INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

September 2022

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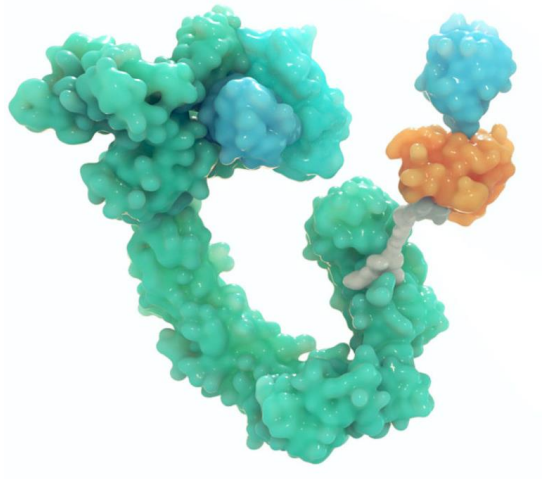
Introduction to Kymera

KYMERA

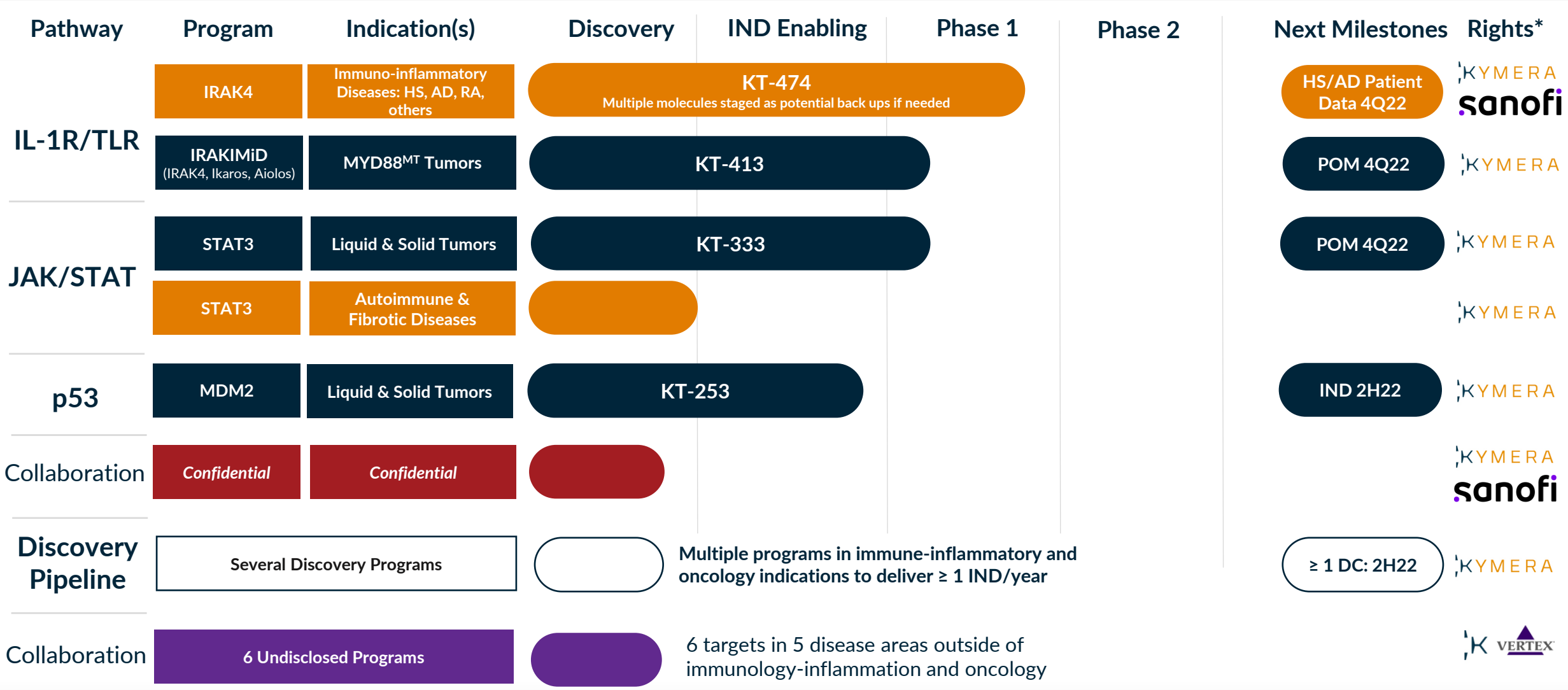


OUR VISION

To be a disease- and technology-agnostic, fully integrated global biopharmaceutical company, using targeted protein degradation to deliver medicines that will transform patients' lives

- **Leader** in Targeted Protein Degradation (TPD)
- Building a **fully-integrated**, global biotech company
- Initial focus in **Immunology/Inflammation and Oncology**, but already a **disease-agnostic platform**
- Accelerating forward integration through **key strategic partnerships**
- Executed **many "firsts"** for TPD with initial clinical programs
- Three clinical stage programs and **a deep pipeline positioned to deliver ≥1 IND/year**
- Focused on **continued innovation** in platform and discovery
- Well capitalized with over **$600 million of cash** as of 8/31/22

Kymera's Pipeline of Novel Protein Degraders



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

Near-Term Milestones Provide Significant Opportunity

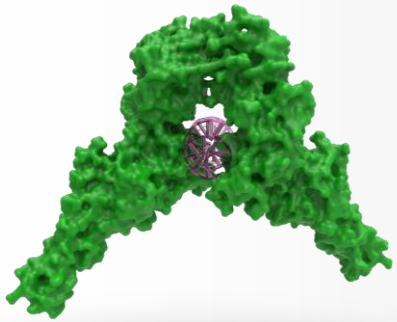
Program	Compound	Indications	Expected Upcoming Milestones
IRAK4	KT-474	AD, HS, RA, others	✓ Establish Phase 1-HS/AD patient cohort dose (2Q22) ✓ Initiate HS/AD patient Part C study (2Q22) • Present Ph1 HS/AD patient cohort data (4Q22) • Provide data package to Sanofi for advancement into Phase 2 (4Q22)
IRAKIMiD (IRAK4, Ikaros, Aiolos)	KT-413	MYD88^{MT} DLBCL	✓ Dose first patient in Phase 1 trial (2Q22) • Present initial Phase 1 safety and proof-of-mechanism data in patients (4Q22) • Present initial Phase 1 anti-tumor proof-of-concept data in patients (2023)
STAT3	KT-333	Liquid & Solid Tumors	✓ Dose first patient in Phase 1 trial (2Q22) • Present initial Phase 1 safety and proof-of-mechanism data in patients (4Q22) • Present initial Phase 1 anti-tumor proof-of-concept data in patients (2023)
MDM2	KT-253	P53wt Liquid & Solid Tumors	• File IND for KT-253 (2H22) • Present new preclinical data elucidating indication expansion opportunities (2H22)
Discovery Programs & Platform			• Continue pipeline expansion by advancing discovery stage programs toward IND-enabling studies • Further expand Pegasus platform to generate novel degrader product candidates for undruggable and inadequately drugged targets • Leverage Whole-Body Atlas to unlock new opportunities across broad therapeutic applications using tissue-sparing, tissue-restricted E3 ligases as well as novel molecular glue mechanisms

● = Oncology ● = Immunology-Inflammation

Kymera's Differentiated Approach to TPD

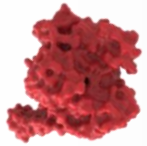
TARGET SELECTION

Unique approach focused on undrugged or not fully drugged targets with broad indication potentials



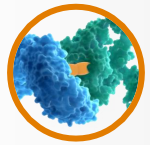
PLATFORM

Significantly differentiated investments



Tissue-selective E3 Ligases

Enabling a whole new generation of clinical programs

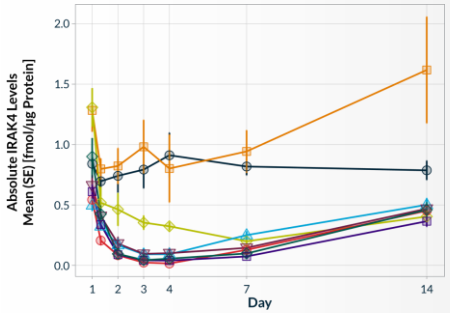


New Molecular Glue Approach

Novel strategy to address undrugged/ un-ligandable targets

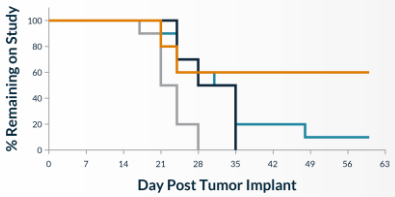
CLINICAL

Innovative clinical trial designs for degrader development



TPD "FIRSTS"

Kymera has accomplished several "firsts" in TPD



KT-474/ IRAK4

FIRST randomized, placebo-controlled trial in healthy volunteers

KT-333/ STAT3

FIRST Hetero-bifunctional degrader against an undrugged transcription factor in clinic

INNOVATION

Serious commitment to constant evolution of our science

How We Select Our Targets

Drug Development Philosophy

Unmet Medical Need

Validated Biology

Undrugged Node

Precision Medicine Approach

Target Types

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

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

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

Therapeutic Profile

Oncology:
- Clear patient stratification
- Clear single agent activity with potential for expansion with combos
- Multiple addressable unmet needs

Immunology:
- Address key unmet needs providing game changing oral therapies
- Key validated signaling pathways with clear degrader advantage

Other Disease Areas:
- Enabled by E3 ligase differential expression
- Key insights from biology and technology expansion
- Some areas enabled by collaborations

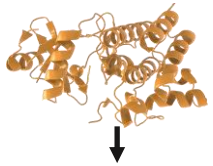
We Want to Drug All Target Classes

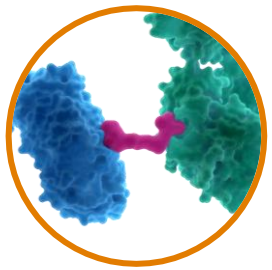
Expanding the Druggable Proteome with TPD

ID Inadequately Drugged Targets with Clear Degrader Advantage

Small molecule binders exist but unable to drug target fully

e.g. IRAK4, MDM2...



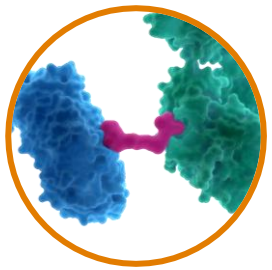


Heterobifunctional Degraders

UD Undrugged Targets

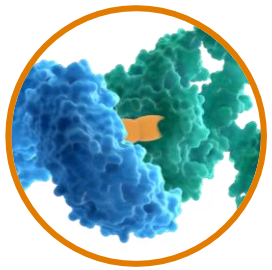
No other technology can drug

Ligandable Proteins
e.g. STAT3...



Heterobifunctional Degraders

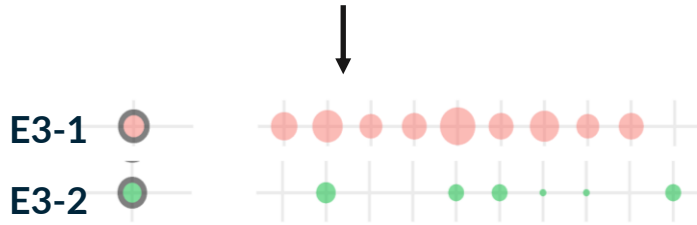
Un-ligandable Proteins
e.g. other transcription factors



Molecular Glues

TR Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression

On target unwanted pharmacology limits clinical application



Tissue sparing or selective E3 ligases eliminate unwanted toxicity and allow full clinical potential

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

LEUKEMIA & LYMPHOMA SOCIETY®

- Blood-based cancers
- Leveraging patient network and access

A-ALPHA BIO

- Established October 2021; upfront, research payments, and downstream milestones
- Leverages AlphaSeq platform to discover novel interactions between E3 ligases and undrugged targets for **molecular glue discovery**

Academic Collaborators

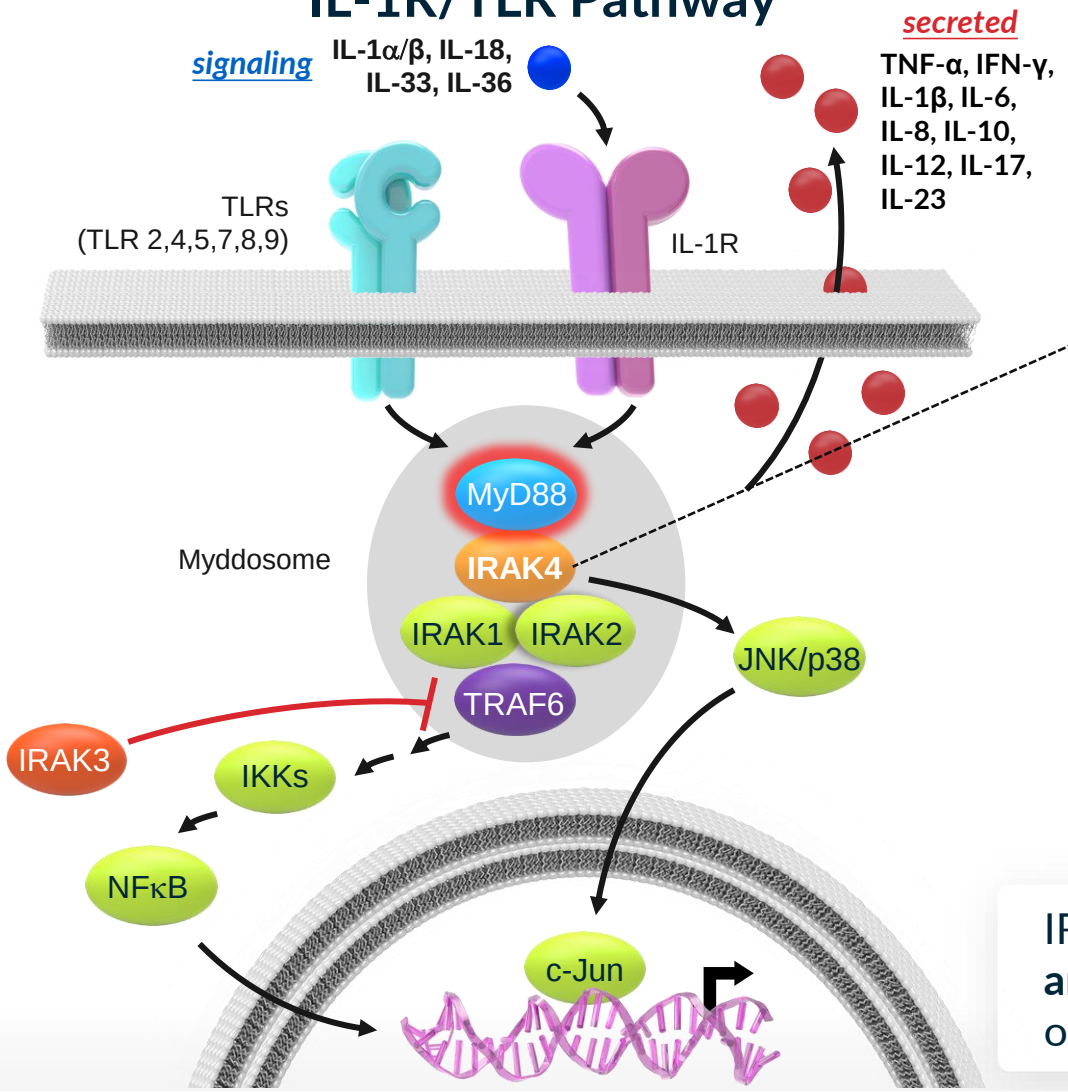
COLUMBIA UNIVERSITY · The Rockefeller University · UCSF · UNIVERSITY OF CALIFORNIA BERKELEY · MAX-PLANCK-GESELLSCHAFT · Yale · UNIVERSITY OF CAMBRIDGE · UNIVERSITY of WASHINGTON · NYU · NATIONAL INSTITUTES OF HEALTH · MAYO CLINIC

IRAK4

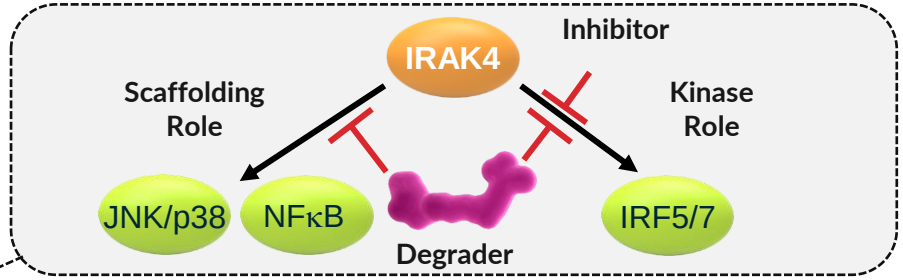
KYMERA

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

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa
IL-1α: Atopic Dermatitis
IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis
IRAK4 SMI: Rheumatoid Arthritis

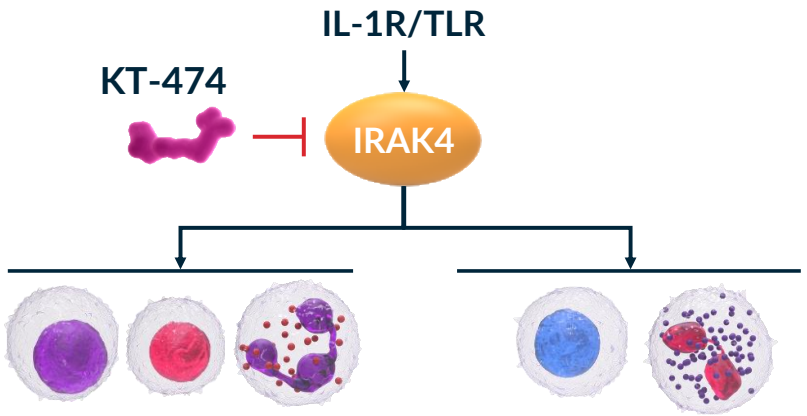
Human Genetics

Adult humans with **IRAK4 Null Mutation are healthy**

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

Potential Best-in-class Oral Small Molecule Mechanism in I/I

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Lupus
- IBD
- Gout
- Psoriasis

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

$ 150B Combined global drug sales

Indication	2021 Prevalence US/EU5/JP	2021 Global Sales
AD	~82.5 M	$5,760 M
HS	~785 K	$1,106 M
RA	~4.6 M	$27,634 M
SLE	~580 K	$1,333 M
IBD	~3.2 M	$21,710 M
Gout	~18.2 M	$1,319 M
Psoriasis	~15.8 M	$23,268 M
Asthma	~87.3 M	$15,664 M
COPD	~61.7 M	$9,960 M
CRSwNP	~20.4 M	$2,622 M

Limitations of Current Therapies

- **Anti-Cytokine/Cytokine Receptor Antibodies**
  - Target only 1-2 cytokines
  - Require injection
- **Small Molecule Inhibitors**
  - Limited pathway blockade (IRAK4 SMI)
  - Safety issues (JAK family)

Source: EvaluatePharma; GlobalData; Dash. Allied Market Research. 2021; Koto. Modern Rheumatology. 2021; Ahn. JAMA Otolaryngol Head Neck Surg. 2016; UC: Ulcerative Colitis; CD: Crohn's Disease.

KT-474 Updated Phase 1 Includes a 28 Day Patient Study

Double-blind, Placebo-controlled SAD and MAD in HV; Open Label Patient Cohort in HS & AD Patients

Parts A & B

Healthy Volunteers SAD and MAD

7 SAD cohorts
- 8 subjects per cohort (6:2 randomization)
- 57 adult healthy subjects dosed

Single dose (25-1600 mg)

4 MAD cohorts
- 12 subjects per cohort (9:3 randomization)
- 48 adult healthy subjects dosed

14x daily doses (25-200 mg)

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin (MAD only)
- *Ex vivo* response of whole blood to TLR agonists (SAD & MAD)

Part C

HS and AD Patients

1 cohort
Up to 20 HS and AD patients

75 mg (fed state)
(~equivalent exposure to 100mg fasted MAD cohort dose level)

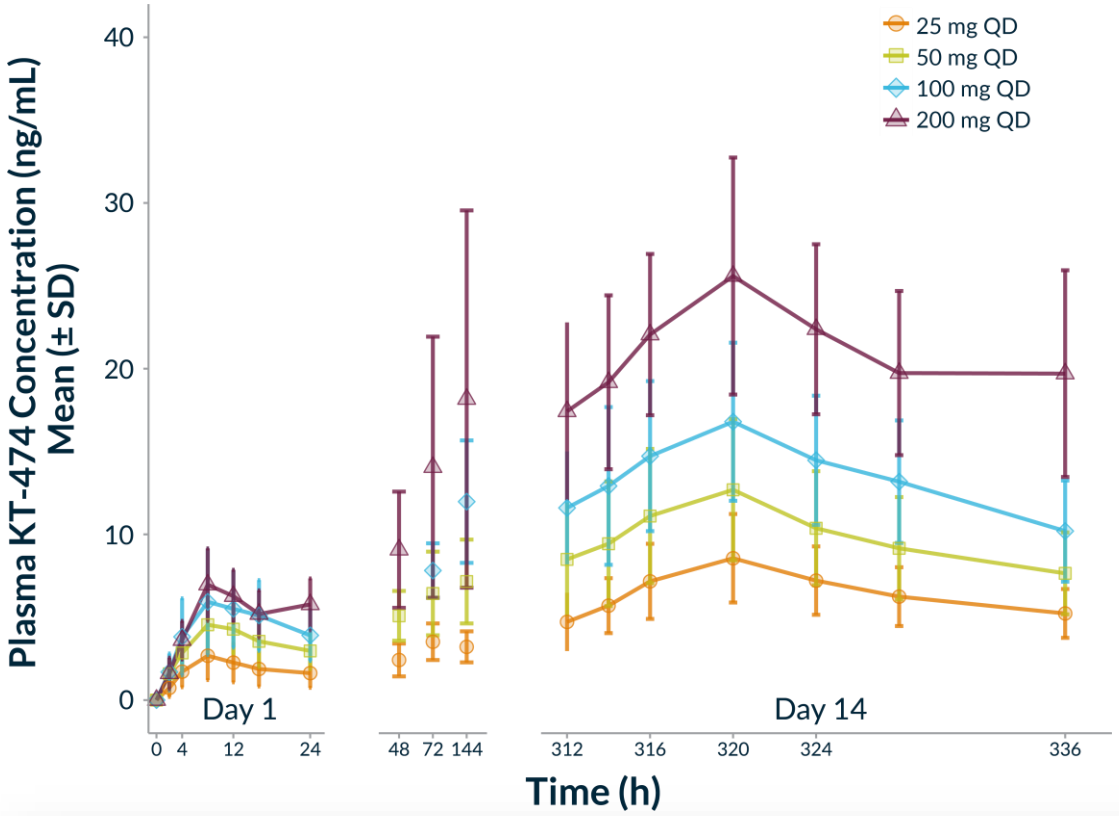
Open-label

28x daily doses

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin
- Change in systemic inflammatory biomarkers and proinflammatory gene transcripts in skin
- *Ex vivo* response of whole blood to TLR agonists
- Clinical endpoints: EASI (AD), Total AN Count (HS), symptom scores and global assessments

MAD Study: Once Daily Dosing Resulted in High Steady-State Exposures



Steady-State (Day 14) PK Parameters

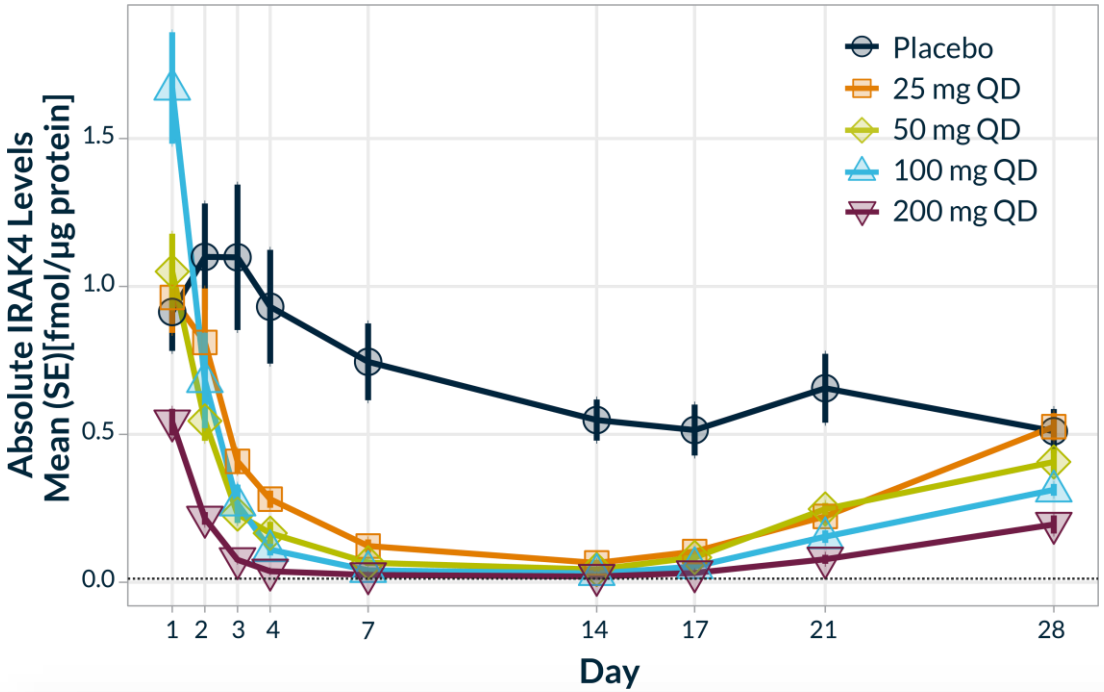
PK Parameter	25 mg QD (n = 9)	50 mg QD (n = 9)	100 mg QD (n = 9)	200 mg QD (n = 9)
C_{max} (ng/mL)	8.20 (34.5)	12.0 (39.1)	16.1 (32.0)	25.2 (26.7)
t_{max} (h)[a]	8.00 (4.0 – 8.0)	8.00 (8.0 – 8.0)	8.00 (8.0 – 12)	8.00 (8.0 – 12)
AUC_{24} (ng*h/mL)	153 (30.8)	224 (39.4)	314 (29.9)	498 (24.0)
C_{trough} (ng/mL)	5.03 (30.3)	7.28 (35.1)	9.81 (30.1)	18.8 (32.6)
Day 14/1 $Ratio_{Cmax}$	3.73 (47.1)	2.64 (26.3)	2.92 (37.7)	3.51 (34.7)
Day 14/1 $Ratio_{AUC}$	4.01 (41.2)	2.97 (23.2)	3.29 (38.9)	4.22 (28.8)

Geometric Mean (%CV) reported for all parameters, except t_{max} where median(range) are presented
Accumulation Ratio represents fold change in exposure from Day 1 to Day 14

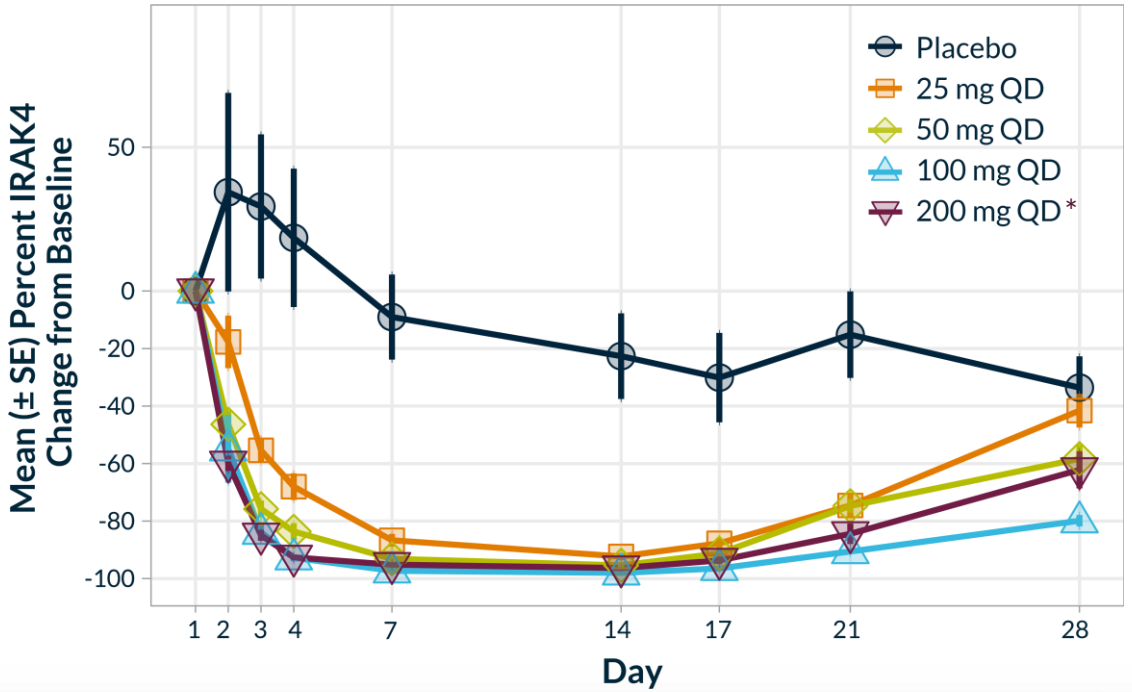
- High steady-state exposures with QD dosing, 3- to 4-fold increase in exposure on Day 14
  - Day 14 Ctrough in range where >90% IRAK4 degradation is expected
- Steady-state reached by Day 7 of dosing

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

Absolute IRAK4 Levels



Mean % Reduction of IRAK4

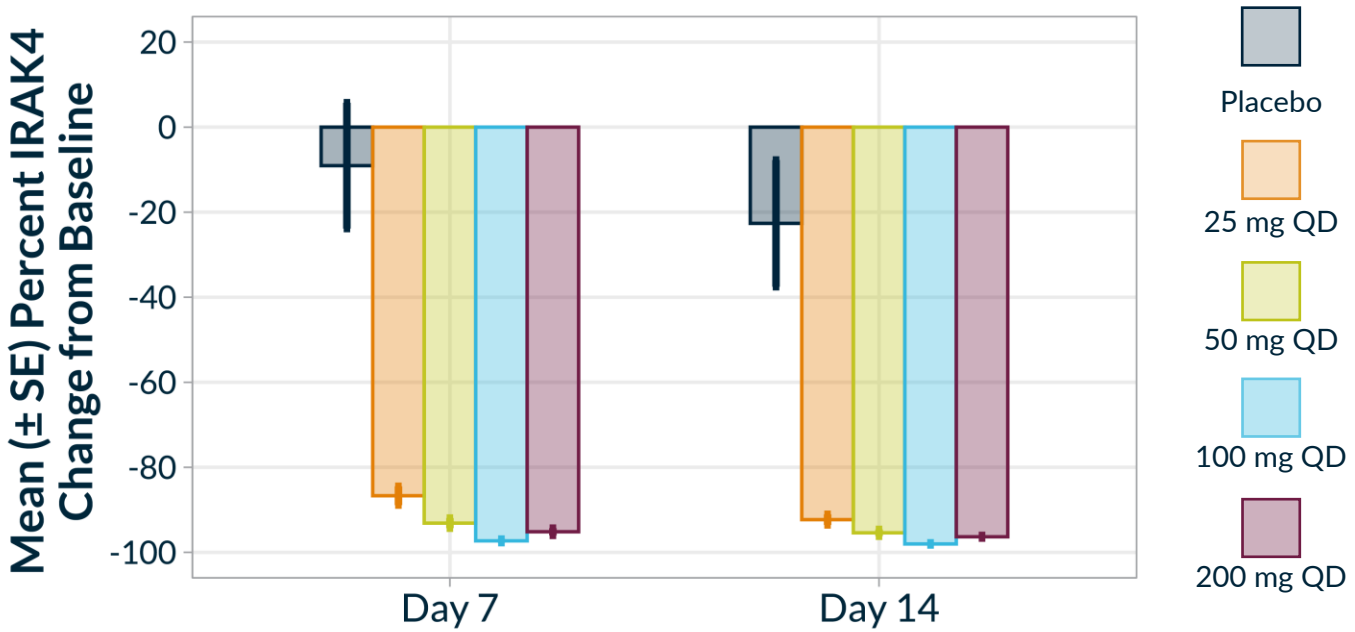


- Detected by mass spectrometry in circulating PBMC
- Steady state IRAK4 reduction achieved between Days 7 and 14
- Recovery towards baseline by Day 28 (2 weeks after last dose)
- MAD 2 through 4 approached Lower Limit of Quantitation (LLOQ)

Lower Daily Doses of KT-474 Achieved >98% IRAK4 Degradation (MS)

