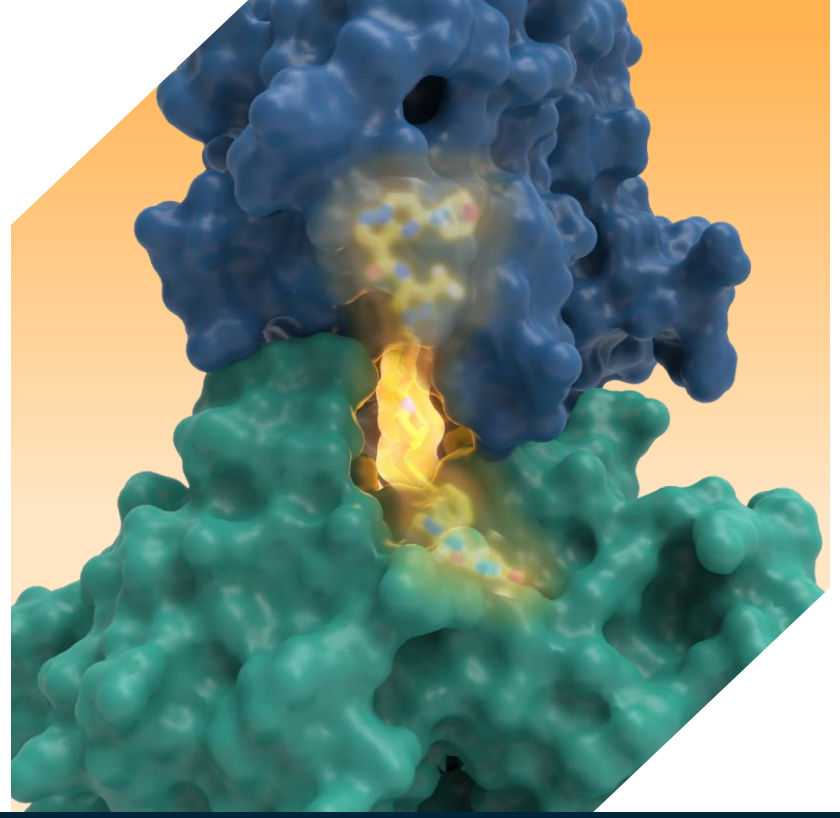


May 9, 2025

KYMERA

Oral Medicines with Biologics-like Activity

Immunology Innovation Day

Agenda

Kymera's Immunology Strategy
Nello Mainolfi, PhD, Founder, President and Chief Executive Officer

STAT6 (KT-621) Update
Jared Gollob, MD, Chief Medical Officer

IRF5 (KT-579): Drugging a Genetically Validated Target
Veronica Campbell, Senior Director, Immunology

Question and Answer Session

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; 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; our ability to deliver additional investigational drugs into the clinic by 2026; 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; any future product candidates; and our financial condition and expected cash runway into the first half of 2028. All statements other than statements of historical facts contained in this presentation, including express or implied statements regarding our strategy, future financial condition, 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," "upcoming," "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.

Any forward-looking statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements including, without limitation, risks associated with: the timing and anticipated results of our current and future preclinical studies and clinical trials, supply chain, strategy and future operations; the delay of any current and future preclinical studies or clinical trials or the development of our drug candidates; the risk that the results of prior preclinical studies and clinical trials may not be predictive of future results in connection with current or future preclinical studies and clinical trials, including those for KT-474/SAR-444656, KT-621 and KT-579; our ability to successfully demonstrate the safety and efficacy of our drug candidates; the timing and outcome of any interactions with regulatory authorities; obtaining, maintaining and protecting our intellectual property; our relationships with existing and future collaboration partners; the impacts of current macroeconomic and geopolitical events. In addition, any forward-looking statements represent Kymera's views only as of today and should not be relied upon as representing its views as of any subsequent date. Kymera explicitly disclaims any obligation to update any forward-looking statements, except as required by law. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. As a result of these risks and others, including those set forth in our filings with the SEC, actual results could vary significantly from those anticipated in this presentation, and our financial condition and results of operations could be materially adversely affected.

Certain information contained in this presentation and statements made orally during this presentation relate to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party studies, publications, surveys and other data to be reliable as of the date of the presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent sources have evaluated the reasonableness or accuracy of the Company's internal estimates or research, and no reliance should be made on any information or statements made in this presentation relating to or based on such internal estimates and research. This presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners.

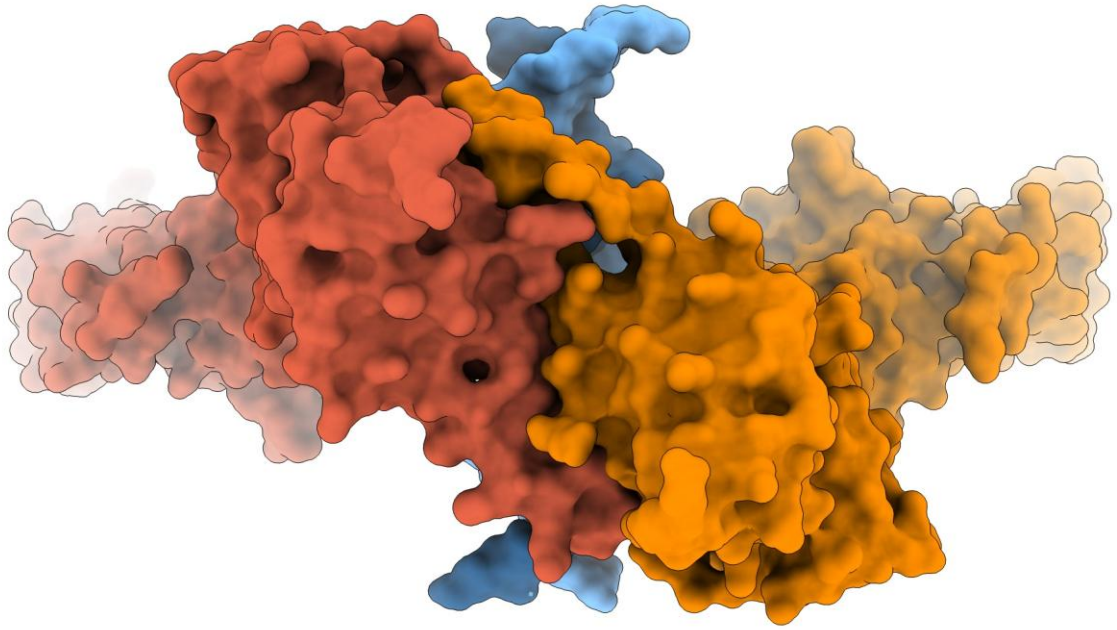
Kymera’s Immunology Strategy

Nello Mainolfi, PhD
Founder, President and CEO

Revolutionizing Immunology: Oral Drugs with Biologics-Like Efficacy

Science-driven Clinical Stage Organization with Industry-leading Oral Immunology Pipeline

- Targeted Protein Degradation (TPD) leader
- Best-in-industry capabilities in hit finding and optimization of oral degraders
- Unique target selection strategy pursuing traditionally undrugged targets in highly validated pathways
- Portfolio poised to disrupt conventional treatment paradigms



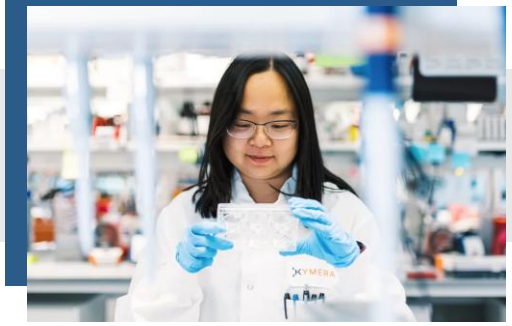
By combining the **"right target" with the disruptive potential of TPD, Kymera is delivering oral therapies with biologics-like profiles** for the first time in industry with the potential to expand access to millions of patients around the world

Clear Vision and History of Strong Execution

VISION

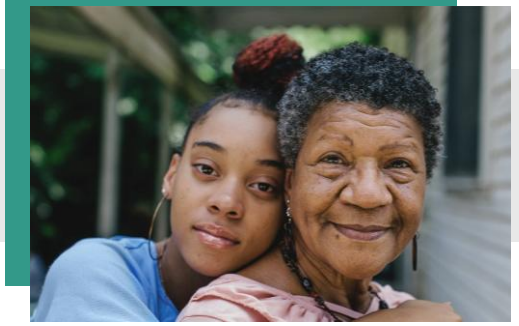
- Reinventing the treatment of human disease **as a fully integrated commercial global biotech**
  - Building a world-class immunology development team to execute on large Phase 2/3 trials
  - **$775M** of cash and equivalents on hand, providing a runway into the first half of 2028

EXECUTION



- Delivered **5 new investigational degrader drugs into the clinic since 2020**, and on path to deliver a total of **10 by 2026**

IMPACT

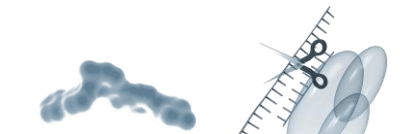


- Dosed **>300 healthy volunteers/patients** to date across clinical pipeline
- Demonstrated excellent fidelity of translation from preclinical to clinical studies:
  - **>90% target degradation in all programs**
  - **Desired safety and efficacy profiles**

Targeted Protein Degradation

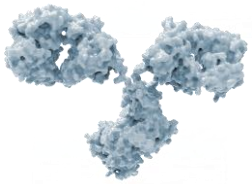
New Modality Expanding the Range of Treatable Disease

Existing modalities have limitations that restrict their application leaving millions of patients without adequate treatment options.



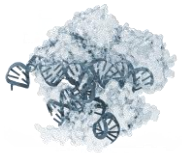
Traditional Small Molecule

RNAi

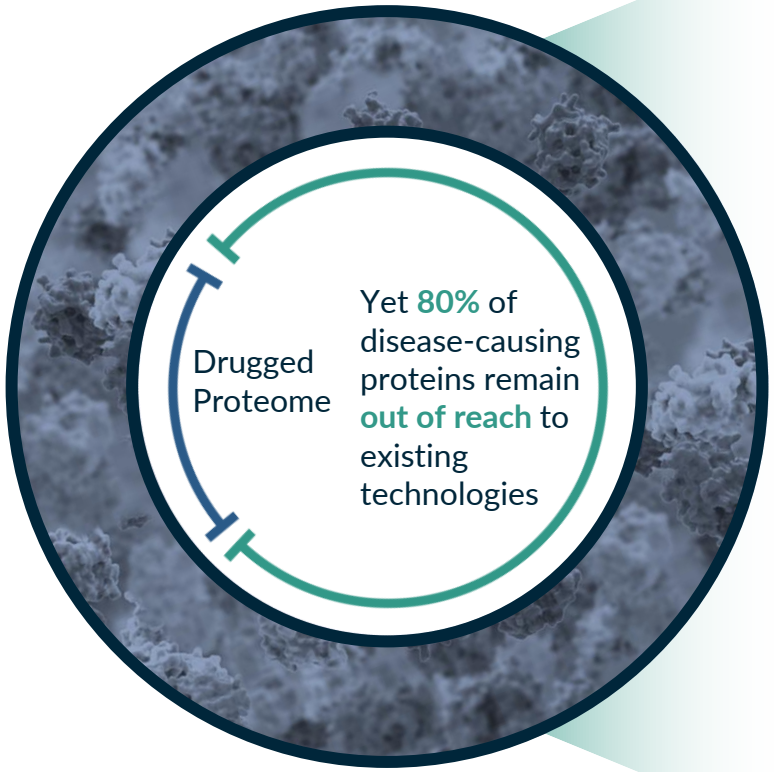


Antibody

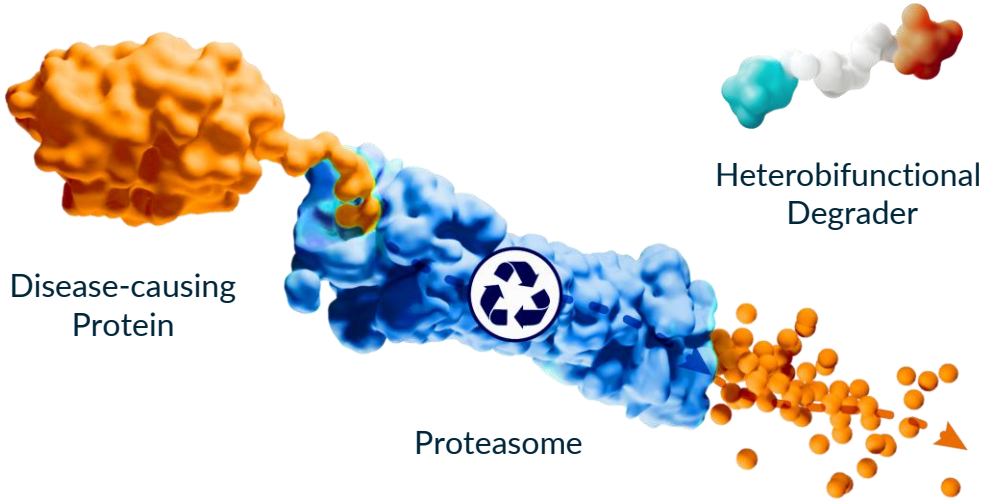
Antisense



Cell/Gene Therapy



Targeted Protein Degradation can unlock the undrugged proteome



- Small molecule-based modality with gene silencing power
- Not limited by target or delivery to specific tissue/organ type; disease agnostic
- Oral dosing with broad tissue distribution
- Efficient development/manufacturing
- **Validated across multiple FDA-approved drugs** with >$17 billion in combined peak WW sales[1]

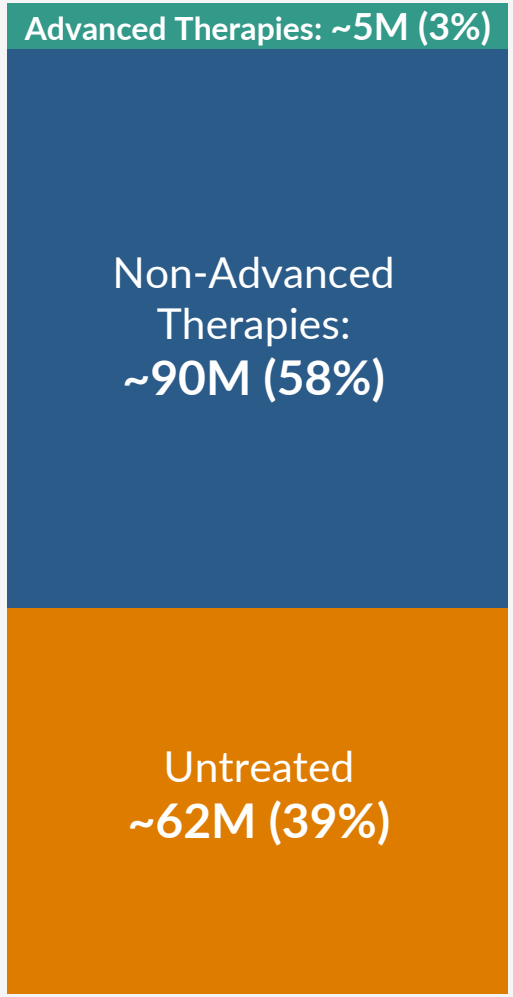
[1]Combined peak WW sales of FDA-approved degrader-based therapies (GlobalData)

Immunology: A Large, Underserved Market

~160M Total Patients Across Key Immunologic Diseases[1]

>$100B

- **~5M patients (3% of total diagnosed)** are on systemic advanced therapies with **>$100B** in annual sales for key I/I indications[2]
- **2/3 of those therapies are injectable biologics**



>$500B?

