Discovery and characterization of potent degraders of IRAK4 and IMiD substrates for oncology indications

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KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

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Biology of Targeted Protein Degradation

Targeted Small Molecule Protein Degraders

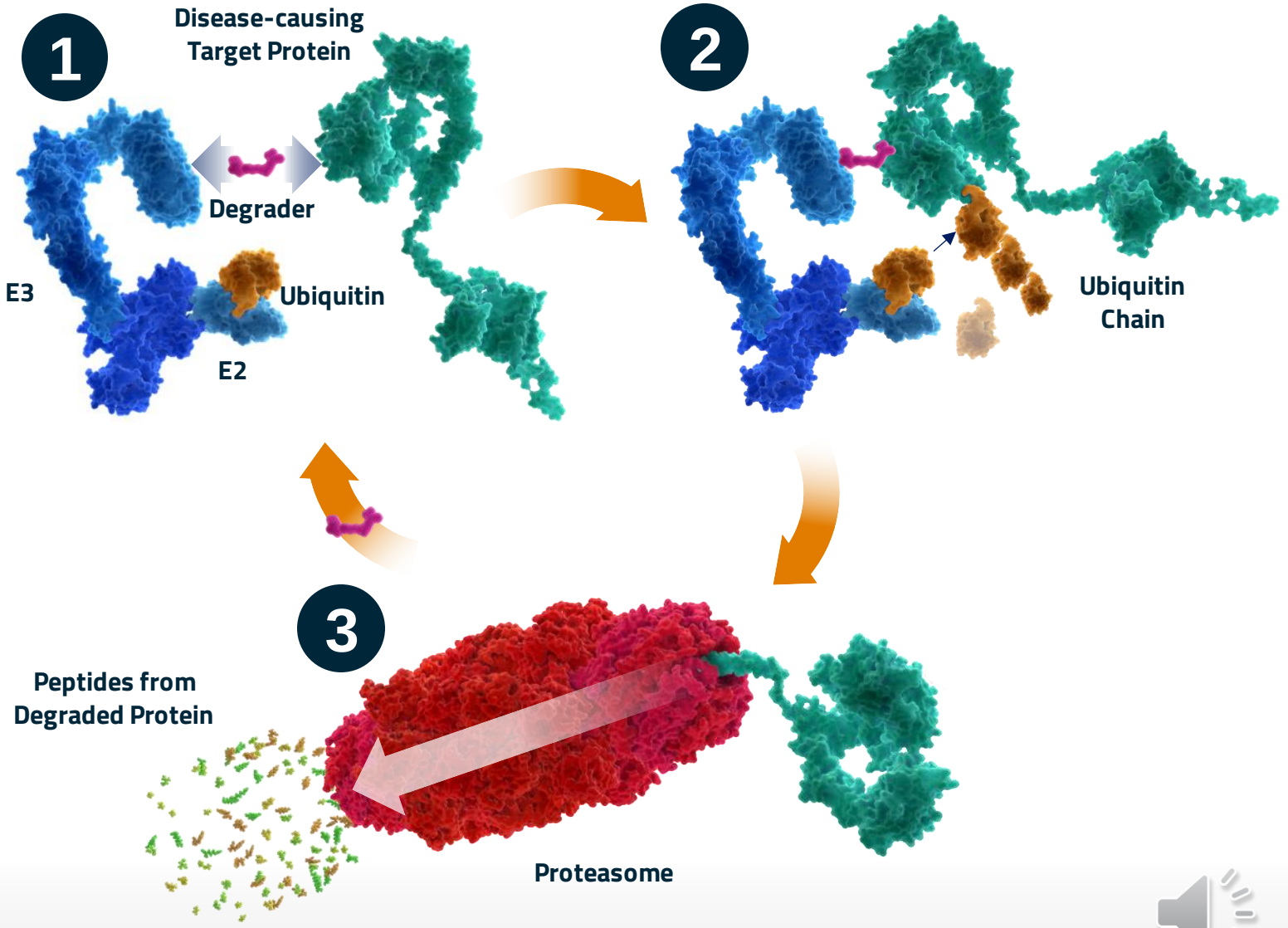
Co-opting a Naturally Occurring Process to Regulate Protein Levels

1. E3 ligase recognizes protein
2. Ubiquitin chain transferred
3. Protein is marked for elimination

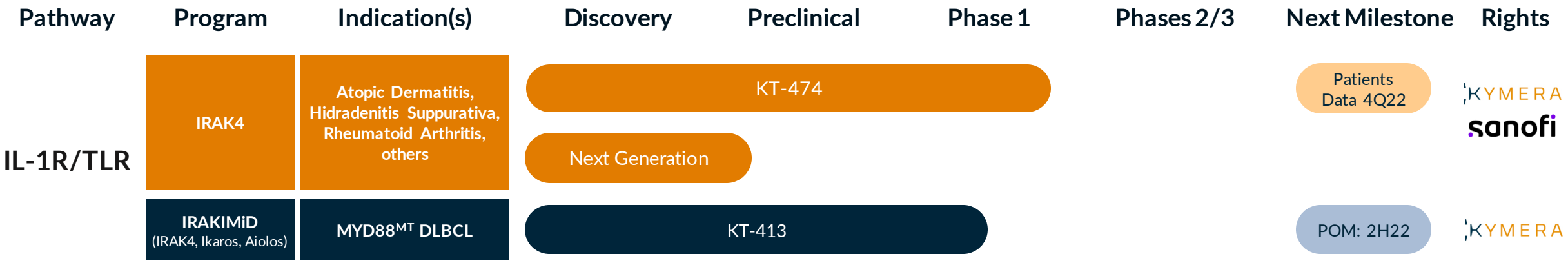
Broad Opportunity
Only Binding Site Required

Efficient
Catalytic

Prolonged Impact
Targeted Protein Degradation



Delivering on the Promise: Building an IRAK4 Franchise



KT-474

Selective heterobifunctional degrader of IRAK4

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

KT-413

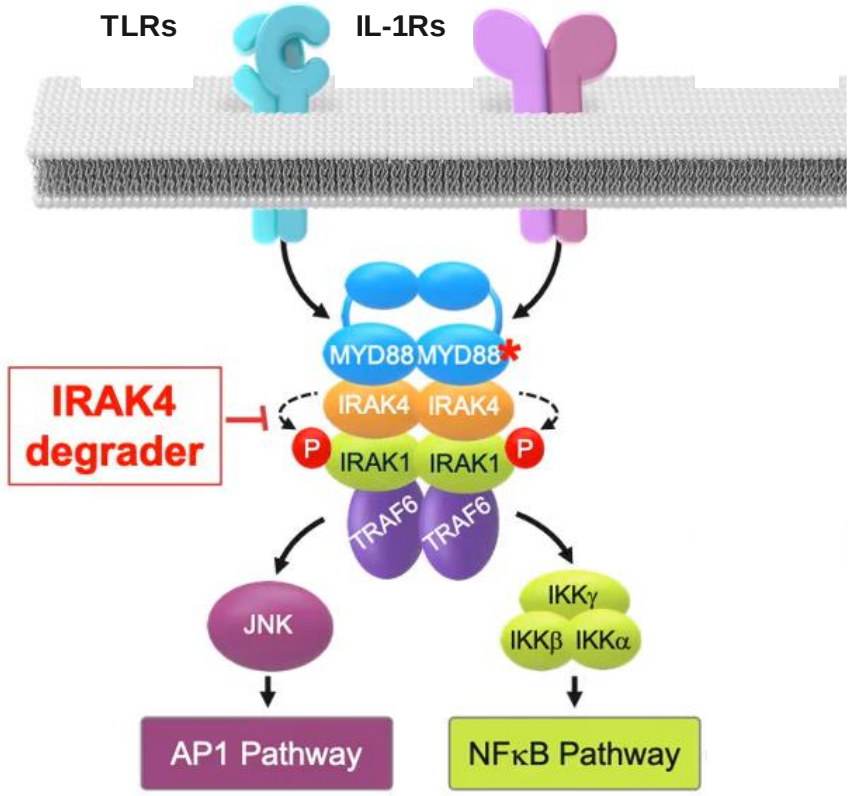
Dual-mechanism degrader of IRAK4 and IMiD substrates

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

(the structures of KT-474 and KT-413 were not disclosed in this presentation)

