Reinventing Medicine with Protein Degradation

October 2024

KYMERA

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. These statements include, but are not limited to, implied and express statements about our strategy, business plans and objectives for our programs; Sanofi's intent to expand the Phase 2 clinical trials of KT-474/SAR-444656, plans and timelines for the preclinical and clinical development of our product candidates, including the therapeutic potential, clinical benefits and safety profiles of such product candidates; expectations regarding timing, success and data announcements of ongoing preclinical studies and clinical trials; our ability to initiate new clinical programs, including plans to submit investigational new drug (IND) applications; the initiation, timing, progress and results of our current and future preclinical studies and clinical trials of our current and prospective product candidates; our plans to develop and commercialize our current and any future product candidates and the implementation of our business model and strategic plans for our business, current and any future product candidates. All statements other than statements of historical facts contained in this presentation, including express or implied statements regarding our strategy, future financial condition, expected cash runway into the first half of 2027, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "assume," "believe," "could," "estimate," "expect," "goal," "intend," "may," "milestones," "objective," "plan," "predict," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. You should not rely upon forward-looking statements as predictions of future events and actual results or events could differ materially from the plans, intentions and expectations disclosed herein.

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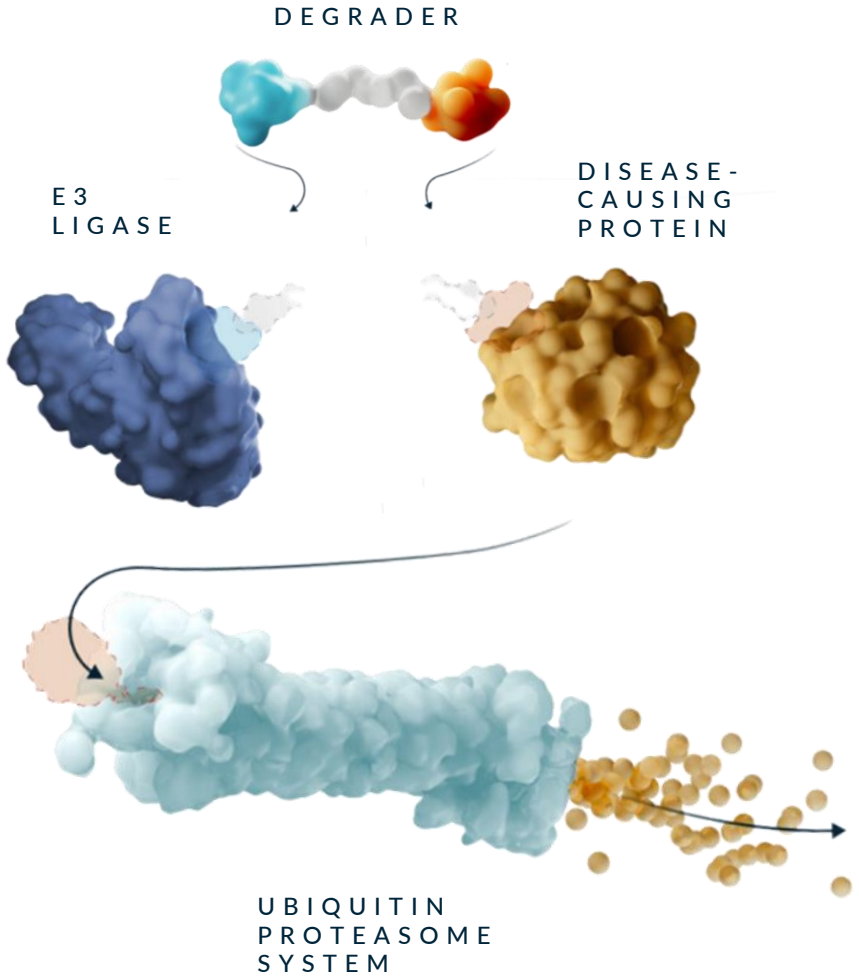
Harnessing a Game-Changing, Novel Modality

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 with $911 million in cash and expected runway into mid 2027, enabling expansion into areas with large clinical and commercial opportunities

Industry Leading Execution

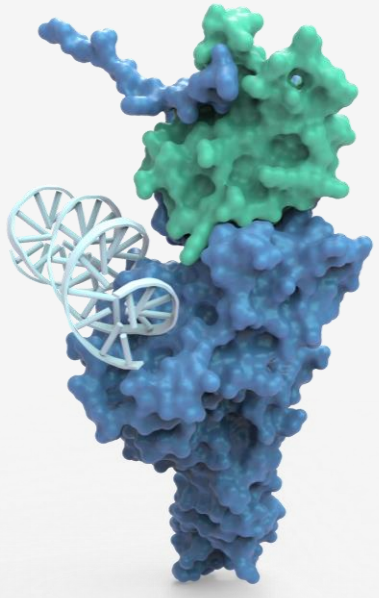
- Since founding Kymera in 2016:
  - Advanced five first-in-class programs to the clinic
  - Demonstrated clinical translation of degradation and safety
  - Achieved early clinical POC in I&I and oncology programs
- Extensive validation of target selection and molecular design
- Successful track record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



Target Selection Strategy

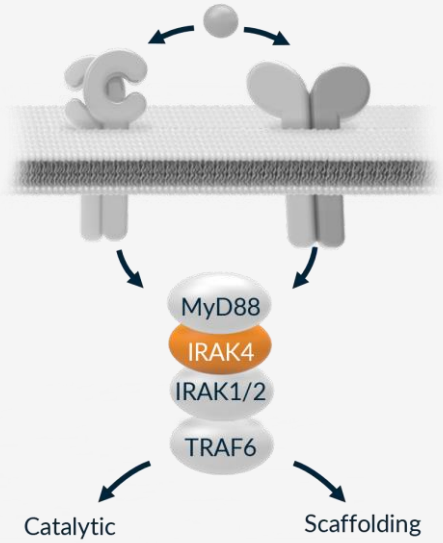
Focus on First- or Best-in-Class Opportunities

Undrugged or Inadequately Drugged targets



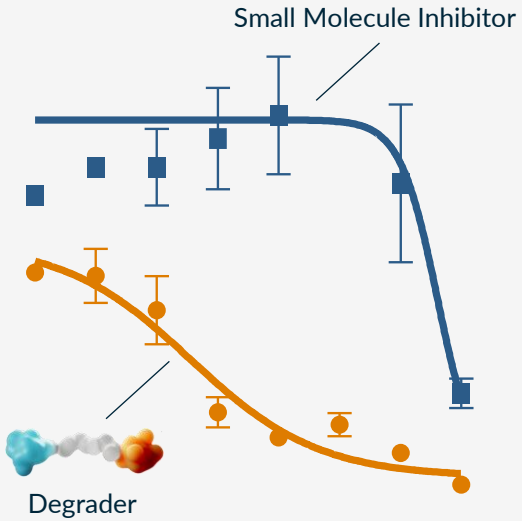
TRANSCRIPTION FACTORS & SCAFFOLDING PROTEINS

Strong Genetic/Pathway Validation



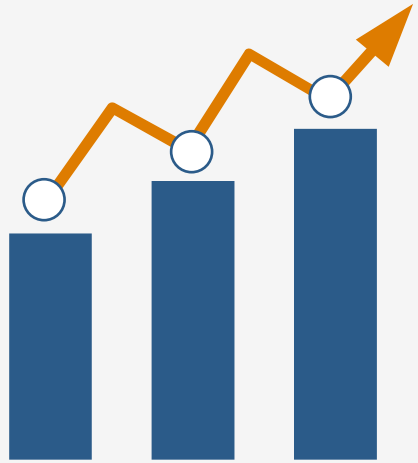
APPROVED DRUGS IN SAME PATHWAY

Clear Path to Early Clinical Differentiation



SUPERIORITY VS PATHWAY DRUGS

Large Clinical/Commercial Opportunities



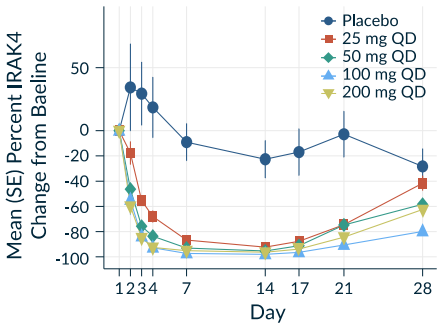
AREAS OF SIGNIFICANT VALUE CREATION

Demonstrating Reproducible and Scalable Clinical Innovation

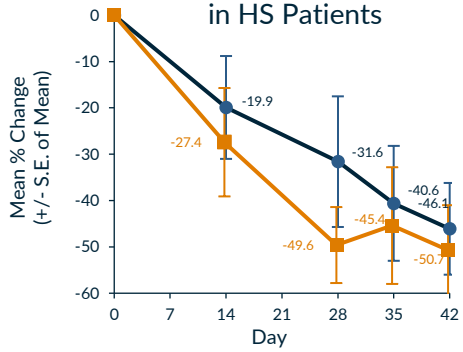
IRAK4 KT-474

IRAK4 Degradation leads to Early POC in HS and AD

IRAK4 Levels



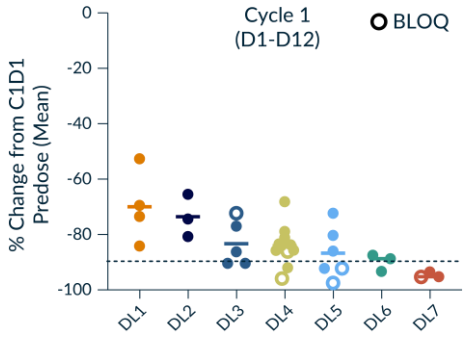
Reduction of AN Counts in HS Patients



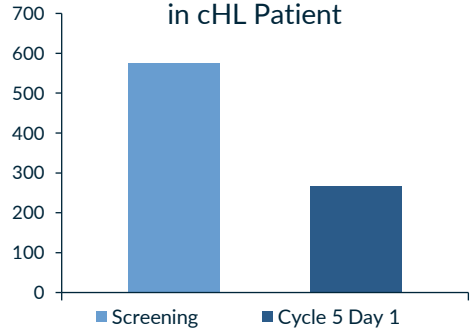
STAT3 Degradation Leads to Major Response in cHL Patient

STAT3 KT-333

STAT3 Levels

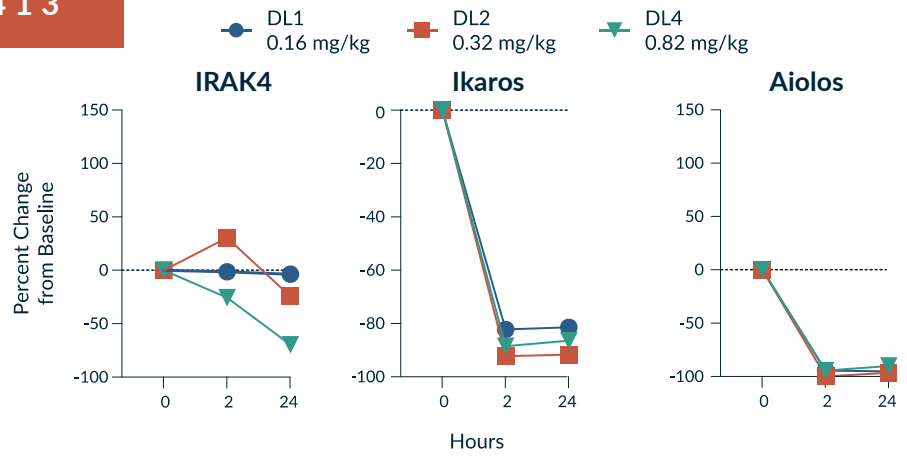


Bone Lesion Size Reduction in cHL Patient



IRAKIMID KT-413

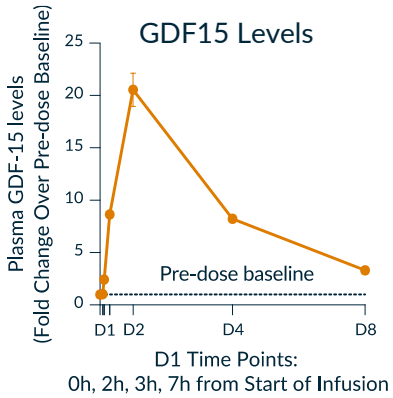
Degradation of IRAK4 and Ikaros/Aiolos



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

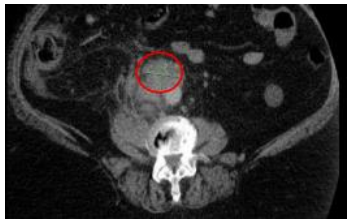
MDM2 KT-253

GDF15 Levels

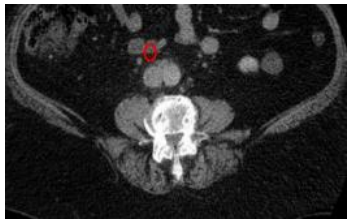


Lesion Size Reduction in MCC Patient

Lesion 2 Pre-Treatment



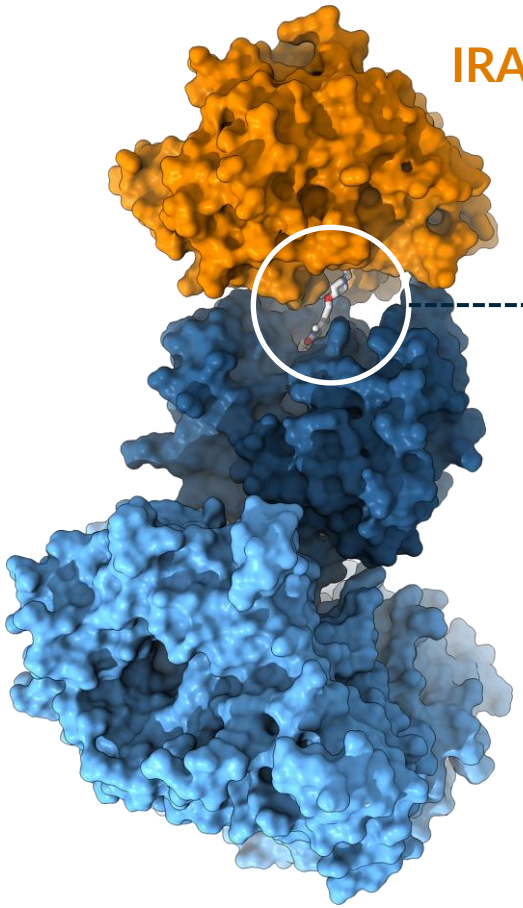
Post-Cycle 2

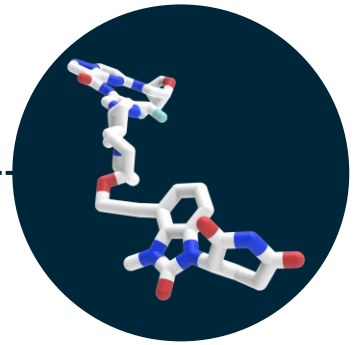


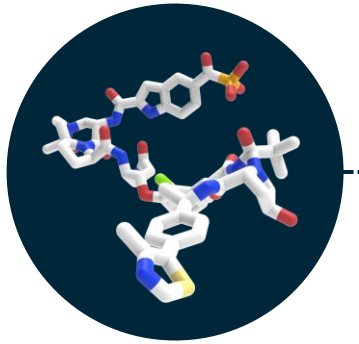
KYMERA

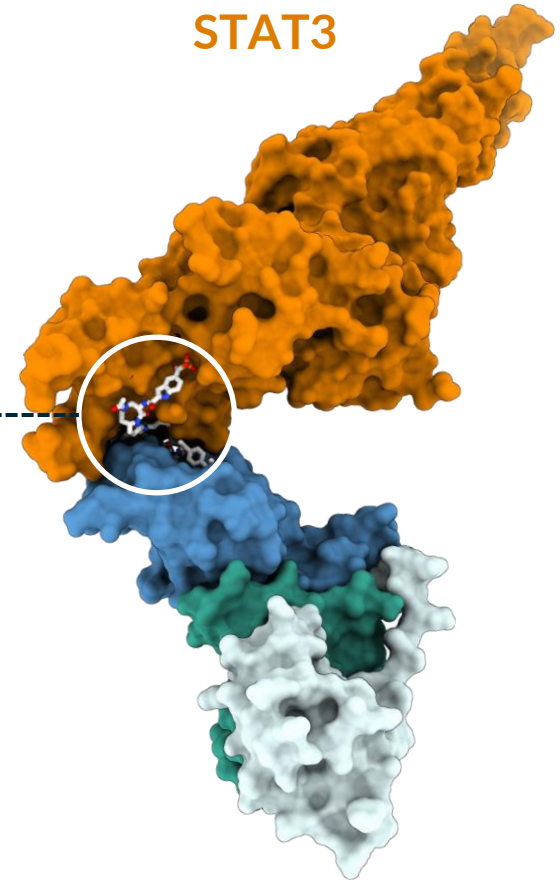
Chemistry and Structural Biology Leadership

Ternary Complex Cryo-EM Structures Enable Design of Highly Specific and Potent Degraders









Command of E3 ligase pairing

Ternary complex Cryo-EM

Advanced accuracy of PK/PD

Optimized chemical matter discovered at Kymera:

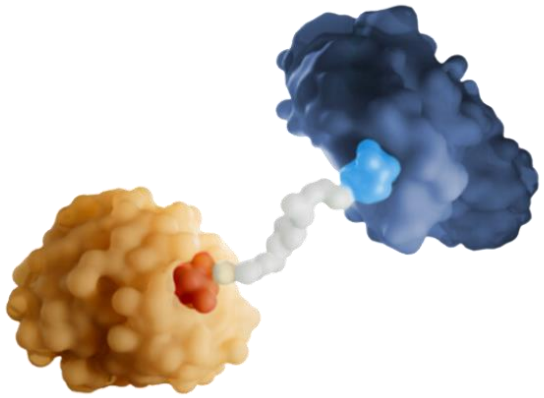
- Unparalleled hit finding capabilities and ability to quickly identify novel ligands for previously undrugged targets through unique screening capabilities, AI/ML, biophysical and proprietary structural approaches
- Ability to fine-tune the potency of our degraders, refine drug-like properties, and comprehensive understanding of PK/PD in all relevant tissues, resulting in impeccable translation of our pipeline in the clinic

Cereblon-(KT-474)-IRAK4

VHL-(KT-333)-STAT3

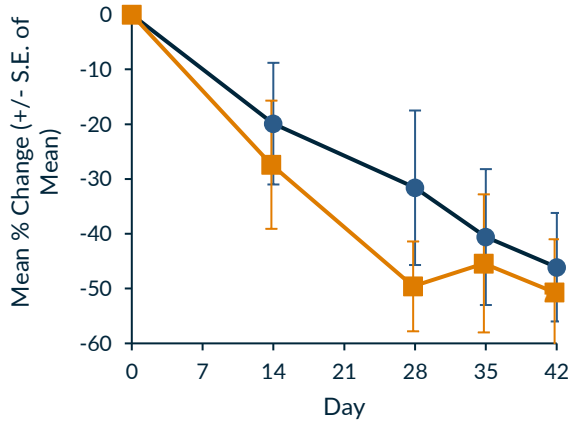
Building a Global Medicines Company

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 potential for 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

Clear Line of Sight to Substantial Patient Impact and Value Creation

	Potential Indications	IND-enabling	Phase 1	Phase 2	Upcoming Milestones	Rights
Immunology – Oral QD Small Molecule Degraders						
IRAK4[1]	HS, AD, RA, Asthma, IBD, others[2]	KT-474 - HS KT-474 - AD			Phase 2b Completion: HS: 1H26 AD: Mid-2026	50/50 US sanofi KYMERA
STAT6	AD, Asthma, COPD, PN, CRSwNP, EoE, BP others	KT-621			Phase 1 Data: 1H25	KYMERA
TYK2	Psoriasis, IBD, PsA, Lupus, others	KT-295			Phase 1 Start: 1H25	KYMERA
Oncology						
STAT3[3]	cHL, PTCL, LGL-L, CTCL, Solid Tumors	KT-333		Phase 1 enrollment completed; Kymera will only advance beyond Phase 1 with a partner		KYMERA
MDM2	Liquid & Solid Tumors	KT-253				KYMERA

[1]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.

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

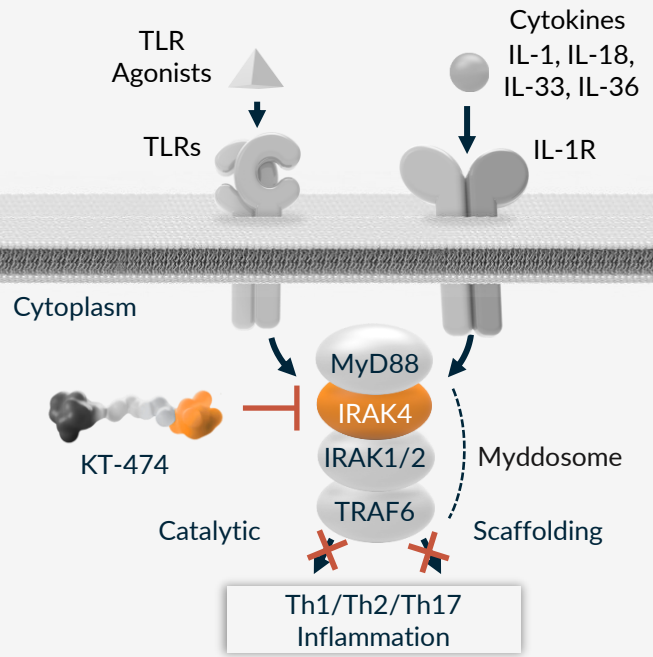
[3]Assessment of STAT3 I/I opportunity is ongoing.

