KYMERA
EST. 2016

INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

Undruggable leaders Forum

Sep 15, 2021

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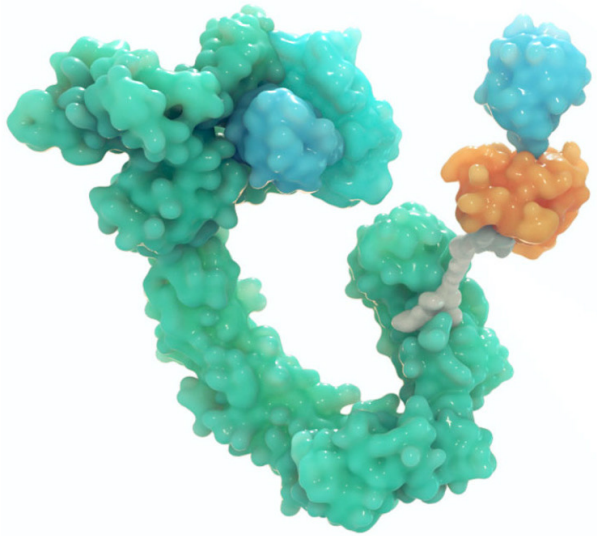
Outline

- Kymera – introduction and pipeline
- IRAK4 degrader KT-474 and clinical degrader proof of mechanism
- Classical undruggable - STAT3 degradation and potential
- Summary

Kymera: A Leading TPD Company

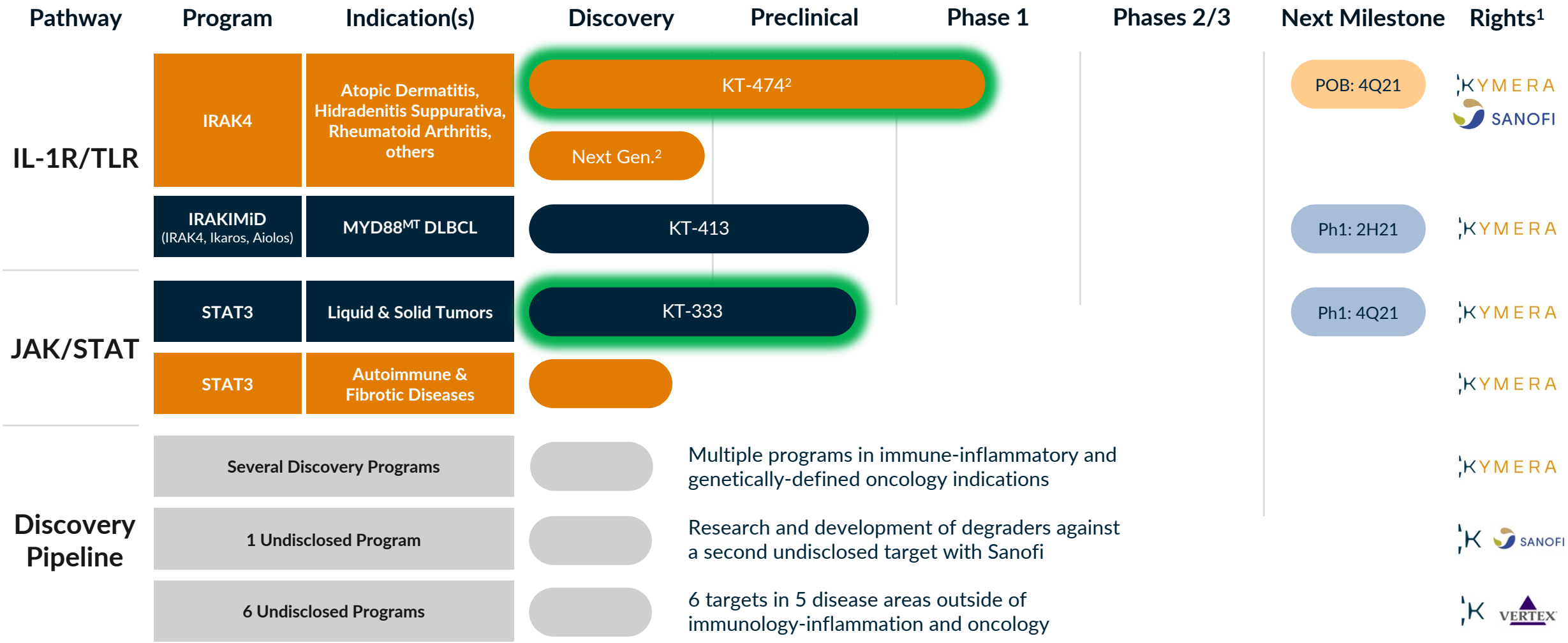
KYMERA



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.

