Identification of Highly Potent and Selective Interleukin-1 Receptor Associated Kinase 4 (IRAK4) Degraders for the Treatment of Autoimmune Disease

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

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IRAK4 Targeting: Clinical Validation, Human Genetics De-risking and Degrader Advantage

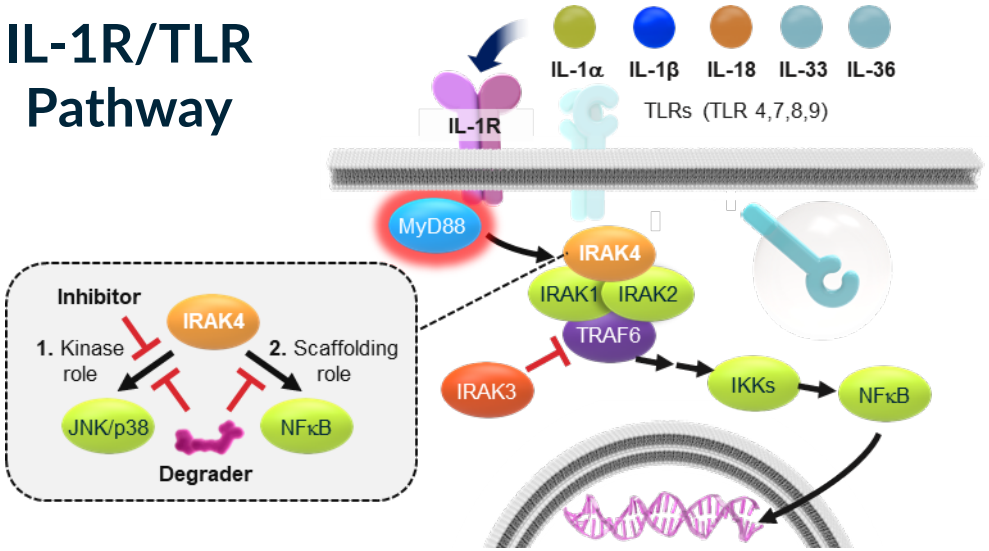
Unmet Medical Need

Validated Biology

Undrugged Node

Precision Medicine Approach

IL-1R/TLR Pathway



Clinical Pathway Validation

IL1-Rα/IL-1β : Rheumatologic Diseases

IL-1α: Atopic Dermatitis

IL-1β: CANTOS Data, Atherosclerosis, Lung Cancer

IL-18: Macrophage Activation Syndrome

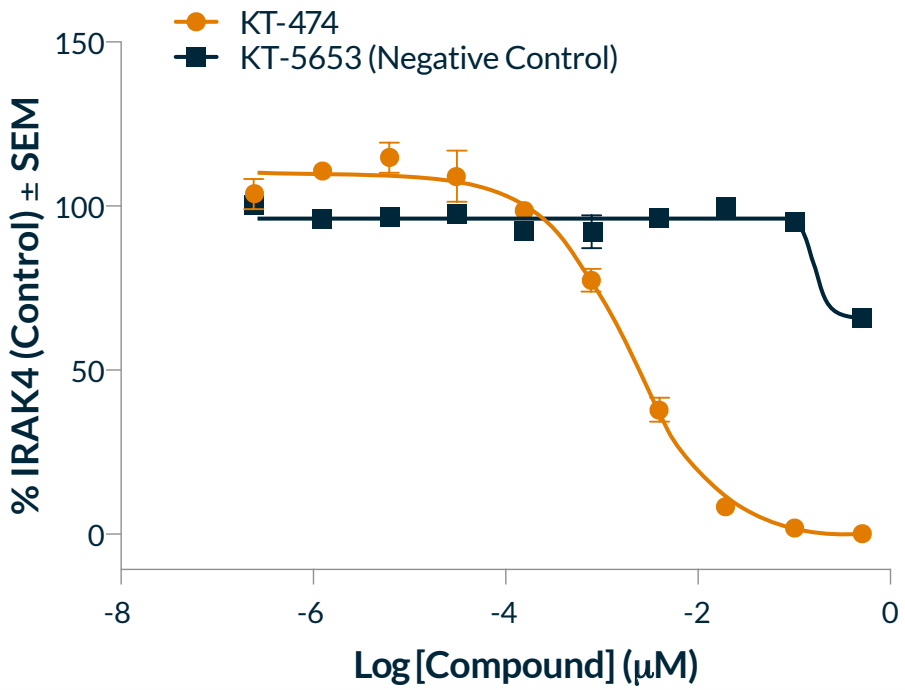
IL-36: Generalized Pustular Psoriasis

IRAK4 SMI: Rheumatoid Arthritis

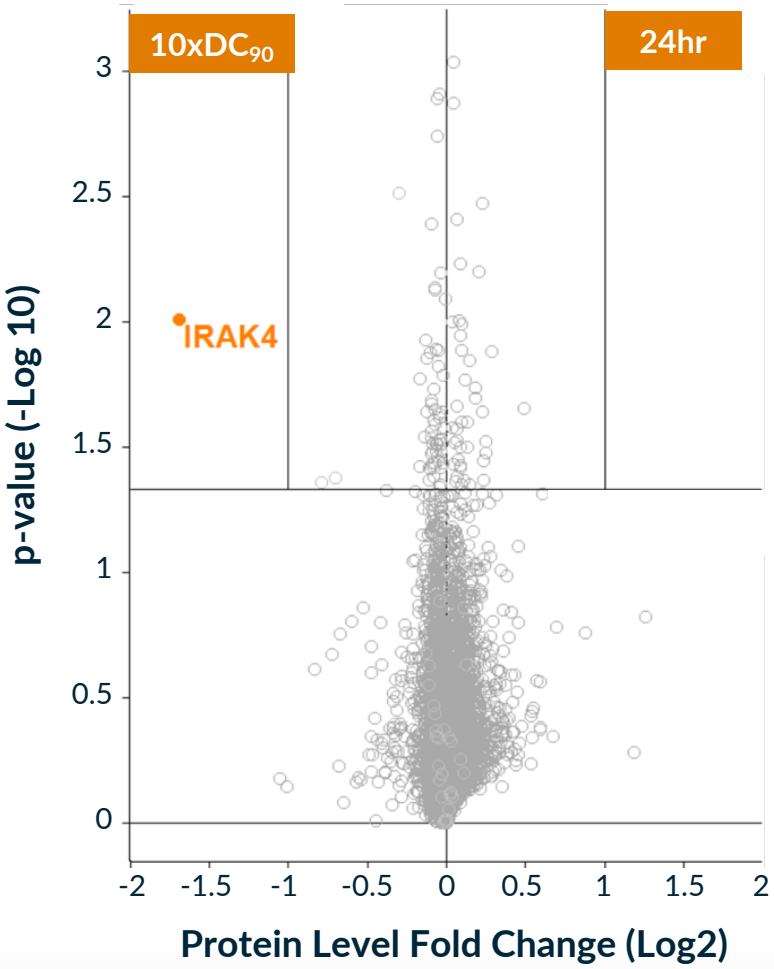
- IRAK4 is a key component of the myddosome protein complex involved in innate immunity that mediates signals through IL-1R and TLRs
- Several commercial and clinical stage drugs have validated this pathway in multiple diseases
- Degrading IRAK4, and fully blocking IL-1R/TLR signaling, is expected to be superior to antibody-based therapies that block only single cytokines, with convenience of a daily oral therapy
- IRAK4 degradation can block pathway fully vs kinase inhibitors that partially block signaling
- Human genetics de-risk safety: adults that lack IRAK4 are healthy

KT-474: Specific IRAK4 Degradation

Degradation in Human Monocytes



Selectivity in Human PBMC

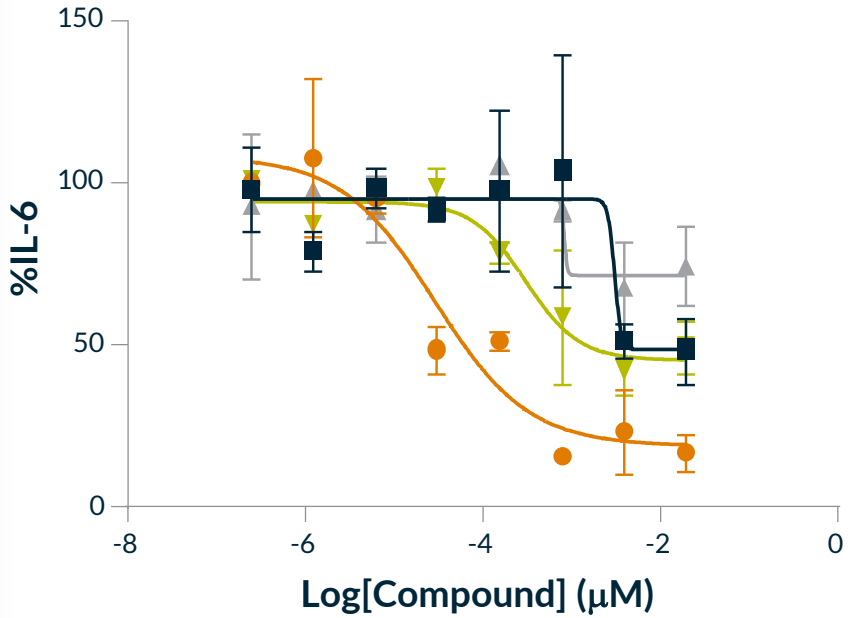


- Calculated DC_{50} of 2.1 nM and E3 ligase dependent degradation of IRAK4 in human immune cells
- IRAK4 was only protein of over 10,000 to be degraded by KT-474 in human immune cells at concentration 10-fold above the DC_{90}

