4th Annual TPD Targeted Protein Degradation

KYMERA EST. 2016

Understanding PK/PD for Development of STAT3 Degraders in Oncology Indications

Chris De Savi, Ph.D. - VP, Head of Drug Discovery

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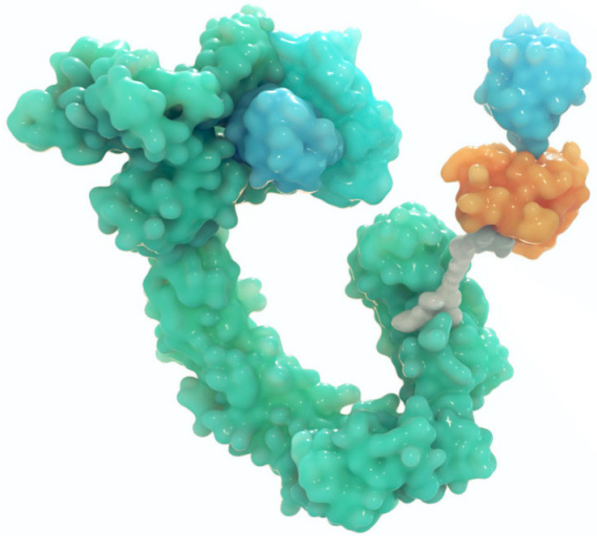
Outline

- Kymera – introduction and pipeline
- STAT3 – tumor intrinsic and tumor extrinsic function
- Characterization of STAT3 degrader KTX-201
- PK-PD/efficacy relationships in ALCL tumor intrinsic models
- Early activity in immuno-oncology tumor extrinsic models and PD
- Summary

Kymera: A Leading TPD Company

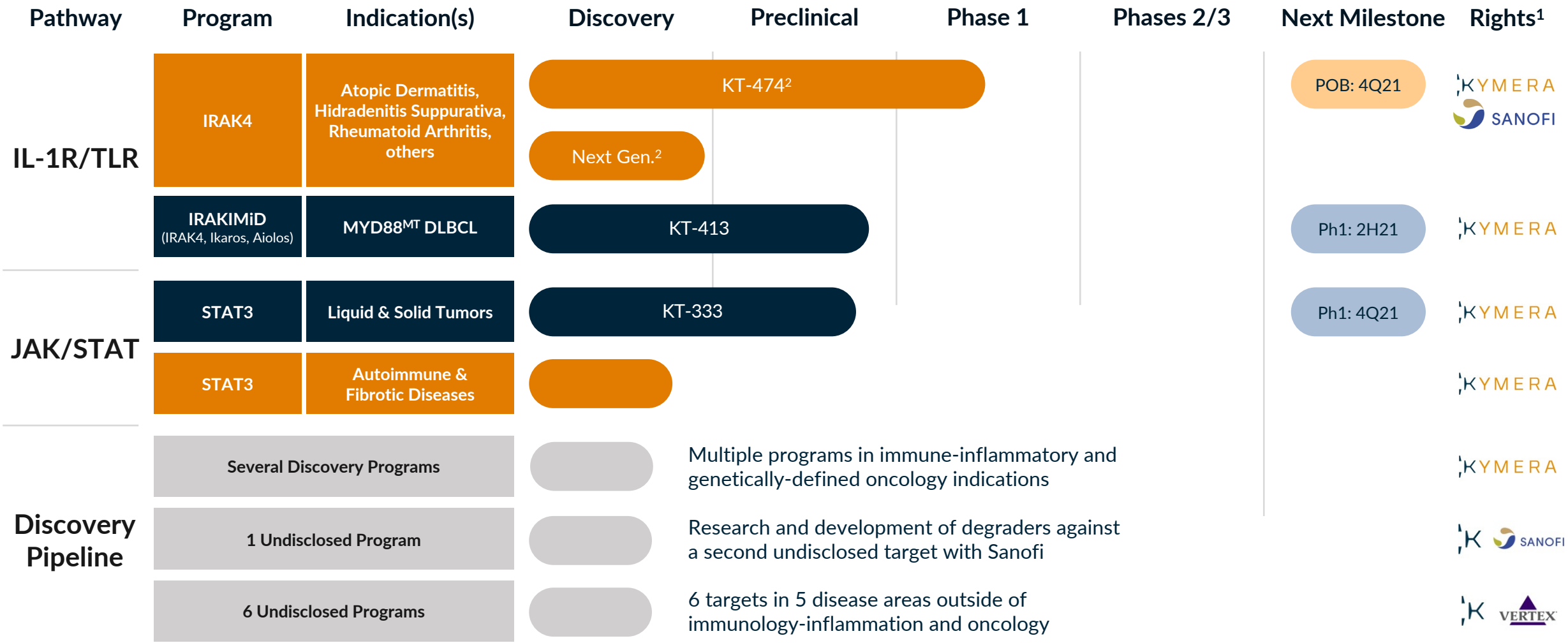
KYMERA



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.

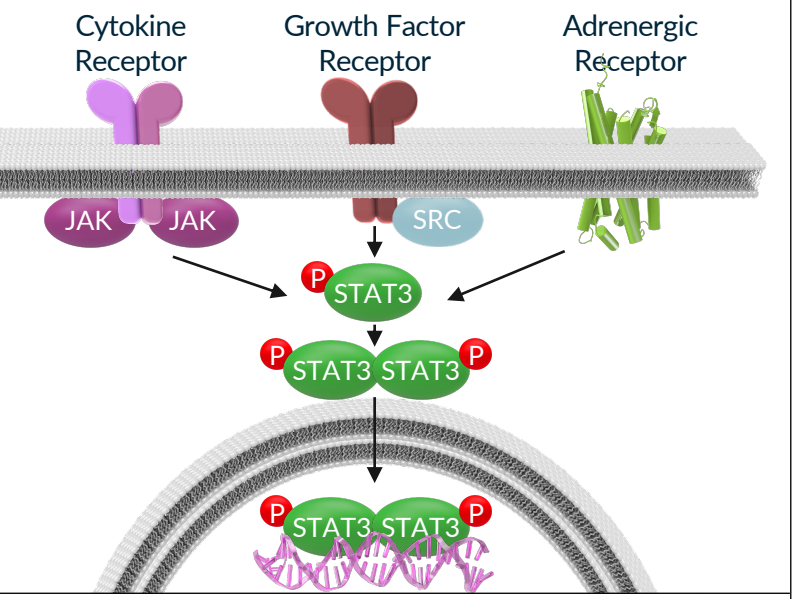
Kymera's Pipeline of Novel Protein Degraders



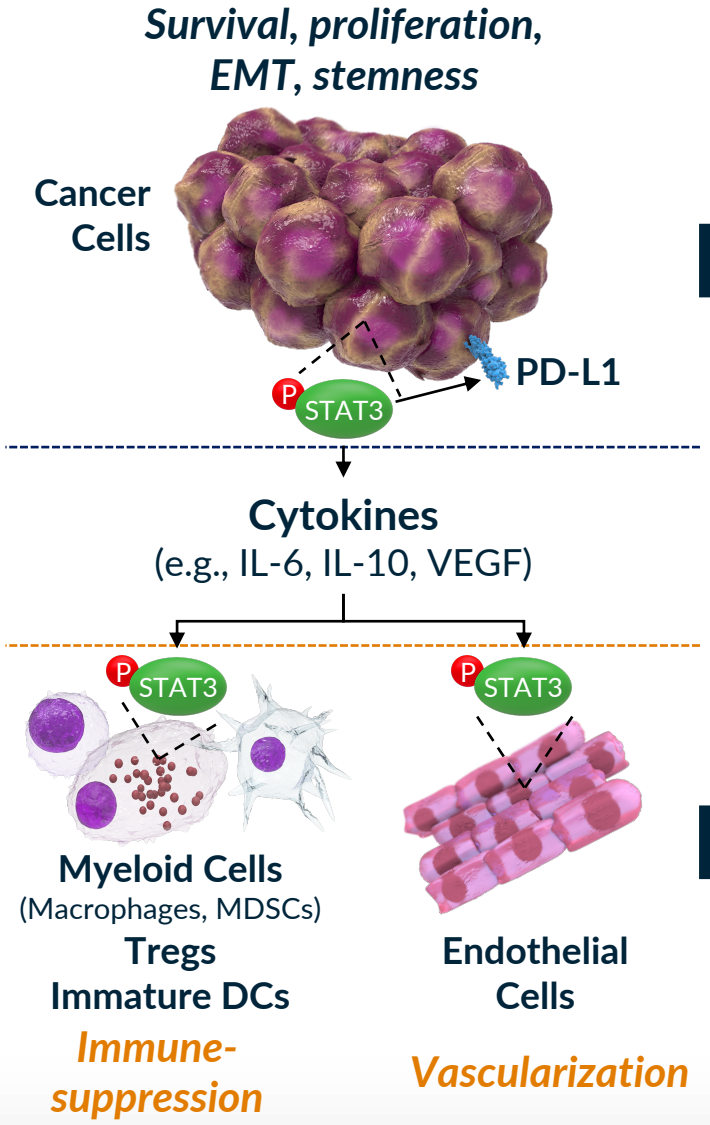
1. Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
2. Sanofi collaboration to develop IRAK4 degrader candidates, including KT-474 (SAR444656), outside of oncology and immuno-oncology fields.