Plateau in IRAK4 Reduction after 14 days in PBMC after 100 mg

Percent IRAK4 Reduction in PBMC by Mass Spectrometry



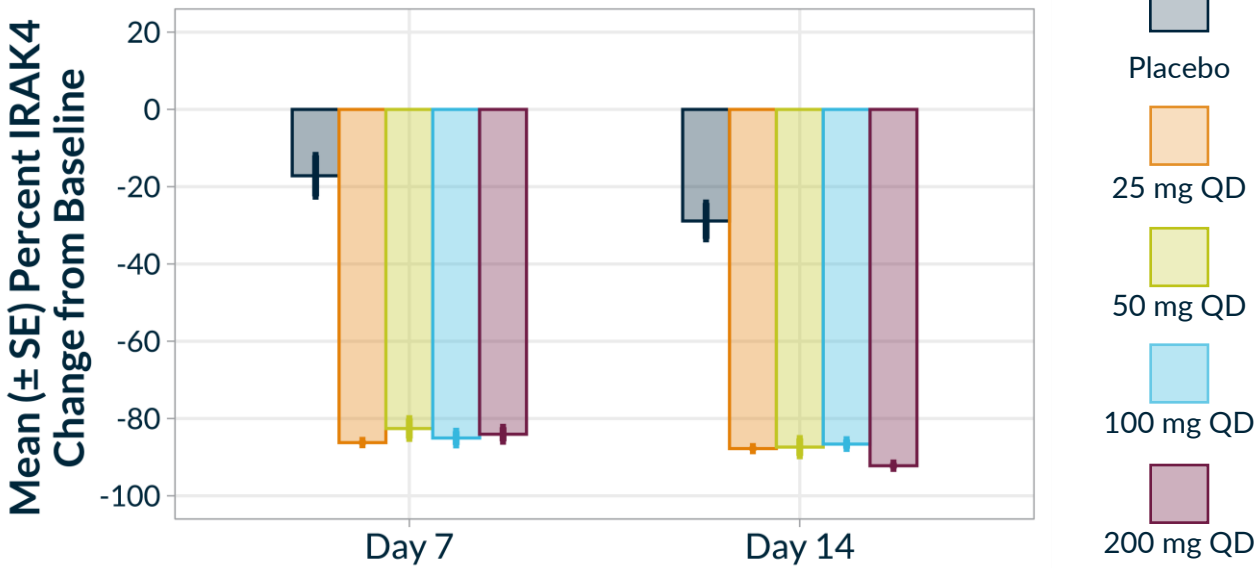
	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-9%	-87%	-93%	-97%	-95%
Mean Day 14	-23%	-92%	-95%	-98%	-96%
*p value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

* p-values relative to placebo

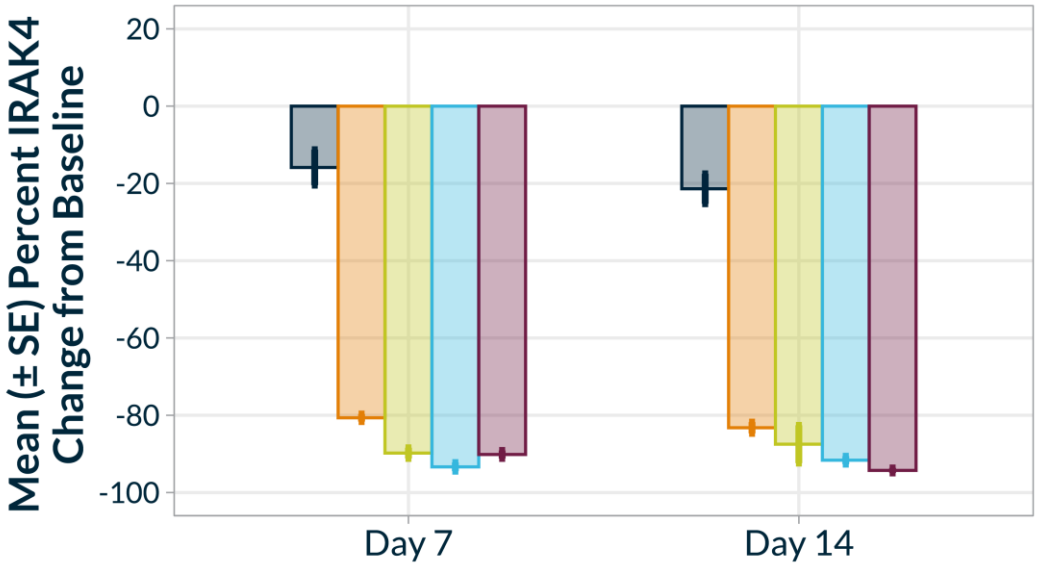
KT-474 Achieved >90% Degradation in Monocytes at ≥ 100 mg (FLOW)

Maximal Degradation in Monocytes in MAD4/200mg at Day 14

Percent IRAK4 Reduction in Lymphocytes



Percent IRAK4 Reduction in Monocytes



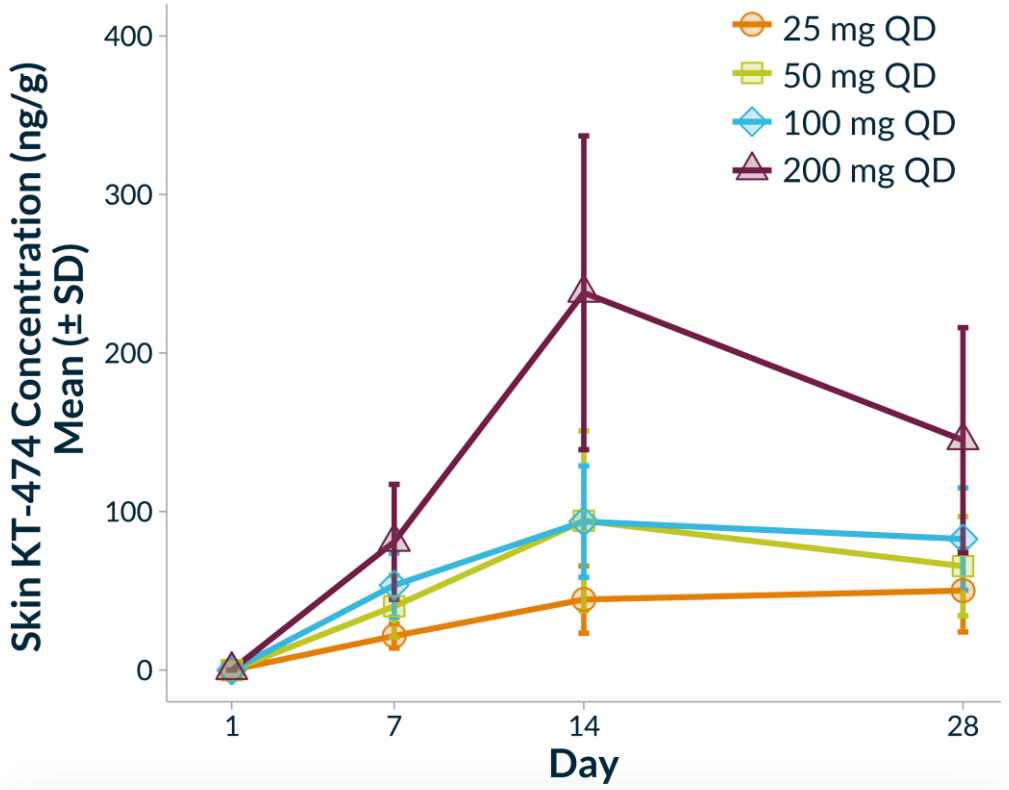
	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-17%	-86%	-83%	-85%	-84%
Mean Day 14	-29%	-88%	-87%	-87%	-92%
*p-value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

	Placebo (n=12)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Mean Day 7	-16%	-81%	-90%	-93%	-90%
Mean Day 14	-21%	-83%	-87%	-92%	-94%
*p-value**		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

* p-values relative to placebo

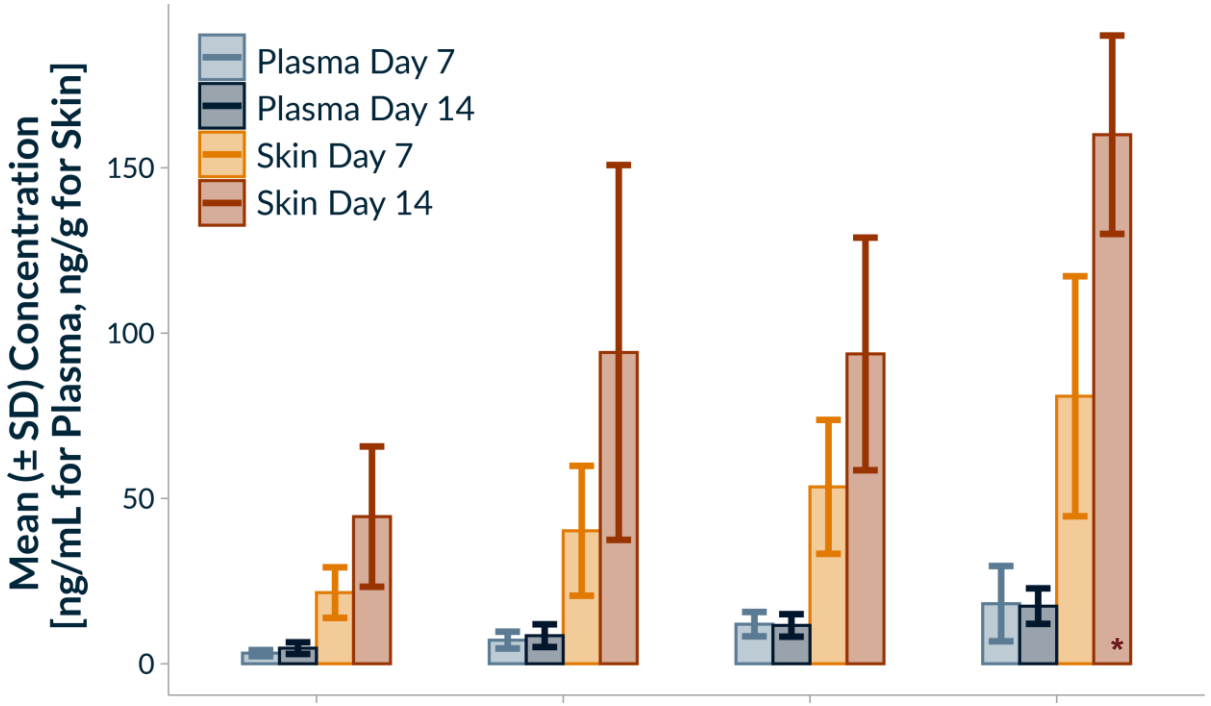
Once Daily Dosing Resulted in High Skin Exposures Exceeding Plasma

KT-474 Levels in Skin



- Increasing exposures through Day 14
- C_{trough} levels in skin ~10-14 fold higher than plasma on Day 14

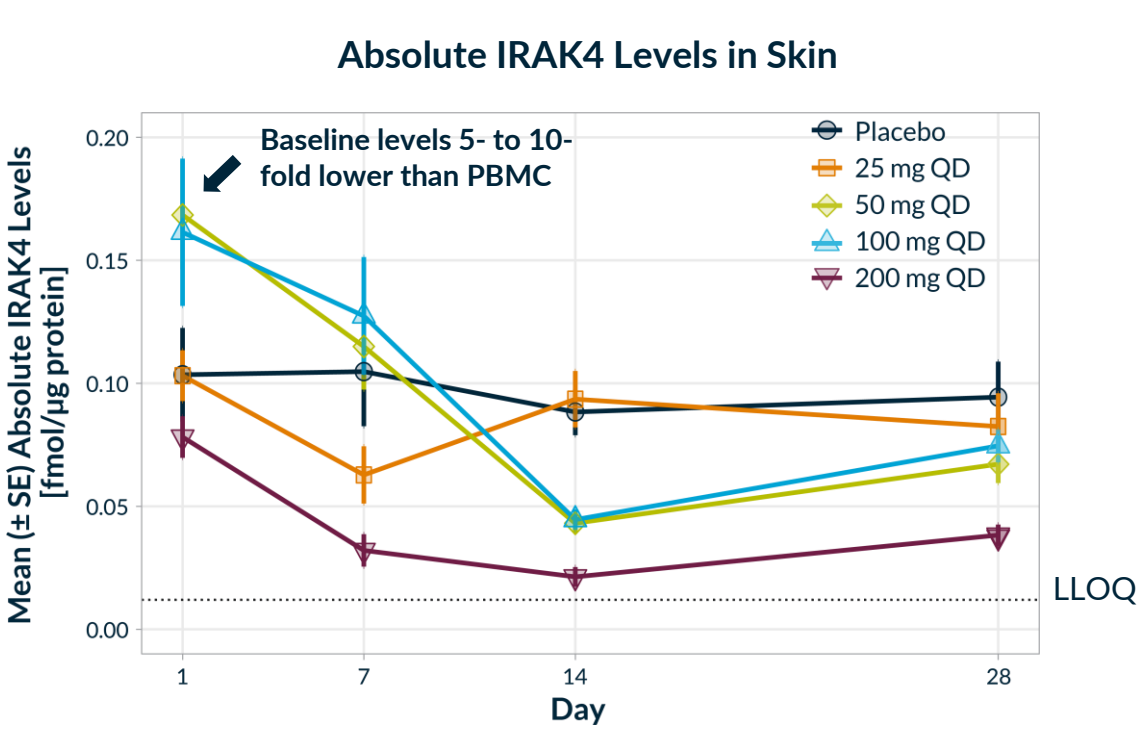
Substantially Larger Skin vs Plasma Exposures at C_{trough}

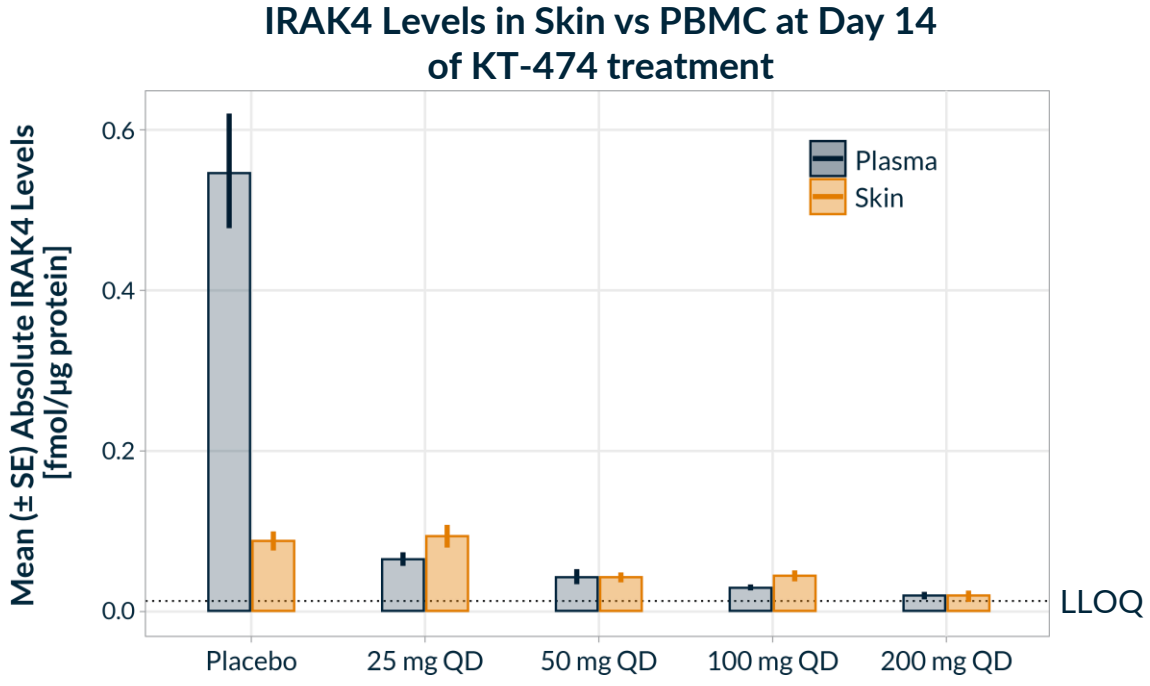


ng/mL (plasma) ng/g (skin)	25 mg QD (n=9)	50 mg QD (n=9)	100 mg QD (n=9)	200 mg QD (n=9)
Plasma Day 7	3.21	7.15	11.9	18.2
Plasma Day 14	4.72	8.49	11.6	17.4
Skin Day 7	21.5	40.2	53.5	80.9
Skin Day 14	44.5	94.2	93.7	238

C_{trough} concentrations shown for Days 1, 7 and 14.

KT-474 Reduced IRAK4 to Near LLOQ in the Skin (MS)

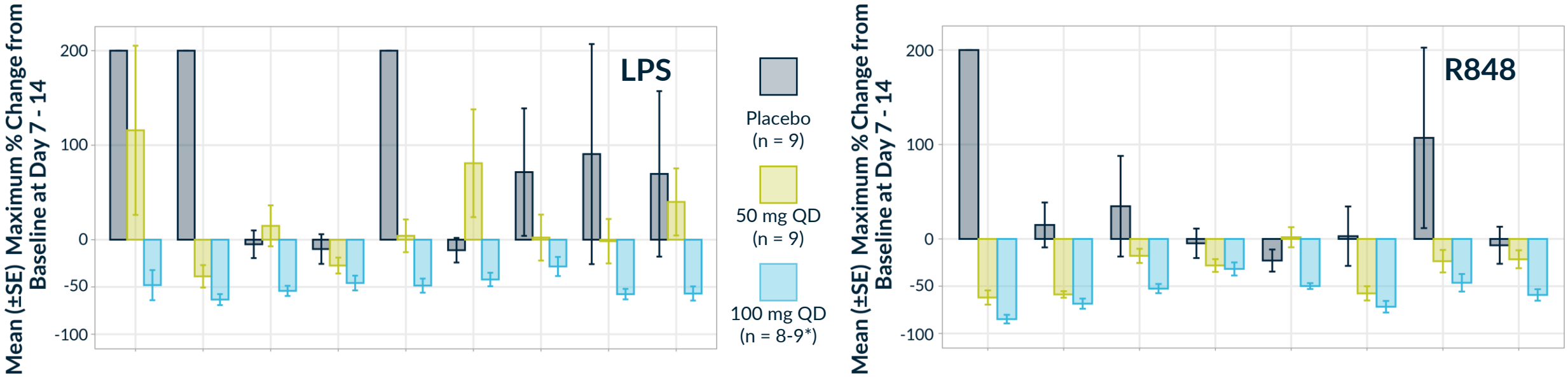




- Baseline IRAK4 levels in skin substantially lower compared to PBMC
- Dose-dependent IRAK4 degradation in skin by mass spectrometry
- Steady-state not yet reached at day 14
- Mean IRAK4 levels at 200 mg dose nearing LLOQ by Day 14, with knockdown up to 90% at 200 mg
- Comparable degradation in PBMC shows that effect of KT-474 is independent of baseline expression level

Ex Vivo Inhibition of 9 Disease-Relevant Cytokines, Day 7-14

Results through MAD3 Showed Dose-Dependent Effect Tracking with Extent of Monocyte IRAK4 Degradation



	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	357%	292%	-5%	-10%	880%	-11%	72%	91%	70%
50 mg QD	116%	-39%	15%	-27%	4%	81%	2%	-2%	40%
100 mg QD	-48%	-63%	-54%	-46%	-49%	-42%	-28%	-58%	-57%

	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	>500%	15%	35%	-5%	-23%	3%	107%	-7%
50 mg QD	-62%	-59%	-18%	-28%	2%	-58%	-24%	-21%
100 mg QD	-85%	-68%	-53%	-32%	-50%	-72%	-46%	-59%

50 mg QD: 93-95% PBMC degradation at Day 7-10; **87-90% Monocyte degradation at Day 7-14**
100 mg QD: 97-98% PBMC degradation at Day 7-10; **92-93% Monocyte degradation at Day 7-14**

*n=8 for LPS, n=9 for R848

Mean values > 200% have been replaced by 200 for visualization purposes

KT-474 Phase 1 Summary

Phase 1 Summary

- Dose escalation completed; 105 healthy volunteers enrolled in initial SAD and MAD portions of trial
- **POM**: IRAK4 degradation in blood and skin to near LLOQ; 95-98% mean IRAK4 reduction in blood at top 3 MAD doses (50mg, 100mg, 200mg)
- **POB**: Over 50% inhibition of up to 9 cytokines with up to 85% inhibition at 100 mg MAD dose
- Ongoing patient cohort study extended to 28 days to explore safety, PK, PD, biomarker impact and exploratory clinical efficacy endpoints in HS and AD patients

Safety Summary

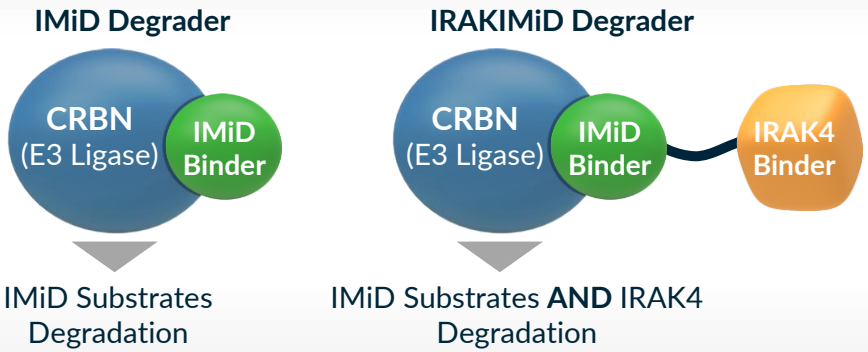
- KT-474 was generally well tolerated, with no SAEs
- MAD TEAEs in 2 or more subjects possibly/probably drug related included Headache (5), Palpitations (3) and Nausea (2)
- A *non-adverse*, non-dose-dependent, self-limiting mean 10-20 msec prolongation of QTc was identified after multi-dosing in MAD, with QTc remaining within normal range (<450 msec).
  - Subsequent analysis suggests weak ion channel binding, not IRAK4 or degradation, as likely cause
  - Not expected to impact development plan

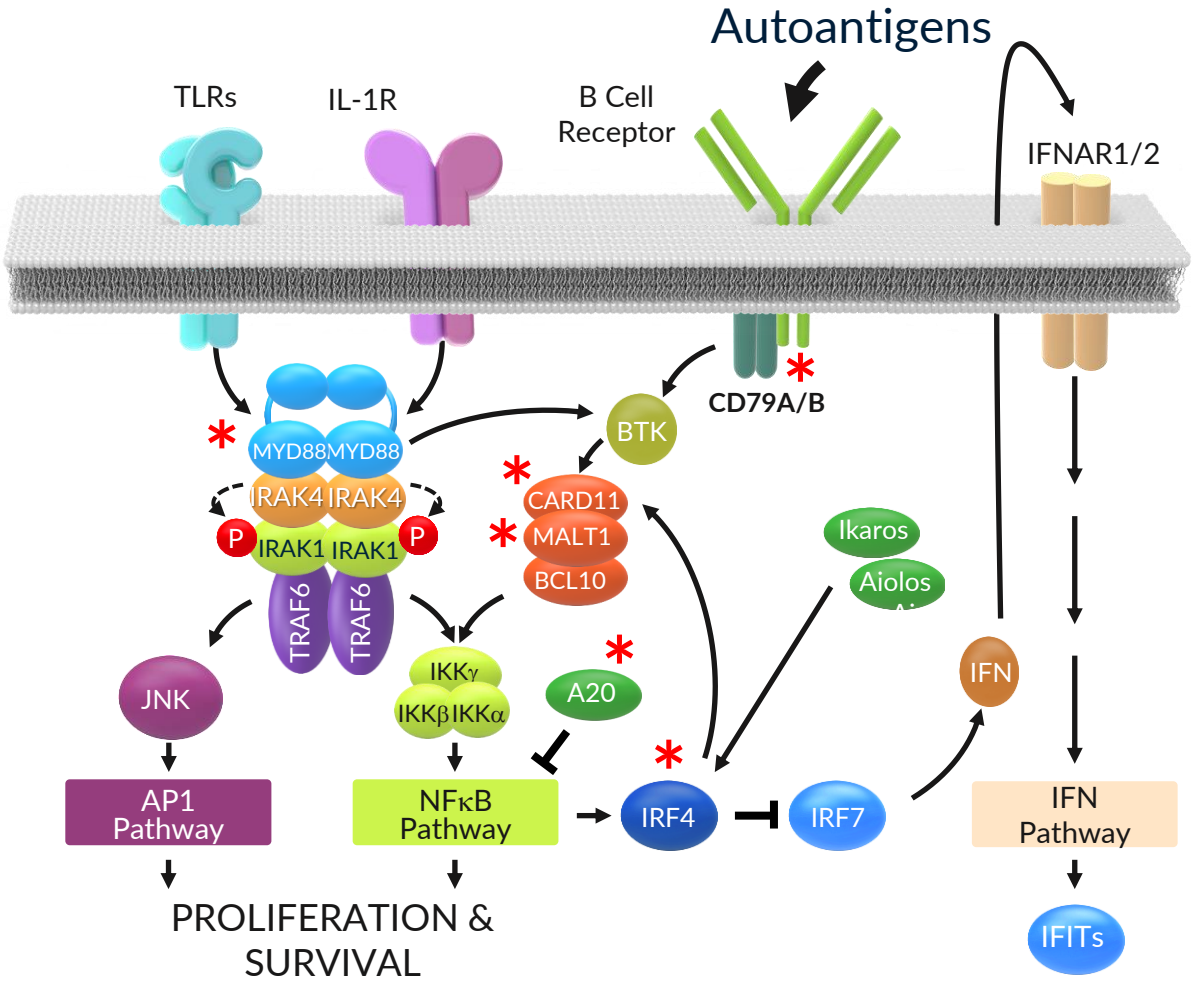
Profile, shared with FDA, supports advancement of KT-474 in further stages of development across immune-inflammatory diseases, starting with 28-day HS and AD patient cohort


IRAKIMiD
KYMERA

IRAKIMiDs are Potent Degraders of IRAK4 and IMiD Substrates Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

- Single-agent therapies that target activated NFκB signaling in DLBCL show limited activity in preclinical or clinical settings
- Redundant NFκB pathway activation and downregulation of Type 1 IFN is common in MYD88^{MT} lymphoma, supporting need to seek combination therapies
- Targeting simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models, supporting this targeted combination





Adapted from Yang et al. (2012) *Cancer Cell* 21, 6, pp723-737

IRAKIMiD: First Precision Medicine in MYD-88 Mutated Cancers

- MYD88 is mutated in ≥ 25% of DLBCL patients, the most common subtype of non-Hodgkin's lymphoma
- DLBCL **5-year survival rate is ~64%**, and MYD88 mutations are associated with poorer survival following frontline R-CHOP chemotherapy
- SOC in relapsed/refractory DLBCL, which includes CAR-T therapy, anti-body drug conjugates (ADC), and anti-CD19 and CD20 compounds, are associated with ORR of 40-80%
- **There are no treatments indicated specifically in MYD88 mutant DLBCL**

- MYD88 is mutated in approximately 90% of **Waldenström's macroglobulinemia** (WM) cases.
- Standard therapy includes ibrutinib-based or zanubrutinib with overall response rates of 80-90% and major response rates (≥ partial response) of approximately 73%

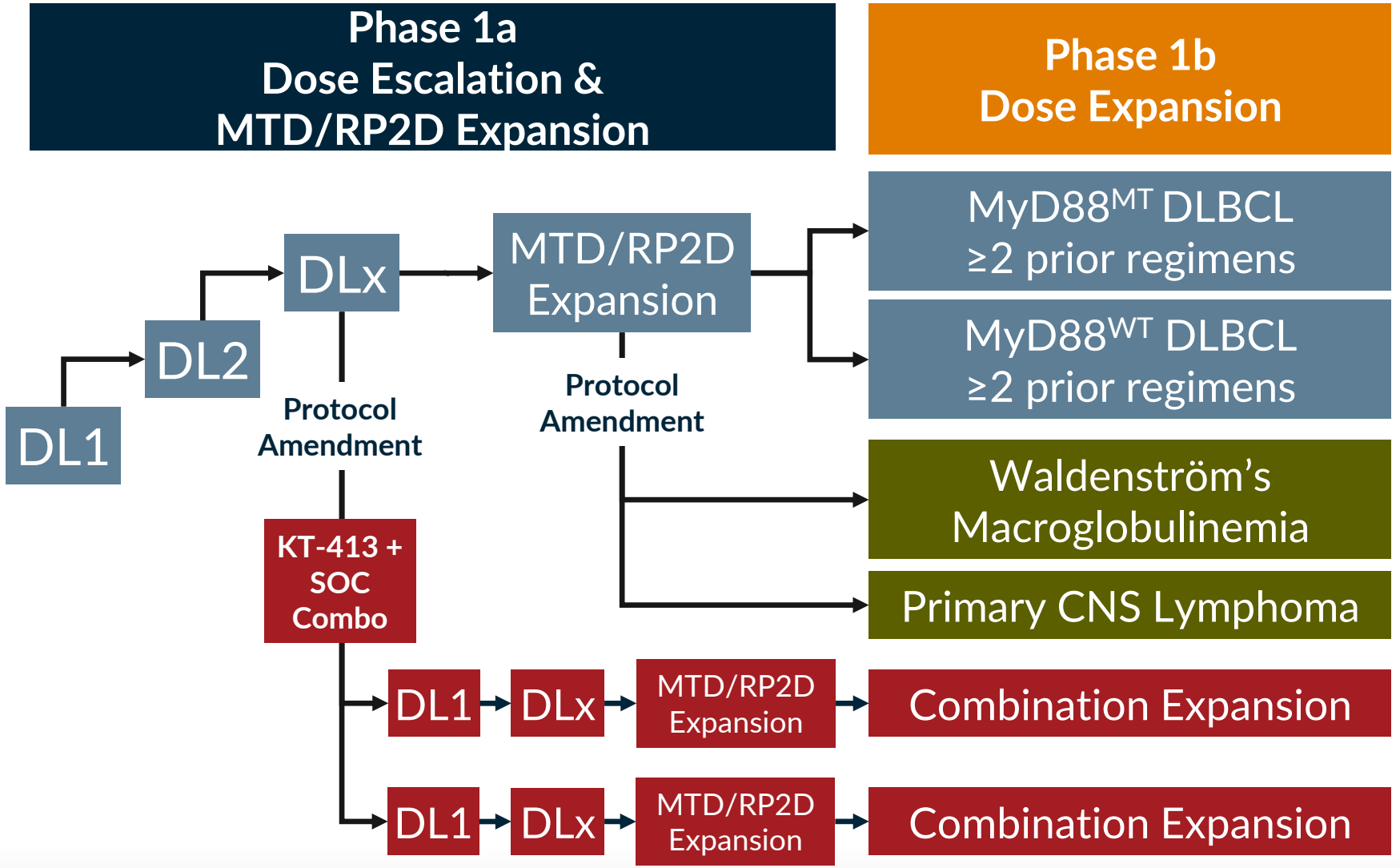
- MYD88 is mutated in approximately 70% of **primary central nervous system lymphoma (PCNSL)**
- Standard therapy in 1L includes high-dose (HD) methotrexate combinations result in overall response rates (ORR) of 53-87%, complete response (CR) in 23-49%, and 2-year PFS rates of 36-61%.
- Approximately 20-30% of patients with PCNSL experience tumor progression within first 6 months of treatment.
- There is no standard of care therapy in relapsed disease

KT-413: Ongoing Clinical Study Design

Key Eligibility Criteria:
R/R B-cell lymphoma
- ≥ 2 prior systemic regimens
- Ineligible or refused CAR-T or ASCT

Primary Objective:
- To evaluate safety, PK/PD, and preliminary efficacy in MYD88 mutant and MYD88 wild-type R/R DLBCL

Study Endpoints:
- Primary: Safety, tolerability, MTD/RP2D
- Secondary: PK, preliminary efficacy
- Exploratory: Target (IRAK4/Ikaros/Aiolos) knockdown and downstream effects in PBMC, and tumor



KT-413 is a Potent Degrader of IRAK4 and IMiD Substrates with Potent Activity in MYD88^{MT} Cell lines

- KT-413 selectively degrades both IRAK4 and IMiD substrates which leads to a profound antitumor effect *in vitro* and *in vivo*