IRAK4 Degradation Superior to Kinase Inhibition in Cytokine Production

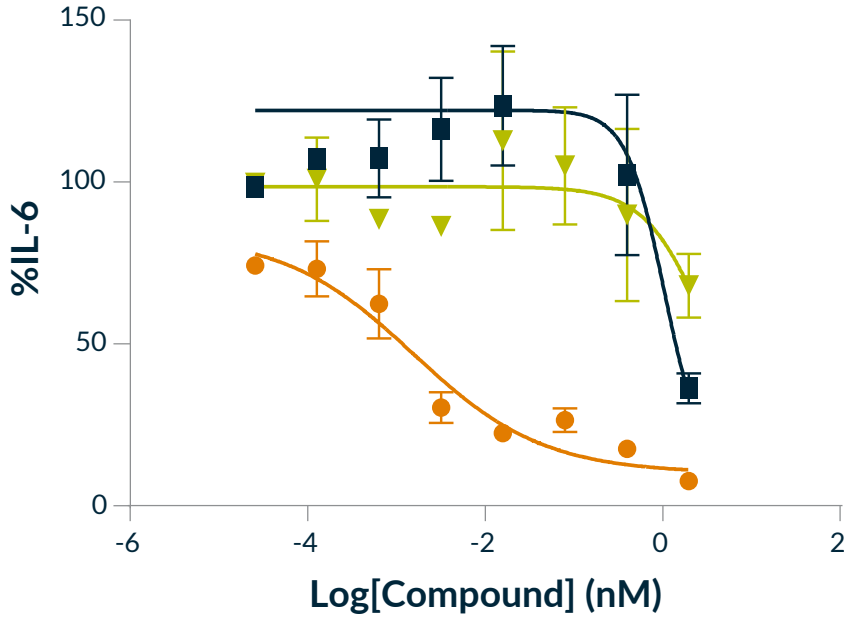
- Functional activity of KT-474 assessed by measuring pro-inflammatory cytokine levels upon activation
- Cells pre-treated with KT-474, a negative control, and small molecule IRAK4 kinase inhibitors
- KT-474 better able to inhibit IL-6 under both LPS and LPS + IL-1B than clinically active IRAK4 SM kinase inhibitor PF-06550833

LPS → IL-6



Legend	Compound	IL-6 IC_{50} (nM)
	KT-474	3
	Negative control	335
	IRAK4 SMI *(PF-06550833)*	N/A
	IRAK4 SMI *(other)*	N/A

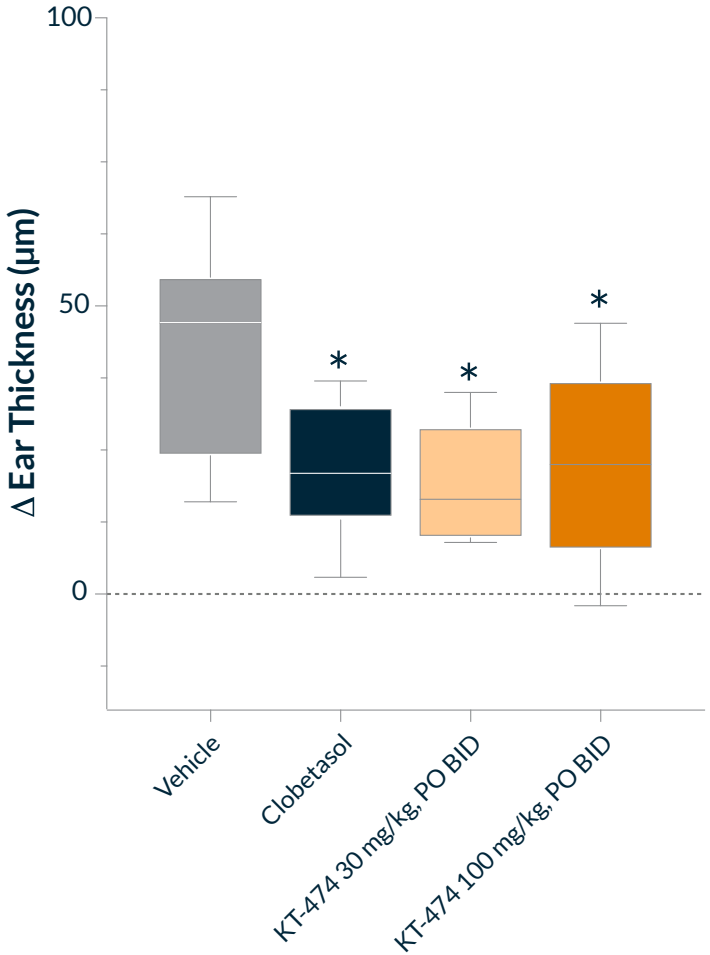
LPS + IL-1B → IL-6

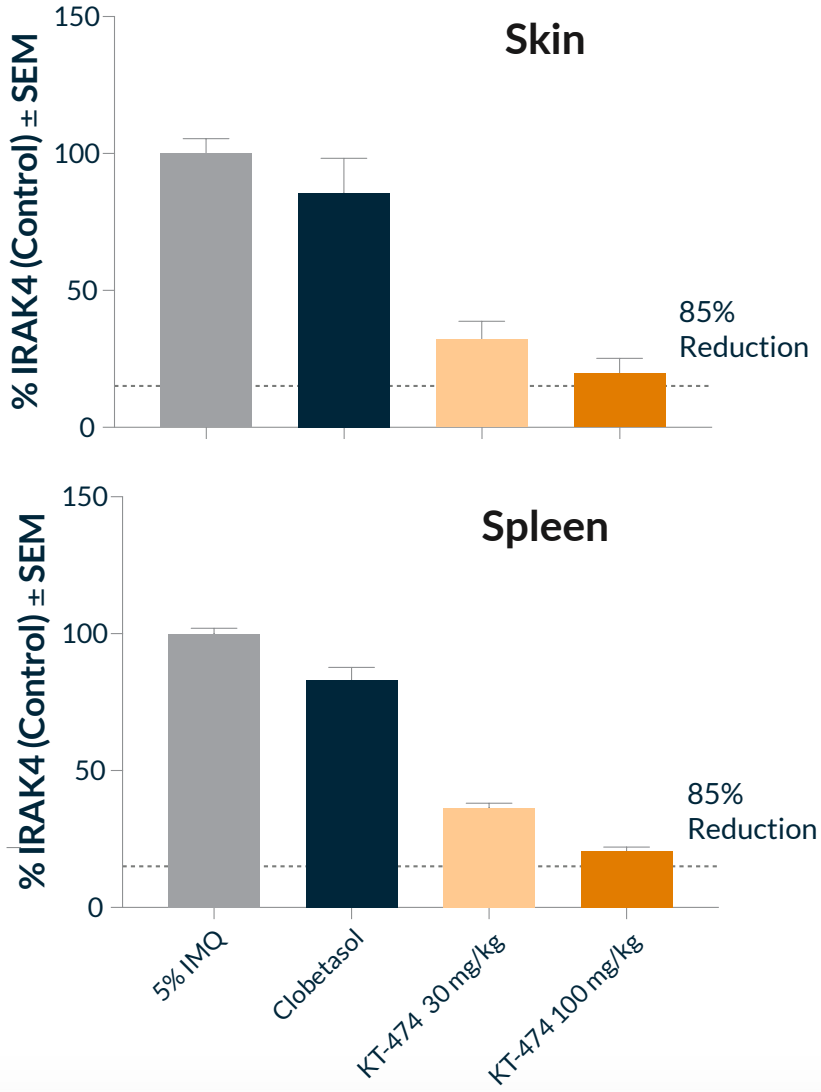


Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

85% IRAK4 Degradation Sufficient for Maximal *In Vivo* Efficacy in Preclinical Models

