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New York City, NY, June 26th – 29th, 2022
Session 1: Integrating Novel Chemical Modalities in Hit-to-lead:
a New Paradigm for Early Drug Discovery

Discovery of IRAKIMiDs: Dual-Mechanism Degraders Targeting IRAK4 and IMiD Substrates for Oncology

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KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

June 26th, 2022

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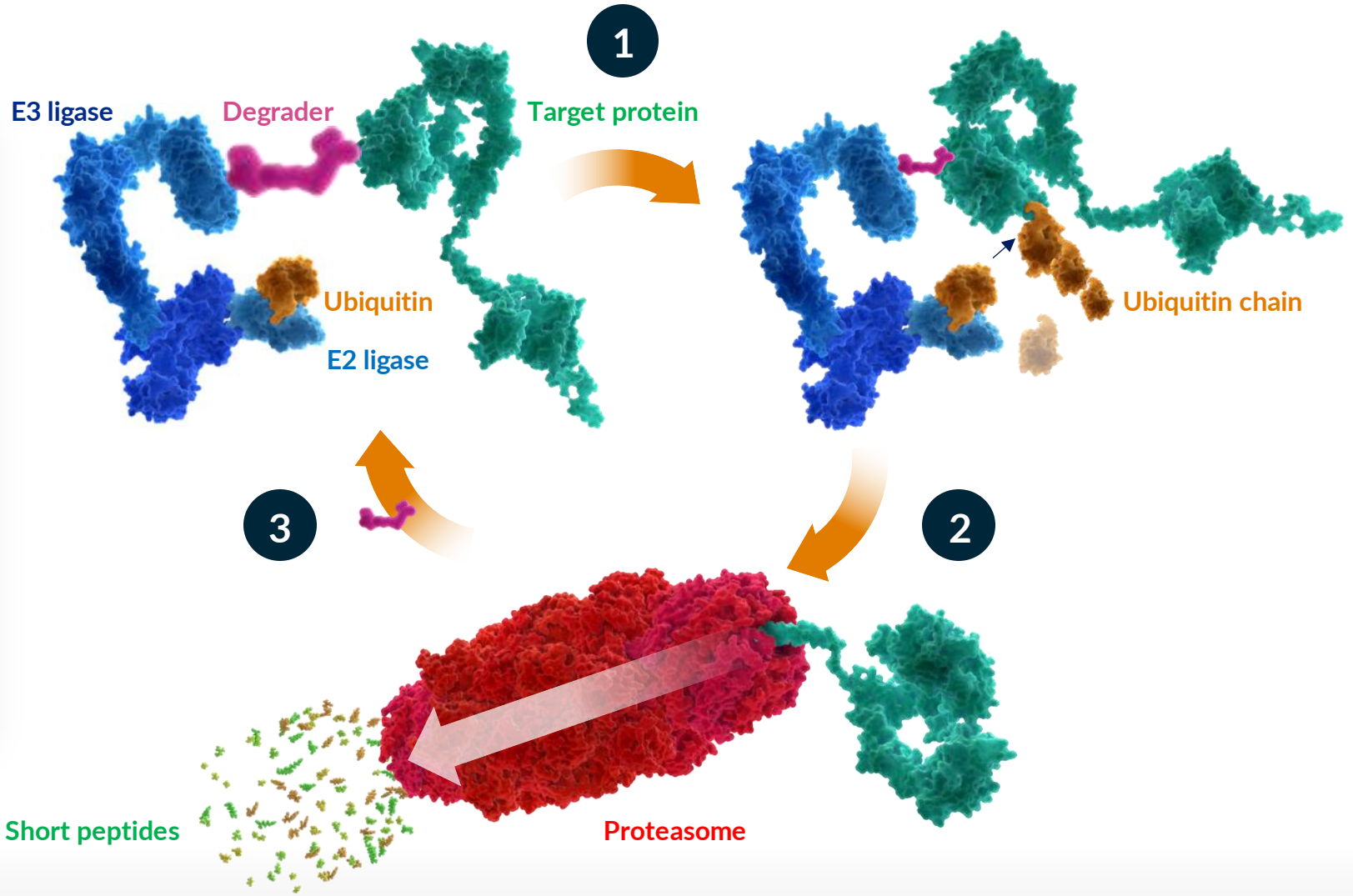
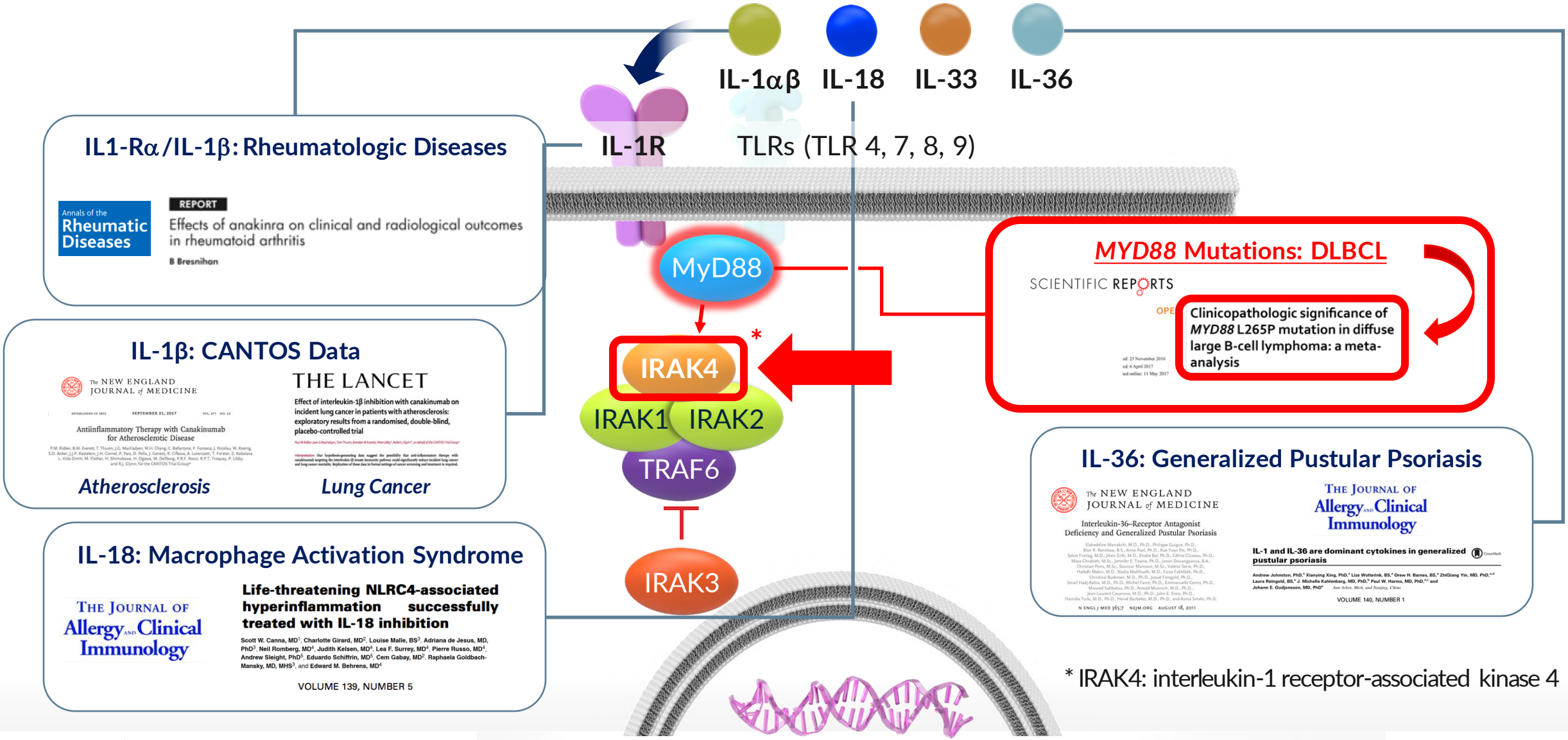
Targeted Protein Degradation