Kymera Immunology Oral Degrader Portfolio

Complementary, First-in-class Mechanisms

IRAK4
SCAFFOLDING KINASE

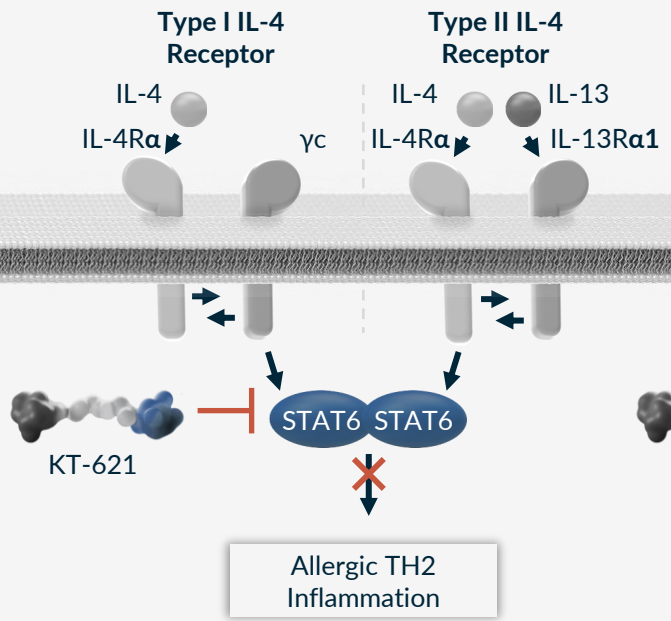
IL-1R/TLR Pathway



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

STAT6
TRANSCRIPTION FACTOR

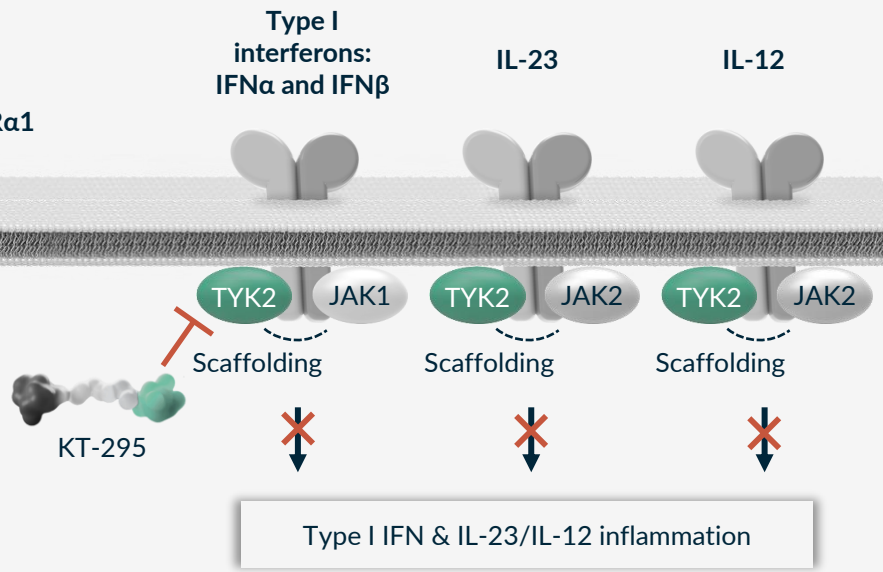
IL-4/13 Pathway



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

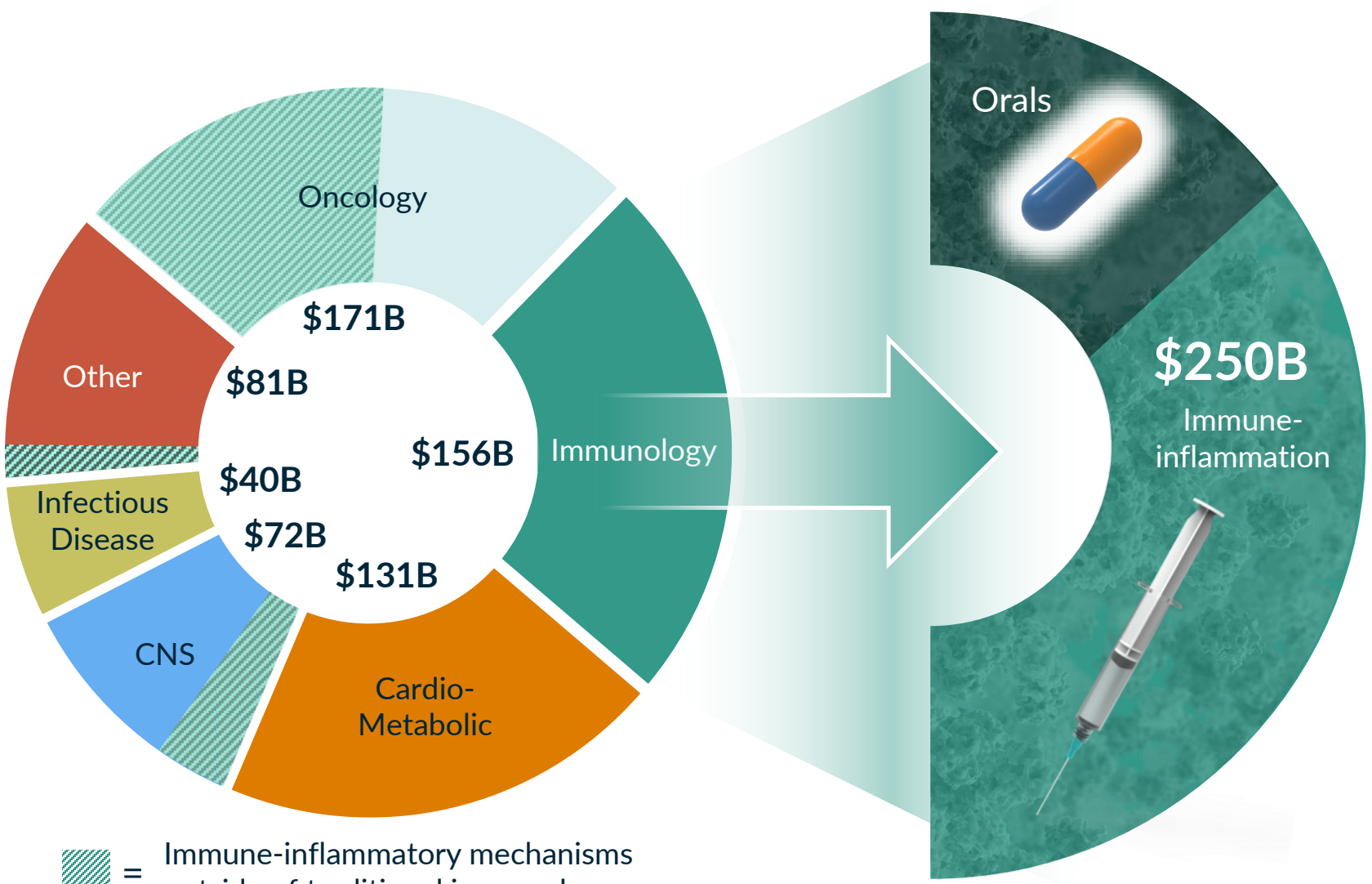
TYK2
SCAFFOLDING KINASE

IL-12/23/IFN Pathways



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

The Opportunity in Immunology



= Immune-inflammatory mechanisms outside of traditional immunology

Immune-inflammation is a **$250B WW market**[1] spanning multiple therapeutic areas.

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

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

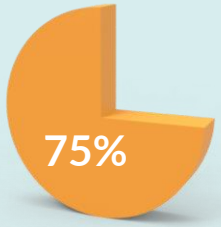
Why Small Molecule Oral Degraders in Immunology

Cosentyx® (secukinumab)

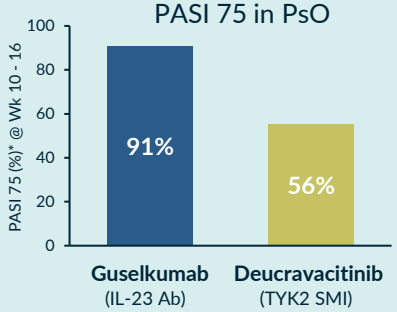
Stelara® (ustekinumab)

DUPIXENT® (dupilumab) Injection

Patients on Biologics that Would Switch to Orals[1]



IL-23 Biologics vs TYK2 SMI[2]
PASI 75 in PsO



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 Activity in a Pill

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

[1]J&J Business Review Dec '23 (survey of N=395 patients with moderate-to-severe psoriasis); [2]Tremfya (IL-23 biologic) package insert, Sotyktu (TYK2 SMI) package insert

Revolutionizing Immunology with Small Molecule Oral Degraders

	IRAK4 (KT-474) SCAFFOLDING KINASE	STAT6 (KT-621) TRANSCRIPTION FACTOR	TYK2 (KT-295) SCAFFOLDING KINASE
Status	• Phase 2b trials in HS and AD with Sanofi	• Phase 1 trial in healthy volunteers	• IND-Enabling
Potential Indications	• HS, AD, RA, Asthma, COPD, IBD, SLE, others[1]	• AD, Asthma, COPD, PN, CRSwNP, EoE, BP, others	• PsO, IBD, PsA, Lupus, others
Next Milestone	• Phase 2b completion: 1H 2026 (HS) and mid-2026 (AD)	• Phase 1 data: 1H 2025	• FIH: 1H 2025
Opportunity	• First-in-class broad anti-inflammatory oral degrader	• Dupilumab-like activity in a pill	• Biologic-like activity in a pill
Commercial Rights	• Up to 50% US with Sanofi, tiered royalties in ROW[2]	• Wholly owned	• Wholly owned

[1]Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities;
[2]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.

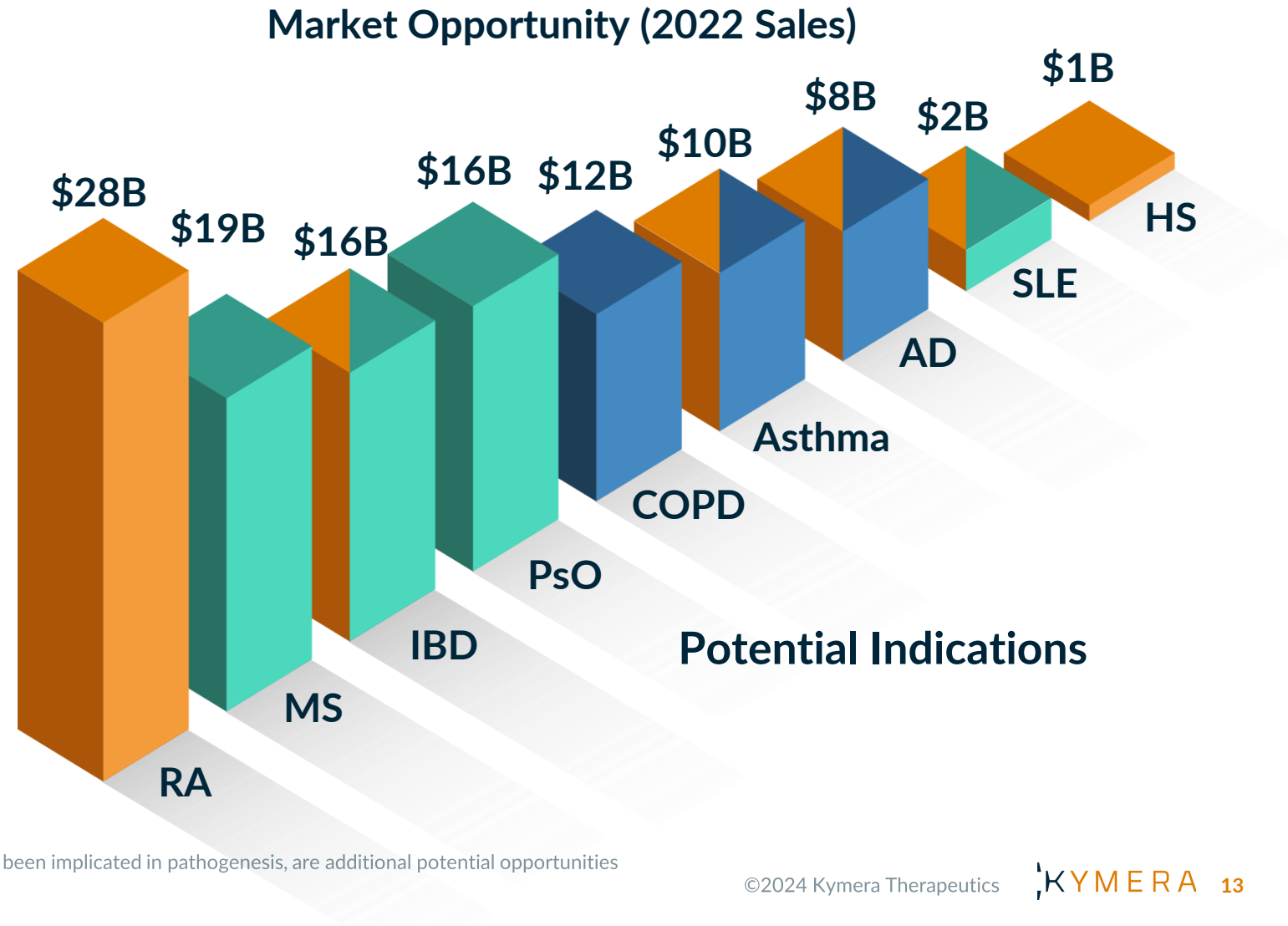
Kymera Immunology Oral Degrader Portfolio

Complementary Mechanisms Each with Mega-blockbuster Potential

IRAK4[1]: **IL-1R/TLR pathway**
Th1/17/Th2 biology

STAT6: **IL-4/13 pathway**
Th2 biology

TYK2: **IL-23/IL-12/IFN pathway**



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

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

First-in-Class Oral IRAK4 Degrader Program

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

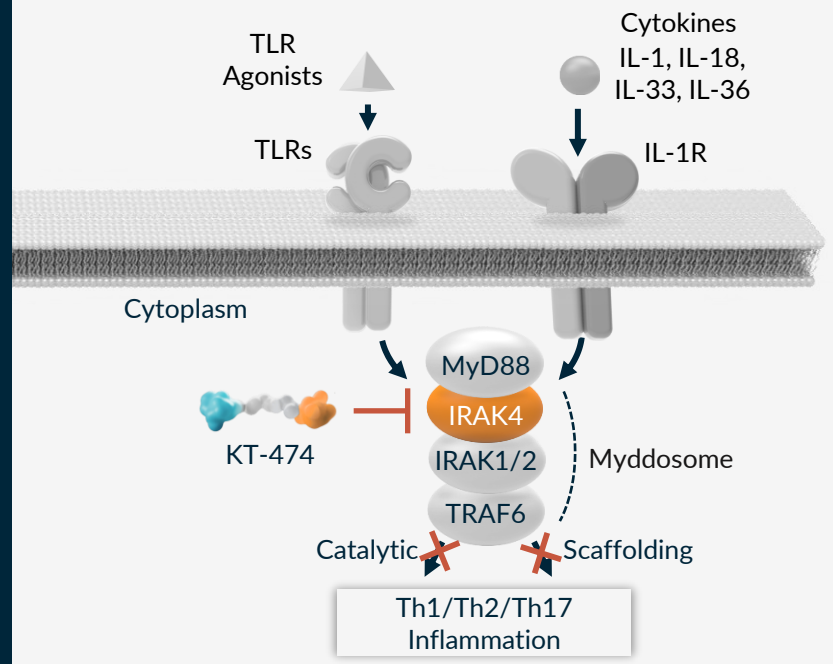
- Adult humans with IRAK4 null mutation are healthy

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 validated[1]:
  - IL-1α/IL-1β : RA, CAPS, HS, AD, Gout
  - IL-18: AD, Macrophage Activation Syndrome
  - IL-36: Generalized Pustular Psoriasis, AD
  - IL-33: Asthma
  - IRAK4 SMI: RA

IRAK4
SCAFFOLDING KINASE

IL-1R/TLR Pathway

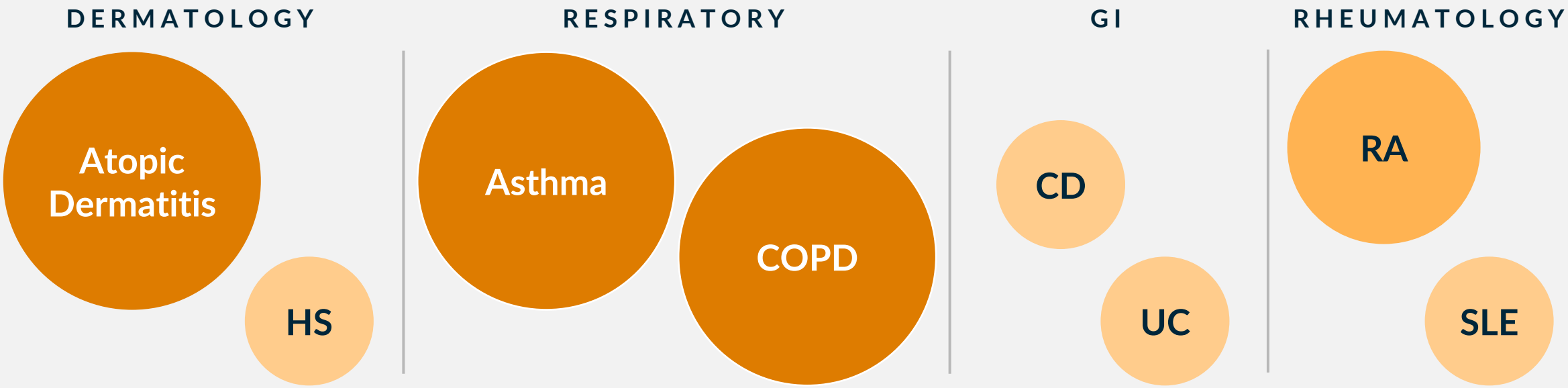


IRAK4 is master regulator of **innate immunity** with scaffolding and kinase functions

Adapted from West NT. Front Immunol 2019

[1]Current 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

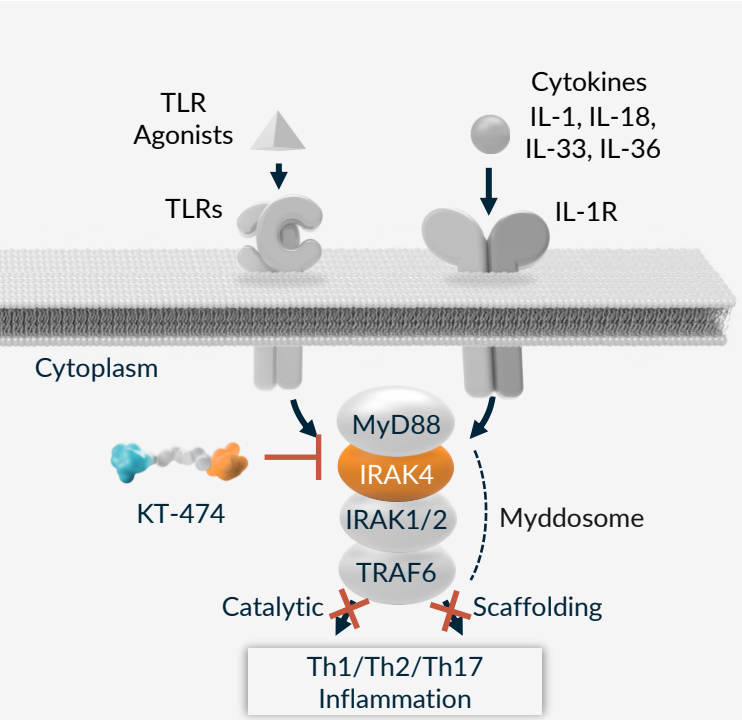


Total Potential Patient Impact[1]: **>150M patients**

- 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

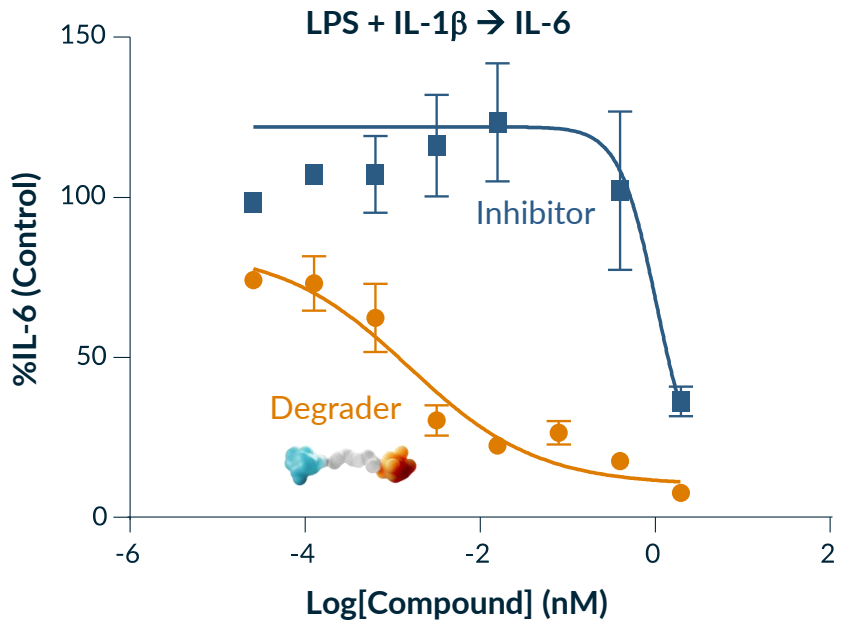
[1]GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)