- Ability to inhibit topical skin thickening induced by imiquimod was measured in a mouse model of psoriasis
- Orally dosed KT-474 inhibited thickening, a reflection of local and systemic inflammation, comparable to a topic corticosteroid after 2 or 4 days of dosing
- Full efficacy at doses achieving at 65-80% IRAK4 reduction in skin and spleen. In other models KT-474 has demonstrated full efficacy with 85% degradation

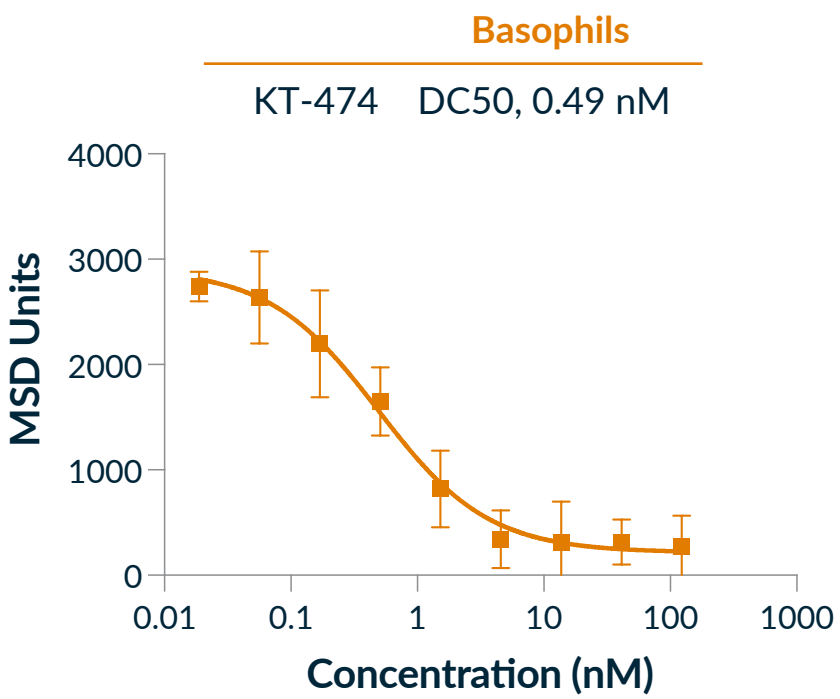




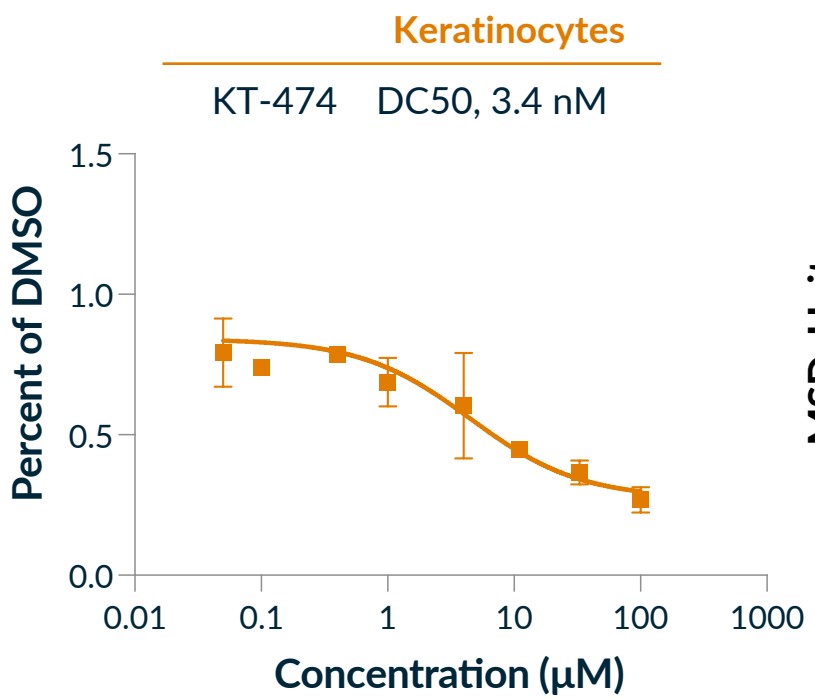
KT-474 Degrades IRAK4 in Cell Types Involved in Skin Inflammation

