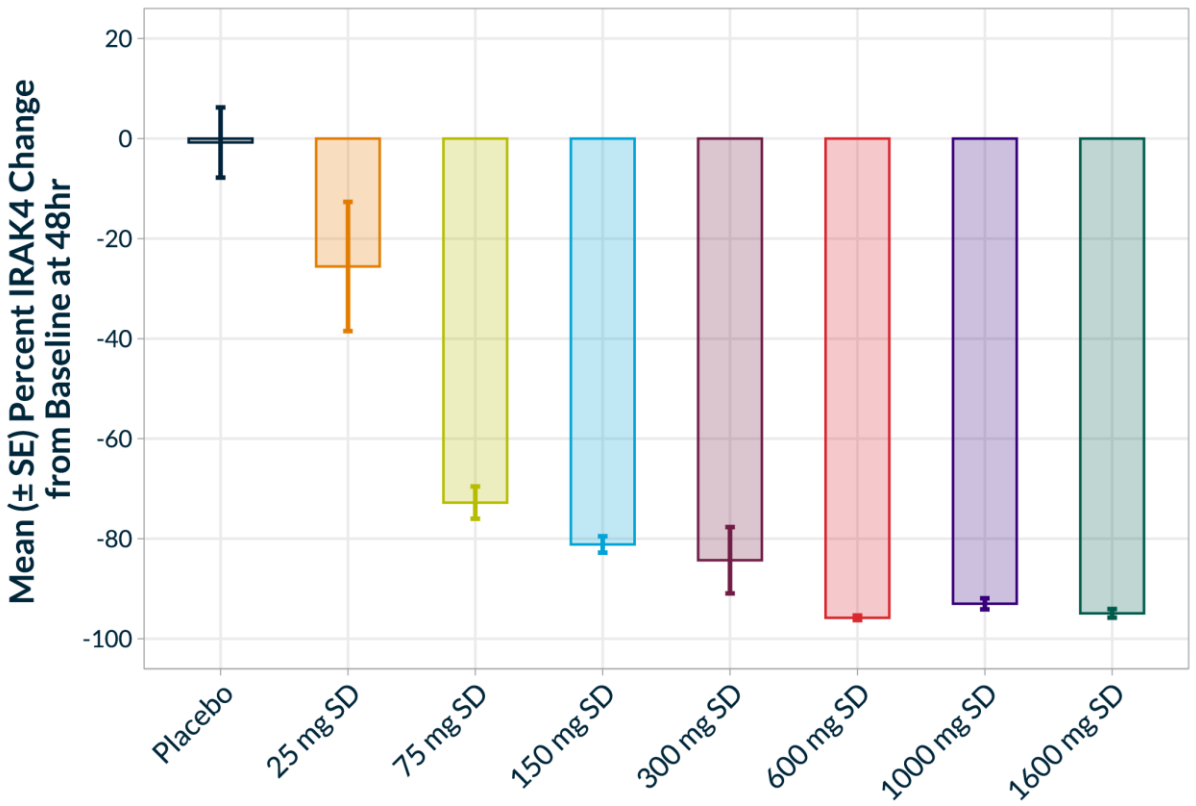


Mean % Reduction of IRAK4



- Detected by Mass Spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours (Day 3-4)
- IRAK4 reduction lasted for at least 6 days post-dose in all dose groups
- SAD 5 through 7 approached or exceeded Lower Limit of Quantitation (LLOQ)

