3rd Annual TPD Targeted Protein Degradation

Targeted Protein Degradation Beyond Oncology

Nello Mainolfi, PhD
Co-Founder, President and CEO

October 2020

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Outline

- Kymera Overview
- Drug Development Principles and Target Selection
- IRAK4 Degradation in Immunology and Inflammation
- Non-Interventional Study in HS and AD patients with IRAK4 Degrader
- Summary

Kymera

Mission to discover, develop & commercialize

transformative therapies using targeted protein degradation (TPD)

Leading targeted protein degradation platform

investing in unique capabilities of our proprietary discovery platform, Pegasus

Focus on un-drugged or inadequately-drugged targets

in clinically validated biological pathways that TPD can potentially unlock

Robust internal pipeline

focused on Oncology and Immunology with three programs projected to enter the clinic in 2021: IRAK4, IRAKIMiD and STAT3

Leveraging synergies in biopharma

collaborations with Vertex and Sanofi to date, to increase disease and patient impact

Experienced management team

of leading scientific innovators

Kymera Corporate Highlights

> 70 Employees in Watertown

> 5 Disease Areas

> $600M Raised

Capital raised since inception, including $220m from partnerships

~$500M Cash On Hand

Strategic Collaborators

gsk

- Collaboration signed April 2018
- Collaboration allows Kymera to access GSK's **DEL capabilities to screen for ligands to targets and E3 ligases**

VERTEX

- Collaboration signed May 2019
- **$70 million** total upfront and **>$1B** of milestones and tiered royalties
- **6 targets in disease areas outside** of Kymera's core areas of focus in oncology and inflammation

SANOFI

- Signed July 2020
- **$150 million** upfront payment and **>$2 billion** and tiered royalties
- **IRAK4 in I/I and a second program**
- Kymera advances IRAK4 through Ph 1; Sanofi Ph 2 and beyond
- Kymera retains U.S. co-dev and co-co opt-in rights for both programs before Ph3
- Kymera retains all rights to IRAK4 in oncology

Academic Collaborators

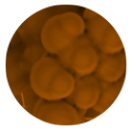
UCSF University of California San Francisco · MAYO CLINIC · COLUMBIA UNIVERSITY · NATIONAL INSTITUTES OF HEALTH · Yale · The Rockefeller University · UNIVERSITY OF CAMBRIDGE

PEGASUS PLATFORM

KYMERA

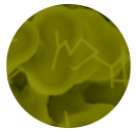
Proprietary Pegasus TPD Platform

Key Capabilities



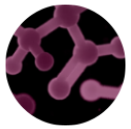
E3 Ligase Whole-Body Atlas

Identification of the **expression profiles of the approximately 600 unique E3 ligases** to match a target protein with the appropriate E3 ligase based on expression, distribution, intracellular localization, and biology.



E3 Ligase Binders Toolbox

Leveraging the E3 Ligase Whole-Body Atlas, **a toolbox of proprietary ligands** designed to bind to novel E3 ligases to design protein degraders with specific degradation profiles for different target disease states.



Ternary Complex Modeling

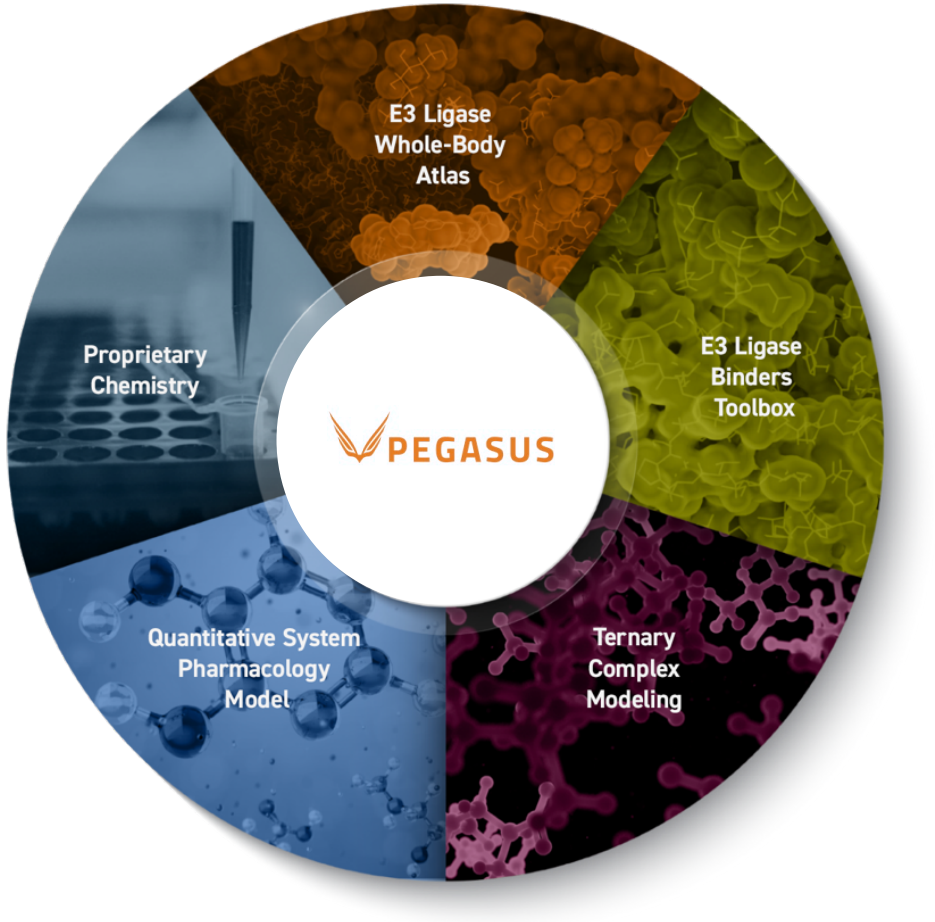
Characterization of ternary complex with both structural biology and biophysical techniques feeds a ternary complex modeling tool to optimize the development of highly efficient, and selective degrader therapeutics.

Quantitative System Pharmacology Model

A model to measure and predict the diverse sets of parameters that impact protein levels. Based on **understanding of PK/PD both *in vitro* and *in vivo***, and across different tissues and cell types.

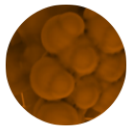
Proprietary Chemistry

Expertise in proprietary chemistry enables the design and optimizes both E3 and target protein binders and convert them into **degraders with optimal pharmaceutical properties** tailored to specific patient populations and diseases.



