TPD Assay Development & Screening Summit
December 6 - 8, 2022 | San Diego, CA

Proteomics enabling TPD Drug Discovery

December 7, 2022

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Agenda

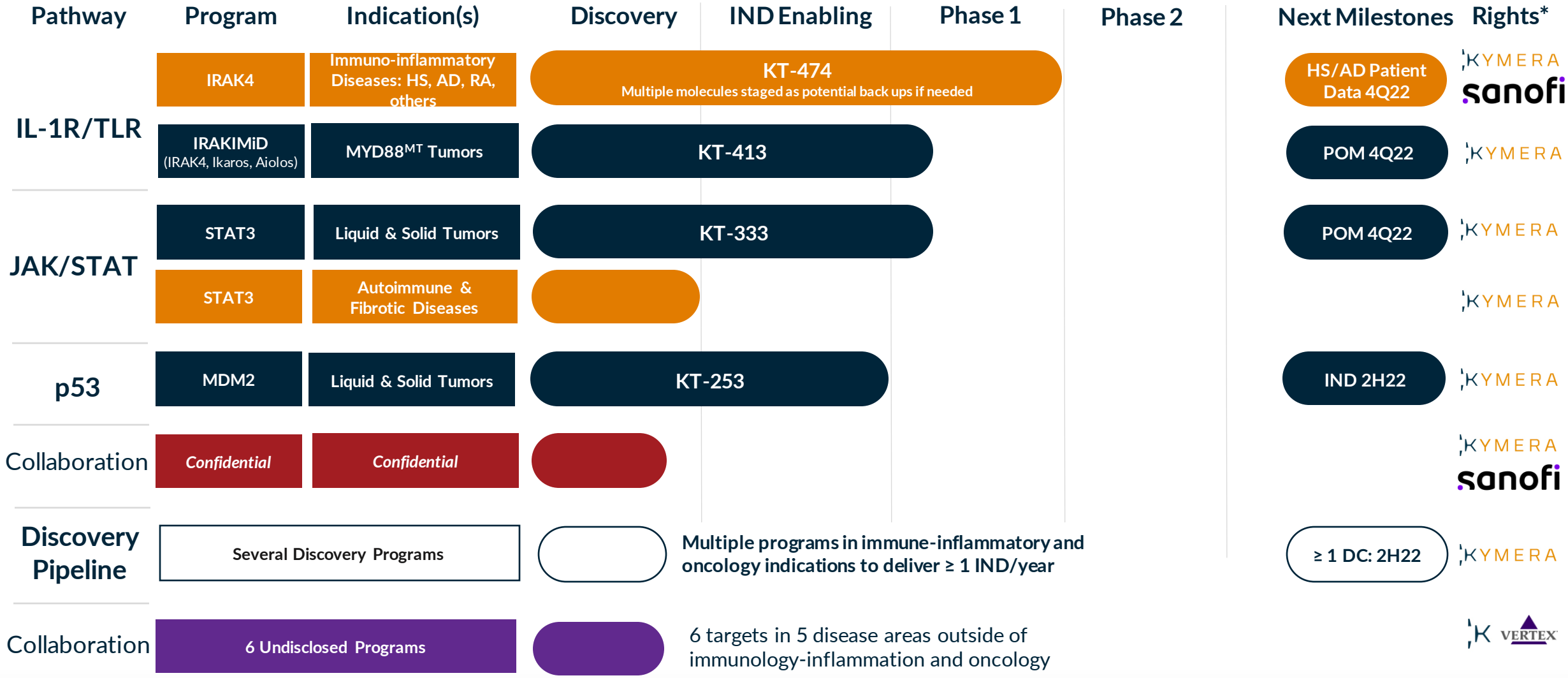
1. Targeted protein degradation at Kymera : enabled by quantitative proteomics
2. Applications:

   Platform - Tissue Restricted Degradation
   - **E**xpression: E3 Expression Atlas
   - **L**igandability: Novel E3 ligands
   - **D**egradability: E3 Biology & Substrates

   Pipeline – Inadequately Drugged Targets: IRAK4

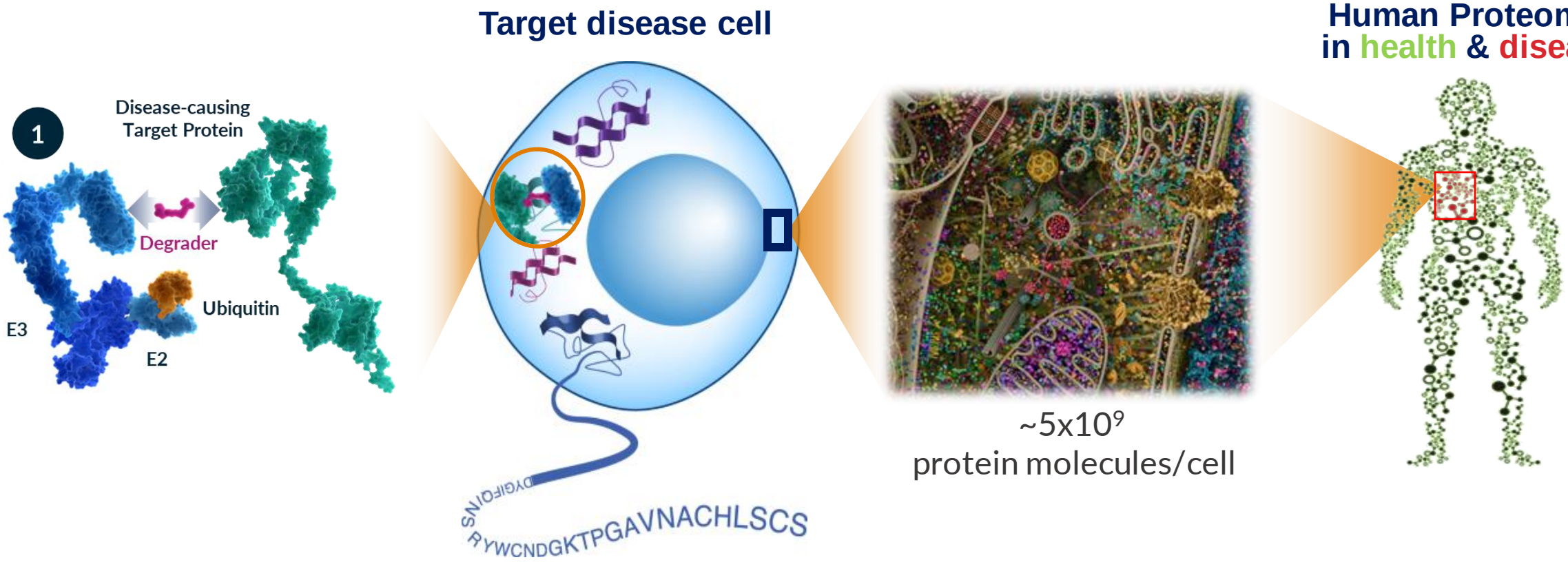
   E3 pairing | Selectivity | PD in (pre)clinical studies
3. Summary & forward looking

Kymera's Pipeline of Novel Protein Degraders



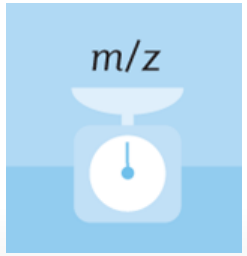
*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US

Proteome Editing By TPD
Empowered By a Technology Enabling Quantitative Assessment Of Proteomes