Rationale for Targeting STAT3 in Oncology

STAT3 as a Target



- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology
- **Traditionally undruggable target**
- **First-in-class** opportunity to address STAT3 driven pathology across large and diverse indications



Tumor Cell Intrinsic

- STAT3 promotes gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells
- In PTCL, activated STAT3 (phospho-STAT3) is detected in many subtypes due to: STAT3 mutation (ALK-ALCL, T-LGLL, NKTCL, AITL, PTCL-NOS), upstream kinase activation (ALK+ALCL, ALK-ALCL), and elevated inflammatory mediators (CTCL)[1-6]

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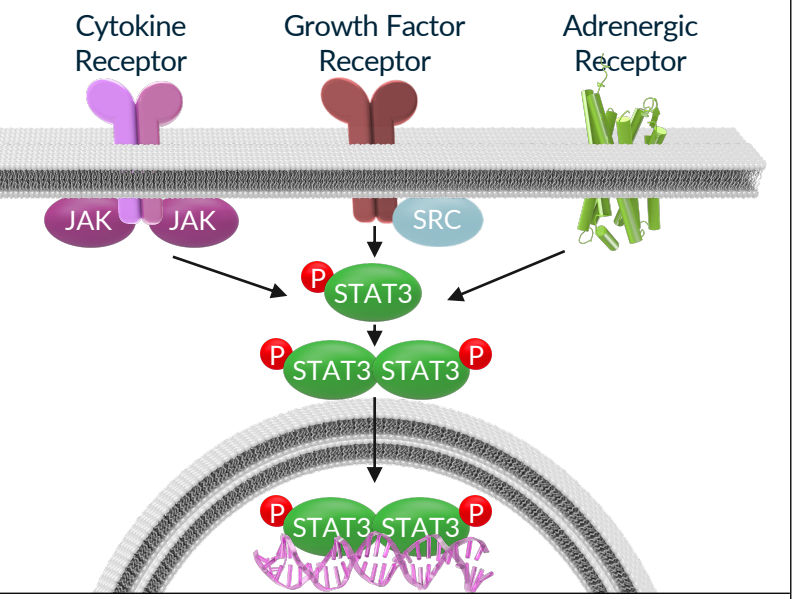

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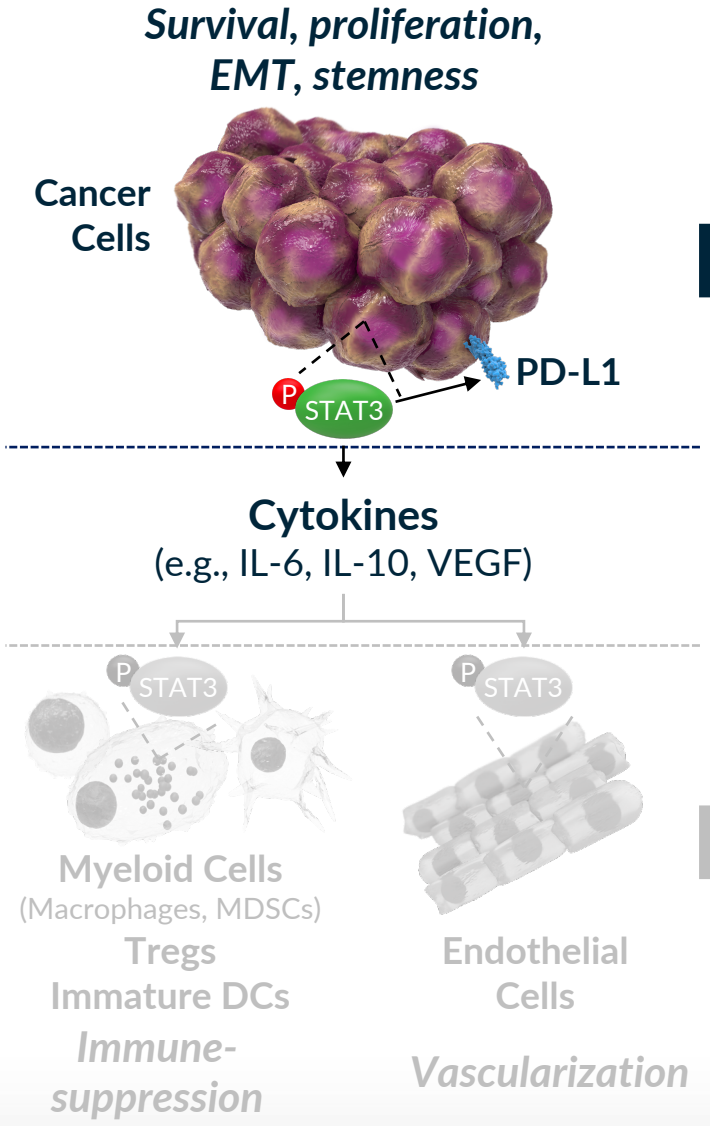

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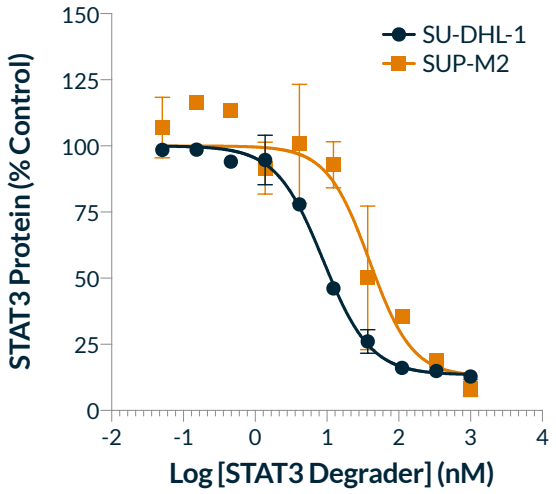
KTX-201 is a Highly Potent and Selective STAT3 degrader

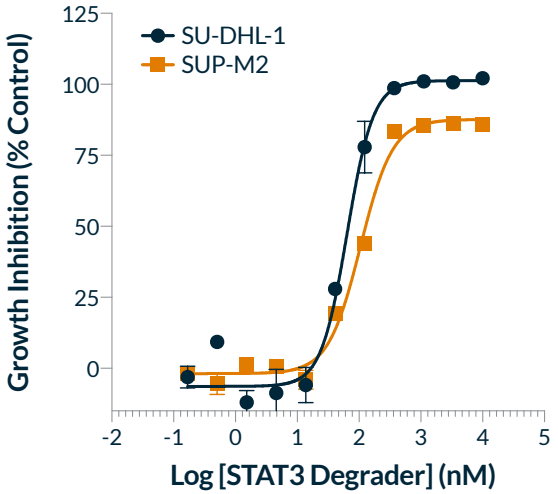
High Potency in SU-DHL-1 and SUP-M2 Cell Lines (ALK+ ALCL)

