Discovery and characterization of IRAKIMiDs: degraders targeting both IRAK4 and IMiD substrates for oncology indications.

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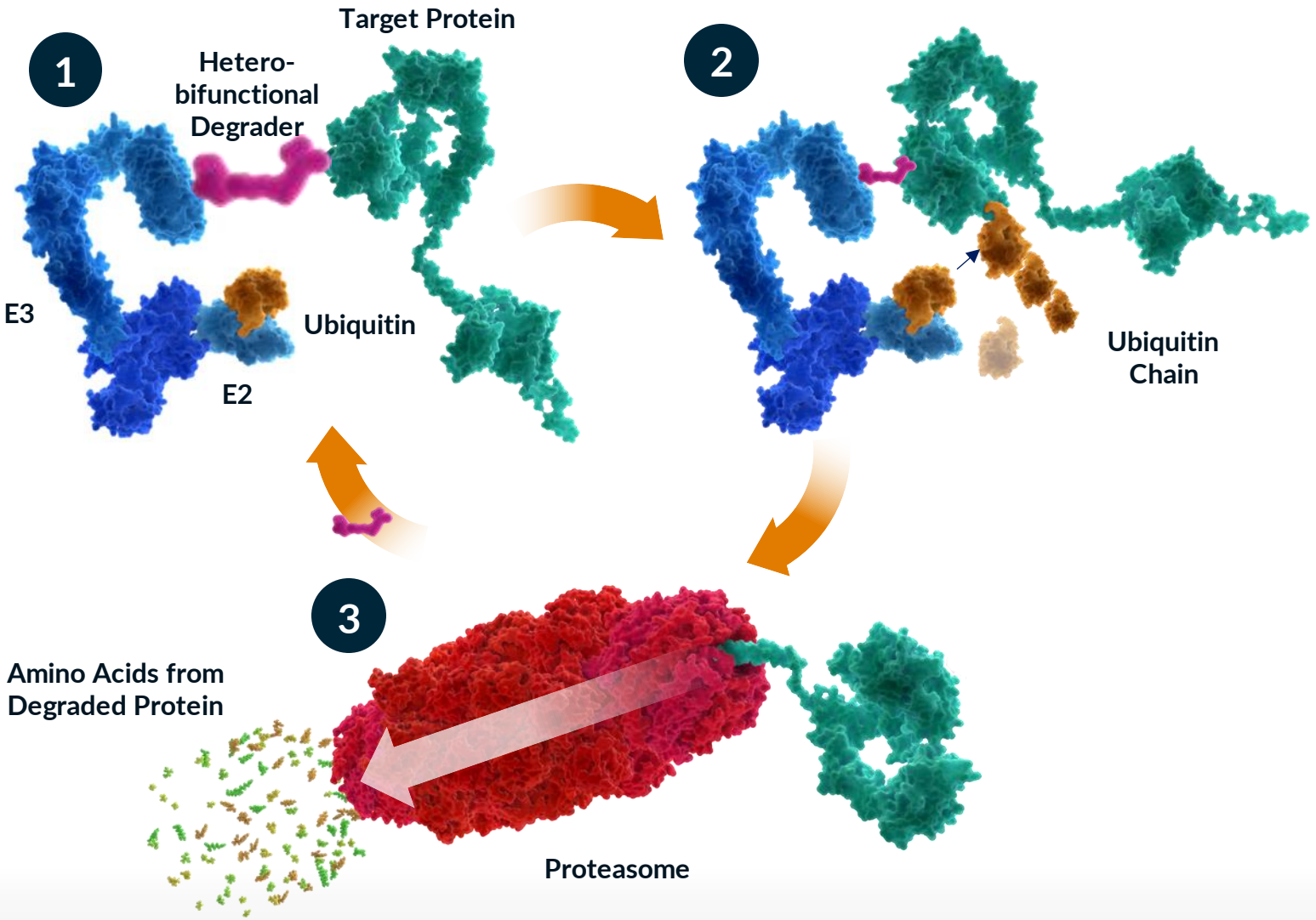
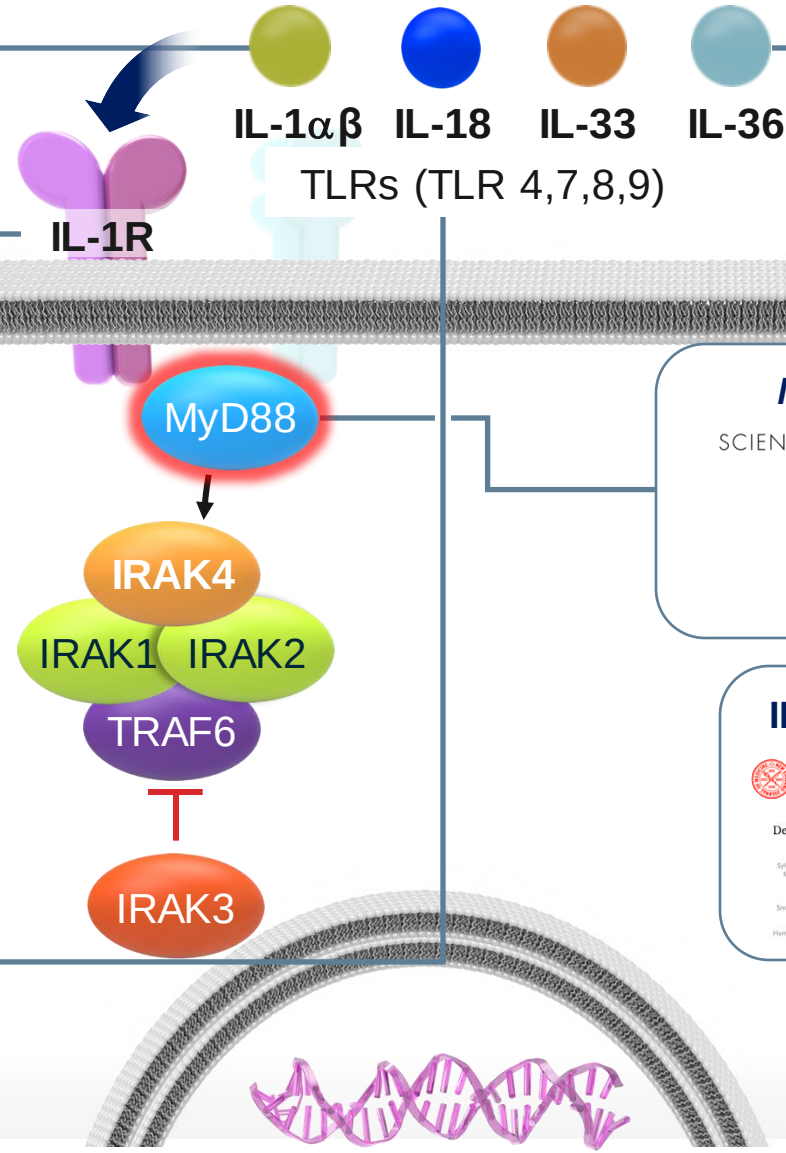
Biology of Targeted Protein Degradation (TPD)



Targeted Protein Degradation

- ONLY binding site required
- Ternary complex-based selectivity
- Sub-stoichiometric, catalytic
- Protein re-synthesis rate limited

Building a Franchise Around IRAK4 Degradation
Clinical and Genetic Validation for Oncologic and Inflammatory Conditions



IL1-Rα/IL-1β: Rheumatologic Diseases

Annals of the Rheumatic Diseases

REPORT

Effects of anakinra on clinical and radiological outcomes in rheumatoid arthritis

B Bresnihan

IL-1β: CANTOS Data

The NEW ENGLAND JOURNAL of MEDICINE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

THE LANCET

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Atherosclerosis *Lung Cancer*

IL-18: Macrophage Activation Syndrome

The Journal of Allergy and Clinical Immunology

Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition

Scott W. Canna, MD[1], Charlotte Girard, MD[2], Louise Malle, BS[3], Adriana de Jesus, MD, PhD[3], Neil Romberg, MD[4], Judith Kelsen, MD[4], Lea F. Surrey, MD[4], Pierre Russo, MD[4], Andrew Sleight, PhD[5], Eduardo Schiffrin, MD[5], Cem Gabay, MD[2], Raphaela Goldbach-Mansky, MD, MHS[3], and Edward M. Behrens, MD[4]

VOLUME 139, NUMBER 5

MYD88 Mutations: Heme Onc

SCIENTIFIC REPORTS

OPEN

Clinicopathologic significance of *MYD88* L265P mutation in diffuse large B-cell lymphoma: a meta-analysis