- The ubiquitin–proteosome system (UPS) can be harnessed for targeted protein degradation
- Only a binding site on the target protein is required
- Target selectivity based on ternary complex formation
- Sub-stoichiometric, catalytic
- Limited by protein re-synthesis rate



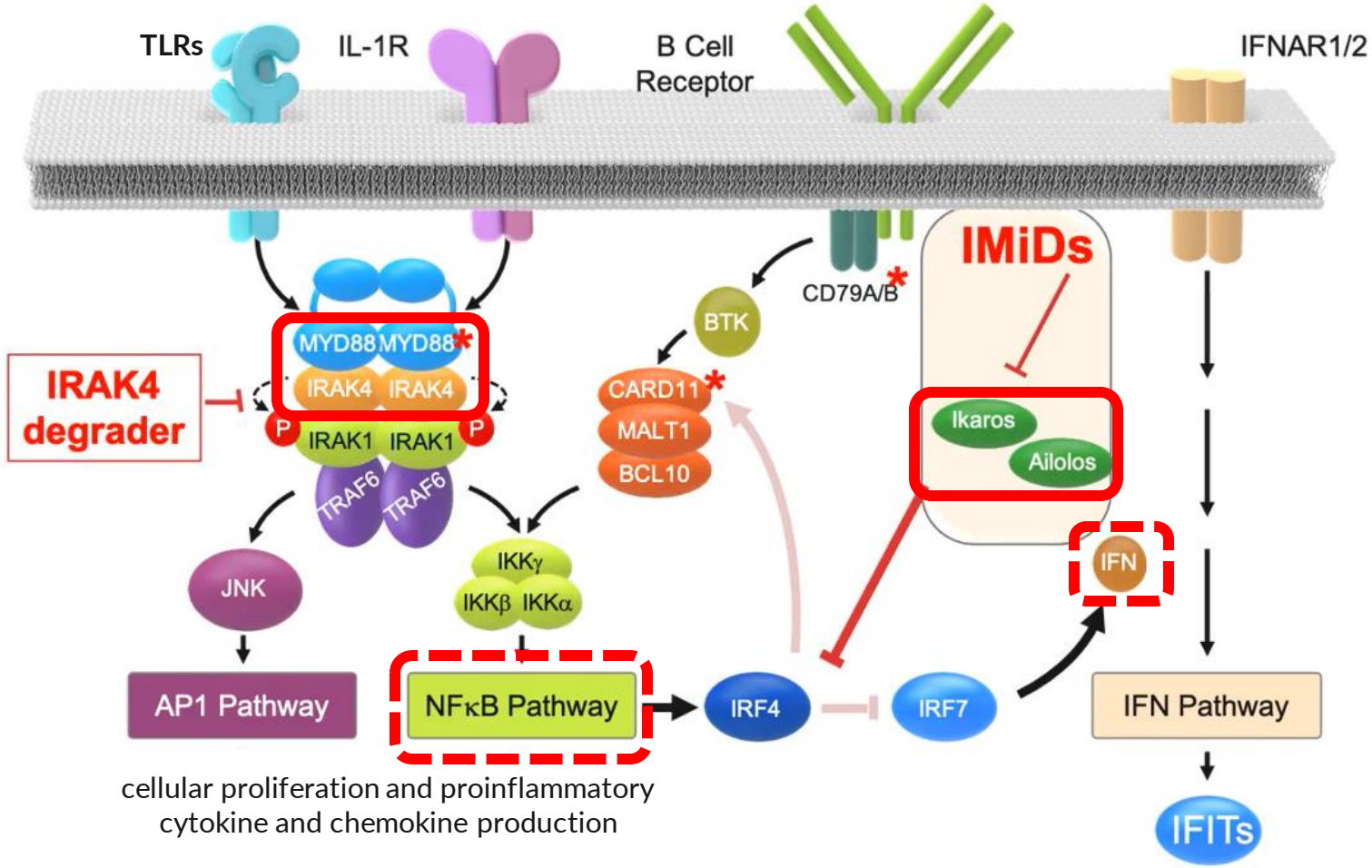
IRAK4 Target Validation



* IRAK4: interleukin-1 receptor-associated kinase 4

Therapeutic Hypothesis

- Disease indication: MYD88^{MT} diffuse large B-cell lymphoma (DLBCL)
- Hypothesis: degraders targeting both IRAK4 and immunomodulatory drug (IMiD) substrates may shutdown two redundant, pro-survival NFκB activation pathways and upregulate Type 1 IFN for improved efficacy versus single-pathway modulators
- Would rely on the E3 ligase cereblon (CRBN) to degrade IMiD substrates

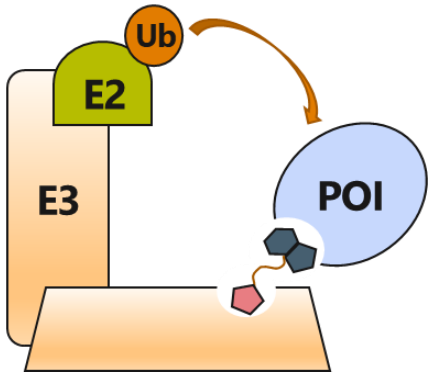


* Frequently mutated proteins in ABC-DLBCL

IRAKIMiD Concept

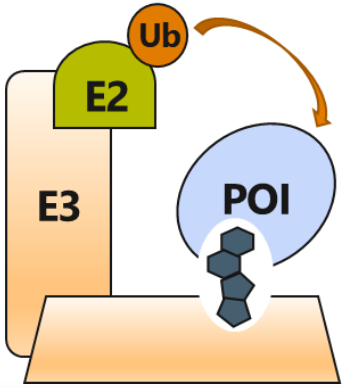
Single-mechanism Degraders:
One Molecule, One Mechanism

Heterobifunctional degrader of a POI

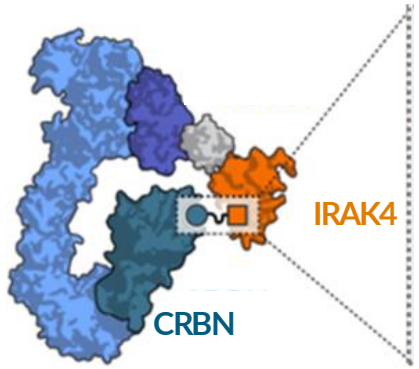


or

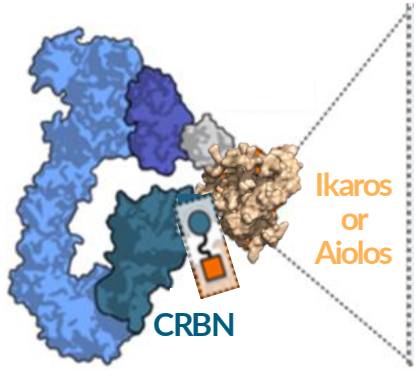
Molecular glue degrader of a POI



Dual-mechanism Degrader:
One Molecule, Two Mechanisms



and



IRAKIMiD:

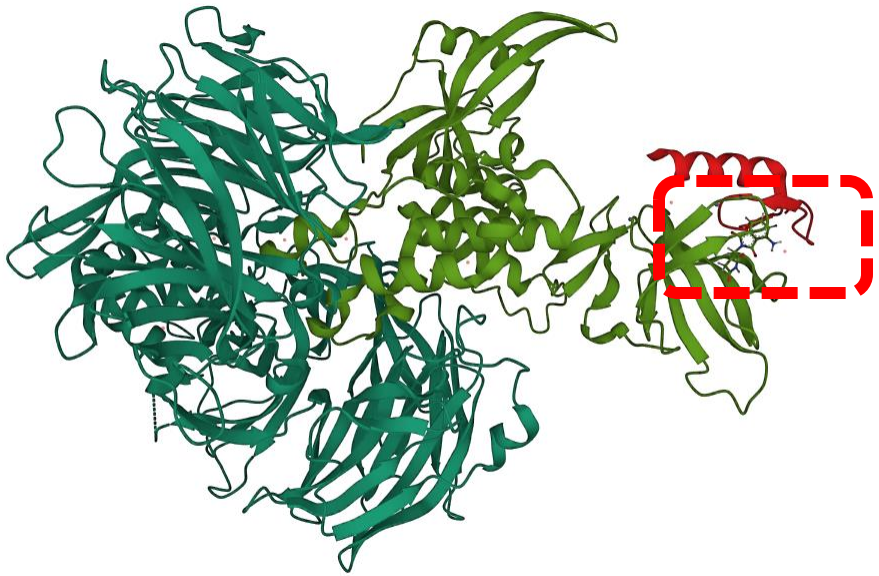
Heterobifunctional degrader of IRAK4

and

Molecular glue degrader of IMiD substrates

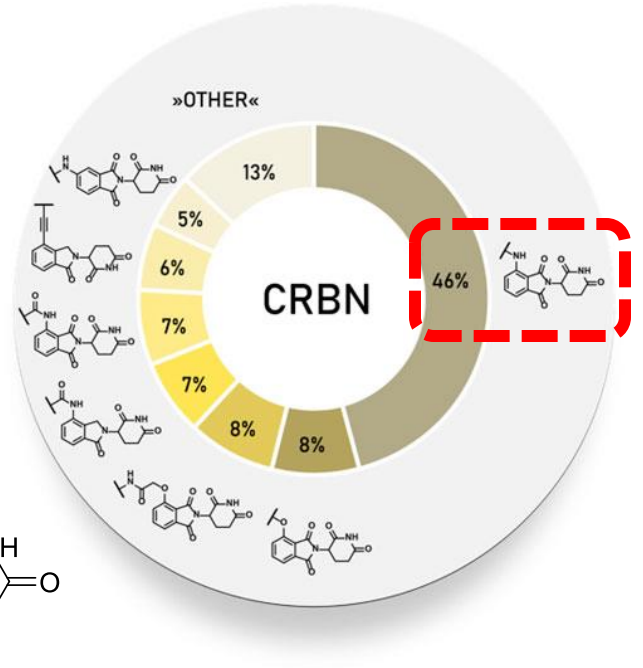
CRBN Ligand Selection

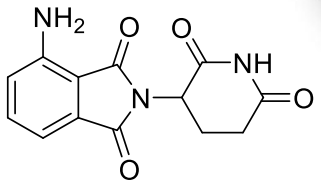
- **Cereblon (CRBN)**
  - Common E3 ligase used for targeted protein degradation (TPD)[1]



X-ray: DDB1$^{\Delta B}$-CRBN$^{\Delta N40}$ bound to pomalidomide and IKZF1^{ZF2} (6H0F)[2]

- **Pomalidomide (POM)**
  - Common CRBN ligand used in heterobifunctional degraders[1]

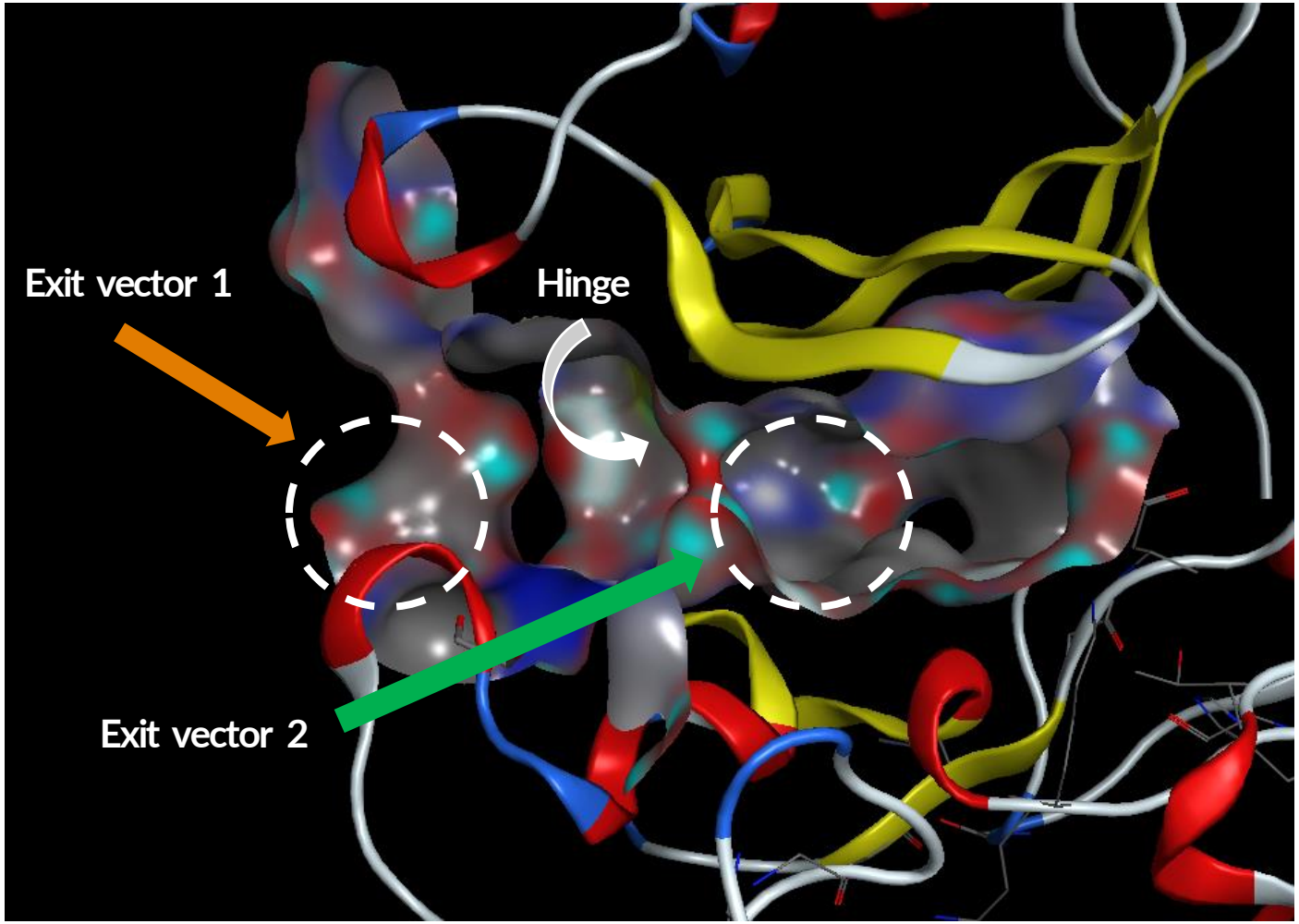




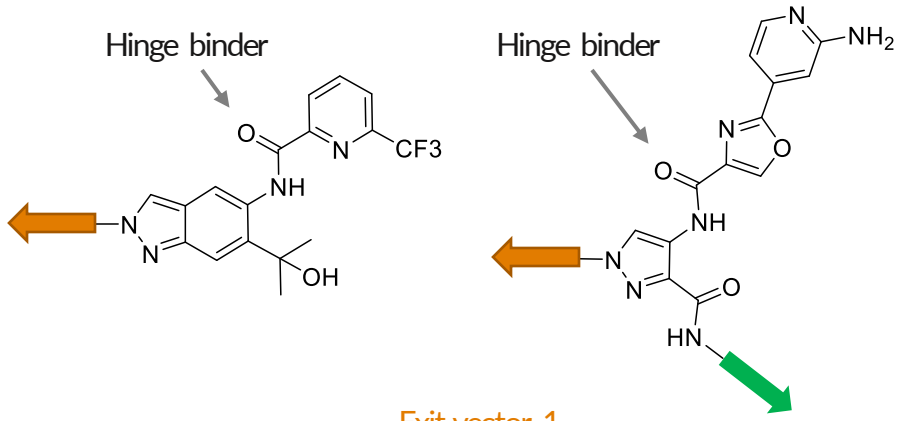
pomalidomide

[1] Gütschow, M.; Sosič, I.; et al. *Front. Chem.* **2021**, *9*, 707317. [2] Ebert, B. L.; Thomä, N. H.; et al. *Science* **2018**, *362*, eaat0572.

