5th Annual TPD Targeted Protein Degradation

Translational & Clinical Track:

Development and Performance of Pharmacodynamic Assays to Demonstrate Proof-of-Mechanism for IRAK4 Degraders in a Phase1 Study

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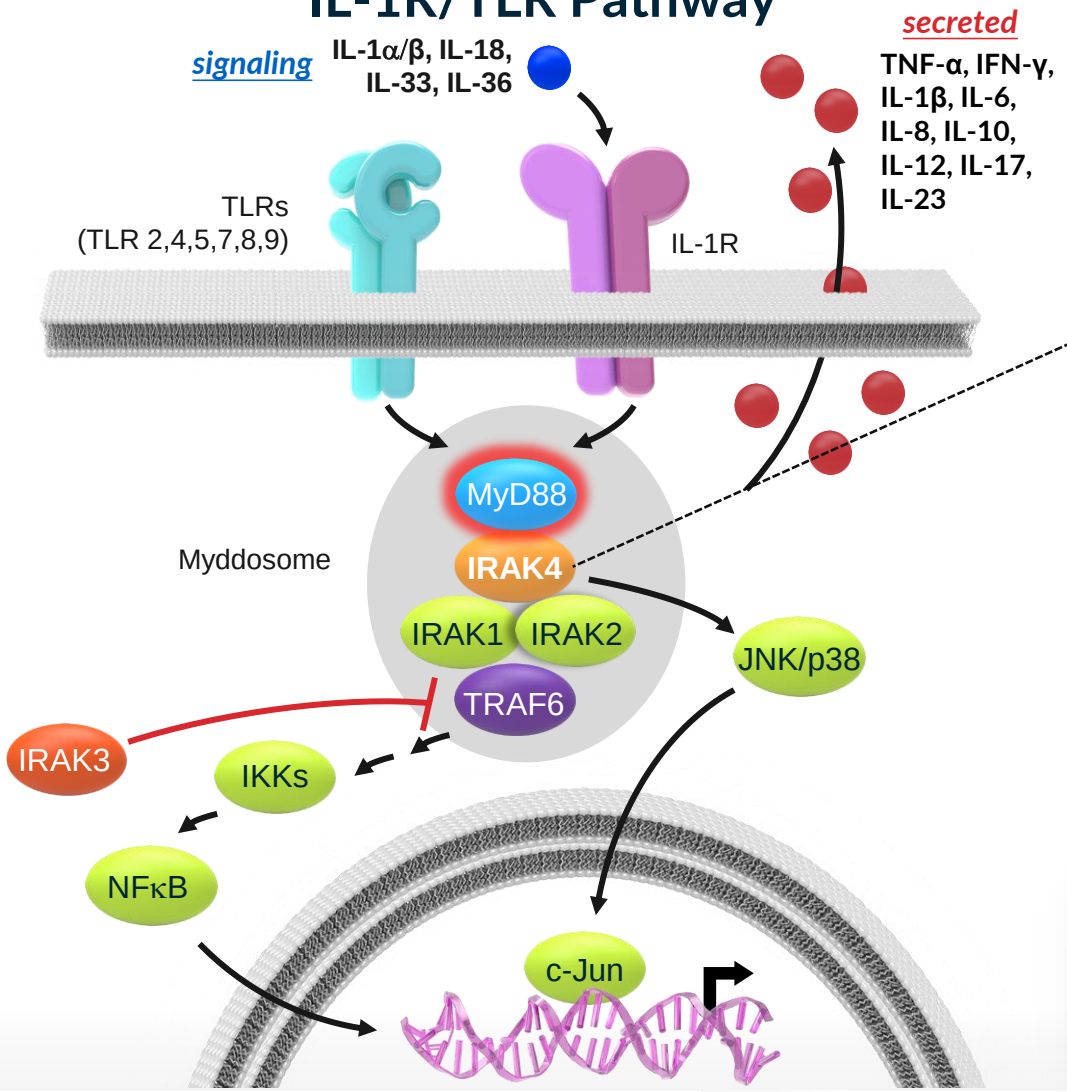
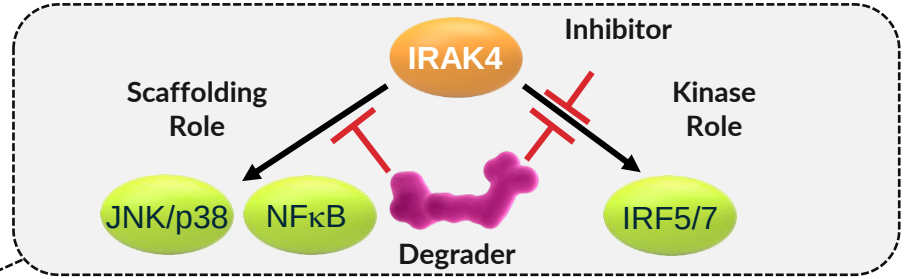
IRAK4 Scientific Rationale & Phase1 Study Design

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

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

KT-474 Phase 1 Trial Design Includes HV and Patients

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

Three-part Phase 1 Design

1 SAD Portion — Healthy Volunteers

- **9** cohorts (up to 68 adult healthy subjects)
- **8** per cohort (6:2 randomization)
- **Single** dosing (starting dose 25 mg)

2 MAD Portion — Healthy Volunteers

- 4 cohorts (up to 48 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
- **28x** 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

Exploratory — MAD Only

- Efficacy in AD and HS patients
- **IRAK4 knockdown in skin biopsies**
- Proinflammatory cytokine and chemokine levels in skin biopsies (Patients only)
- Plasma C-reactive protein and cytokine levels (Patients only)

KT474-HV-101 Sample Collection and Testing
Proof of Mechanism (PoM) and Proof of Biology (PoB)

Blood

PoM

Mass Spec.

FLOW

PBMC

Whole Blood

PoB

Ex vivo Stim.

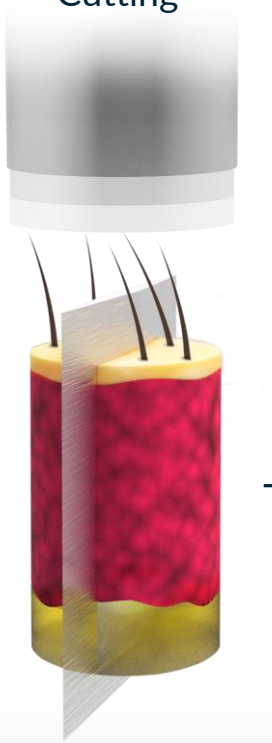
Plasma

Trial Participants

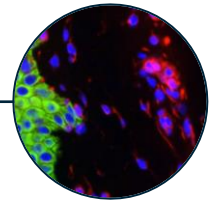
Skin

PoM & PoB

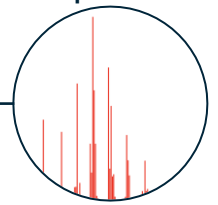
Biopsy and Cutting



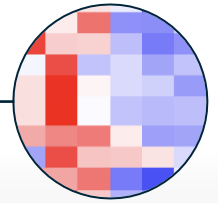
Immunofluorescence Fixed (FFPE)



Mass Spec. Frozen



RNAseq Frozen

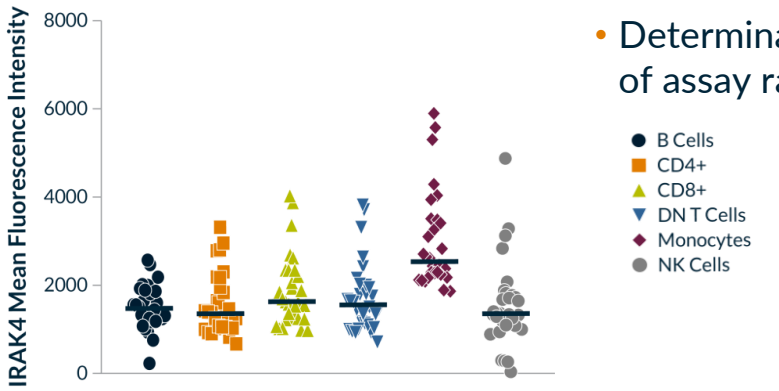


IRAK4 Degradation in Blood

Methods Development: Measuring Degradation in Blood

FLOW in Whole Blood

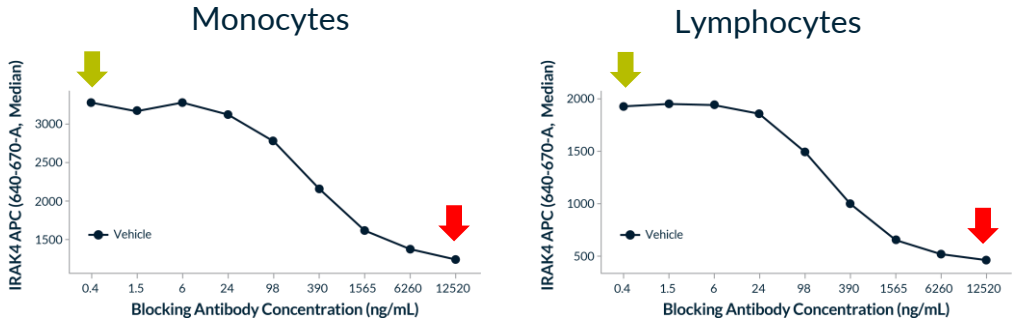
Pre-dose Samples Provide Baseline IRAK4 Values