Degradation Potency



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

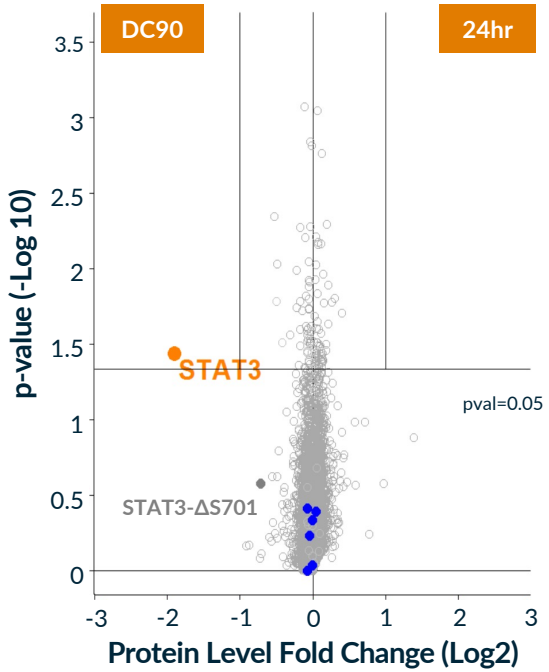
Growth Inhibition Potency



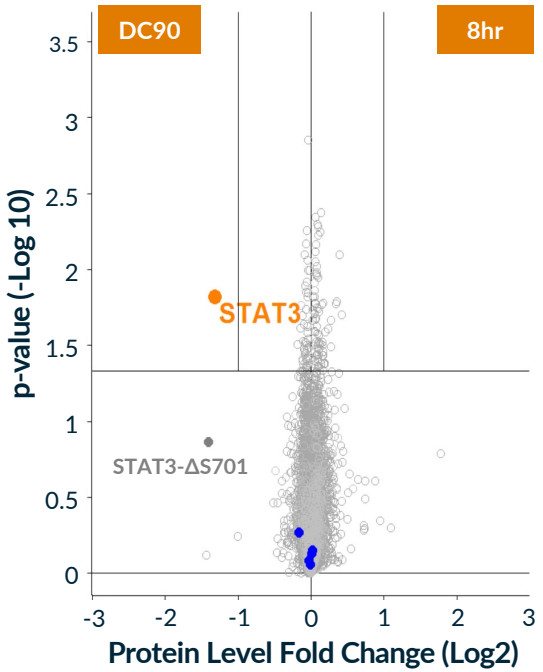
SU-DHL-1 IC_{50} 64 nM
SUP-M2 IC_{50} 105 nM

High Selectivity in huPBMCs and SUDHL-1 (ALK+ ALCL)

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

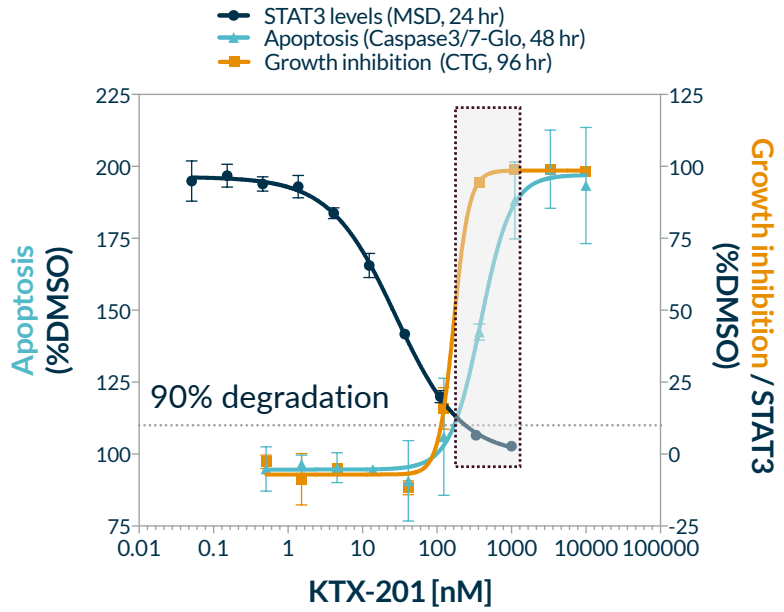
KTX-201 is Highly Soluble and Has Low Clearance *in vivo*

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**

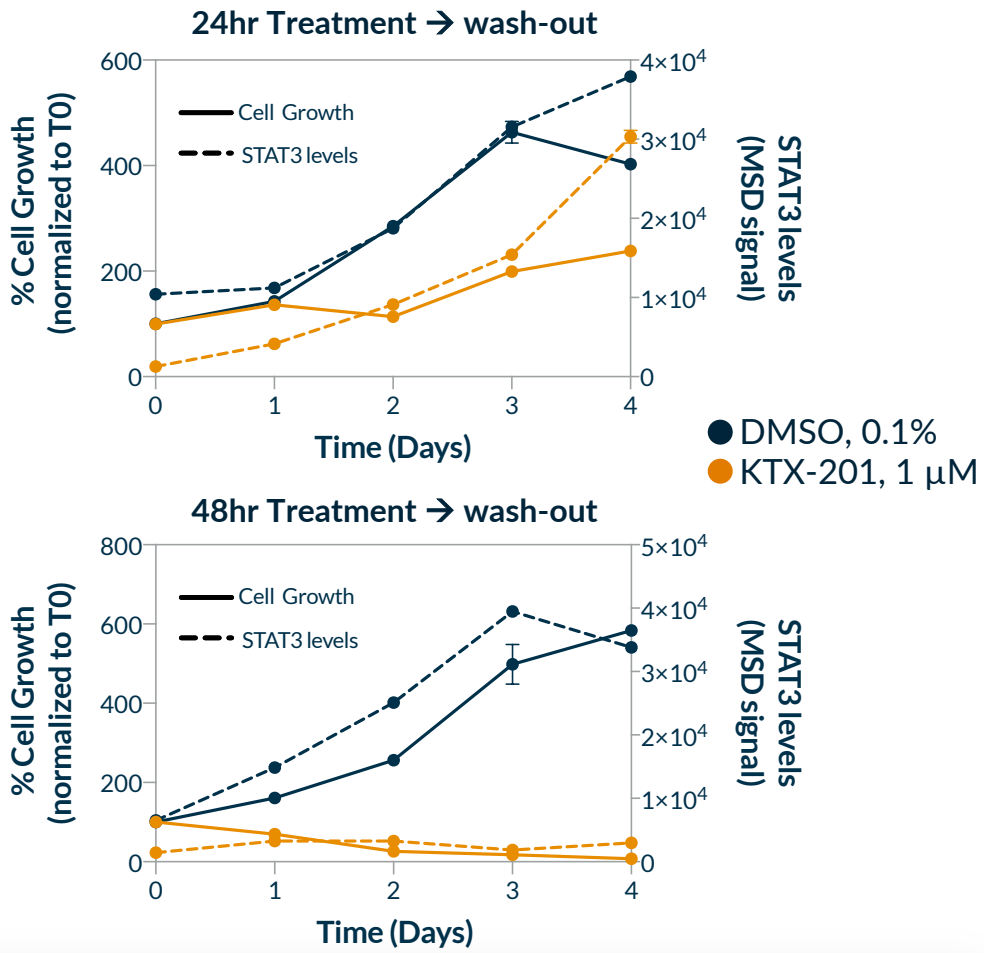
1. KTX-201 is a potent and selective STAT3 degrader tool molecule