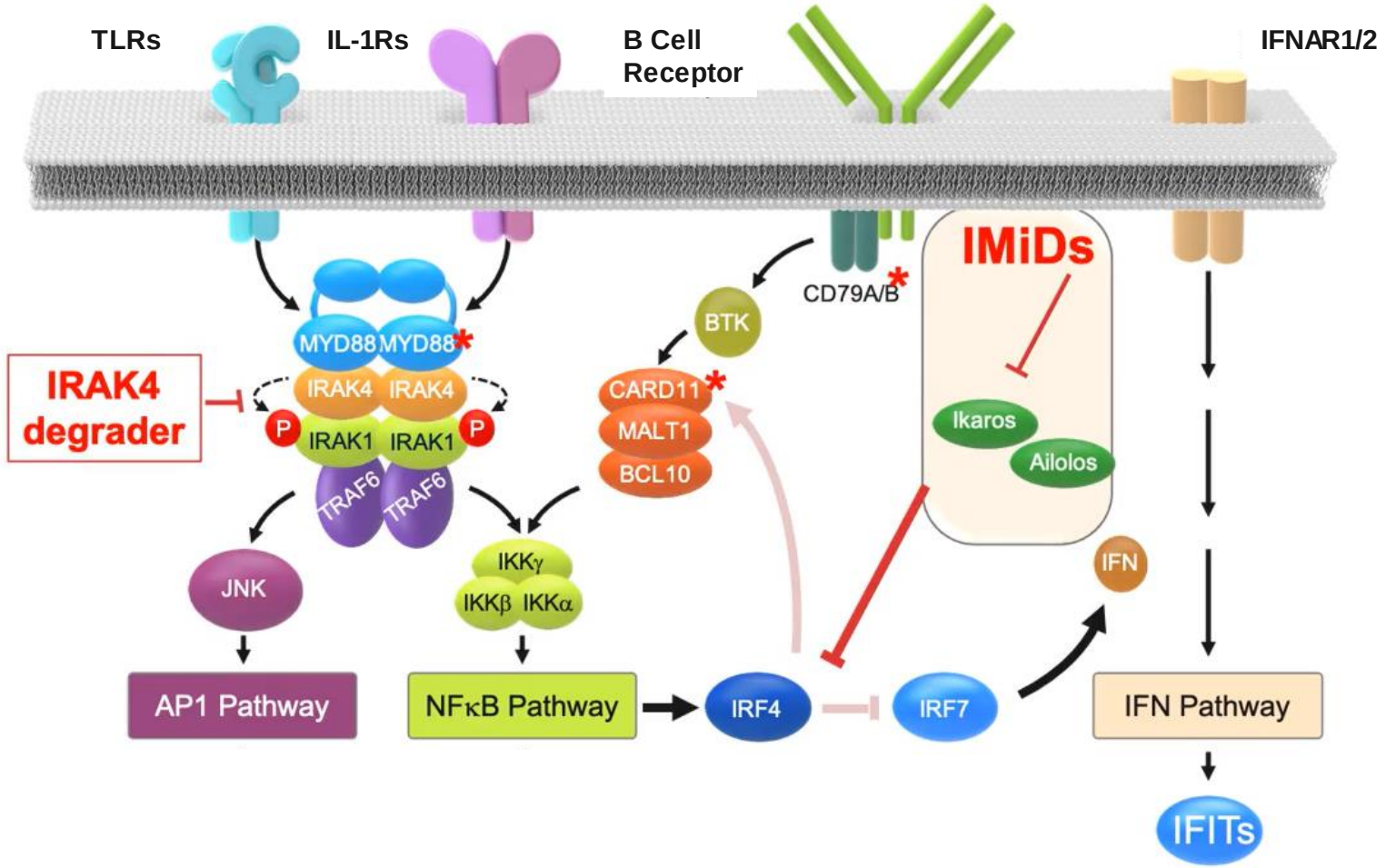
Degradation of IRAK4: Modulating Proinflammatory Cytokines and Cellular Proliferation

- 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



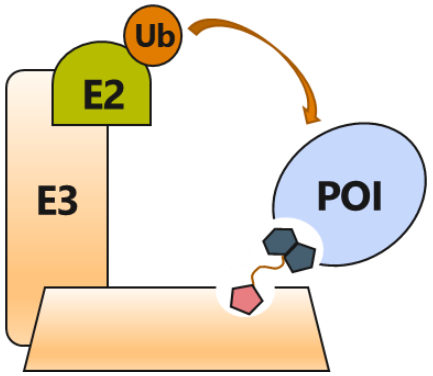
Degradation of IRAK4 and IMiD Substrates: Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

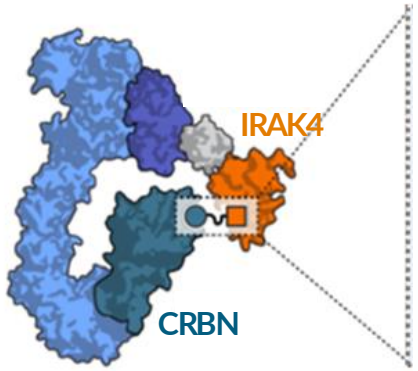
- MYD88 L265P is a gain-of-function driver mutation which results in constitutive activation of the anti-apoptotic NFkB signaling pathway
- Single-agent therapies that target activated NFκB signaling in DLBCL show limited activity in preclinical or clinical settings
- Redundant NFκB pathway activation 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



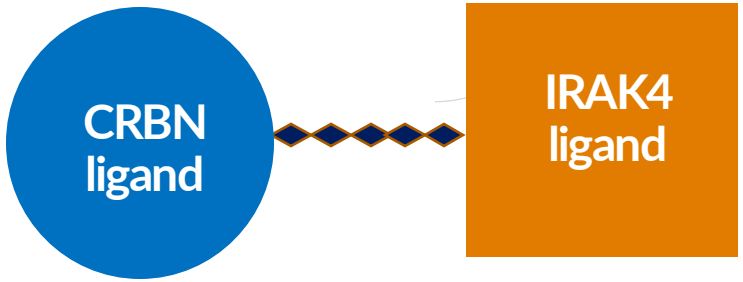
IRAKIMiD:
Functioning as a Heterobifunctional Degrader & a Molecular Glue