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

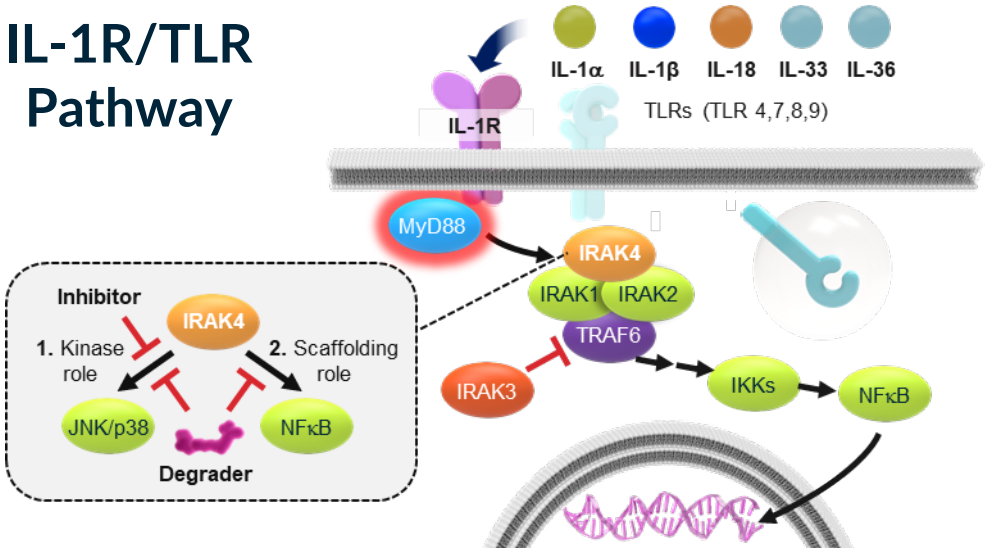
Unmet Medical Need

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

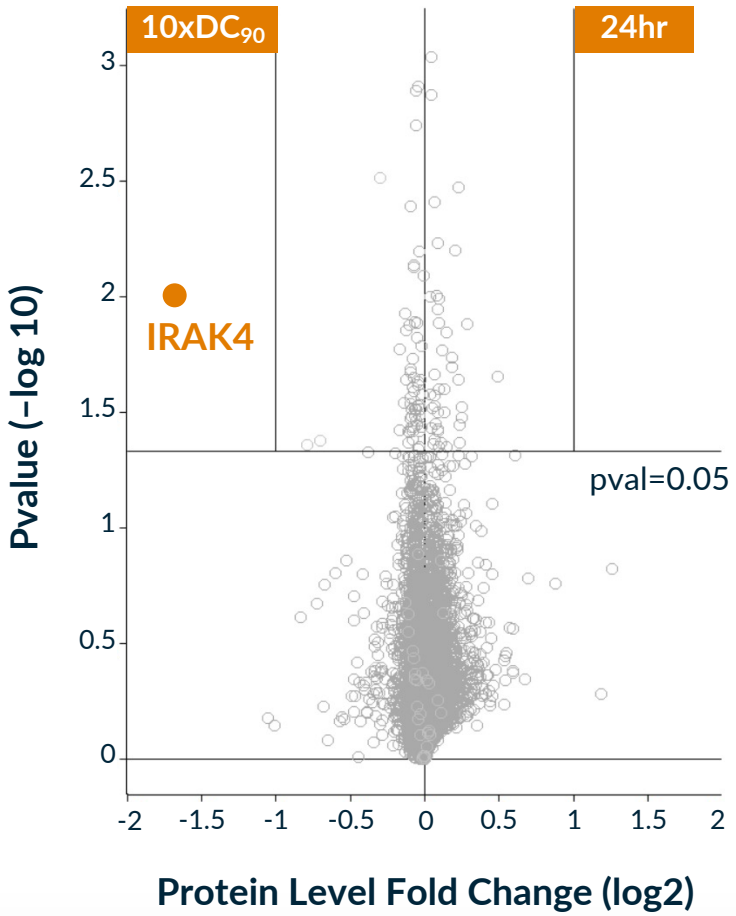
IL-36: Generalized Pustular Psoriasis

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

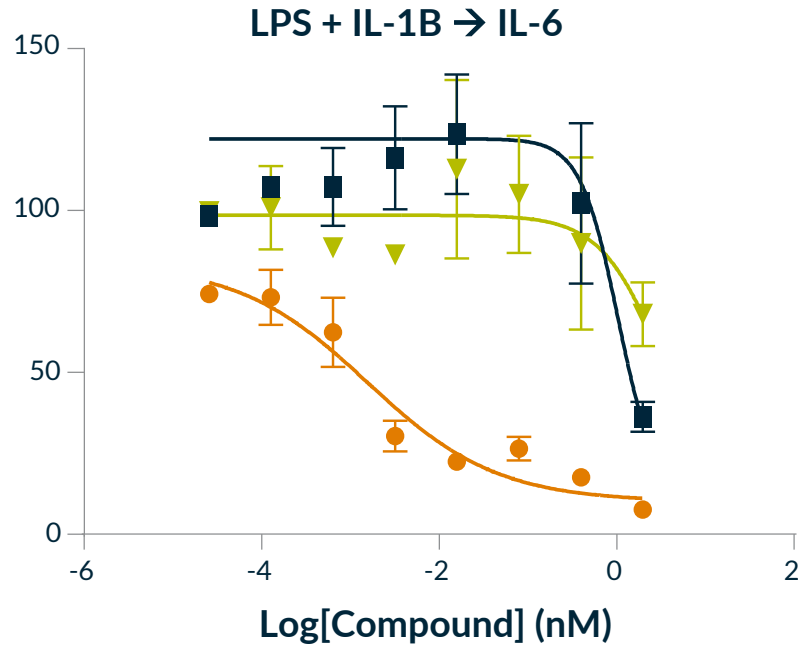
KT-474: Potent and Specific IRAK4 Degradation Superior to Kinase Inhibition