IRAK4 Degradation *In Vitro* by KT-474

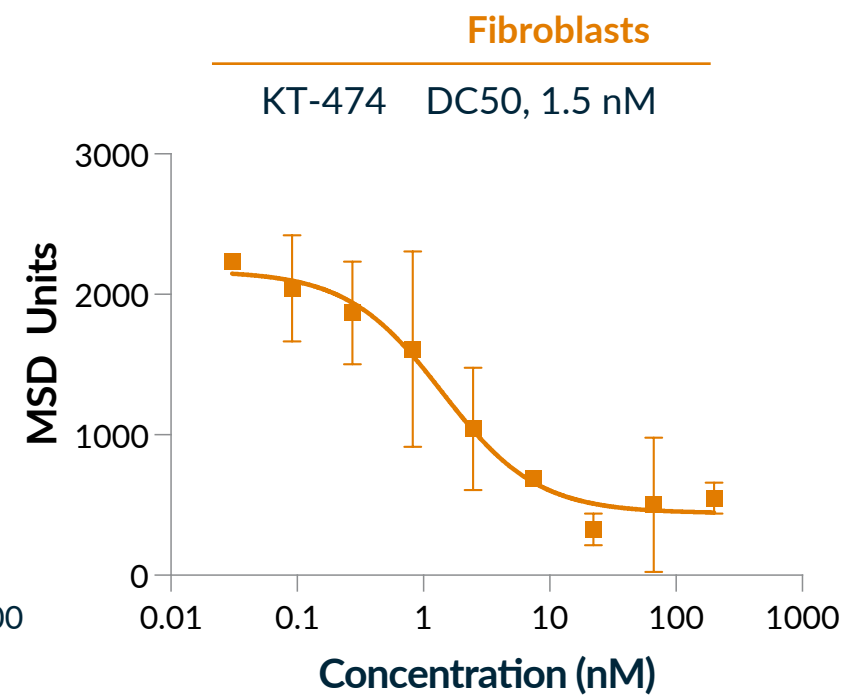
Basophils



Keratinocytes

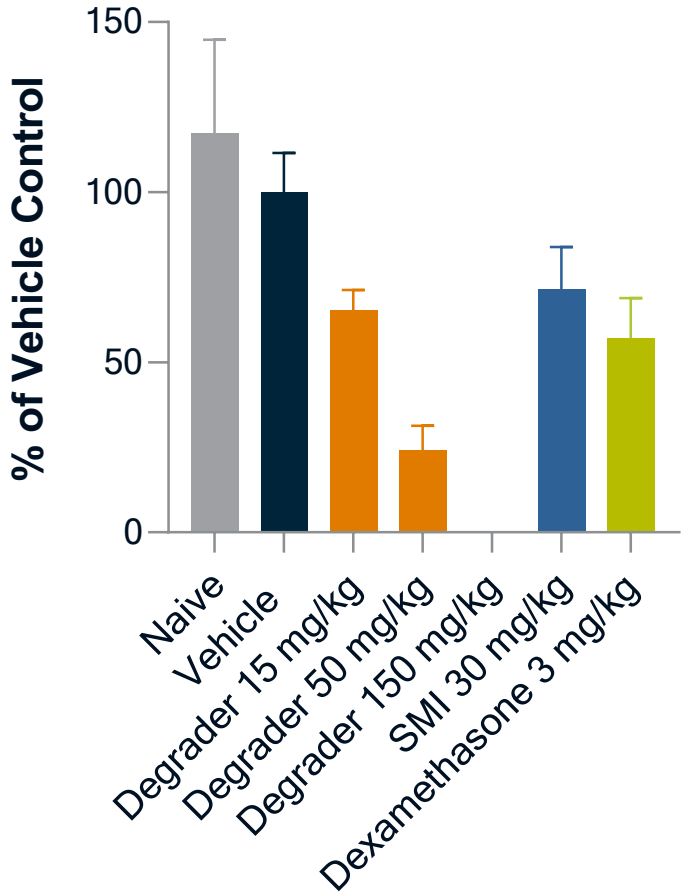


Fibroblasts

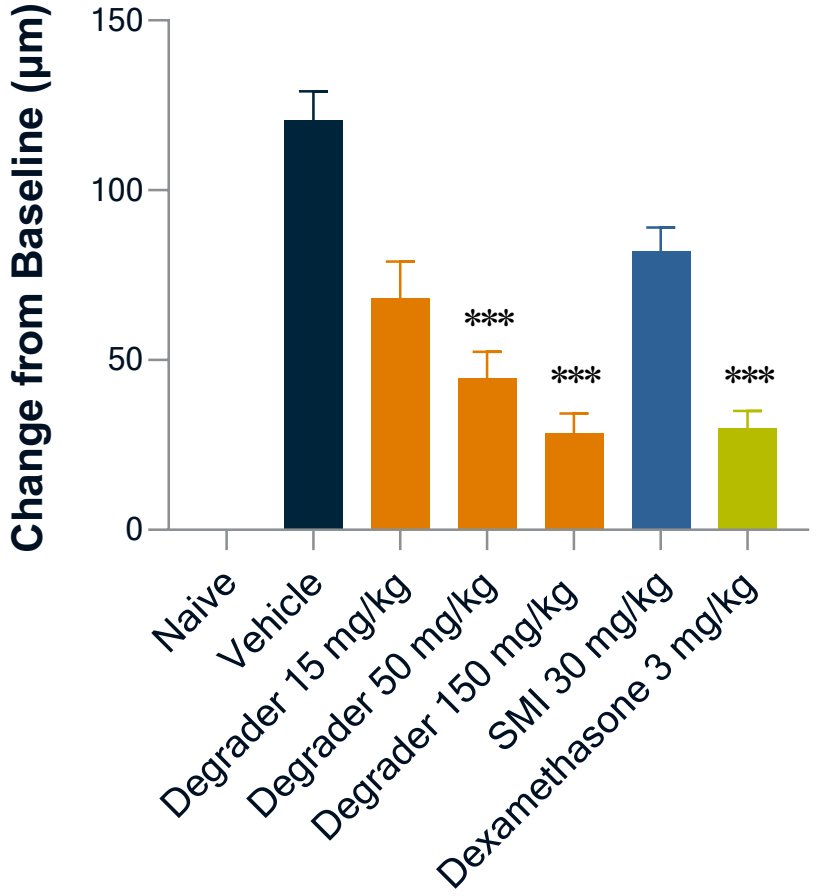


Skin Inflammation in Rodents Induced by IL-33 is Abrogated by KT-474

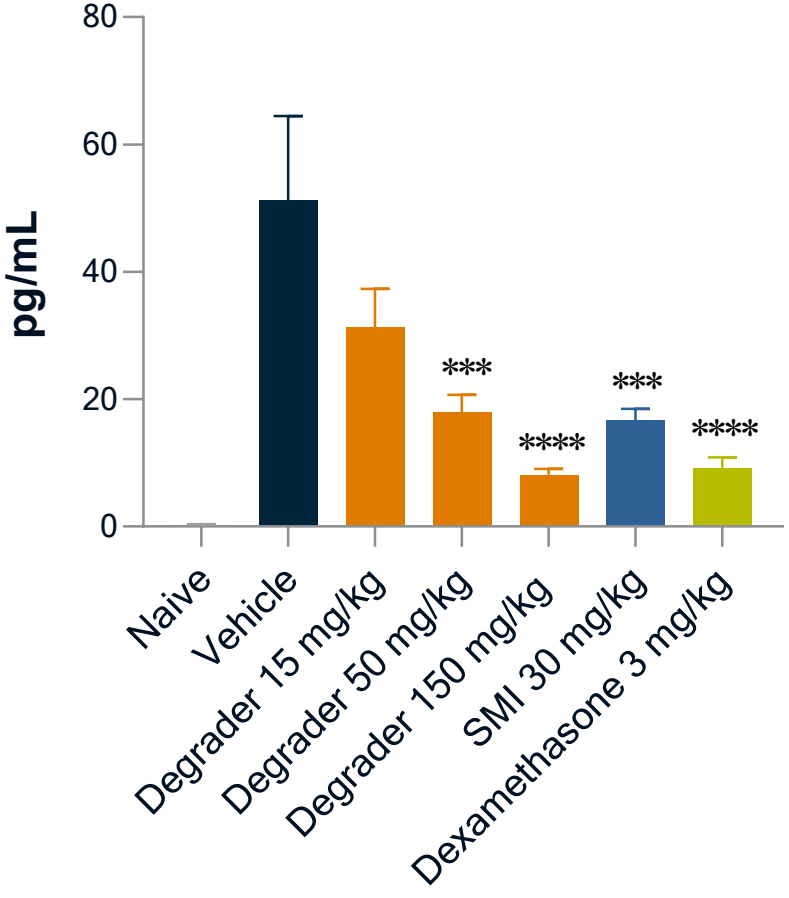
In vivo IRAK4 Degradation in Whole Blood



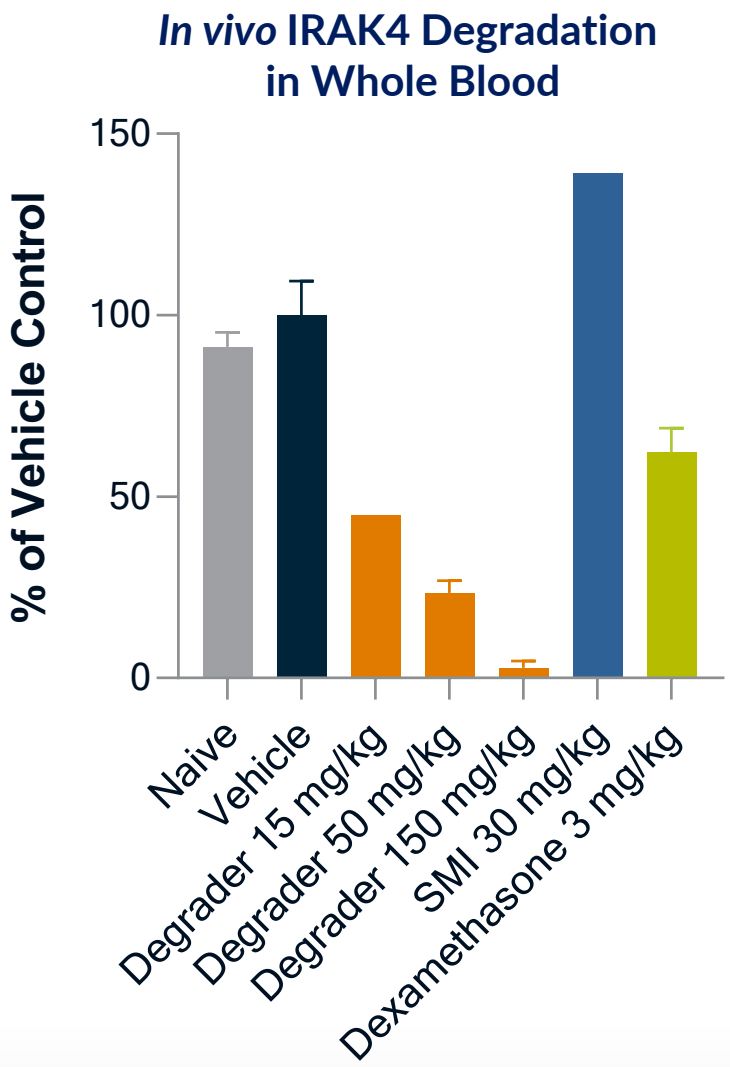
Ear Thickness (Day 14)