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**

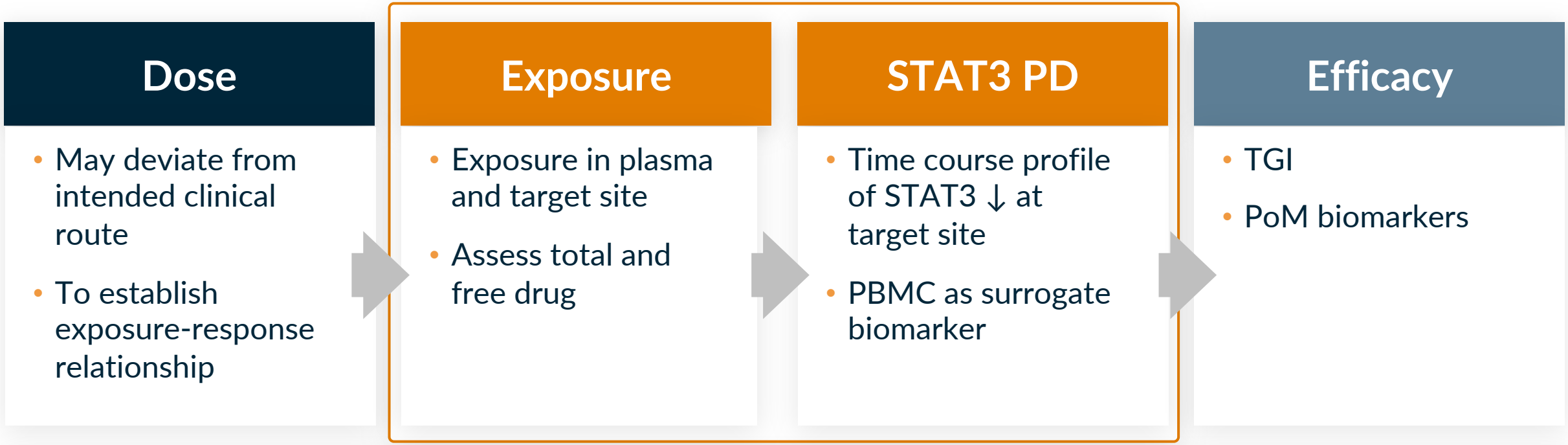
- A decrease of STAT3 by 90% is necessary to induce SU-DHL-1 apoptosis and inhibit cell growth



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

Understanding PK/PD Relationship in ALK+ ALCL Xenograft Model to Enable Human Translation

PK/PD Relationship in vivo

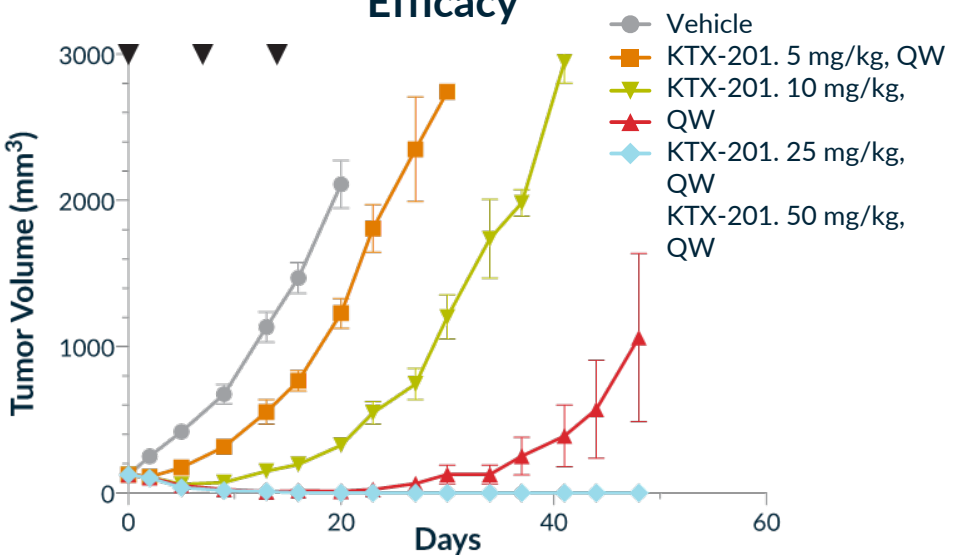


Account for species difference in translation

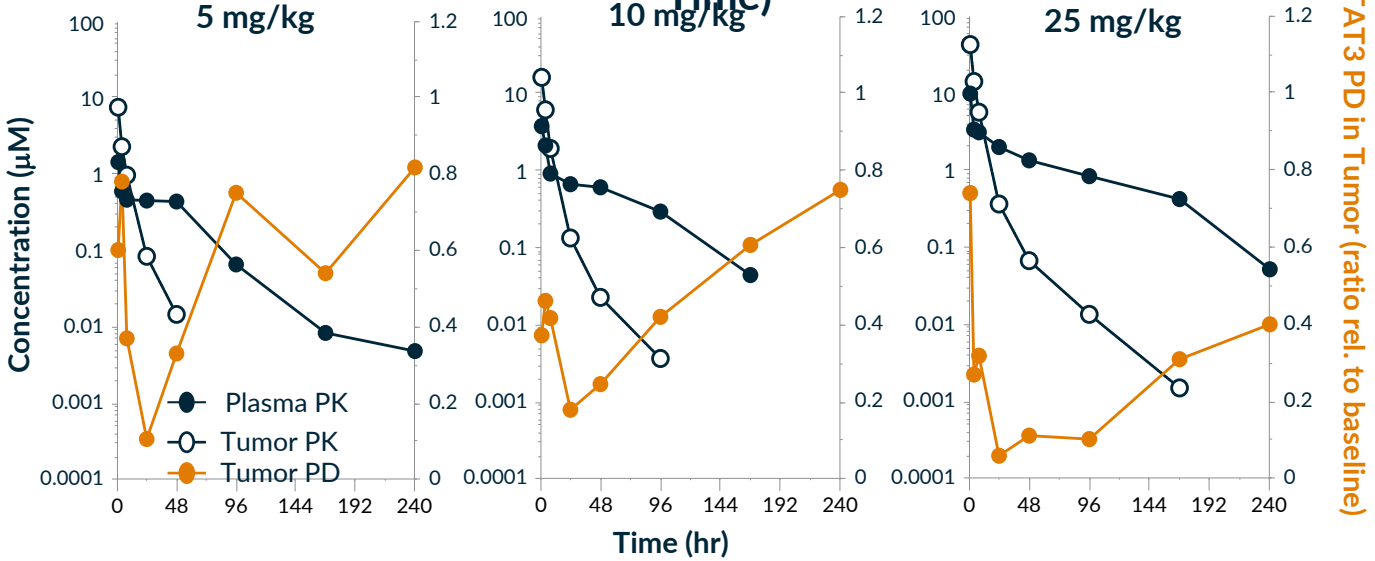
- Pharmacokinetics: drug metabolism and disposition
- Drug distribution in tissues and its kinetics
- Target protein properties:
  - Turnover rate (synthesis and degradation)
  - Disease status

Intermittent QW Dosing is Sufficient to Drive Efficacy in STAT3-Dependent ALK+ ALCL Models

SU-DHL-1 Mouse Xenograft Tumor Efficacy



PK-PD Relationship (KTX-201 Concentration vs Time)



- KTX-201 in SUDHL-1 XG mouse
  - IV bolus at 5 to 50 mg/kg
  - Weekly dosing
  - Treatment on D1, D8, D15
- The treatments were well tolerated, with no significant body weight loss

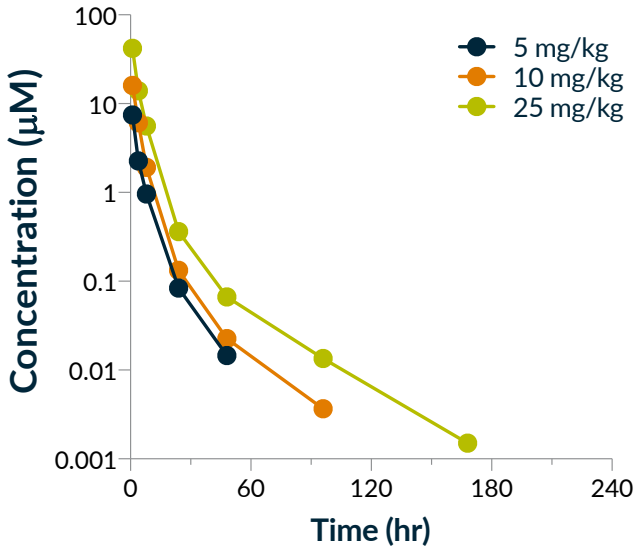
- Maximal STAT3 degradation occurred at 24 hr post dose for all doses
- Maximal degradation is >90% at 25 mg/kg
- Prolonged degradation in tumor is partially due to longer drug $t_{1/2}$ in tumor
- $T_{½}$ of STAT3 return to baseline is dose-dependent → higher dose/higher exposure/prolonged degradation