Quantitative Proteomics

Mass spec (a fancy weighting scale!) based ID & quant of entire proteomes

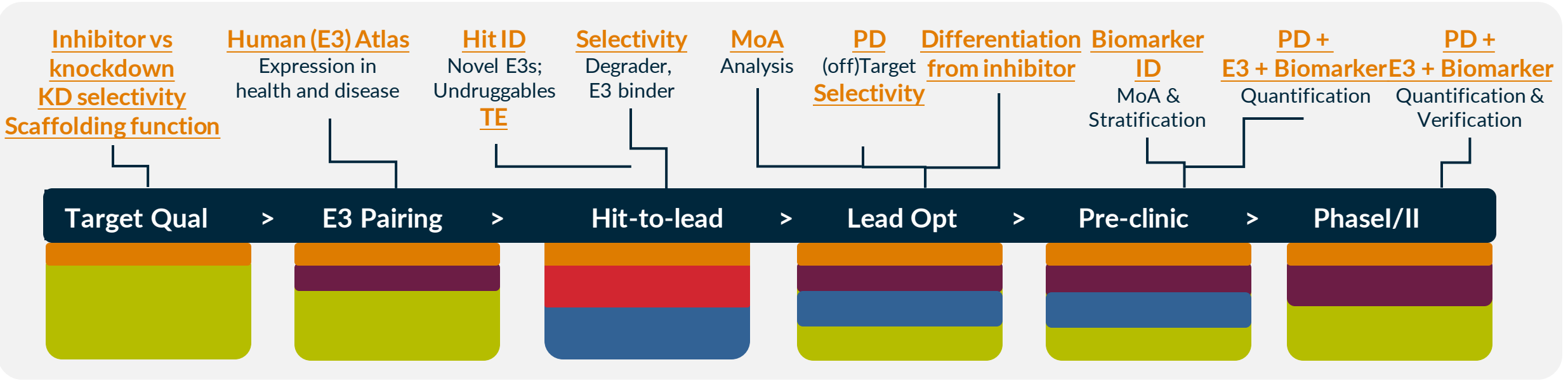


Key challenges in measuring proteome

- >10,000 proteins in cells (accurate ID)
- Dynamic range: 10 copies to >10^6 copies/cell (sensitivity)
- >1 million measurements/proteome (speed)

Proteomics in TPD drug discovery

Enabled by multiple 'types' of proteomics



Global PTM/Proteome, PPI analysis

Targeted Proteomics

Chemoproteomics

Computational Proteomics

Selectivity Analysis

Discovery Proteomics

Agenda

1. Targeted protein degradation at Kymera : enabled by quantitative proteomics

2. Example Applications:

   Platform - Tissue Restricted Degradation

   - **E**xpression: E3 Expression Atlas
   - **L**igandability: Novel E3 ligands
   - **D**egradability: E3 Biology & Substrates

   Pipeline – Inadequately Drugged Targets: IRAK4

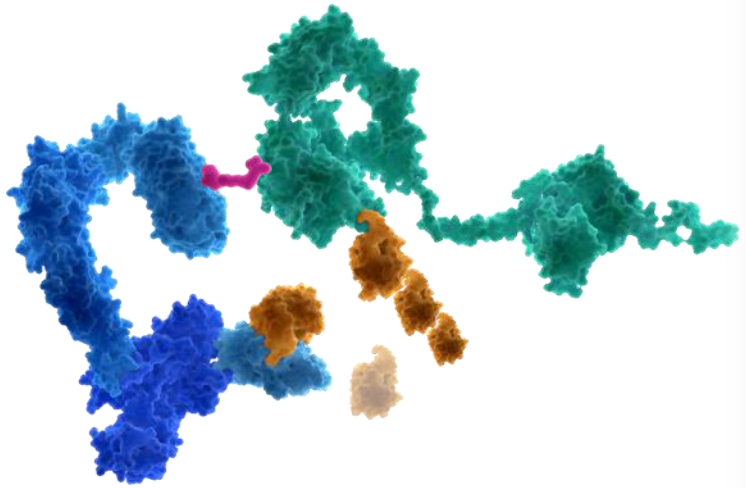
   E3 pairing | Selectivity | PD in (pre)clinical studies

3. Summary & forward looking

Expanding the Druggable Proteome with TPD

Proteome Editing with TPD

Small molecule binds to E3 & disease-causing target protein to **induce its degradation**



Medical knock down strategy with **flexibility of a small molecule drug** (oral & systemic)

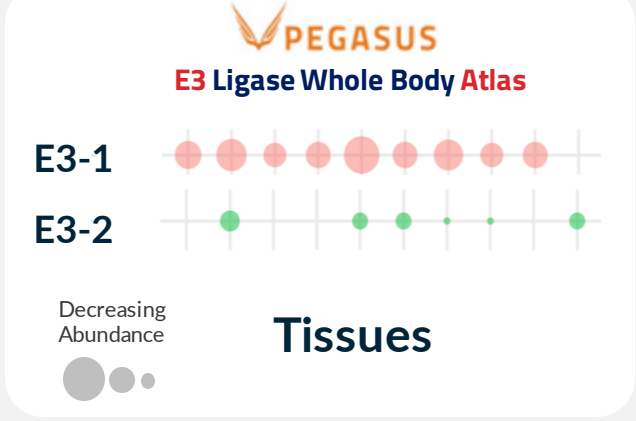
Target Types

ID **Inadequately Drugged Targets with Clear Degrader Advantage**
e.g. IRAK4*, MDM2

UD **Undrugged Targets by any other technology**
e.g. STAT3*

TR **Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression**

Tissue restricted degradation **via restrictively expressed E3s eliminates unwanted on-target toxicity** in certain heathy tissues



Tissue sparing or selective E3 ligases allow **full clinical potential**

* Kymera Degraders **in Clinic**

The 'Why', 'What' and 'How' of E3 Atlas

Why?	**Tissue Restricted**	**Differentiated** investment in **high value E3** Ligases
What?	**Human E3 Ligase Whole-Body Atlas**	Determine **expression profiles of ~600 unique E3 ligases (+ drug targets)** in both **health and disease**
How?	**Desired Features**	Determine the ideal approach

Approach: Proteomics + Novel Algorithm

- **Speed @ Budget:** *no* upfront reagent build cost ✓
- **Reliable:** protein level directly (+ QC) ✓
- **Deep Coverage:** all E3 ligases (& POIs) ✓
- **Scope:** human, whole body in health & disease ✓
- **Absolute abundance & stoichiometry** ✓

Development of a Human Whole Body Protein Expression Atlas

Strong Industry-Academia Collaboration

KYMERA

MAX PLANCK INSTITUTE OF BIOCHEMISTRY

Jürgen Cox Lab

Breakthroughs

- Algorithm for global concentration profiles
- Can tackle very heterogeneous quantitative proteomics data
- Computational scalability and feasibility
- Consolidated Atlas clusters globally by biology, not by technology

>4,000 Proteomes Integrated

>460 acquired @ Kymera
>3,400 published, e.g.

>40 Healthy Tissues

>560 Primary Tumor Samples (CPTAC)

>15+ Cell Types Relevant for Tox
(GI organoids, cardiomyocytes, hepatocytes…)

250 CCLE Cancer Cell Lines

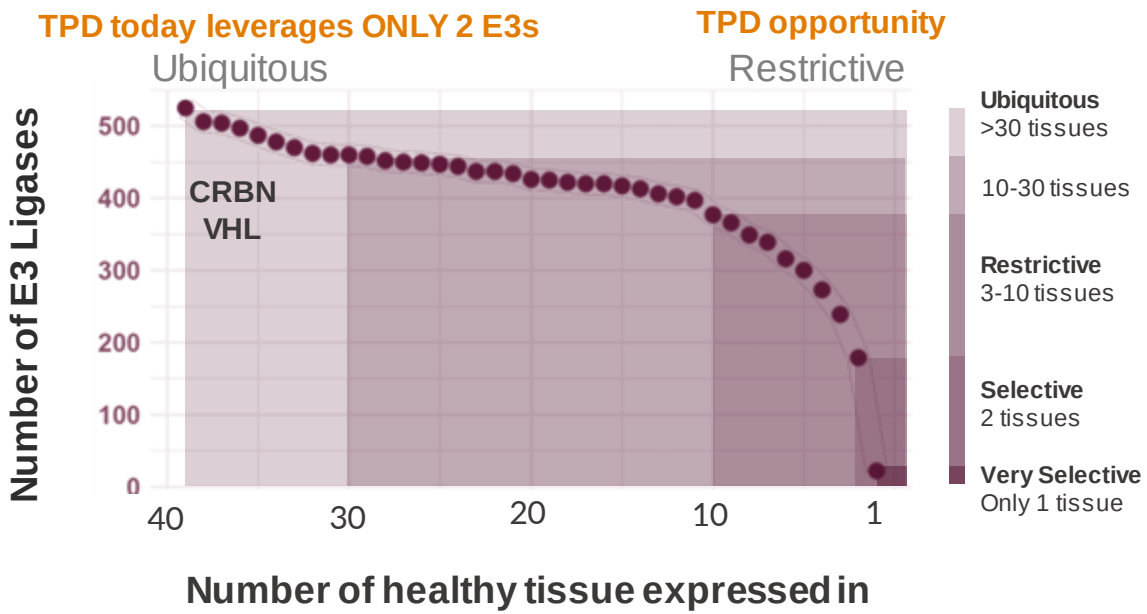
Skin Layers and Cell Types

Immune and Structural Cell Types
(T cells, B cells, keratinocytes, fibroblasts …)