Pegasus

E3 Ligase Whole-Body Atlas



E3 Ligase Whole-Body Atlas

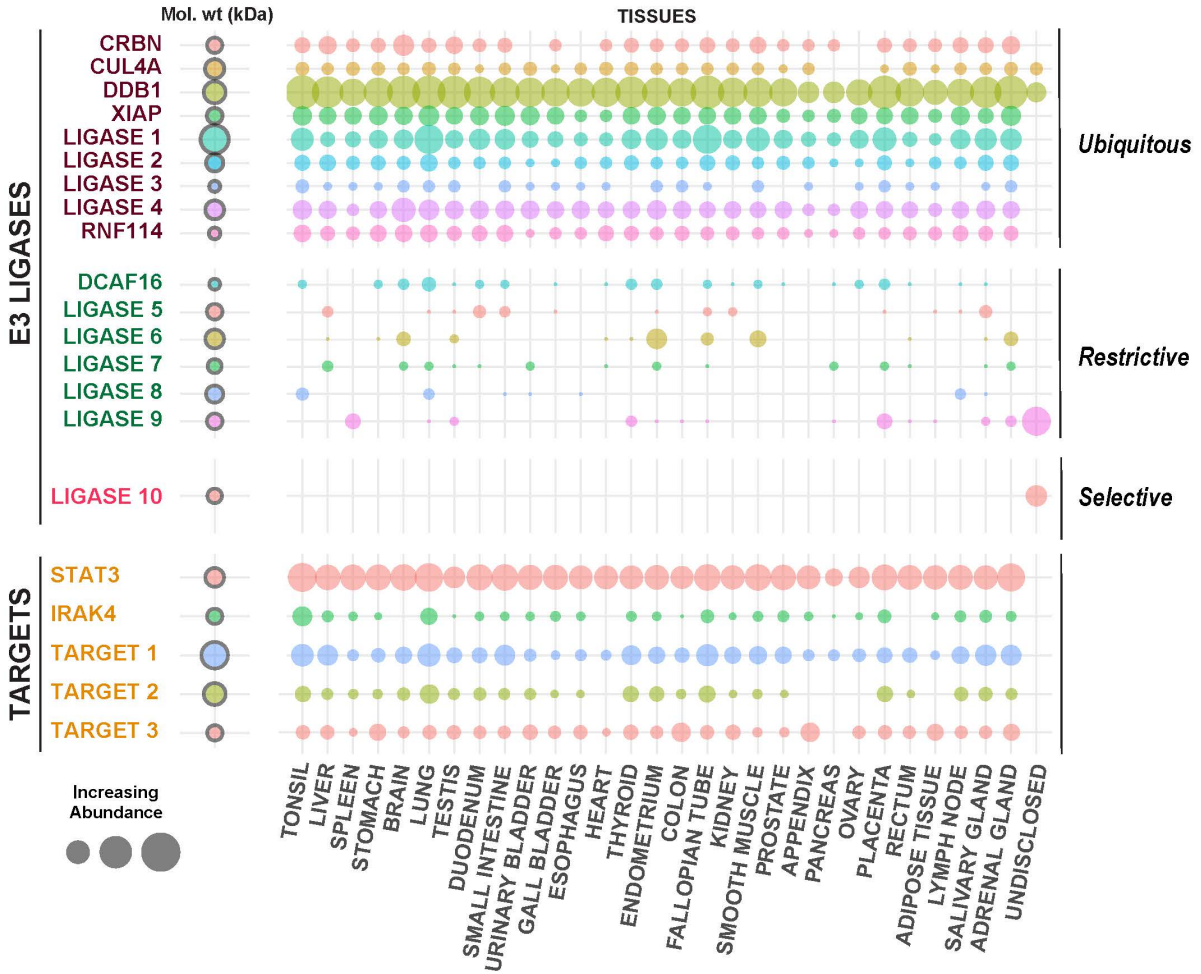
E3 Ligase Binders Toolbox

Ternary Complex Modeling

Quantitative System Pharmacology Model

Proprietary Chemistry

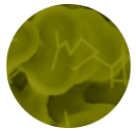
- Focused on determining the expression profiles of ~600 unique E3 ligases
- Patterns mapped in both disease and healthy contexts
- Ability to match a target protein with appropriate E3 ligase based on expression, and biology
- Vision to develop tissue selective or tissue restricted degraders to enable novel therapeutics opportunities



Pegasus

E3 Ligase Binders Toolbox

E3 Ligase Whole-Body Atlas



E3 Ligase Binders Toolbox

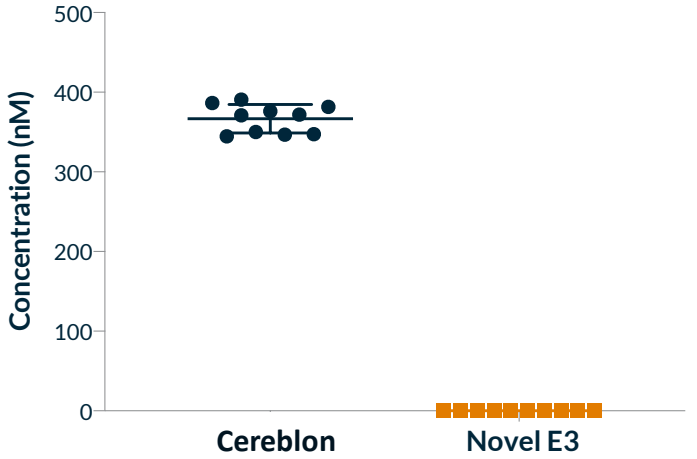
Ternary Complex Modeling

Quantitative System Pharmacology Model

Proprietary Chemistry

- E3 Ligase Whole Body Atlas queried to identify a tissue sparing E3 ligase based on target protein unwanted pharmacology (i.e. bone marrow for a particular target of interest)
- A Bone marrow sparing E3 ligase identified
- Screening and optimization lead to a novel binder to a previously unliganded E3 ligase (E3 ligase binders toolbox)
- A novel degrader based on a bone marrow sparing E3 ligase demonstrated target degradation

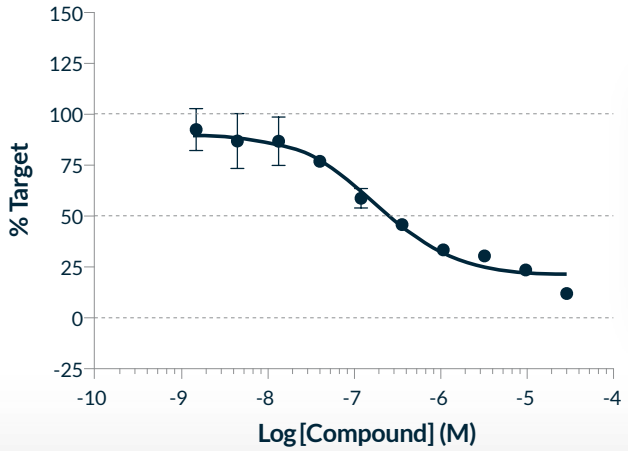
This E3 Ligase is Not Expressed in Bone Marrow



Bone marrow: CD34+ from five donors

Ligand Identification

TPD with Bone Marrow Sparing Novel E3 Ligase



Target	Target Protein
DC_{50} (nM)	206
Dmax (%)	88

Drug Development Principles

UNMET MEDICAL NEED

Many unmet medical needs across various cancers and rheumatological, dermatological disorders

VALIDATED BIOLOGY

Clinically validated across several disease areas: oncology, immunology, fibrosis