KTX-201 Exhibited Prolonged Half-life in Tumor

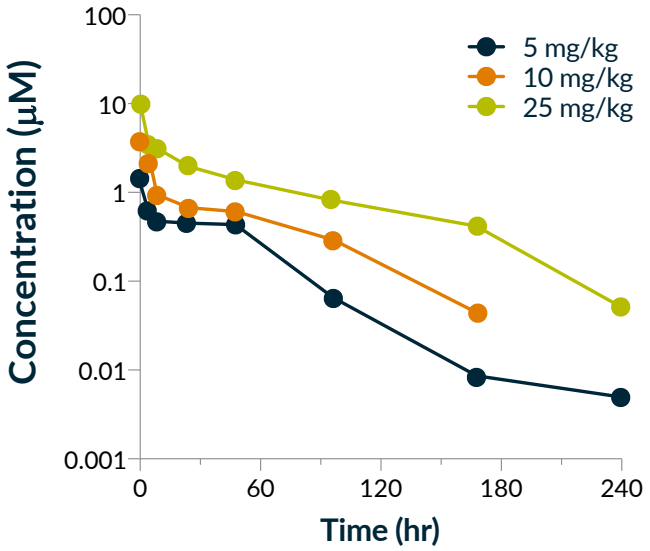
PK in Plasma and Tumor

- Plasma and tumor exposure increase as increase of dose
- T½ 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



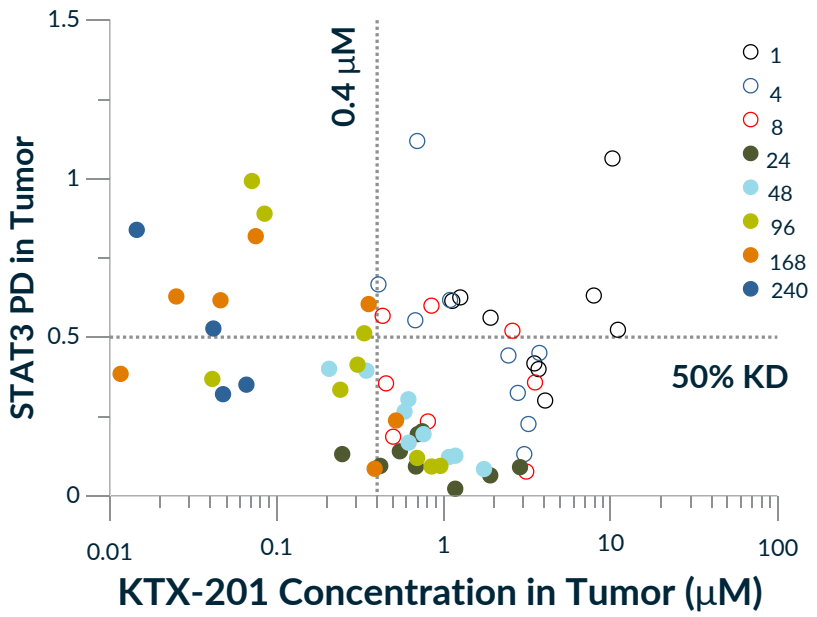
KTX-201 Tumor PK Profiles

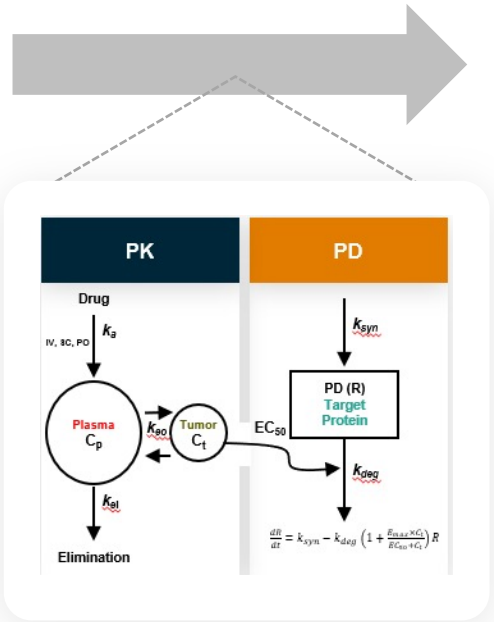


KTX-201		5 mg/kg		10 mg/kg		25 mg/kg	
PK Parameters	Unit	Plasma	**Tumor**	Plasma	**Tumor**	Plasma	Tumor
$T_{½}$	hr	6.8	**24**	16	**31**	16	**36**
AUC_{last}	µM*h	40	**36**	87	**78**	229	**231**

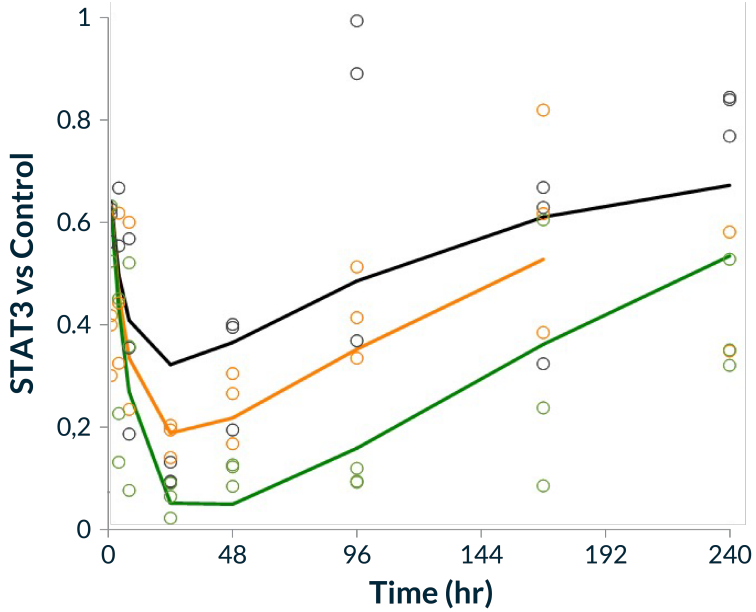
Important *in vivo* Parameters Can be Derived from PK/PD Modelling to Enable Human Dose Projections

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)

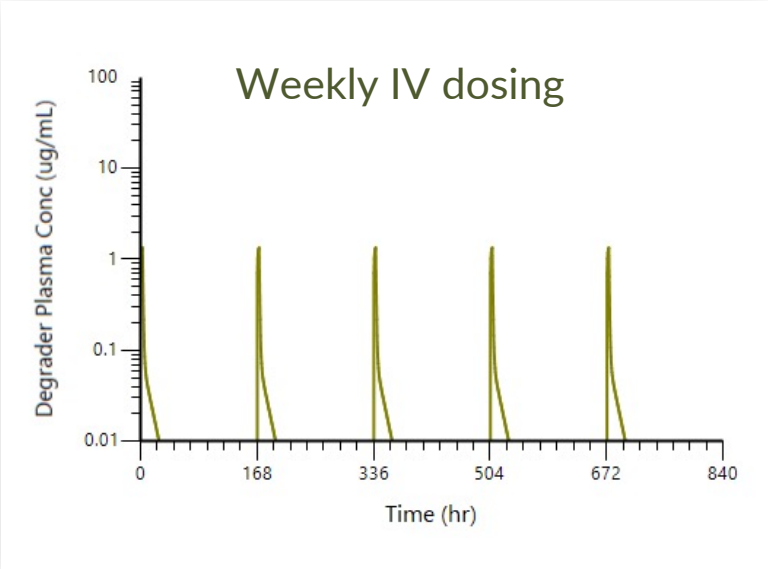
*10% FBS fu = 0.15; SUDHL-1 fu,t = 0.0049

