7536 KYM-001, first-in-class oral IRAK4 protein degraders, induce tumor regression in a xenograft model of MYD88-mutant ABC DLBCL alone and in combination with BTK inhibition LB-272

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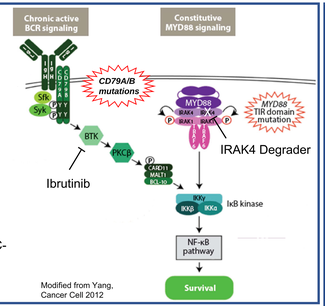
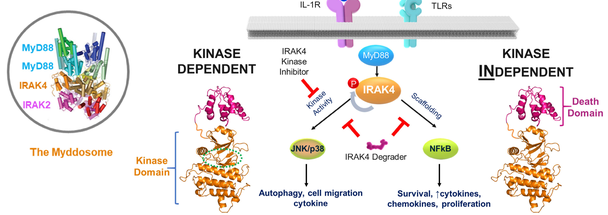
Introduction:

- Recurrent mutations in MYD88 drive 30-40% of ABC-DLBCL; MYD88 L265P is the most prevalent
- IRAK4 is a critical component of the Myddosome; IRAK4 catalytic and scaffolding functions are essential for full signaling to NFκB and MAPK pathways
- Kymera Therapeutics is developing heterobifunctional small molecule degraders of IRAK4 with drug-like properties, typified here with series KYM-001 Compounds A and B.
- IRAK4 Degrader Compounds A and B are close analogs, differing mainly in PK properties
- Activating mutations in CD79A and CD79B cause BTK-dependent activation of NFκB signaling in ABC-DLBCL, and often co-occur with MYD88 mutation, prompting exploration of combinations of IRAK4 degradation with BTK inhibition

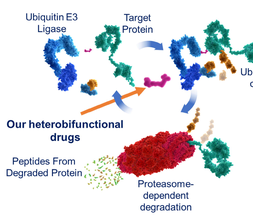


IRAK4 is a key node in IL-1R and TLR signaling downstream of MYD88, with kinase-dependent and kinase-independent functions



Overview of targeted protein degradation with heterobifunctional small molecules

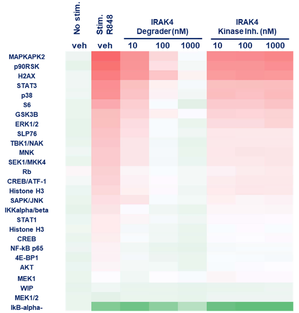
Mechanism of action:
- Bind simultaneously to Target Protein and to ubiquitin E3 ligase, bringing into physical proximity
- E3 ligase transfers ubiquitin to Target Protein
- Ubiquitinated Target is degraded by proteasome



Key features for developing therapeutics:
- Only a binding site is required
- Ternary complex-based selectivity
- Sub-stoichiometric, catalytic
- Protein re-synthesis rate limited
- Irreversible protein degradation

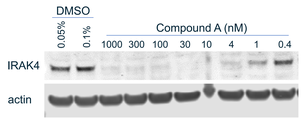
IRAK4 degradation is superior to IRAK4 kinase inhibition

TLR7/8 Induced Phosphoproteins in hPBMC

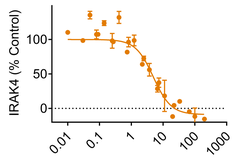


IRAK4 Degrader causes potent and highly selective depletion of IRAK4 in MYD88/CD79 double mutant human ABC-DLBCL cell line OCI-LY10

Immunoblot in OCI-LY10 at 24 h



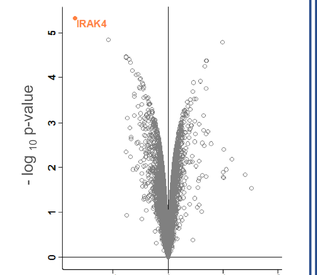
IRAK4 in OCI-LY10 MSD Assay at 4 h



In Vitro Degradation (DC_{90}, μM)
OCI-LY10 at 4 h: 0.02

Similar results were obtained with Compound B

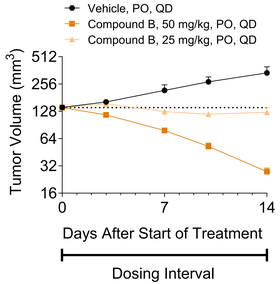
Deep TMT proteomics in OCI-LY10 at 8 h



Number of unique proteins groups	11,231
Number of quantified proteins groups	10,992
Number of proteins with >1 unique peptides and quantified	9,526

TMT = Tandem Mass Tag

IRAK4 Degrader administered PO once daily causes tumor xenograft regression in association with ≥ 75% IRAK4 reduction in OCI-LY10

