Targeted protein degradation in oncology and beyond

Xiaozhang Zheng, PhD
Senior Director of Chemistry

KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

February 2021

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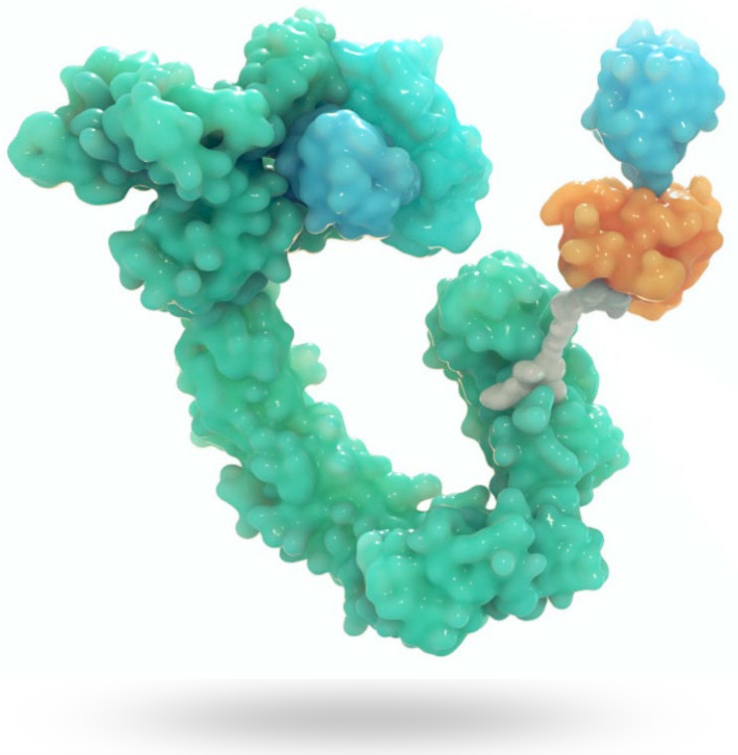
Outline

- Kymera introduction, platform and pipeline
- IRAK4 Degradation in Immunology and Inflammation
- Summary

Kymera: A Leading Targeted Protein Degradation Company

Founded:	2016
NASDAQ:	KYMR
Employees:	~75
Cash balance at Q4'20*:	~$458M
Cash runway*:	2025

KYMERA



- Premier protein degrader discovery platform
- Key partnerships:

  SANOFI VERTEX gsk
- Initial focus in immune-inflammation and oncology
- Expect **3 INDs** and clinical initiations by end of **2021**
- Dosing HV, I/I and cancer patients with first proof-of-biology in humans in **2021**

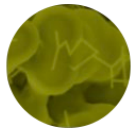
* Kymera expects that its cash, cash equivalents, and investments as of 12/31/2020, excluding any future potential milestones from collaborations, will enable the Company to fund its operational plans into 2025. This cash estimate is based on information currently available, and may differ from the actual cash balance to be included in the Company's audited financial statements

Proprietary Pegasus™ TPD Platform

Key capabilities

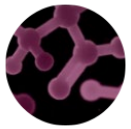
E3 Ligase Whole-Body Atlas

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



E3 Ligase Binders Toolbox

- **Toolbox of proprietary ligands** leverages the E3 Ligase Whole-Body Atlas



Ternary Complex Modeling

- Ternary complex modeling tool **optimizes the development** of highly efficient and selective degrader therapeutics

Quantitative System Pharmacology Model

- Model **measures and predicts 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

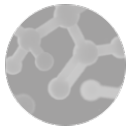
- Proprietary chemistry expertise enables the design and optimization of both E3 ligases and target protein binders
- Ability to convert them into degraders with optimal pharmaceutical properties tailored to specific patient populations and diseases

Pegasus

E3 Ligase Whole-Body Atlas

E3 Ligase Whole-Body Atlas

E3 Ligase Binders Toolbox

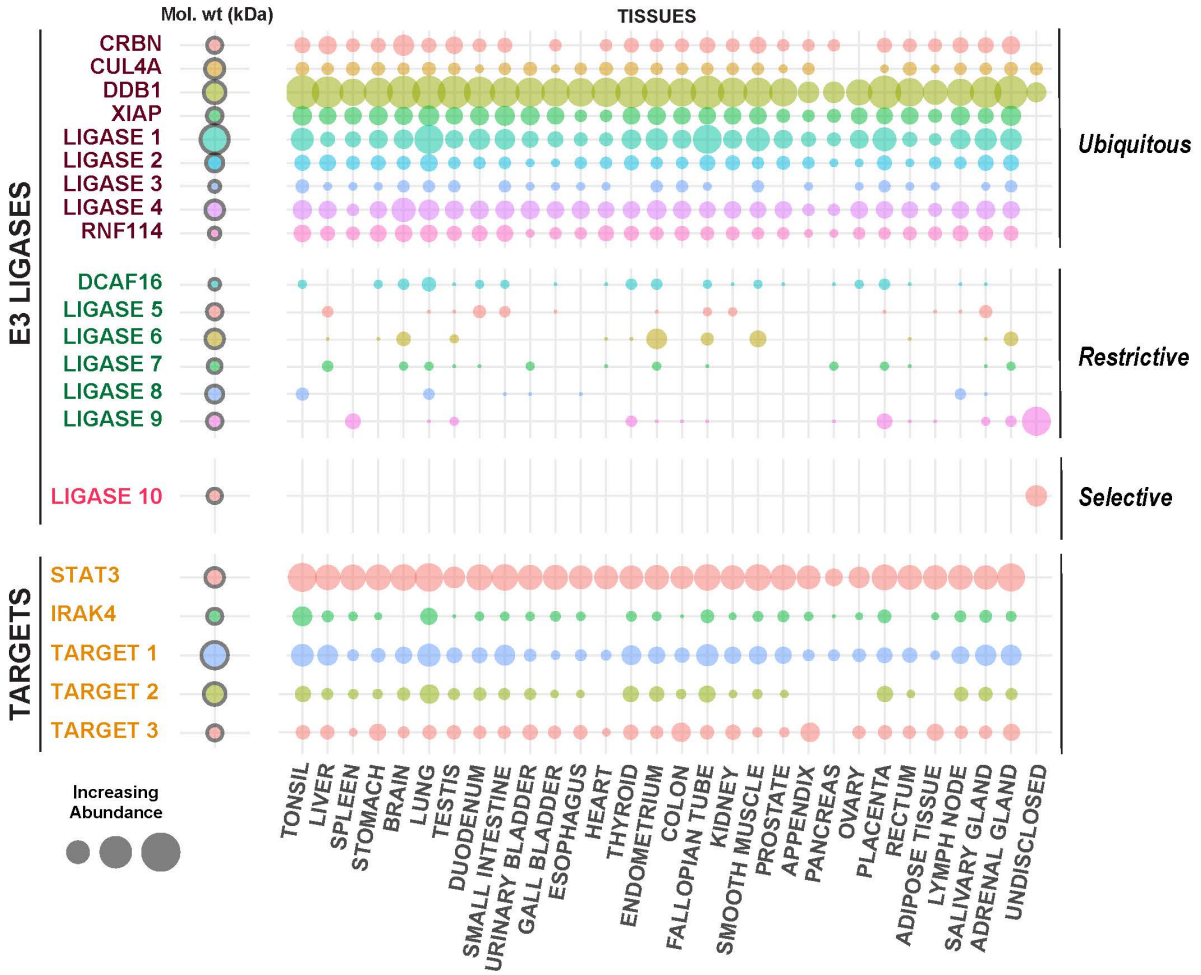


Ternary Complex Modeling

Quantitative System Pharmacology Model

Proprietary Chemistry

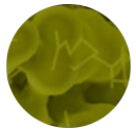
- Focused on determining the expression profiles of ~600 unique E3 ligases
- Patterns mapped in both disease and healthy contexts
- Ability to match a target protein with appropriate E3 ligase based on expression, and biology
- Vision to develop tissue selective or tissue restricted degraders to enable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