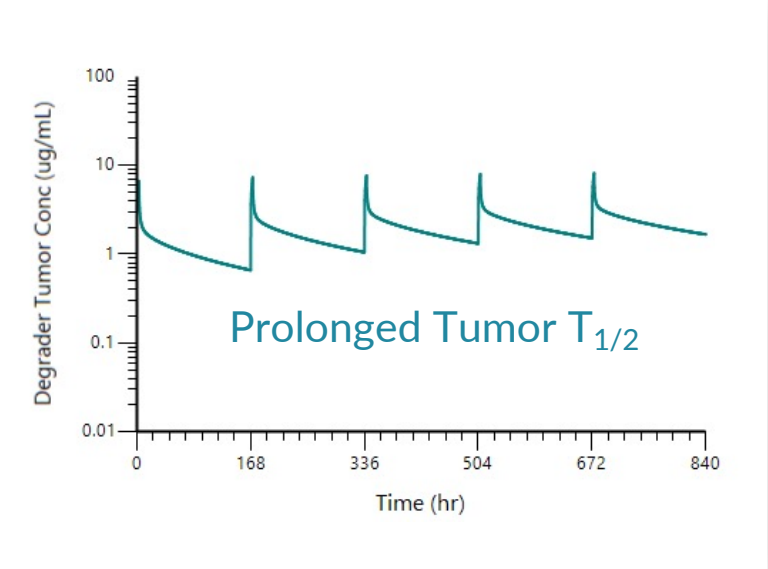
PK/PD Parameters	Description	Estimate	CV
k_{deg}	Degradation Rate	0.0356 hr^{-1} ($t_{½}$ 19 hr)	17%
E_{max}	*In vivo* max. effect	14	16%
EC_{50}	*In vivo* potency	2.5 µM	16%

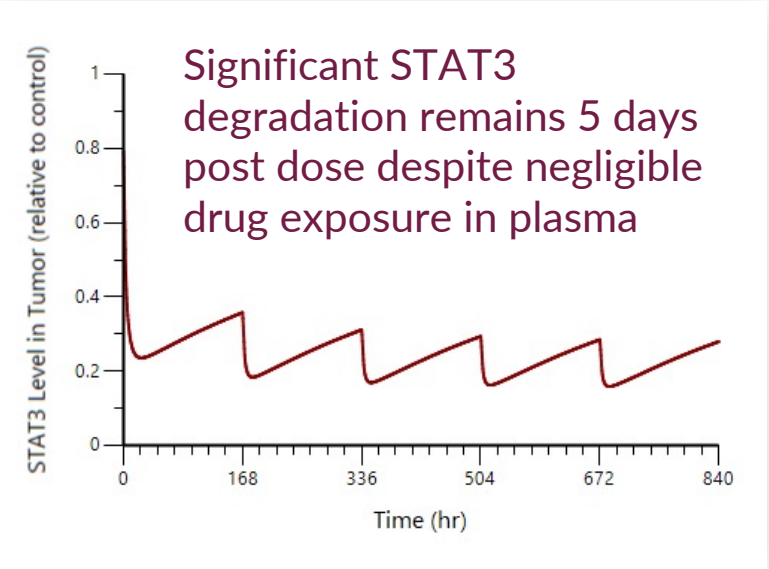
These PK/PD parameters are used to project human degradation profiles

Mechanistic Modeling to Project Tumor STAT3 Degradation in Human

Simulated Plasma PK Profile in Human → **Simulated Tumor PK Profile in Human** → **Simulated Tumor PD Profile in Human**



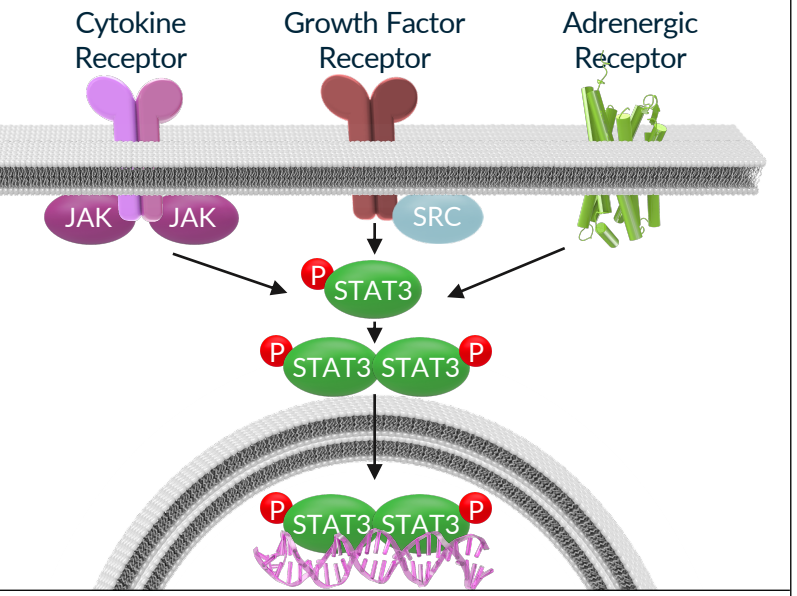




Integration of human PK, tissue distribution, and *in vivo* degradation potency (EC_{50}) and efficacy (E_{max}) enables projection of target protein degradation in human for dose optimization in clinic.

Rationale for Targeting STAT3 in Oncology

STAT3 as a Target



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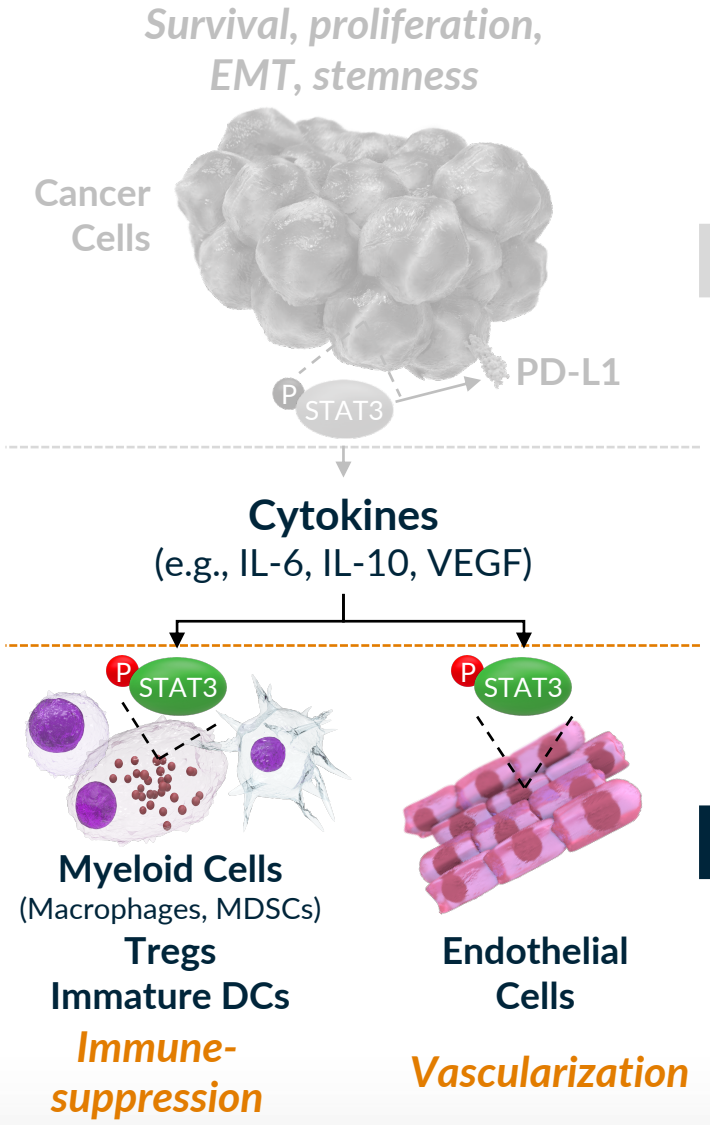