- ~ **97%** of the diseased population does not have access to advanced therapies
- Enormous untapped market potential

Oral Degraders with Biologics-Like Profiles Can Disrupt the Immunology Market

- **Displace injectable biologics**
- **Offer a convenient highly effective advanced therapy** to the 97% unserved and underserved patients

[1]Diagnosed prevalent patient population for US/EU5/JP (GlobalData; 2023); key immunologic diseases includes AD, Asthma, COPD, HS, MS, PsO, PsA, RA, SLI, UC, CD; [2]Market Forecasts for US/EU5/JP (GlobalData; 2023)

Small Molecule Oral Degraders Can Transform Immunology

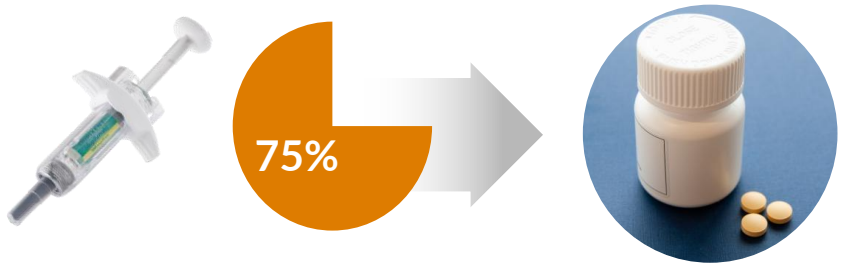
Potentially Superior Profile to Injectable Biologics and Traditional Small Molecule Inhibitors

Biologics can have several limitations, making orals preferred by most patients

DUPIXENT® (dupilumab) Injection

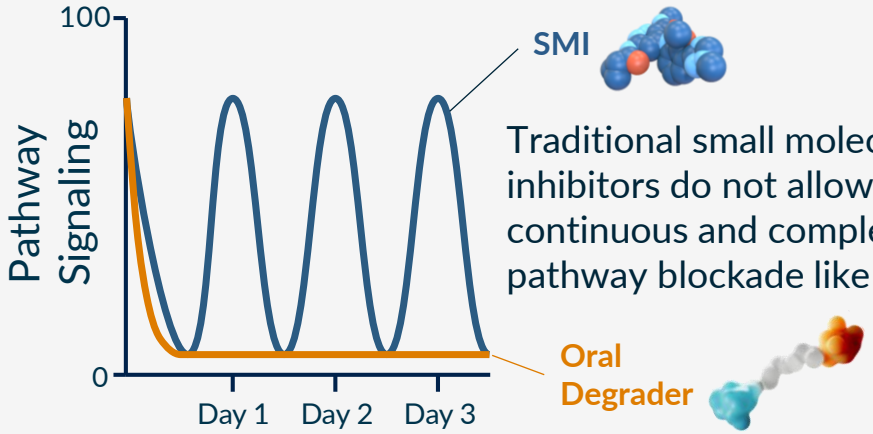
Skyrizi® risankizumab-rzaa

- Expensive, challenging to prescribe/reimburse
- Immunogenicity
- Cold storage
- Inconvenient and/or painful route of administration for patients

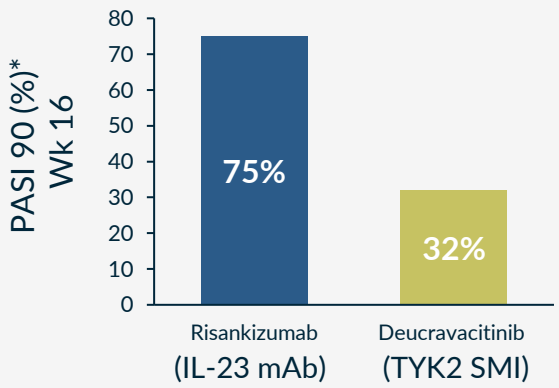


In industry surveys[1], **75%** of patients would switch from injectable biologics to oral with similar profile

Traditional SMI's insufficiently block pathways, which can limit efficacy



Traditional small molecule inhibitors do not allow continuous and complete pathway blockade like degraders



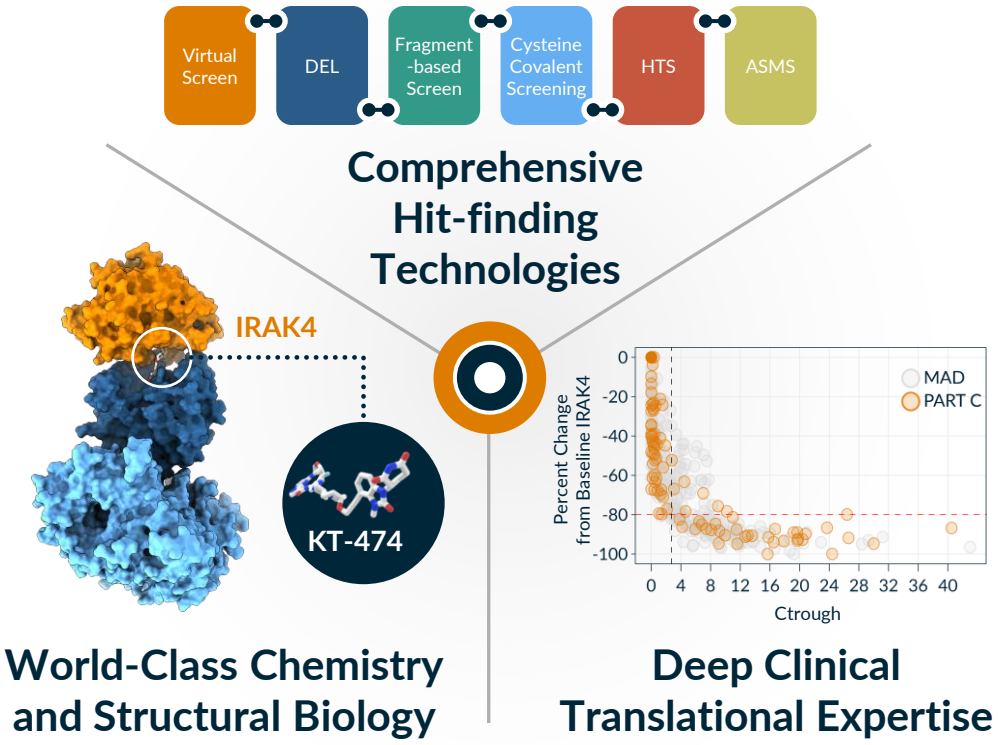
Anti IL-23 biologic dramatically more effective than TYK2 SMI in PsO[2]

[1]J&J Business Review Dec '23 (survey of N=395 patients with moderate-to-severe psoriasis); [2]Skyrizi (IL-23 mAb) and Sotyktu (TYK2 SMI) package inserts

Kymera, Industry Leader at Developing Oral Degrader Drugs

Established Drug Discovery Engine to Address Historically Undrugged/Inadequately Drugged Proteins

Key Capabilities



Proven Results

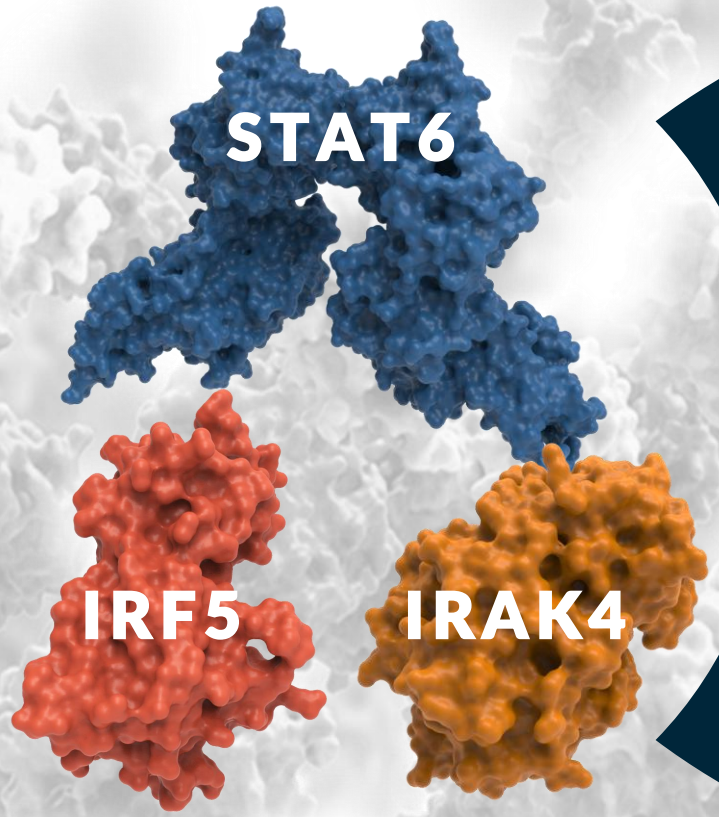
- **Productivity**
  Kymera has delivered **>9 development candidates**, including **4 transcription factors in past 5 years**
- **Drug Properties**
  Highly potent degraders (sub-nanomolar) with refined drug-like properties (orally bioavailable with systemic distribution to all target tissues)
- **Translation**
  Comprehensive understanding of PK/PD, resulting in impeccable translation of our pipeline into the clinic across programs

Reproducible and scalable innovation for high value immunology targets

Unique Target Selection Strategy Drives Best-In-Class Pipeline

Undrugged or inadequately drugged targets

Strong genetic/clinical validation



Clear path to early clinical differentiation

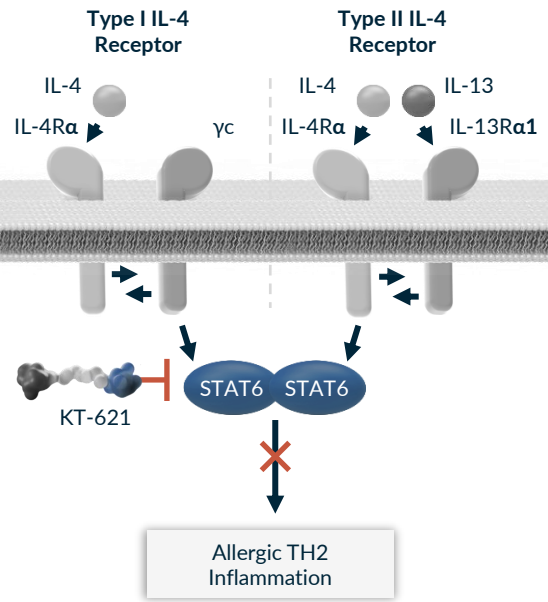
Large clinical/ commercial opportunities

FOCUS ON FIRST- AND BEST-IN-CLASS OPPORTUNITIES

Complementary First-in-Class Mechanisms in Highly Validated Pathways

STAT6 TRANSCRIPTION FACTOR

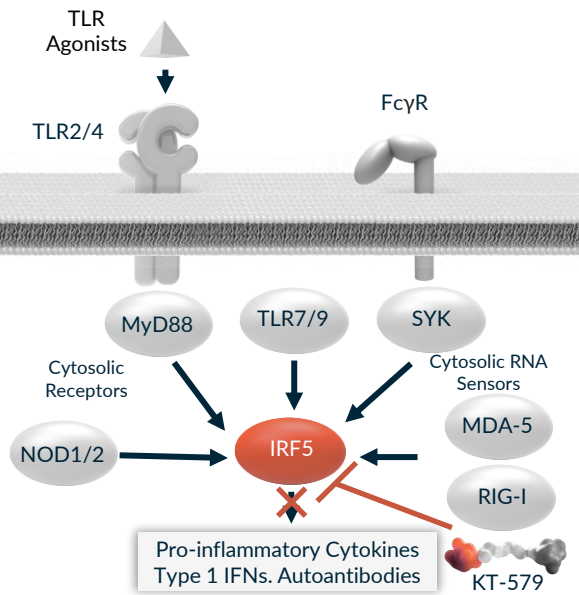
IL-4/13 Pathway



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

IRF5 TRANSCRIPTION FACTOR

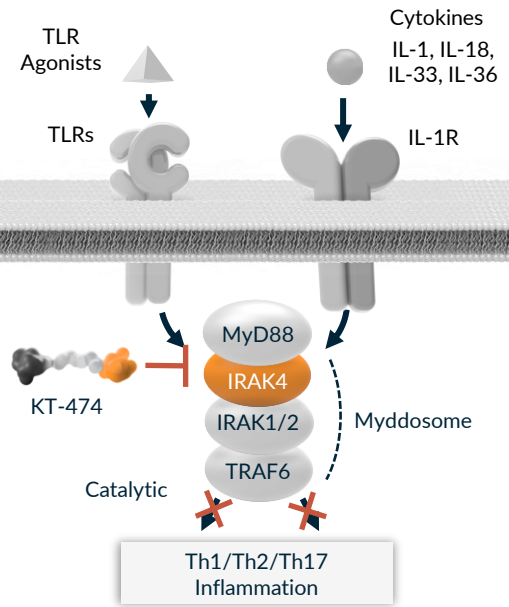
Type I IFN, cytokines (TNFα, IL-6, IL-12/23) and autoantibodies



IRF5 is a genetically validated transcription factor and a master regulator of immunity

IRAK4 SCAFFOLDING KINASE

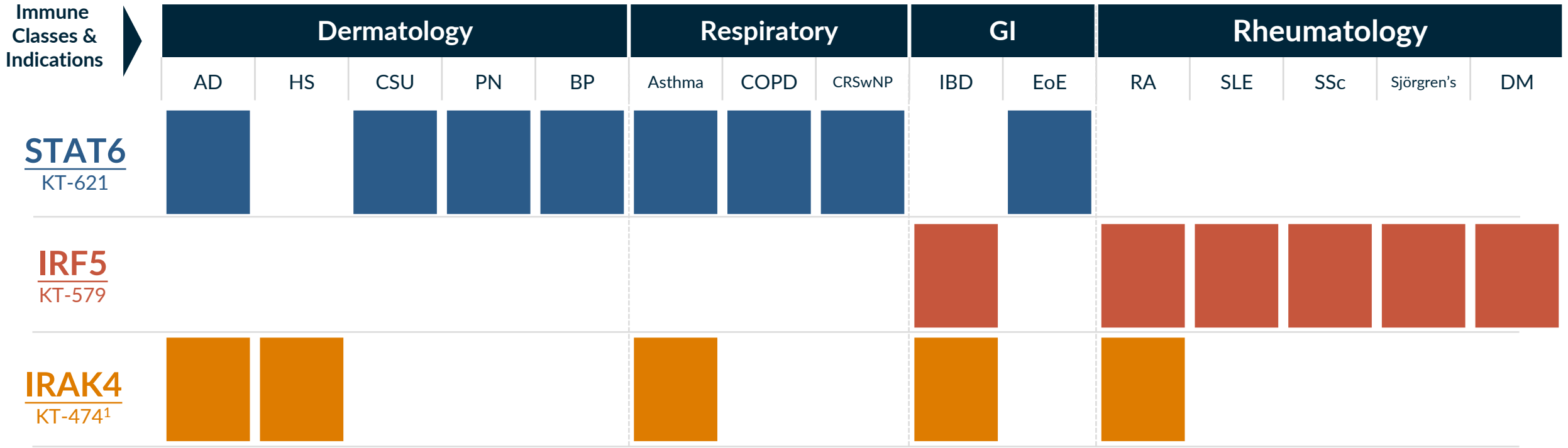
IL-1R/TLR Pathway



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

Addressing Major Immunology Indications

Orals with Biologics-Like Activity to Transform Immunology



Synergies and know-how **across key immunological pathways** creates multiple development and combination opportunities and positions Kymera to expand access to systemic advanced therapies for broad patient populations

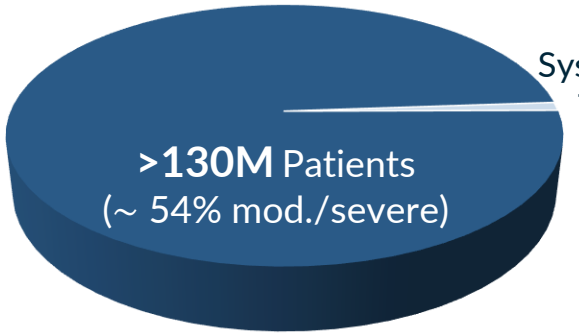
AD: atopic dermatitis; HS: hidradenitis suppurativa; CSU: chronic spontaneous urticaria; PN: prurigo nodularis; BP: bullous pemphigoid; COPD: chronic obstructive pulmonary disease; CRSwNP: chronic rhinosinusitis with nasal polyps; IBD: inflammatory bowel disease; EoE: eosinophilic esophagitis; UC: ulcerative colitis; CD: Crohn's disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; DM: dermatomyositis;
[1]Current indications: HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities.

Oral Degraders with Biologics-like Efficacy Can Transform Immunology

Existing Therapies Address 10% or Less of Diagnosed Patients[1]

STAT6
TRANSCRIPTION FACTOR

Key Indications: AD, Asthma, COPD, CRSwNP, EoE, CSU, PN

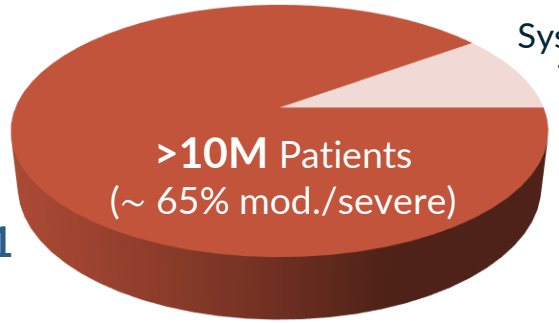


Systemic Advanced Therapies: 1%

>$10B[1]

IRF5
TRANSCRIPTION FACTOR

Key Indications: SLE, RA, UC, CD, Sjögrens, SSc, DM

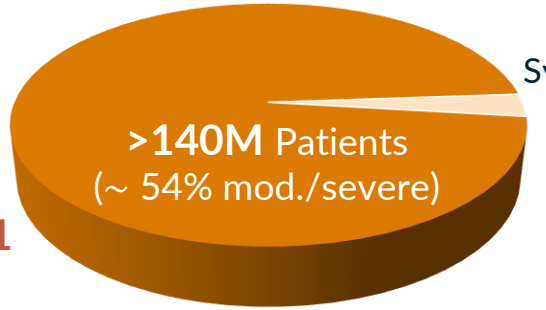


Systemic Advanced Therapies: 7%

>$45B[1]

IRAK4
SCAFFOLDING KINASE

Key Indications[2]: HS, AD, Asthma, COPD, RA, SLE, UC, CD

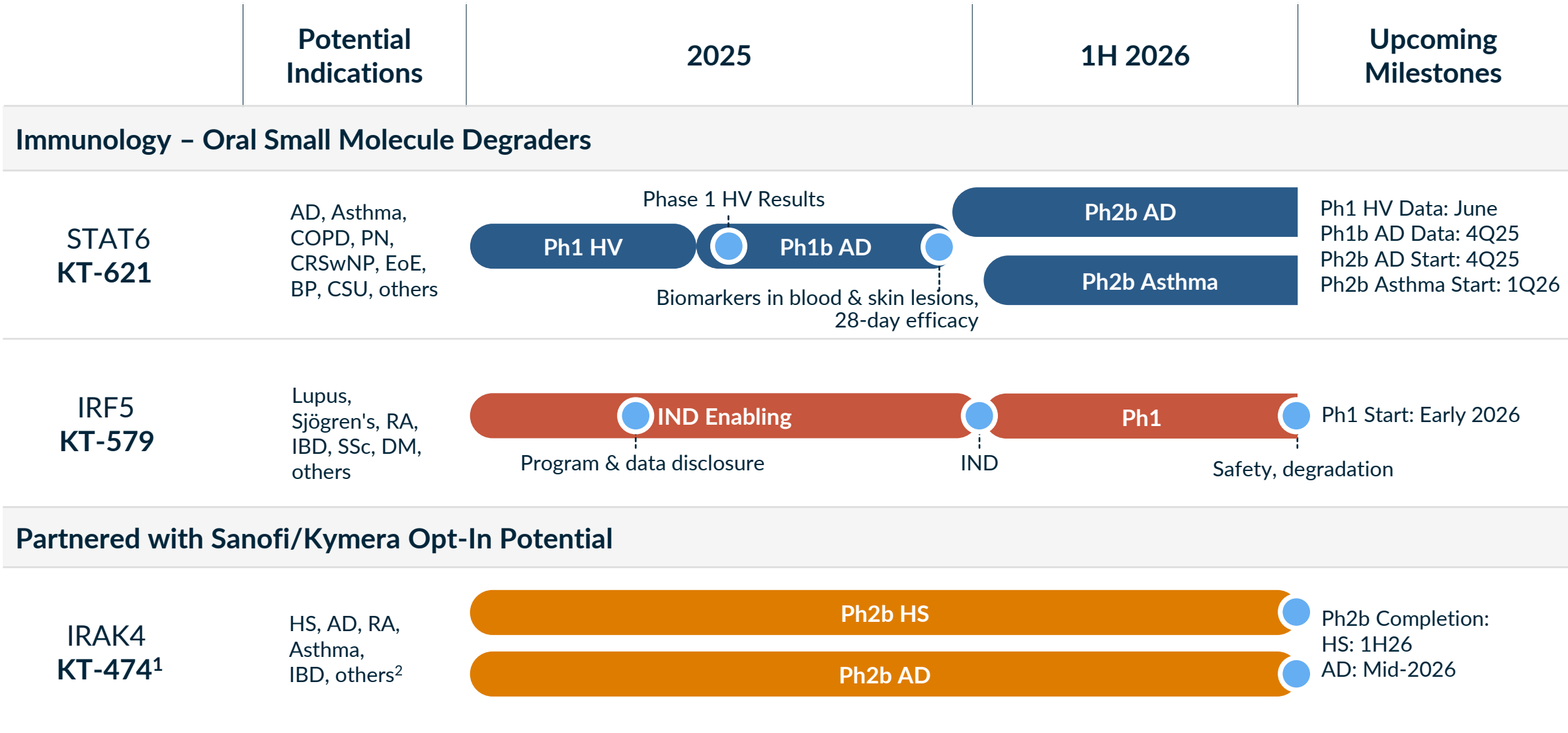


Systemic Advanced Therapies: 3%

>$55B[1]

[1]GlobalData (2023 diagnosed prevalent patient population and forecasted sales for approved systemic advanced therapies in US/EU5/JP
STAT6 estimates include only AD, Asthma, COPD; IRF5 estimates include only SLE, RA, UC, CD; IRAK4 estimates include all noted indications).
[2]Current 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



[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.