IRAK4 Ligands and Exit Vectors Identification

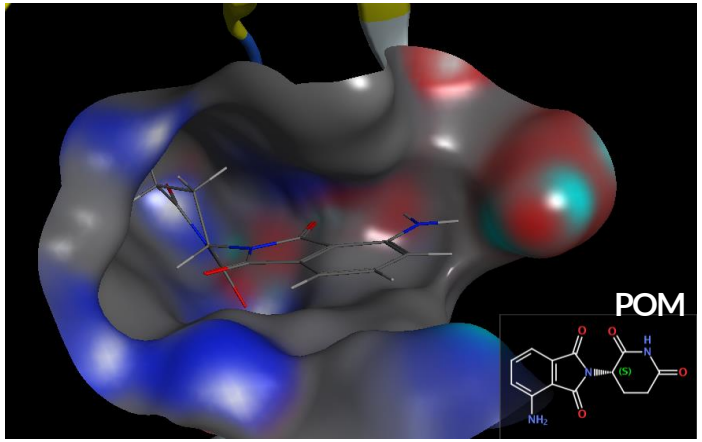


Subset of IRAK4 Ligands Incorporated into Exploratory Tool Degraders of IRAK4

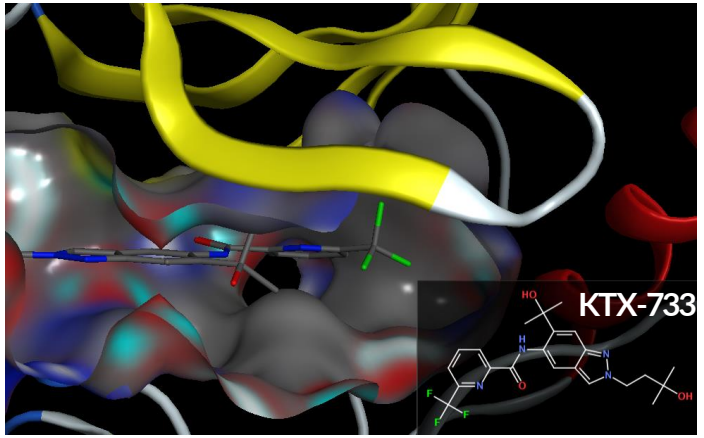


Exploratory studies showed IRAK4 degradation using multiple IRAK4 ligands and multiple exit vectors

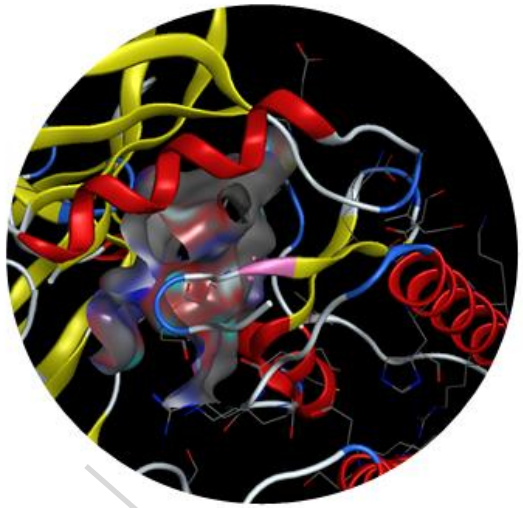
Ternary Complex Modeling



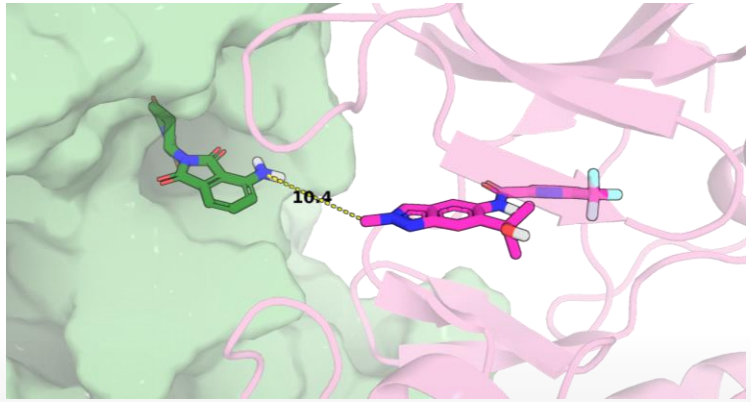
X-ray: POM bound to CRBN-DDB1



X-ray: KTX-733 bound to IRAK4



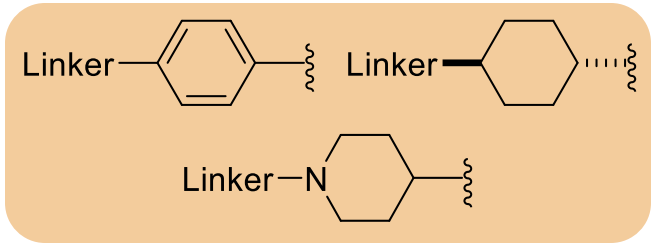
X-rays and exploratory SAR inform design of ternary complex model

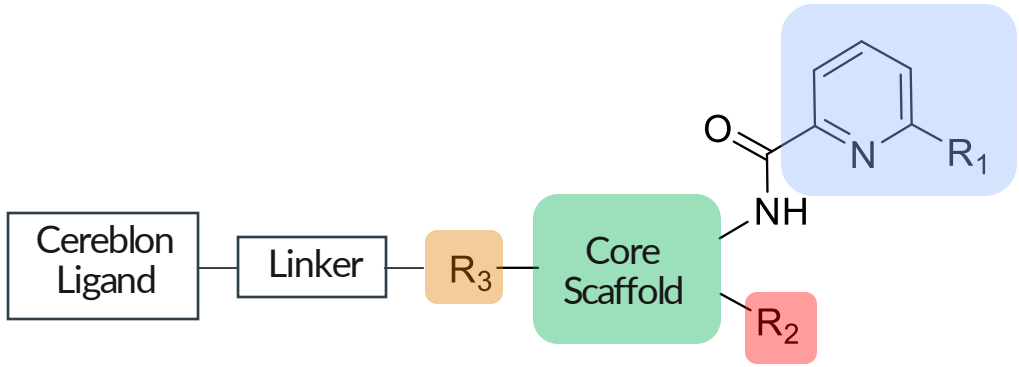


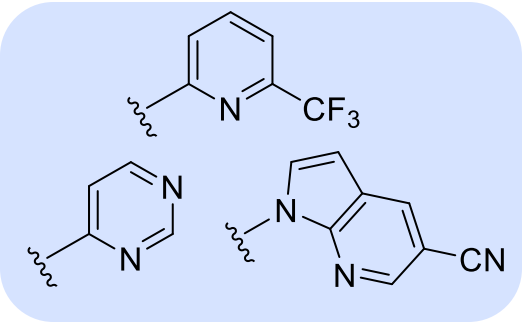
Ternary complex model to guide and inspire degrader design

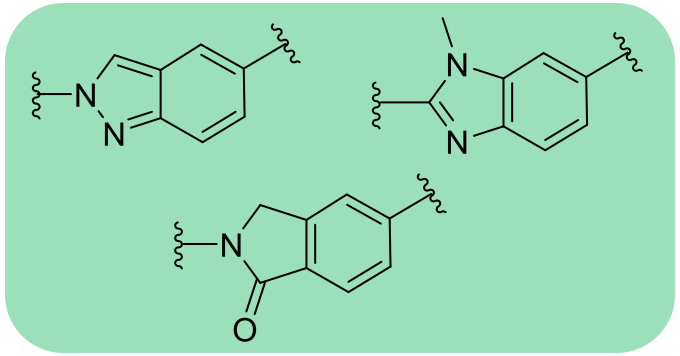
Representative Motifs Explored

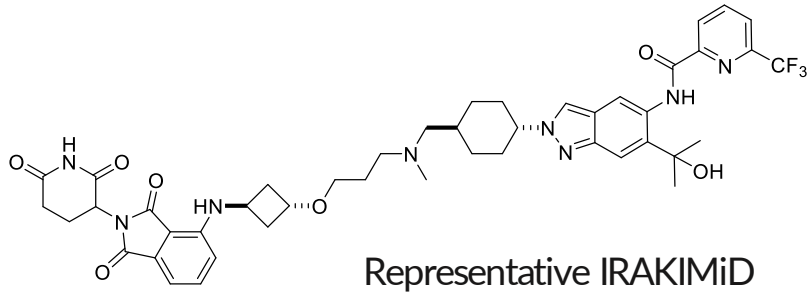
- Extensive exploration of IRAK4 ligand and linker required to probe SAR for both IRAK4 and IMiD substrate degradation
- Indazole scaffold became primary focus due to kinome selectivity, modularity, and ability to tune properties