IRAK4 Degrader Advantage



IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation

Only Degrader 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-κB 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**

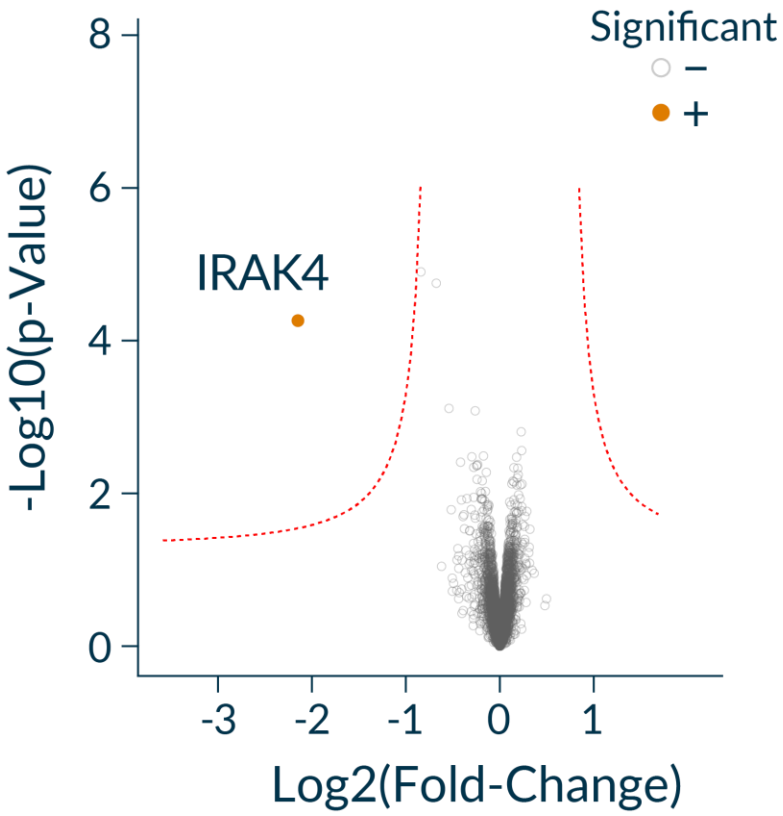
Clinical Data *(Nature Medicine*)*

- 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 Degrader Active in Multiple Cell Types

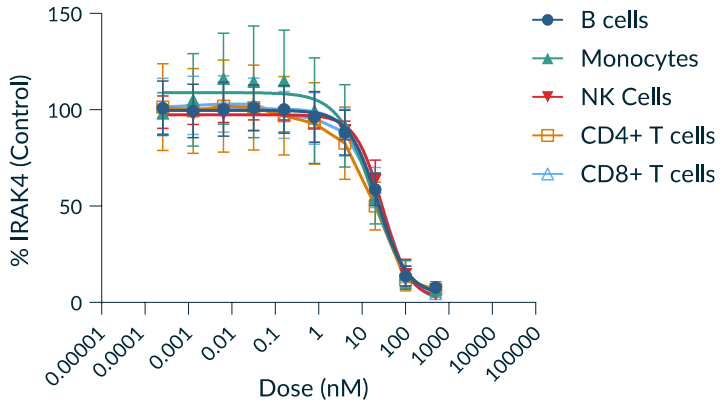
Selectivity in PBMC



- 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-1β-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



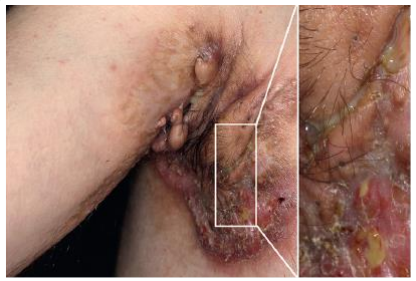
Cell type (Human)	Source	KT-474 DC_{50} (nM)
Monocytes	Blood	2.6
B cells	Blood	2.7
CD4 T cells	Blood	1.5
CD8 T cells	Blood	1.5
NK cells	Blood	1.8
Fibroblasts	Skin	1.5
Keratinocytes	Skin	7.8

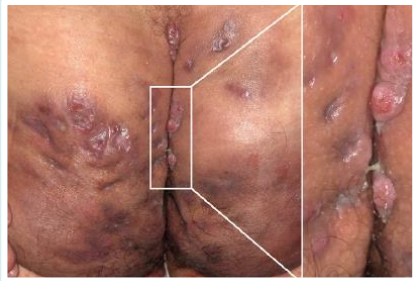
Initial Clinical Focus for KT-474: Moderate to Severe HS and AD

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

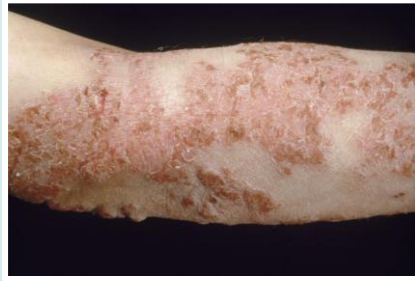
Lesions characterized by pleotropic inflammation with Th1/Th17 skewing; bacterial infection and tissue destruction leading to TLR activation; IL-1 and IL-36 production

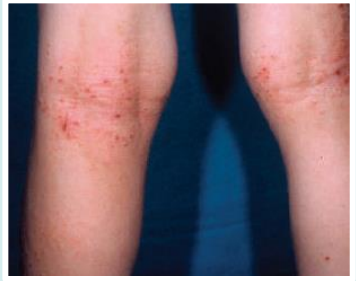
Active agents approved or in development target TNF-α, IL-17 and JAK/STAT pathways

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/JP[1]

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

[1]GlobalData – 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

Lindsay Ackerman[1], Gerard Acloque[2], Sandro Bacchelli[3], Howard Schwartz[4], Brian J. Feinstein[5], Phillip La Stella[6], Afsaneh Alavi[7], Ashwin Gollerkeri[8], Jeffrey Davis[8], Veronica Campbell[8], Alice McDonald[8], Sagar Agarwal[8], Rahul Karnik[8], Kelvin Shi[8], Aimee Mishkin[8], Jennifer Culbertson[8], Christine Klaus[8], Bradley Enerson[8], Virginia Massa[8], Eric Kuhn[8], Kirti Sharma[8], Erin Keaney[8], Randy Barnes[8], Dapeng Chen[8], Xiaozhang Zheng[8], Haojing Rong[8], Vijay Sabesan[8], Chris Ho[9], Nello Mainolfi[8], Anthony Slavin[8] & Jared A. Gollob[8]


News & views

Targeted therapy https://doi.org/10.1038/s41591-023-02622-y

PROTACs reach clinical development in inflammatory skin disease

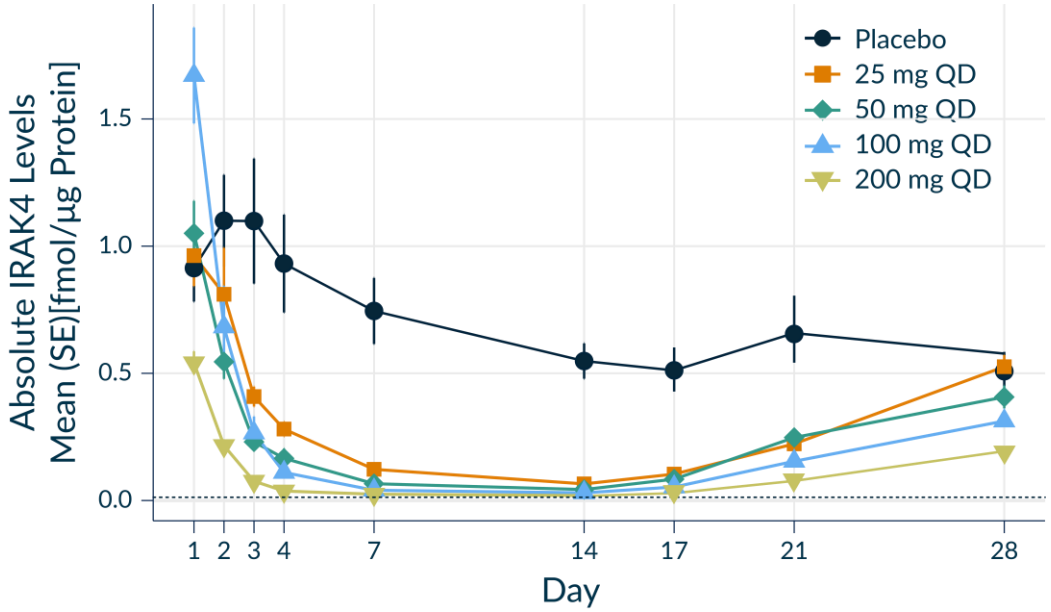
Fleur M. Ferguson

Check for updates

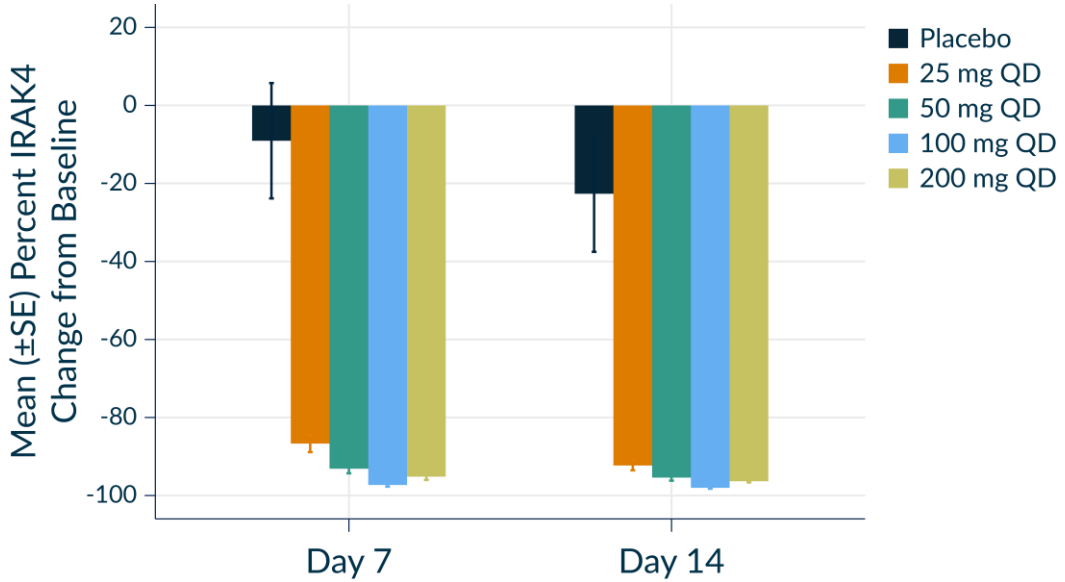
A phase 1 trial of an IRAK4-targeted protein degrader in patients with chronic inflammatory skin diseases hits an important milestone for the safe application of this drug class beyond oncology.

Phase 1 MAD HV: KT-474 Achieved Robust and Sustained IRAK4 Degradation with Multiple Daily Oral Doses (14 Days)

Absolute IRAK4 Levels



Percent IRAK4 Reduction at Steady State



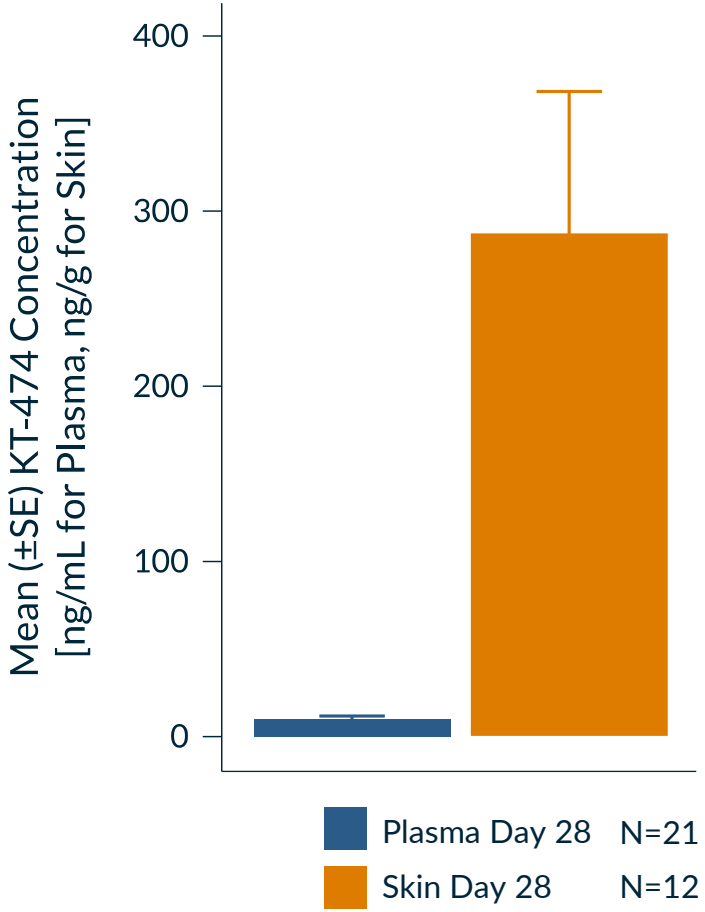
- Detected by mass spectrometry in circulating PBMC
- Steady state IRAK4 reduction achieved between Days 7 and 14
- Recovery towards baseline by Day 28 (2 weeks after last dose)
- MAD 2 through 4 approached Lower Limit of Quantitation (LLOQ)

	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

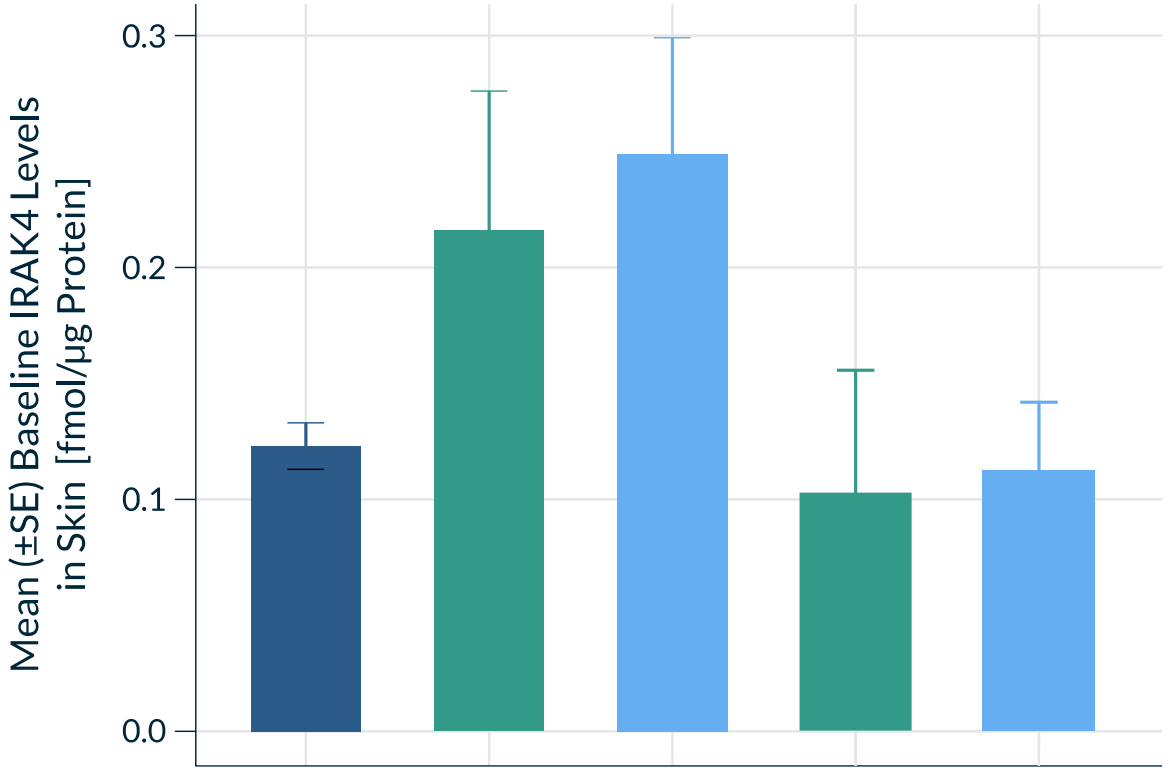
* p-values relative to placebo

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

High KT-474 Exposure in HS and AD Patients Skin



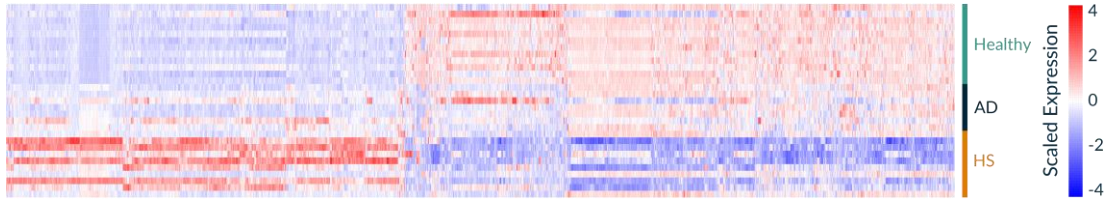
Reduced IRAK4 in Skin Lesions of AD and HS Patients

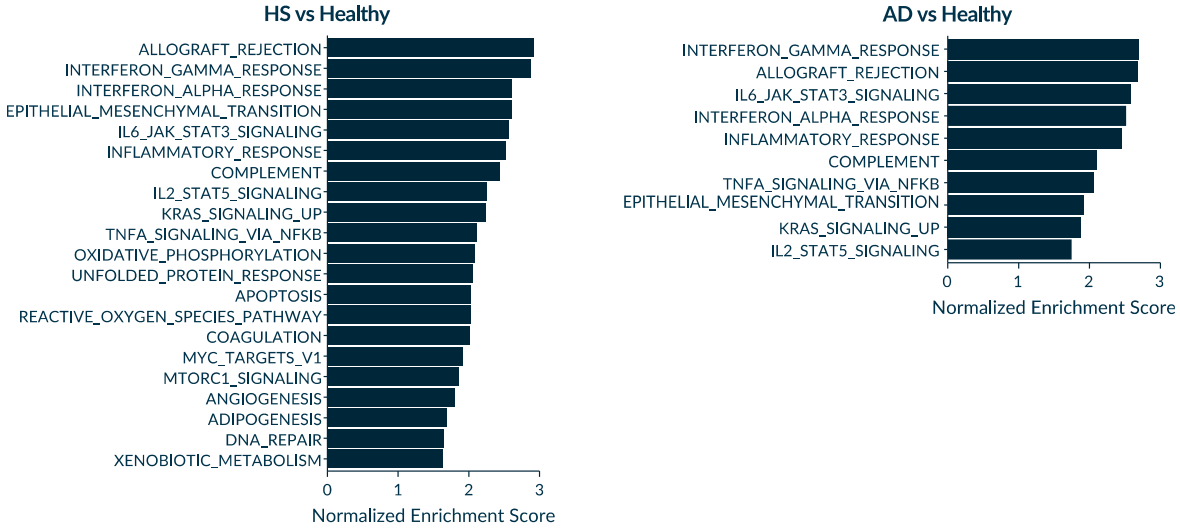


	MAD Healthy Subjects **(Baseline)**	AD Patients **(Baseline)**	HS Patients **(Baseline)**	AD Patients **(Day 28)**	HS Patients **(Day 28)**
N	46	7	11	6	9
Mean	0.12	0.22	0.24	0.1	0.11