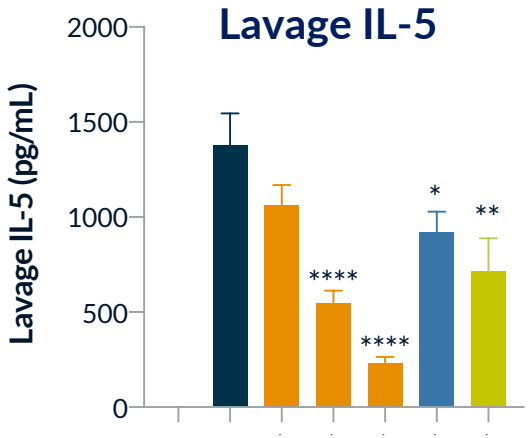


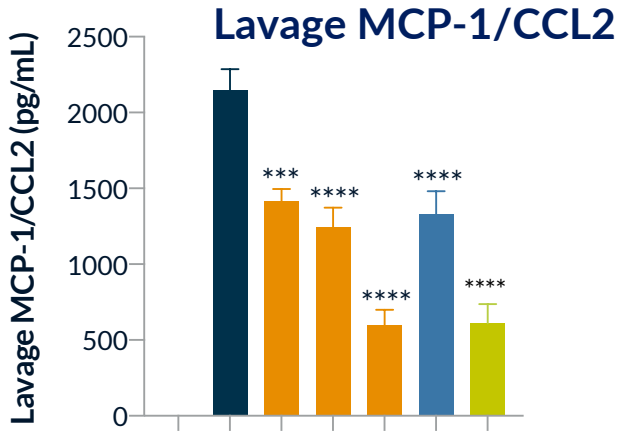
IL-5 in Ear Tissues

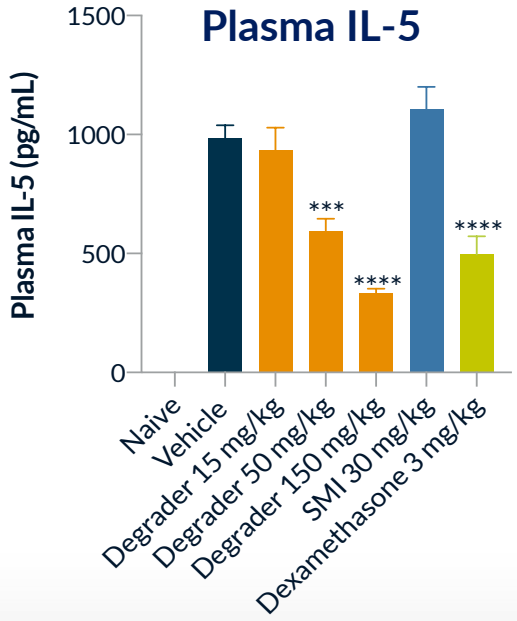


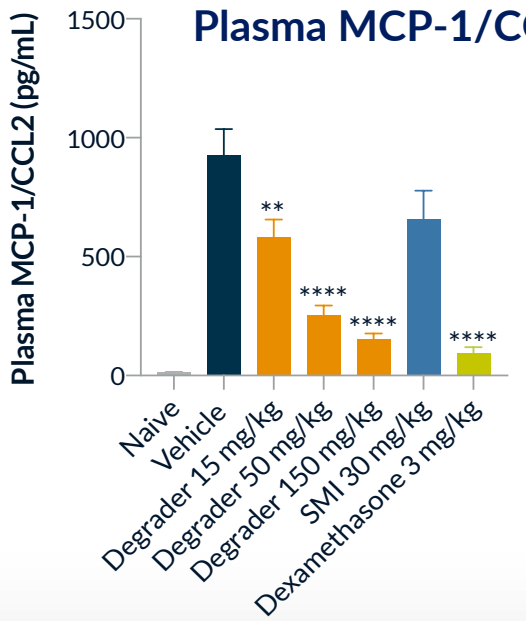
IRAK4 Degradation by KT-474 is Superior to Kinase Inhibition at Reducing IL-33 Induced Local and Systemic Cytokines



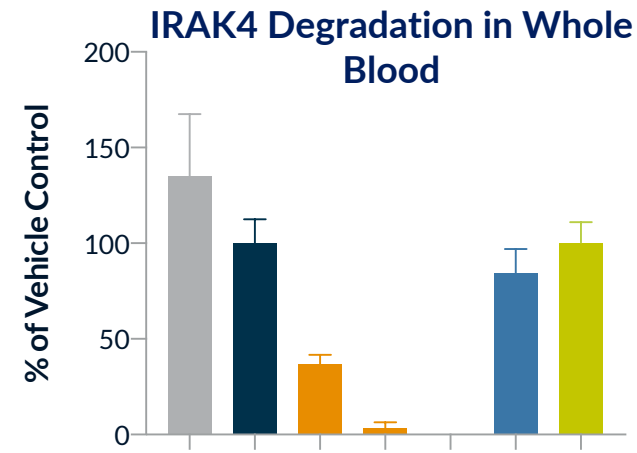


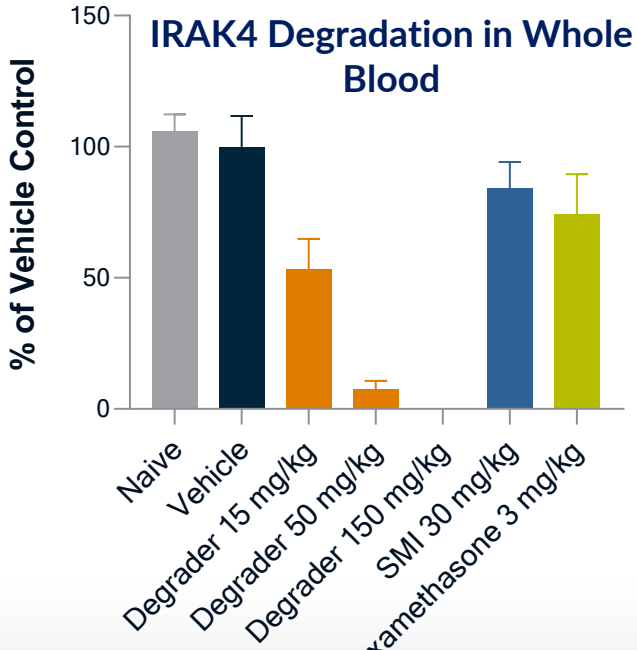


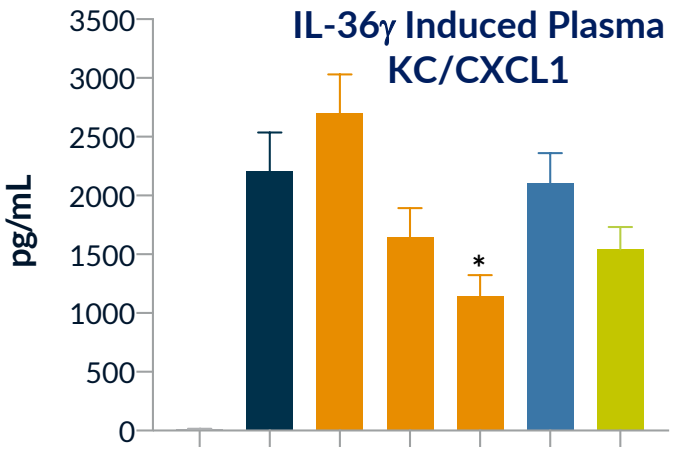


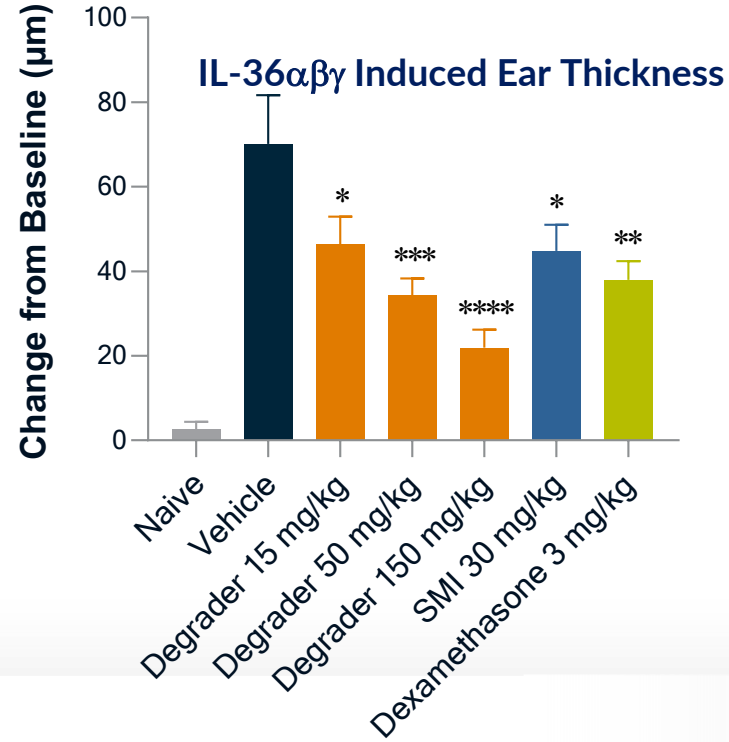


Inhibition of IL-36 induced Local and Systemic Inflammation Following IRAK4 Degradation with KT-474 is Superior to Kinase Inhibition