Ju-Han Lee, Hoiseon Jeong, Jung-Woo Choi, HwaEun Oh & Young-Sik Kim

IL-36: Generalized Pustular Psoriasis

The NEW ENGLAND JOURNAL of MEDICINE

Interleukin-36–Receptor Antagonist Deficiency and Generalized Pustular Psoriasis

The Journal of Allergy and Clinical Immunology

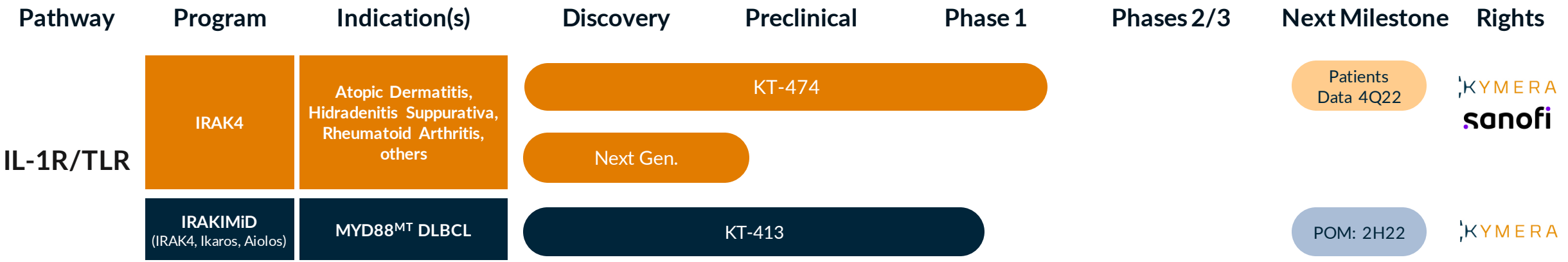
IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis

Andrew Johnston, PhD,* Xianying Xing, PhD,* Liza Wolterink, BS,* Drew H. Barnes, BS,* ZhiQiang Yin, MD, PhD,*,† Laura Reingold, BS,* J. Michelle Kahlenberg, MD, PhD,‡ Paul W. Harms, MD, PhD,*,† and Johann E. Gudjonsson, MD, PhD*

Ann Arbor, Mich, and Nanjing, China

VOLUME 140, NUMBER 1

Building a Franchise Around IRAK4 Degradation: Heterobifunctional Degraders KT-474 and KT-413



KT-474
Highly selective IRAK4 degrader

- First proof-of-mechanism for TPD in a randomized, placebo-controlled healthy volunteer study
- Demonstrated >95% IRAK4 degradation in humans

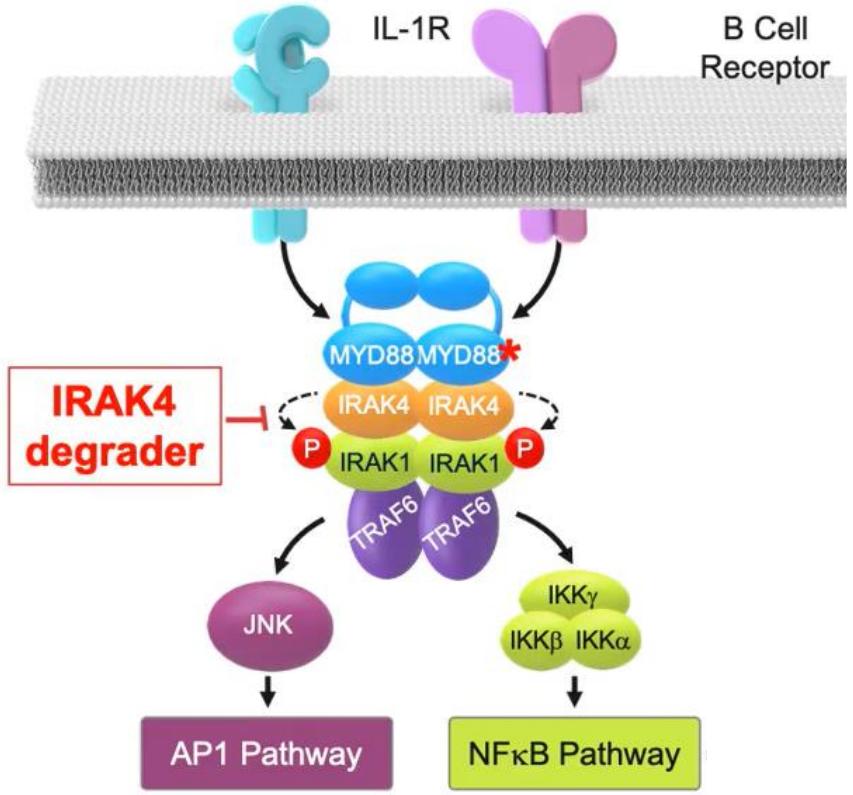
KT-413
Targets Degradation of IRAK4 and IMiD substrates

- Phase 1 clinical trial in R/R B cell lymphomas ongoing

(structures of KT-474 or KT-413 will not be disclosed in this presentation)

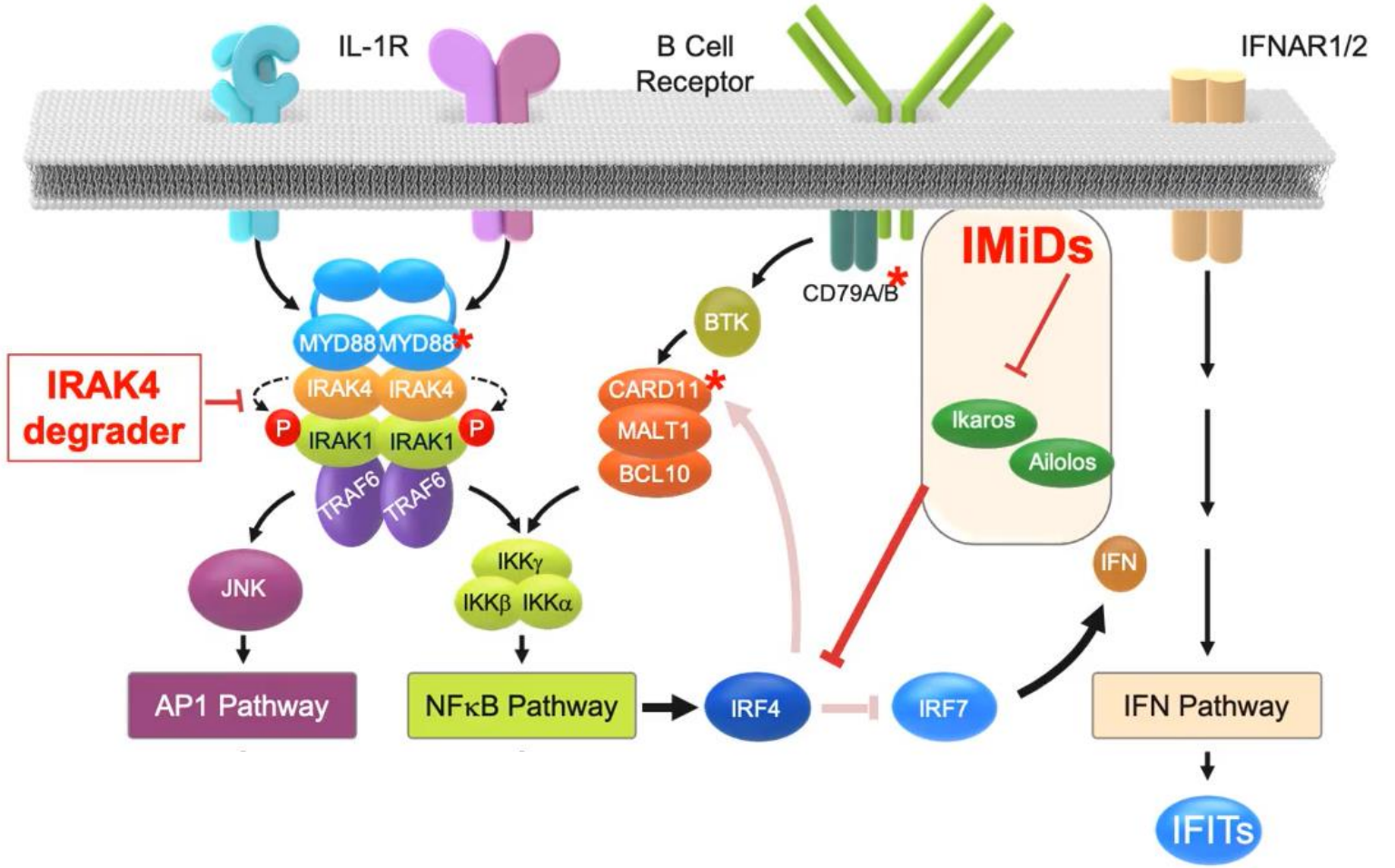
Degradation of IRAK4: Modulating Proinflammatory Cytokines and Cellular Proliferation

- IRAK4 is a key component of the myddosome and its function is dependent on both its kinase activity and on its scaffolding properties
- Activation of downstream pathways drive the scaffolding function of IRAK4 and are key drivers of cellular proliferation and proinflammatory cytokine and chemokine production



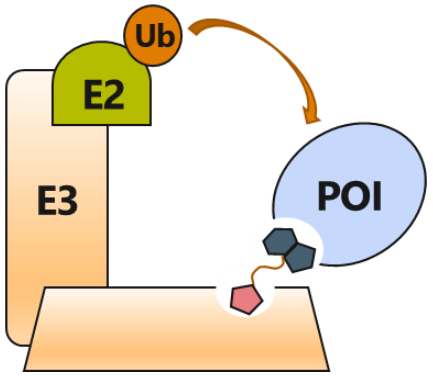
Degradation of IRAK4 and IMiD Substrates: Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