STAT6 (KT-621): Dupilumab-like Activity in a Pill

Jared Gollob, MD
Chief Medical Officer

STAT6 Degrader: Opportunity for Dupilumab-Like Activity in a Pill

Highly Validated but Undrugged Target

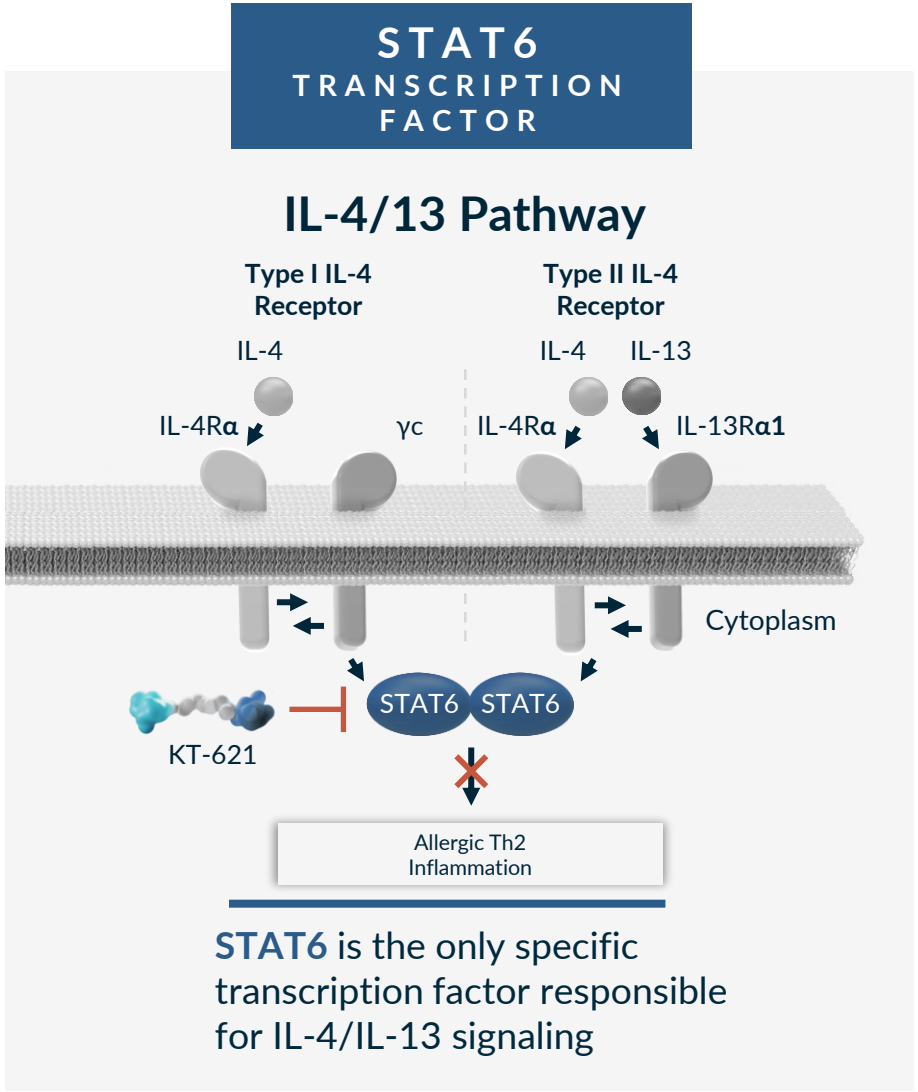
- IL-4/IL-13 pathway highly validated by **dupilumab (IL-4Rα mAb): approved in 7 Th2 allergic indications, >$15B of yearly sales**
- STAT6 is **the specific transcription factor for IL-4/IL-13 signaling**
- **STAT6 targeting should phenocopy IL-4/IL-13 targeting**
- Human **gain-of-function of STAT6 causes severe allergic disease**[1]
- Human heterozygous **LOF are healthy** and protected against Th2 inflammation[2]
- STAT6 KO mice develop normally, are viable and fertile

Clear Degrader Advantage

- **Only STAT6 degradation** has the potential to fully block IL-4/IL-13 signaling with an oral daily drug

Access Large Patient Populations

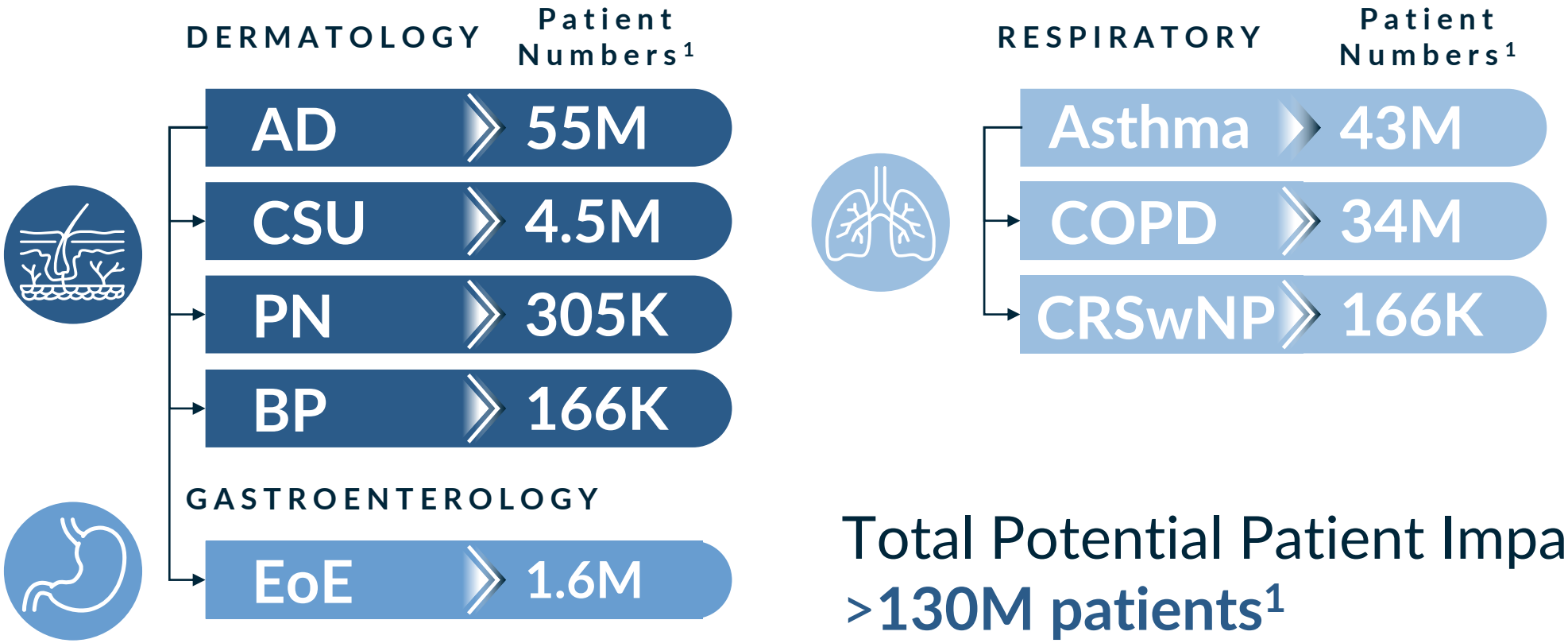
- Dupilumab indications include AD, Asthma, COPD, CRSwNP, CSU, EoE, PN
- Mega-blockbuster potential for a safe and active oral drug



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

[1]Sharma et al. *J Exp Med*. 2023; Suratannon et al. *J Allergy Clin. Immunol*. 2022; Takeuchi et al. *J Allergy Clin Immunol*. 2022
[2]Kristjansdottir et al. *Journal of Allergy and Clinical Immunology*. 2024

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



Total Potential Patient Impact:
>130M patients[1]

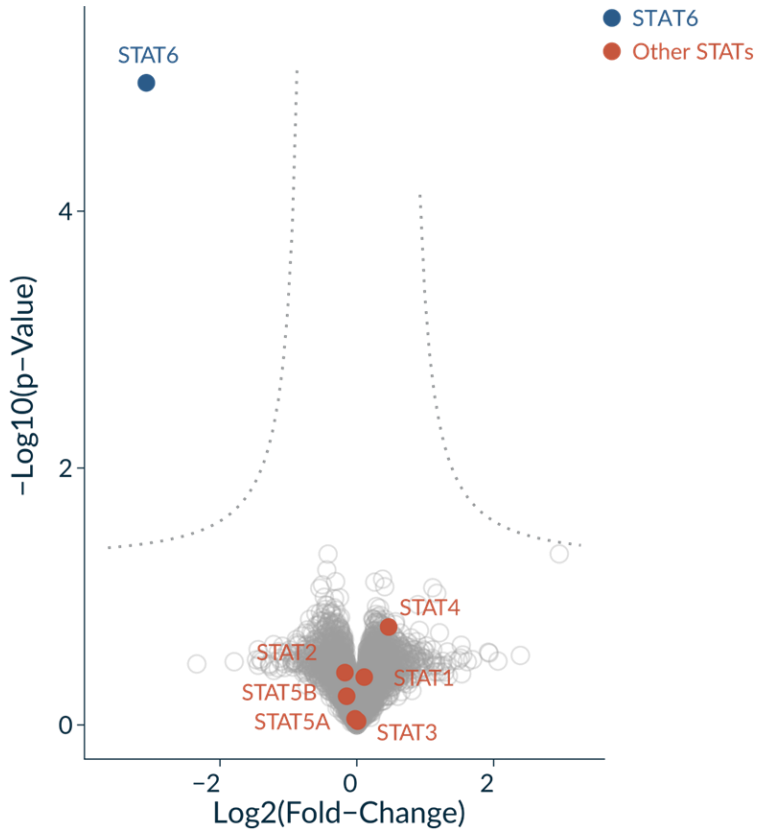
Numerous indications/therapeutic areas that are de-risked by dupilumab create a unique opportunity for KT-621 to reach broad patient populations

[1]GlobalData (2023 diagnosed prevalent patient population in US/EU5/JP; Total Patient Impact estimate includes only AD, Asthma, COPD)

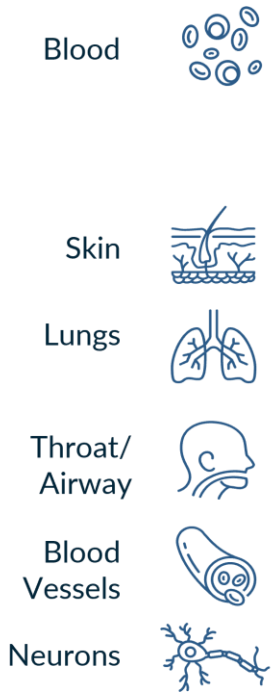
KT-621: Kymera's First-in-Class STAT6 Degrader

Excellent Degradation Potency and Selectivity

Complete STAT6 Degradation Selectivity in Human PBMC Proteosome at 100 x DC_{90}



Picomolar Potency and Consistent Degradation Across all Disease-Relevant Cell Types Evaluated

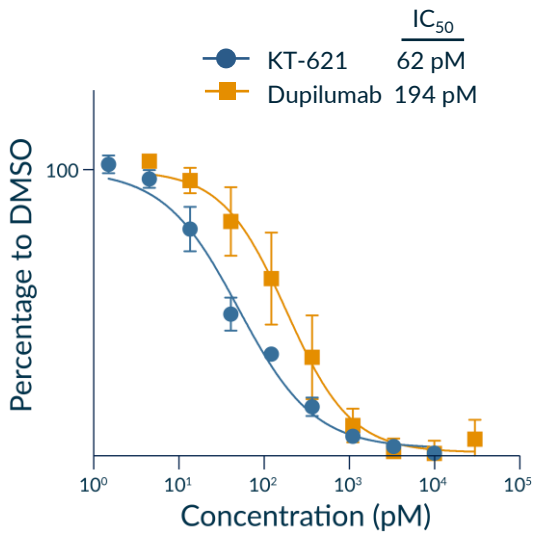


Human Primary Cell Type	KT-621, DC_{50} (pM)
Hematopoietic cell (all Th2 diseases)	
Human PBMC	13
Human CD3 T cell	36
Human CD14 monocyte	60
Human CD19 B cell	86
Human eosinophil	99
Epithelial cell (AD, CSU, asthma, COPD)	
Human keratinocyte (adult)	22
Human keratinocyte (neonatal)	18
Human bronchial 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

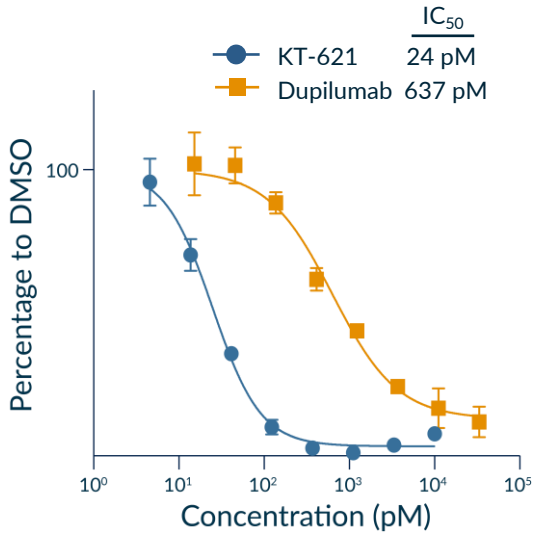
KT-621 Has Preclinical Activity Comparable or Superior to Dupilumab

KT-621 Fully Blocks IL-4/13 Pathway in Human Th2 Functional Assays with IC_{50}'s Lower than Dupilumab

IL-4 Induced TARC Release in Human PBMC

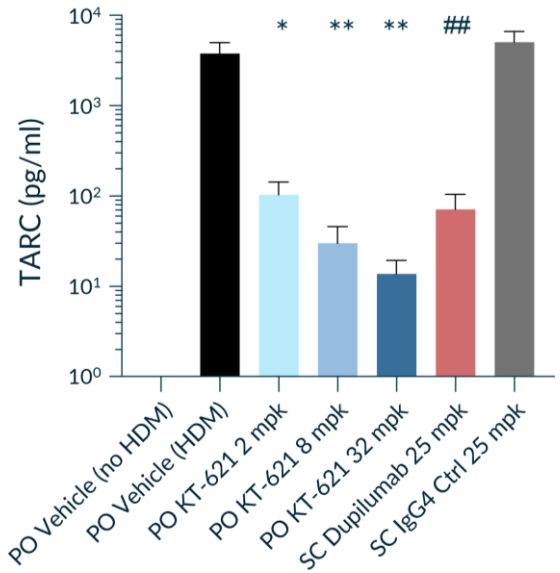


IL-13 Induced Periostin Release in Human Bronchial Smooth Muscle Cells

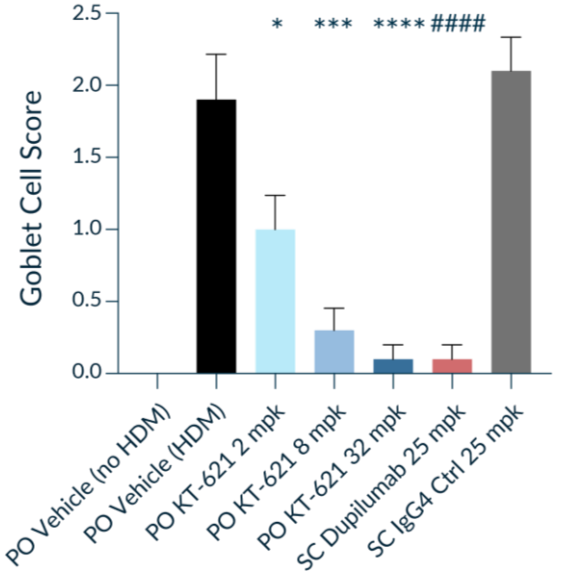


KT-621 Blocks Th2 Inflammation *in Vivo* Equal to/Better than a Saturating Dose of Dupilumab in Mouse HDM Asthma Model[1]