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

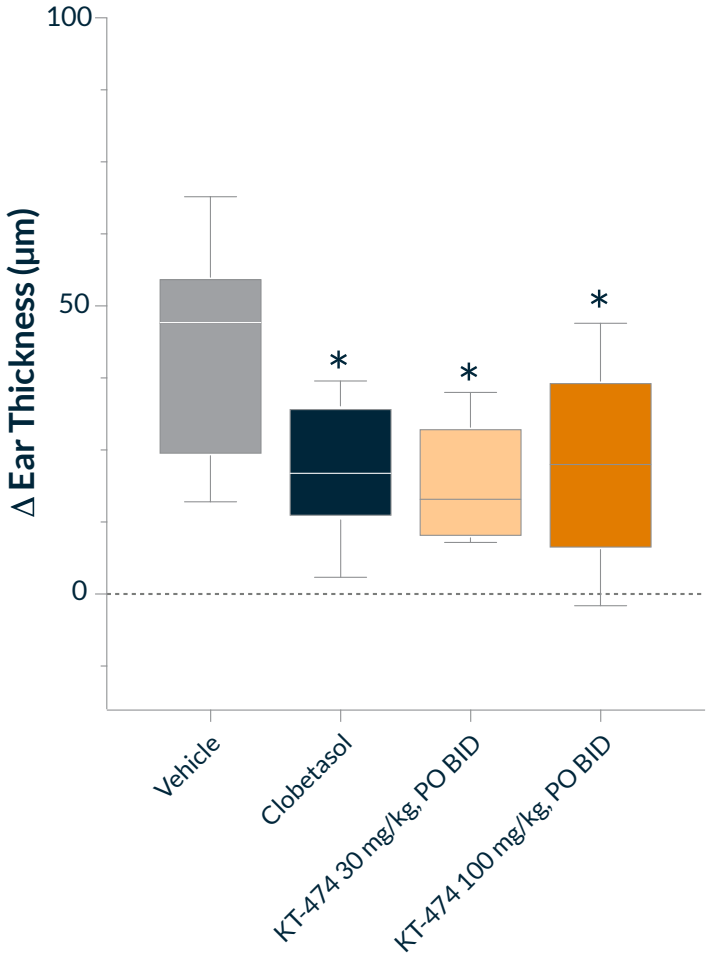
Superiority over SM kinase Inhibitor

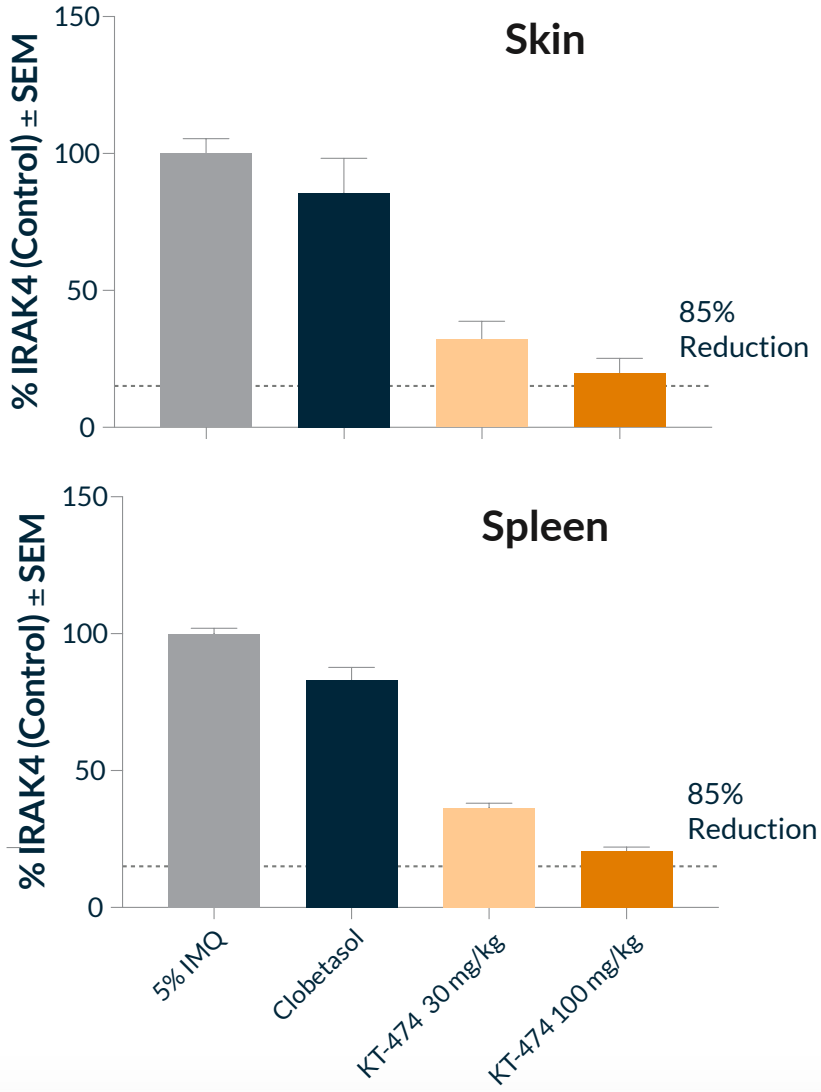


Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

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

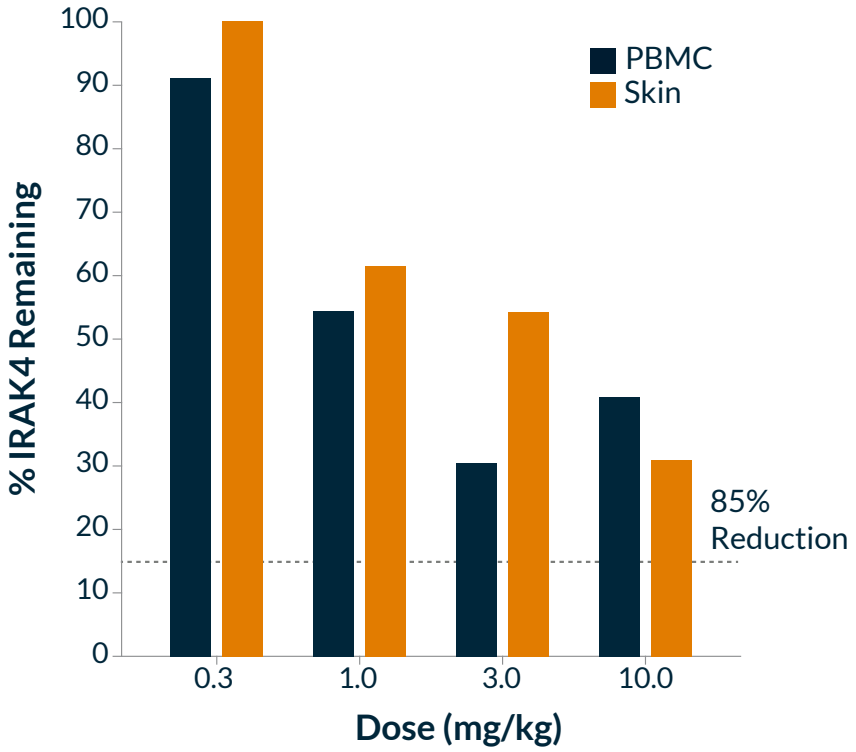




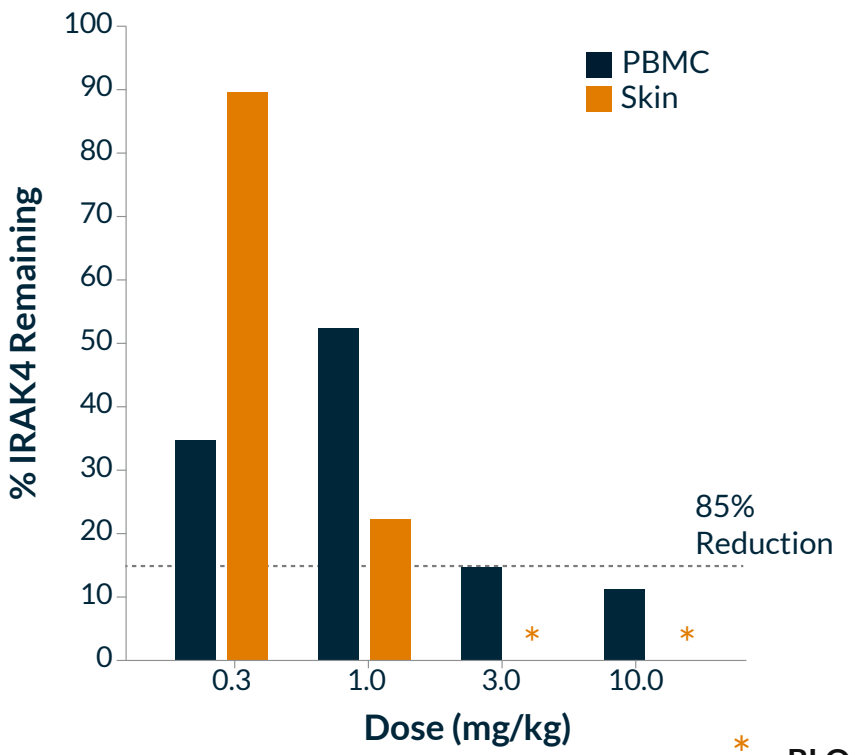
KT-474 in Dog: Multi-dosing Required to Achieve Target Degradation

- 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 cell (PBMC) and skin measurements

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



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



* = BLQ

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
SAD & MAD

- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC

Secondary
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 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

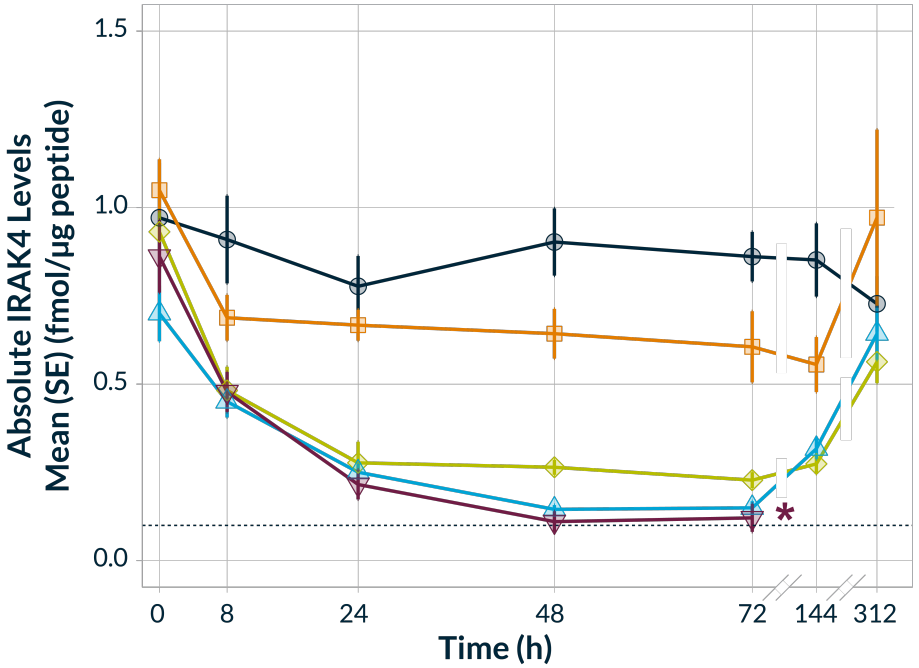
- PK profile consistent with oral daily dosing
- Predictable, dose-dependent plasma exposures after single oral KT-474
- Half-life:
  25-32 hours

Safety & Tolerability

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

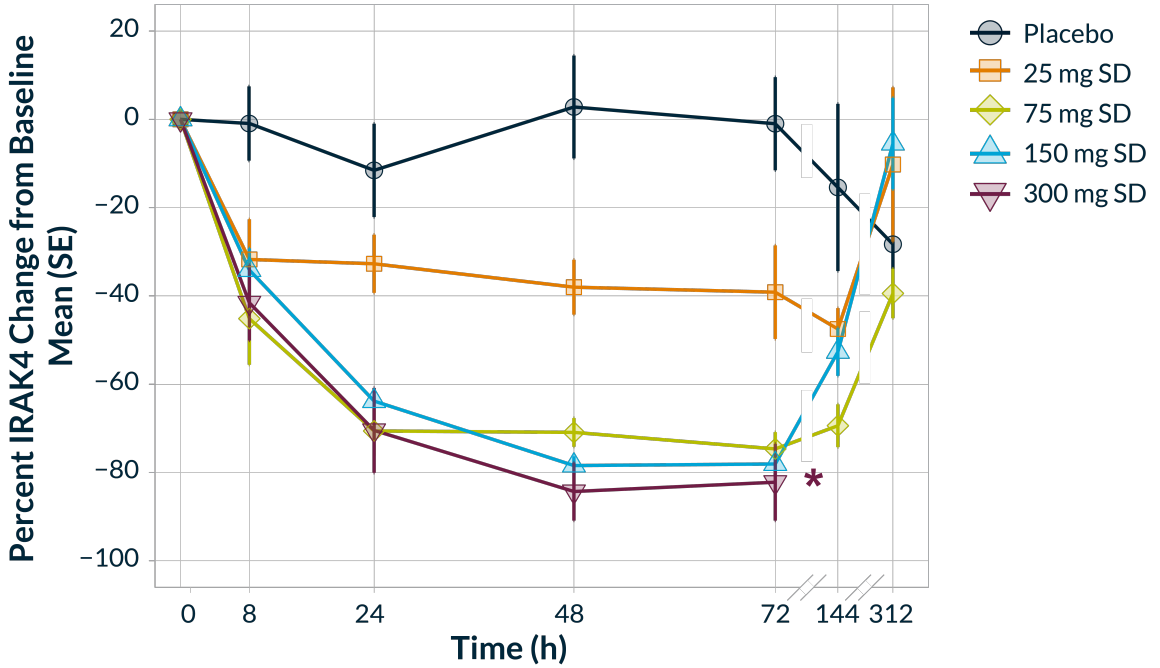
KT-474 Achieved Profound IRAK4 Degradation after Single Oral Dose that Lasted for at Least 6 Days