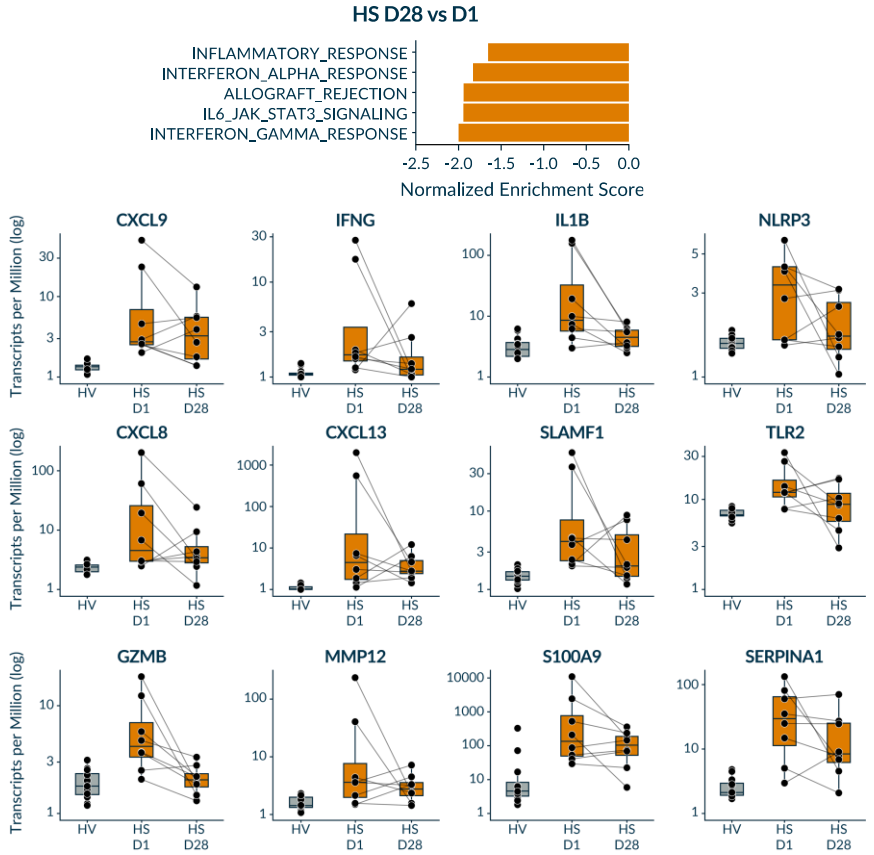
Upregulation of Multiple Inflammatory Pathways in HS and AD Skin Lesions and Impact of KT-474 Treatment

Upregulation of Inflammatory Genes/Pathways in HS and AD





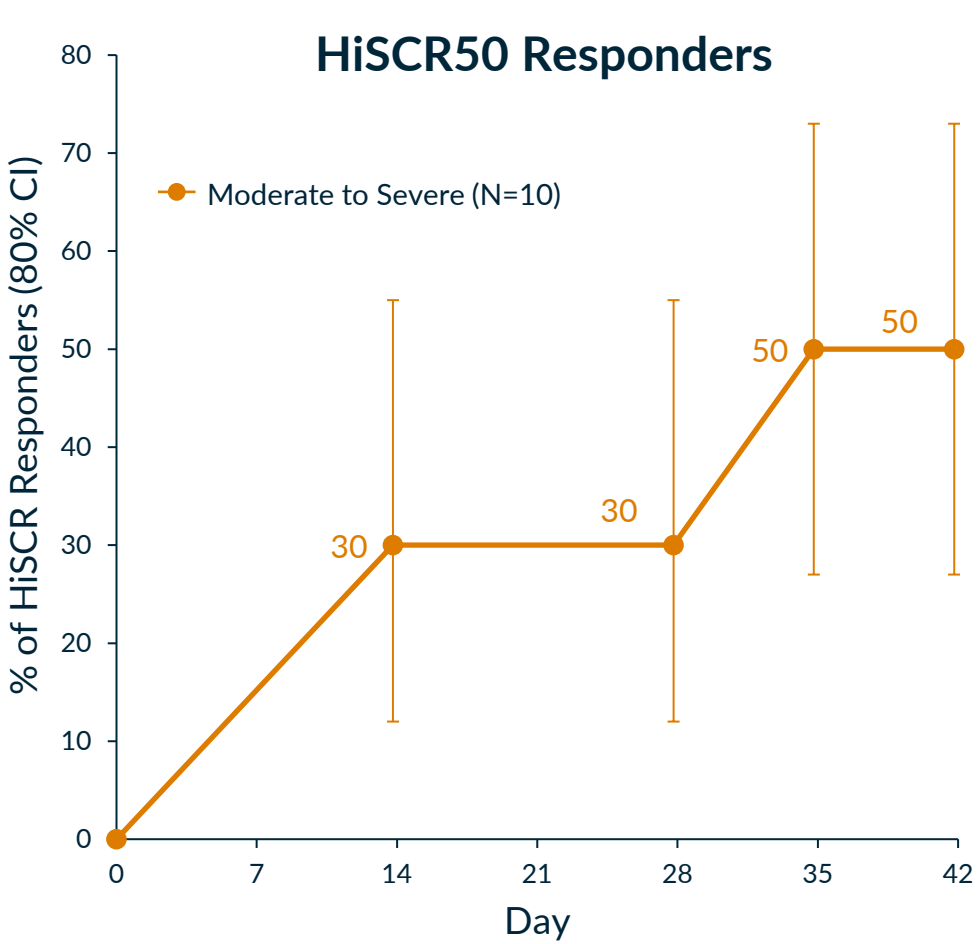
Anti-inflammatory Effect of KT-474 Treatment in HS

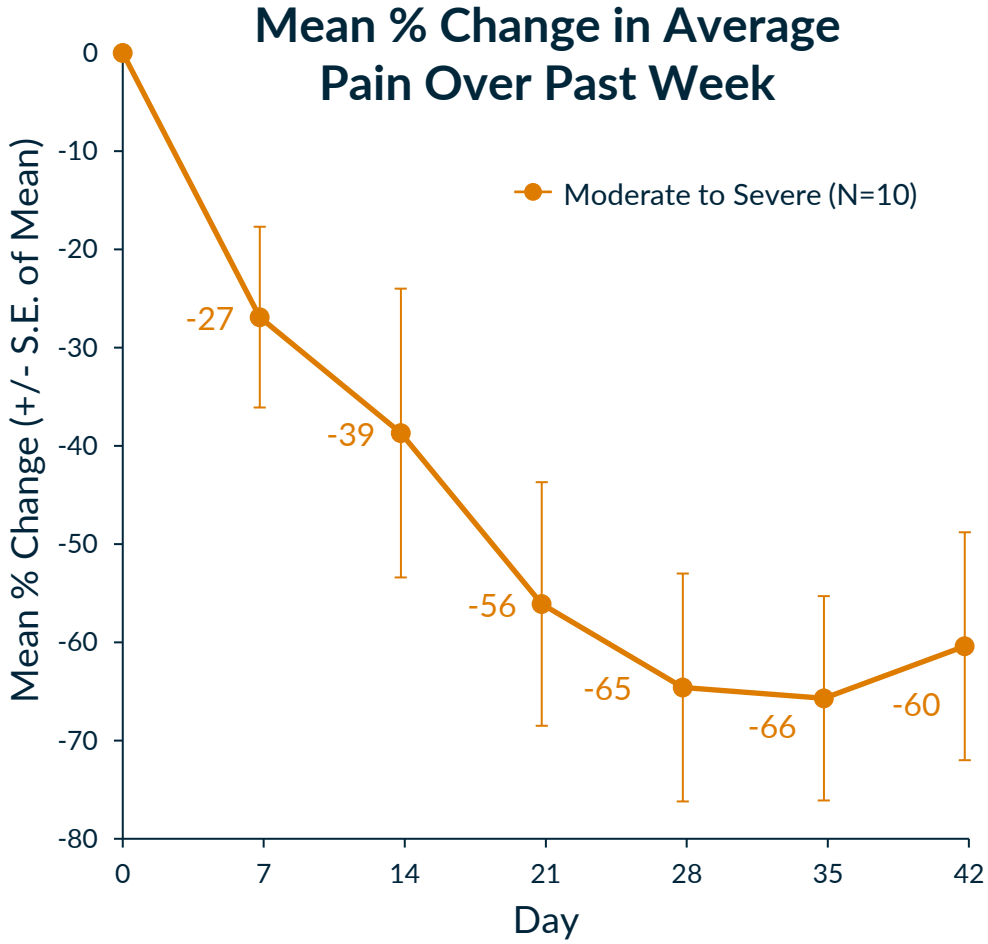


- Upregulation of pro-inflammatory genes and pathways in HS and AD skin lesions relative to healthy subjects
- Inflammatory burden greater in HS compared to AD, facilitating detection of downregulation following KT-474 treatment
- Multiple Th1 and innate immunity genes linked to IRAK4-controlled IL-1R and TLR pathways downregulated in HS

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

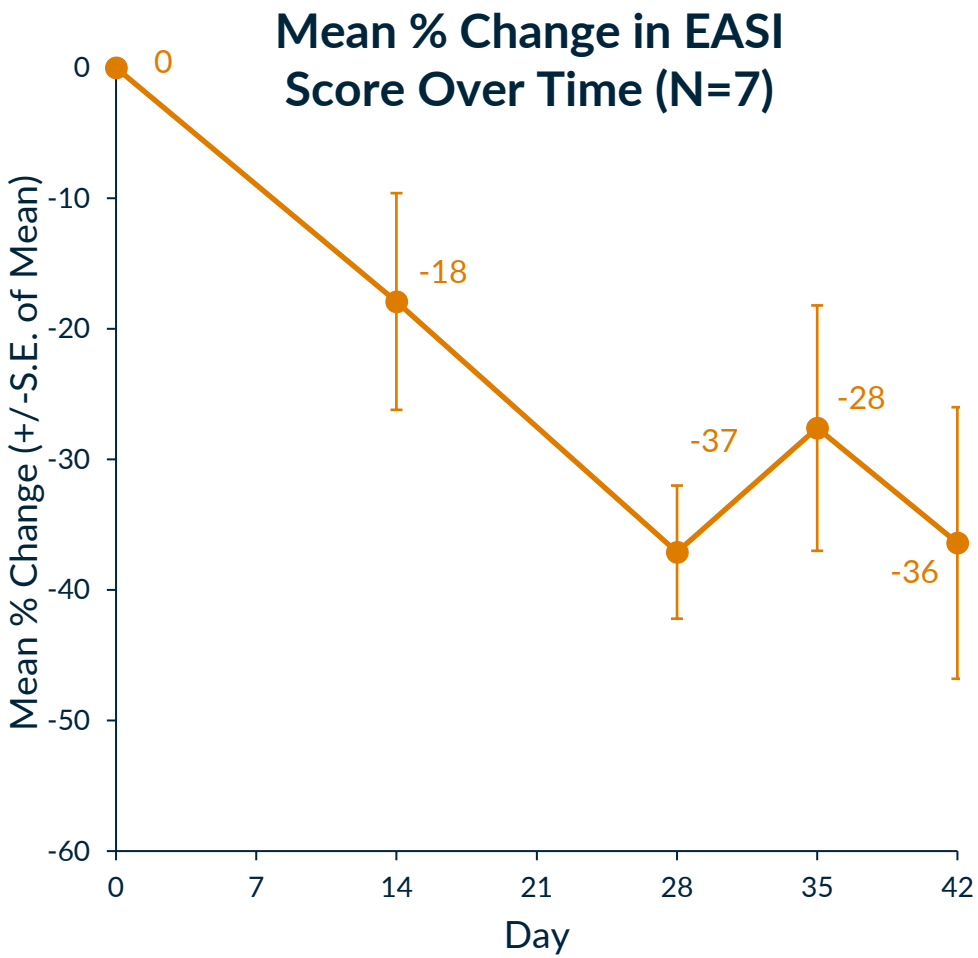
Robust Clinical Impact in HS After Only 28 Days of Dosing

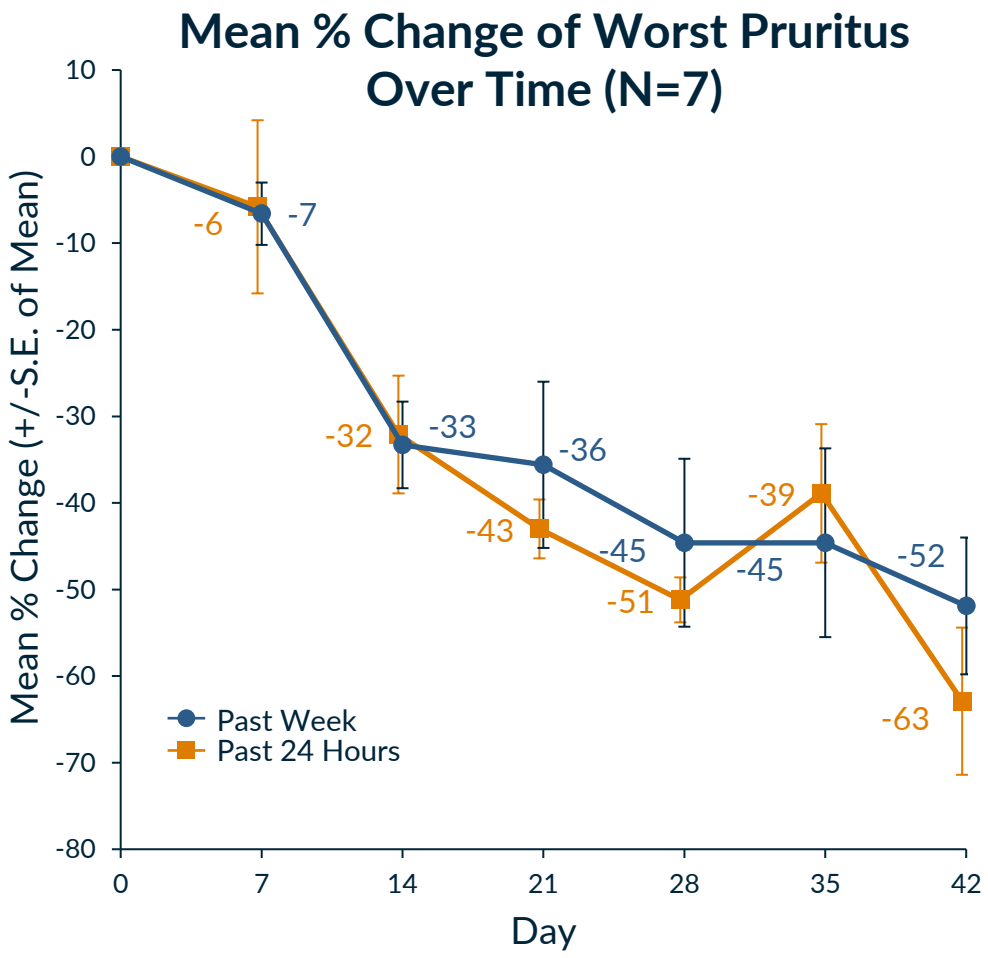




HiSCR50 response rate of up to 50% and pain reduction of up to 66% in moderate to severe HS patients

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 2b HS Trial
(ZEN)

- Double-blind, placebo-controlled
- Up to 156 patients, dosed for 16 weeks
- 2 KT-474 dose arms, 1 placebo arm
- Primary endpoint: % Change in AN Count
- Additional endpoints (select):
  - HiSCR50, IHS4, HS-Skin Pain-NRS30
- Primary completion (est.): 1H 2026

Phase 2b AD Trial
(ADVANTA)

- Double-blind, placebo-controlled
- Up to 200 patients, dosed for 16 weeks
- 3 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.): Mid-2026

Sanofi, following a safety/efficacy IA, has expanded the ongoing Phase 2 trials by adding additional doses to more rapidly progress toward pivotal trials

Additional information on the Phase 2 studies can be found at www.clinicaltrials.gov; identifier NCT06028230 (HS) and NCT06058156 (AD); Study Sponsor: Sanofi

Oral IRAK4 Degrader: 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 sales[1] opportunity

Large potential for oral degraders with best in pathway efficacy

KT-474 Progress

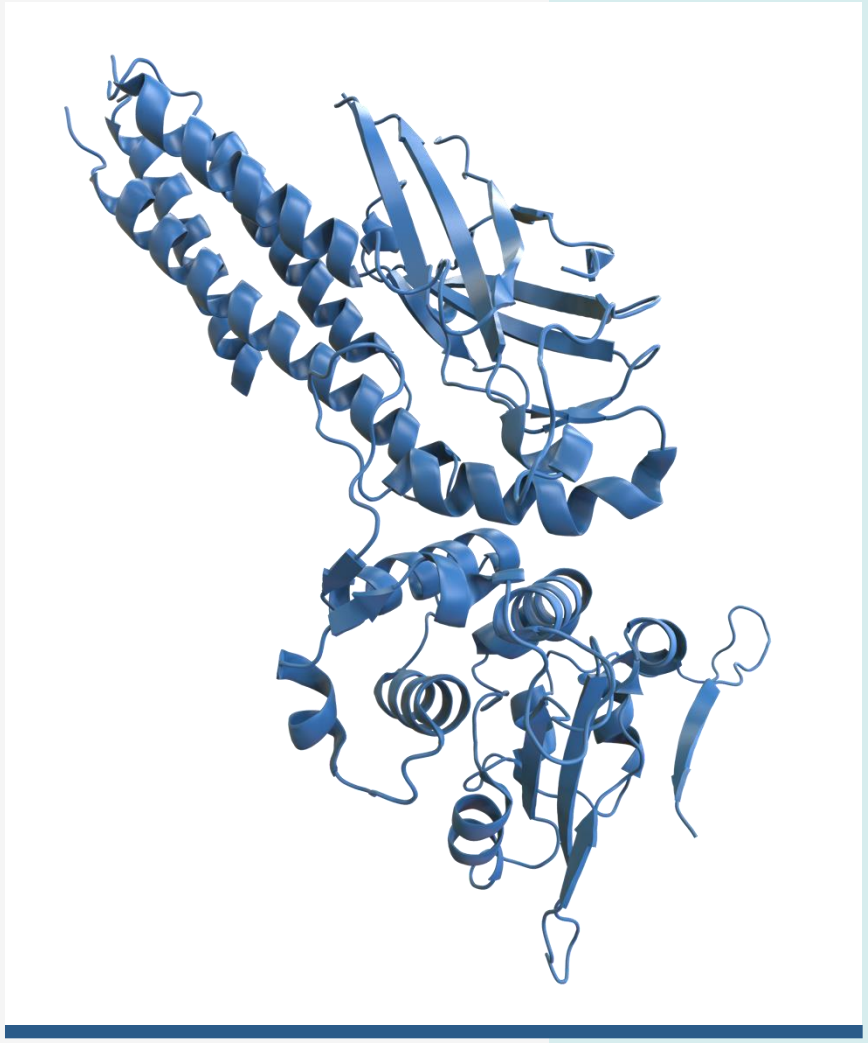
Phase 1 complete:

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

Partner Sanofi, after safety/efficacy IA, has expanded the ongoing Phase 2 trials in HS and AD by adding additional doses to accelerate overall development timelines and inform future pivotal trials; primary completion expected 1H26 for HS and mid-2026 for AD

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

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



First-in-Class Oral STAT6 Degrader Program

STAT6 Biology and Target Rationale

Target Biology and rationale

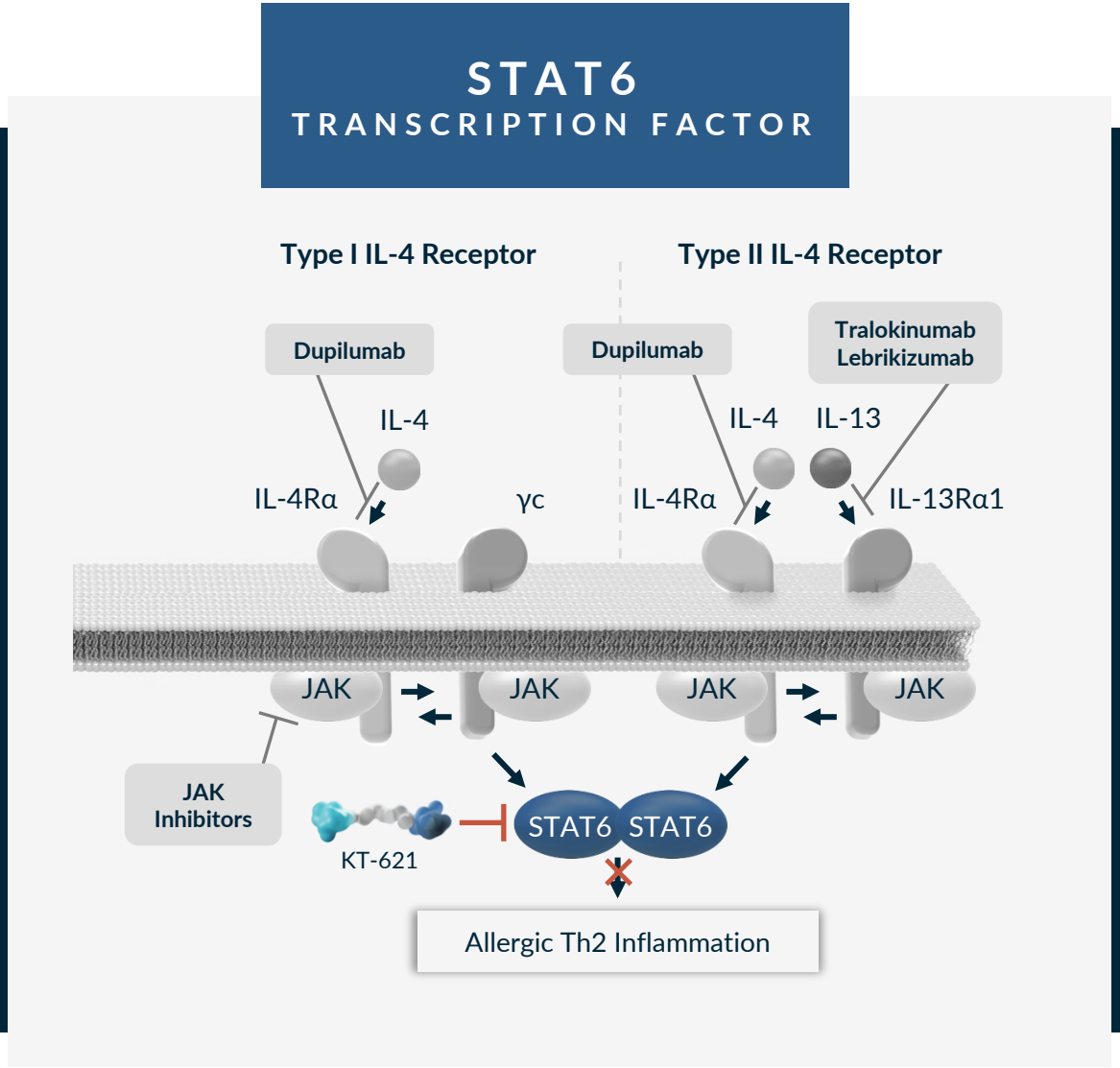
- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases

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

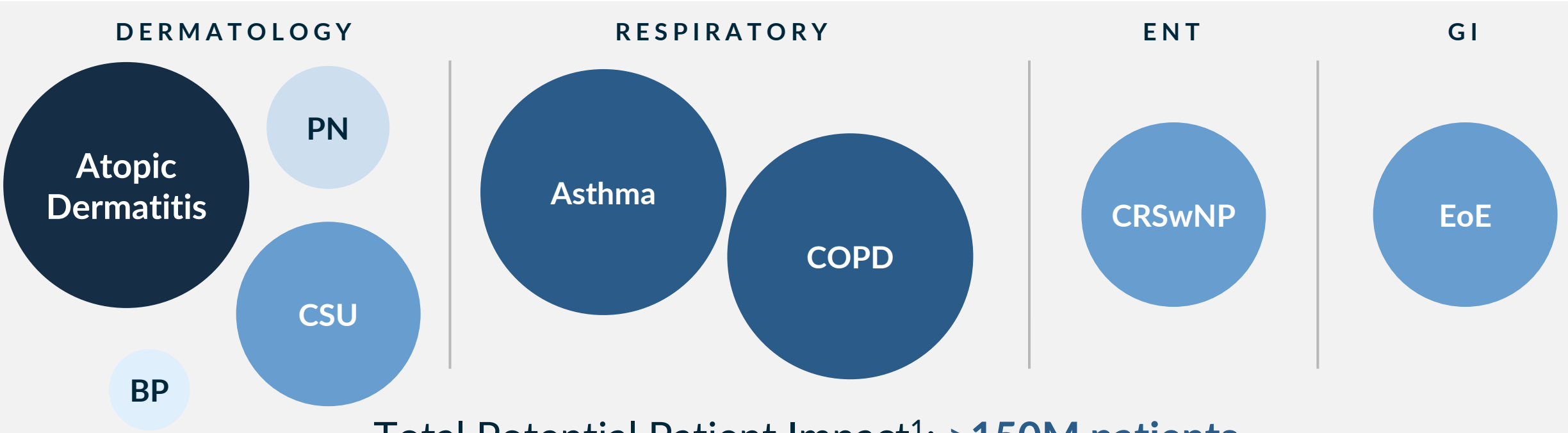
Clinical Pathway Validation

- Dupilumab, an IL-4Rα monoclonal Ab that blocks IL-4/IL-13 signaling, has been approved in: Atopic dermatitis, Asthma, COPD, CRSwNP, Eosinophilic Esophagitis, Prurigo Nodularis, and has positive Phase 3 data in Bullous Pemphigoid and is in development for multiple additional indications
- STAT6 degradation can fully block IL-4/IL-13 signaling*



Adapted from Junttila. Front Immunol. 2018; Sharma et al. J Exp Med. 2023; Suratannon et al. J Allergy Clin. Immunol. 2022; Takeuchi et al. J Allergy Clin Immunol. 2022
*Statements regarding STAT6 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

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

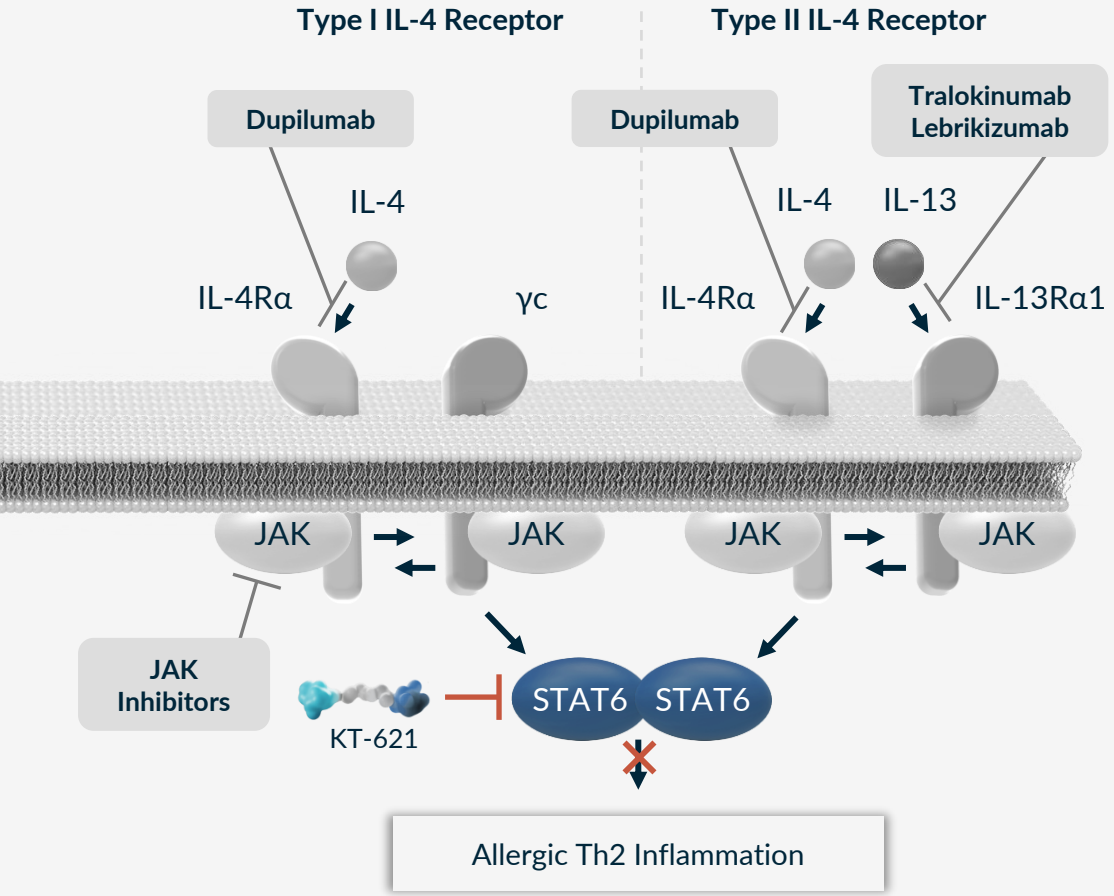


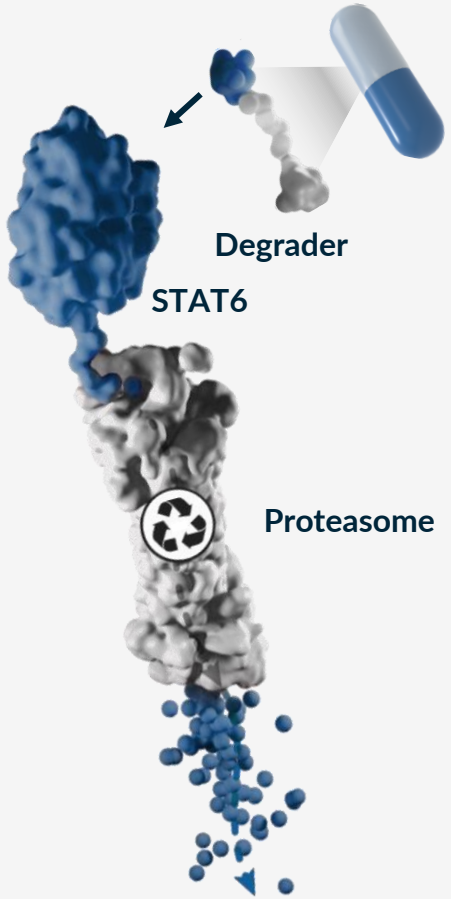
Total Potential Patient Impact[1]: >150M patients

- 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

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

STAT6 Degrader 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
- However, degradation of STAT6 can fully block IL-4/IL-13 signaling *in vitro* and *in vivo*

KT-621: A Picomolar Degrader of STAT6

Consistent Degradation Across All Disease Relevant Cell Types Evaluated

Blood

Skin

Lungs

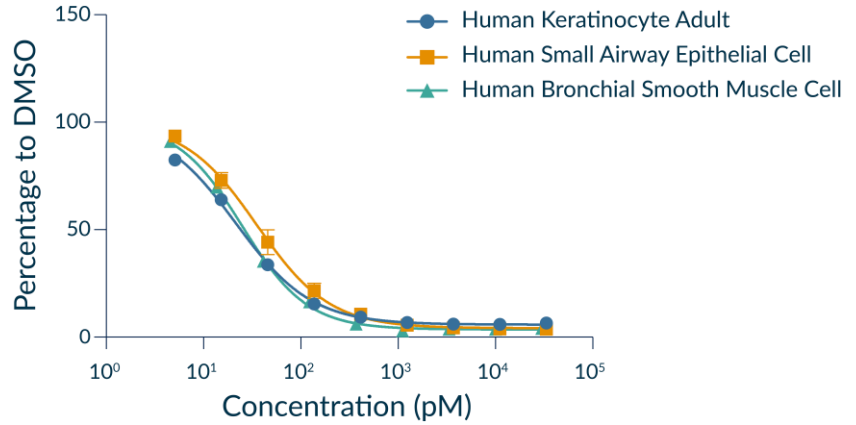
Throat/ Airway

Blood Vessels

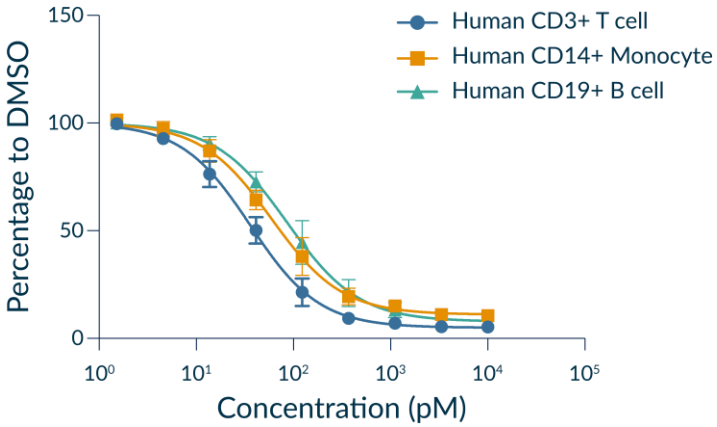
Neurons

Human Primary Cell Type	KT-621, DC_{50} (pM)
Hematopoietic cell (all TH2 diseases)	
Human PBMC	13
Human CD3 T cell	36
Human CD14 monocyte	60
Human CD19 B cell	86
Human eosinophil	99
Epithelial cell (AD, CSU, asthma, COPD)	
Human keratinocyte (adult)	22
Human keratinocyte (neonatal)	18
Human bronchial tracheal epithelial cell	33
Human small airway epithelial cell	35
Smooth muscle cell (asthma, COPD, EoE)	
Human bronchial smooth muscle cell	25
Human esophageal smooth muscle cell	33
Endothelial cell (all TH2 diseases)	
Human vascular endothelial cell	46
Neuron (AD, PN, CSU)	
Human iPSC derived sensory neuron	22

STAT6 Degradation in Hematopoietic Cells



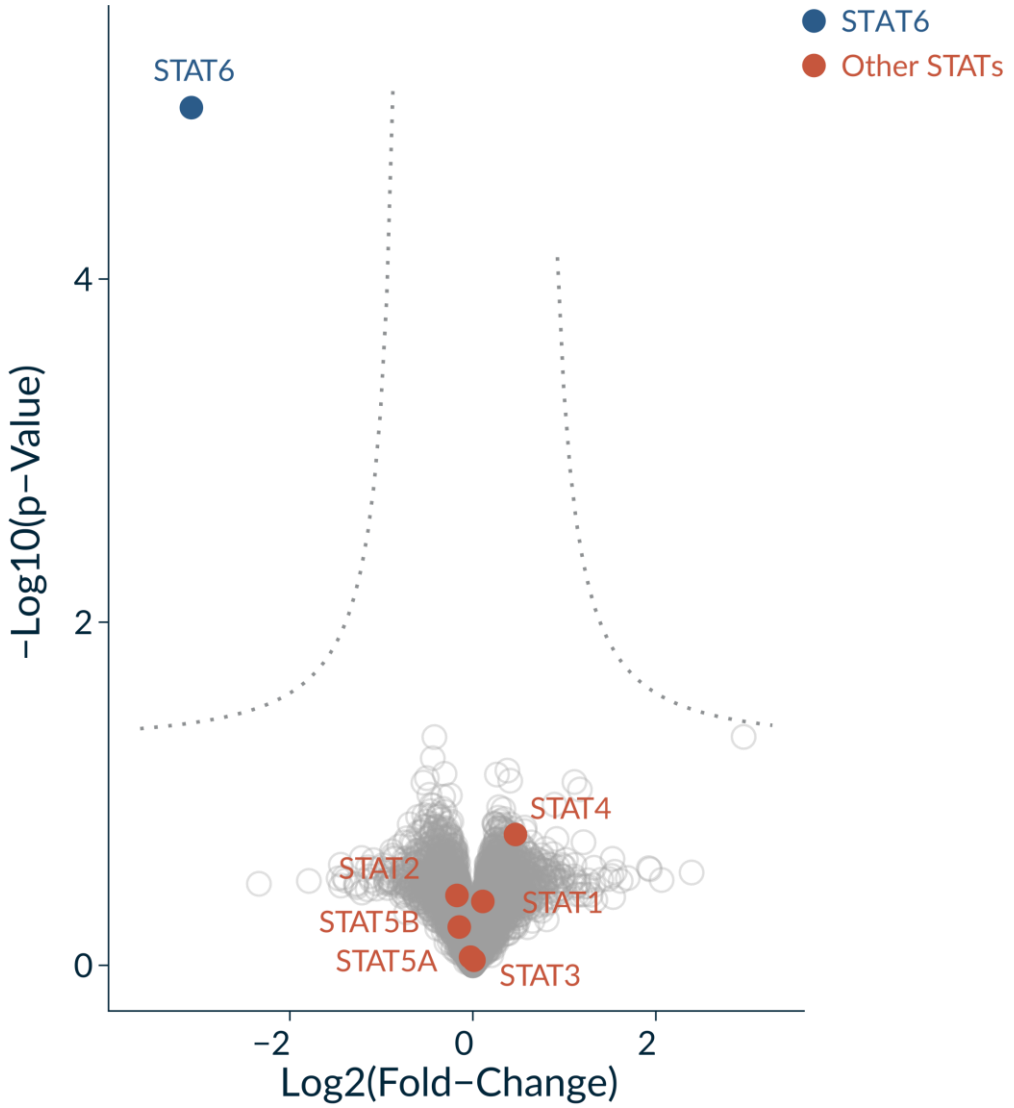
STAT6 Degradation in Tissue Cells



KT-621: Exquisite Degradation Selectivity for STAT6

Complete STAT6 degradation selectivity in human PBMC proteome at 100 x DC_{90}

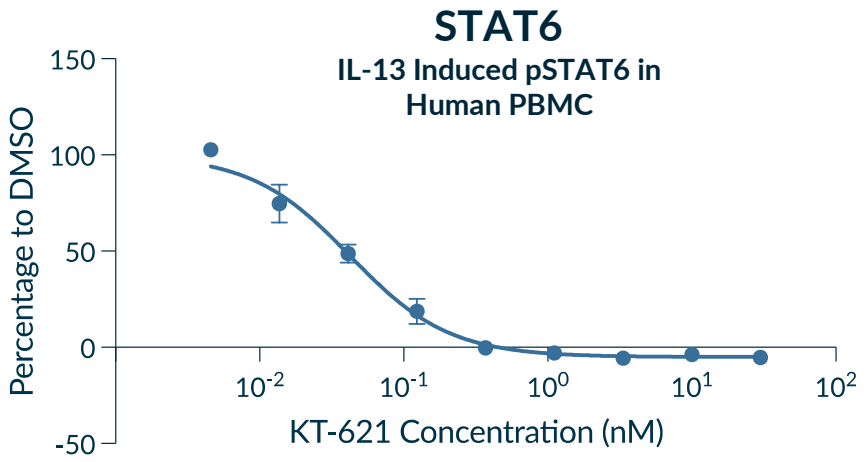
No other STATs are degraded to any extent

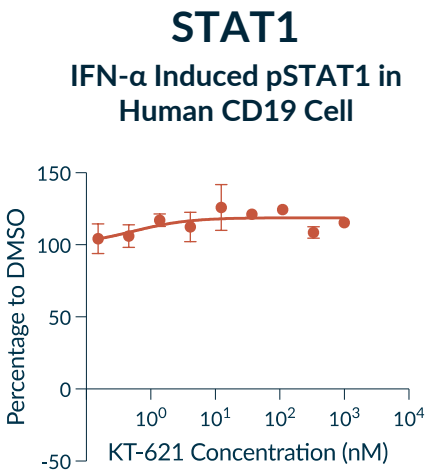


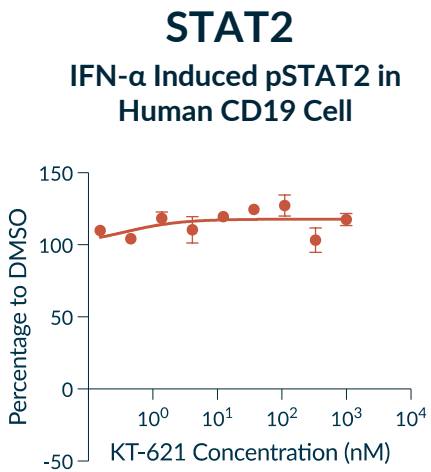
KT-621: Exquisite Pathway Selectivity for STAT6

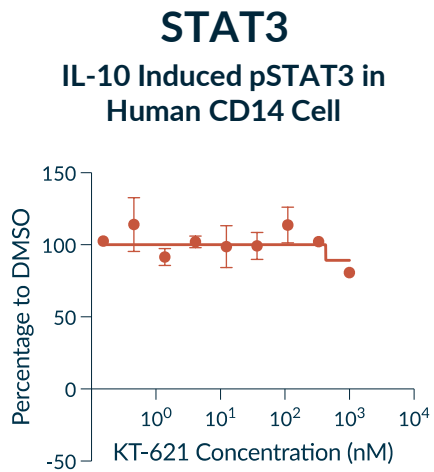
No Impact on Any Other STAT Pathway Observed

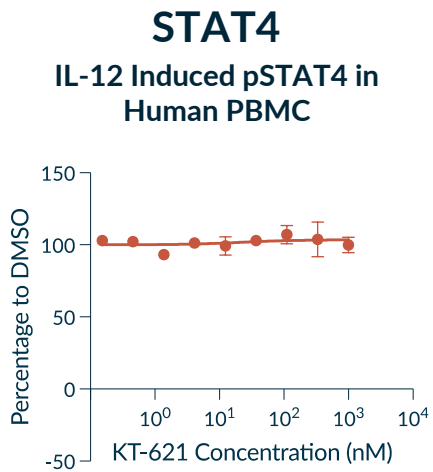
STAT assays	KT-621, IC_{50} (nM)
IFN-α induced pSTAT1	> 1000
IFN-α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042