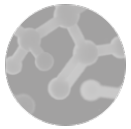


Pegasus

E3 Ligase Binders Toolbox


E3 Ligase Whole-Body Atlas


E3 Ligase Binders Toolbox

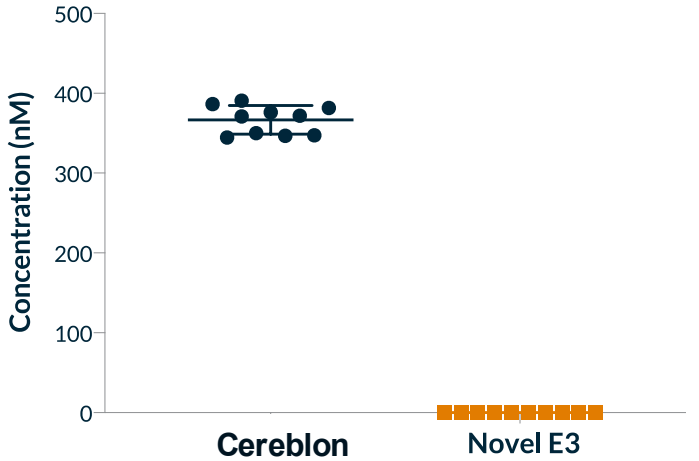

Ternary Complex Modeling


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

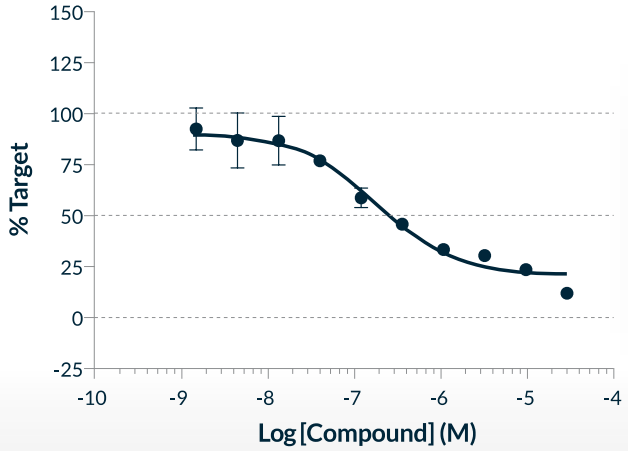
This E3 Ligase is Not Expressed in Bone Marrow