Absolute IRAK4 Levels



LOD

Mean % Reduction of IRAK4

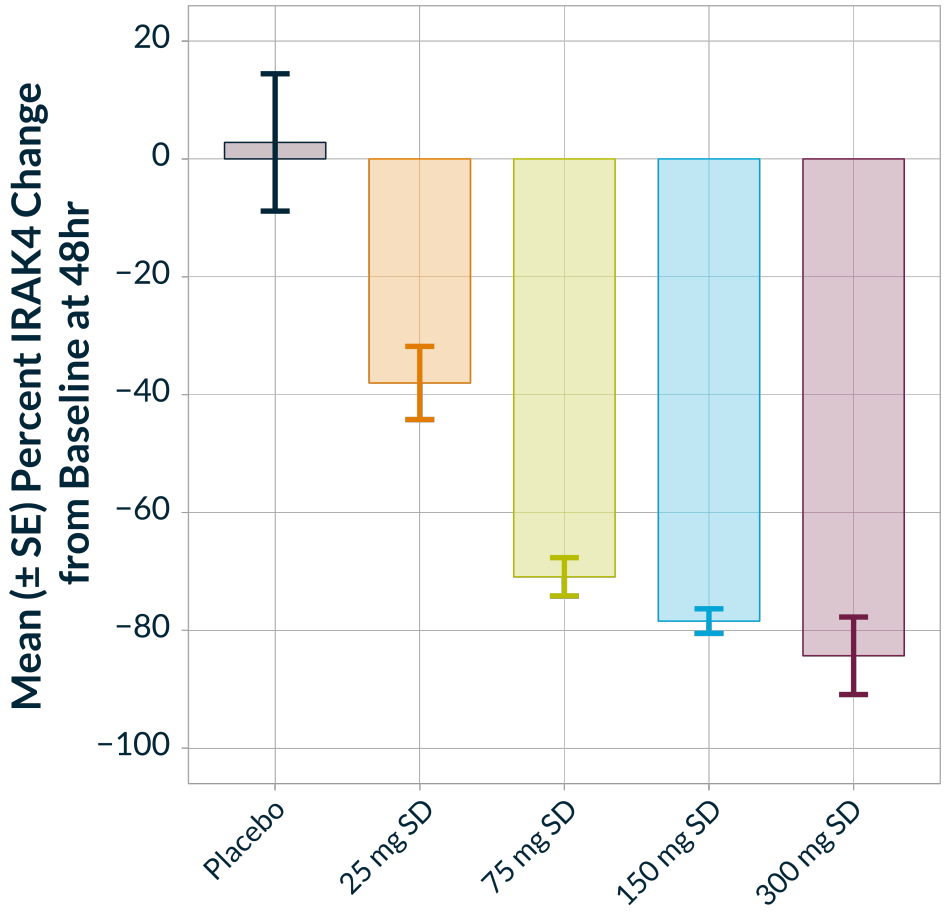


LOD = limit of detection

* SAD4 144/312 h PD timepoints pending

- Detected 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

KT-474 Reached >85% IRAK4 Degradation After Single 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

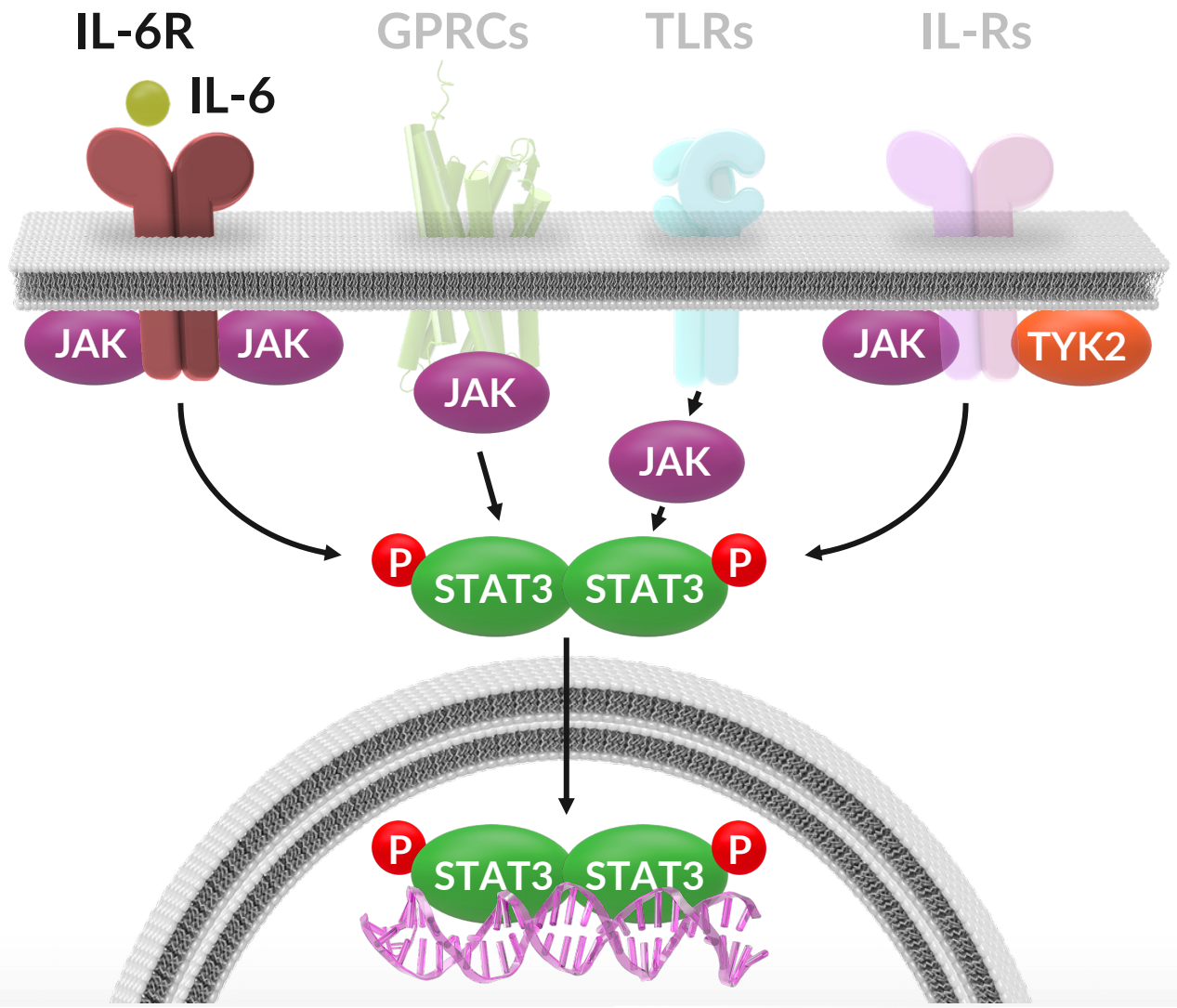
Summary and Next Steps

- **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 48h 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; MAD starting dose of 25mg
  - Demonstrated oral bioavailability, predictable, dose-dependent and efficacious plasma exposures, and a half-life supportive of oral daily dosing
  - No treatment-related adverse events or serious adverse events observed to date
  - Exceeding Phase 1 target degradation of at least 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

- **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
  - Dose from MAD healthy volunteer portion to be selected for evaluation in an open label a cohort of patients with atopic dermatitis and hidradenitis suppurativa

