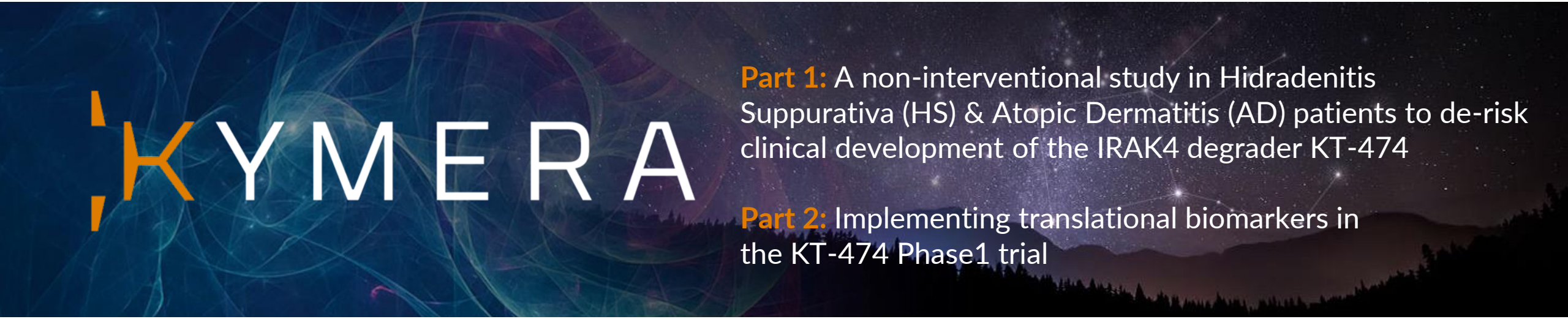
4th Annual TPD Targeted Protein Degradation

KYMERA EST. 2016

TPD Workshop C:
De-risking Clinical Development of a Novel Protein Degrader

Alice McDonald



Part 1: A non-interventional study in Hidradenitis Suppurativa (HS) & Atopic Dermatitis (AD) patients to de-risk clinical development of the IRAK4 degrader KT-474

Part 2: Implementing translational biomarkers in the KT-474 Phase1 trial

Workshop Agenda & Goals

INTRODUCTION to Kymera and IRAK4 TPD program – 8:30-8:40

PART1 8:40-9:10

- Summarize the non-interventional (NI) study and biomarker end points
  - **Discussion topics:** Other opportunities / experiences from participants
- Define IRAK4 baseline expression levels and localization
  - **Discussion topics:** Gaining support for both qualitative and quantitative assays
- Establish KT-474 degrader Proof of Mechanism (PoM) ex vivo
  - **Discussion topics:** Assessing assay dynamic range and defining values for samples < LLOQ
- Demonstrate how the NI study supported IRAK4 biological Proof of Concept (PoC) in HS
  - **Discussion topics:** Considerations moving from pre-clinical PoC into the clinic

PART 1 Discussion: 9:10-9:25

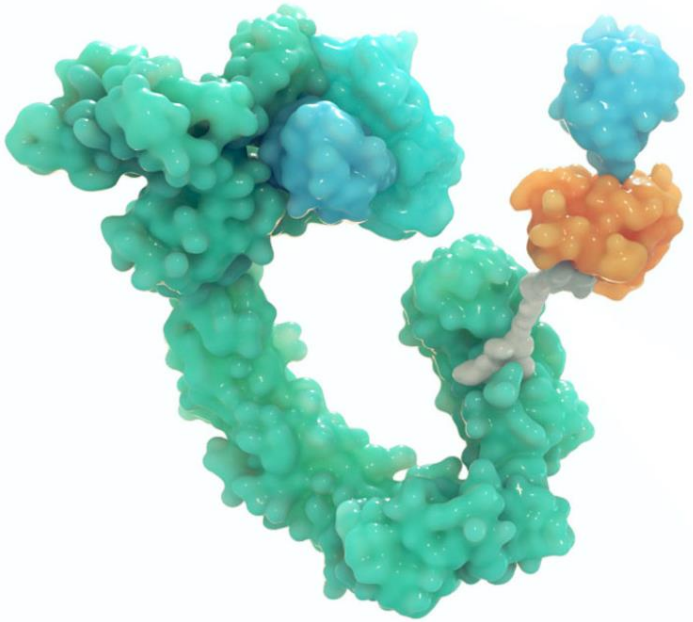
BREAK: 9:25-9:35

PART2 9:35-10:05

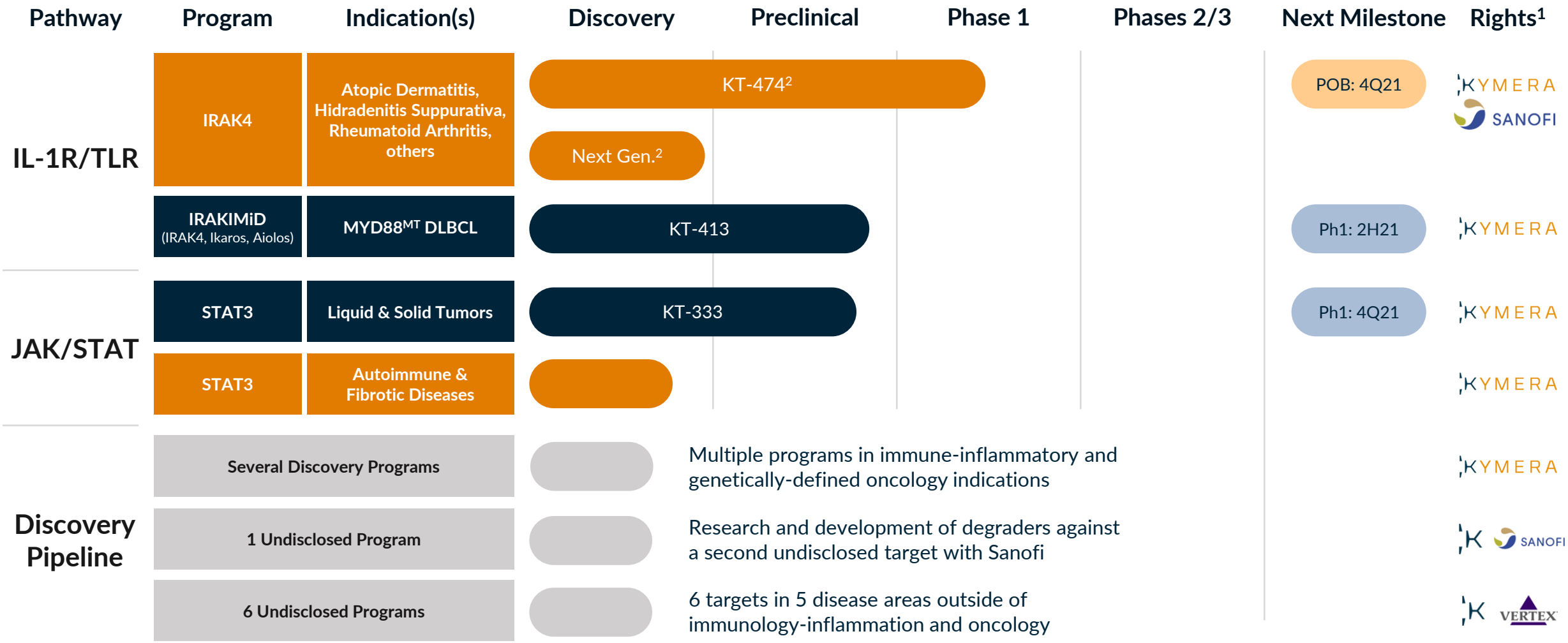
- Introduce KT-474 Phase1 study and exploratory endpoints
  - **Discussion topics:** Secondary vs exploratory endpoints for translational assays
- Demonstrate successful implementation of KT-474 Phase 1 PD assays
  - **Discussion topics:** Additional methods for monitoring proof of degradation
- Present additional KT-474 Phase 1 PD assays not evaluated in NI Study
  - **Discussion topics:** High level considerations when implementing translational biomarkers in clinical studies

PART2 Discussion 10:05-10:30

KYMERA



Kymera's Pipeline of Novel Protein Degraders

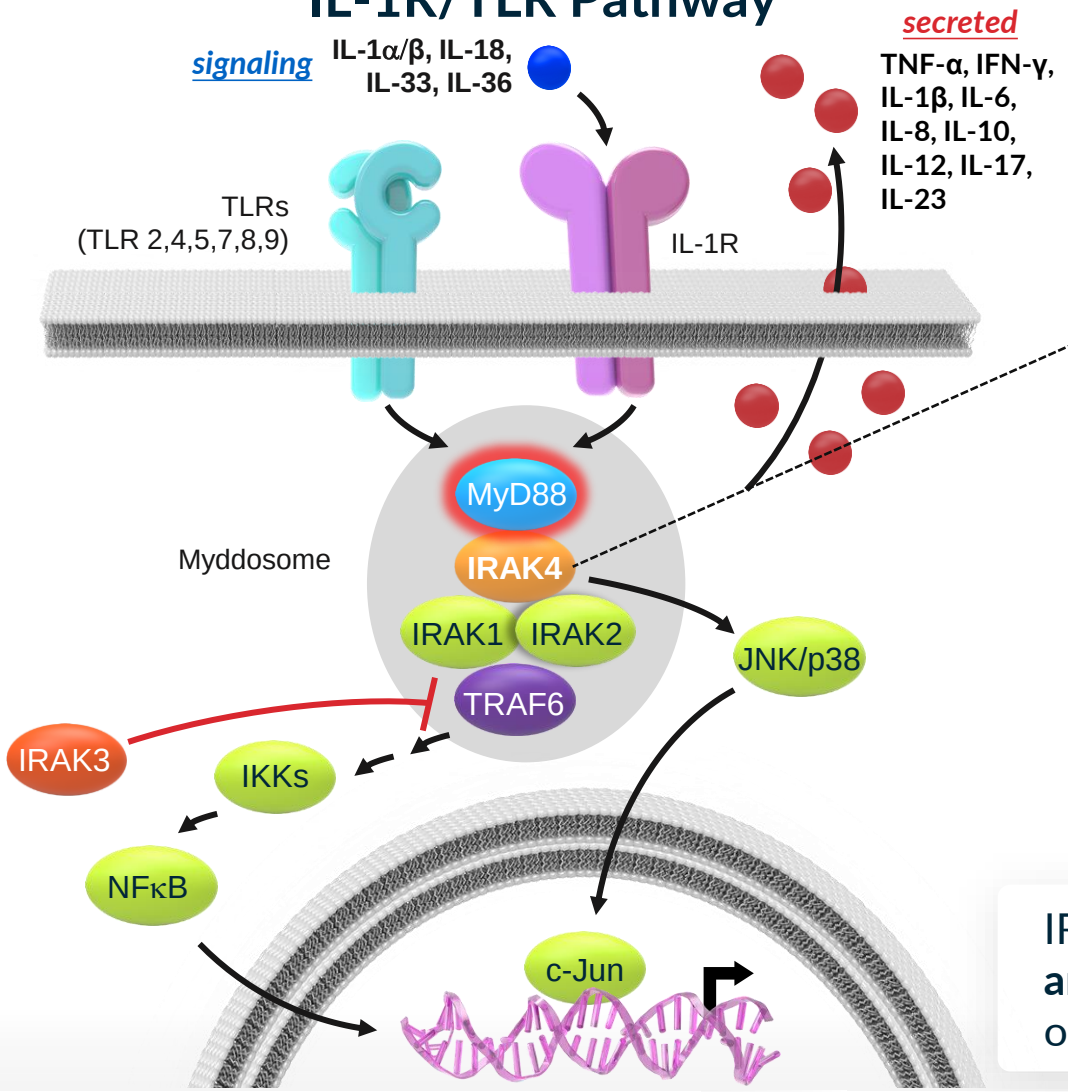


1. Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
2. Sanofi collaboration to develop IRAK4 degrader candidates, including KT-474 (SAR444656), outside of oncology and immuno-oncology fields.

