

A close-up photograph of a female scientist with blonde hair, wearing a white lab coat and blue nitrile gloves. She is using a pipette to transfer liquid into a small vial. The lab coat has a 'KYMERA' logo on the left chest pocket. The background is a blurred laboratory environment with various equipment and containers.

KYMERA

2024 IMMUNOLOGY R&D DAY

January 4, 2024



Welcome

Justine Koenigsberg

Vice President, Investor Relations

Forward Looking Statements

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Agenda

Welcome

Justine Koenigsberg, Vice President, Investor Relations

10:00 - 10:05

Revolutionizing Immunology with Small Molecule Oral Degraders

Nello Mainolfi, Ph.D., Founder, President and CEO

10:05 - 10:25

Paving the Way: KT-474, a First-in-Class Oral IRAK4 Degradar

Jared Gollob, M.D., Chief Medical Officer

10:25 - 10:35

Dupilumab-like Activity in a Pill: KT-621, a First-in-Class Oral STAT6 Degradar

Amy Wang, Ph.D., Senior Director and Program Lead, Immunology

10:35 - 10:55

Degrading a Proven Target: KT-294, a First-in-Class Oral TYK2 Degradar

Juliet Williams, Ph.D., Head of Research

10:55 - 11:15

Closing Remarks: Solving Big Problems with Small Molecules

Nello Mainolfi, Ph.D., Founder, President and CEO

11:15 - 11:20

Q&A

11:20 - 12:00



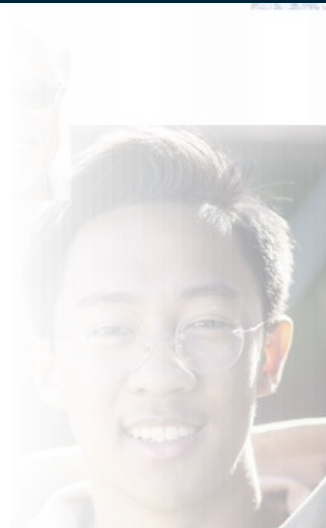
Revolutionizing Immunology with Small Molecule Oral Degraders

Nello Mainolfi, Ph.D.,
Founder, President and CEO



Mission

Build a global medicines company that harnesses novel modalities to revolutionize healthcare



What I Will Cover

- Targeted Protein Degradation: Harnessing a Game-Changing Novel Modality

- Demonstrating Reproducible and Scalable Clinical Innovation

- Our Target Selection Strategy

- Why Oral Degraders in Immunology

- Our Two New Programs

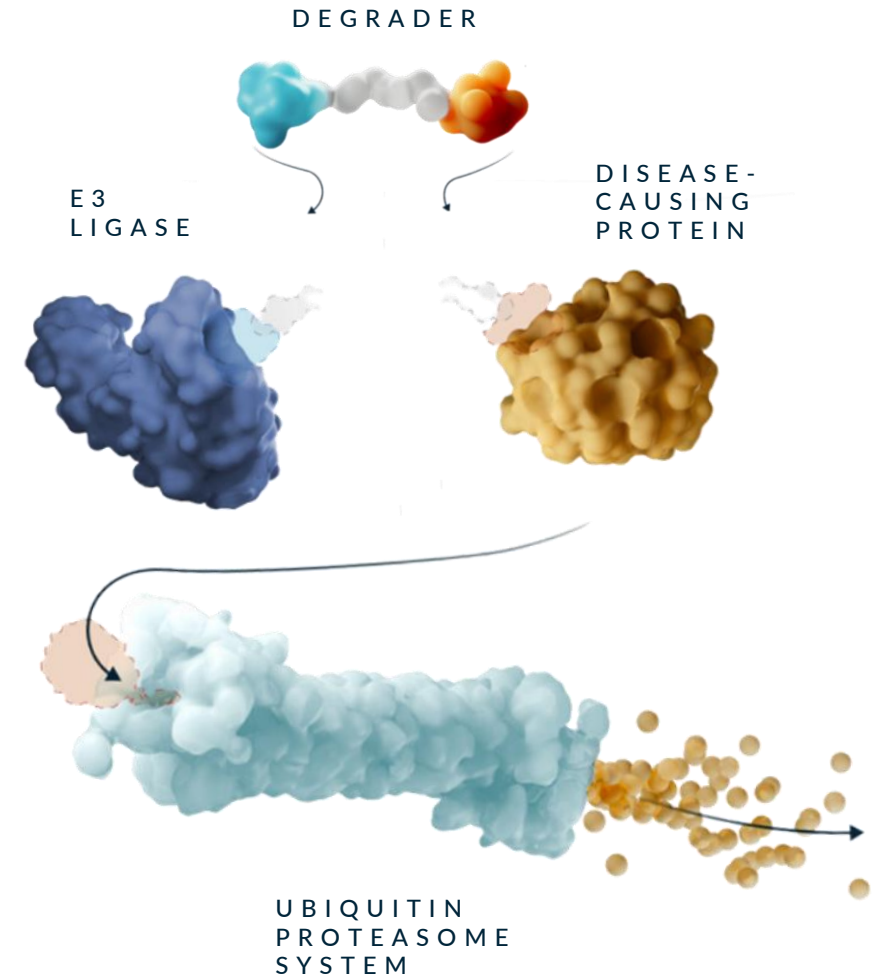
Harnessing a Game-Changing, Novel Modality

Kymera, a Leader in Targeted Protein Degradation

- Focused on unlocking high value, undrugged targets using TPD
- Highly productive and reproducible platform for discovery of innovative medicines
- Leading platform and pipeline IP, developed internally
- Well-capitalized, enabling expansion into areas with large clinical and commercial opportunities

Industry Leading Execution

- Since founding Kymera in 2016:
 - Advanced four first-in-class programs to the clinic
 - Demonstrated clinical translation of degradation and safety
 - Achieved early clinical POC in I&I and oncology programs
- Extensive validation of target selection and molecular design
- Successful track record delivering multiple new drug mechanisms in clinic, expecting up to 10 novel INDs within first 10 years



Target Selection Strategy

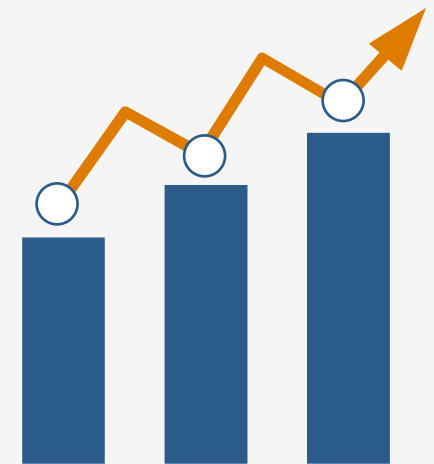
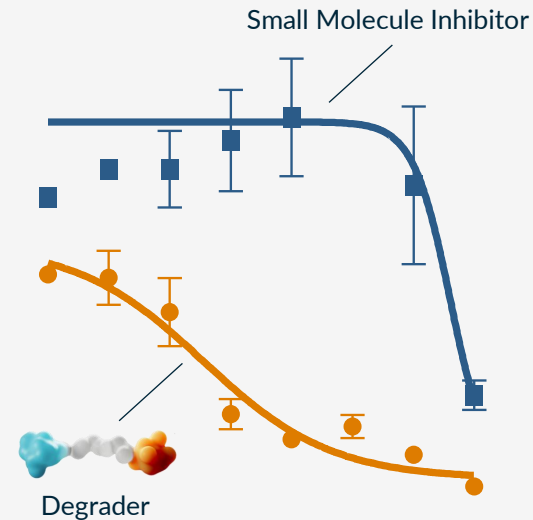
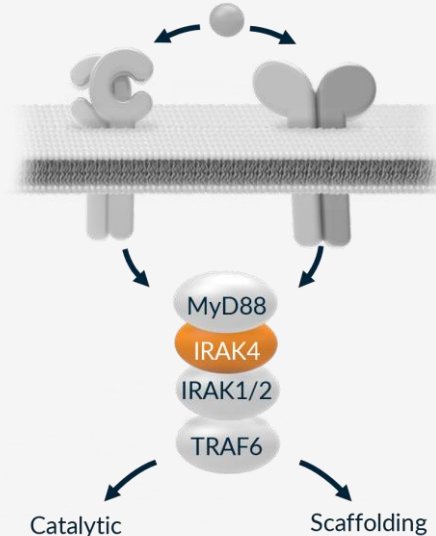
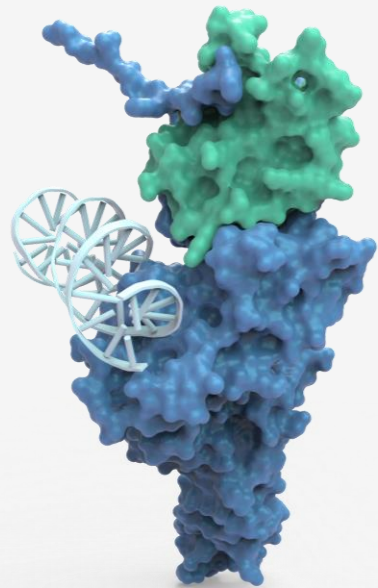
Focus on First- or Best-in-Class Opportunities

Undrugged or Inadequately Drugged targets

Strong Genetic/Pathway Validation

Clear Path to Early Clinical Differentiation

Large Clinical/Commercial Opportunities



TRANSCRIPTION FACTORS & SCAFFOLDING PROTEINS

APPROVED DRUGS IN SAME PATHWAY

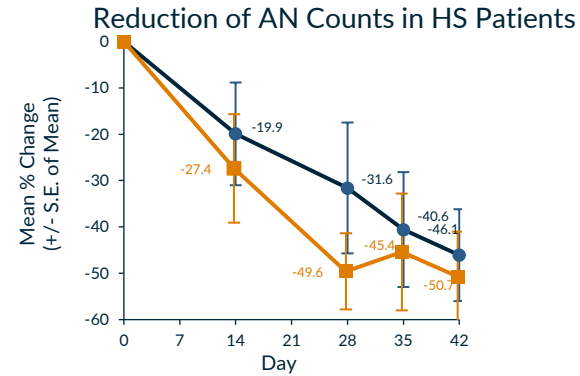
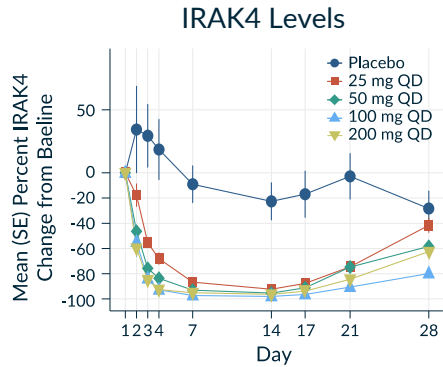
SUPERIORITY VS PATHWAY DRUGS

AREAS OF SIGNIFICANT VALUE CREATION

Demonstrating Reproducible and Scalable Clinical Innovation

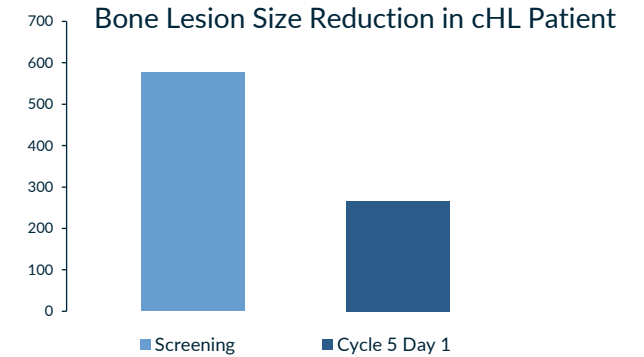
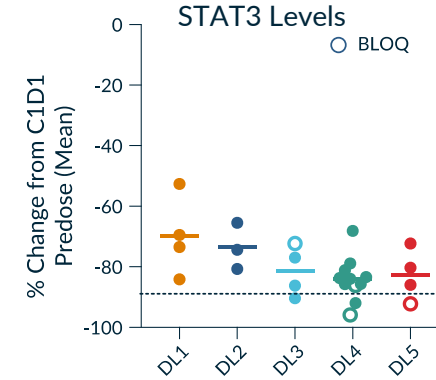
IRAK4 KT-474

IRAK4 Degradation leads to Early POC in HS and AD



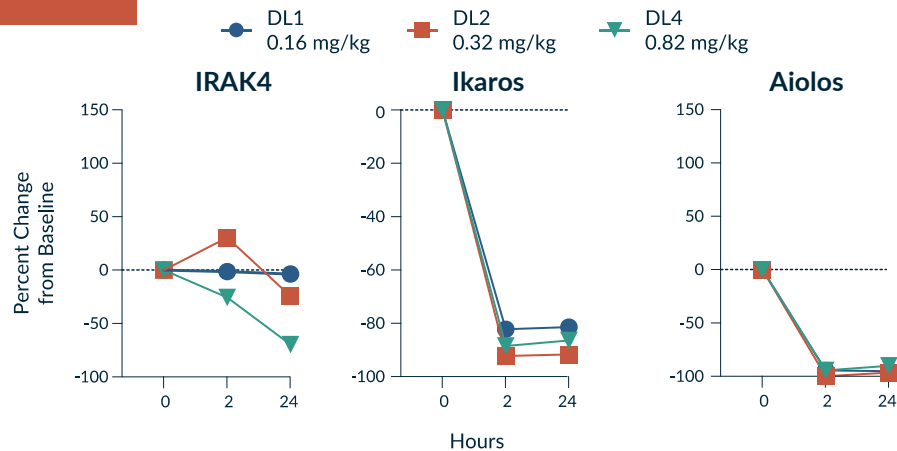
STAT3 Degradation Leads to Major Response in cHL Patient

STAT3 KT-333



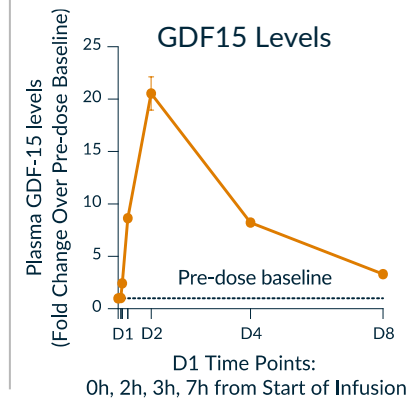
IRAKIMID KT-413

Degradation of IRAK4 and Ikaros/Aiolos in Humans was Well Tolerated

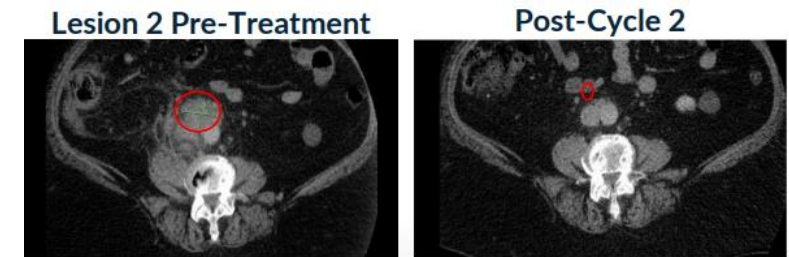


MDM2 Degradation Leads to Major Response in MCC Patient with no Heme-tox

MDM2 KT-253

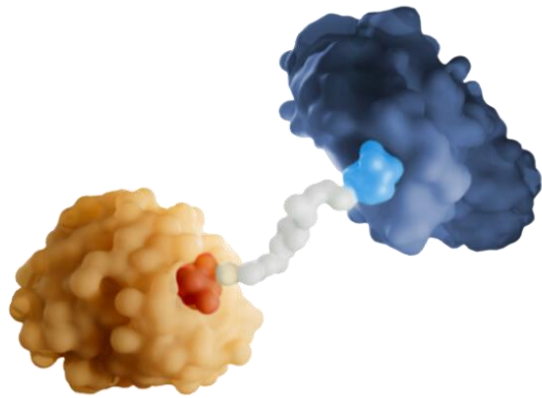


Lesion Size Reduction in MCC Patient



Building a Global Medicines Company

Pioneering a new modality
2016-2020

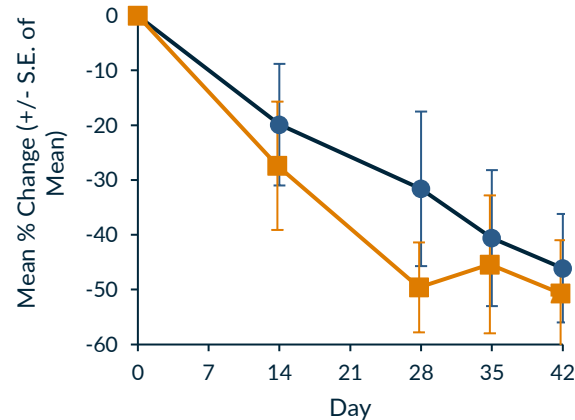


Focused on undrugged targets within clinically validated pathways

Forged multiple strategic partnerships to forward integrate (>\$3B total value)

Developed industry leading capabilities in TPD and novel E3s

Demonstrating early POC
2021-2023



Advanced four drug candidates into clinic demonstrating clinical activity in oncology and immunology

Initiated two Phase 2 studies in significant immunology indications with Sanofi

Demonstrated biological and clinical superiority of degrader vs. SMIs

Delivering a new generation of medicines
2024-2028



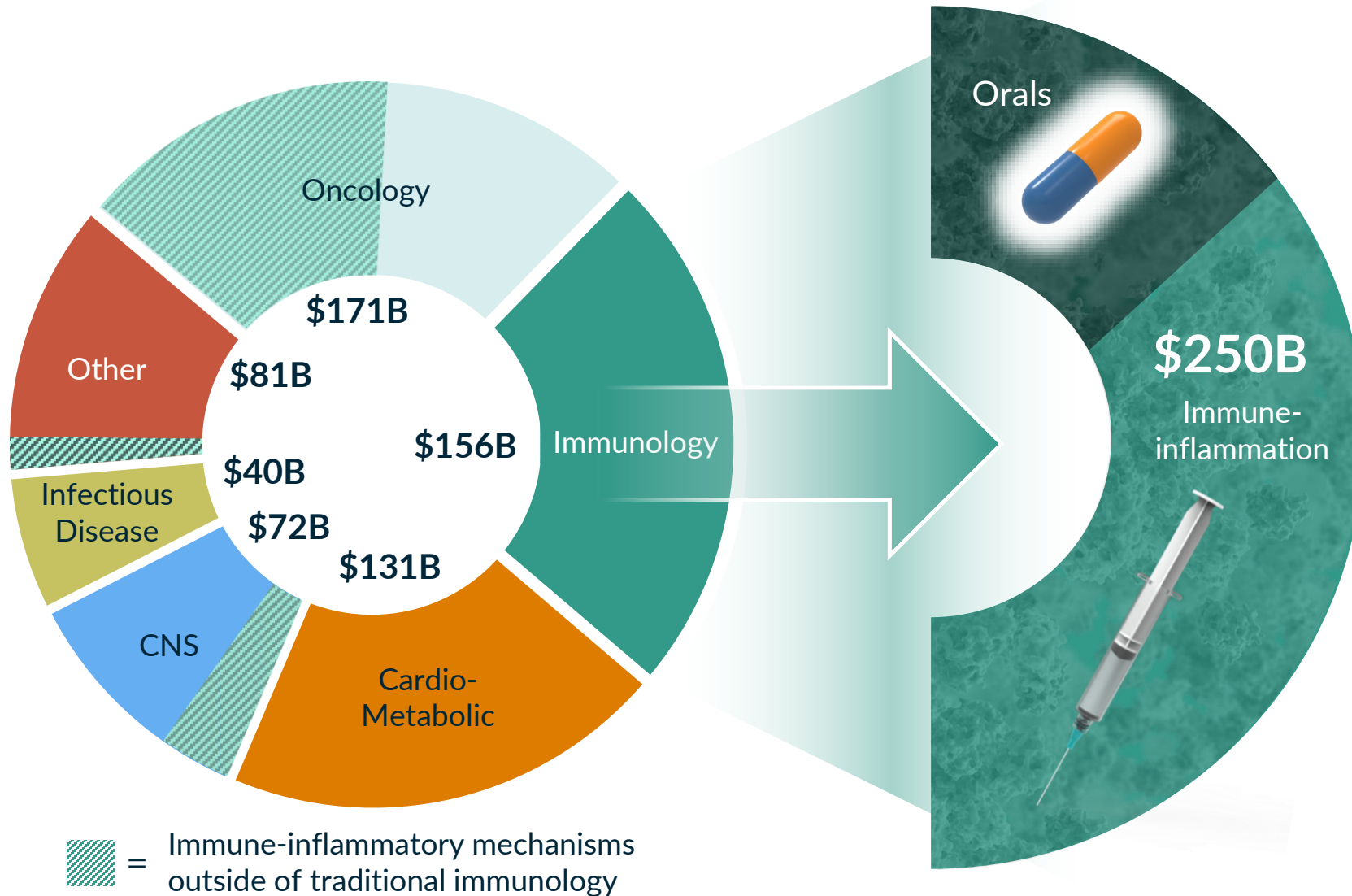
Focus on large clinical/commercial opportunities with oral degraders

Increase investments in I&I

Complete multiple POC studies in large indications and launch several registrational studies

Build towards a fully integrated global biotech

The Opportunity in Immunology



Immune-inflammation is a **\$250B WW market¹** spanning multiple therapeutic areas.

Injectables dominate, comprising >75% of the established market.