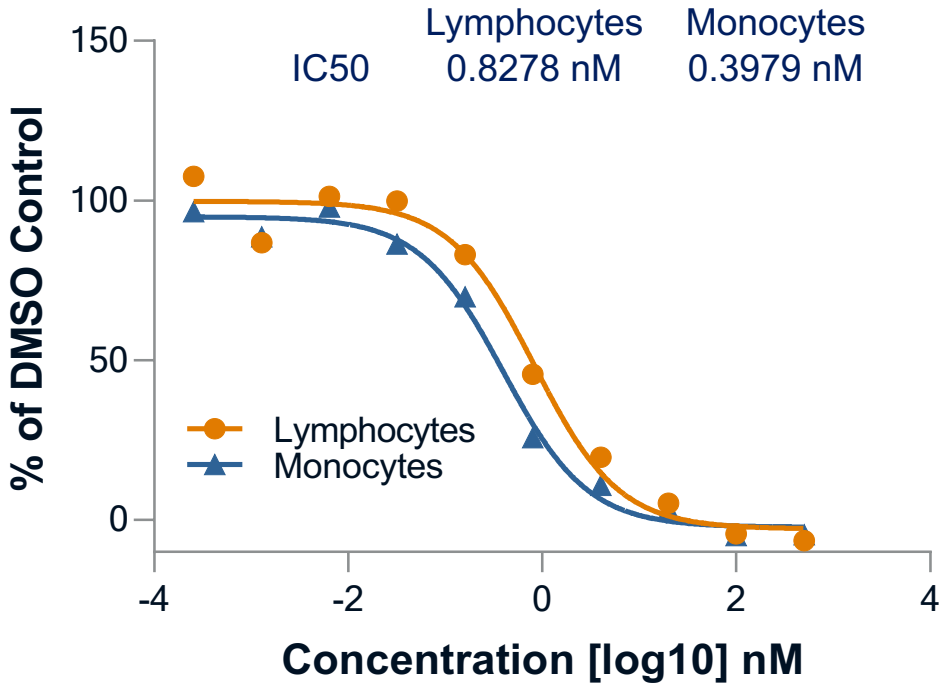




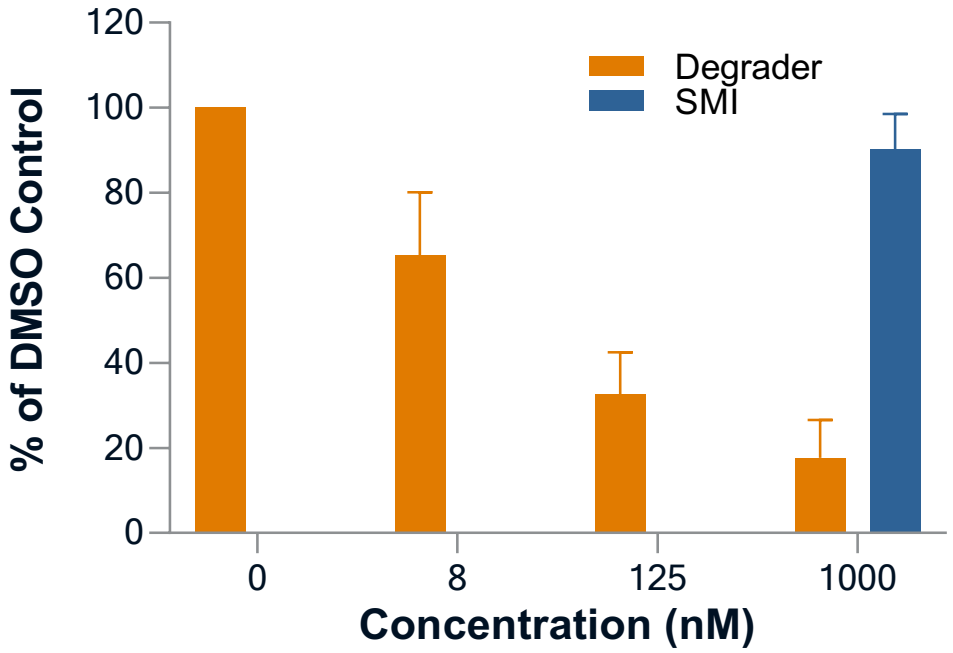


IRAK4 Degradation By KT-474 Potently Inhibits IL-17 production *In Vitro*

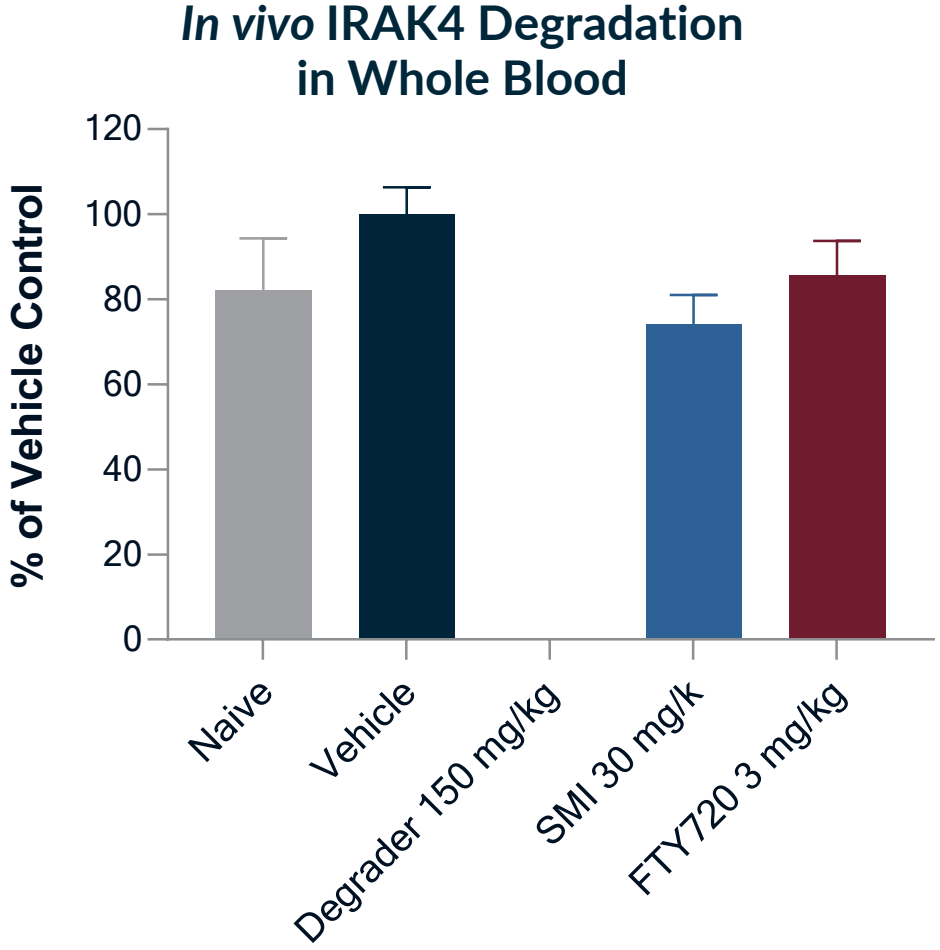
IRAK4 Degradation in PBMC

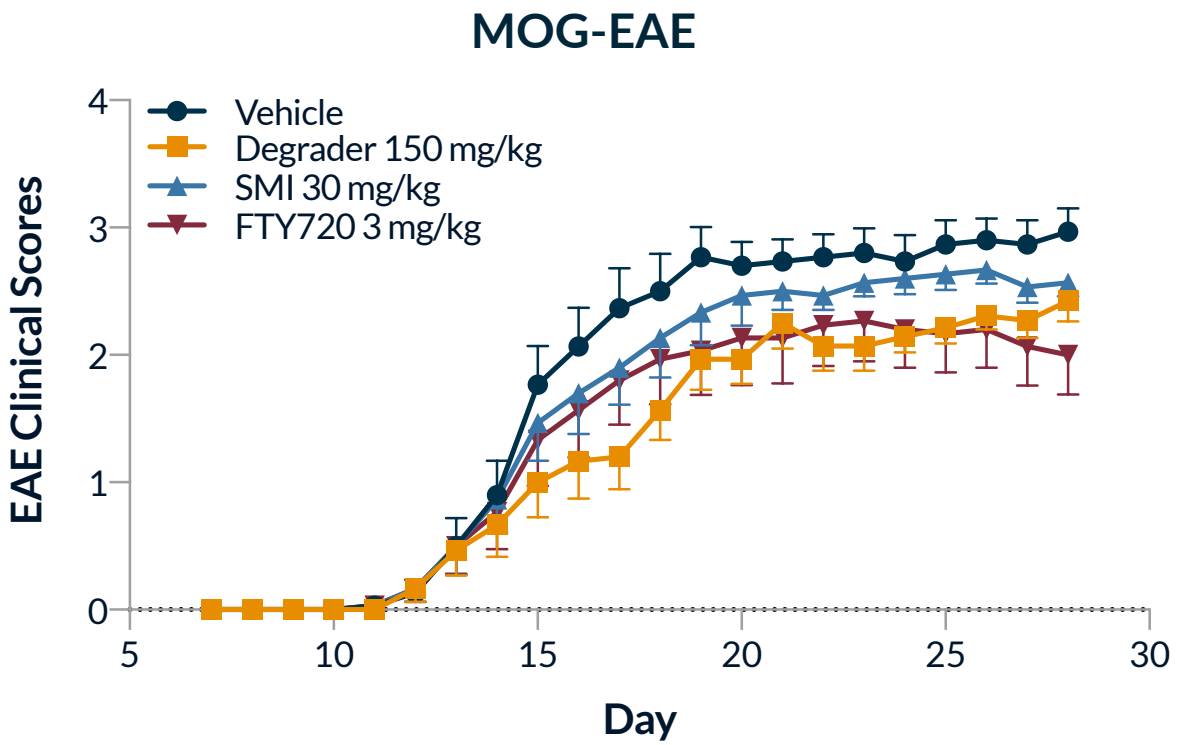


IL-17 Release by CD4+ Th17 Cells



KT-474 Reduces Severity of Th17 Model of CNS Inflammation



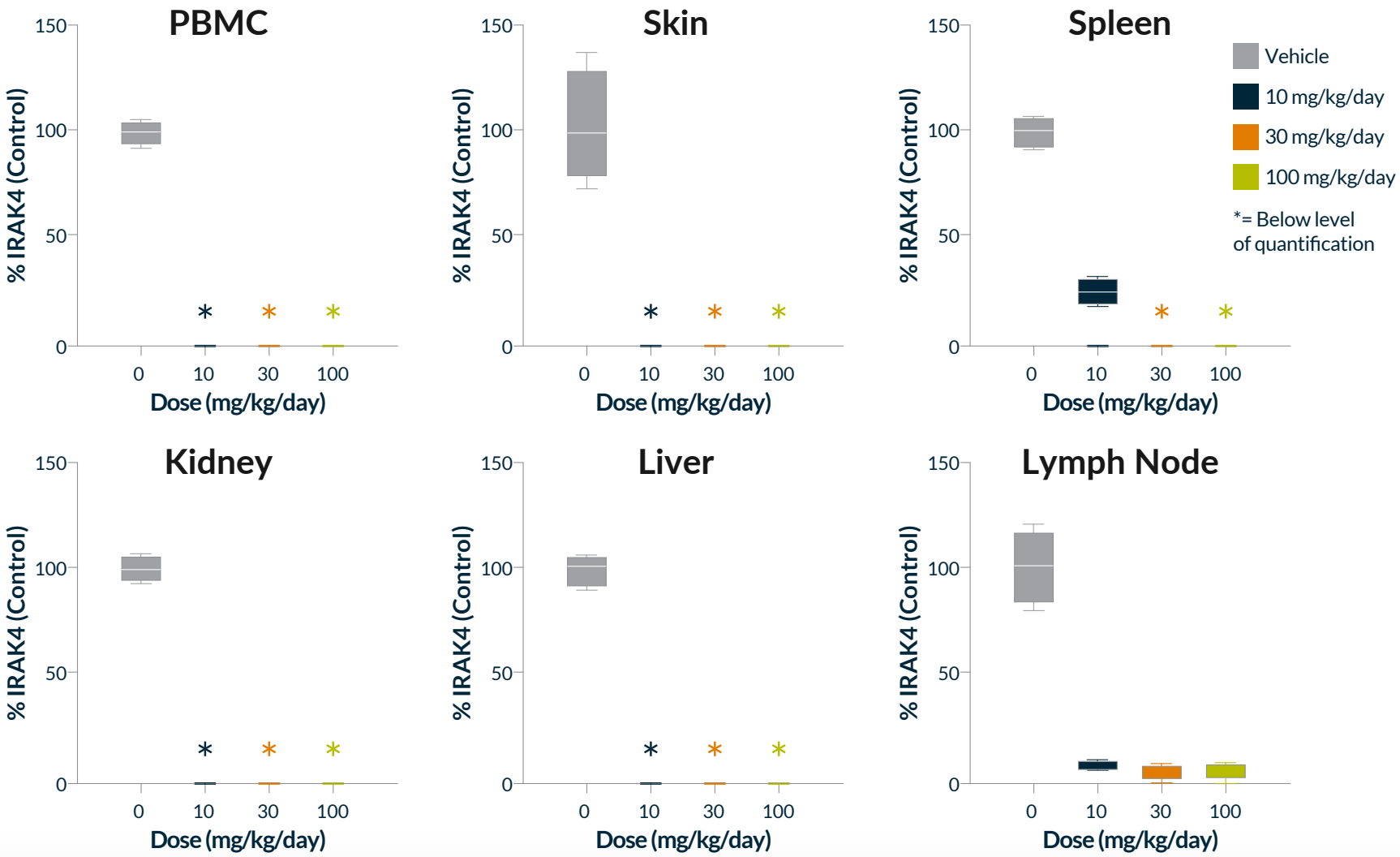


Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

IRAK4 degraders administered therapeutically (d13-d28) proved as efficacious as FTY720, whereas IRAK4 SMI did not reduce disease scores significantly.

KT-474: Close to Complete IRAK4 Degradation and Well Tolerated in Preclinical Non-rodent Model

- Orally-administered KT-474 evaluated in a 14-day non-GLP tox and PKPD study in rodent and non-rodents (shown).
- Almost complete knockdown demonstrated across multiple tissues at multiple doses
- Compound well-tolerated at all doses up to 600 mg/kg for rodents and 100 mg/kg for non-rodents



KT-474 Phase 1 Trial Design