Bone marrow: CD34+ from five donors

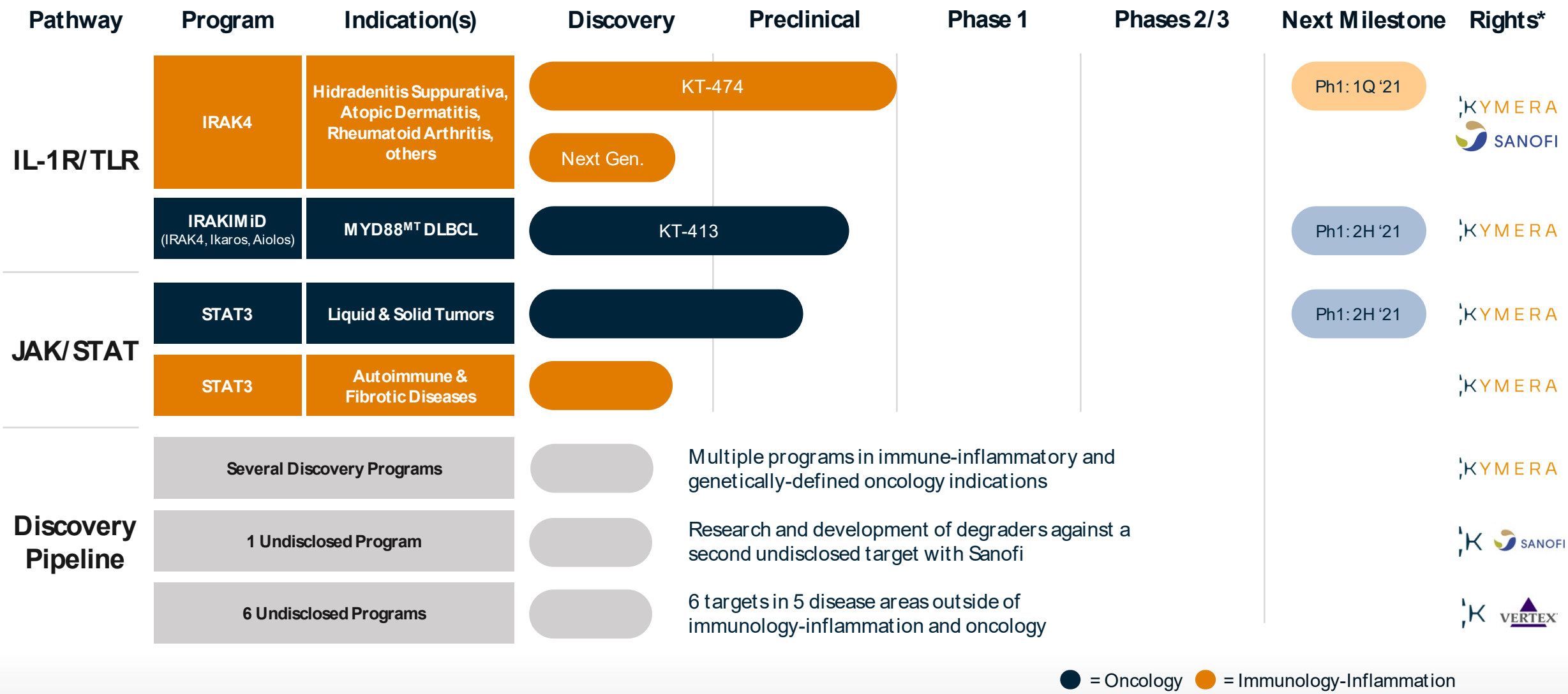
Ligand Identification

TPD with Bone Marrow Sparing Novel E3 Ligase



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

Kymera's Pipeline of Novel Protein Degraders



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

IRAK4

KYMERA

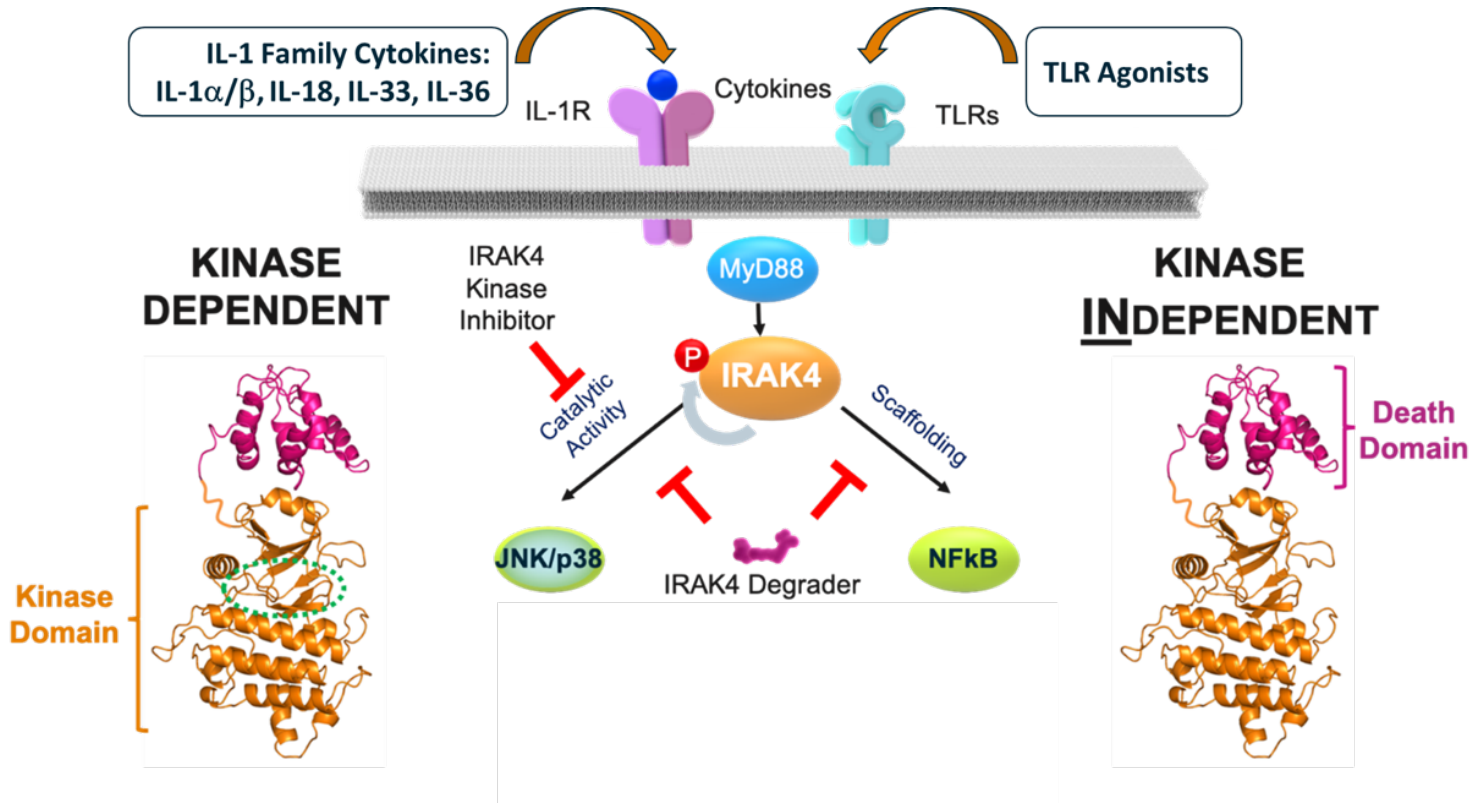
IRAK4 Biology and Degrader Rationale

- IRAK4 is a key component of the myddosome protein complex
- Myddosome is 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
- Believe degrading IRAK4 can provide a single oral small molecule solution to many diseases impacted by this pathway
- Sanofi collaboration on development of degraders targeting IRAK4 outside oncology and immuno-oncology

Indications/ Expected Timeline

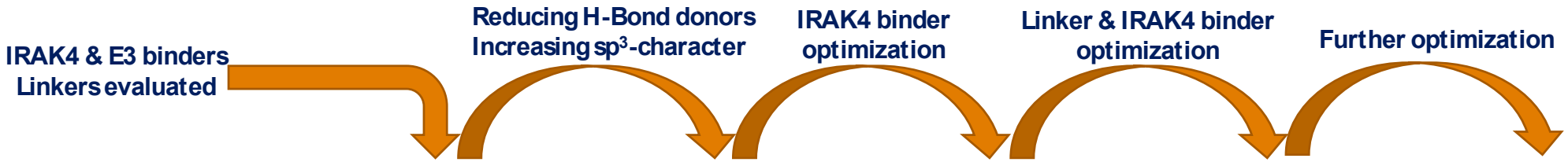
HS, AD, RA

Phase 1 SAD initiation: 1Q 2021
Phase 1 MAD enrollment: 2H 2021*
Phase 1 proof-of-biology in healthy volunteers: 4Q 2021



*Plan to initiate SAD portion of Phase 1 trial in 1Q 2021. Initiation of MAD portion of Phase 1 trial is on partial clinical hold pending FDA review of interim SAD data.

IRAK4: Road to development candidate KT-474



Key Milestones	Cpd-1	Cpd-2	Cpd-3	Cpd-4	KT-474
IRAK4 DC_{50} (nM)	40	7	7	41	
h-/r-LM Cl_{int} (µL/min/mg)	317 / 193	< 1.4 / 5	74 / 22	5.9 / 5.0	
P_{app} (10^{-6} cm/s)	ND	2.6	6.0	14	
Rat PK: CL (mL/min/kg) / %F	ND	40 / 11	35 / 8	19 / 14	
Proteomics: degradation over 10,000 proteins	ND	> 10	2	1	
Monkey PK: CL (mL/min/kg) / %F	ND	ND	129 / 1	33 / 45	

*Plan to initiate SAD portion of Phase 1 trial in 1Q 2021. Initiation of MAD portion of Phase 1 trial is on partial clinical hold pending FDA review of interim SAD data.