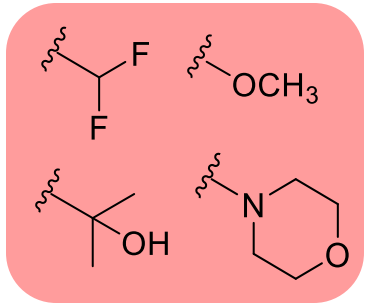




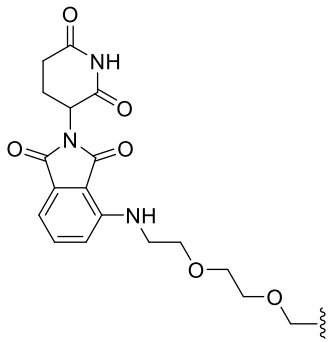


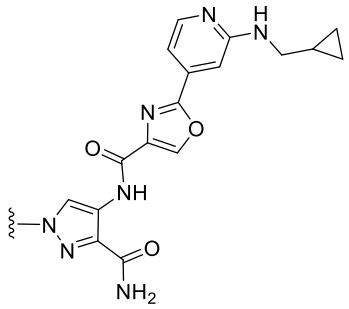


Representative IRAKIMiD

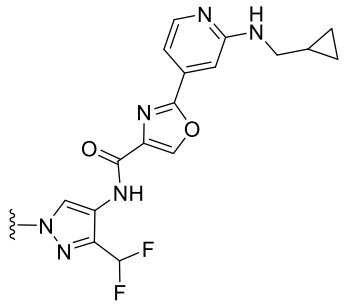


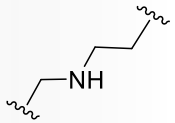
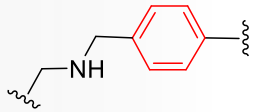
Improving IRAK4 Degradation Potency

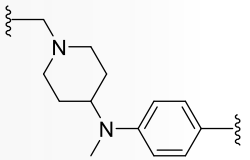
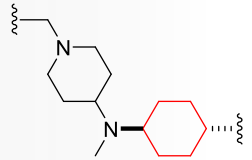




CRBN Ligand

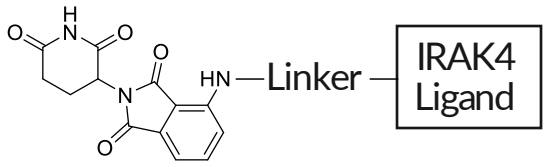


Parameter	KTX-671	KTX-315
Linker		
OCI-Ly10 Cell IRAK4 DC_{50}(nM)	**> 1,000**	**22**

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

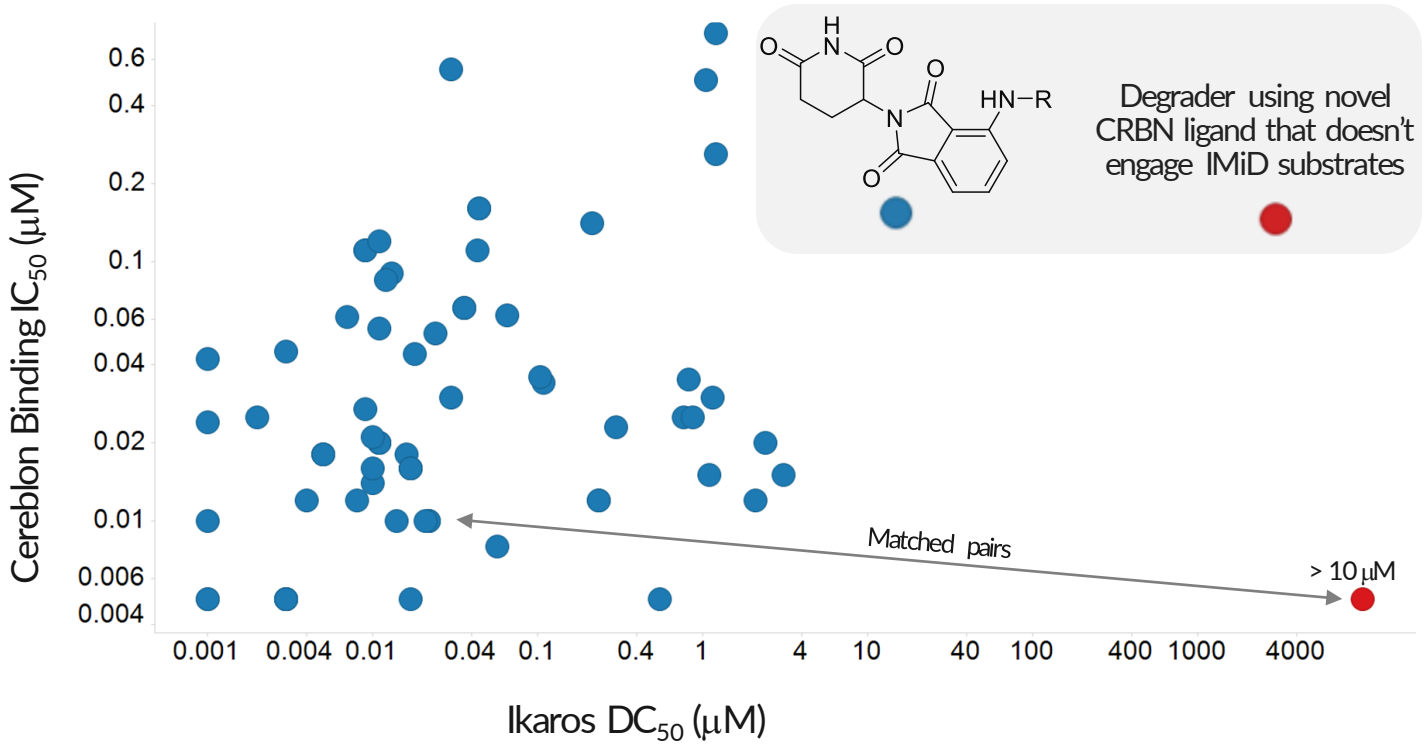
Linker modifications to alter POI exit vector directionality and rigidity can improve IRAK4 degradation potency
(All compounds have the same binding affinity for CRBN and IRAK4)

Degradation Potency Versus Binding Affinity



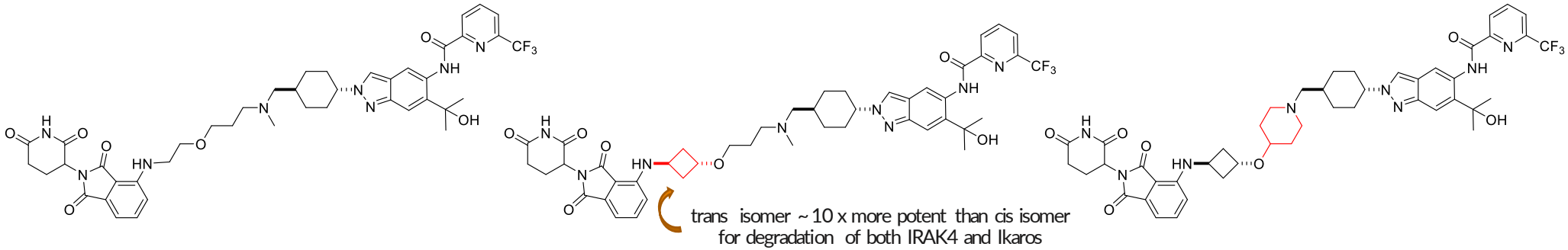
Parameter	KTX-326	KTX-951	KTX-178
IRAK4 Ligand	**Ligand A**	**Ligand B**	**Ligand C**
IRAK4 K_d (nM)	**0.30**	**3.5**	**28**
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**8.0**	**18**	**15**