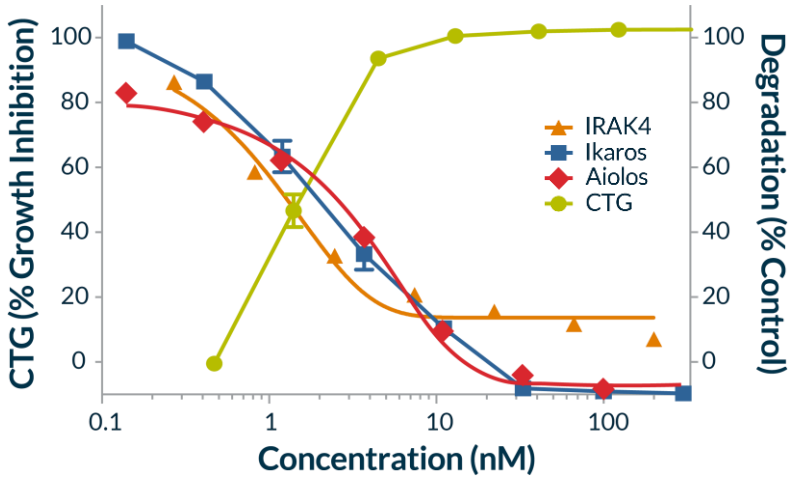
KT-413

IRAK4 DC_{50} = 6 nM

Ikaros DC_{50} = 2 nM

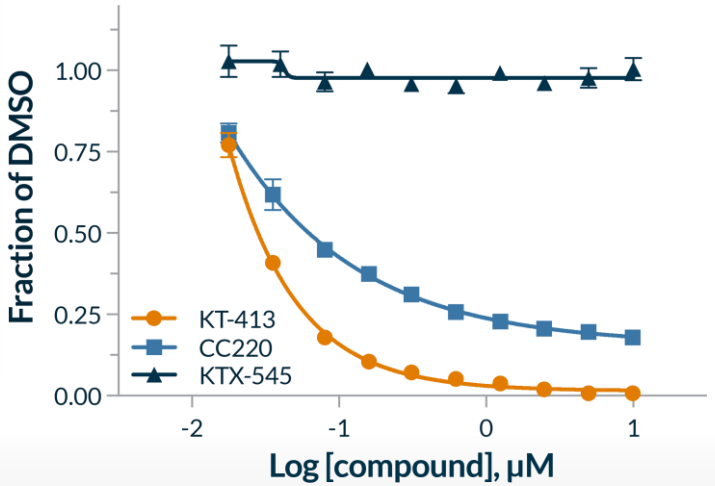
Aiolos DC_{50} = 2 nM

OCI-Ly-10 (MYD88^{MT} DLBCL) EC_{50} = 1 nM

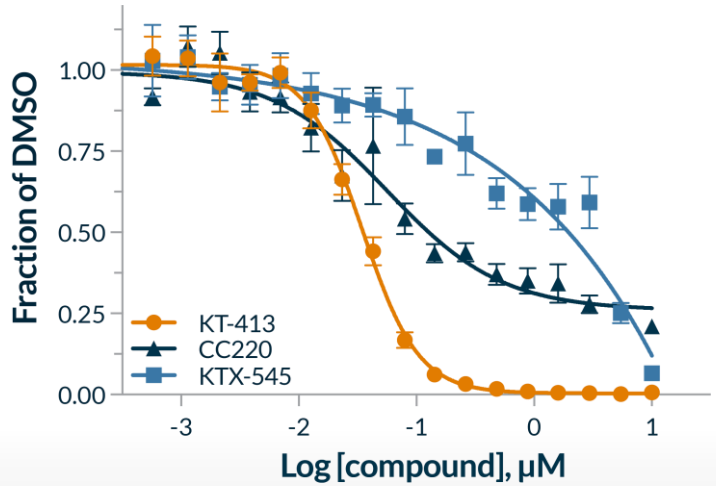


- KT-413 is more active in MYD88^{MT} DLBCL cells than the clinically active IMiD, CC-220, and IRAK4-selective degrader, KTX-545

OCI-Ly10 (MYD88^{L265P})



SUDHL2 (MYD88^{S222R})



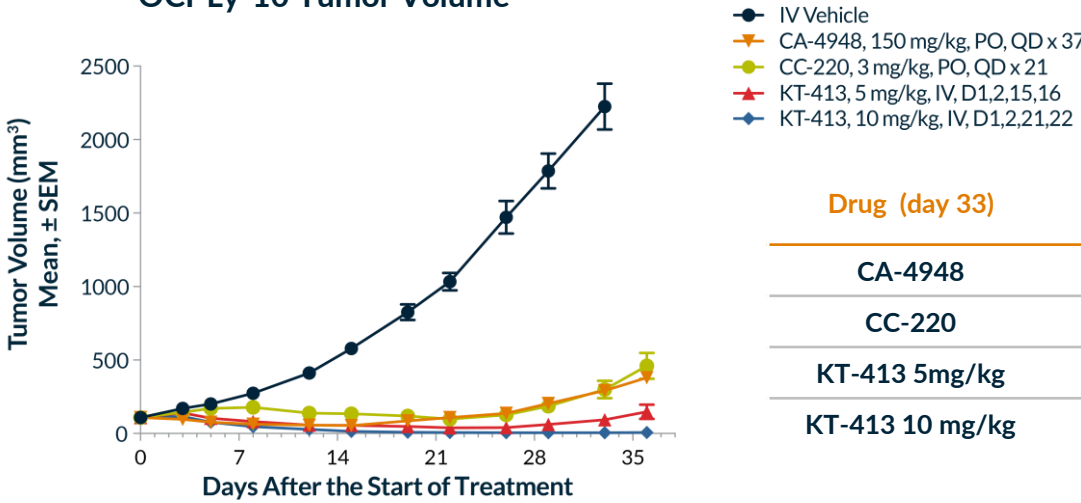
KT-413 is Highly Active on Intermittent Dosing Regimens

- 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 IMiD CC-220 alone**

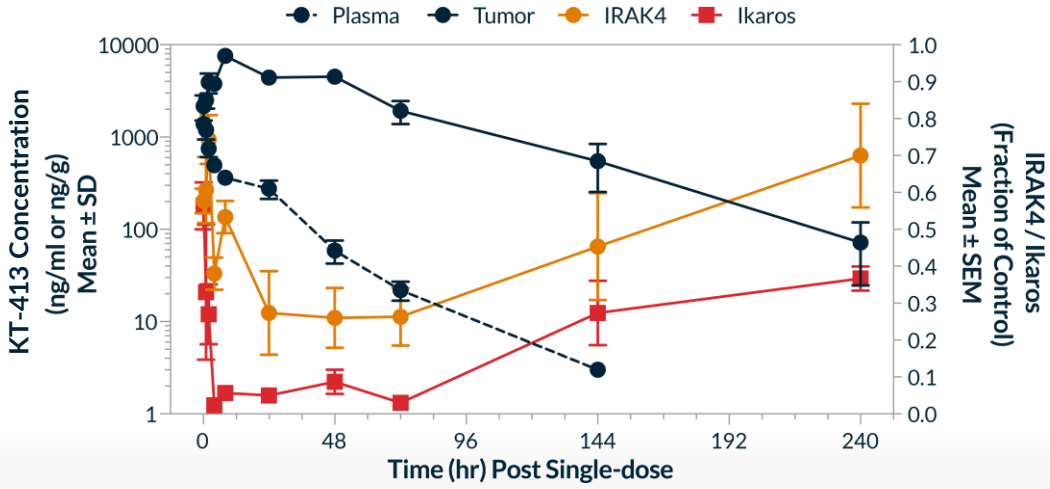
- Single 10 mg/kg dose showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for least 72hr
- Single 10 mg/kg dose Q3W had robust anti-tumor activity

Superior Anti-tumor activity

OCI-Ly-10 Tumor Volume

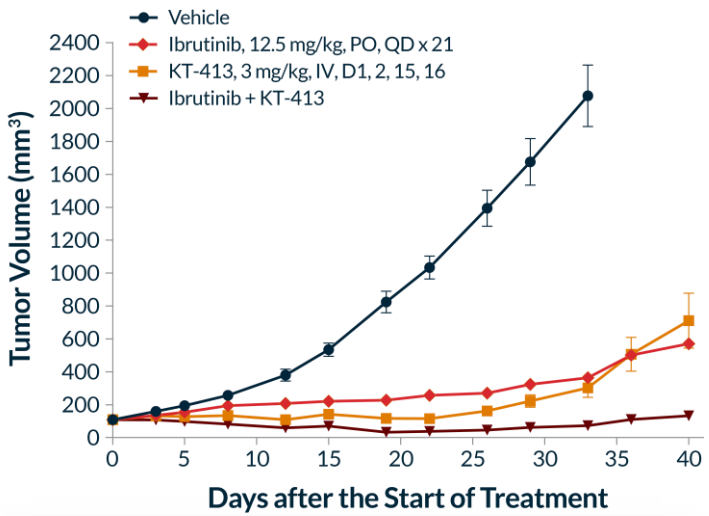


Drug (day 33)	T/C% (REG%)	CR	PR	SD	PD
CA-4948	9	0	0	0	7
CC-220	9	0	0	0	7
KT-413 5mg/kg	(14)	1	0	3	3
KT-413 10 mg/kg	(94)	5	2	0	0



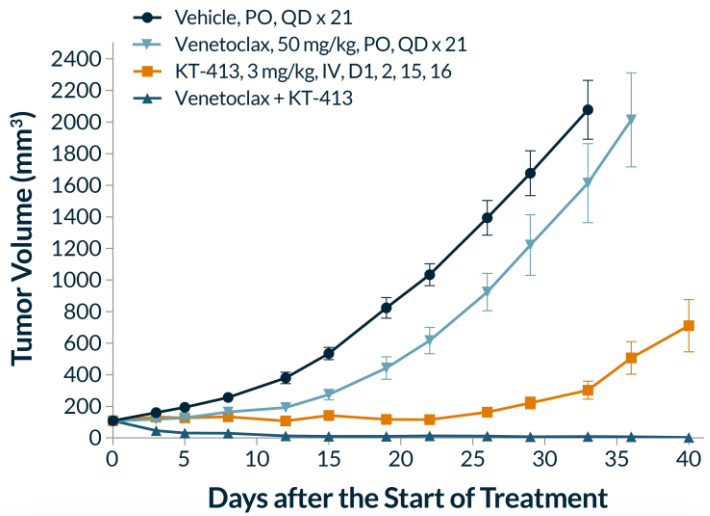
KT-413 Has Strong Activity in Combination in MYD88^{MT} OCI-Ly10 Xenografts

with BTK Inhibitor



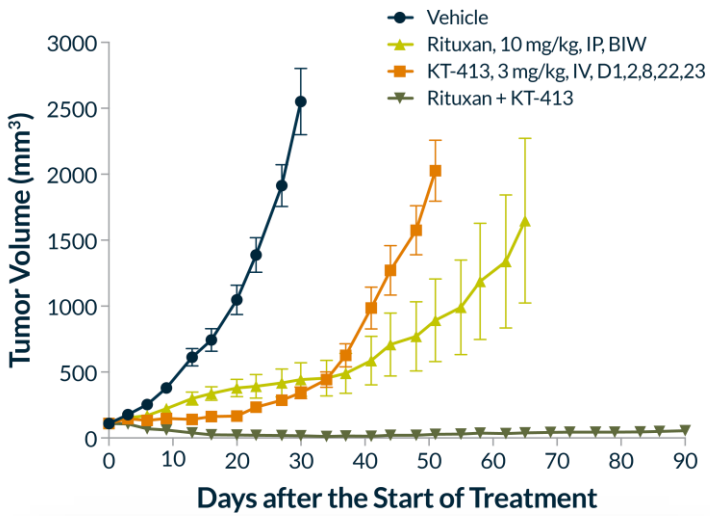
- KT-413 administered on intermittent schedules leads to strong regressions in combination with the BTK inhibitor Ibrutinib

with BCL-2 Inhibitor



- KT-413 administered on intermittent schedules leads to deep and durable regressions in combination with the BCL-2 inhibitor, Venetoclax

with Rituxan



- KT-413 administered on intermittent schedules leads to deep and durable regressions in combination with Rituxan

Data support potential for KT-413 in combination in earlier lines of therapy

IRAKIMiD Degrader KT-413 has Potential to be First Precision Medicine in DLBCL to Target a Genetically-defined Population (MYD88MT)

- Profound **antitumor activity** in preclinical models both **in single agent** and **combination**
- Clinical strategy in place to enable accelerated approval:

Monotherapy

  - $MYD88^{MT}$ DLBCL for most direct path to registration
  - Other $MYD88^{MT}$ lymphomas of interest include PCNSL, WM

Combinations

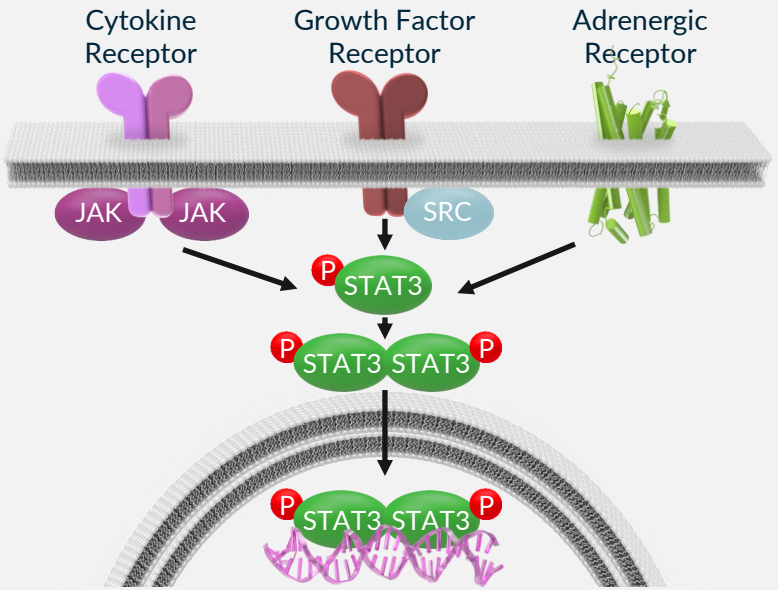
  - With SOC agents in $MYD88^{MT}$ DLBCL to enable earlier line therapy

STAT3

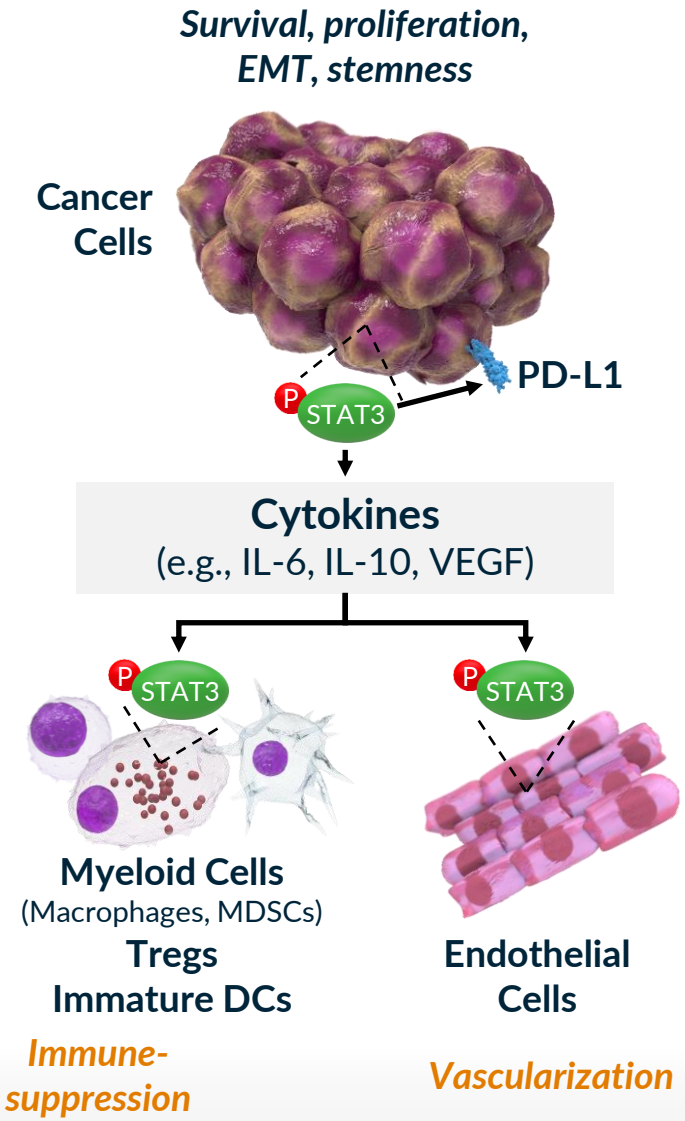
KYMERA

STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

STAT3 as a Target



- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported by >25k publications
- Traditionally undrugged target
- First-in-class opportunity to address STAT3 driven pathology across large and diverse indications



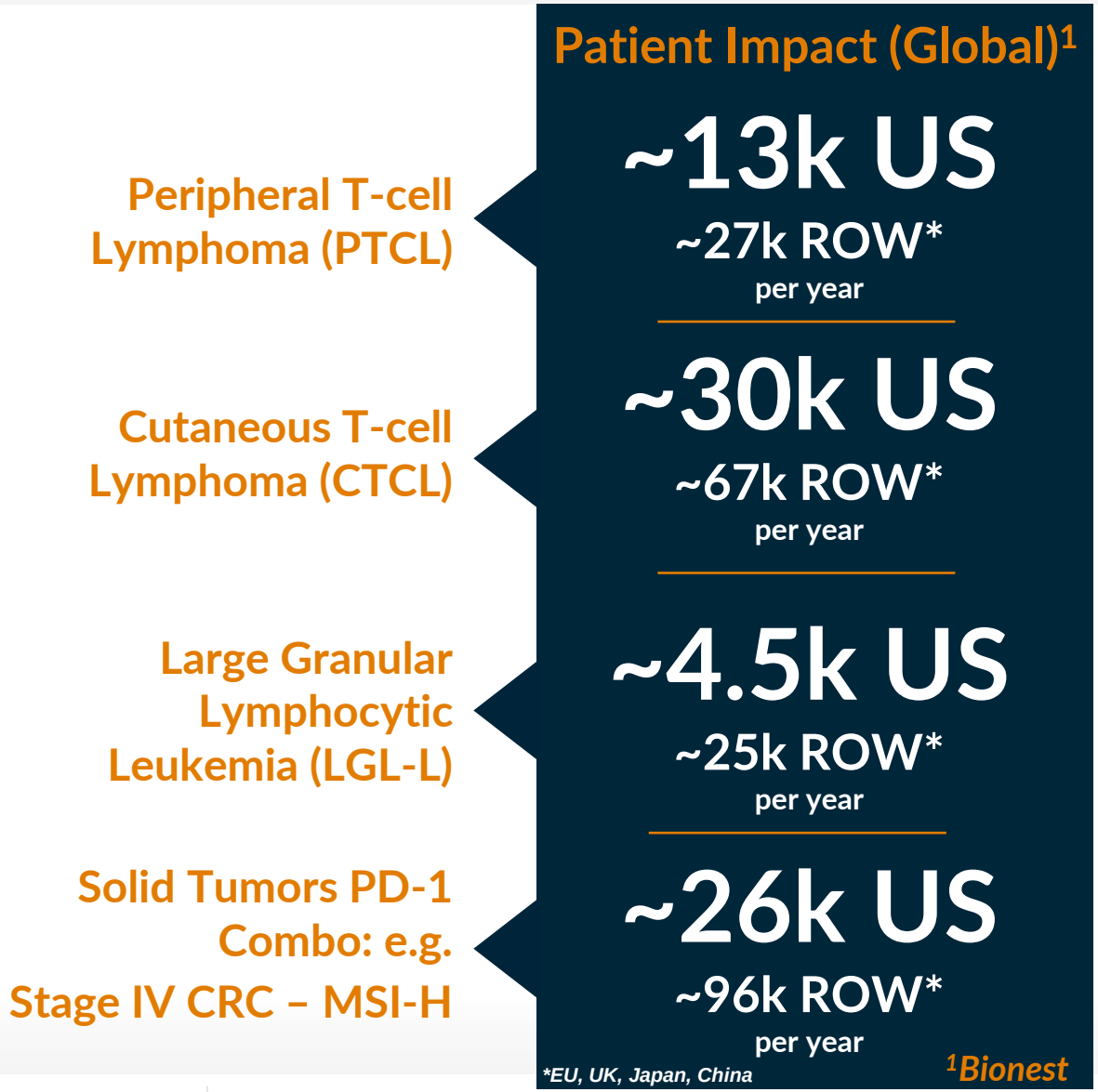
Tumor Cell Intrinsic

- Hyperactivation of STAT3 via either receptor signaling, or hotspot mutations promotes gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells
- Opportunities in STAT3-dependent malignancies (e.g., T cell malignancies, DLBCL, AML) and drug resistant tumors (e.g., TKI resistant oncogene-driven solid tumors)

Tumor Cell Extrinsic

- STAT3 promotes the differentiation and activity of immunosuppressive and endothelial cells, resulting in an immunosuppressive tumor microenvironment.
- Opportunities in multiple heme and solid tumor indications that are not responsive to immune checkpoint inhibitors.

First-in-class Opportunity to Address STAT3-driven Pathology Across Diverse indications



- Abnormal activation of JAK/STAT pathway occurs in nearly all T-cell lymphomas
- STAT3 is most frequent mutation among JAK/STAT pathway
- Standard therapies in relapsed/refractory PTCL including result in ORRs ~25%, CR rate of ~10% and mDOR of approximately 9 months

- Advanced stages of disease associated with constitutively activated STAT3
- Standard therapies in relapsed/refractory CTCL result in ORRs of ~30% with few CRs and mPFS of 5-8 months

- STAT3 mutations in up to 70% cases
- Constitutively active STAT signaling in nearly all cases
- No approved agents in LGL-L; SOC in 1L which includes methotrexate and cyclophosphamide result in ORRs ~60%
- No SOC in ≥2L

- STAT3 decreases inflammatory state in tumor, degradation of STAT3 sensitizes to PD1/L1 activity
- PD1 inhibitors approved as single agents or in combination with CTLA4 inhibitor in 1L and in later lines following chemotherapy in patients with metastatic MSI-H CRC

KT-333: Ongoing Clinical Study Design

Key Eligibility Criteria:

R/R B-cell lymphoma

- ≥ 2 prior systemic regimens
- Ineligible or refused CAR-T or ASCT

Advanced solid tumors

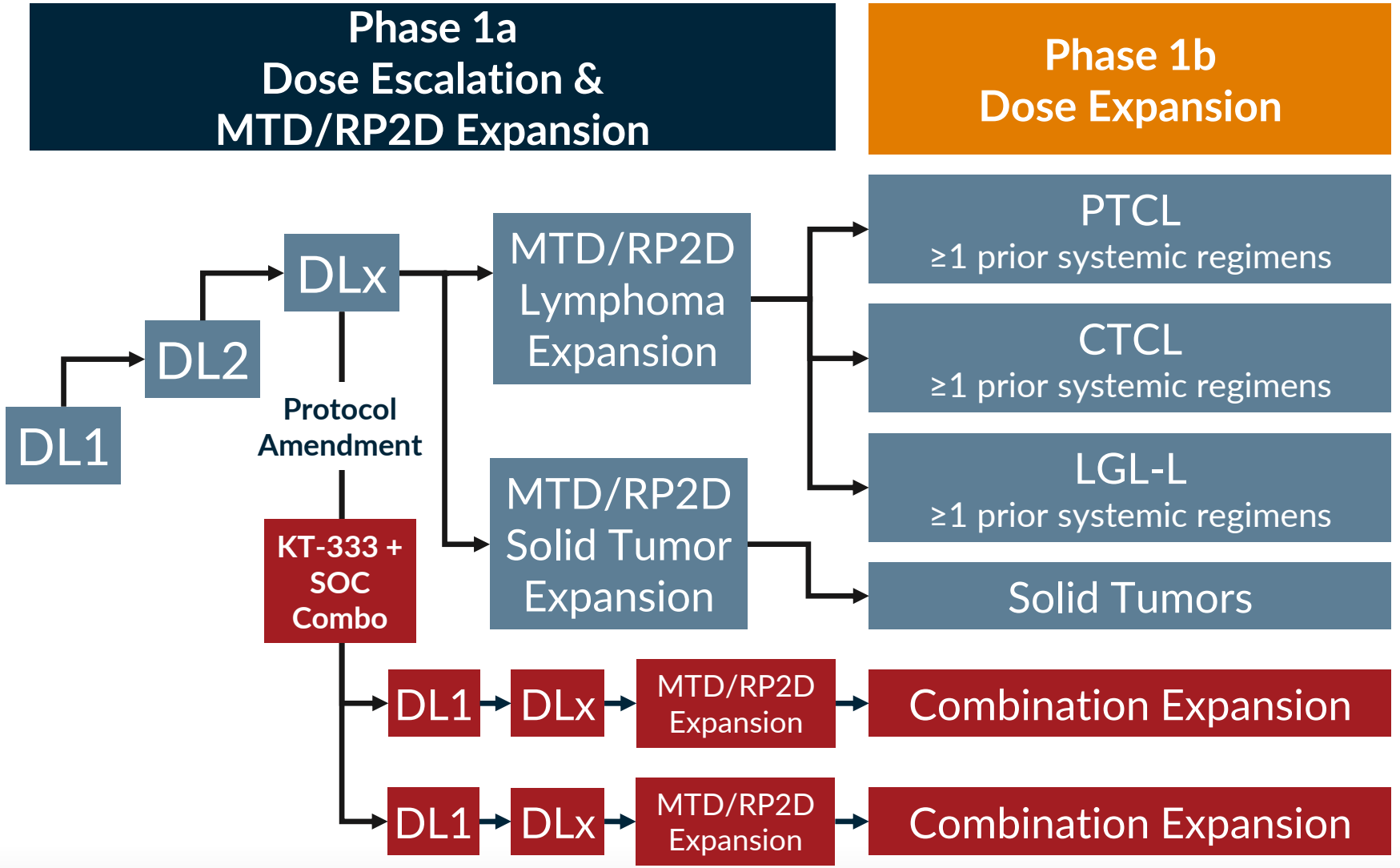
- ≥ 2 prior systemic regimens or no available SOC

Primary Objective:

- To evaluate safety, PK/PD, and preliminary efficacy in PTCL, CTCL, LGL-L and solid tumors

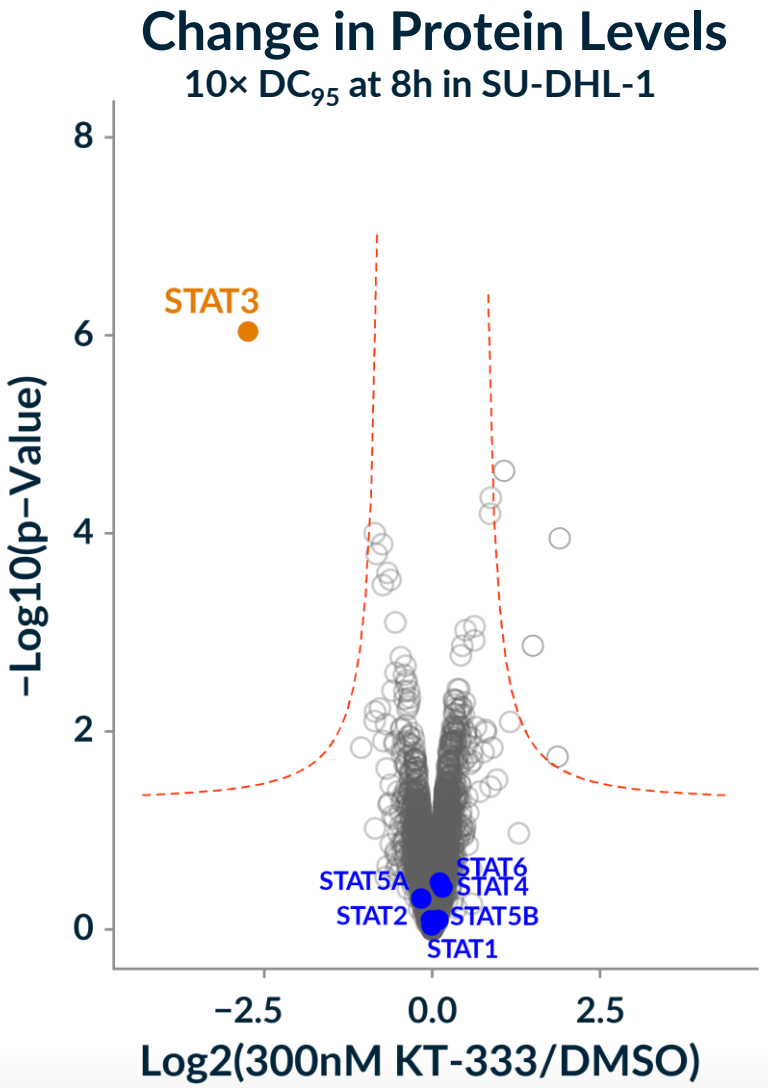
Study Endpoints:

- Primary: Safety, tolerability, MTD/RP2D
- Secondary: PK, preliminary efficacy
- Exploratory: STAT3 knockdown and downstream effects in PBMC and tumor



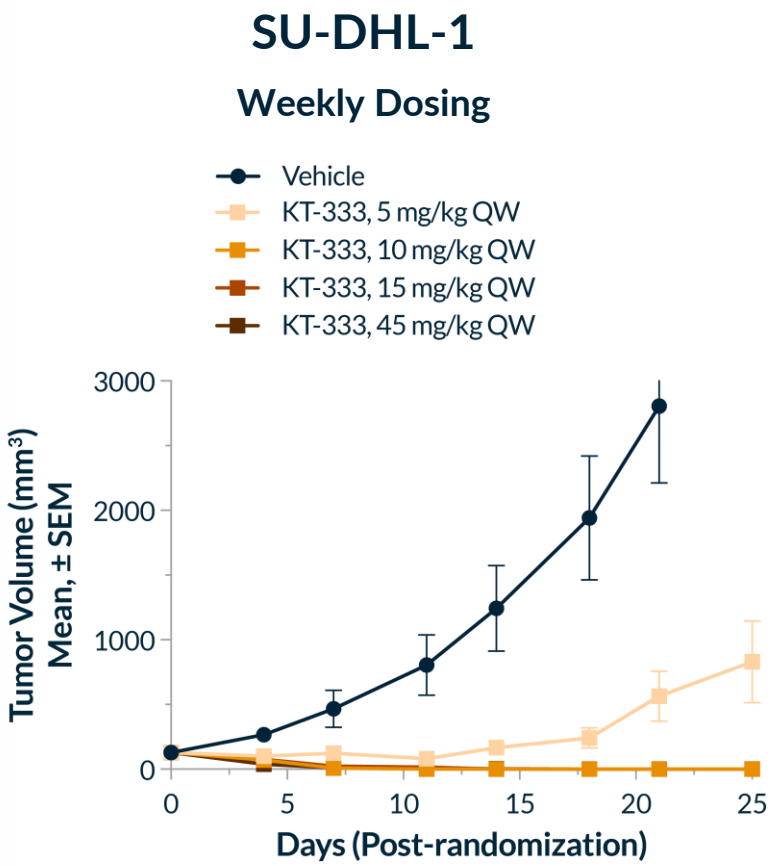
KT-333 Demonstrates Highly Selective Degradation of STAT3

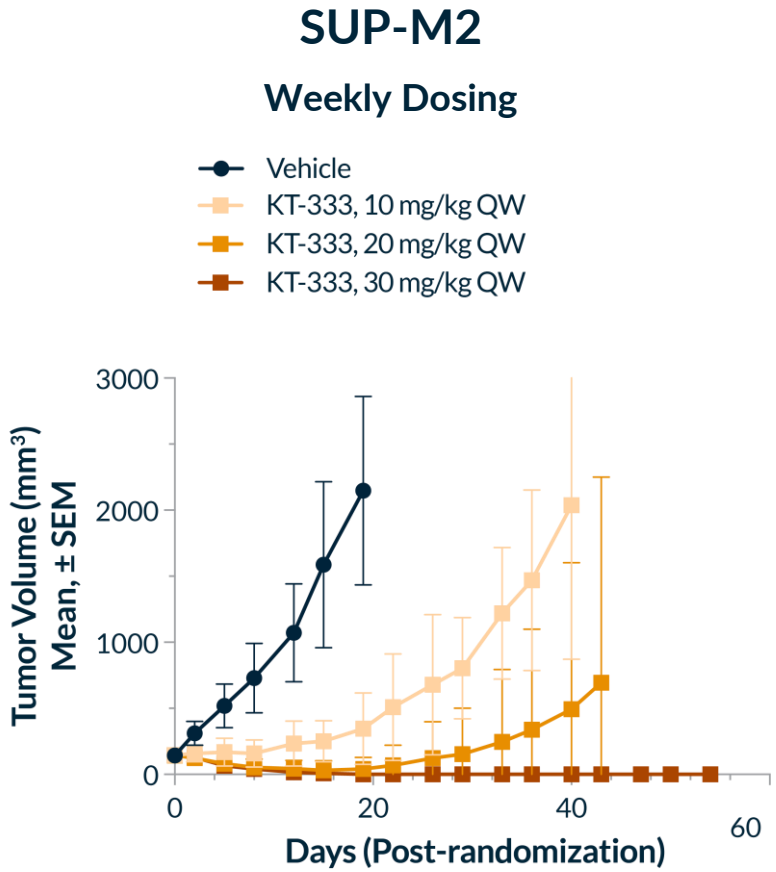
- Deep mass spectrometry-based proteomics to assess STAT3 selectivity performed
- In hPBMC and SU-DHL-1 cancer line (shown), treatment with KT-333 degrader led to selective degradation of only STAT3 protein



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

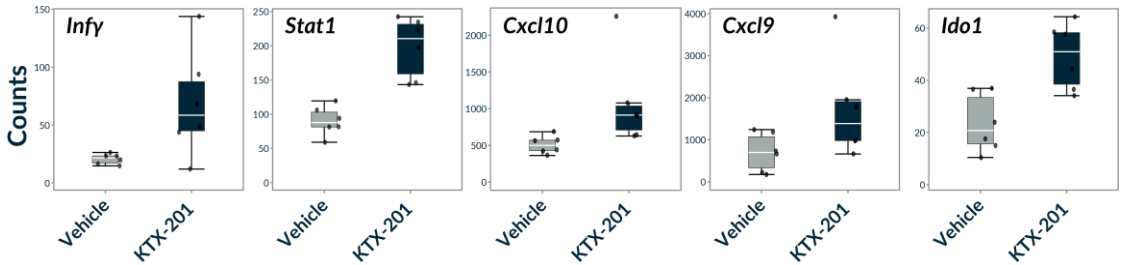
- Mice bearing STAT3-dependent ALK+ ALCL SU-DHL-1 or SUP-M2 tumor xenografts dosed with STAT3 degrader
- Dose- and degradation dependent tumor growth inhibition observed with once-a-week dosing
- 10 mg/kg sufficient to drive full tumor regression in SU-DHL- 1 that was durable for multiple weeks after the last dose (on day 14)