Oral exposure has been achieved across multiple species

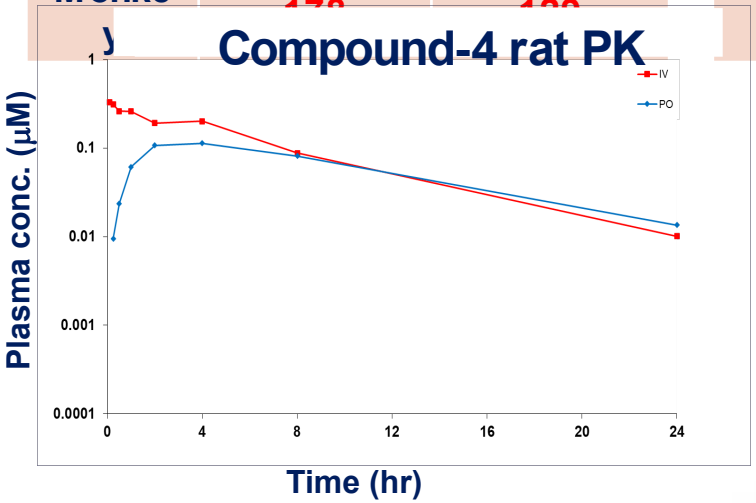
Compound-3

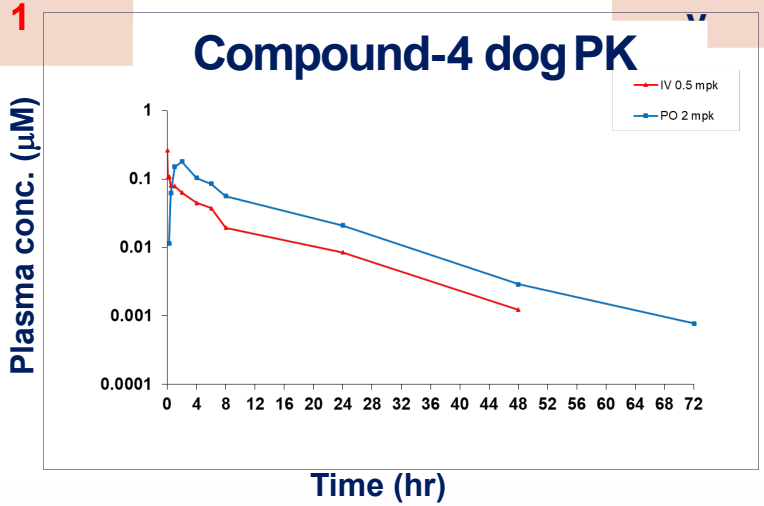
Species	LM Cl_{int} (µL/min/mg)	iv Cl (mL/min/Kg)	po %F
Rat	22	14	11
Dog	32	69	28
Monkey	178	120	1

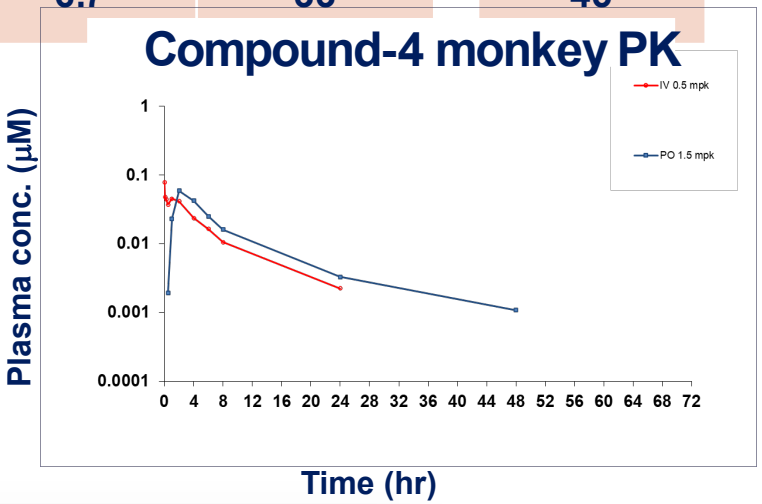
Linker & IRAK4 binder optimization

Compound-4

Species	LM Cl_{int} (µL/min/mg)	iv Cl (mL/min/Kg)	po %F
Rat	5.0	19	14
Dog	< 1.4	16	58
Monkey	6.7	33	45



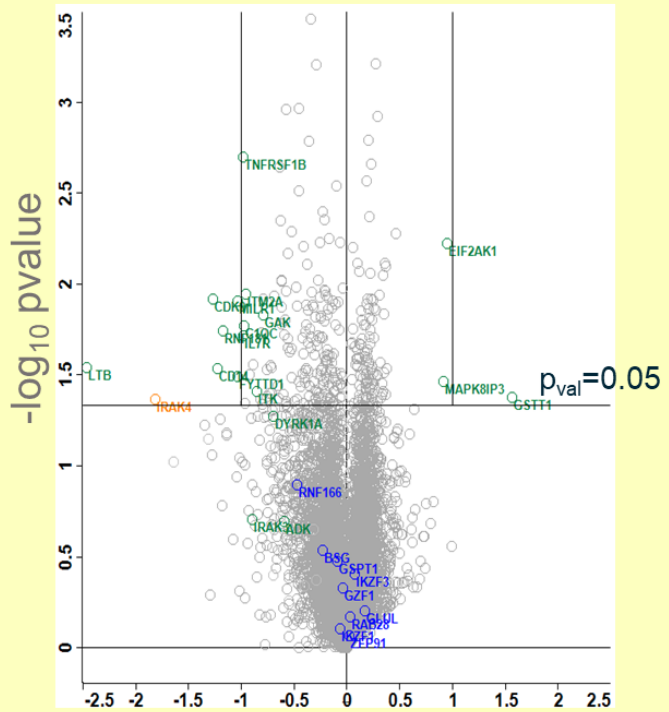




- Reducing clearance has increased oral bioavailability

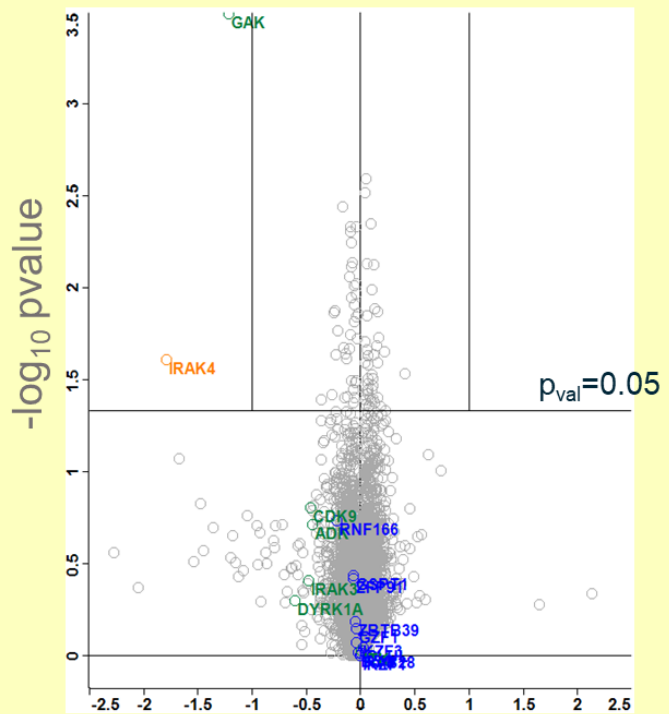
IRAK4 protein is selectively degraded over 10,000 proteins