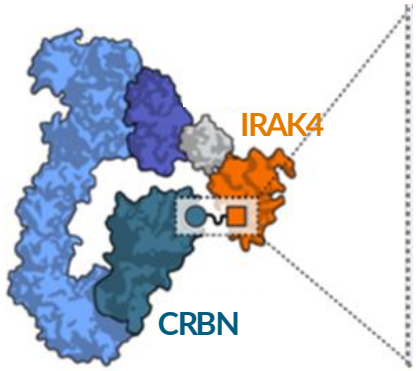
- MYD88 L265P is a gain-of-function driver mutation which results in constitutive activation of the anti-apoptotic NFkB signaling pathway
- Single-agent therapies that target activated NFκB signaling in DLBCL show limited activity in preclinical or clinical settings
- Redundant NFκB pathway activation and downregulation of Type 1 IFN is common in MYD88^{MT} lymphoma, supporting need to seek combination therapies
- Targeting simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models, supporting this targeted combination



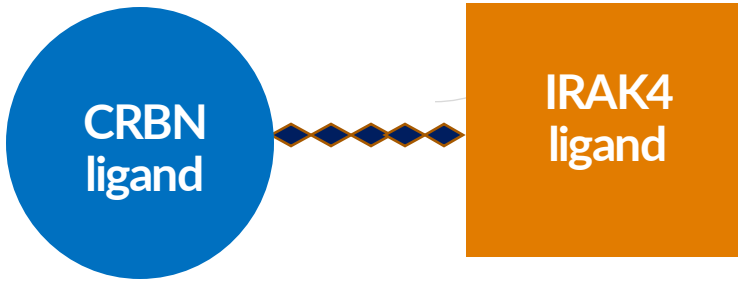
IRAKIMiD:
Functioning as a Heterobifunctional Degrader & a Molecular Glue

Heterobifunctional Degrader

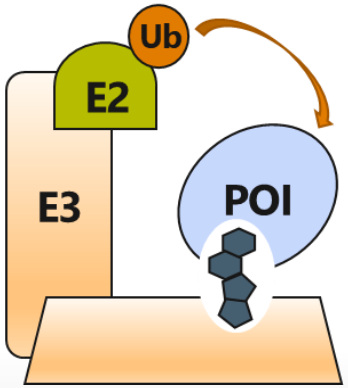


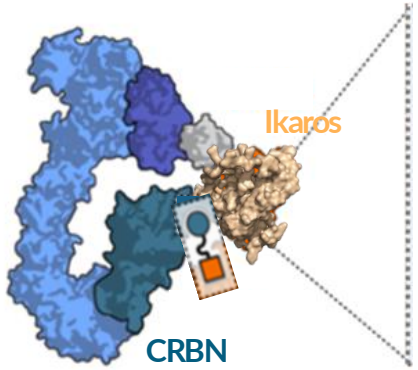


Degradation of IRAK4



Molecular Glue



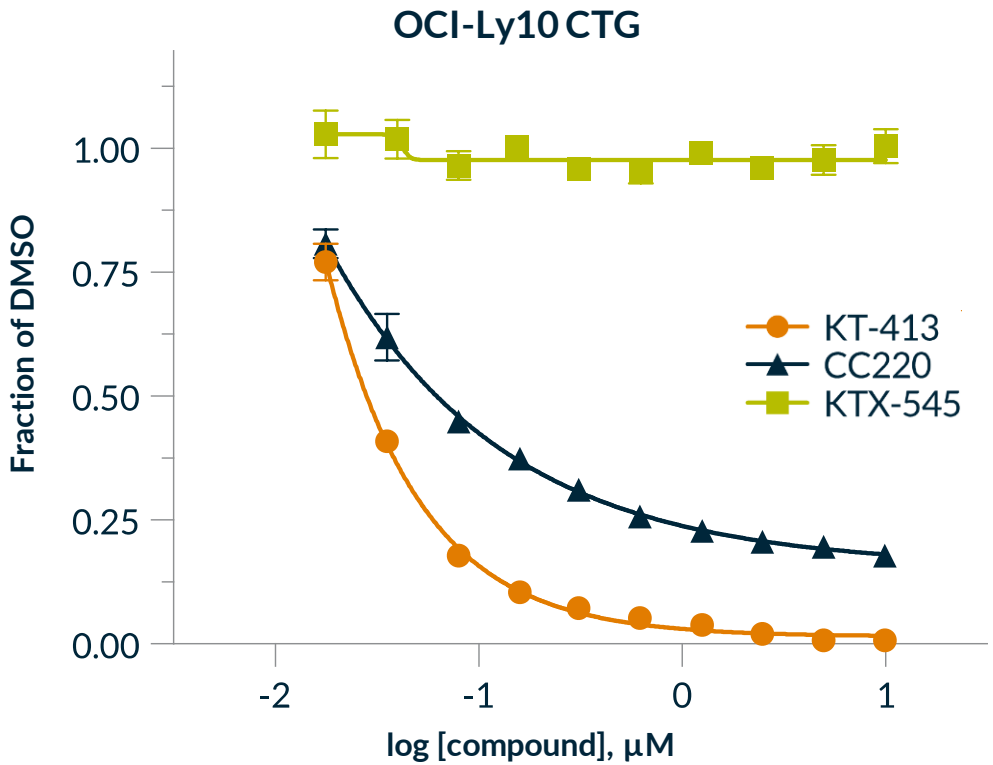


Degradation of IMiD substrates
(i.e., Ikaros and Aiolos)

Differential Biology of Selective IRAK4 Degraders and IRAKIMiDs

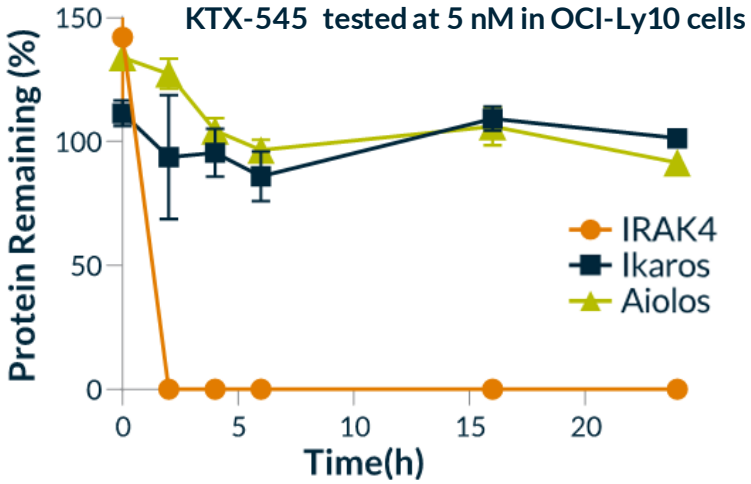
- OCI-Ly10: DLBCL line expresses most prevalent mutation found in MYD88 (L265P)
- Selective IRAK4 degrader (e.g., KTX-545) exhibits no anti-proliferative effect on OCI-Ly10 cells
- Dual degrader of IRAK4 and IMiD substrates Ikaros and Aiolos (e.g. KT-413) shows robust cell killing of OCI-Ly10
- IRAKIMiDs can show strong and broad activity across a number of MYD88 mutant lines

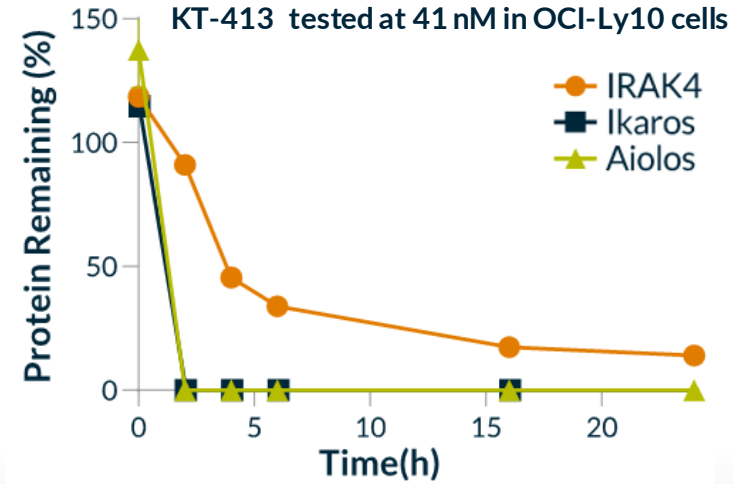
	KTX-545	KT-413
	Selective IRAK4 Degrader	IRAKIMiD Degrader
IRAK4 DC_{50} (OCI-Ly10; nM)	**1**	**6**
Ikaros DC_{50} (OCI-Ly10; nM)	**>1,000**	**2**
Aiolos DC_{50} (OCI-Ly10; nM)	**>1,000**	**2**
OCI-Ly10 CTG IC_{50} (nM)	**>10,000**	**9**



Differential Biology of Selective IRAK4 Degraders and IRAKIMiDs

	KTX-545	KT-413
	Selective IRAK4 Degrader	IRAKIMiD Degrader
IRAK4 DC_{50} (nM)	**1**	**6**
Ikaros DC_{50} (nM)	**>1,000**	**2**
Aiolos DC_{50} (nM)	**>1,000**	**2**