¹Revenues from Top 1,000 worldwide brands by revenue; Source: GlobalData; 2022 Non-Covid, Non-Vaccine Rx Market

Why Small Molecule Oral Degraders in Immunology



Key pathways/cytokines validated as drivers of many diseases in I&I

Biologics blocking these pathways/cytokines have revolutionized treatment

Biologics are injected, can be inconvenient for patients and costly to manufacture

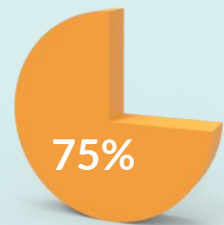
Traditional small molecule inhibitors insufficiently block these pathways, limiting efficacy

Oral Degraders Can Offer Biologic-like Efficacy in a Pill

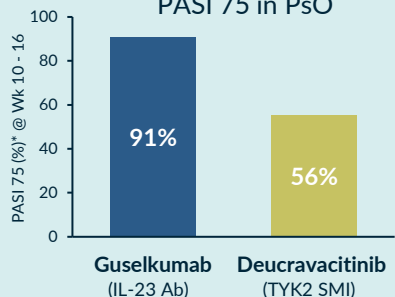


Degraders can provide comparable pathway inhibition to biologics, convenience of oral dosing, ease of manufacturing and potentially access broader populations

Patients on Biologics that Would Switch to Orals¹

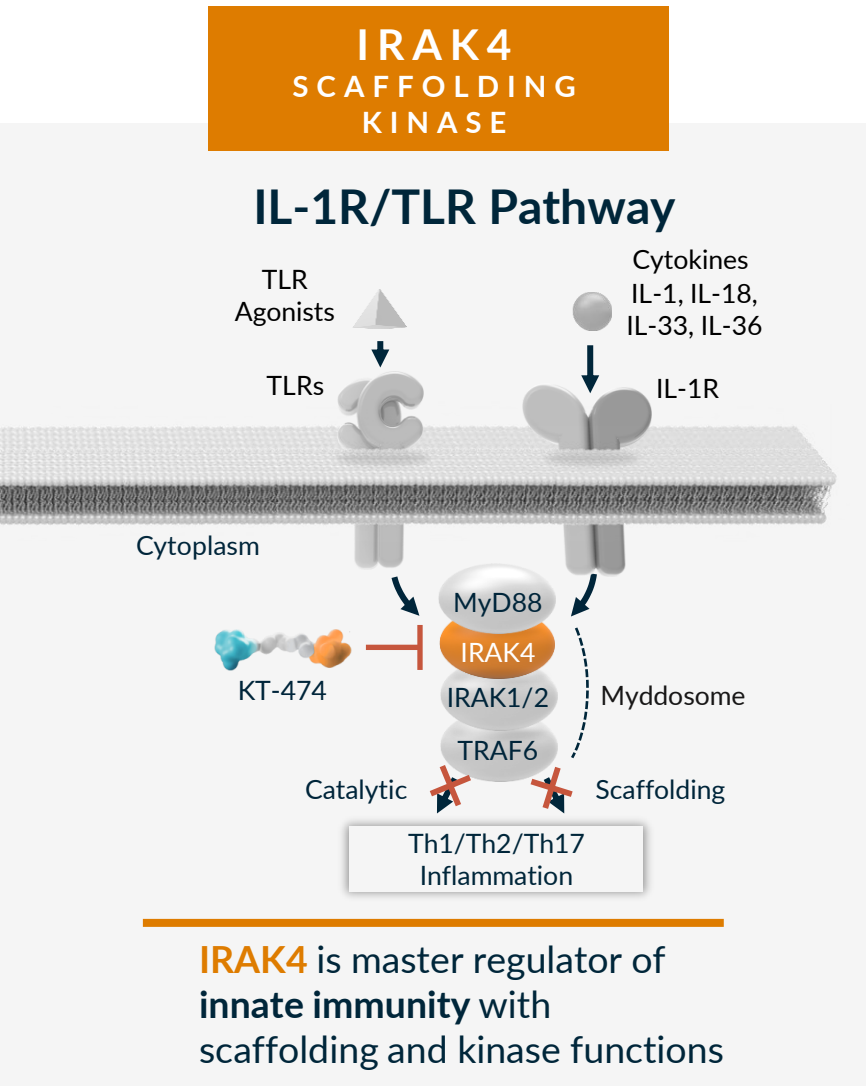


IL-23 Biologics vs TYK2 SMI²
PASI 75 in PsO



Revolutionizing Immunology with Oral Degraders

Our IRAK4 Example



BEST-IN-PATHWAY MECHANISM

Clinical pathway validation



IL-1, IL-18, IL-33, IL-36 biologics

Human genetics



IRAK4 null adults: healthy

Undrugged/inadequately drugged by other technologies



Scaffolding kinase, only TPD can address

Best-in-pathway profile opportunity



Superior to single cytokine upstream blockers: IL-1/18/33/36

Clear path to early clinical de-risking



Superiority in Phase 1/2

Access large clinical and commercial opportunities



HS, AD, RA, Asthma, COPD, IBD, others¹

¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

Revolutionizing Immunology with Oral Degraders

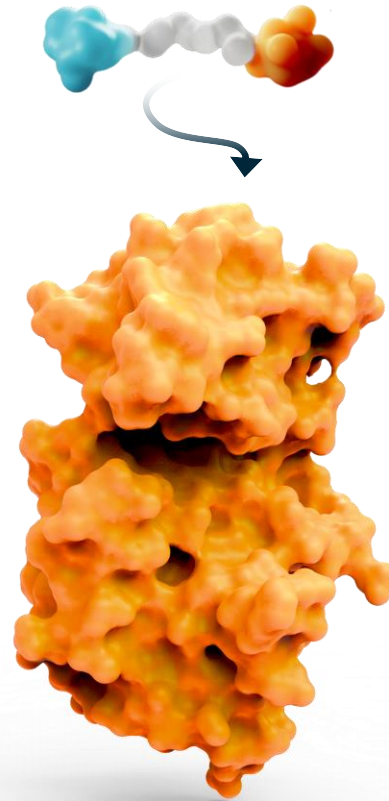
WHAT WE HAVE LEARNED FROM KT-474



Strong
PK/PD
Correlation



Safety

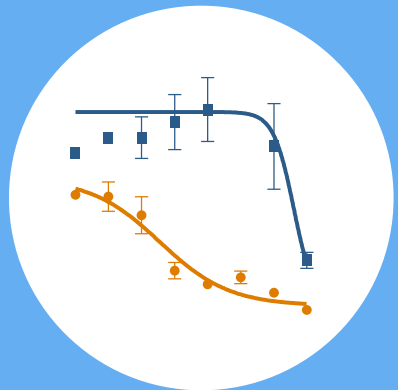


IRAK4
SCAFFOLDING
KINASE

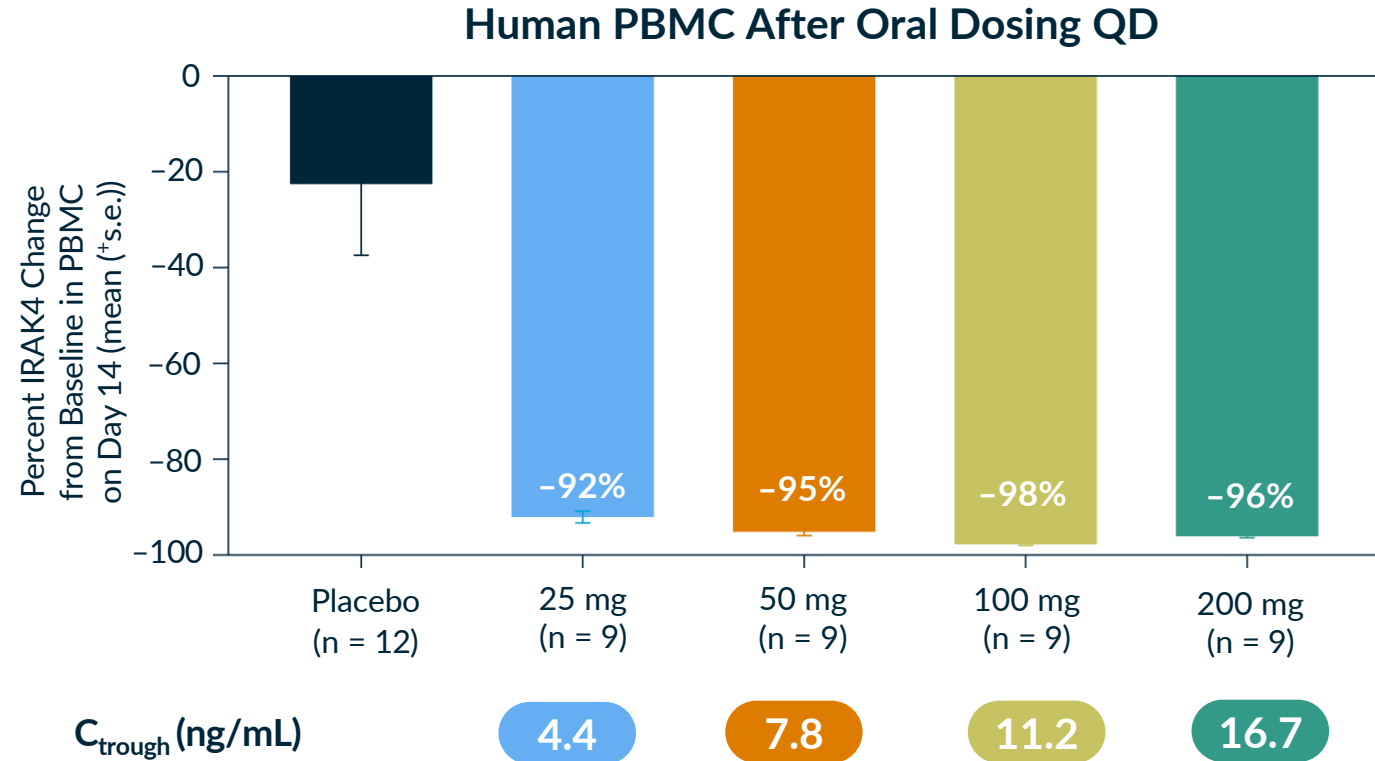
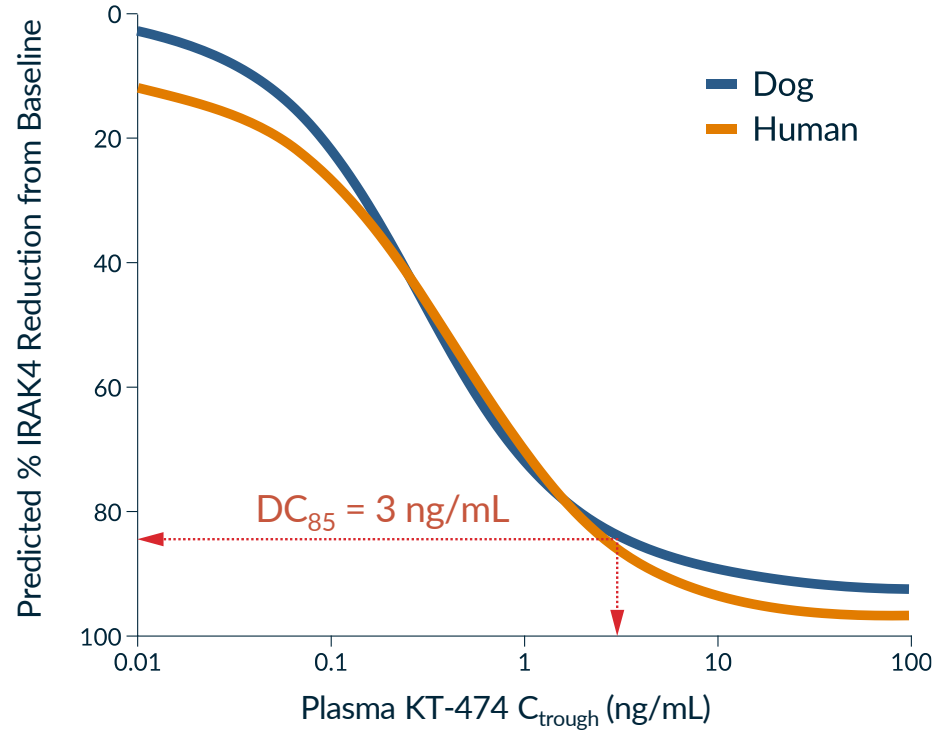
Early Signs
of Clinical
Activity



Differentiated
vs. SMI



KT-474: Fidelity of Translation from Preclinical to Clinical Profile



PK/PD modeling of observed data predicts **comparable DC_{85} (~3 ng/mL) in dog and human** showing excellent preclinical to clinical translation and predictability of IRAK4 degradation

Revolutionizing Immunology with Small Molecule Oral Degraders

Our Two New Programs

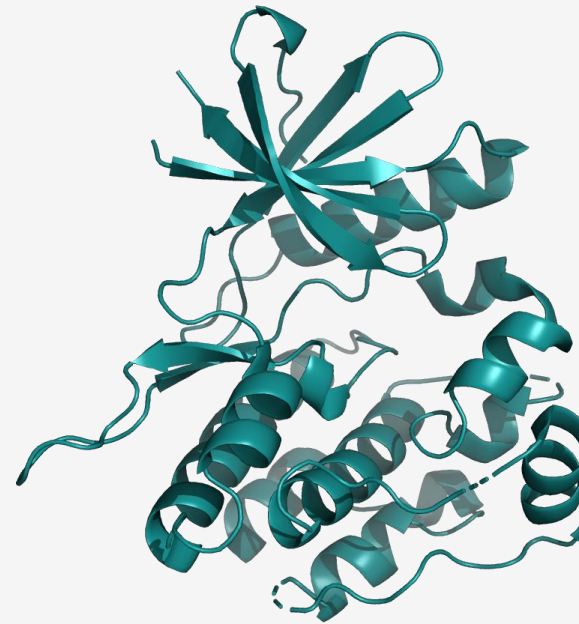
SPECIFIC IL-4/13
TRANSCRIPTION FACTOR

STAT6

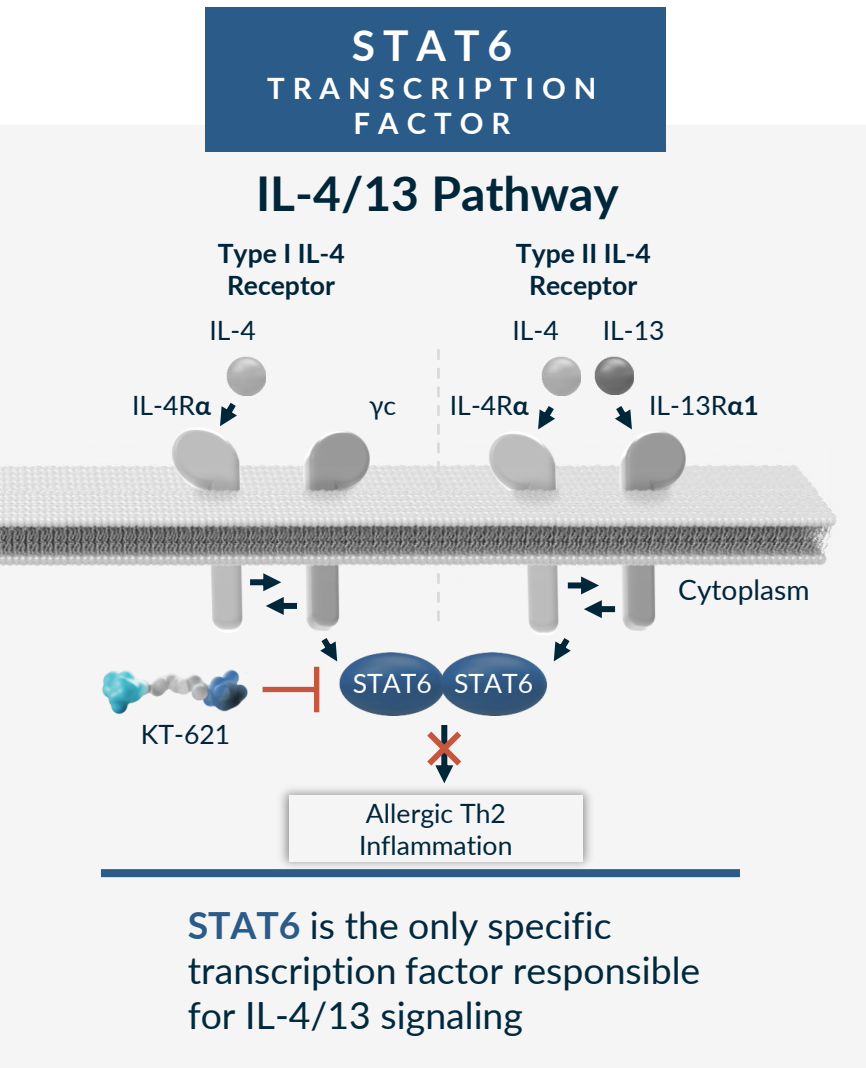


SPECIFIC IL-23/IFN
SCAFFOLDING KINASE

TYK2



STAT6 Degradator: Dupilumab-like Activity in a Pill



BEST-IN-PATHWAY MECHANISM

Clinical pathway validation



Dupilumab

Human genetics



Gain of function variants cause severe allergic diseases; KO phenotype (mouse) normal

Undrugged/inadequately drugged by other technologies



Transcription factor, TPD can fully block target/pathway

Best-in-pathway profile opportunity



Dupilumab-like activity with oral small molecule profile

Clear path to early clinical de-risking



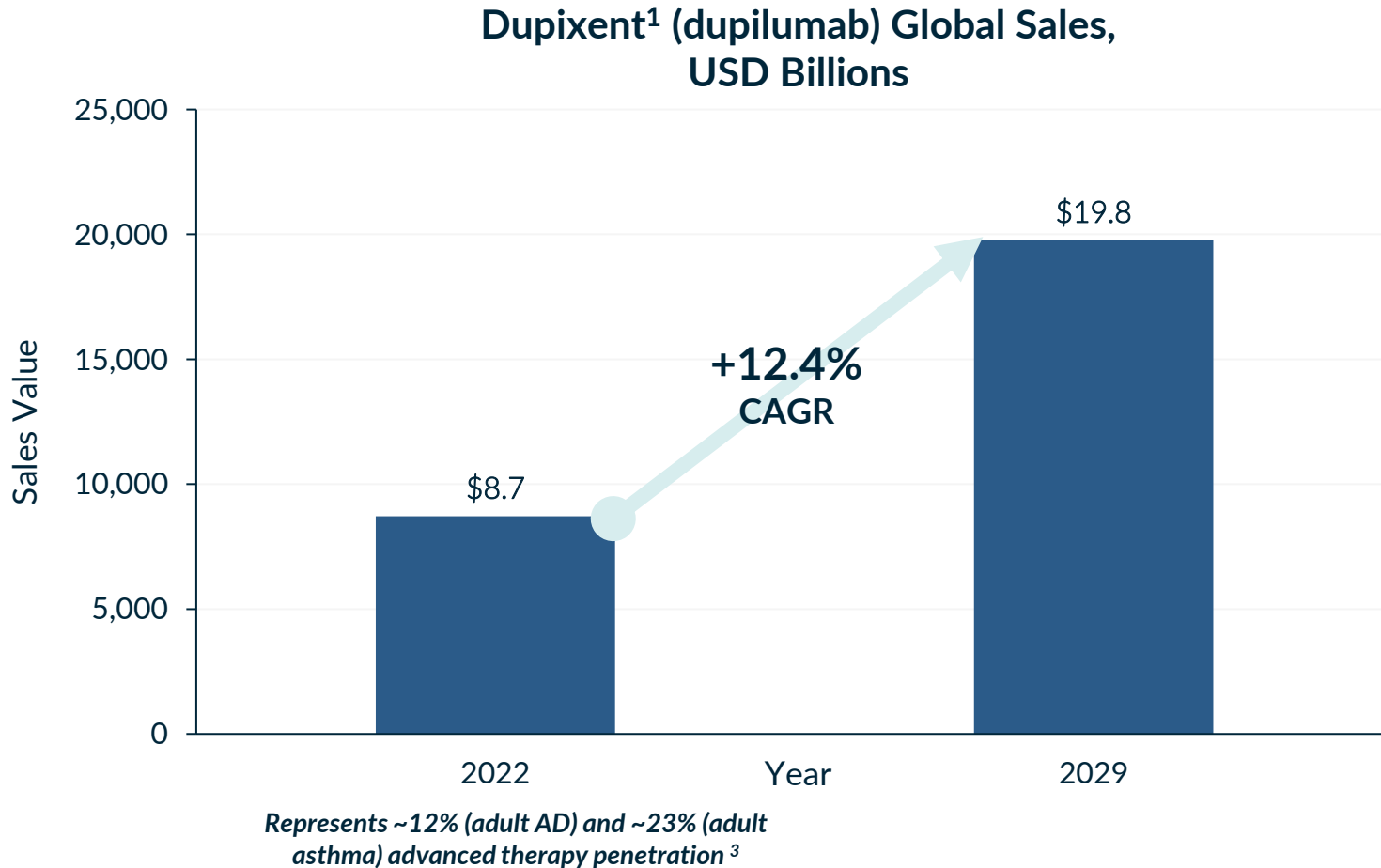
Phase 1/2 efficacy

Access large clinical and commercial opportunities



Dupilumab indications (AD, Asthma, COPD, CRSwNP, EoE, PN, others), mega-blockbuster potential

STAT6: Significant Potential Across Multiple I&I Indications



MARKET OPPORTUNITY

Total IL-4/IL-13 biologics² sales expected to double by 2029

- >\$10B in 2023
- >\$23B by 2029

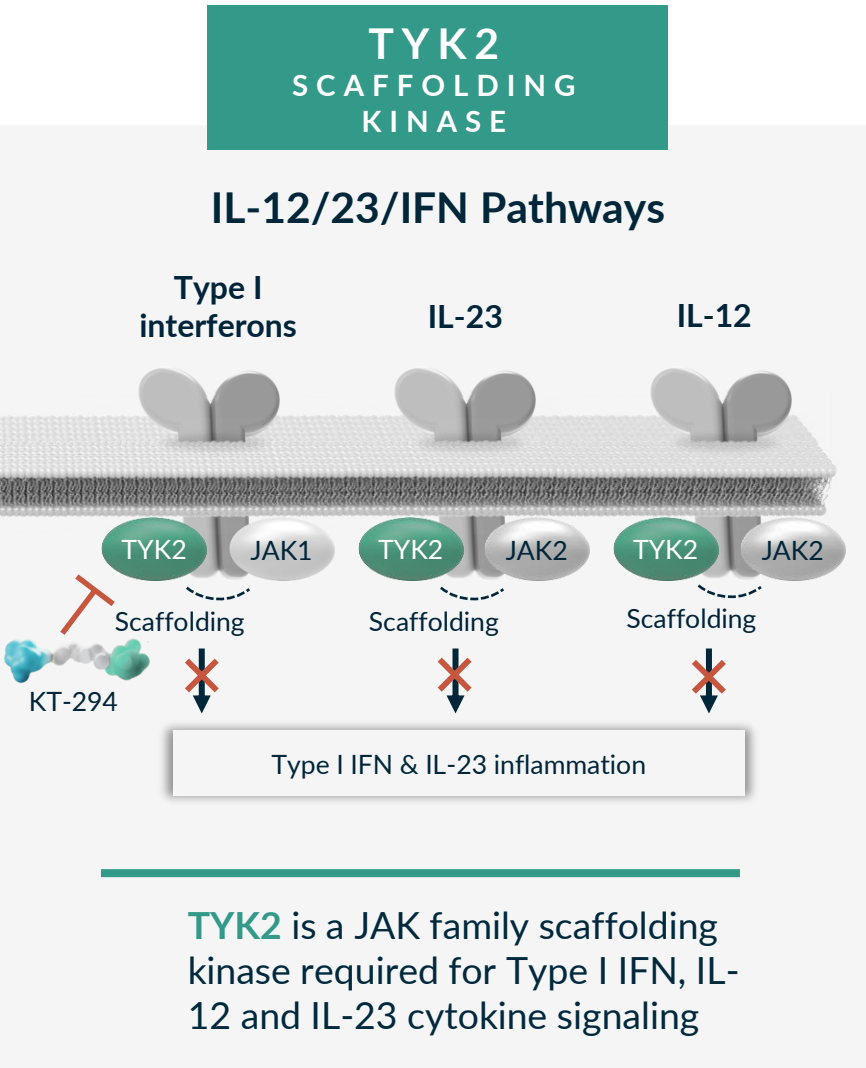
Currently approved indications of IL-4/IL-13 agents are dominated by biologics

Oral STAT6 degrader has potential for dupilumab-like activity with convenience of an oral pill

Oral STAT6 degrader could have broader access beyond biologics-eligible patients and impact much larger populations

¹dupilumab/Dupixent indications: Approved – Atopic Dermatitis, Asthma, CRSwNP, EoE, PN; Investigational – COPD, CSU, BP, CPUO, EoG, UC; ²IL-4/IL-13 = dupilumab, tralokinumab, and lebrikizumab; ³Sanofi 2Q23 Earnings; GlobalData

TYK2 Degradator: Degrading a Proven Target for a Best-in-Class Profile



BEST-IN-PATHWAY MECHANISM

Clinical pathway validation



IL-23 biologics (ustekinumab), TYK2 inhibitor (deucravacitinib) approved, others

Human genetics



LOF variant is protective in immunological diseases and generally normal

Undrugged/inadequately drugged by other technologies



Scaffolding kinase, SMLs do not fully block pathway

Best-in-pathway profile opportunity



TYK2 degrader recapitulates LOF phenotype: biologic-like activity and convenience of oral pill