Compound-2 proteomics



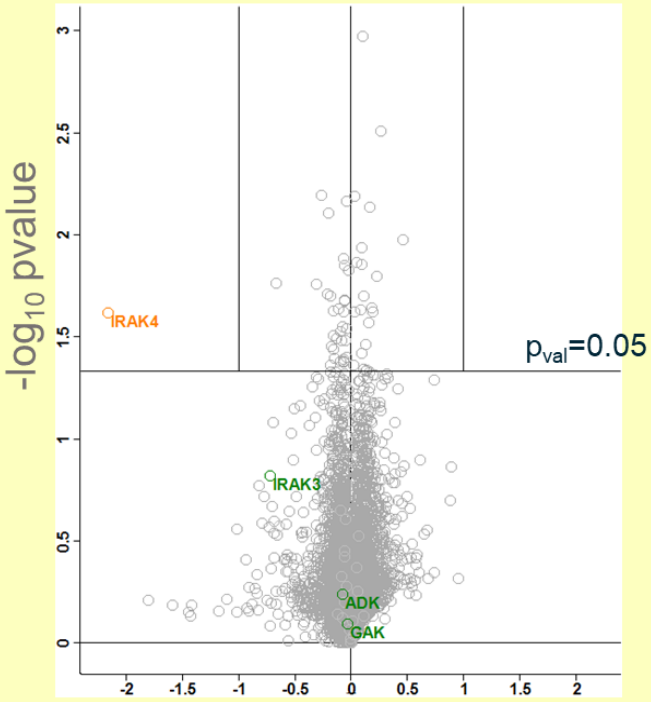
multiple proteins are degraded over 10,000

Compound-3 proteomics



two proteins are degraded over 10,000

Compound-4 proteomics



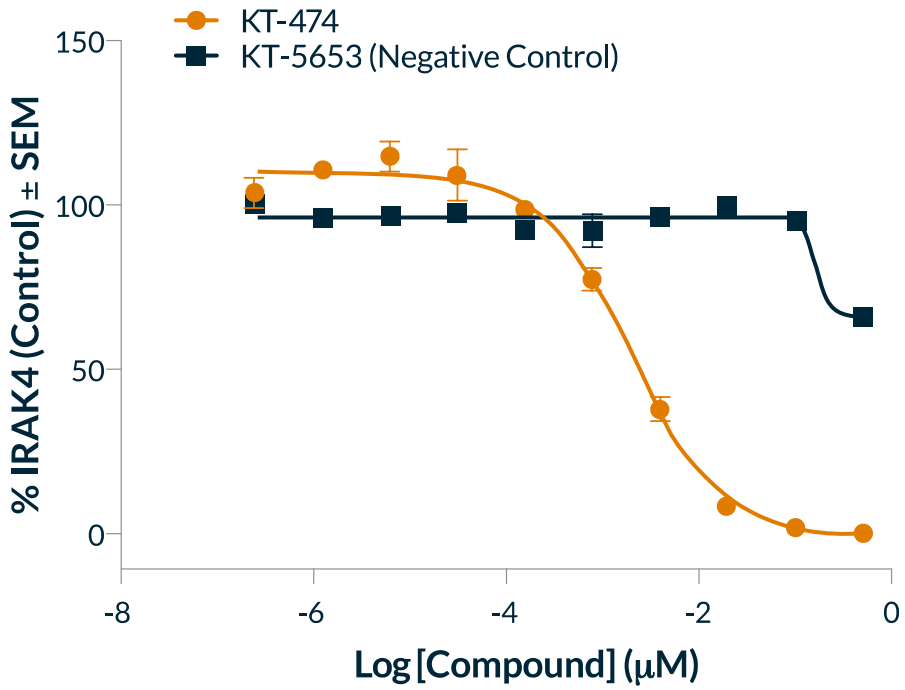
one protein is degraded over 10,000

- Proteomics in PBMC @10x DC_{90}

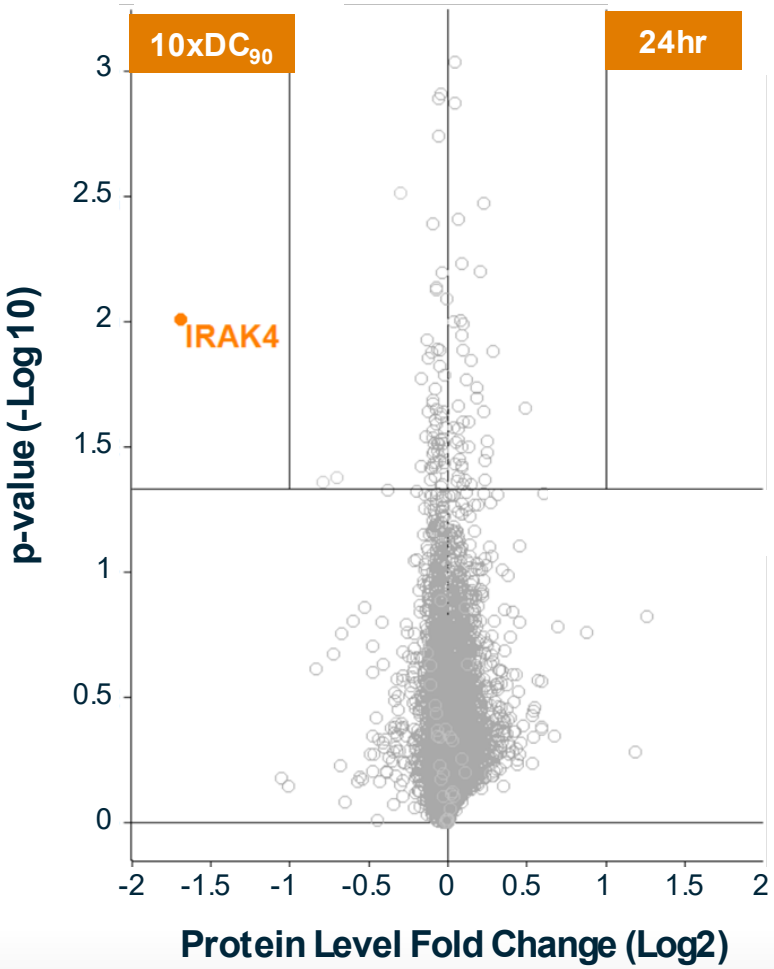
- IRAK4 binder and linker modification led to protein degradation selectivity improvement

KT-474: Specific IRAK4 Degradation

Degradation in Human Monocytes



Selectivity in Human PBMC

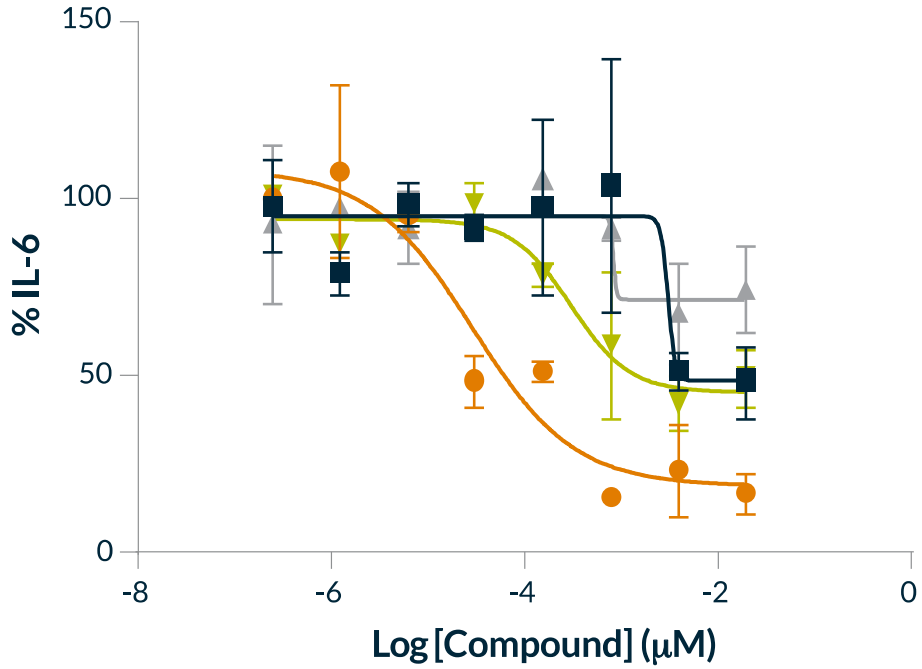


- Calculated DC_{50} of 2.1 nM and E3 ligase dependent degradation of IRAK4 in human immune cells
- IRAK4 was only protein of over 10,000 to be degraded by KT-474 in human immune cells at concentration 10-fold above the DC_{90}