TARC (CCL17) Reduction in Lungs



Reduction in Lung Goblet Cell Metaplasia

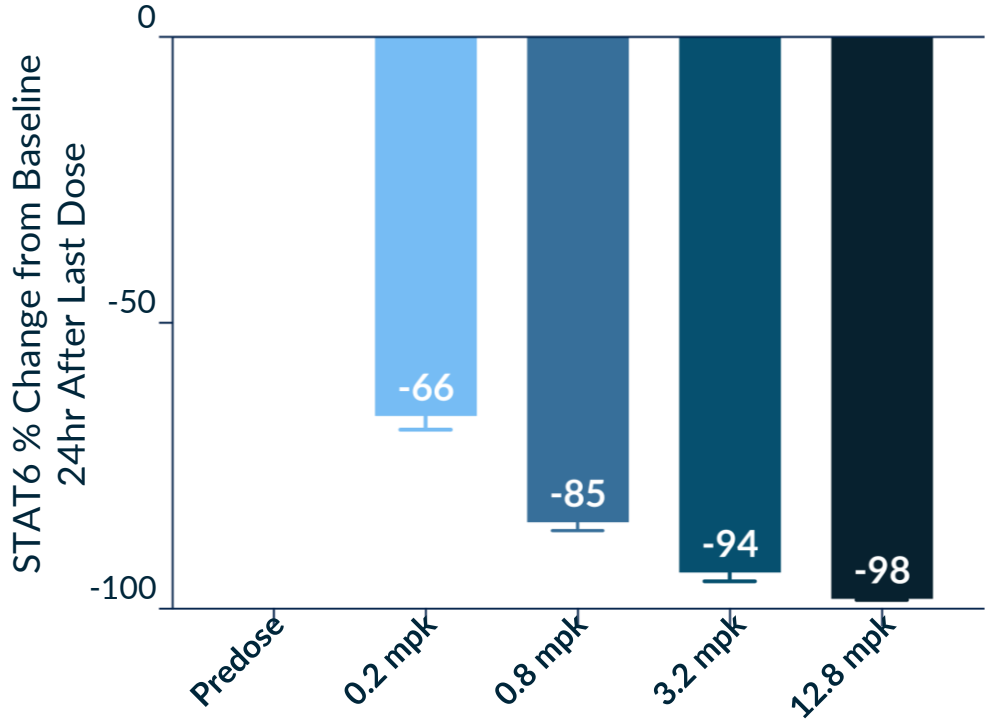


2/8/32 mpk doses showed 72/85/91% STAT6 degradation respectively in mouse spleen

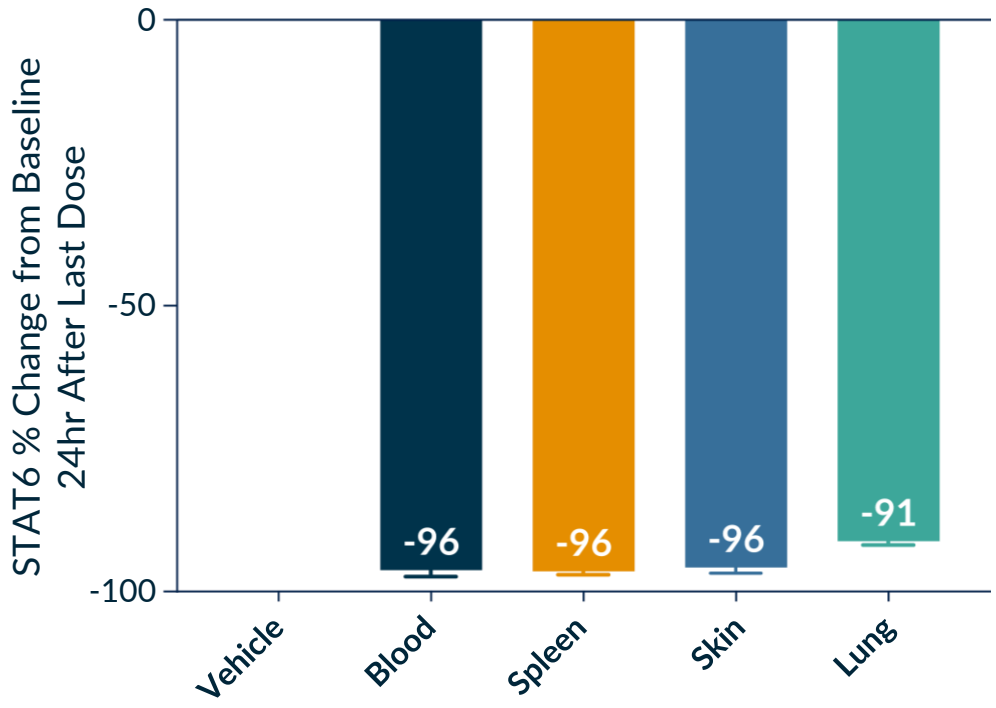
[1]A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. *Allergy*. 2020); *Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

KT-621 Degrades STAT6 at Low Oral Doses in All Relevant Tissues

Dose Responsive STAT6 Degradation in Dog Blood Post 7 Days of KT-621 QD Oral Dosing



STAT6 Degradation in All Relevant Tissues in NHP Post 14 Days of KT-621 (10 mpk QD) Oral Dosing



No adverse safety findings in any doses of 4-week GLP tox studies in NHP and rodents

KT-621 Development Plan Enables Efficient Path to Registration Across all Th2 Diseases

Initial Parallel Phase 2b Trials in Moderate/Severe Atopic Dermatitis (AD) and Asthma are Expected to Support Subsequent Phase 3 Trials Across Multiple Dermatology, GI and Respiratory Indications

Ph1 HV
SAD-MAD

✓*Completed*

- Safety & tolerability
- STAT6 degradation
- Th2 biomarkers

Ph1b AD
Single Arm, Open Label

Ongoing

- Dosing for 28 days
- Biomarkers in blood & skin lesions
- Clinical activity

Ph2b AD
Dose Ranging

Start in Q4 2025

Ph2b Asthma
Dose Ranging

Start in Q1 2026

- Efficacy and safety in two initial Th2 diseases
- Ph3 dose selection for franchise

Ph3 dose

Ph3 AD, CSU, PN, BP, EoE

Ph3 dose

Ph3 Asthma, COPD, CSRwNP

- Ph3 dose selected for AD can be used for other indications in derm/GI such as PN, BP, CSU, EoE while the Ph3 asthma dose can be used for other respiratory indications such as COPD and CRSwNP

KT-621: Phase 1a Trial

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

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 (MAD)
- Th2 biomarkers

June 2025

Phase 1 Healthy Volunteer Data

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

Phase 1 HV SAD/MAD complete. Data presentation in June

KT-621: BroADen Phase 1b Trial

Single Arm, Open Label in Atopic Dermatitis Patients

BROADEN STUDY

Adult, Moderate to Severe AD Patients

Baseline entry criteria:
EASI ≥ 16;
IGA ≥ 3;
Pruritus NRS ≥4;
BSA ≥10%;
Documented TCS failure for AD

Design
- Single arm, open label
- ~20 patients
- Daily dose for 28 days; 14-day safety follow-up

Dosing
- Single dose selected based on Phase 1 HV data

Endpoints
- Safety, PK, STAT6 degradation,Th2 biomarkers in blood and skin lesions, clinical activity (EASI, pruritus, IGA)

4Q 2025

Phase 1b AD Patient Data

Key trial aim:

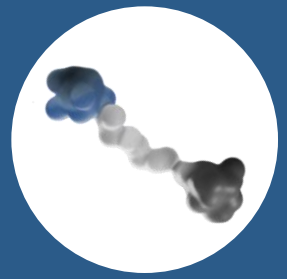
Demonstrate that **KT-621 has a dupilumab-like biomarker signature in blood and skin lesions**

Status update:

First Patient dosed in April; recruitment ongoing. Data expected in 4Q 2025

KT-621 Summary

Dupilumab-like Activity in a Pill



KT-621 is the **first highly selective and potent STAT6 degrader** in the clinic

- In preclinical *in vitro and in vivo* studies, it **is equal or superior to dupilumab**
- STAT6 degradation **was well-tolerated in multiple preclinical safety studies** at >40x efficacious concentration

OPPORTUNITY

- **Over 130M**[1] potential patient impact; only ~1% has access to advanced systemic therapies
- Market projected to **reach $23B+** w/new indications/entrants[1]
- An **oral pill with dupi-like efficacy** can transform the treatment paradigm of Th2 diseases

→ **Potential to access patients beyond biologics-eligible, across all disease severities and ages**

STATUS

- Phase 1 SAD/MAD HV completed
- Phase 1b AD patient study enrolling patients

UPCOMING MILESTONES

- Phase 1 SAD/MAD HV data: June 2025
- Phase 1b AD patient data: 4Q 2025
- Phase 2b expected trial initiations:
  AD - 4Q 2025
  Asthma - 1Q 2026

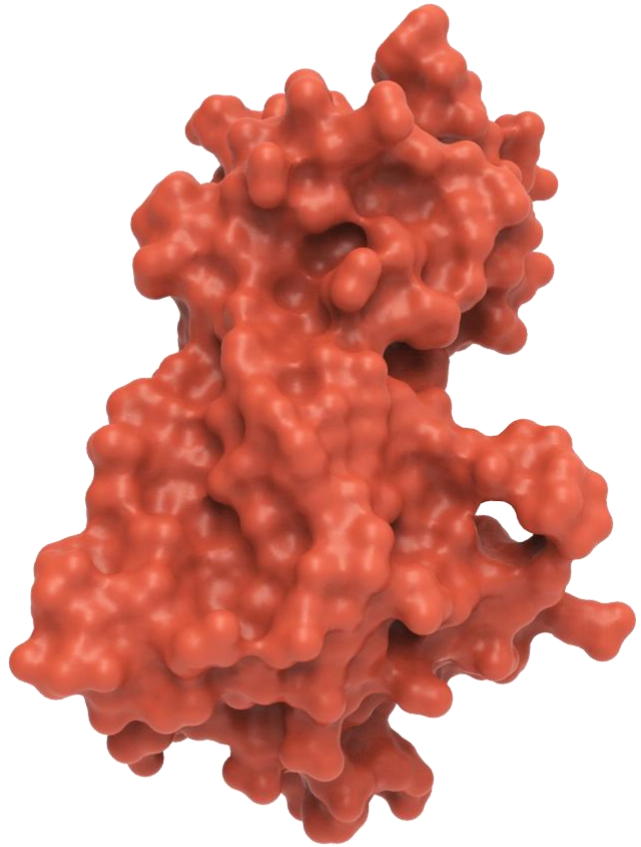
[1]GlobalData (2023 diagnosed prevalent patient population and forecasted sales of systemic advanced therapies for AD, Asthma, and COPD only in US/EU5/JP)

IRF5 (KT-579): Drugging a Genetically Validated Transcription Factor with an Oral Degrader

Veronica Campbell
Senior Director, Immunology

IRF5: Agenda

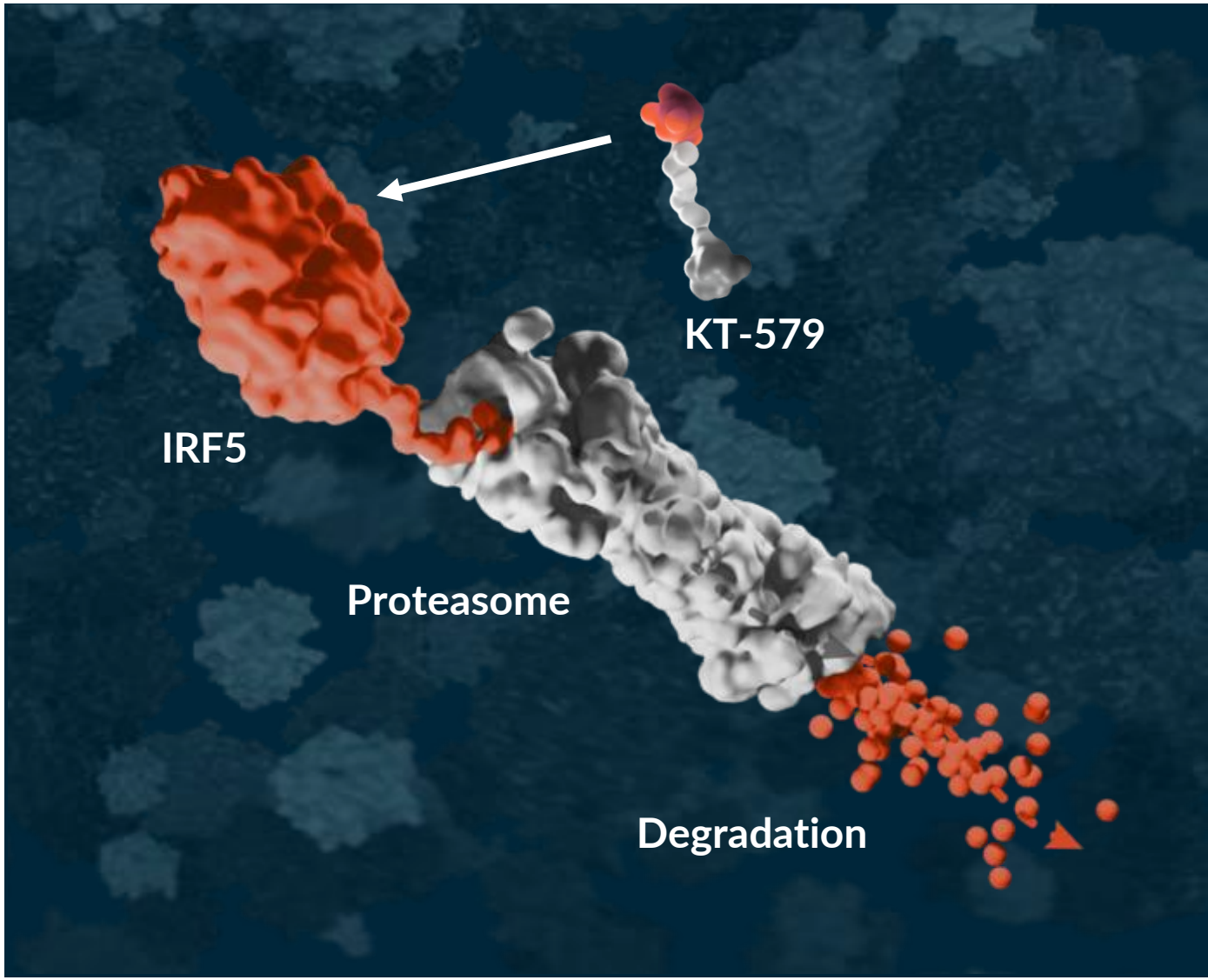
- Value proposition
- Biological function, genetics and clinical validation
- Opportunity in I&I
- KT-579: A highly potent and selective IRF5 degrader
- *In vitro* and *in vivo* data
- Next steps



KT-579: a First-in-Class IRF5 Oral Degrader

- A potent, selective, oral IRF5 degrader with broad potential utility across multiple diseases
- Robust activity in:
  - Primary human cells
  - Lupus patient donor cells
  - *In vivo models* of Lupus and RA
- Well-tolerated in safety studies up to 200-fold above the predicted human efficacious concentration

IND enabling studies ongoing, with Phase 1 start expected early 2026



IRF5: Targeting a Genetically Validated Undrugged Transcription Factor

An Undrugged Transcription Factor, Master Regulator of Immunity

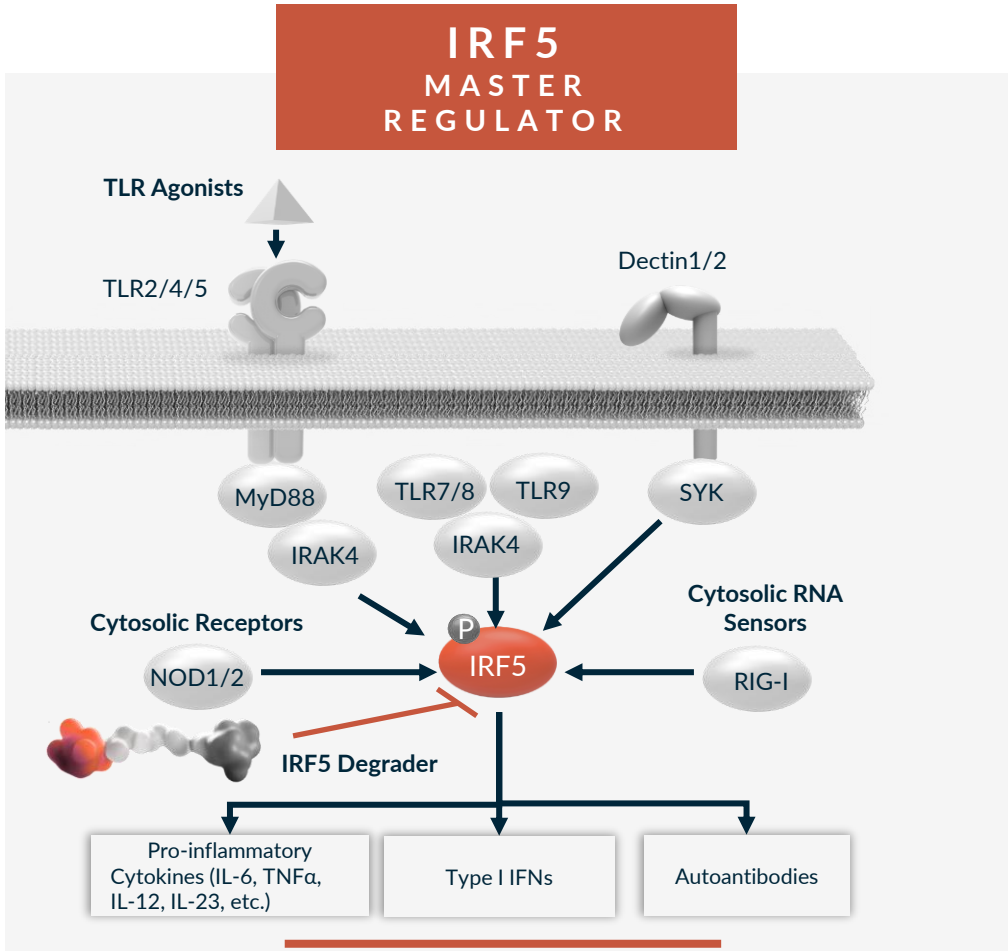
- IRF5 regulates pro-inflammatory cytokines, Type I IFN production and autoantibody production in a cell and activation-specific manner
- Targeting IRF5 has the potential to block cell-specific immune dysregulation while sparing normal cell function

Genetically and Clinically Validated

- IRF5 functional risk variants associate with increased susceptibility to SLE, Sjögren's, RA, IBD, and SSc[1, 2]
- IRF5 regulated pathways have been clinically validated by multiple drugs (i.e. anti-IFN, -TNF, IL-6, IL-12, IL-23 Ab, B cell targeting agents)

Why a Degrader

- Conventional approaches have failed to effectively and selectively block IRF5 due to multiple activation steps and IRF family member homology
- TPD allows for a single and specific binding event to drive depletion of the protein and disrupt all IRF5 signaling