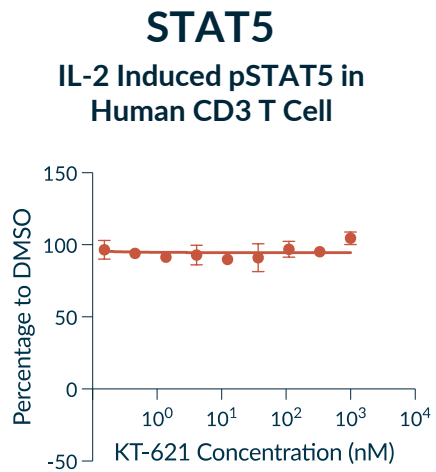








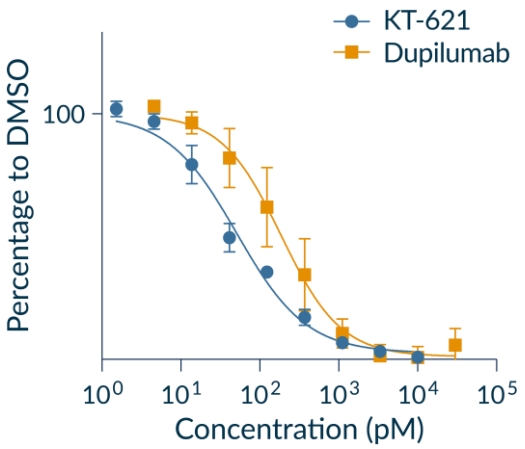




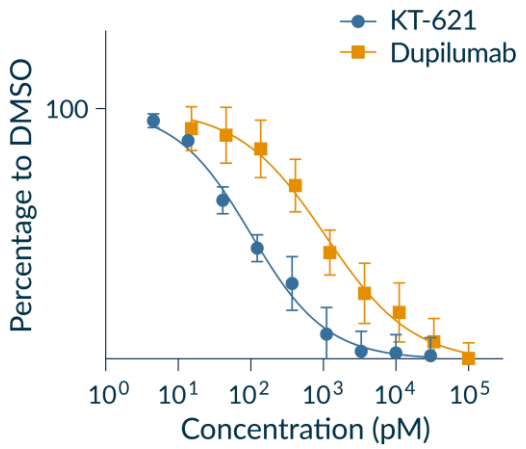
KT-621 Fully Blocks IL-4/13 Pathway in Human TH2 Functional Assays with IC_{50}'s Lower than Dupilumab

		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
TAC1 NPPB	Neuropeptides related to itch transmission in sensory neurons	IL-13 TAC1 expression in iPSC derived human sensory neuron	**89**	1027
		IL-13 NPPB expression in iPSC derived human sensory neuron	**121**	5714

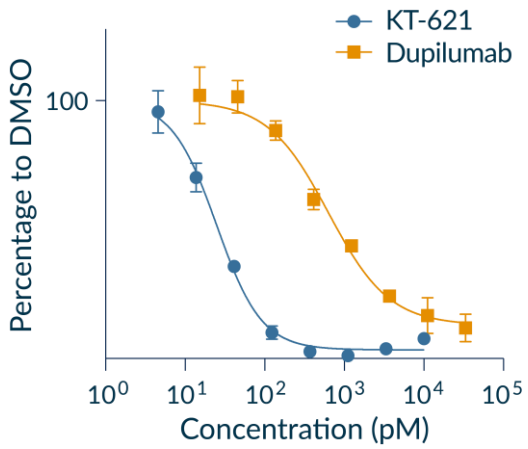
IL-4 Induced TARC Release in Human PBMC



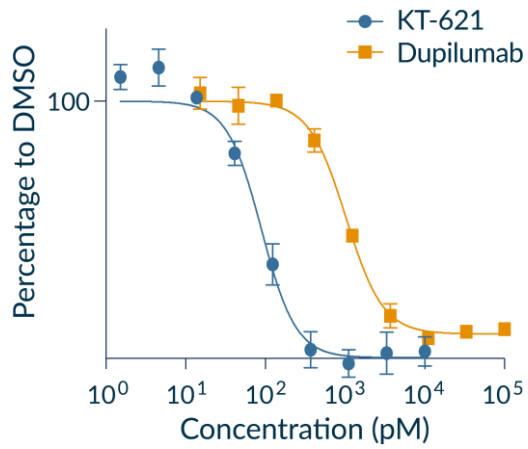
IL-13 Induced CD23 Expression in Human CD19 B Cell



IL-13 Induced Periostin Release in Human Bronchial Smooth Muscle Cell



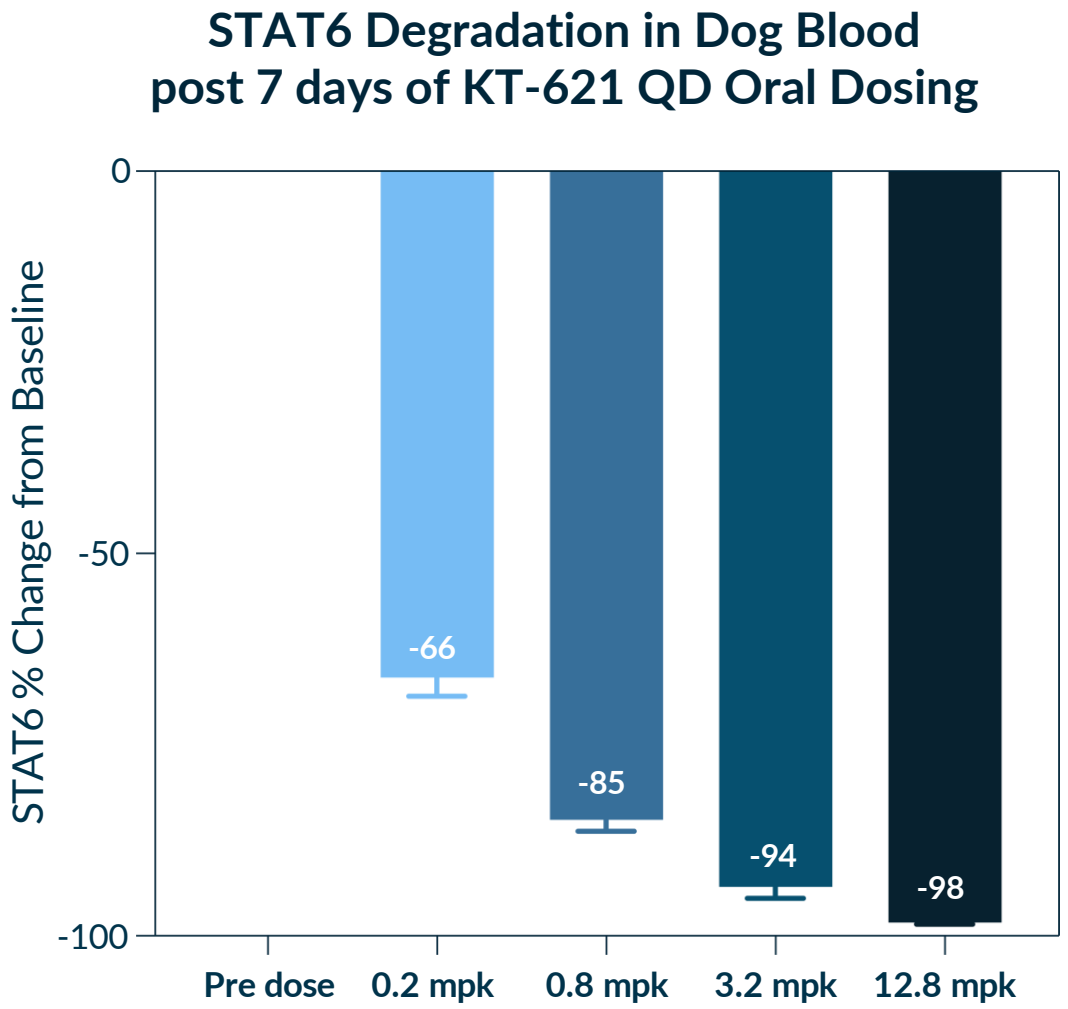
IL-13 Induced TAC1 Expression in iPSC Derived Human Sensory Neuron



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

KT-621 potently degrades STAT6 across multiple preclinical species

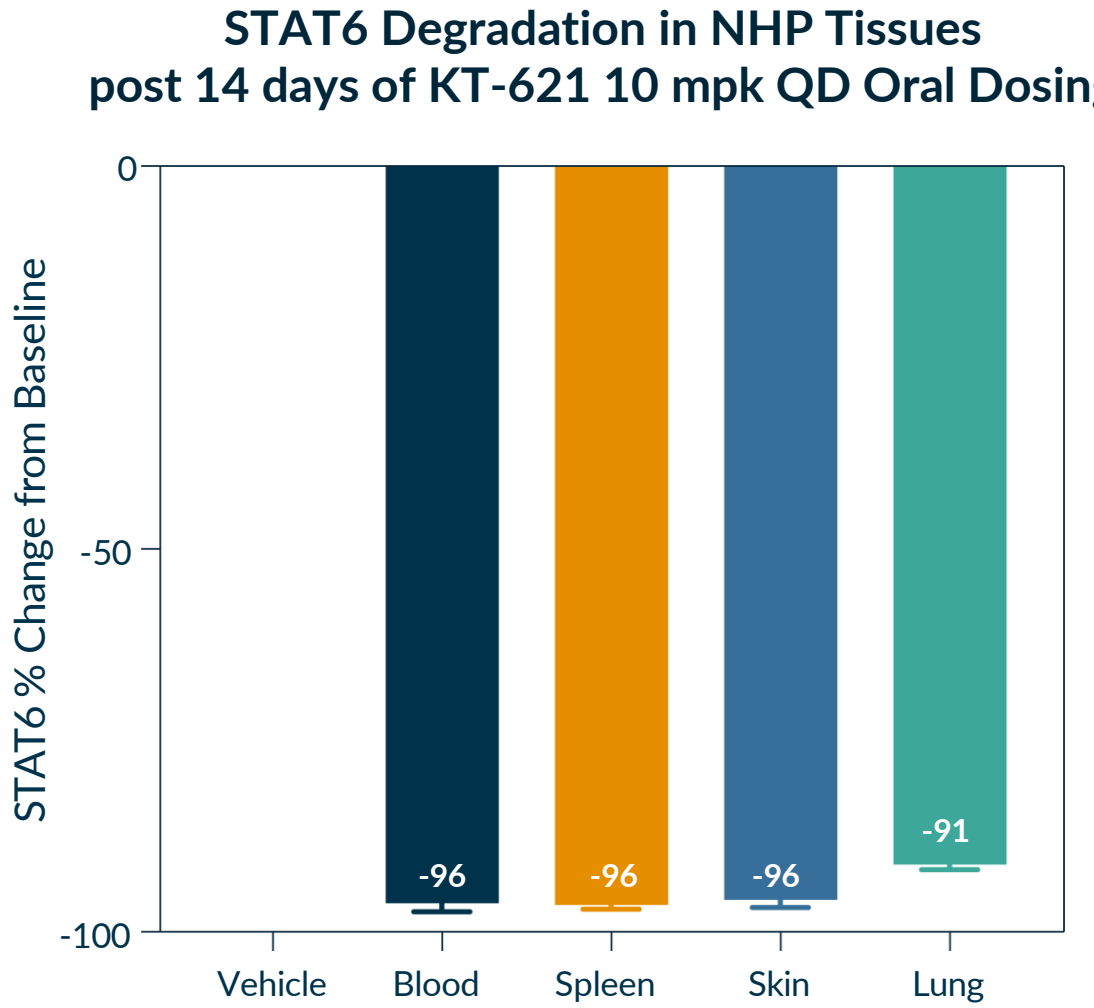
KT-621 can degrade STAT6 to depletion with low oral doses



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

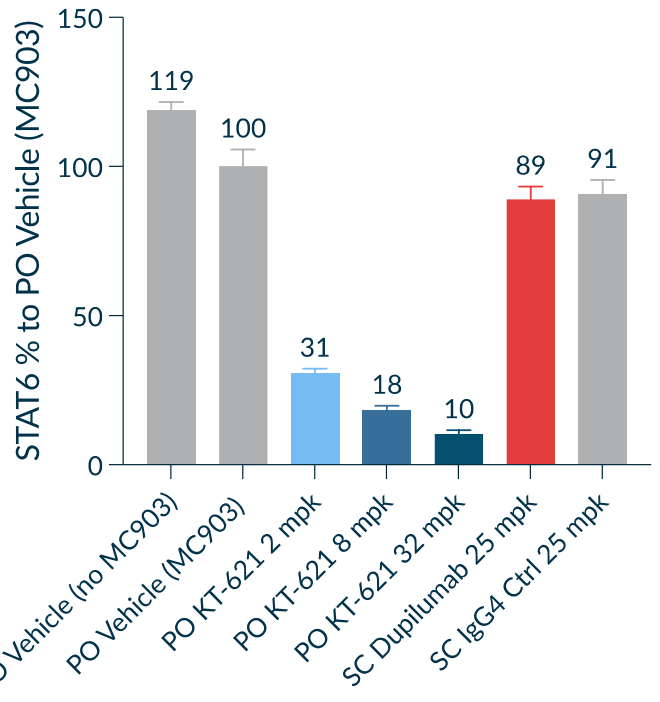


KT-621 Has Comparable *in vivo* Activity to IL-4Rα Saturating Dose of Dupilumab in the MC903 Atopic Dermatitis Model

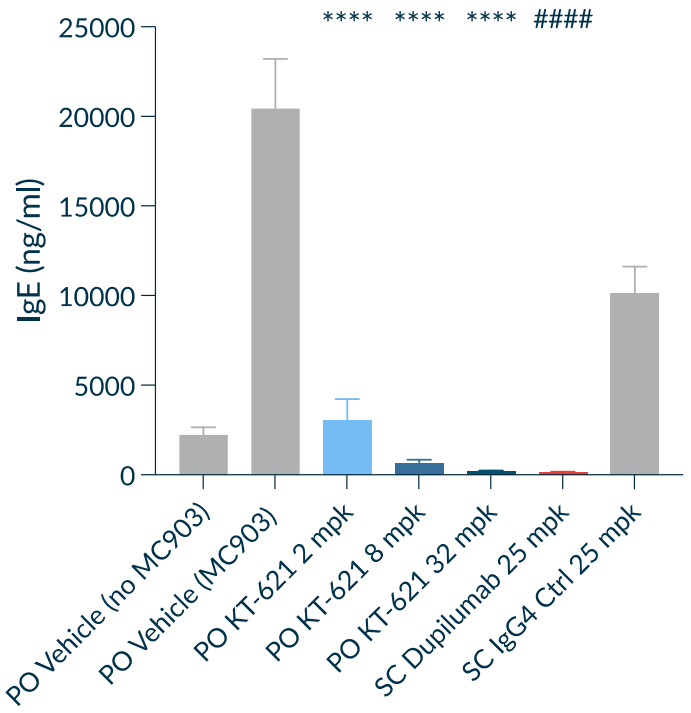
An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

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

STAT6 Degradation in Mouse Spleen



Total Serum IgE

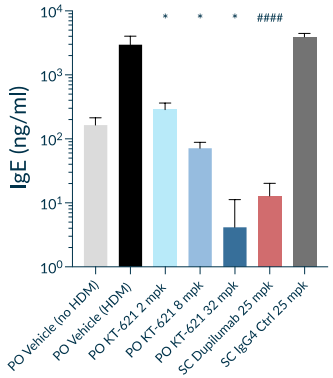


* Significance to PO vehicle (MC903); # Significance to SC IgG4 25 mpk BIW

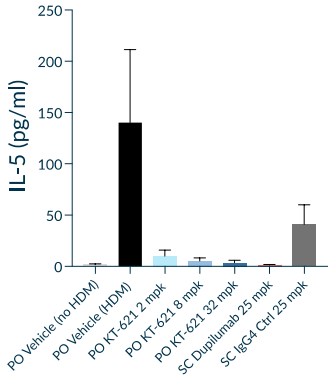
KT-621 Blocks TH2 Inflammation *in vivo* Equally or Better than an IL-4Rα Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model

Serum IgE and Lung Cytokine

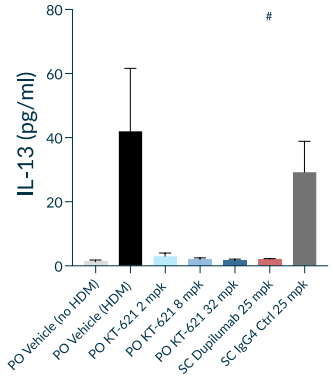
Total Serum IgE



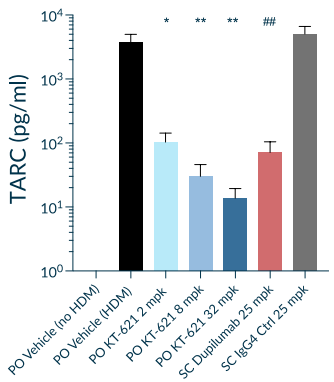
BAL IL-5



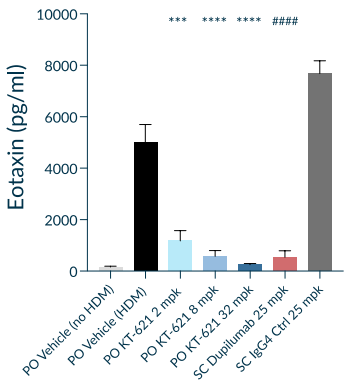
BAL IL-13



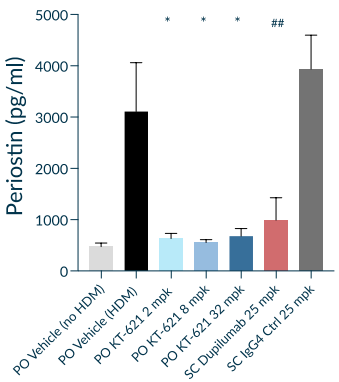
BAL TARC (CCL17)



BAL Eotaxin (CCL11)

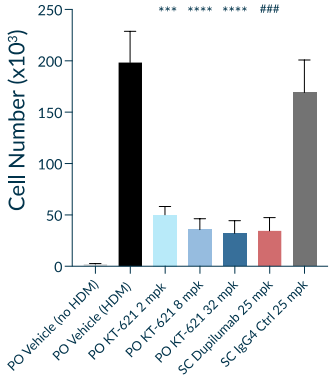


BAL Periostin

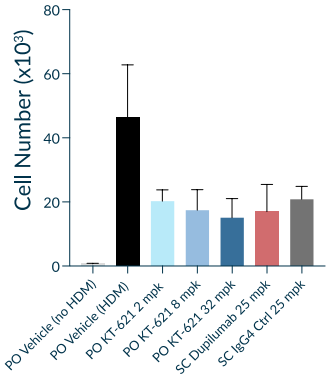


Inflammatory Infiltrate

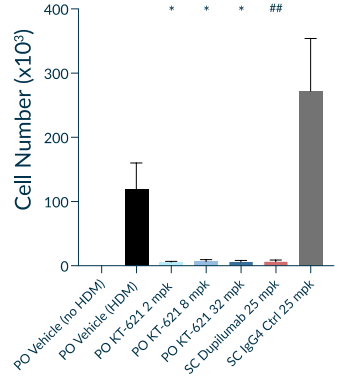
BAL CD4+ T Cell



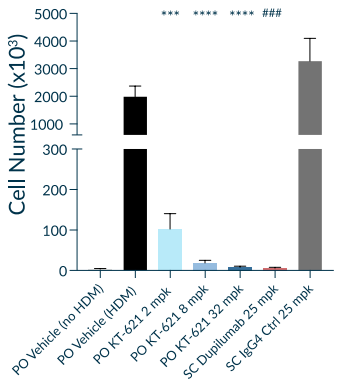
BAL CD8+ T Cell



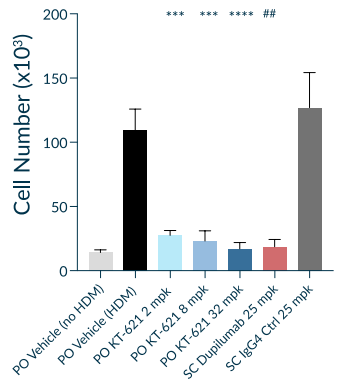
BAL Activated B Cell



BAL Eosinophil



BAL Dendritic Cell



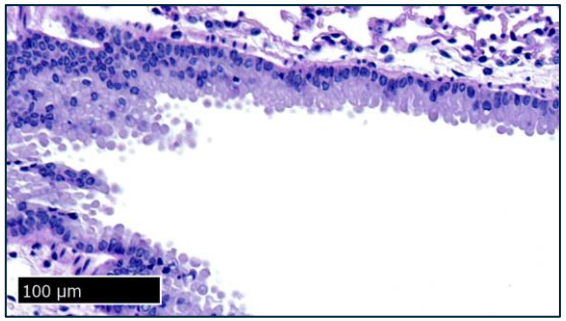
- **KT-621 dosed QD orally for 31 days. 2/8/32 mpk** doses showed **72/85/91% STAT6 degradation** respectively in mouse spleen
- **Dupilumab dosed 9 times subcutaneously**, 25 mpk BIW (IL-4Rα saturating dose), **effect equivalent to 300 mg every other week in human**

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);
BAL – bronchoalveolar lavage; *Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

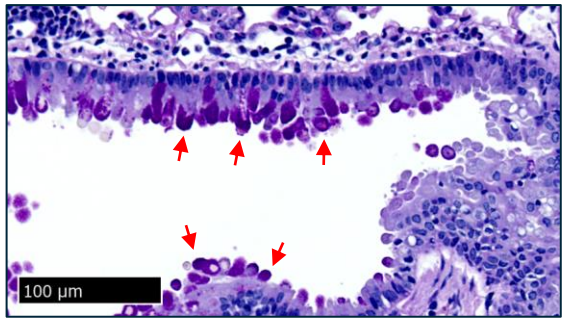
KT-621 Reduced Disease Severity in the Lung in the Intranasal HDM Asthma Model

Lung Remodeling: Goblet Cell Metaplasia (Arrow)