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



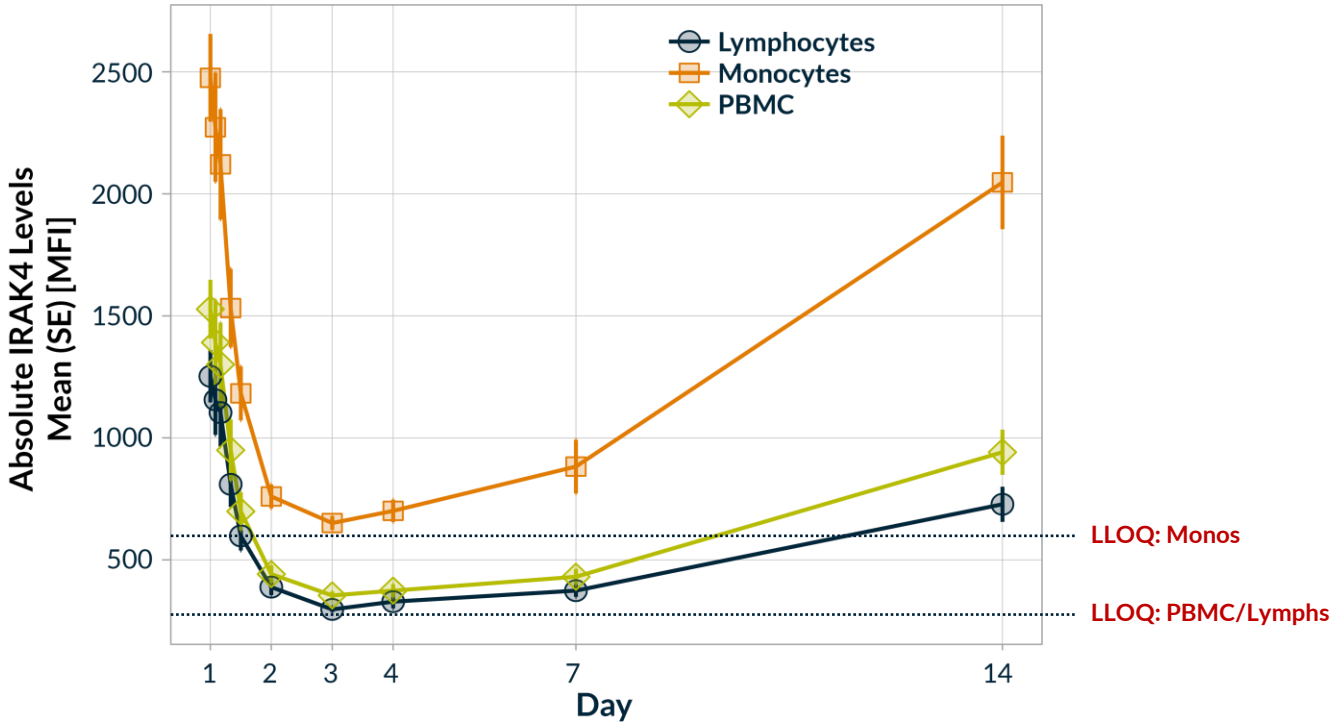
Percent IRAK4 Reduction in PBMC at 48 Hours Post-Dose using Mass Spectrometry

	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*

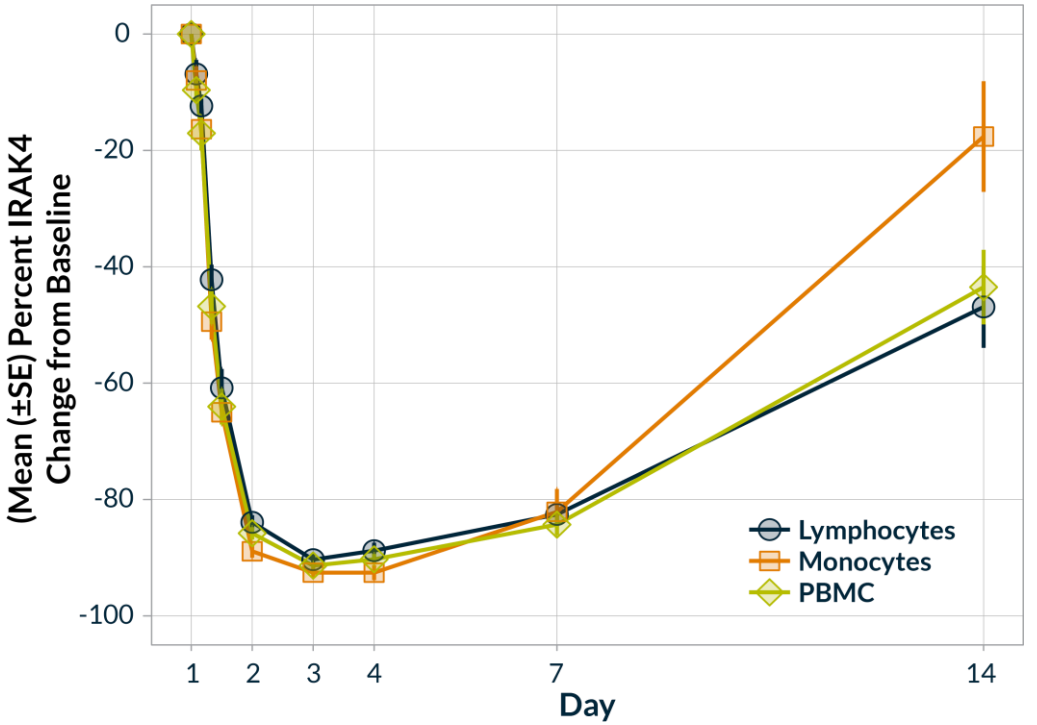
* p-values relative to placebo

Robust IRAK4 Degradation Observed in Lymphocytes and Monocytes: Flow Cytometry Results at SAD 7

