KYMERA
EST. 2016

INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

September 2021

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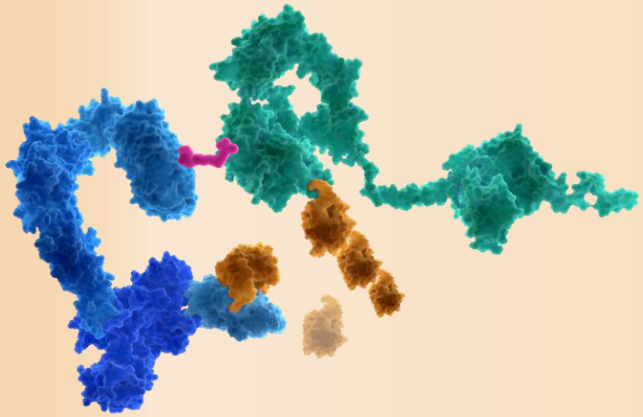
Targeted Protein Degradation

Next Potential Breakthrough Modality to Expand Drugged Proteome

Targeted Protein Degradation



Human Proteome

Existing Modalities

✓	**Undruggable Targets** Scaffold, transcript factor, multiple functions	✓
✓	**Efficient** Development / Manufacturing	X
✓	**Systemic** Exposure	X
✓	**Oral** Bioavailability	X

Kymera: A Leading TPD Company

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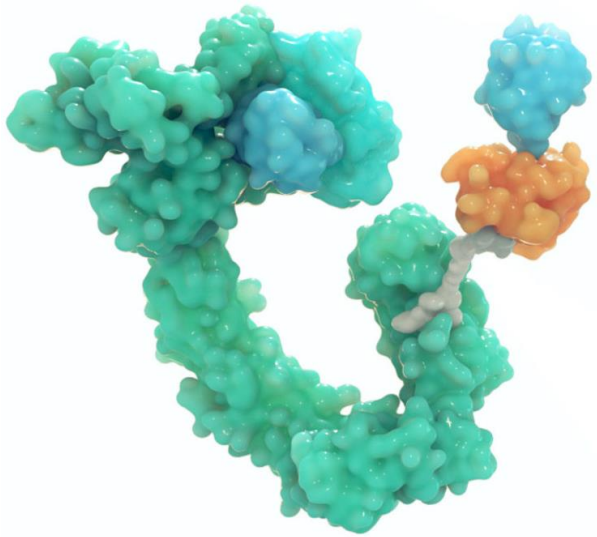
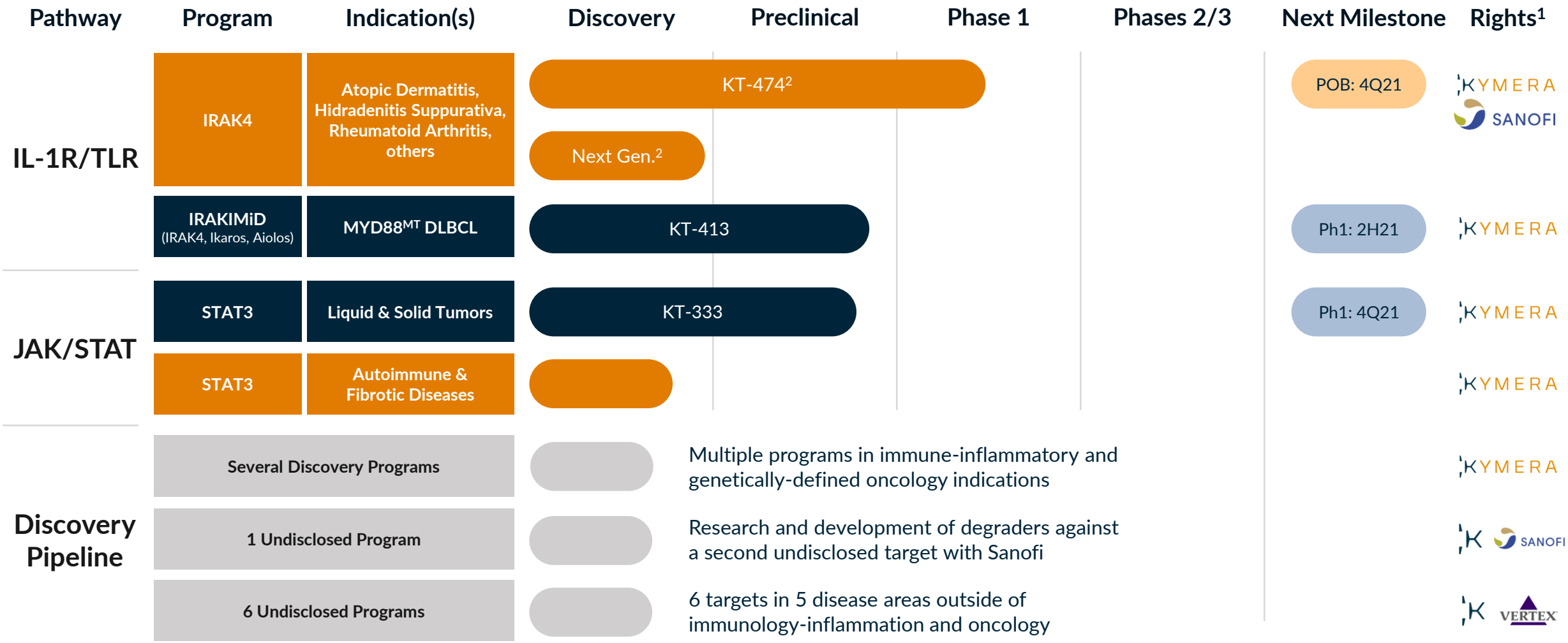


VISION	Fully integrated, **disease agnostic** protein degrader medicine company
KEY PARTNERSHIPS	SANOFI VERTEX gsk
INITIAL FOCUS	**Immune inflammation (I/I)** and **oncology**
FIRST-IN-CLASS	**First** to show **placebo-controlled** degrader **proof-of-mechanism**
CLINICAL PIPELINE	**2** additional **INDs** and clinical initiations expected by end of **2021**
PROOF-OF-BIOLOGY	To be established in humans in **2021**
WELL-POSITIONED	**$647M** cash balance*

* Based on reported cash at June 30, 2021, pro forma for the follow-on financing completed July 6, 2021.

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

Pegasus™ TPD Platform

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Targeted Protein Degradation

Biology

Co-opting a Naturally Occurring Process to Regulate Protein Levels

1. E3 ligase recognizes protein
2. Ubiquitin chain transferred
3. Protein is marked for elimination

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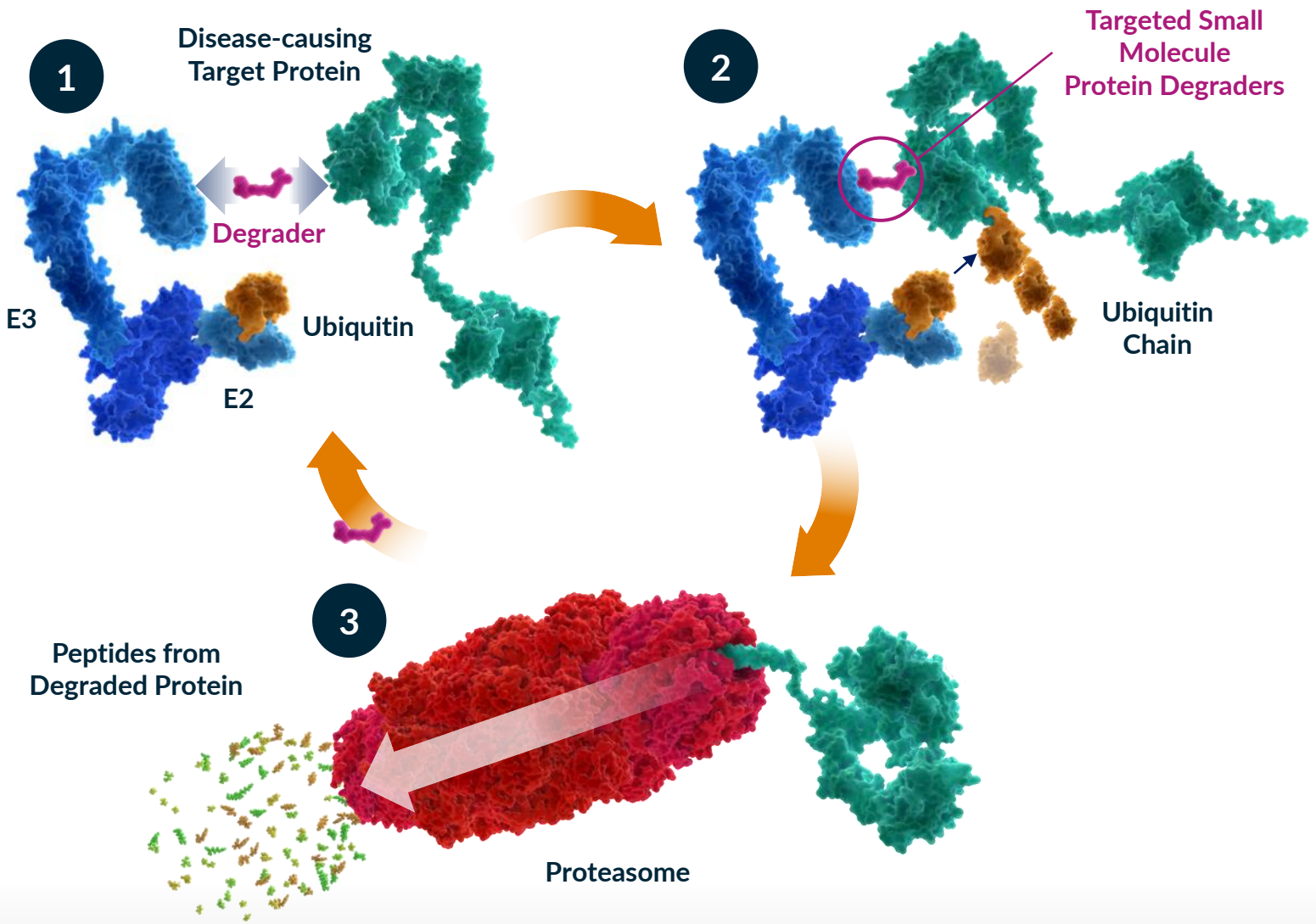
Broad Opportunity
Only Binding Site Required

Efficient
Catalytic

Prolonged Impact
Targeted Protein Degradation

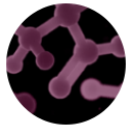


Proprietary Pegasus™ TPD Platform

Key capabilities

Expanded E3 ligase toolbox

- **E3 ligase Whole-Body Atlas**: Identification of the **expression profiles of ~600 unique E3 ligases**
- Match target protein with appropriate E3 ligase based on expression, distribution, intracellular localization, and biology
- **Toolbox of proprietary ligands** leverages the E3 Ligase Whole-Body Atlas



Understanding degradation (PK/PD) across tissue types

- **Ternary complex modeling tool optimizes the development** of highly efficient and selective degrader therapeutics
- **Quantitative System Pharmacology Model** measures and predicts 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

- **Comprehensive hit finding technologies toolbox**: chemoproteomics, DEL, fragment screens, *in silico*
- **Proprietary chemistry expertise** enables the design and optimization of both E3 ligases and target protein binders
- Ability to convert into degraders with optimal pharmaceutical properties tailored to specific patient populations

Pegasus: E3 Ligase Whole-Body Atlas

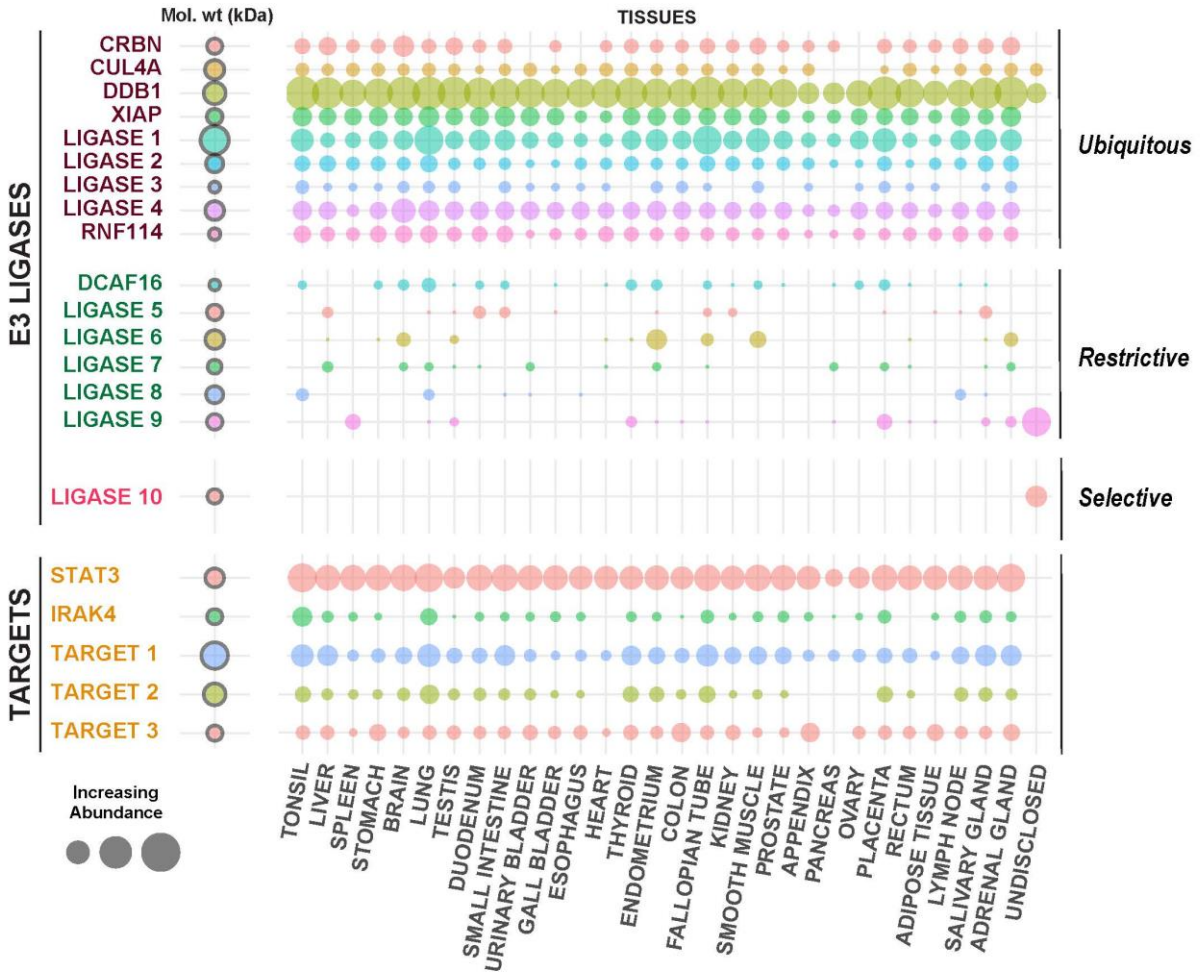
Different expression profiles of E3's provide opportunity for tissue selective/restricted degradation

Expanded E3 ligase toolbox

Understanding degradation (PK/PD) across tissue types

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 therapeutic opportunities



IRAK4 Degrader KT-474

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IRAK4 Targeting: Clinical Validation, Human Genetics De-risking and Degrader Advantage

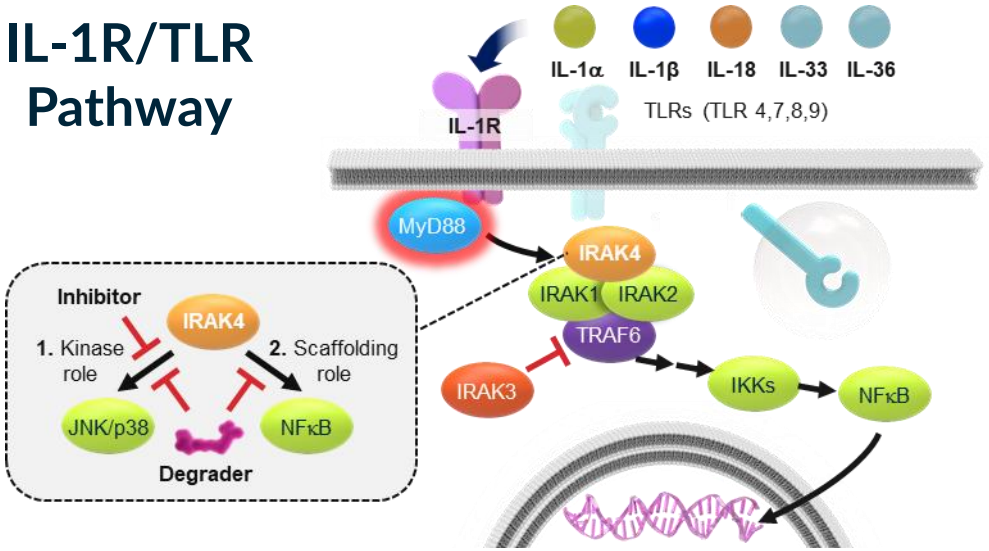
Unmet Medical Need

Validated Biology

Undrugged Node

Precision Medicine Approach

IL-1R/TLR Pathway



Clinical Pathway Validation

IL1-Rα/IL-1β : Rheumatologic Diseases

IL-1α: Atopic Dermatitis

IL-1β: CANTOS Data, Atherosclerosis, Lung Cancer

IL-18: Macrophage Activation Syndrome

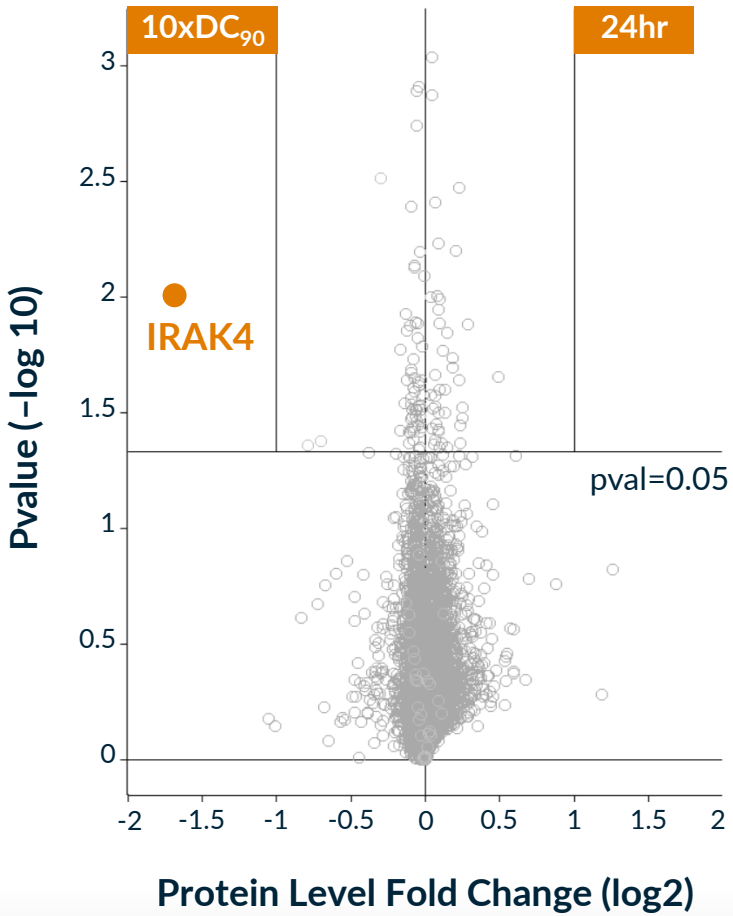
IL-36: Generalized Pustular Psoriasis

IRAK4 SMI: Rheumatoid Arthritis

- IRAK4 is a key component of the myddosome protein complex involved in innate immunity that mediates signals through IL-1R and TLRs
- Several commercial and clinical stage drugs have validated this pathway in multiple diseases
- Degrading IRAK4, and fully blocking IL-1R/TLR signaling, is expected to be superior to antibody-based therapies that block only single cytokines, with convenience of a daily oral therapy
- IRAK4 degradation can block pathway fully vs kinase inhibitors that partially block signaling
- Human genetics de-risk safety: adults that lack IRAK4 are healthy