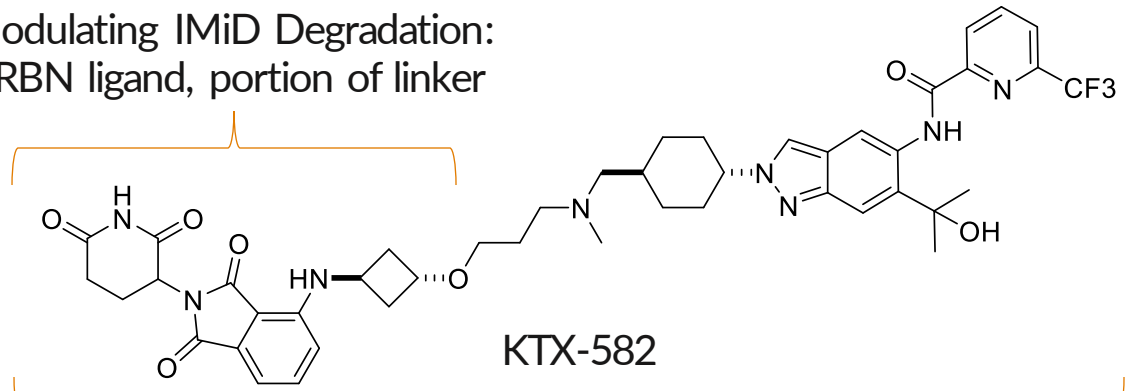
- Selective IRAK4 degrader KTX-545 exhibits no effect on levels of Ikaros or Aiolos
- IRAKIMiD KT-413 induces strong degradation of IRAK4, Ikaros and Aiolos
- Degradation of proteins by KT-413 is hierarchical, with IRAK4 degradation being slower than that of either Ikaros or Aiolos

Identification and Optimization of IRAKIMiDs: Multi-Parameter Optimization

- Challenges associated with IRAKIMiDs:
  - Independent SAR for the degradation of IRAK4 *and* IMiD substrates
  - Optimization of the physicochemical properties and pharmacokinetics in space beyond the rule of 5 (bRo5)
  - Developing and using appropriate assays is critical
- Embracing the linker is critical to identifying heterobifunctional degraders with high levels of potency, selectivity and drug-like properties.

Modulating IRAK4 Degradation:
CRBN Ligand, Linker, IRAK4 Ligand

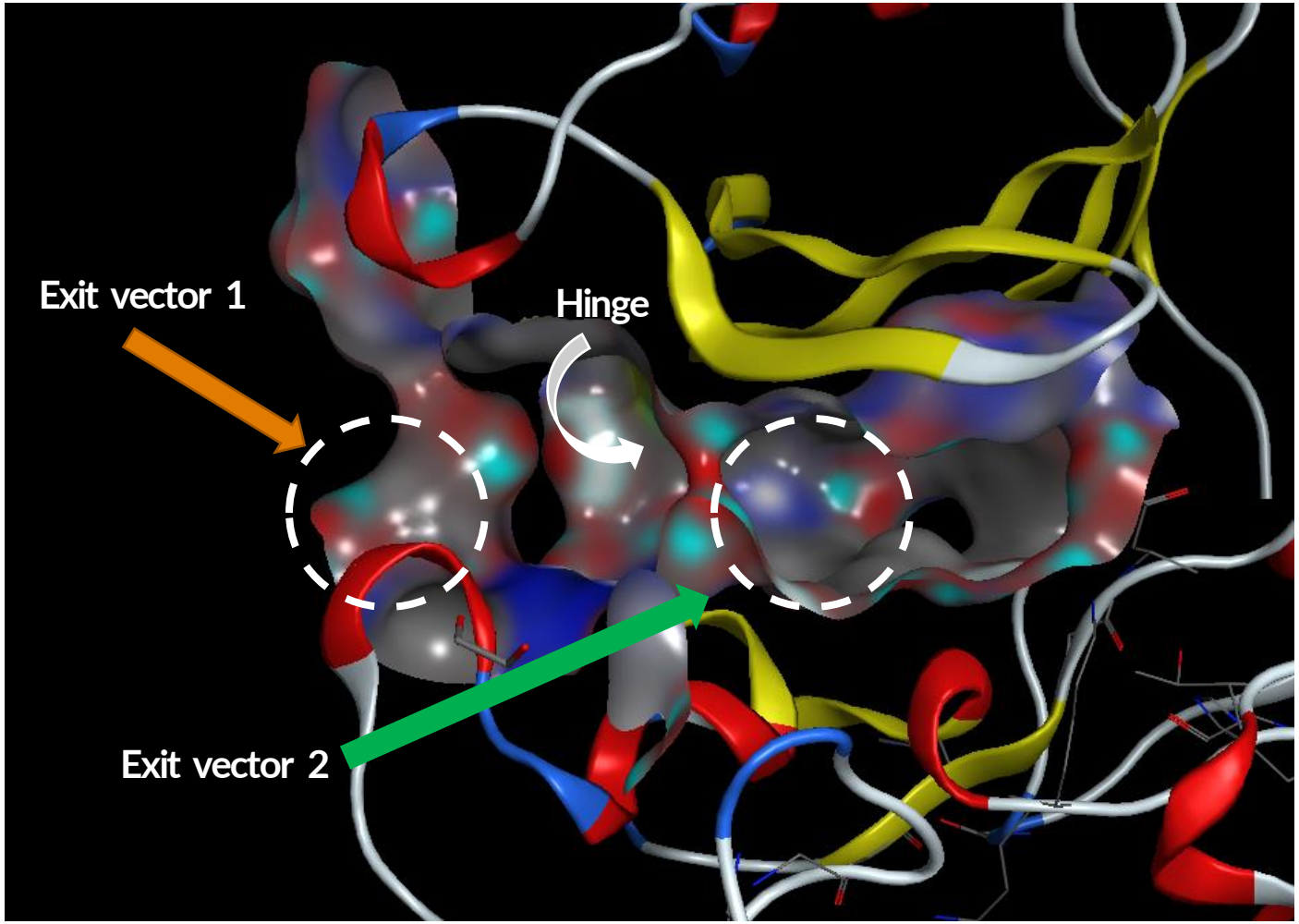
Modulating IMiD Degradation:
CRBN ligand, portion of linker



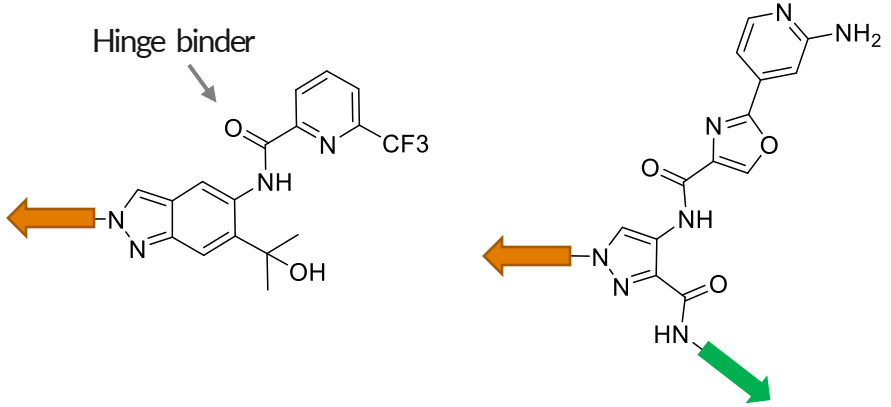
KTX-582

Modulating Pharmacokinetics and Safety:
CRBN Ligand, Linker, IRAK4 Ligand

Identifying Scaffolds and Vectors for Linker Attachment: IRAK4 Degradation Achieved with Multiple Scaffolds and Vectors



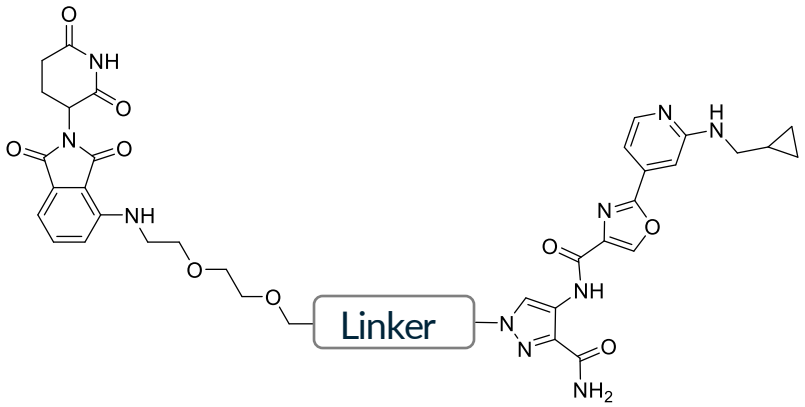
Subset of IRAK4 Ligands Capable of Inducing Degradation of IRAK4

