ACS FALL 2023
HARNESSING THE POWER OF DATA

Discovery of KT-474, a potent, selective, and orally bioavailable IRAK4 degrader for the treatment of autoimmune diseases

Xiaozhang Zheng, Ph.D.
Executive Director of Chemistry

KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

August 16th, 2023

Forward-looking Statements

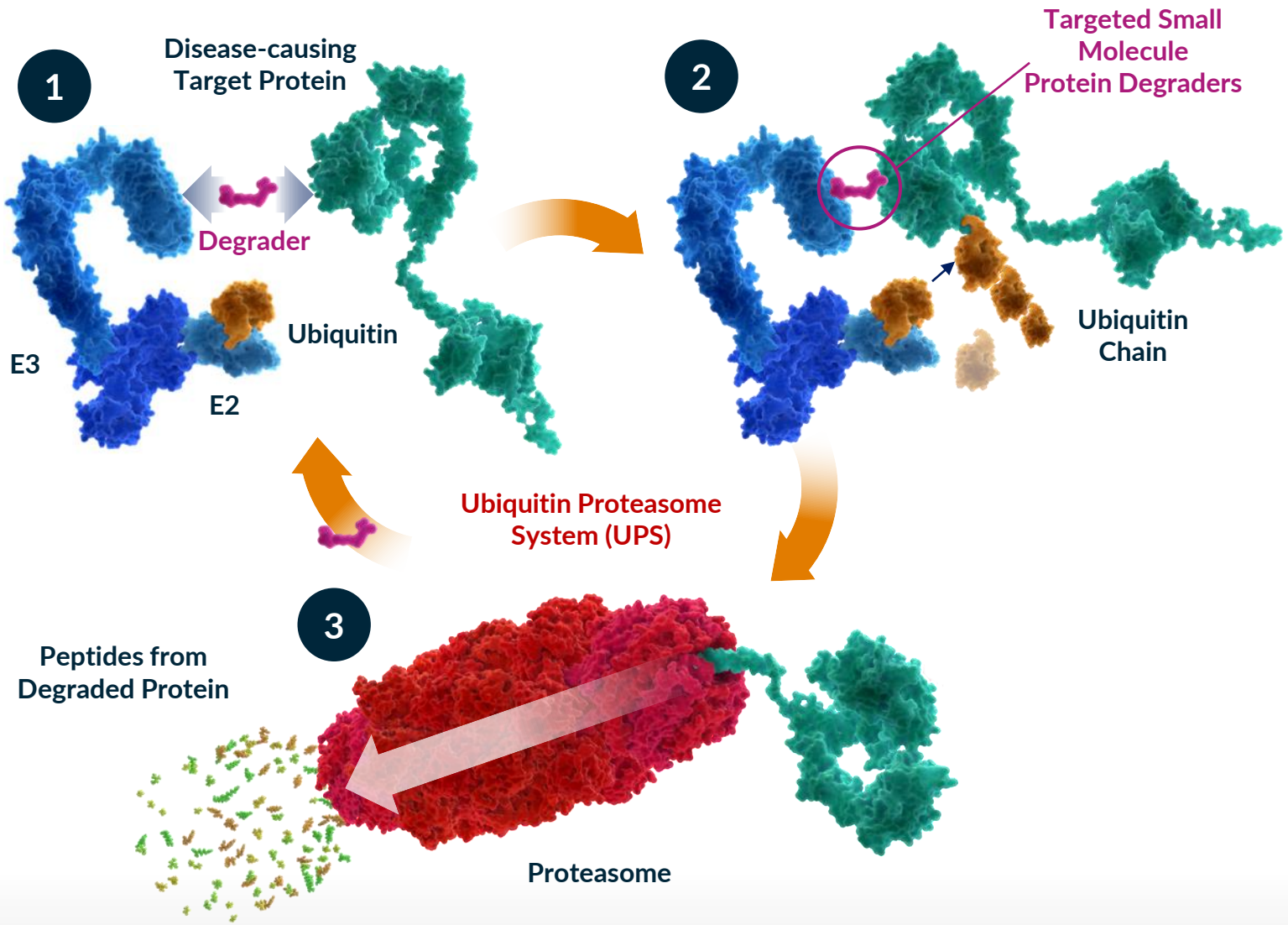
This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 (PSLRA) and other federal securities laws. These statements include information about our current and future prospects and our operations and financial results, which are based on currently available information. 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 "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "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. These forward-looking statements include statements about the initiation, timing, progress and results of our current and future clinical trials and current and future preclinical studies of our product candidates and of our research and development programs; our plans to develop and commercialize our current product candidates and any future product candidates and the implementation of our business model and strategic plans for our business, current product candidates and any future product candidates. 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.

Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise. As a result of these risks and others, including those set forth in our most recent and future filings with the Securities and Exchange Commission, actual results could vary significantly from those anticipated in this presentation, and our financial condition and results of operations could be materially adversely affected. This presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners.

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 has 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.