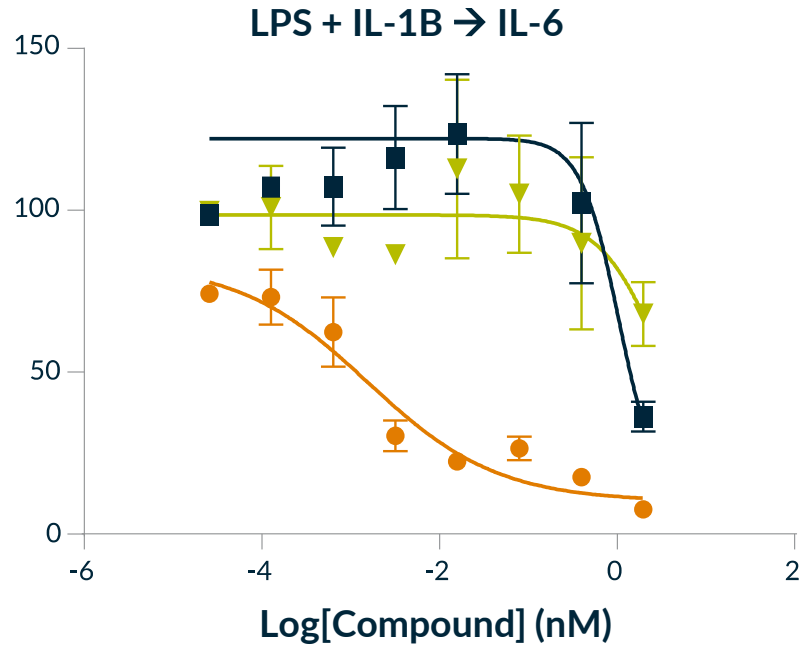
KT-474: Potent and Specific IRAK4 Degradation Superior to Kinase Inhibition

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-1B 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

KT-474 Opportunity

Immune-inflammatory disorders collectively impacting millions of patients in the U.S.

	Total Prevalence (U.S.)	
Atopic Dermatitis (AD)	>16.0M [1]	• Chronic, pruritic **inflammatory skin disease** • Large unmet need for safe and effective oral agents for patients with AD
Rheumatoid Arthritis (RA)	>1.3M [2]	• Chronic, systemic **autoimmune disease** that can cause irreversible joint damage • Multiple therapies targeting the **IL-1R/TLR pathway** are approved
Hidradenitis Suppurativa (HS)	>325K [3]	• Chronic and debilitating inflammatory skin disease • **~25%** of patients with moderate-to-severe disease[4] • Adalimumab is approved, which provides some benefit to **~50% of patients** with moderate-to-severe disease[5]
Additional Opportunities	→	• Immune-inflammatory diseases impacted by **IL-1R/TLR pathway**

1. Chiesa Fuxench et al. J Invest Dermatol. 2019 Mar;139(3):583-590.
2. Hunter et al. Rheumatol Int . 2017 Sep;37(9):1551-1557.
3. Garg et al. JAMA Dermatol. 2017;153(8):760-764.
4. Calao et al. PLoS One. 2018; 13(7): e0200683.
5. Kyriakou et al. Dermatol Reports. 2018 Oct 1; 10(2): 7859.

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
MAD only

- IRAK4 knockdown in skin biopsies
- Proinflammatory cytokine and chemokine levels in skin biopsies
- C-reactive protein and cytokine levels in plasma
- *Ex vivo* response of whole blood to TLR agonists and IL-1β

KT-474 Phase 1 Trial Goals

Establishing proof-of-mechanism and proof-of-biology

De-risking Milestones

1 SAD Portion
Healthy Volunteers

Oral Bioavailability and Proof-of-Mechanism

- Efficacious plasma exposures that are safe and well-tolerated
- Proof-of-mechanism with IRAK4 knockdown following single KT-474 dose
- Predictable PK/PD supporting oral daily dosing regimen

2 MAD Portion
Healthy Volunteers

Optimal IRAK4 Reduction and Proof-of-Biology

- ≥85% IRAK4 knockdown in skin and blood with daily dosing x 14 days that is safe and well-tolerated
- Proof-of-biology with systemic anti-inflammatory effect: reduction in plasma hsCRP and inhibition of whole blood *ex vivo* response to TLR agonists and IL-1β
- Establishment of maximum effective dose

3 MAD Portion
Patient Cohort

Establish Proof-of-Biology in Patients

- ≥85% IRAK4 degradation in diseased skin and blood
- Anti-inflammatory effect in diseased skin and reduction of plasma cytokines and hsCRP
- Confirmation of dose for subsequent Phase 2 studies

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

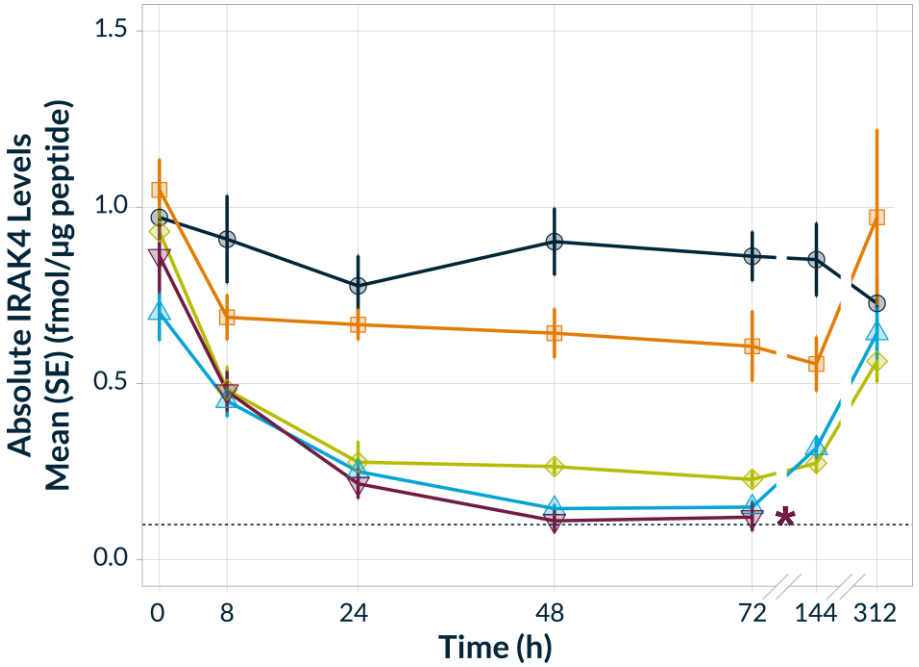
- PK profile consistent with oral daily dosing
- Predictable, dose-dependent plasma exposures after single oral dose of KT-474
- Half-life:
  25-32 hours

Safety & Tolerability

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

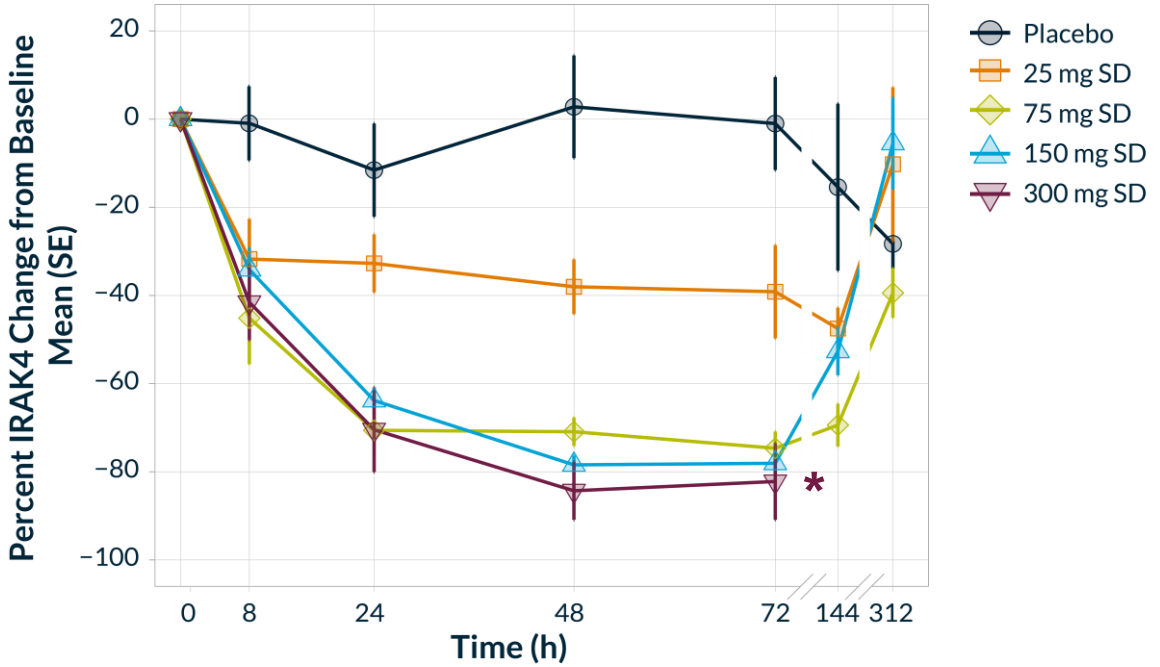
KT-474 Achieved Profound IRAK4 Degradation after Single Oral Dose that Lasted for at Least 6 Days

Absolute IRAK4 Levels



BLQ

Mean % Reduction of IRAK4

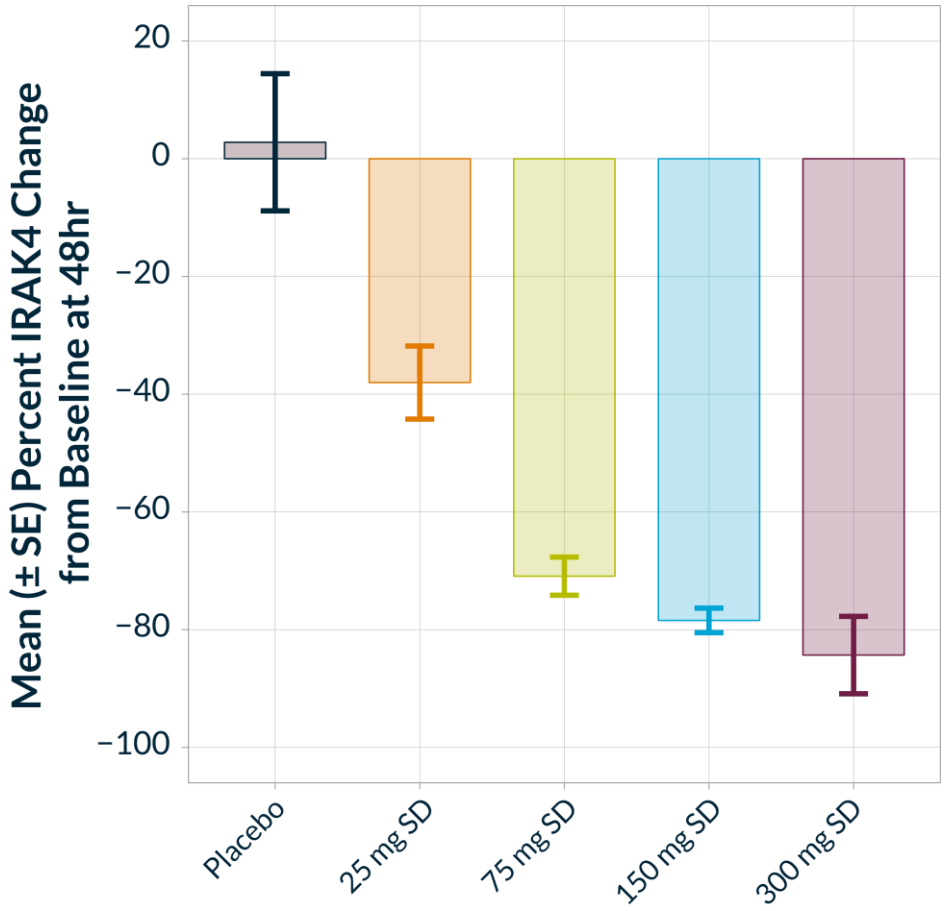


BLQ = Below Limit of Quantitation

* SAD4 144/312 h PD timepoints pending

- Measured by mass spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours
- IRAK4 reduction lasted for at least 144h (6 days post-dose) in all dose groups

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*

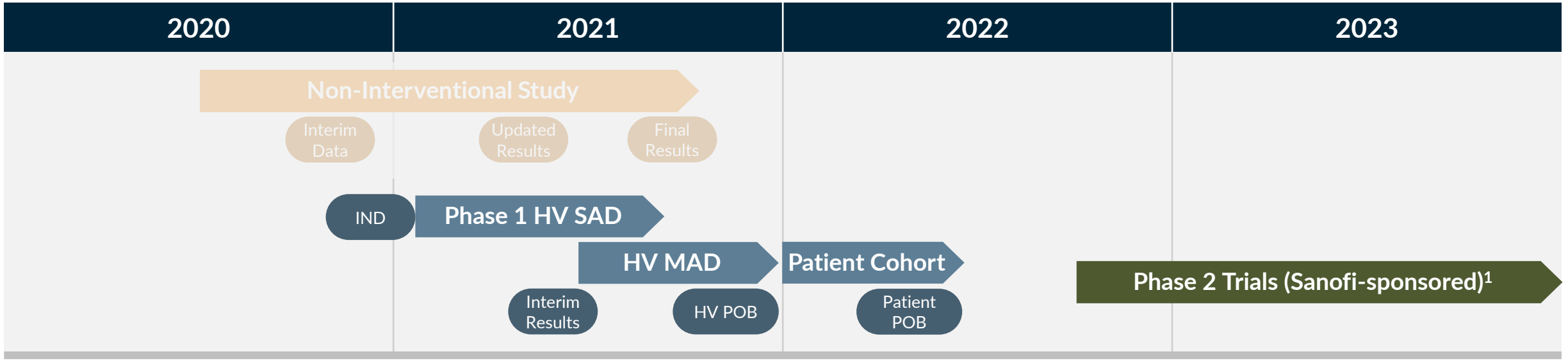
** p-values relative to placebo*

Interim Results from Phase 1 Healthy Volunteer SAD

Summary and Next Steps

- **KT-474 interim Phase 1 results demonstrate degrader proof-of-mechanism, first time for TPD in a placebo-controlled study**
  - Median IRAK4 reduction of 90% ($p<0.0001$ vs placebo) and maximum reduction of 94% at 48 hours following single dose of 300 mg, with sustained degradation that lasted for at least 6 days at all dose levels
  - Based on potency, PK and PD profiles with deep and sustained multiday degradation, expect to achieve biologically relevant (85%) level of degradation with repeat dosing at lower doses; selected MAD starting dose of 25 mg
  - Demonstrated predictable, dose-dependent and biologically active plasma exposures, and half-life that supports oral daily dosing
  - No treatment-related adverse events or serious adverse events observed to date
  - Demonstrating Phase 1 target degradation of >85% de-risks KT-474 ability to reach clinically relevant biological effects in future development as a potential best-in-class anti-inflammatory oral drug
- **FDA lifted partial clinical hold following review of interim healthy volunteer SAD results**
  - Dose escalation in SAD portion of Phase 1 to continue, including assessment of food-effect
  - In July, initiated MAD portion of Phase 1 in healthy volunteers assessing daily dosing of KT-474 for 14 days
- **Expect to present updated results from healthy volunteer SAD/MAD portions in Q4'21**
  - Data to include IRAK4 degradation in skin and PBMC and effects on inflammatory biomarkers after repeat dosing
  - Optimal dose from MAD healthy volunteer portion to be evaluated in an open label cohort of patients with atopic dermatitis and hidradenitis suppurativa

KT-474 Development Plan



Non-Interventional

- 40 patients (HS n=30; AD n=10)
- Biomarker endpoints in blood and skin: IRAK4, cytokines, acute phase reactants
- Data updates:
  - Interim: **Oct 2020**
  - Updated HS: **May 2021**
  - Final AD: **2H21**

Phase 1

- SAD dosing initiated **1Q21**
- SAD/MAD studies: healthy volunteers (HV) and AD/HS patients
- Endpoints: primary - **Safety**; secondary - **Proof-of-Biology**
- Data updates:
  - Interim SAD proof-of-mechanism: **June 2021**
  - HV proof-of-biology: **4Q21**
  - Patient proof-of-biology: **1H22**