Clear path to early clinical de-risking



Phase 1 differentiation

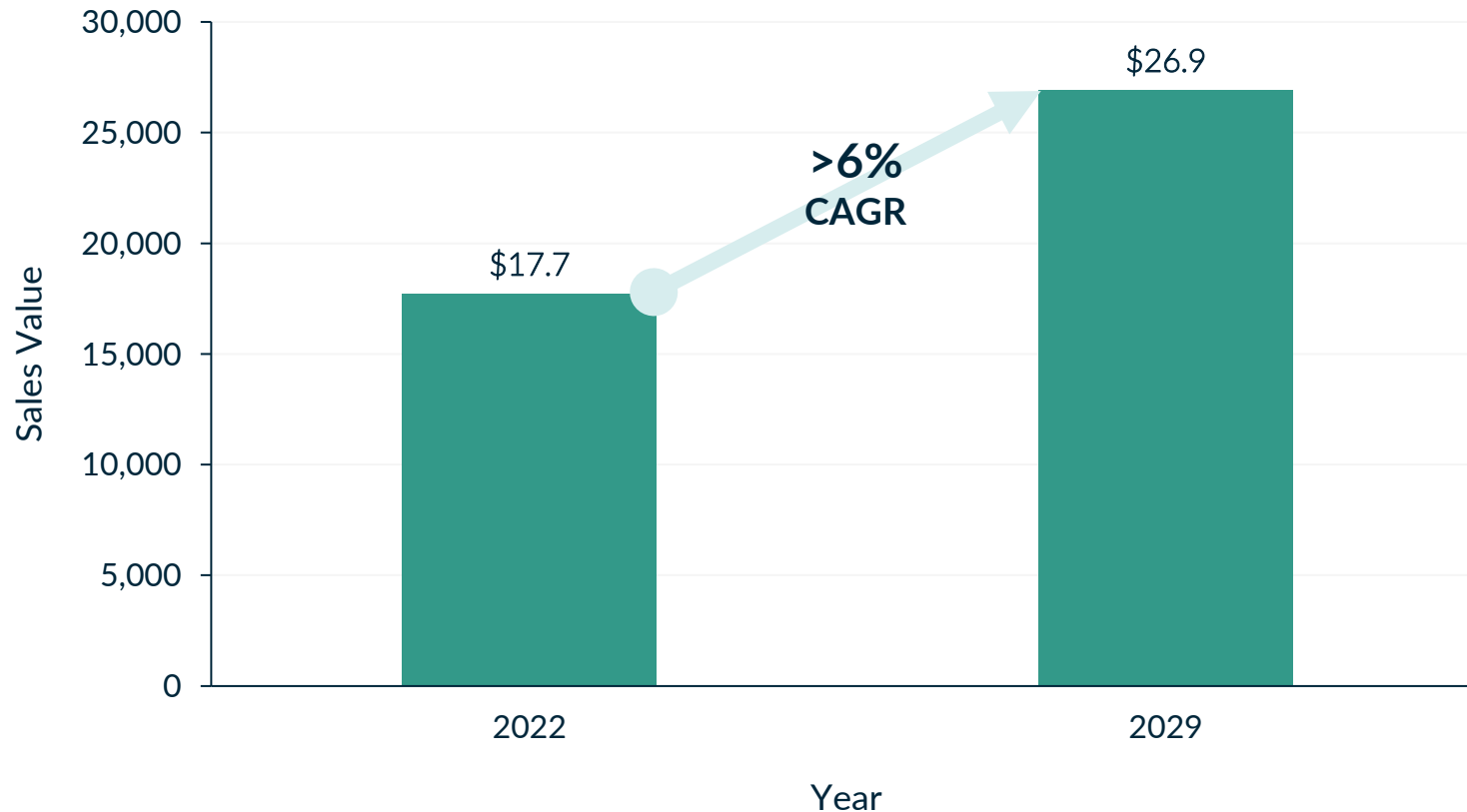
Access large clinical and commercial opportunities



IL-23, IFN indications, beyond: IBD, PsO, PsA, Lupus, others

TYK2: Significant Potential Across Multiple I&I Indications

IL-23 and Type I IFN Annual Market
USD Billions



MARKET OPPORTUNITY

Total IL-23 and Type I IFN biologics¹ sales expected to grow by over \$9B by 2029

- ~\$18B in 2022
- ~\$27B by 2029

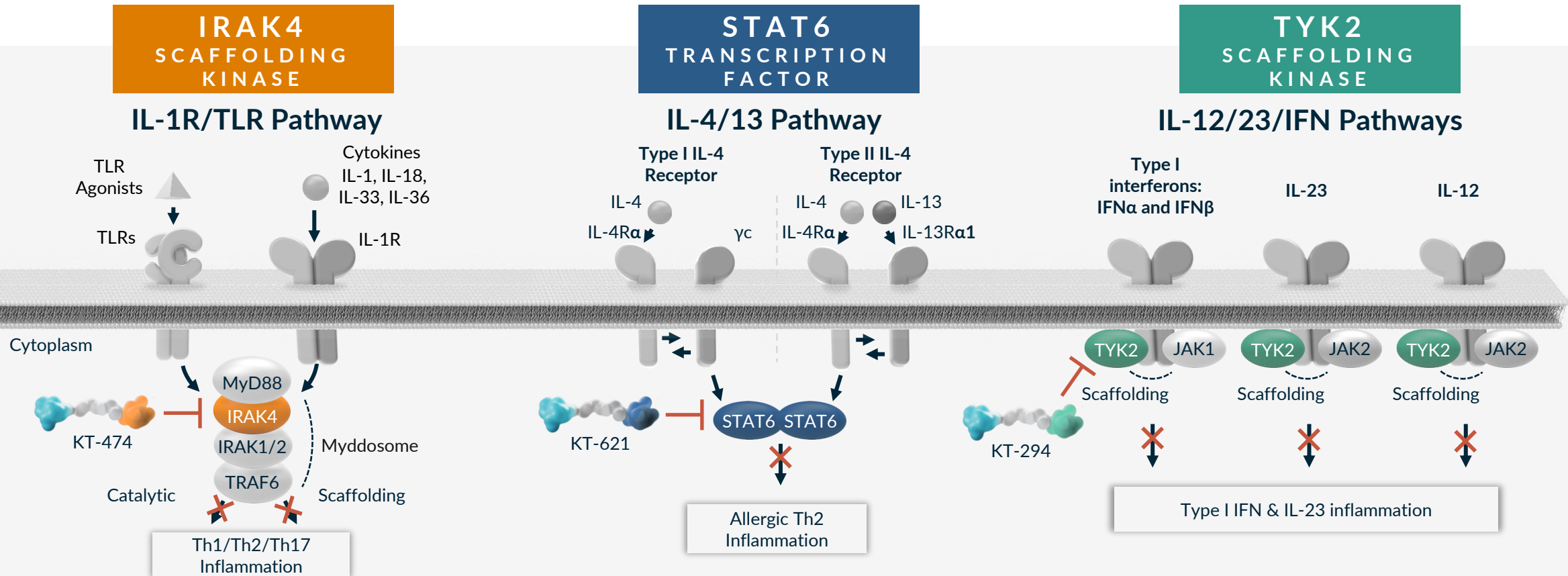
Currently approved indications dominated by biologics, with oral options challenged by efficacy and/or safety

TYK2 degrader has potential for biologic-like efficacy with convenience of oral pill

¹IL-23 = ustekinumab, risankizumab, guselkumab and tildrakizumab; Type 1 interferon = anifrolumab; GlobalData

Kymera Immunology Oral Degradable Portfolio

Complementary, First-in-class Mechanisms



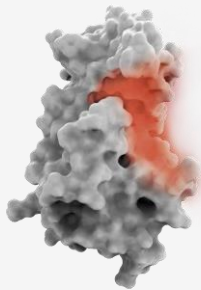
IRAK4 is master regulator of innate immunity with scaffolding and kinase functions

STAT6 is the only specific transcription factor responsible for IL-4/13 signaling

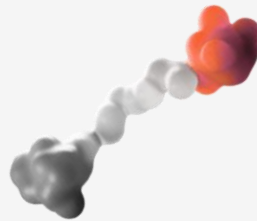
TYK2 is a JAK family scaffolding kinase required for Type I IFN, IL-12 and IL-23 cytokine signaling

Industry-leading Oral Immunology Pipeline

Three Fundamental Immune-inflammatory Pathways with Large Market Potential



High value undrugged/
inadequately drugged
targets



Next generation oral
drugs with potential
best-in-class profiles



Building the industry-
leading oral
immunology portfolio

IRAK4 (KT-474) SCAFFOLDING KINASE

Potential Indications

- HS, AD, RA, Asthma, COPD, IBD, others¹

Opportunity

- **First-in-class broad anti-inflammatory oral degrader**

Commercial Rights

- Up to 50% US with Sanofi, tiered royalties in ROW²

STAT6 (KT-621) TRANSCRIPTION FACTOR

- AD, Asthma, COPD, CRSwNP, EoE, PN, others

- **Dupilumab-like activity in a pill**

- Wholly owned

TYK2 (KT-294) SCAFFOLDING KINASE

- IBD, PsO, PsA, Lupus, others

- **Biologic-like activity in a pill**

- Wholly owned

¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities; ²KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.

WHAT TO EXPECT TODAY

Vision for our I/I portfolio and Kymera's unique ability to capitalize on power of TPD

Update on IRAK4 program

Detailed overview of STAT6 and TYK2 programs

- Clinical opportunities
- Degradator advantage
- Compelling preclinical data package
- Timelines to clinic





Paving the Way: KT-474, a First-in-Class IRAK4 Oral Degradator

Jared Gollob, M.D.,
Chief Medical Officer

IRAK4: What We Will Cover

- Pathway Biology and Validation

- Clinical Development/Commercial Opportunities

- Degradation Profile and Advantage

- Our Clinical Data and Fidelity of Translation

- Our Ongoing Phase 2 Studies

IRAK4 Biology and Target Rationale

Target Rationale

- IRAK4 is an obligate node in IL-1R/TLR signaling, and its degradation is the only approach to fully block the pathway

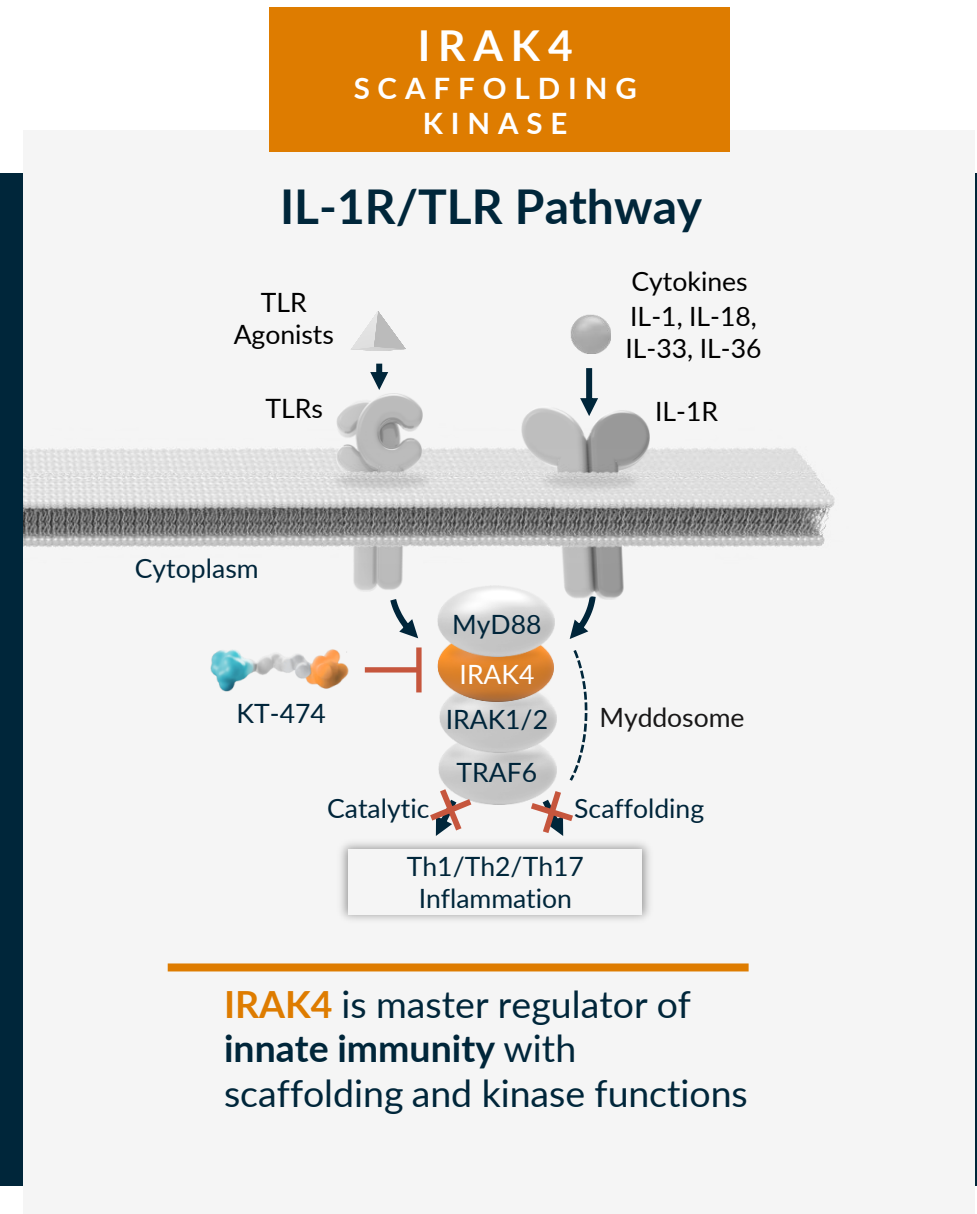
Human Genetics

- Adult humans with IRAK4 null mutation are healthy

Clinical Pathway Validation

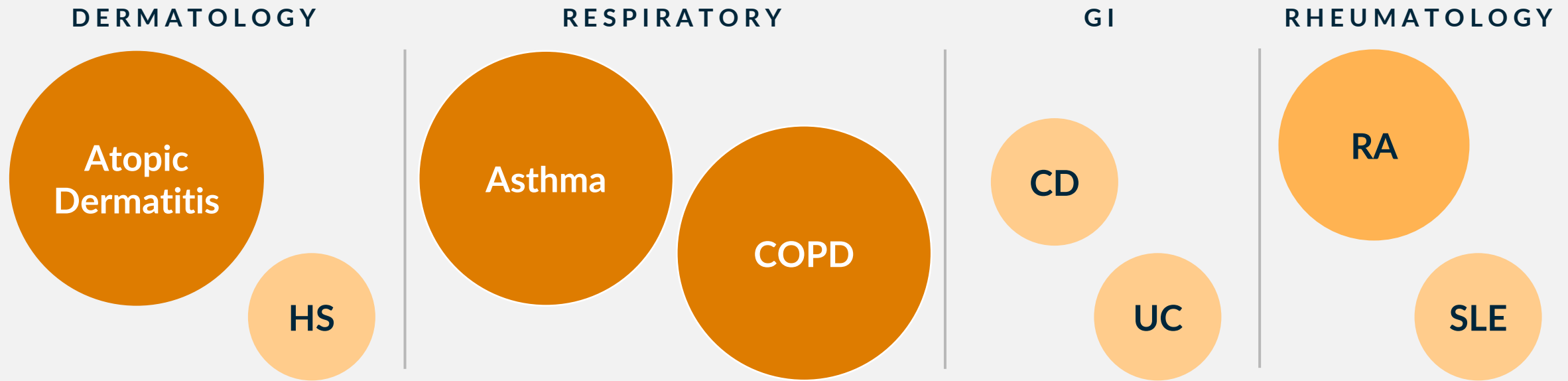
- IRAK4 degradation has the potential to achieve a broad, well-tolerated anti-inflammatory effect
- Multiple development opportunities in immune-inflammatory diseases which signal through MyD88/IRAK4 have been validated¹:
 - IL-1 α /IL-1 β : RA, CAPS, HS, AD, Gout
 - IL-18: AD, Macrophage Activation Syndrome
 - IL-36: Generalized Pustular Psoriasis, AD
 - IL-33: Asthma
 - IRAK4 SMI: RA

Adapted from West NT. Front Immunol 2019



¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

IL-1R/TLR Pathway Potential Impact Across Multiple Immune-Inflammatory Diseases



Total Potential Patient Impact¹: **>150M patients**

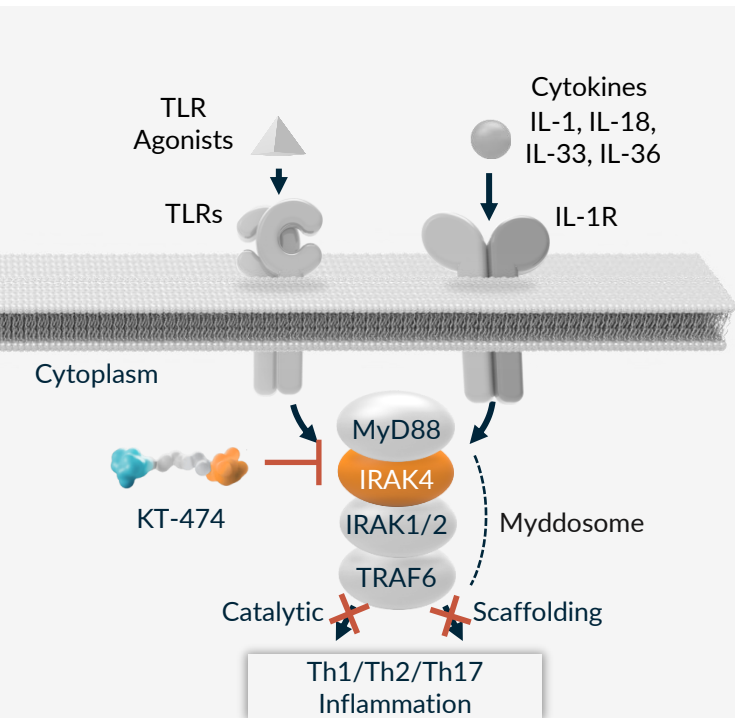
Numerous indication opportunities across multiple therapeutic areas validated by sub-optimal pathway inhibitors

IRAK4 degradation leading to full pathway inhibition has the potential to deliver superior profile to upstream biologics

Oral degrader medicines offer opportunity to reach broader patient populations

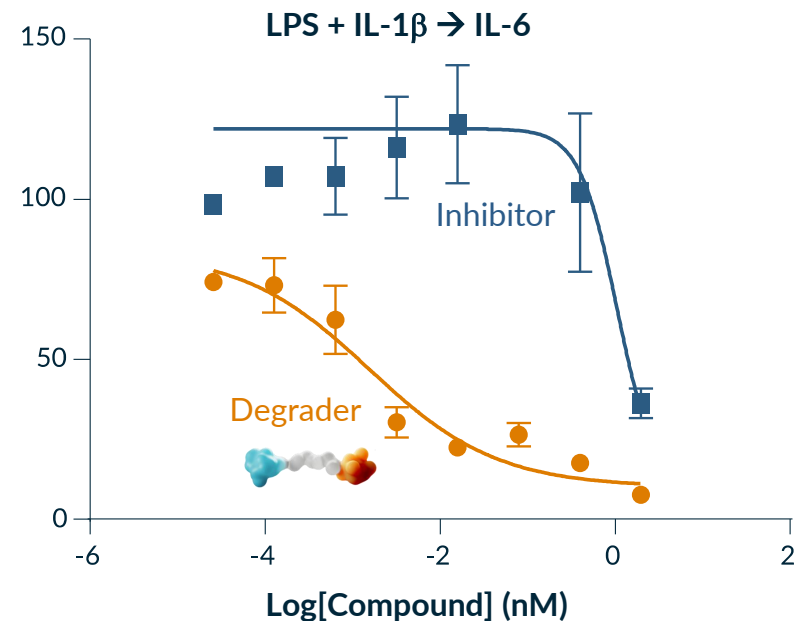
¹GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)

IRAK4 Degradation Advantage



IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation

Only Degradation Can Fully Block Inflammation



Preclinical Data (Kymera IRAK4 Backgrounder)

- IRAK4 KO is able to block TLR activation unlike the kinase dead rescue
- IRAK4 **scaffolding function** is critical in Myddosome formation and pathway signaling
- IRAK4 degradation, but not kinase inhibition, can **block TLR induced NF- κ B translocation** and **IL1R+TLR activation**
- IRAK4 degradation is superior to kinase inhibition at **blocking downstream phosphoproteome**
- IRAK4 degradation is superior to inhibition in a **variety of preclinical efficacy models**

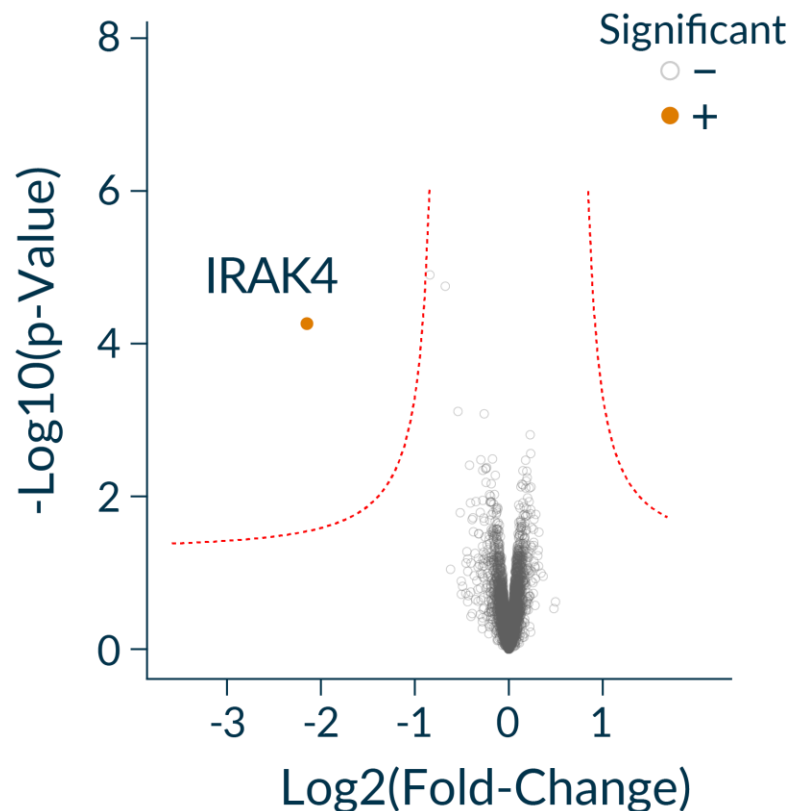
Clinical Data (Nature Medicine*)

- IRAK4 degradation **reduces signs and symptoms of HS and AD**, while IRAK4 SMI inactive in Phase 2 HS trial
- IRAK4 blocks inflammation in blood and skin of HS and AD patients

*Ackerman, et al., Nature Medicine (2023).