Heterobifunctional Degrader

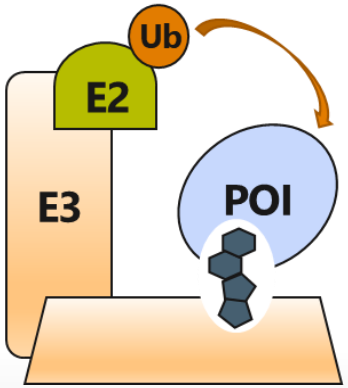


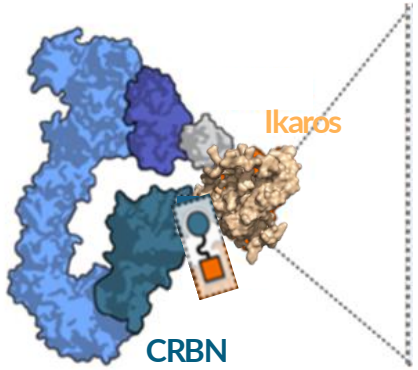


Degradation of IRAK4



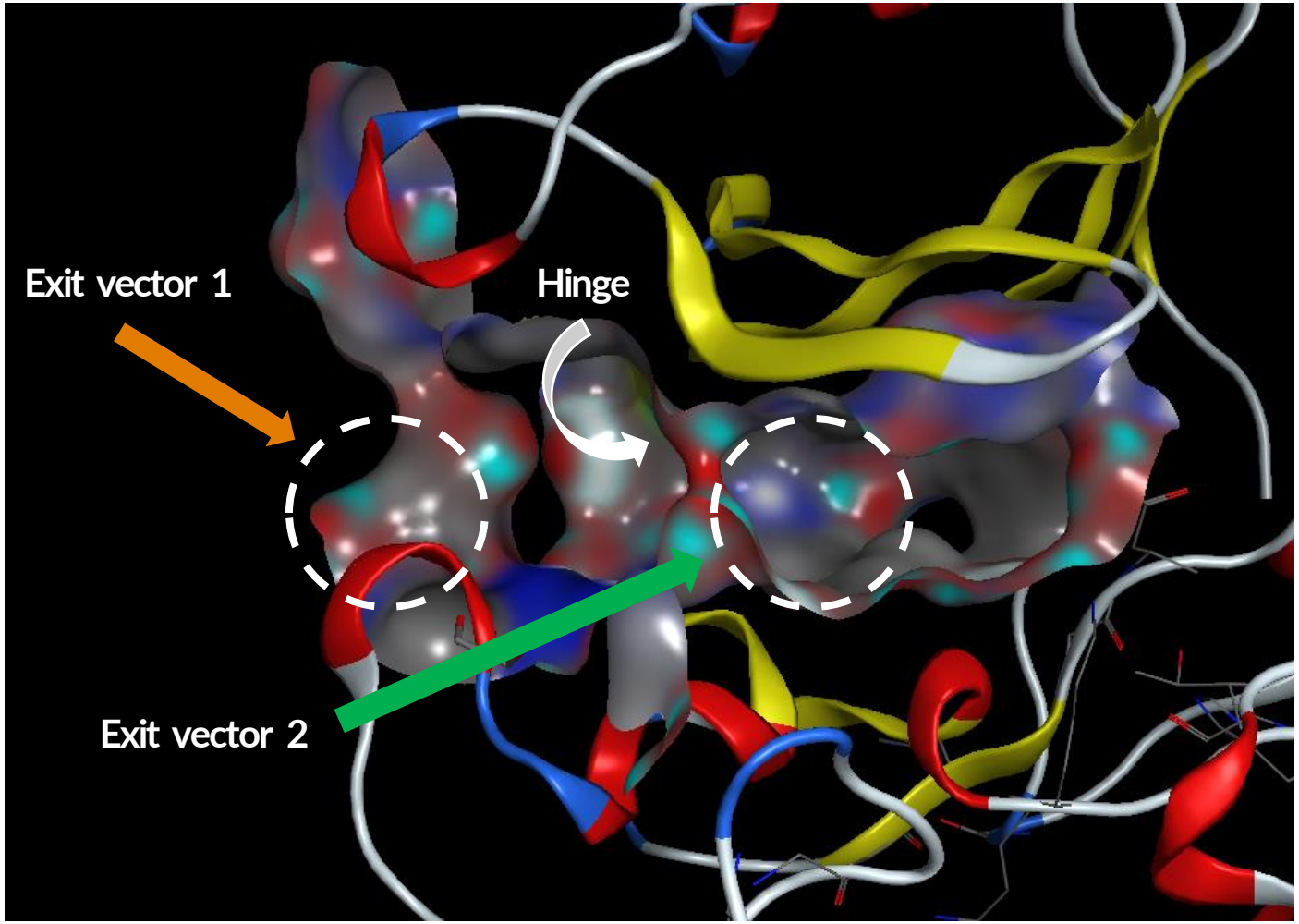
Molecular Glue



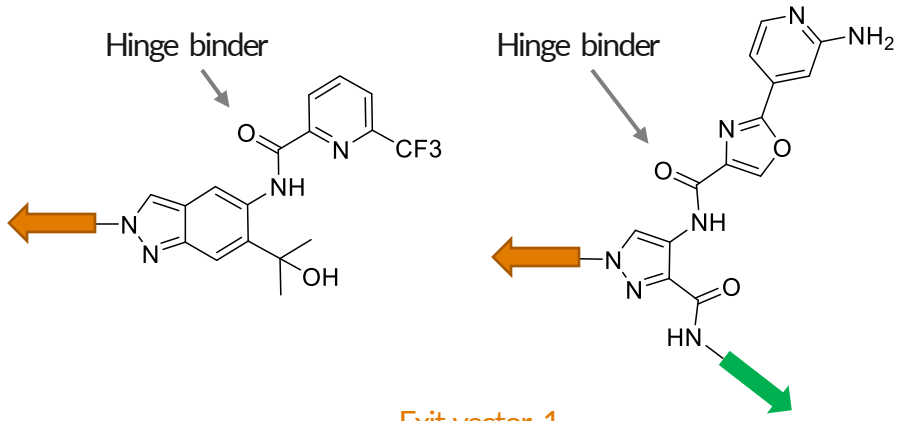


Degradation of IMiD substrates
(i.e., Ikaros and Aiolos)

IRAK4 Ligand and Exit Vector Identification

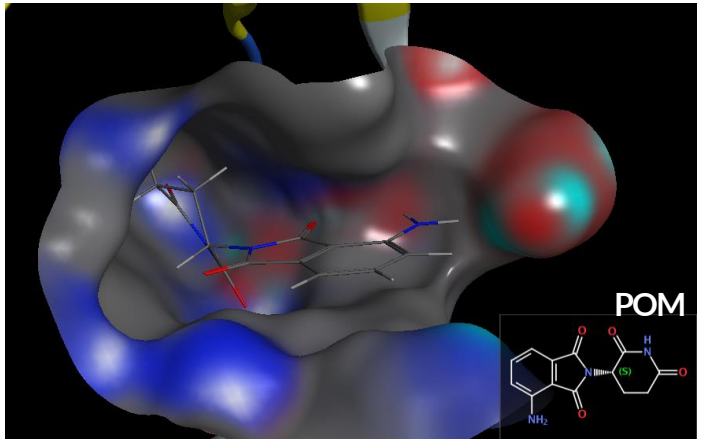


Subset of IRAK4 Ligands Incorporated into Exploratory Tool Degraders of IRAK4

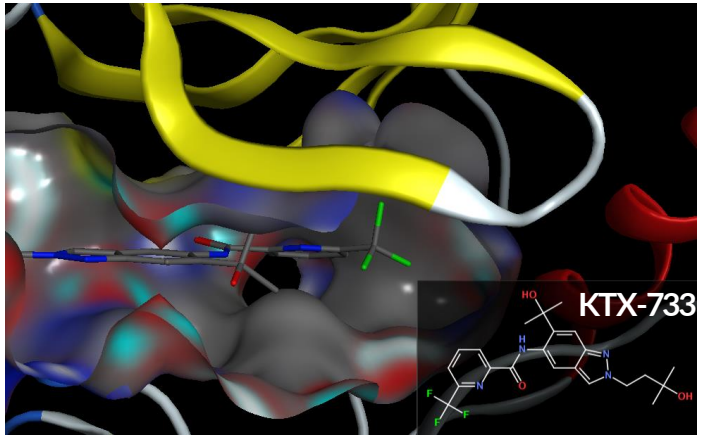


Exploratory studies showed IRAK4 degradation using multiple IRAK4 ligands and multiple exit vectors

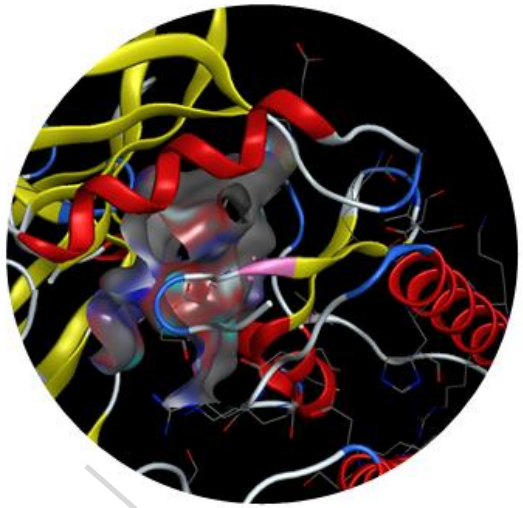
Ternary Complex Modeling



X-ray: POM bound to CRBN-DDB1

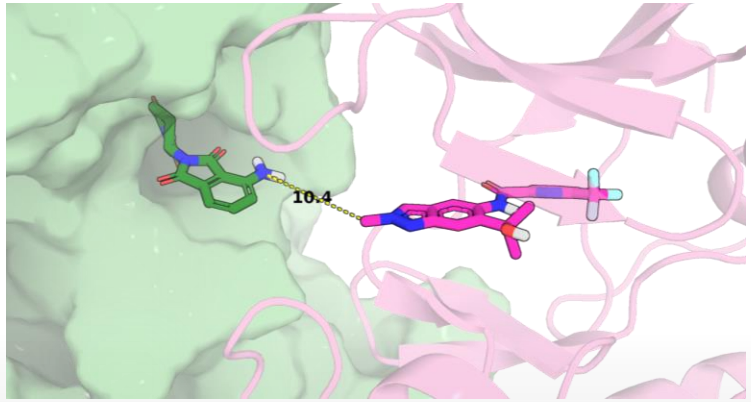


X-ray: KTX-733 bound to IRAK4



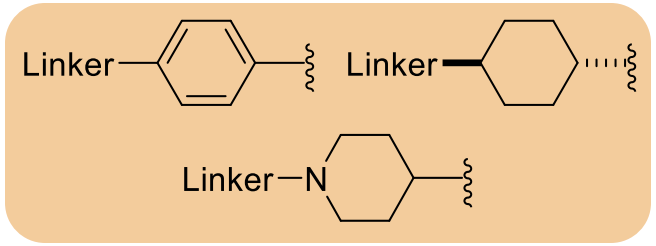
X-rays and exploratory SAR inform design of ternary complex model