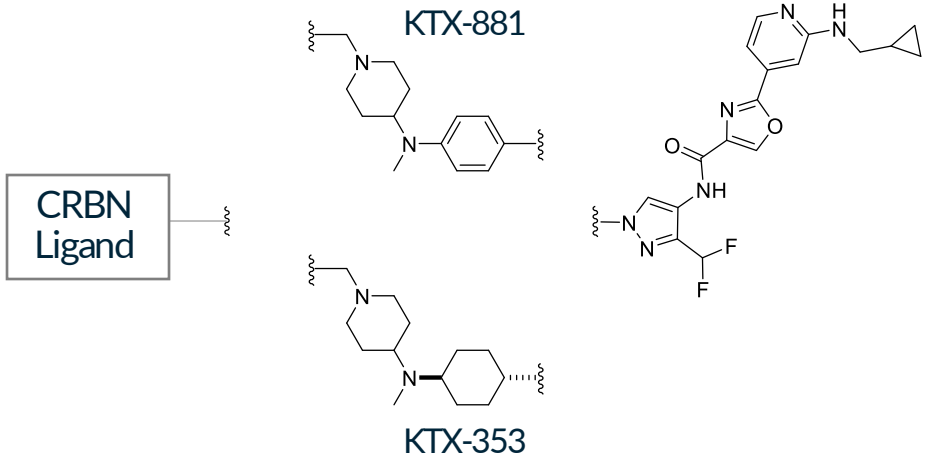


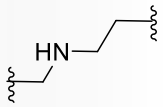
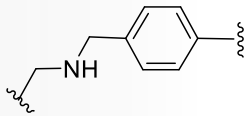
Demonstrated the ability to induce degradation of IRAK4 using multiple vectors off of multiple different scaffolds

Improving Degradation Efficiency and Selectivity

- Incorporation of a functional handles to control the directionality of the vector from POI can significantly increase the efficiency of POI degradation



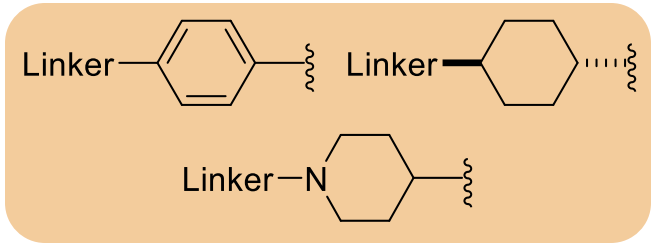


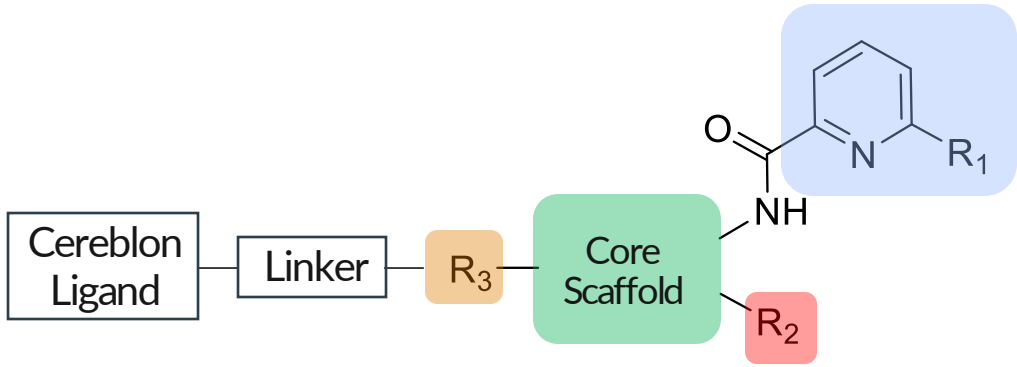
	KTX-671	KTX-315
Linker		
IRAK4 DC_{50} (nM)	**>1,000**	**22**

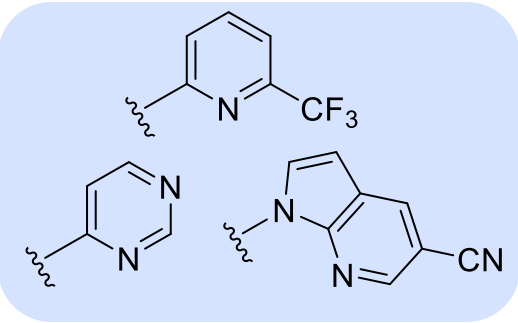
	KTX-881	KTX-353
IRAK4 DC_{50} (nM)	**23**	**6**

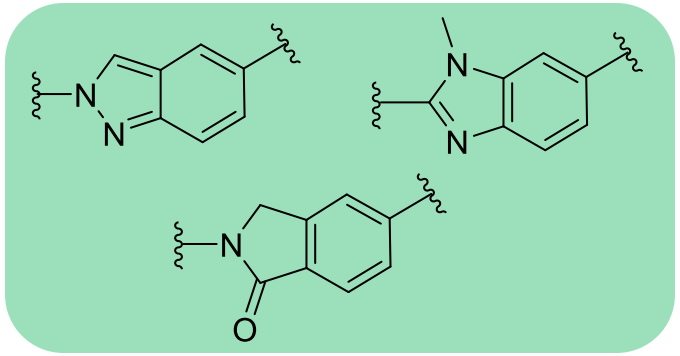
Optimizing IRAKIMiDs: Representative Motifs Explored

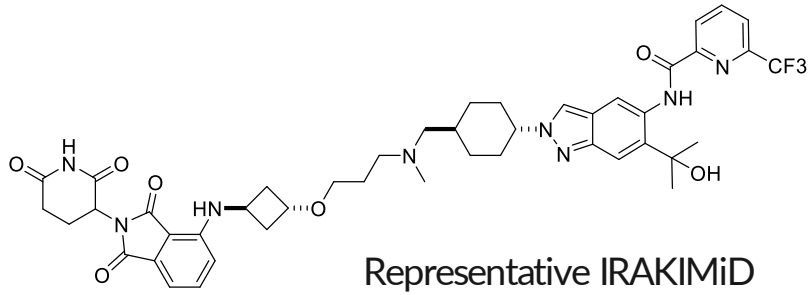
- Extensive exploration of the IRAK ligand and linker required to accommodate SAR associated with both IRAK and IMiD degradation
- Indazole scaffold chosen due to kinome selectivity, modularity and ability to easily modulate properties



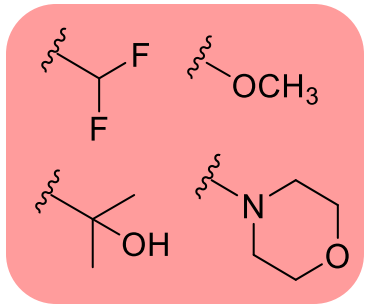








Representative IRAKIMiD



Embracing the Linker: Modulating Potency, Selectivity and Physicochemical Properties

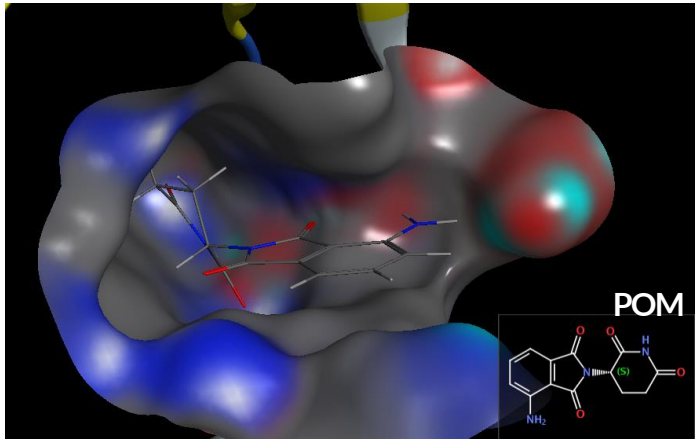
- **Linker can serve as a handle to modulate every aspect of a heterobifunctional degrader**

- **Some of the lessons we have learned around linker design**

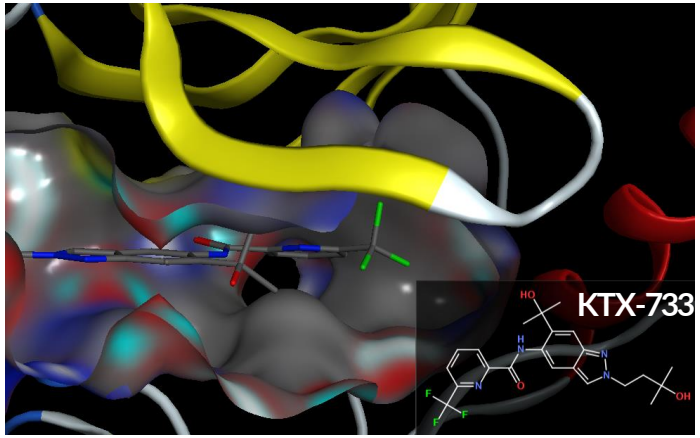
  - **Potency and Selectivity**
    - Linker modulation can significantly impact degradation efficiency and selectivity
    - Leverage ternary complex modelling to inform design
    - Subtle modifications in both POI ligand and linker can have a drastic impact on degradation efficiency

  - **Pharmacokinetics and oral absorption**
    - Amide generally has a negative impact on oral absorption
    - Modulating the composition of the linker can be leveraged to significantly impact all pharmacokinetic parameters

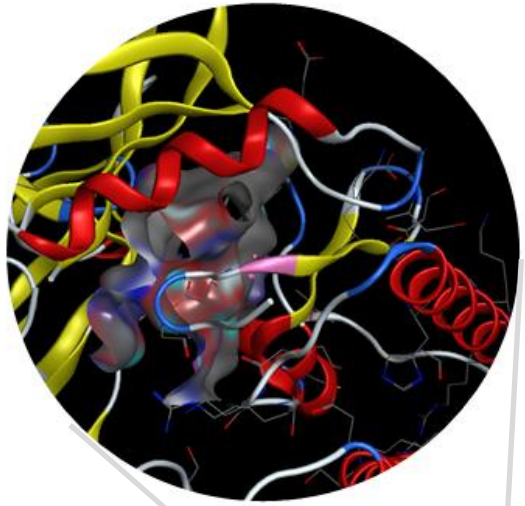
Building and Leveraging a Ternary Complex Model: Enabling a Rational Degrader Design Strategy