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



- Ikaros degradation potency not correlated with CRBN ligand binding affinity

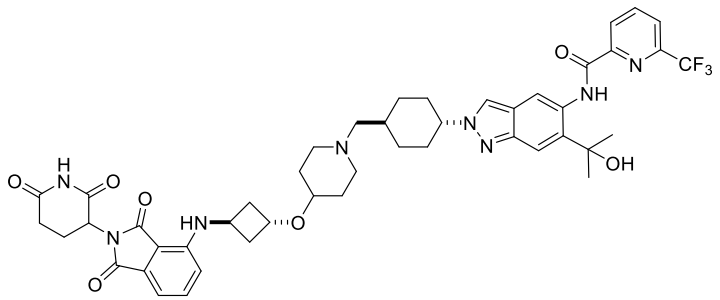
Modulating IRAKIMiD Potency and Intrinsic Clearance

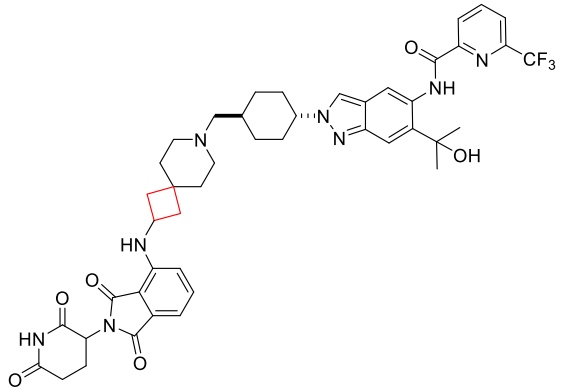


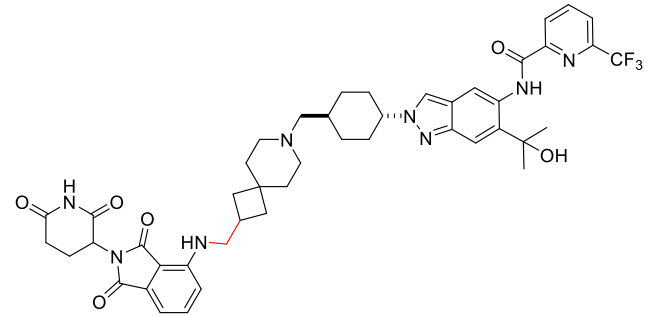
Parameter	KTX-435	KTX-582	KTX-955
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**18**	**4.0**	**5.0**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**12**	**5.0**	**130**
HLM CL_{int} (µL/min/mg)	**60**	**48**	**4.0**

Linker modifications can positively impact IRAK4 degradation potency and intrinsic clearance, but can negatively impact Ikaros and Aiolos degradation potency

Merging IRAKIMiD Potency and Intrinsic Clearance



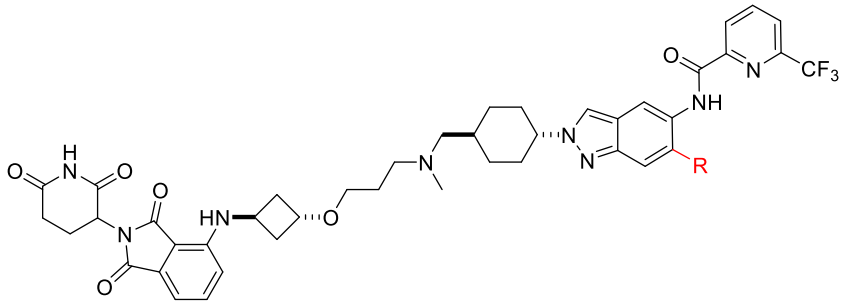


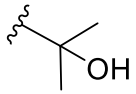
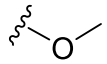


Parameter	KTX-955	KTX-497	KTX-612
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	5.0	3.0	7.0
OCI-Ly10 Cell Ikaros DC_{50} (nM)	130	25	6.0
HLM CL_{int} (µL/min/mg)	4.0	1.0	3.0
RLM CL_{int} (µL/min/mg)	4.0	3.0	2.0
Rat PPB (f_u)	0.096	0.079	0.026
Rat IV CL (mL/min/kg)	7.0	13	14
Rat PO %*F* (AUC, µM*hr)	29 (5.3)	17 (1.4)	1.0 (0.060)

More exposed PSA of NH group of KTX-612 relative to KTX-497 may lead to lower oral absorption

Balancing IRAKIMiD Potency and Metabolic Stability

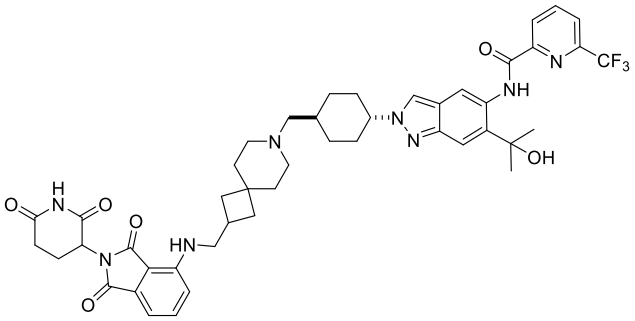


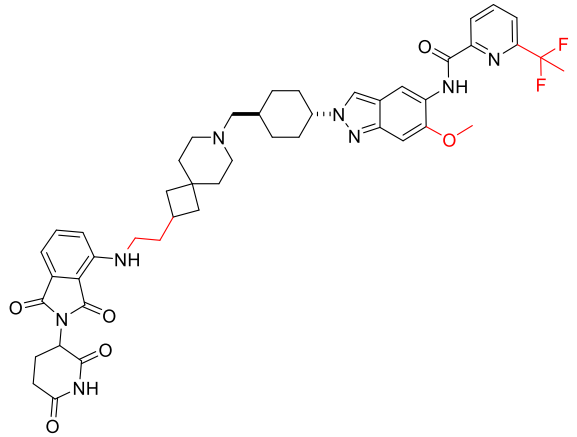
R =  R = 

Parameter	KTX-582	KTX-961
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**4.0**	**19**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**5.0**	**28**
HLM CL_{int} (µL/min/mg)	**48**	**4.0**
RLM CL_{int} (µL/min/mg)	**26**	**10**
MDCK Cell P_{app} A→B (x 10^{-6} cm/s)	**4.9**	**2.1**
Rat PPB (f_u)	**0.039**	**0.066**
Rat IV CL (mL/min/kg)	**34**	**19**
Rat PO %*F* (AUC, µM*hr)	**37 (2.0)**	**21 (1.1)**

- Tertiary alcohol analogues consistently show better potency
- Methoxy analogues consistently show better metabolic stability
- Both tertiary alcohol and methoxy analogues could provide access to compounds with moderate clearance and good oral bioavailability

Achieving IRAKIMiD Potency and Oral Absorption

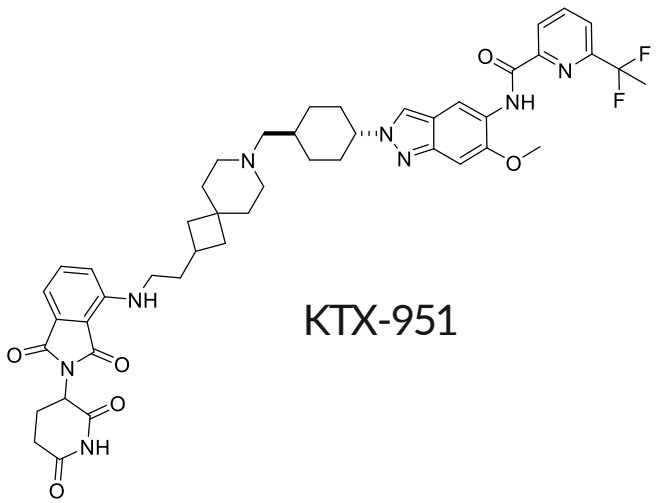




Parameter	KTX-612	KTX-951
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**7.0**	**13**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**6.0**	**14**
OCI-Ly10 Cell Aiolos DC_{50} (nM)	**4.0**	**13**
HLM CL_{int} (µL/min/mg)	**3.0**	**2.0**
RLM CL_{int} (µL/min/mg)	**2.0**	**3.0**
Rat PPB (f_u)	**0.026**	**0.073**
Rat IV CL (mL/min/kg)	**14**	**4.0**
Rat PO %*F* (AUC, µM*hr)	**1.0 (0.060)**	**22 (2.6)**