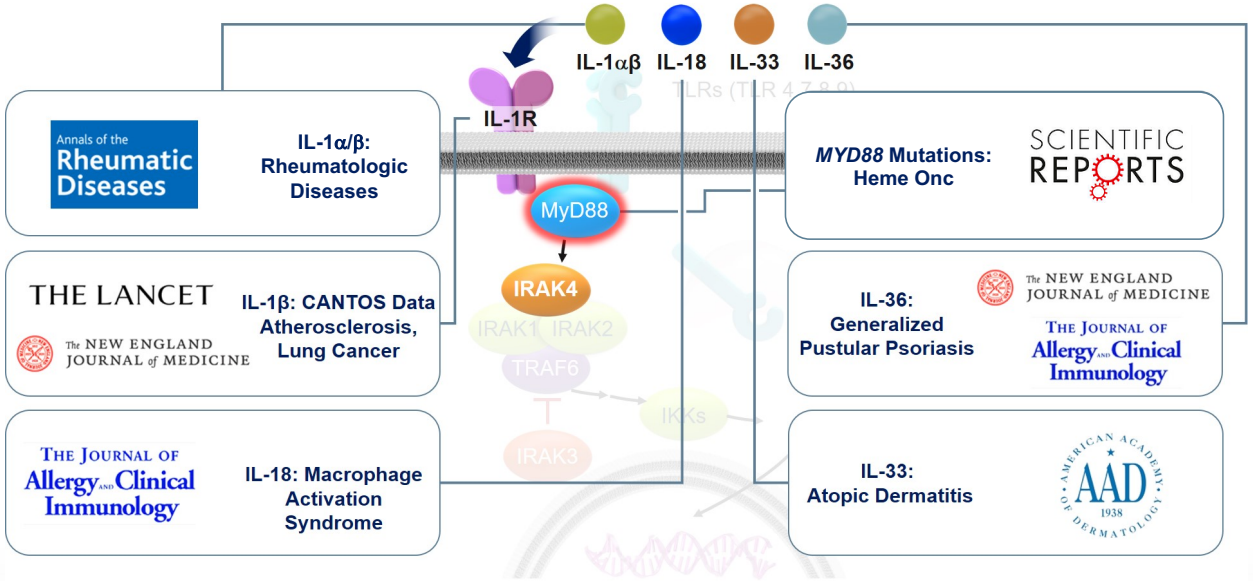
UN-DRUGGED NODE

Key un-drugged or inadequately drugged nodes that TPD can unlock

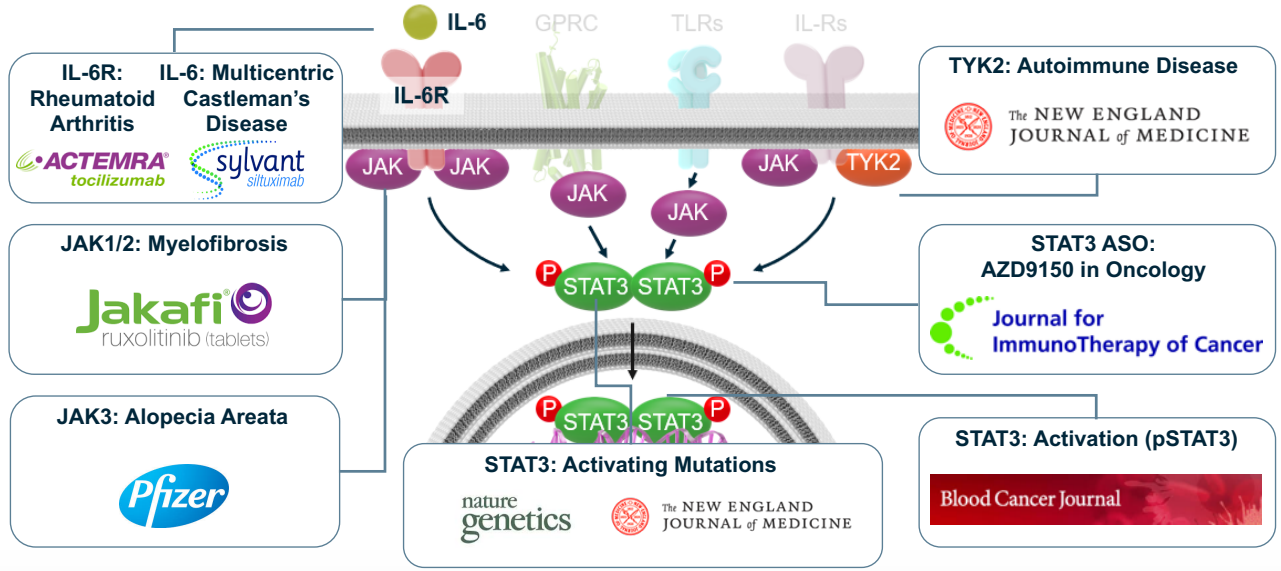
PRECISION MEDICINE APPROACH

Targeted to a genetically defined patient population

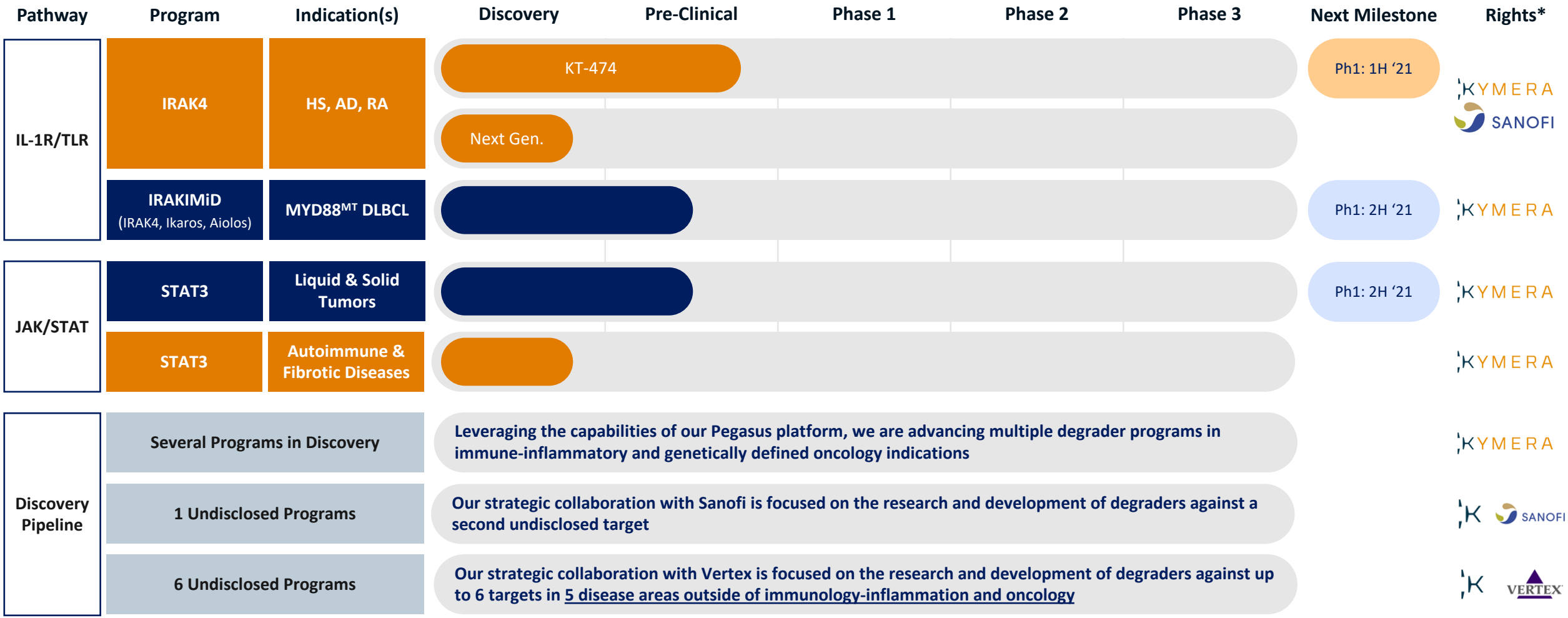
IL-1R/TLR Pathway



JAK-STAT Pathway



Kymera Pipeline



**Kymera will have the option to participate equally in the development and commercialization of Sanofi-partnered programs in the US*

= Oncology = Immunology-Inflammation

IRAK4

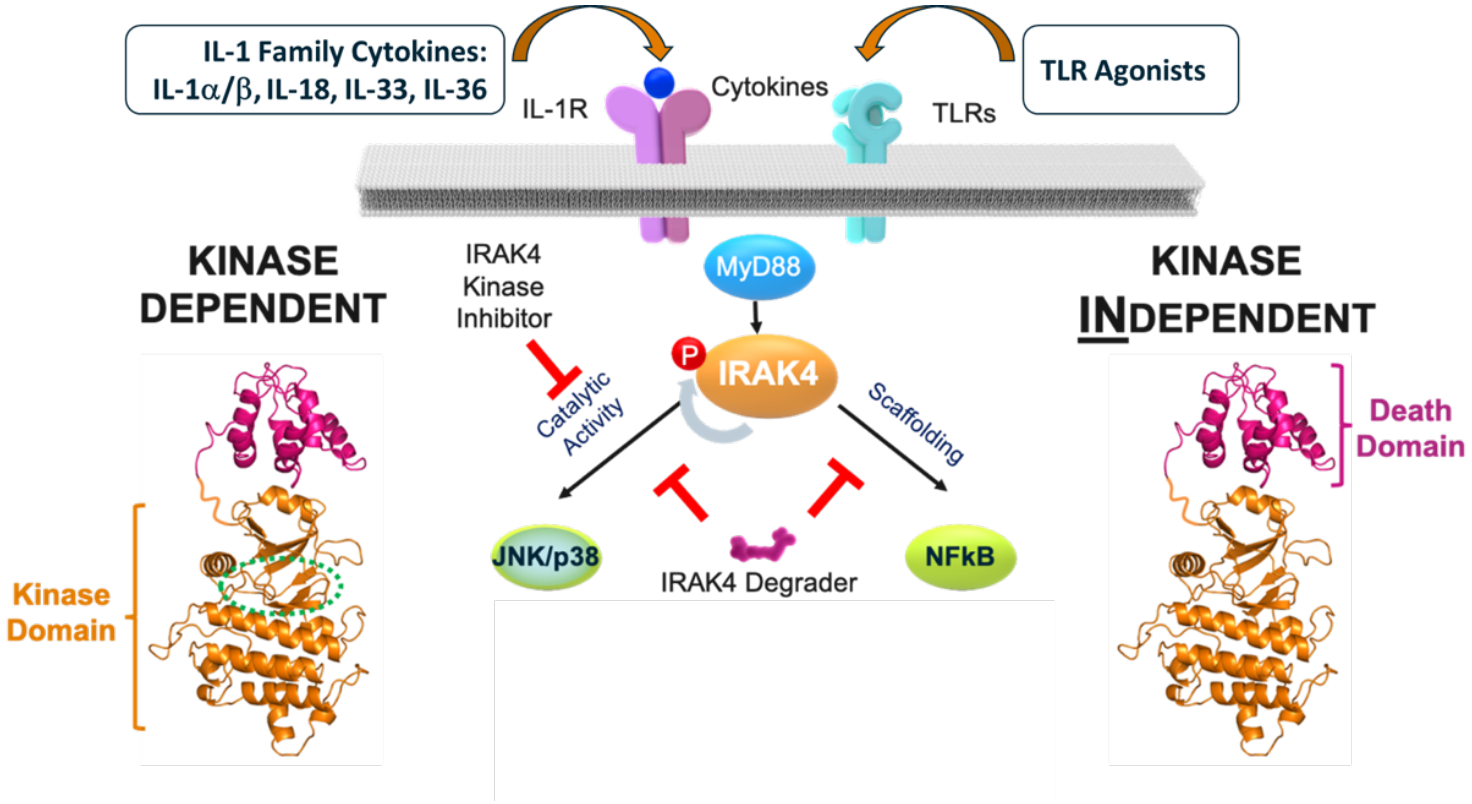
KYMERA

IRAK4 Biology and Degrader Rationale

- IRAK4 is a key component of myddosome protein complex
- Myddosome involved in innate immunity that mediates signals through IL-1R and TLRs
- IL-1R/TLR signaling through the myddosome complex is dependent on IRAK4 kinase and scaffolding functions
- Degrading IRAK4 we believe can provide a single oral small molecule solution to many diseases impacted by this pathway