STAT3 Biology and Degrader Rationale

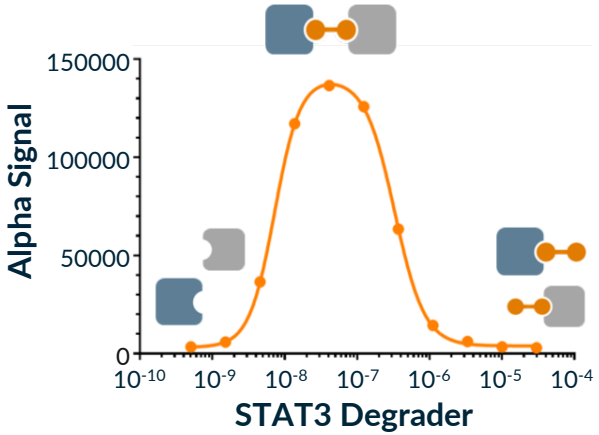
- STAT3 is a traditionally largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAKs mediated mechanisms
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported also by numerous publications
- STAT3 plays a role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



Specific and Potent STAT3 Degradation

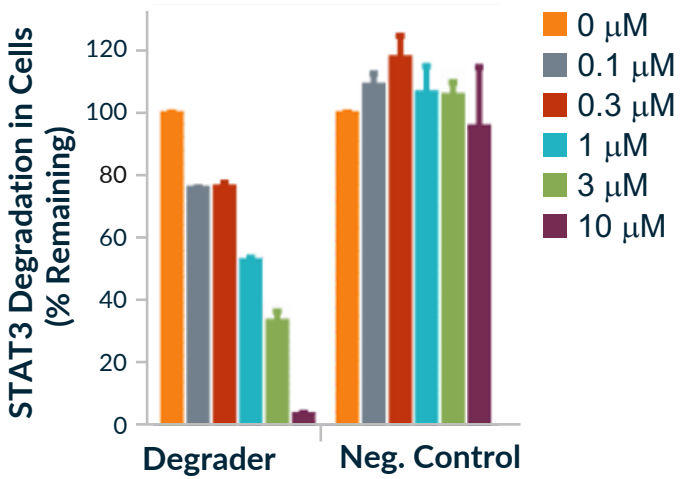
Kymera binders recruit STAT3 to E3 ligase and affect ubiquitination

Efficient Ternary Complex Formation



Efficient Ubiquitination of Cellular STAT3

Potent, E3-Dependent Degradation



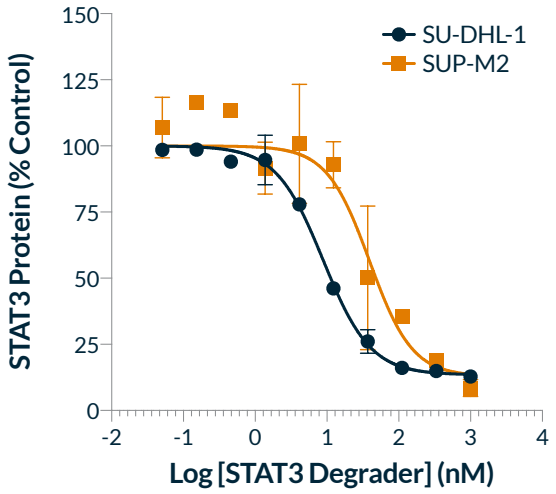
Potent Degradation

Inactive analog of degrader (Unable to bind E3 ligase)

KTX-201 Exhibited High Potency and Selectivity

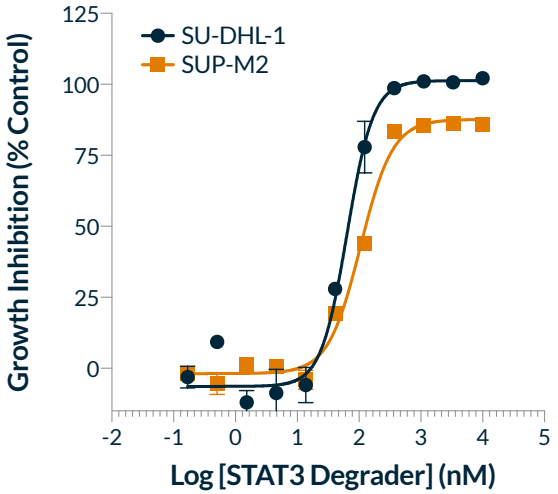
High Potency in SU-DHL-1 and SUP-M2 Cell Lines (ALK+ ALCL)

Degradation Potency



SU-DHL-1 24h DC_{50} 15 nM
SUP-M2 24h DC_{50} 86 nM

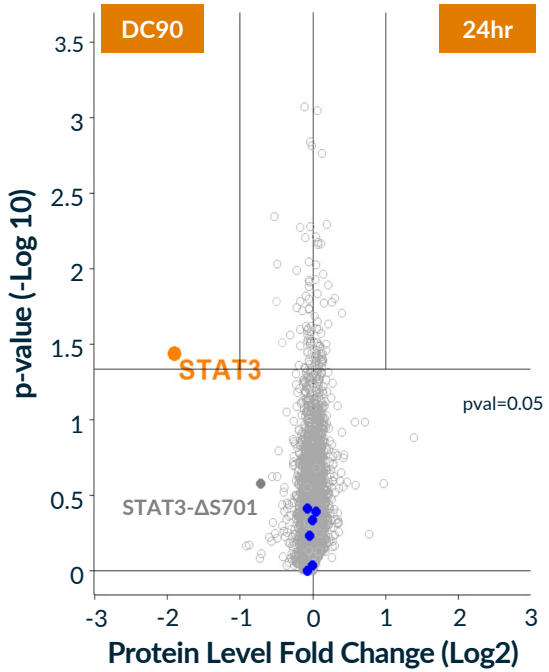
Growth Inhibition Potency



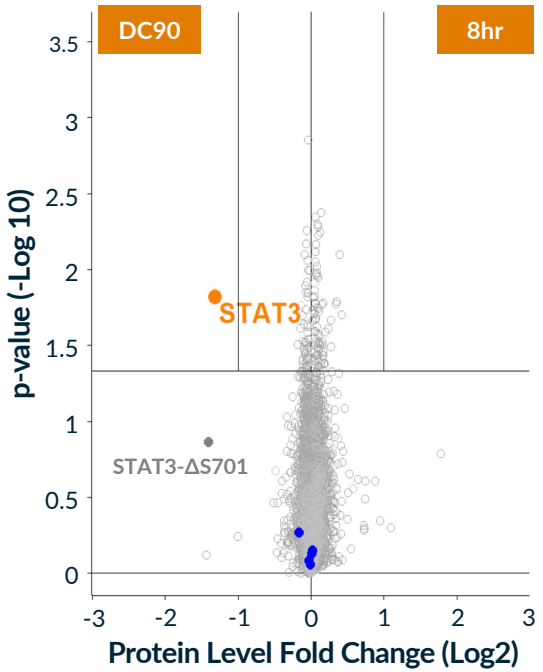
SU-DHL-1 IC_{50} 64 nM
SUP-M2 IC_{50} 105 nM

High Selectivity in huPBMCs and SUDHL-1 Cell

huPBMCs



SU-DHL-1



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

1. KTX-201 is a potent and selective STAT3 degrader tool molecule

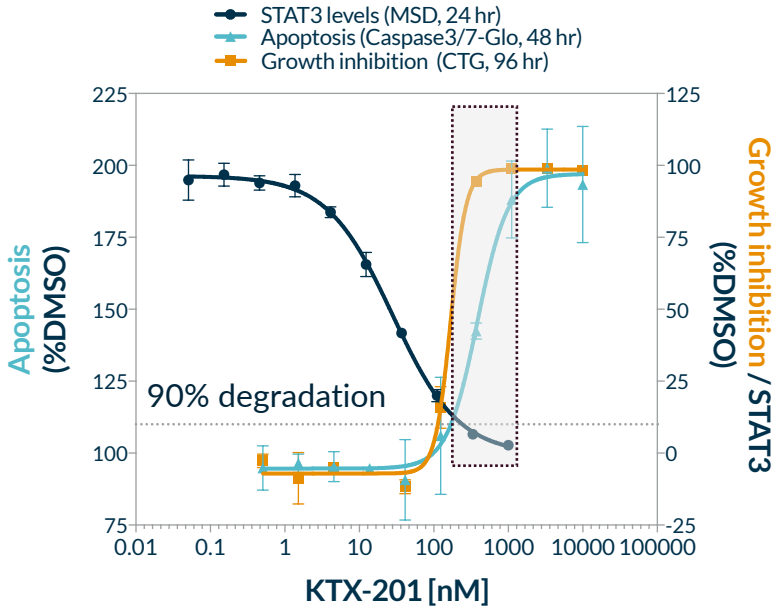
KTX-201 is Highly Soluble and Has Low Clearance *in vivo*