>16.5k unique gene IDs in Atlas

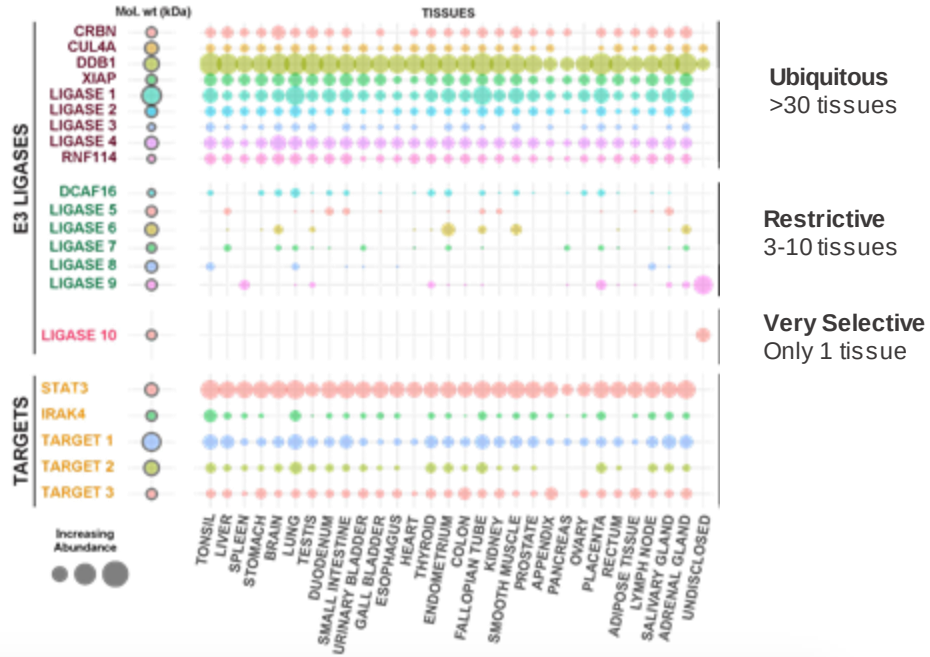
Novel E3 Ligases to Drug a New Generation of Targets

A Third of E3 Ligases are Selectively Detected in 1-2 Tissues



PEGASUS
E3 Ligase Whole Body Atlas

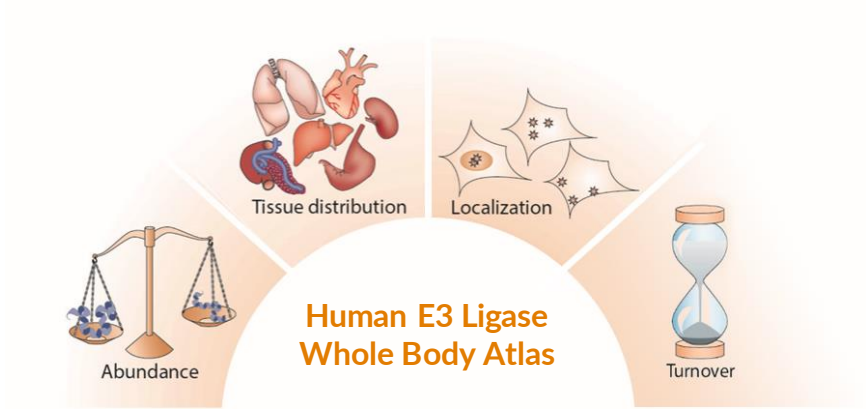
578 E3 Ligases
(Unique Gene IDs)

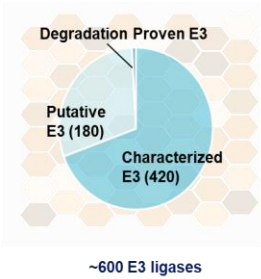


- Determined the expression profiles of ~600 unique E3 ligases
- Patterns mapped in both disease and healthy contexts
- Ability to match a target protein with appropriate E3 ligase based on expression and biology via a machine learning algorithm
- Vision to develop tissue-selective or tissue-restricted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

First Human E3 (& POI) Absolute Expression Atlas in Health & Disease

Invest in E3s with Tissue Sparing Potential for Targets with Unmet Clinical Need





E3 Ligase Matching TA or Target Criteria

- Pan expressed
- Differentially expressed
- Disease-specific
- Tissue-specific
- Tissue-sparing

MaxQuantAtlas

Relative Abundance in Health and Disease

- Tissue sparing or Ubiquitous
- Expression in disease: Broad or restricted

Absolute Abundance

- Benchmarking expression of novel E3s vs CRBN/VHL
- E3: target stoichiometry to predict efficiency of ternary complex formation

Subcellular Localization

- Match E3 and POI subcellular location
- ID colocalized (interacting) partners for compartment specific degradation approaches