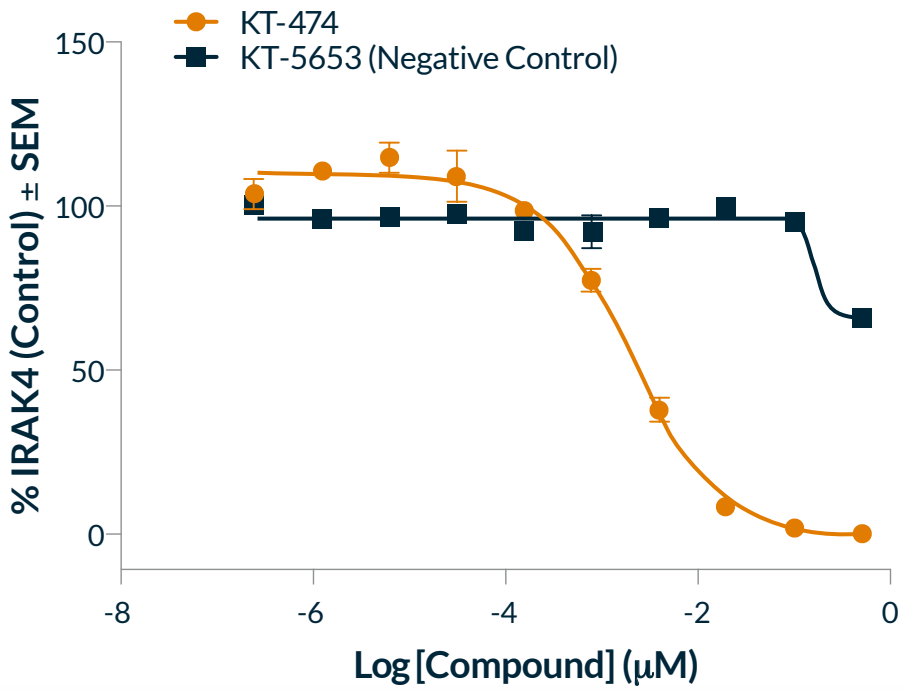
Indications/Timeline

AD, Hidradenitis Suppurativa (HS), RA
Current: IND enabling studies
Expected IND submission: 1H 2021
Expected P1: 1H 2021

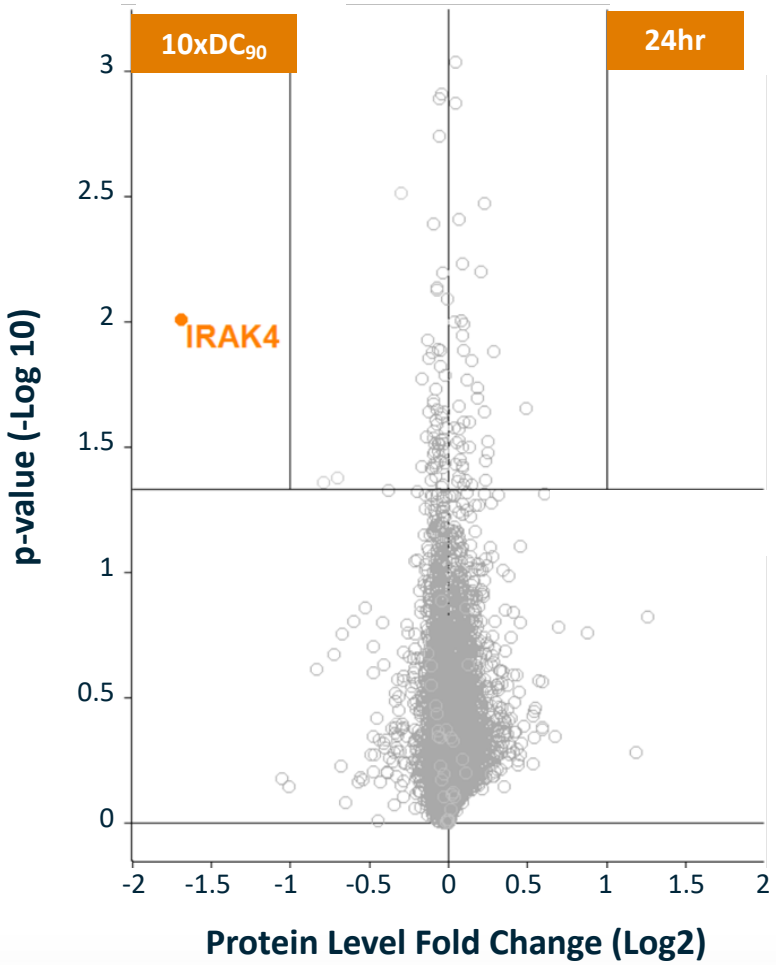


KT-474: Specific IRAK4 Degradation

Degradation in Human Monocytes



Selectivity in Human PBMC

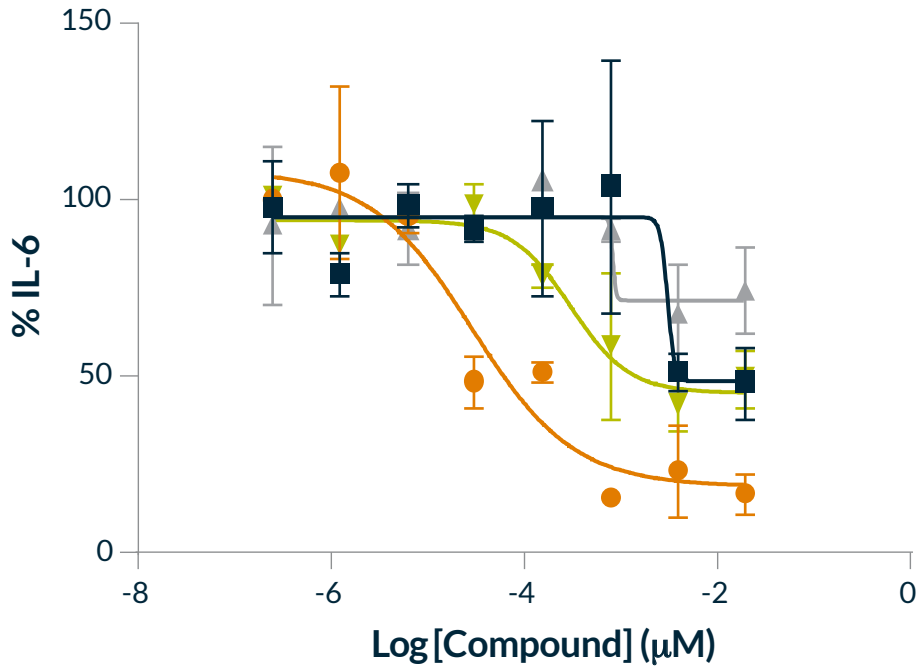


- Calculated DC_{50} of 2.1 nM and E3 ligase dependent degradation of IRAK4 in human immune cells
- IRAK4 was only protein of over 10,000 to be degraded by KT-474 in human immune cells at concentration 10-fold above the DC_{90}