KT-474: Selective and Potent IRAK4 Degradator Active in Multiple Cell Types

Selectivity in PBMC



KT-474 selectively degrades IRAK4 in human immune cells at concentration 10-fold above the DC_{90}

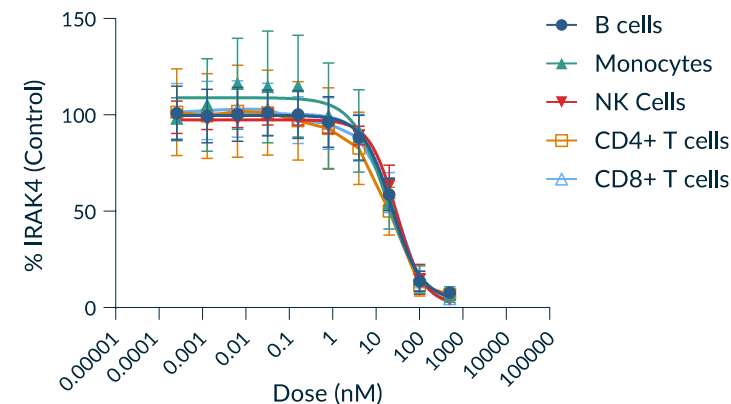
Potent degradation in PBMC subsets and skin cells including fibroblasts, with single-digit nM DC_{50}

Associated with functional inhibition of TLR- and IL-1 β -stimulated cytokine production

Comprehensive understanding of degradation kinetics across cell types to enable human translation

Potency in Blood and Skin Cells

KT-474 Degradation Across Immune Cell Types



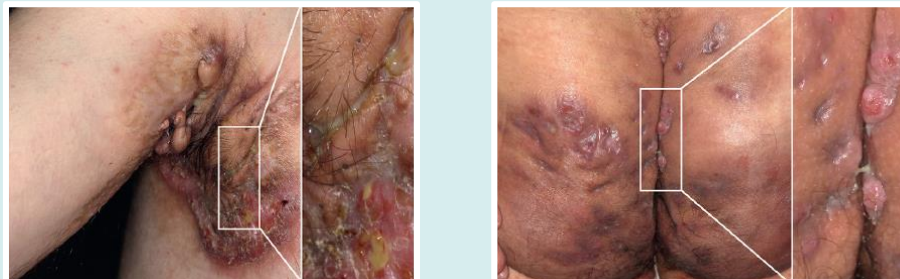
Cell type (Human)	Source	KT-474 DC_{50} (nM)
Monocytes	Blood	2.6
B cells	Blood	2.7
CD4 T cells	Blood	1.5
CD8 T cells	Blood	1.5
NK cells	Blood	1.8
Fibroblasts	Skin	1.5
Keratinocytes	Skin	7.8

Initial Clinical Focus for KT-474: Moderate to Severe HS and AD

Hidradenitis Suppurativa (HS)

Chronic and debilitating skin disease with painful nodules, abscesses and draining fistulae/tunnels

Major QoL impact: Pain, itching, depression, social isolation



Many diagnosed in their 20s/30s; more common in females (~3:1); prevalence estimated to be up to 1-3% of population in US and EU

Lesions characterized by pleotropic inflammation with Th1/Th17 skewing; bacterial infection and tissue destruction leading to TLR activation; IL-1 and IL-36 production

Active agents approved or in development target TNF- α , IL-17 and JAK/STAT pathways

Atopic Dermatitis (AD)

Chronic inflammatory skin disease with scaly, dry, erythematous lesions; intense itching/scratching, predisposition to infections

Major QoL impact: Itching, pain, sleep disturbance



Onset usually in early childhood; affects an estimated 98 million adults in US/EU5/JP¹

Lesions characterized by pleotropic inflammation with Th2 skewing; bacterial infection and skin barrier breakdown leading to TLR activation; IL-33 and IL-1 production

Active agents approved or in development target IL-4/IL-13, JAK/STAT and OX40/OX40-L pathways

KT-474 Opportunity: Potential for broad anti-inflammatory effect, competitive efficacy vs. pathway biologics and convenience of once-daily oral dosing

¹GlobalData – undiagnosed, all-age prevalence

KT-474 Phase 1: Compelling Data and Early POC in HS and AD

Healthy Volunteers (HV): SAD and MAD

- Evaluated safety, tolerability and pharmacokinetics in 105 healthy volunteers
 - SAD: Oral doses of 25-1600 mg
 - MAD: Escalating doses up to 200 mg were administered for 14 consecutive days
- Robust (>95%) and sustained IRAK4 degradation with single and multiple daily doses
- Broad inhibition of *ex vivo* TLR-mediated cytokine induction
- Generally well-tolerated across all dose groups



HS and AD Patient Cohort

- Open label study in 21 patients with HS and AD
- Dose: 75 mg QD with food (equivalent exposure to 100 mg fasted), administered for 28 consecutive days
- Safety, PK and PD comparable to healthy volunteers
- Robust IRAK4 degradation in blood and skin with associated systemic anti-inflammatory effect in HS and AD patients
- Promising clinical activity observed in HS and AD

nature medicine



Article

<https://doi.org/10.1038/s41591-023-02635-7>

IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial

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[Check for updates](#)

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News & views

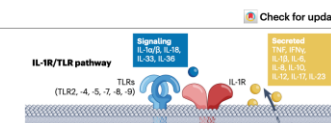
Targeted therapy

<https://doi.org/10.1038/s41591-023-02622-y>

PROTACs reach clinical development in inflammatory skin disease

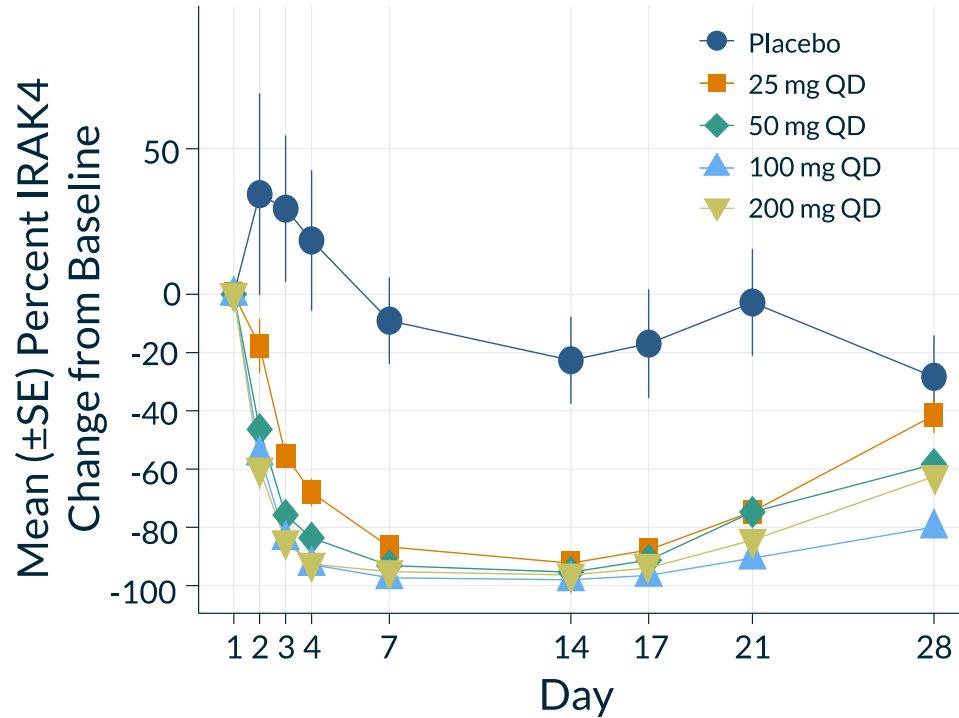
Fleur M. Ferguson

A phase 1 trial of an IRAK4-targeted protein degrader in patients with chronic inflammatory skin diseases hits an important milestone for the safe application of this drug class beyond oncology.

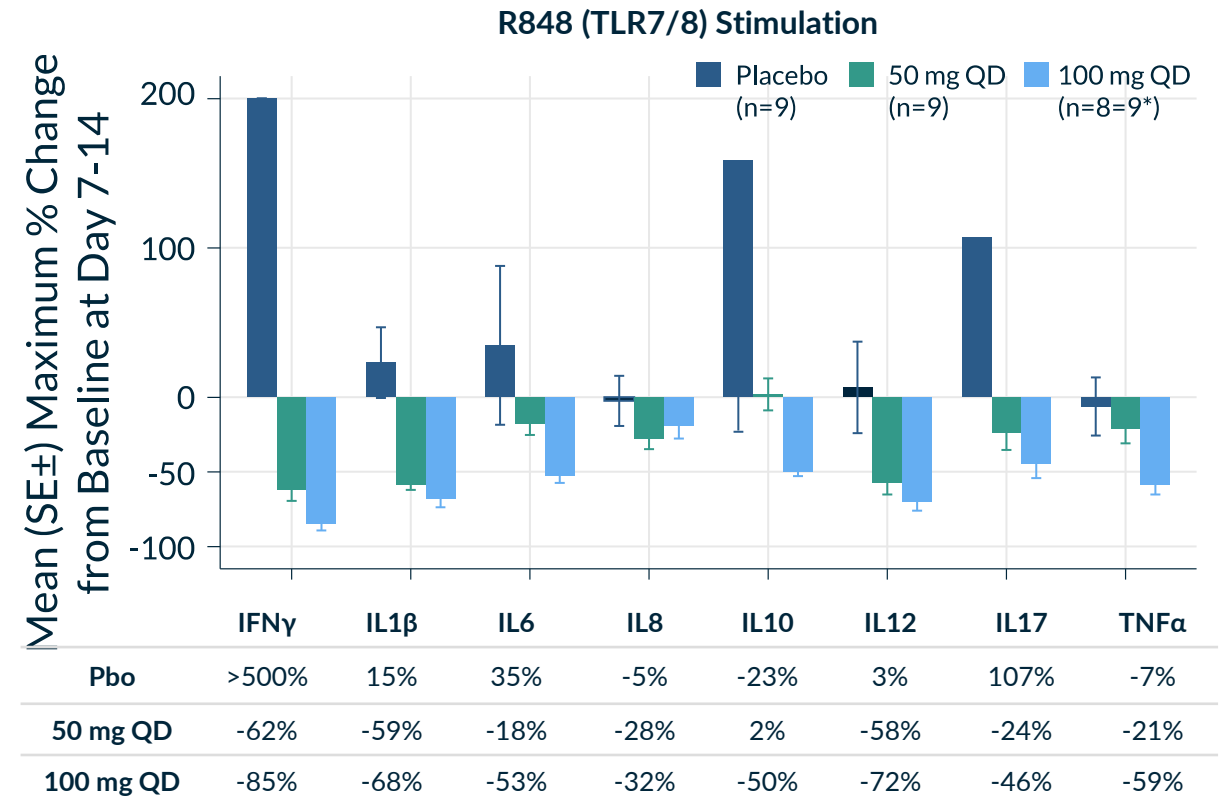


Near-Complete Degradation and Broad Cytokine Impact in Healthy Volunteers

Mean % Reduction of IRAK4
(Daily oral doses for 14 days)



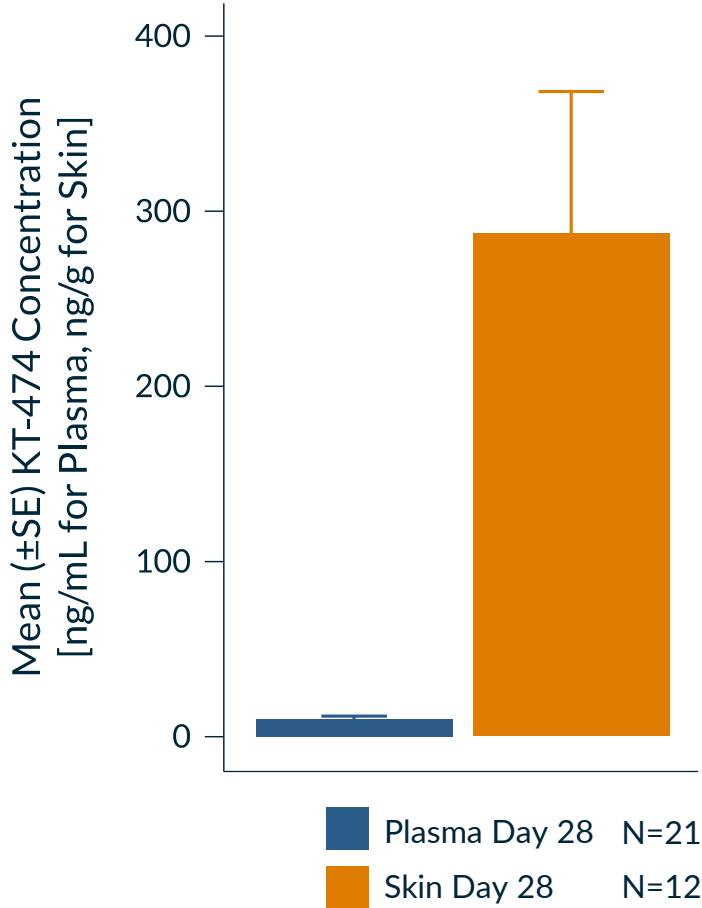
Ex Vivo Inhibition of 9 Disease-Relevant Cytokines, Day 7-14



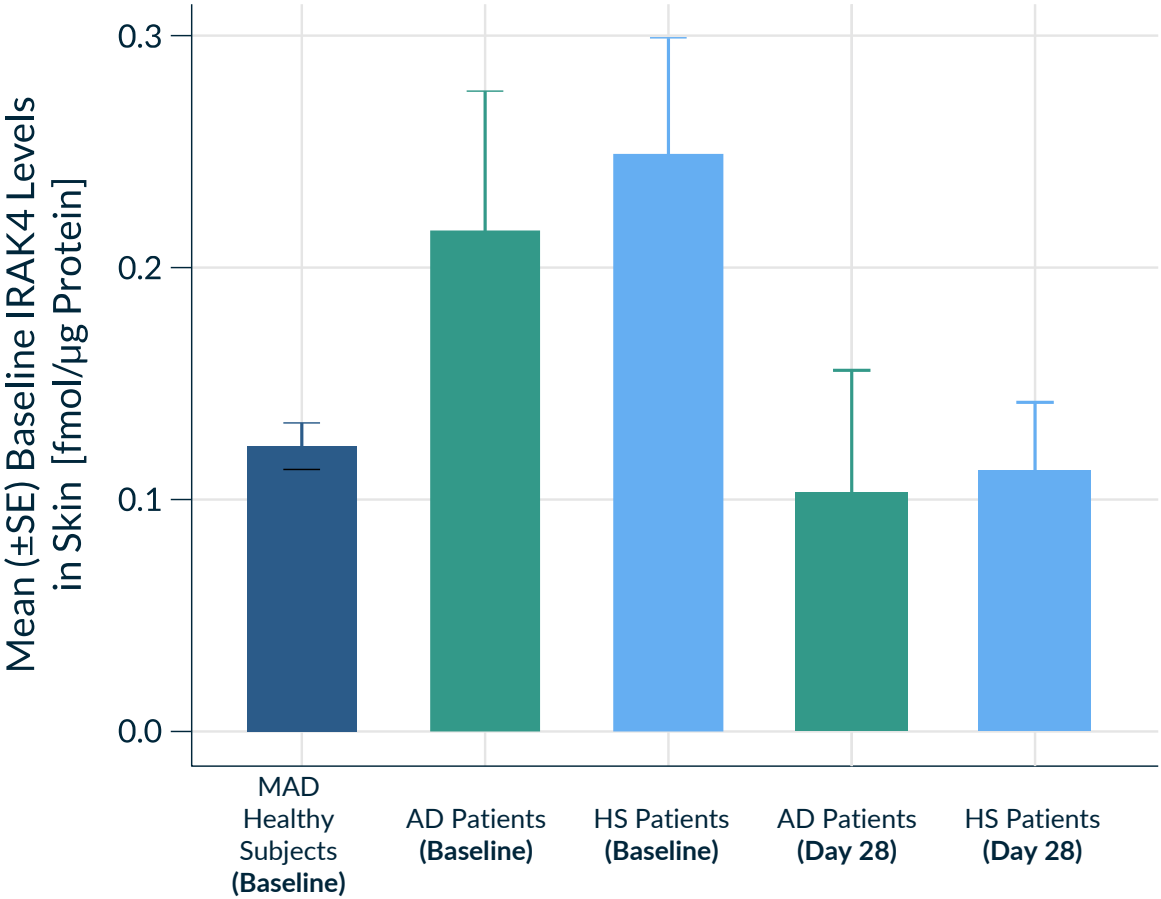
- High fidelity of PKPD translation from preclinical species to humans.
- Human efficacious concentrations (C_{trough} 3 ng/mL) and doses (50-200 mg) were correctly predicted

High Skin Exposure and Degradation in Skin of HS and AD Patients

High KT-474 Exposure in HS and AD Patients Skin

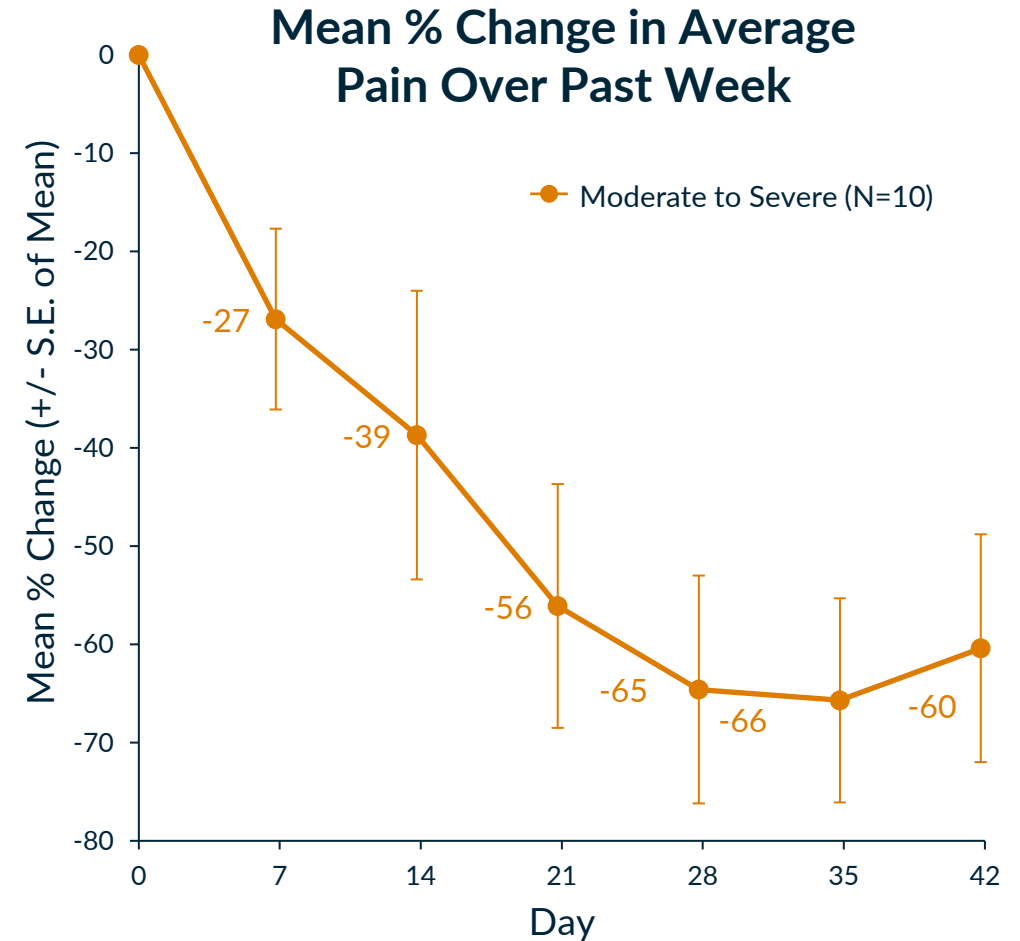
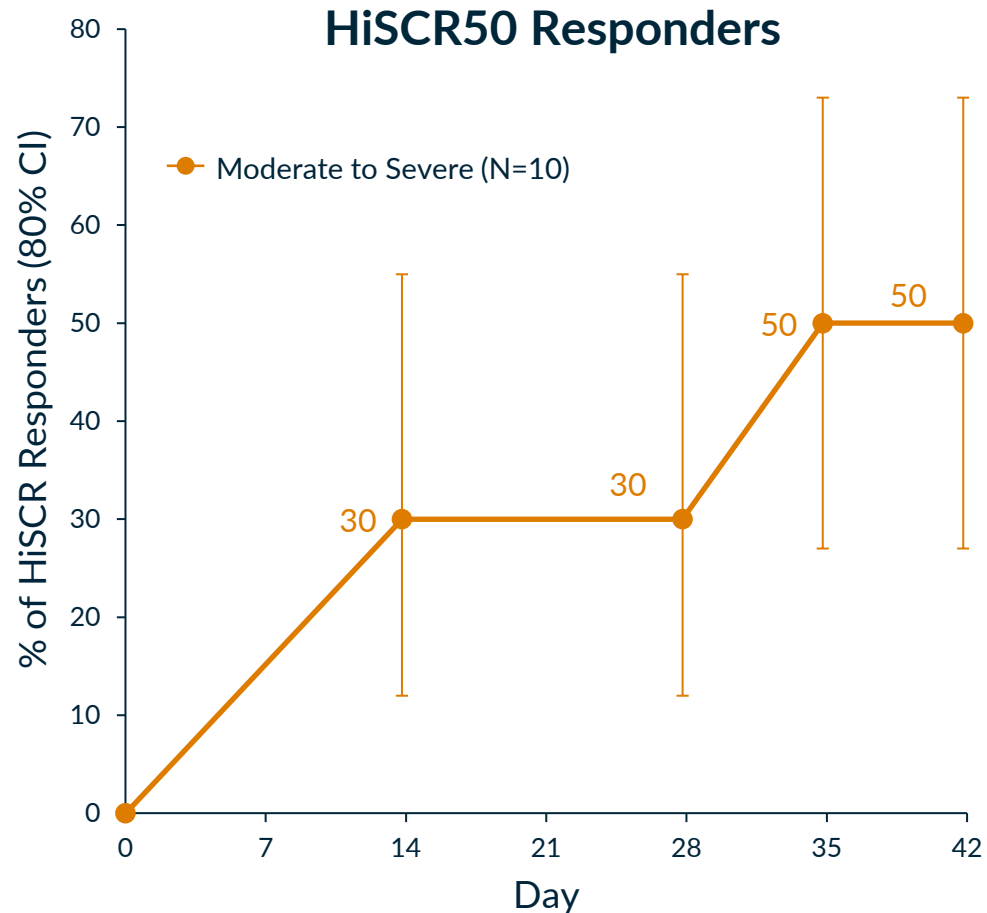