IRF5 is a genetically validated transcription factor and a master regulator of immunity

[1]Santana-de Anda et al. *Autoimmunity Reviews*. 2011; [2]Eames et al. *Translational Research*. 2016

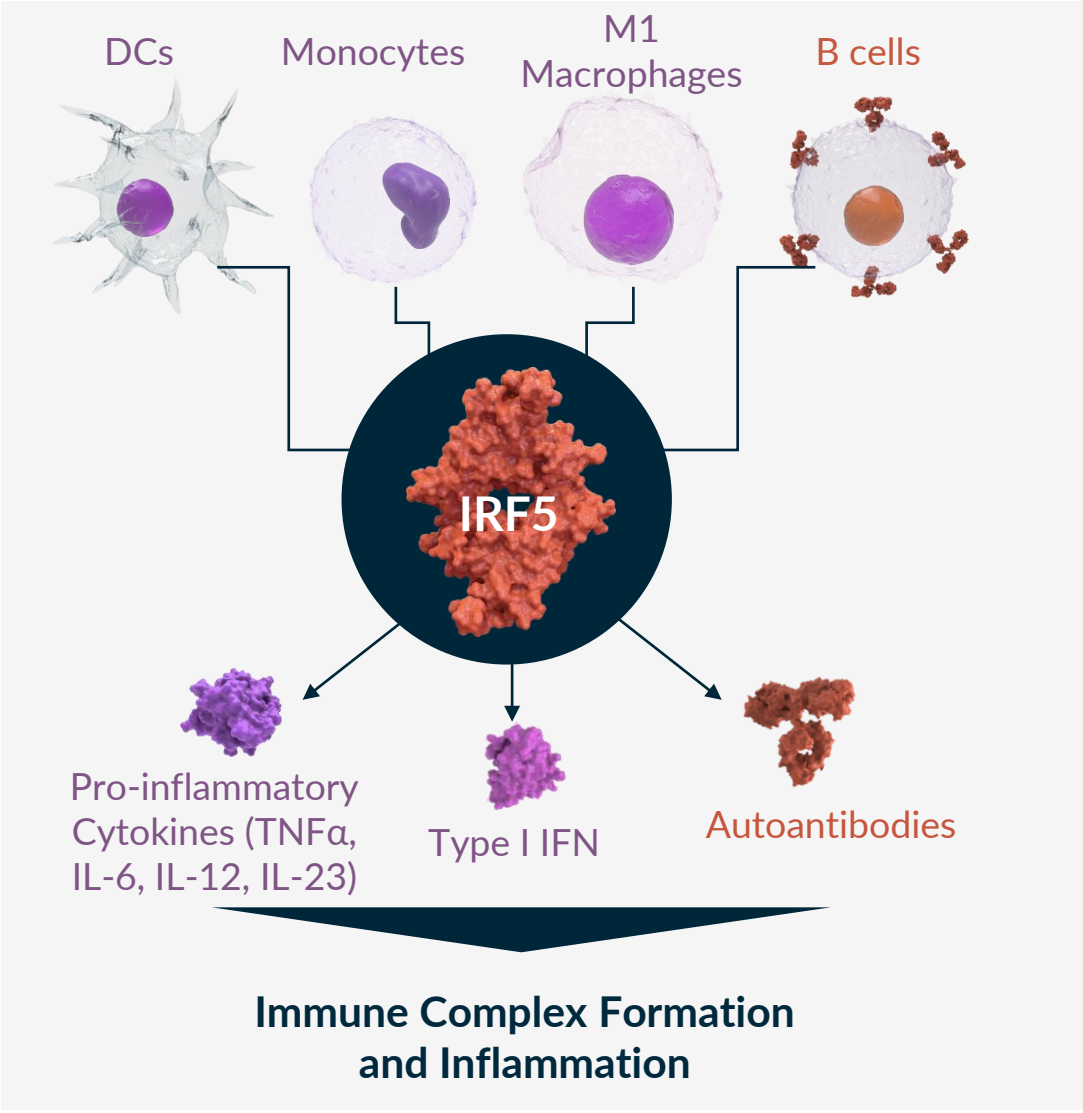
IRF5: Master Regulator of Innate and Adaptive Immune Responses

IRF5 Expression and Activation

- IRF5 is selectively expressed and activated in specific cell types: Dendritic Cells (DCs), Monocytes, Macrophages, and B cells
- IRF5 is activated by pattern recognition receptors (PRRs) during immune responses or when dysregulated in autoimmune diseases
- The cell and activation-specific profile has the potential to block cell-specific immune dysregulation while sparing normal cell function

IRF5 Function

- A master regulator of innate and adaptive responses by controlling pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-23), B cell activation (autoantibody production) and Type I IFN



IRF5 Genetically Validated in Multiple Autoimmune Diseases

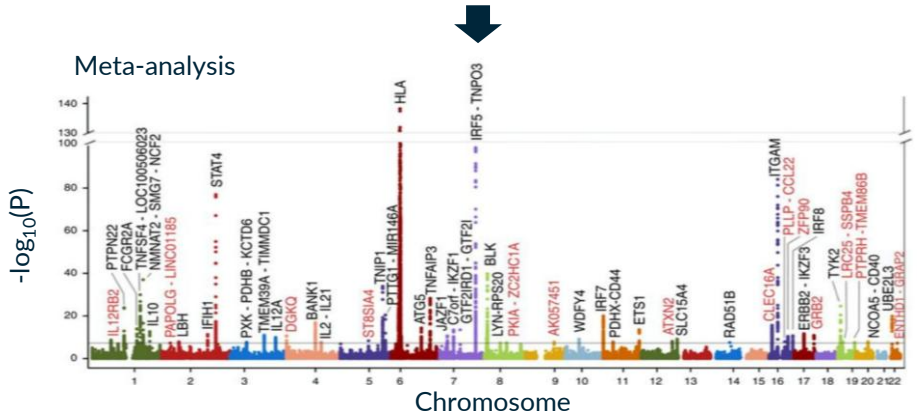
Human Genetics

- Multiple GWAS studies identify IRF5 as an autoimmune susceptibility gene[1]
- IRF5 risk haplotypes and hyperactivated IRF5 levels in SLE patients associated with high serum IFNα levels, anti-dsDNA or anti-RNA binding protein antibodies
- Genetic associations and functional variants also identified in RA, IBD, SSc, and MS

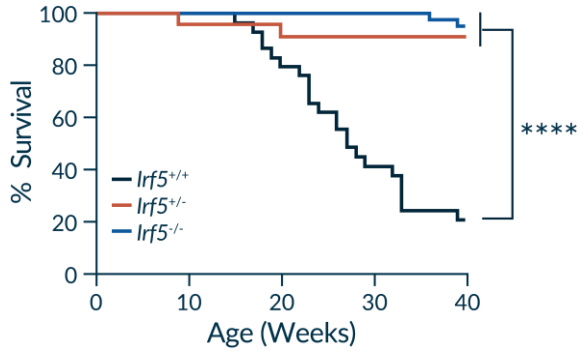
Mouse IRF5 KO Studies

- KO mice are viable and fertile; with normal B cell development
- IRF5 KO mouse can protect or attenuate disease in models of SLE, SSc, RA and IBD
- In a mouse model of lupus (FcγIIB-/-, Yaa) IRF5 plays an essential role in lupus pathogenesis, that is independent of Type I IFN pathways[2]

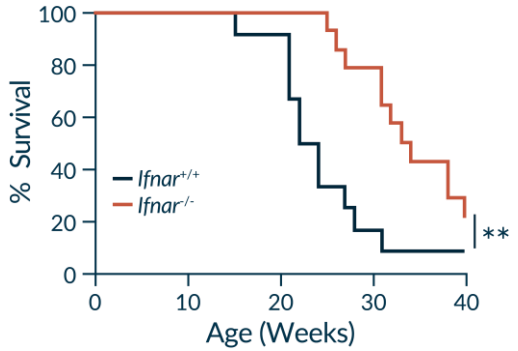
Meta-analyses Identified IRF5 as a Risk Locus for SLE



IRF5 KO Increases Survival and has Essential Role in Lupus



Type I IFN Modestly Protects Against Lupus



[1]Santana-de Anda et al. *Autoimmunity Reviews*. 2011; [2]Richez et al. *J Immunol*. 2010.; ****$p < 0.0001$; **$p = 0.0043$

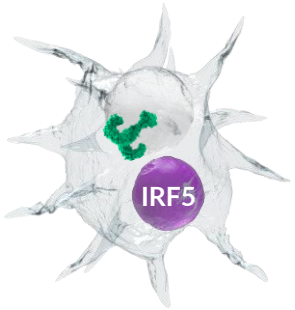
Stimuli and Cell Specific IRF5 Activation in Clinically Validated Pathways

IRF5 degradation has the potential to selectively block inflammation and restore immune regulation by inhibiting pro-inflammatory cytokines, Type I IFN and autoantibody production

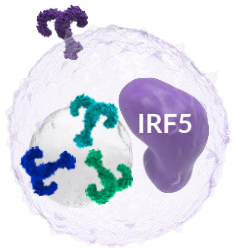
Activation by: TLR2, -4, -5, -7, -8, -9, Dectin 1, -2

Activation by TLR7, -8, -9

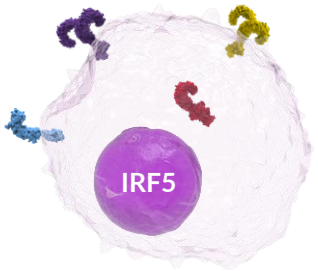
Cell-Specific IRF5 Activation By Pattern Recognition Receptors



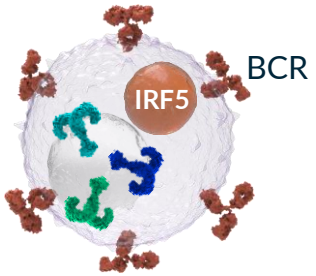
Dendritic Cells



Monocytes



M1 Macrophages



B cells

Pathogenic Immune Response

Pro-inflammatory Cytokines
TNFα, IL-1b, IL-6, **IL-12p40, IL-23**

Type I IFNs

Autoantibodies

Clinical Pathway Validation

HUMIRA® adalimumab

Stelara® (ustekinumab)

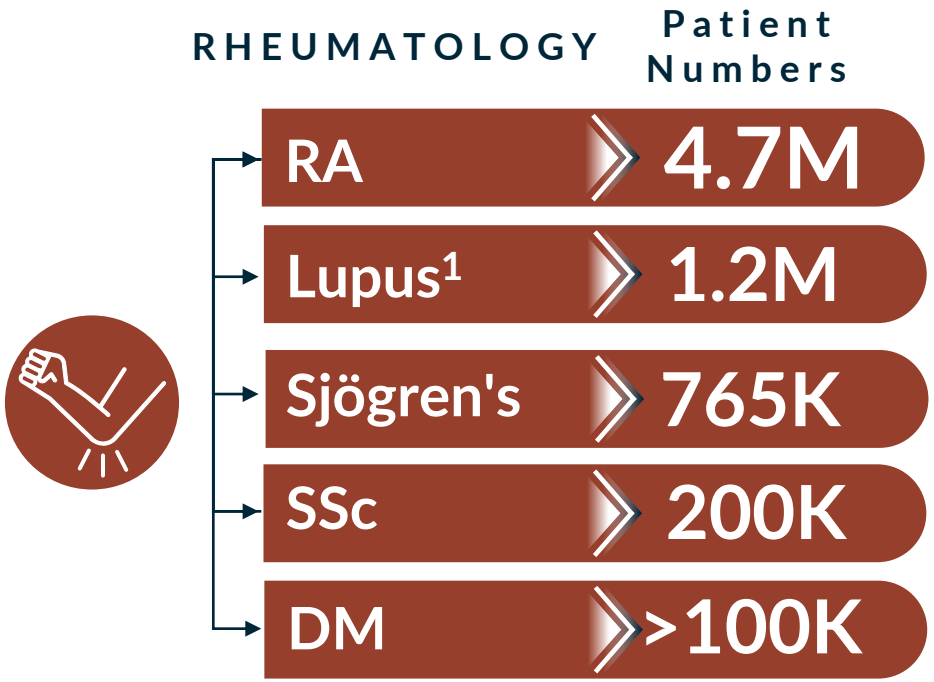
Saphnelo®

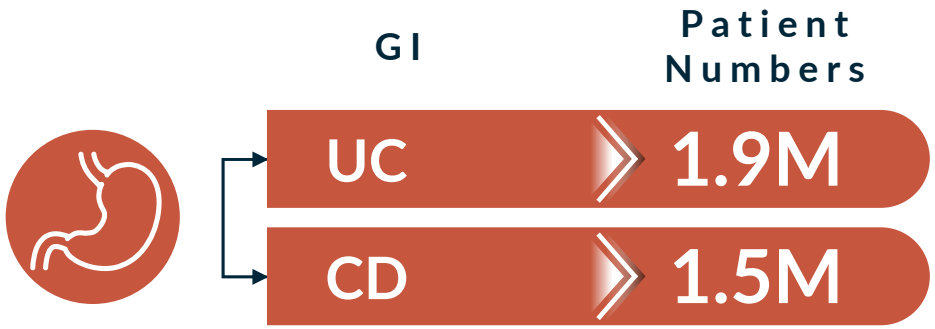
Benlysta® (belimumab)

Rituxan® Rituximab

Blocking IRF5 activity has the potential for more effective, tolerated and durable responses in autoimmune diseases such as **SLE**, **Sjögren's, RA,** and **IBD**

IRF5: A Novel Mechanism in High Unmet Need Indications in I&I





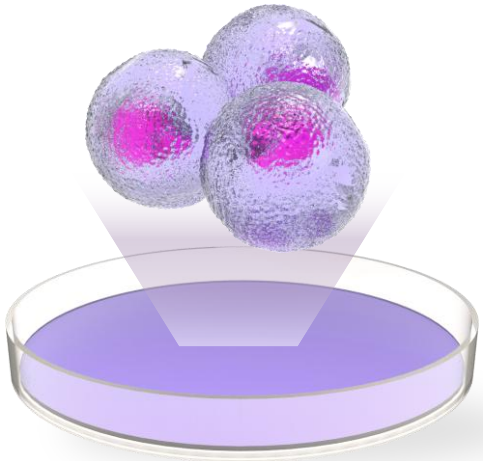
Total Potential Patient Impact[2]:
>10M patients

IRF5 functional risk variants associate with increased susceptibility to multiple diseases, and IRF5 regulated pathways have been clinically validated by multiple drugs

[1]Lupus includes SLE, CLE, LN; [2]GlobalData (2023 diagnosed prevalent patient population US/EU5/JP)

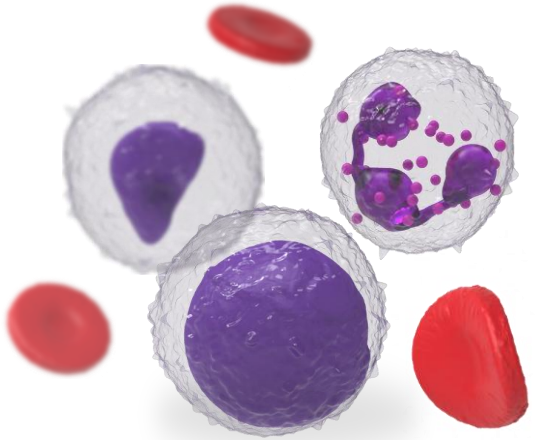
KT-579 Preclinical Characterization

Human Primary Cells (Healthy)



- ✓ Degradation and selectivity
- ✓ Pro-inflammatory cytokines inhibition
- ✓ Type-I IFN inhibition

SLE Patient Samples



Inhibition of:

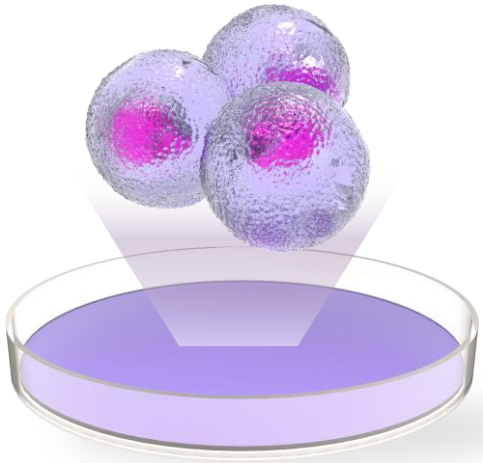
- ✓ Pro-inflammatory cytokines
- ✓ Type-I IFN
- ✓ Autoantibodies

In Vivo Disease Models

- ✓ Inhibition of pro-inflammatory cytokines *in vivo*
- ✓ MRL/lpr Lupus model
- ✓ NZBW1 Lupus model
- ✓ AIA (antigen-induced) RA model

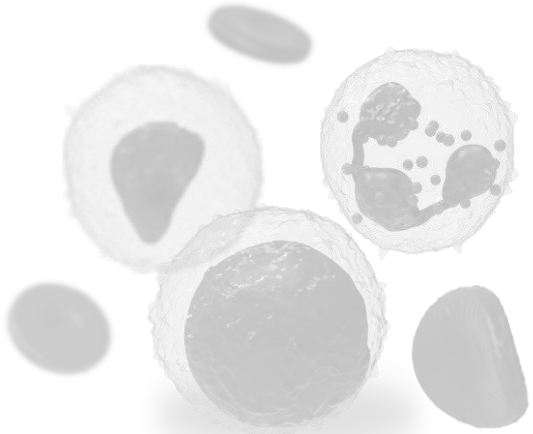
KT-579 Preclinical Characterization

Human Primary Cells (Healthy)



- ✓ Degradation and selectivity
- ✓ Pro-inflammatory cytokines inhibition
- ✓ Type-I IFN inhibition

SLE Patient Samples



Inhibition of:

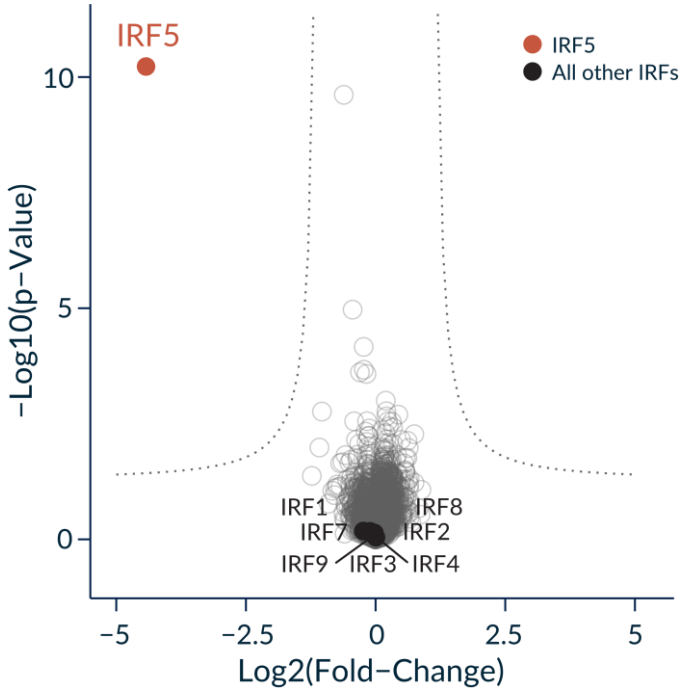
- ✓ Pro-inflammatory cytokines
- ✓ Type-I IFN
- ✓ Autoantibodies

In Vivo Disease Models

- ✓ Inhibition of pro-inflammatory cytokines *in vivo*
- ✓ MRL/lpr Lupus model
- ✓ NZBW1 Lupus model
- ✓ AIA (antigen-induced) RA model

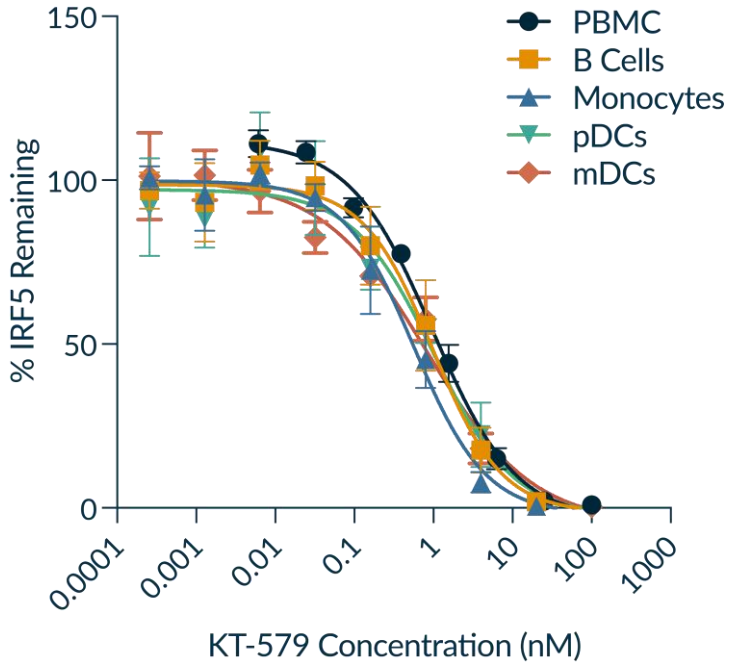
KT-579: An Exquisitely Selective and Picomolar Oral IRF5 Degrader

KT-579: 10xDC_{90} in hPBMCs @ 24 hrs



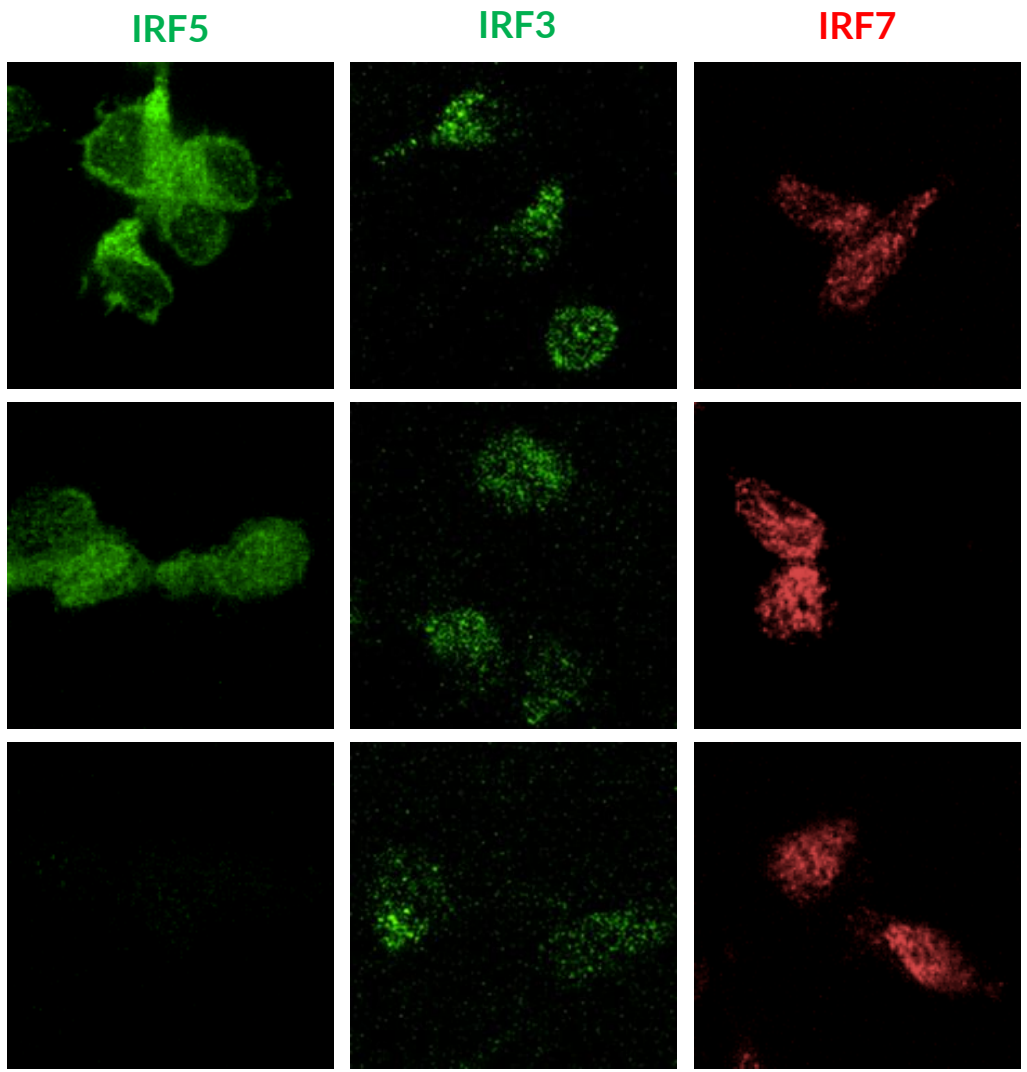
Selectivity Binding and Cellular Assays	KT-579
IRF3, 4, 6, 7, 8 SPR binding, Kd (nM)	>10,000
IRF3 Degradation DC_{50} (nM)	>10,000
IRF7 Degradation DC_{50} (nM)	>10,000

Equipotent Degradation in Relevant hPBMC Subsets @ 24hrs



Cell Subsets	KT-579 DC_{50} (nM)
PBMC	0.8
CD19+ B cells	1.0
CD14+ Monocytes	0.6
HLA-DR+CD123+ pDCs	0.9
HLA-DR+CD11c mDCs	0.9

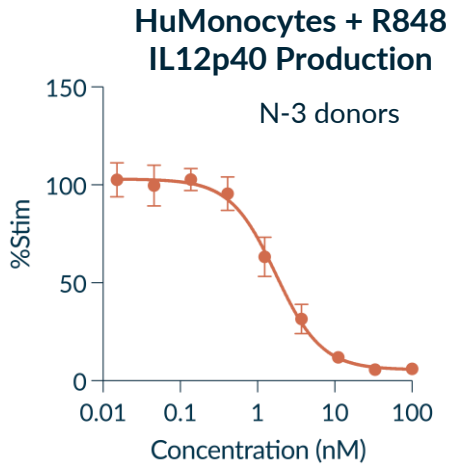
KT-579 Selectively Depletes IRF5 Downstream of TLR Activation

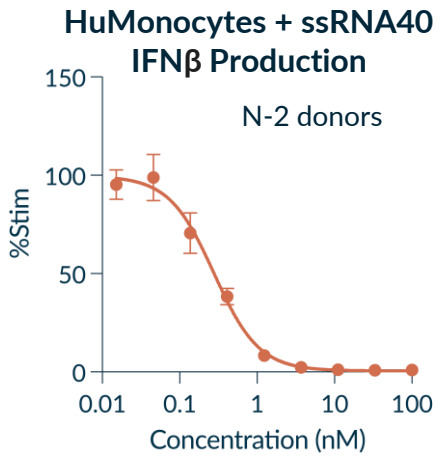


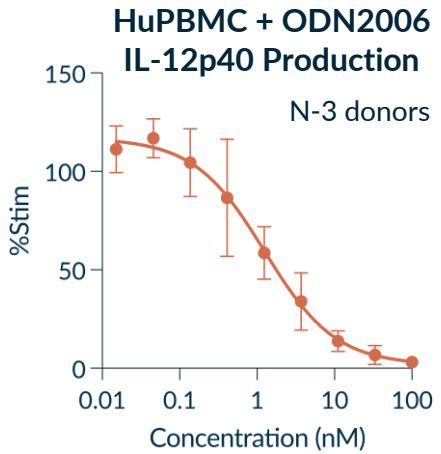
IRF5 degradation in human monocytes selectively depletes TLR7/8 induced IRF5 nuclear translocation, while sparing IRF7 and IRF3

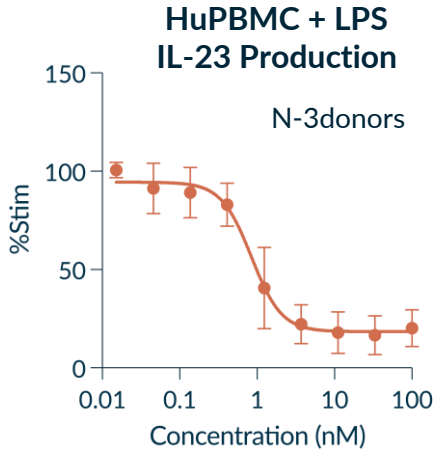
KT-579 Potently Inhibits Production of Key Pro-Inflammatory Cytokines and Type I IFN in Human Primary Cellular Assays

Biology	Receptor	Stim	Cell	Cytokine Readout	KT-579 DC_{50} (nM)
Type I IFN Production	**TLR8**	**ssRNA40**	**Monocytes**	**IFNβ**	**0.3**
	TRL7/8	R848	Monocytes	IFNβ	0.4
	TLR9	ODN2006	PBMC	IFNβ	0.8
Pro-inflammatory Cytokine Production	TLR7/8	R848	PBMC	TNFα	1.5
	TLR7/8	R848	B cells	TNFα	0.4
	TLR8	ssRNA40	Monocytes	TNFα	1.3
	TL7/8	**R848**	**Monocytes**	**IL-12p40**	**0.5**
	TLR9	**ODN2006**	**PBMC**	**IL-12p40**	**1.8**
	TLR7/8	R848	Monocytes	IL-1b	0.15
	TLR4	**LPS**	**PBMC**	**IL-23**	**1.1**





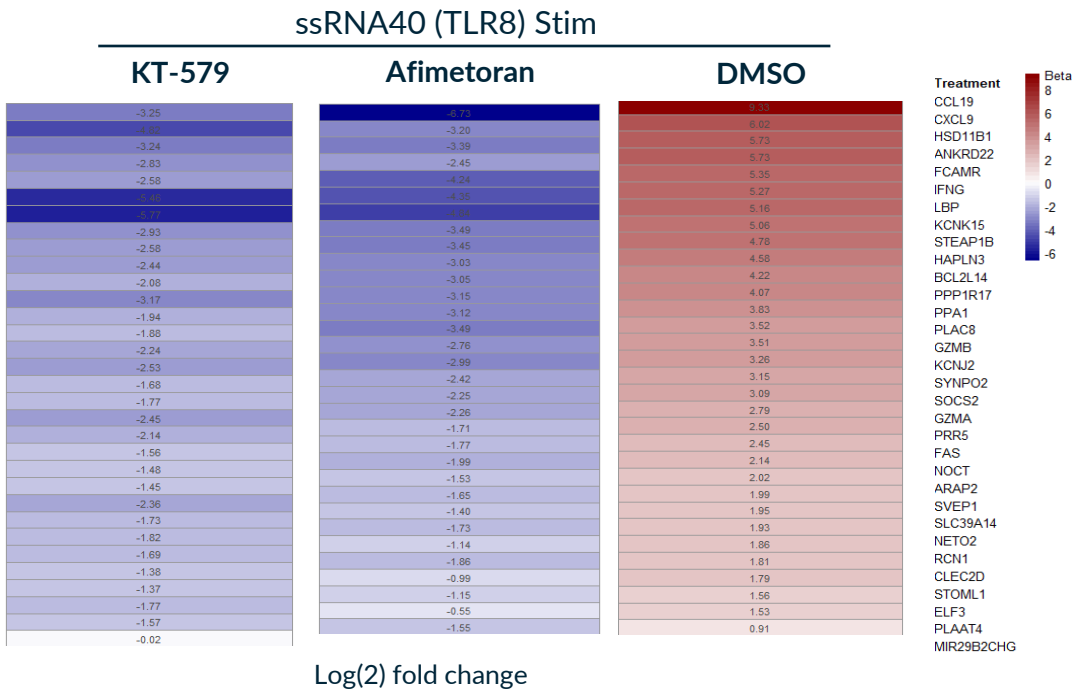




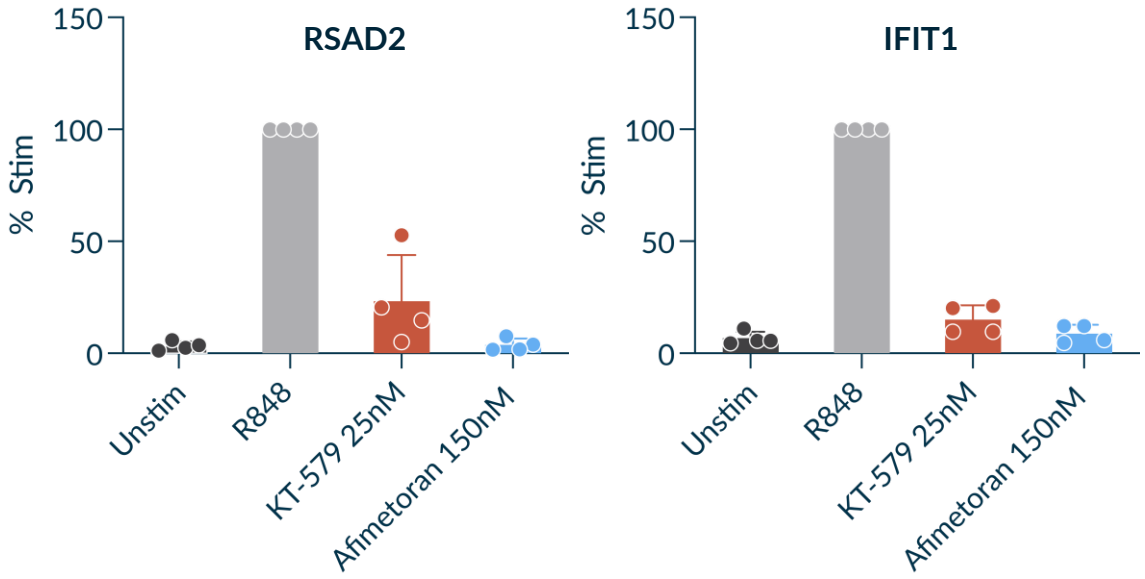
IRF5 degradation inhibits proinflammatory cytokines (TNFα, IL-12, IL-23, IL-1) and Type I IFN (IFNβ) downstream of TLR4, TLR7, TLR8, and TLR9 activation

KT-579 Dampens Type I IFN Downstream Response

Impact on Type I Response Following TLR8 Activation



Inhibition of Select Downstream Interferon-Stimulated Genes (ISGs)



KT-579 blocks Type I IFN dependent genes at least as effectively as an anti-TLR7/8 drug (Afimetoran)

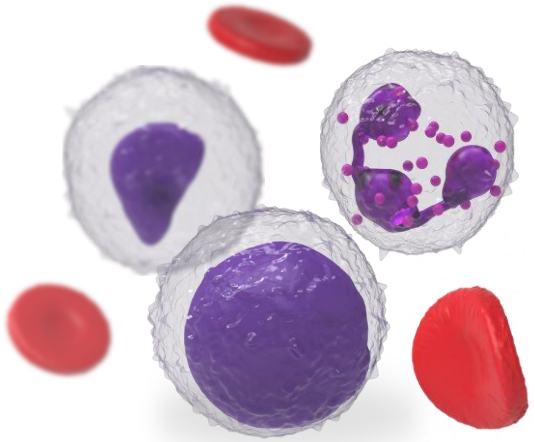
KT-579 inhibits TLR7/8 induced ISGs that are associated with increased disease activity in SLE

KT-579 Preclinical Characterization

Primary Cells

- ✓ Degradation and selectivity
- ✓ Pro-inflammatory cytokines inhibition
- ✓ Type-I IFN inhibition