- Determination of assay range

Blocking Antibody Utilized to Define the Assay Floor

Max IRAK4 signal (no block) Min IRAK4 signal (block)



Each subject sample is stained +/- block

Mass Spec in Isolated PBMCs

- Identification of most sensitive analytes
- Defining the linear range of the assay

Peptide 1

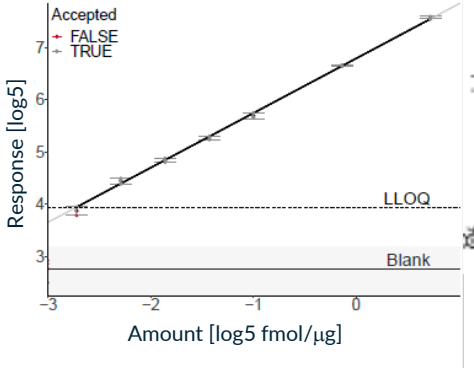
Assay Characterization Results

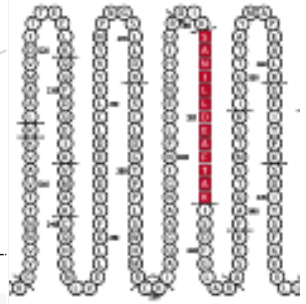
Parameter	Value	Unit
LLOQ	0.0125	fmol/ug
Average CV > LLOQ	6.94	%
Minimal Tested Concentration	0.0125	fmol/ug
Maximal Tested Concentration	3.2	fmol/ug
R^2	0.998	
Slope (Linear Range)	1.04	
Intercept (Linear Range)	6.79	

Assay Characterization Settings

Parameter	Value
q-value Filter	< 0.05
Zero Calibrator Filter	2 x blank intensity
Accuracy Filter	–
Precision Filter	< 20 % CV

Assay Characterization Plot





Peptide 2

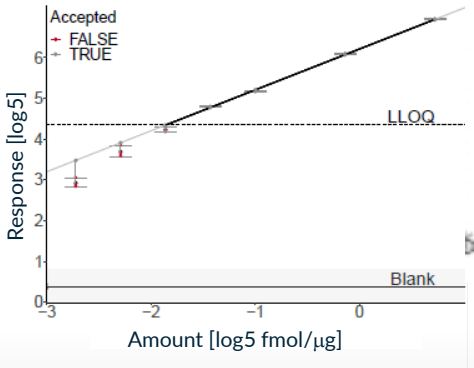
Assay Characterization Results

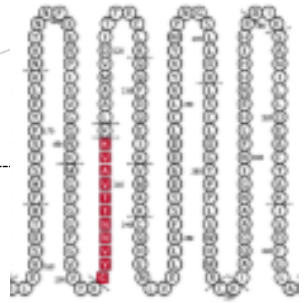
Parameter	Value	Unit
LLOQ	0.05	fmol/ug
Average CV > LLOQ	3.87	%
Minimal Tested Concentration	0.0125	fmol/ug
Maximal Tested Concentration	3.2	fmol/ug
R^2	0.999	
Slope (Linear Range)	1	
Intercept (Linear Range)	6.21	

Assay Characterization Settings

Parameter	Value
q-value Filter	< 0.05
Zero Calibrator Filter	2 x blank intensity
Accuracy Filter	–
Precision Filter	< 20 % CV

Assay Characterization Plot





Method Development of IRAK4 Flow Assay in Whole Blood from Healthy Donors

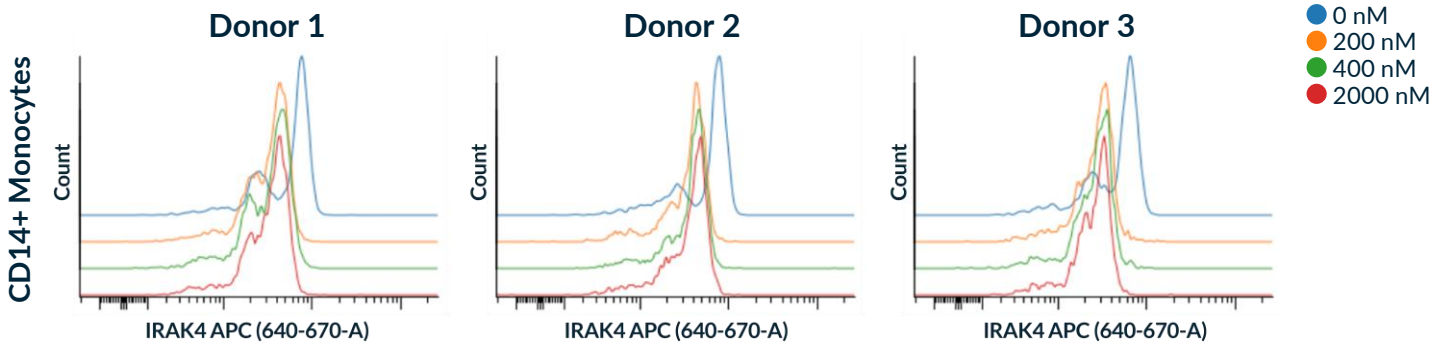
Objective: **Detect IRAK4 levels in circulating lymphocyte subsets and monocytes in whole blood**

Flow Immune Panel

CD14+: Monocytes
CD16CD56+: NK cells
CD19+: B cells
CD3+: T cells (total)
CD4+: T helper cells
CD8+: Cytotoxic T cells
IRAK4

Assay Parameters	Final Recommendation
Anti-coagulant	Na Heparin
Shipping conditions	Ship @ 4C within 30 minutes of draw

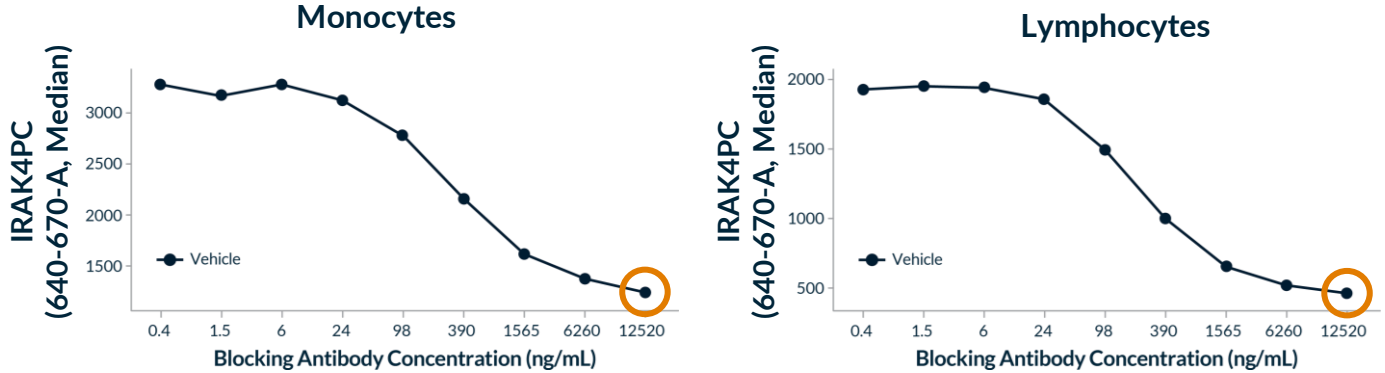
Equal Degradation of KT-474 at 200, 400 and 2000nM



Results from this study helped determine ex-vivo treatment conditions in NI trial

- KT-474 at 200nM for 24 hours

Blocking Control to Determine Floor of Assay



Stain immune panel with IRAK4 +/- Blocking control concentration pre-determined in optimization experiments

Developing MS Method in Isolated Healthy Donor PBMCs

Phase 1 blood draw limitations prevented a separate sample collection for MS

- Solution: retain cell layer after PK plasma collection & process within 4 hours

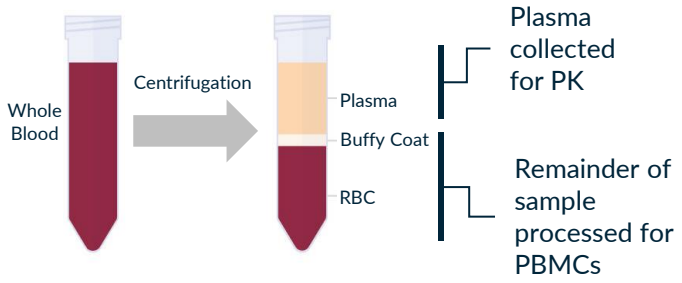
On site processing could not be performed immediately after blood draw

- Pilot study confirmed no loss of IRAK4 from 0-4 hrs. post collection
- KT-474 ex-vivo treatment of donor blood confirmed that PD can be measured

Comparison of IRAK4 levels in donor PBMCs to healthy donor tissue

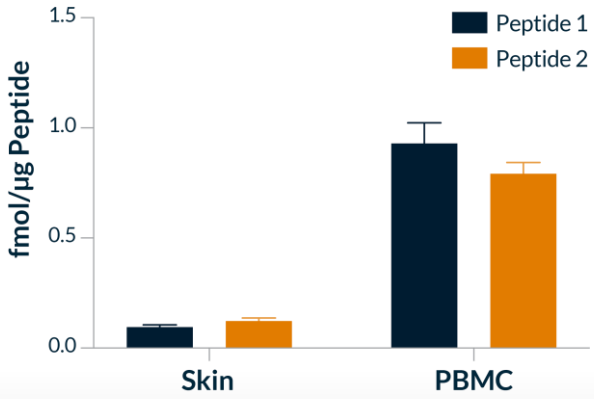
- PBMC expression levels are higher than human skin