Phase 2

- Randomized, placebo-controlled trials in patients in potential indications such as AD, HS, RA, others

1. Estimated clinical development timeline.


IRAKIMiD
KYMERA

IRAKIMiD

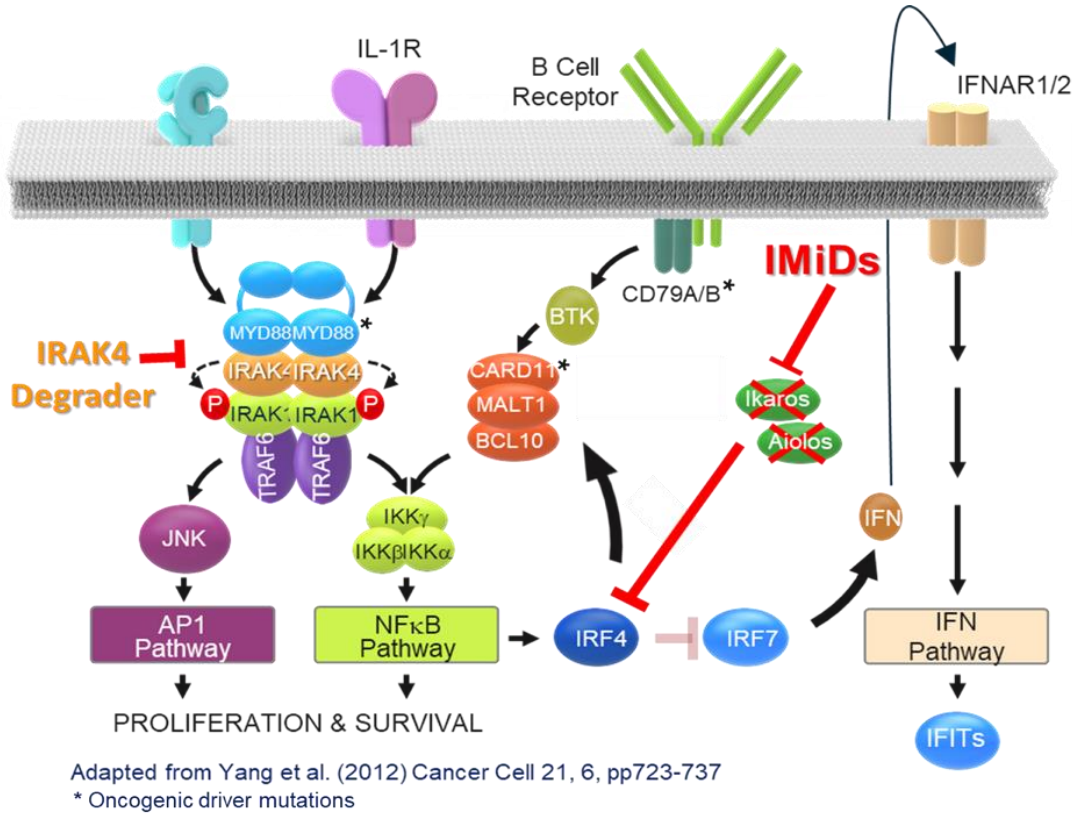
A combo in a single molecule

- MYD88 mutation drives differentiation and proliferation in ~25% of diffuse large B cell lymphoma (DLBCL)
- IMiDs downregulate IRF4, increasing IFN signaling and further suppressing NFkB activation and show activity in lymphoma
- Inhibiting both MYD88 and IRF4-dependent NFkB and activating IFN signaling drive cell death in MYD88-mutant lymphomas and leads to full and durable responses *in vivo*
- Combining two therapeutically relevant pathways in a single molecule has the potential to be first single agent targeted therapy agent in lymphoma (MYD88-mut)

Indications/Expected Timeline

MYD88-mutant DLBCL
Current: KT-413 in IND-enabling activities
IND/Phase 1 initiation: 2H 2021
Phase 1 proof-of-biology in patients: 2022

Pathway



IRAK4 + Ikaros/Aiolos

KT-413 Opportunity

Potential to be first precision medicine in DLBCL to target a genetically defined population (MYD88-mut)

	Patient Impact (U.S.)	
MYD88-mutant DLBCL	**~7.0k**[1] per year	• MYD88 is mutated in at least 25% of DLBCL patients, the most common subtype of non-Hodgkin's lymphoma[1] • Front-line treatment includes **R-CHOP** (chemo/rituximab) • DLBCL **5-year survival rate is ~64%**, and MYD88 mutations in DLBCL are associated with poorer survival following frontline R-CHOP chemotherapy[3]
Other MYD88-mutant B cell Lymphomas	**>1.0k**[2] per year	• MYD88 is mutated in approximately 90% of **Waldenström's macroglobulinemia** cases and 70% of primary central nervous system lymphoma[4,5]
Additional Cancers	→	• **IL1R/TLR/NFκB**-driven cancers, AML & MDS subsets with long isoform of IRAK4 (IRAK4L)

1. Lee et al. Sci Rep. 2017; 7: 1785.
2. https://www.lls.org/sites/default/files/file_assets/waldenstrommacroglobulinemia.pdf
3. https://seer.cancer.gov/statfacts/html/dlbcl.html.
4. Varettoni et al. Blood (2013) 121 (13): 2522–2528.
5. Hattori et al. Cancer Sci. 2018 Jan; 109(1): 225–230.

KT-413 Shows Regressions in MYD88^{MT} Patient-Derived Xenograft Models

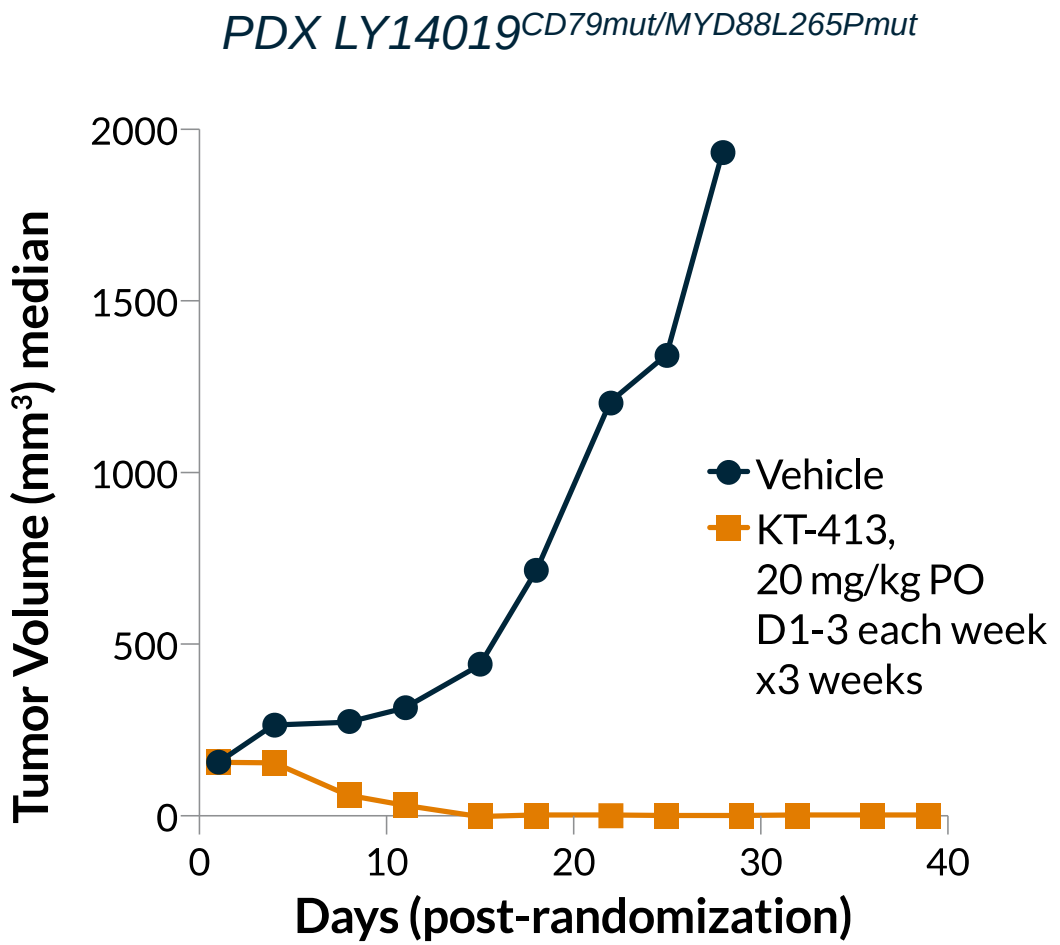
Model	MYD88	CD79B	TNFAIP3	Other	KT-413 (%TGI)
LY14019	L265P	MT	MT		**100**
LY2264	L265P	MT		IRF4	**100**
LY2298	L265P	MT		BCL2/BCL6	**90**
LY12699	L265P	MT			**87**
LY2345	WT		MT		**70**
LY2301	WT				**30**
LY0257	L265P			BCL2/BCL6/IKZF3	**0**

KT-413 dosed orally shows strong tumor growth inhibition (>85% TGI) in 4/5 MYD88-Mutated DLBCL PDX Models

- Activity is observed regardless of co-mutations that activate NFkB and IRF4 pathways
- The non-responsive MYD88^{MT} model LY0257 harbors a mutation in Aiolos and is reported to be insensitive to lenalidomide
- The functional consequence of Aiolos mutations in IRAKIMiD and IMiD response is being investigated

Some level of tumor growth inhibition observed in MYD88-WT PDX

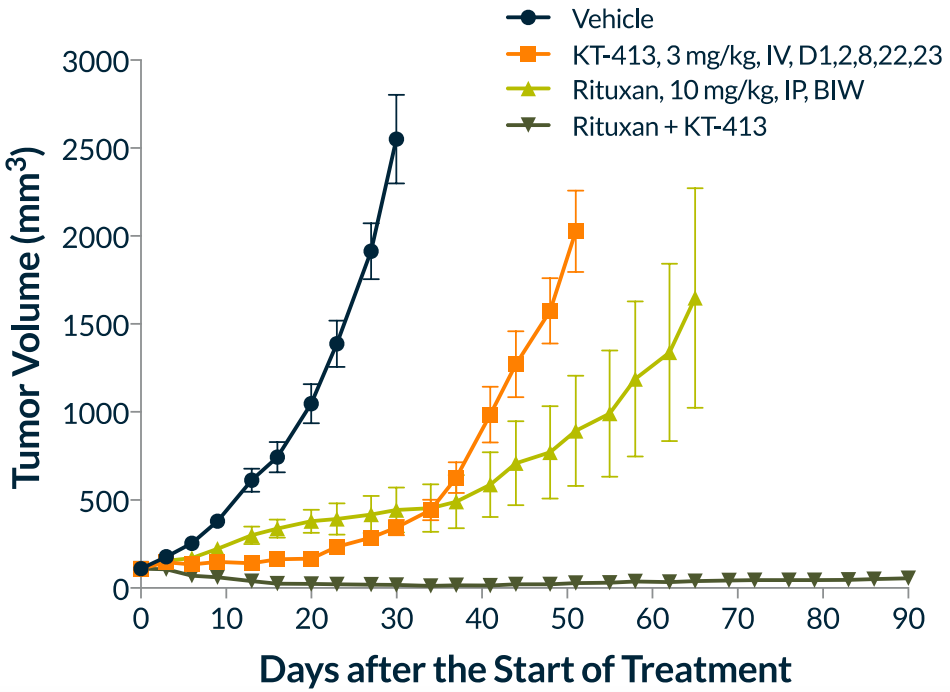
- May be consistent with IMiD activity of KT-413



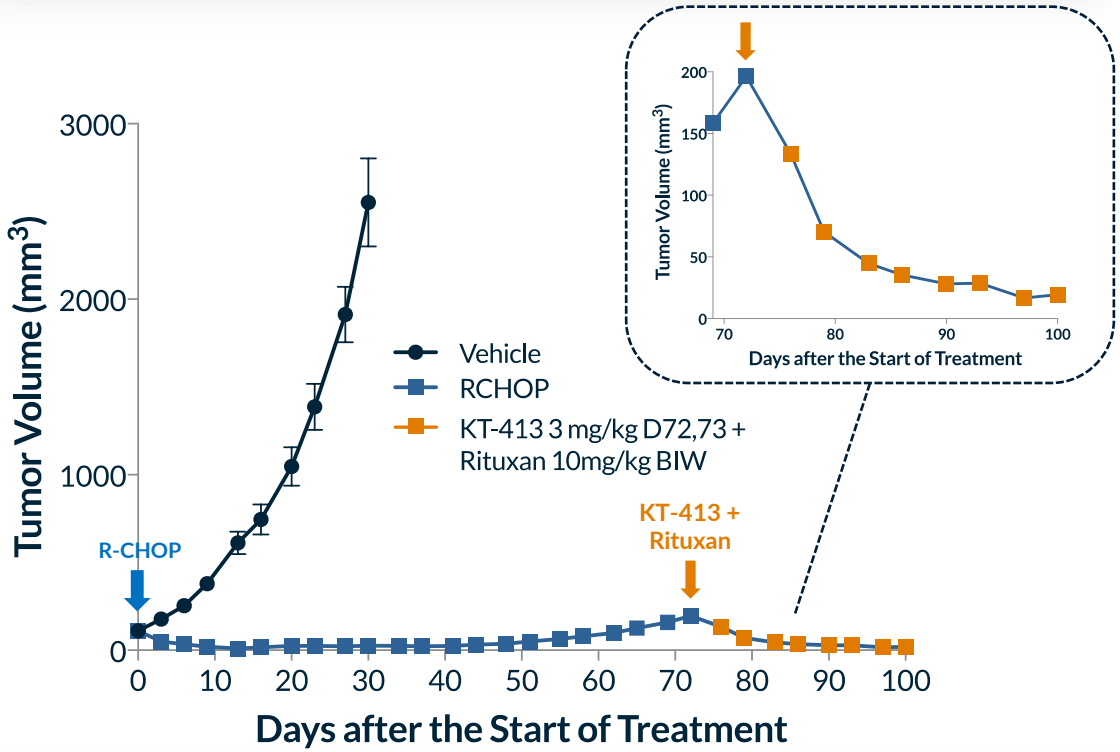
PDX models run at Crown Biosciences

KT-413 has Synergistic Activity in Driving Deep Tumor Regressions in Combination with Other Therapies in Preclinical Models

- KT-413 administered on intermittent schedules demonstrated deep and durable regressions in combination with rituximab in MYD88MT OCI-Ly10 xenografts

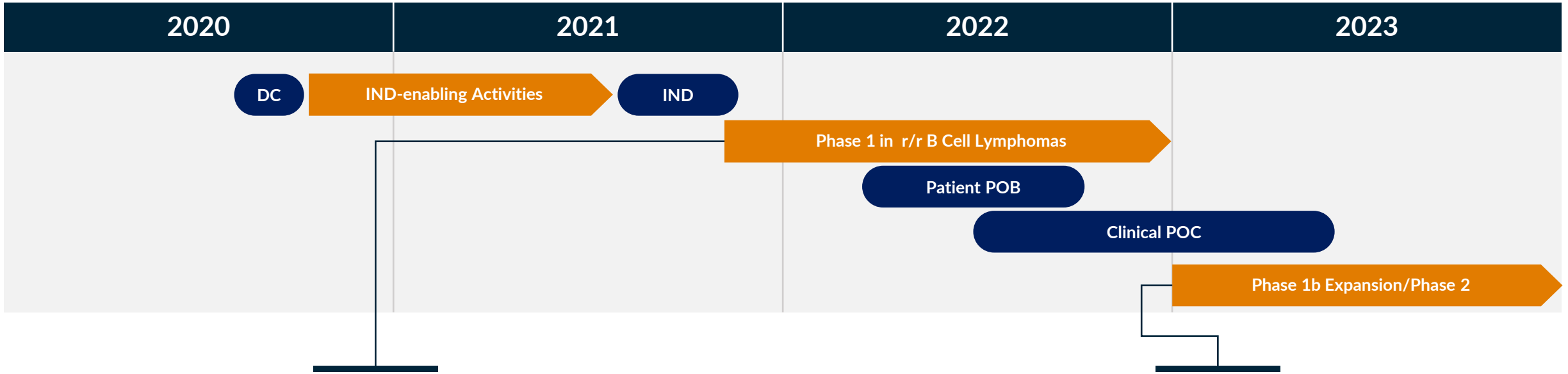


- KT-413 + rituximab showed strong tumor regressions in tumors that relapsed following initial R-CHOP treatment



*Determined by Bliss Independence method

KT-413 Development Plan



- **Multi-center Phase 1 dose escalation study (US sites) start in 2H21**
- Relapsed/refractory B cell lymphomas, including MYD88-mutant DLBCL
- Objectives include safety, tolerability, PK and PD (proof-of-biology) and preliminary clinical activity
- Clinical and biomarker endpoints
- **POB to be presented in 2022**