Double-blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) trial

Three-part Phase 1 Design

1 SAD Portion
Healthy Volunteers

- **7** cohorts (up to 56 adult healthy subjects)
- **8** per cohort (6:2 randomization)
- **Single** dosing (starting dose 25 mg)

2 MAD Portion
Healthy Volunteers

- **5** cohorts (up to 60 adult healthy subjects)
- **12** per cohort (9:3 randomization)
- **14x** daily doses (starting dose 25 mg)

3 MAD Portion
Patient Cohort

- **1** cohort (up to 20 AD and HS patients)
- Open-label
- **14x** daily doses

Endpoints

Primary

- Safety & tolerability

Secondary
SAD & MAD

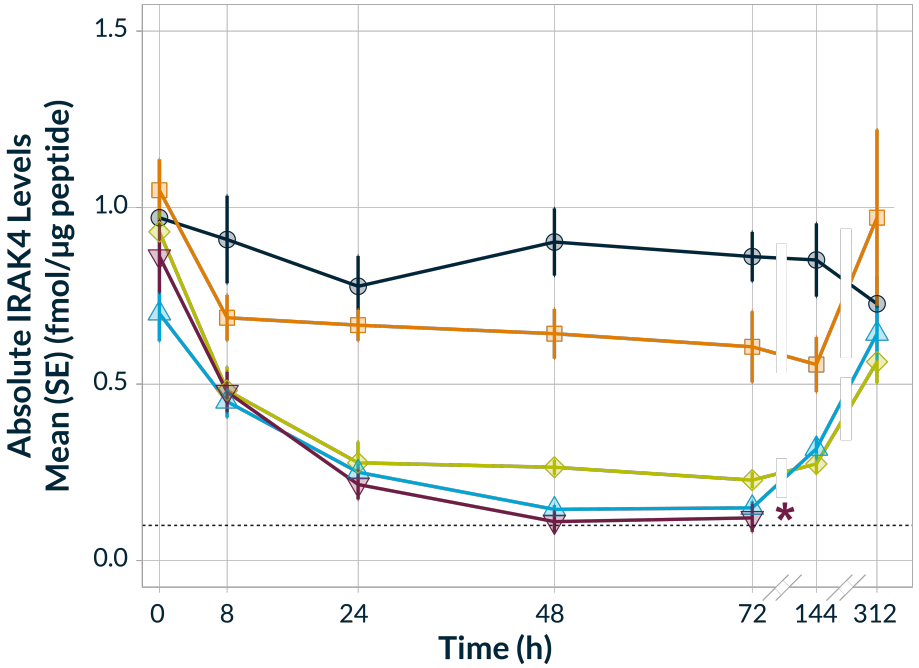
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC

Secondary
MAD only

- IRAK4 knockdown in skin biopsies
- Proinflammatory cytokine and chemokine levels in skin biopsies
- C-reactive protein and cytokine levels in plasma
- *Ex vivo* response of whole blood to TLR agonists and IL-1β

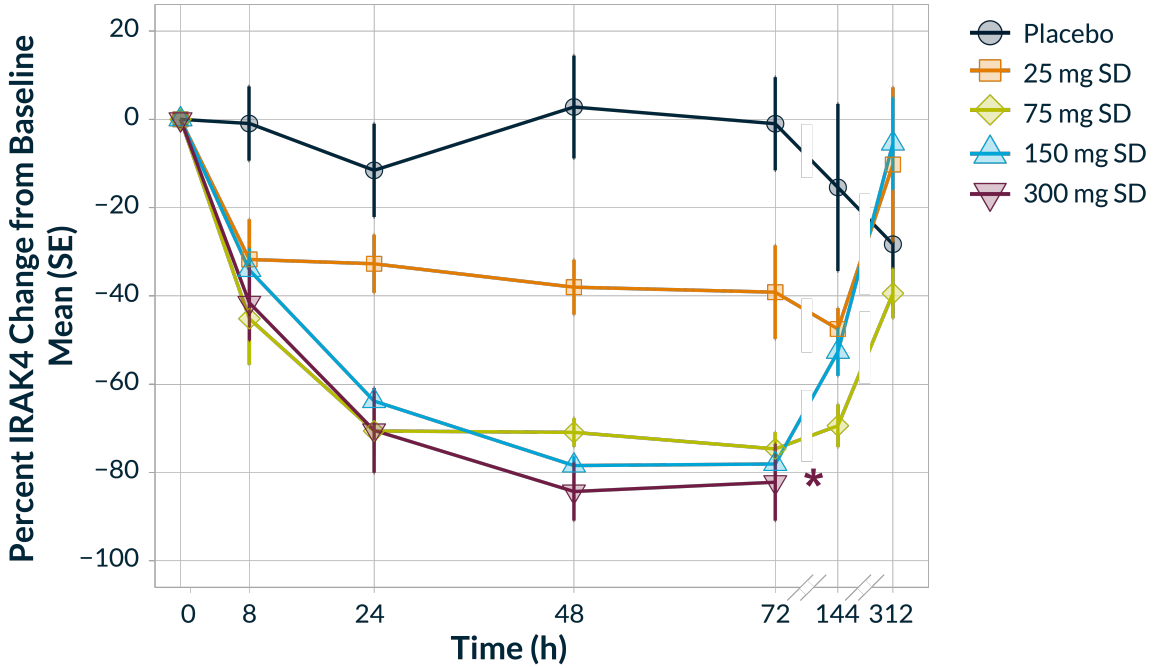
KT-474 Achieved Profound IRAK4 Degradation after Single Oral Dose that Lasted for at Least 6 Days