SLE Patient Samples



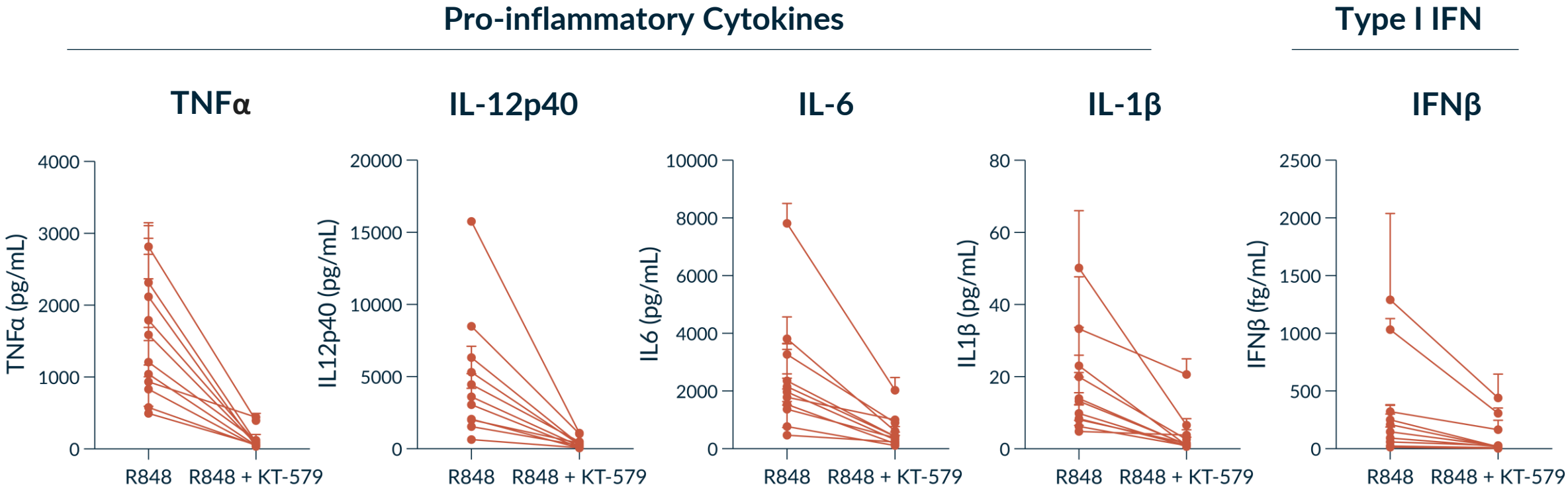
Inhibition of:

- ✓ Pro-inflammatory cytokines
- ✓ Type-I IFN
- ✓ Autoantibodies

In Vivo Disease Models

- ✓ Inhibition of pro-inflammatory cytokines *in vivo*
- ✓ MRL/lpr Lupus model
- ✓ NZBW1 Lupus model
- ✓ AIA (antigen-induced) RA model

KT-579 Effectively Blocks Pro-inflammatory Cytokines and Type I IFN Induction in SLE Patient Samples

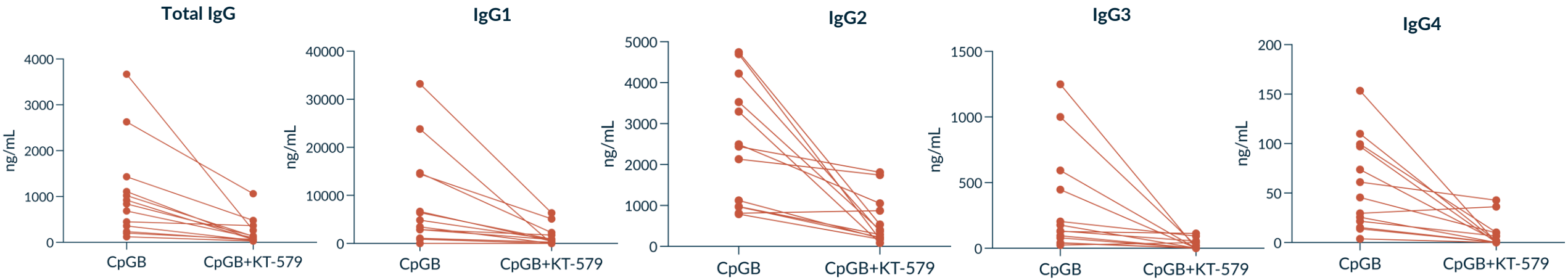


Degrader Treatment (100nM) for 24h, Followed by 24h of R848 (TLR7/8) Stimulation

KT-579 inhibits pro-inflammatory cytokines and Type I IFN that are commonly elevated in autoimmune diseases

KT-579 Significantly Inhibits IgG Levels in Human SLE Patient Samples

KT-579 Inhibits IgG Levels After TLR9 Activation (CpG-B)



7-day B cell culture with CpG-B (TLR9) + 100nM degrader treatment

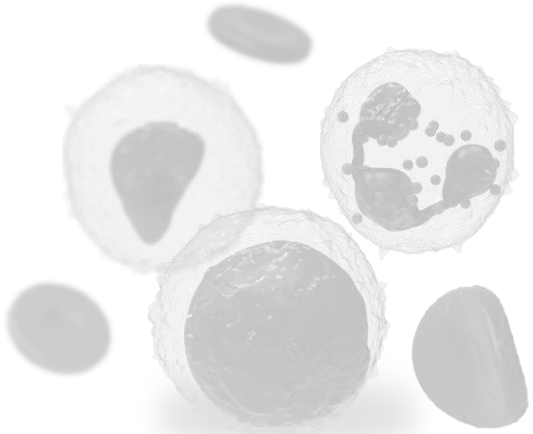
KT-579 reduces TLR9 (CpG-B) induced plasmablast differentiation and inhibits IgG production in SLE derived B cells

KT-579 Preclinical Characterization

Primary Cells

- ✓ Degradation and selectivity
- ✓ Pro-inflammatory cytokines inhibition
- ✓ Type-I IFN inhibition

SLE Patient Samples



Inhibition of:

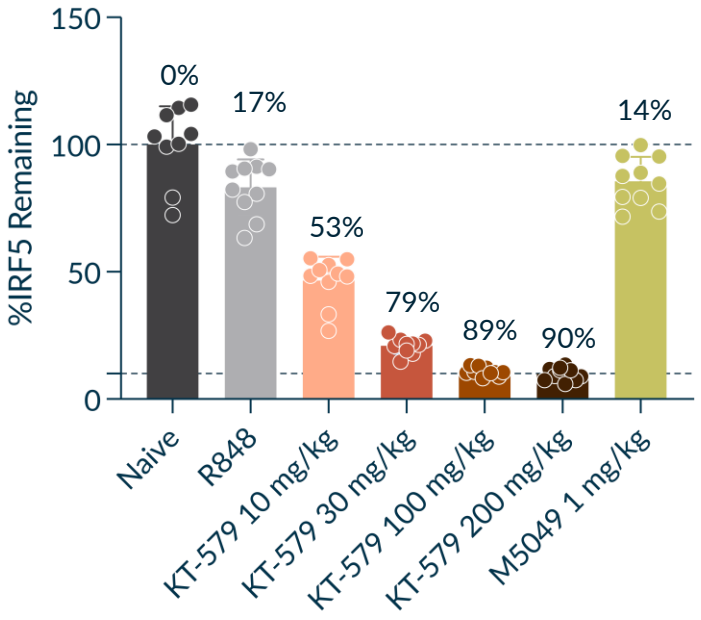
- ✓ Pro-inflammatory cytokines
- ✓ Type-I IFN
- ✓ Autoantibodies

In Vivo Disease Models

- ✓ Inhibition of pro-inflammatory cytokines *in vivo*
- ✓ MRL/lpr Lupus model
- ✓ NZBW1 Lupus model
- ✓ AIA (antigen-induced) RA model

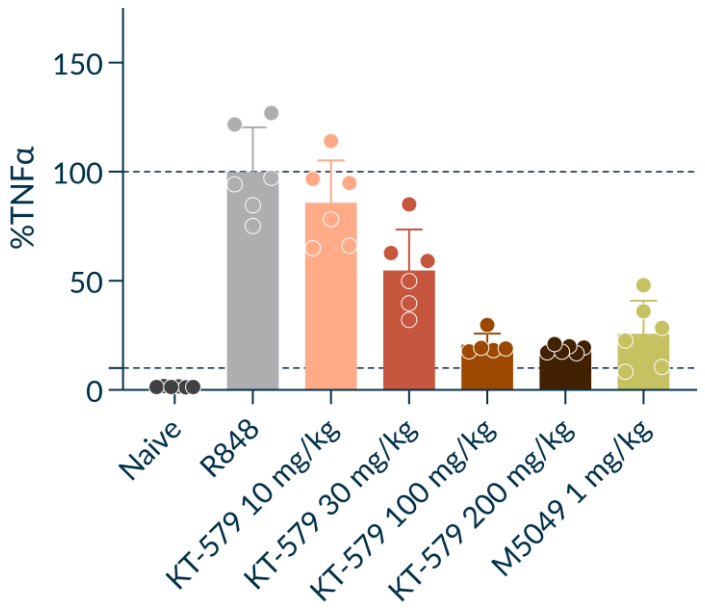
KT-579 Effectively Blocks Circulating Cytokines In Mouse Model[1]

IRF5 Degradation in Mouse Spleen Following 4 Days of Oral Dosing

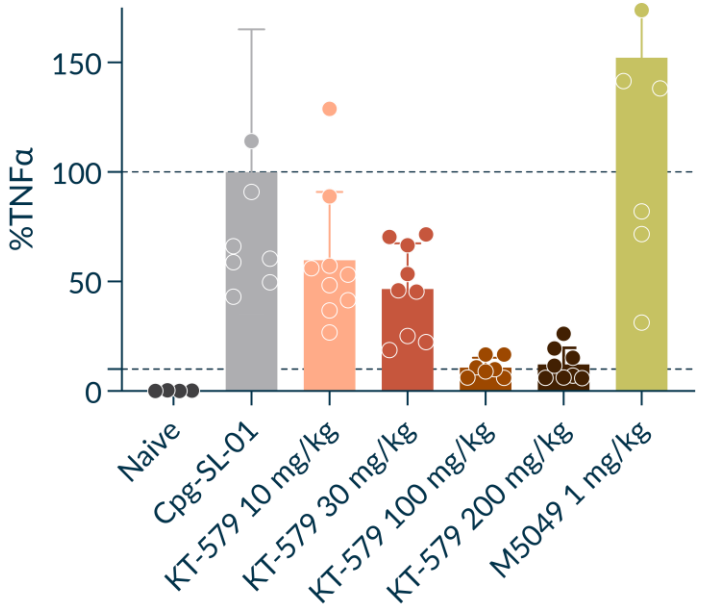


KT-579 Leads to Significant Dose-dependent Inhibition of TLR7-R848 and TLR9-CpG-B Cytokine Production in Mouse

TLR7-R848



TLR9-CpGB-SL01



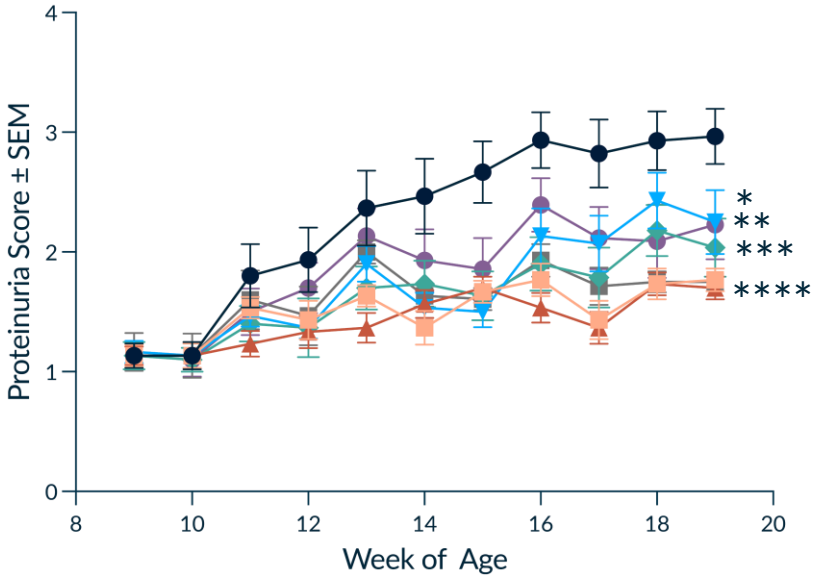
M5049=TLR7/8 SMI

KT-579, not M5049 (TLR7/8 SMI), blocks both TLR7 and TLR9 induced cytokines, including TNFα (shown), IL-6, IL-12p40, IFNβ (not shown)

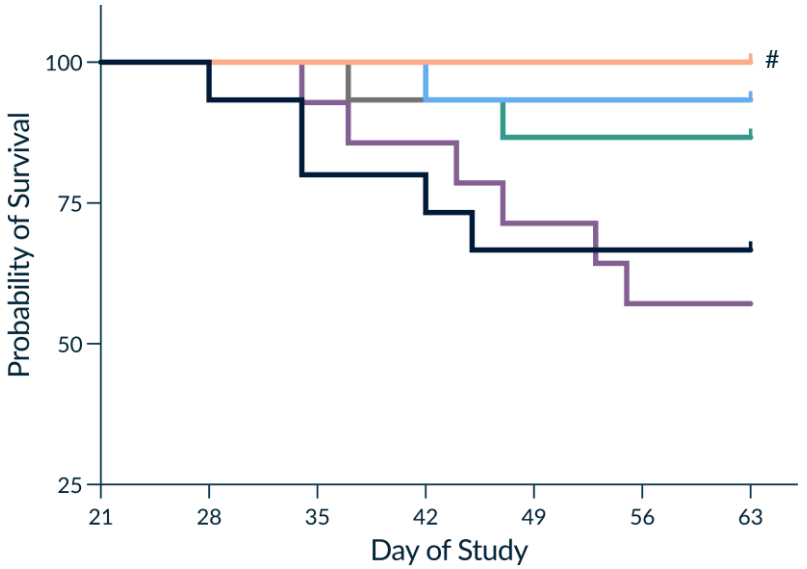
[1]As in other Kymera programs, degraders require higher doses in mouse vs. other species due to higher PPB and lower affinity (see slide 48 for NHP in vivo degradation)

KT-579 Demonstrated Generally Better Outcomes than Approved or Clinically Active Drugs in MRL/lpr[1] Model of Lupus

Proteinuria



Survival



Treatment	#Total survival
Vehicle	10/15
KT-579 50 mg/kg, p.o.	15/15
KT-579 200 mg/kg, p.o.	15/15
Afimetoran, 10 mg/kg, p.o.	14/15
Deucravacitinib, 30 mg/kg, p.o.	13/15
Cyclophosphamide, 50 mg/kg, i.p.	14/15
Anti-IFNAR mAb, 20 mg/kg, s.c.	9/15

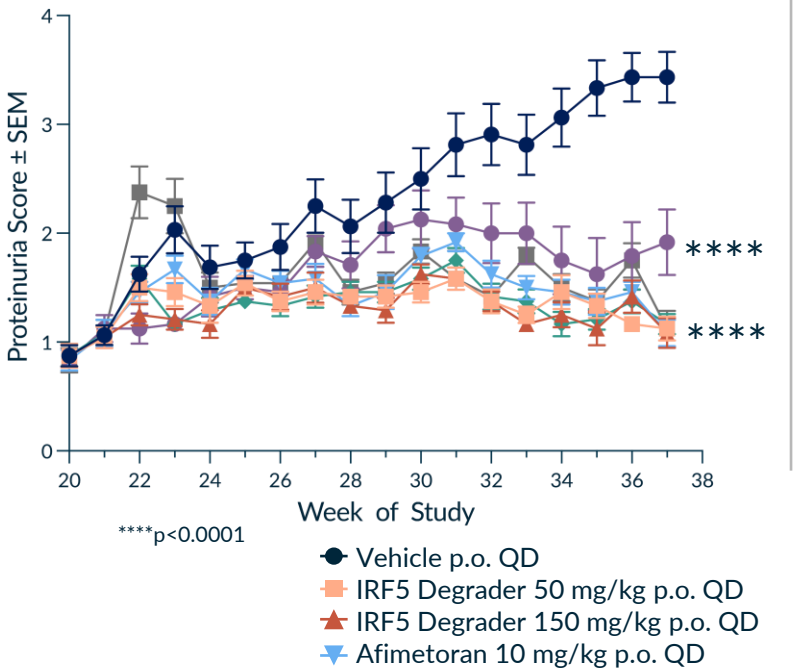
*p=0.0116, **p0.0019, ***0.004, ***<0.0001

KT-579, dosed once a day for 63 days, leading to 85% and >90% IRF5 degradation, reduced proteinuria (key disease marker) and prevented disease associated mortality better than all other approved or clinically active agents tested

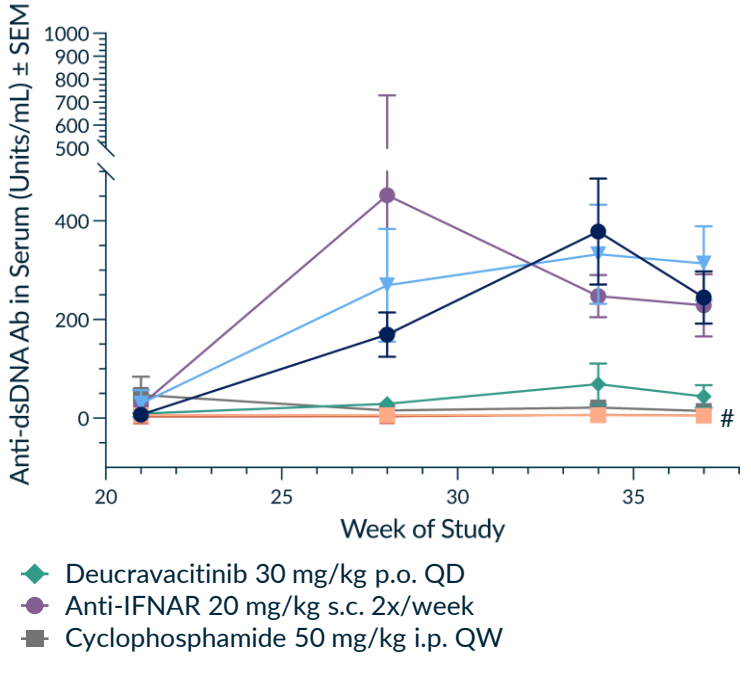
[1]MRL/lpr mice have a susceptible genetic background and single inactivating mutation in Fas gene, quickly developing lupus-like symptoms and manifestations.
#KT-579 50 mg/kg p.o. and 200 mg/kg p.o. lines are overlapping

IRF5 Degradation Demonstrated Generally Better Outcomes than Approved or Clinically Active Drugs in NZBW1 Spontaneous[1] Mouse Lupus Model