Proteome Editing with Targeted Protein Degradation

A Nobel Prize (2004) Inspired Technology

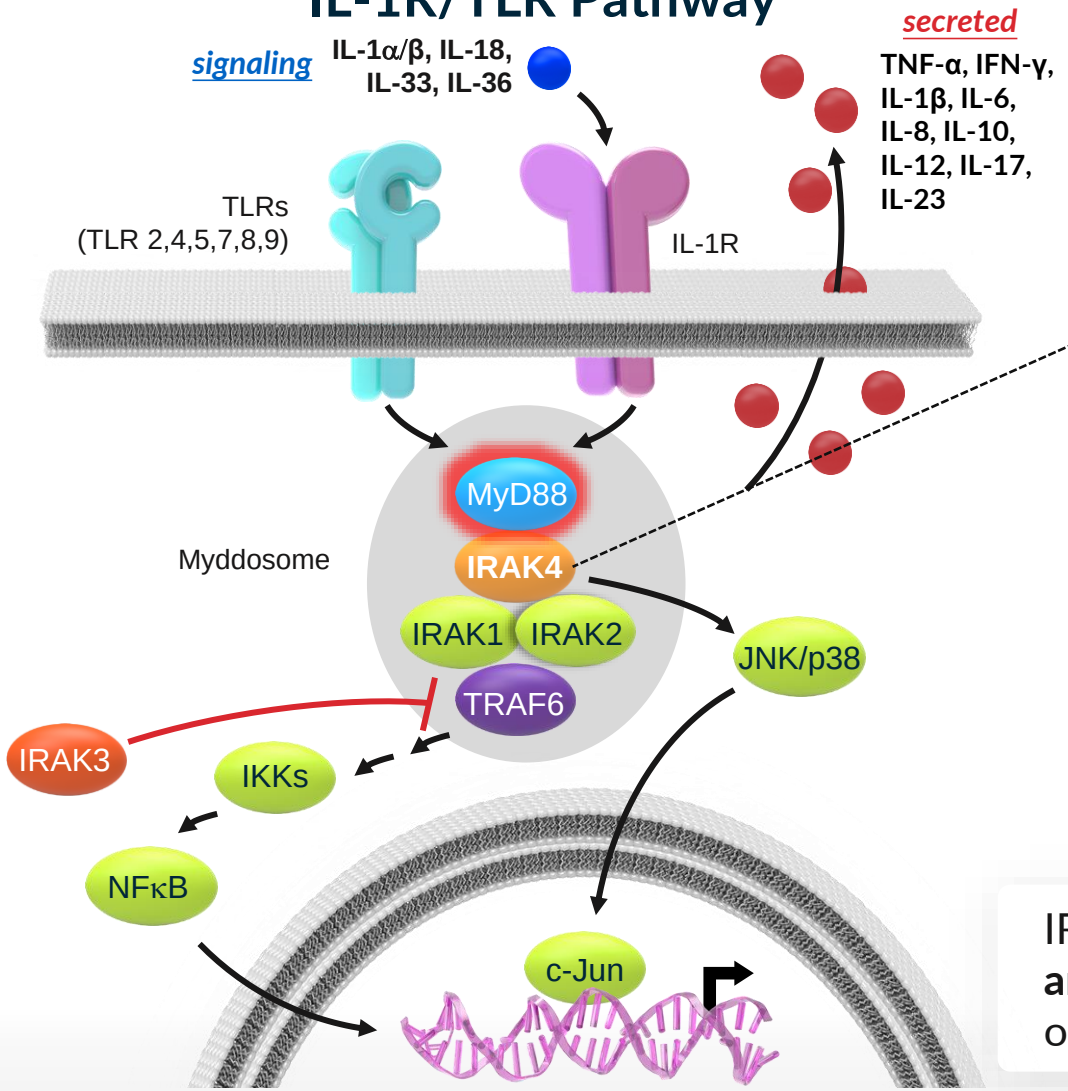


Expanded Opportunities

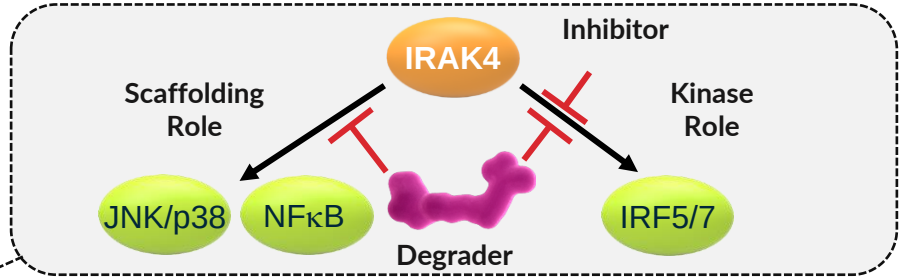
- Small molecule binds to E3 and target protein to enable its degradation
- Small Molecule only needs to bind to protein anywhere
  Not inhibit function
- Highly potent/catalytic:
  Small amount of drug needed
- Highly specific
- Genetic–like knock-down effects
- Advantage of small molecule development: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

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

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

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

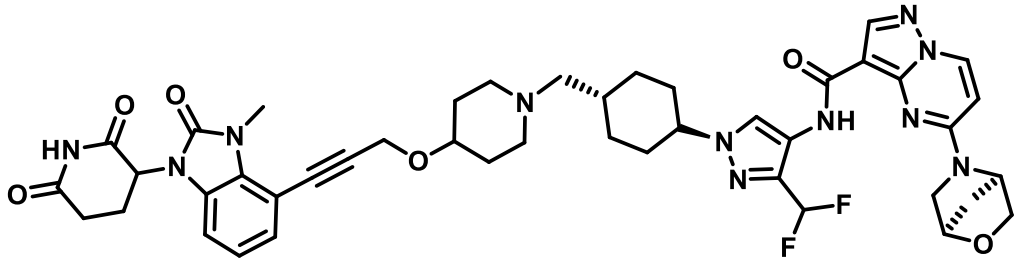
Human Genetics

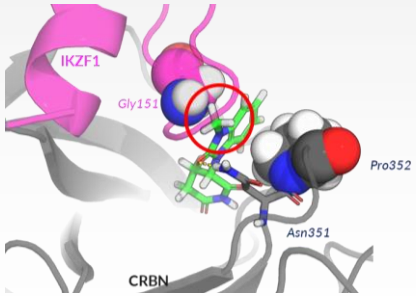
Adult humans with **IRAK4 Null Mutation are healthy**

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

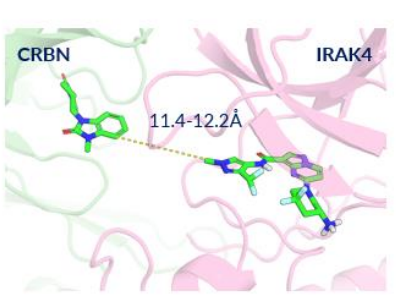
The Discovery of KT-474

- First of **four development candidates advanced into humans** by Kymera
- First **randomized, placebo-controlled trial in healthy volunteers** for a heterobifunctional degrader
- First **heterobifunctional degrader with evidence of clinical activity, outside of oncology**, in patients with HS and AD
- First demonstration of biological and clinical differentiation of **degrader vs. small molecule inhibitor**

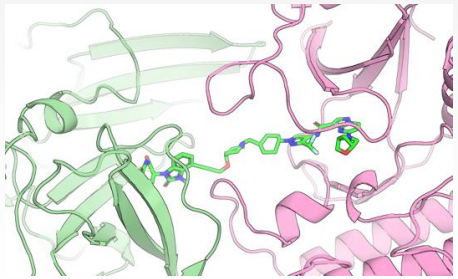




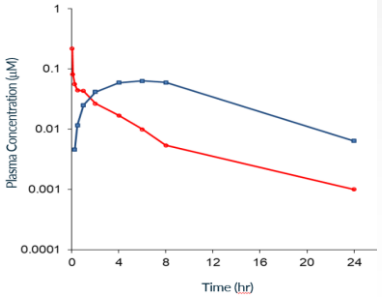
Novel CRBN Ligand



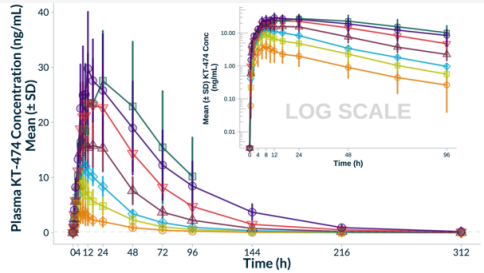
Ternary Complex Modelling



IRAK4:KT-474:CRBN/DDB1 Cryo-EM



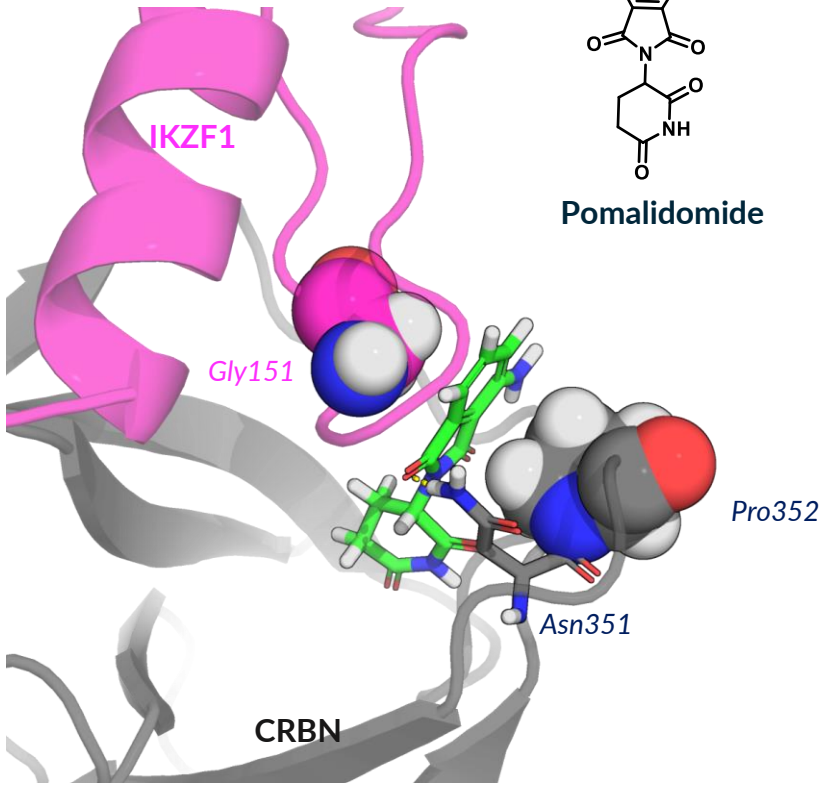
Favorable Preclinical PK Profile



Demonstrated Robust Human PK\PD

Discovery of a Novel CRBN Binder: Dialing Out IMiD Activity

Analysis of POM interactions with degron shows key role of benzene in binding to degron and CRBN