Absolute IRAK4 Levels

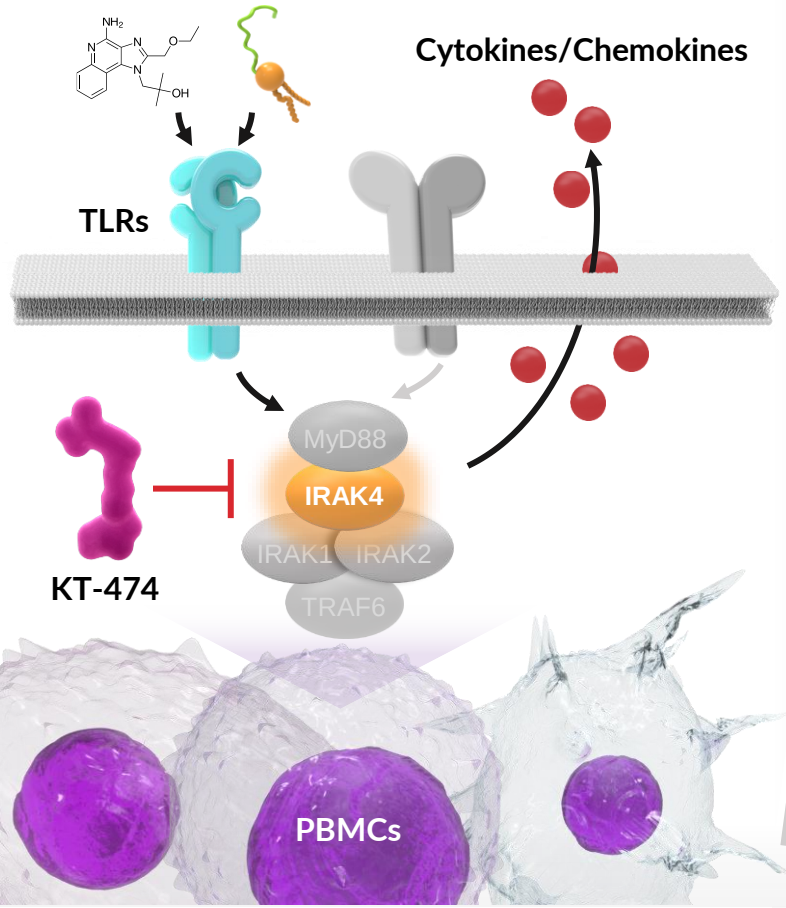


Mean % Reduction of IRAK4



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

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

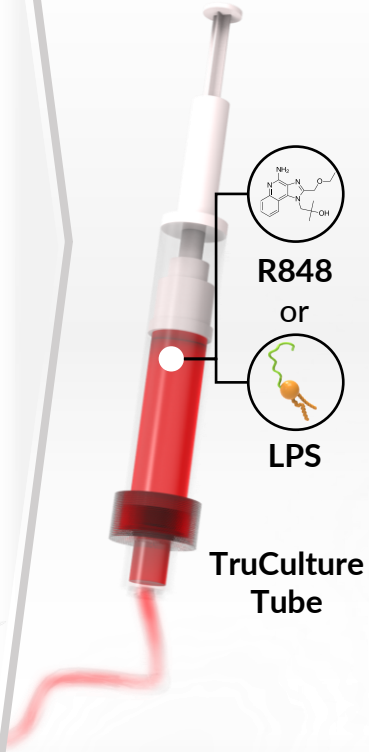


1 Blood Draw Pre-/Post-Dose

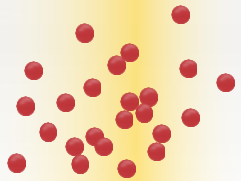
2 Overnight Incubation (37°)