Properties suitable for IV dosing route-of-administration (RoA)

Physical and DMPK properties	KTX-201
cLogD	**-1.3**
Solubility at pH 7.4 (μM)	**259**
Solubility in PBS pH 7.4 (mg/mL)	**>28**
HLM / RLM / DLM / MkLM (μL/min/mg)	**3.4 / <1.4 / 4.6 / <1.4**
PPB (hu / rat / dog / Mk)	**95.8% / 99.1% / 97.1% / 97.3%**
CYP3A4 / 2C9 / 2C19 / 2D6 inhibition (IC_{50})	**All > 50 μM**
Mouse Cl (mL/min/kg) / Vdss / $t_{1/2}$ (hr)	**2.4 / 0.39 / 4.1**
Dog Cl (mL/min/kg) / Vdss / $t_{1/2}$ (hr)	**3.2 / 0.66 / 9.2**
Monkey Cl (mL/min/kg) / Vdss / $t_{1/2}$ (hr)	**5.5 / 0.68 / 5.6**

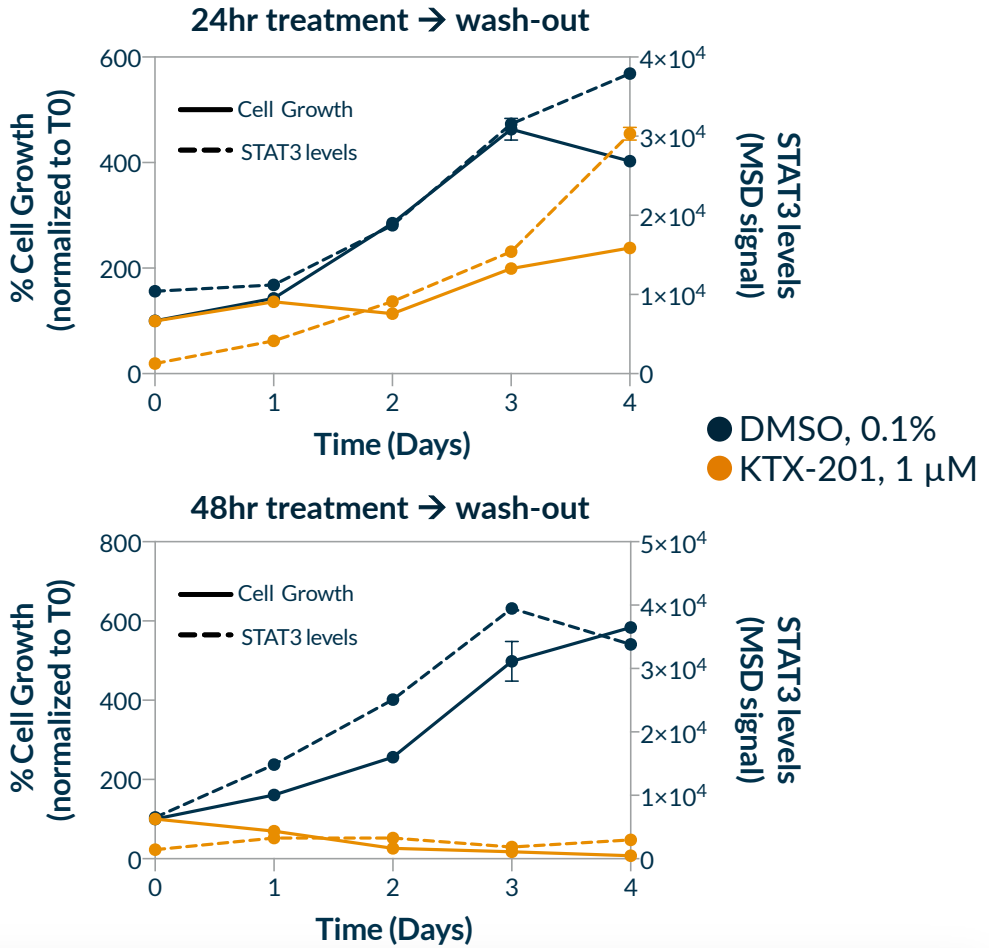
1. KTX-201 is a potent and selective STAT3 degrader tool molecule

Sustained and Robust Degradation of STAT3 with KTX-201 is Necessary to Induce SU-DHL-1 Apoptosis and Inhibit Cell Growth



Assay	SU-DHL-1
STAT3 levels, MSD DC_{90} (μM) at 24 hr	**0.15**
Apoptosis, Caspase3/7-Glo IC_{50} (μM) at 48hr	**0.38**
Growth inhibition, CTG IC_{50} (μM) at 96 hr	**0.167**

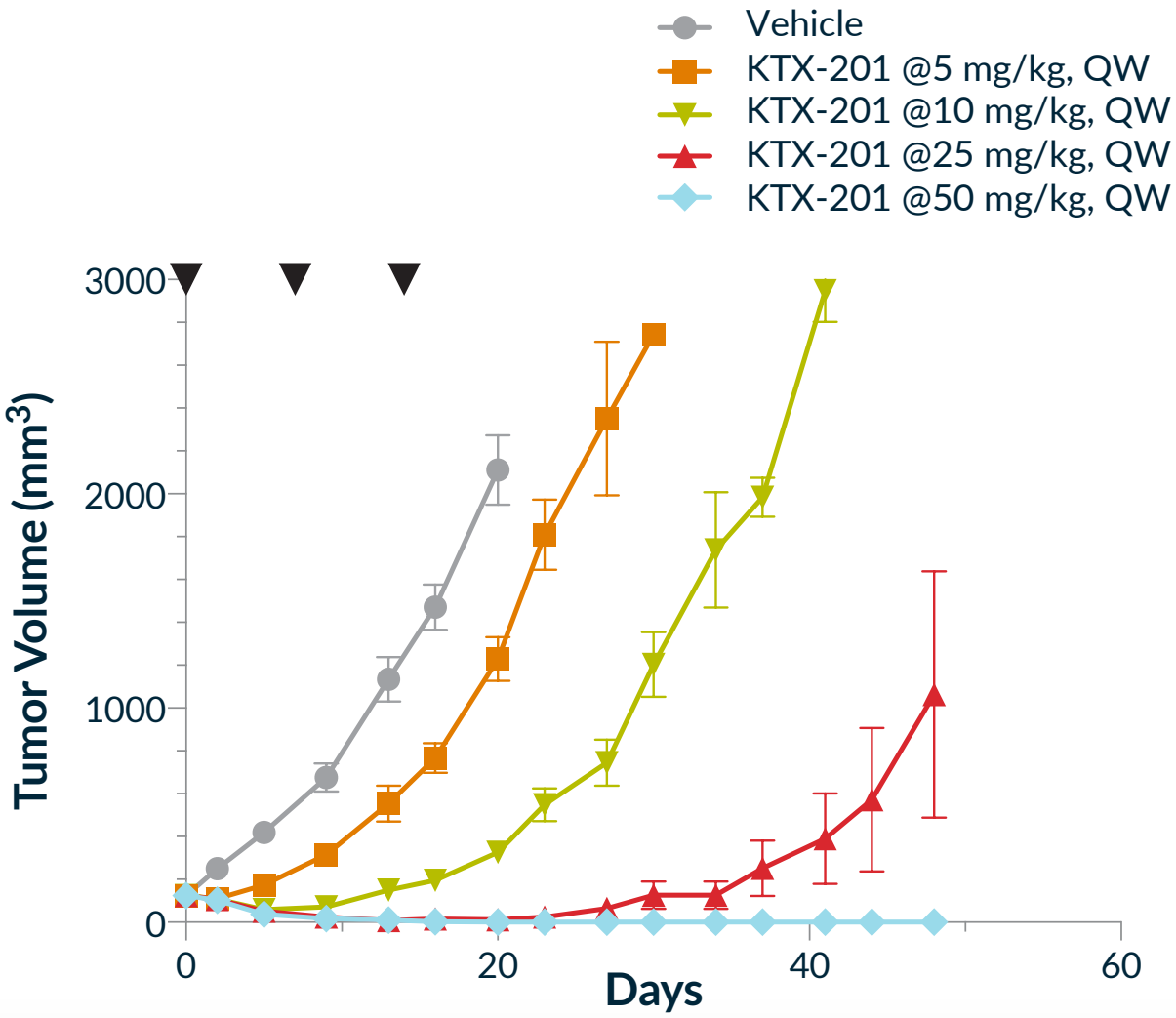
- A decrease of STAT3 by 90% is necessary to induce SU-DHL-1 apoptosis and inhibit cell growth