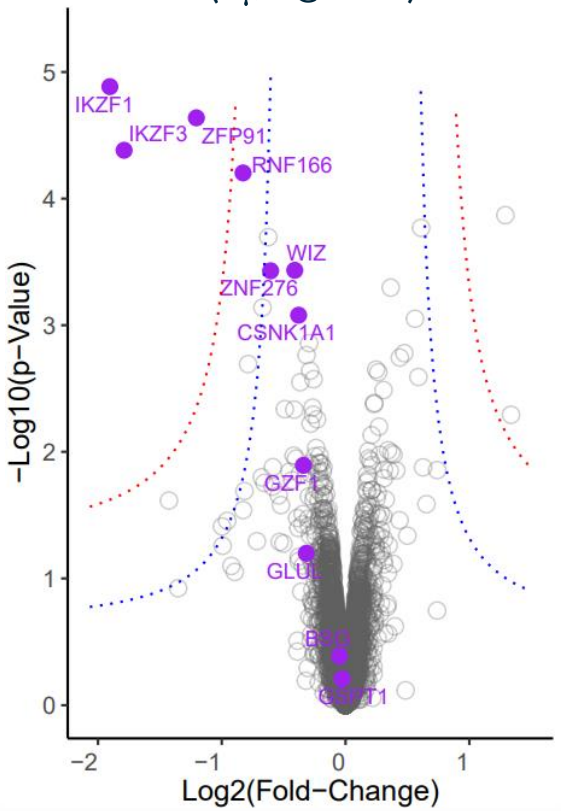


Pomalidomide

X-ray structure of CRBN:Pomalidomide:IKZF1 (6H0F)

Pomalidomide serves as a molecular glue to degrade IMiD substrates

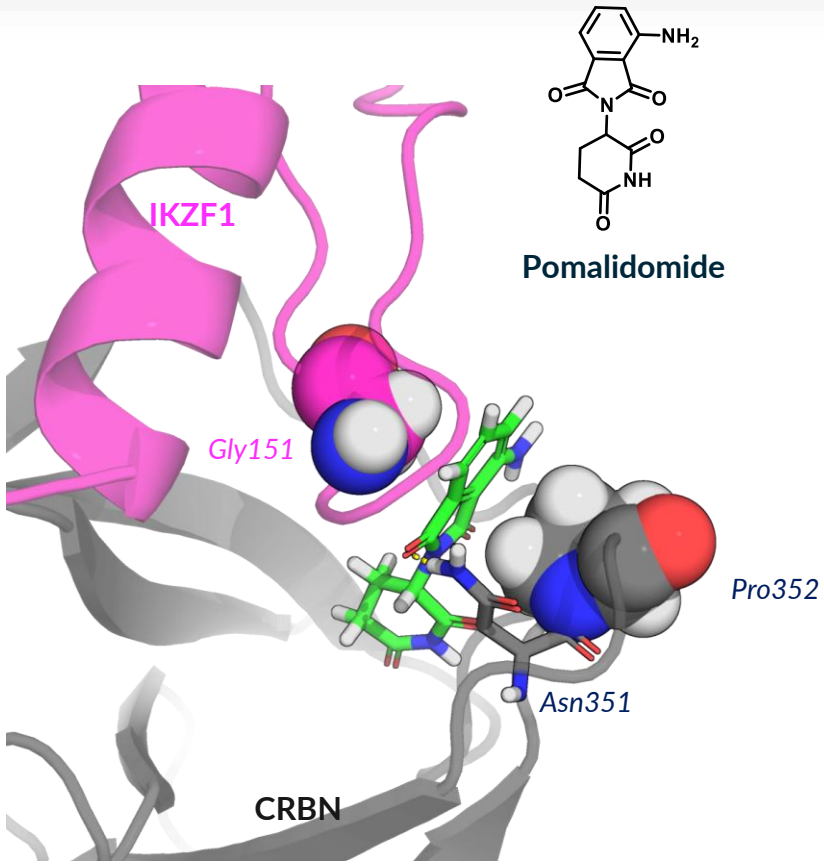
Global Proteomic Analysis of POM in human PBMCs (1 µM @ 24 hrs)



IMiD substrates in purple

Discovery of a Novel CRBN Binder: Dialing Out IMiD Activity

Analysis of POM interactions with degron shows key role of benzene in binding to degron and CRBN

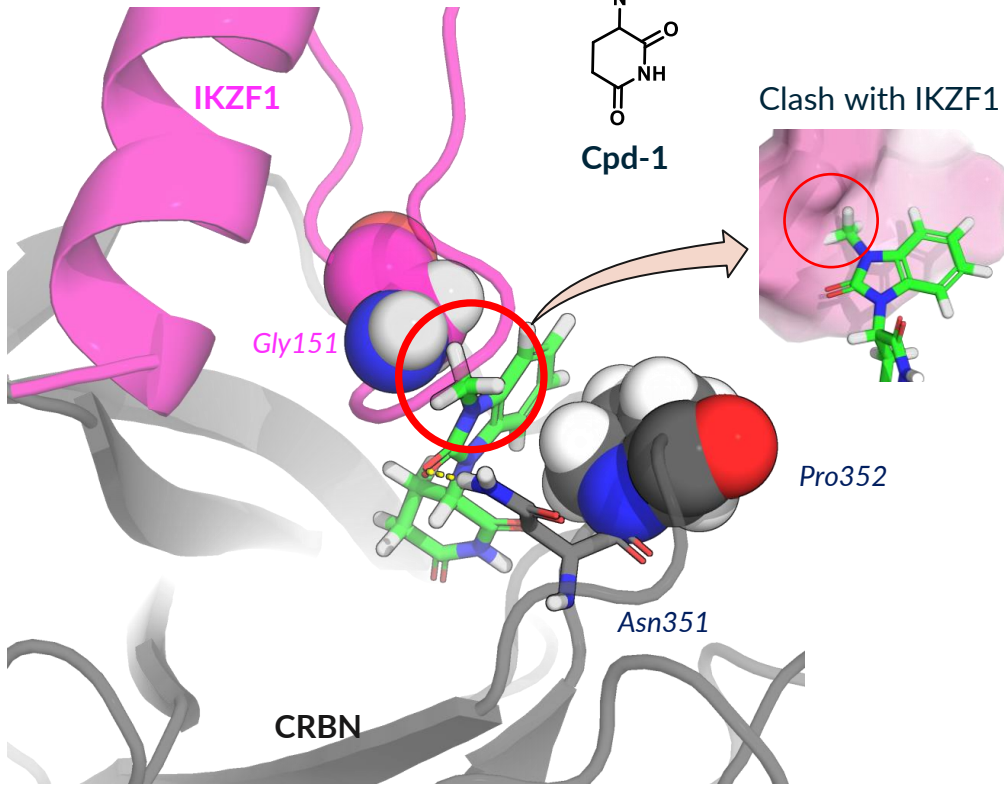


Pomalidomide

Design strategies to remove IMiD biology

- Reduce degron interactions
- Introduce methyl to further disengage degron

Cpd-1 lacks favorable engagement with degron and contains methyl to introduce clash

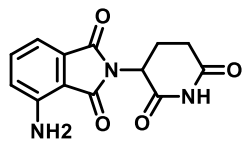


Cpd-1

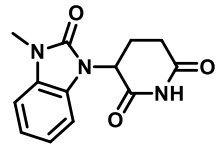
X-ray structure of CRBN:Pomalidomide:IKZF1 (6H0F)