Proposed Clinical Process



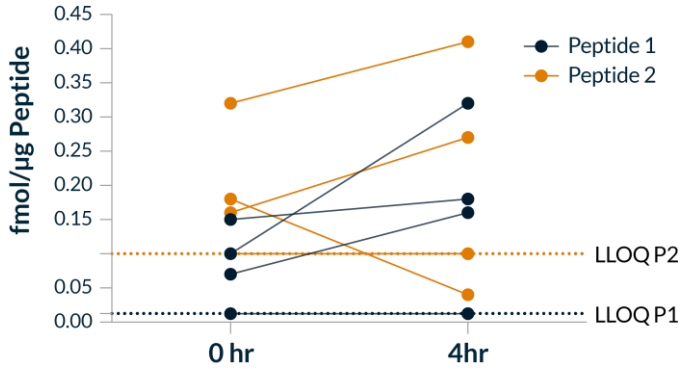
Measurements of Donor Tissue and Blood

IRAK4 Expression in Skin vs PBMC

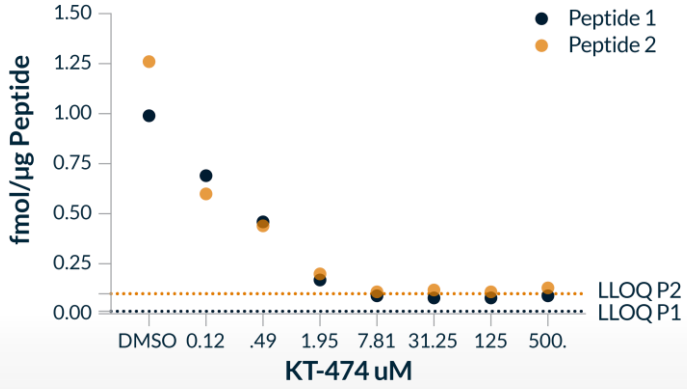


Pilot Mimicking Clinical Process with Donor Blood

Comparison IRAK4 Levels Post Draw



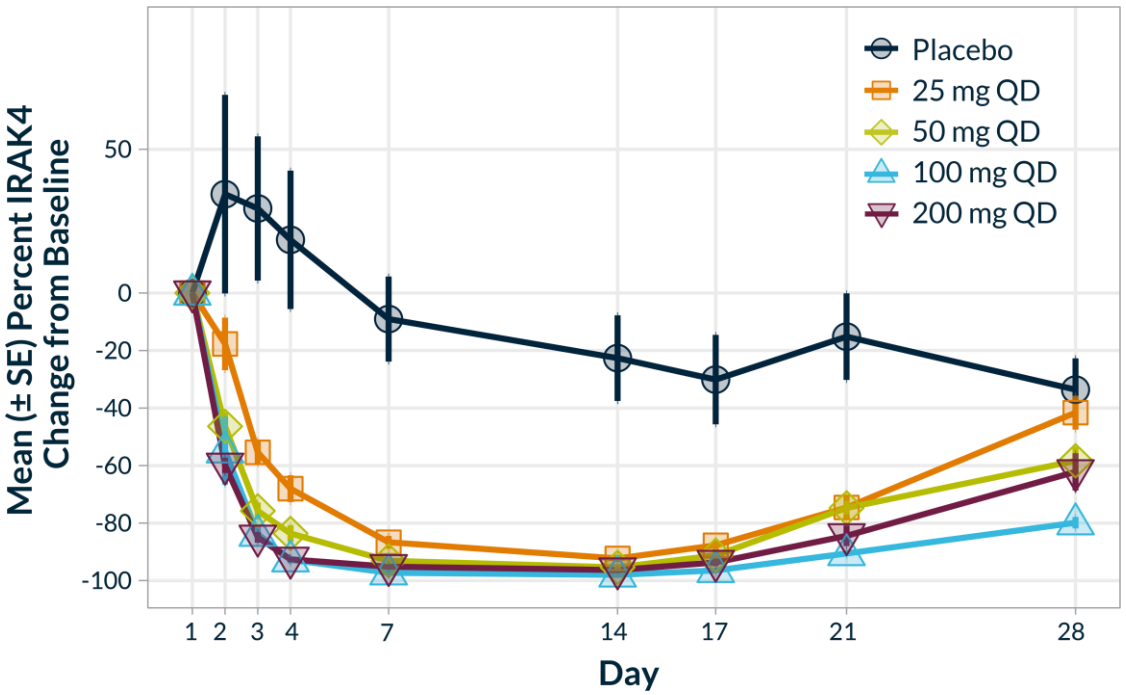
IRAK4 KD in PBMCs Isolated after Ex Vivo Treatment of Whole Blood with KT-474



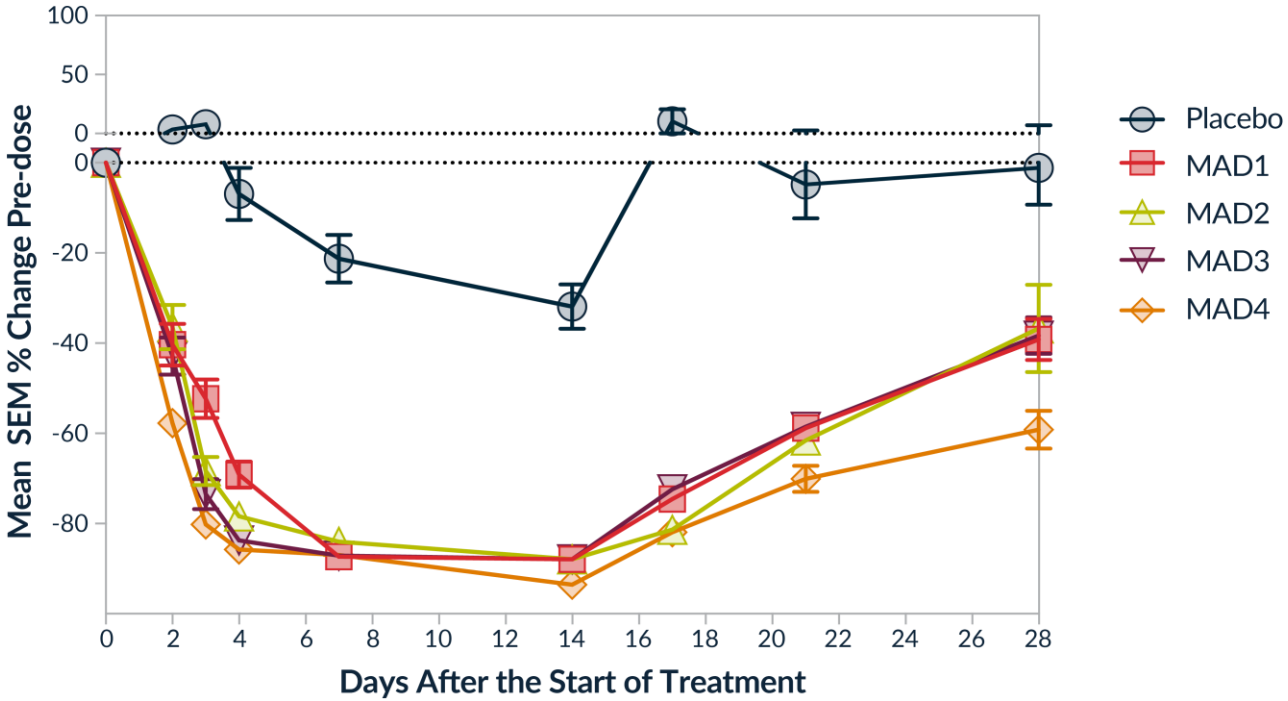
POM by MS and FLOW in KT-474 Phase 1 MAD Cohorts: Orthogonal Methods for Demonstrating IRAK4 Degradation in PBMC