Reducing number of HBDs may contribute to improved oral absorption in some instances

Attaining Favorable Pharmacokinetic Profiles in Rat and Dog



KTX-951

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

Parameter	Value
MDCK Cell P_{app} A→B (x 10^{-6} cm/s)	**1.1**
FaSSIF solubility (μM)	**21**
FeSSIF solubility (μM)	**20**

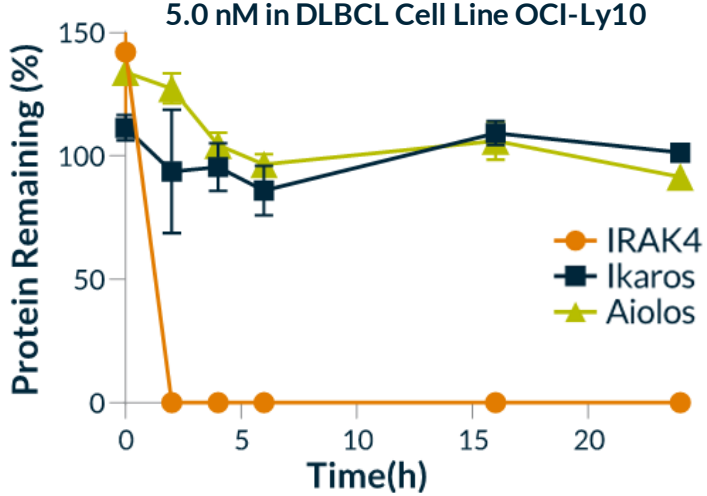
Good oral bioavailability may be attainable, despite modest solubility and permeability

IRAK4 Degrader vs IRAKIMiD Degrader: Degradation

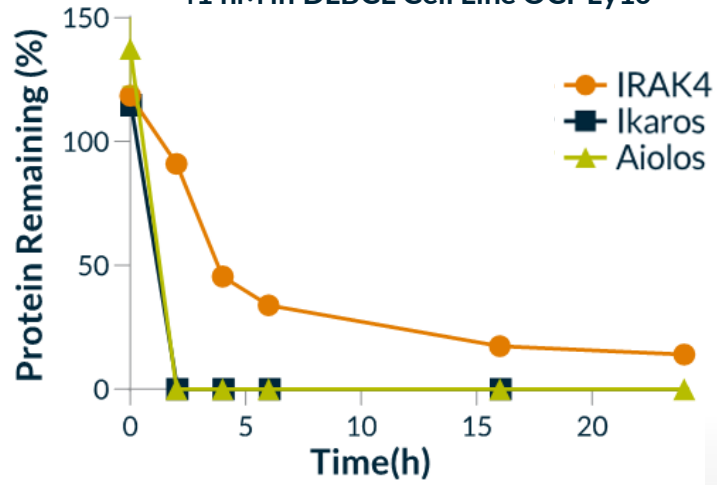
Parameter	KTX-545	KT-413
	IRAK4 Degrader (Tool Compound)	IRAKIMiD Degrader (Clinical Compound)
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**1.0**	**6.0**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell Aiolos DC_{50} (nM)	**> 1,000**	**2.0**

- 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

Degradative Activity of IRAK4 Degrader KTX-545
5.0 nM in DLBCL Cell Line OCI-Ly10



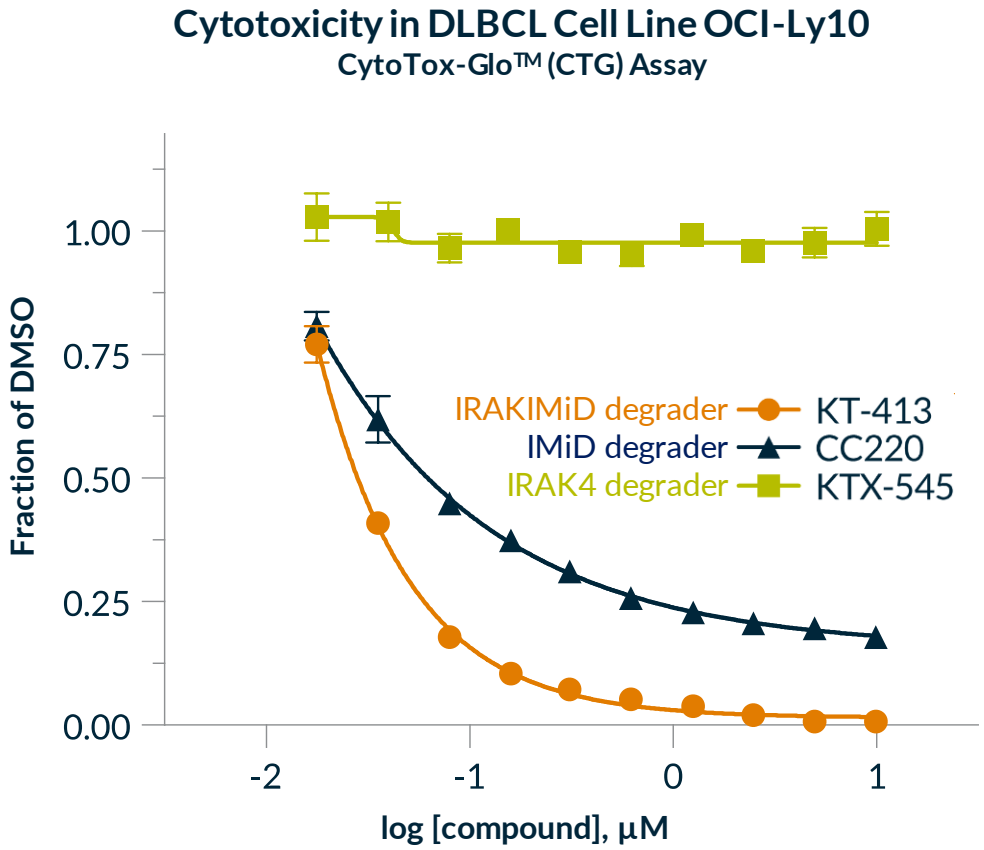
Degradative Activity of IRAKIMiD Degrader KT-413
41 nM in DLBCL Cell Line OCI-Ly10



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

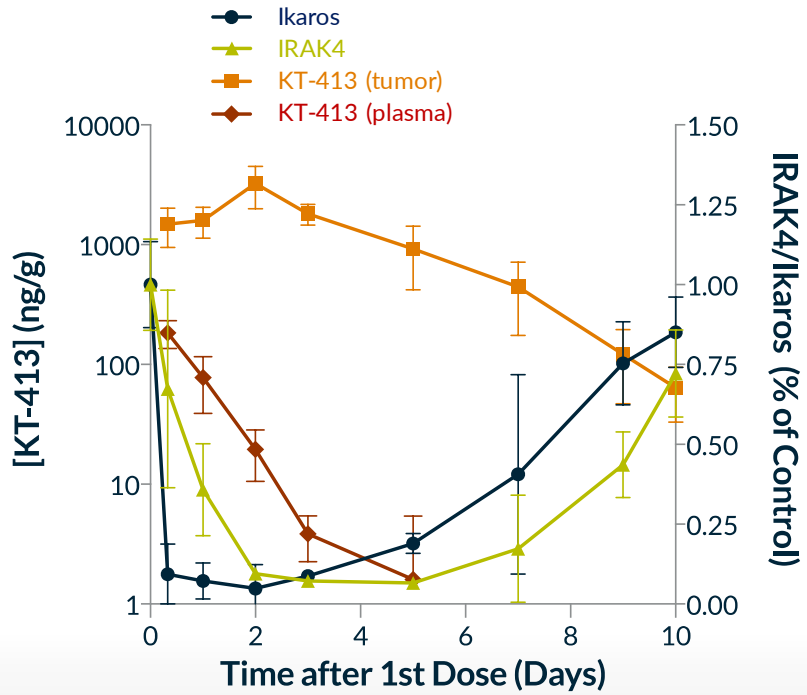
Parameter	KTX-545	KT-413
	IRAK4 Degrader (Tool Compound)	IRAKIMiD Degrader (Clinical Compound)
OCI-Ly10 Cell IRAK4 DC_{50} (nM)	**1.0**	**6.0**
OCI-Ly10 Cell Ikaros DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell Aiolos DC_{50} (nM)	**> 1,000**	**2.0**
OCI-Ly10 Cell CTG IC_{50} (nM)	**> 10,000**	**9.0**