Half-Life

- E3 and POI(s): QSP modeling and covalent hit strategies

Advanced Uses: e.g., Targeted Delivery of Degraders

- Selected expression of differentially expressed surface expressed proteins

Developing Next Gen Degrader for Precision Medicine

Well-established tox profiles

Clinically Validated Targets

High POS for TPD application

Ligases with varying Sparing potential

Multiple hit finding efforts

Degrader for Precision Medicine

Ligandability; **E**xpression; **D**egradation

Proteomics Enabling LED for a Bone Marrow Sparing E3 Ligase

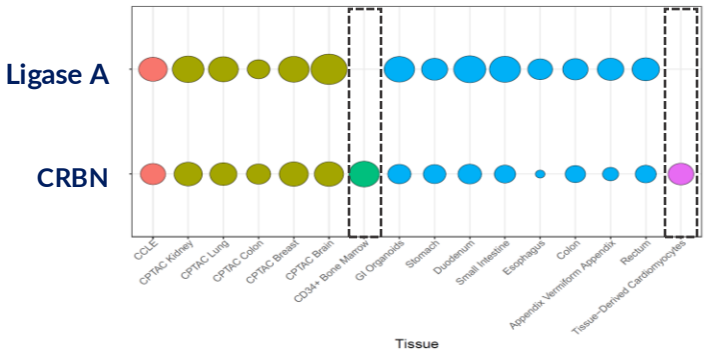
Expression
E3 Ligase
Whole Body
Atlas

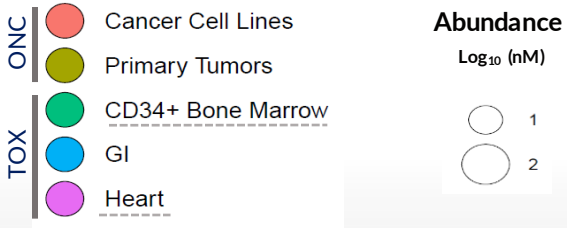
Ligandability
Chemoproteomics

Degradation
Novel Method –
E3 substrates ID

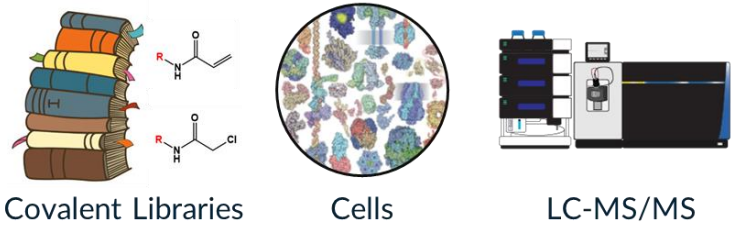
ID of Tissue Sparing E3s

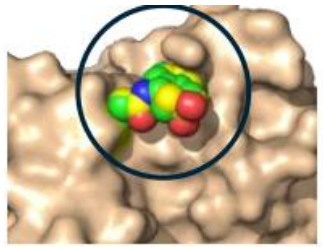
Expression in health & disease





Covalent Ligand Screening



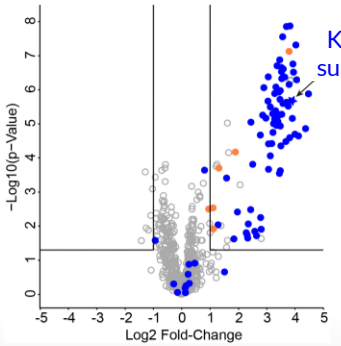


Novel covalent ligand to Ligase A

E3 Substrate ID

- Degradative Potential?
- E3 Biology?
- Degron ID→ DEL Screens

Substrate ID for Ligase A



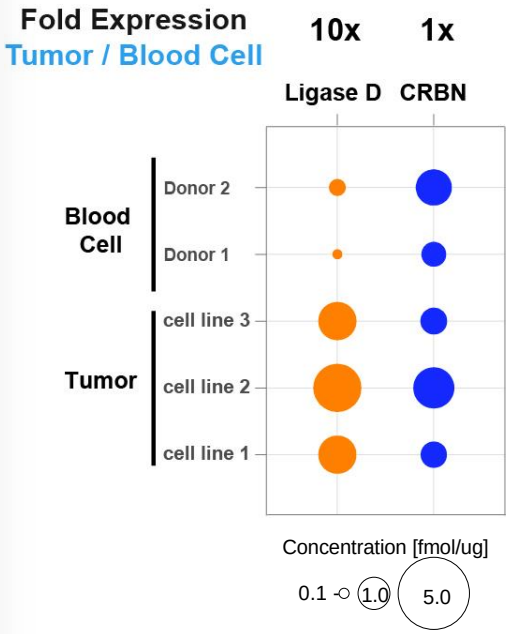
Ligase A / Control

E3 ubiquitinates almost exclusively expected protein class of substrates.

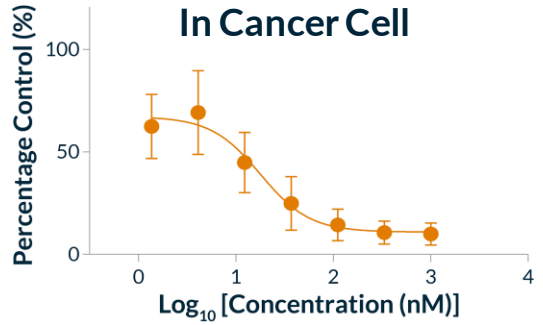
Unlocking a Clinically Validated Target by a Tissue Sparing E3

- Kymera has characterized an E3 ligase that is expressed broadly but NOT in ONE blood cell type
- A clinically validated oncology target has dose limiting toxicity driven by on-target pharmacology in the same blood cell type where this E3 ligase is absent/very low

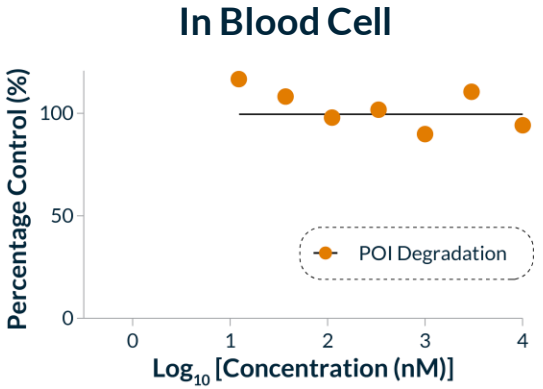
E3 Ligase is Almost Absent in One Blood Cell Type



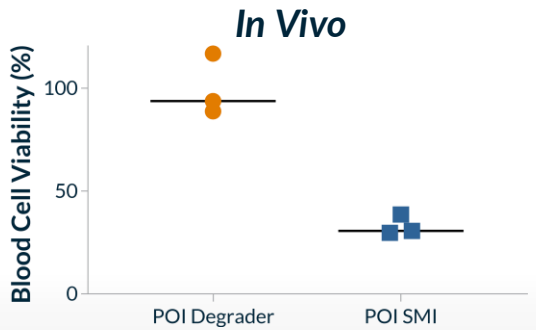
Optimization and Degrader Program



Kymera's degrader using this E3 ligase **degrades target in cancer cells**



Kymera's degrader using this E3 ligase **DOES NOT degrade target in one blood cell type**



In a pharmacologically active dose *in vivo* a **degrader allows blood cells to survive** while SMI leads to substantial cell death

POI = protein target of interest

Agenda

1. TPD at Kymera : empowered by quantitative proteomics
2. Applications

   Platform - Tissue Restricted Degradation
   - **L**: Chemoproteomics: Novel E3s ligands
   - **E**: E3 Expression Atlas
   - **D**: E3 Biology & Substrates

   Pipeline – Inadequately Drugged Targets: IRAK4

   E3 pairing | Selectivity | PD in (pre)clinical studies
3. Summary & forward looking

Expanding the Druggable Proteome with TPD

Target Types

ID **Inadequately Drugged Targets with Clear Degrader Advantage**
e.g. IRAK4*, MDM2

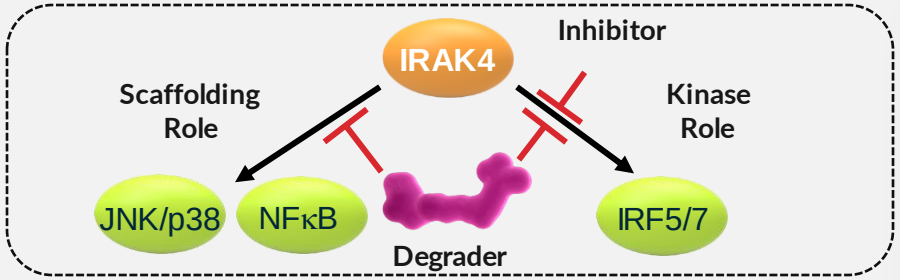
UD **Undrugged Targets by any other technology**
e.g. STAT3*

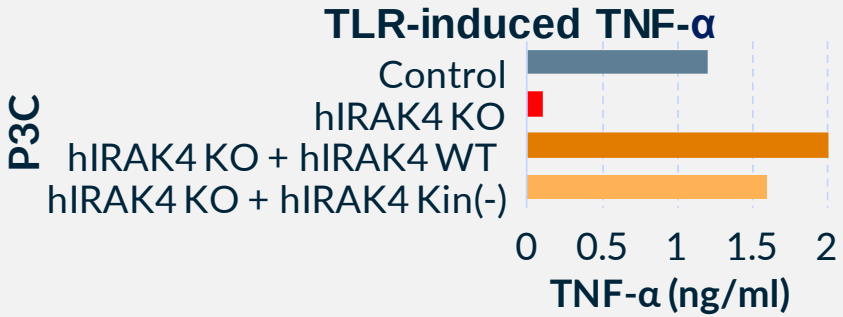
TR **Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression**

* Kymera Degraders **in Clinic**

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

Degrader Advantage





Source: Sun, et al. *Science Signaling*, 2016

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

IRAK4 : E3 Pairing

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Considerations for E3 Ligase Pairing of Immunology Targets

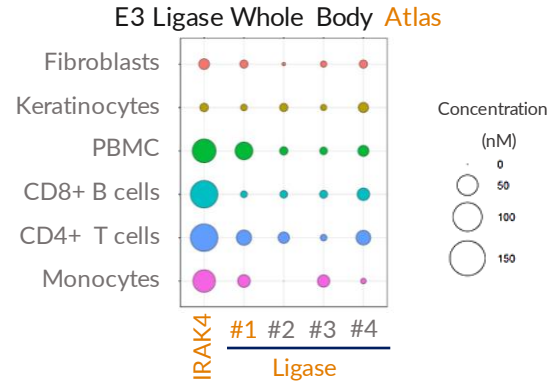
- What is the desired degradation profile for chronic inflammatory disease target?
  - Is the target ubiquitous?
  - What are the pharmacology relevant cell types?
  - How safe is your target?
- What are the desired properties of the E3 Ligands?