Reduced IRAK4 in Skin Lesions of AD and HS Patients



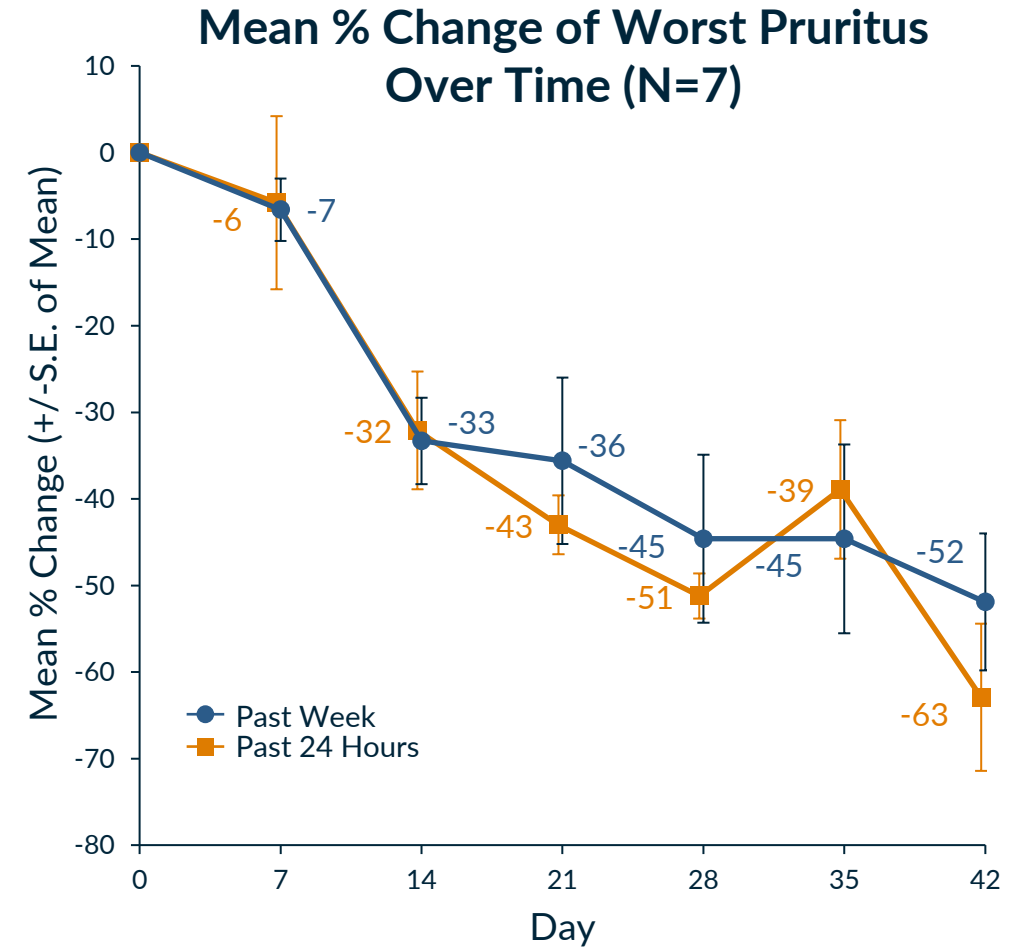
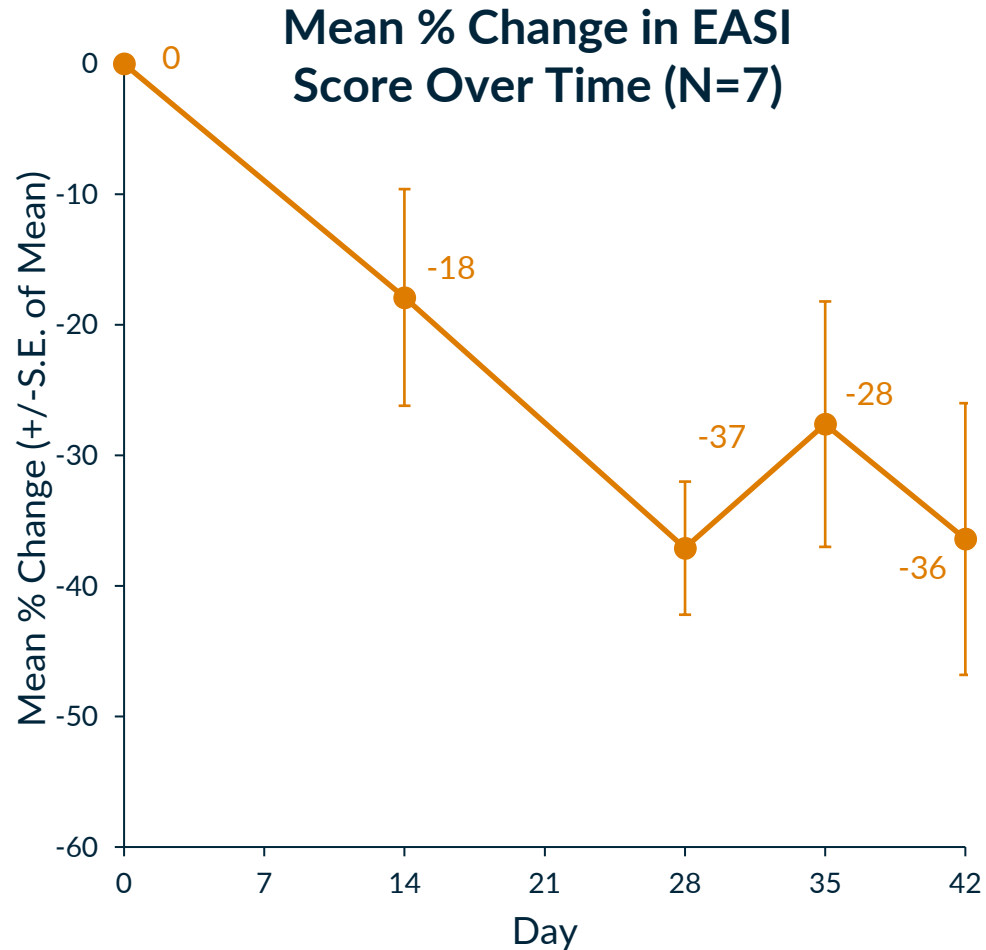
	MAD Healthy Subjects (Baseline)	AD Patients (Baseline)	HS Patients (Baseline)	AD Patients (Day 28)	HS Patients (Day 28)
N	46	7	11	6	9
Mean	0.12	0.22	0.24	0.1	0.11

Robust Clinical Impact in HS After Only 28 Days of Dosing



HiSCR50 response rate of up to 50% and pain reduction of up to 66% in moderate to severe HS patients

Robust Clinical Impact in AD After Only 28 Days of Dosing



EASI score reduction of up to 36% and pruritus reduction of up to 63% in moderate to severe AD patients

KT-474/SAR444656: Positioned for Clinical Success



Phase 2 HS Trial (ZEN)

- Double-blind, placebo-controlled
- Up to 99 patients, dosed for 16 weeks
- 1 KT-474 dose arm, 1 placebo arm
- Primary endpoint: % Change in AN Count
- Additional endpoints (select):
 - HiSCR50, IHS4, HS-Skin Pain-NRS30
- Primary completion (est.): February 2025

Phase 2 AD Trial (ADVANTA)

- Double-blind, placebo-controlled
- Up to 115 patients, dosed for 16 weeks
- 2 KT-474 dose arms, 1 placebo arm
- Primary endpoint: % Change in EASI
- Additional endpoints (select):
 - EASI 50/75/90, vIGA-AD, PP-NRS
- Primary completion (est.): January 2025

Topline data expected 1H 2025

Oral IRAK4 Degradator: KT-474

A best-in-pathway broad oral anti-inflammatory agent for multiple inflammatory diseases



Validated Biology

Mediates signaling through IL-1 and toll-like receptors

Upstream cytokine blockers with proven clinical activity across many diseases

Scaffolding kinase at the interface of innate and adaptive immune responses with a variety of functions

Competitive Profile

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases

>\$50B in combined global drug sales¹ opportunity

Large potential for oral degraders with best in pathway efficacy

KT-474 Progress/Next Steps

Phase 1 complete:

- Robust IRAK4 degradation
- Favorable safety profile
- Systemic suppression of proinflammatory cytokines and chemokines
- Early signs of strong clinical activity

Partner Sanofi conducting Phase 2 trials in HS and AD

Phase 2 data expected in 1H 2025

Activity and fidelity of translation of TPD platform in KT-474 Phase 1 trial informs probability of success with STAT6 and TYK2 immunology programs

¹GlobalData (2022 sales for AD, HS, Asthma, COPD, UC, CD, RA, SLE)



Dupilumab-like activity in a pill: KT-621, a First-in-class Oral STAT6 Degradar

Amy Wang, Ph.D.,
Senior Director, Biology Project Lead

What We Will Cover

- STAT6 Biology and Target Rationale

- Clinical Development/Commercial Opportunities

- Degradation Advantage

- Preclinical Data

- Next Steps

STAT6 Biology and Target Rationale

Target Biology and rationale

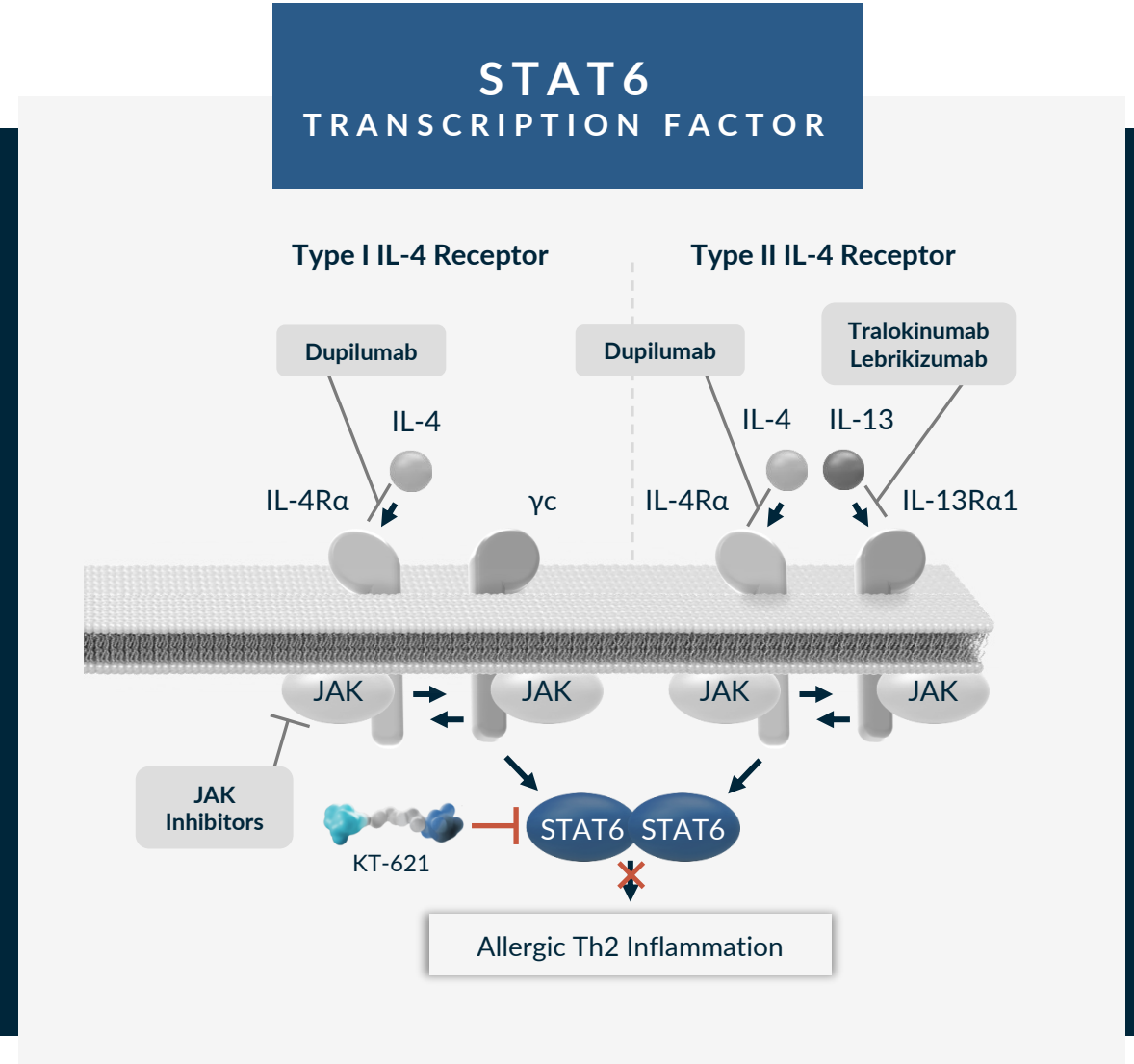
- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases

Human and Mouse Genetics

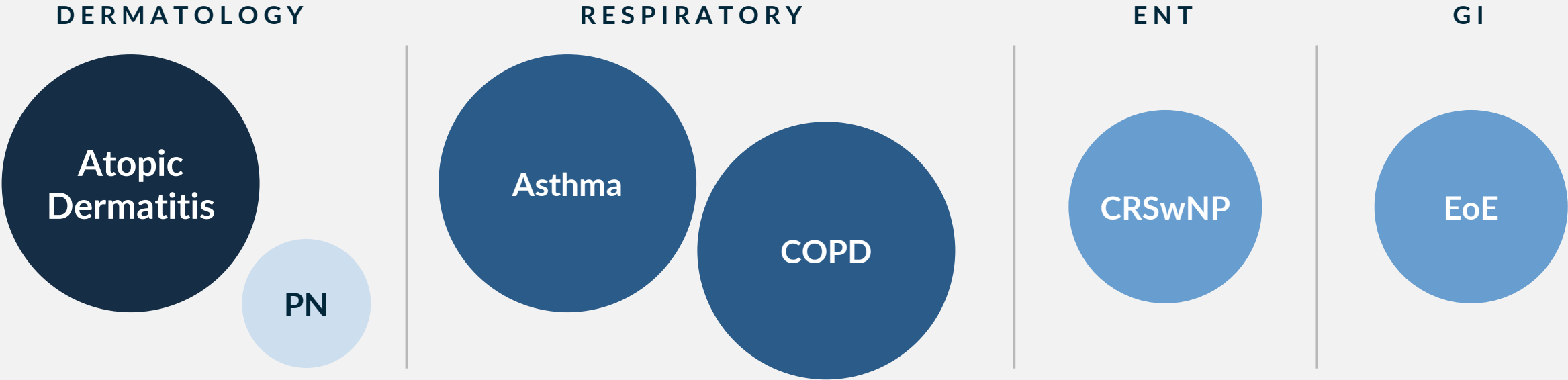
- Gain of function (GOF) mutations of STAT6 cause severe allergic diseases in human
- STAT6 KO mice develop normally, are viable and fertile

Clinical Pathway Validation

- Dupilumab, an IL-4R α monoclonal Ab has been approved in: Atopic dermatitis, Asthma, CRSwNP, Eosinophilic Esophagitis, Prurigo Nodularis, has positive Phase 3 data in COPD and is in development for multiple additional indications
- STAT6 degradation can achieve dupilumab-like pathway inhibition



Oral STAT6 Degraders Can Transform Treatment Paradigm in Multiple Indications De-risked by Dupilumab



Total Potential Patient Impact¹: >150M patients

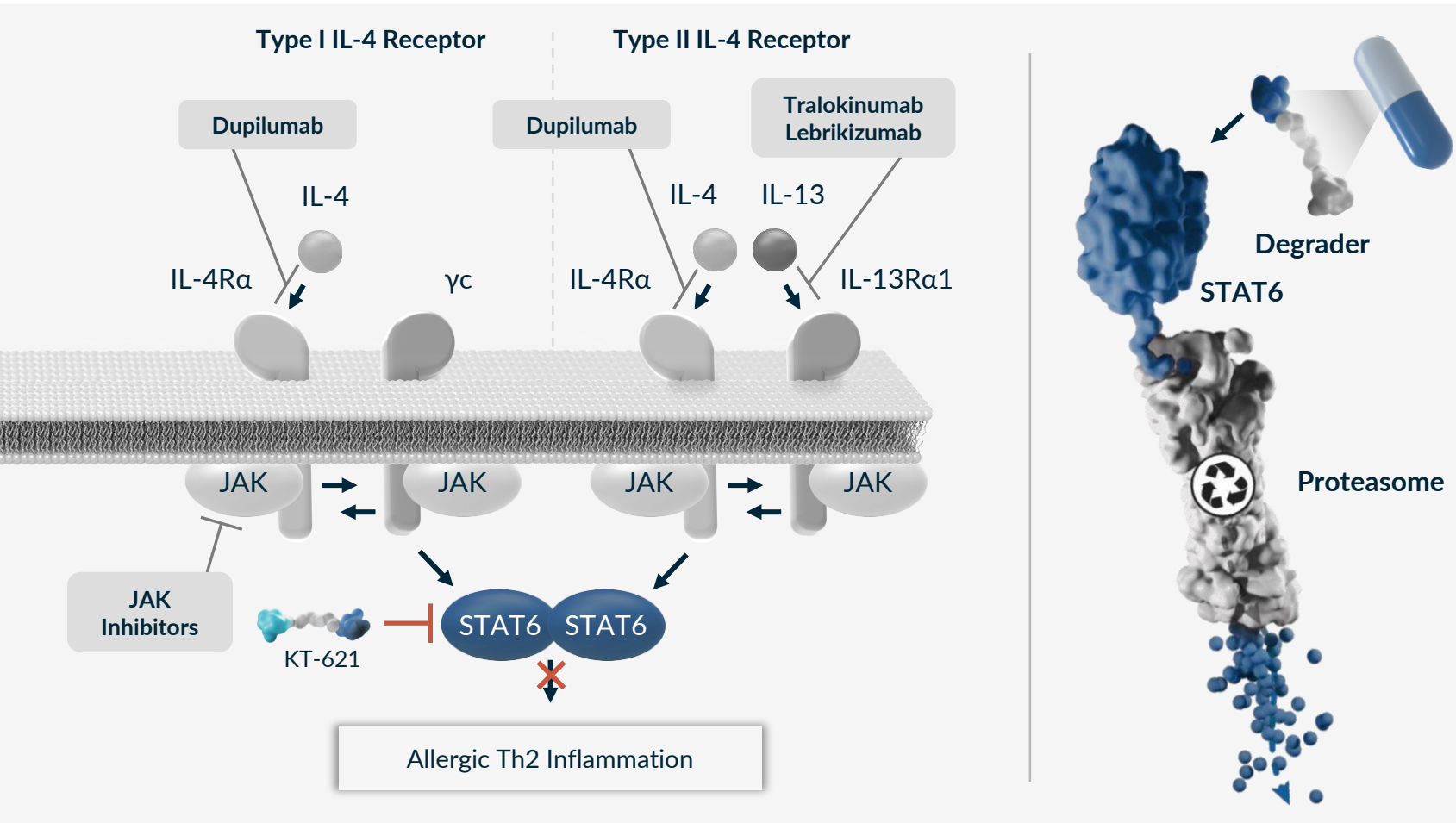
Numerous indication opportunities across multiple therapeutic areas de-risked by dupilumab

STAT6 degradation leading to full pathway inhibition has the potential to deliver dupilumab-like activity

Oral degrader medicines offer opportunity to reach broader patient populations

¹GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)






STAT6 Degradation Advantage



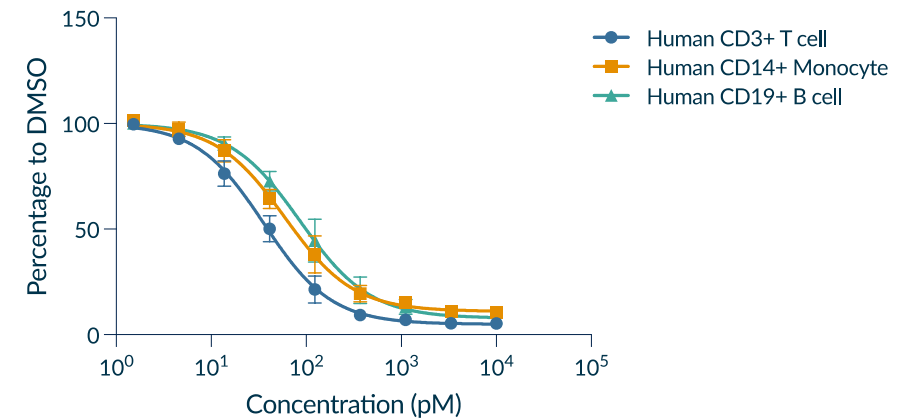
- STAT6 is the specific and essential transcription factor in the IL-4/13 pathway
- Occupancy based approaches (e.g., SMI) unlikely to block pathway fully in a pharmacologically relevant manner
- Only degradation of STAT6 can block its activity fully and match dupilumab pathway blockade *in vitro* and *in vivo*

KT-621: A Picomolar Degradator of STAT6

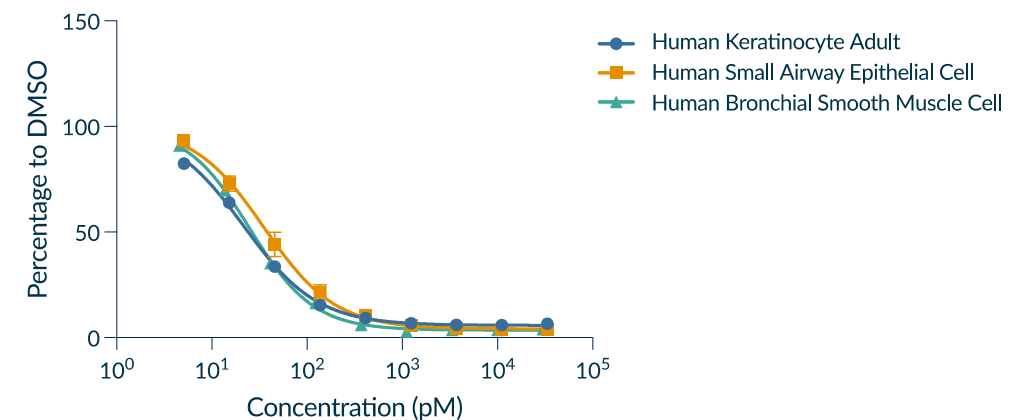
Consistent Degradation Across All Disease Relevant Cell Types Evaluated

		Human Primary Cell Type	KT-621, DC ₅₀ (pM)
Hematopoietic cell (all TH2 diseases)			
 Blood		Human PBMC	13
		Human CD3 T cell	36
		Human CD14 monocyte	60
		Human CD19 B cell	86
		Human eosinophil	99
Epithelial cell (AD, CPG, CU, asthma, COPD)			
 Skin		Human keratinocyte (adult)	22
		Human keratinocyte (neonatal)	18
 Lungs		Human bronchial tracheal epithelial cell	33
		Human small airway epithelial cell	35
Smooth muscle cell (asthma, COPD, EoE)			
 Throat/ Airway		Human bronchial smooth muscle cell	25
		Human esophageal smooth muscle cell	33
Endothelial cell (all TH2 diseases)			
 Blood Vessels		Human vascular endothelial cell	46