Co-crystal POM (CRBN-DDB1)

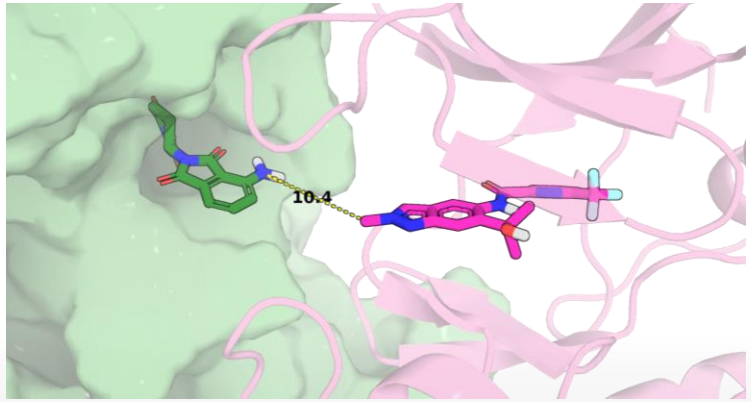


Co-crystal KTX-733 and IRAK4

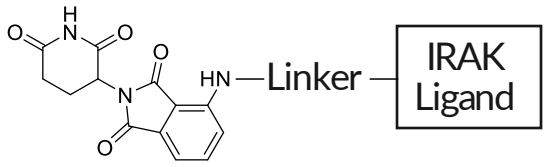


Ternary complex model to enable rationale linker design

Early SAR informs design of ternary complex model

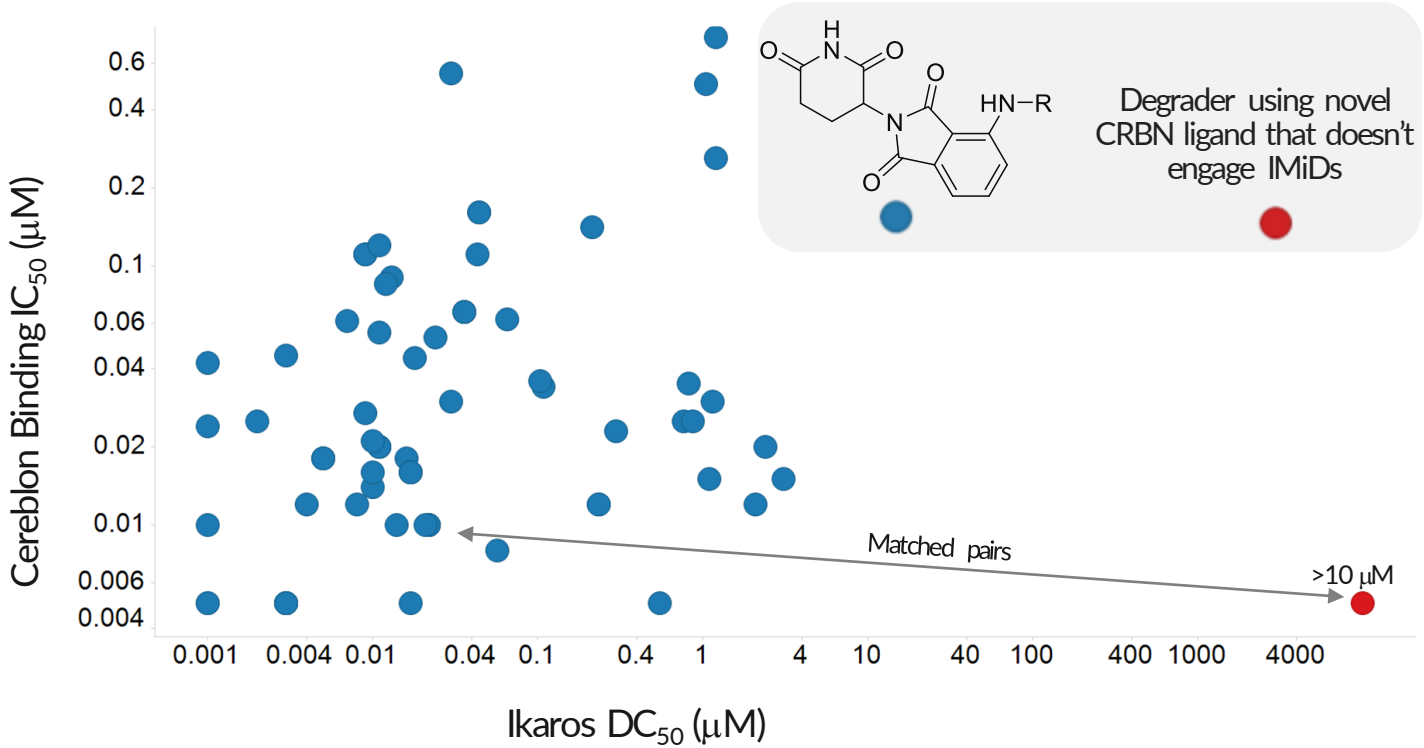


Affinity of Ligands Doesn't Always Correlate with Degradation Efficiency



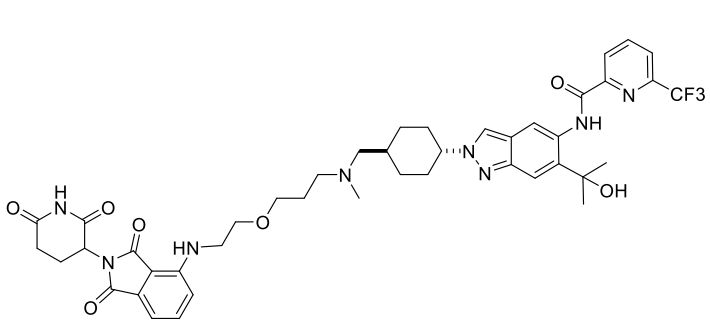
	KTX-326	KTX-951	KTX-178
IRAK Ligand	**Ligand A**	**Ligand B**	**Ligand C**
IRAK4 Kd (nM)	**0.3**	**3.5**	**28**
IRAK4 DC_{50} (nM)	**8**	**18**	**15**

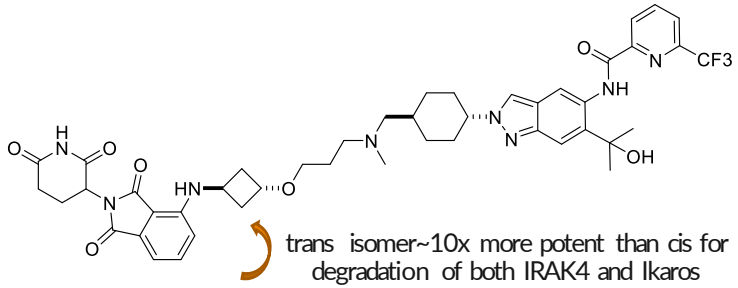
- IRAK4 degradation efficiency is not always correlated with ligand binding affinity
- Comparable IRAK4 degradation can be achieved with heterobifunctional degraders having significantly different affinity for IRAK4



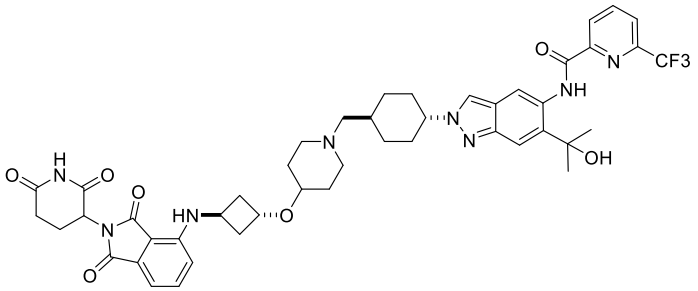
- Degradation of Ikaros is not correlated to affinity of ligand to CRBN

Modulating Potency and Intrinsic Stability





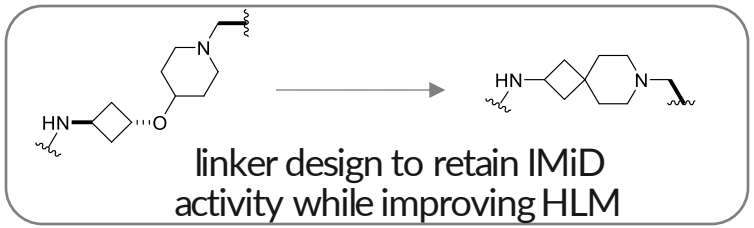
trans isomer~10x more potent than cis for degradation of both IRAK4 and Ikaros