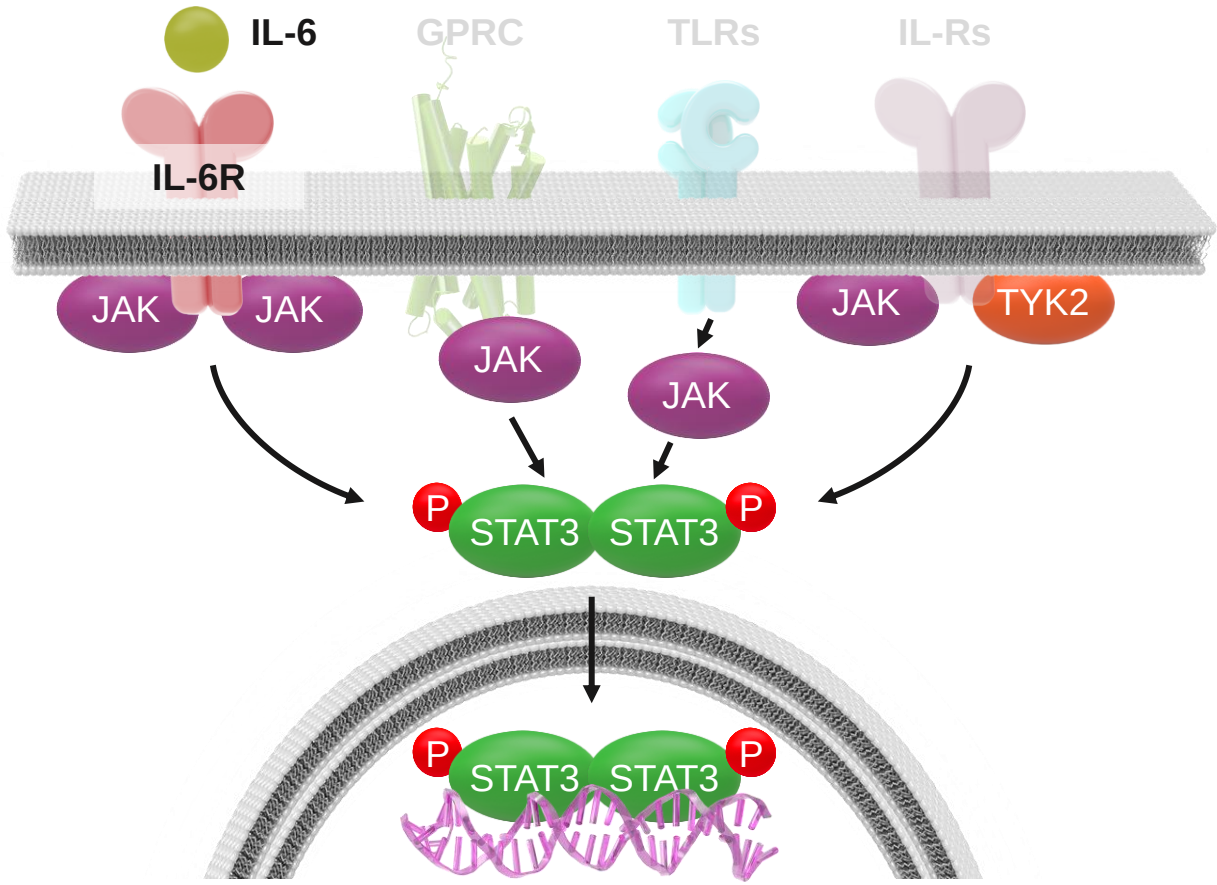
- Phase 1b expansion cohorts in DLBCL (MYD88-mut and –wt) and other MYD88-mut lymphomas, including Waldenstrom's macroglobulinemia and primary central nervous system lymphoma
- Objectives include safety, tolerability and clinical activity of monotherapy and select combinations
- Clinical and biomarker endpoints
- Potential expansion in other indications

STAT3

KYMERA

STAT3 Biology and Degrader Rationale

- STAT3 is a traditionally largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAKs mediated mechanisms
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported also by numerous publications
- STAT3 plays a role in tumor biology, evasion of immune surveillance and inflammation/fibrosis
- No known drugs specifically affect STAT3 broadly across all relevant cell types



Indications/Expected Timeline

Hematological Malignancies/Solid Tumors and Autoimmune/Fibrosis

Nomination of development candidate: 1Q 2021 ✓

IND/Phase 1 initiation: 4Q 2021

Phase 1 proof-of-biology in patients: 2022

STAT3 Opportunity in Oncology & Autoimmunity

First-in-class opportunity to address STAT3-driven pathology across large and diverse indications

Patient Impact (U.S.)

Cancer

~5.0k per year[1]
Peripheral T-cell Lymphoma

~2.0k per year[2]
Cutaneous T-cell Lymphoma

~200.0k per year[3]
NSCLC

Liquid Tumors

Solid Tumors

I/I Fibrosis

>40.0k[4]
Systemic Sclerosis

>16.0M[5]
Atopic Dermatitis

>40.0k[6]
Idiopathic Pulmonary Fibrosis

Autoimmune

Fibrosis

Genetically-defined STAT3 mutation and/or hyperactivation
PTCL, CTCL, T-LGL leukemia

STAT3 activation and dependency
DLBCL, AML, multiple myeloma

Cell Intrinsic: STAT3 role in EMT/TKI resistance
Combinations in TKI / chemotherapy resistant settings

Cell Extrinsic: STAT3 role in IO
T-cell infiltrated tumors. Combinations with immune-modulators

STAT3 GOF syndrome
Genetically-defined population characterized by enteropathy, arthritis, dermatitis, lung disease

Immune-inflammatory
Systemic sclerosis, atopic dermatitis, rheumatoid arthritis, Crohn's disease/ulcerative colitis

Chronic inflammation / fibrosis
Idiopathic pulmonary fibrosis, CKD/renal fibrosis

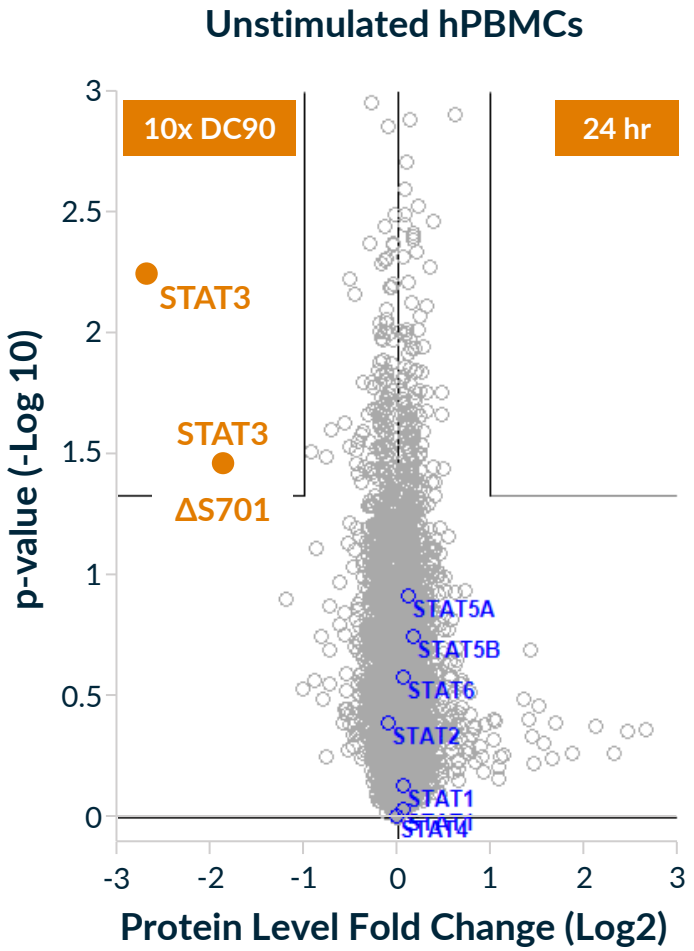
1. Marchi and O'Connor. CA CANCER J CLIN 2020;70:47–70.
2. Criscione and Weinstock. Arch Dermatol. 2007 Jul;143(7):854-9.
3. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html.
4. Bergamasco et al. Clin Epidemiol. 2019; 11: 257–273.
5. Chiesa Fuxench et al. J Invest Dermatol. 2019 Mar;139(3):583-590.
6. Nalysynk et al. European Respiratory Review. 2012 21: 355-361.

KT-333 Highly Specific Degradation of STAT3

CANCER
- Liquid Tumors
- Solid Tumors

I/I FIBROSIS
- Autoimmune
- Fibrosis

- Deep mass spectrometry-based proteomics to assess STAT3 specificity performed
- hPBMC and tumor cells (SU-DHL-1) treated with KT-333 degrader
- STAT3 was the only protein to be degraded with statistical significance
- Data demonstrate highly selective degradation profile



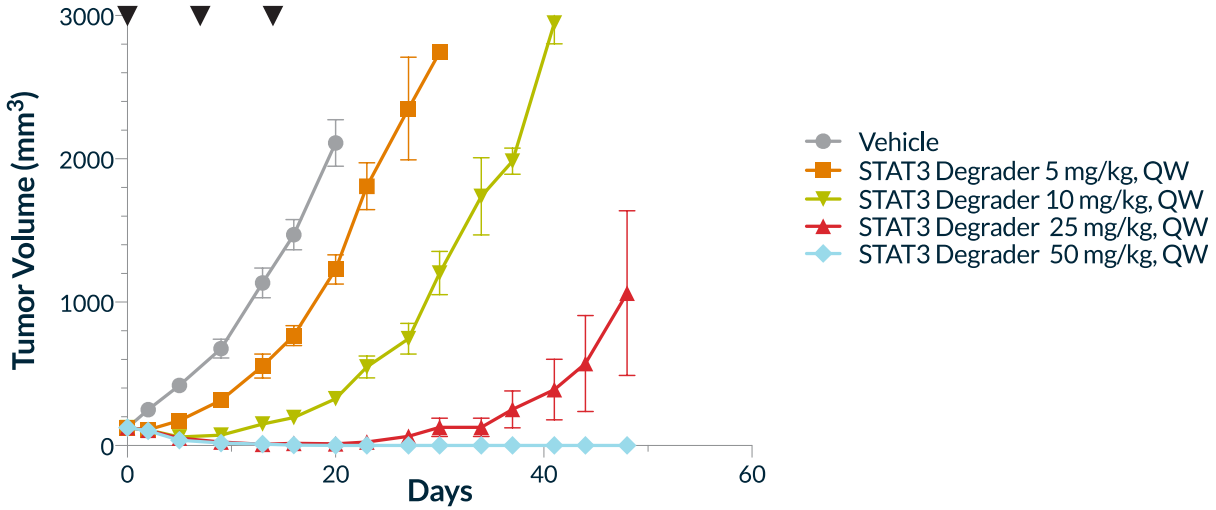
● STAT Family Members: **STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6**

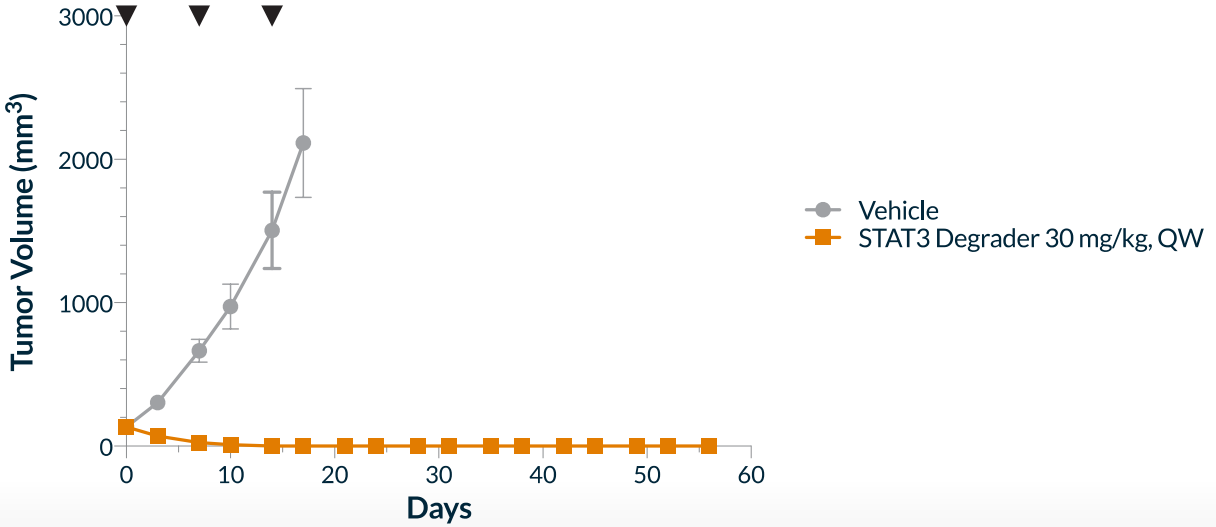
Full and Durable Regressions Across Multiple *in vivo* Preclinical Tumor Models

CANCER
- Liquid Tumors
- Solid Tumors

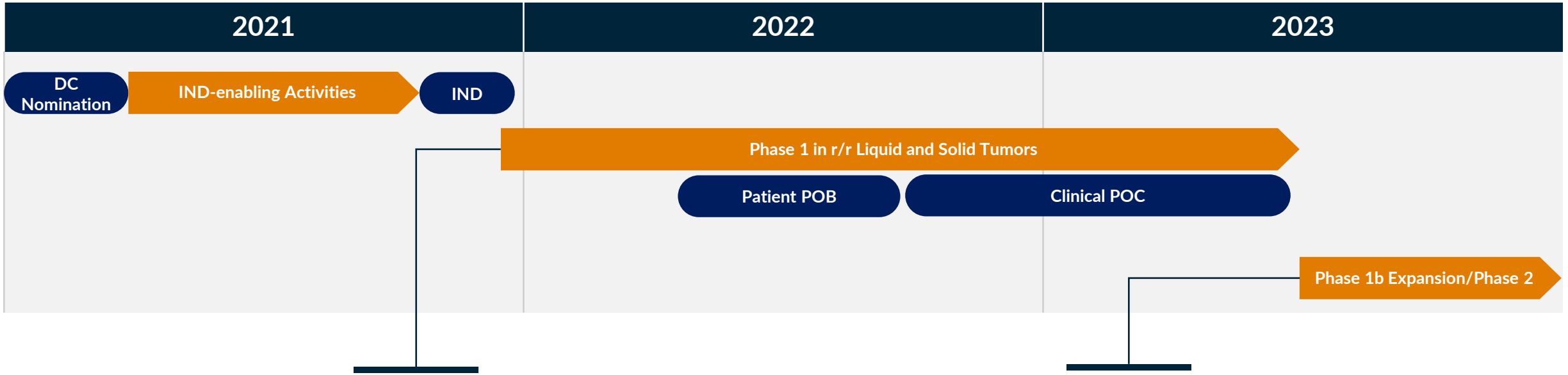
I/I FIBROSIS
- Autoimmune
- Fibrosis

- Mice bearing STAT3-dependent ALK+ ALCL SU-DHL-1 (above) and STAT3-driven ALK+ ALCL xenograft model SUP-M2 (below) tumors dosed with STAT3 degrader
- Dose and degradation dependent tumor growth inhibition observed with once-a-week IV dosing
- 30 mg/kg sufficient to drive full tumor regression that was durable for multiple weeks after the last dose





STAT3 Degrader Development Plan in Liquid & Solid Tumors



- **Multi-center Phase 1 dose escalation study start in 4Q21**
- Safety, tolerability, PK and PD (proof-of-biology) and preliminary clinical activity
- Clinical and biomarker endpoints
- **POB to be presented in 2022**

- Phase 1b expansion cohorts in STAT3-dependent liquid tumors
- Objectives include safety, tolerability and clinical activity of monotherapy and select combinations
- Separate Phase 2 in solid tumors

Near-Term Milestones Provide Significant Opportunity

Program	Compound	Indication(s)	Expected Upcoming Milestones
IRAK4	KT-474	AD, HS, RA, others	✓ Initiated SAD portion of Phase 1 trial in healthy volunteers (Feb 2021) ✓ Established degrader proof-of-mechanism in healthy volunteer SAD portion of Phase 1 trial (June 2021) ✓ Initiate enrollment in MAD portion of Phase 1 trial (July 2021) • Establish Phase 1 proof-of-biology in healthy volunteers (4Q21) • Establish Phase 1 proof-of-biology in patient cohort (1H22)
IRAKIMiD (IRAK4, Ikaros, Aiolos)	KT-413	$MYD88^{MT}$ DLBCL	✓ Presentation of preclinical data updates at AACR, ICML meetings (2Q21) • Submit IND to initiate Phase 1 clinical trial in r/r B cell lymphomas (2H21) • Present additional KT-413 preclinical data and potential expansion strategies (2H21) • Establish Phase 1 proof-of-biology in patients (2022) • Establish Phase 1 initial clinical proof-of-concept in patients (2022)
STAT3	KT-333	Liquid & Solid Tumors	✓ Nominated development candidate for liquid & solid tumor indications (1Q21) • Present additional preclinical data in liquid & solid tumor indications (2H21) • Submit IND to initiate Phase 1 clinical trial in liquid and solid tumors (4Q21) • Establish Phase 1 proof-of-biology in patients (2022) • Establish Phase 1 initial clinical proof-of-concept in patients (2022)
Discovery Programs & Platform			• Continue pipeline expansion by advancing early-stage discovery programs toward IND-enabling studies • Further expand Pegasus platform to generate novel degrader product candidates • Leverage Whole-Body Atlas to unlock new opportunities across broad therapeutic applications

● = Oncology ● = Immunology-Inflammation

Appendix

KYMERA

What We Are Building

Vision

A fully integrated **degrader medicines company** that discovers, develops, and commercializes transformative medicines while leading the evolution of targeted protein degradation (TPD)

Opportunity

- Potential to **expand the druggable proteome dramatically**

Platform

- Advancing **TPD beyond current opportunities**

Strategy

- Focusing on undrugged targets and clinical indications with **high unmet medical need and franchise potential**

Team

- Driven by a **culture of scientific innovation**

Strategic Partnerships to Accelerate Growth

Supports discovery, development, and commercialization within and outside of core therapeutic areas

Strategic Collaborators

SANOFI

- Established July 2020; **$150M** upfront; **>$2B** of potential milestones, plus tiered royalties
- Focused on **IRAK4 in I/I** + 2nd program; KYMR advances IRAK4 through Ph 1; Sanofi Ph 2 and beyond
- KYMR retains U.S. co-dev and co-co opt-in rights, and rights to IRAK4 in oncology

VERTEX

- Established May 2019; **$70M** total upfront; **>$1B** of potential milestones, plus tiered royalties
- **6 targets** in 5 disease areas
- Outside of Kymera's core focus areas in oncology and immune-inflammatory

gsk

- Established April 2018
- Gained access to GSK's **DEL capabilities** to screen for ligands to targets and E3 ligases