IRAK4 Degradation Superior to Kinase Inhibition in Cytokine Production

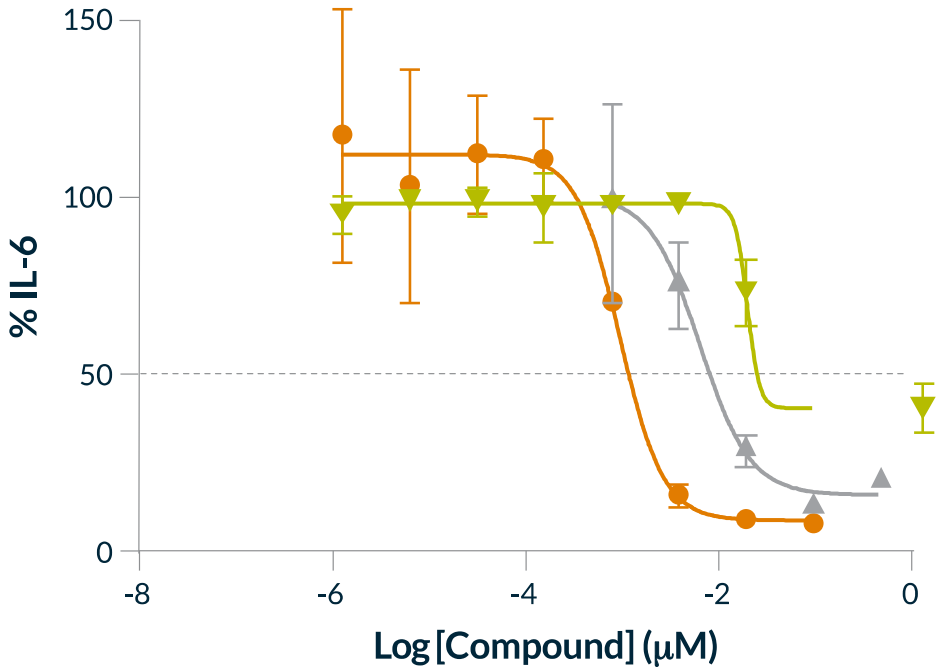
- Functional activity of KT-474 assessed by measuring pro-inflammatory cytokine levels upon activation
- Cells pre-treated with KT-474, a negative control, and two small molecule IRAK4 kinase inhibitors
- KT-474 better able to inhibit IL-6 under both LPS and R848 than clinically active IRAK4 SM kinase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