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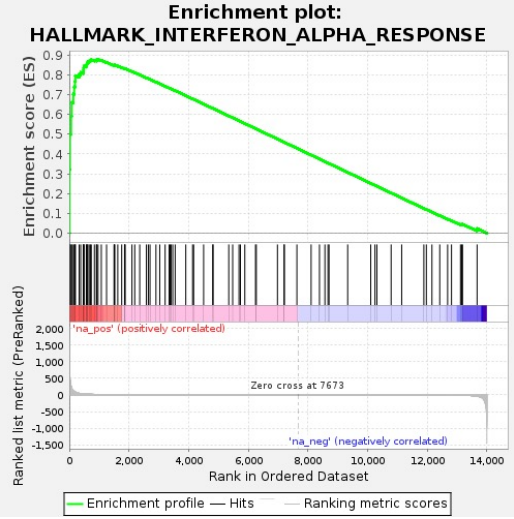
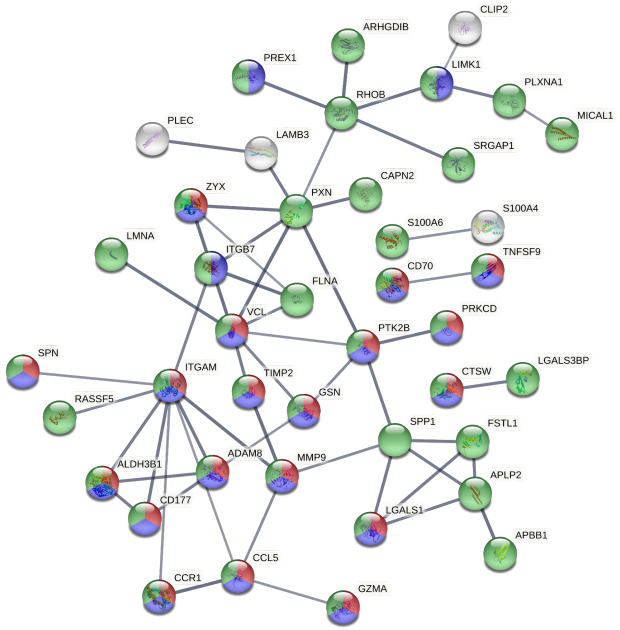
STAT3 Degradation Modulates Proteins Involved with Immune Suppression in Both Immune and Tumor Cells

STAT3 Degradation Upregulates Interferon Response and Immune Pathways in SUDHL-1 Cells

RNAseq



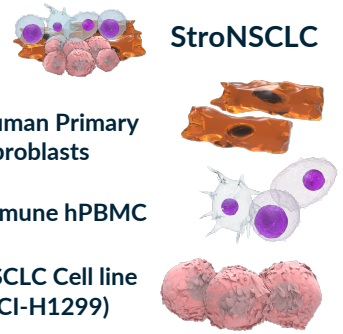
Proteomics

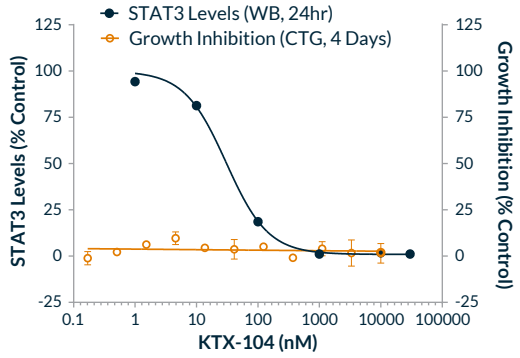


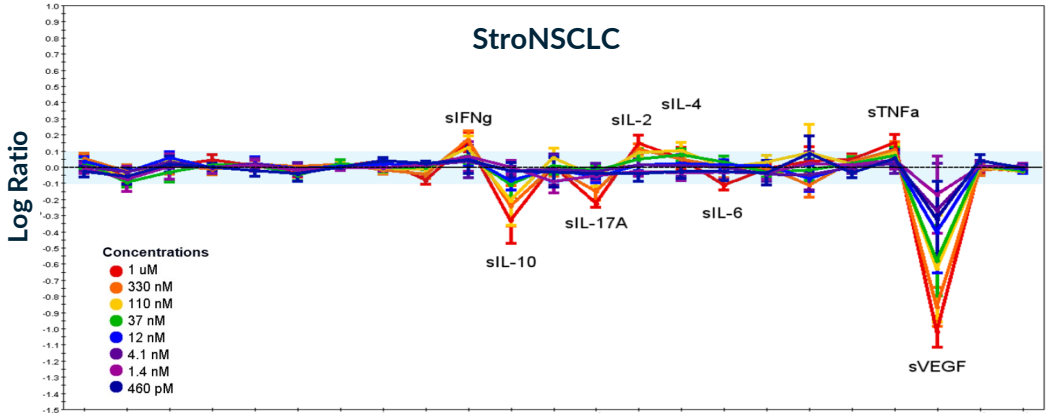
Biological Process (Gene Ontology)				
GO-term	description	count in network	strength	false discovery rate
GO:0006955	immune response	32 of 1560	0.56	2.23e-07
GO:0002376	immune system process	40 of 2370	0.47	2.23e-07
GO:0050896	response to stimulus	77 of 7824	0.24	3.50e-07

STAT3 Degradation Reverses Immune Suppression in the Biomap Co-culture Model of the TME

BioMAP NSCLC Panel





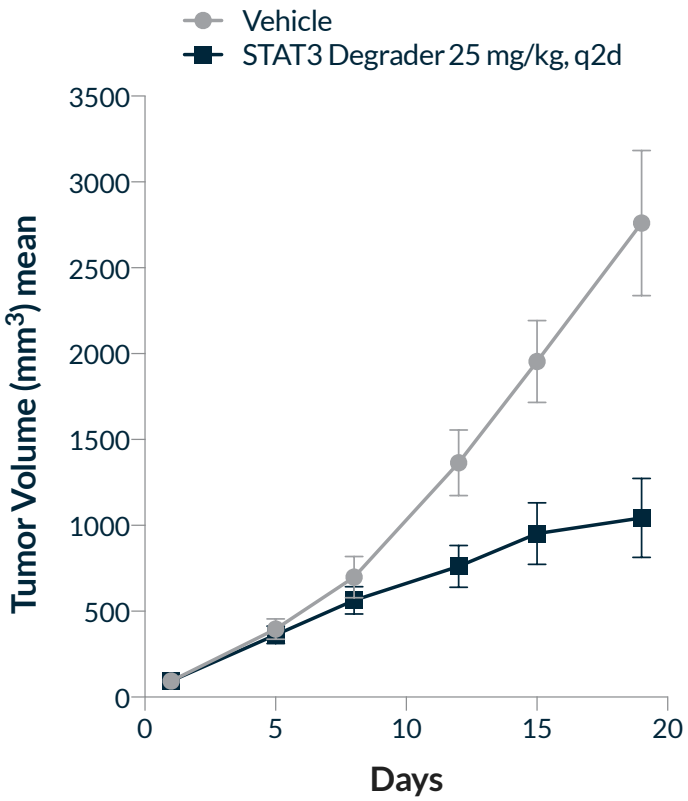


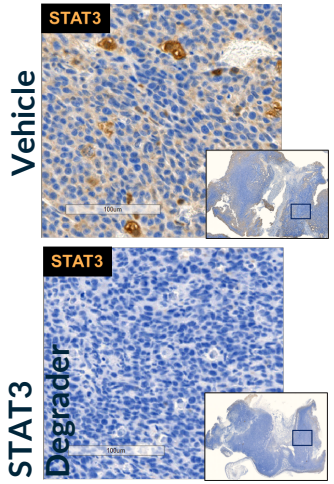
- KTX-104 induces anti-tumorigenic factor including IL-2, TNFa and IFNg while reducing immune suppressive and pro-tumorigenic factors IL-10, IL-6 and VEGF