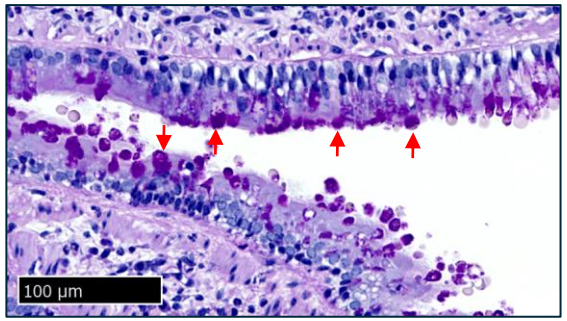
PO Vehicle (no HDM)



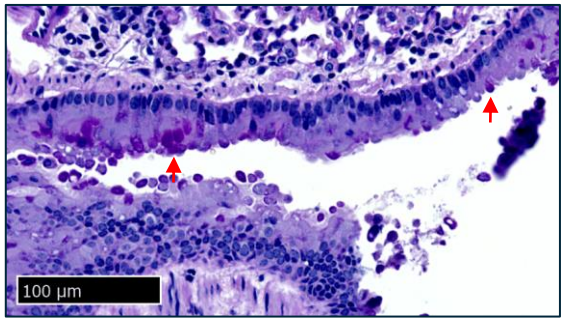
PO Vehicle (HDM)



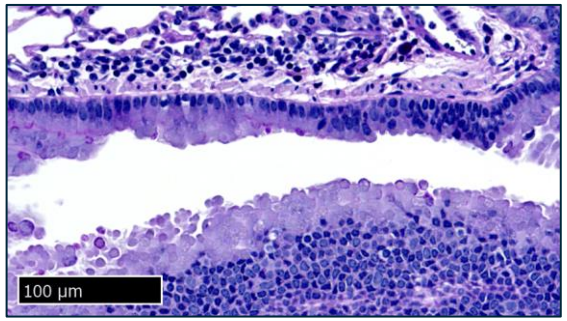
SC IgG4 Ctrl 25 mpk



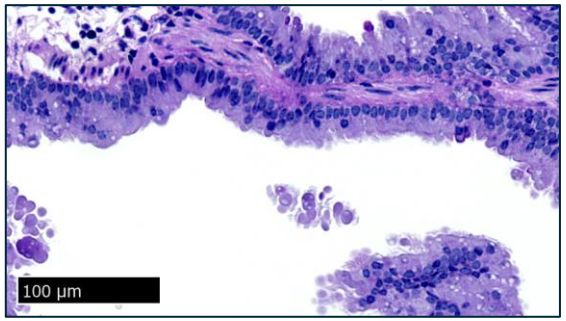
PO KT-621 2 mpk



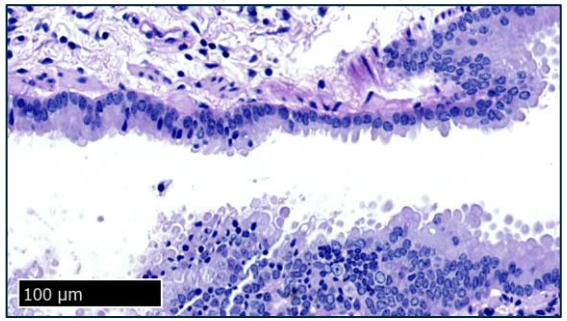
PO KT-621 8 mpk



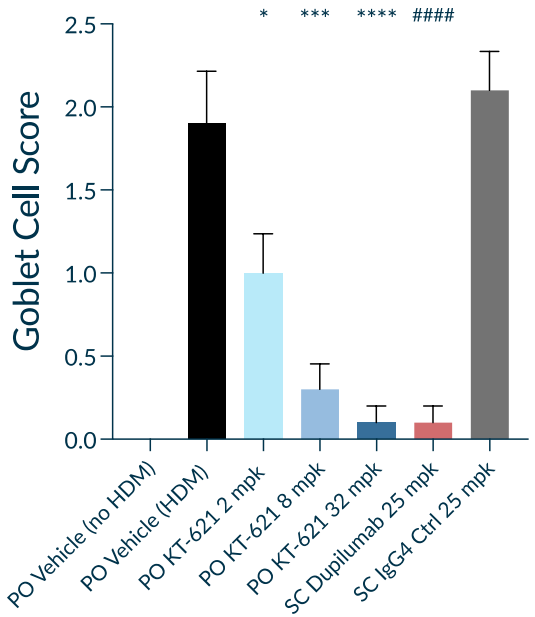
PO KT-621 32 mpk



SC Dupilumab 25 mpk



Lung Goblet Cell Metaplasia



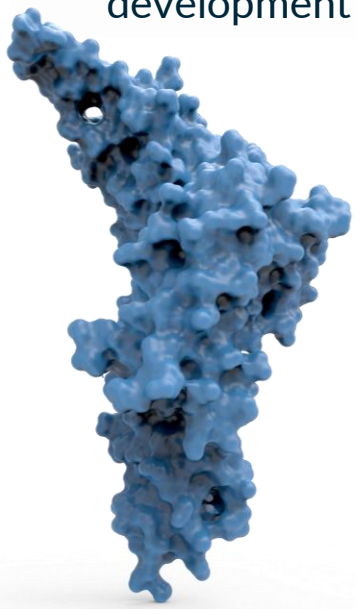
Amelioration of lung remodeling seen after low daily oral doses of KT-621 comparable to dupilumab

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

KT-621 First-in-Human Phase 1 Clinical Trial

Double-blind, Placebo-controlled SAD and MAD in Healthy Volunteers

First STAT6 directed medicine in clinical development



Part A
Single Ascending Dose
(SAD)

Part B
Multiple Ascending Dose
(MAD)
14x daily doses

Primary
- Safety & tolerability of escalating single and multiple doses of KT-621

Secondary
- Pharmacokinetic measures

Exploratory
- STAT6 protein levels in blood and skin
- TH2 biomarkers

Key study aim is to show that **KT-621 can robustly degrade STAT6 in blood and skin at doses that are safe and well-tolerated**

Oral STAT6 Degrader: KT-621

Potential for dupilumab-like activity 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 in allergic diseases

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

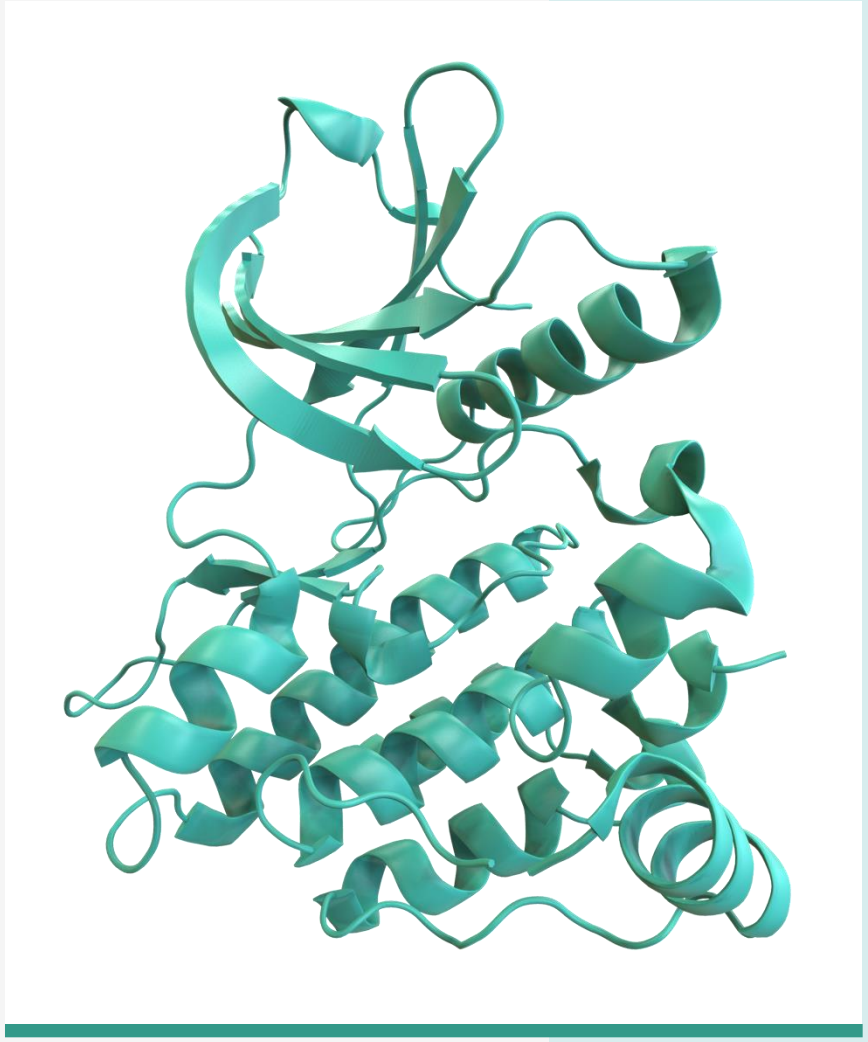
Phase 1 Data: 1H 2025

Full IL-4 and IL-13 functional inhibition with picomolar IC_{50}'s superior to dupilumab

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

STAT6 degradation was well-tolerated in multiple preclinical safety studies (including GLP-tox) at >40x efficacious concentration

Phase 1 trial ongoing in healthy volunteers, with data expected in 1H25



First-in-Class Oral TYK2 Degrader Program

TYK2 Biology and Target Rationale

Target Biology and Rationale

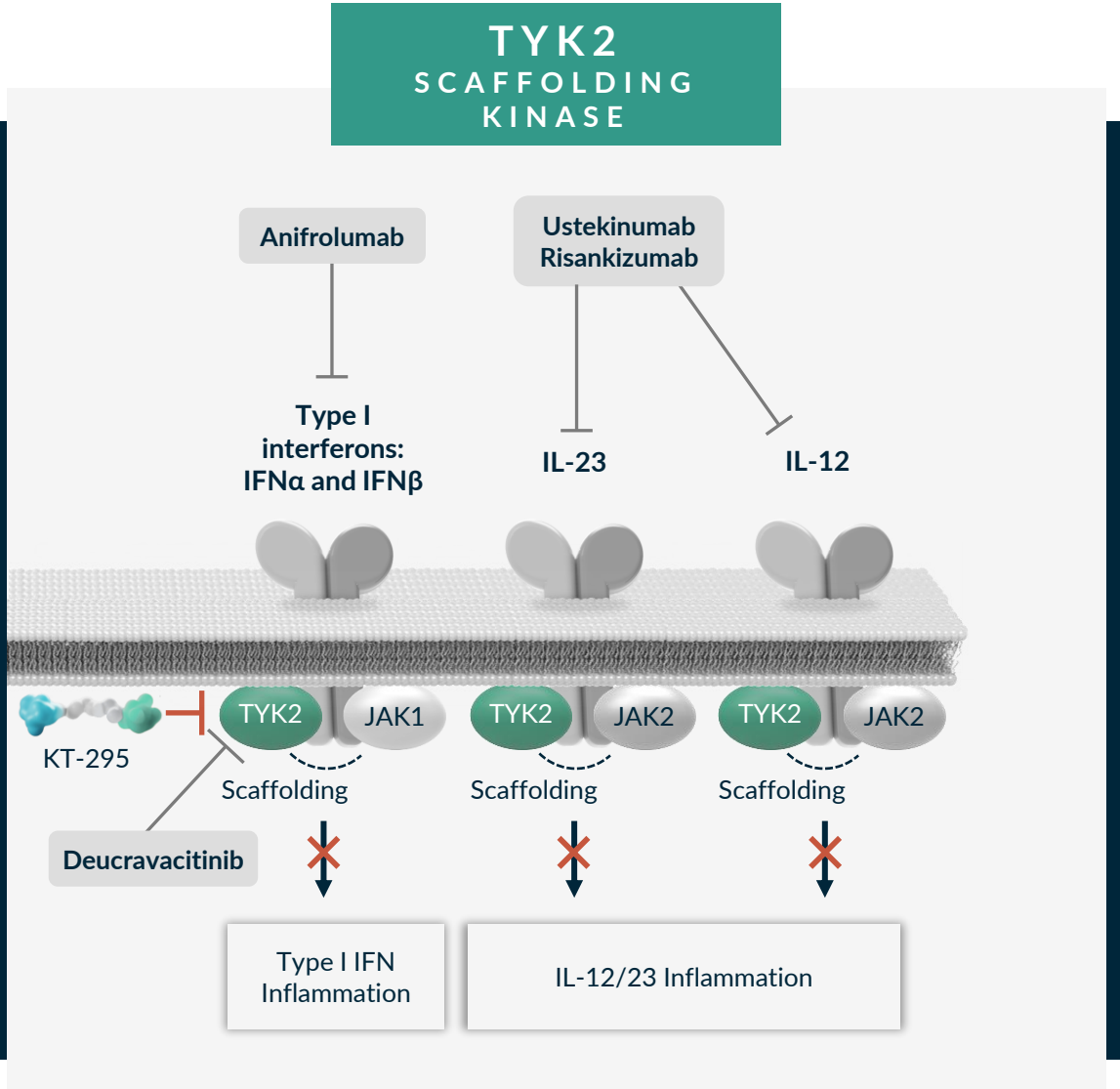
- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 regulated cytokines are clinically validated targets for autoimmune and inflammatory diseases

Human Genetics

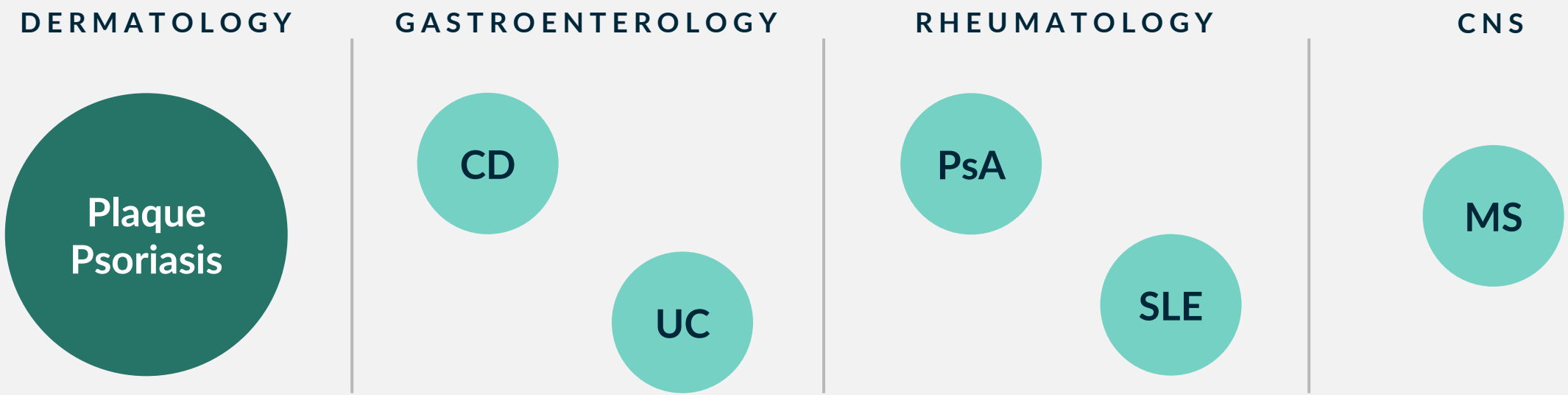
- Loss-of-function variant of TYK2 is protective in autoimmune and inflammatory diseases

Clinical Pathway Validation

- IL-23 (± 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



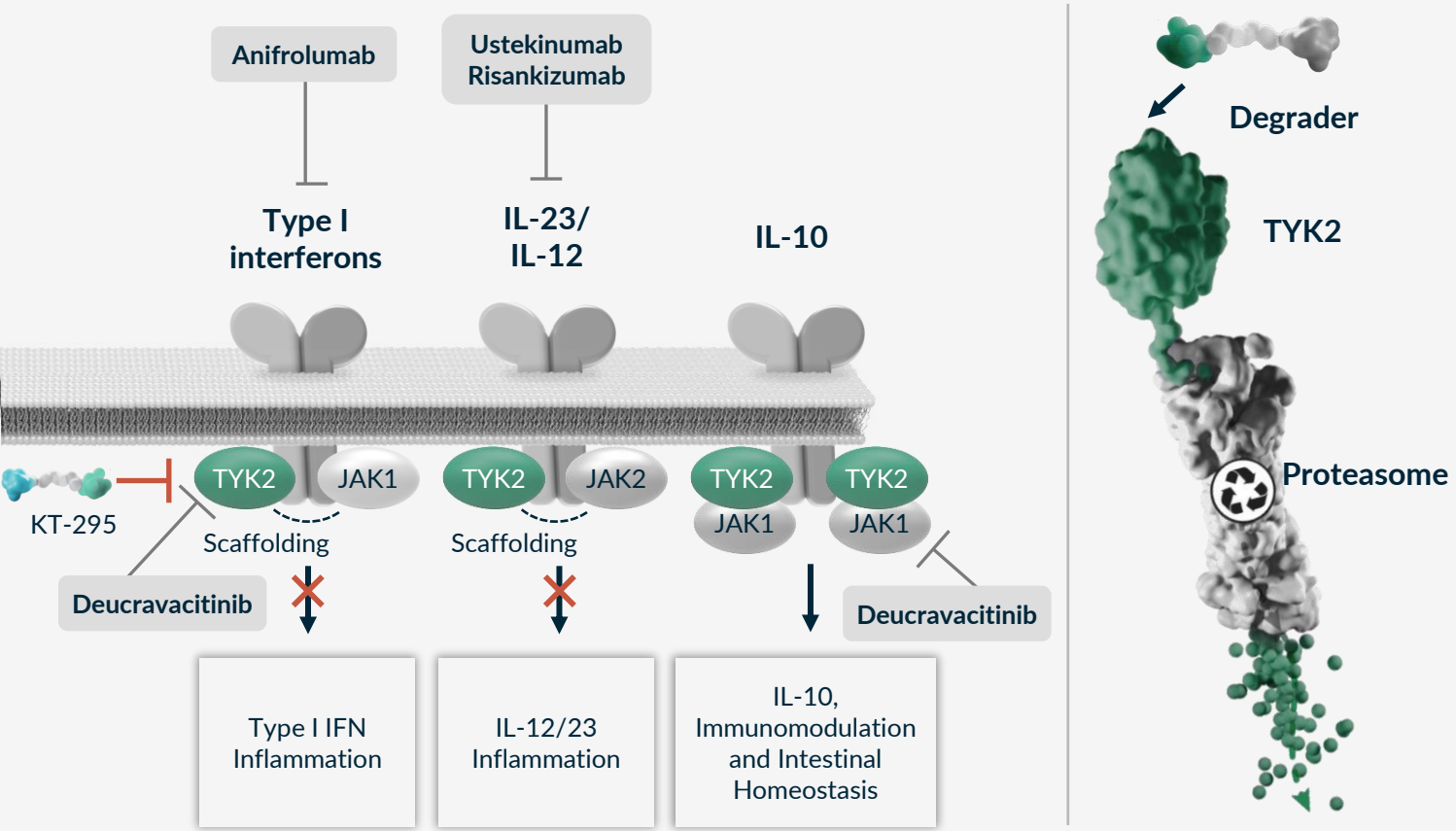
Total Potential Patient Impact[1]: > 20M patients

- 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

[1]GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)
*Statements regarding TYK2 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

TYK2 Degrader Advantage

Only TYK2 Degraders Can Achieve 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, TYK2 degradation does not inhibit IL-10, which is important in IBD
  - Compared to TAK-279, TYK2 degradation fully inhibits Type I IFN
- Full TYK2 degradation leads to pathway inhibition superior to existing SMIs with potential for biologics-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	+	++++	++++	++++

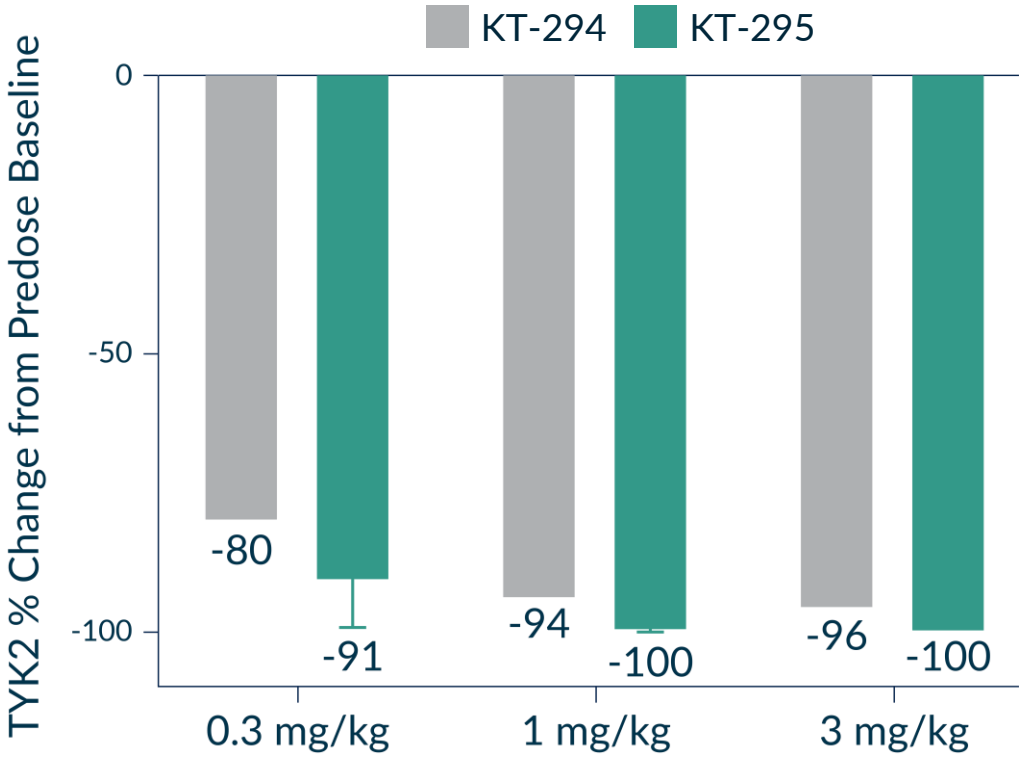
Degrading TYK2 is the only small molecule approach to potentially eliminate all scaffolding and catalytic functions of TYK2, fully recapitulating the human TYK2-/- biology