STAT6 Degradation in Hematopoietic Cells



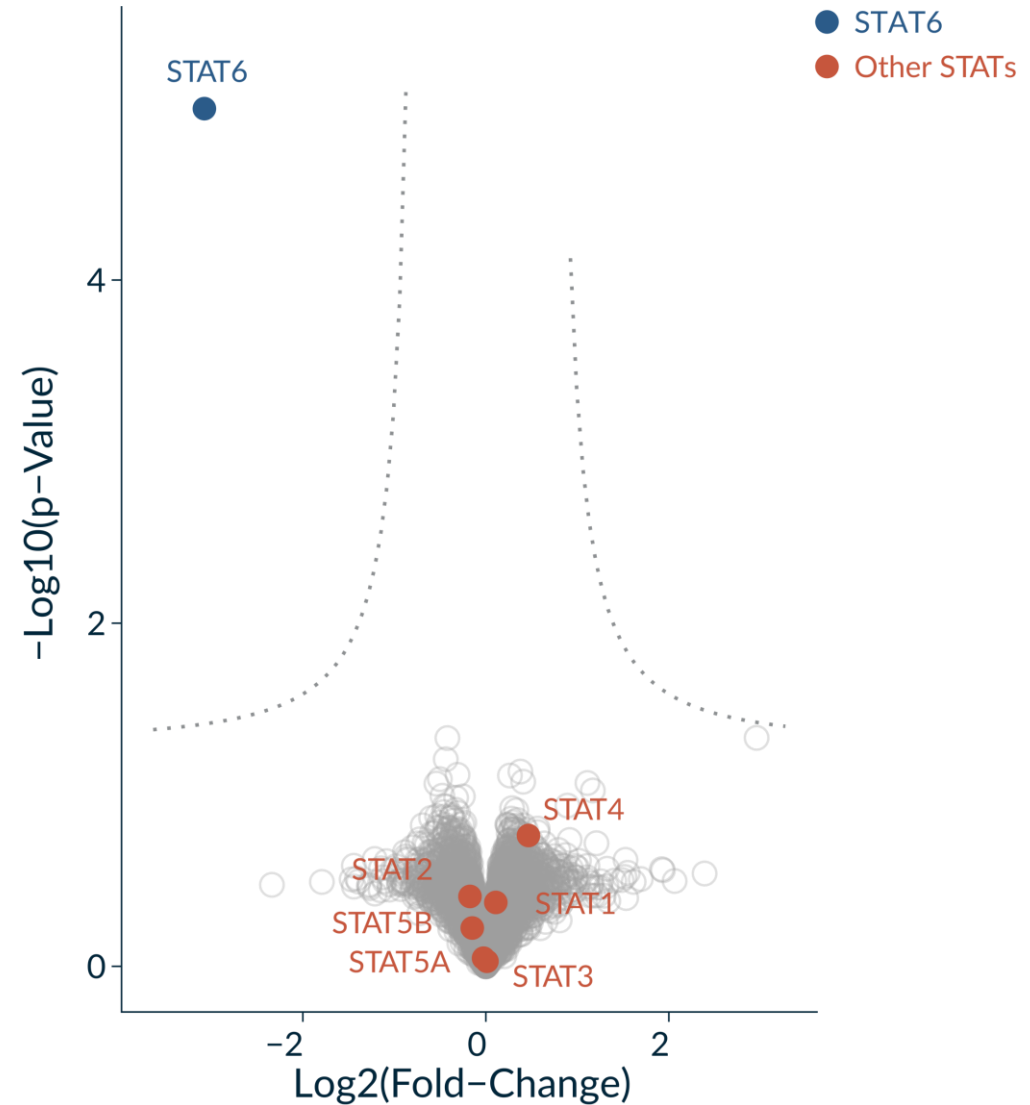
STAT6 Degradation in Tissue Cells



KT-621: Exquisite Degradation Selectivity for STAT6

Complete STAT6 degradation selectivity in human PBMC proteome at 100 x DC₉₀

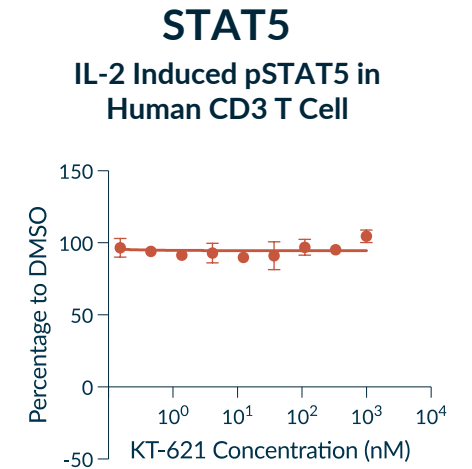
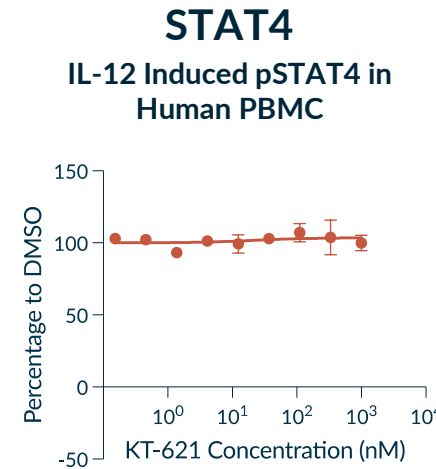
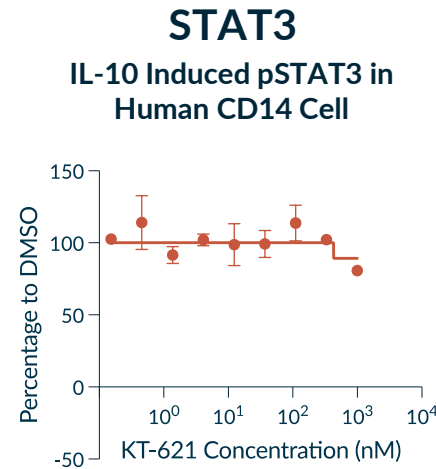
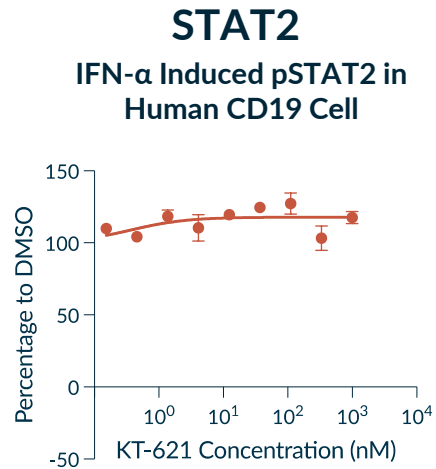
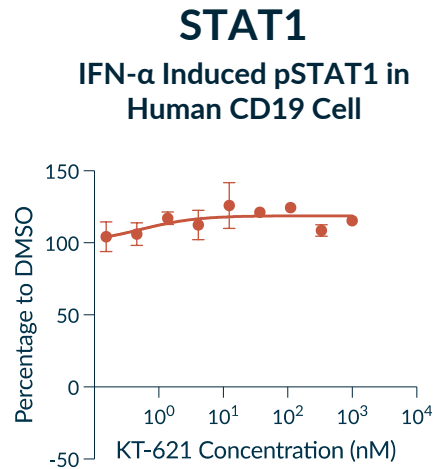
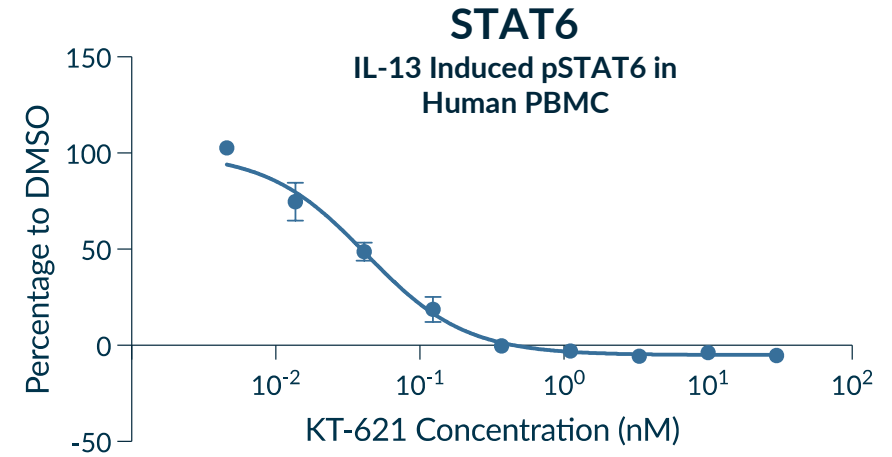
No other STATs are degraded to any extent



KT-621: Exquisite Pathway Selectivity for STAT6

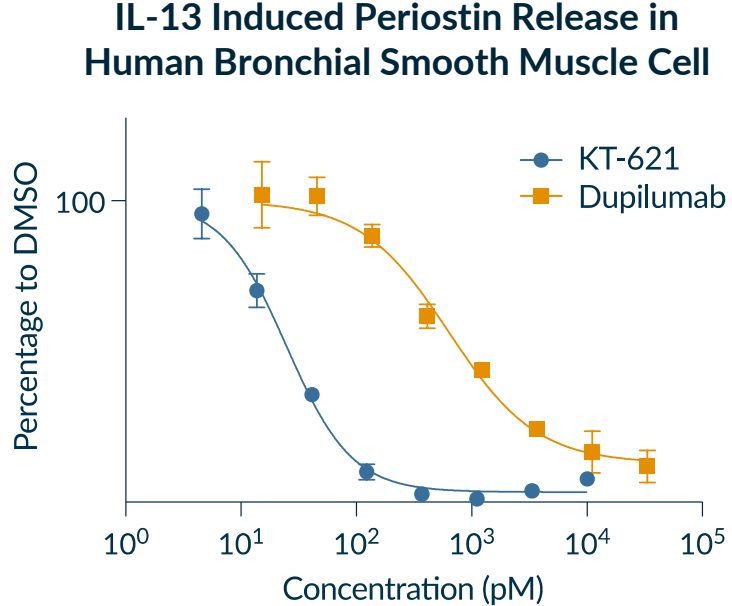
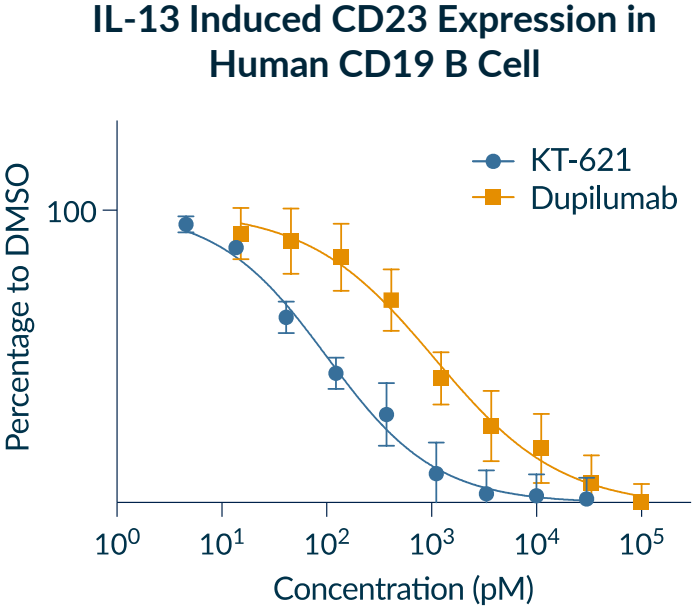
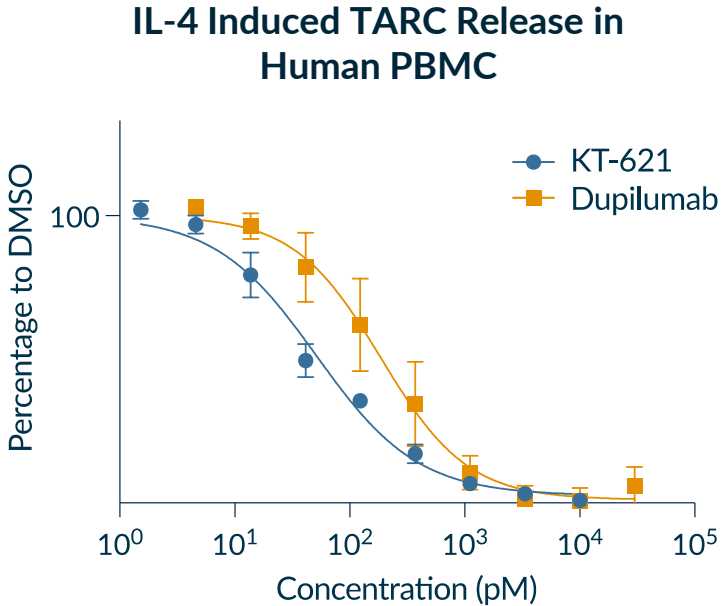
No Impact on Any Other STAT Pathway Observed

STAT assays	KT-621, IC ₅₀ (nM)
IFN- α induced pSTAT1	> 1000
IFN- α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042



KT-621 Fully Blocks IL-4/13 Pathway, More Potently than Dupilumab

		Cellular Functional Assay	KT-621 IC ₅₀ (pM)	Dupilumab IC ₅₀ (pM)
TARC	Serum Th2 biomarker, chemoattractant for Th2 cell	IL-4 TARC release in human PBMC	62	194
		IL-13 TARC release in human PBMC	43	113
CD23	B cell activation marker, correlates with IgE class switch	IL-4 CD23 expression in human CD19 B cell	125	354
		IL-13 CD23 expression in human CD19 B cell	98	1070
PERIOSTIN	Serum Th2 biomarker and ECM protein associated with tissue remodeling in atopic diseases	IL-13 Periostin release in human bronchial smooth muscle cell	24	637
		IL-13 Periostin release in human esophageal smooth muscle cell	39	431

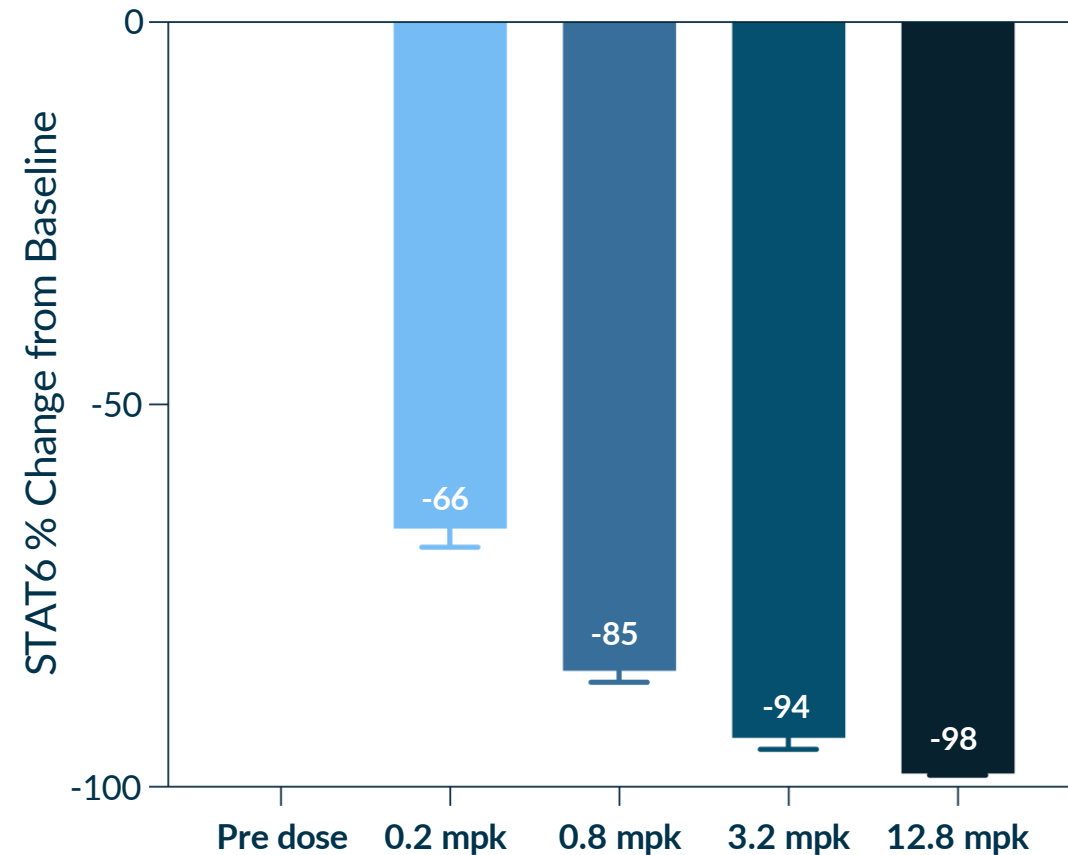


KT-621 Achieves Dose Dependent Deep Degradation of STAT6 *in vivo* with Low Oral Doses

KT-621 potently degrades STAT6 across multiple preclinical species

KT-621 can degrade STAT6 to depletion with low oral doses

STAT6 Degradation in Dog Blood post 7 days of KT-621 QD Oral Dosing

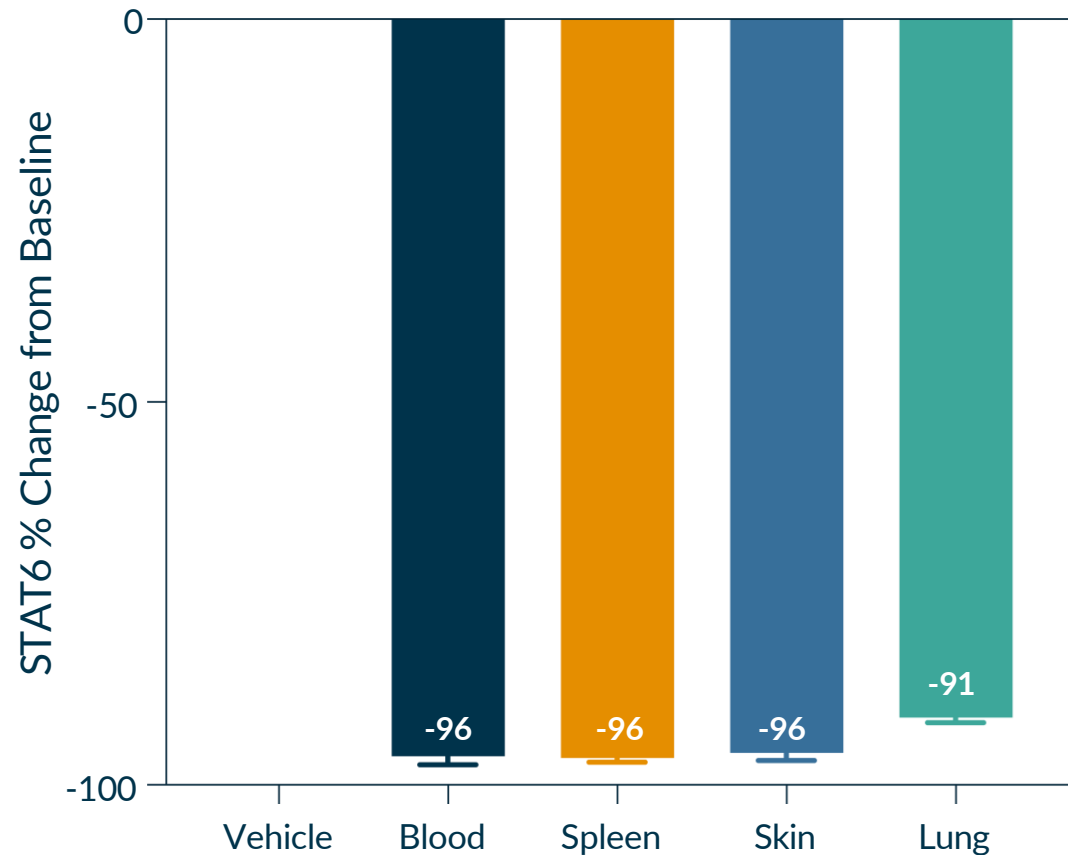


KT-621 Degrades STAT6 in Disease Relevant Tissues in NHP

Deep degradation of STAT6 in NHP after 14 days of daily oral dosing

STAT6 is degraded in key disease-relevant tissues: blood, spleen, skin and lung

STAT6 Degradation in NHP Tissues post 14 days of KT-621 10 mpk QD Oral Dosing

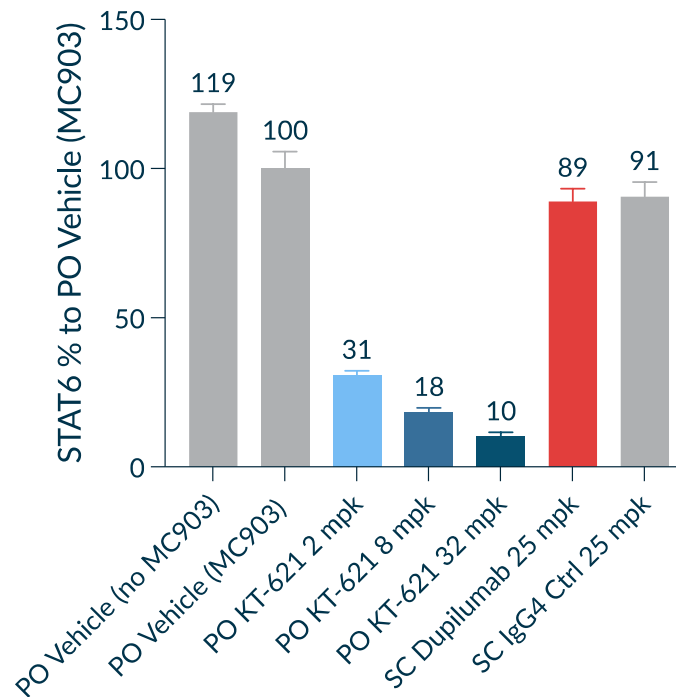


KT-621 Has Comparable *in vivo* Efficacy to IL-4R α Saturating Dose of Dupilumab in the MC903 Atopic Dermatitis Model

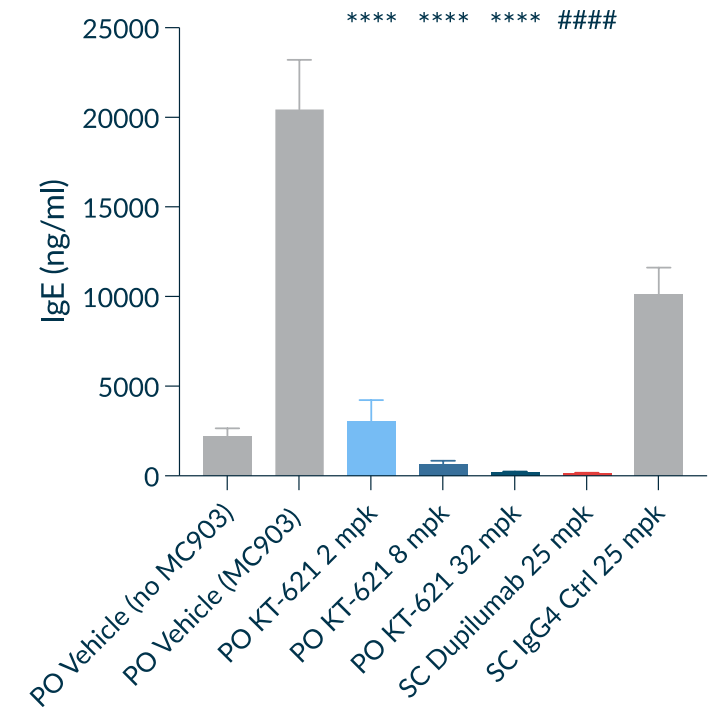
An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

- **KT-621 dosed QD orally for 11 days**
- **Dupilumab dosed 4 times subcutaneously, 25 mpk twice a week (IL-4R α saturating dose); effect equivalent to 300 mg every other week in human**

STAT6 Degradation in Mouse Spleen



Total Serum IgE

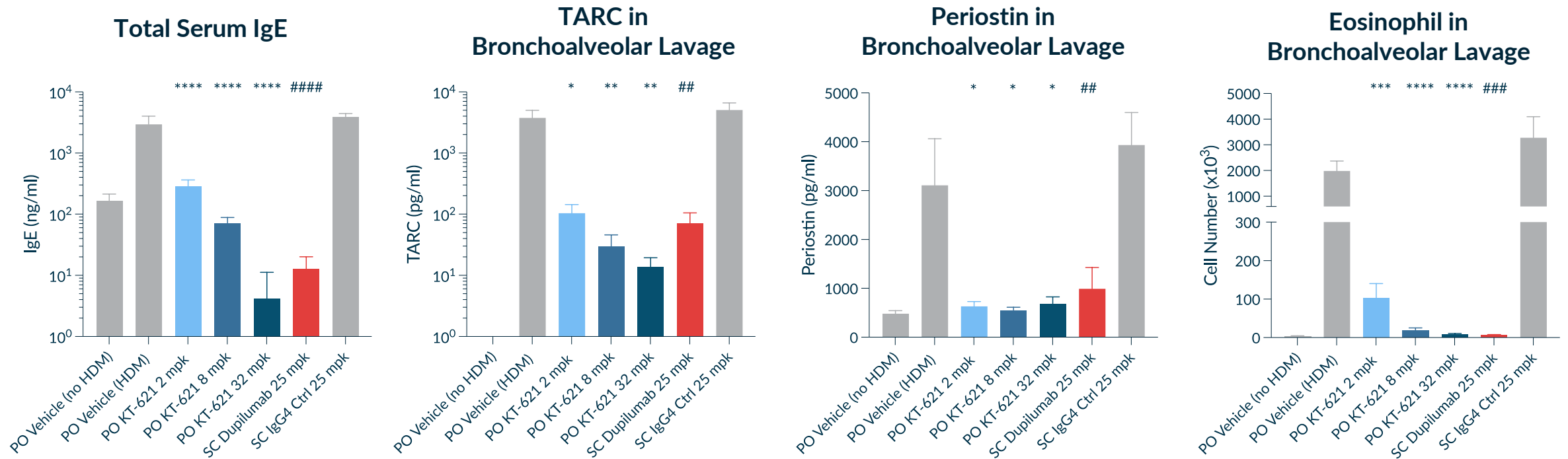


* Significance to PO vehicle (MC903); # Significance to SC IgG4 25 mpk BIW

KT-621 Has Comparable or Superior *in vivo* Efficacy to IL-4R α Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model

A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. *Allergy*. 2020)

- KT-621 dosed QD orally for 31 days. 2/8/32 mpk doses showed 72/85/91% STAT6 degradation respectively in mouse spleen
- Dupilumab dosed 9 times subcutaneously, 25 mpk BIW (IL-4R α saturating dose), effect equivalent to 300 mg every other week in human



*Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk

Oral STAT6 Degradator: KT-621

Dupilumab-like efficacy with oral small molecule profile



Validated Biology

Specific and essential transcription factor in IL-4 and IL-13 signaling pathways

Central driver of Th2 inflammation

STAT6 validated by human genetics

Pathway validated by human genetics and dupilumab across multiple indications

Competitive Profile

WW IL-4/IL-13 biologic market currently \$10B+ annually

Estimated to grow to \$23B+ with expanded indications and new entrants

Mega-blockbuster potential for oral degraders with dupilumab-like efficacy and good safety

Potential to access beyond biologics-eligible patients and much larger population

KT-621, FIH: 2H 2024

Full IL-4 and IL-13 functional inhibition with picomolar IC50s superior to dupilumab

Robust efficacy shown in *in vivo* models of atopic dermatitis and lung inflammation equal or superior to dupilumab