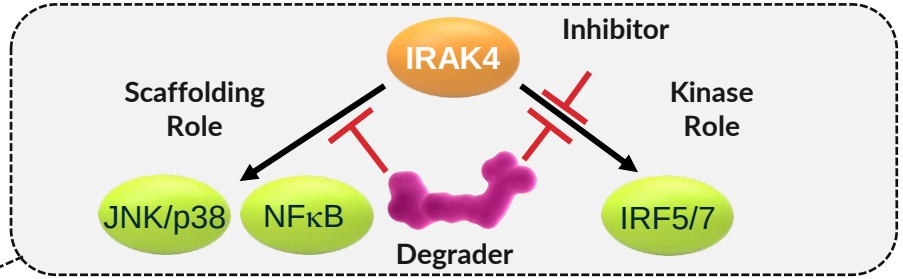
● = Oncology ● = Immunology-Inflammation

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
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

TPD Workshop C: De-risking Clinical Development of a Novel Protein Degrader

Part 1: A non-interventional study in Hidradenitis Suppurativa (HS) & Atopic Dermatitis (AD) patients to de-risk clinical development of the IRAK4 degrader KT-474

Non-interventional Study of IRAK4 and Inflammatory Biomarkers in HS and AD Patients

Design

Number of Sites	Single center (York Dermatology Clinic and Research Center, Ontario, Canada) PIs: Dr. Afsaneh Alavi, MD, MSch, FRCPC, Mayo Clinic Dr. Michael Cecchini, MD York Dermatology
Number of Patients	40 (30 HS and 10 AD)
Inclusion Criteria	1. Age 18 or older 2. Active Hidradenitis Suppurativa (HS) or Atopic Dermatitis (AD), diagnosed by PI 3. Mild, moderate, and severe HS (by IHS4 score) or AD (by EASI score) patients
Exclusion Criteria	1. Patients currently on a biologic or other immunosuppressive treatment for HS or AD 2. Use of biologic treatment for HS or AD within 3 months or 5 half-lives, whichever is longer 3. Use of non-biologic immunosuppressive treatment (e.g. Cyclosporin) in the last 4 weeks.
Data Collection at Study Entry	Medical history, disease severity in HS (Hurley, PGA, IHS4, HASI) and AD (EASI), prior treatments, comorbidities, duration of disease
Sample Collection	Whole blood, plasma, skin (Lesion [L], Peri-lesion [PL: <2 cm away from lesion], Non-lesion [NL: >10 cm away from lesion])

Baseline Demographics & Biomarkers

Study Duration	• FPI: 28May2020 • Completed: 24Mar2021
Patients Enrolled to Date	• 30 HS: 9 mild, 10 moderate, 11 severe • 10 AD: 8 mild, 1 moderate, 1 severe
Demographics	• Age 19-78 yrs. • 13 male, 27 Female • Duration of disease: 1-56 years • Race: 98% were non-Hispanic or Latino
Biomarker Endpoints	• **Targeted MS of IRAK4 in skin biopsies** • **IRAK4 immunofluorescence in skin biopsies** • **Proinflammatory gene transcripts in skin biopsies** • **Flow cytometry for IRAK4 in ex vivo treated whole blood** • **Cytokines from *ex vivo* treated whole blood**
Reporting Status	• October 2020 SHSA Meeting: Interim data on IRAK4 expression in HS skin and blood • May 2021 SID Meeting: Complete HS skin dataset for IRAK4 protein and proinflammatory gene transcripts as well as healthy skin and monocyte controls

PART 1: De-Risking KT-474 Phase 1

Key Goals of Non-Interventional Study

Define IRAK4 expression and localization in skin of diseased patients & healthy subjects

- Provide understanding of baseline IRAK4 expression and localization among healthy and diseased patient skin biopsies

Measure IRAK4 knock down in PBMC following ex vivo treatment with degrader

- Establish degrader POM in patient samples

Assess immune biomarkers in HS & AD lesion and non-lesion skin biopsies

- Demonstrate biological PoC:
  - Expression pattern of proinflammatory genes
  - Correlation of proinflammatory gene expression with IRAK4 protein expression

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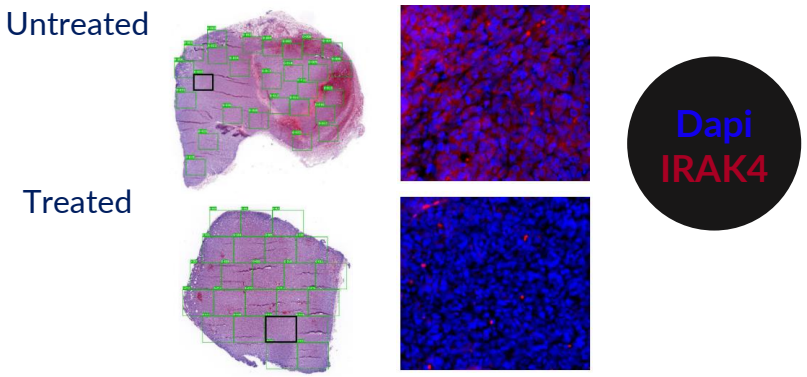
IRAK4 Detection Method Development in Skin

Detection & Knock Down in Treated Samples

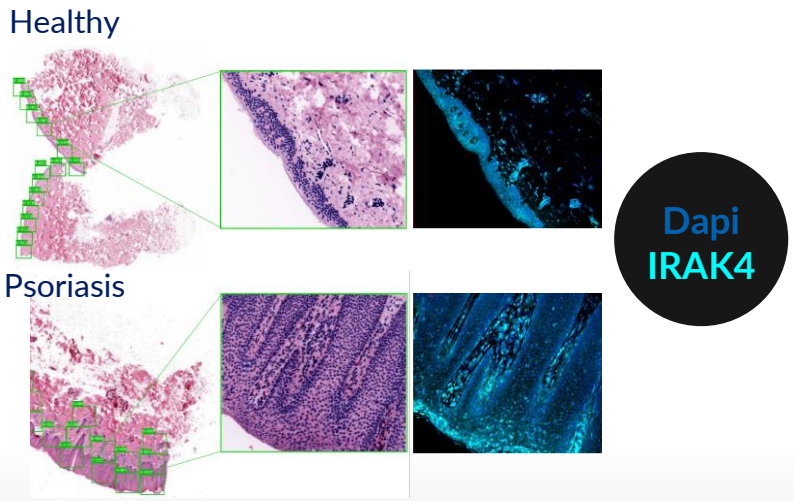
Detection In Healthy & Inflamed Tissues

Immunofluorescence

Xenograft Studies

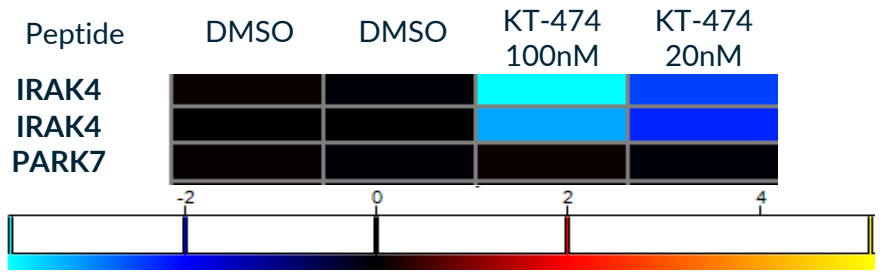


Banked Tissues

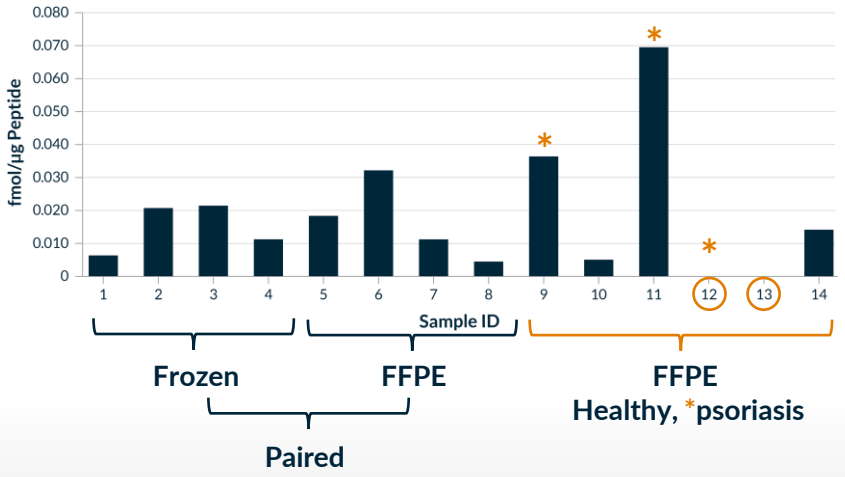


Mass Spec

Treated cells

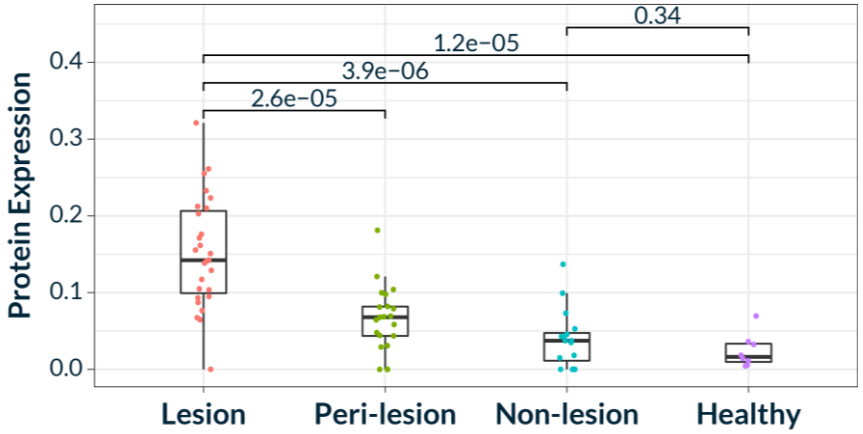


Banked Tissues: IRAK4 Absolute Quantities

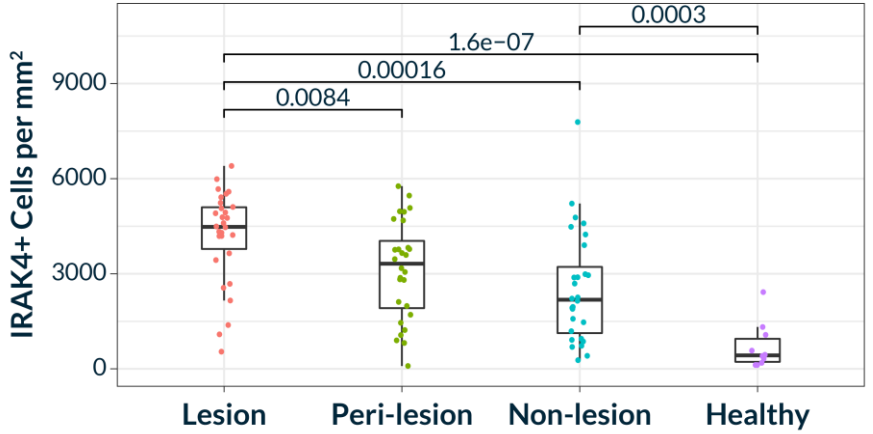


IRAK4 Protein Expression is Elevated in HS Skin Compared to Skin from Healthy Subjects

Mass Spectrometry (MS)



Immunofluorescence (IF)



Immunofluorescence (IF)

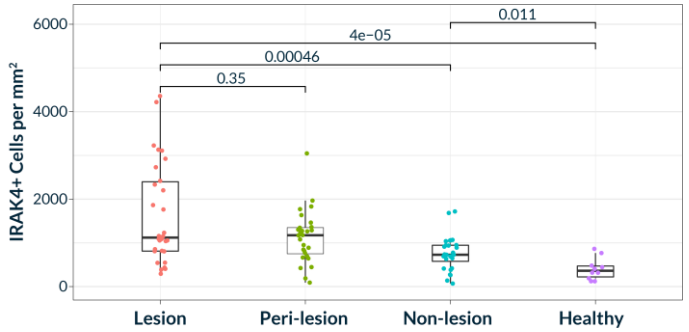
- Concordance between IF and MS for HS patients
- HS patients: Lesion > Peri-lesion > Non-lesion
- Significant difference between HS Non-lesion skin and Healthy subject skin