Phase1 MAD dosing period: QD Day 1-14

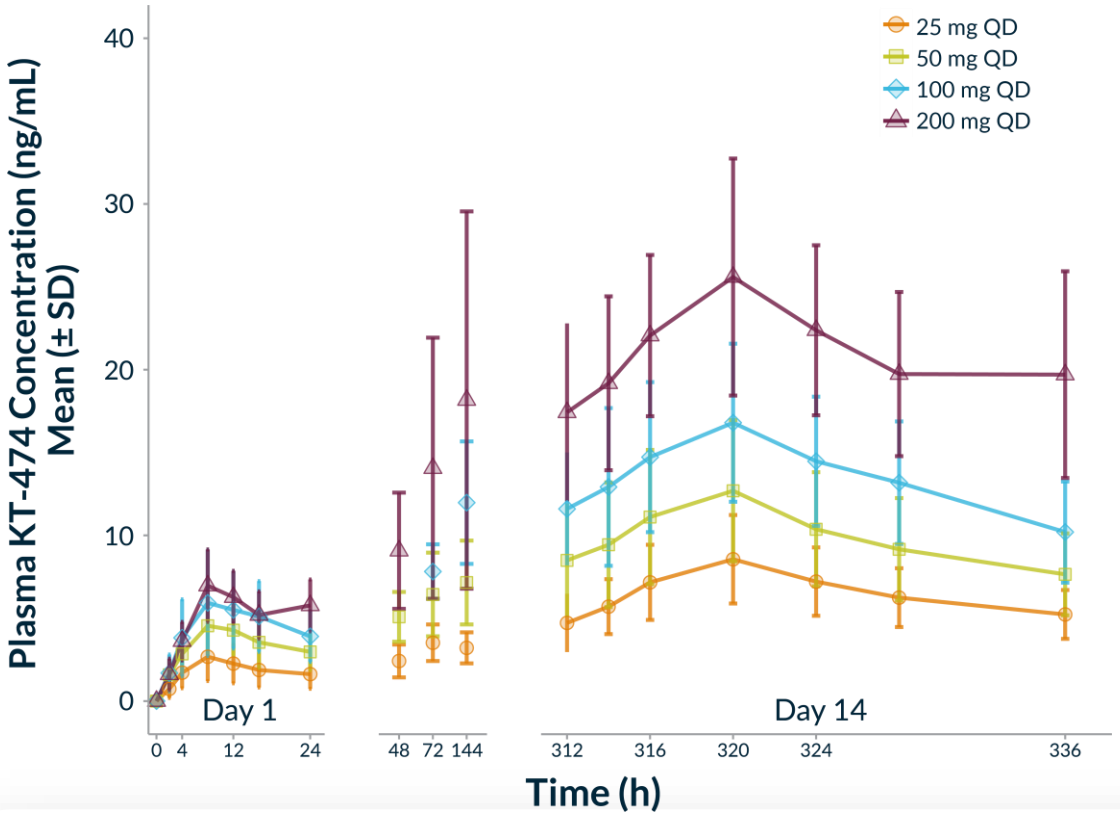
Mass Spec on Isolated PBMCs



FLOW on PBMCs in Whole Blood



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)

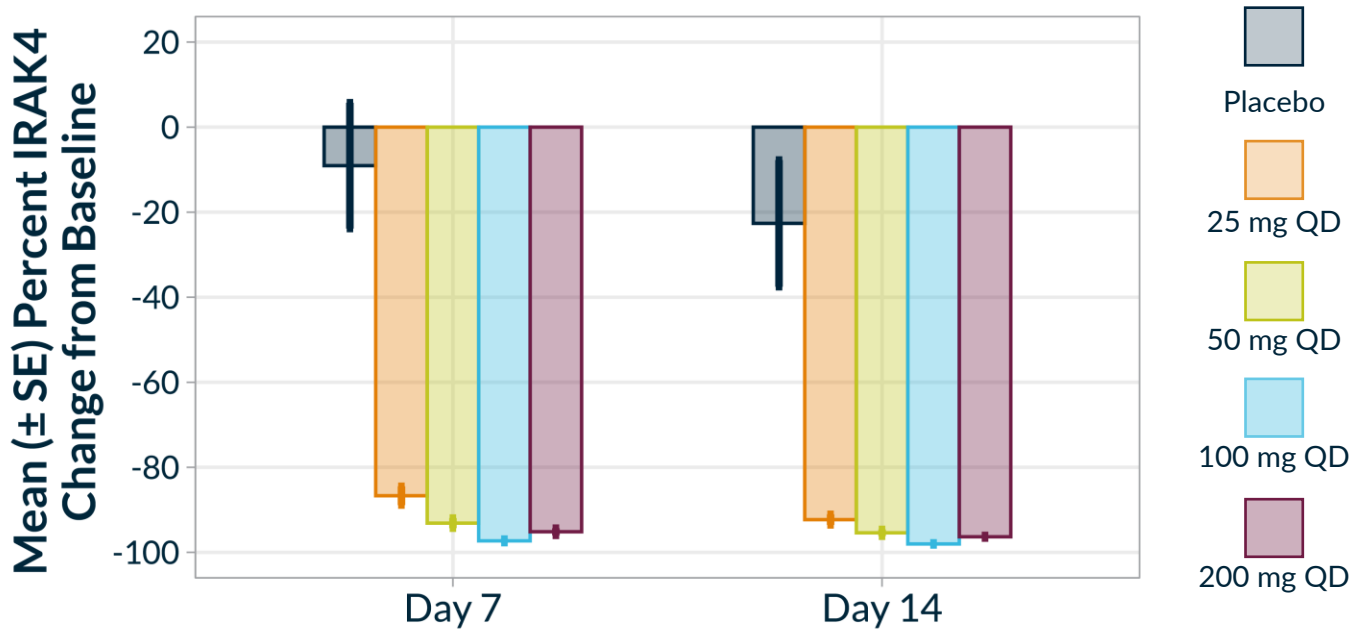
Geometric Mean (%CV) reported for all parameters, except t_{max} where median(range) are presented
Accumulation Ratio represents fold change in exposure from Day 1 to Day 14

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

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



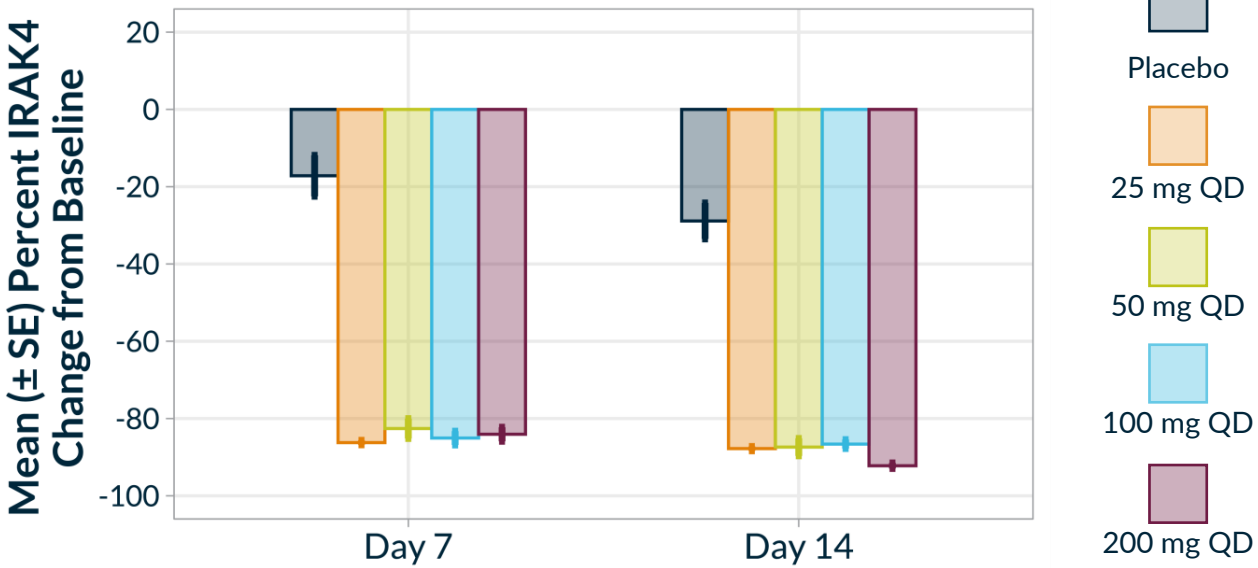
	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
*p value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

* p-values relative to placebo

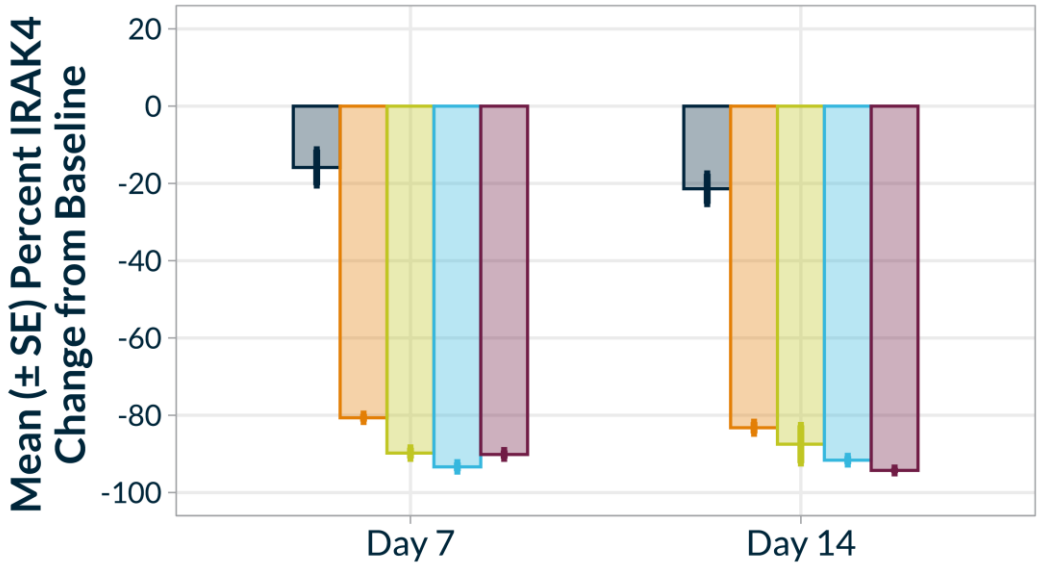
KT-474 Achieved >90% Degradation in Monocytes at ≥ 100 mg (FLOW)