X-ray structure of CRBN:Cpd-1 overlayed with IKZF1

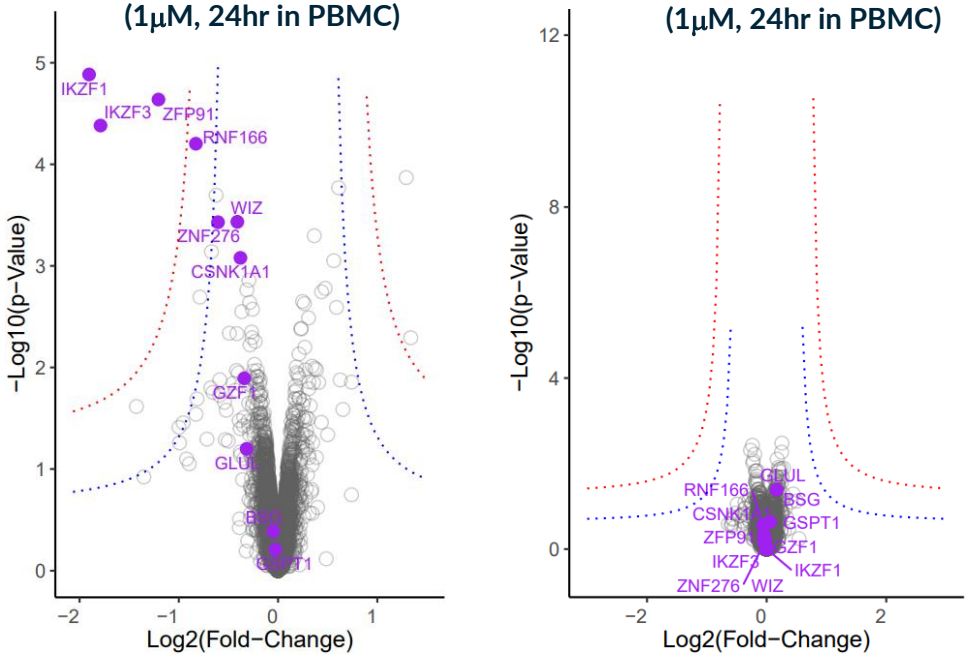
Compound-1 Demonstrates Improved Selectivity and Favorable ADME Properties



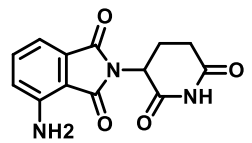
Pomalidomide
(1μM, 24hr in PBMC)

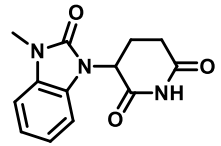


Cpd-1
(1μM, 24hr in PBMC)



IMiD substrates in purple



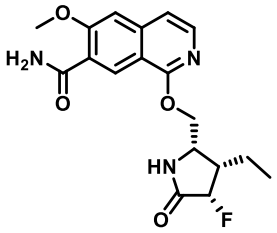


	Pomalidomide	Cpd-1
MW / cLogD / tPSA	273 / 0.65 / 110	259 / 0.93 / 73
CRBN HTRF IC_{50} (mM)	1.51	0.20
Papp (10^{-6} cm/s) / MDR1 Efflux ratio	30 / 0.9	19 / 1.3
Ikaros / Aiolos DC_{50} (mM)	0.17 / 0.01	>10 / >10
Rat PK:		
CL (mL/min/kg)	5.5	7.7
Vss (L/kg)	0.8	1.0
%F	109	126

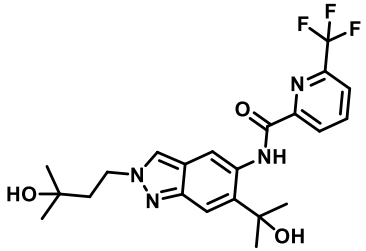
IV / PO dose (mg/kg)= 2 / 10

- Cpd-1 exhibits comparable physicochemical properties, in vitro and in vivo pharmacokinetics, improved affinity for CRBN and is devoid of any IMiD activity
- Ligand provides opportunities to explore multiple exit vectors; all of which are devoid of IMiD activity

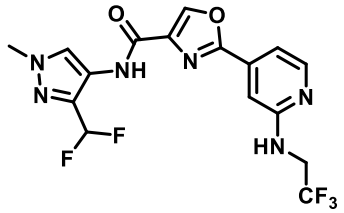
Achieving IRAK4 Degradation with Range of IRAK4 Binders and Vectors



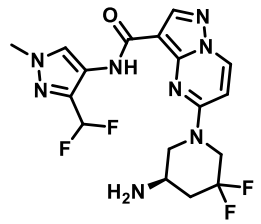
binder-1



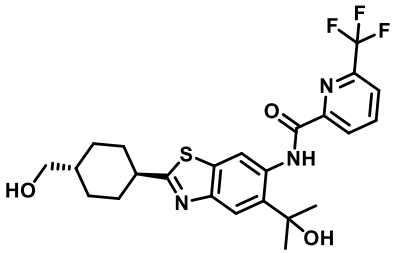
binder-2



binder-3



binder-4



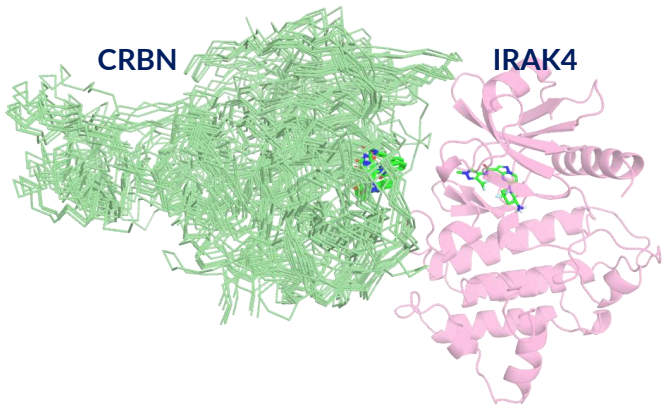
binder-5

	binder-1	binder-2	binder-3	binder-4	binder-5
MW	361	450	409	426	395
cLogD	1.05	3.30	1.47	-0.73	3.69
tPSA	104	100	104	106	75
IRAK4 K_d (nM)	0.05	0.31	0.04	0.03	0.81

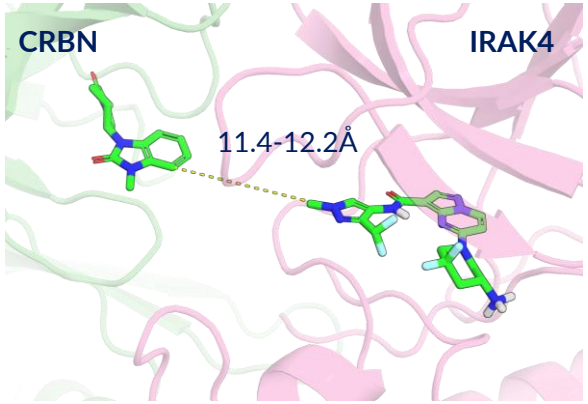
- Successfully degraded IRAK4 utilizing multiple different ligands and multiple different exit vectors

Initial Degrader Design Utilized Ternary Complex Modeling

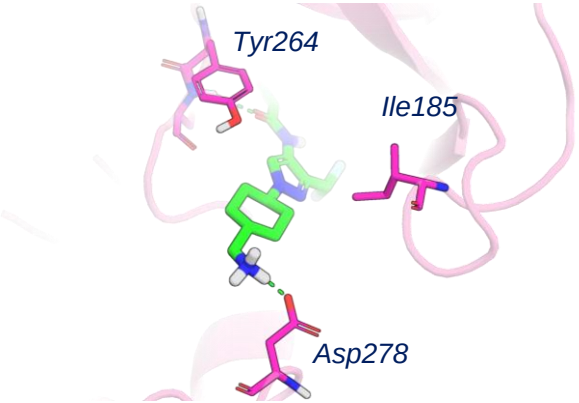
TCM identifies likely encounter complexes

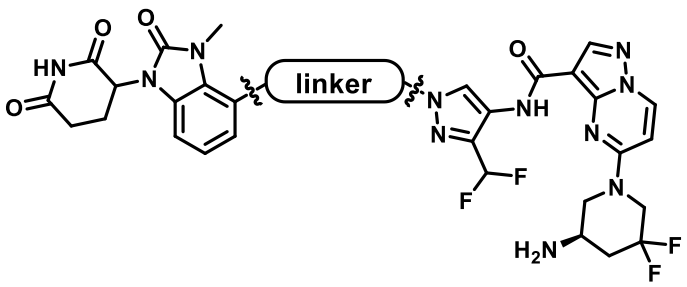


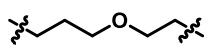
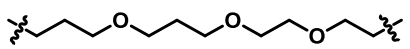
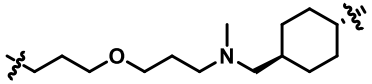
TCM ensemble suggests ideal linker distances to be 11.4-12.2A