Similar expression across disease severity*

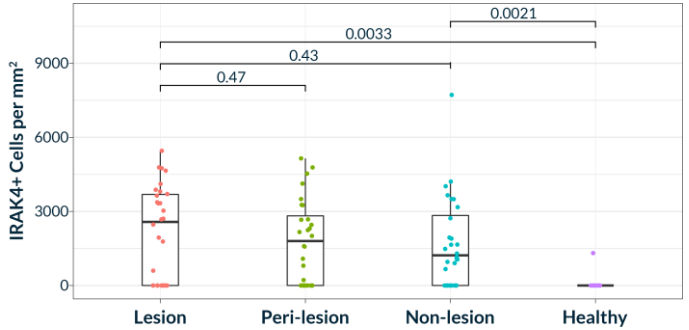
*By IHS4 severity score

IF: Localization of IRAK4 Expression in Skin

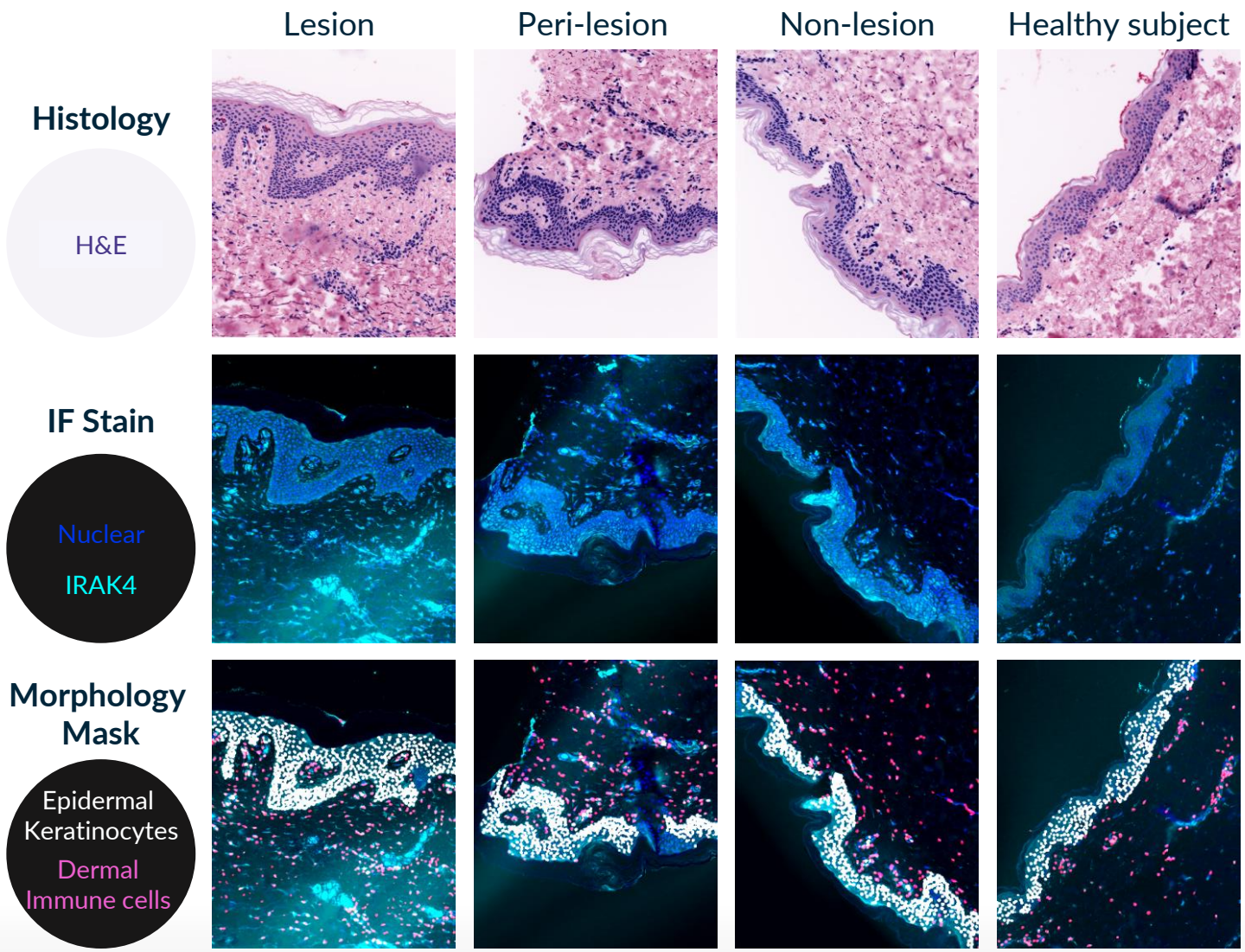
Dermal Immune Cells



Epidermal Keratinocytes



IF developed for use in PH1 skin biopsies to assess KT-474 knock down in dermal immune vs epidermal compartments of the skin



PART 1: De-Risking KT-474 Phase 1

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- Provide understanding of baseline IRAK4 expression and localization among healthy and diseased patient skin biopsies

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- Demonstrate biological PoC:
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Biomarker Endpoints

- **Targeted MS of IRAK4 in skin biopsies**
- **IRAK4 immunofluorescence in skin biopsies**
- **Proinflammatory gene transcripts in skin biopsies**
- **Flow cytometry for IRAK4 in ex vivo treated whole blood**

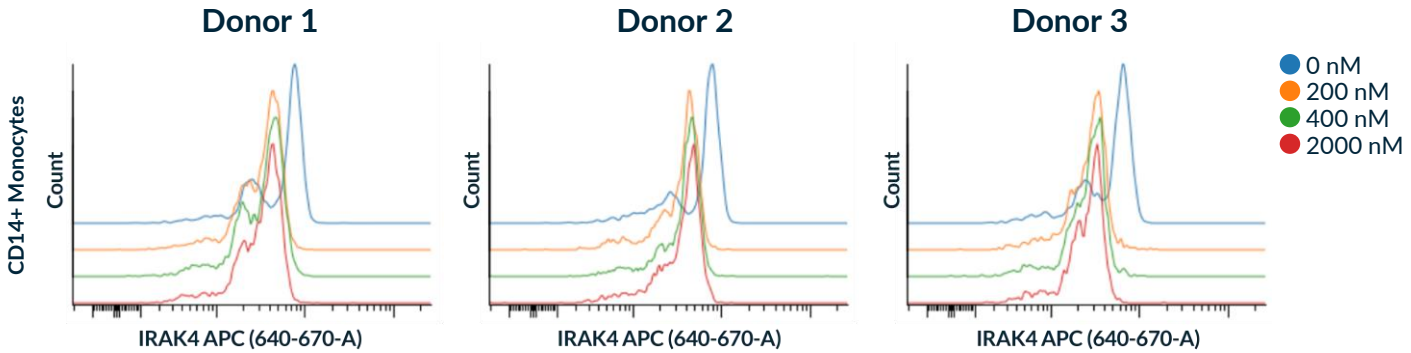
Method Development of IRAK4 Flow Assay in Blood from Healthy Donors

Objective: Detect IRAK4 levels in circulating lymphocyte subsets and monocytes

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

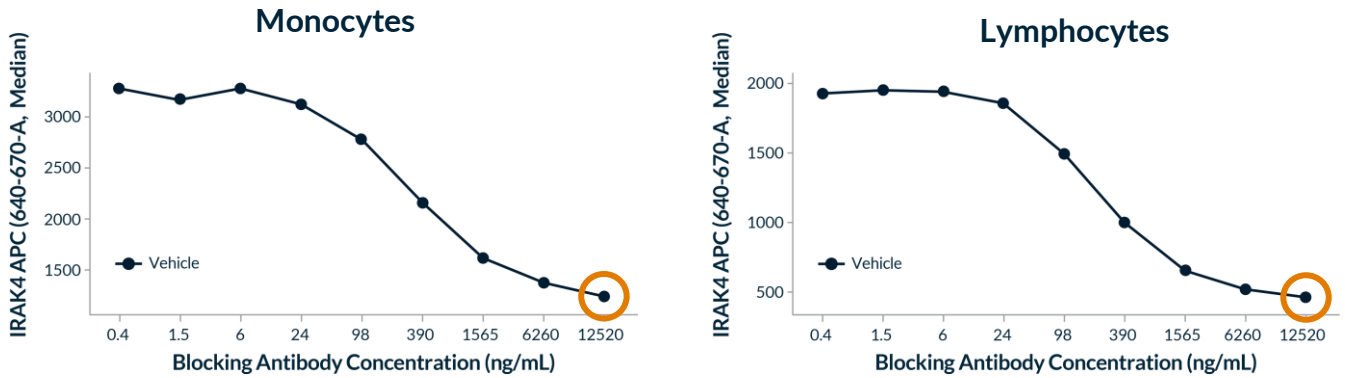
Assay Parameters	Final Recommendation
Anti-coagulant	Na Heparin
Shipping conditions	Ship @ 4C within 30 minutes of draw
Cell pellet stability	over 72 hours @-20
Cell stability @ -80C	Up to 28 days with no sign of degradation

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

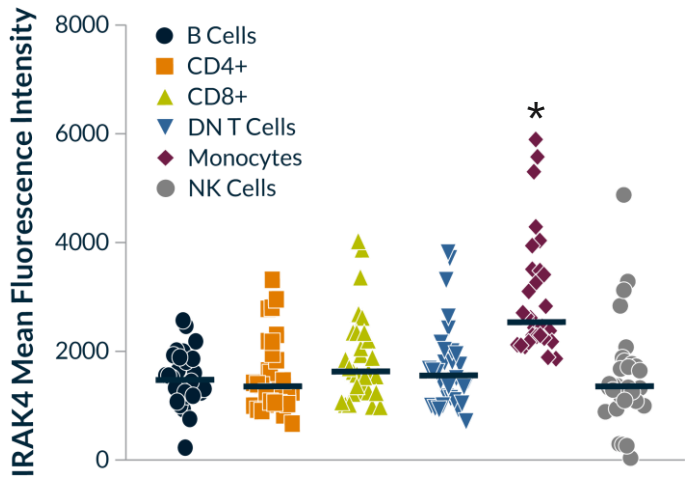
Blocking Control to Determine Floor of Assay



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

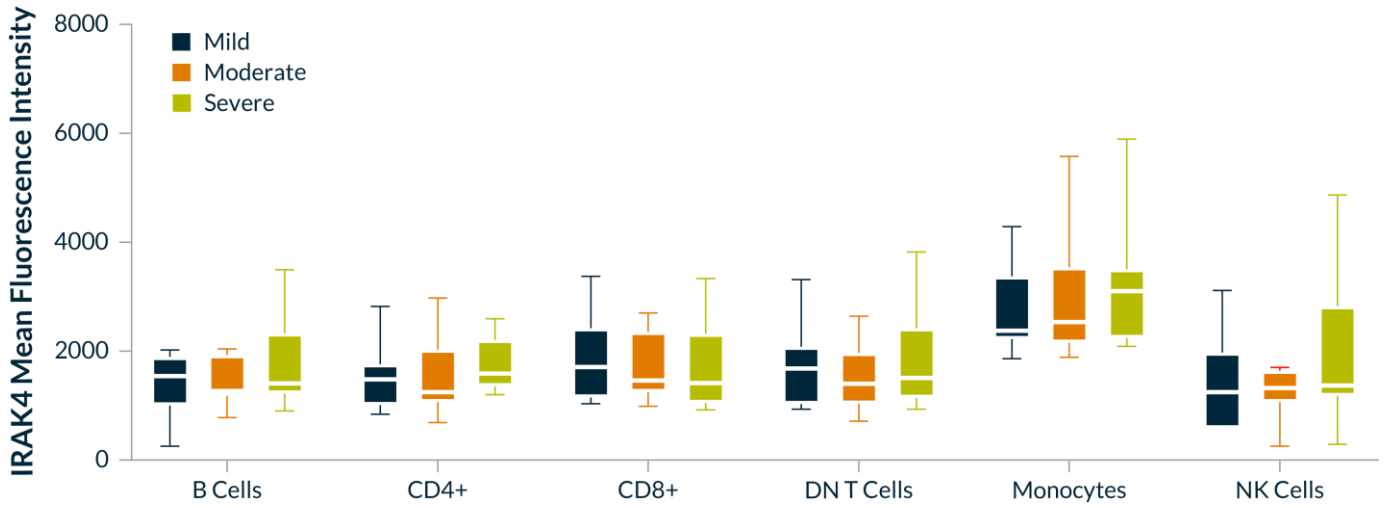
FLOW Assay Defined Baseline IRAK4 Expression in Immune Cells from HS Patients