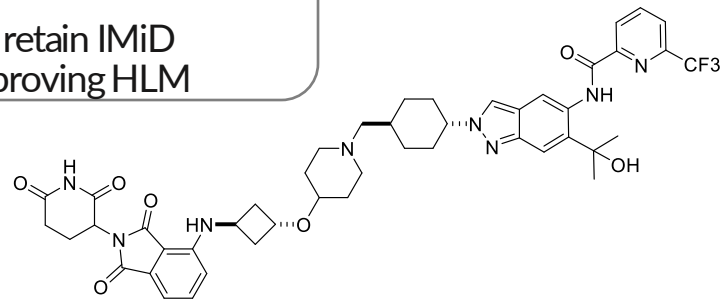


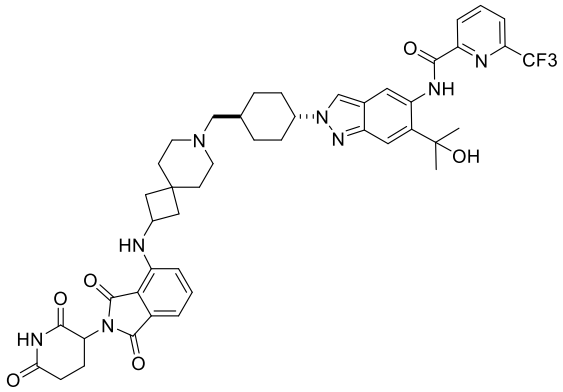
	KTX-435	KTX-582	KTX-955
IRAK4 DC_{50} (nM)	18	4	5
Ikaros DC_{50} (nM)	12	5	130
OCI-Ly10 CTG IC_{50} (nM)	270	28	1,800
HLM (μL/min/mg)	60	48	4

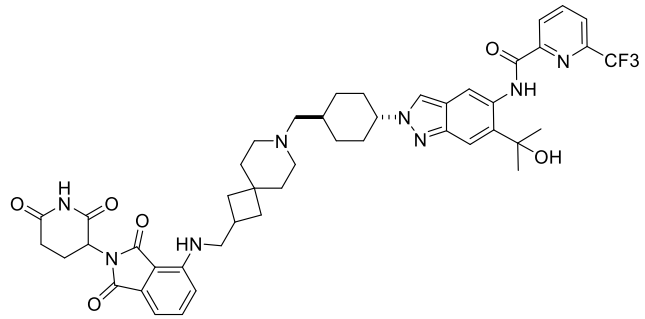
Linker modifications could enable an improvement on IRAK4 degradation efficiency and intrinsic stability but could significantly impact ability to degrade Ikaros and Aiolos

Merging Intrinsic Stability with IMiD Activity: Impact on Oral Absorption



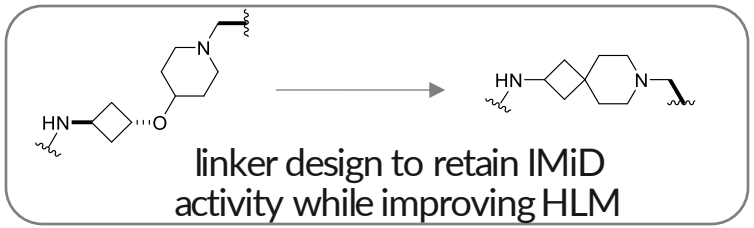


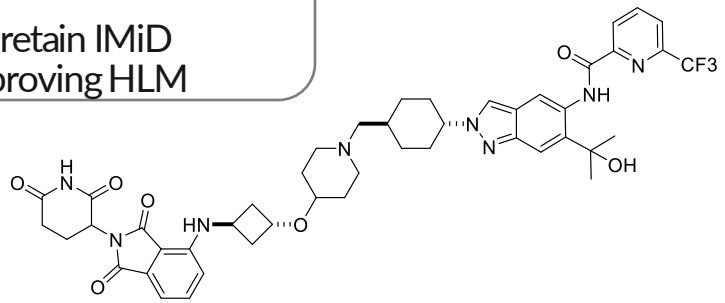


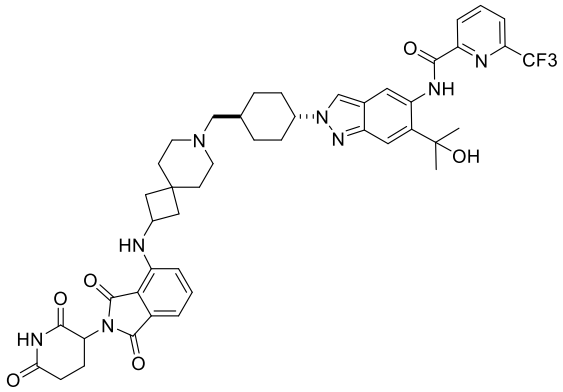


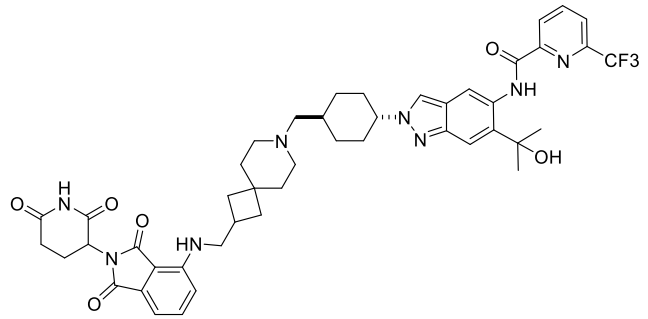
	KTX-955	KTX-497	KTX-612
IRAK4 DC_{50} (nM)	5	3	7
Ikaros DC_{50} (nM)	130	25	6
HLM (μL/min/mg)	4	1	3
RLM (μL/min/mg)	4	3	2

Merging Intrinsic Stability with IMiD Activity: Impact on Oral Absorption





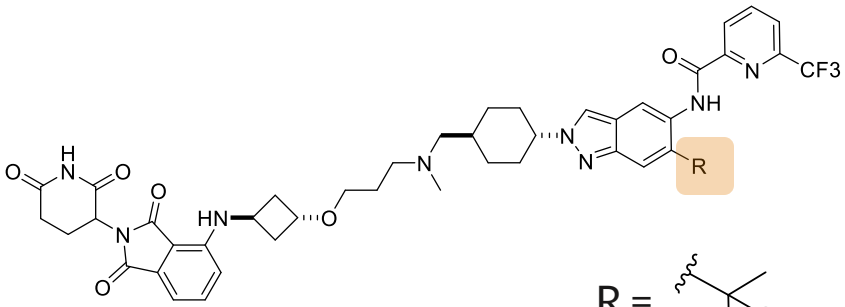




	KTX-955	KTX-497	KTX-612
IRAK4 DC_{50} (nM)	5	3	7
Ikaros DC_{50} (nM)	130	25	6
HLM (µL/min/mg)	4	1	3
RLM (µL/min/mg)	4	3	2
Rat PPB (Fu)	0.096	0.079	0.026
Rat IV CL (mL/min/kg)	7.0	13	14
Rat PO PK (10 mg/kg)			
%F	29	17	1
AUC (µM*hr)	5.3	1.4	0.060

Exposed PSA of KTX-612 relative to KTX-497 significantly impacted oral absorption

Balancing Metabolic Stability and Potency



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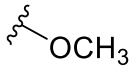
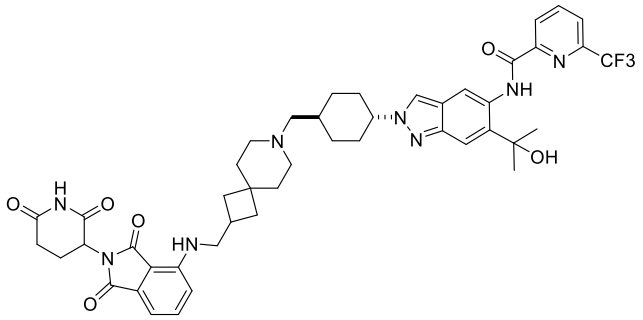
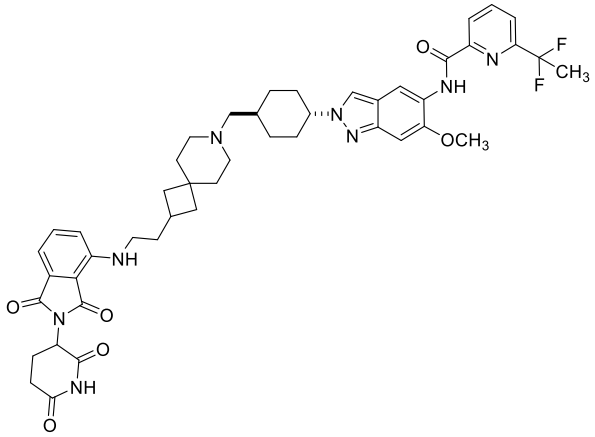
R = 

	KTX-582	KTX-961
IRAK4 DC_{50} (nM)	4	19
Ikaros DC_{50} (nM)	5	28
HLM (µL/min/mg)	48	4
MDCK Passive Perm. (x10-6 cm/s)	4.9	2.1
Rat PPB (Fu)	0.039	0.066
Rat IV PK: CL (mL/min/kg)	34	19
Rat PO PK (10 mg/kg) %F AUC (µM*hr)	 37 2.0	 21 1.1

- Methoxy analogs consistently more metabolically stable than their tertiary alcohol counterparts
- Tertiary alcohols consistently demonstrate improved potency; an impact of improved permeability and solubility
- Both alcohol and methoxy containing analogs could provide access to compounds with moderate clearance and good oral absorption