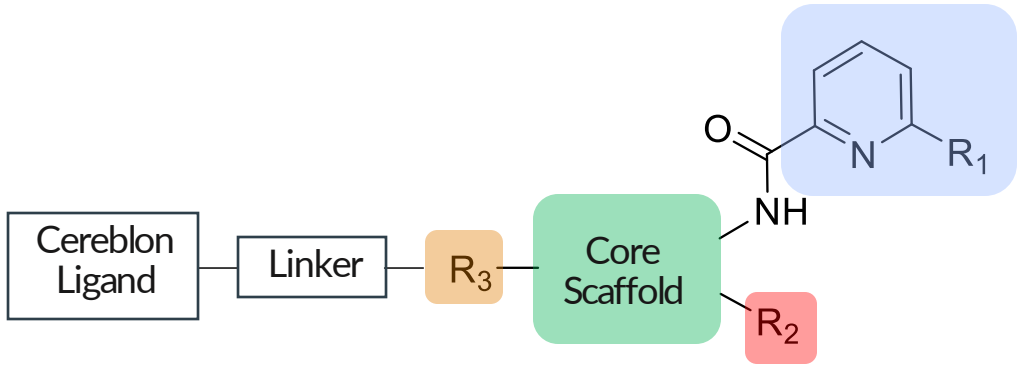
Ternary complex model to guide and inspire degrader design

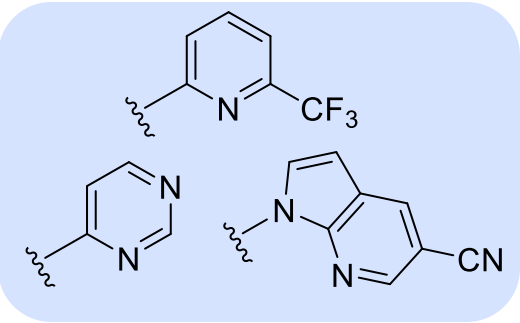


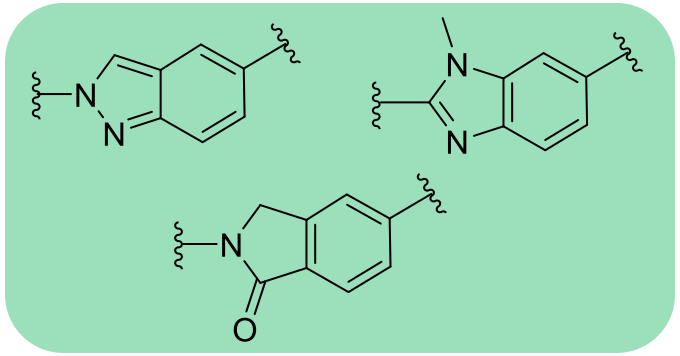
Representative Motifs Explored

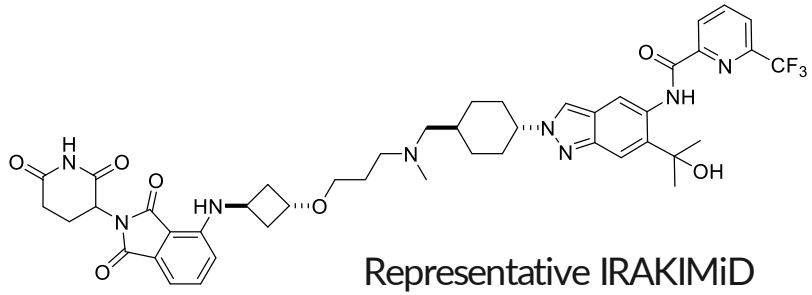
- Extensive exploration of IRAK4 ligand and linker required to probe SAR for both IRAK4 and IMiD substrate degradation
- Indazole scaffold became primary focus due to kinome selectivity, modularity, and ability to tune properties



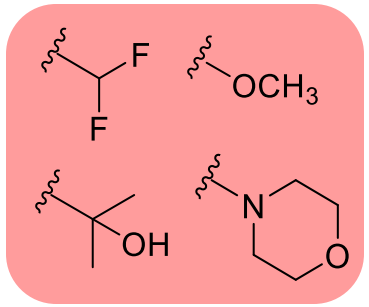




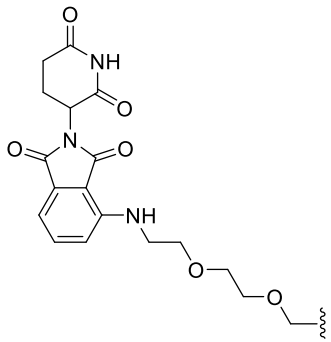


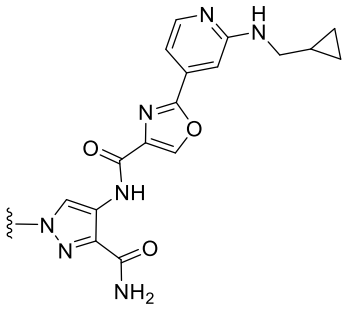


Representative IRAKIMiD

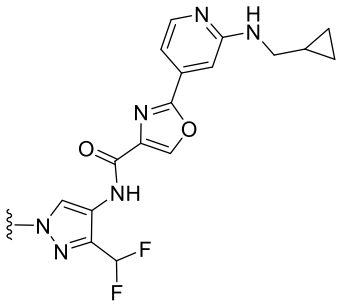


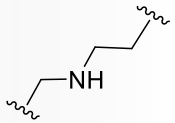
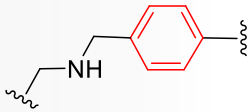
Improving IRAK4 Degradation Potency

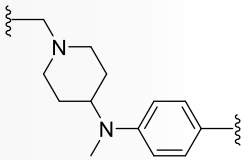
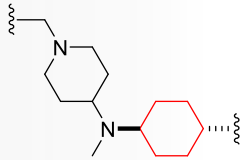




CRBN Ligand

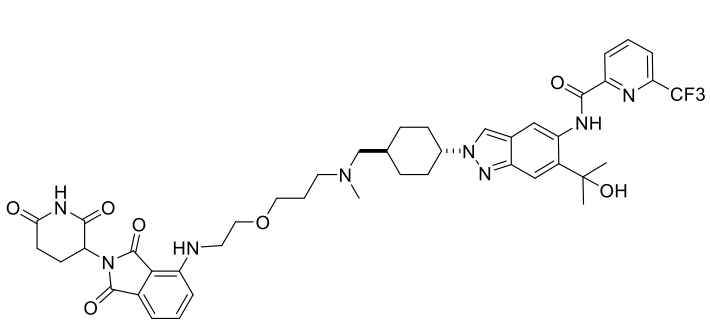


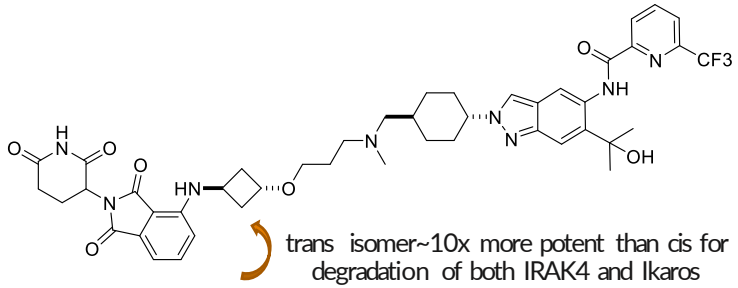
Parameter	KTX-671	KTX-315
Linker		
OCI-Ly10 Cell IRAK4 DC_{50}(nM)	**> 1,000**	**22**

Parameter	KTX-881	KTX-353
Linker		
OCI-Ly10 Cell IRAK4 DC_{50}(nM)	**23**	**6.0**

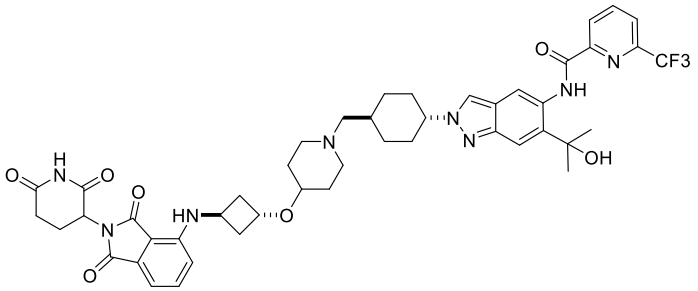
Linker modifications to alter POI exit vector directionality can improve IRAK4 degradation potency

Modulating Potency and Intrinsic Stability





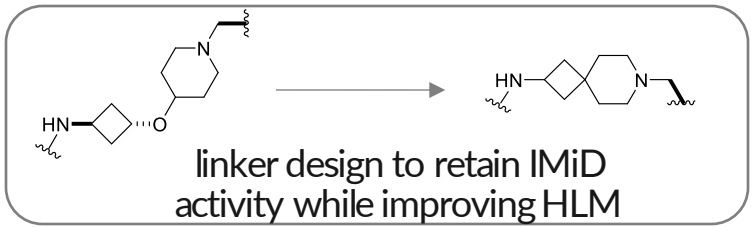
trans isomer~10x more potent than cis for degradation of both IRAK4 and Ikaros