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)



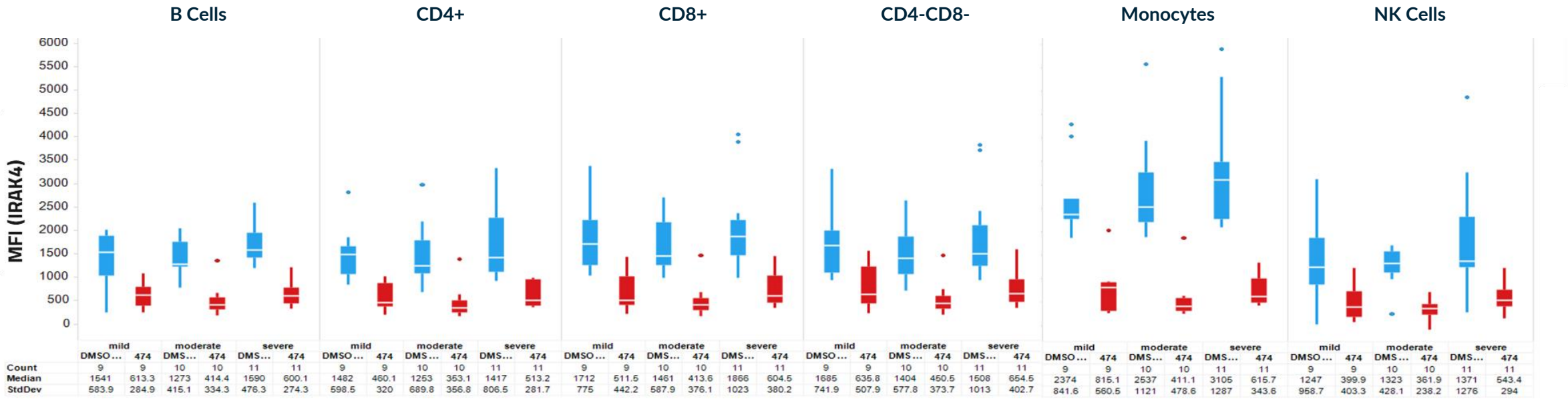
- IRAK4 levels detected in circulating cells from HS patients
- Monocytes express IRAK4 at significantly higher levels compared to other immune subsets

- 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

Ex-vivo Treatment of KT-474 Leads to IRAK4 Knockdown (POM)

IRAK4 Degradation is Similar Across Different Immune Subsets in HS Patients

DMSO (no block)
IRAK4 Degrader



	B Cells						CD4+					
	mild		moderate		severe		mild		moderate		severe	
	DMSO...	474	DMS...	474	DMS...	474	DMSO...	474	DMS...	474	DMS...	474
Count	9	9	10	10	11	11	9	9	10	10	11	11
Median	1541	613.3	1273	414.4	1590	600.1	1482	460.1	1253	353.1	1417	513.2
StdDev	583.9	284.9	415.1	334.3	476.3	274.3	598.5	320	689.8	356.8	806.5	281.7

	CD8+						CD4-CD8-					
	mild		moderate		severe		mild		moderate		severe	
	DMSO...	474	DMS...	474	DMS...	474	DMSO...	474	DMS...	474	DMS...	474
Count	9	9	10	10	11	11	9	9	10	10	11	11
Median	1712	511.5	1461	413.6	1866	604.5	1685	635.8	1404	450.5	1508	654.5
StdDev	775	442.2	587.9	376.1	1023	380.2	741.9	507.9	577.8	373.7	1013	402.7

	Monocytes						NK Cells					
	mild		moderate		severe		mild		moderate		severe	
	DMSO...	474	DMS...	474	DMS...	474	DMSO...	474	DMS...	474	DMS...	474
Count	9	9	10	10	11	11	9	9	10	10	11	11
Median	2374	815.1	2537	411.1	3105	615.7	1247	399.9	1323	361.9	1371	543.4
StdDev	841.6	560.5	1121	478.6	1287	343.6	958.7	403.3	428.1	238.2	1276	294

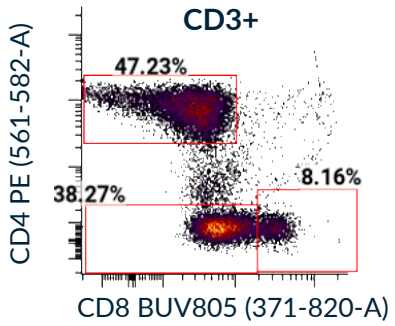
- Treatment with KT-474 leads to reduction of IRAK4 to a similar level across multiple immune subsets, regardless of baseline expression level or disease severity
- Up to an average of 80% ± 9% knockdown of IRAK4 was observed with ex vivo KT-474 treatment

Immunophenotyping Strategy with HS Patient Samples Led to 2nd Generation Panel Development for Phase I

1st Generation Panel:

CD14+/CD16CD56+/CD19+/CD3+/CD4+/CD8+

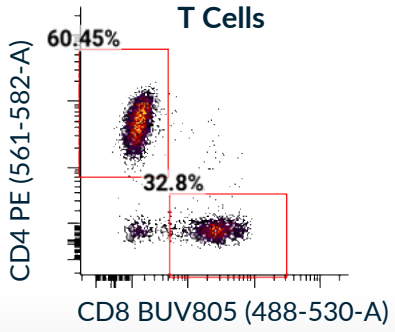
Resolution of T cell subsets was Suboptimal in patient samples



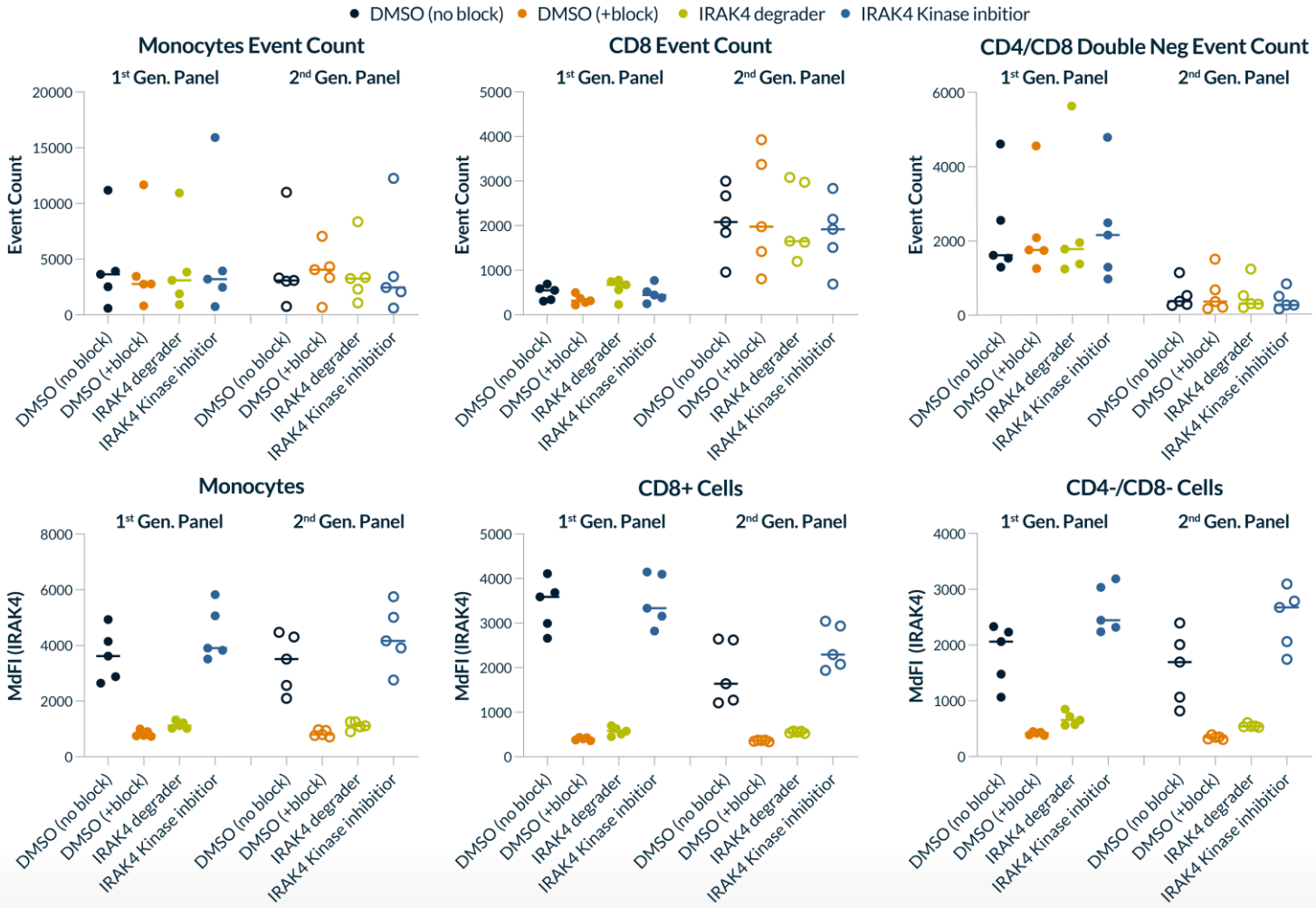
2nd Generation Panel:

CD45+/CD14+/CD16/CD56+/CD19+/CD3+/CD4+/CD8+

Improved identification of CD4+ and CD8+ cells



Increased Frequency of CD8+ Cells Led to a Decrease in IRAK4 MFI, and Less DN T cells



PART 1: De-Risking KT-474 Phase 1

Key Goals of Non-Interventional Study

Define IRAK4 expression and localization in skin of diseased patients & healthy subjects

- Provide understanding of baseline IRAK4 expression and localization among healthy and diseased patient skin biopsies

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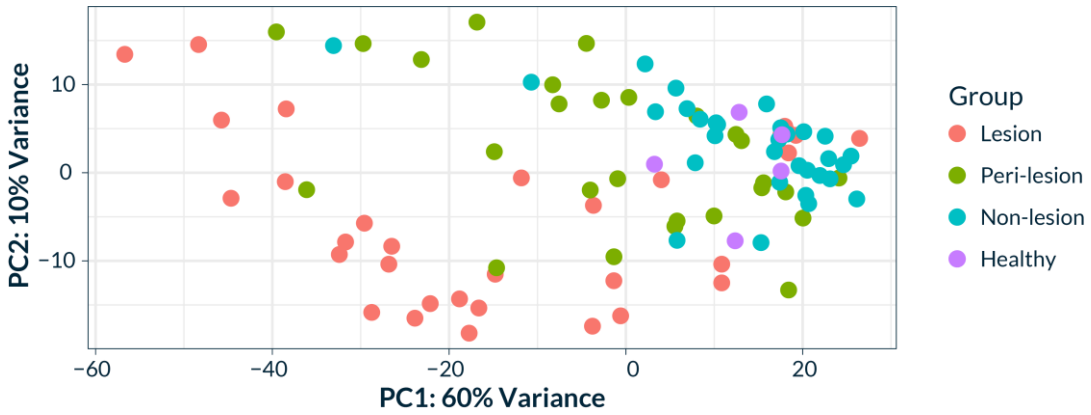
Biomarker Endpoints