E3 Ligase Pairing: IRAK4

Key Questions:

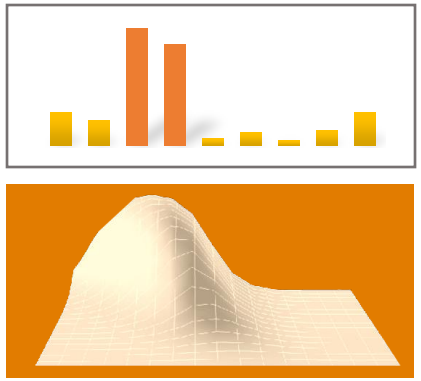
1. Can we achieve degradation in primary human cells?
2. Can we achieve equal potency in key cell types?

Select E3s expressed across all relevant cell types



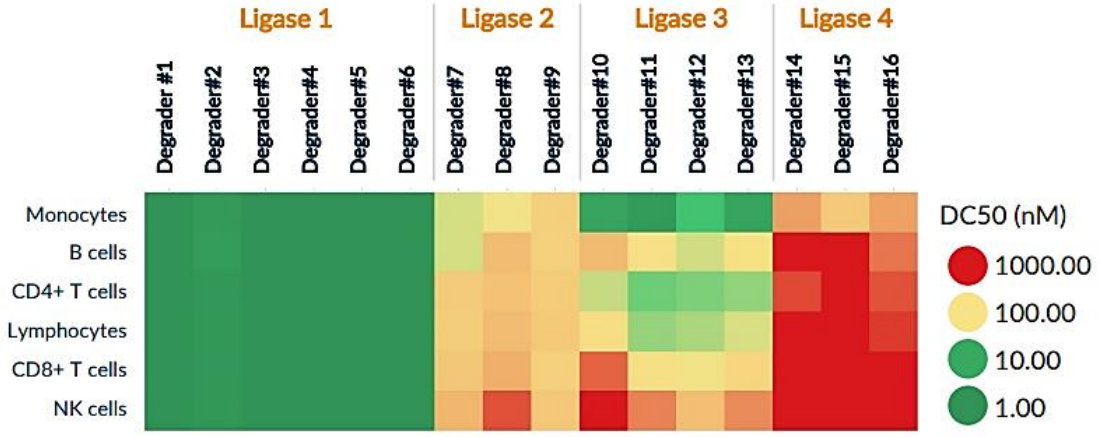
Relative Expression across Primary Immune & Tissue Cell Types

Predict E3s with best ternary complex kinetics



QSP Modeling
Absolute Expression E3 & Target + Cooperativity

Confirm IRAK4 Degradation



Flow Screening Assay

- Different IRAK4 degradation profiles in peripheral immune subsets based on E3 pairing
- Ligase 1 provides desired potency and degradation profile

IRAK4 : Degradation Selectivity

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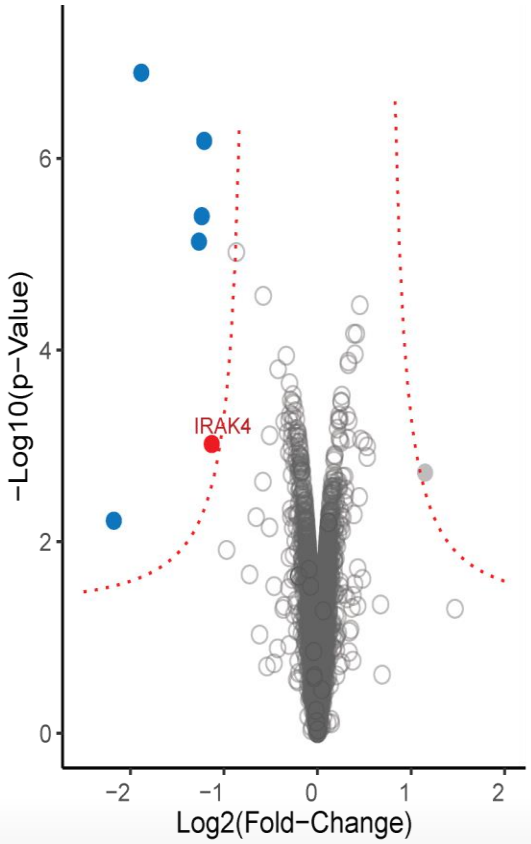
IRAK4 Selective Degraders Identified Using Discovery Proteomics

