Targeting MYD88-Mutant DLBCL with IRAKIMiDs: A Comparison to IRAK4 Kinase Inhibition and Evaluation of Synergy with Rational Combinations

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Disclosures:

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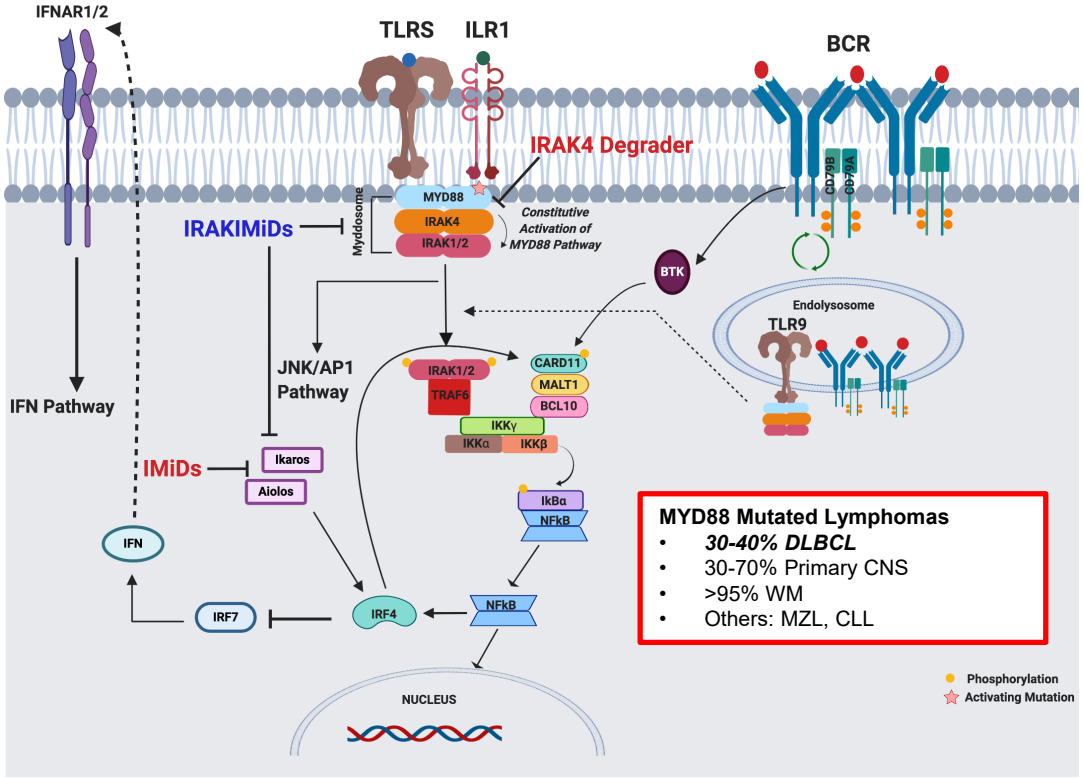
Role of IRAK4 in Lymphomagenesis

IRAKIMiDs are a Novel Therapeutic Option to Target MYD88-Mutated DLBCL



MYD88 Mutated Lymphomas

- ***30-40% DLBCL***
- 30-70% Primary CNS
- >95% WM
- Others: MZL, CLL

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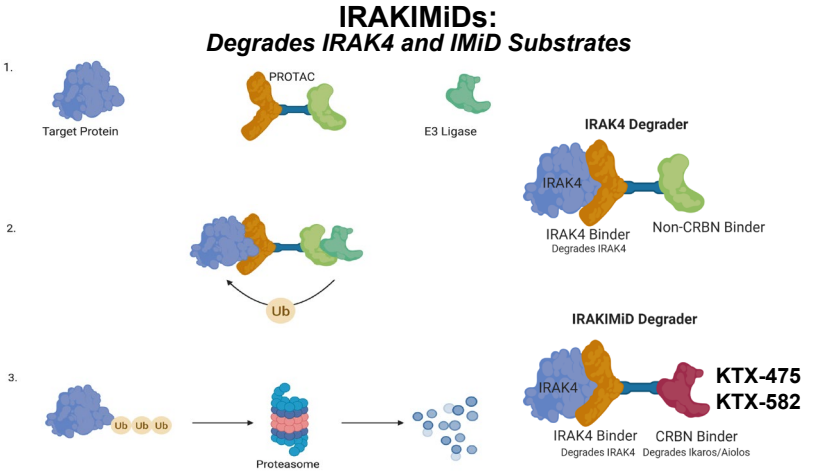