Predicted model indicates Ile185 & Asp278 provide opportunity to improve affinity

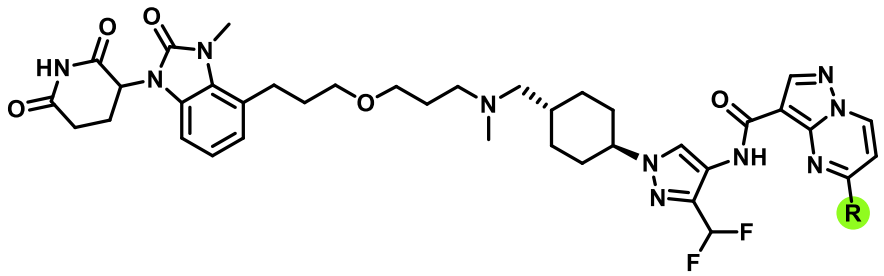


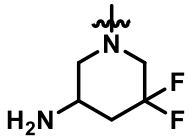
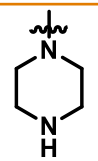
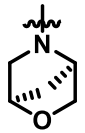
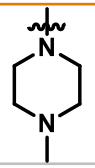


	Cpd-2	Cpd-3	Cpd-4
Linker			
IRAK4-IRAK4i AlphaLISA IC_{50} (nM)	13	19	0.5
AlphaLISA TCF (AUC)	0	1,015,700	1,063,052
IRAK4 DC_{50} (nM)	>10,000	72	7

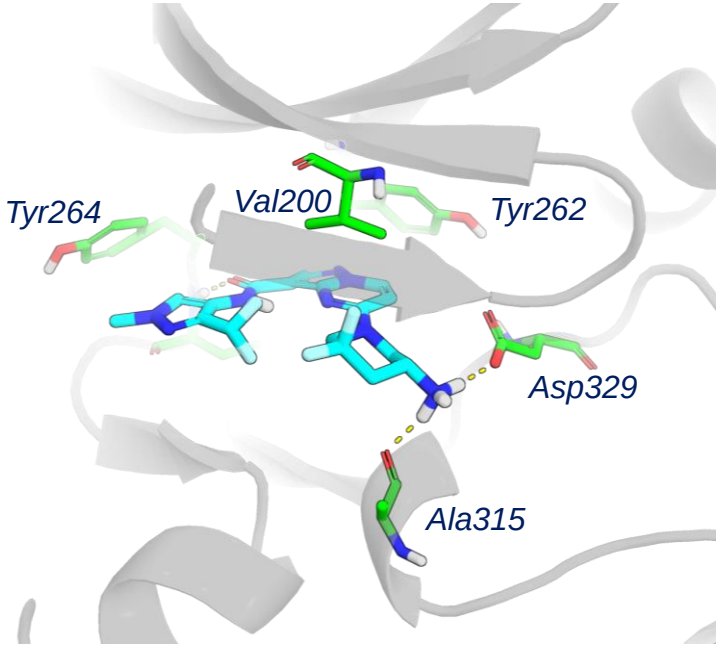
- Degradation data validated design hypotheses
- Incorporation a basic amine in linker to engage Asp278 and a cyclohexyl ring to engage Ile185

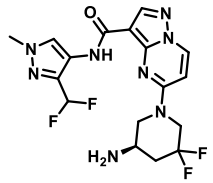
Modulating Permeability and Efflux via Optimization of the IRAK4 Binder



	Cpd-4	Cpd-5	Cpd-6	Cpd-7
R				
tPSA / # HBD	192 / 4	178 / 3	175 / 2	169 / 2
IRAK4-IRAK4i AlphaLISA IC_{50} (nM)	0.5	4.3	40	61
IRAK4 DC_{50} (nM)	7	18	9	>200
Papp (10^{-6} cm/s) / MDR1 Efflux Ratio	6.5 / 35	3.7 / 29	16 / 14	11 / 11
HLM / RLM (µL/min/mg)	497 / 196	46 / 20	267 / 40	104 / 43
Rat PK: CL (mL/min/kg) Vss (L/kg) %F	 124 47 0.0		 67 6.2 3.2	

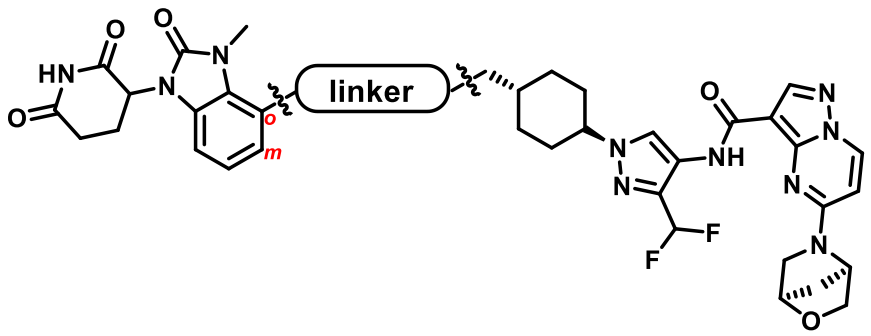
Cpd-4 IRAK4 binder -IRAK4 modeling

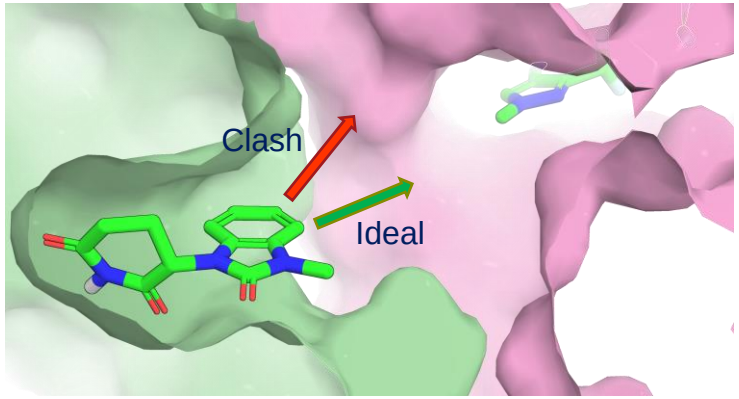




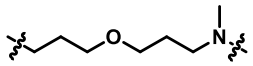
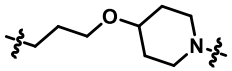
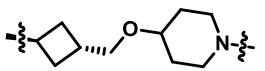
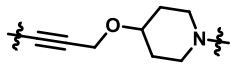
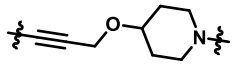
- Modifying the IRAK4 binder to improve properties
  - Removal of HBD leads to improved permeability and reduced efflux ratio