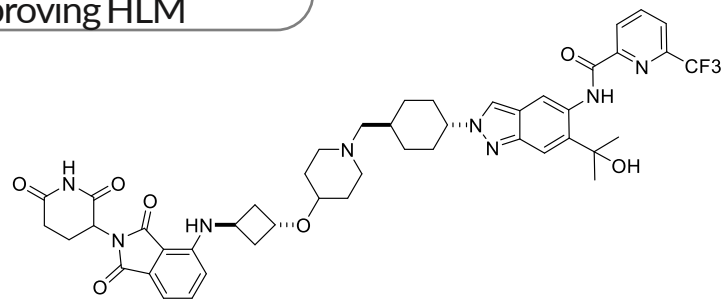


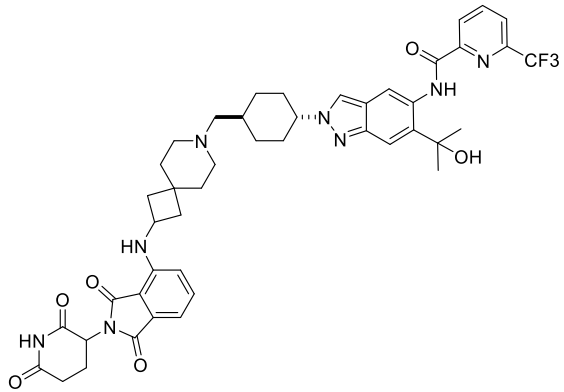
	KTX-435	KTX-582	KTX-955
IRAK4 DC_{50} (nM)	18	4	5
Ikaros DC_{50} (nM)	12	5	130
OCI-Ly10 CTG IC_{50} (nM)	270	28	1,800
HLM (μL/min/mg)	60	48	4

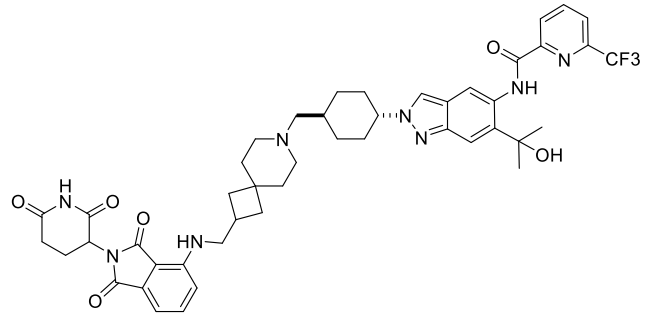
Linker modifications could enable an improvement on IRAK4 degradation efficiency and intrinsic stability but could significantly impact ability to degrade Ikaros and Aiolos

Merging Intrinsic Stability with IMiD Activity





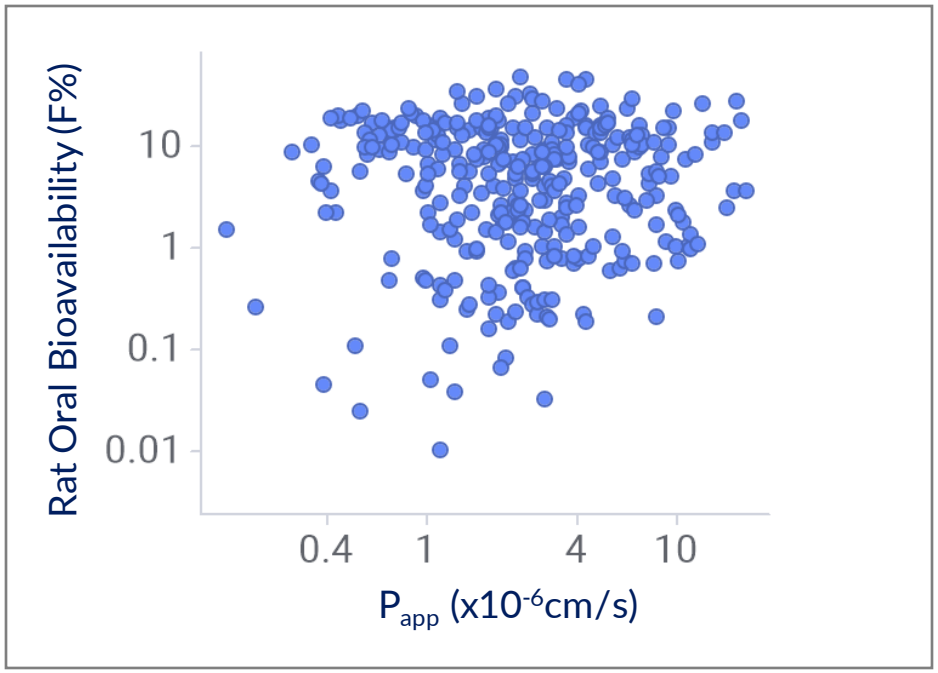




	KTX-955	KTX-497	KTX-612
IRAK4 DC_{50} (nM)	5	3	7
Ikaros DC_{50} (nM)	130	25	6
HLM (μL/min/mg)	4	1	3
RLM (μL/min/mg)	4	3	2

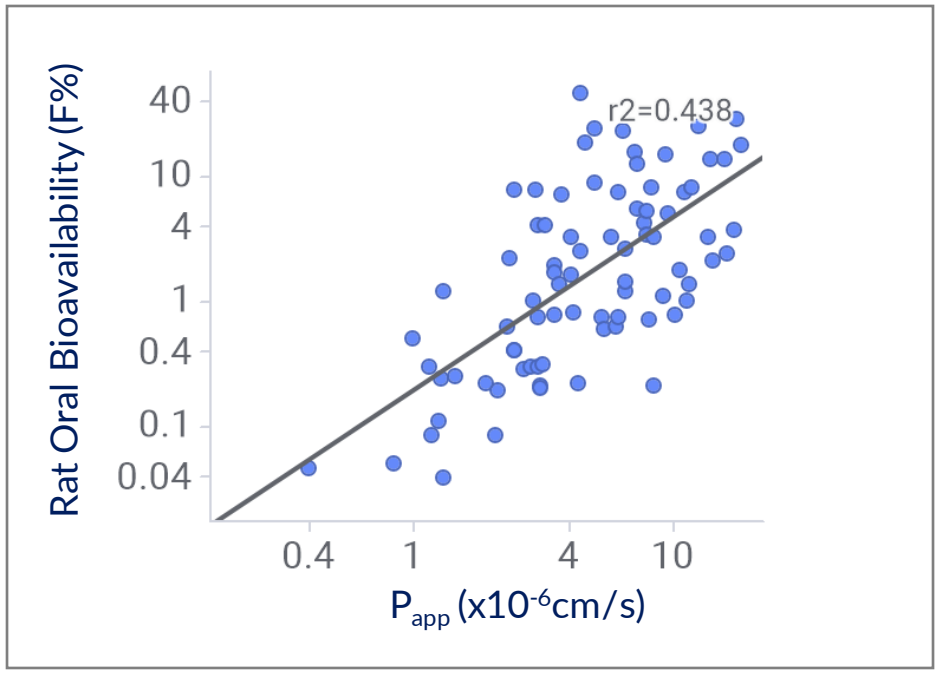
Understanding and Leveraging Permeability Data

Evaluation of IRAK4 degraders in rat PK studies: 10 mg/kg, PO



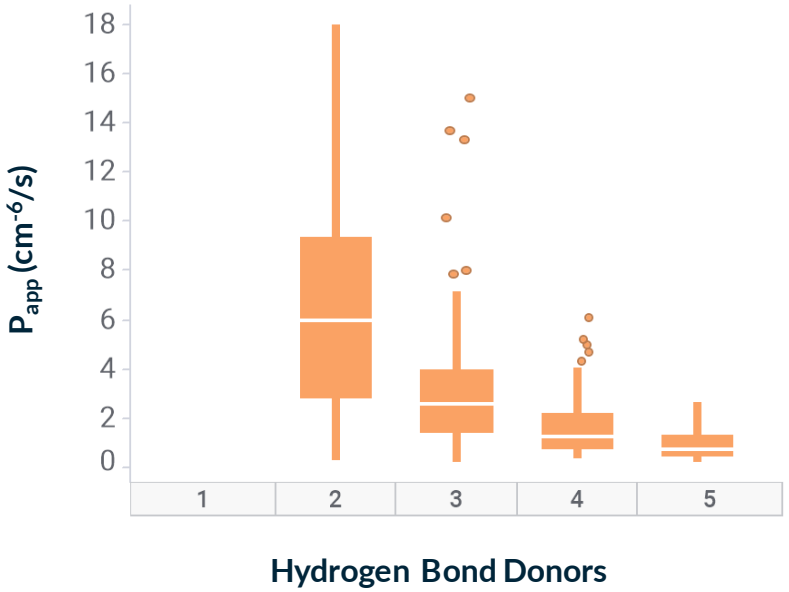
No correlation between oral absorption and passive permeability