LEUKEMIA & LYMPHOMA SOCIETY®

- Blood-based cancers
- Leveraging patient network and access

Academic Collaborators

COLUMBIA UNIVERSITY

The Rockefeller University 1901

UCSF

Yale

UNIVERSITY OF CAMBRIDGE

NATIONAL INSTITUTES OF HEALTH

MAYO CLINIC

Pegasus™ Platform and R&D Approach

KYMERA

Pegasus: E3 Ligase Whole-Body Atlas

A Bone Marrow Sparing E3 Ligase

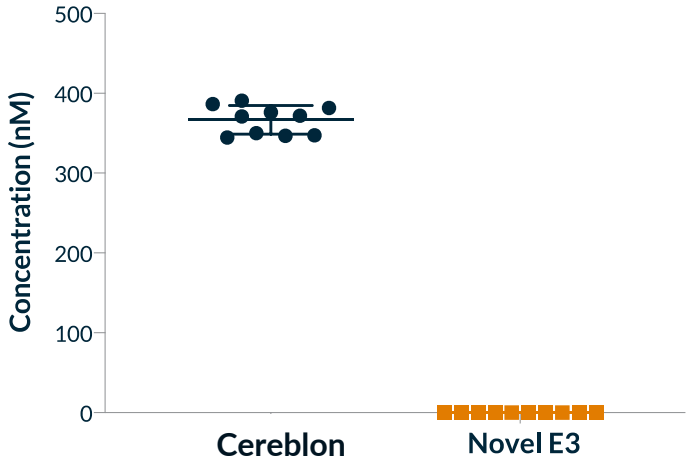
Expanded E3 ligase toolbox

Understanding degradation (PK/PD) across tissue types

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

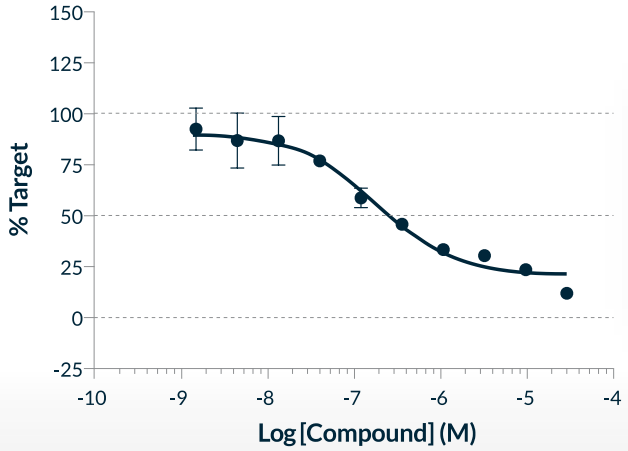
This E3 Ligase is Not Expressed in Bone Marrow



Bone marrow: CD34+ from five donors

Ligand Identification

TPD with Bone Marrow Sparing Novel E3 Ligase



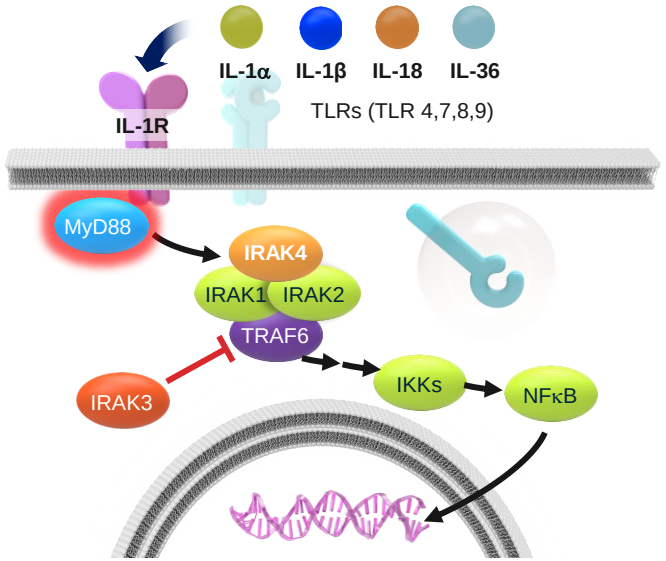
Target	Target Protein
DC_{50} (nM)	206
Dmax (%)	88

Kymera Drug Development Principles

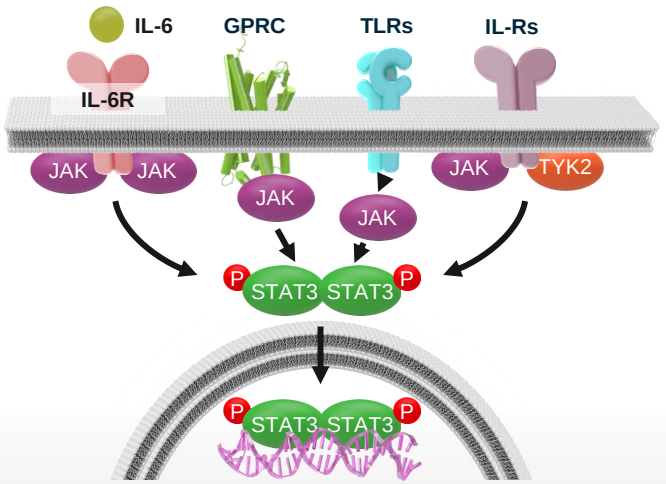
Initial focus on pathways that have been clinically and commercially validated with undrugged nodes

- **Unmet Medical Need**
- **Validated Biology**
- **Undrugged Node**
- **Precision Medicine Approach**

IL-1R/TLR Pathway



JAK-STAT Pathway



Clinical Pathway Validation

IL1-Rα/IL-1β : Rheumatologic Diseases
IL-1α: Atopic Dermatitis
IL-1β: CANTOS Data, Atherosclerosis, Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis
IRAK4 SMI: Rheumatoid Arthritis

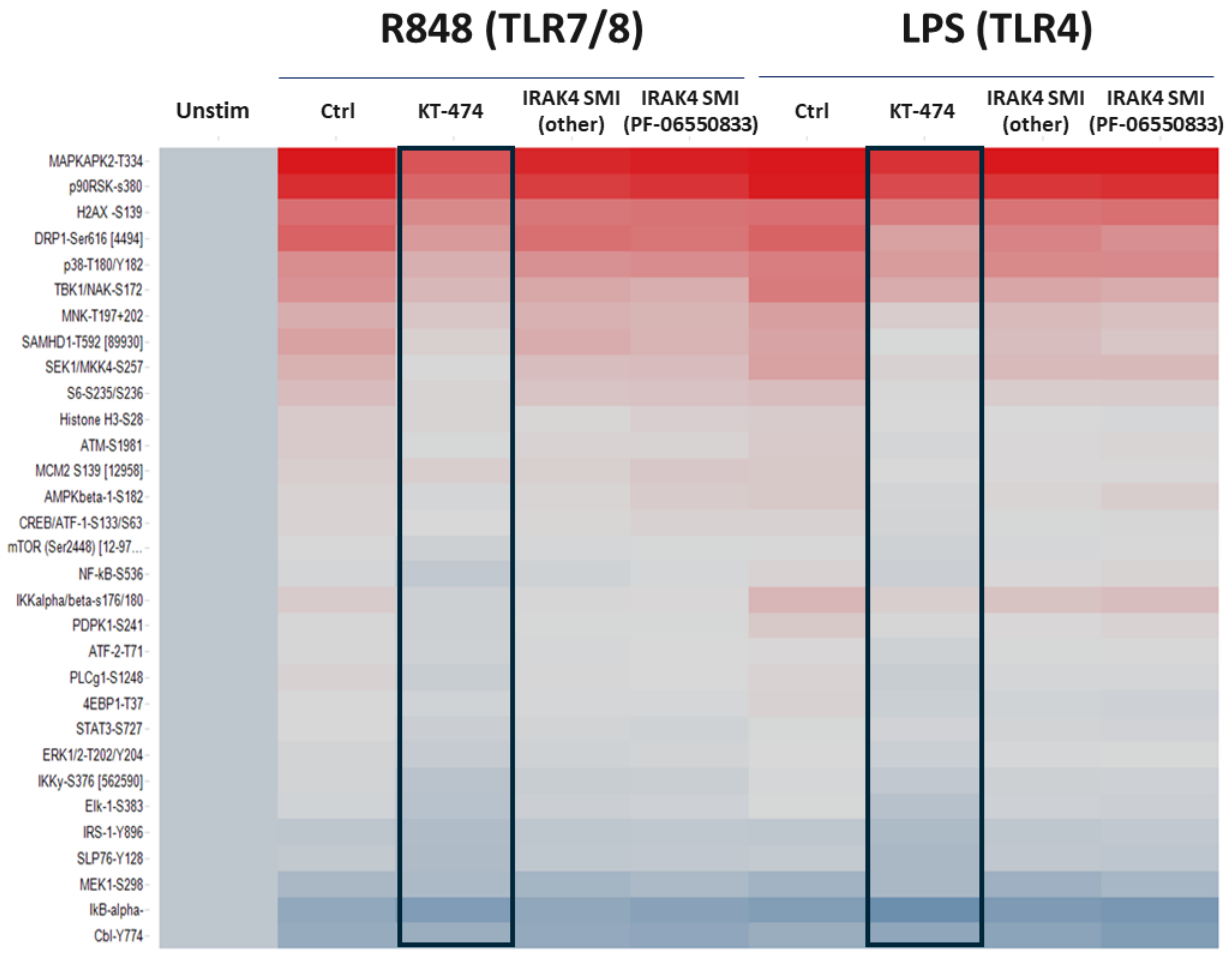
IL-6R: Rheumatoid Arthritis
IL-6: Multicentric Castleman's Disease
JAK1/2: Myelofibrosis
JAK3: Alopecia Areata
TYK2: Autoimmune Diseases
STAT3 ASO: AZD9150 in Oncology

IRAK4

KYMERA

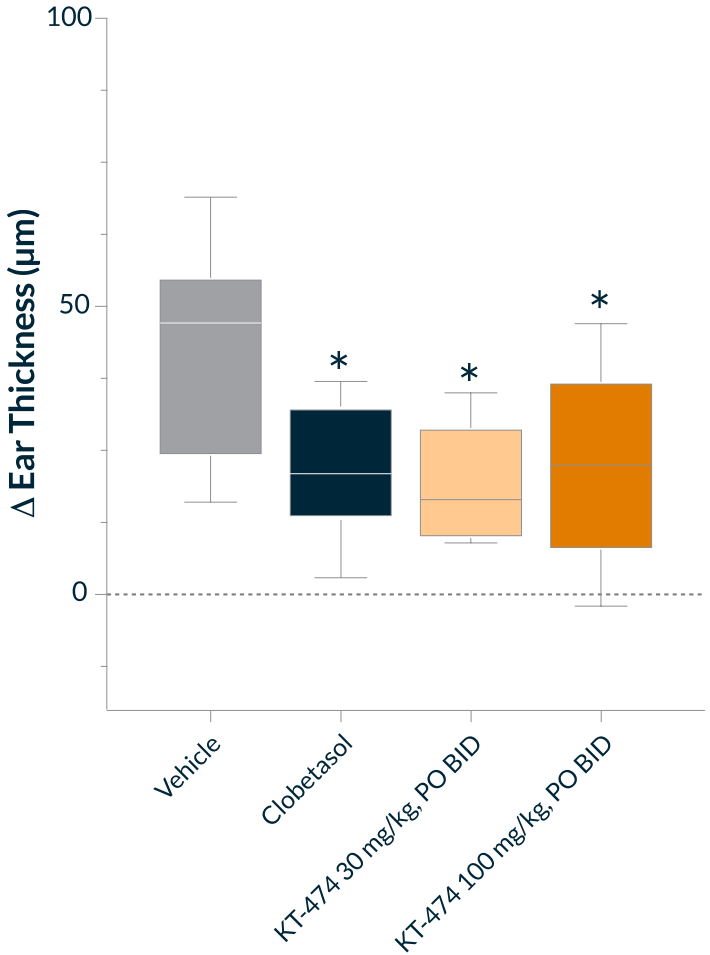
IRAK4 Degradation Superior to Kinase Inhibition in Intracellular Signaling

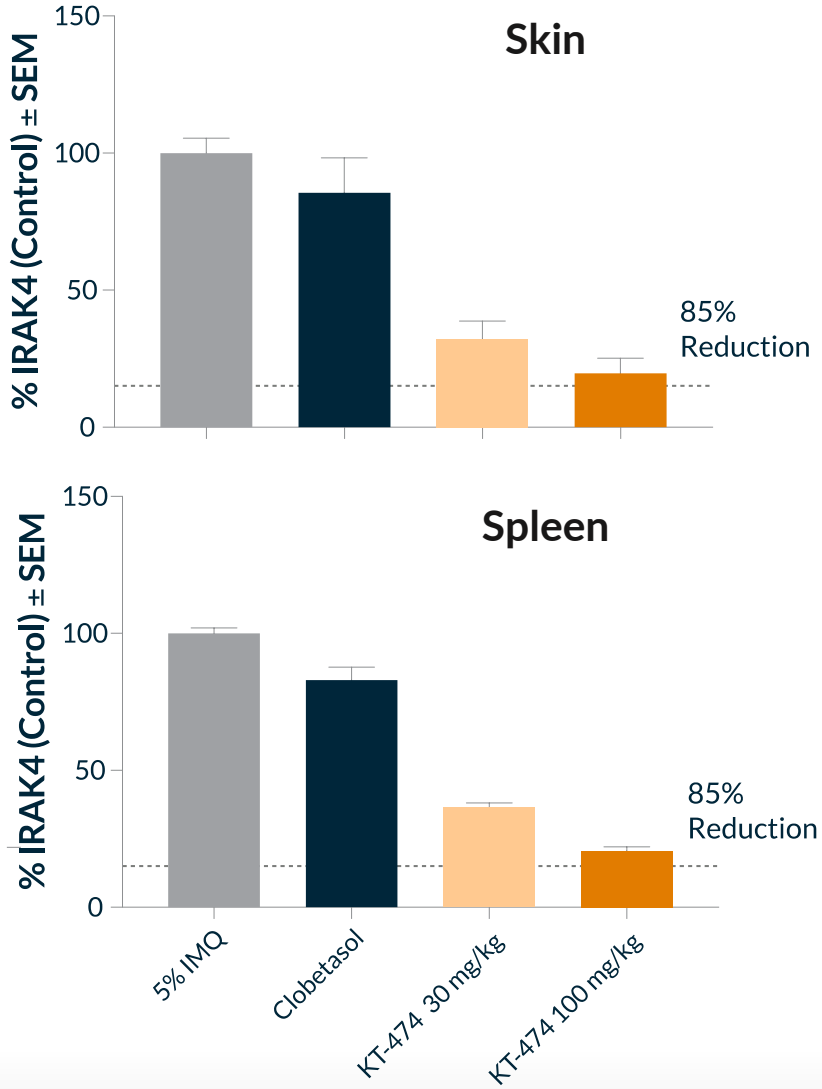
- Phosphorylation events upon TLR activations monitored using flow cytometry
- KT-474 inhibited pro-inflammatory phosphorylation events in a superior manner to small-molecule inhibitors including clinically active PF-compound



85% IRAK4 Degradation Sufficient for Maximal *In Vivo* Efficacy in Preclinical Models

- 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
- Full efficacy at doses achieving at 65-80% IRAK4 reduction in skin and spleen. In other models KT-474 has demonstrated full efficacy with 85% degradation

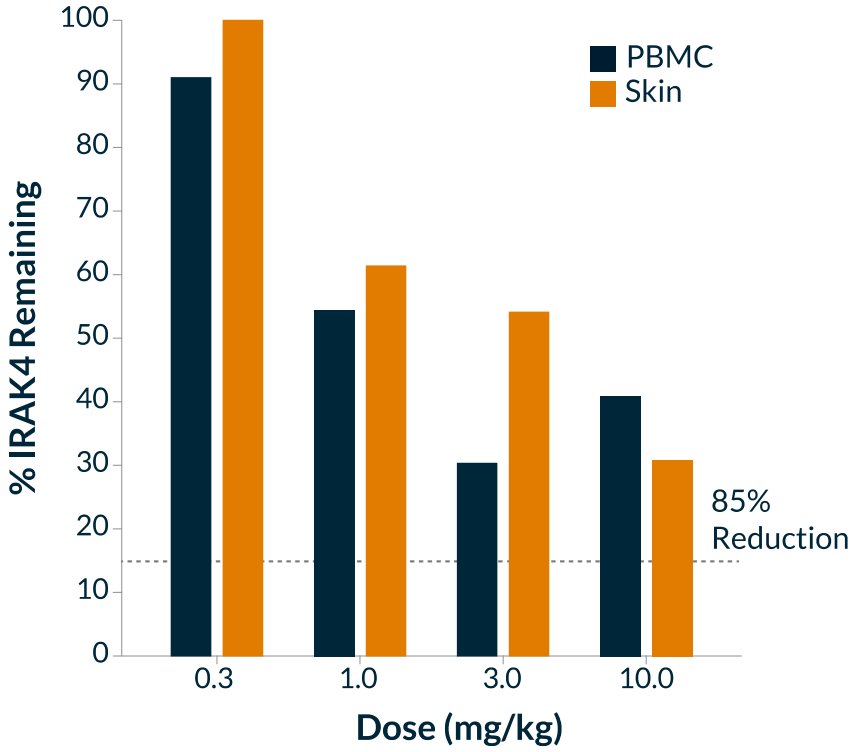




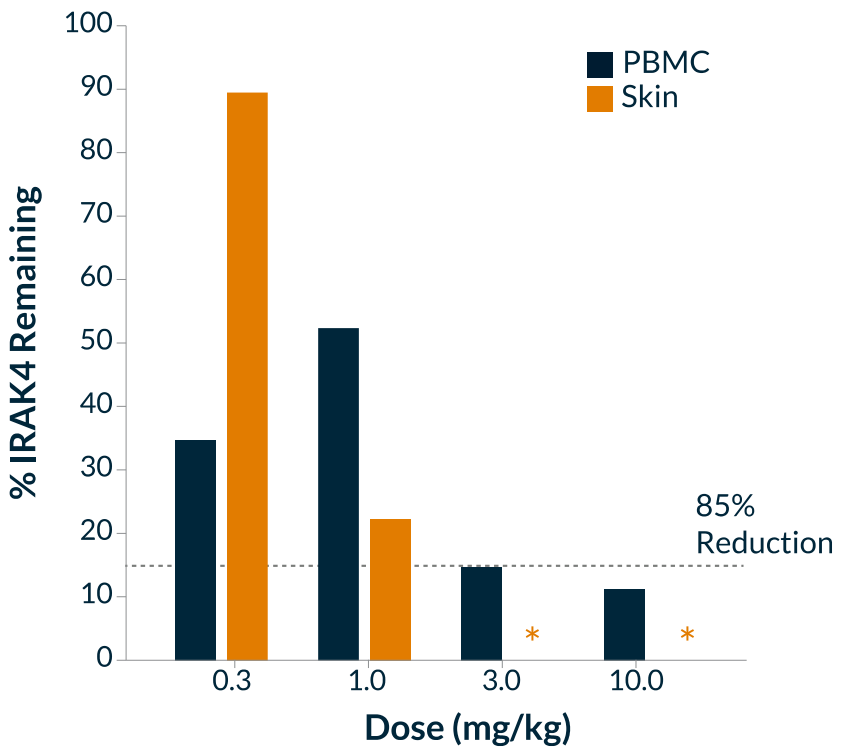
KT-474 in Dog: Multi-dosing Required to Achieve Target Degradation