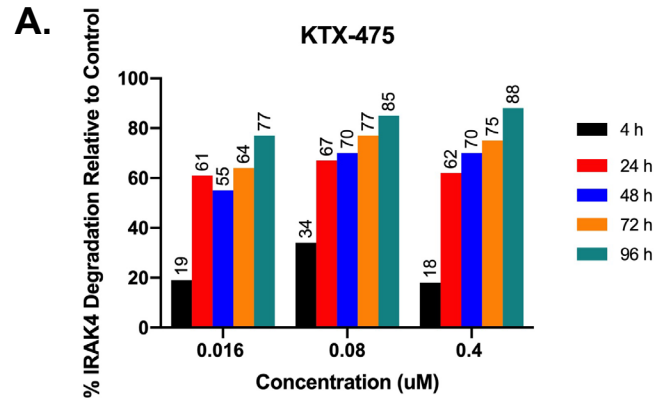
Hypothesis:

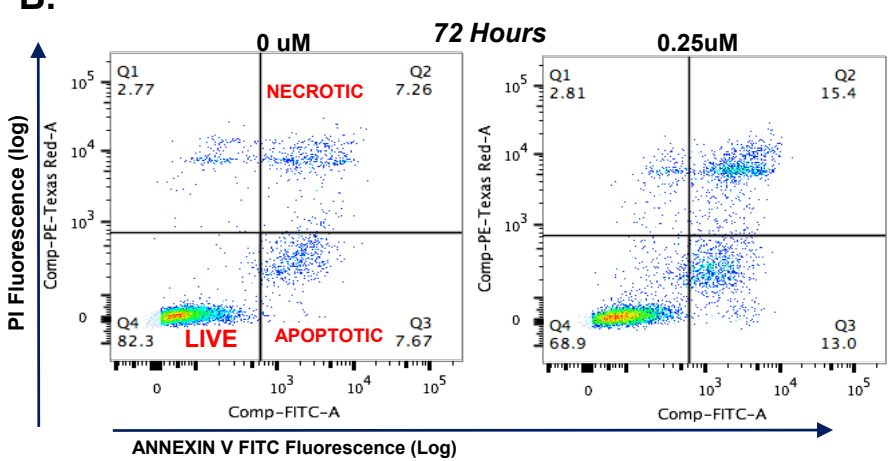
If recurrent mutations in MYD88 are associated with inferior prognosis in a subset of DLBCL patients, then targeting the degradation of IRAK4 and IMiD substrates will lead to potent cytotoxicity and serve as a potential therapeutic platform for the treatment of MYD88-addicted lymphomas

Lin SC et al. Nature 2010;465:885-90.
Phelan JD et al. Nature 2018;560:387-91

IRAKIMiDs Degrade IRAK4 and Induce Apoptosis

OCI-LY10 (MYD88/CD79A Mut)