Ogishi et al. JEM. 2022

KT-295, a Potent, Selective, Once Daily Oral TYK2 Degrader

Key Data	KT-294	KT-295
Human PBMC degradation DC_{50}	**0.08 nM**	**0.08 nM**
IL-23 pathway		
IL-23/IL-1β IFN-γ release in human PBMC	**2.4 nM**	**3.6 nM**
Type I IFN pathway		
IFN-α pSTAT2 in human CD19 B cells	**15 nM**	**14 nM**
IL-12 pathway		
IL-12/IL-18 IFN-γ release in human PBMC	**10 nM**	**14 nM**
IL-10/22 pathways		
IL-10 pSTAT3 in human CD14 monocytes	**>1000 nM**	**>1000 nM**
IL-22 pSTAT3 in HT29 cells	**>1000 nM**	**>1000 nM**
Human dose prediction	-	**Lower human dose prediction compared to KT-294**

TYK2 Degradation in NHP Blood Post 7-day QD Oral Dosing for KT-294 and KT-295

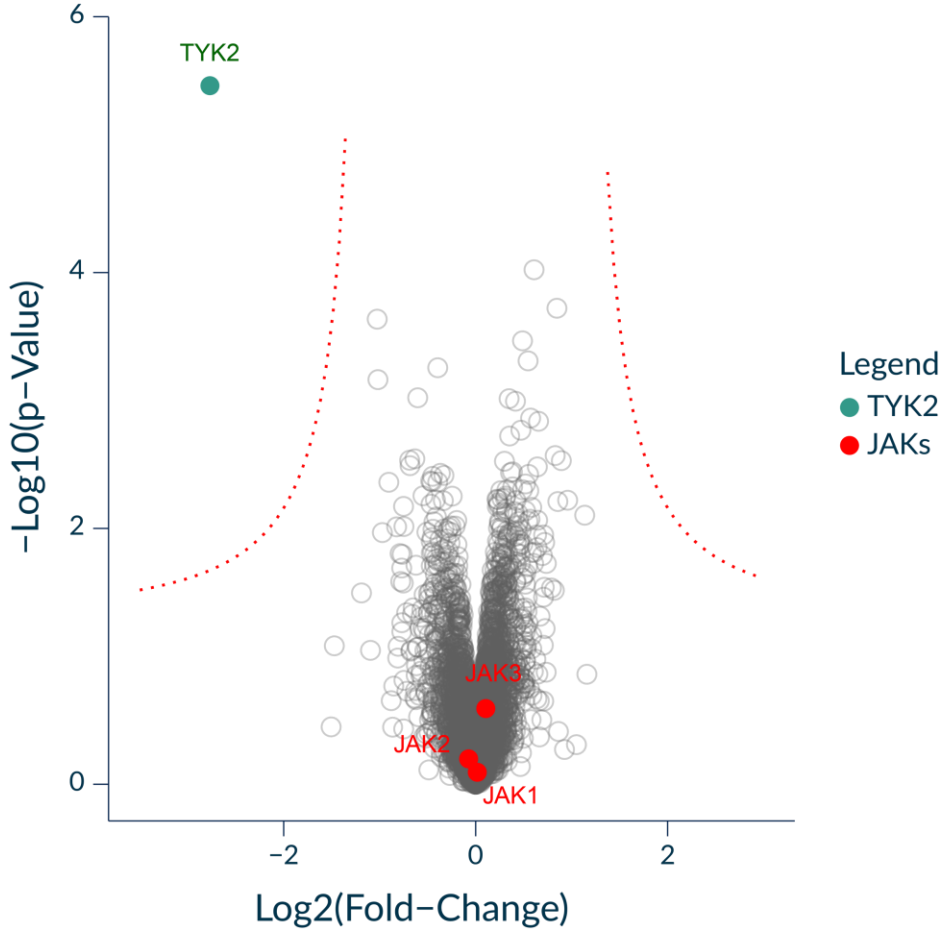


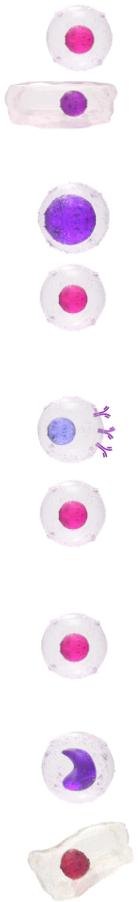
KT-295 has comparable high selectivity and picomolar potency but greater *in vivo* activity in preclinical animal models compared to KT-294, Kymera's previously identified TYK2 degrader

KT-295, a Highly Selective Picomolar TYK2 Degrader, 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-295 in hPBMC Proteome at 10x DC_{90}



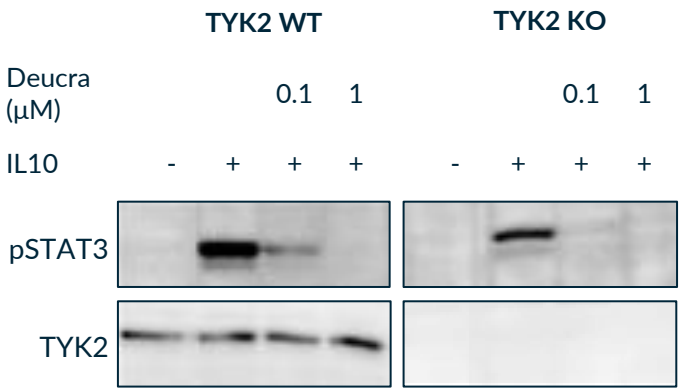


Cellular Degradation/Functional Assay	KT-295 DC_{50}/IC_{50} (nM)
Human PBMC degradation	**0.08**
Human keratinocyte	**0.06**
IL-23 pathway	
IL-23 pSTAT3 in human CD3+CD161high TH17 cell	**1.3**
IL-23/IL-1β IFN-γ release in human PBMC	**3.6**
Type I IFN pathway	
IFN-α pSTAT1 in human CD19 B cell	**10**
IFN-α pSTAT2 in human CD19 B cell	**14**
IFN-α IP10 release in human PBMC	**37**
IL-12 pathway	
IL-12/IL-18 pSTAT4 in human PBMC	**1.1**
IL-12/IL-18 IFN-γ release in human PBMC	**14**
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**

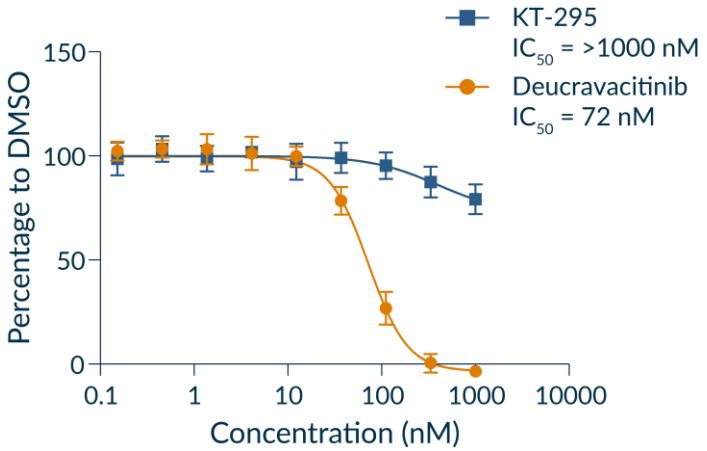
Unlike Allosteric TYK2 Inhibitor Deucravacitinib, KT-295 Does Not Inhibit IL-10

- 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 because of its anti-JAK1 activity; KT-295 spares IL-10 as a result of TYK2 selectivity

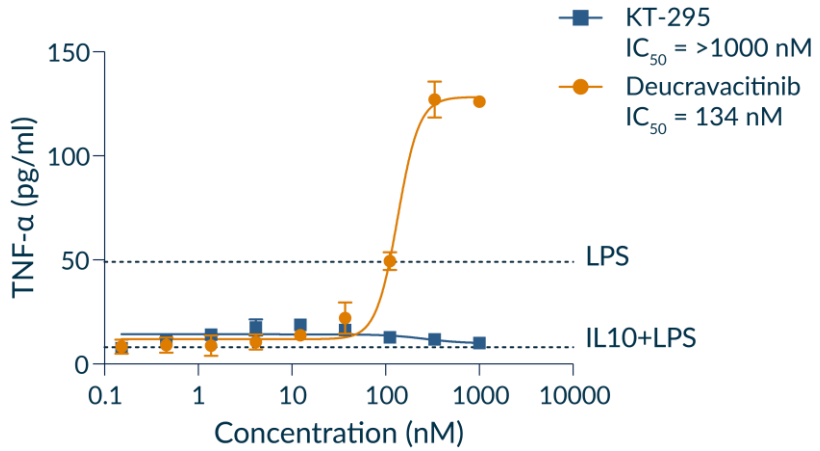
Deucravacitinib Inhibited IL-10 induced pSTAT3 in TYK2 KO EBV B Cell



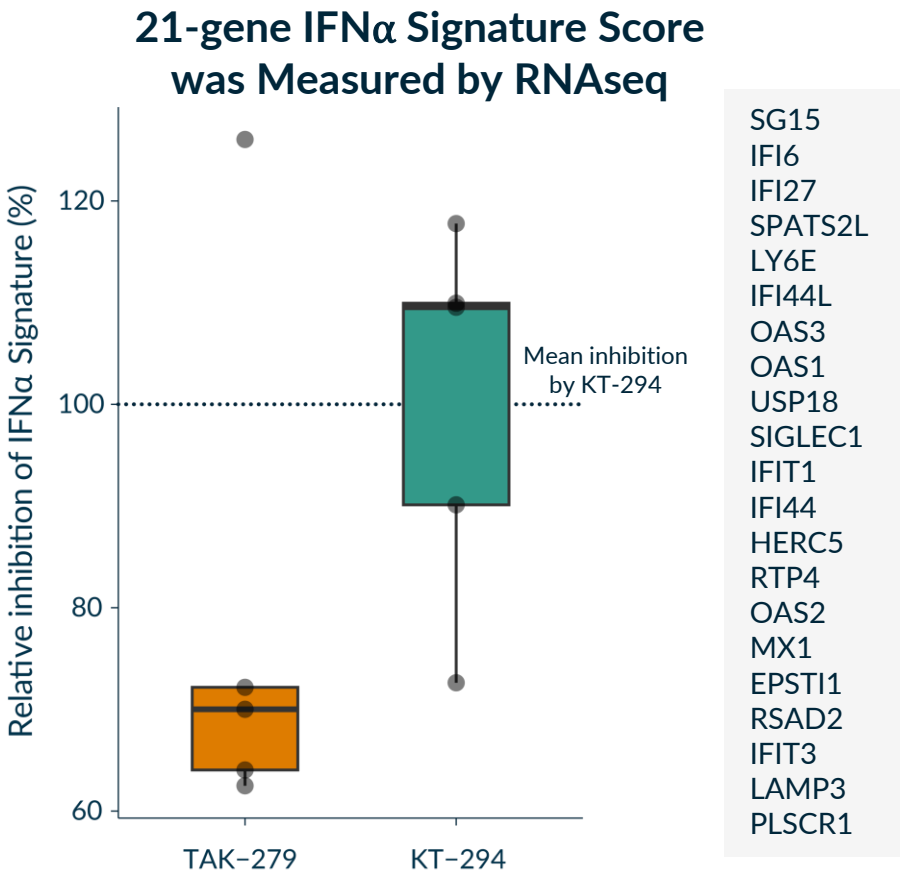
Deucravacitinib Inhibited IL-10 Induced pSTAT3 in Human CD14 Monocyte

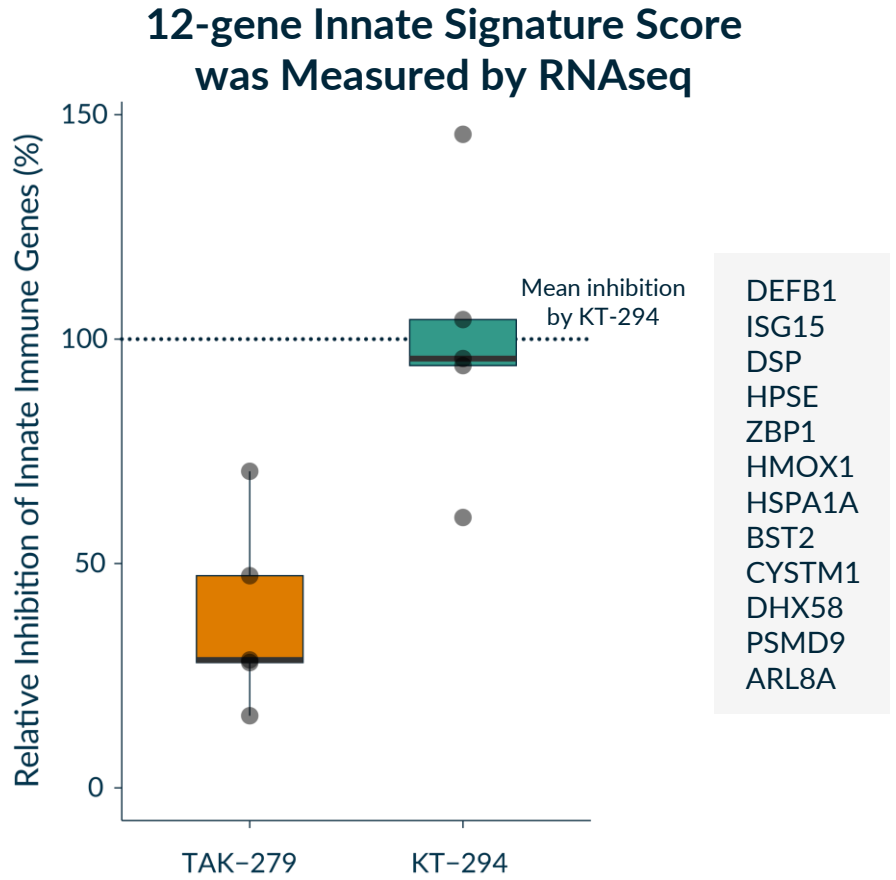


Deucravacitinib Inhibits IL-10's Function of Suppressing LPS Induced TNF-α Release in Human CD14 Monocyte



Superior Inhibition of Type I IFN Pathway and Innate Immunity by Degrader vs. Inhibitor





Doses Used:

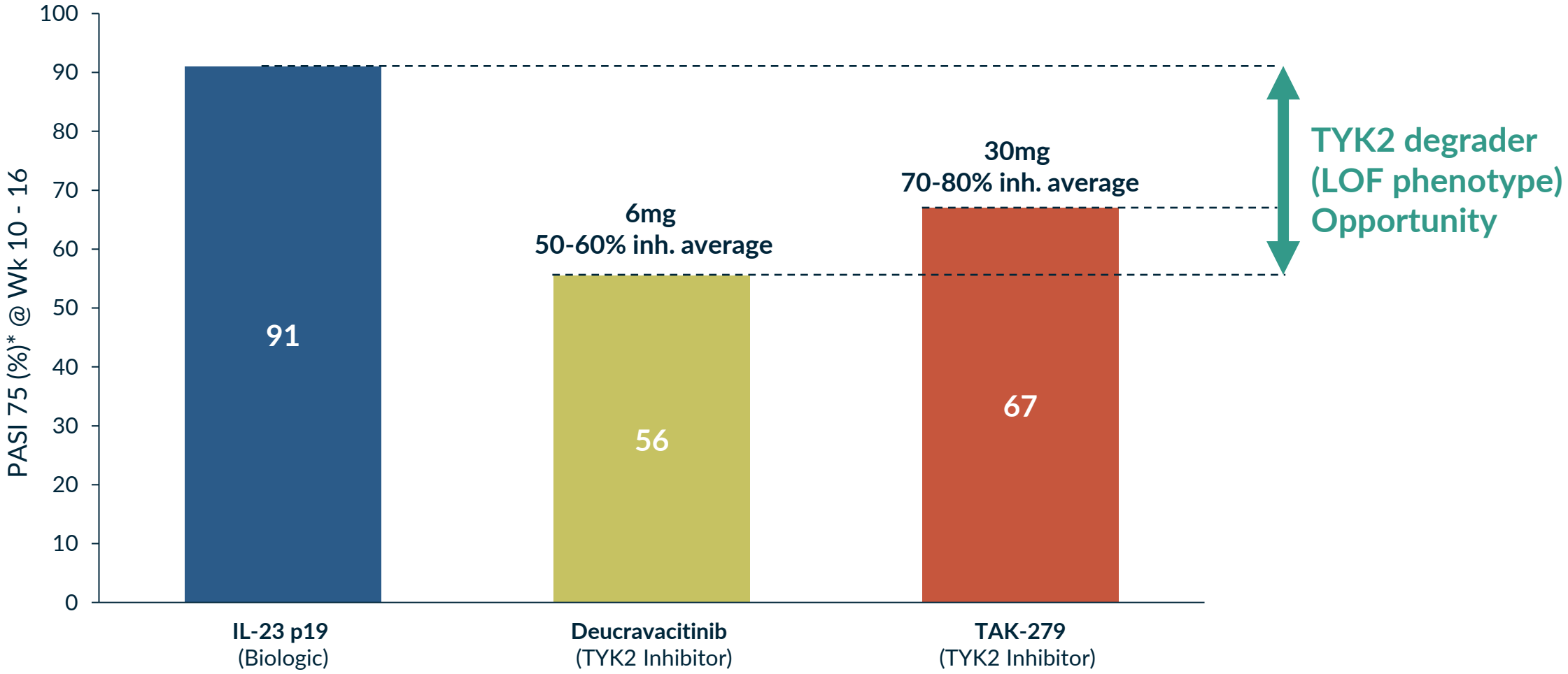
- TYK2 Inhibitor (TAK-279) = 422nM (IFNα stimulated pSTAT2 IC_{95}). Clinical exposure Cmax (free) at 35mg[1] = ~ 77 nM
- TYK2 Degrader (KT-294) = 56nM (IFNα stimulated pSTAT2 IC_{95})

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

[1]Gangolli et al., SID 2022

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-295 IL12/23, IFN	*KT-295, unlike TYK2 SMI, can replicate the TYK2 deficient phenotype and result in potent Type I IFN, IL-12/23 inhibition fully while sparing IL-10* **WITH FOLLOWING EXPECTED CLINICAL DIFFERENTIATION:**
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 Degrader: KT-295

Potential Best-in-Class Opportunity with Biologics-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 biologics-like activity that is superior to TYK2 SMI

FIH: 1H 2025

Degrades TYK2 in human cells with pM potency

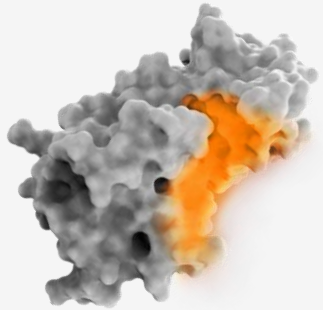
Recapitulates the phenotype of TYK2 human deficiency showing potent IFN-α, IL-12 and IL-23 inhibition and sparing IL-10

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

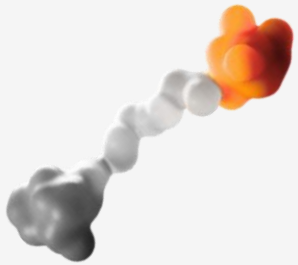
Currently in IND enabling studies

2024 Summary

Advancing our Best-in-Industry Pipeline of Degrader Therapeutics



High value undrugged/ inadequately drugged targets



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

Building the industry-leading oral immunology portfolio

- Dosing in the **KT-621** Phase 1 clinical trial initiated, with data expected in the first half of 2025
- Sanofi expanding **KT-474** Phase 2 clinical trials in HS and AD to dose ranging Phase 2b studies to accelerate overall development timelines, with completion of both trials expected by mid-2026
- **KT-295**, a new TYK2 degrader, selected as the development candidate to advance into Phase 1 clinical trial in the first half of 2025, in line with prior program guidance
- **Advancing additional novel, high value immunology programs,** in validated pathways for areas of significant patient need, to be shared in the near future
- Company to shift focus and resources from oncology to its expanding immunology pipeline, and will only advance **KT-333 and KT-253** oncology degrader programs beyond Phase 1 with a partner

Thank You

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Abbreviations

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

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
WW	Worldwide