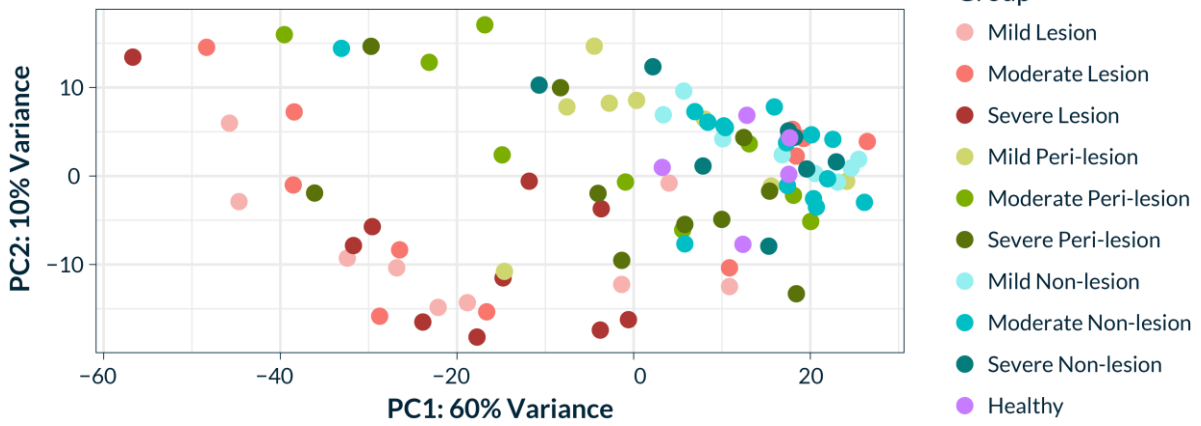
- **Targeted MS of IRAK4 in skin biopsies**
- **IRAK4 immunofluorescence in skin biopsies**
- **Proinflammatory gene transcripts in skin biopsies**
- **Flow cytometry for IRAK4 in ex vivo treated whole blood**

Transcriptional Profiling of Inflammatory Gene Transcripts in HS Skin Identified Biomarkers to Monitor in Patients on KT-474 Phase 1 Trial

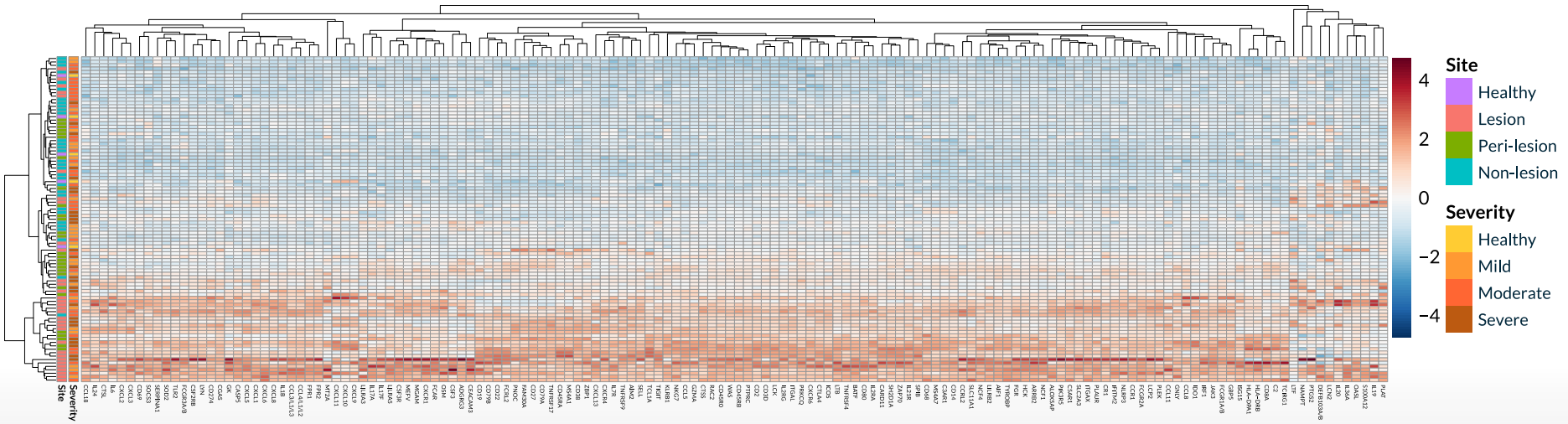
Lesion Samples Cluster Separately in PCA Plot of Transcript Profiles



Transcript Profiles are not Differentiated by Disease Severity



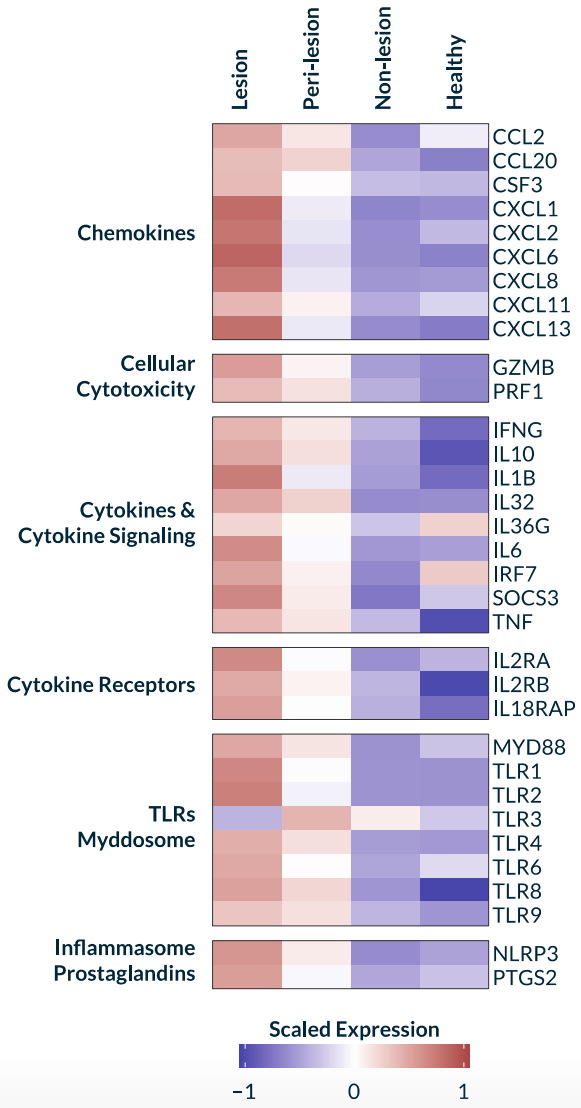
Differentially Expressed Genes – Lesion vs Non-lesion

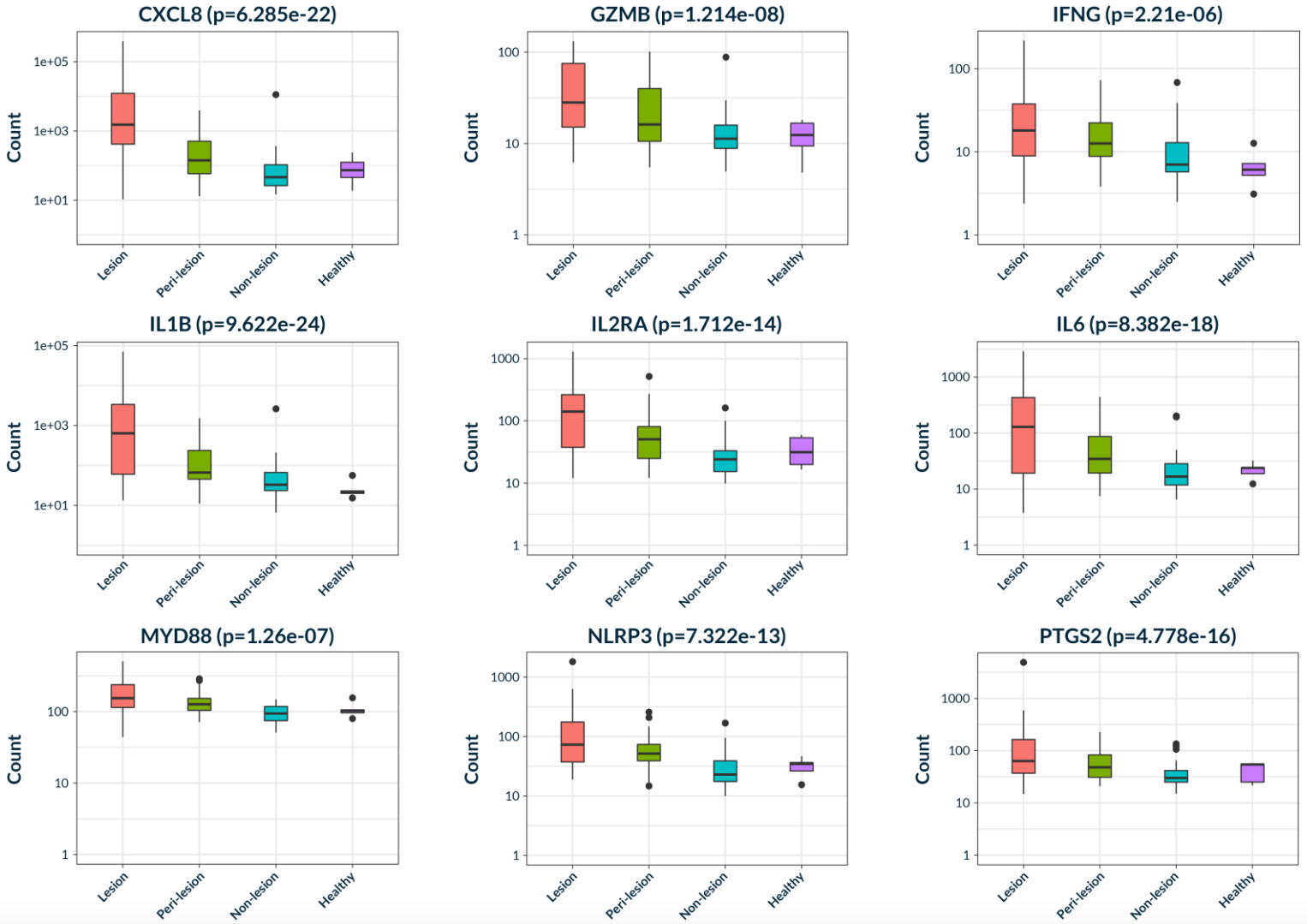


p-value < 0.0001,
fold change >= 4

Lesion samples show many upregulated genes relative to Peri- and Non-lesion samples