IRAK4 Degradation Superior to Kinase Inhibition in Cytokine Production

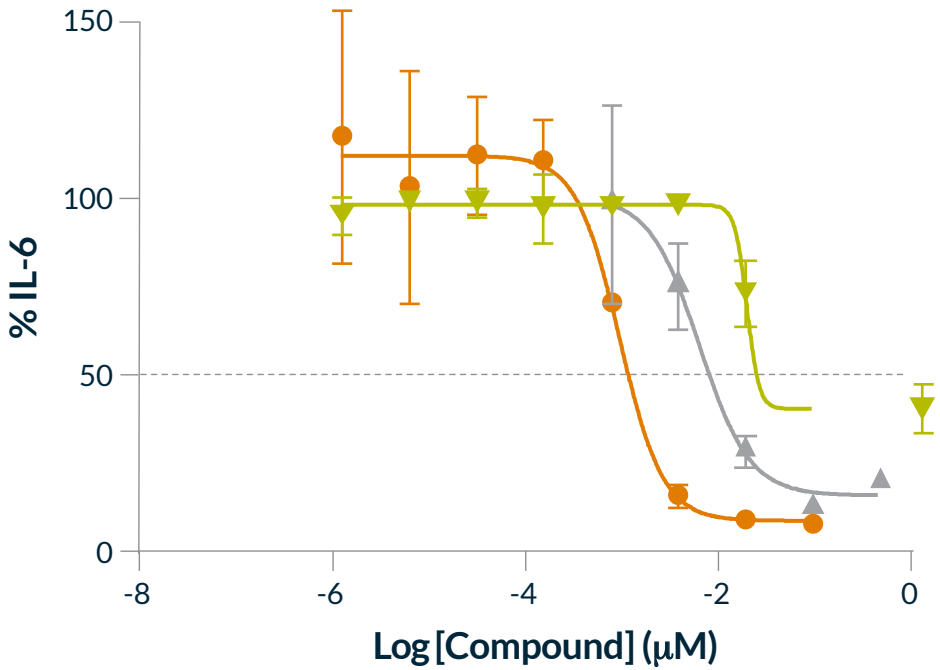
- Functional activity of KT-474 assessed by measuring pro-inflammatory cytokine levels upon activation
- Cells pre-treated with KT-474, a negative control, and two small molecule IRAK4 kinase inhibitors
- KT-474 better able to inhibit IL-6 under both LPS and R848 than clinically active IRAK4 SM kinase inhibitor PF-06550833

LPS → IL-6



Legend	Compound	IL-6 IC_{50} (nM)
	KT-474	**3**
	Negative control	**335**
	IRAK4 SMI *(PF-06550833)*	**N/A**
	IRAK4 SMI *(other)*	**N/A**

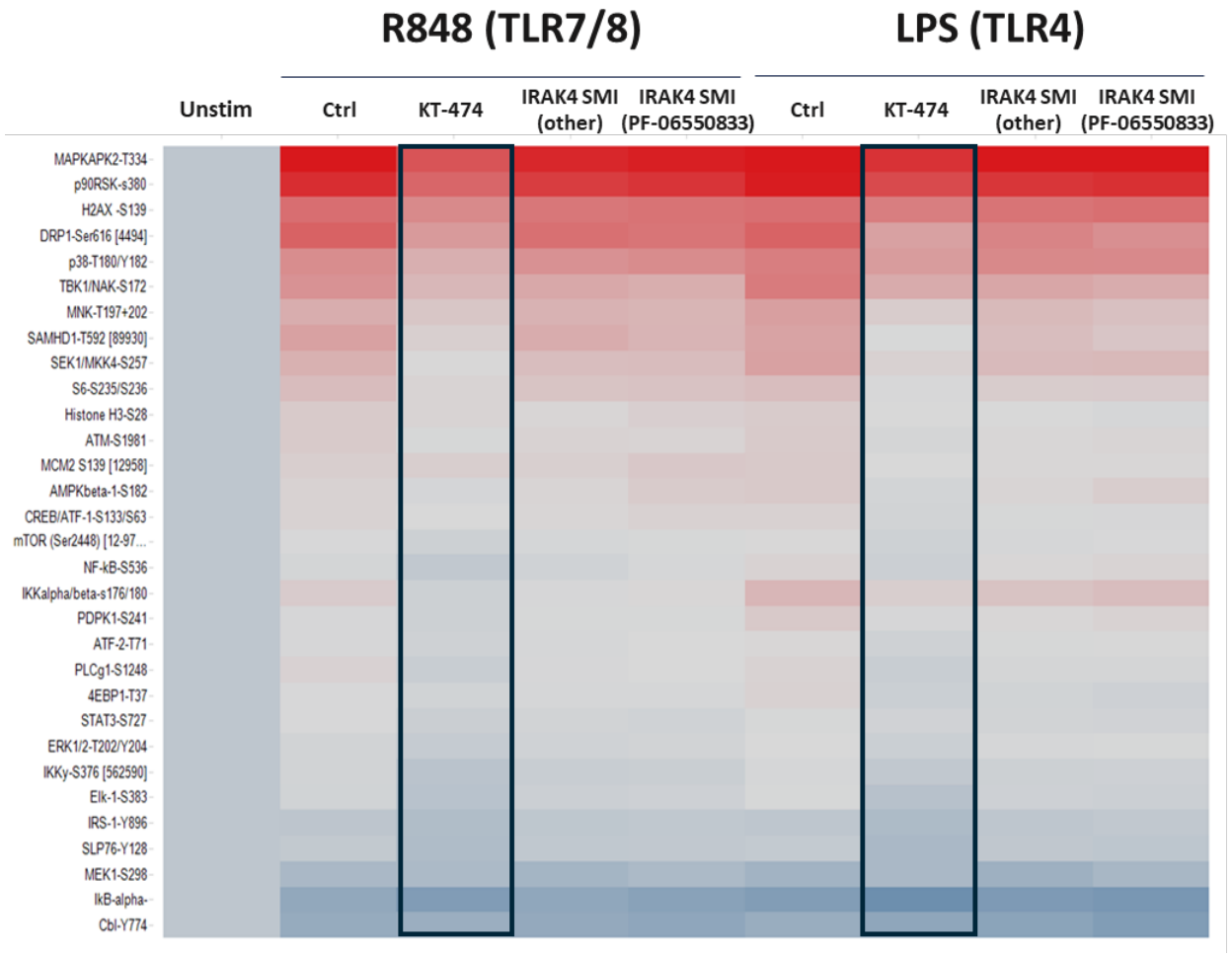
R848 → IL-6



Legend	Compound	IL-6 IC_{50} (nM)
	KT-474	**0.7**
	IRAK4 SMI *(PF-06550833)*	**5**
	IRAK4 SMI *(other)*	**49**

IRAK4 Degradation Superior to Kinase Inhibition in Intracellular Signaling

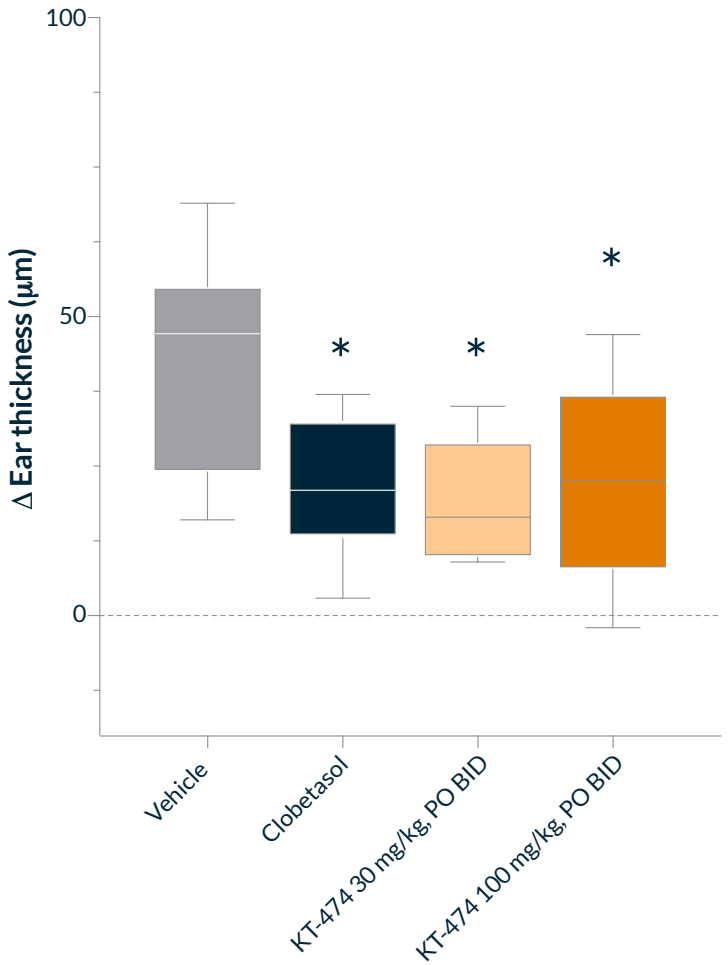
- Phosphorylation events upon TLR activations monitored using flow cytometry
- KT-474 inhibited pro-inflammatory phosphorylation events in a superior manner to small-molecule inhibitors including clinically active PF-compound