Restrict to only datapoints where recovery >70%

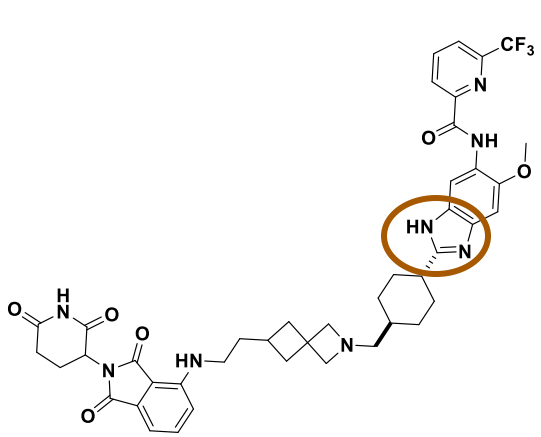


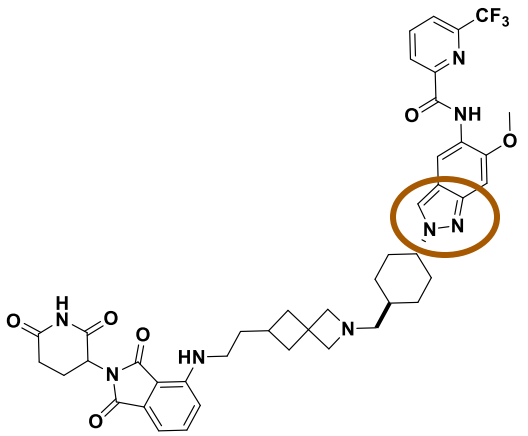
Passive permeability trends with oral bioavailability

Number of HBDs Impacts Passive Permeability and Efflux



- **Reduction in hydrogen bond donors (HBDs) trends toward improved passive permeability and reduced MDR1-mediated efflux**



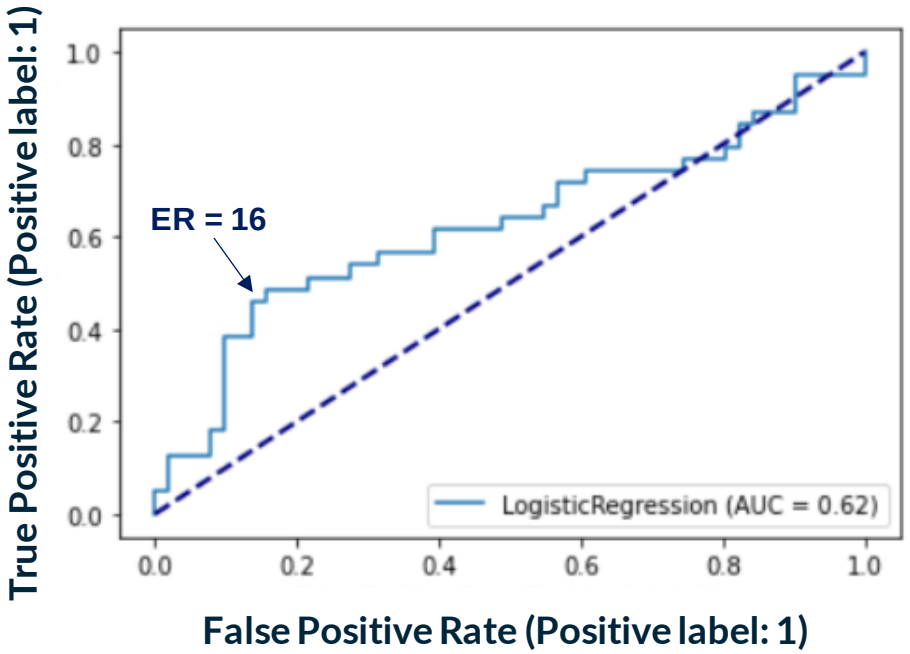


	KTX-088	KTX-109
IRAK4 DC_{50} (nM)	54	8
Hydrogen bond donors (#)	4	3
MDCK P_{app} (10^{-6} cm/s)	0.4	1.0
MDCK-MDR1 efflux ratio	8	0.3
R_{gyr} (Å)	9.2	9.2
Rat IV CL (mL/min/kg)	67	30
Rat PO PK (10 mg/kg) %F AUC (μM*hr)	 0 0	 4.2 0.13

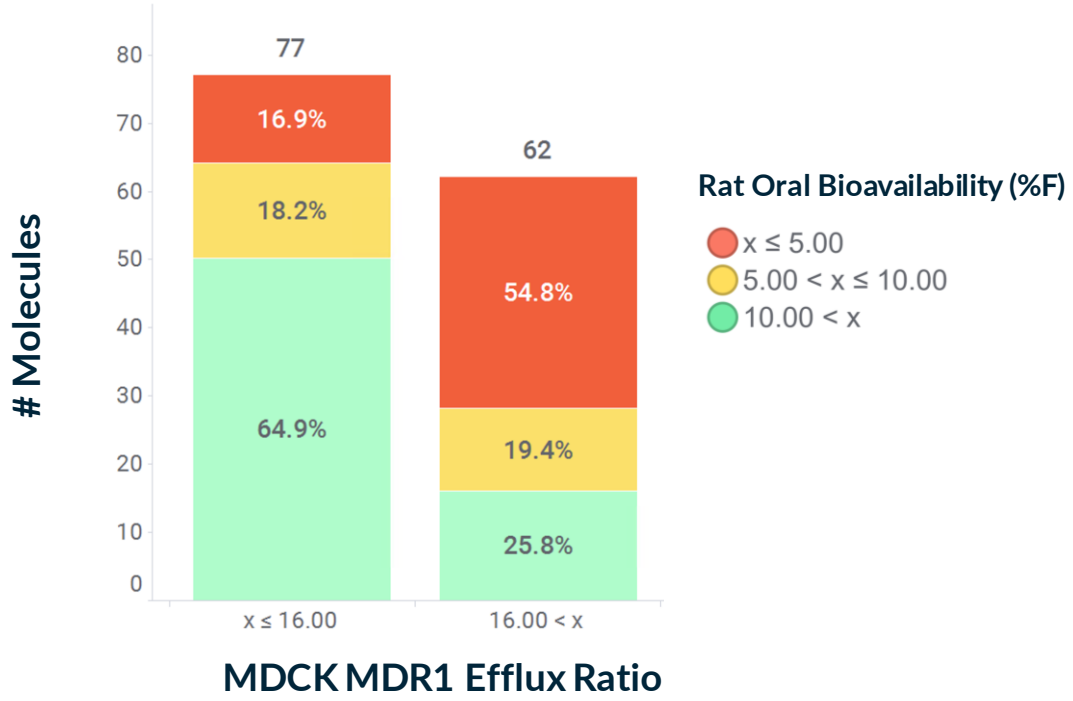
Efflux Has Critical Impact on Oral Bioavailability

- In vivo MoA study indicated efflux has critical impact on oral bioavailability

Machine learning analysis to determine the most effective ER threshold to achieve oral F>10%

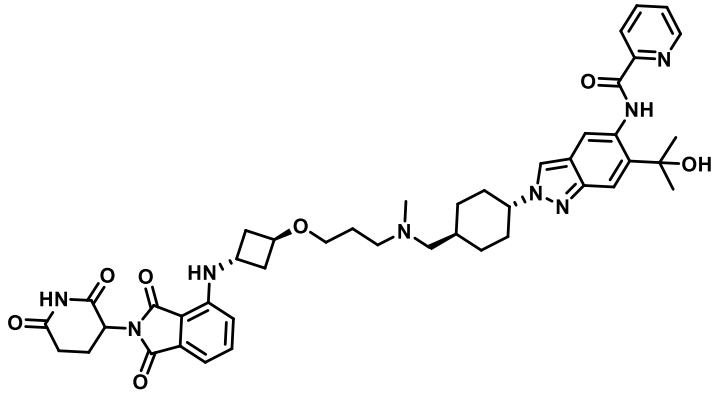


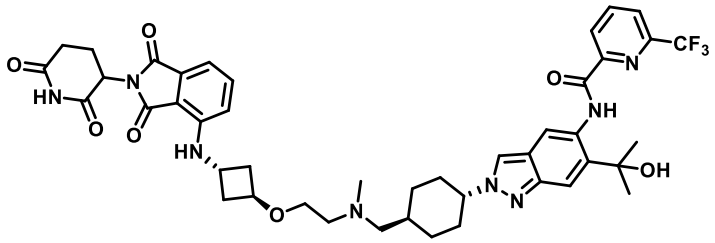
ROC plot for LOW (F<5%) and HIGH (F>10%) bioavailability classes