Identification of KT-474: Leveraging Linker Modifications



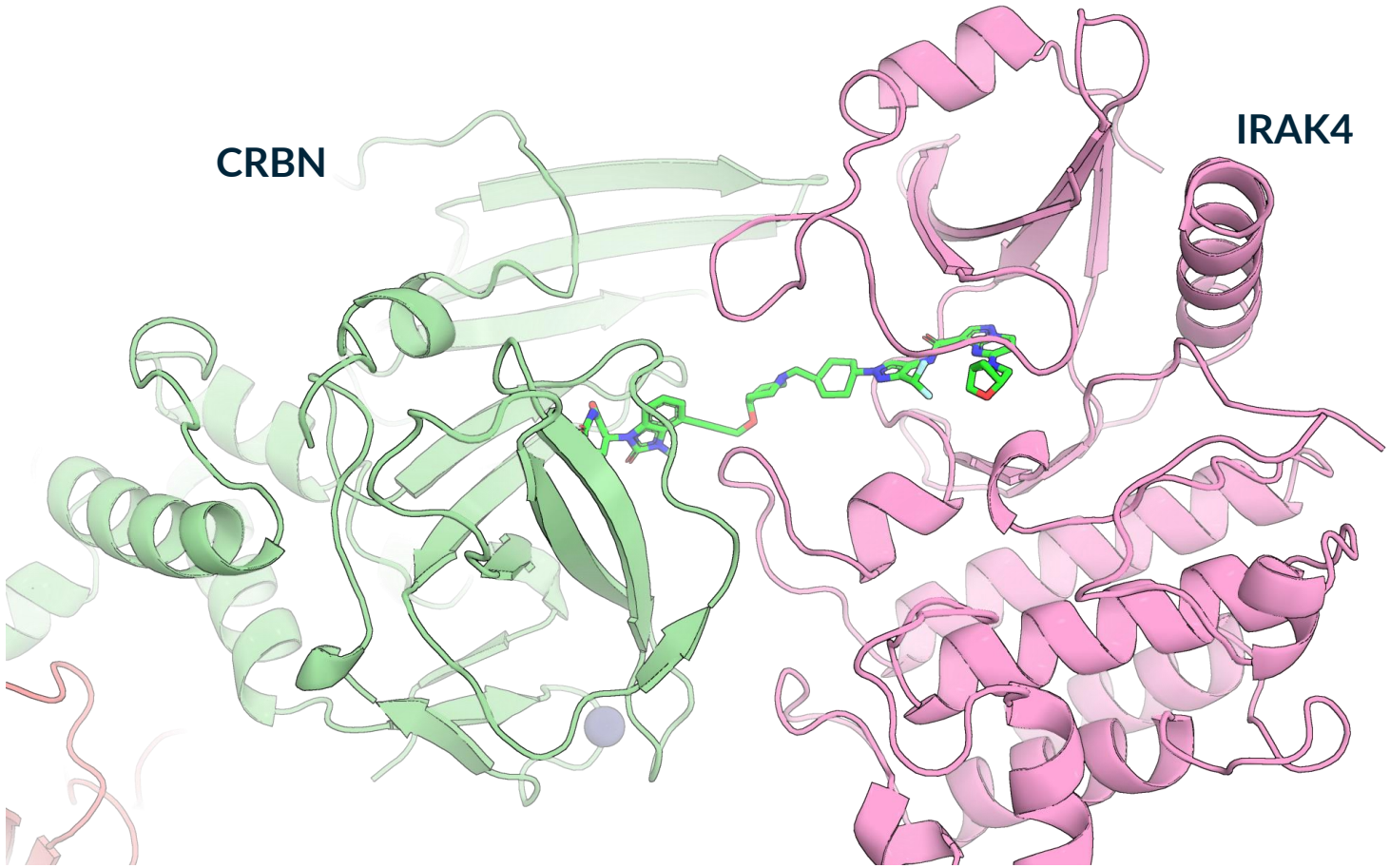


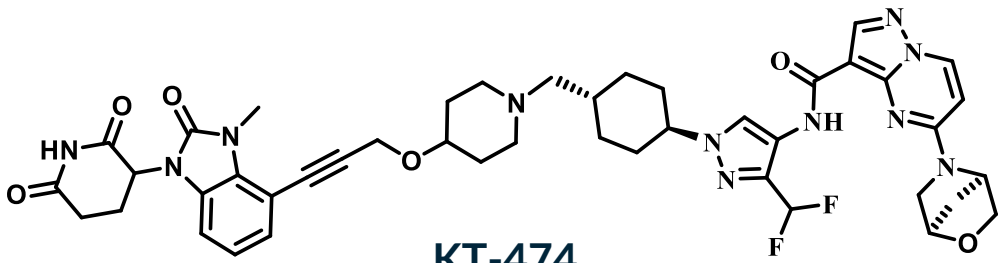
Representative IRAK4:CRBN TCM

	Cpd-6	Cpd-8	Cpd-9	KT-474	Cpd-10
Linker				 (*o*-position)	 (*m*-position)
IRAK4 DC_{50} (nM)	9	7	5	2	>200
Papp (10^{-6} cm/s) / MDR1 Efflux Ratio	16 / 14	6.4 / 8.0	3.9 / 9.5	8.1 / 2.8	9.2 / 3.2
HLM / RLM (µL/min/mg)	267 / 40	111 / 19	83 / 28	30 / 27	31 / 13
Rat PK: CL (mL/min/kg) / Vss (L/kg) / %F	67 / 6.2 / 3.2	20 / 4.8 / 4.1	22 / 5.5 / 2.8	61 / 10 / 15	NA

- Permeability & efflux are key drivers of bioavailability
- Linker rigidification leads to improved intrinsic clearance & efflux issue

IRAK4:KT-474:CRBN/DDB1 Ternary Complex





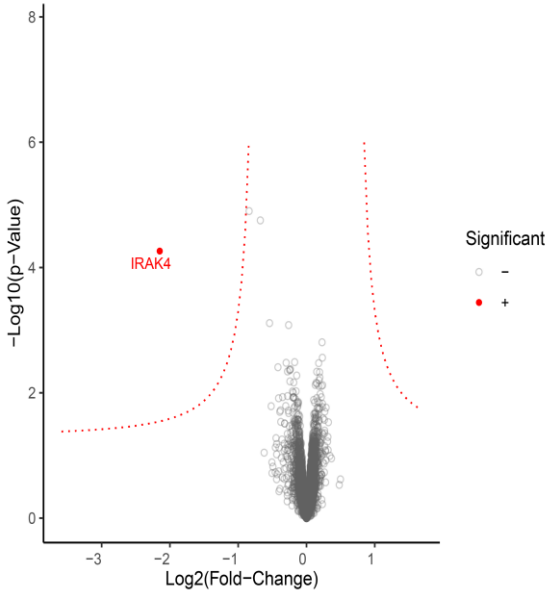
KT-474

- First reported heterobifunctional Cryo-EM ternary complex structure
- IRAK4:KT-474:CRBN/DDB1 ternary complex confirms the design hypotheses
- Structure significantly enabled optimization

KT-474: A Potent and Specific IRAK4 Degrader is Superior to Kinase Inhibitor in Both In Vitro & Vivo Models

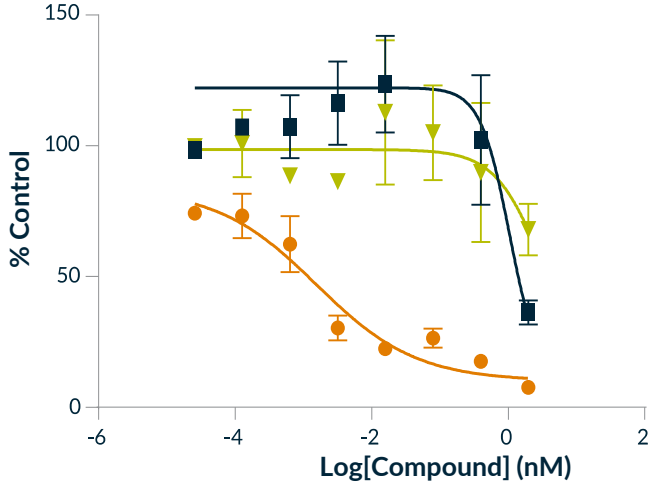
Degradation and Selectivity

Human PBMCs @ 300 nM (10x DC_{90})