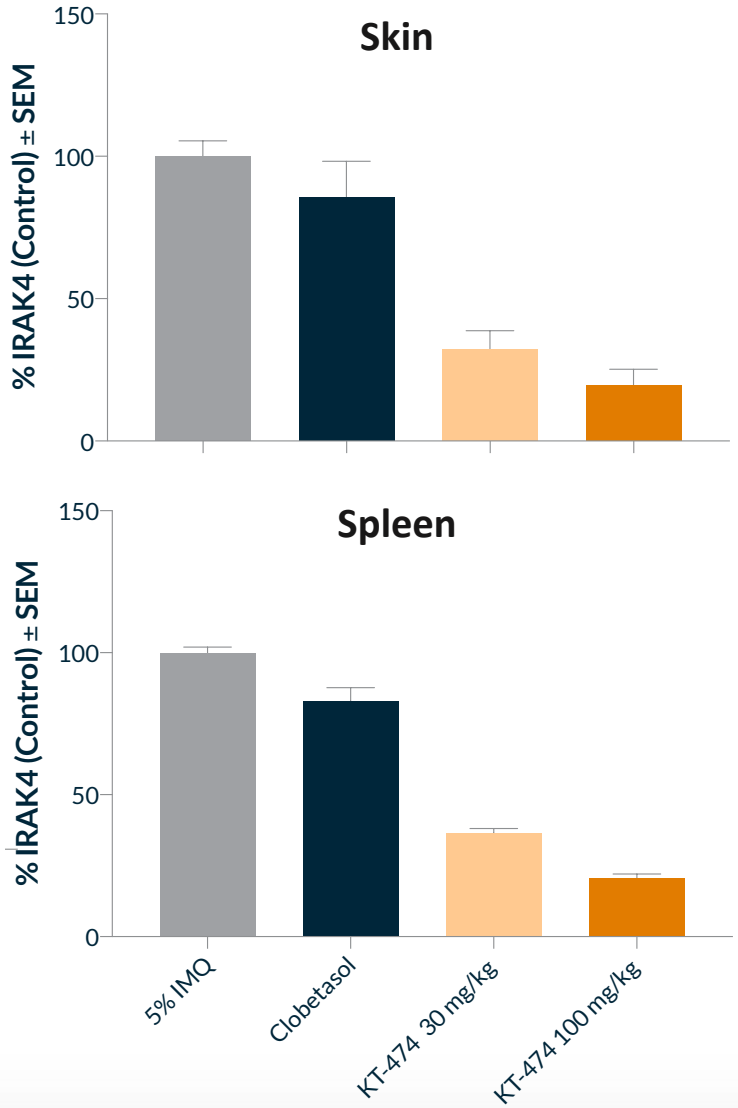


IRAK4 Degradation *In Vivo* Active in Preclinical Mouse Psoriasis Model

IL-1R/TLR driven

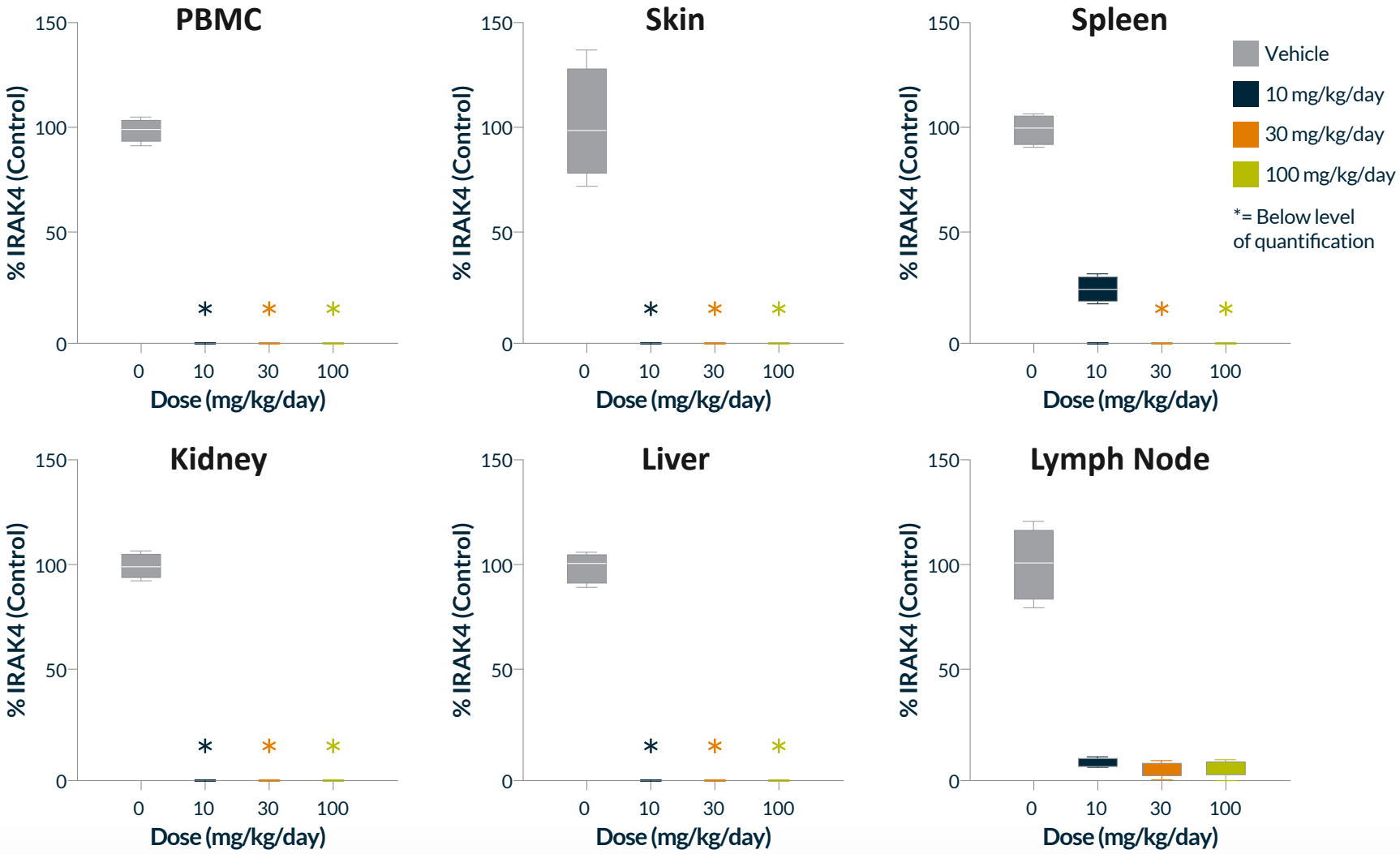
- Ability to inhibit topical skin thickening induced by imiquimod was measured in a mouse model of psoriasis
- Orally dosed KT-474 inhibited thickening, a reflection of local and systemic inflammation, comparable to a topic corticosteroid after 2 or 4 days of dosing
- Inhibition shown at doses achieving at least 60-70% IRAK4 knockdown in skin and spleen





KT-474: Close to Complete IRAK4 Degradation and 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 Development Plan

NI Study

Target Date	Milestones
H1 2020	Study Start
H2 2020/H1 2021	Data readouts from skin and blood

- *Single-site non-interventional study*
- *Whole blood, plasma and skin biopsies collected at single time point*
- ***HS: n=30***
  AD: n=10
- *Biomarker endpoints in blood and skin: IRAK4, cytokines, acute phase reactants*

IND

Phase 1 NHV SAD/MAD

Target Date	Milestones
H1 2021	IND Filing and Study Start
H2 2021	NHV SAD/MAD data
H2 2021	Patient cohort in MAD

- *Randomized, pbo-controlled, dose escalation study*
- *SAD and MAD (14 daily doses)*
- *Up to 100 adult healthy volunteers*
- *Primary endpoint: Safety*
- *Secondary endpoints: PK and PD (POB)*
  - *IRAK4 levels in blood and skin*
  - *Levels of pro-inflammatory cytokines*
  - *Ex-vivo stimulation of PBMC*
  - *Plasma levels of hsCRP*
- *Small patient cohort of top MAD dose to confirm PKPD*