Maximal Degradation in Monocytes in MAD4/200mg at Day 14

Percent IRAK4 Reduction in Lymphocytes



Percent IRAK4 Reduction in Monocytes



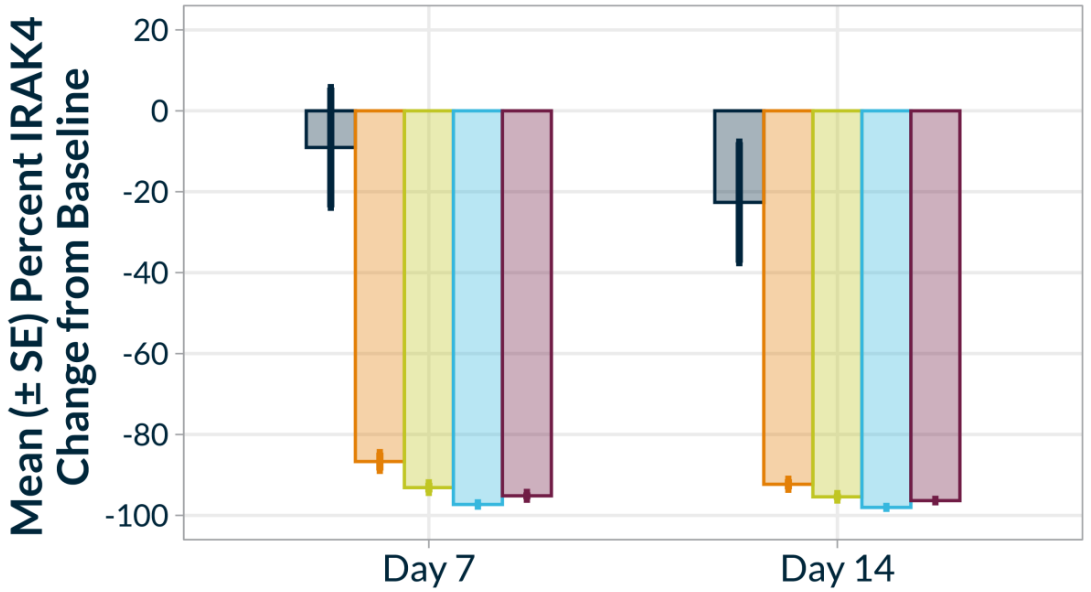
	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-17%	-86%	-83%	-85%	-84%
Mean Day 14	-29%	-88%	-87%	-87%	-92%
*p-value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

	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	-16%	-81%	-90%	-93%	-90%
Mean Day 14	-21%	-83%	-87%	-92%	-94%
*p-value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

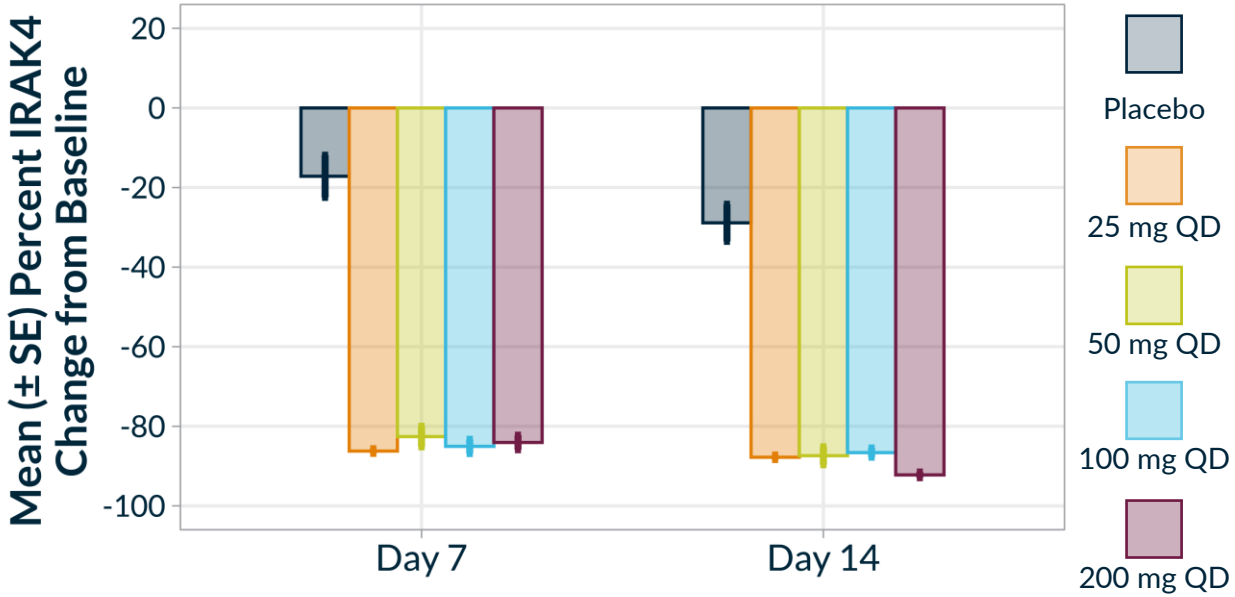
* p-values relative to placebo

KT-474 Lead to Maximum KD of IRAK4 at Day 14 Observed in both Mass Spectrometry and FLOW

Percent IRAK4 Reduction in PBMC by Mass Spectrometry



Percent IRAK4 Reduction in PBMCs by FLOW

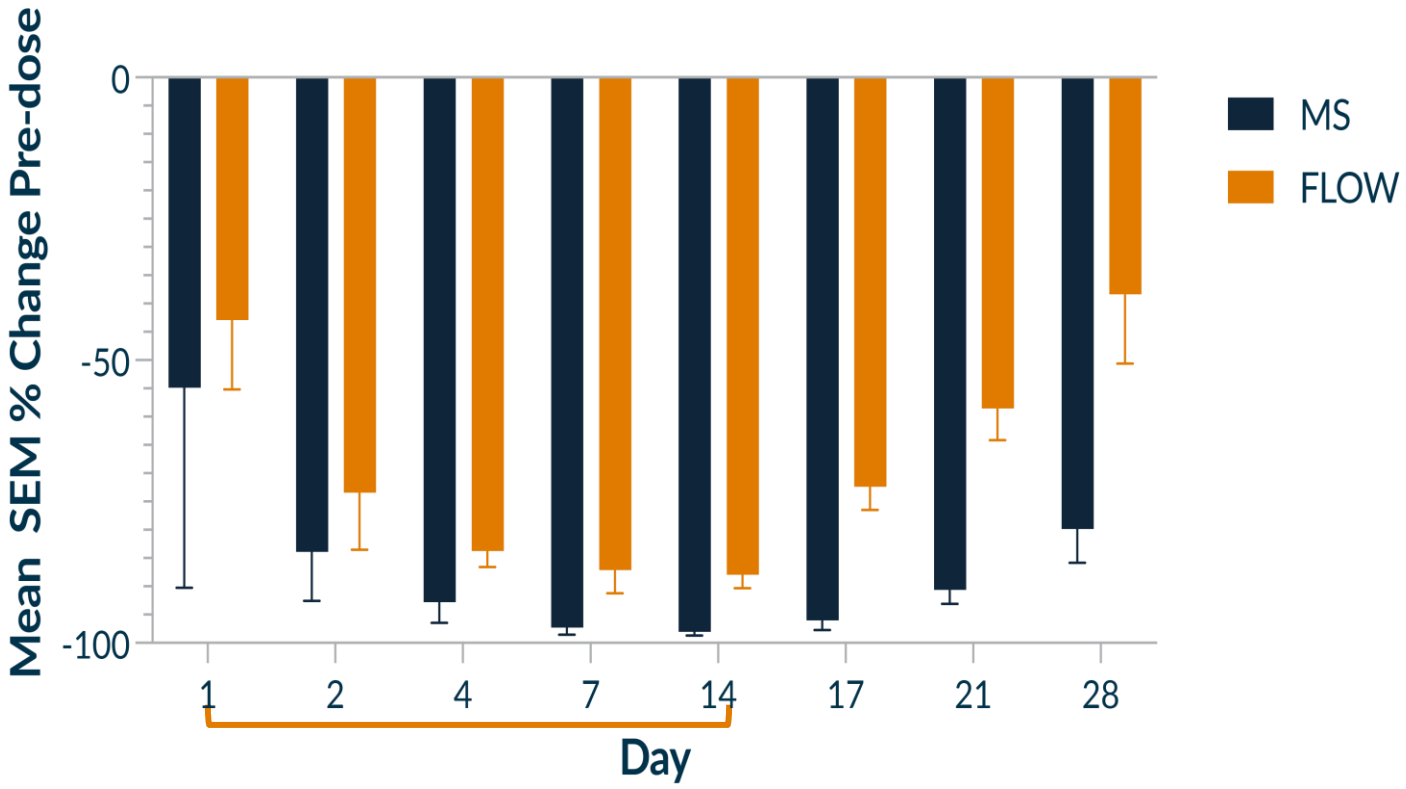


MS	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
*p value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

FLOW	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	-17%	-87%	-84%	-87%	-87%
Mean Day 14	-29%	-88%	-88%	-88%	-94%
*p-value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