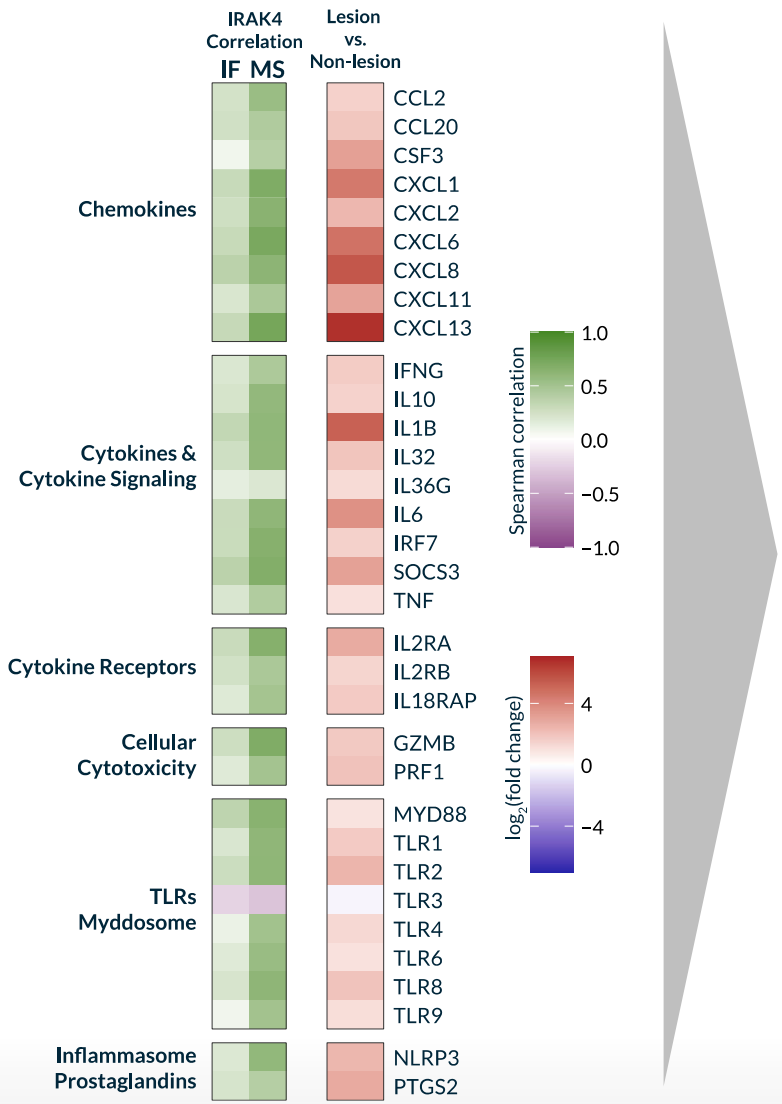
Transcripts for Multiple Mediators of Inflammation are Upregulated in HS Skin Lesions

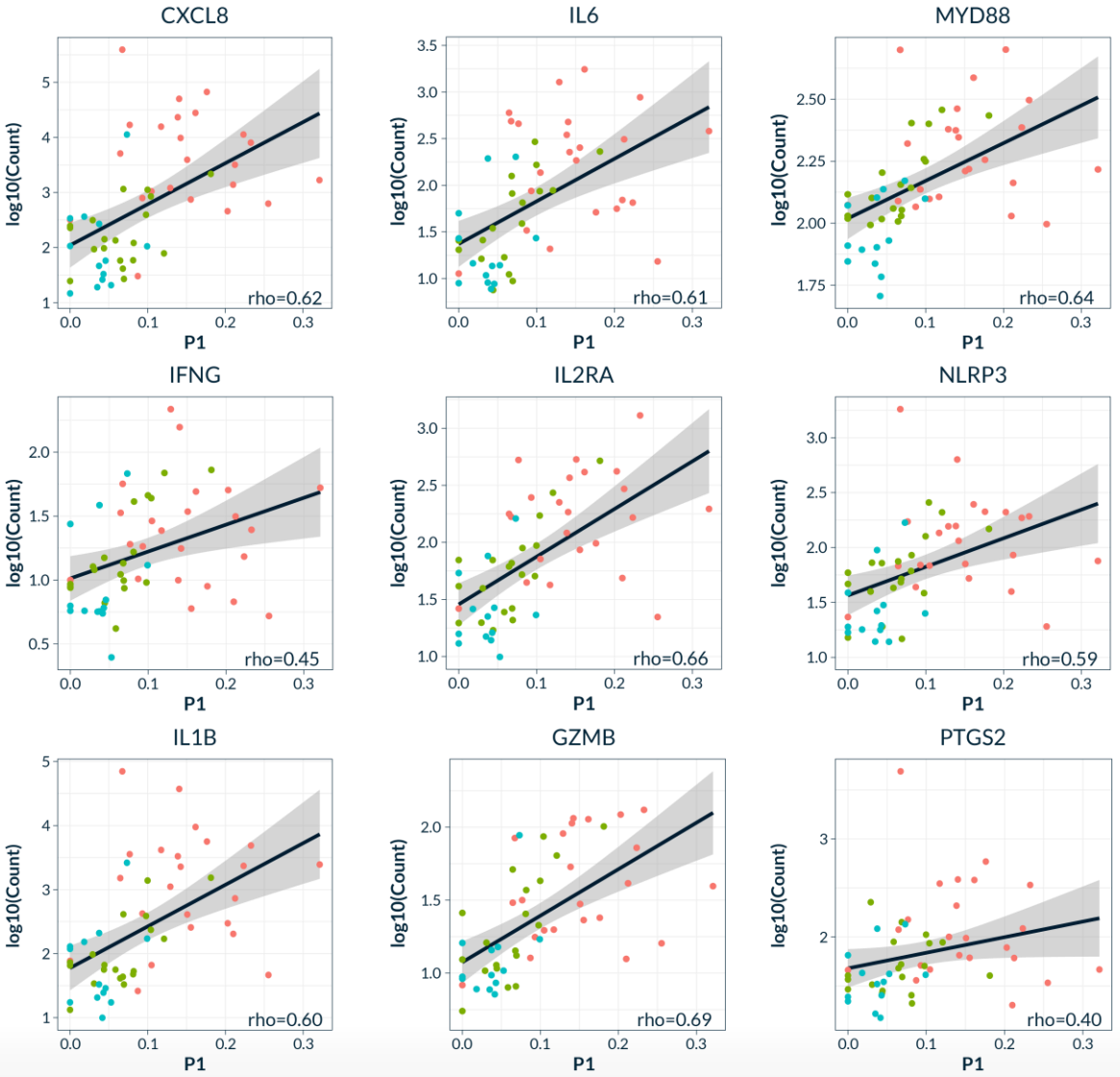




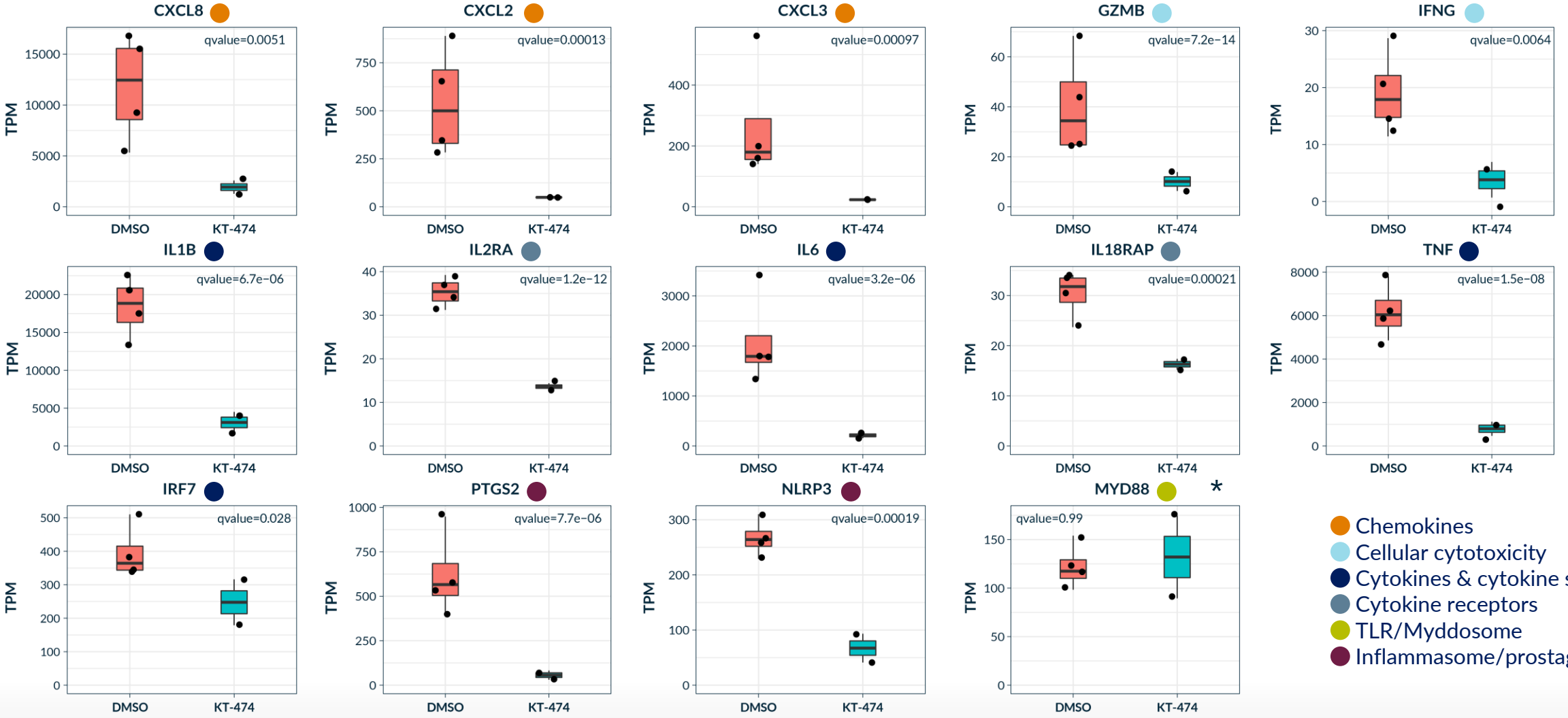
All p-values are for differential expression in Lesions vs Non-lesions

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





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

PART 1: De-Risking KT-474 Phase 1

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Workshop Agenda & Goals

INTRODUCTION to Kymera and IRAK4 TPD program

PART1

- Summarize the non-investigational study and biomarker end points
  Discussion topics: Other opportunities / experiences from participants
- Define IRAK4 baseline expression levels and localization
  Discussion topics: Gaining support for both qualitative and quantitative assays
- Establish KT-474 degrader PoM ex vivo
  Discussion topics: Assessing assay dynamic range and defining values for samples < LLOQ
- Demonstrate how the NI study supported IRAK4 biological PoC in HS
  Discussion topics: Considerations moving from pre-clinical PoC into the clinic

PART2

- Introduce KT-474 Phase1 study and exploratory endpoints
  Discussion topics: Secondary vs exploratory endpoints for translational assays
- Demonstrate successful implementation of KT-474 Phase 1 PD assays
  Discussion topics: Additional methods for monitoring proof of degradation
- Present additional KT-474 Phase 1 PD assays not evaluated in NI Study
  Discussion topics: High level considerations when implementing translational biomarkers in clinical studies

Part 1

BREAK 9:25-9:35

KYMERA

TPD Workshop C: De-risking Clinical Development of a Novel Protein Degrader

Part 2: Implementing translational biomarkers in the KT-474 Phase1 trial

4th Annual TPD Summit

October 26, 2021

PART 2: Implementing Translational Biomarkers in the KT-474 Phase1 Trial

Key Goals

Introduce KT-474 Phase1 study and exploratory endpoints

- **Discussion topics:** Secondary vs exploratory endpoints for translational assays

Demonstrate PoM results from the Phase 1 interim SAD analysis

- **Discussion topics:** Additional methods for monitoring degradation

Present additional Phase 1 PD assays not evaluated in NI Study

- **Discussion topics:** Considerations for ex-vivo experiments

High Level considerations when implementing translational biomarkers in clinical studies

- **Discussion topics:** Quality control, Data TAT, Implementing changes when feasible and appropriate

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)

KT-474 Interim Phase 1 Healthy Volunteer SAD Overview

Interim Results (Cohorts 1-4)

- **32** subjects randomized
- **24** subjects administered KT-474
- **8** subjects administered placebo

Dosing

- Single dose administration of oral KT-474 tablet
- Dose levels (mg):
  25
  75
  150
  300

Pharmacokinetic (PK) Features

- PK profile consistent with oral daily dosing
- Predictable, dose-dependent plasma exposures after single oral dose of KT-474
- Half-life:
  25-32 hours

Safety & Tolerability

- No treatment-related adverse events
- No Serious Adverse Events

Data shared June 28th 2021, Investor presentation

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Methods Development: Measuring Degradation in PBMCs