POB

Phase 2

Target Date	Milestones
2H 2022/ 1H 2023	Clinical POC

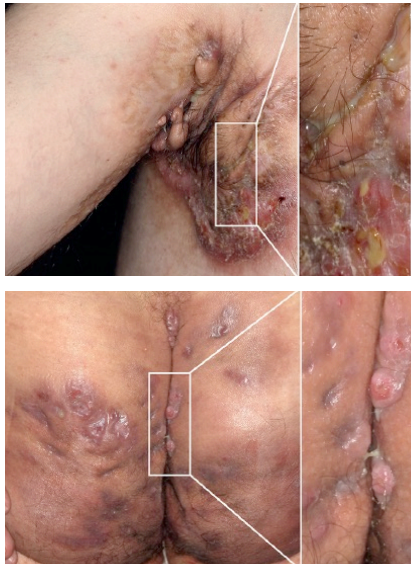
- *Randomized, pbo-controlled, study in pts in indications such as **HS, AD, RA***

POC

Hidradenitis Suppurativa

Clinical Presentation, Epidemiology and Treatment

- Painful, chronic, suppurative process involving the skin and subcutaneous tissue



- Onset usually in 2nd and 3rd decades, more common in females (~3.5:1)
- Primarily occurs on intertriginous skin: axilla, inguinal area, inner thighs, perineal and perianal regions, mammary and inframammary skin, and buttocks
- Recurrent, painful and inflamed nodules, leading to rupture, inflammatory plaques, epithelialized sinuses, end-stage “tombstone” comedones, and “rope-like” scarring
- Significant impact on QOL due to pain, scarring and malodorous discharge
- Severity measures: Hurley clinical staging system (I-III), inflammatory lesion (nodules and abscesses) count
- Diagnosis: clinical, based on typical lesions in typical locations as well as relapses and chronicity

- **Epidemiology**
  - Prevalence of 0.1-2%; ~325K in US, ~25% with moderate-to-severe disease (total abscess and inflammatory nodule count ≥ 3)
  - Incidence in US: 11.4/100,000
- **Treatment**
  - Adalimumab (anti-TNF-a) approved in 2015 for moderate-to-severe disease; ~50% respond, but only 20-30% with durable responses
  - Other treatments include: antibiotics, steroids and surgery

INTERIM RESULTS FROM NON-INTERVENTIONAL STUDY

To Evaluate Cutaneous & Circulating Biomarkers for a Novel IRAK4-Targeted Therapeutic

IN PATIENTS WITH HIDRADENITIS SUPPURATIVA

***Afsaneh Alavi*[1, 2], *Sara Chavoshi*[1], *Veronica Campbell*[3], *Alice McDonald*[3], *Jeffrey Davis*[3], *Anthony Slavin*[3], *Nello Mainolfi*[3], *Jared Gollob*[3]**

[1]York Dermatology Clinical and Research Center, Ontario, Canada; [2]Department of Dermatology, Mayo Clinic, Rochester, MN; [3]Kymera Therapeutics, Watertown, MA

LEARNING OBJECTIVES

CHARACTERIZE
IRAK4 expression in the skin and blood of patients with HS

HIGHLIGHT
the *ex vivo* pharmacodynamic activity of an IRAK4 degrader on peripheral blood mononuclear cells (PBMC) from patients with HS

Study Design and Baseline Demographics

Design

Number of Sites	Single center (York Dermatology Clinic and Research Center, Ontario, Canada) PI: Dr. Afsaneh Alavi, MD, MSch, FRCPC
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 patients (by IHS4 score), and moderate to severe AD (by EASI score)
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 (eg. 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 (lesional, peri-lesional, non-lesional)

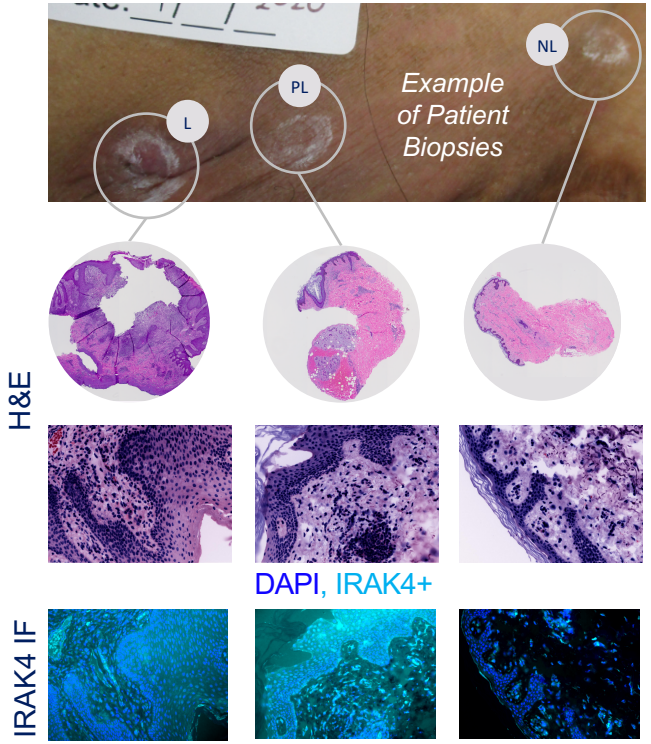
Baseline Demographics & Biomarkers

Study Duration	• FPI: 28May2020 • HS accrual completed; enrollment of AD patients ongoing
Patients Enrolled to Date	• 30 HS: 9 mild, 10 moderate, 11 severe • 2 AD
Demographics	• Age 19-56 yrs • 9 male, 23 Female • Duration of disease: 1-38 years • Race: 97% were non-Hispanic or Latino
Biomarker Endpoints	• Flow cytometry for IRAK4 in ex vivo treated whole blood • Targeted MS of IRAK4 in skin biopsies • IRAK4 immunofluorescence in skin biopsies • Cytokines from ex vivo treated whole blood • Plasma cytokines and acute phase reactants • Cytokines in skin biopsies

IRAK4 Expression is Highest in Lesional (L) & Peri-Lesional (PL) Skin

IRAK4 Immunofluorescence (IF)

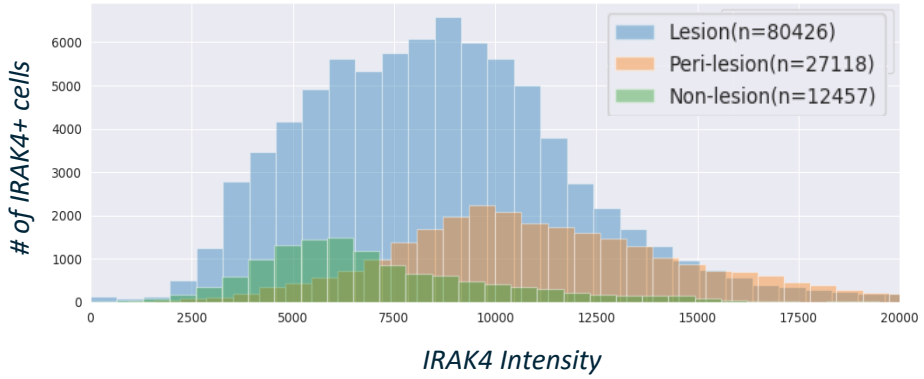
N=10 | **IHS4 severity:** 4 mild, 3 moderate, 3 severe



IF Analysis

- L, PL, NL IRAK4 positive cells counted and binned into intensity ranges as depicted by the horizontal bars below
- Cell counts per intensity bin were summed from the 3 biopsy locations

Cell count by intensity per biopsy location



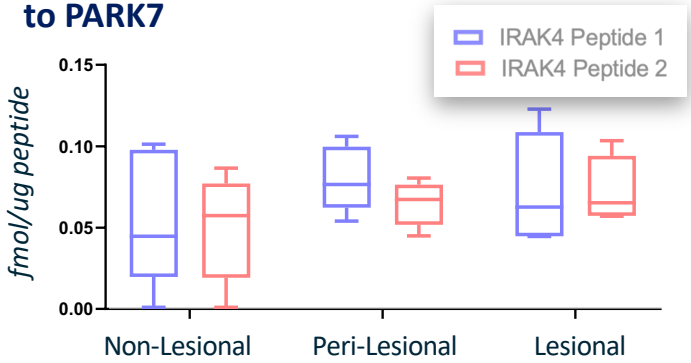
IRAK4 Mass Spectrometry (MS)

N=5 | **IHS4 severity:** 0 mild, 2 mod, 3 severe

MS Analysis

- Two peptides were chosen providing strong concordance in absolute quantification
- Plot represents the range of fmol/ug peptide across the 3 biopsy locations