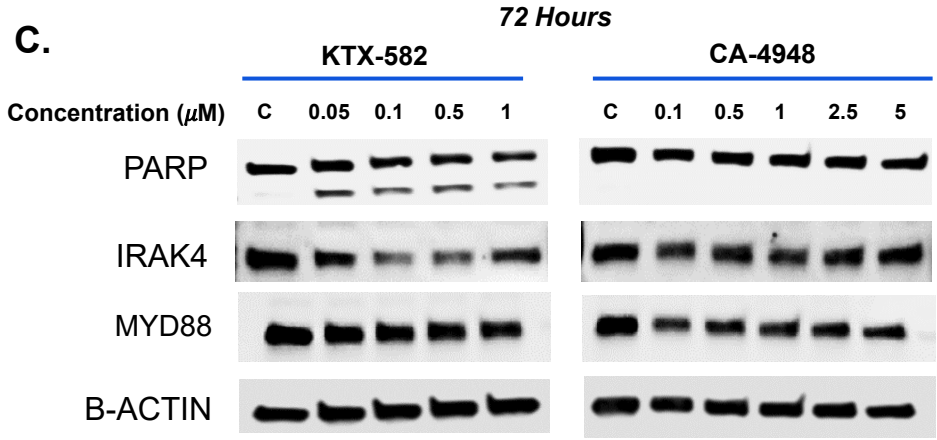
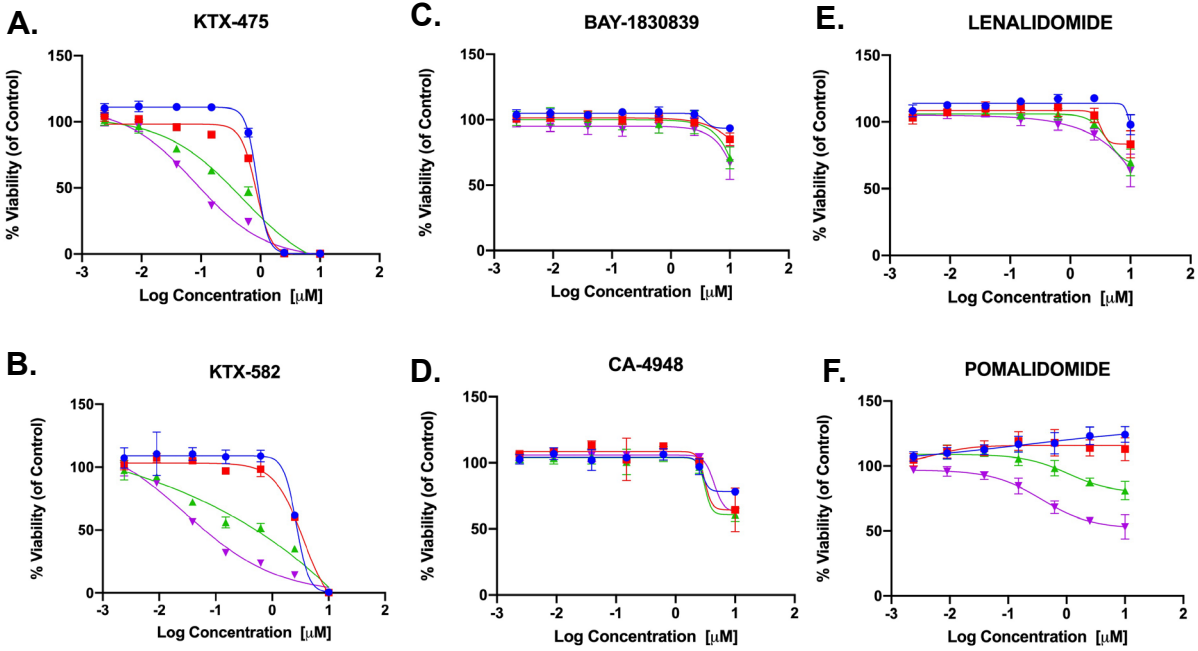


Figure 2:

A. After single administration of KTX-475, IRAK4 degradation is observed as early as 4 hours and is time and concentration dependent as assessed by flow cytometry
B. Apoptosis was confirmed after exposure to KTX-475 using flow cytometry
C. At equimolar concentrations, KTX-582 induces apoptosis (PARP cleavage) whereas the IRAK4 kinase inhibitor, CA-4948, does not