Within this specific series of degraders, an MDR1 efflux ratio of 16 was identified as the threshold above which oral absorption was significantly impacted

Efflux Ratio Impact on Oral Bioavailability



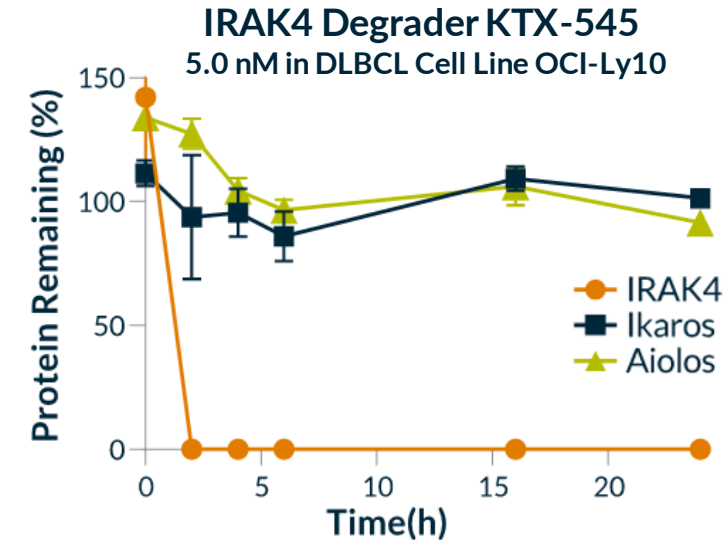


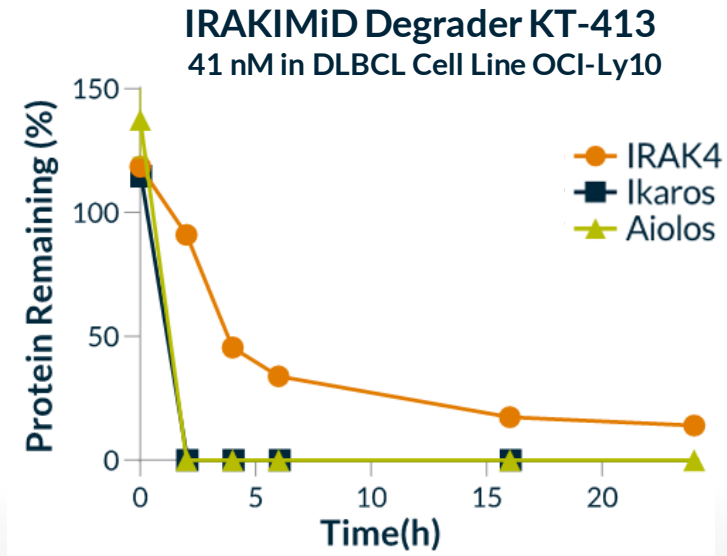
	KTX-037	KTX-045
IRAK4 DC_{50} (nM)	7	9
#HBD	4	4
P_{app} (10^{-6} cm/s)	19	4.9
Efflux ratio	35	10
R_{gyr} (Å)	5.8	6.1
RLM (μL/min/mg)	19	< 12
Rat PPB (Fu)	0.0024	0.0013
Rat IV CL (mL/min/kg)	22	21
Rat PO PK (10 mg/kg) %F AUC (μM*hr)	 4 0.35	 14 1.2

IRAK4 Degrader vs IRAKIMiD Degrader: Degradation

Parameter	KTX-545	KT-413
	IRAK4 Degrader	IRAKIMiD Degrader
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**1.0**	**6.0**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell Aiolos DC_{50} (nM)	**> 1,000**	**2.0**

- IRAK4 degrader KTX-545 exhibits no effect on levels of Ikaros or Aiolos
- IRAKIMiD degrader KT-413 induces strong degradation of IRAK4, Ikaros, and Aiolos
- IRAKIMiD degrader KT-413 degrades IRAK4 more slowly than Ikaros and Aiolos

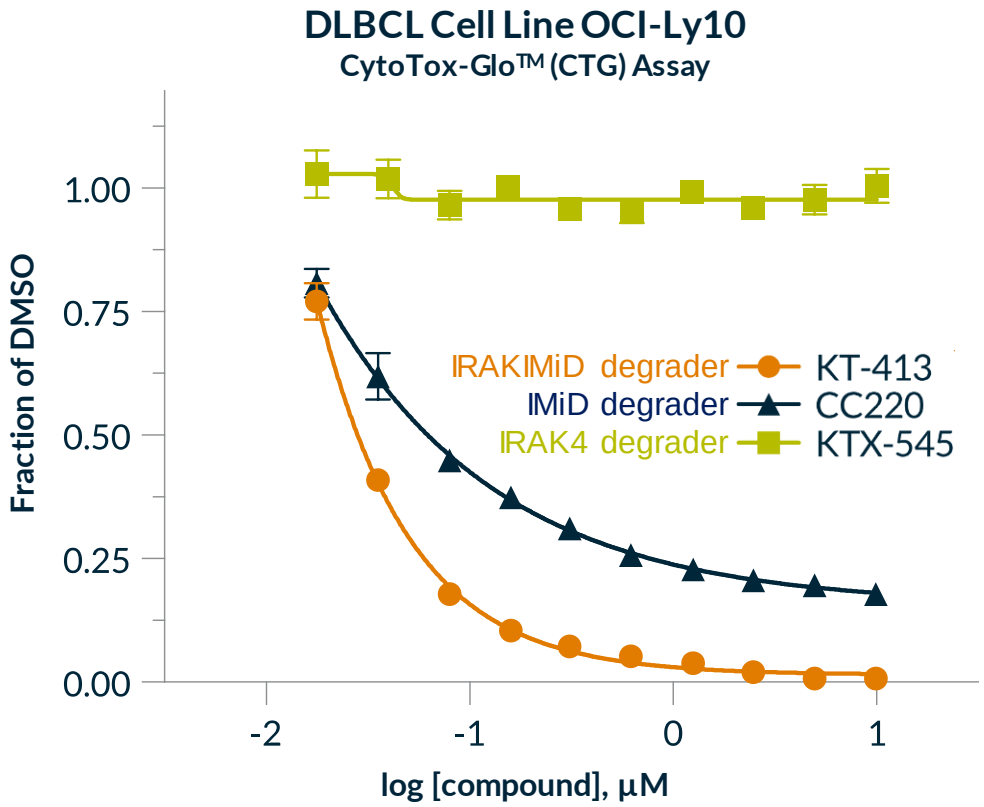




IRAK4 and IMiD Degraders vs IRAKIMiD Degrader: Cytotoxicity

- DLBCL cell line OCI-Ly10 expresses most prevalent MYD88 mutation (L265P)
- IRAK4 degrader KTX-545 exhibits no OCI-Ly10 cytotoxicity
- IRAKIMiD degrader KT-413 shows robust OCI-Ly10 cytotoxicity
- IRAKIMiD degraders can show strong and broad activity across several MYD88 mutant cell lines

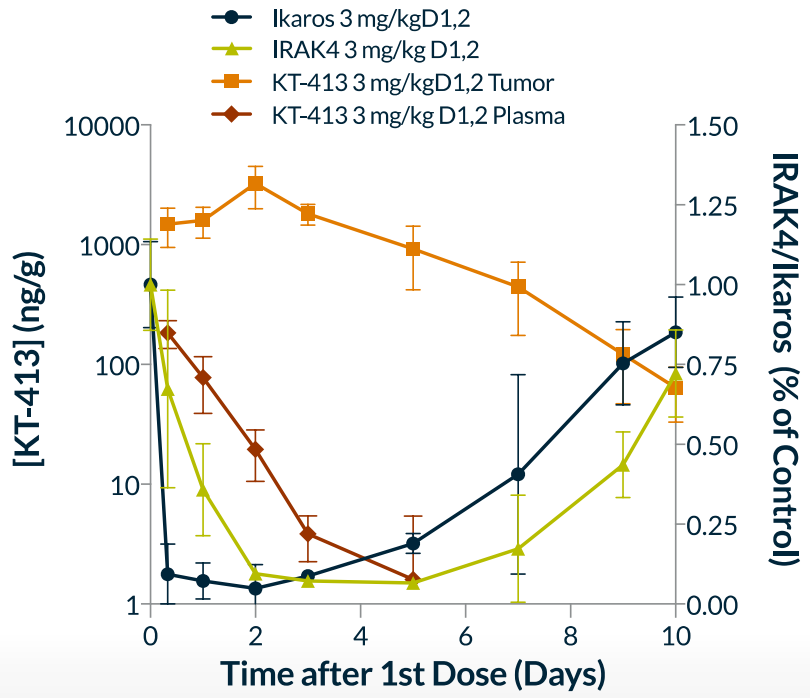
Parameter	KTX-545	KT-413
	IRAK4 Degrader	IRAKIMiD Degrader
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**1.0**	**6.0**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell Aiolos DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell CTG IC_{50} (nM)	**> 10,000**	**9.0**