STAT3 Degrader's Role in Immuno-Oncology: Sensitization of Tumors to Anti PD-1

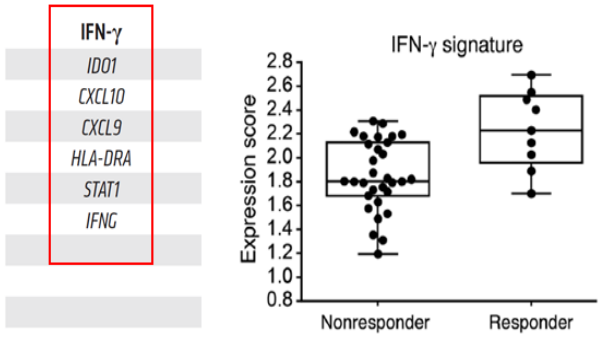
IFNγ-dependent Gene Signature Induced by STAT3 Degrader Monotherapy in CT-26 Tumors



CT-26: Veh or KTX-201 25 mg/kg q2D IP; n=6/grp; t = Day 11

- STAT3 degradation remodels the CT-26 TME to be more immune-favorable with upregulation of anti-tumor immunity genes previously identified as predictors of clinical response to pembrolizumab

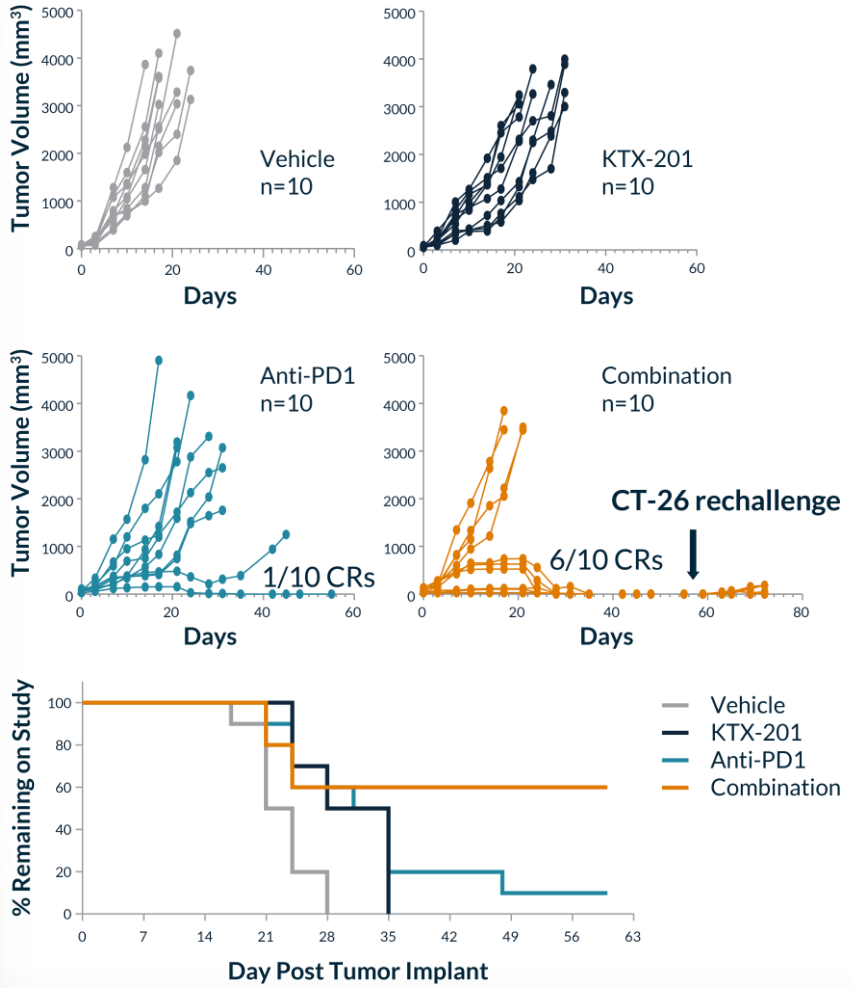
IFN-γ and Expanded Immune Gene Signature



Source: Ayers et al., *JCI*, 2017

STAT3 Degradation and Anti-PD-1 Synergy

- KTX-201 synergizes with anti-PD-1 leading to 60% complete responses in CT-26 model
- Complete responders reject tumor rechallenge demonstrating development of long-term immune memory
- Combination extends survival

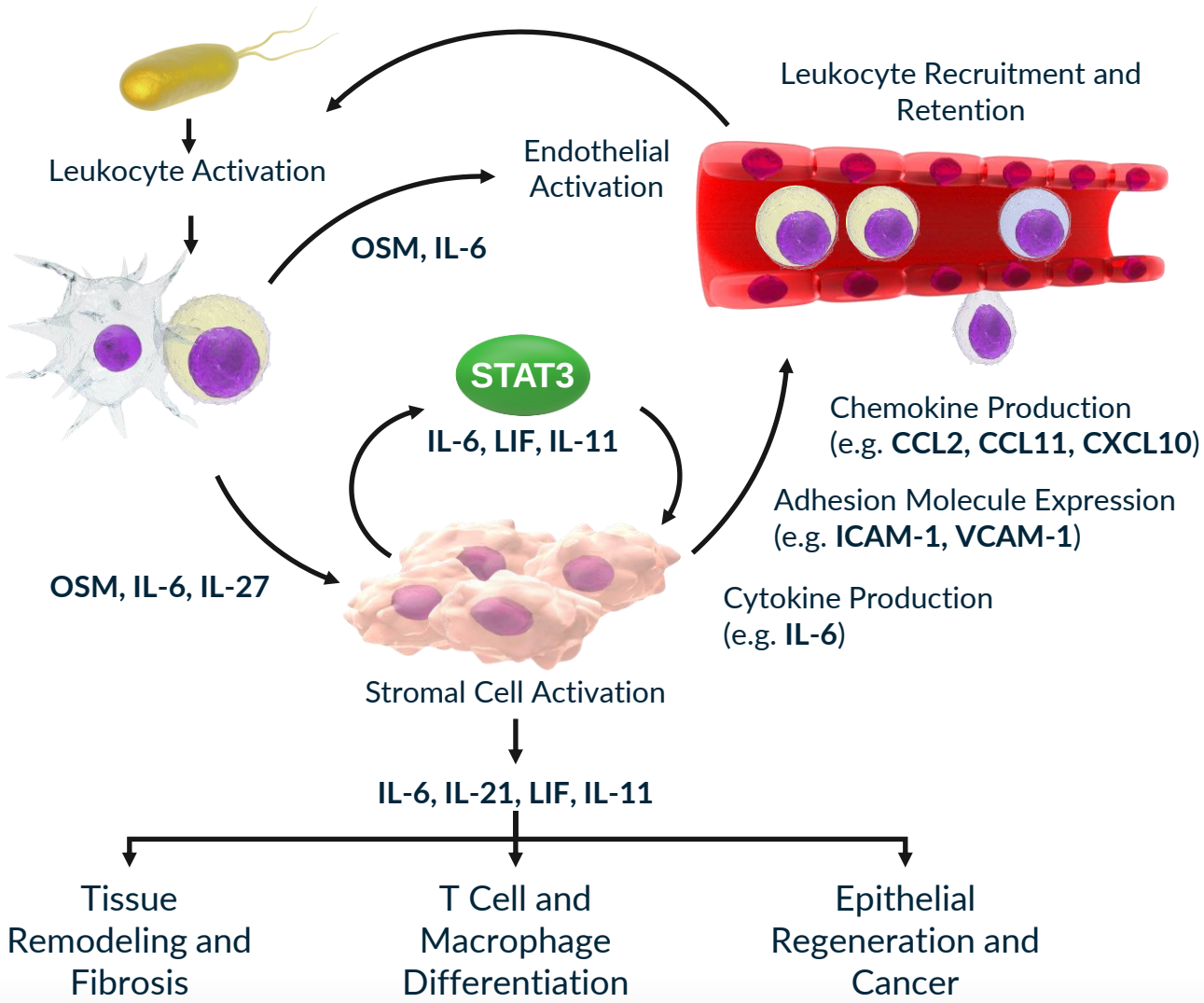


STAT3 Degrader KT-333, First-in-class Opportunity to Address STAT3-driven Pathology Across Diverse Indications

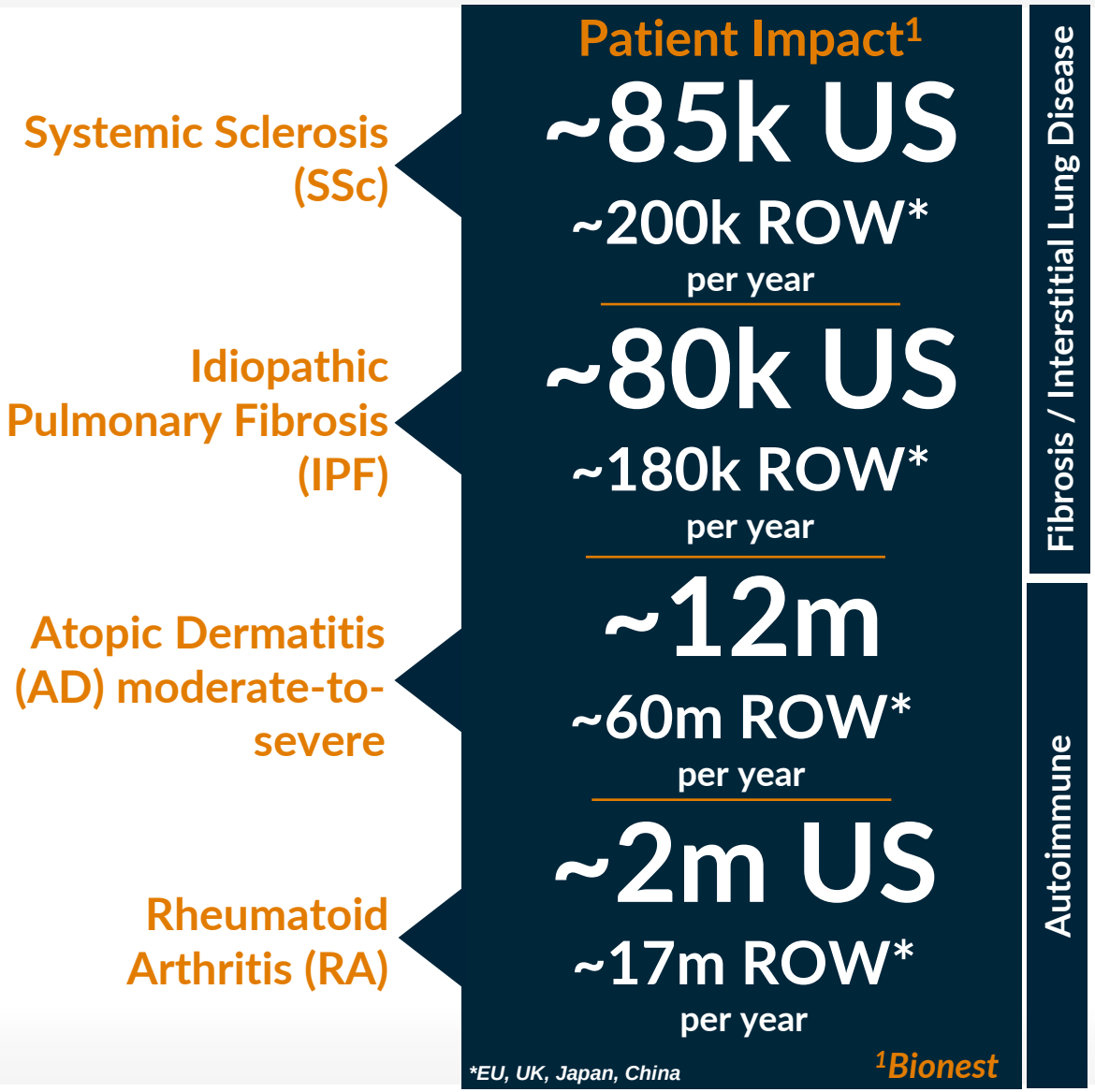
- First heterobifunctional degrader against an **undrugged target in the clinic**
- Profound **single agent activity** in liquid tumor and **promising combo activity** with anti-PD1 in liquid and solid tumors
- Clinical development strategy includes **direct registrational path in STAT3 pathway** activated heme malignancies
- Opportunity for **expansion into solid tumors** in combination with immune checkpoint inhibitors

Role of STAT3 in Inflammatory Processes

- STAT3 is activated by multiple tyrosine kinases and plays a critical role in the signaling of cytokines, hormones, and growth factors including IL-6, IL-21, IL-11, OSM, TGF-**β**, VEGF
- STAT3 gain-of-function mutations lead to a poly-autoimmunity with clinical manifestations that include interstitial lung disease (ILD), arthritis, scleroderma and eczema
- Increased STAT3 activation is associated with disease severity in chronic inflammation including SSc, RA, AS, MS, IBD, Psoriasis
- STAT3 activation is also implicated in conditions defined by intense stromal remodeling in the absence of overt inflammation, e.g. IPF, PAH, NAFLD, and Diabetic Kidney Disease



STAT3 Degraders Have Applicability in Serious Inflammatory and Fibrotic Diseases



- Increased STAT3 and pSTAT3 observed in SSc skin and lung biopsies
- Aberrant IL6/JAK/STAT3 gene signature in biopsies from SSc patients
- Tocilizumab no effect on mRSS but change from baseline in FVC at week 48 (observed FVC and %pFVC) in patients with SSc/ILD

- STAT3 dependent cytokines (e.g. IL-11) upregulated in lung of IPF patients and are associated with disease severity
- IL-6/gp130 stimulation is mitogenic for IPF fibroblasts but no normal fibroblasts
- SoC reduces the annual rate of FVC decline

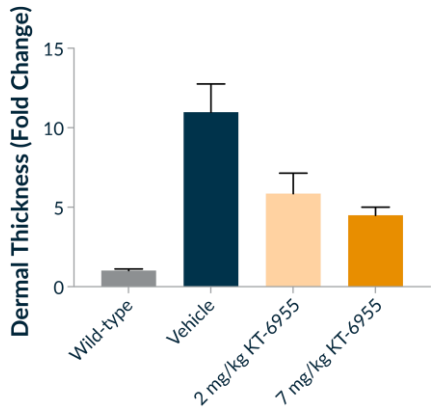
- STAT3 GoF patients exhibits signs of dermatitis
- TSLP receptor activates STAT3
- Pruritis is linked to mechanical and IL-31R activation of STAT3
- Fibrotic changes associated with AD is associated with STAT3 activation

- STAT3 mRNA and pSTAT3 are significantly higher in blood of RA patients
- STAT3 target genes (BCL3, SOCS3 and PIM1) are upregulated in early RA
- Constitutive STAT3 phosphorylation in circulating $CD4^+$ T cells correlates to IL-6 levels in recent-onset RA
- ~30% of SoC therapies in moderate to severe RA achieve ACR70 at week 52

Our STAT3 Degraders Robustly Reduce Disease in Models of Systemic Sclerosis, Arthritis and CNS Inflammation

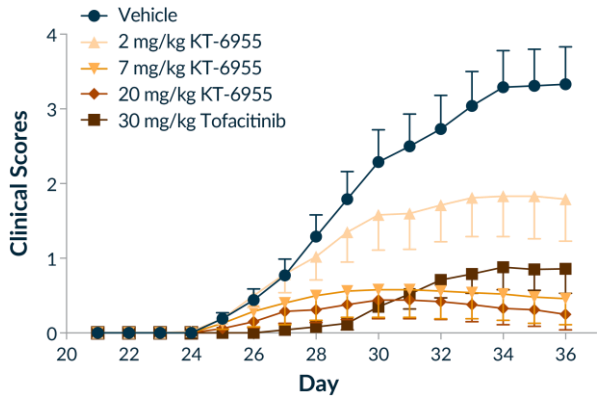
In Vivo Tight Skin Model (Fibrosis)

TSK ± Mice (BIW Dosing)



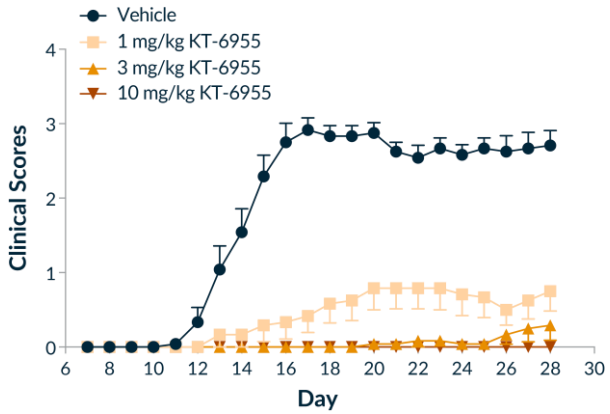
In Vivo CIA Model (RA)

Collagen-induced Arthritis (BIW Dosing)



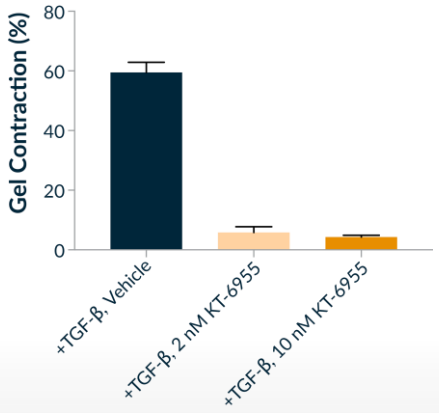
In Vivo MS Model

Experimental Autoimmune Encephalomyelitis (BIW Dosing)

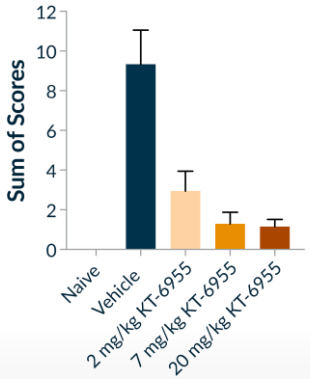


Cellular Fibrosis Model

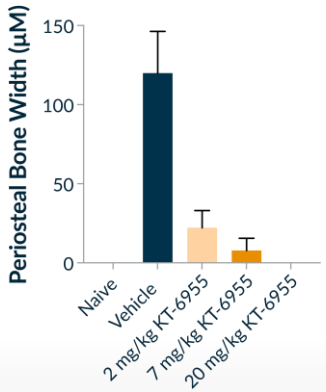
TGF-β Stimulated SSc Fibroblasts (72h)



Pathology Score



Periosteal Bone Growth

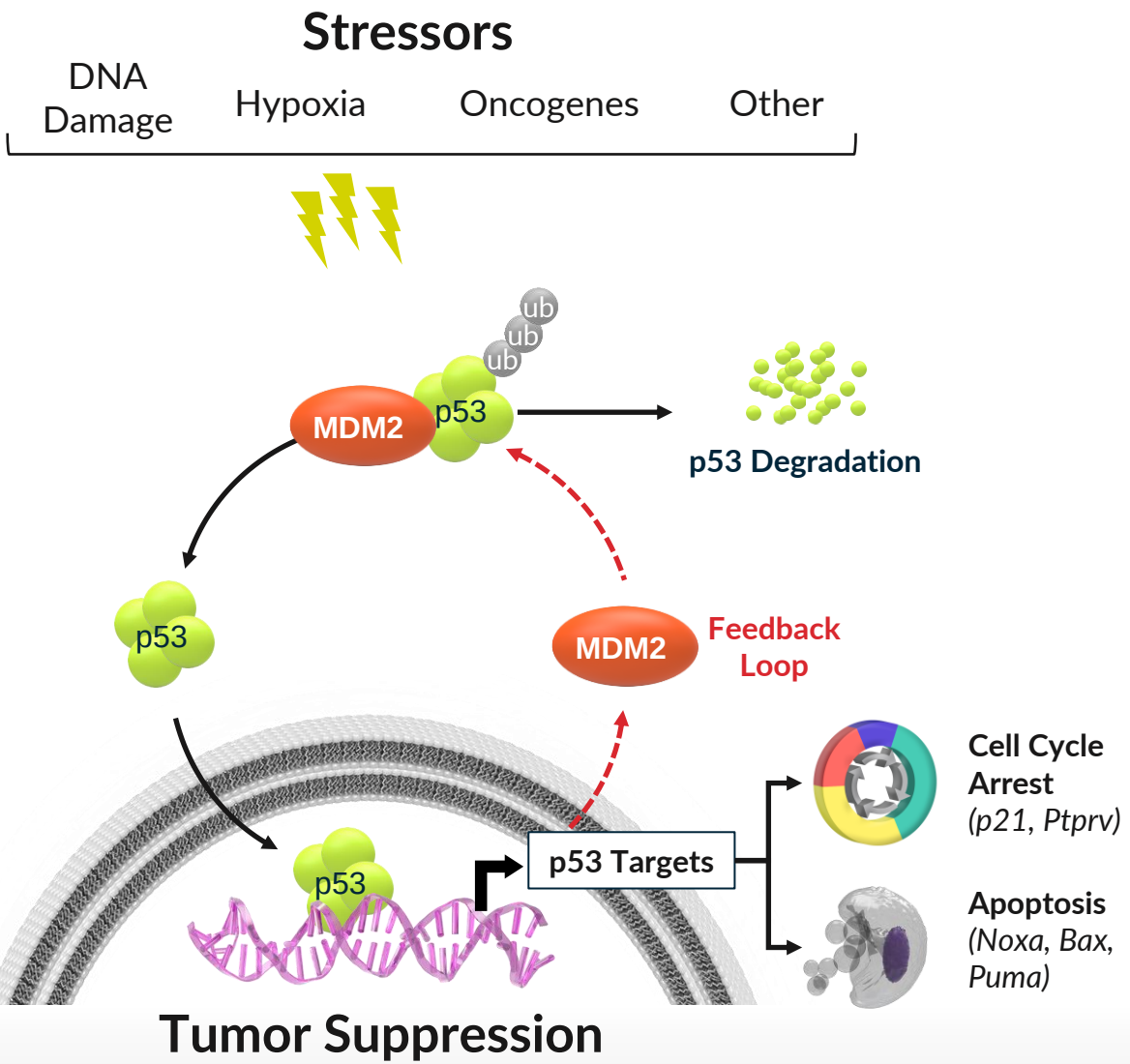


Treatment	EAE Incidence (%)	Median Day of Onset	End Score (+/- SD)
Vehicle	100.0%	13.0	2.71 +/- 0.69
1 mg/kg KT-6955	66.7%	23.0	0.75 +/- 0.92
3 mg/kg KT-6955	16.7%	>28.0*	0.29 +/- 0.69
10 mg/kg KT-6955	0.0%	>28.0*	0.00 +/- 0.00

MDM2

KYMERA

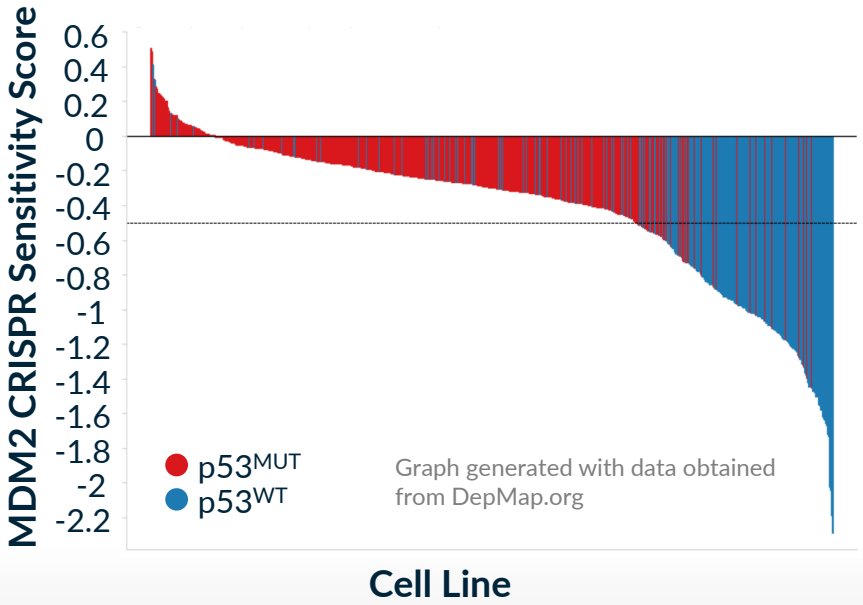
MDM2 is the E3 Ligase that Modulates P53, the Largest Tumor Suppressor



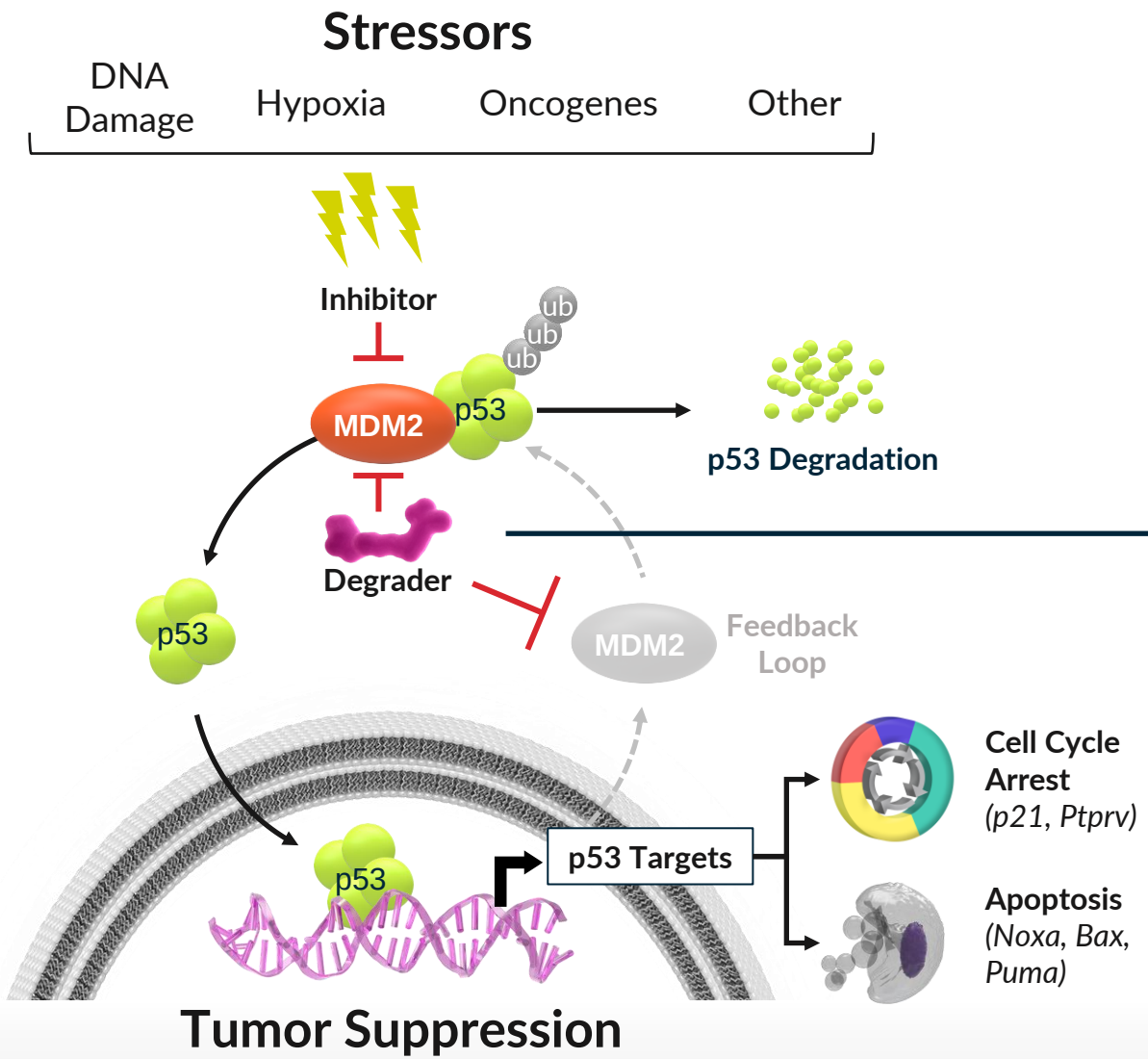
Cancer Genetics

- p53 is **NOT mutated** in almost 50% of tumors
- MDM2 overexpression and amplification can inactivate p53
- Large opportunity in wide variety of cancers

Dependency of p53^{WT} cells on MDM2



MDM2 Degradation, Not Inhibition, Efficiently Restores p53



Clinical Validation

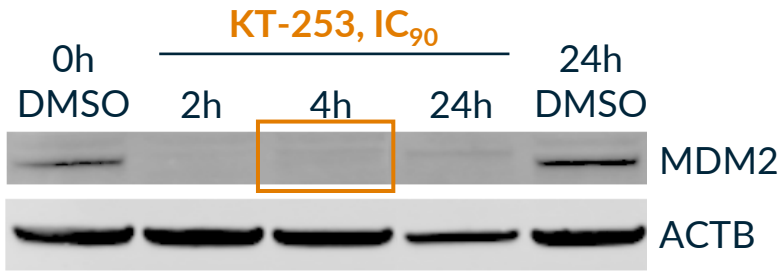
- **MDM2 small molecule inhibitors** of MDM2/p53 interaction **show activity in the clinic**..
- **...but they induce MDM2 feedback loop** resulting in limited impact on pathway

Degrader Advantage

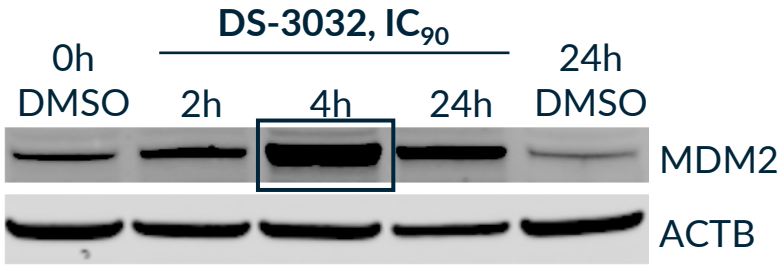
- **MDM2 degraders**, by removing the protein, **can overcome the p53-dependent feedback loop that upregulates MDM2**
- MDM2 degrader can induce an acute apoptotic response in tumor cells, **increasing efficacy and therapeutic index vs a small molecule inhibitor**

KT-253, Unlike Small Molecule Inhibitors, Overcome the MDM2 and p53 Autoregulatory Feedback Loop

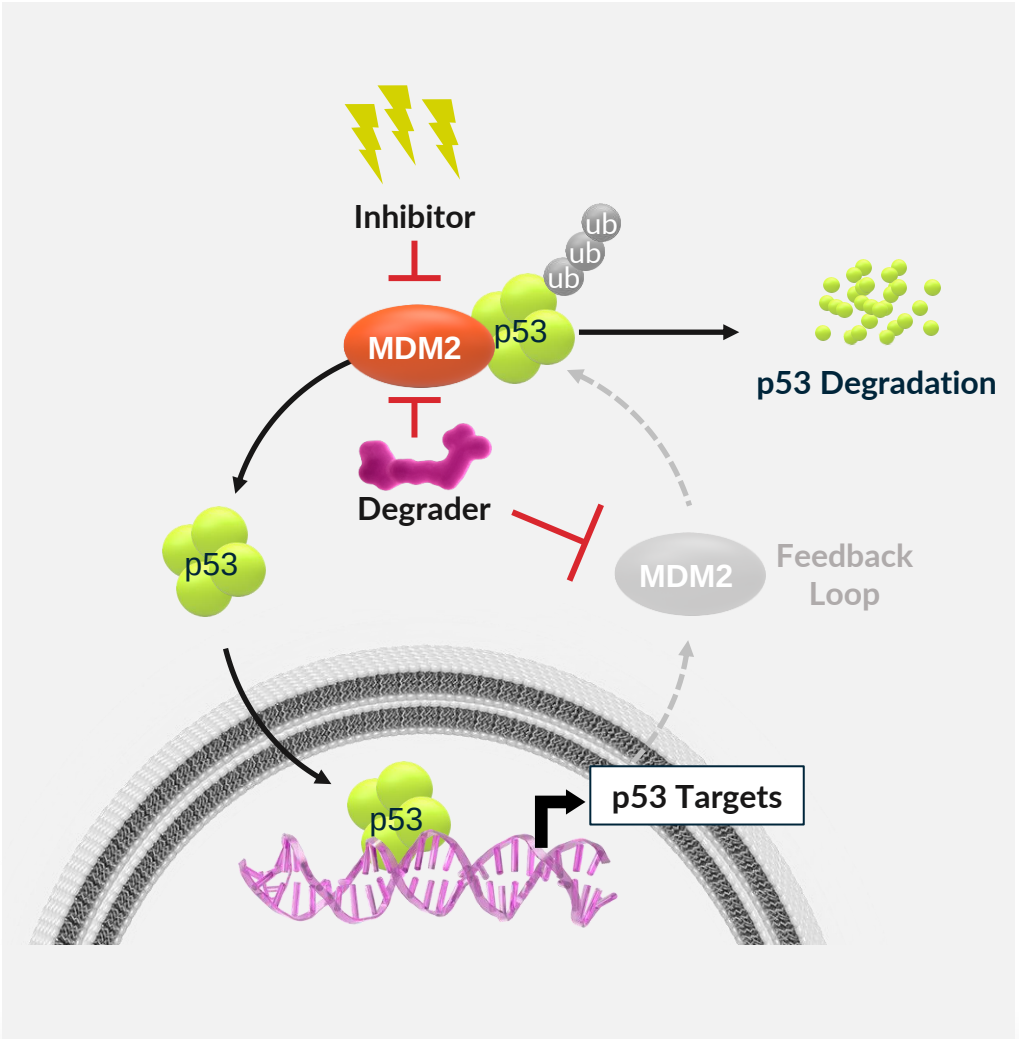
Degrader Overcomes MDM2 Feedback Loop



MDM2 levels are kept at undetectable levels with MDM2 degrader KT-253, leading to p53 stabilization