- Orally-administered KT-474 achieves >85% knockdown of IRAK4 at Day 7 with repeat dosing in MAD study
- Multiple doses (MAD) lead to optimal degradation profile vs SAD upon reaching steady-state
- Consistency of IRAK4 knockdown observed across peripheral blood mononuclear cells (PBMC) and skin tissue

Dog Single Ascending Dose (SAD)
IRAK4 Knockdown at Day 1



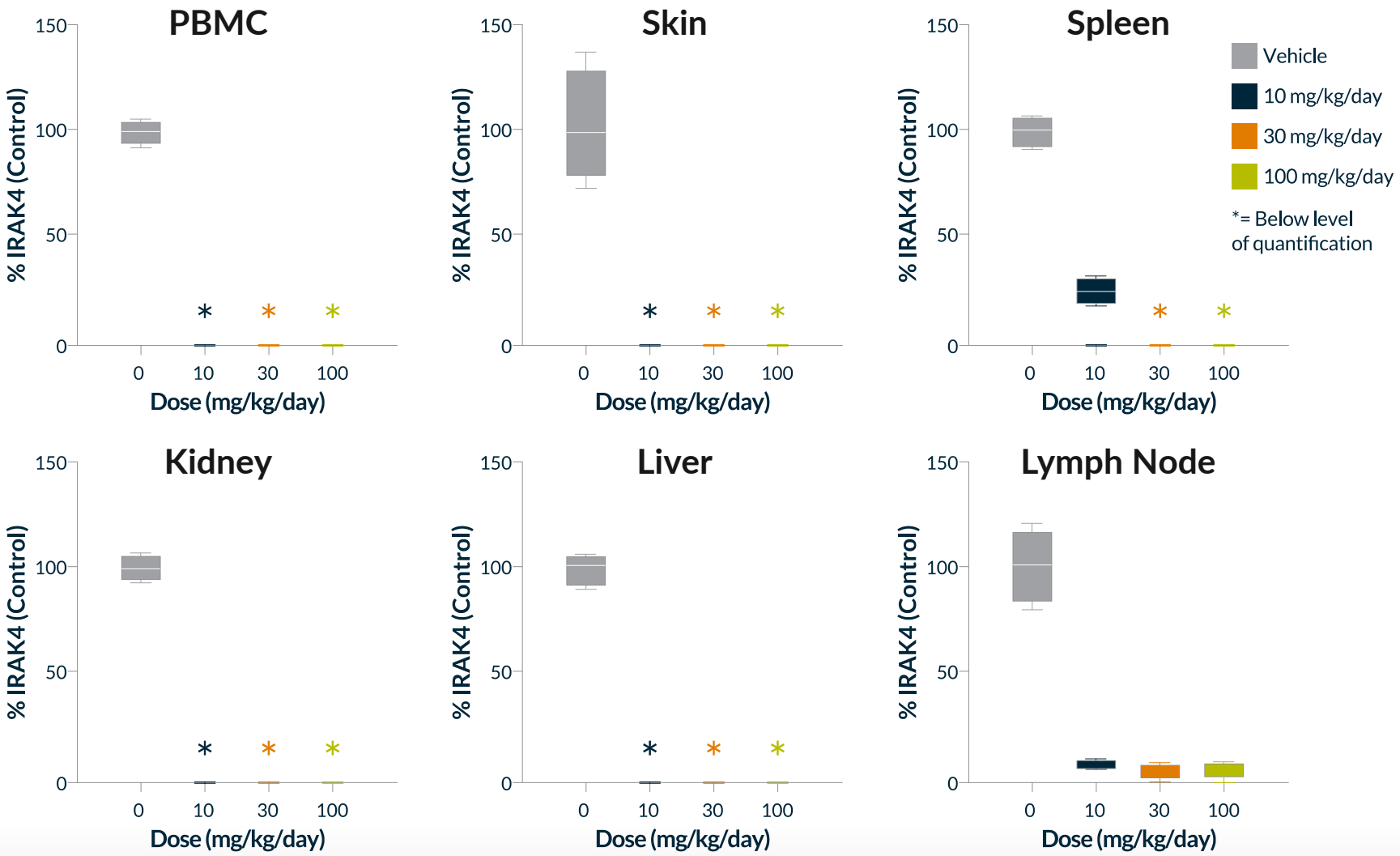
Dog Multiple Ascending Dose (MAD)
IRAK4 Knockdown at Day 7



* = Below Limit of Quantitation

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

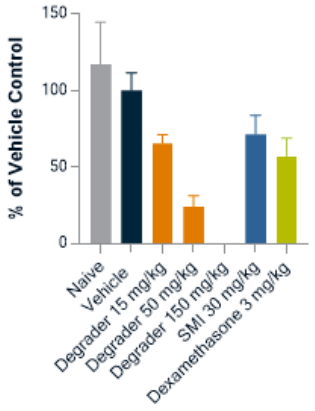


KT-474 is Superior to IRAK4 Kinase Inhibitors Across Multiple Preclinical Immune-inflammatory *In Vivo* Models

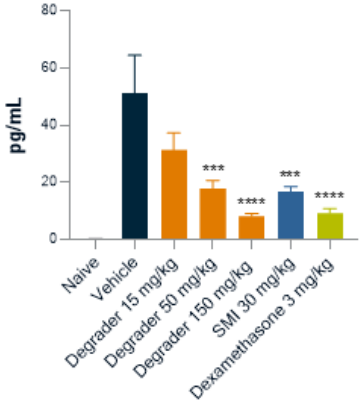
- KT-474's efficacy and superiority to IRAK4 small molecule inhibitors in models of IL-33, IL-36 and Th17-mediated inflammation
- In IL-33 and IL-36 models, KT-474 dose-dependently reduced IRAK4 levels in blood cells and inhibited skin inflammation and/or systemic as well as local cytokine production to the same extent as a potent corticosteroid (dexamethasone) and more potently than an IRAK4 small molecule inhibitor
- In a mouse model of Th17-mediated multiple sclerosis, KT-474 was superior to IRAK4 kinase inhibition and similar to FDA-approved fingolimod (FTY720) in significantly reducing clinical disease scores

rmIL-33 Intradermal Challenge Model

***In vivo* IRAK4 Degradation in Whole Blood**

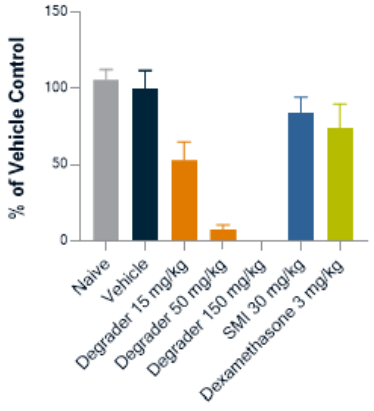


IL-5 in Ear Tissues

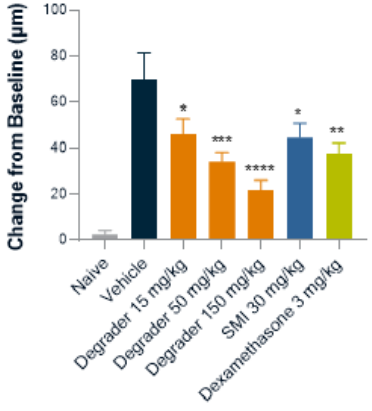


rhIL-36αβγ Intradermal Challenge Model

***In vivo* IRAK4 Degradation in Whole Blood**

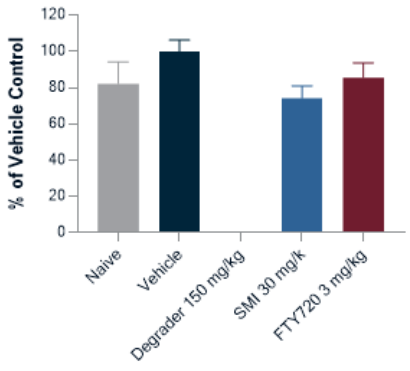


Ear Thickness

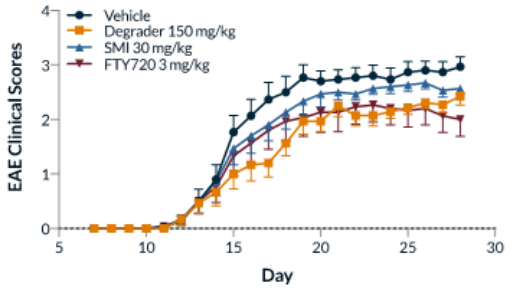


Th17-mediated Multiple Sclerosis Model

***In vivo* IRAK4 Degradation in Whole Blood**



MOG-EAR[1]



Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

1. Myelin Oligodendrocyte Glycoprotein-induced Experimental Autoimmune Encephalomyelitis (MOG-EAR) Model

IRAK4 Non-Interventional Study

KYMERA

Non-interventional Study in HS and AD Patients

Designed to characterize IRAK4 expression and its relationship to inflammatory biomarkers

Study Design

Patients Enrolled	• 30 HS: 9 mild, 10 moderate, 11 severe • 10 AD: 8 mild, 1 moderate, 1 severe
Inclusion Criteria	• Age 18 or older • Active Hidradenitis Suppurativa (HS) or Atopic Dermatitis (AD) • Mild, moderate, and severe HS (IHS4 score) or AD (EASI score)
Exclusion Criteria	• Patients currently on a biologic or other immunosuppressive treatment for HS or AD • Use of biologic treatment for HS or AD within 3 months or 5 half-lives, whichever is longer • Use of non-biologic immunosuppressive treatment in last 4 weeks
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 • Plasma cytokines and acute phase reactants
Reporting Status	• Interim data on IRAK4 expression in HS skin and blood presented in October 2020 at SHSA Meeting • **Updated data presented in May 2021 at SID Meeting on full HS skin dataset for IRAK4 protein and proinflammatory gene transcripts as well as healthy skin and monocyte controls**

Non-interventional Study Methods

HS Skin Biopsies (N=30)

Lesion (L), Peri-lesion (PL), Non-lesion (NL)

IRAK4
Immunofluorescence (IF)
Localization/ Semi-quant

1. Expression in L vs PL vs NL
2. Expression by disease severity
3. Expression in Epidermis vs Dermis

IRAK4
Mass Spectrometry (MS)
Whole Tissue/Quantitative

1. Expression in L vs PL vs NL
2. Expression by disease severity

NanoString
Gene Expression Profiling (GEP)
Whole Tissue

1. Significantly elevated genes in L vs NL
2. Spearman correlation of elevated genes with IRAK4 protein levels by MS and IF

Control Methods

Healthy Subject Skin Biopsies (N=10)

IRAK4
Immunofluorescence (IF)

1. Expression in Healthy vs HS
2. Expression in Epidermis vs Dermis

IRAK4
Mass Spectrometry (MS)

1. Expression in Healthy vs HS

NanoString
Gene Expression Profiling (GEP)

1. Significantly elevated genes in HS vs Healthy
2. Spearman correlation of elevated genes with IRAK4 protein levels by MS and IF

Ex-vivo R848-Stimulated Monocyte Methods

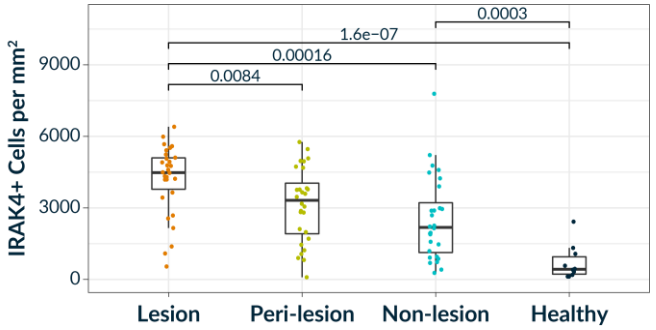
1. Mechanistic study designed to evaluate impact of IRAK4 degradation on response of healthy monocytes to TLR7/8 agonist R848
2. Monocytes isolated from blood of healthy donors (N=3), treated overnight with 500nM of IRAK4 degrader KT-474, and then stimulated with R848
3. For RNA-seq, cells were collected at 2 hours following stimulation
4. Analysis of KT-474 effect on R848 upregulation of subset of genes overexpressed in HS skin lesions that correlate with IRAK4 protein levels

IRAK4 Protein is Overexpressed in HS Skin Compared to Skin from Healthy Subjects

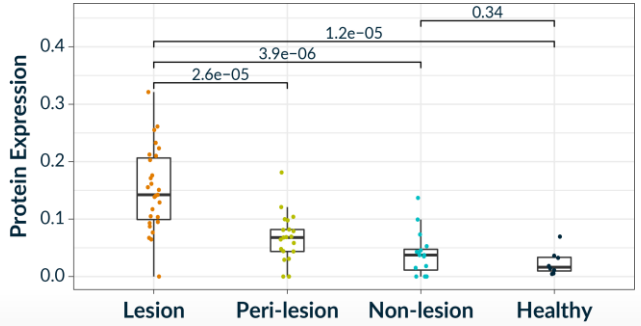
- IRAK4 protein levels overexpressed in HS patient skin lesions
- Concordance between IF and MS

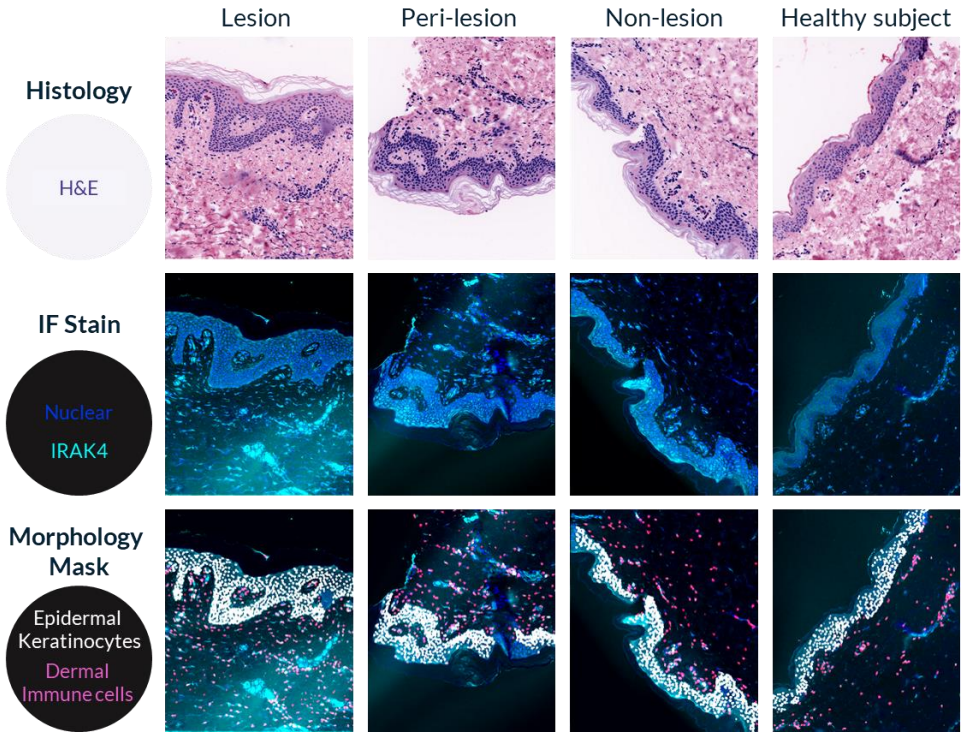
- IRAK4 expression is upregulated in dermis and epidermis of HS patients relative to healthy subject skin
- Higher overall IRAK4 expression in HS lesions and peri-lesion skin was due primarily to an increase in the dermal immune cell infiltrate

Immunofluorescence (IF)

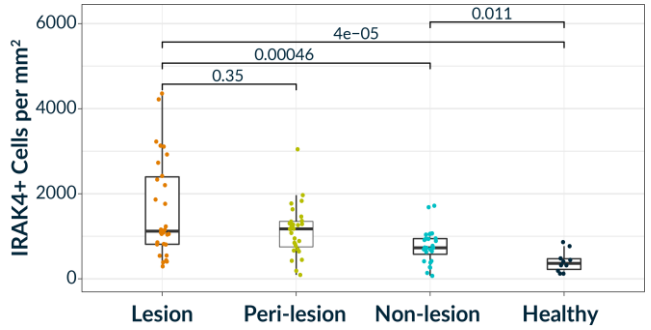


Mass Spectrometry (MS)