Mass Spec

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

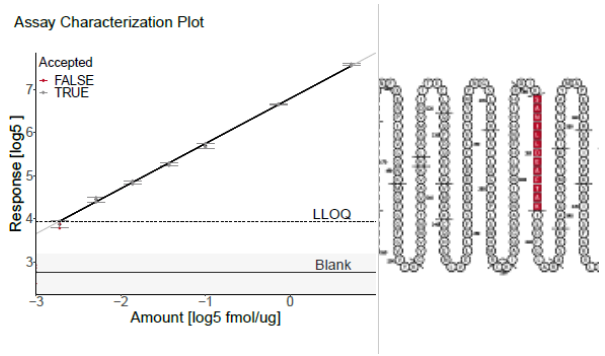
Peptide 1

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



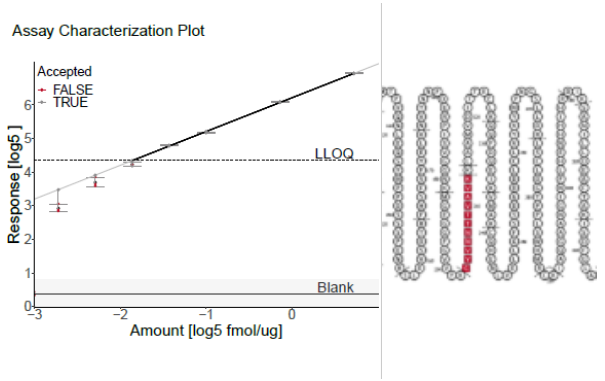
Peptide 2

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

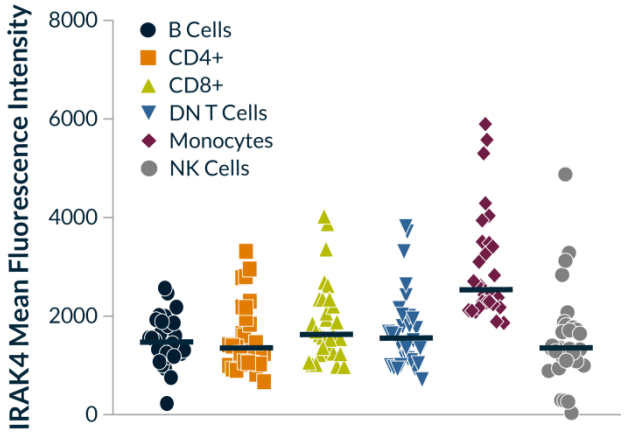
Parameter	Value
q-value Filter	< 0.05
Zero Calibrator Filter	2 x blank intensity
Accuracy Filter	–
Precision Filter	< 20 % CV



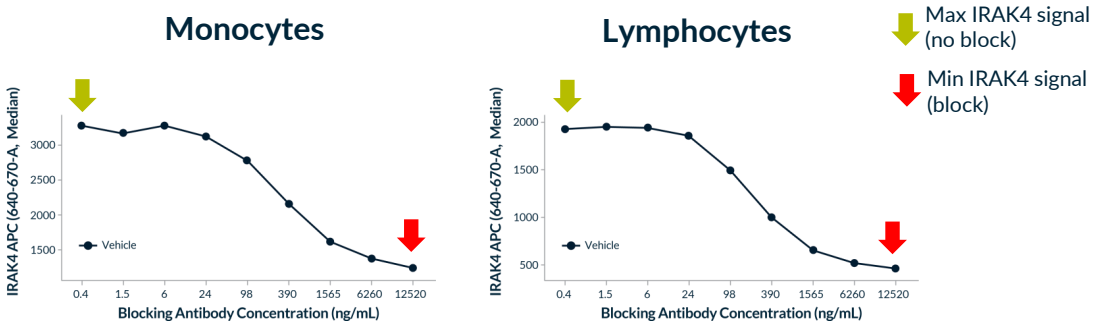
FLOW

- Determination of assay range

Pre-dose Samples Provides Baseline IRAK4 Values



Blocking Antibody Utilized to Define the Assay Floor



Each subject sample is stained +/- block

Developing MS Method in 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

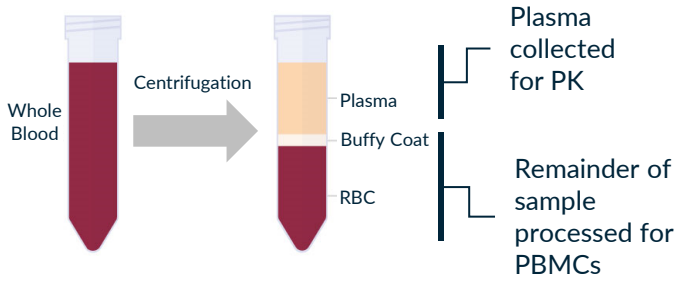
On site processing could not be performed immediately after blood draw

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

Comparison of IRAK4 levels in donor PBMCs to healthy donor tissue

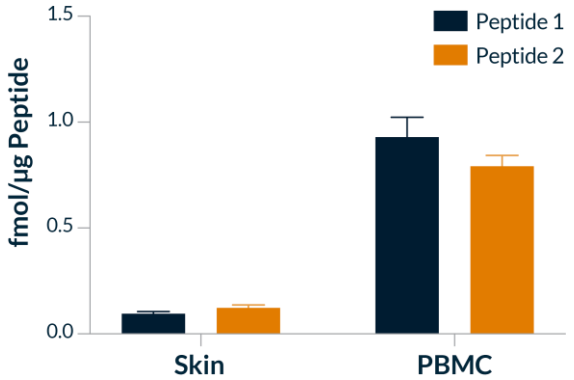
- PBMC expression levels are higher than human skin

Proposed Clinical Process



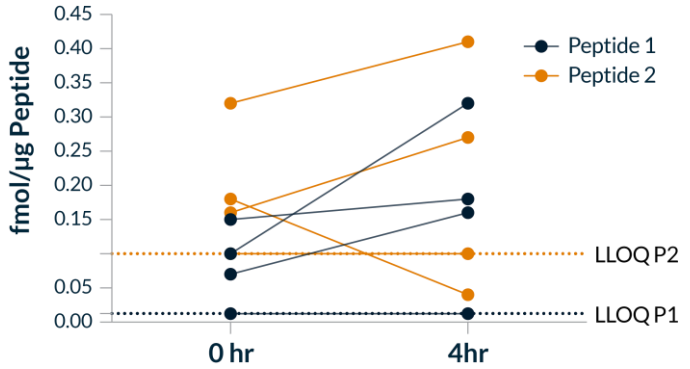
Measurements of Donor Tissue and Blood

IRAK4 Expression in Skin & PBMC

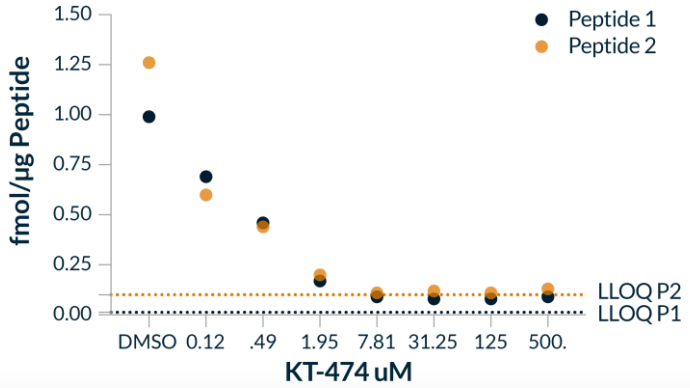


Pilot Mimicking Clinical Process with Donor Blood

Comparison IRAK4 Levels Post Draw



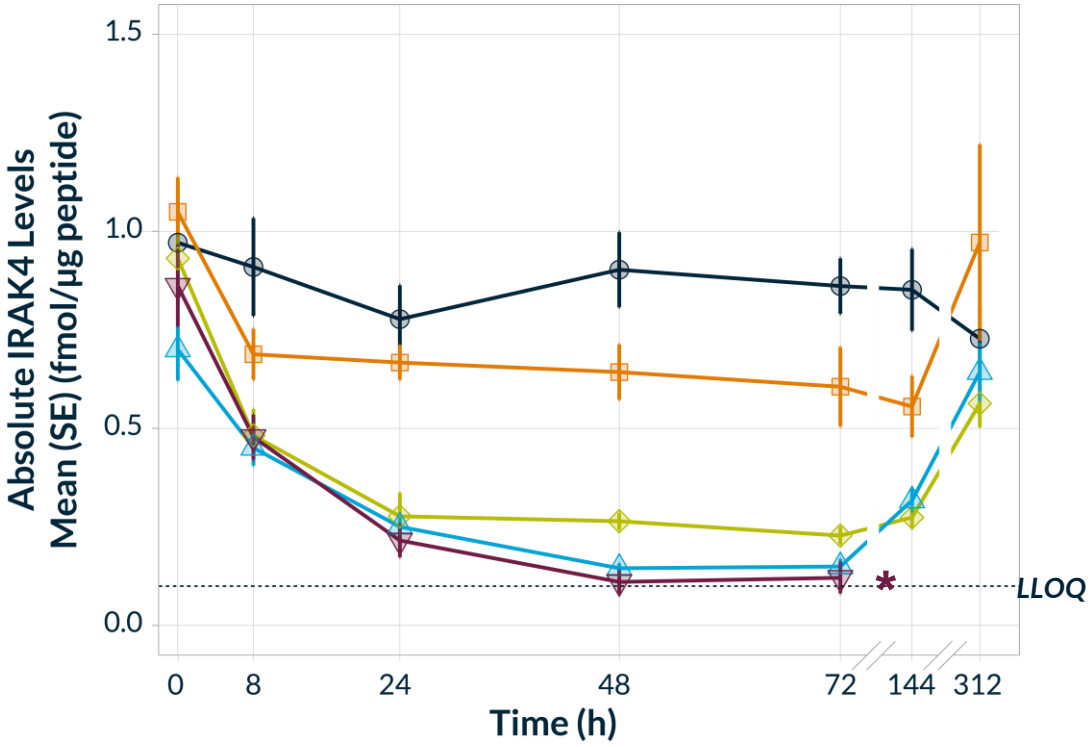
Pilot KT-474 Treated and Isolated PBMCs



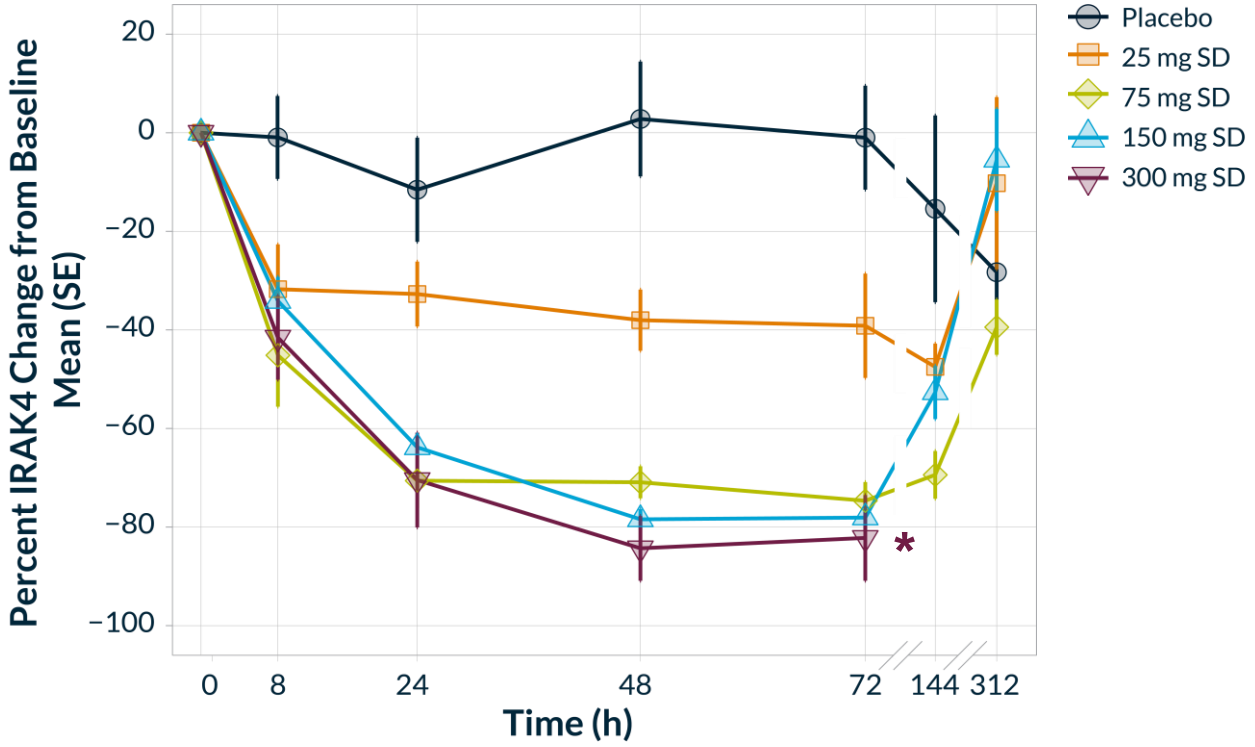
Successful Execution of IRAK4 MS Assay in Clinic