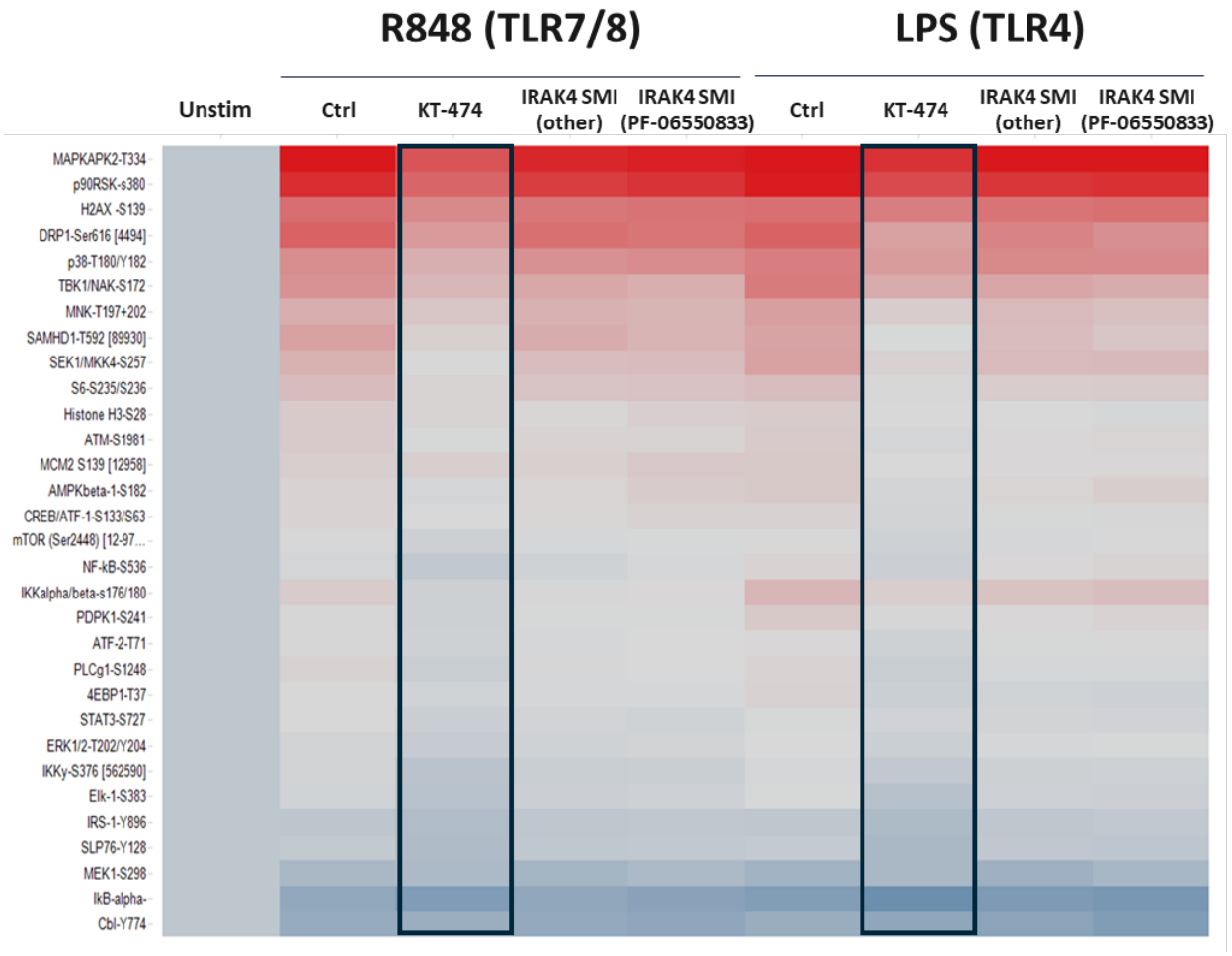
R848 → IL-6



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

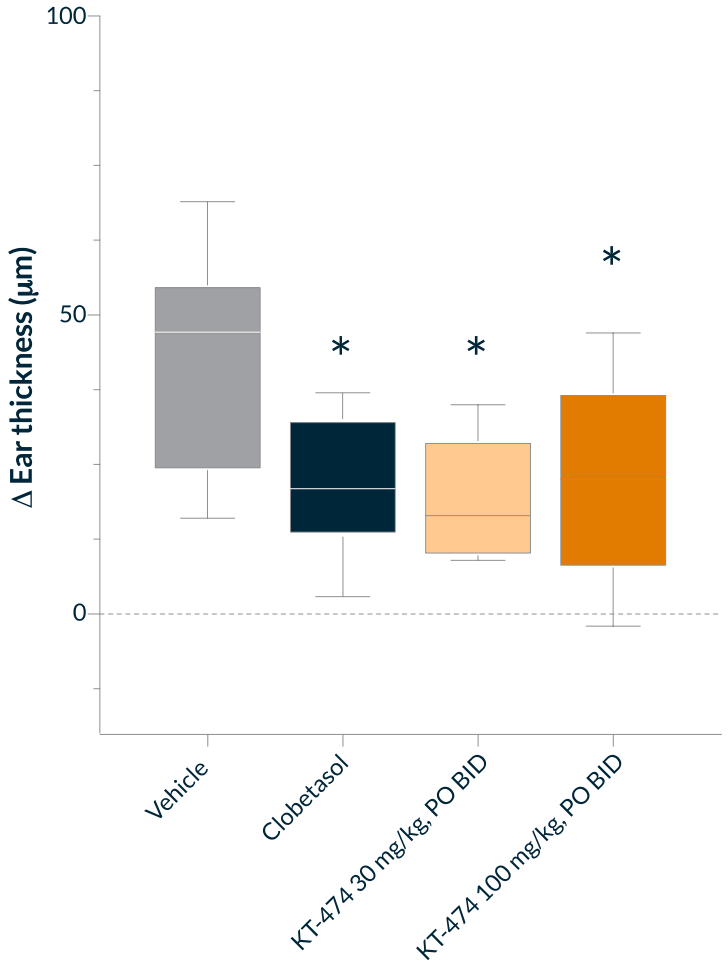
- Phosphorylation events upon TLR activations monitored using flow cytometry
- KT-474 inhibited pro-inflammatory phosphorylation events in a superior manner to small-molecule inhibitors including clinically active PF-compound