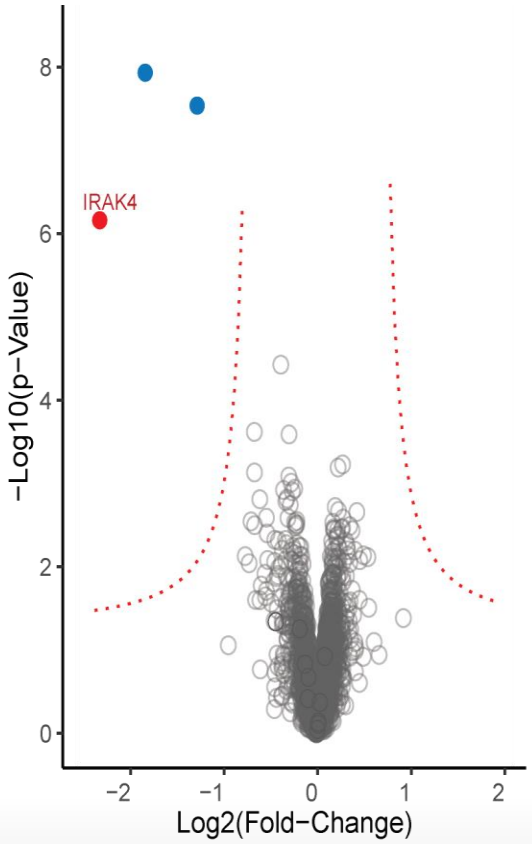
IRAK4 Degrader Selectivity

Less selective → **Highly selective**

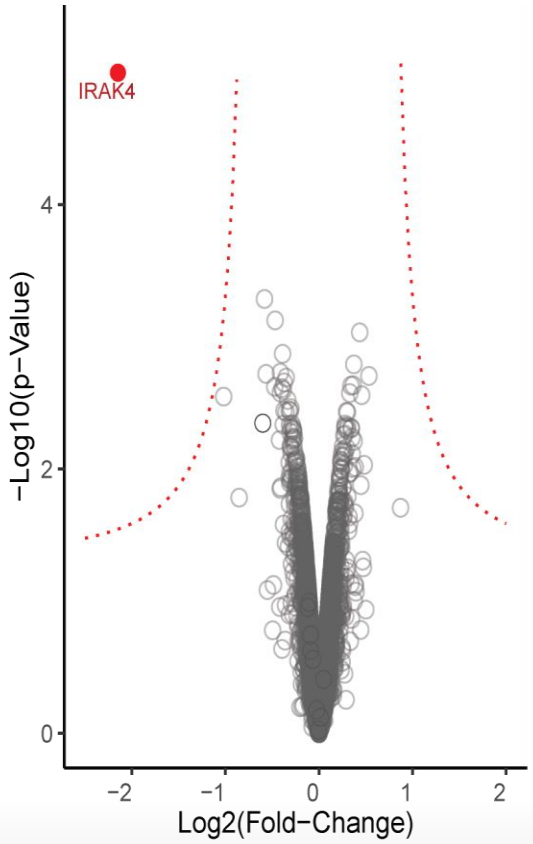
Series A



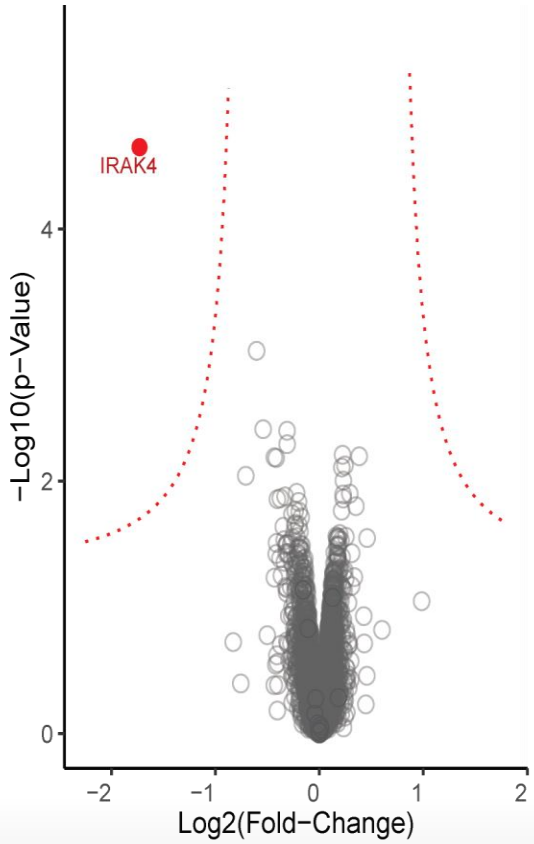
Series B



Series C



Series D

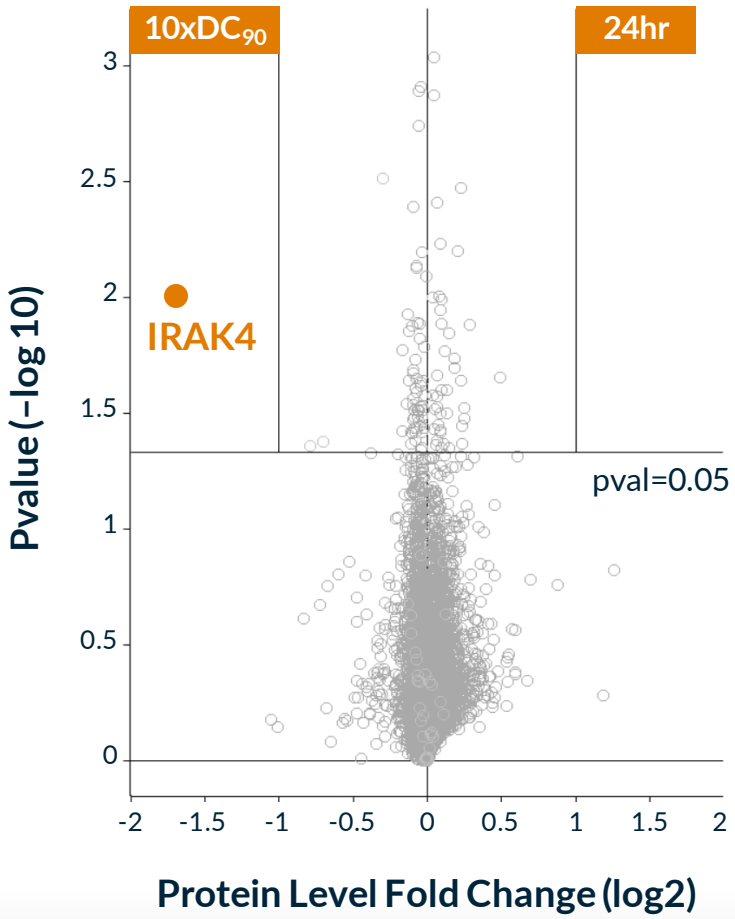


IRAK4

Legend
- IRAK4
- Significantly Upregulated Proteins
- Other Significantly Downregulated Proteins
- Significance Cutoff

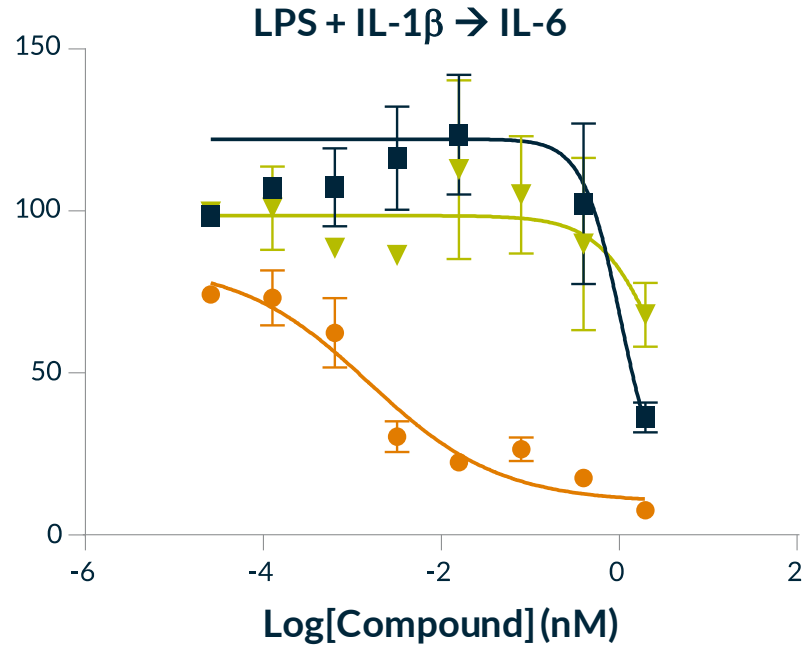
KT-474: Clinical DC shows Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

Degradation and Selectivity



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

Superiority over SM kinase Inhibitor



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

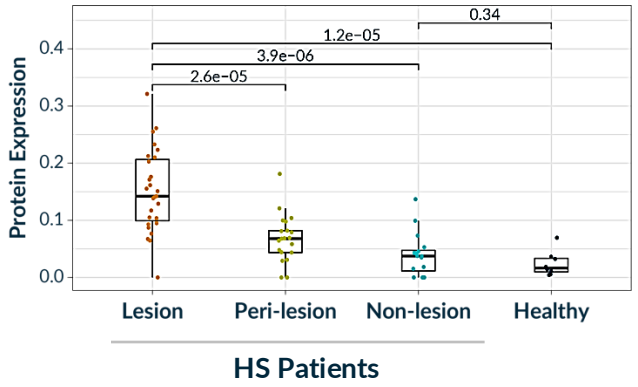
IRAK4:
Expression & Degradation Analysis in (Pre)Clinical Studies by Targeted MS

KYMERA

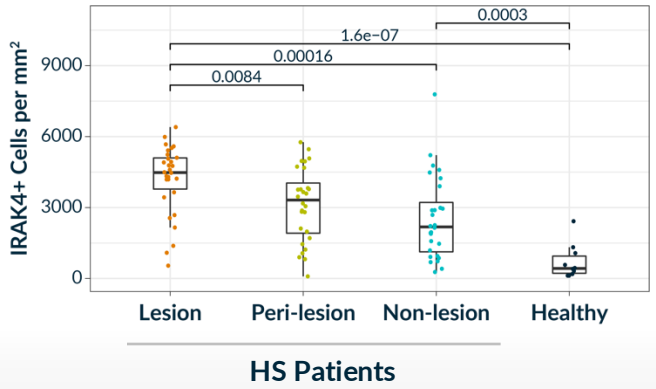
IRAK4 Protein Expression in Autoimmune Diseases: Upregulation in Skin of HS Patients Compared to Healthy Subjects