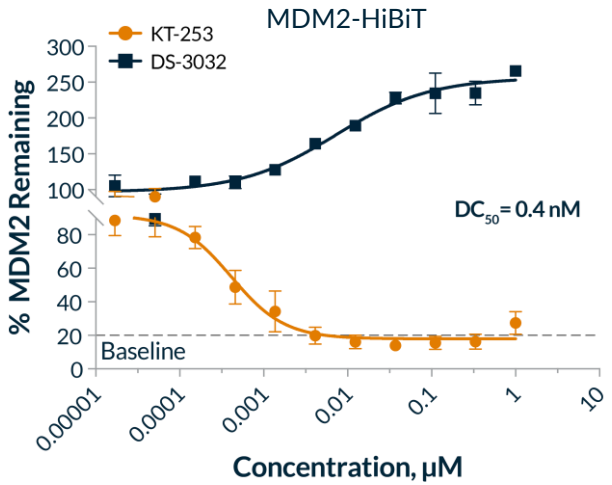


MDM2 levels are increased by the small molecule inhibitor (feedback loop), impairing p53 stabilization

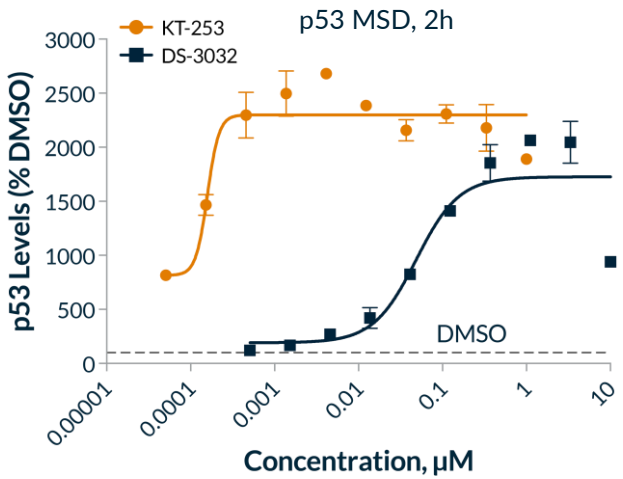


Kymera's MDM-2 Degrader Development Candidate, KT-253 is Superior to MDM2/p53 Small Molecule Inhibitors

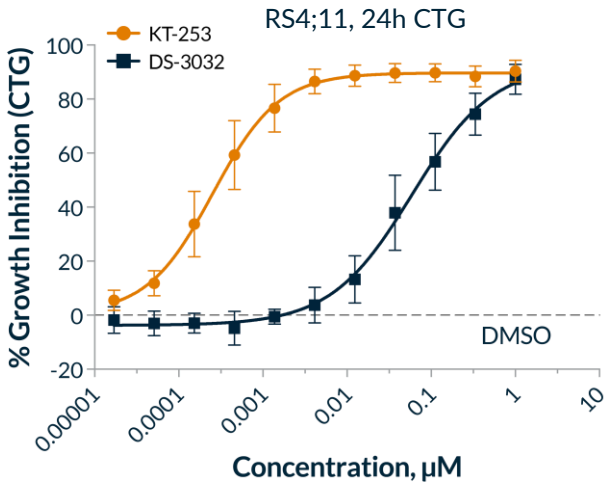
KT-253 is a potent MDM2 degrader



KT-253, unlike SMI's such as DS-3032, strongly stabilizes p53…



… which leads to superior tumor cell killing (pM range)



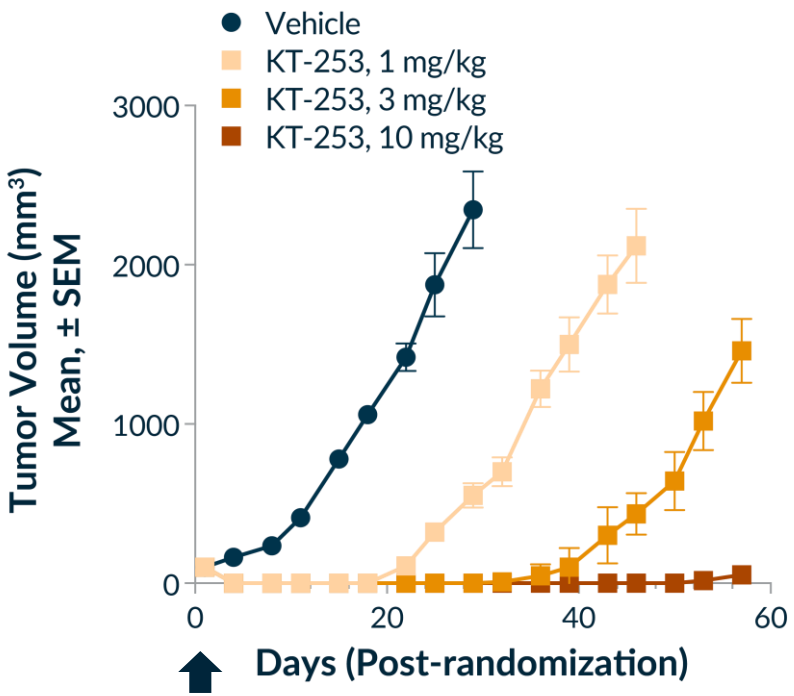
Compound	KT-253	DS-3032	RG7388	SAR405838	HDM201	AMG-232
Company	Kymera	Sankyo/Rain	Roche	Sanofi	Novartis	Amgen/Kartos
Clinical stage	IND enabling	Ph II / combo AML	Ph II / III	Paused	Ph I / II	Multiple Ph II; combo AML
RS4-11 IC_{50} (nM) (AML Cell Killing)	0.3	67	220	620	163	280
MDM2-HiBiT, DC_{50} (nM) (Degradation)	0.4	-	-	-	-	-

- KT-253 is **>200-fold more potent** in tumor cell killing assays than SMI's due to its mechanism of action
- Proteomics show selective degradation of KT-253

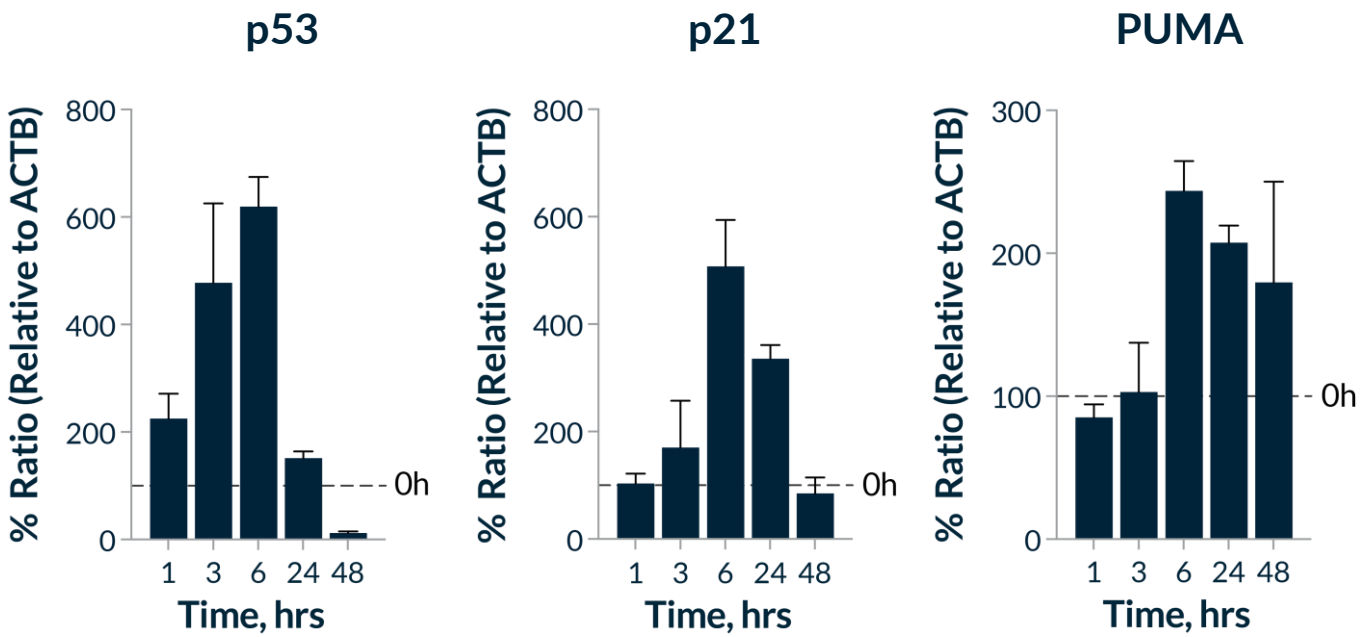
Single Dose of KT-253 Leads to Sustained Tumor Regression

Single Dose of KT-253 Achieves Sustained Tumor Regression

Rs4;11 XGs



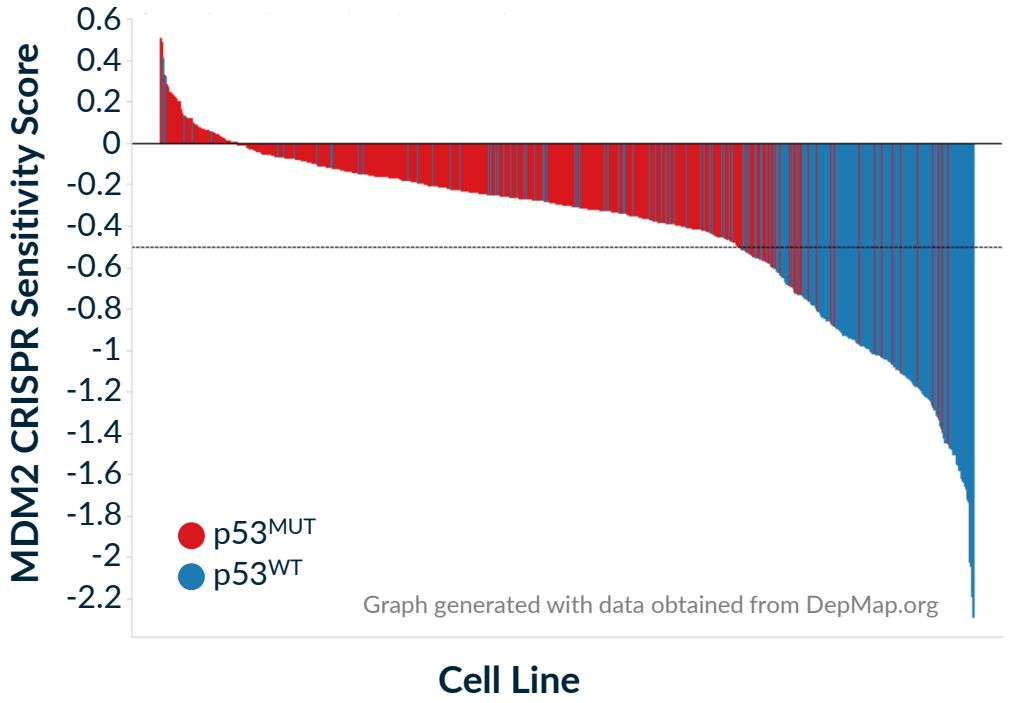
MDM2 Degradation (KT-253, 1 mg/kg) Leads to Fast Increase in p53, p21, and PUMA (Key Apoptotic Biomarker)



- Clinical equivalent doses of small molecule inhibitors have no significant *in vivo* impact in these xenograft models

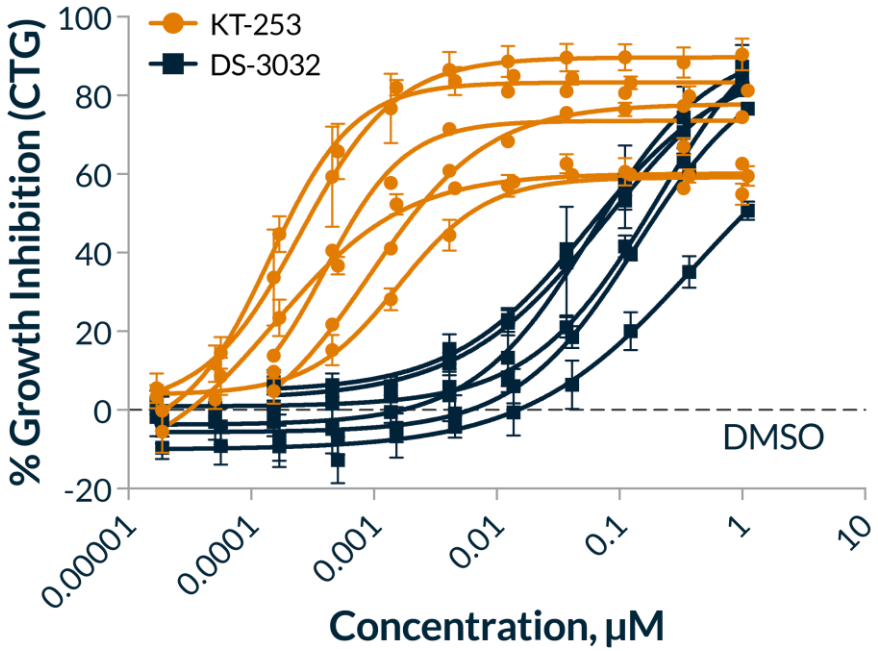
MDM2 Dependency Seen Across a Large Subset of Tumor Types Large Franchise Potential in Liquid and Solid Tumors

Dependency of p53^{WT} Cell Lines on MDM2



MDM2 Degrader Superior to SMI Across Cell Line Panel

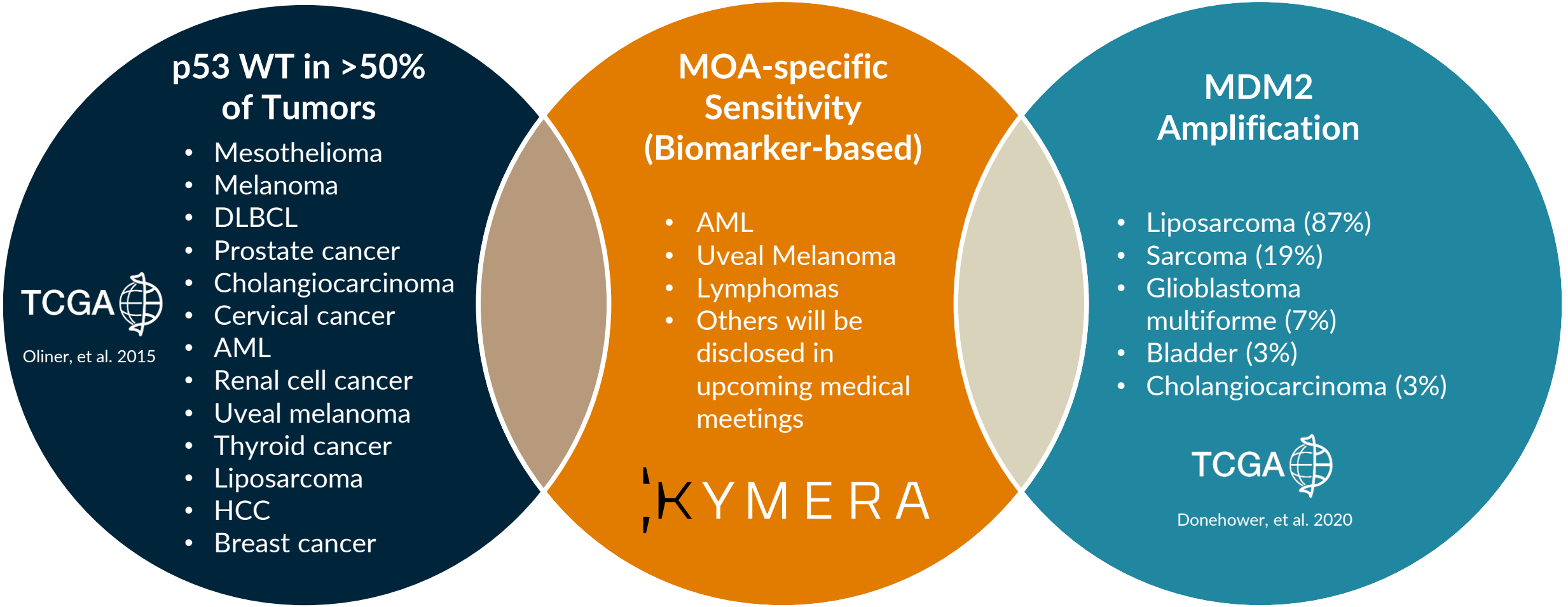
Heme & Solid Cell Lines



Tumor Types: Uveal melanoma, Bile Duct, Bladder, Bone, Brain, Breast, Colon, Endometrial/Uterine, Gastric, Kidney, Liver, Lung, Ovarian, Pancreatic, Rhabdoid, Sarcoma, Leukemia, Lymphoma

p53WT cell lines sensitive: ALL, AML, DLBCL, Uveal Melanoma
p53 mutant cell lines were not sensitive to KT-253 or DS-3032 as expected

Focus on Indications Where MDM2 Degradation Leads to Acute Apoptotic Response



KT-253 is a Potent MDM2 Degrader and a Best-in-Class p53 Stabilizer with Potential to Treat Numerous p53 WT Tumors

- KT-253 inhibits tumor cell growth with **picomolar potency** and is more **than 200-fold more potent** than clinically active MDM2 small molecule inhibitors
- KT-253, unlike small molecule inhibitors, **blocks the feedback loop** which up-regulates MDM2 production and in doing so more effectively stabilizes the tumor suppressor p53
- **Short term high exposures of KT-253** are enough to induce apoptosis in cell lines and *in vivo* xenografts, which ensures high activity and improved therapeutic index vs SMI's
- Broad franchise opportunities available for this mechanism (p53 WT is present in >50% tumors), Kymera is focused on indications with **specific sensitivity to degrader mechanism**, such as AML, Uveal melanoma and others through a biomarker strategy
- Projected IND filing in **2022**

Pegasus™ Platform and R&D Approach

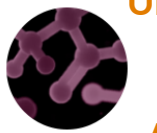
KYMERA

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



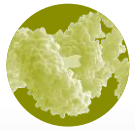
Understanding Degradation (PK/PD) Across Tissue Types

- **Quantitative System Pharmacology Model**
- Understanding and **Translating PK/PD** from preclinical systems into humans

Proprietary Chemistry

- **Comprehensive hit finding technologies toolbox**
- **Proprietary chemistry expertise, AI enabled optimization**
- Ability to convert into **degraders with optimal pharmaceutical properties**

NEW



Center for Molecular Glue Discovery

- **Identification of novel E3 ligases** to degrade high value “undrugged and un-ligandable” proteins
- **With external collaborators** enable differentiated approach to molecular glues discovery

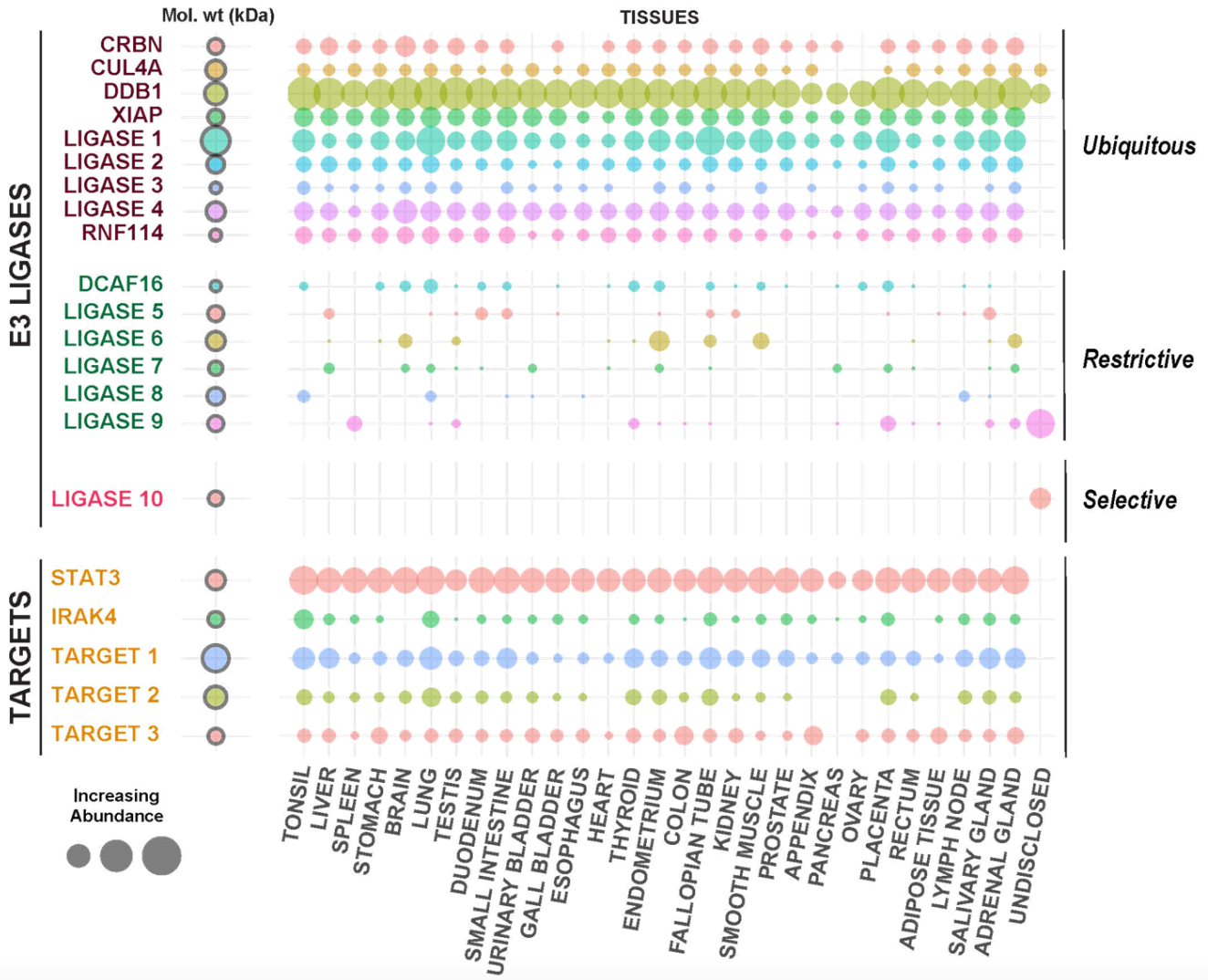
Novel E3 Ligases to Drug a New Generation of Targets

TR

Clinically Validated Targets Unlocked by E3 Ligase Differential Expression

On target unwanted pharmacology limits clinical application

- 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 via a machine learning algorithm
- Vision to develop tissue-selective or tissue-restricted degraders to enable novel therapeutic opportunities

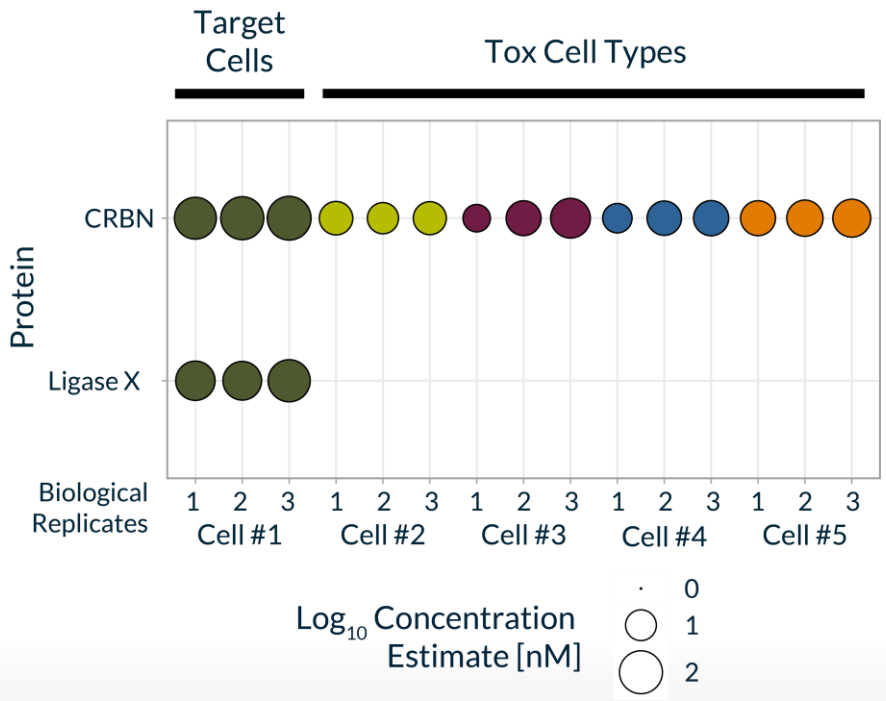


Source: Kymera's Proprietary E3 Expression Atlas

Kymera has Engaged a Broadly Expressed Protein in Only One Cell Type Using a Tissue Selective E3 Ligase

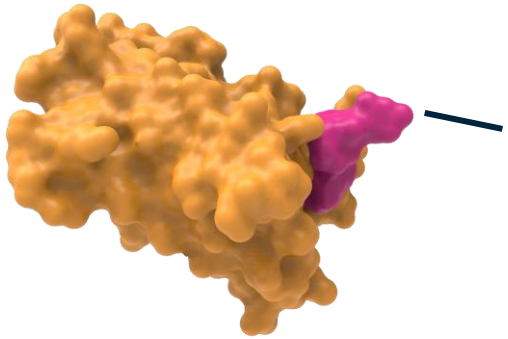
Kymera Has Identified an E3 Ligase that is Expressed Almost Exclusively in One Cell Population

Protein Expression Profile (Proprietary E3 Atlas)



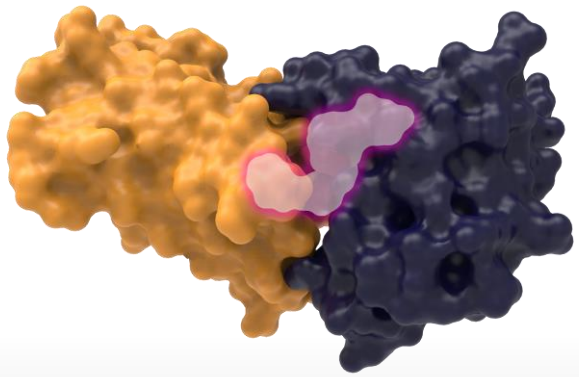
Ligand Identification and Optimization

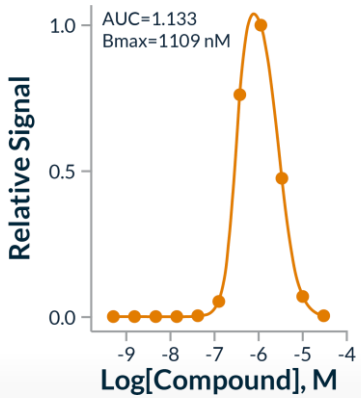
Small Molecule Ligand Bound to a Tissue-selective E3 Ligase



Lead Compound
Affinity K_D = < 1 uM

Leads to an Active Ternary Complex with a Protein of Interest

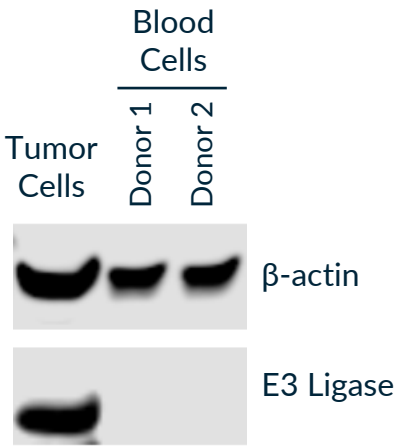




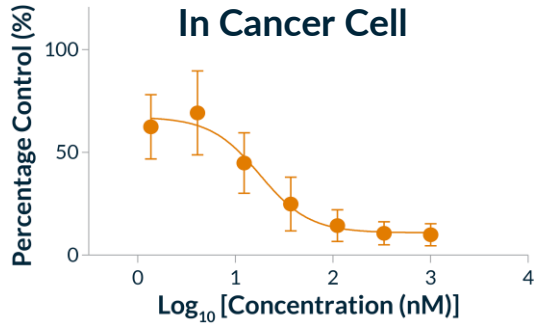
Tissue-Selective Degradation Drives Increase of Therapeutic Index

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

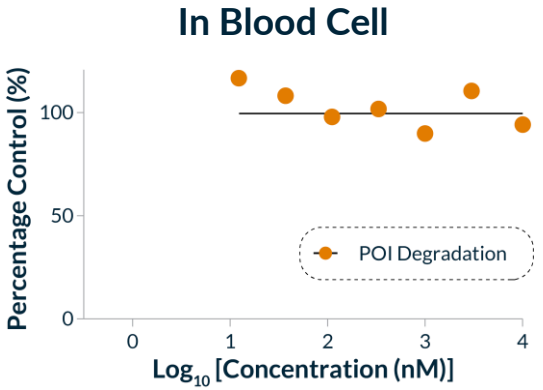
E3 Ligase is Almost Absent in One Blood Cell Type



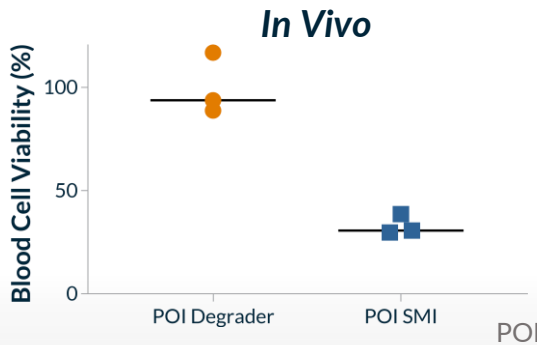
Optimization and Degrader Program



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



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

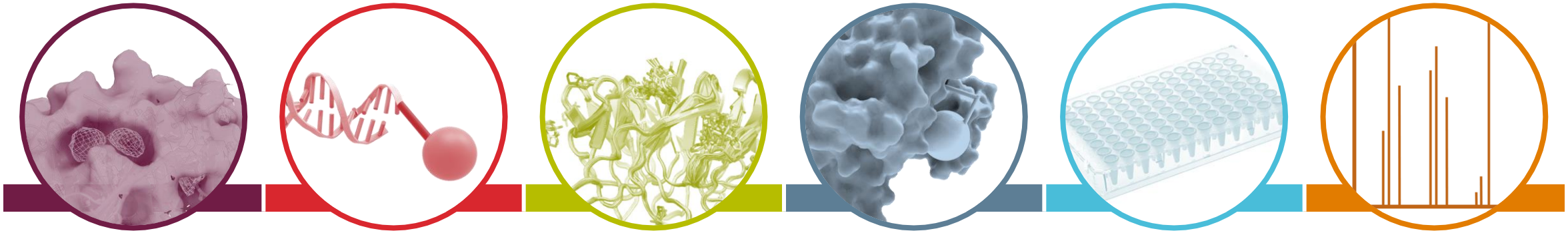


In a pharmacologically active dose *in vivo* a **degrader allows blood cells to survive** while SMI leads to substantial cell death

- This program is projected to nominate a development candidate in 2022

POI = protein target of interest

A Comprehensive Hit Finding Toolbox Rapidly Enables New Ligand Discovery Against All Target Classes



Virtual Screen

Criteria
- Availability of structure or homology model

Approaches
- DB ~8 million purchasable cpds
- Cloud enables screen < 24hrs
- AI to improve enrichment

DEL

Criteria
- High quality protein
- Ideal QC profile (single-species by SEC; <5% aggregation by DLS)

Fragment-Based Screen

Criteria
- Availability of high quality (crystallization-grade) protein
- Robust crystallization system

Approaches
- SPR, NMR
- X-ray
- LC/MS (covalent)

Cysteine Covalent Screening

Criteria
- Proteins have reactive cysteines

Approaches
- Covalent fragment screening on recombinant protein
- Whole cell covalent fragment screening

HTS

Criteria
- Available high-throughput assay format

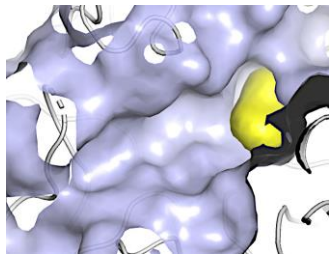
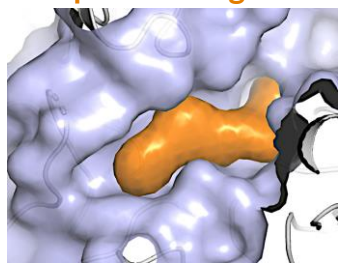
Approaches
- Focused library
- Diversity set