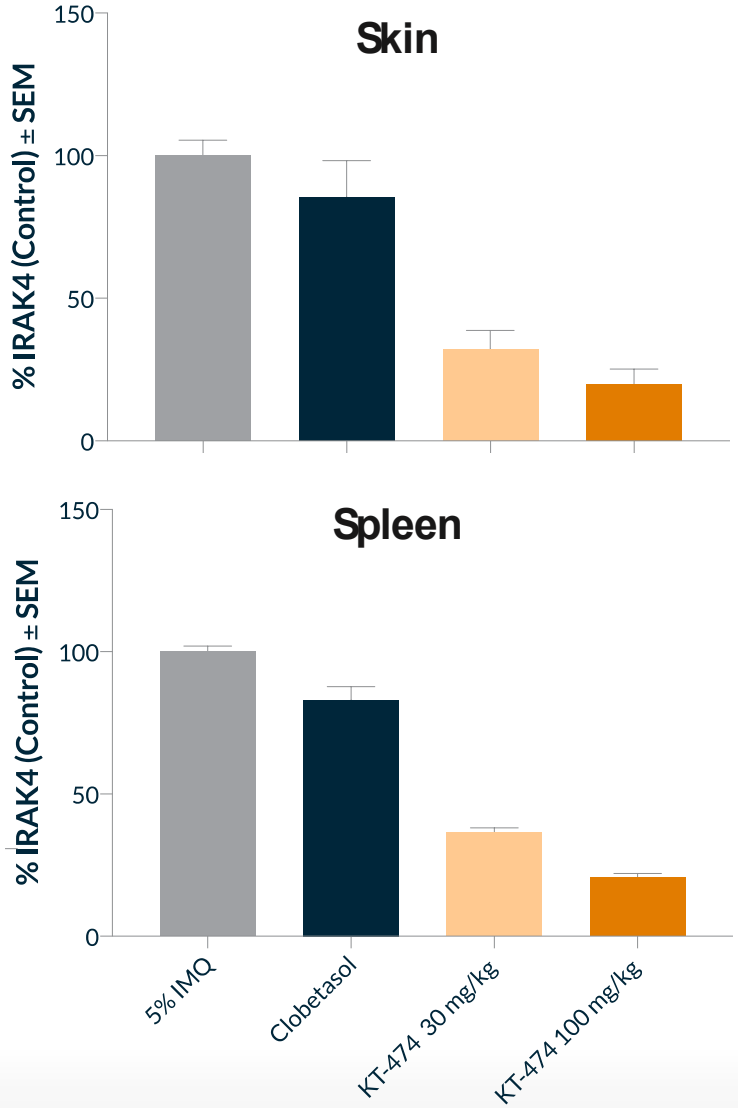


IRAK4 Degradation *In Vivo* Active in Preclinical Mouse Psoriasis Model

IL-1R/TLR driven

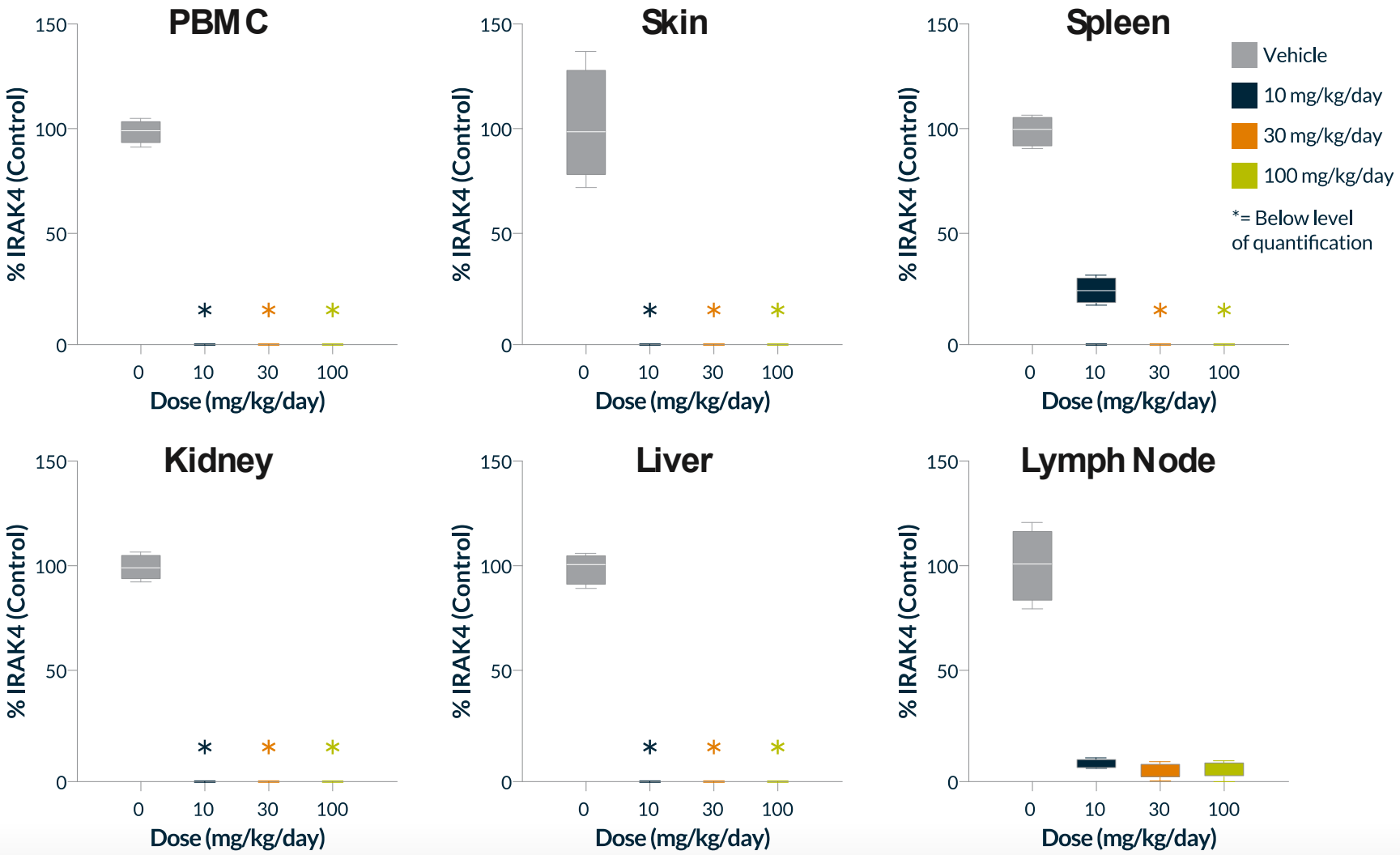
- Ability to inhibit topical skin thickening induced by imiquimod was measured in a mouse model of psoriasis
- Orally dosed KT-474 inhibited thickening, a reflection of local and systemic inflammation, comparable to a topic corticosteroid after 2 or 4 days of dosing
- Inhibition shown at doses achieving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





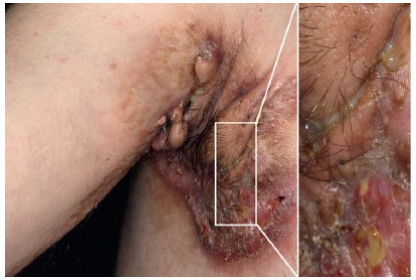
KT-474: Close to Complete IRAK4 Degradation and Well Tolerated in Preclinical Non-rodent Model

- 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



Hidradenitis Suppurtiva (HS) and interim results from Non-interventional study in HS

HS is a painful, chronic, suppurative process involving the skin and subcutaneous tissue



- Onset in 2nd & 3rd decades, more common in females
- Primarily occurs on intertriginous skin
- Recurrent, painful & inflamed nodules, leading to rupture, inflammatory plaques, and scarring
- Severity measures: Hurley clinical staging system (I-III), inflammatory lesion (nodules and abscesses) count

Epidemiology

- Prevalence of 0.1-2%; ~325K in US, ~25% with moderate-to-severe disease
- 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 : antibiotics, steroids and surgery

IRAK4 degrader downregulates IRAK4 expression across all PBMC subsets in HS patient blood

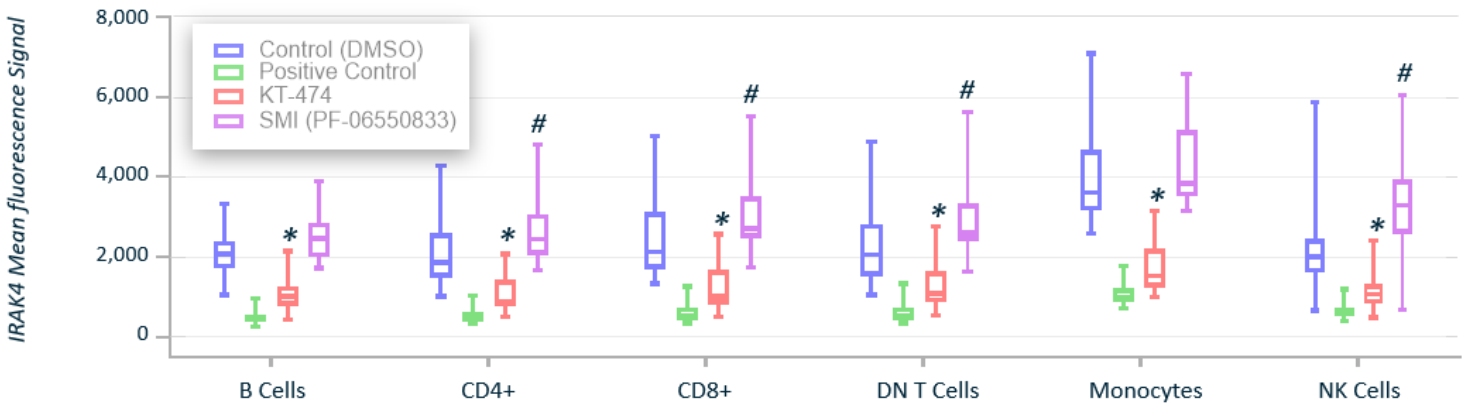
Patient blood was treated with DMSO control or 200nM of KT-474 IRAK4 degrader or 200nM of IRAK4 kinase inhibitor (PF-06550833)

Blood was incubated overnight at 37◦C (16-24 hr) and shipped and processed for IRAK4 lineage specific cell surface staining by flow

Treatment with an IRAK4 degrader led to reduction of IRAK4 to a similar level approaching lower limits of detection as determined by an anti-IRAK4 blocking antibody across all PBMC subsets in HS patient blood, irrespective of baseline IRAK expression intensity

Treatment with an IRAK4 kinase inhibitor led to an increase in IRAK4 levels up to 2.6 fold in T and NK cells

IRAK4 Levels Following Treatment with IRAK4 Degrader or Kinase Inhibitor



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

IRAK4 Summary

- Kymera has generated deep know-how to develop protein degraders (e.g. compound optimization for potency and oral bioavailability, in vivo PK/PD)
- IRAK4 is a well validated pathway involved in multiple IL-1R/TLR-driven immune-inflammatory diseases
- IRAK4 degradation is superior to inhibition
- *Ex vivo* incubation of HS blood with the IRAK4 degrader KT-474 reduces IRAK4 across all PBMC subsets
- Pre-clinical data and findings from non-interventional study support the clinical development KT-474 in HS (Phase I SAD: 1Q 2021; MAD enrollment: 2H 2021*)

*Plan to initiate SAD portion of Phase 1 trial in 1Q 2021. Initiation of MAD portion of Phase 1 trial is on partial clinical hold pending FDA review of interim SAD data.

Q & A

THANK YOU

February 2021