PBMCs Exhibit KT-474-driven IRAK4 Degradation after Single Oral Dose

Absolute IRAK4 Levels



Mean % Reduction of IRAK4

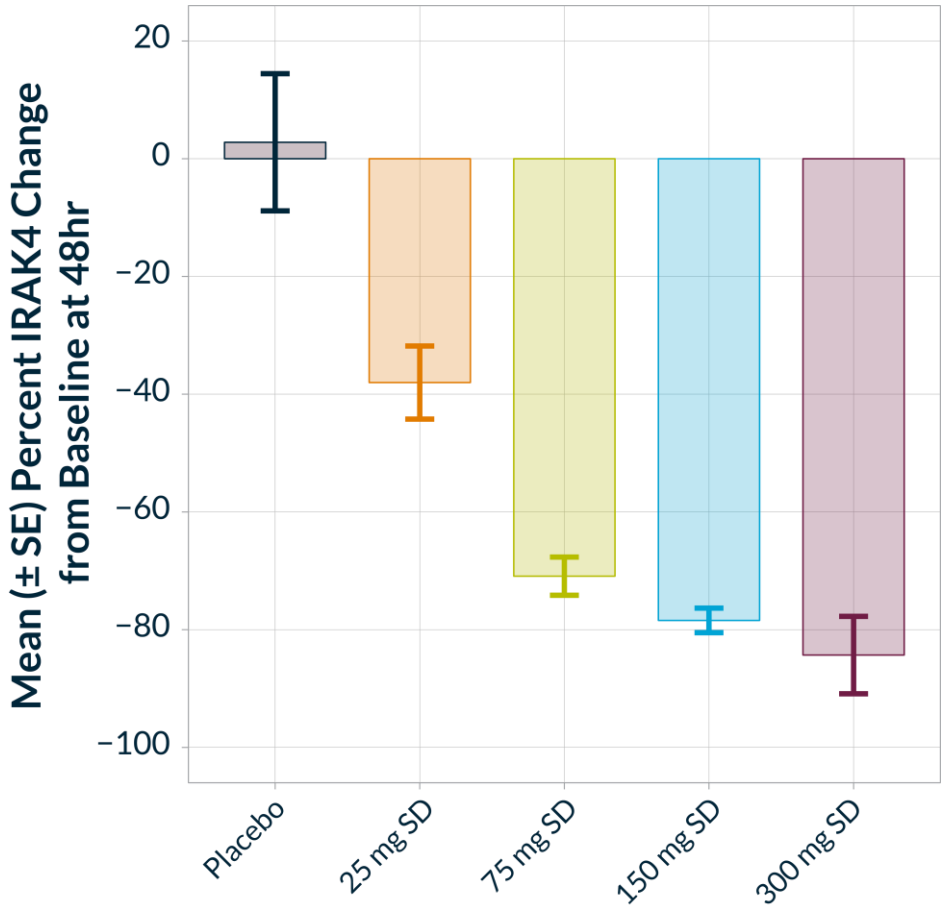


LLOQ = Lower Limit of Quantitation

* SAD4 144/312 h PD timepoints pending

Data shared June 28th 2021, Investor presentation

IRAK4 Degradation >85% Achieved Following Single KT-474 Dose



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

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	-	25 mg	75 mg	150 mg	300 mg
Mean IRAK4 Change	+3%	-38%	-71%	-78%	-84%
Median IRAK4 Change	+16%	-41%	-71%	-78%	-90%
*p value**		*0.0057*	*<0.0001*	*<0.0001*	*<0.0001*

** p-values relative to placebo*

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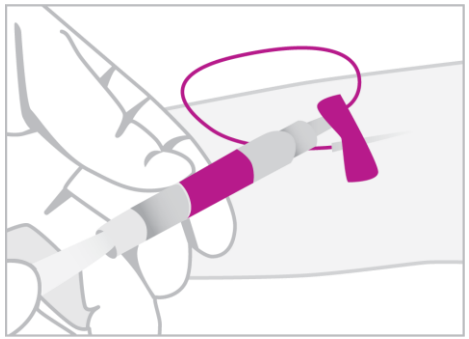
Whole Blood Ex Vivo Cytokine Stimulation Assay

TruCulture Tubes

- Null – 782-001086
- *S. aureus* enterotoxin type B (SEB) – 782-001124
- Lipopolysaccharide (LPS) – 782-001087
- Anti-CD3 and Anti-CD28 – 782-001125
- CytoStim™ – 782-001333
- Gardiquimod (GDQ) – 782-001269

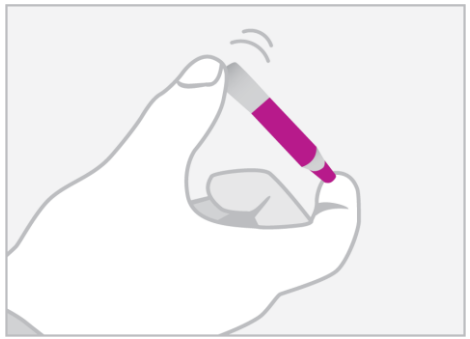
OptiMAP – 13 Analyte Multiplex Assay

ENA-78	**IFN-γ**	**IL-12p70**	**TNF-α**
IL-8	**IL-2**	**IL-10**	**IL-6**
	IL-17	**IL-23**	**IL-1β**
	IL-13	**GM-CSF**	



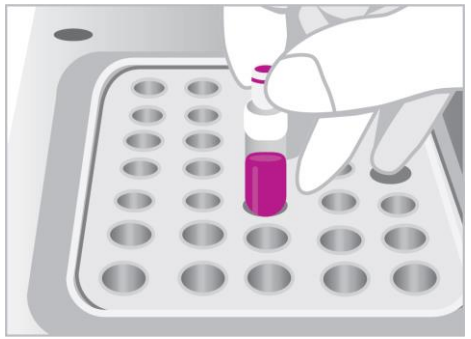
1. COLLECT

Draw 1 mL of blood directly into the TruCulture Tube and break off the plunger.



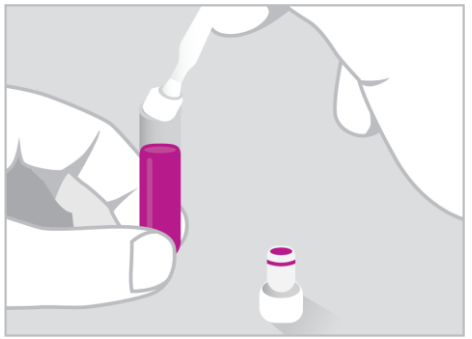
2. MIX

Gently invert tube to mix 3 to 5 times.



3. INCUBATE

Place tube in 37°C heat block for up to 24 hours.



4. SEPARATE

Manually insert valve to separate supernatant from the cells. Collect supernatant and cell layer for downstream analysis.

Source: MyriadRBM.com/TruCulture

Cytokine Fold Induction of Healthy Donor Blood Stimulated with R848 or LPS TruCulture Tubes

Donor Blood

	ENA-78	IL-1β	IL-6	IL-8	IL-10	IL-13	TNFα
Donor A_LPS	3.9	20.2	3.6	5.5	2.2	1.2	19.1
Donor B_LPS	13.0	13.2	17.3	36.2	31.6	1.4	X
Donor A_R848	0.4	8.7	3.4	2.7	1.7	1.1	39.6
Donor B_R848	1.0	17.5	17.5	14.7	33.8	1.7	X

Preclinical assessment of TruCulture tubes using healthy donor blood:

- ≥3fold induction over baseline (unstim) detected for IL-1**β**, IL-8, IL-6, IL-10 and TNF**α**
- Level of induction is donor dependent but still robust and measurable
- In the clinic, collection of pre-dose sample will serve as each subject/patient control

Pressure Testing Ex-vivo Treatment of Whole Blood Prior to Incubation in TruCulture System

TRUCULTURE PROCEDURE

1. DRAW BLOOD
Directly into truculture tube

2. INCUBATE
in 37°C heat block for 24hours

3. SEPARATE
Supernatant from cells and collect for cytokine analysis

PILOT PROCEDURE

1. SOURCE WB
Healthy donor blood

2. EX-VIVO HOLD
0 or 8 hours

3. TRANSFER
WB to truculture

4. INCUBATE
in 37°C heat block for 24hours

5. SEPARATE
Supernatant from cells and collect for cytokine analysis

Stimulated Day 1

LPS Day 1

	1	2	3
ENA78	4000.0	3200	4400
IL-1b	827	983	398
IL-6	620	1440	508
IL-8	1240	1530	378
TNFa	469	945	417
GM-CSF	<33	<33	<33
IFNg	<13	<13	21
IL-2	<62	<62	<62
IL-10	<6.6	7.6	<6.6
IL-12p70	<75	<75	<75
IL-13	<5.2	<5.2	<5.2
IL-17	<4.3	<4.3	<4.3
IL-23	<2.4	<2.4	<2.4

R848 Day 1

	1	2	3
ENA78	4400	2600	4700
IL-1b	1480	1750	1090
IL-6	3020	3230	1580
IL-8	722	2060	560
TNFa	3450	4420	2800
GM-CSF	<33	<33	<33
IFNg	<13	<13	85
IL-2	<62	<62	83
IL-10	29	196	135
IL-12p70	<75	158	79
IL-13	<5.2	<5.2	<5.2
IL-17	<4.3	<4.3	5.9
IL-23	<2.4	<2.4	<2.4

Stimulated Day 2

LPS Day 2

1	2	3
1000.0	830	840
56	241	28
325	528	21
1040	2940	876
211	417	<74
<33	<33	<33
<13	<13	<13
<62	<62	<62
<6.6	<6.6	<6.6
<75	<75	<75
<5.2	<5.2	<5.2
<4.3	<4.3	<4.3
<2.4	<2.4	<2.4

R848 Day 2

1	2	3
960	960	1200
24	<21	<21
48	11	<11
1340	1020	329
<74	<74	<74
<33	<33	<33
<13	<13	<13
<62	<62	<62
<6.6	<6.6	<6.6
<75	<75	<75
<5.2	<5.2	<5.2
<4.3	<4.3	<4.3
<2.4	<2.4	<2.4

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High Level considerations when implementing translational biomarkers in clinical studies

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Workshop Agenda & Goals

INTRODUCTION to Kymera and IRAK4 TPD program

PART1

- Summarize the non-investigational study and biomarker end points
  - Discussion topics: Other opportunities / experiences from participants
- Define baseline expression levels and localization
  - Discussion topics: Gaining support for both qualitative and quantitative assays
- Establish KT-474 degrader PoM
  - Discussion topics: Assessing assay dynamic range and defining values for samples < LLOQ
- Demonstrate how the study supported IRAK4 biological PoC in HS
  - Discussion topics: Considerations moving from pre-clinical PoC into the clinic

PART2

- Introduce KT-474 Phase1 study and exploratory endpoints
  - Discussion topics: Secondary vs exploratory endpoints for translational assays
- Demonstrate successful implementation of KT-474 Phase 1 PD assays
  - Discussion topics: Additional methods for monitoring proof of degradation
- Present additional KT-474 Phase 1 PD assays not evaluated in the NI study
  - Discussion topics: High level considerations when implementing translational biomarkers in clinical studies