STAT6 degradation was well-tolerated in multiple preclinical safety studies at >40x efficacious concentration

Currently in IND enabling studies



Degrading a Proven Target: KT-294, a First-in-Class Oral TYK2 Degradator

Juliet Williams, Ph.D.,
Head of Research

What We Will Cover

- TYK2 Biology and Target Rationale

- Clinical Development/Commercial Opportunities

- Degradation Advantage

- Preclinical Data

- Next Steps

TYK2 Biology and Target Rationale

Target Biology and Rationale

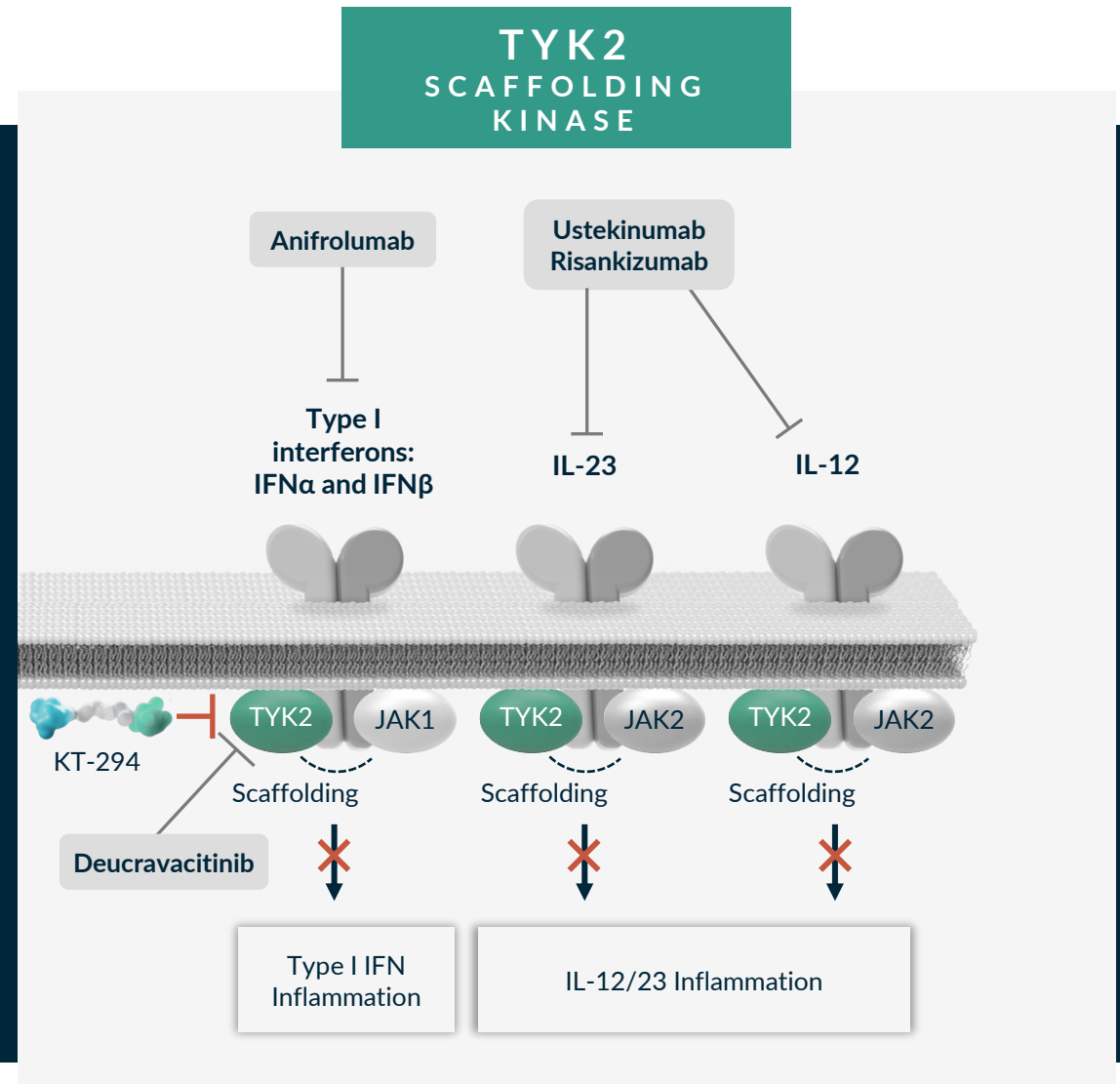
- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 regulated cytokines are clinically validated targets for autoimmune and inflammatory diseases

Human Genetics

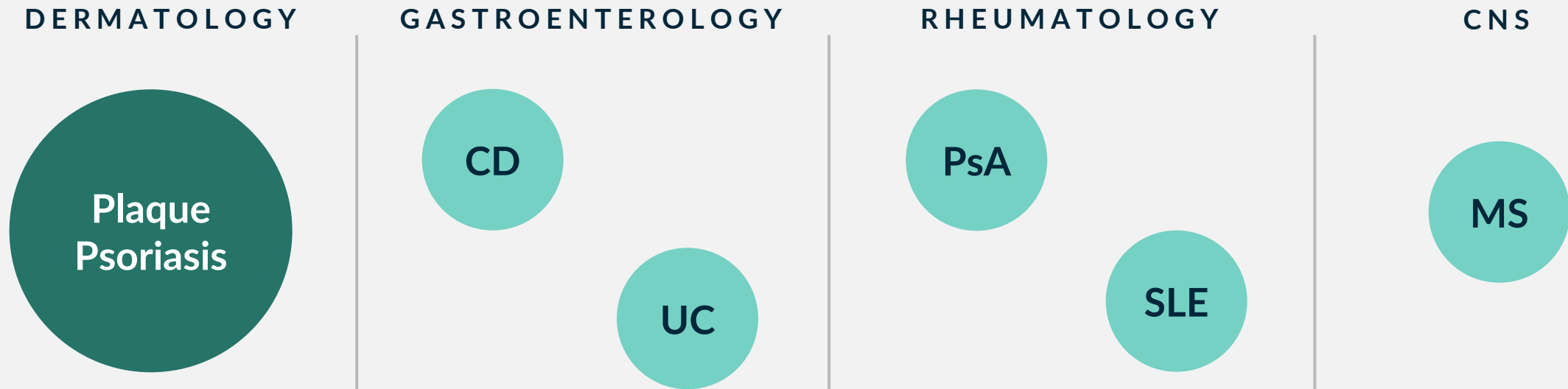
- Loss-of-function variant of TYK2 is protective in autoimmune and inflammatory diseases

Clinical Pathway Validation

- IL-23 (\pm IL-12)-targeting agents include ustekinumab, risankizumab, guselkumab, and tildrakizumab, with approvals in PsO, PsA, CD, UC
- Type I IFN-targeting agents include anifrolumab with approval in SLE
- TYK2 SMI deucravacitinib recently approved in PsO



Patient Impact of TYK2: Potential Best-In-Class Opportunity in I&I



Total Potential Patient Impact¹: > 20M patients

Numerous indication opportunities across multiple therapeutic areas de-risked by biologics and deucravacitinib

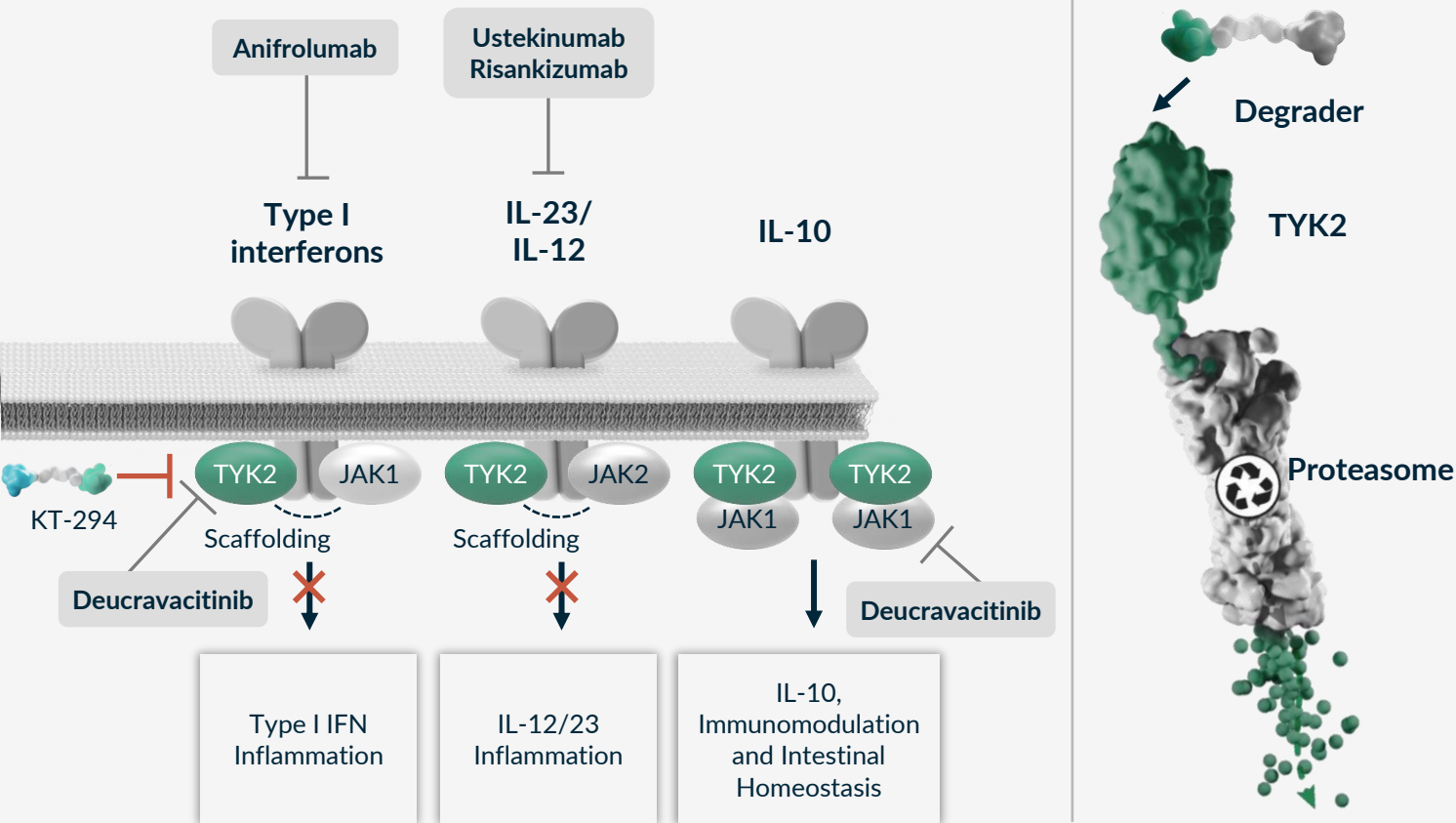
TYK2 degradation, differentiated from inhibition, leads to full pathway inhibition with potential to deliver biologic-like activity

Oral degrader medicines offer opportunity to reach broader patient populations

¹GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)

TYK2 Degradator Advantage

Only TYK2 Degraders Can Reach Biologics-like Activity



- TYK2 has a well-established scaffolding function that is responsible for cytokine receptor surface expression and activation
- Unlike SMIs, only TYK2 degradation recapitulates the human LOF phenotype of full pathway inhibition of Type I IFN, IL-12 and IL-23 and sparing of IL-10
 - Unlike deucravacitinib, which inhibits IL-10 through JAK1, KT-294 does not inhibit IL-10, which is important in IBD
 - Compared to TAK-279, KT-294 fully inhibits Type I IFN
- Full TYK2 degradation demonstrated by KT-294 leads to superior pathway inhibition to existing SMIs and potentially reach biologic-like activity

TYK2 Has Well-Established Scaffolding Function

- TYK2 complete deficiency severely impairs IL-23, Type I IFN, and IL-12 signaling but spares IL-10 in humans
- TYK2 scaffolding functions are demonstrated by differential pathway inhibitions in complete TYK2 deficiency vs a kinase dead variant in humans
- TYK2 deficient humans are generally healthy with only increased risk of some mycobacteria and viral infections that are relatively mild, curable and tend not to recur, de-risking safety for TYK2 degradation

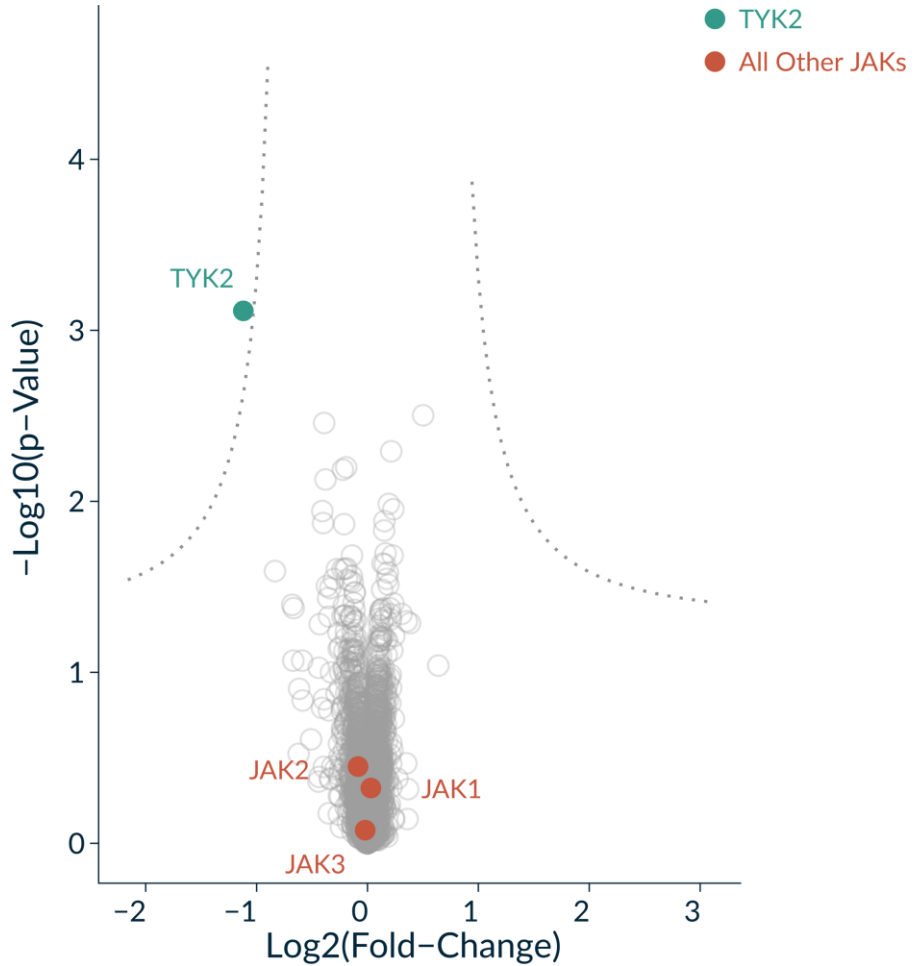
Cytokine Pathway	IL-23	Type I IFN	IL-12	IL-10
WT TYK2	++++	++++	++++	++++
Complete deficiency TYK2 -/-	+	+	+	+++
TYK2 Kinase dead P1104A/P1104A	+	++++	++++	++++














Degrading TYK2 is the only small molecule approach to eliminate all scaffolding and catalytic functions of TYK2, fully recapitulating the human TYK2-/- biology

KT-294, a Highly Selective Picomolar TYK2 Degradator, Recapitulates TYK2 Human Deficiency Biology

Fully Inhibits of Type I IFN and IL-12/23 and Spares IL-10/22

Selective TYK2 Degradation by KT-294 in hPBMC Proteome at 10x DC₉₀



Cellular Degradation/Functional Assay	KT-294 DC ₅₀ /IC ₅₀ (nM)
 Human PBMC degradation	0.08
 Human keratinocyte (neonatal and adult)	0.07
IL-23 pathway	
 IL-23 pSTAT4 in human PBMC	0.7
 IL-23 pSTAT3 in human CD3+CD161high TH17 cell	2.1
 IL-23/IL-1β IFN-γ release in human PBMC	2.4
Type I IFN pathway	
 IFN-α pSTAT1 in human CD19 B cell	13
 IFN-α pSTAT2 in human CD19 B cell	15
 IFN-α IP10 release in human PBMC	4.9
IL-12 pathway	
 IL-12/IL-18 pSTAT4 in human PBMC	1.3
 IL-12/IL-18 IFN-γ release in human PBMC	10
IL-10 and IL-22 pathways	
 IL-10 pSTAT3 in human CD14 monocyte	> 1000
 IL-22 pSTAT1 in HT29 cell	> 1000
 IL-22 pSTAT3 in HT29 cell	> 1000

KT-294, Unlike Allosteric TYK2 Inhibitor Deucravacitinib, Does not Inhibit IL-10

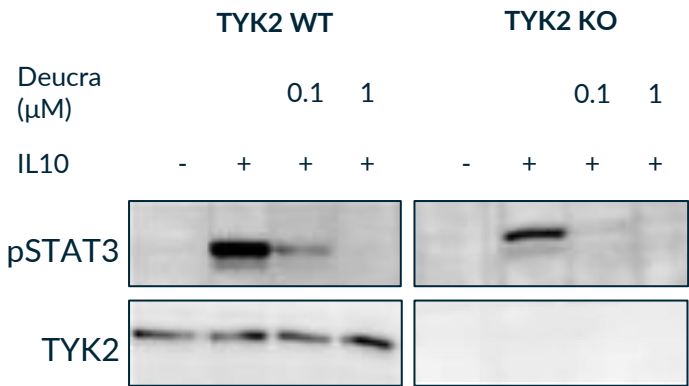
IL-10 has essential roles in intestinal homeostasis

- Loss of function mutations of the IL-10 pathway cause early onset refractory colitis in humans

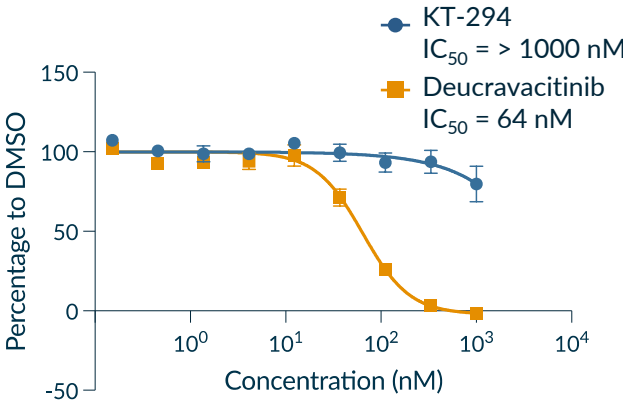
Deucravacitinib inhibits IL-10 through JAK1

- Deucra JAK1 Ki = 0.33 nM (Burke et al. Sci Transl Med. 2019)
- KT-294 JAK1 Ki = > 1000 nM

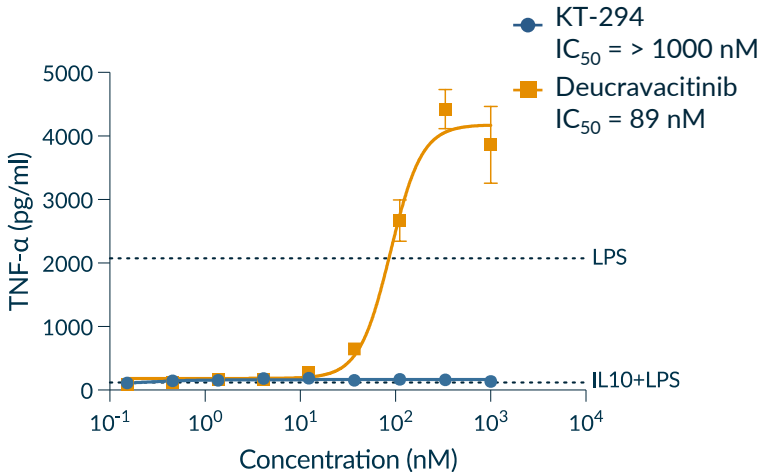
Deucra Inhibited IL-10 induced pSTAT3 in TYK2 KO EBV B Cell



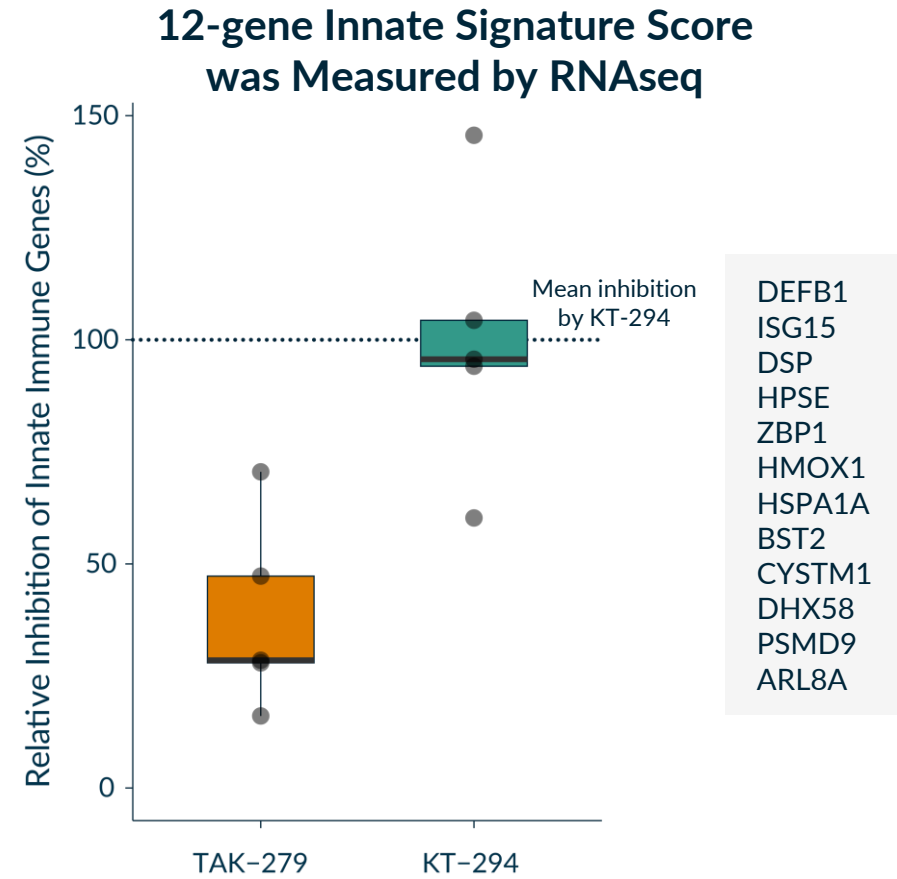
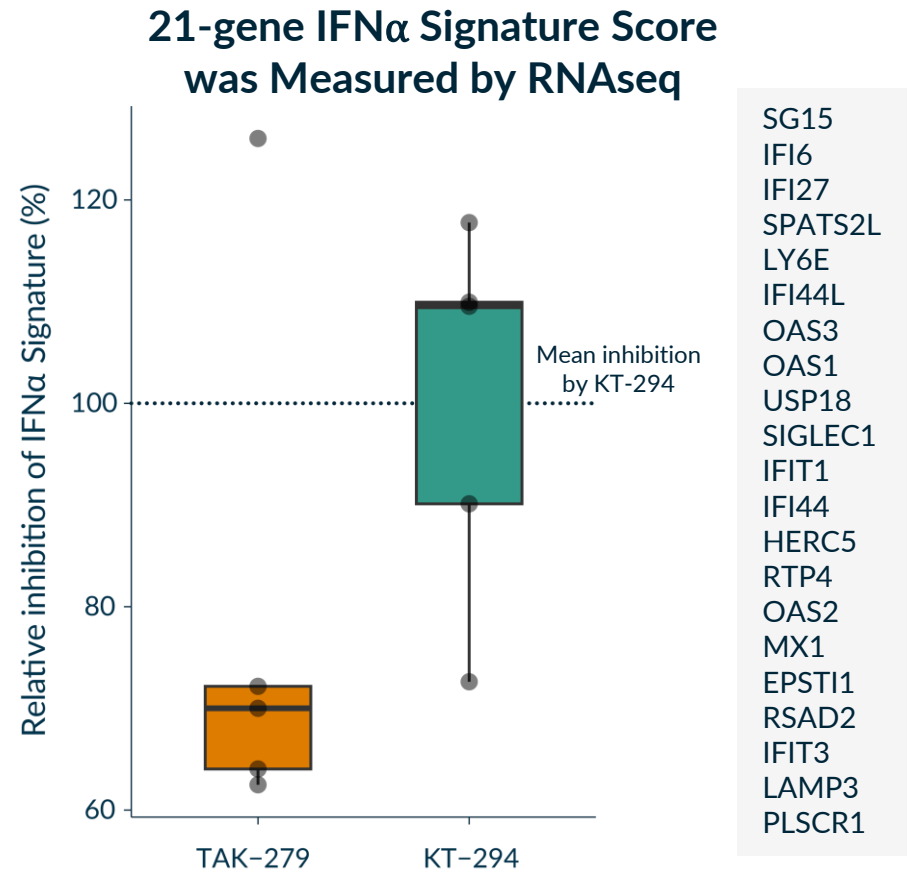
Deucra Inhibited IL-10 Induced pSTAT3 in Human CD14 Monocyte