IRAK4 protein levels in skin

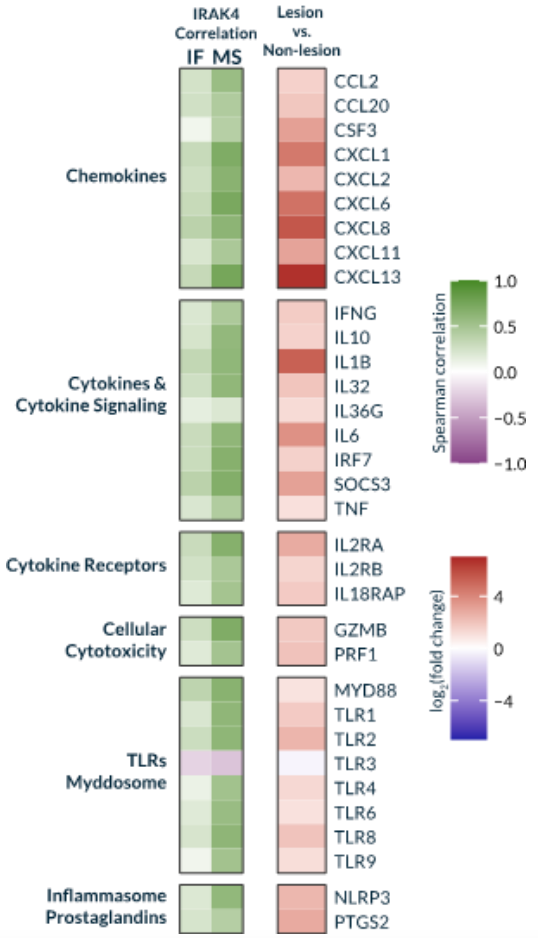
Targeted Proteomics



Immunofluorescence (IF)



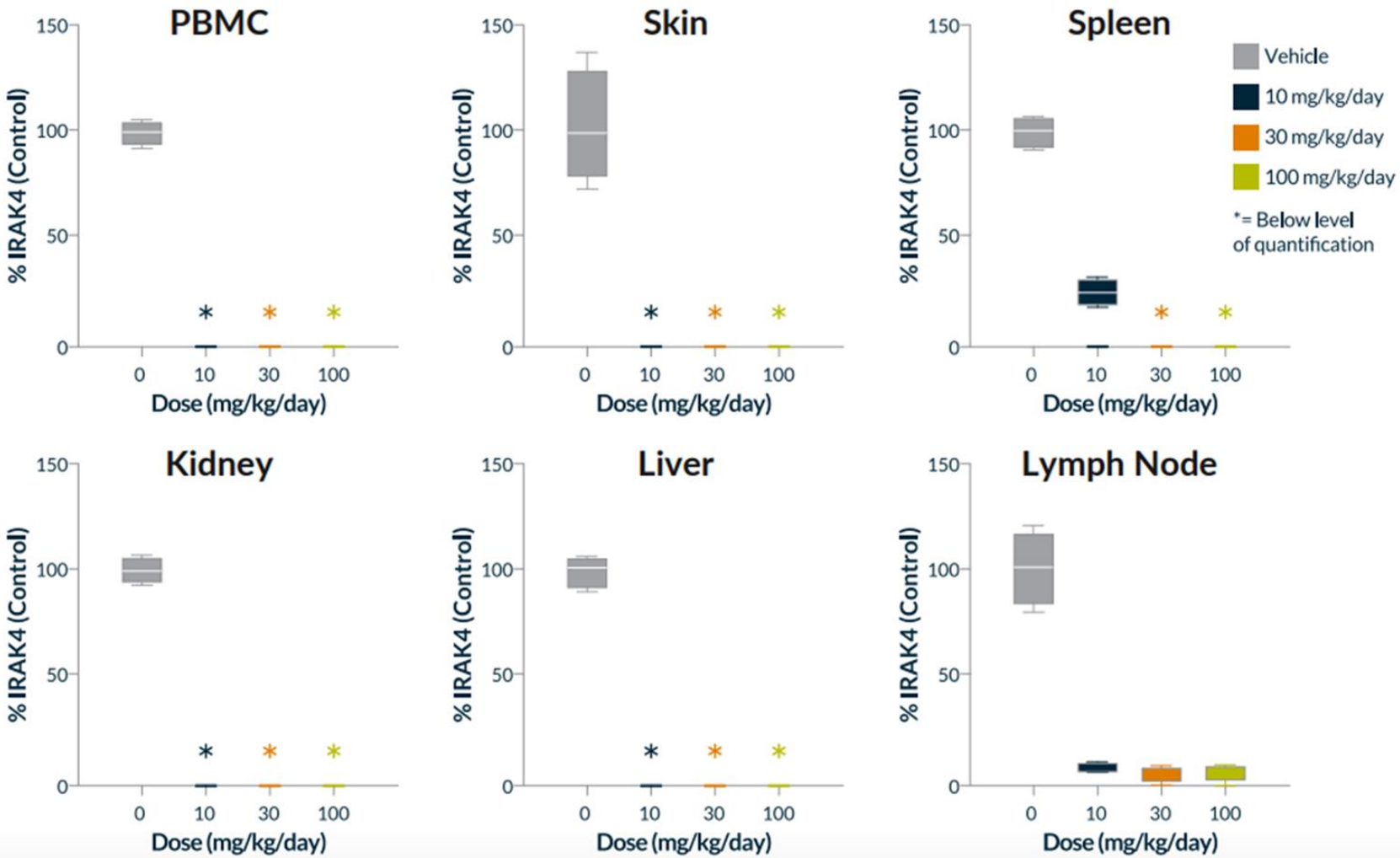
Proinflammatory Mediators Vs IRAK4 Protein Levels in HS Skin Lesions



IF: immunofluorescence; MS: mass spectrometry

- IRAK4 protein levels upregulated in HS patient skin lesions relative to healthy subject skin
- 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

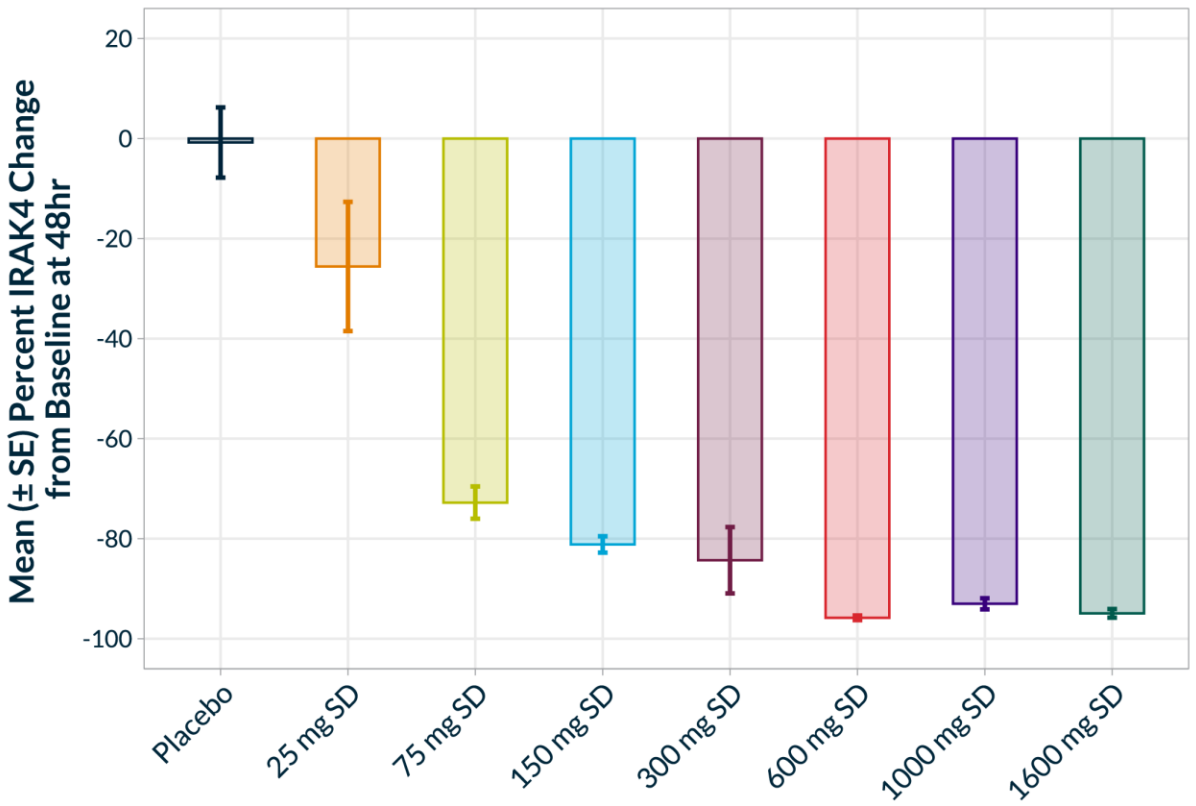
Systematic IRAK4 Degradation to Assay Detection Limits is Well Tolerated in Preclinical Non-rodent Model