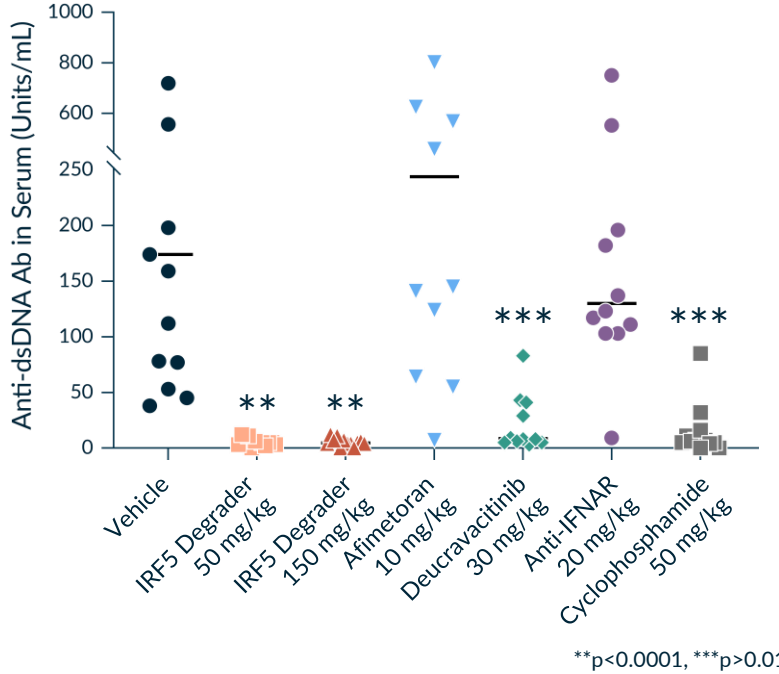
Decreased Proteinuria



Early, Sustained and Complete Reduction in Anti-dsDNA Abs



Superior Activity Reducing Anti-dsDNA at Week 37



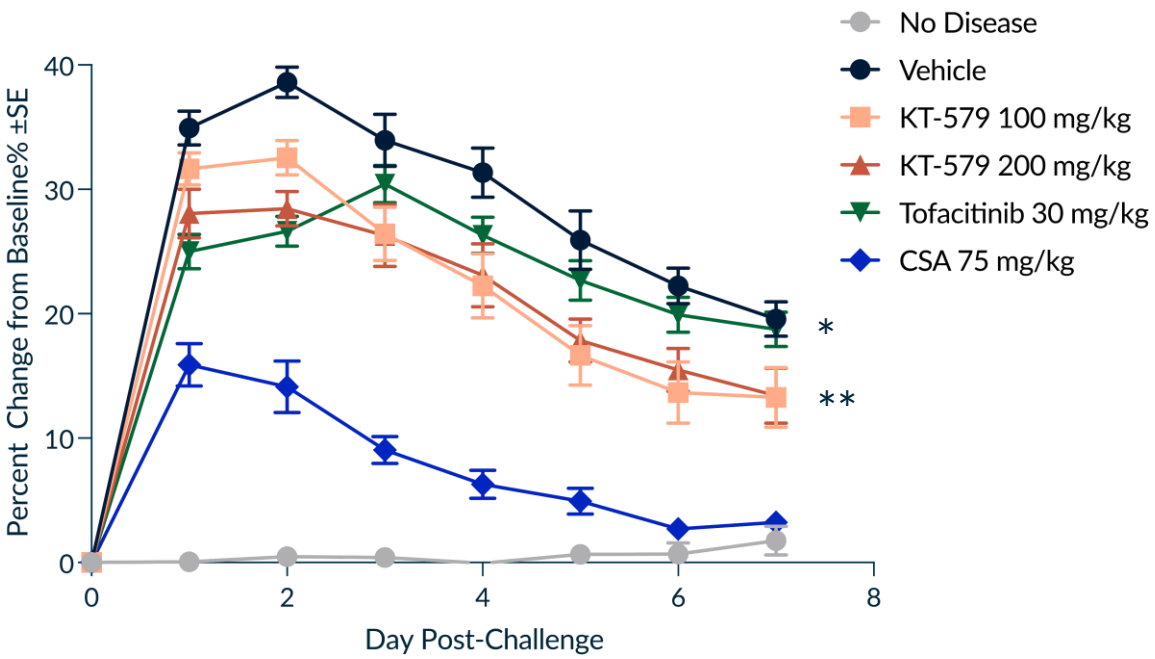
IRF5 degrader, dosed once a day for 107 days, leading to 80% and >90% IRF5 degradation, led to decreased proteinuria and near complete reduction of serum anti-dsDNA Abs superior to standard of care, approved and clinically active agents tested

[1]NZBW1 mice develop a similar disease to human SLE, characterized by anti-dsDNA ANA production, and immune complex mediated nephritis due to defects in multiple genes

#IRF5 Degrader 50 mg/kg p.o. and 150 mg/kg p.o. lines are overlapping

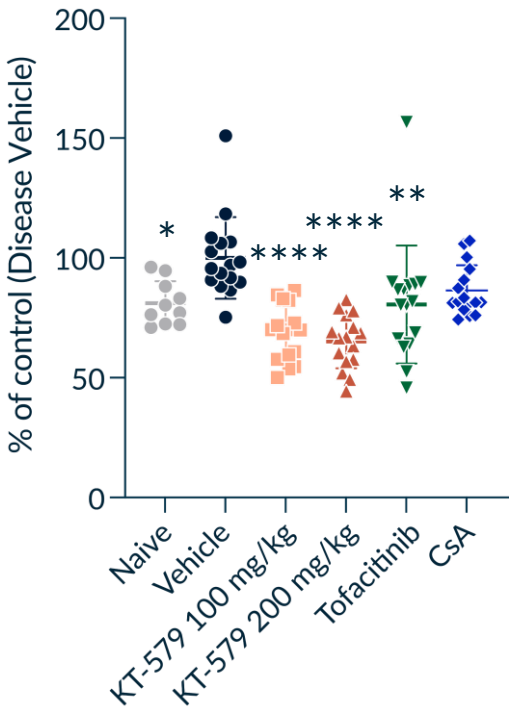
KT-579 Reduces Joint Swelling in a Mouse Model of RA

Treatment with KT-579 Leads to Significant Reduction in Joint Swelling Comparable to Tofacitinib in the AIA[1] Mouse Model of RA

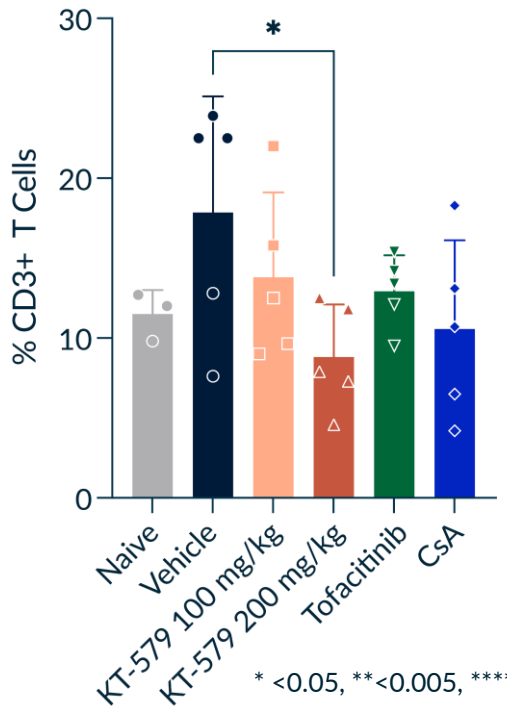


Reduction in Circulating IL-12 Levels and Infiltrating Synovial IFNγ+ Th1 Cells

IL-12p40 Serum Levels Day 2



IFNγ+ CD4+ T Cells Day 7



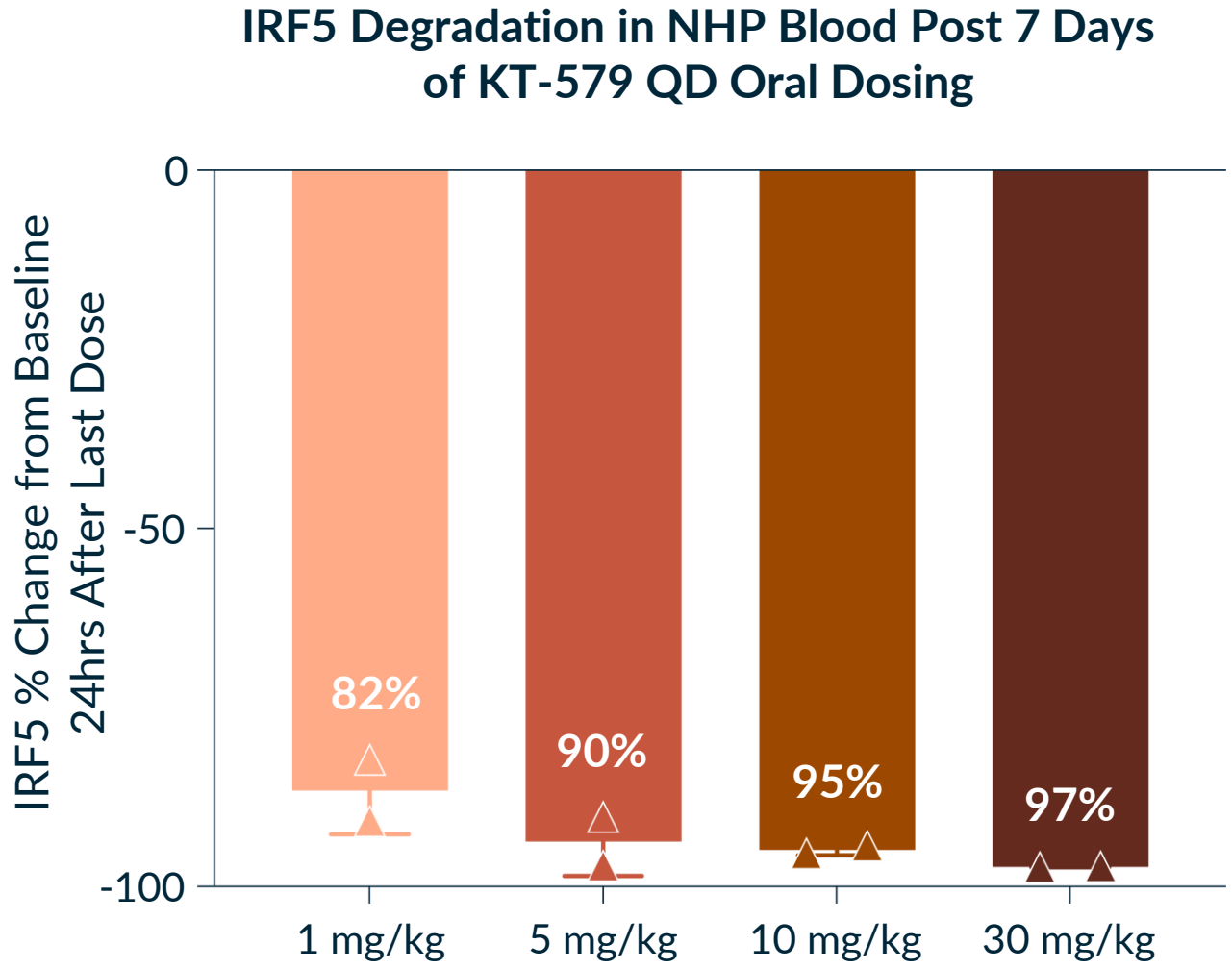
* <0.05, **<0.005, ****<0.0001

Daily oral dosing of KT-579, leading to ~90% IFR5 degradation, results in significant reduction of circulating pro-inflammatory cytokines, joint swelling and pathogenic infiltrating T cells

[1]Antigen induced arthritis (AIA) model was established by sensitization with methylated bovine serum albumin (mBSA). 14 days later mice were challenged with mBSA (Day 0) that induced rapid inflammation and swelling at site of injection. Samples for analysis collected on Day 2 and Day 7.

KT-579 Potently Degrades at Low Oral Doses in NHP with an Excellent Safety Profile

- KT-579 potently degrades IRF5 across multiple preclinical species with low oral doses
- KT-579 completed non-GLP toxicity studies in NHP and rodents with no adverse effects at up to 200-fold predicted human efficacious exposure

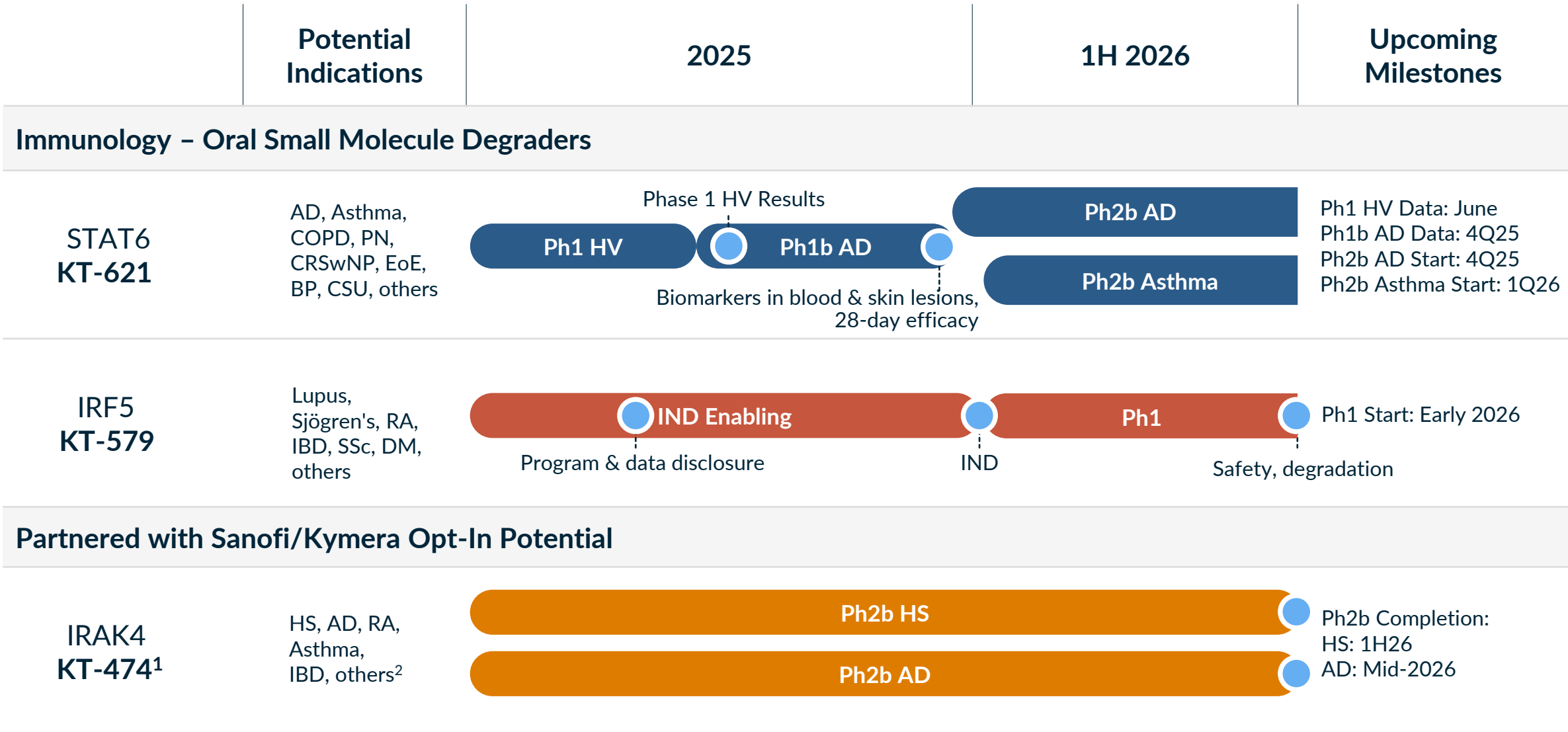


IRF5 Program Executive Summary

Vision: KT-579 is a first-in-class, oral IRF5 degrader to target debilitating diseases driven by Type 1 interferon, pro-inflammatory cytokines (TNFα, IL-1b, IL-6, IL-12p40, IL-23) and autoantibodies such as SLE, Sjögren's disease, dermatomyositis, RA, IBD and potentially others

- IRF5 has the potential to be the first broad anti-inflammatory to affect immune dysregulation while sparing normal cell function
- Human and mouse genetics and preclinical validation point to potential best-in-class profile in Lupus (as well as B cell mediated and Type 1 IFN diseases) and RA
- KT-579 is the first highly selective, potent, oral IRF5 degrader development candidate
- IRF5 degradation *in vivo* leads to robust cytokine inhibition and *in vivo* efficacy in models of lupus and RA superior to approved drugs in the space
- KT-579 fully degrades IRF5 across multiple preclinical species and in all relevant tissues with a favorable safety profile (no AEs in non-GLP tox studies)
- IND-enabling studies ongoing and initiation of a Phase 1 trial is expected early 2026

Pipeline with Clear Line of Sight to Large Value Creation



[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.

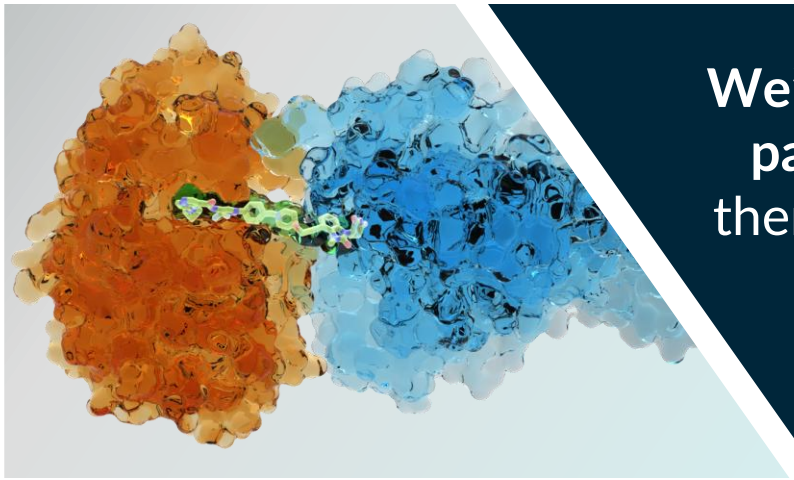
A Powerful Strategy for Patients

Harnessing the powerful mechanism of TPD to develop innovative, differentiated medicines that address critical health problems in immunology

Demonstrated consistent and compelling preclinical packages across our immunology programs

Established unique capabilities to tackle high value undrugged targets in validated pathways linked to several diseases

Advancing accelerated and innovative clinical strategies that position our programs for key inflection points near term



We're always innovating for patients - advancing oral therapies with biologics-like profiles to transform treatment paradigms

Thank You

Q&A

KYMERA THERAPEUTICS
500 North Beacon Street, 4th Floor
Watertown, MA 02472

KYMERA