IRAKIMiDs Display Superior Efficacy Compared to IRAK4 Kinase Inhibitors and IMiDs



	COO	MYD88	CD79A/B
OCI-LY10	ABC	L265P	CD79A Mut

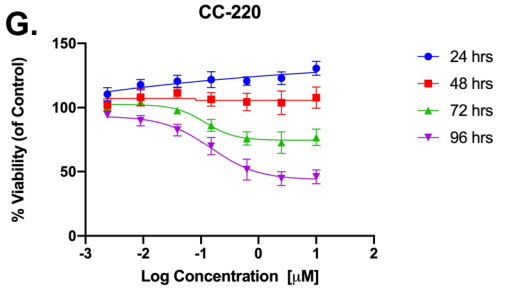


Figure 3:
A-G: As assessed by Cell-Titer Glo, IRAKIMiDs (KTX-475, KTX-582) can impair cell viability more effectively than IRAK4 Kinase inhibitors (BAY-1830839, CA-4948), and IMiDs (lenalidomide, pomalidomide, CC-220) at equimolar concentrations
H. Summary of IC50s at 48-96 hours in OCI-LY10 cell line

H.

IC50 (μM)																				
KTX-475 IRAKIMiD			KTX-582 IRAKIMiD			Bay-1830839 Kinase Inhibitor			CA-4948 Kinase Inhibitor			Lenalidomide IMiD			Pomalidomide IMiD			CC-220 IMiD		
48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H
0.71	0.26	0.08	3.36	0.34	0.05	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	0.35

Exposure to IRAKiMIDs leads to Superior Activity Compared to IRAK4 Kinase Inhibition and IMiDs in a Panel of DLBCL Cell Lines

		IC50 (μM)																			
		KTX-475			KTX-582			Bay-1830839			CA-4958			Lenalidomide			Pomalidomide			CC-220			
		48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	48H	72H	96H	
GCB	OCI-LY7 *TP53 Mut*	0.54	0.23	0.19	0.91	0.46	0.26	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	1.64	>5.0	>5.0	0.44	Wild type MYD88
GCB	SUDHL-10 *TP53 Mut/MYC Mut*	0.61	0.11	0.08	0.92	0.18	0.10	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	0.86	0.16	>5.0	1.70	1.46	Wild type MYD88
	RIVA *TP53 Mut*	1.51	0.82	0.85	3.42	2.04	1.91	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	>5.0	Wild type MYD88
	U-2932 *Hemizygous A20 deletion*	3.51	1.99	1.27	2.76	2.57	1.60	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	>5.0	Wild type MYD88
ABC	OCI-LY10 *MYD88L265P/CD79Mut*	0.71	0.26	0.08	3.36	0.34	0.05	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	0.35	Mutated MYD88
ABC	OCI-LY3 *MYD88L265P/CD79Mut/CARD11Mut*	0.55	0.39	0.07	3.64	0.20	0.08	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	0.14	> 5.0	> 5.0	3.46	>5.0	>5.0	0.38	Mutated MYD88
ABC	HBL-1 *MYD88L265P/CD79Mut*	1.58	1.99	2.09	2.35	2.23	2.77	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	>5.0	Mutated MYD88
ABC	SUDHL-2 *MYD88S222R/A20Mut*	0.70	0.53	0.44	1.57	0.65	0.61	>3.3	>3.3	>3.3	>3.3	>3.3	>3.3	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	> 5.0	>5.0	>5.0	>5.0	Mutated MYD88

1. *IRAKIMiDs lead to superior cytotoxicity (lower IC50) compared to IRAK4 Kinase Inhibitors and IMiD compounds*
2. *IRAKIMiDs demonstrate activity in GCB-DLBCL cell lines paralleling activity observed with newer generation IMiDs alone*
3. *Within the ABC-DLBCL cell lines, MYD88-mutated DLBCL are more sensitive to IRAKIMiDs compared to MYD88-WT*

Mutational profiling: NSG Lymphoma Focus Panel

KTX-475 is Synergistic with Rational Compounds that Target ABC-DLBCL Biology

OCI-LY10 (MYD88/CD79A Mut)

A.