Absolute IRAK4 Levels



LOD

Mean % Reduction of IRAK4

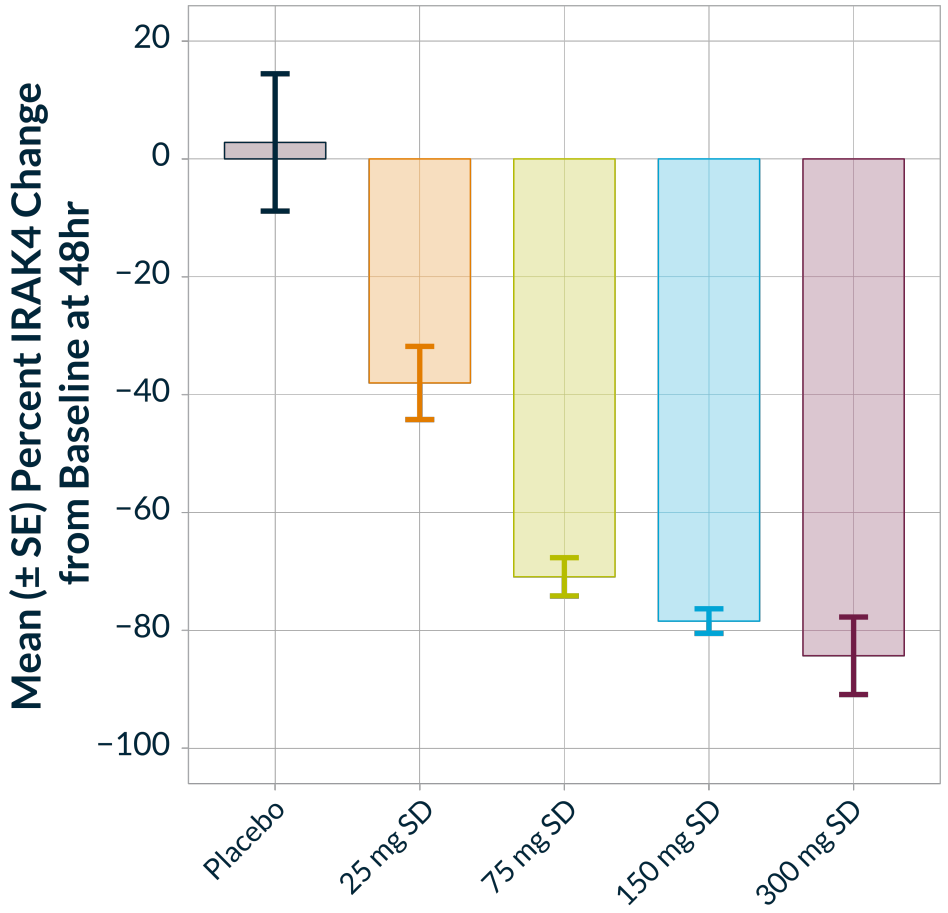


LOD = limit of detection

* SAD4 144/312 h PD timepoints pending

- Detected by Mass Spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours
- IRAK4 reduction lasted for at least 144h (6 days post-dose) in all dose groups

KT-474 Reached >85% IRAK4 Degradation After Single Dose

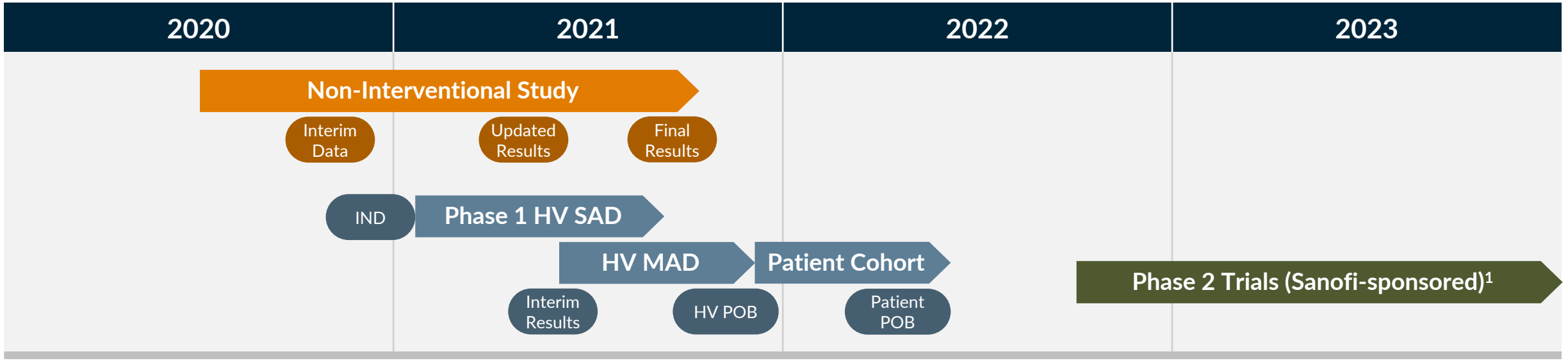


Percent IRAK4 Reduction in PBMC at 48 Hours Post-Dose using Mass Spectrometry

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	-	25 mg	75 mg	150 mg	300 mg
Mean IRAK4 Change	+3%	-38%	-71%	-78%	-84%
Median IRAK4 Change	+16%	-41%	-71%	-78%	-90%
*p value**		*0.0057*	*<0.0001*	*<0.0001*	*<0.0001*

** p-values relative to placebo*

KT-474 Development Plan



Non-Interventional

- 40 patients (HS n=30; AD n=10)
- Biomarker endpoints in blood and skin: IRAK4, cytokines, acute phase reactants
- Data updates:
  - Interim: **Oct 2020**
  - Updated HS: **May 2021**
  - Final AD: **2H21**

Phase 1

- SAD dosing initiated **1Q21**
- SAD/MAD studies: healthy volunteers (HV) and AD/HS patients
- Endpoints: primary - **Safety**; secondary - **Proof-of-Biology**
- Data updates:
  - Interim SAD proof-of-mechanism: **June 2021**
  - HV proof-of-biology: **4Q21**
  - Patient proof-of-biology: **1H22**

Phase 2

- Randomized, placebo-controlled trials in patients in potential indications such as AD, HS, RA, others

1. Estimated clinical development timeline.

KT-474 an IRAK4 Degrader for the Treatment of Autoimmune Disease

- Kymera has developed a first-in-class potent, selective and orally active IRAK4 degrader, KT-474, with franchise potential across a wide variety of immune-inflammatory diseases such as HS, RA, AD and others
- KT-474 is more potent and more broadly active than leading IRAK4 small molecule kinase inhibitors and has demonstrated activity in a variety of preclinical models with a promising activity and safety profile
- In these studies, KT-474 inhibited cytokine production and skin inflammation upon IL-33 or IL-36 injection more potently than IRAK4 SMI
- In a classic model of antigen-induced, Th17-driven neuroinflammation (MOG-EAE), IRAK4 degraders reduced clinical scores similarly to FTY720 (a standard of care for MS), and more robustly than IRAK4 SMI.
- Kymera has initiated Phase 1 trial of KT-474, including SAD and MAD healthy volunteer portions
- KT-474 interim Phase 1 results demonstrate degrader proof-of-mechanism, first time for TPD in a placebo-controlled study
- Median IRAK4 reduction of 90% ($p<0.0001$ vs placebo) and maximum reduction of 94% at 48h following single dose of 300 mg, with sustained degradation that lasted for at least 6 days at all dose levels
- Expect to present updated results from healthy volunteer SAD/MAD portions in Q4'21

THANK YOU

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