Correlation MS to FLOW in MAD Cohorts Exhibits XX Correlation

MAD3 FL vs MS



VISIT	R Value % Change FLOW and MS
Day 2 Post-dose 24 Hours	0.418
Day 3 Post-dose 48 Hours	0.719
Day 4 Post-dose 72 Hours	0.697
Day 7 Post-dose 144 Hours	0.801
Day 14 Post-dose 312 Hours	0.725
Day 17 Post-dose Follow-up	0.618
Day 21 Post-dose Follow-up	0.689
Day 28 Post-dose Follow-up	0.244

Detection of IRAK4 Degradation in Skin

IRAK4 Detection Method Development in Skin

Detection & Knock Down in Treated Samples

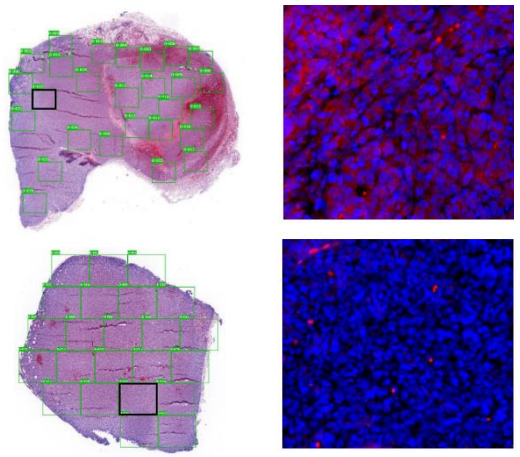
Detection In Healthy & Inflamed Tissues

Immunofluorescence

Xenograft DLBCL Tumors Treated with IRAK4 Degrader

Untreated

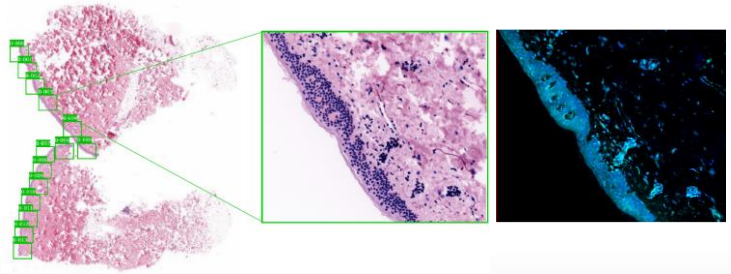
Treated



Dapi
IRAK4

Banked Tissues

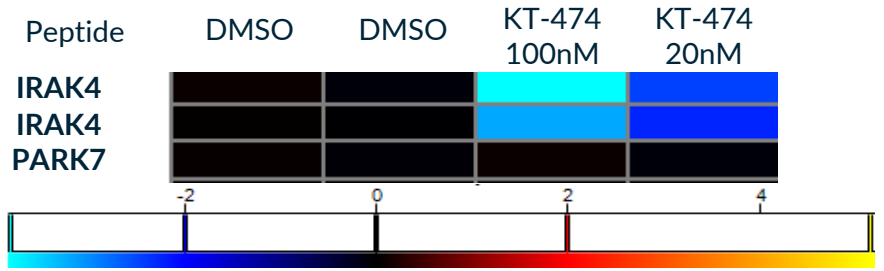
Healthy Skin



Dapi
IRAK4

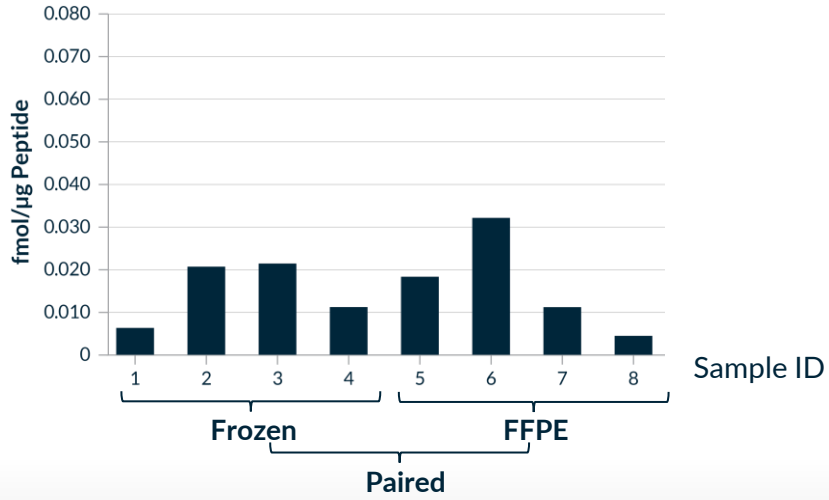
Mass Spec

Treated FFPE DLBCL Xenografts



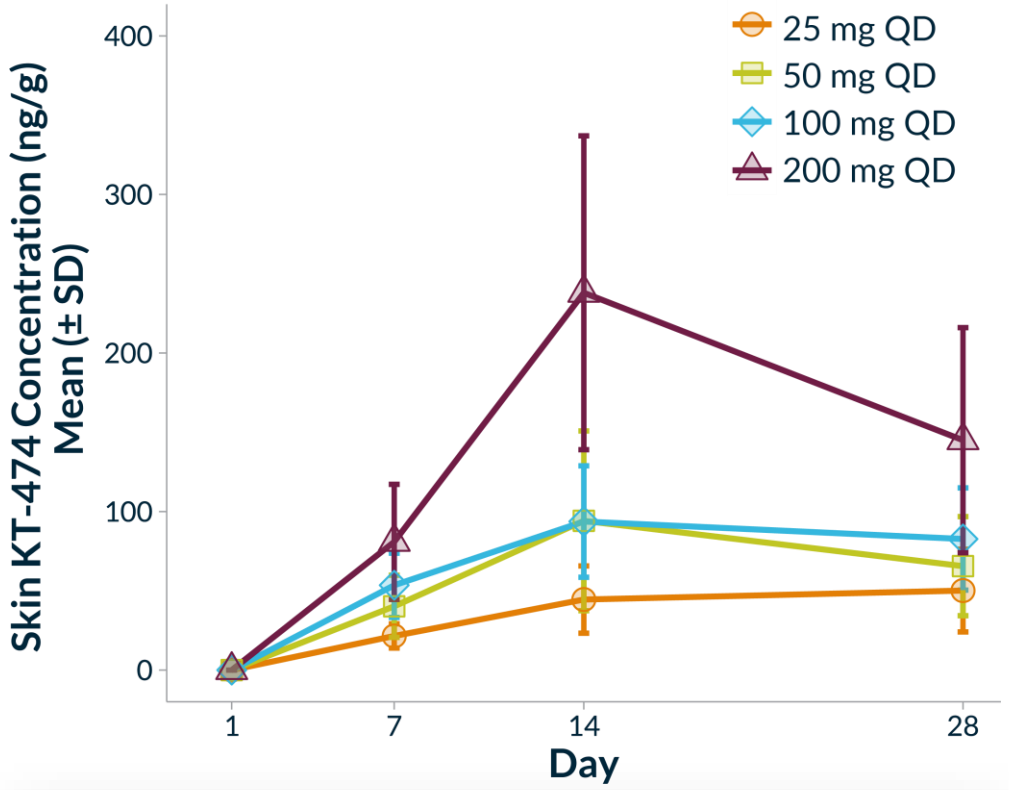
Log 2 fold change over DMSO

Banked HV Skin: IRAK4 Absolute Quantities



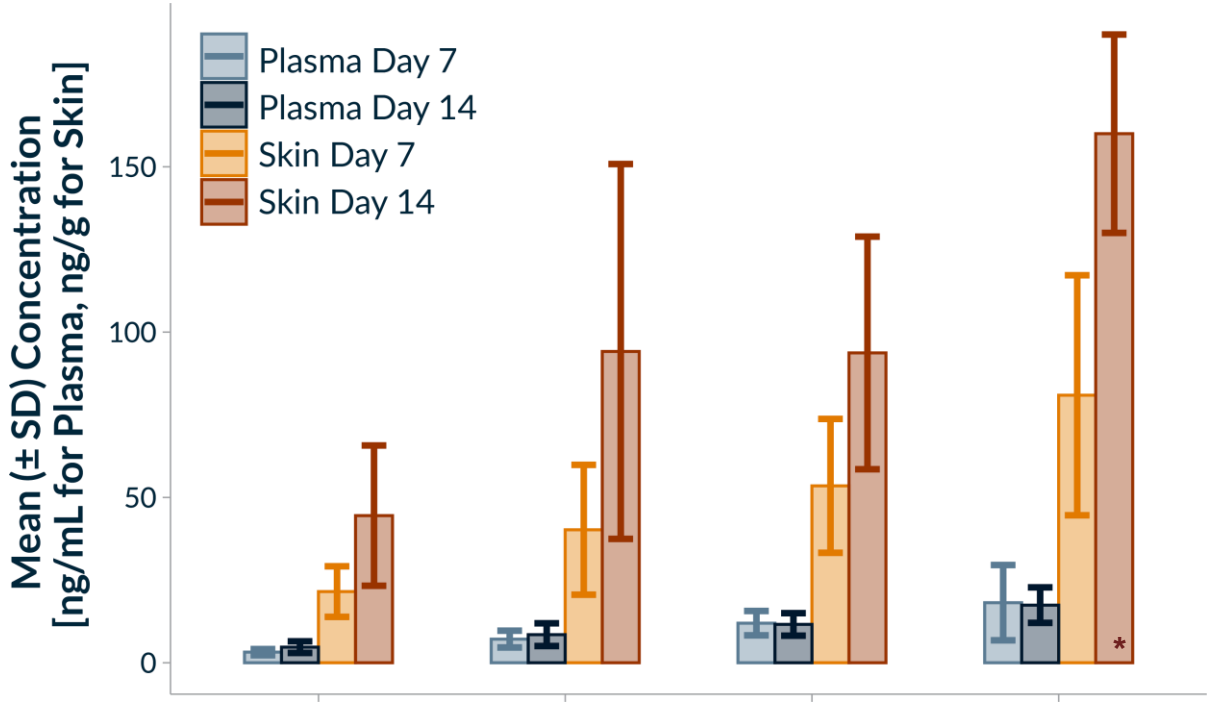
Once Daily Dosing Resulted in High Skin Exposures Exceeding Plasma