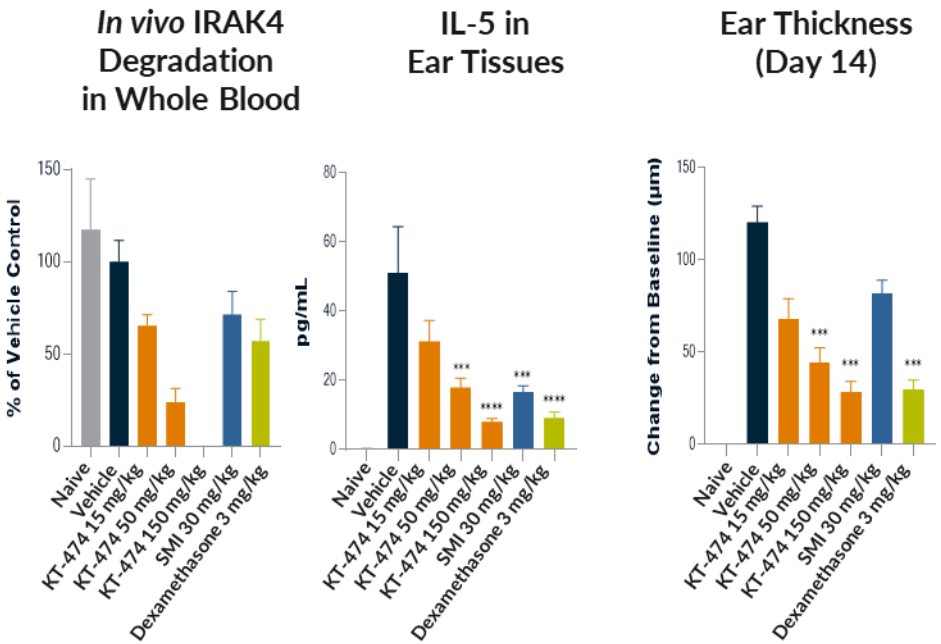
Superiority Over SM kinase Inhibitor

LPS + IL-1β → IL-6 in human PBMC



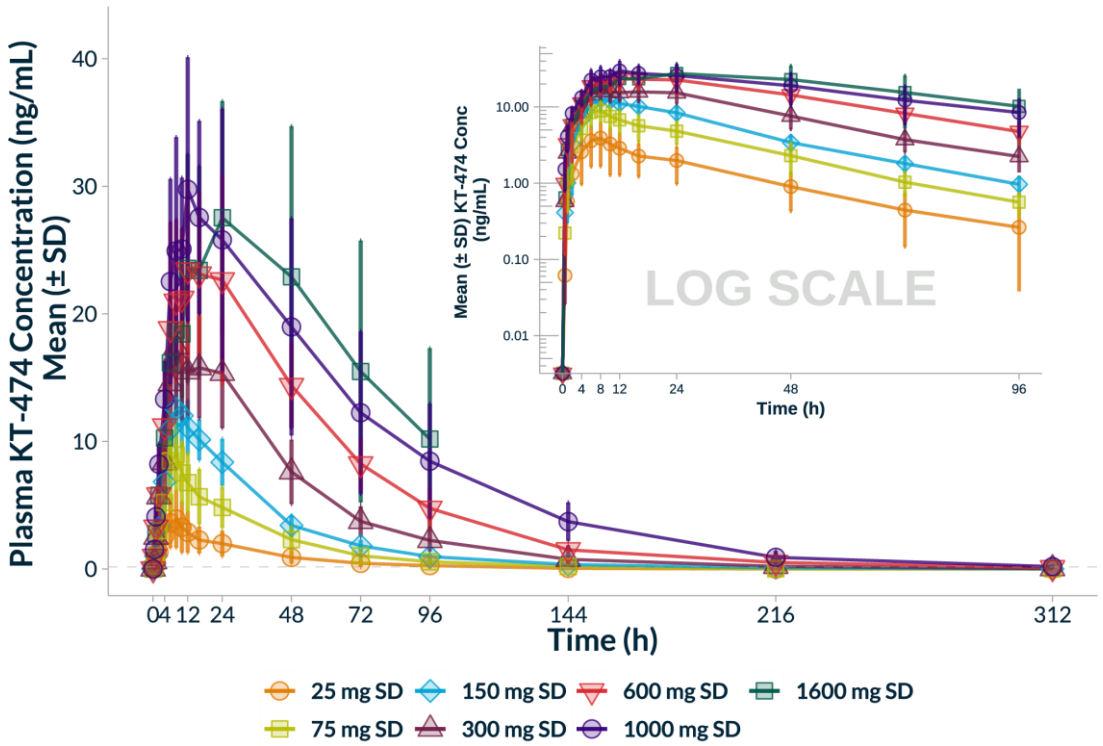
Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

rmIL-33 Intradermal Challenge Model



- DC_{50} = 2.1 nM (DC_{90} = 30 nM) in human immune cells
- Highly selective degradation of IRAK4 across the proteome (>10,000 proteins) @ 10x IRAK4 DC_{90}
- More efficacious than IRAK4 small molecule inhibitor (SMI)
- KT-474 induced knockdown of ≥85% IRAK4 in whole blood achieved superior anti-inflammatory effect relative to IRAK4 SMI

KT-474 Single Ascending Dose: Favorable PK



SAD #	Dose	Cmax (ng/mL)	t_{max} (h)	AUC (ng.h/mL)	$t_{1/2}$ (h)
1	25 mg	3.49 (61.2)	8.0 (6.0-8.0)	112 (65.4)	25.2 (27.0)
2	75 mg	9.08 (36.6)	7.0 (6.0-8.0)	288 (36.7)	28.7 (10.1)
3	150 mg	12.7 (25.7)	9.0 (8.0 - 10.0)	483 (21.9)	31.6 (22.1)
4	300 mg	17.4 (29.6)	8.0 (8.0 – 24.0)	869 (31.4)	36.4 (13.1)
5	600 mg	24.2 (27.5)	12.0 (6.00 – 24.0)	1530 (18.6)	40.9 (18.2)
6	1000 mg	27.8 (34.4)	20.0 (6.0 – 24.0)	1890 (60.8)	38.8 (7.0)
7	1600 mg	27.3 (36.2)	24.0 (12.0 – 48.0)	1920 (43.0)	36.4 (46.9)

Geometric Mean (%CV) reported for all parameters, except t_{max} where median (range) are presented

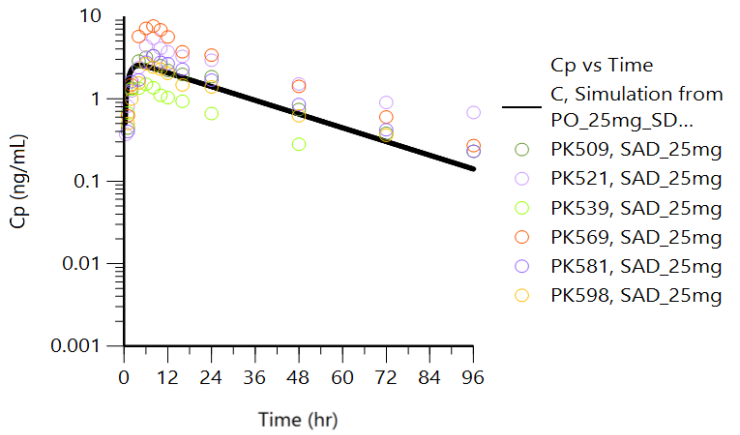
- Consistent PK after single dosing: C_{max} achieved between 7-24 hours, half-life = 25-40 hours
- Dose dependent exposure increases, plateauing after the 1000 mg dose
- Low to moderate inter-subject variability in exposure

KT-474: Preclinical Pharmacokinetics Predictive of Human PK

Parameter	Rat	Dog	Monkey
Plasma CL (mL/min/kg)	60.7	25.5	34.5
Plasma V_{ss} (L/kg)	13.6	10.6	11.1
Oral Bioavailability (%)	12.1	34.8	13.1
IV MRT_{inf} (hrs)	3.64	7.20	5.36
PO MRT_{inf} (hrs)	4.65	8.88	NC
Plasma Protein Binding ($f_{u,p}$)	0.0511	0.0409	0.0325
Blood:plasma ($K_{blood}/_{plasma}$)	1.33	1.19	1.86