Deucra Inhibits IL-10's Function of Suppressing LPS Induced TNF-α Release in Human CD14 Monocyte



Superior Inhibition of Type I IFN Pathway and Innate Immunity by KT-294 vs TAK-279



Doses Used:

- TAK-279 = 422nM (IFN α stimulated pSTAT2 IC₉₅). Clinical exposure C_{max} (free) at 35mg = ~ 77 nM
- KT-294 = 56nM (IFN α stimulated pSTAT2 IC₉₅)

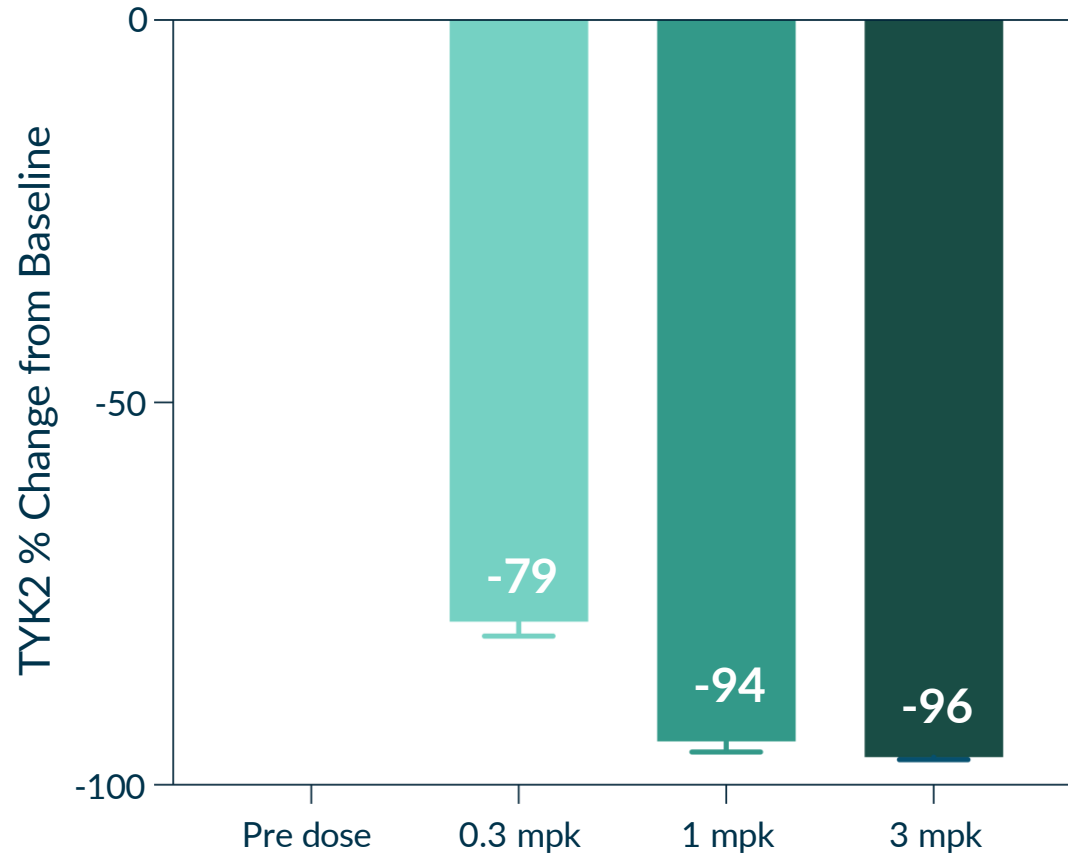
At concentrations where TAK-279 and KT-294 block pathway 95%, degrader demonstrates superior biological effect. (TAK-279 does not reach these exposures in clinic)

KT-294 Achieved Dose Dependent Deep Degradation of TYK2 *in vivo* with Low Oral Doses

KT-294 potently degrades TYK2 across multiple preclinical species

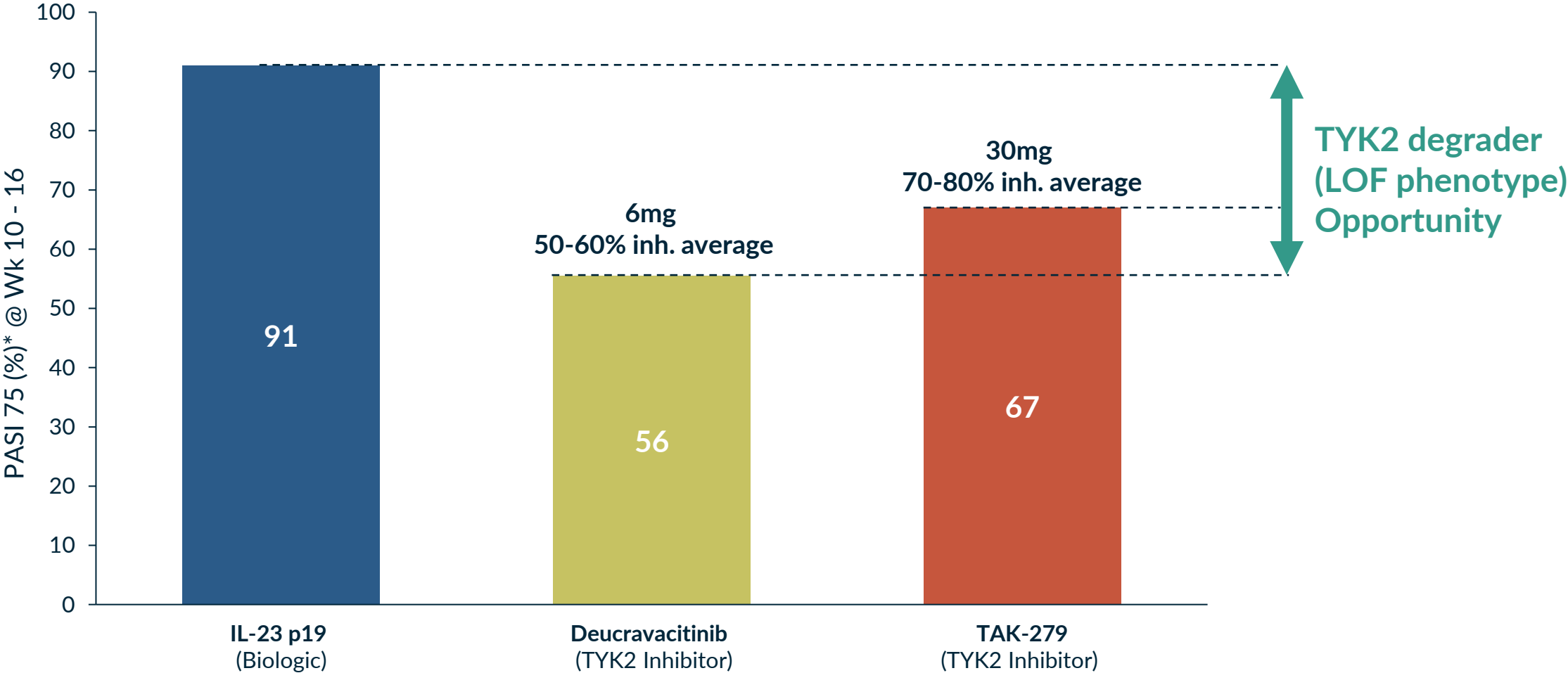
In NHP, KT-294 can degrade TYK2 to depletion with low oral doses

TYK2 Degradation in NHP Blood Post 7 days of KT-294 QD Oral Dosing



TYK2 SMI's Do Not Reach Maximal Target Engagement

Clinical Efficacy In Psoriasis is Target Engagement Dependent



Company presentations and package inserts; * total observed response rate for primary endpoint cut-off ranges from Wk 10 to Wk 16.

Biological and Clinical Differentiation

TYK2 Clinical Opportunities	Deucravacitinib IL12/23, IFN, IL10	TAK-279 IL12/23, ~IFN	KT-294 IL12/23, IFN	<p><i>KT-294, unlike TYK2 SMI, can replicate the TYK2 deficient phenotype and result: potent Type I IFN, IL-12/23 inhibition fully while sparing IL-10</i></p> <p>WITH FOLLOWING EXPECTED CLINICAL DIFFERENTIATION:</p>
Psoriasis	++	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)
Psoriatic Arthritis	++	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)
IBD	-	++	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile), + sparing IL-10
Lupus & interferonopathies	++	+	+++	>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile) + best anti-IFN profile

Oral TYK2 Degradator: KT-294

Potential Best-in-Class Opportunity with Biologic-like Profile

Validated Biology

TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling

Pathway validated by upstream biologics (i.e. ustekinumab) and TYK2 SMI across many diseases

TYK2 validated by human genetics

Competitive Profile

IL-23 and Type 1 IFN-based biologic market currently ~\$18B annually

Estimated to grow to ~\$27B with expanded indications and new entrants

TYK2 SM inhibitors have limitations due to selectivity (deucravacitinib) or lack of potent IFN- α activity (TAK-279) and limited clinical target engagement (both)

Mega-blockbuster potential for oral degrader with biologic-like activity that is superior to TYK2 SMI



KT-294, FIH: 1H 2025

Degrades TYK2 in human cells with pM potency

Recapitulates the phenotype of TYK2 human deficiency showing potent IFN- α , IL-12 and IL-23 inhibition and sparing IL-10

Dosed orally, shows complete TYK2 degradation in NHP providing a path to full target engagement in clinic, unlike current SMI

Currently in IND enabling studies



Solving Big Problems with Small Molecules

Nello Mainolfi, Ph.D.,
Founder, President and CEO

A Powerful Strategy That Puts Patients First

We focus on genetically validated targets/pathways that are either undrugged or inadequately drugged, where TPD is the best or the only solution

With a growing understanding of the underlying biology and many key pathways/targets validated by biologics, I&I offers large clinical/commercial opportunities

TPD can provide a unique solution with biologic-like specificity and efficacy, with the flexibility of oral small molecules

Our unique approach and capabilities have generated a best-in-industry oral I&I pipeline of first-in-class, highly valuable programs



Revolutionizing Immunology with Small Molecule Oral Degraders

IRAK4 (KT-474) SCAFFOLDING KINASE

STAT6 (KT-621) TRANSCRIPTION FACTOR

TYK2 (KT-294) SCAFFOLDING KINASE

Status	<ul style="list-style-type: none"> Phase 2 Trials in HS and AD with Sanofi 	<ul style="list-style-type: none"> IND-Enabling 	<ul style="list-style-type: none"> IND-Enabling
Potential Indications	<ul style="list-style-type: none"> HS, AD, RA, Asthma, COPD, IBD, others¹ 	<ul style="list-style-type: none"> AD, Asthma, COPD, CRSwNP, EoE, PN, others 	<ul style="list-style-type: none"> IBD, PsO, PsA, Lupus, others
Next Milestone	<ul style="list-style-type: none"> HS and AD Ph2 data: 1H 2025 	<ul style="list-style-type: none"> FIH: 2H 2024 	<ul style="list-style-type: none"> FIH: 1H 2025
Opportunity	<ul style="list-style-type: none"> First-in-class broad anti-inflammatory oral degrader 	<ul style="list-style-type: none"> Dupilumab-like activity in a pill 	<ul style="list-style-type: none"> Biologic-like activity in a pill
Commercial Rights	<ul style="list-style-type: none"> Up to 50% US with Sanofi, tiered royalties in ROW² 	<ul style="list-style-type: none"> Wholly owned 	<ul style="list-style-type: none"> Wholly owned

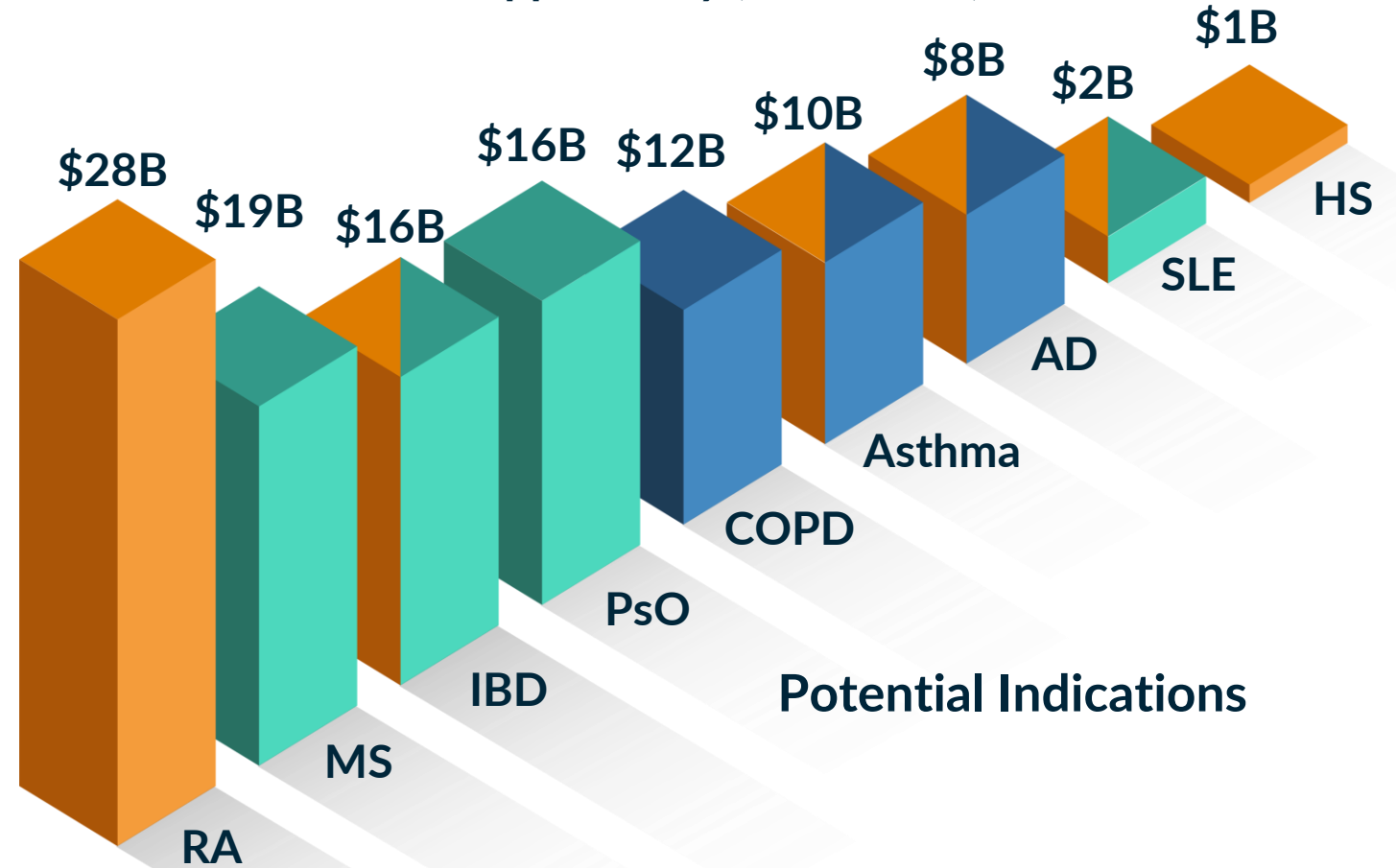
¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities; ²KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.

Kymera Immunology Oral Degradator Portfolio

Complementary Mechanisms Each with Mega-blockbuster Potential

Market Opportunity (2022 Sales)

- **IRAK4¹:** IL-1R/TLR pathway
Th1/17/Th2 biology
- **STAT6:** IL-4/13 pathway
Th2 biology
- **TYK2:** IL-23/IFN pathway



Potential Indications

GlobalData, focused only on large markets based on 2022 sales of approved drugs

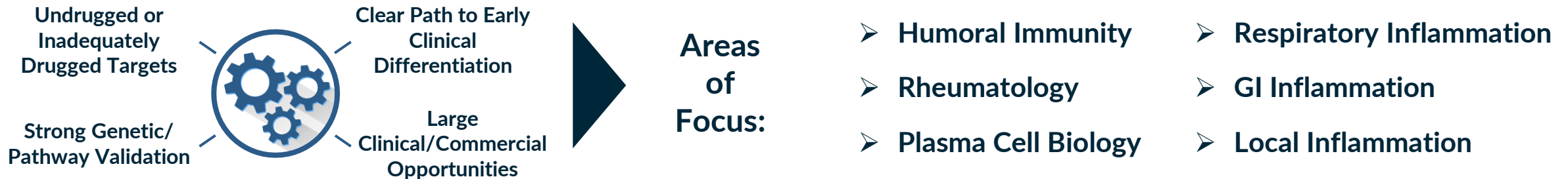
¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

Immunology Pipeline with Clear Line of Sight to Large Value Creation

	Potential Indications	2024	2025	2026+	Upcoming Milestones	Rights
Oral QD Small Molecule Degraders						
IRAK4* KT-474	HS, AD, RA, Asthma, IBD, other ¹	HS Ph2	▲ HS Late Development		Ph2 HS & AD Data 1H 2025	sanofi KYMERA 50/50 US
		AD Ph2	▲ AD Late Development			
STAT6 KT-621	AD, Asthma, COPD, PN CRSwNP, EoE	IND	Ph1	▲ Mid-Late Development	Ph1 Start 2H 2024	KYMERA
TYK2 KT-294	Psoriasis, IBD, PsA, Lupus, other	IND	Ph1	▲ Mid-Late Development	Ph1 Start 1H 2025	KYMERA

*KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW

Our Discovery Engine in Immunology



▲ = key data readout

¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

Pipeline with Clear Line of Sight to Large Value Creation

	Potential Indications	2024	2025	2026+	Upcoming Milestones	Rights
Immunology - Oral QD Small Molecule Degraders						
IRAK4* KT-474	HS, AD, RA, Asthma, IBD, other ¹	HS Ph2	▲ HS Late Development		Ph2 HS & AD Data 1H 2025	sanofi KYMERA 50/50 US
		AD Ph2	▲ AD Late Development			
STAT6 KT-621	AD, Asthma, COPD, PN CRSwNP, EoE	IND	Ph1	▲ Mid-Late Development	Ph1 Start 2H 2024	KYMERA
TYK2 KT-294	Psoriasis, IBD, PsA, Lupus, other	IND	Ph1	▲ Mid-Late Development	Ph1 Start 1H 2025	KYMERA

*KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW

Oncology						
STAT3** KT-333	PTCL, LGL-L, CTCL, Solid Tumors	Ph1	▲ Mid-Late Development		Ph1 Data 2024	KYMERA
MDM2 KT-253	Liquid & Solid Tumors	Ph1	▲ Mid-Late Development		Ph1 Data 2024	KYMERA

**Assessment of STAT3 I/I opportunity is ongoing

▲ = key data readout

¹Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

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2024 PRIORITIES

- Completion of enrollment in IRAK4 oral degrader KT-474 Phase 2 trials in HS and AD by partner Sanofi (topline data 1H 2025)
- Initiation of oral STAT6 degrader KT-621 Phase 1
- IND ready for oral TYK2 degrader KT-294
- Additional oncology proof-of-concept data for the STAT3 degrader KT-333 and MDM2 degrader KT-253

Thank You

Q&A

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Abbreviations

Ab	Antibody	FIH	First-in-Human	KO	Knockout
AD	Atopic Dermatitis	GDF15	Growth Differentiation Factor 15	LGL-L	Large Granular Lymphocytic Leukemia
AN Count	Abscess and Inflammatory Nodule Count	GI	Gastrointestinal	LOF	Loss of Function
CAGR	Compound Annual Growth Rate	GOF	Gain of Function	LPS	Lipopolysaccharide Solution
CAPS	Cryopyrin-Associated Periodic Syndrome	HDM	House Dust Mite	MAD	Multiple Ascending Dose Study
CD	Crohn's Disease	HiSCR	Hidradenitis Suppurativa Clinical Response	MCC	Merkel Cell Carcinoma
cHL	Classic Hodgkin's Lymphoma	hPBMC	Human Peripheral Blood Mononuclear Cells	MDM2	Mouse Double Minute 2
CNS	Central Nervous System	HS	Hidradenitis Suppurativa	MS	Multiple Sclerosis
COPD	Chronic Obstructive Pulmonary Disease	HV	Healthy Volunteers	MYD88	Myeloid Differentiation Primary Response Protein 88
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps	I&I	Immunology and Inflammation	NF-kB	Nuclear Factor Kappa B
CTCL	Cutaneous T-Cell Lymphoma	IBD	Inflammatory Bowel Disease	nM	Nanomolar
Ctrl	Control	IC_#	Inhibitory Concentration	NRS	Numerical Rating Scale
C_{trough}	Trough Concentration	IFN	Interferon	PASI	Psoriasis Area and Severity Index
CU	Chronic Urticaria	IHS4	International Hidradenitis Suppurativa Severity Score	PBMC	Peripheral Blood Mononuclear Cells
DC_#	Degradation Concentration	IL	Interleukin	Pbo	Placebo
DMSO	Dimethyl Sulfoxide	IND	Investigational New Drug Application	Ph	Phase
EASI	Eczema Area and Severity Index	IP	Intellectual Property	PK/PD	Pharmacokinetics/Pharmacodynamics
EBV	Epstein-Barr Virus	IRAK4	Interleukin 1 Receptor Associated Kinase 4	PN	Prurigo Nodularis
ECM	Extracellular Matrix	IRAKIMiD	IRAK4 and IMiD substrates	POC	Proof-of-Concept
ENT	Ear Nose Throat	JAK	Janus Kinase	PP-NRS	Peak Pruritus Numerical Rating Scale
EoE	Eosinophilic Esophagitis	JP	Japan	PsA	Psoriatic Arthritis
EU	European Union				

Abbreviations

PsO	Psoriasis
pSTAT	Signal Transducer and Activator of Transcription
PTCL	Peripheral T-Cell Lymphoma
QD	Once a day
QoL	Quality of Life
R&D	Research and Development
RA	Rheumatoid Arthritis
RNAseq	Ribonucleic Acid Sequencing
ROW	Rest of World
SAD	Single Ascending Dose study
SLE	Systemic Lupus Erythematosus
SMI	Small Molecule Inhibitor
STAT	Signal Transducer and Activator of Transcription
STAT3	Signal Transducer and Activator of Transcription 3
STAT6	Signal Transducer and Activator of Transcription 6
TARC	Thymus and Activation-Regulated Chemokine
Th1	Type 1
Th2	Type 2
Th17	Type 17
TLR	Toll-like Receptors
TPD	Targeted Protein Degradation
TYK2	Tyrosine Kinase 2

UC	Ulcerative Colitis
US	United States
vIGA	Validated Investigator Global Assessment for AD
WT	Wildtype
WW	Worldwide