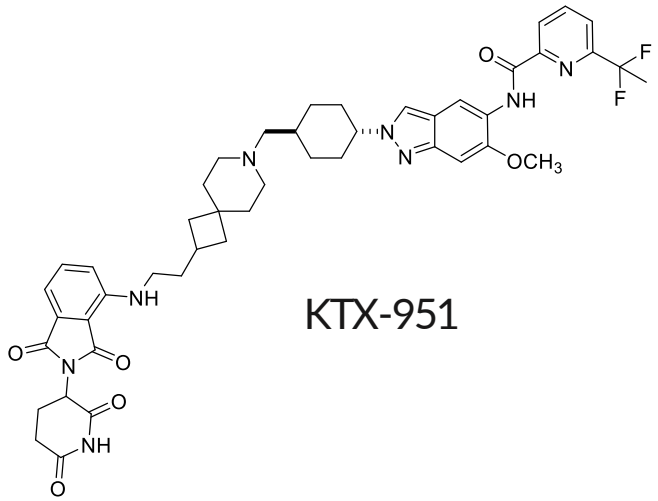
Potency and Pharmacokinetics
Reducing H-Bond Donors to Improve Oral Absorption





	KTX-612	KTX-951
IRAK4 DC_{50} (nM)	7	13
Ikaros DC_{50} (nM)	6	14
Aiolos DC_{50} (nM)	4	13
OCI-Ly10 CTG IC_{50} (nM)	10	35
HLM (μL/min/mg)	3	2
RLM (μL/min/mg)	2	3
Rat PPB (Fu)	0.026	0.073
Rat IV CL (mL/min/kg)	14	4.0
Rat PO PK (10 mg/kg)		
%F	1	22
AUC (μM*hr)	0.06	2.6

KTX-951: Favorable Pharmacokinetics Across Species



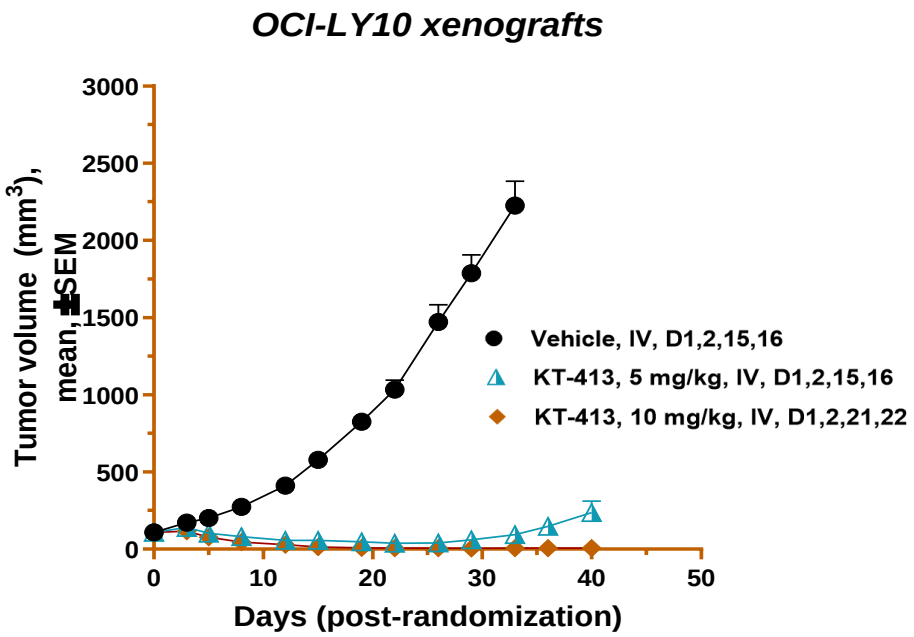
KTX-951

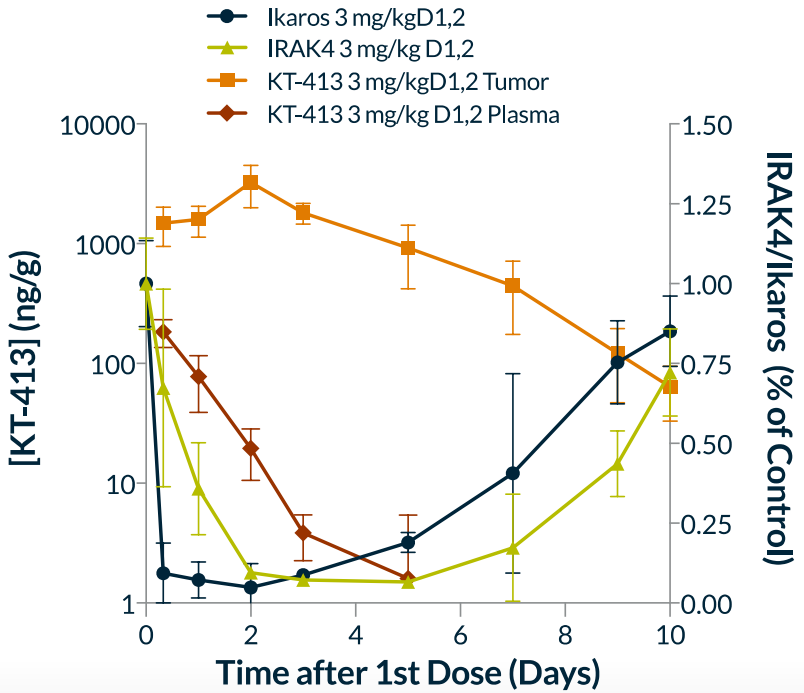
	Human	Rat	Dog
PPB (Fu)	**0.12**	**0.073**	**0.072**
IV CL (mL/min/kg)	--	**4.0**	**4.4**
PO %F (10 mg/kg)	--	**22**	**57**

MDCK Passive Permeability (x10-6 cm/s)	**1.1**
FaSSIF solubility (μM)	**21**
FeSSIF solubility (μM)	**20**

KT-413 is Highly Active on Intermittent Dosing Regimens

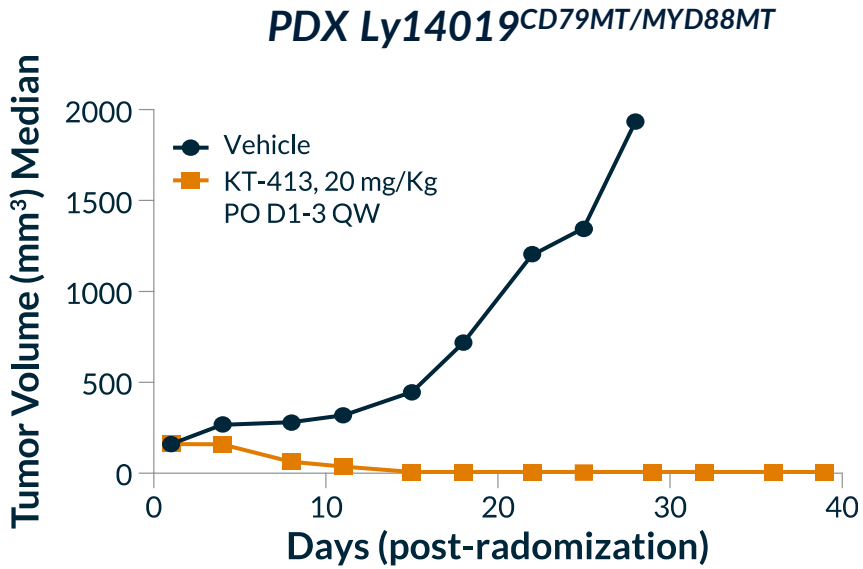
- In the OCI-Ly10 MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete or partial regressions
- Minimally active dose of 3 mg/kg D1,2 showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for at least 72h





KT-413 Shows Regressions in MYD88^{MT} Patient-Derived Xenograft (PDX) Models

Model	MYD88	CD79B	TNFAIP3	Other	KT-413 (%TGI)
LY14019	L265P	MT	MT		**100**
LY2264	L265P	MT		IRF4	**100**
LY2298	L265P	MT		BCL2/BCL6	**90**
LY12699	L265P	MT			**87**
LY2345	WT		MT		**70**
LY2301	WT				**30**
LY0257	L265P			BCL2/BCL6/IKZF3	**0**



KT-413 shows strong tumor growth inhibition (>85% TGI) in 4/5 MYD88-Mutated DLBCL PDx Models

- Activity is observed regardless of co-mutations that activate NFkB and IRF4 pathways
- The non-responsive MYD88^{MT} model LY0257 harbors a mutation in Aiolos and is reported to be insensitive to lenalidomide. The functional consequence of Aiolos mutations in IRAKIMiD and IMiD response is being investigated

Building an IRAK4 Franchise: Delivering on the Promise of Targeted Protein Degraders

- Selective IRAK4 degrader KT-474
  - First proof-of-mechanism for TPD in a randomized, placebo-controlled healthy volunteer study
- IRAKIMiD KT-413
  - Potent degrader of IRAK4 and IMiD substrates
  - PK/PD shows sustained, >80% degradation of both IRAK4 and IMiD substrates that correlates with tumor regressions in CDX models
  - Tumor regressions in multiple $MYD88^{MT}$ CDX and PDx models in both PO and IV schedules with intermittent dosing
  - Phase 1 clinical trial with KT-413 has been initiated
- Kymera has developed know-how to work within the beyond Ro5 to turn potent and selective heterobifunctional protein degraders into drugs to help patients in need

Acknowledgments