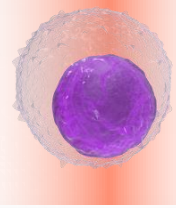
3 Plasma Isolation

4 Cytokine/Chemokine Measurement



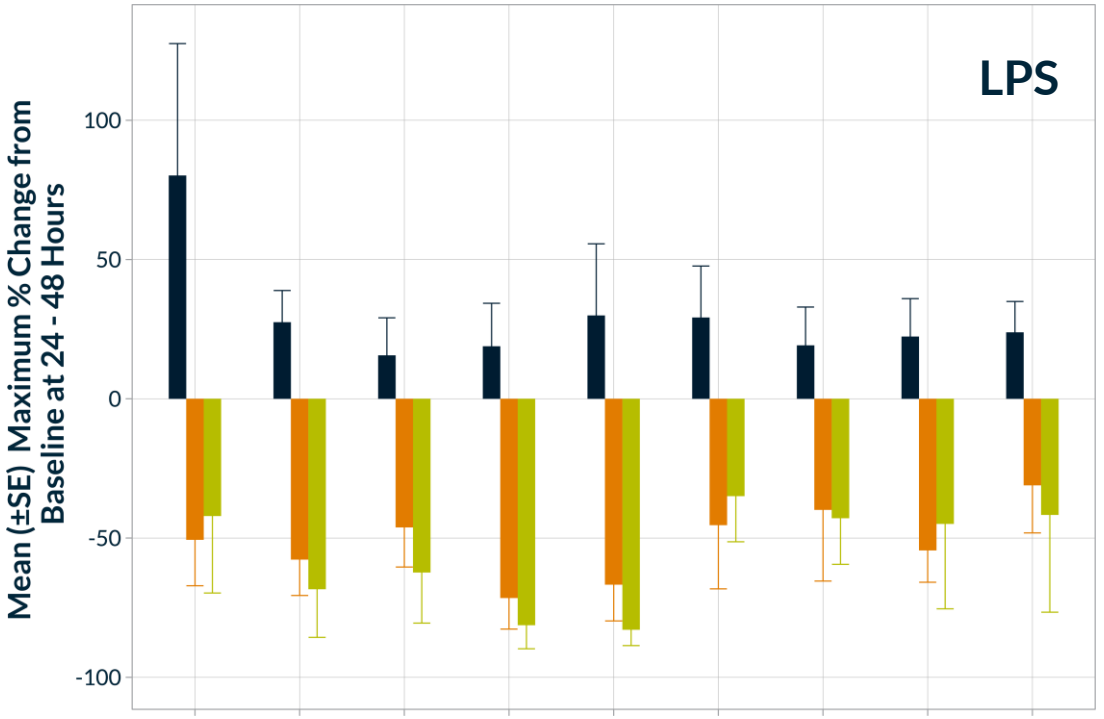
TNF-α, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23