- IRAK4 levels monitored using targeted MS assays
- Findings from this non-GLP dog study were used to project doses in subsequent preclinical dose range finding & human studies

Phase 1 Study
KT-474 Achieved >95% IRAK4 Degradation After Single Dose

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

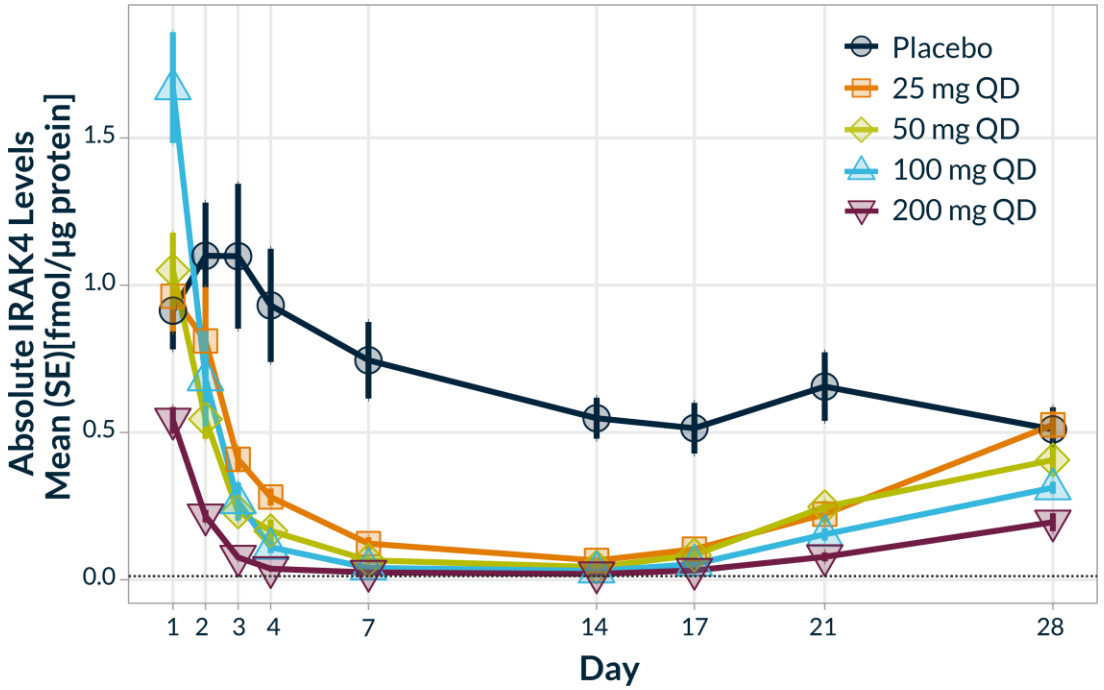


	N	Mean IRAK4 Change	Median IRAK4 Change	p value
Placebo	13	-1%	-2%	--
25 mg	6	-26%	-39%	0.1
75 mg	6	-73%	-75%	<0.0001
150 mg	6	-81%	-82%	<0.0001
300 mg	6	-84%	-89%	<0.0001
600 mg	7	-96%	-96%	<0.0001
1000 mg	5	-93%	-94%	<0.0001
1600 mg	6	-95%	-95%	<0.0001

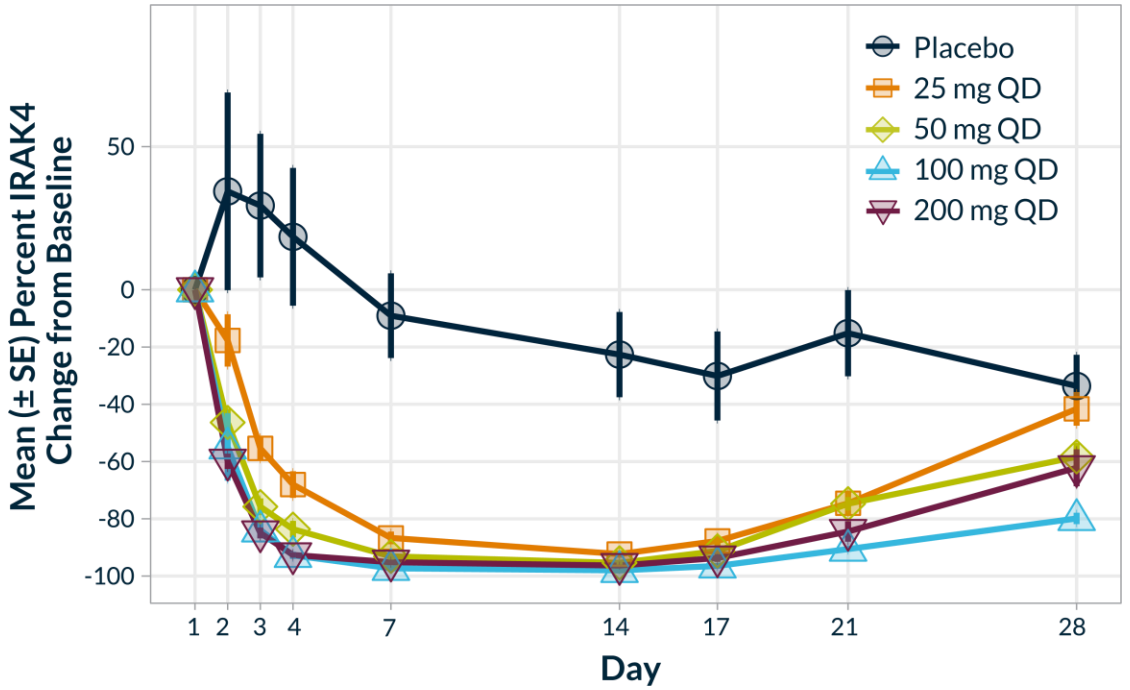
* p-values relative to placebo

Phase 1 Study : KT-474 Achieved Robust and Sustained IRAK4 Degradation with Multiple Daily Oral Doses (14 Days)

Absolute IRAK4 Levels in PBMC



Mean % Reduction of IRAK4



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

Summary

- Kymera intends to expand the druggable proteome under **all target classes** using TPD

- We routinely apply proteomics technology and innovate, as needed, to address key scientific questions across the TPD drug discovery process – Pipeline & Platform
  - Targeted proteomics for (pre) clinical applications & Kymera Selectivity Analysis Pipeline
  - Continued **Innovation** (E3 Atlas, Chemoproteomics, E3 substrate ID)

- Deep understanding of **degrader selectivity**
- Ability to routinely **monitor & quantify protein degradation** in preclinical & clinical programs
- E3 Ligase Whole Body Atlas **routinely used to identify tissue sparing E3 ligases** in a disease agnostic manner.
- Through **Pegasus Platform**, Kymera is able to chemically harness biology of identified novel tissue restricted E3 ligases.

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Lead Discovery

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