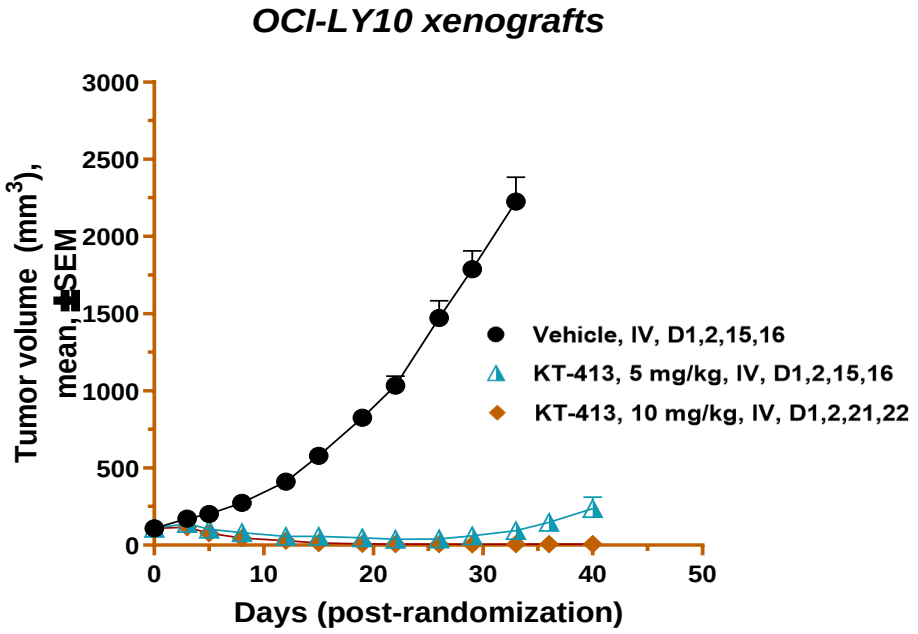
KT-413 Highly Active on Intermittent Dosing Regimens

- Minimally active dose of 3.0 mg/kg D1,2 showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for at least 72 h
- In the OCI-Ly10 cell MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete or partial regressions

DLBCL Cell Line OCI-Ly10 CDX Tumor PK–PD in Mouse

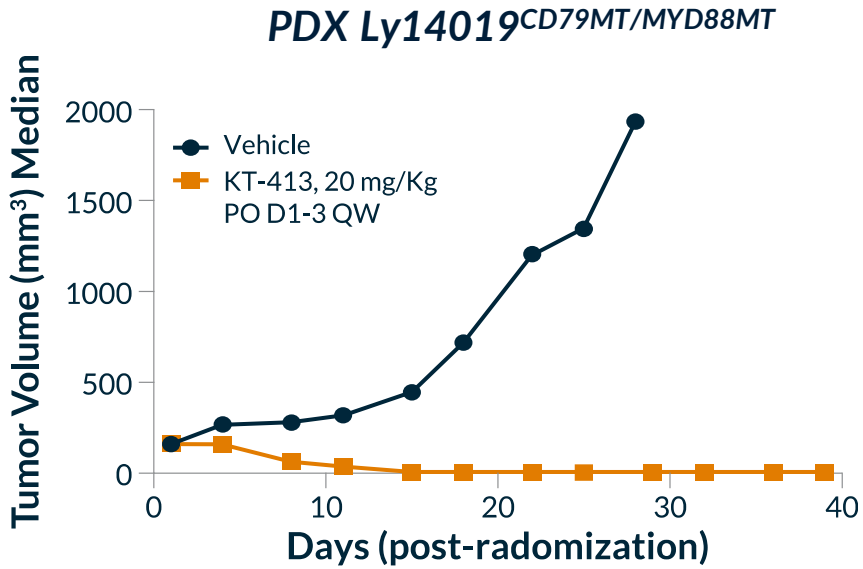


DLBCL Cell Line OCI-Ly10 CDX Efficacy in Mouse



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

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**

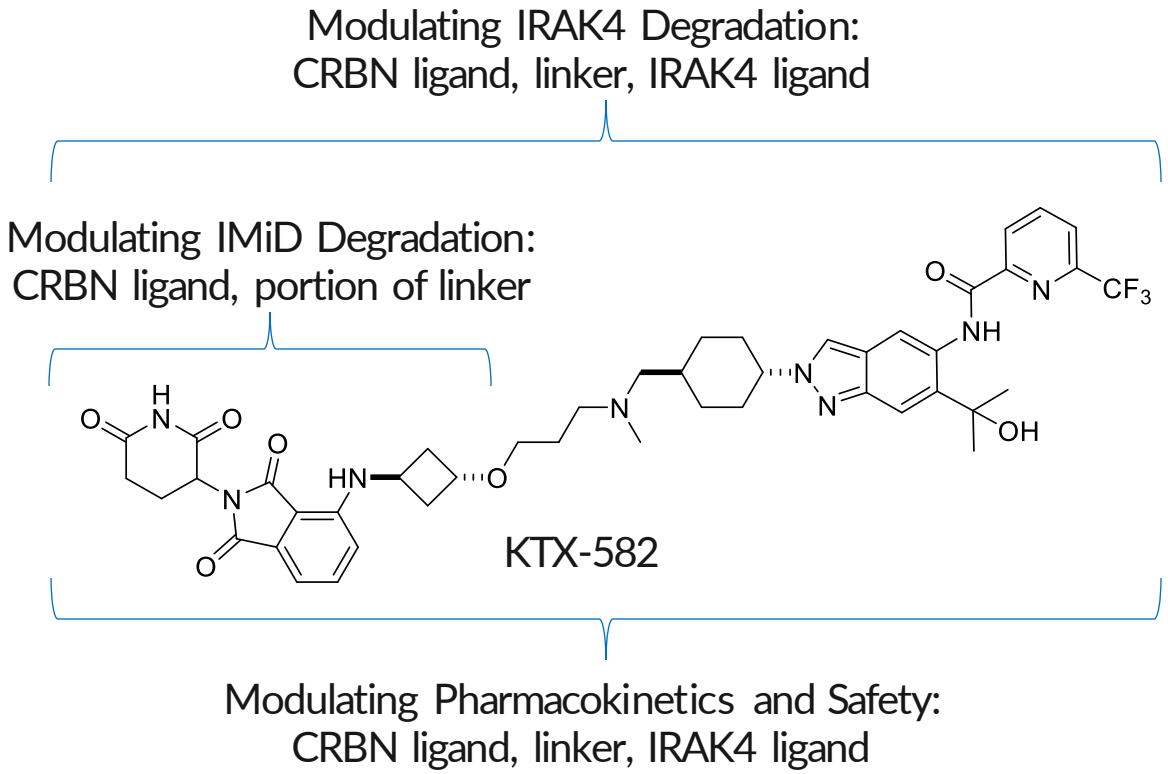


KT-413 shows strong tumor growth inhibition (> 85% TGI) in 4/5 MYD88-Mutated DLBCL PDX Models in mouse

- 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

Lessons Learned in the Optimization of IRAKIMiDs

- Challenges:
  - Managing independent SAR for degradation of IRAK4 and IMiD substrates
  - Optimizing physicochemical and pharmacokinetic properties in bRo5 chemical space
  - Developing appropriate in vitro assays for evaluating pharmacological properties
- Opportunities:
  - Embracing the linker: it is not just a bystander
  - Leveraging subtle structure modifications to POI ligand or linker for profound impact on degradation potency
  - Exploiting minor structure modifications to linker for large impact on selectivity, oral bioavailability and pharmacokinetics
  - Using ternary complex modeling to inspire design
  - Understanding parameters (e.g. permeability, efflux ratio, etc.) that have impact on oral bioavailability and developing models to predict those parameters



Acknowledgments