IRAK4 absolute quantification normalized to PARK7



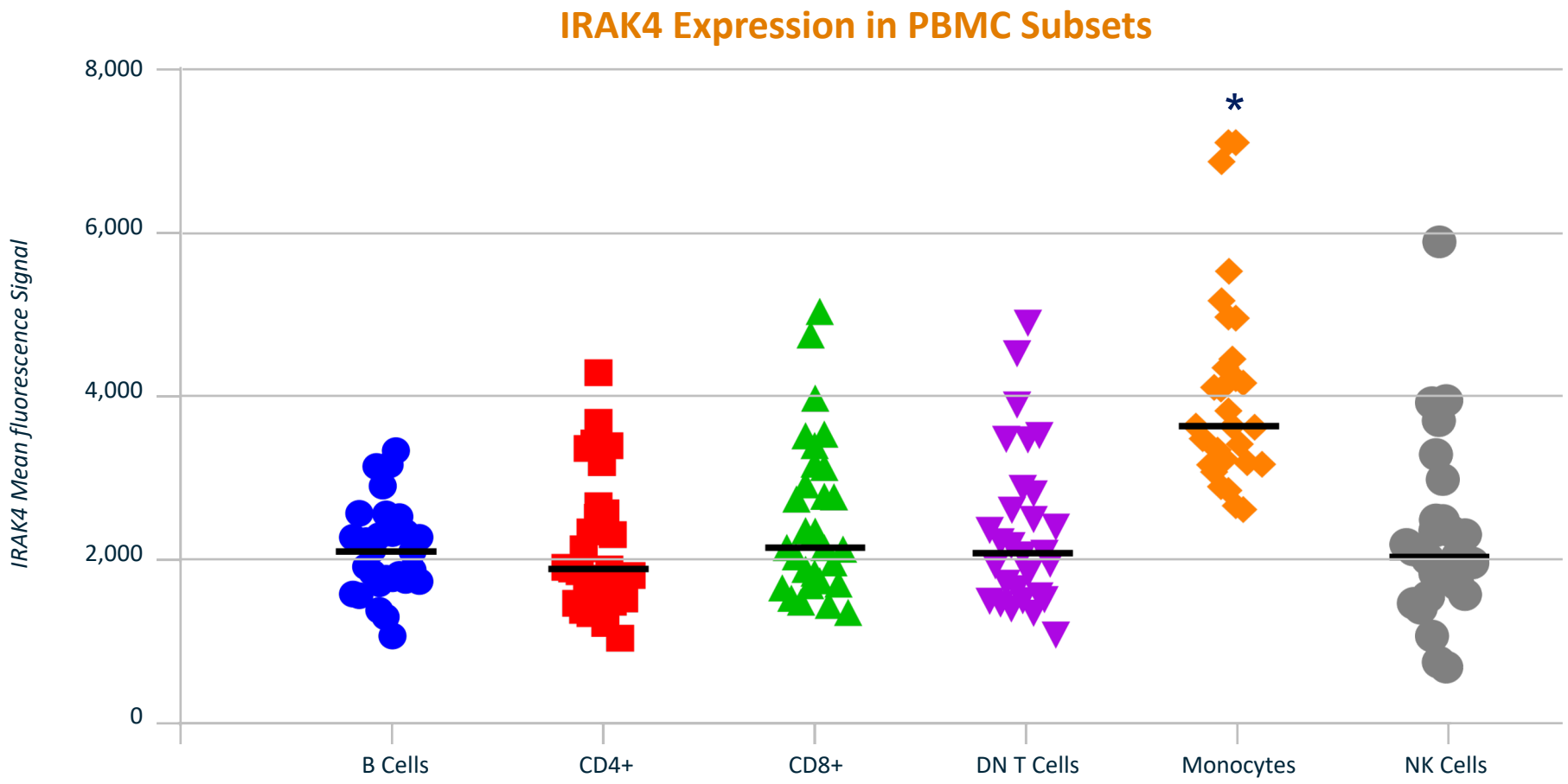
CONCLUSIONS

Lesional and Peri-lesional biopsies have more IRAK4+ cells and higher intensity IRAK4 staining than Non-Lesional as measured by IF.
MS with trend towards higher level of IRAK4 in L and PL compared to NL.

IRAK4 Expression in Peripheral Blood Mononuclear Cells

is Highest in Monocytes

- IRAK4 levels are significantly higher in monocytes compared to other PBMC subsets



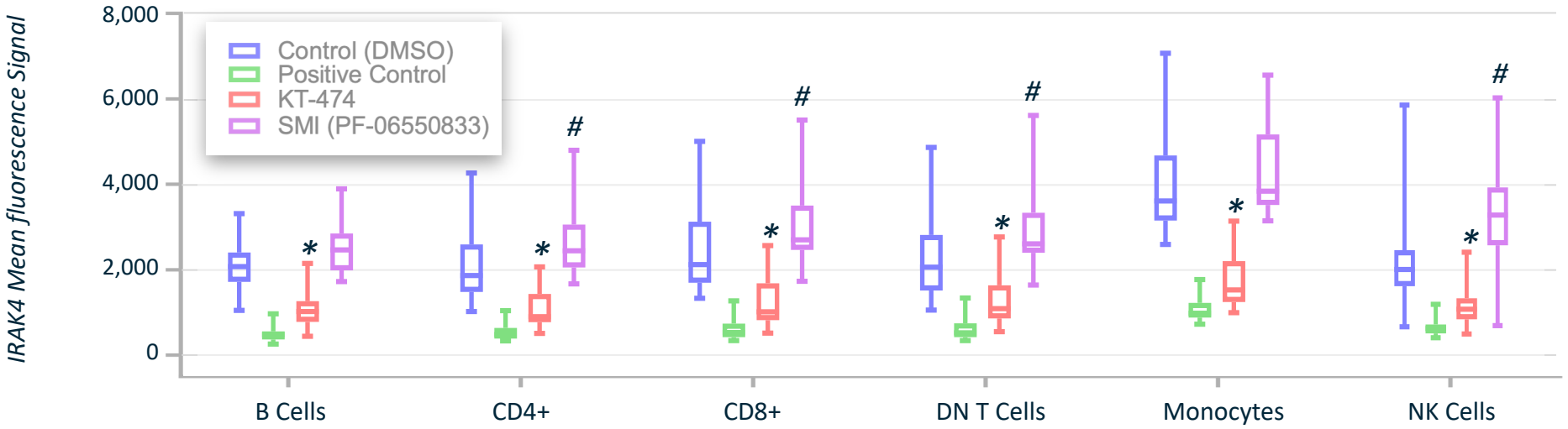
*N=30 (IHS4 severity: 9 mild, 10 moderate, 11 severe); *One-way ANOVA p≤0.0006*

IRAK4 Degrader Downregulates IRAK4 Expression Across All PBMC Subsets

Ex Vivo Blood Treatment

- Patient blood was treated with DMSO control or 200nM of KT-474 IRAK4 degrader or 200nM of IRAK4 kinase inhibitor (PF-06550833)
- Blood was incubated overnight at 37◦C (16-24 hours)
- Blood was shipped and processed for IRAK4 and lineage specific cell surface staining by flow

IRAK4 Levels Following Treatment with IRAK4 Degrader or Kinase Inhibitor



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

KEY TAKEAWAYS

- **Treatment with an IRAK4 degrader (KT-474) led to reduction of IRAK4 to a similar level approaching the lower limits of detection as determined by an anti-IRAK4 blocking antibody (Positive Control) across all PBMC subsets in HS patient blood, irrespective of baseline IRAK4 expression intensity**
- **Treatment with an IRAK4 kinase inhibitor led to an increase in IRAK4 levels of up to 2.6-fold in T and NK cells**

Conclusions

1. **TPD is a disease and target agnostic modality**
   Kymera is committed to demonstrate its impact across several diseases

2. **IRAK4 degradation fulfills Kymera's Drug Development Principles**
   Validated pathway in several immune-inflammatory diseases with key undrugged or not well drugged node

3. **IRAK4 degradation superior to inhibition**
   In blocking secretion of cytokines as well as in intracellular signaling

4. **IRAK4 levels are higher in L and PL skin compared to NL skin**
   supporting the relevance of the IRAK4 signaling pathway in HS

5. **Ex vivo incubation of HS blood with the IRAK4 degrader KT-474 reduces IRAK4**
   to a level approaching the lower limits of detection across all PBMC subsets, irrespective of baseline expression intensity, whereas an IRAK4 kinase inhibitor increases IRAK4 levels in T and NK cells

6. **Findings supports clinical development of KT-474 in HS** and other IL-1R/TLR-driven inflammatory diseases, with plans to **initiate Phase 1 in H1 2021**

THANK YOU

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