		KTX-475								
		48 Hours			72 Hours			96 Hours		
	nM	12.5	25	50	12.5	25	50	12.5	25	50
Ibrutinib	0.20	-4.49	-0.76	-2.53	0.83	4.21	9.07	9.82	17.84	18.17
	0.40	-8.22	-4.03	-7.30	-0.77	1.46	1.23	2.66	9.22	6.54
	0.50	3.26	-4.42	-4.48	-8.43	-3.10	-2.23	-5.71	0.13	0.00
Venetoclax	0.25	20.67	25.47	16.79	23.55	26.15	28.41	33.71	33.25	27.95
	0.50	8.23	17.40	31.21	28.58	34.68	39.84	39.81	46.60	37.05
	1.00	36.07	49.30	51.51	45.30	51.85	49.98	59.87	57.02	39.92
Umbralisib	4.00	6.31	5.03	8.24	-1.42	-4.68	1.45	-1.16	6.76	6.67
	10.00	-2.15	-2.10	-4.23	-2.97	-6.07	-3.64	-4.42	-1.40	-0.13
	20.00	-1.49	-2.32	-2.33	-12.87	-13.06	-9.55	0.82	9.21	3.82

EOB: 0

Synergy >0

B.

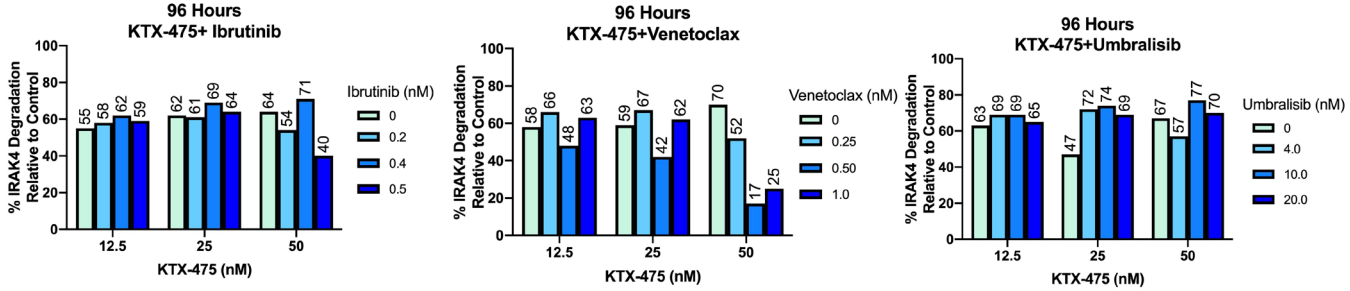


Figure 5:

A. Co-administration of KTX-475 and ibrutinib, venetoclax, or umbralisib led to synergy as assessed by Excess Over Bliss (EOB) method. (EOB>0 defines synergy)

B. Addition of ibrutinib, venetoclax or umbralisib does not significantly impact the degradation of IRAK4 by IRAKIMiDs over 96 hours of exposure

Conclusions

- Novel heterobifunctional degraders that target both IRAK4 and IMiD biology (IRAKIMiDs) leads to potent cell kill in DLBCL cell line models
- IRAKIMiDs induced superior cellular toxicity compared to IRAK4 kinase inhibition as determined by lower IC50s and induction of apoptosis
- MYD88-mutated ABC-DLBCL cell lines are more sensitive to IRAKIMiD exposure as compared to wild type
- Combination of IRAKIMiD in conjunction with ibrutinib, venetoclax and umbralisib is synergistic in the OCI-LY10 cell line model
- A lead IRAKIMiD candidate has been identified, and plans for first-in-human clinical trial in B-cell lymphomas is planned for second half of 2021

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THANK YOU!

Questions?

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