- Wash-out study demonstrates sustained degradation is required for SU-DHL-1 cells to commit to death

KTX-201 Showed Significant Anti-Tumor Activity *in vivo* with Weekly Dosing Regimen

- KTX-201 in SUDHL-1 XG Mouse
  - IV bolus at 5 to 50 mg/kg
  - Weekly dosing
  - Treatment on D1, D8, D15
- KTX-201 showed significant anti-tumor activity
- The treatments were well tolerated, with no significant body weight loss
- Three doses sufficient to drive durable complete responses

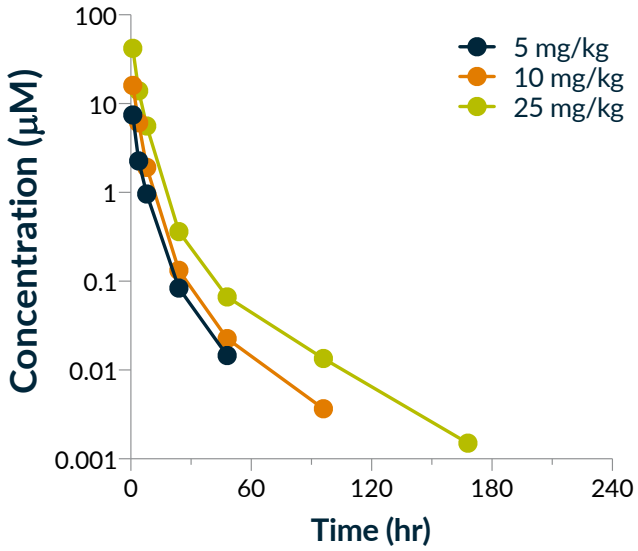


KTX-201 Exhibited Prolonged Half-life in Tumor

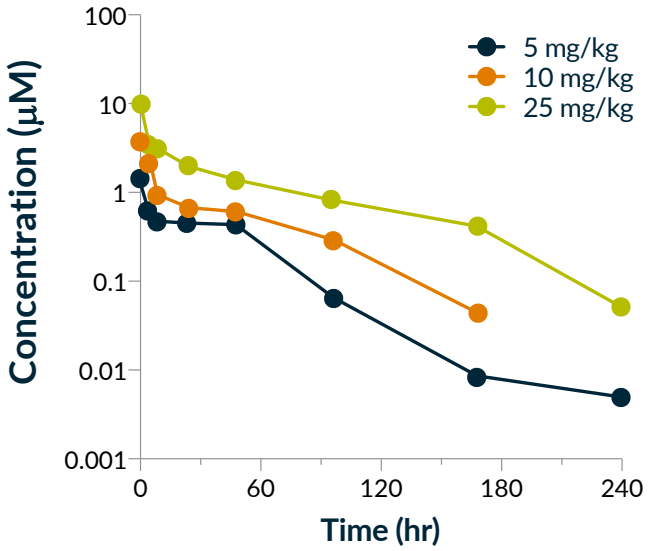
PK in Plasma and Tumor

- Plasma and tumor exposure increase as increase of dose
- $T_{½}$ in tumor > plasma
- Tumor/Plasma AUC ratio *Kp* ~1; consistent across 5 mg/kg to 25 mg/kg dose range

KTX-201 Plasma PK Profiles



KTX-201 Tumor PK Profiles

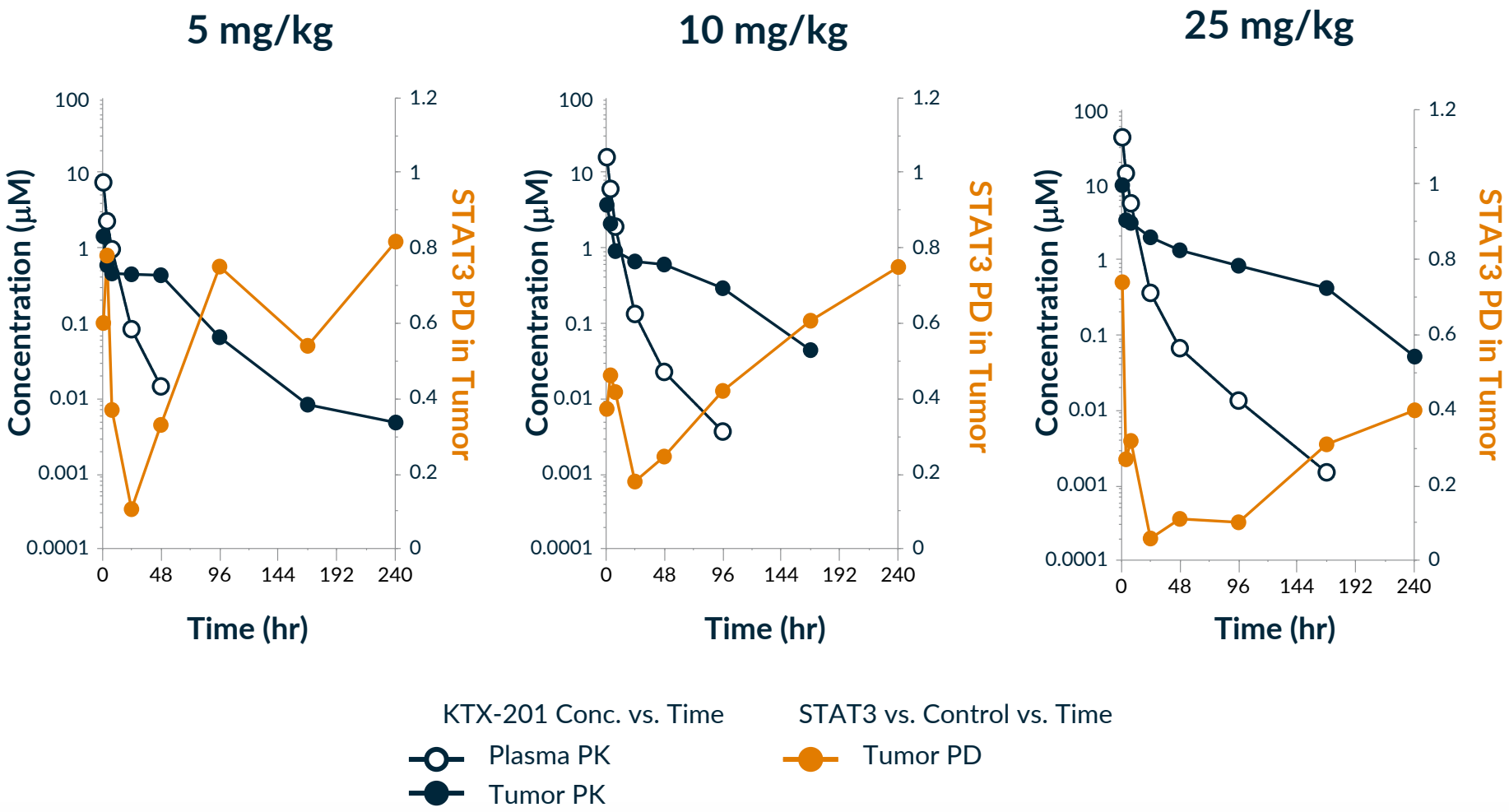


KTX-201		5 mg/kg		10 mg/kg		25 mg/kg	
PK Parameters	Unit	Plasma	**Tumor**	Plasma	**Tumor**	Plasma	Tumor
$T_{½}$	hr	6.8	**24**	16	**31**	16	**36**
AUC_{last}	µM*h	40	**36**	87	**78**	229	**231**