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}

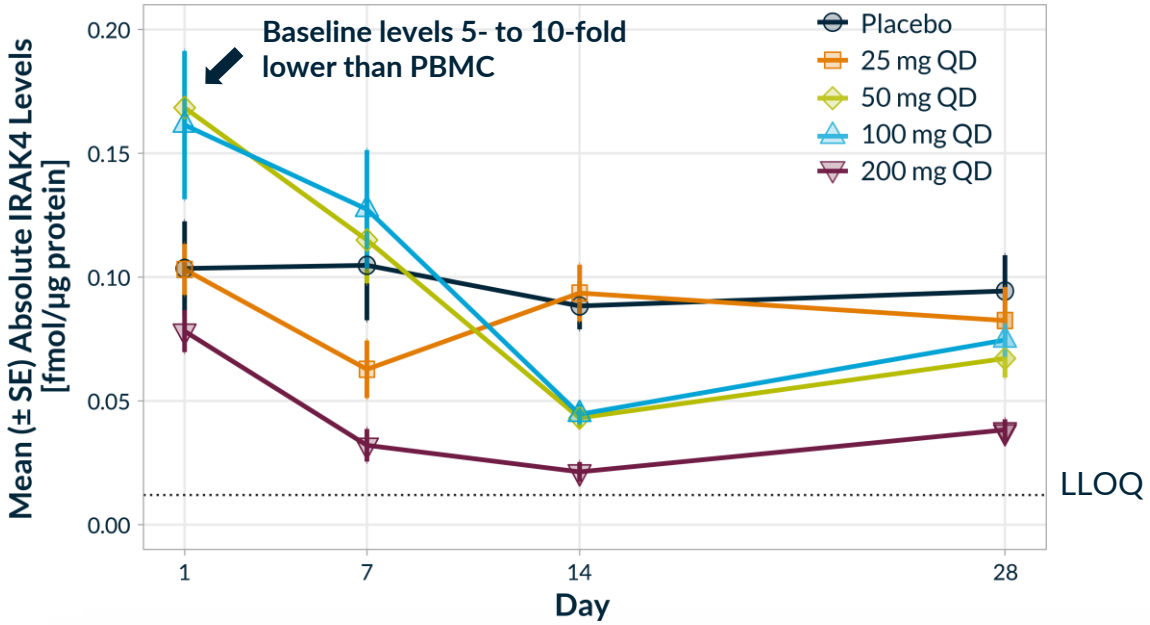


ng/mL (plasma) ng/g (skin)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Plasma Day 7	3.21	7.15	11.9	18.2
Plasma Day 14	4.72	8.49	11.6	17.4
Skin Day 7	21.5	40.2	53.5	80.9
Skin Day 14	44.5	94.2	93.7	238

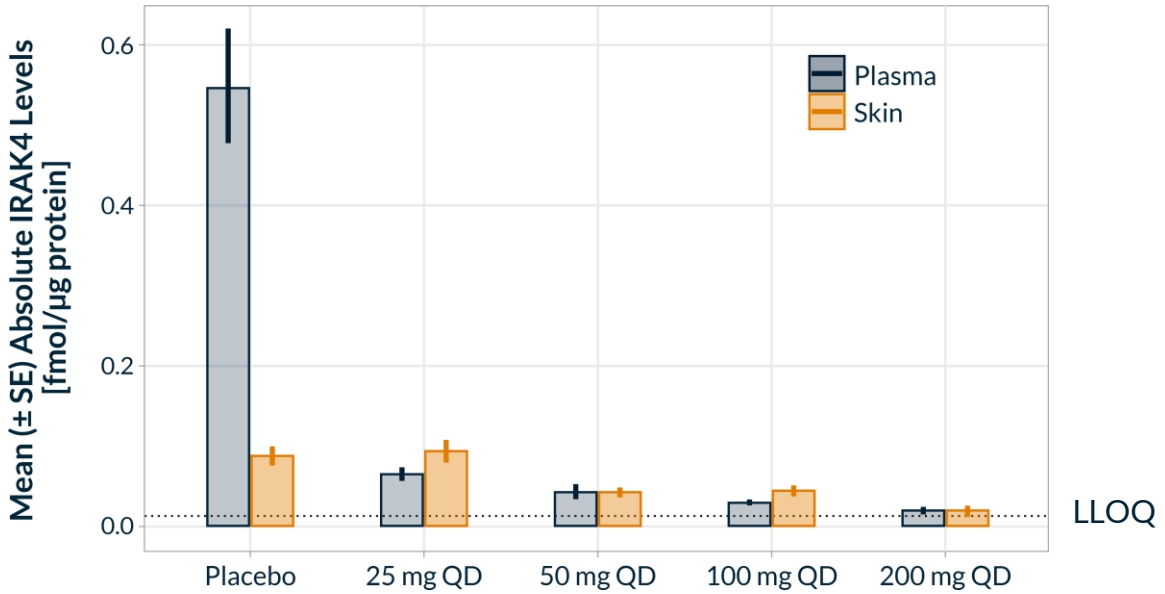
C_{trough} concentrations shown for Days 1, 7 and 14.