NC: not calculable due to poor terminal phase curve fit for in vivo PK data

Overlay of **Predicted** and Observed PK profiles of KT-474 in human at 25 mg PO

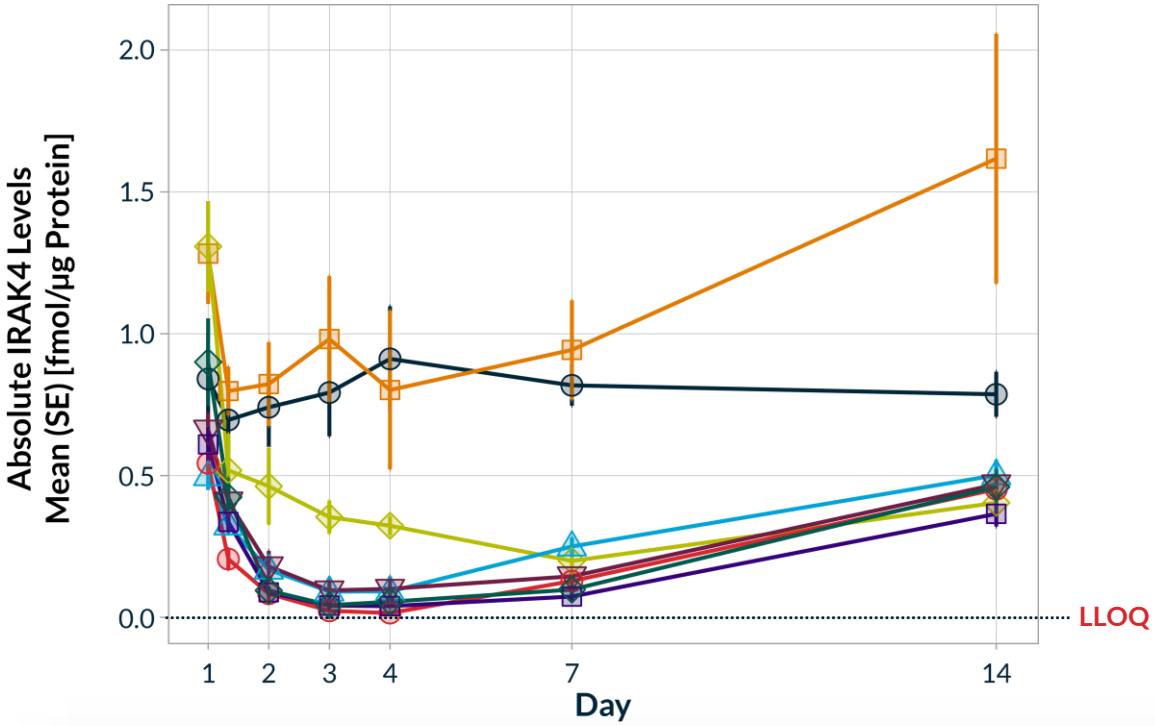


- KT-474 is orally bioavailable in rats, dogs, and monkeys
- The predicted KT-474 human PK parameters (AUC, C_{max}, T_{max}, $T_{1/2}$) were within 2-fold of the observed data

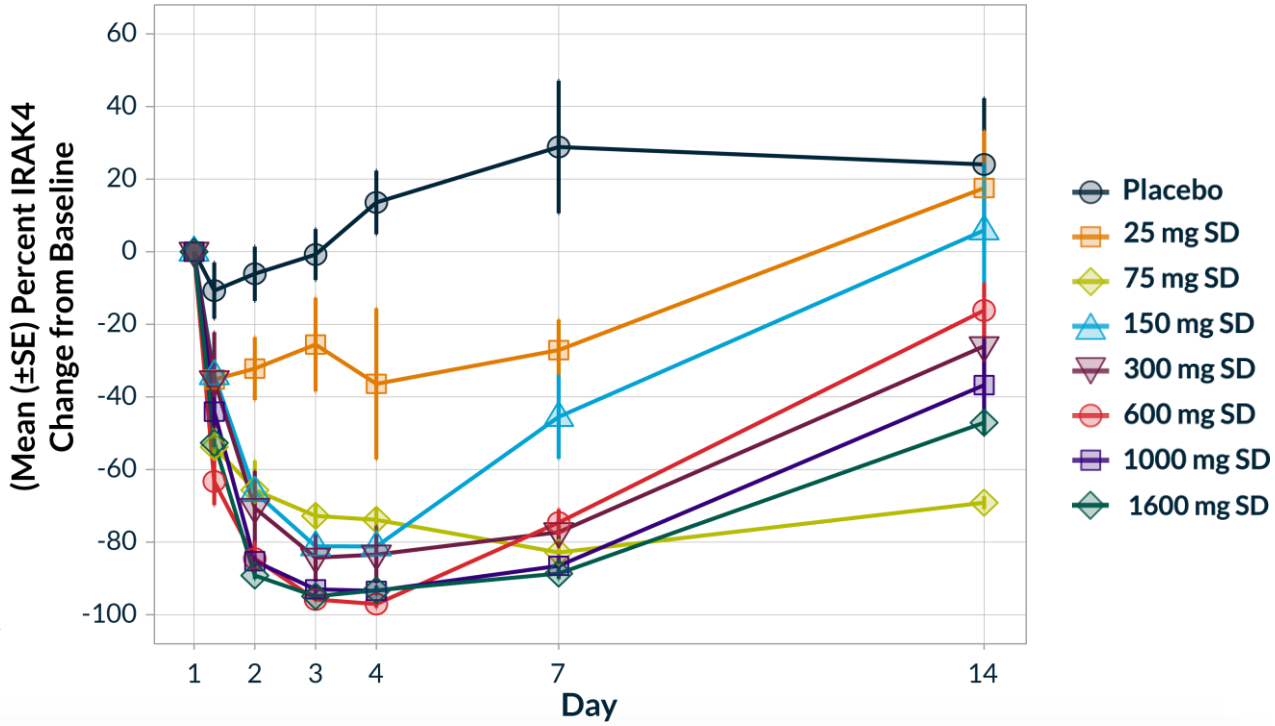
KT-474 25 mg, PO	Projected	Observed
C_{max} (ng/mL)	2.5	3.5
T_{max} (hr)	4.1	7.3
AUC∞ (ng/mL*hr)	91	112
$T_{1/2}$ (hr)	22	25

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

Absolute IRAK4 Levels

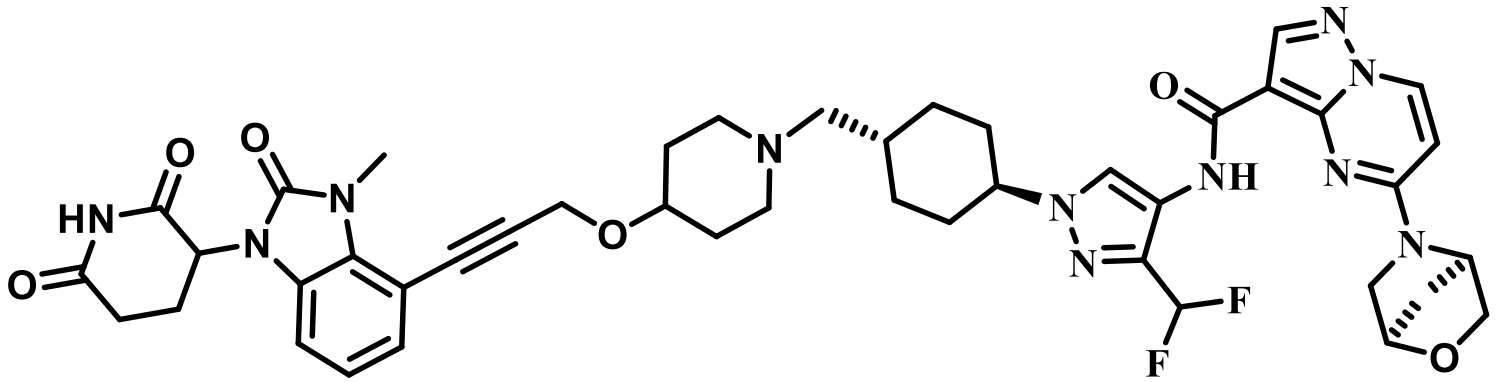


Mean % Reduction of IRAK4



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

Discovery of KT-474: Innovation in the TPD Space



- Modeling guided design led to the discovery of novel CRBN binder devoid of IMiD biology
- Leveraged ternary complex modelling to expedite the advancement of the IRAK4 project
- KT-474 is a highly potent, selective and orally bioavailable IRAK4 degrader and represents the first heterobifunctional degrader evaluated in a non-oncology indication and dosed to healthy human volunteers
- KT-474 (SAR444656): Preliminary clinical activity seen in HS and AD patients in Ph1 and plan for separate pbo-controlled Ph2 trials in HS and AD to start Q4 2023

KYMERA

Thank you
Q&A

This work was completed under collaboration agreement with Sanofi.