STAT3 Degradation in Tumor Was Exposure-Dependent

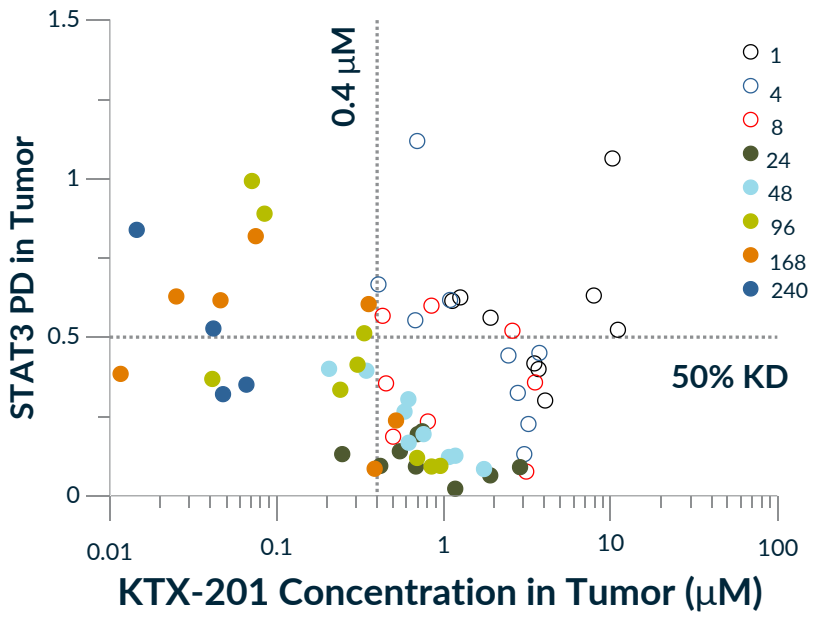
KTX-201 dose-dependent PD

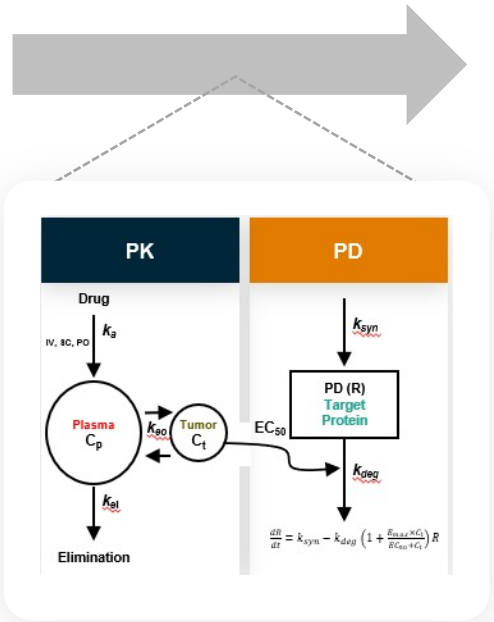
- Maximal STAT3 degradation occurred at 24 hr post dose for all doses
- Maximal degradation is >90% at 25 mg/kg
- Prolonged degradation in tumor is partially due to longer drug $t_{1/2}$ in tumor
- $T_{½}$ of STAT3 return to baseline is dose-dependent → higher dose/higher exposure/ prolonged degradation



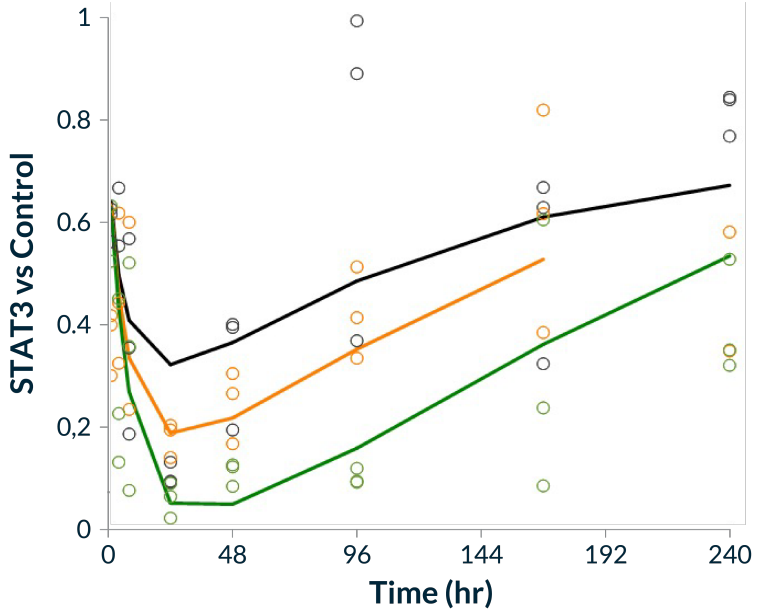
Important *in vivo* Parameters Can be Derived from PK/PD Modelling to Enable Human Dose Projections

KTX-201 Exposure-response in SU-DHL-1





KTX-201 PK/PD Model in SU-DHL-1



5, 10, 25 mg/kg

Solid lines (simulation)

Open circles (observed)

- Hysteresis observed
- >0.4 uM $[KTX-201]_{tumor}$ leads to >50% STAT3 degradation
- *in vivo tumor* DC_{50} is expected to be 0.46 µM (using *in vitro* DC_{50} with PPB correction)

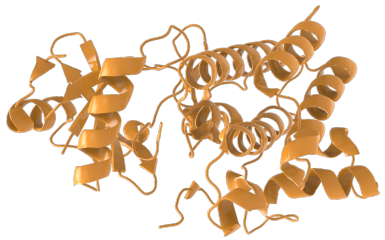
*10% FBS fu = 0.15; SUDHL-1 fu,t = 0.0049

PK/PD Parameters	Description	Estimate	CV
k_{deg}	Degradation Rate	0.0356 hr^{-1} ($t_{½}$ 19 hr)	17%
E_{max}	*In vivo* max. effect	14	16%
EC_{50}	*In vivo* potency	2.5 µM	16%

These PK/PD parameters are used to project human degradation profiles

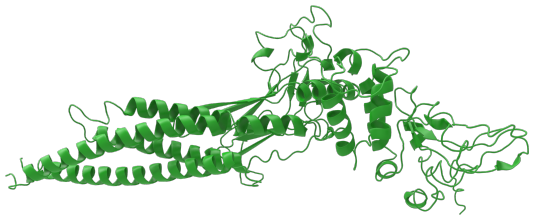
Summary

IRAK4



- IRAK4 is a well validated pathway involved in **multiple IL-1R/TLR-driven immune-inflammatory diseases**
- IRAK4 degradation is **superior** to inhibition
- 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% and maximum reduction of 94% at 48h** following single dose of 300 mg, with sustained degradation that lasted for at least 6 days at all dose levels
- Kymera expect to **present updated results** from healthy volunteer SAD/MAD portions in **Q4'21**

STAT3



- Kymera has developed potent and highly selective **STAT3 degraders** which are active in models of **heme malignancies and solid tumors** which support these as potential indications for clinical development
- Sustained STAT3 degradation of **90% or greater** leads to **apoptosis induction** and **cancer cell death** within 48 hr *in vitro* and *in vivo*
- **PK/PD modeling** is a useful tool to understand STAT3 degradation and efficacy relationships and also allows projection of STAT3 degradation profiles in human
- Kymera expect to submit **IND application** to evaluate **KT-333** in Ph I clinical trial in relapsed liquid and solid tumors this year

THANK YOU

KYMERA