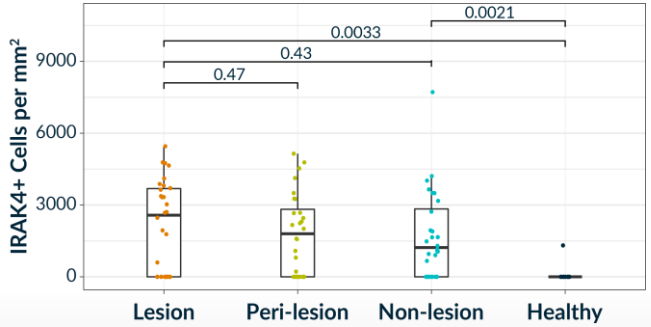




Dermal Immune Cells

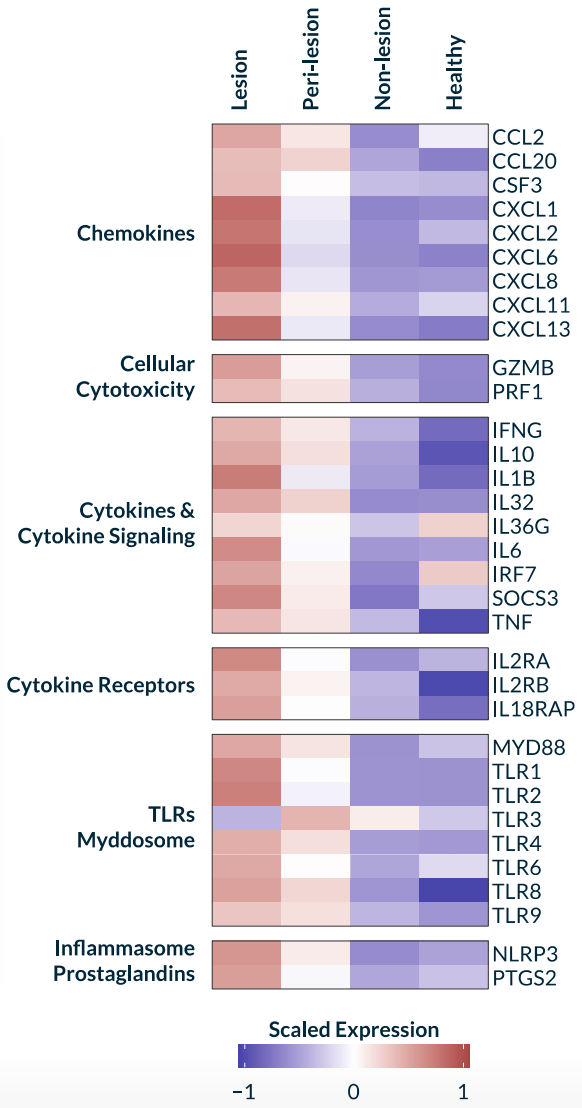


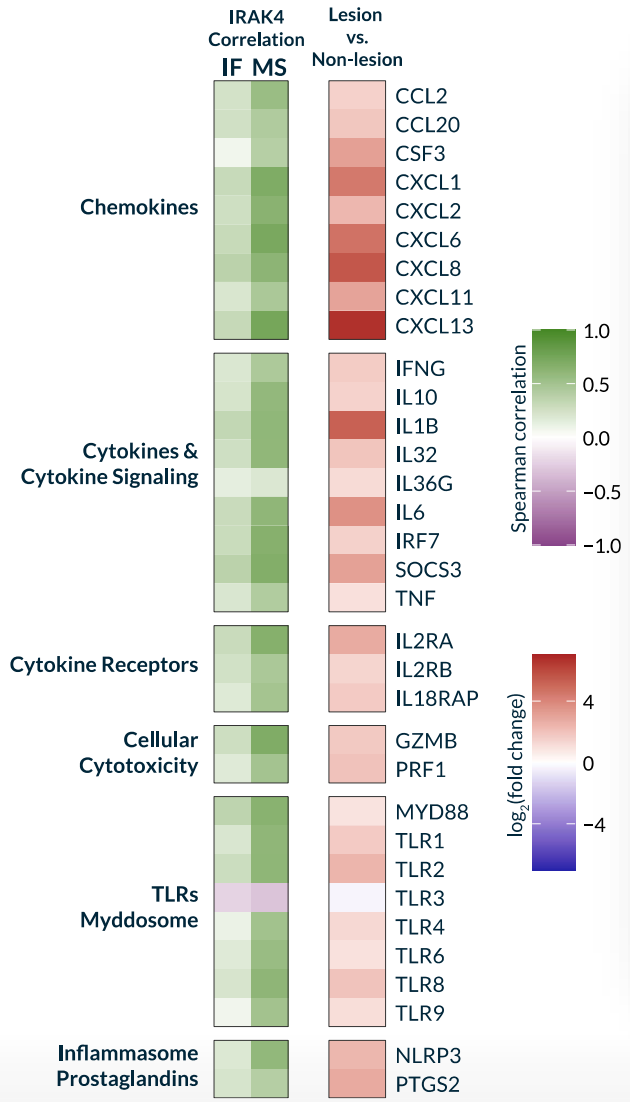
Epidermal Keratinocytes



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

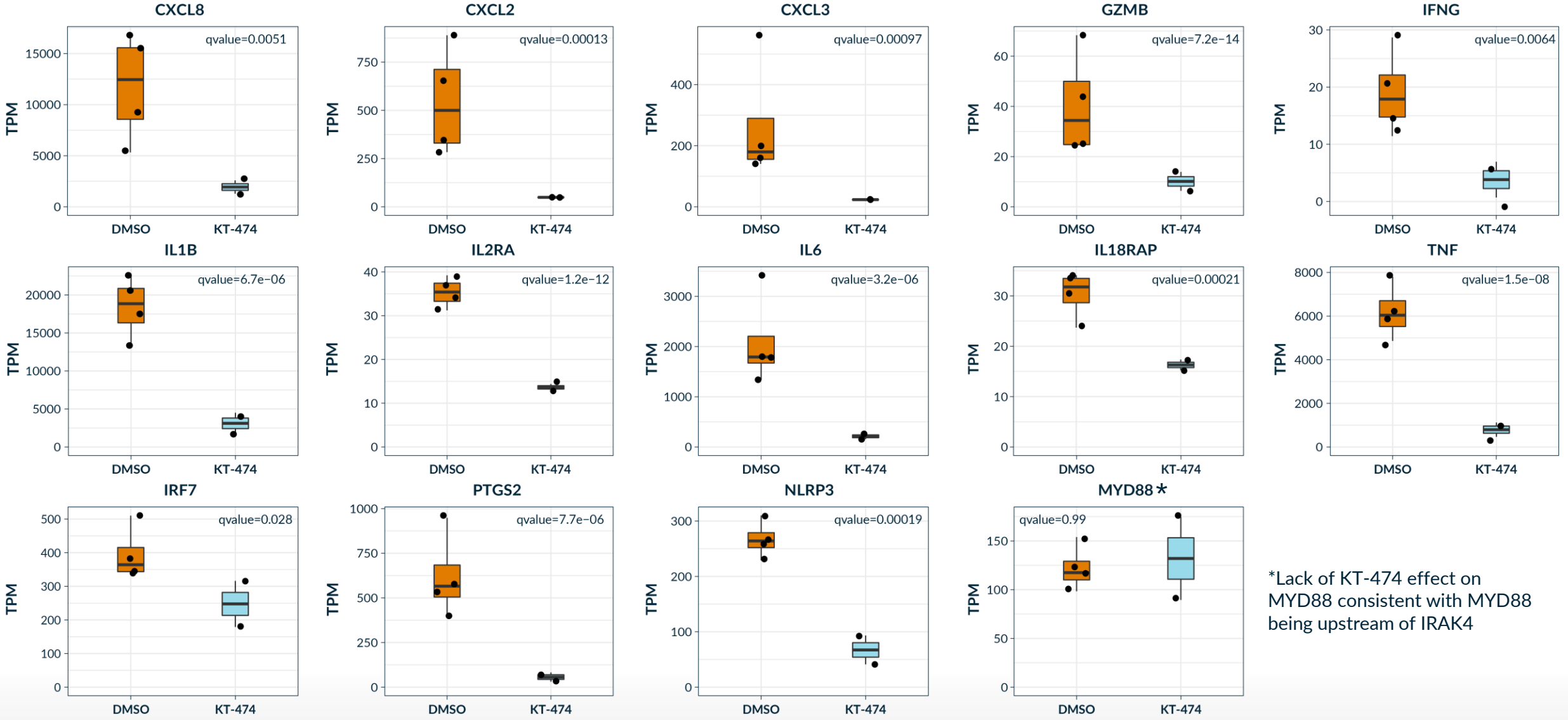
- Gene expression profiling showed upregulation of multiple mediators of inflammation in HS skin lesions
- Inflammatory gene transcripts significantly upregulated in HS skin lesions included genes involved in TLR/myddosome signaling, inflammasome activity, prostaglandin generation, Th1 and Th17 inflammation, and monocyte/neutrophil migration and activation





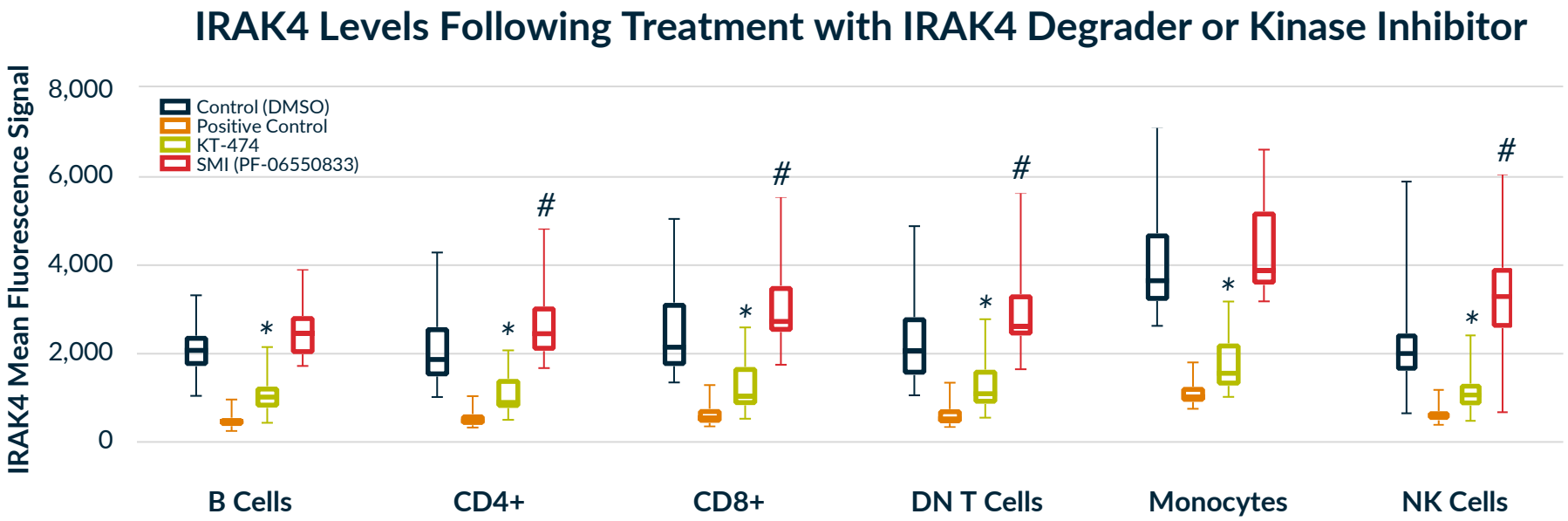
- Almost all of these same inflammatory gene transcripts upregulated in HS skin lesions positively correlated with IRAK4 protein expression by both IF and MS, as did multiple other proinflammatory genes
- TLR3, which is the only TLR that does not signal through IRAK4, was not upregulated in HS lesions and negatively correlated with IRAK4

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

IRAK4 Degrader Downregulates IRAK4 Expression Across All PBMC Subsets



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

KEY TAKEAWAYS

- *Ex vivo* incubation of HS blood with KT-474 reduced IRAK4 to a level approaching the lower limits of detection across all PBMC subsets, irrespective of baseline expression intensity, whereas an IRAK4 kinase inhibitor increased IRAK4 levels in T and NK cells
- Treatment with an IRAK4 kinase inhibitor led to an increase in IRAK4 levels of up to 2.6-fold in T and NK cells

Non-interventional Study Conclusions

- **IRAK4 is overexpressed in HS skin relative to healthy subjects due to increase in number of IRAK4+ dermal immune cells and epidermal keratinocytes**
  - Higher expression in active HS skin Lesions compared to peri-lesion and/or non-lesion skin associated with increase in infiltrating IRAK4+ dermal immune cells
  - Higher expression in dermis and epidermis of non-lesion skin compared to skin of healthy subjects raises possibility that IRAK4 overexpression may predispose to inflammatory lesion formation in HS
- **Gene expression profiling shows upregulation of multiple mediators of inflammation in HS skin lesions that correlates with IRAK4 protein overexpression**
  - Includes genes involved in TLR/myddosome signaling, inflammasome activity, prostaglandin generation, Th1 and Th17 inflammation, and monocyte/neutrophil migration and activation, thereby linking IRAK4 to the pleiotropic inflammation in HS
  - Neither proinflammatory gene expression nor IRAK4 protein expression correlated with disease severity, suggesting common pathophysiology underlying inflammation in active lesions irrespective of disease stage
- **IRAK4 degrader KT-474 inhibits TLR-stimulated upregulation of HS-overexpressed inflammatory genes in monocytes from healthy subjects**
  - Provides further evidence for role of IRAK4 in overexpression of these mediators of inflammation in HS skin lesions and rationale for targeting IRAK4 with KT-474 for the treatment of patients with HS
  - Phase 1 trial of KT-474 in healthy volunteers and patients with HS or AD is ongoing and includes pre- and post-treatment skin biopsies and blood sampling to assess the effect of KT-474 on the expression of IRAK4 and associated biomarkers of inflammation


IRAKIMiD
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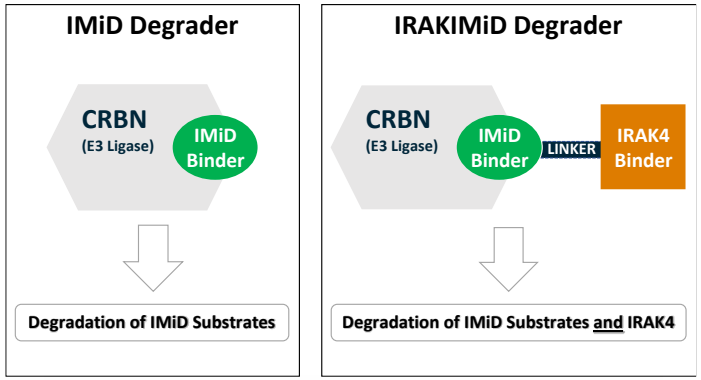
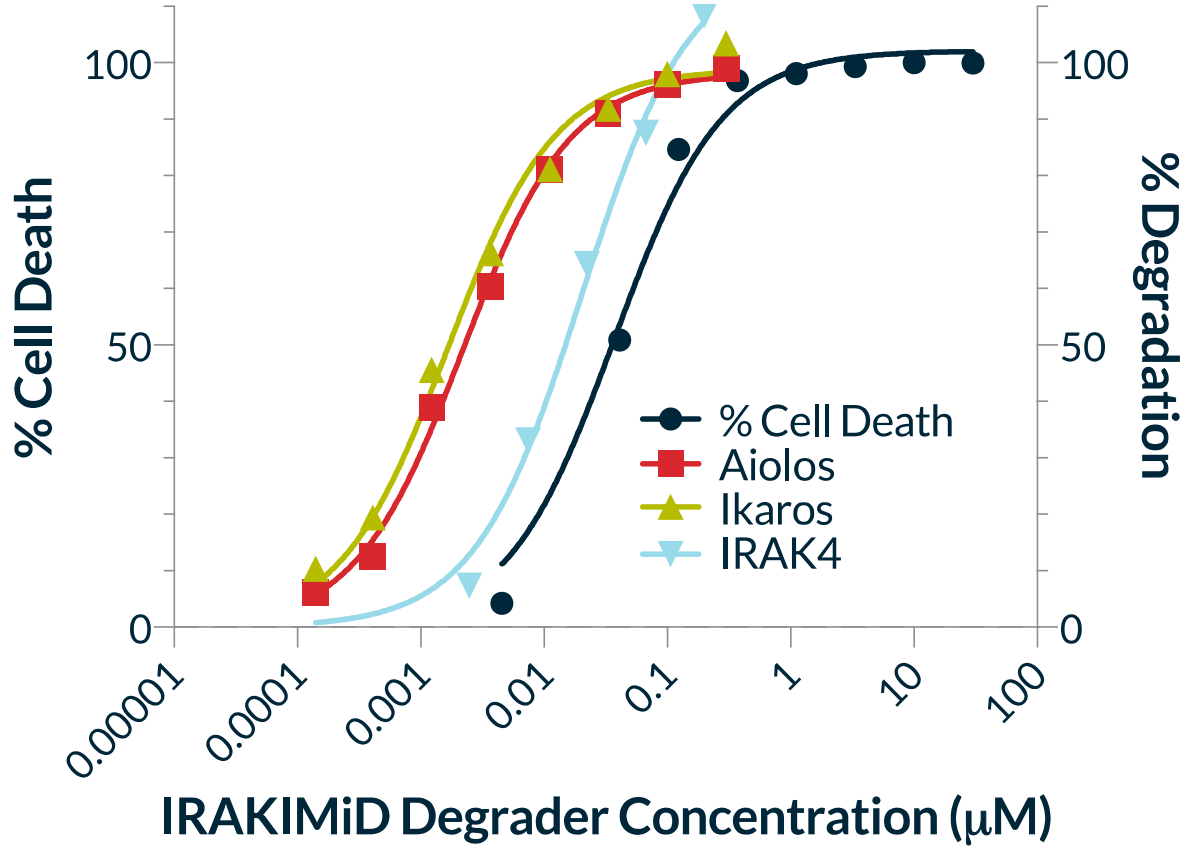
Degradation of IRAK4, Ikaros and Aiolos Correlates to Cell Killing

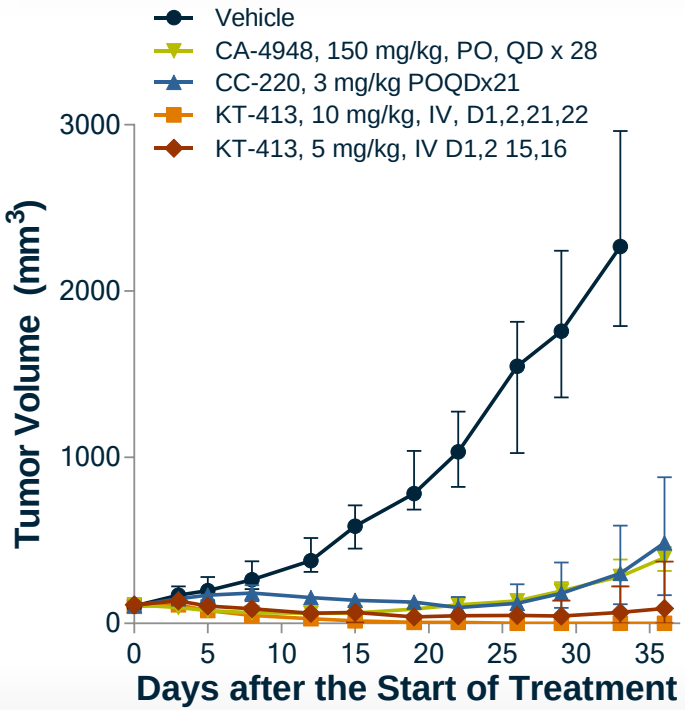


- IRAK4, Ikaros and Aiolos degradation measured in MYD-88-mutated OCI-Ly10 cells after 24 h of drug exposure
  - *IRAK4 DC_{50} = 4 nM*
  - *Ikaros/Aiolos DC_{50} = 2/2 nM*
- Degradation correlates with cell killing effects
  - *IC_{50} = 31 nM*