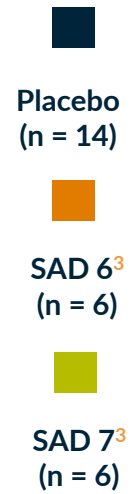


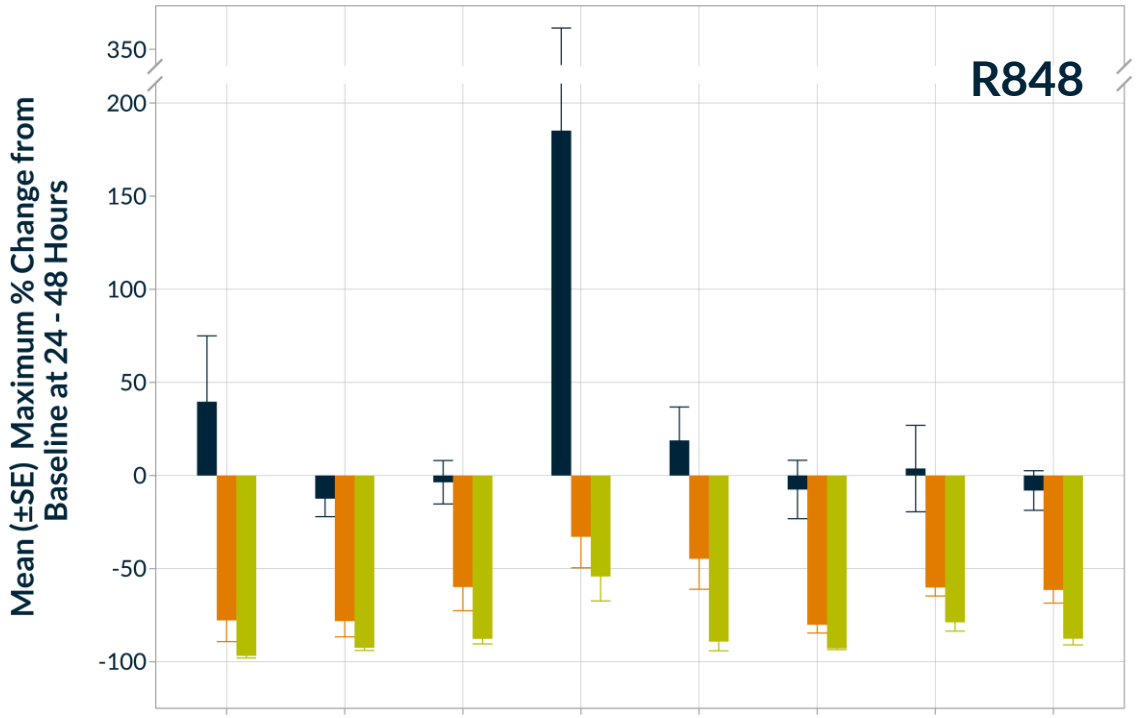


Up to 97% Maximum *Ex Vivo* Cytokine Inhibition 24-48h Post-Dose

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

Blinded SAD Safety Summary

- **No SAEs**
- **Treatment-related AEs observed only in SAD 5 and SAD 6; all were self-limiting and resolved**
  - No treatment-related AEs in SAD 7
- **No significant ECG changes**

Possibly or Probably Treatment-Related AEs* (>1 Subject)

AE Term	#AEs (subjects)	Severity	Cohort
Headache	**4 (3)**	Moderate (x2)	SAD 5, SAD 6
		Mild (x2)	SAD 5
Nausea	**2 (2)**	Mild (x2)	SAD 6

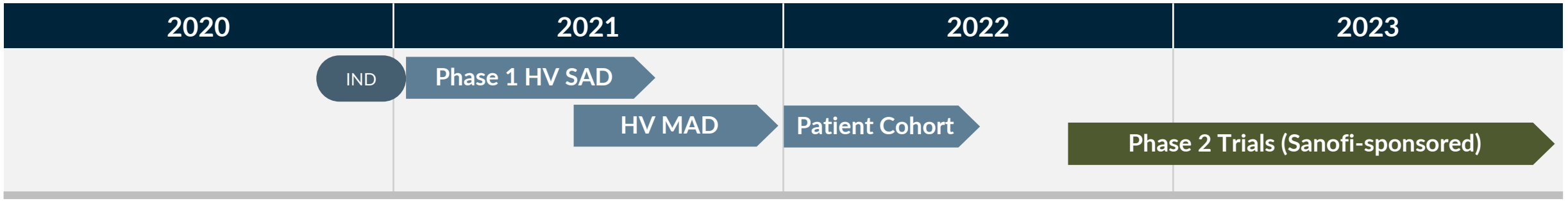
** per investigator assessment*

SAD Summary

- SAD dose escalation completed
- Single doses resulting in sustained pharmacodynamic effect were well-tolerated, with mild-moderate self-limiting headache and GI symptoms the most common treatment-related AEs seen at doses ≥ 600 mg
- **Robust, dose-dependent IRAK4 reduction in PBMC maintained for at least 6 days, with mean 93-96% KD (approaching or exceeding lower limit of quantification)** at 48 hours plateauing after 600 mg; expectation during multi-dosing is to reach these levels at much lower dose
- **Proof-of-biology established** with demonstration of broad and potent *ex vivo* cytokine inhibition in whole blood
  - Up to **79-97% inhibition of R848 or LPS induction of 8 different pro-inflammatory cytokines**, including: IFN-γ (97%), IL-12 (93%), IL-1β (92%), IL-10 (89%), IL-6 (88%), TNF-α (88%), IL-8 (81%) and IL-17 (79%)
  - Maximum cytokine effects seen with KT-474 exposures corresponding to **≥*85%* degradation in PBMC**

KT-474 SAD Phase 1 results demonstrate degrader proof-of-mechanism and proof-of-biology, first time for TPD in a placebo-controlled study

KT-474 Phase 1 Trial: Next Steps



Data readouts:
- *Oct 2021:* HV SAD POM/POB
- *Before end of 2021:* HV MAD POM/POB
- *Mid 2022:* Patients POM/POB

- Healthy volunteer MAD enrollment ongoing
  - Anticipate maximizing **IRAK4 knockdown and impact on downstream biomarkers at substantially lower doses** with daily dosing based on PK and PD and as shown in preclinical models
  - Plan to present safety, PK, and PD data before year end
  - PD includes: IRAK4 levels in blood and skin, *ex vivo* cytokine stimulation, plasma hsCRP
  - On track to complete by year-end
- Cohort of AD and HS patients (up to 20) to start enrolling in Q1'22
  - Data readout planned for mid-year