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

Absolute IRAK4 Levels in Skin

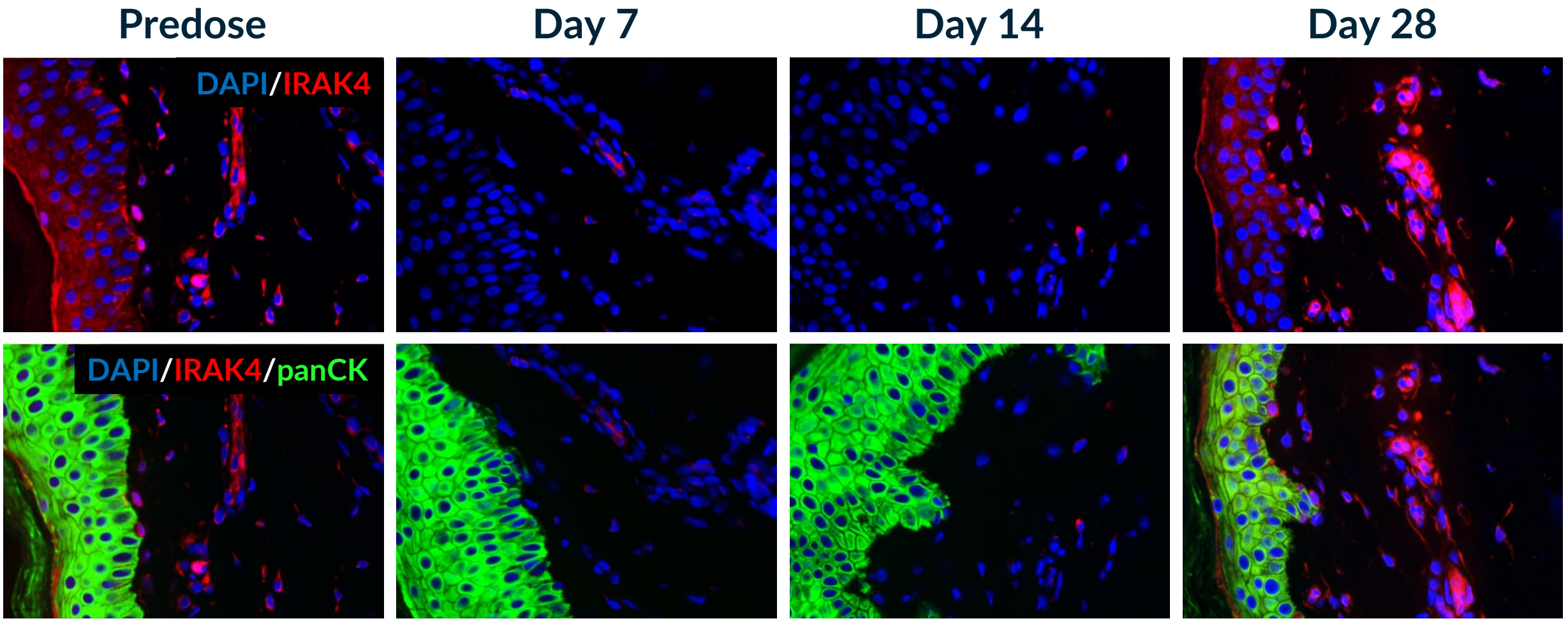


IRAK4 Levels in Skin vs PBMC at Day 14 of KT-474 treatment



- 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

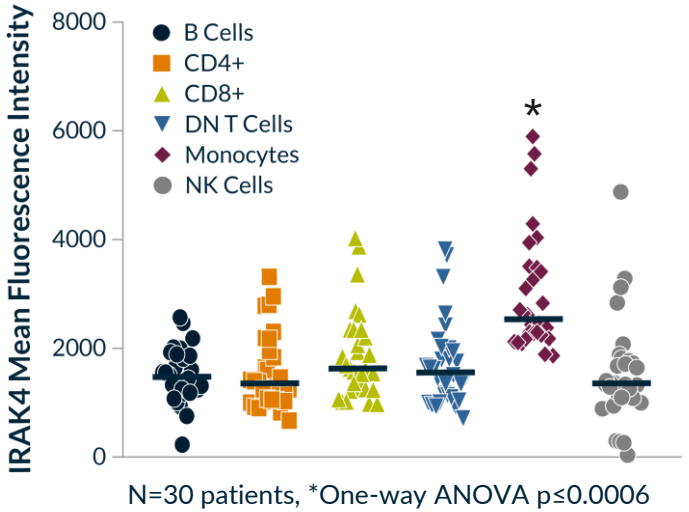
IRAK4 Localization and Subsequent Degradation Observed in Skin of Healthy Volunteers treated with KT-474



Feasibility to Detect IRAK4 Degradation in Patient Samples

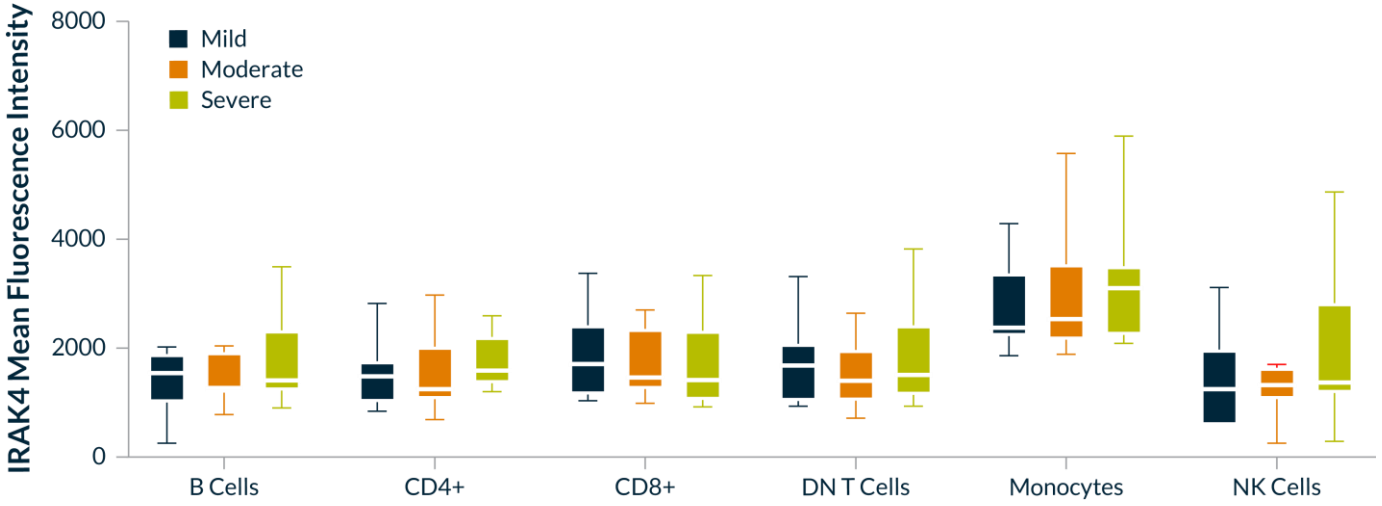
FLOW Assay Defined Baseline IRAK4 Expression in Immune Cells from HS Patients

IRAK4 Expression in Blood Immune Cells



N=30 patients, *One-way ANOVA p≤0.0006

IRAK4 Expression in Blood Immune Cells by HS Disease Severity (IHS4)



- IRAK4 levels detected in circulating cells from HS patients
- Monocytes express IRAK4 at significantly higher levels compared to other immune subsets

- IRAK4 levels remain the same in patients across disease severity (same results obtained with HS-PGA and Hurley (Max) staging), with a trend of higher IRAK4 median expression in patients with more severe disease

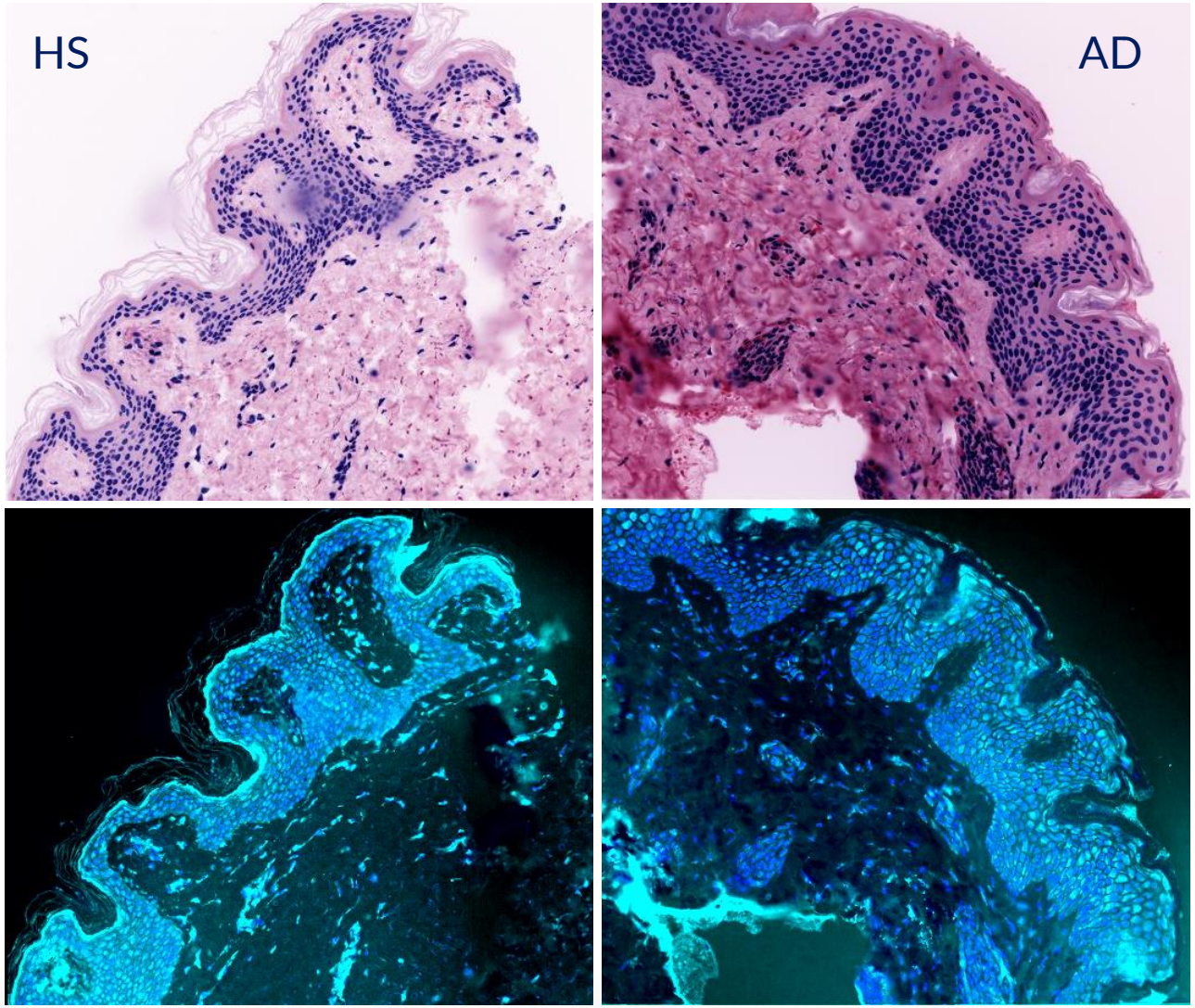
IF: IRAK4 Expression is Detectable in Lesions from HS and AD Skin Biopsies

Histology

H&E

IF Stain

Nuclear IRAK4



Data presented @ SID May 2021

Summary KT-474 Pharmacodynamic Assays

- Multiple methodologies were developed to measure on-target knock down of IRAK 4 degraders in blood and tissue
- Successful implementation of pharmacodynamic assays in the healthy volunteer portion of the study demonstrating POM in blood and skin
  - Blood assays (MS and FLOW) had a high correlation with MS measuring greater degree of degradation compared to FLOW
  - Skin assays (MS and IF) were comparable with MS measuring greater degree
- Baseline evaluation of IRAK4 levels in blood and skin lesion samples from subjects with hidradenitis suppurativa have been established with PD assays
- Plans to apply these assays to blood and skin samples from HS and AD patients in recently completed Phase 1 patient cohort

KYMERA

Thank You!

*This work was done under collaboration agreement with Sanofi