KTX-201 is Active in PD-1/L-1 Refractory Solid Tumor Model

- KTX-201 assessed in solid tumor models (CT-26) known to be refractory to approved immunotherapies
- KTX-201 significantly reduced tumor growth
- STAT3 was degraded in tumor cells and TME
- STAT3 degradation in vitro did not impact CT-26 viability highlighting the TME's role in the anti-tumor response
- Analysis of tumors showed modulation of immune cells (M2/M1 and T cells) within TME to favor an anti-tumor response

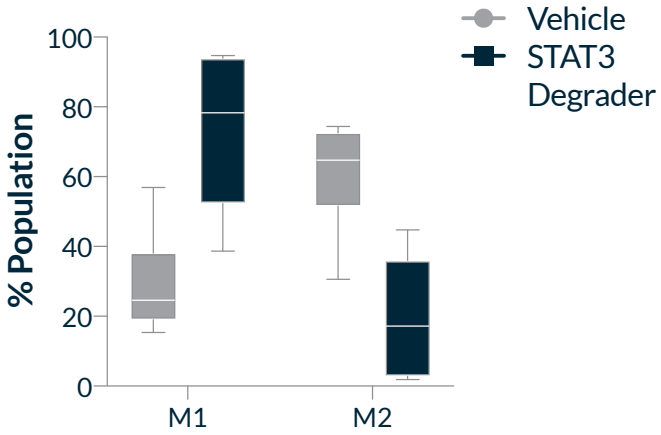
CT-26 Syngeneic Model



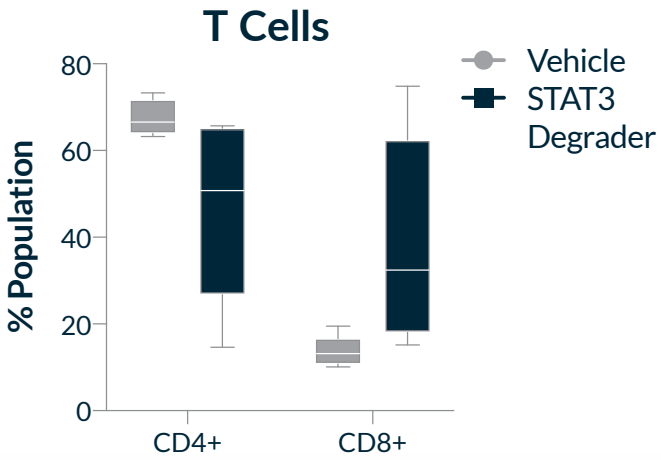


Combination data with anti-PD1 to be presented at Society for Immunotherapy of Cancer (SITC), November 10-14, 2021, Washington, D.C.

Macrophages (M1/M2)



T Cells

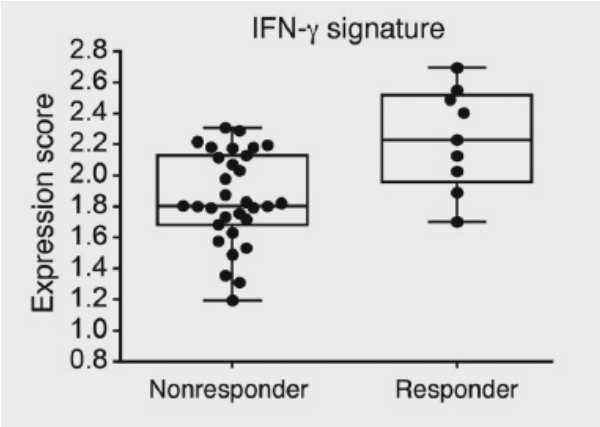


STAT3 Degradation Remodels TME to Sensitize to PD-1 Inhibition

IFNγ Related Signature Predicts Clinical Response to PD-1 Blockade[1]

IFNγ Gene Signatures

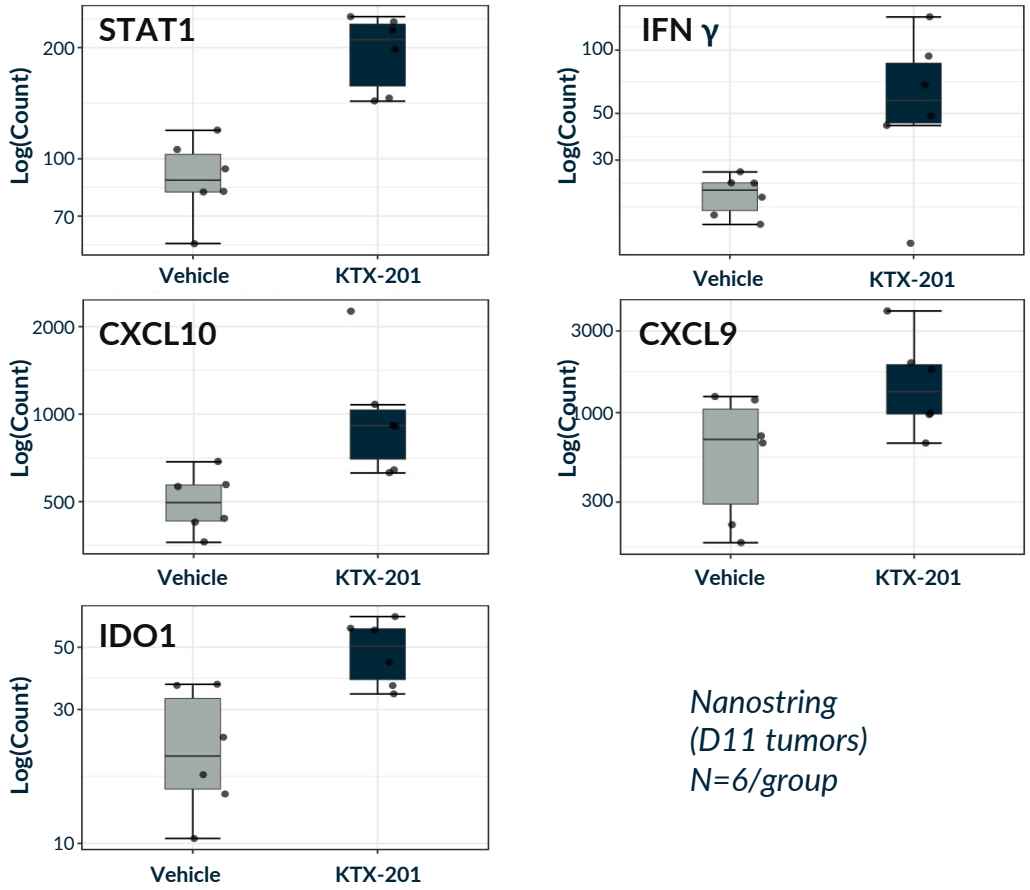
IFNγ
IDO1
CXCL10
CXCL9
HLA-DRA
STAT1
IFNG



220 patients, 9 cancer types from clinical studies of pembrolizumab

STAT3 ASO treatment leads to upregulation of IFNγ signature in DLBCL patients[2]
(IFNγ, STAT1, CXCL10, CXCL9, IDO1)

STAT3 Degrader-treated CT-26 Tumors Also Show Increased Expression of IFNγ Signature Genes



Nanostring
(D11 tumors)
N=6/group

Ongoing work underway to elucidate PK/PD/efficacy relationships in TME

1. Ayers et. Al. JCI 2017
2. Proai et. Al. Clin Can Res 2020

Summary

- STAT3 is a transcription factor member of the STAT family and possesses both **tumor intrinsic** and **extrinsic** functions
- STAT3 promotes gene expression programs involved with **survival, proliferation, stemness and metastasis** of **tumor** cells and differentiation and **activity of immunosuppressive** and endothelial cells, resulting in pro-tumorigenic environment
- 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* in ALK+ ALCL models
- **PK/PD modeling** is a useful tool to understand STAT3 degradation and efficacy relationships and also allows projection of STAT3 degradation profiles in human
- STAT3 degradation **remodels TME** to sensitize to PD-1 inhibition and ongoing work is underway to understand **PK/PD/efficacy** relationships
- We expect to submit an **IND application** to evaluate **KT-333** in Ph I clinical trial in relapsed liquid and solid tumors this year

KYMERA

THANK YOU