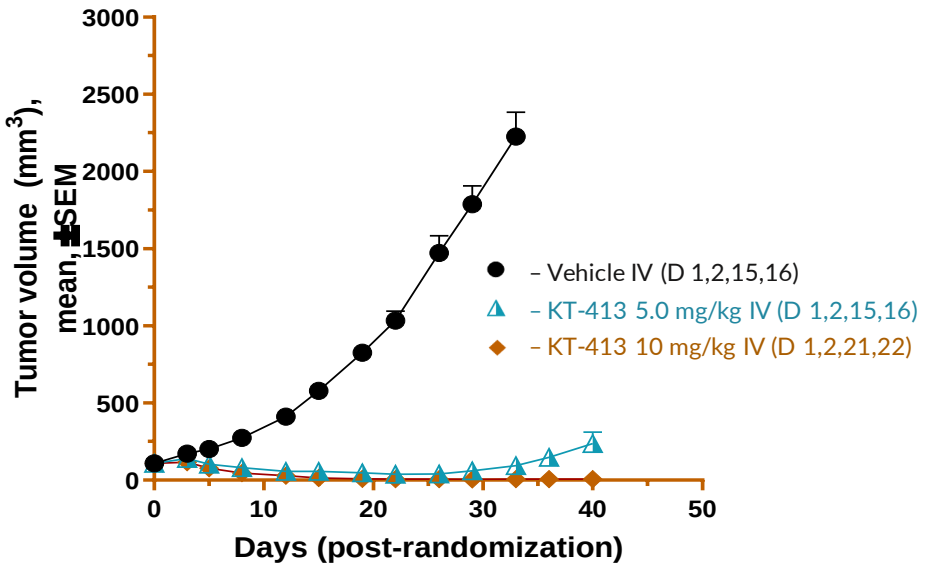
KT-413 Is Highly Active on Intermittent Dosing Regimens in a Cell-derived Xenograft Model (CDX) in Mouse

- In the DLBCL cell line OCI-Ly10 (MYD88^{MT}) xenograft model, minimally active dose of 3.0 mg/kg D 1,2 showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates, maintained for at least 72 h
- Intermittent dosing of KT-413 induced strong antitumor activity, including complete or partial regressions

PK–PD in Mouse CDX Model
DLBCL Cell Line OCI-Ly10 (3.0 mg/kg IV, D 1,2)

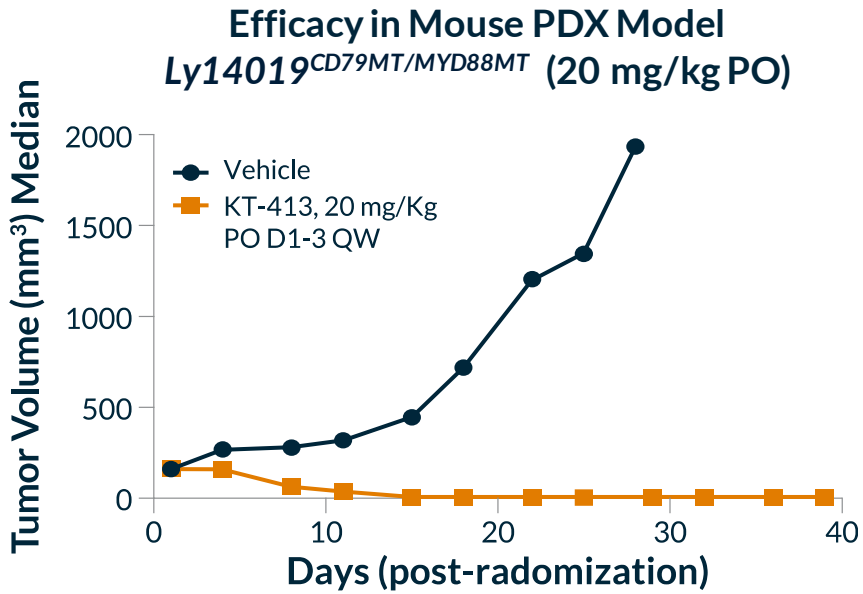


Efficacy in Mouse CDX Model
DLBCL Cell Line OCI-Ly10 (5.0 or 10 mg/kg IV)



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

Model	MYD88	CD79B	TNFAIP3	Other	% 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**

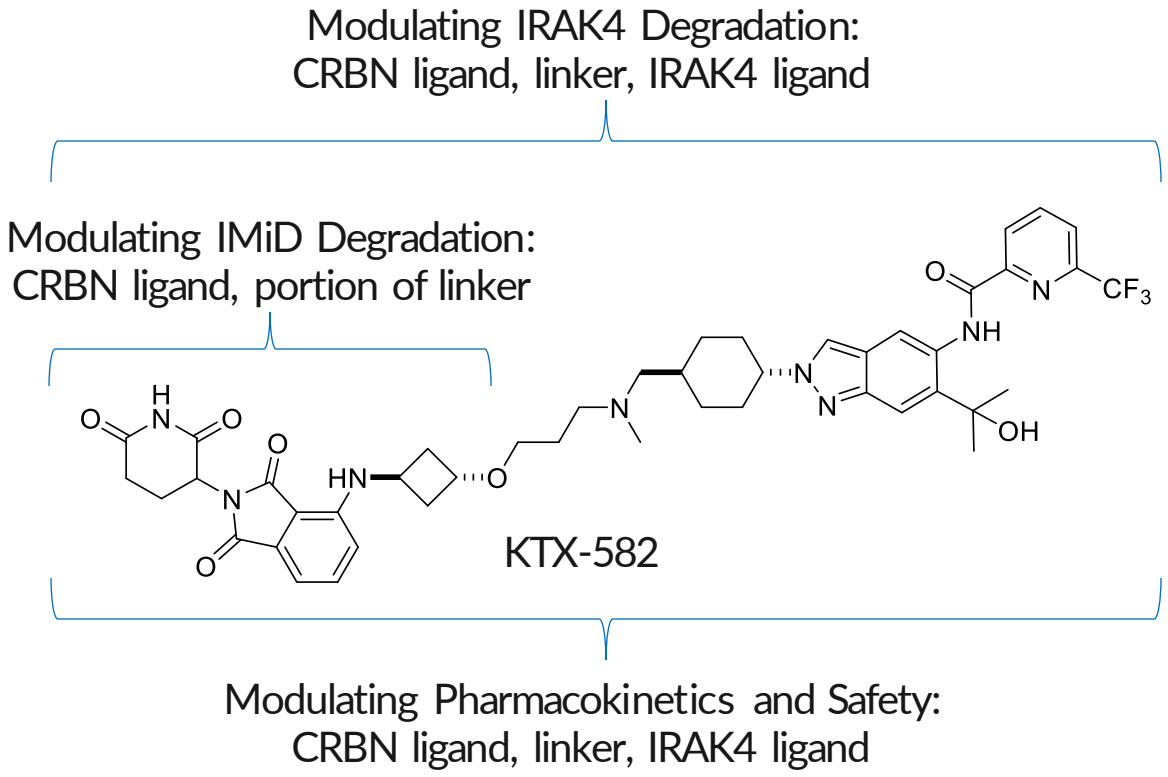


KT-413 shows strong tumor growth inhibition (> 85% TGI) in 4/5 MYD88-mutated DLBCL PDX models in mouse

- 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 ikaros and aiolos
  - 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



Acknowledgments