ASMS

Criteria
- Availability of high-quality protein

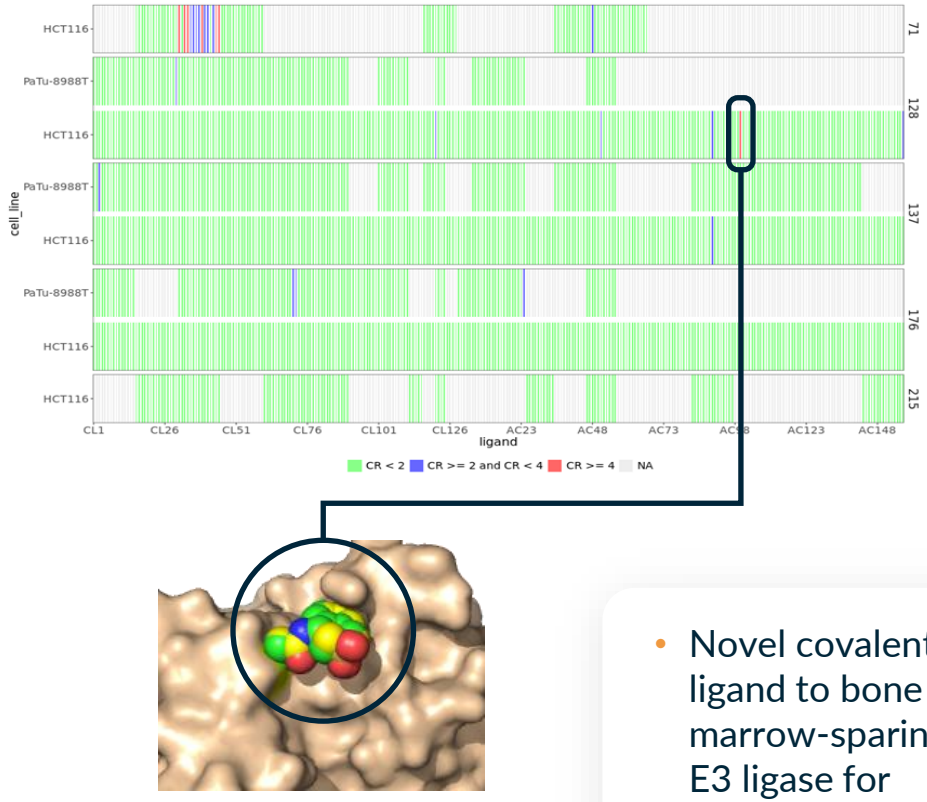
Successful Examples of Fragment and Covalent Screens

Fragment Based Virtual Optimization

	HTRF	X-ray with Fragment
Fragment bound X-ray structure	IC_{50} > 1 mM	
Rational design to explore SAR	IC_{50} < 30 µM	
In silico library evaluation & synthesis	IC_{50} < 5 µM	X-ray with Optimized Ligand 
Rational design to optimize library hits	IC_{50} = < 0.1 µM MW <400 clogP 0.7	

Total # of virtual compounds evaluated	40K
Total # of crystal structures	18
Total # of compounds made	195

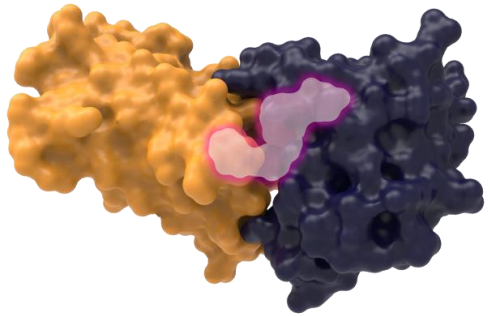
Covalent Ligand E3 Ligase Hit Finding



- Novel covalent ligand to bone marrow-sparing E3 ligase for multiple oncology programs

Kymera Can Develop Degraders with Predictable Drug-Like Properties

Pre-clinical Optimization of Degraders Leads to High Oral Bioavailability Across Pre-clinical Species



Ternary Complex Modeling (TCM)

Harnessing the power of cloud computing and AI to evaluate millions of TCM models

Molecular Chameleonicity

Accurately capturing the chameleonic nature of degraders to predict ADME/PK profile

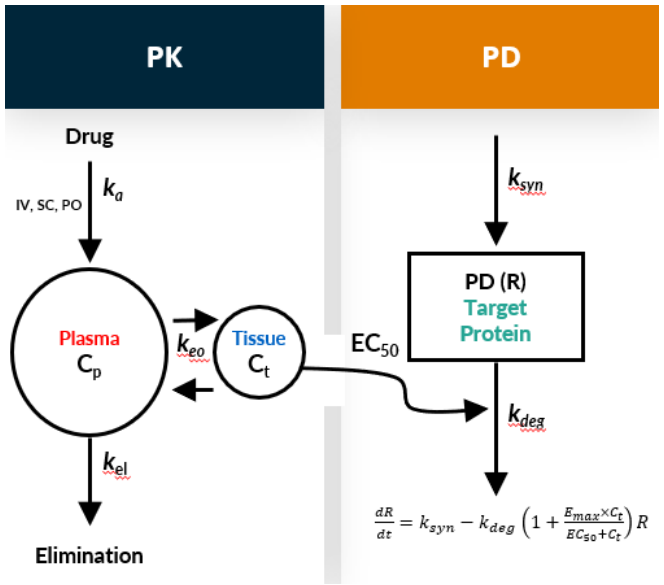
AI-driven Insights

Leveraging deep-learning to derive design insights from *in silico* and *in vitro* data

DMPK Properties	Degrader 1	Degrader 2	Degrader 3	Degrader 4
HLM / RLM (μL/min/mg)	317 / 193	74 / 22	<12 / <12	<12 / <12
P_{app} (10^{-6} cm/s) / Efflux Ratio	ND / ND	6.0 / 1.3	14 / 21	4.3 / 2.0
Rat Cl (mL/min/kg) / Vdss / F%	ND	35 / 9 / 8	19 / 7 / 14	7 / 3 / 18
Dog Cl (mL/min/kg) / Vdss / F%	ND	69 / 19 / 9	15 / 11 / 58	6 / 4 / 60
Monkey Cl (mL/min/kg) / Vdss / F%	ND	129 / 16 / 1	33 / 16 / 45	9 / 6 / 62

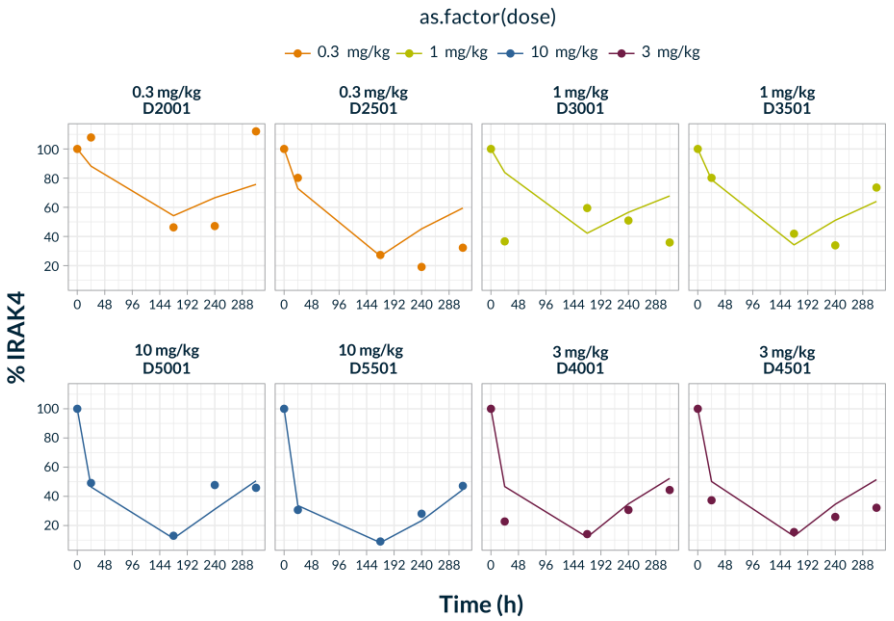
Mechanistic Modeling Allowed Kymera to Accurately Predict Human PK and PD from Preclinical Dog Data for Clinical Candidate KT-474

Mechanistic PK/PD Modeling Describes the MoA of TPD

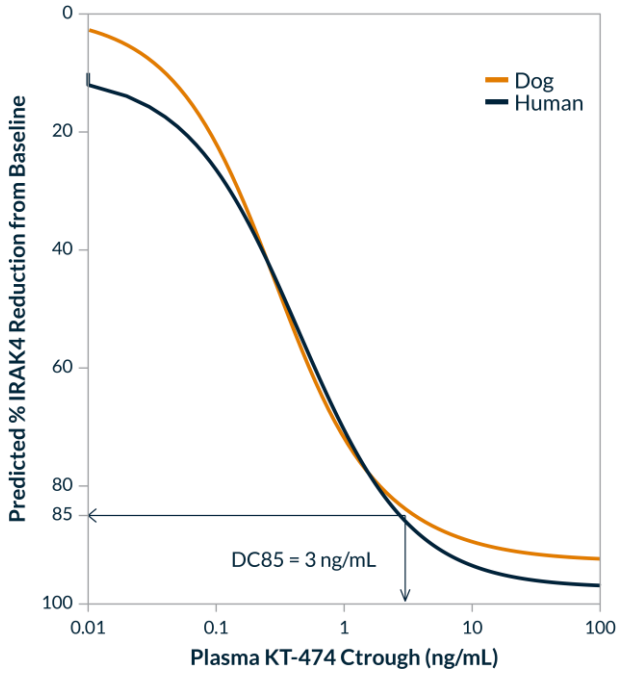


Preclinical Species Models for PK/PD

KT-474 in Dog



Model Predicts Human PK/PD



Rationally Designing Molecular Glues to Drug Historically Undrugged/Unligandable Targets

To drug all genetically validated but **undrugged and un-ligandable** proteins through the discovery of novel E3 ligases and small molecule glues

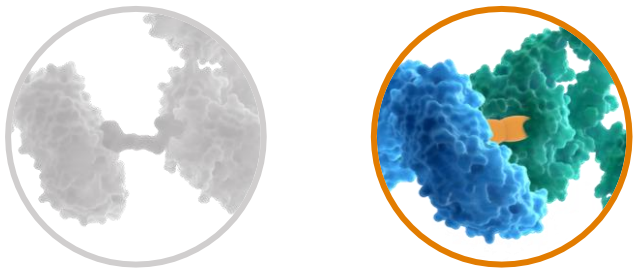
UD

Undrugged Targets

No other technology can drug

Ligandable Proteins
e.g. STAT3

Un-ligandable Proteins
e.g. other transcription factors



Heterobifunctional Degraders

Molecular Glues

Our Approach:

- We are **NOT** iterating on CRBN/IMiD Scaffold
- Identifying the best matched pairs between targets of interests and E3 ligases exploiting **natural affinity augmented with small molecule glues**
- Established a platform that uses high content genetic-based screens, structural insights, biological pathways deconvolution, degron discovery, computational knowledge expansion
- Multiple programs in discovery stage
- Strategic partnerships with:

A-ALPHA BIO

UNIVERSITY of WASHINGTON

NYU

Expanding the Druggable Proteome with TPD

- Kymera intends to drug **all target classes** using targeted protein degradation
- A comprehensive **hit finding toolbox** has been developed to identify ligands against novel E3 and undrugged targets
- Our capabilities have evolved to **accurately predict human active doses** and compound properties
- We have developed **know-how and technologies** to drug **inadequately drugged** targets such as IRAK4 and MDM2, **undrugged targets** such as STAT3 and have for the first time in TPD drugged targets in a **tissue selective manner** using our E3 ligase toolbox.
- Kymera has established a new discovery unit to identify **new molecular glue degrader drugs** focused on undrugged/un-ligandable high value protein targets
- Multiple **strategic collaborations** have been established to enable MG Discovery

KYMERA
EST. 2016

Thank You

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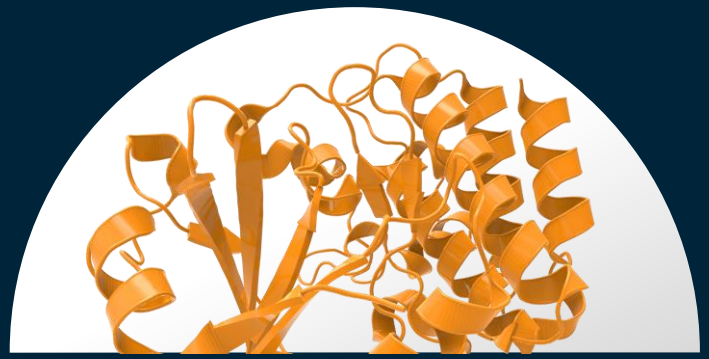
Photography courtesy of Nasdaq, Inc.

Appendix – IRAK4

KYMERA

IRAK4 Degradation vs Inhibition
Overview

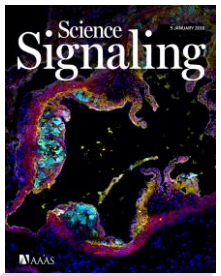


We and others have shown that IRAK4 degradation **is required to block IL1R/TLR pathway activation,** especially in high-inflammatory states where small molecule kinase inhibitors fail

- IRAK4 KO is able **to block TLR activation** unlike the kinase dead rescue (*Slide 64*)
- IRAK4 **scaffolding function** is critical in Myddosome formation and pathway signaling (*Slide 65*)
- IRAK4 degradation, but not kinase inhibition, can **block TLR induced NF-κB translocation** (*Slide 66*)
- IRAK4 degradation, but not kinase inhibition, can **block IL1R+TLR activation** (*Slides 67, 68*)
- IRAK4 degradation is superior to kinase inhibition at **blocking downstream phosphoproteome** (*Slide 69*)
- IRAK4 degradation **is active in all blood cell types** in HS patients while SMI can increase IRAK4 levels (*Slide 70*)
- IRAK4 degradation is superior to inhibition in a **variety of preclinical efficacy models** (*Slide 71*)

IRAK4 KO/Degradation Differentiated Over Kinase Inhibition in TLR Activation – External Data

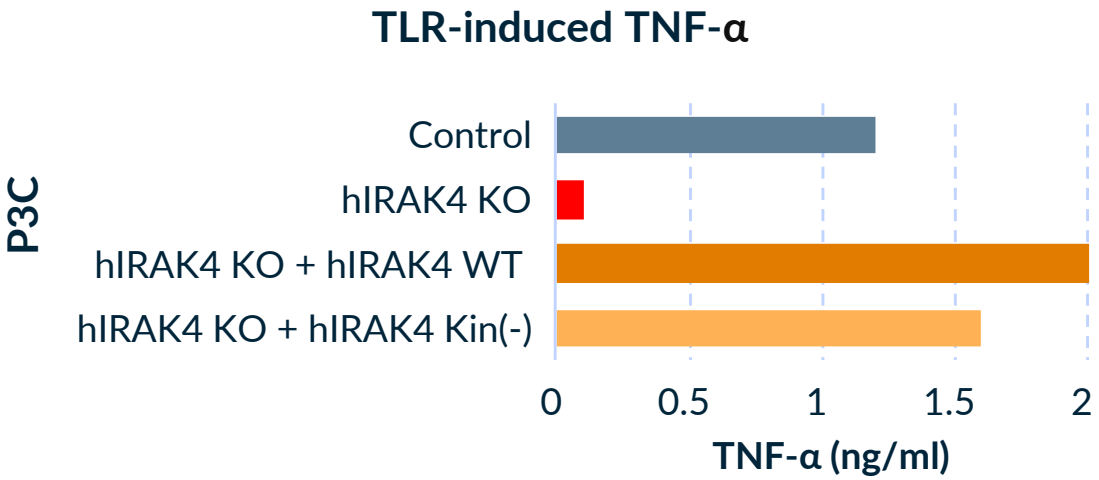
Science Signaling



Comprehensive RNAi-based screening of human and mouse TLR pathways identifies species-specific preferences in signaling protein use

JING SUN, NING LI, KYU-SEON OH, BHASKAR DUTTA, SHARAT J. VAYTTADEN, BIN LIN, THOMAS S. EBERT, DOMINIC DE NARDO, JOIE DAVIS, RUSTAM BAGIRZADEH, NICOLAS W. LOUNSBURY, CHANDRASHEKHAR PASARE, EICKE LATZ, VEIT HORNUNG, AND IAIN D. C. FRASER

Toll-like receptors (TLRs) are a major class of pattern recognition receptors, which mediate the responses of innate immune cells to microbial stimuli. To systematically determine the roles of proteins in canonical TLR signaling pathways, we conducted an RNA interference (RNAi)–based screen in human and mouse macrophages. We observed a pattern of conserved signaling module dependencies across species, but found notable species-specific requirements at the level of individual proteins. Among these, we identified unexpected differences in the involvement of members of the interleukin-1 receptor–associated kinase (IRAK) family between the human and mouse TLR pathways. Whereas TLR signaling in mouse macrophages depended primarily on IRAK4 and IRAK2, with little or no role for IRAK1, TLR signaling and proinflammatory cytokine production in human macrophages depended on IRAK1, with knockdown of IRAK4 or IRAK2 having less of an effect. Consistent with species-specific roles for these kinases, IRAK4 orthologs failed to rescue signaling in IRAK4-deficient macrophages from the other species, and only mouse macrophages required the kinase activity of IRAK4 to mediate TLR responses. The identification of a critical role for IRAK1 in TLR signaling in humans could potentially explain the association of IRAK1 with several autoimmune diseases. Furthermore, this study demonstrated how systematic screening can be used to identify important characteristics of innate immune responses across species, which could optimize therapeutic targeting to manipulate human TLR-dependent outputs.



- IRAK4 KO has a strong response to TLR activation
- A kinase dead and a WT rescue behave similarly
- This demonstrate that kinase function has no impact on TLR activation response

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

Scaffolding Function of IRAK4 is Critical for Myddosome Formation – External Data

JCB Journal of Cell Biology

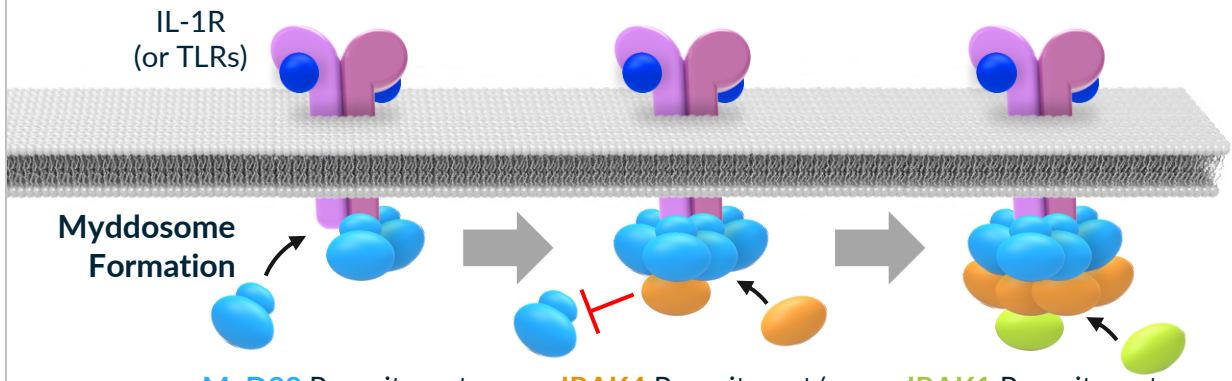
MyD88 oligomer size functions as a physical threshold to trigger IL1R Myddosome signaling

Rafael Deliz-Aguirre*, Fakun Cao*, Fenja H.U. Gerpott, Nichanok Auevechanichkul, Mariam Chupanova, YeVin Mun, Elke Ziska, and Marcus J. Taylor

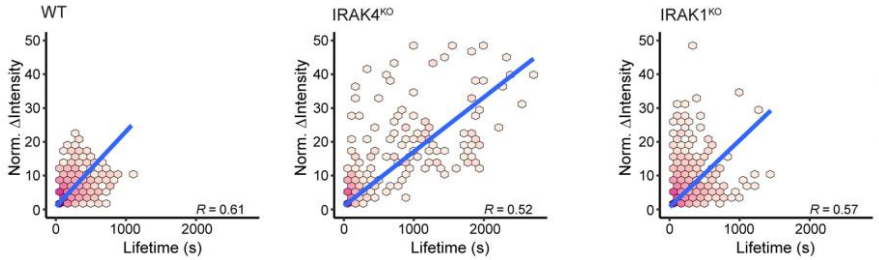
A recurring feature of innate immune receptor signaling is the self-assembly of signaling proteins into oligomeric complexes. The Myddosome is an oligomeric complex that is required to transmit inflammatory signals from TLR/IL1Rs and consists of MyD88 and IRAK family kinases. However, the molecular basis for how Myddosome proteins self-assemble and regulate intracellular signaling remains poorly understood. Here, we developed a novel assay to analyze the spatiotemporal dynamics of IL1R and Myddosome signaling in live cells. We found that MyD88 oligomerization is inducible and initially reversible. Moreover, the formation of larger, stable oligomers consisting of more than four MyD88s triggers the sequential recruitment of IRAK4 and IRAK1. Notably, genetic knockout of IRAK4 enhanced MyD88 oligomerization, indicating that IRAK4 controls MyD88 oligomer size and growth. MyD88 oligomer size thus functions as a physical threshold to trigger downstream signaling. These results provide a mechanistic basis for how protein oligomerization might function in cell signaling pathways.

"…indicating that IRAK4 controls MyD88 oligomer size and growth. MyD88 oligomer size thus functions as a physical threshold to trigger downstream signaling."

IRAK4 Scaffolding Role Functions to Limit MYD88 Oligomer Size and Trigger Myddosome Formation



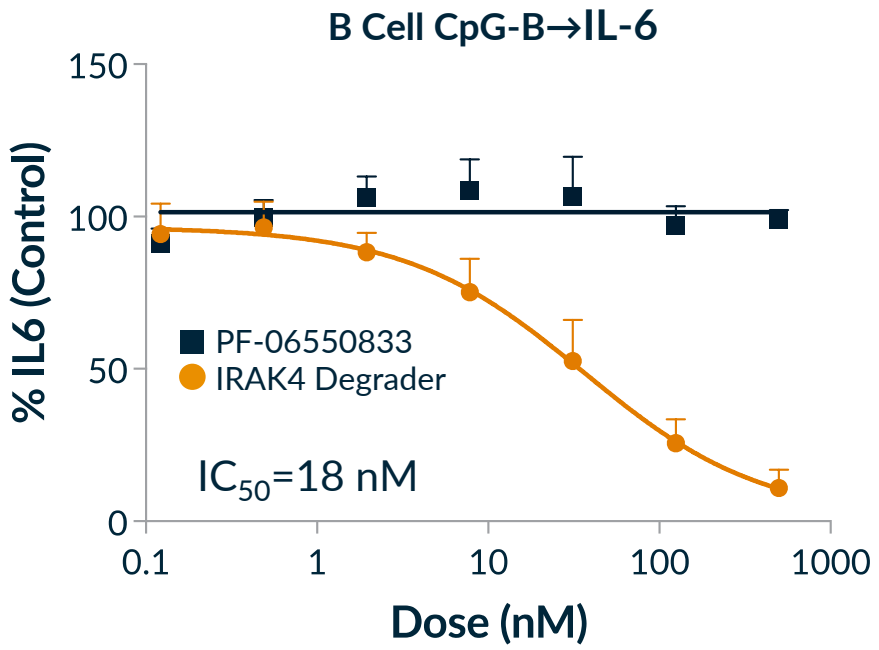
- IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation
- Macromolecular assembly of proteins **in itself** can be considered a signal transduction step

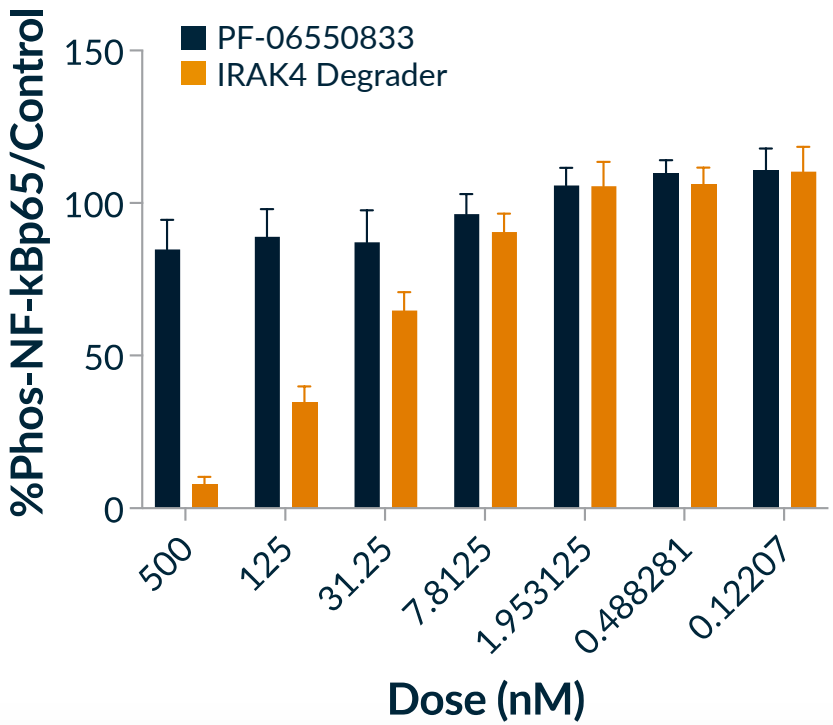


Source: Deliz-Aguirre, et al. *J. Cell Biol.*, 2021

Scaffolding Function of IRAK4 is Critical for Pathway Signaling Through NF-κB – Kymera Data

IRAK4 Scaffolding Function, Not Kinase Activity, is Required for TLR9-mediated Activation of NF-κB in Human B cells

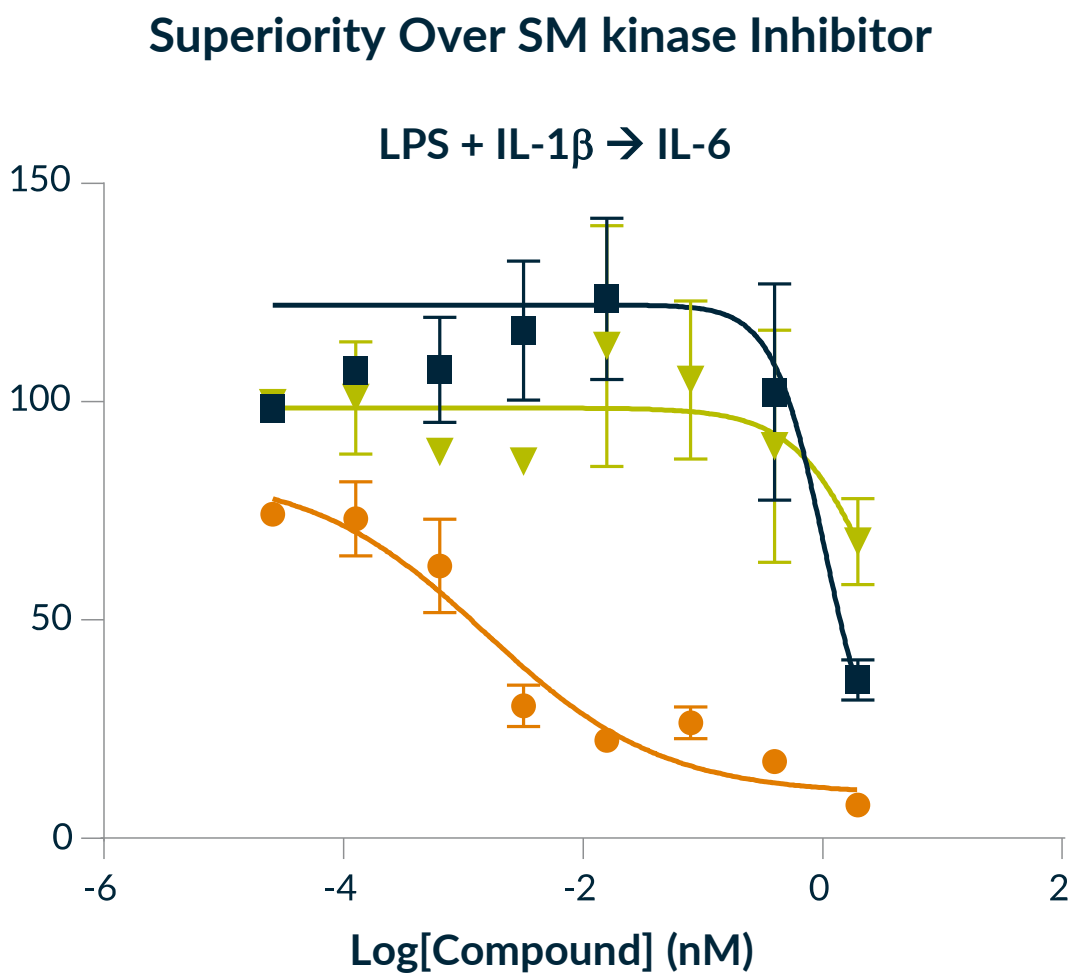




- IRAK4 degradation leads to inhibition of TLR9/ CpG-B induced phos-p65 and IL-6

- Pathway engagement result in downstream signaling that include NF-κB which only a degrader can block.

Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition – Kymera Data

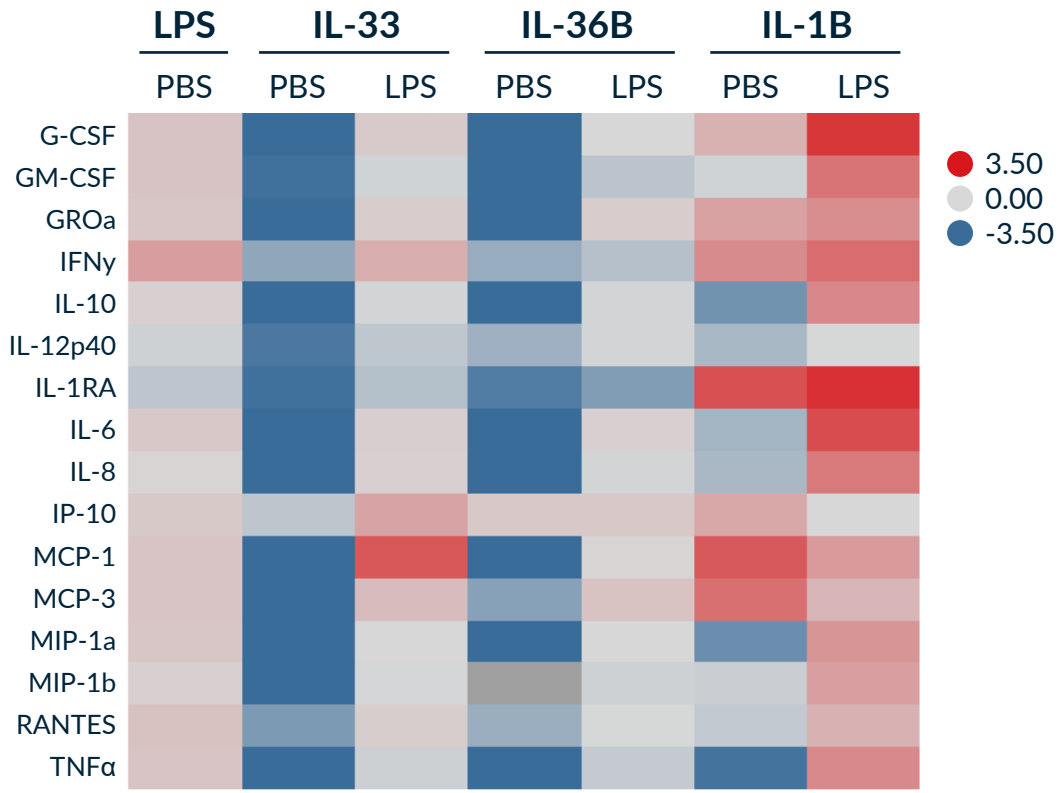


Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

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

Degrader More Effective than Kinase Inhibitors Against Cytokine/Chemokine Induction by IL-1b + LPS – Kymera Data

IL-1β+LPS Combination Induces Enhanced Levels of Inflammation

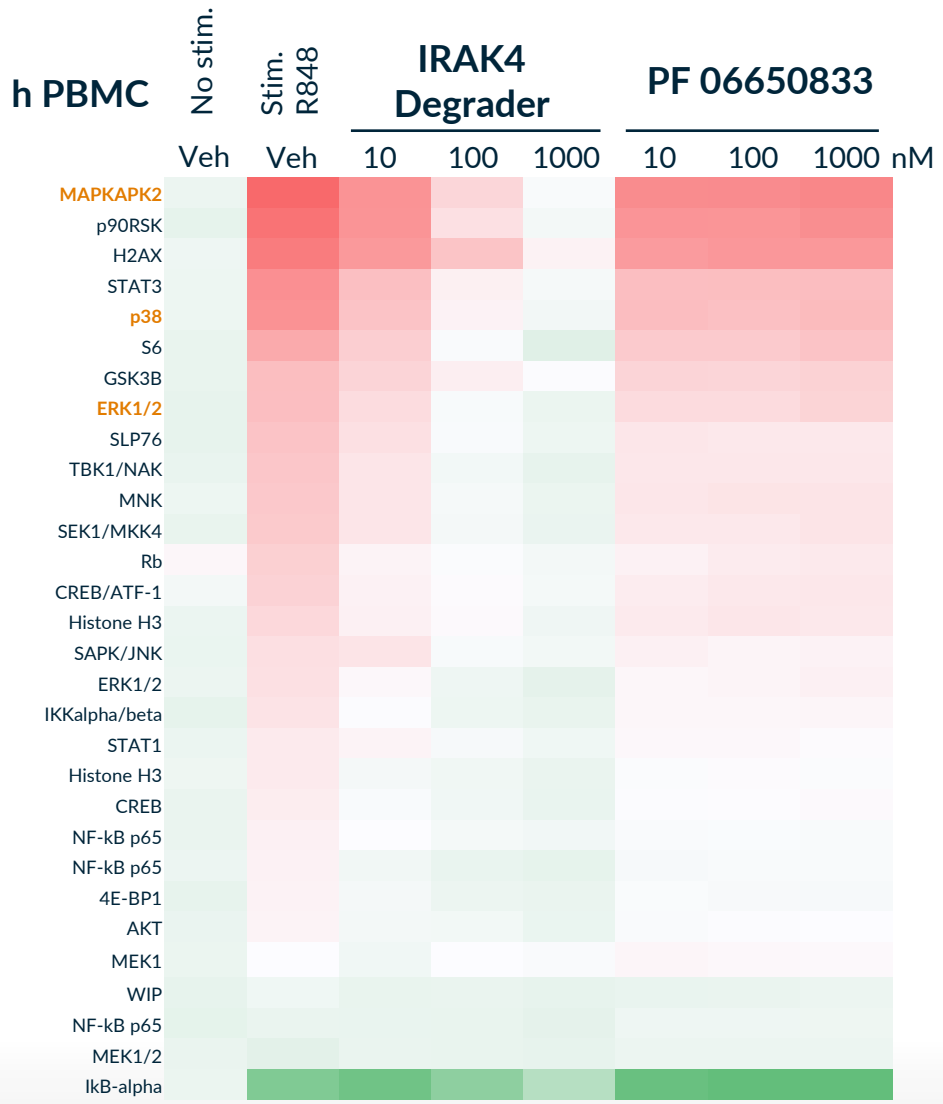


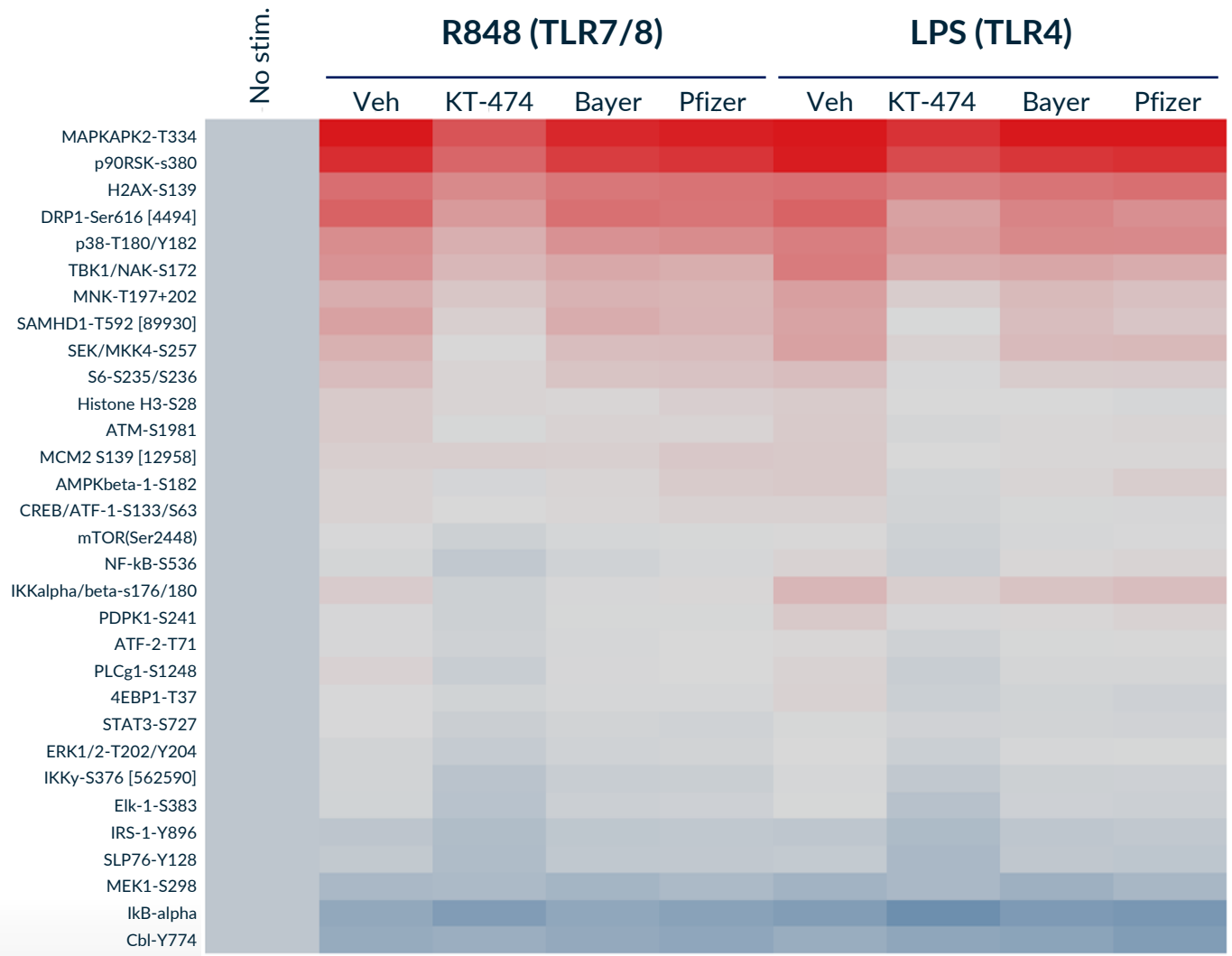
Only IRAK4 Degrader Can Block Pathway Stimulated by IL-1B + LPS

Cytokine/ Chemokine Induced by IL-1b + LPS	IRAK4 Degrader [IC_{50}] nM	E3-ve Control [IC_{50}] nM	PF-06550833 [IC_{50}] nM	BAYER Inh. [IC_{50}] nM
IL-6	**0.8**	427.5	>2000	>2000
IL-8	**0.08**	>2000	1400	>2000
G-CSF	**0.5**	>2000	>2000	>2000
GM-CSF	**2.6**	161.6	8.1	464.9
CXCL1 (GROα)	**76.4**	1100	>2000	>2000
CCL3 (MIP-1α)	**42.3**	1977	>2000	>2000

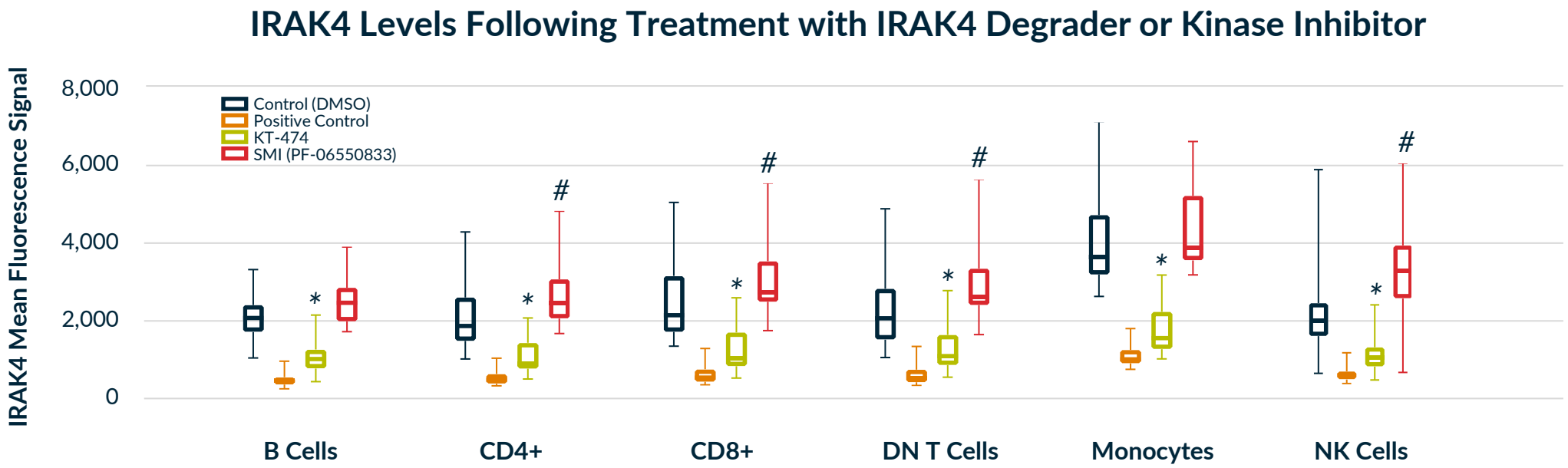
E3-ve Control = an IRAK4 degrader molecule that is not enabled to degrade IRAK4 and functions as an inhibitor

IRAK4 Degradation Reverses Phosphoproteomic Response to Pathway Action Unlike SMI





IRAK4 Degrader Downregulates IRAK4; SMI can Increase it in HS Patients Blood – Non-Interventional Study Data Kymera



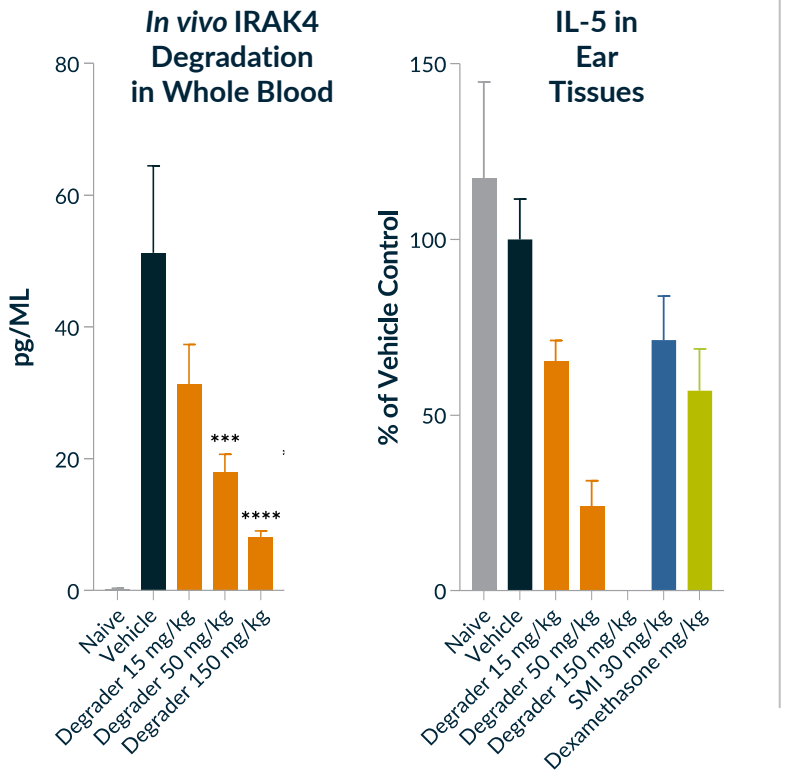
N=30 patients, One-way ANOVA* KT-474 vs DMSO Control p≤0.0001, #SMI (PF-06550833) vs DMSO Control p≤0.02
Positive Control: cells treated with IRAK4 blocking antibody prior to IRAK4 staining

KEY TAKEAWAYS

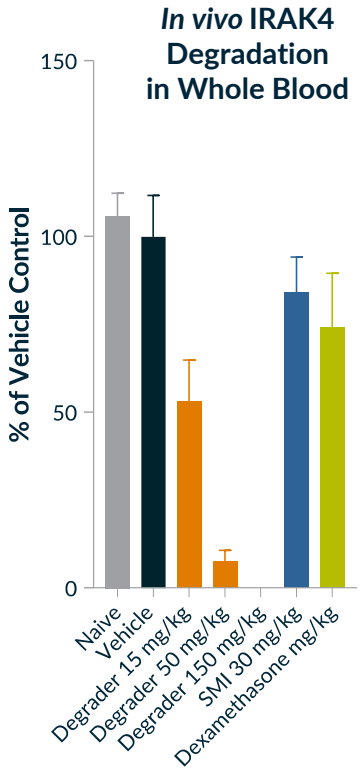
- *Ex vivo* incubation of HS blood with KT-474 reduced IRAK4 to a level approaching the lower limits of detection across all PBMC subsets, irrespective of baseline expression intensity, whereas an IRAK4 kinase inhibitor increased IRAK4 levels in T and NK cells
- **Treatment with an IRAK4 kinase inhibitor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

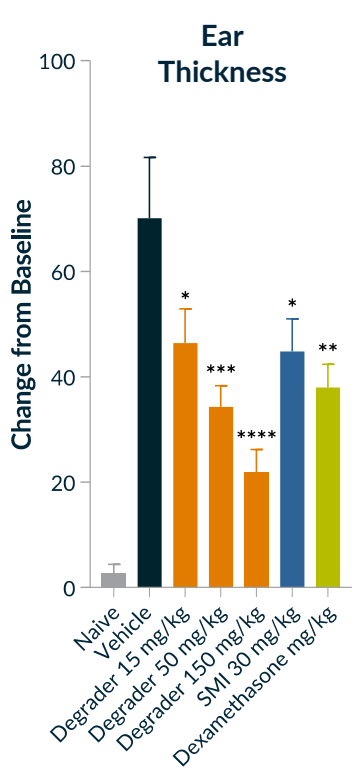
KT-474 is Superior to IRAK4 Small Molecule Inhibitor (SMI) Across Multiple Preclinical Immune-inflammatory *in vivo* Models

rmIL-33 Intradermal Challenge Model

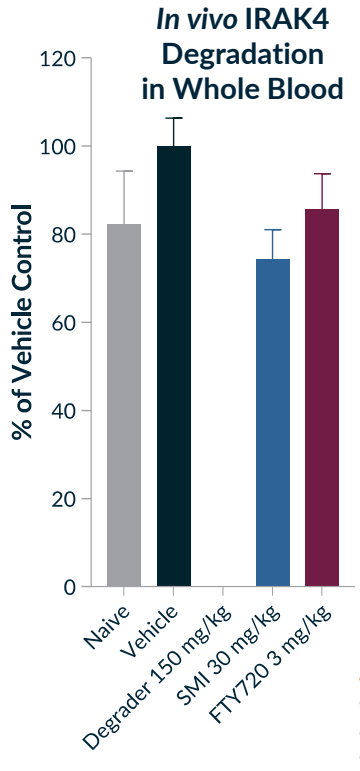


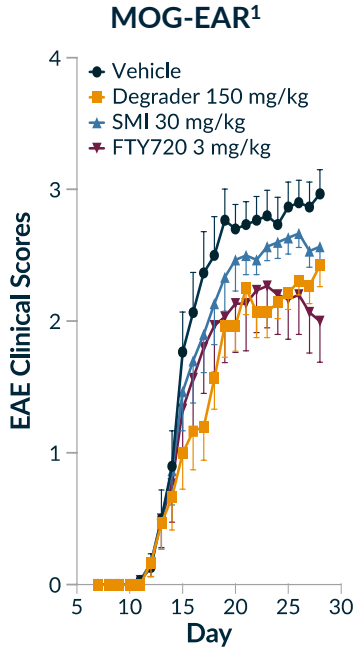
rhIL-36αβγ Intradermal Challenge Model





Th17-mediated Multiple Sclerosis Model





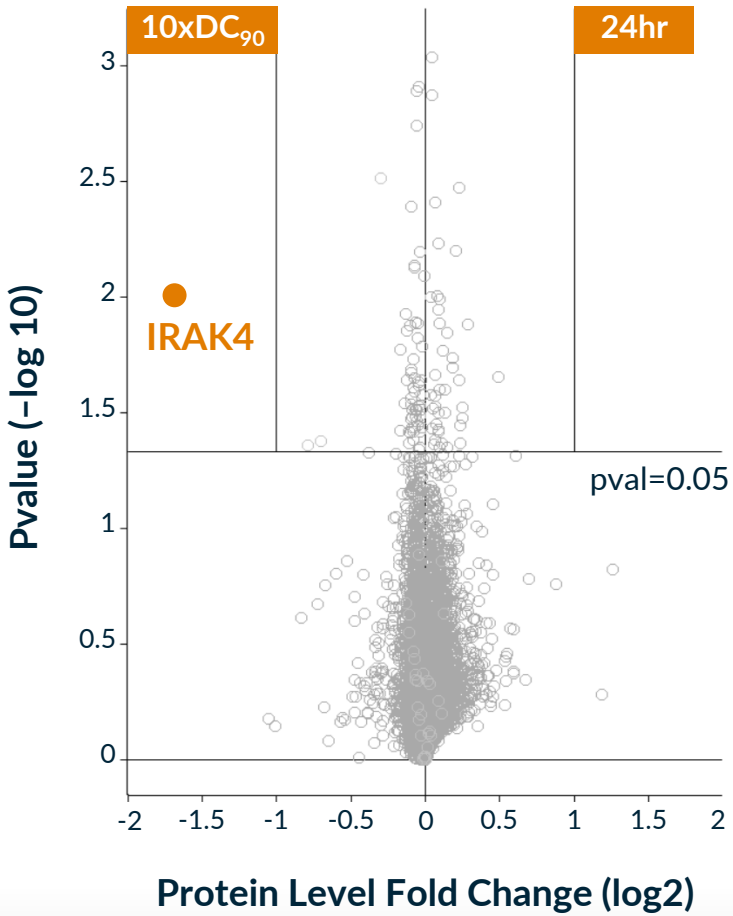
Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

IRAK4 knockdown of ≥85% in whole blood achieved anti-inflammatory effect comparable to potent corticosteroids or approved standard of care drugs in these models as well as in models of TLR4 (MSU-Gout) or TLR7/8 (Imiquimod-Psoriasis) activation that was superior to IRAK4 small molecule inhibitor

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

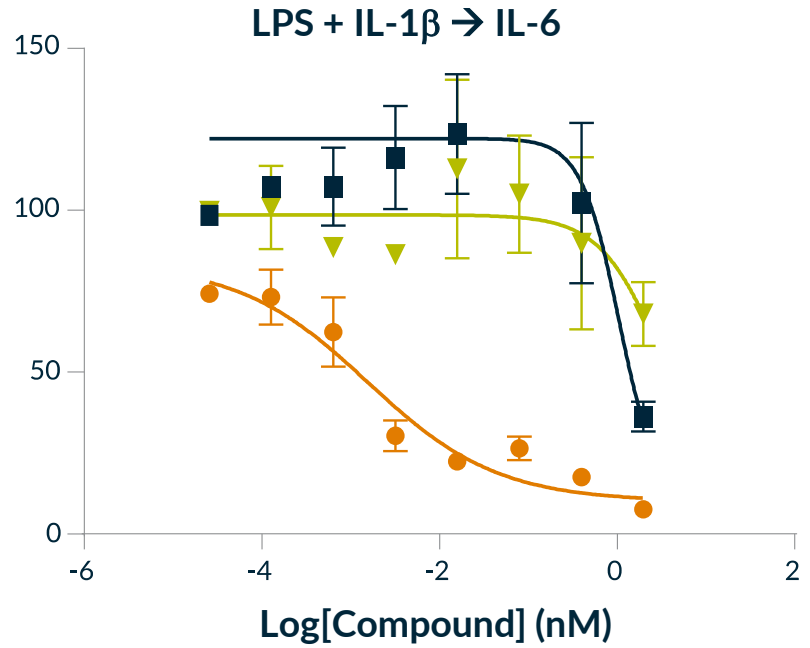
KT-474: Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

Degradation and Selectivity



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

Superiority over SM kinase Inhibitor



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

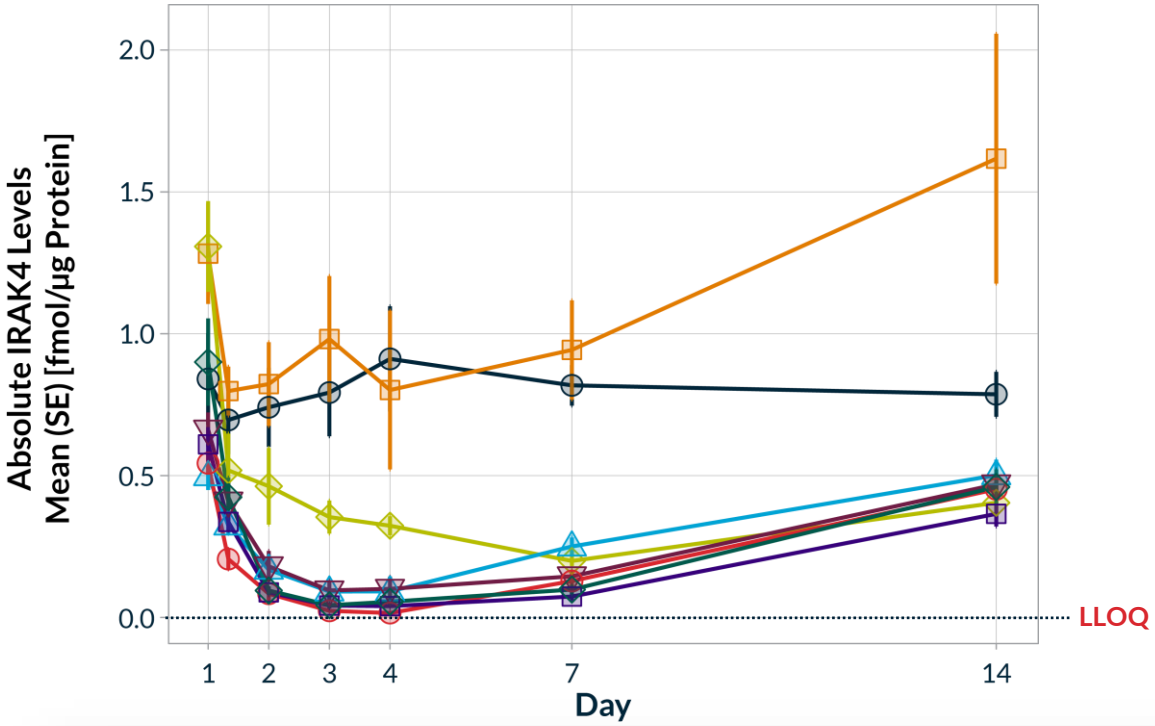
SAD/MAD Enrollment Status and Demographics

	SAD 1-7 (n=57)	MAD 1-4 (n=48)
Gender		
Female	29	9
Male	28	39
Median age, years (range)	38.0 (20-55)	37.5 (20-55)
Ethnicity		
• Hispanic or Latino	42	34
• Black or African American	8	8
• Non-Hispanic or Latino- White	5	6
• Asian	2	0

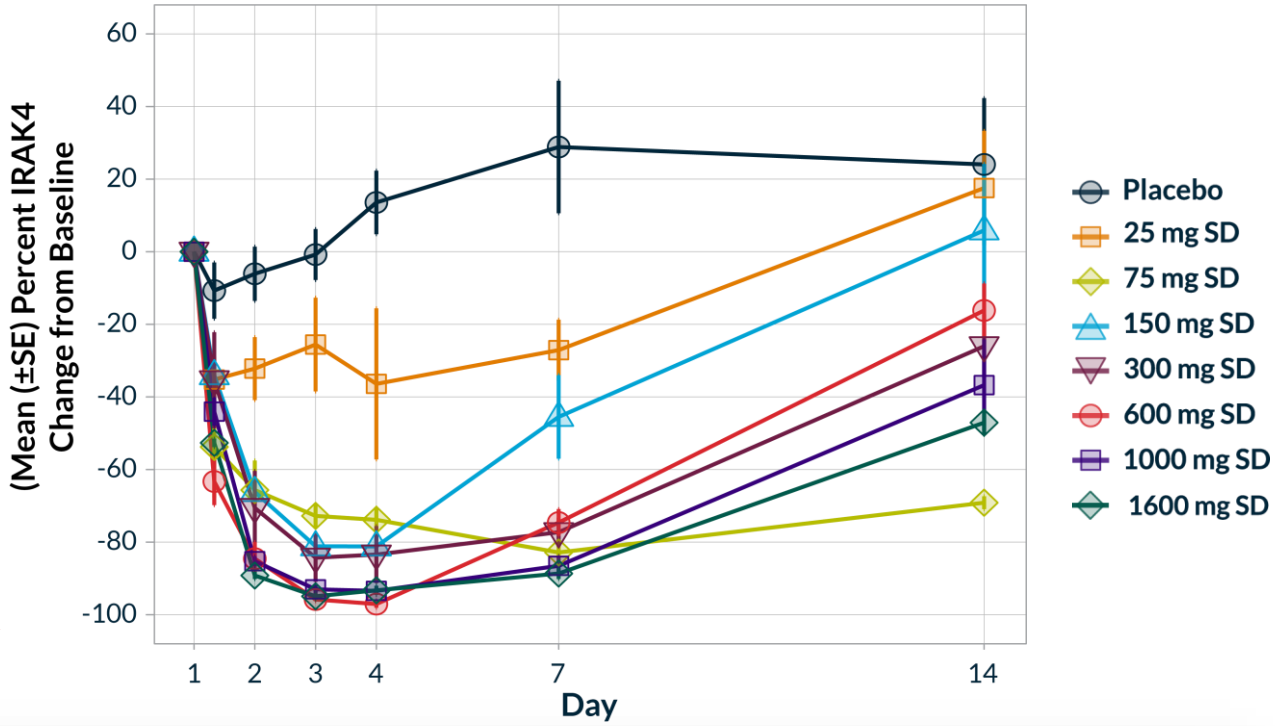
IRAK4 SAD

KT-474 Achieved Deep and Dose-Dependent IRAK4 Degradation after Single Oral Doses that Lasted for at Least 6 Days

Absolute IRAK4 Levels



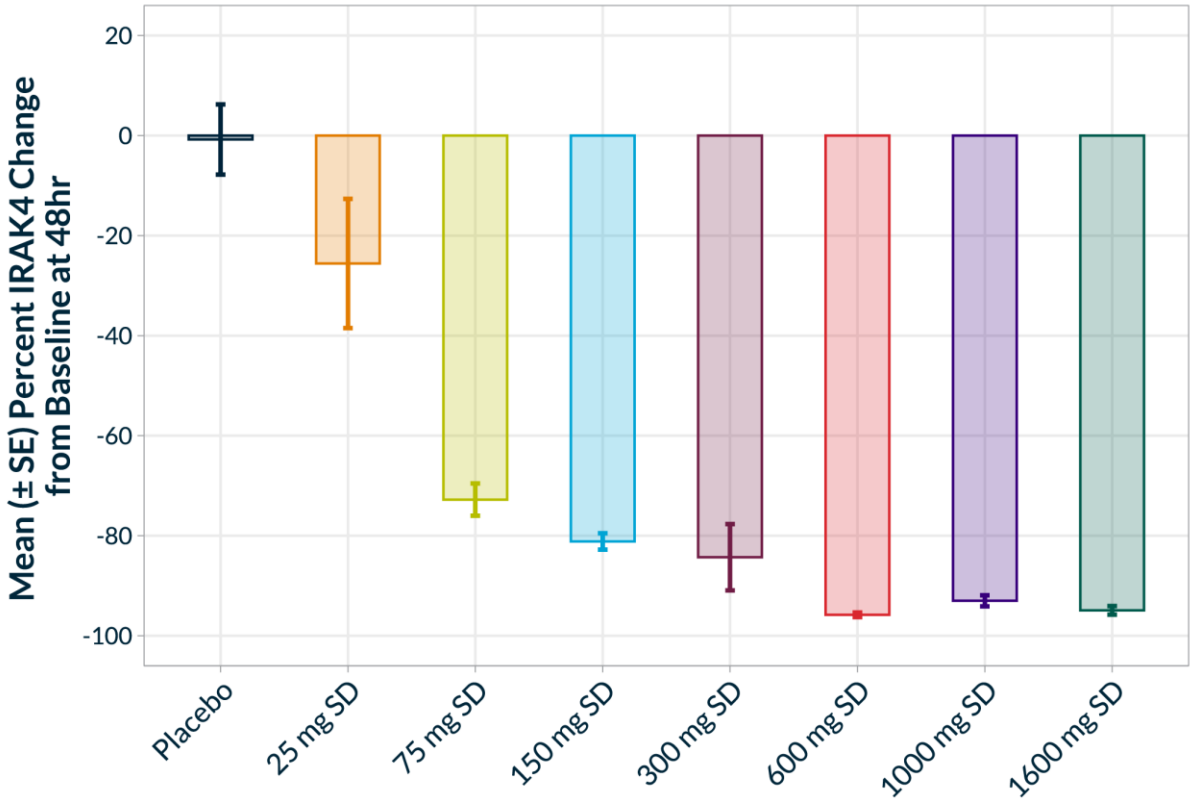
Mean % Reduction of IRAK4



- Detected by Mass Spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours (Day 3-4)
- IRAK4 reduction lasted for at least 6 days post-dose in all dose groups
- SAD 5 through 7 approached or exceeded Lower Limit of Quantitation (LLOQ)

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

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

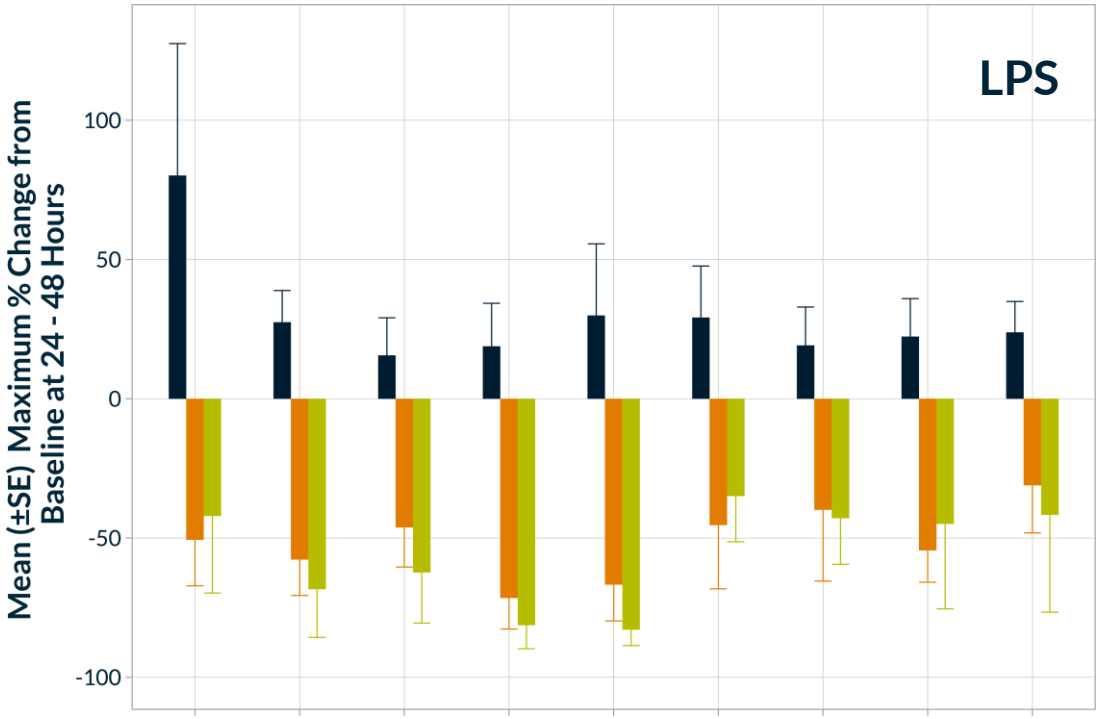


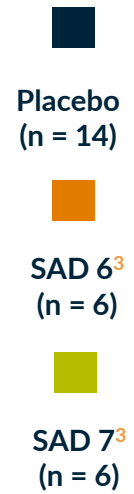
	N	Mean IRAK4 Change	Median IRAK4 Change	p value
Placebo	13	-1%	-2%	--
25 mg	6	-26%	-39%	0.1
75 mg	6	-73%	-75%	<0.0001
150 mg	6	-81%	-82%	<0.0001
300 mg	6	-84%	-89%	<0.0001
600 mg	7	-96%	-96%	<0.0001
1000 mg	5	-93%	-94%	<0.0001
1600 mg	6	-95%	-95%	<0.0001