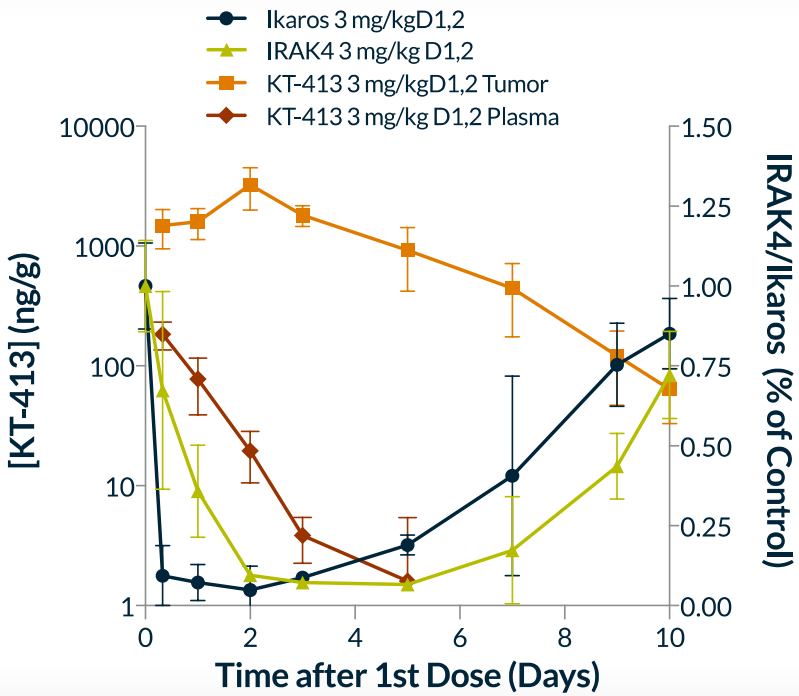
KT-413 is Highly Active on Intermittent Dosing Regimens and Superior to Clinically Active CA-4948 and CC-220

- In the OCI-Ly10 MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete or partial regressions
  - Superior activity compared to the clinically active IRAK4-inhibitor CA-4948 or the latest generation IMiD CC-220 alone
- Minimally active dose of 3 mg/kg D1,2 showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for at least 72h



Drug	CR	PR	SD	PD
CA-4948	0	0	3	4
CC-220	0	1	4	2
KT-413 (5 mpk)	2	2	3	-
KT-413 (10 mpk)	5	2	-	-

CR: <10mm^3 tumor on D26
PR: >50% regression from baseline
SD: <50% regression to 20% increase in tumor volume
PD: >20% tumor growth on D26



STAT3

KYMERA

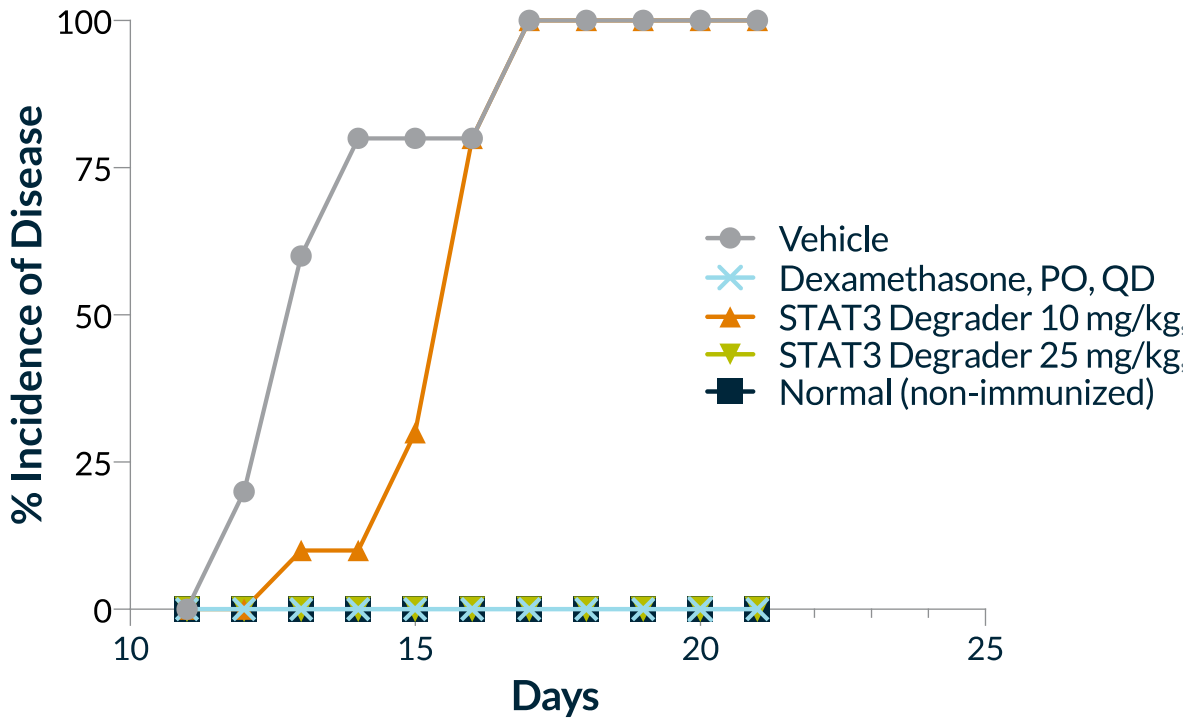
STAT3 Degrader Active in T Cell Activation Preclinical *In Vivo* Model

Multiple Sclerosis Model

CANCER
- Liquid Tumors
- Solid Tumors

I/I FIBROSIS
- Autoimmune
- Fibrosis

- A preclinical model of experimental autoimmune encephalomyelitis (T cell activation) was used to evaluate STAT3 degradation
- Kymera STAT3 Degrader completely prevented onset of the disease in mice



STAT3 Degradation and Downstream Effects Across Tumor Cells

CANCER

Liquid Tumors

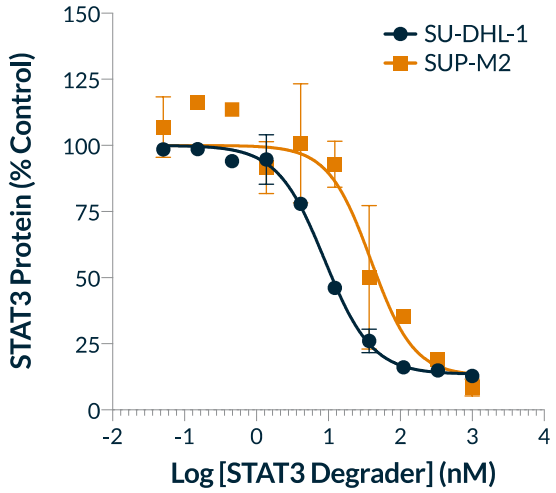
Solid Tumors

I/I FIBROSIS

Autoimmune

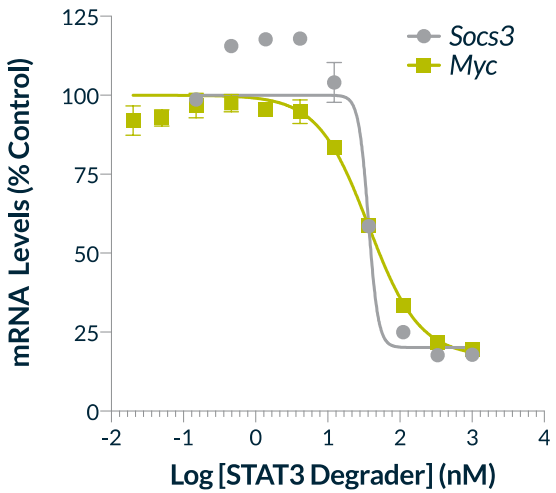
Fibrosis

STAT3 Degradation



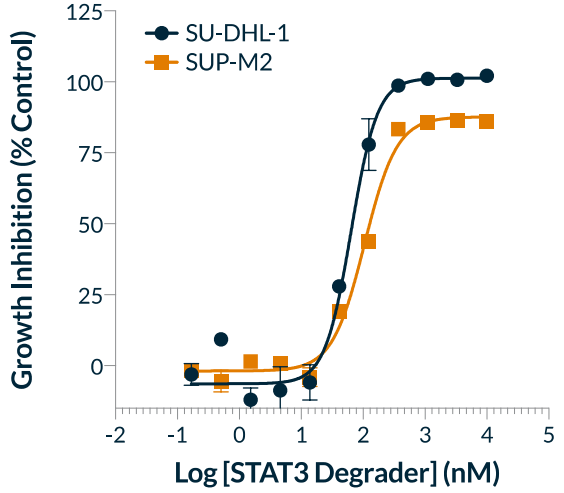
- STAT3 protein levels measured in two STAT3-dependent cell lines
- STAT3 degrader decreased levels of STAT3 by greater than 95% with DC_{50} of 15nM and 86 nM, respectively

Gene Transcription Effects



- Expression of STAT3 downstream target genes in SU-DHL-1 cells measured
- Treatment with STAT3 degrader for 24 hours led to significant downregulation of STAT3 target genes, including SOCS3 (IC_{50} = 36 nM) and MYC (IC_{50} = 37 nM)

Cell Viability Effects



- Impact of STAT3 degradation on viability of lymphoma cells measured
- Inhibited growth of SU-DHL-1 and SUP-M2 cells with IC_{50} values of 64 and 105 nM, respectively

Effects of STAT3 Degradation on Tumor Microenvironment

CANCER

I/I FIBROSIS

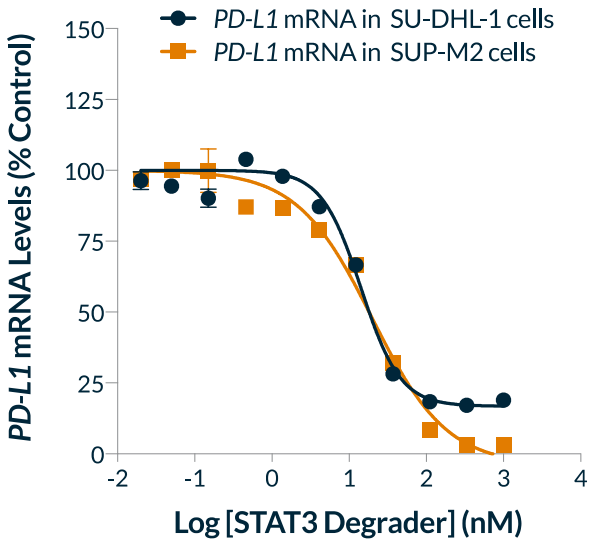
Liquid Tumors

Solid Tumors

Autoimmune

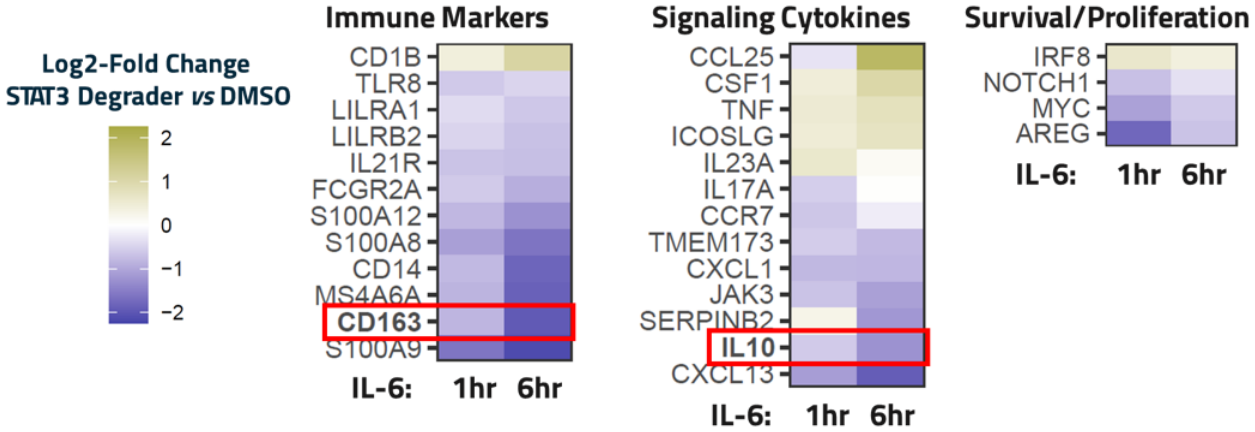
Fibrosis

PD-L1 Downregulation



- Treatment of cells with Kymera's STAT3 degrader reduced transcription of PD-L1 mRNA
- STAT3 degradation may reverse a key tumor intrinsic mechanism for immune suppression

Increased Inflammation in Tumor Associated Immune Cells



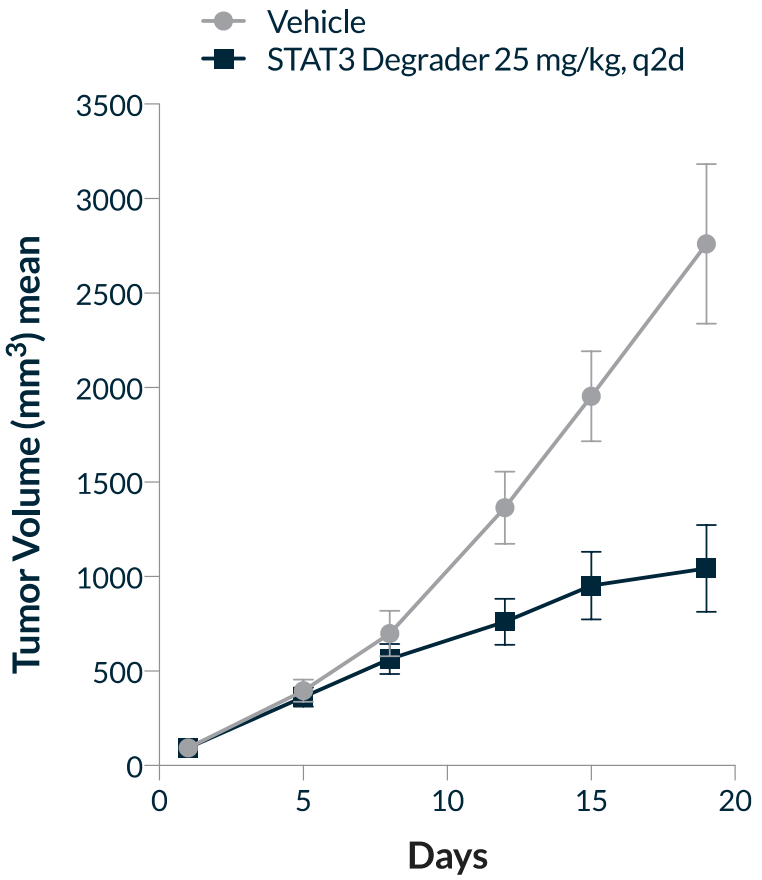
- STAT3 degrader blocked IL-6-induced increases in gene expression in hPBMC
- Data suggest degradation of STAT3 reverses expression of genes contributing to immune suppression

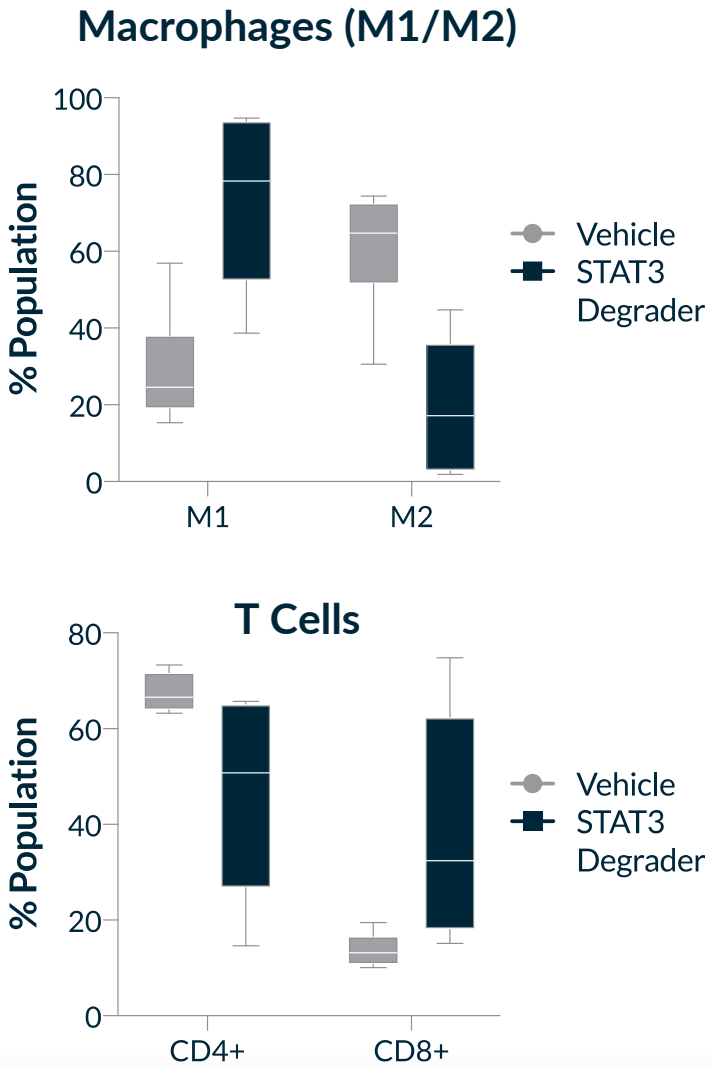
STAT3 Degrader *In Vivo* Active in Preclinical PD-1/L-1 Refractory Solid Tumor Model

CANCER
- Liquid Tumors
- Solid Tumors

I/I FIBROSIS
- Autoimmune
- Fibrosis

- Kymera's STAT3 degrader assessed in colorectal cancers (CT-26) known to be refractory to approved immunotherapies
- STAT3 degrader significantly reduced tumor growth when administered every two days
- Analysis of tumors showed synergistic modulation of immune cells (M2/M1 and T cells) within the tumor microenvironment to favor an anti-tumor response





THANK YOU

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