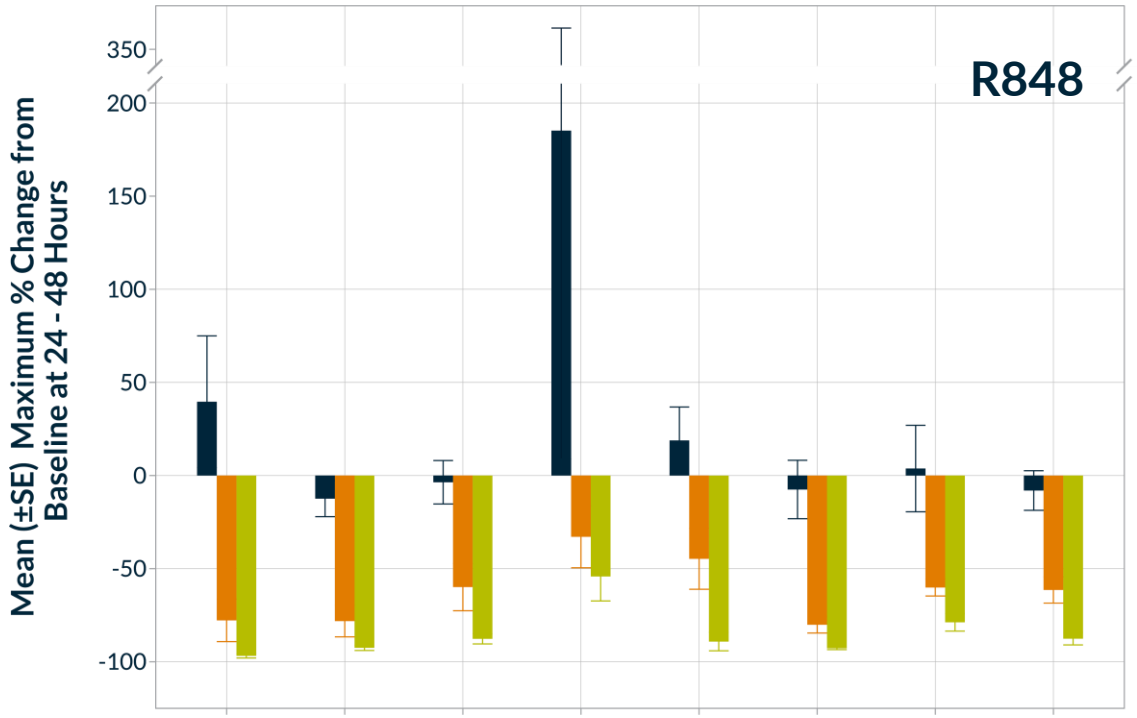
* p-values relative to placebo

Broad and Deep Inhibition of Disease Relevant Cytokines

Effect Against LPS (TLR4)- or R848 (TLR7/8)-Stimulated Cytokine Induction in Whole Blood







	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	80%	27%	16%	19%	30%	29%	19%	22%	24%
SAD 6 85-93% Degr*	-51%	-58%[1]	-46%[2]	-72%[1]	-67%[2]	-45%[2]	-40%[2]	-54%[2]	-31%
SAD 7 89-95% Degr*	-42%	-68%[1]	-62%[1]	-81%[1]	-83%[1]	-35%[2]	-43%[2]	-45%[2]	-42%[2]

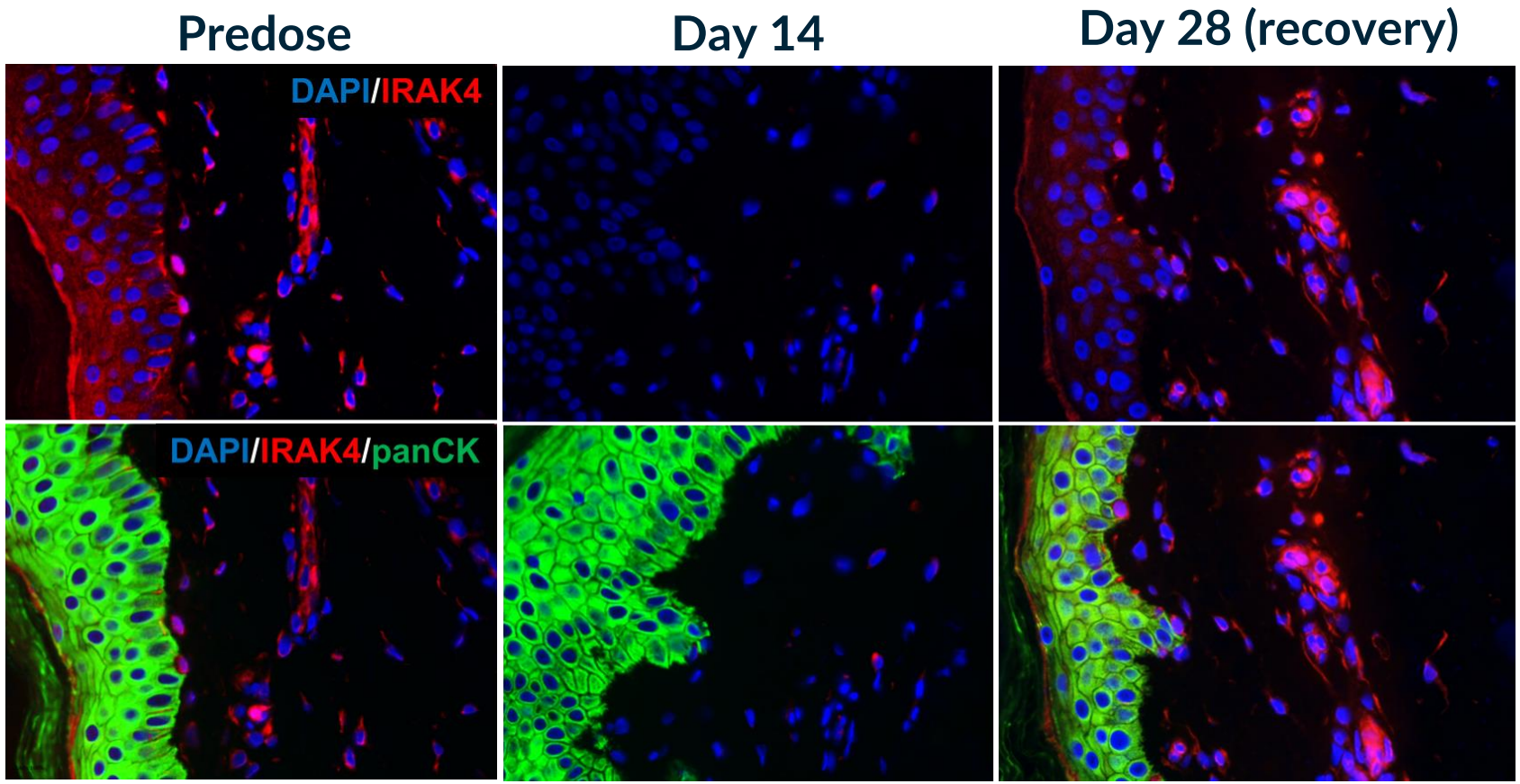
	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	40%	-12%	-4%	185%	19%	-7%	4%	-8%
SAD 6	-78%	-78%[1]	-60%[1]	-33%	-45%	-80%[1]	-60%[1]	-61%
SAD 7	-97%[2]	-92%[1]	-88%[1]	-54%	-89%[1]	-93%[1]	-79%[1]	-88%[2]

[1] = p value < 0.01; [2] = p value < 0.05

*Mean IRAK4 degradation in PBMC at 24-48h

[3]*Ex vivo* cytokine assay was performed at 48h nadir (maximal degradation) only in cohorts 6-7

Substantial IRAK4 Degradation in Skin Observed in Dermis and Epidermis (IRAK4 = Red)



Pan cytokeratin (panCK) is used as the epidermal marker

Representative images from subject in 50 mg cohort

KT-474 Demonstrates Broadest Anti-inflammatory Effect Compared to Other Clinical Agents

Inhibition of *Ex Vivo* Disease Relevant Cytokine/Chemokine Stimulation by Anti-Inflammatory Agents in Ph1 Studies

Agent/Stimulus	Target	IFNγ	TNFα	IL-1β	IL-6	IL-8	IL-17	IL-12	IL-23	IL-10
KT-474/LPS	**IRAK4 (degrader)**	✓	✓	✓	✓	✓	✓	✓	✓	✓
KT-474/R848	**IRAK4 (degrader)**	✓	✓	✓	✓	✓	✓	✓		✓
CA-4948/R848	IRAK4* (inhibitor)				✓					
GS-5718/R848	IRAK4 (inhibitor)		✓							
ATI-450/LPS	MK2		✓	✓	✓	✓				
ATI-450/IL-1β	MK2		✓		✓	✓				
LY2775240/LPS	PDE4		✓							
Iberdomide/LPS	Ikaros/ Aiolos			✓						
JNJ-61803534/ T cell activation	RORγ						✓			

* Non-selective

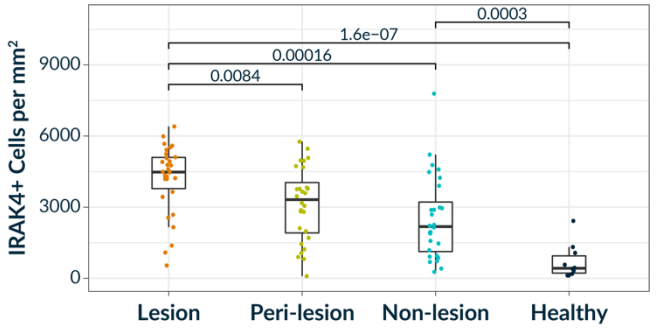
Iberdomide: Schafer PH, et al. *Ann Rheum Dis* 2018;77:1516–1523; **LY2775240**: Patel DR, et al. *Clin Transl Sci.* 2021;14:1037–1048; **JNJ61803534**: Xue X, et al. Sci Rep 2021;11:11066-80; **MK2**: Aclaris 2021 Company Overview; **CA-4948**: Booher RN, et al. ASH Annual Meeting 2018, Poster #4168; **GS-5718**: Roedder S, et al. ACR Convergence 2021, Poster #0185

IRAK4 Non-Interventional

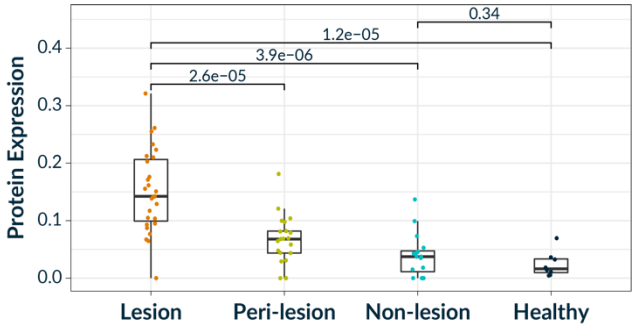
IRAK4 Protein Expression in Autoimmune Diseases: Upregulation in Skin of HS Patients Compared to Healthy Subjects

IRAK4 protein levels overexpressed in HS patient skin lesions

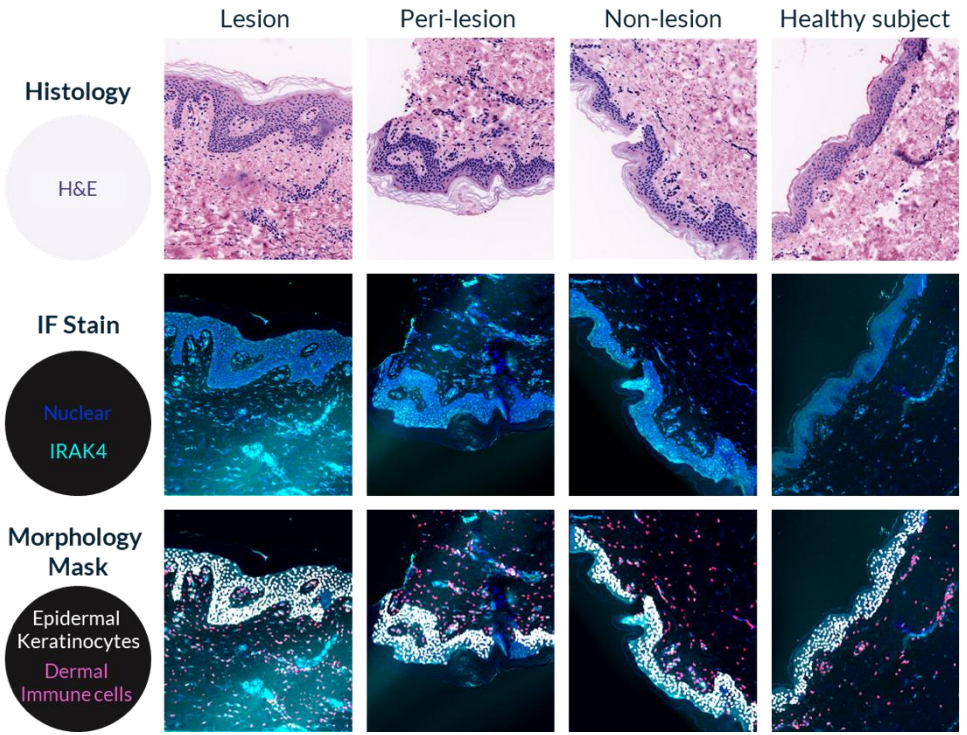
Immunofluorescence (IF)



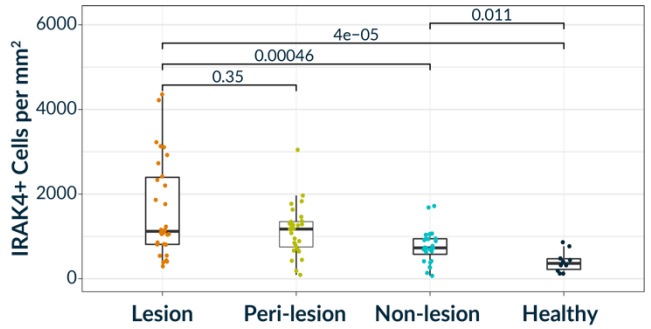
Mass Spectrometry (MS)



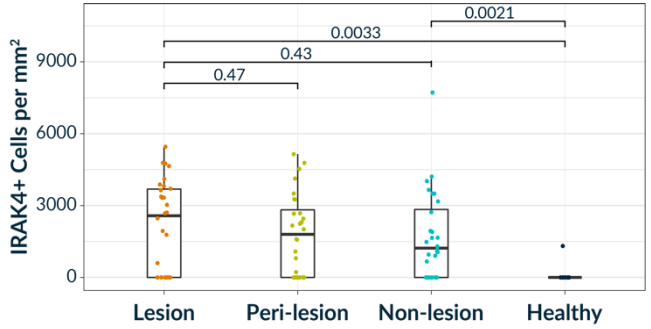
IRAK4 expression is upregulated in dermis and epidermis of HS patients relative to healthy subject skin



Dermal Immune Cells



Epidermal Keratinocytes



Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

IRAK4 Non-Interventional

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

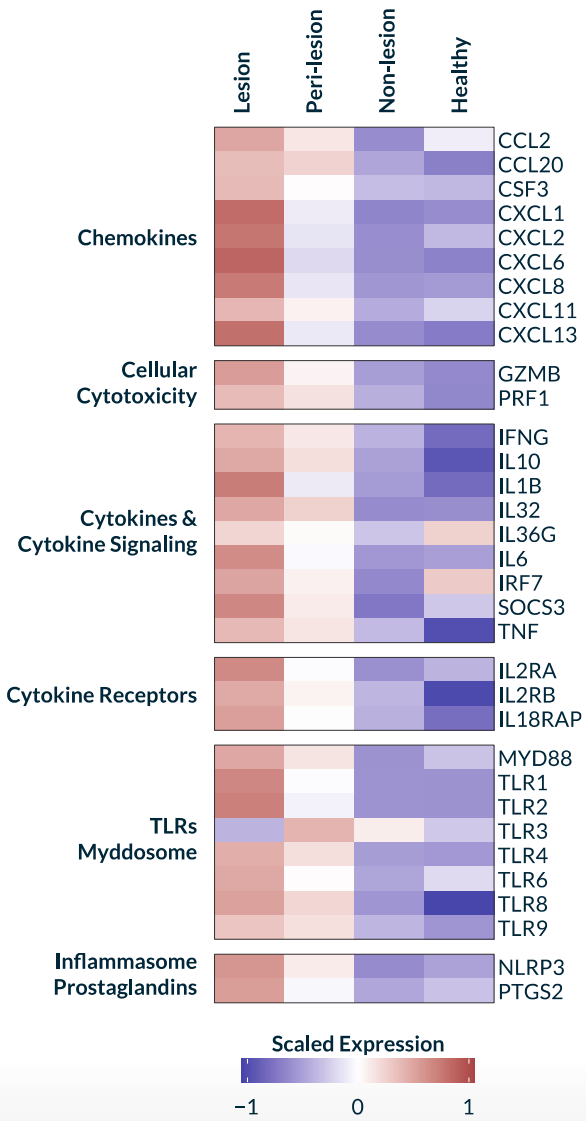
NanoString
Gene Expression Profiling (GEP)

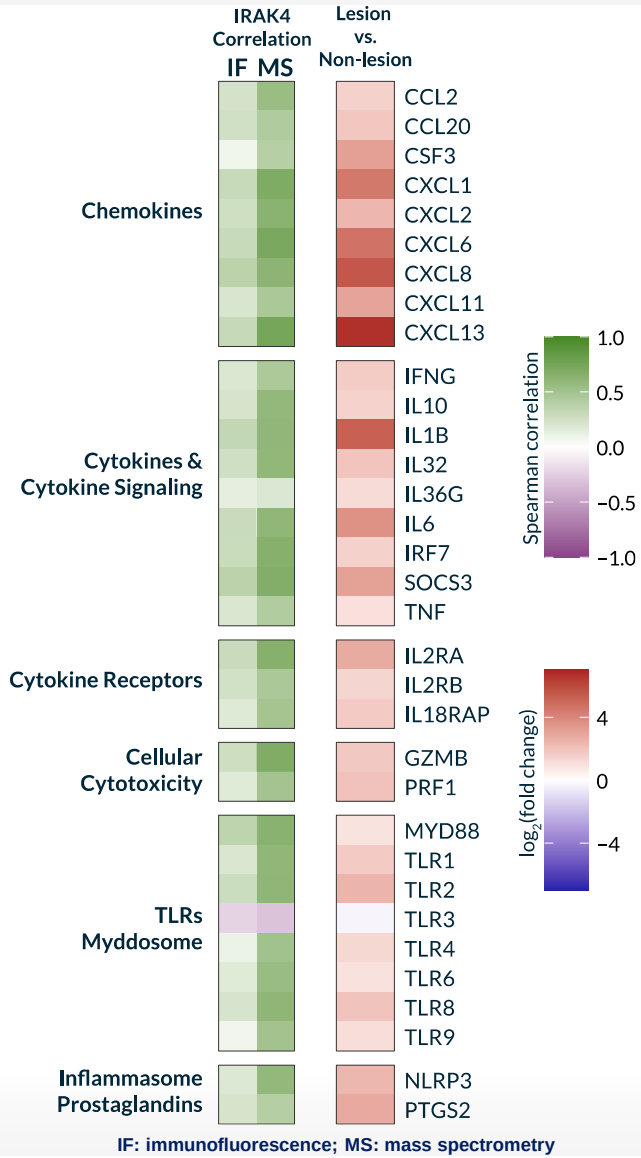
1. Significantly elevated genes in HS vs Healthy
2. Spearman correlation of elevated genes with IRAK4 protein levels by MS and IF

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

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



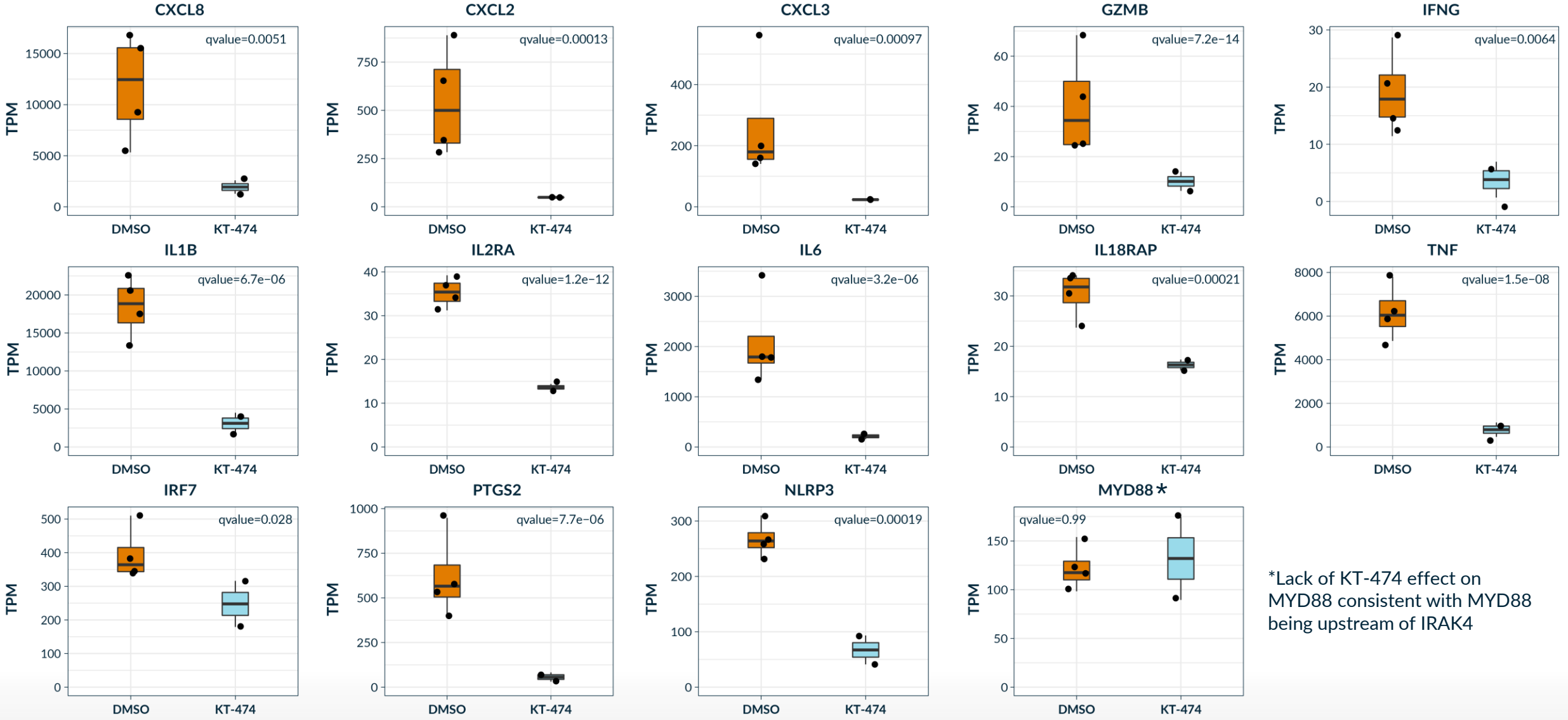


IF: immunofluorescence; MS: mass spectrometry

- Upregulation of TLRs, IL-1β/IL-36, MYD88, and multiple additional drivers of inflammation that all correlate with IRAK4 protein expression
- Highlights potential of IRAK4 targeting to treat diseases like HS characterized by marked pleiotropic inflammation

Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

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

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

Appendix – Corporate

KYMERA

Proteome Editing is the New Frontier of Medicine

Genome

- Essentially **static**
- Alterations are responsible for **some** diseases
- Editing is **irreversible**

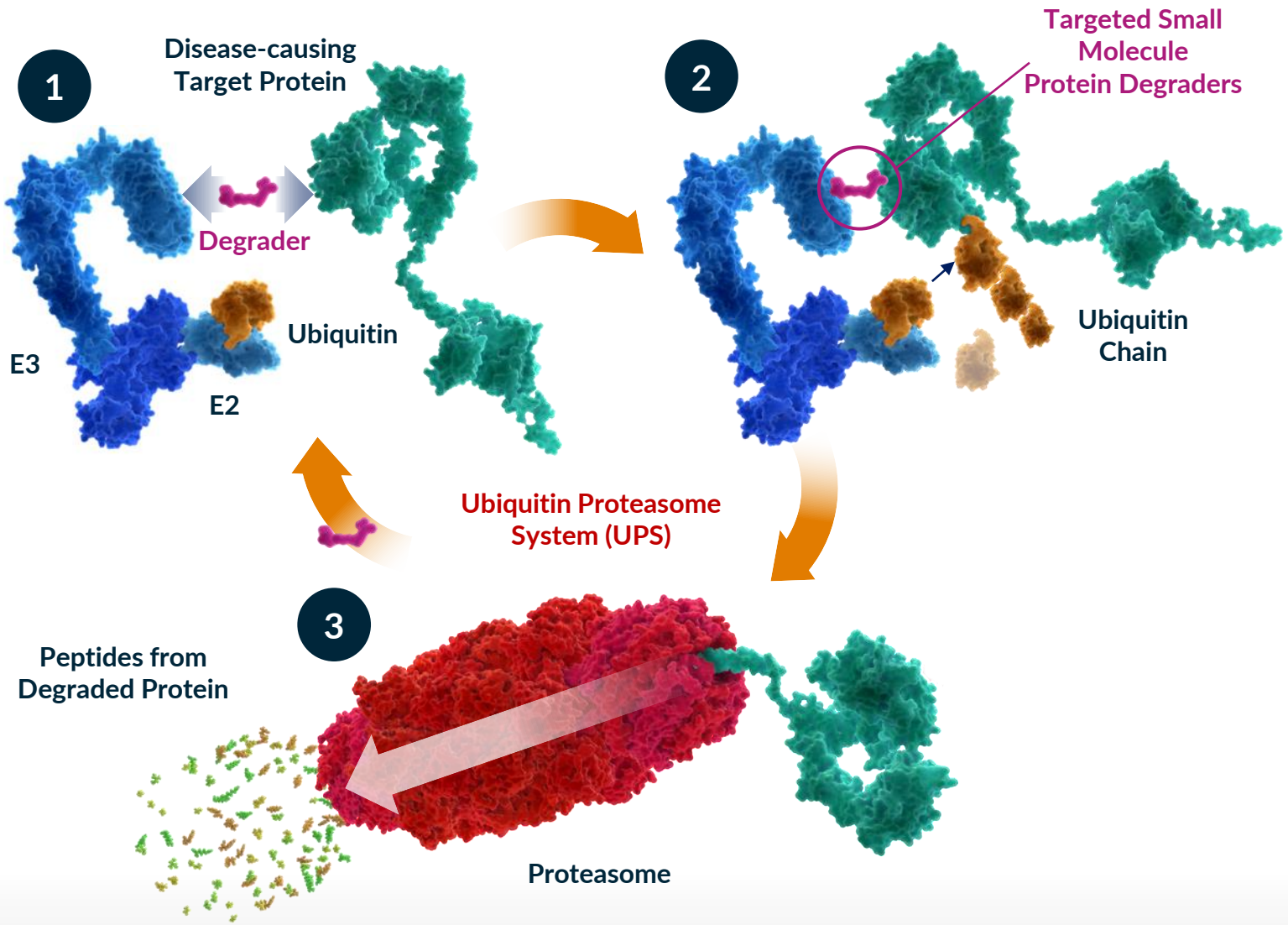
Encodes

Proteome

- **Changes** based on internal (genetic) and external (epigenetic) events
- Alterations are responsible for **all** diseases
- Editing is **reversible**

Proteome Editing with Targeted Protein Degradation

A Nobel Prize (2004) Inspired Technology

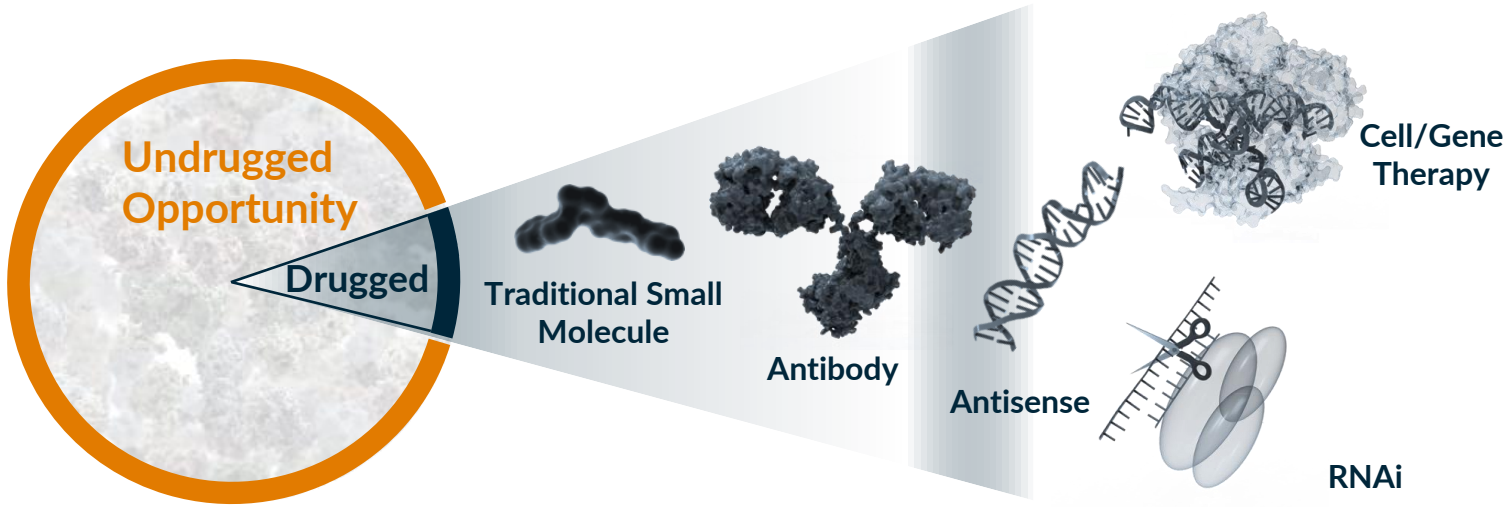


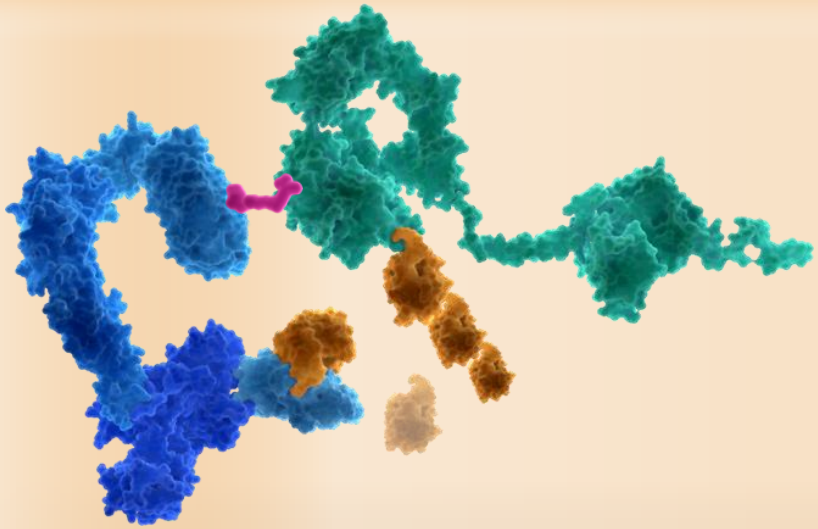
Expanded Opportunities

- Small molecule binds to E3 and target protein to effect its degradation
- Small Molecule only needs to "weakly" bind to protein:
  Not inhibit function
- Highly potent/catalytic:
  Small amount of drug needed
- Highly specific
- Genetic–like knock-down effects
- Advantage of small molecule development:
  Route of administration, manufacturing
- Agnostic to protein type and disease

Expanding Druggable Proteome with Targeted Protein Degradation

All therapeutic modalities to date **only drug up to 20%** of proteome





Kymera **is expanding the drugged proteome** with Targeted Protein Degradation (TPD)

Exponential Clinical Pipeline Growth of Degraders

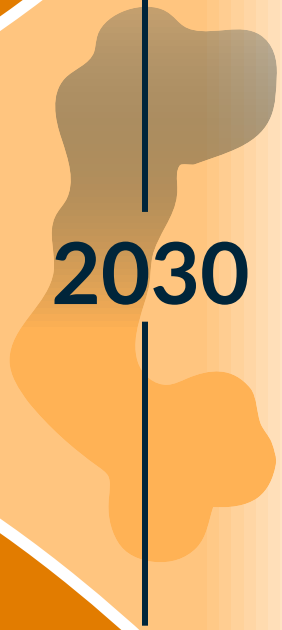
Existing Modalities

Therapeutic Modality	Drugs FDA Approved
Small molecule inhibitor	>2000
Antibody	>100
ASO	~10
Cell Therapy	~5
Gene Therapy	~4
RNAi	~3
Gene editing	0

Targeted Protein Degradation

	Drugs FDA Approved	Drugs in Clinical Development
Degraders	4	>15

2010 2020 2030



- Elucidation of MOA of thalidomide **circa 2010** has **profoundly** accelerated TPD
- Clinical programs with protein degraders have grown exponentially in the past 12 months
- This growth will continue in foreseeable future

What We Expect in 2022

- **Completion of Ph1 patient cohort for KT-474 and transition to Sanofi**
- **Proof of mechanism in patients for KT-413 and KT-333 oncology Ph1 studies**
- **IND filing for KT-253**
- **First tissue restricted E3 ligase enabled program in development**
- **Additional programs in oncology and immunology reaching development**
- Expanded recognition as a leader in TPD with a disruptive innovation engine across the biotech sector
- Multiple scientific contributions in medical meetings and in peer reviewed publications
- Continued investment in providing our employees, collaborator and partners the best experience

Our Vision: Where Kymera Will Be in 2026

KYMERA

A fully-integrated biotech company with a disease and technology agnostic pipeline and capabilities

Path to NDA for at least **1 program**

At least **8 clinical stage programs** across different development stages and disease areas

Pipeline positioned to deliver **at least 1 new IND per year**

Clinical proof-of-concept established in **tissue-selective/restricted degradation** and **undrugged** targets

Disease and technology-agnostic pipeline and capabilities

Expand technology platform to wholistically address undrugged proteome

Continued commitment to **innovation** and **first-in-class** science and medicines

Commercial organization **build up** in progress