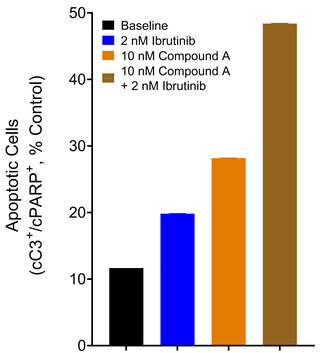


PO Dose (mg/kg)	Total Plasma Exposure (μM)	Tumor IRAK4↓ (% Control ± SD, day 5)
25	0.15	65.4 ± 8.2
50	0.34	75.3 ± 3.5

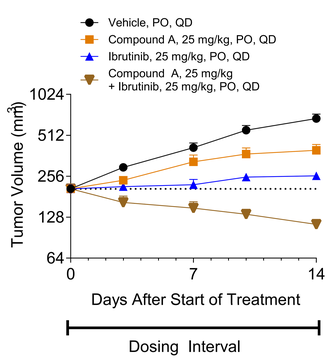
Similar results were obtained with Compound A

IRAK4 Degrader and ibrutinib show strong combination activity for induction of apoptosis in OCI-LY10 *in vitro* and induce tumor xenograft regression when used together *in vivo* at suboptimal dose of IRAK4 Degrader

Apoptosis in OCI-LY10 at 72 h *in vitro*



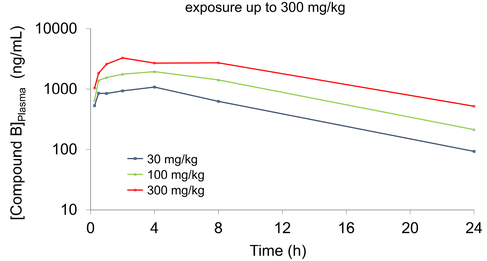
OCI-LY10 tumor xenograft growth *in vivo*



Similar results were obtained with Compound B *in vitro*

IRAK4 Degrader shows dose proportional oral exposure in mouse and is orally bioavailable in rat, dog and monkey

Compound B dosed orally in mice shows dose-proportional exposure up to 300 mg/kg



Compound B Shows promising PK characteristics in CD1 Mice

Species	Dose (mg/Kg)	Route	Cl (mL/min/Kg)	T½ (h)	AUC_{inst} (h*ng/mL)	%F
Mouse	2	IV	15	7.1	2050	-
	10	PO	-	5.4	2831	27

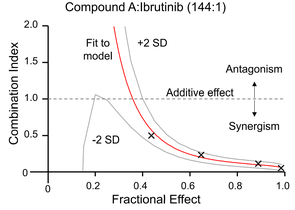
Compound A also shows dose proportional oral bioavailability in mouse

Compound B has oral bioavailability across species

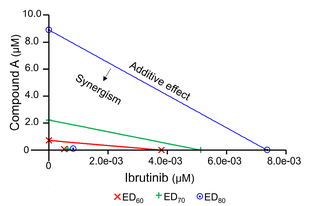
Species	%F
Mouse	27
Rat	35
Dog	35
Monkey	14

IRAK4 degradation is synergistic with inhibition of BTK by ibrutinib in 4-day Cell Titer Glo *in vitro* cell viability assay in OCI-LY10

Compound A:Ibrutinib (144:1)



Isobologram



Similar results were obtained with Compound B

Conclusions

- IRAK4 Degrader induced potent and selective E3 ligase-dependent degradation of IRAK4, with 90% degradation at concentrations less than 100 nM.
- IRAK4 degradation was highly selective compared to >10,000 other proteins quantified by tandem mass tagged proteomics in MYD88 L265P/CD79 double mutant ABC DLBCL cell line OCI-LY10.
- IRAK4 Degrader has dose proportional oral exposure in plasma at doses up to 300 mg/kg in mice
- IRAK4 Degrader has oral bioavailability in rat, dog and monkey, enabling pre-clinical safety studies
- Oral dosing of an IRAK Degrader showed dose-dependent antitumor activity against OCI-LY10, with ≥75% degradation of IRAK4 correlating with tumor regression in xenograft-bearing mice.
- In OCI-LY10, IRAK Degrader synergized with BTK inhibition by ibrutinib to decrease cell viability *in vitro*, as measured using 4-day Cell Titer Glo assay
- *In vitro*, the combined activity of an IRAK4 Degrader and Ibrutinib resulted in a greater than additive increase in apoptosis within 72 h in OCI-LY10
- *In vivo*, the combined activity of an IRAK4 Degrader and ibrutinib drove regression of OCI-LY10 at concentration of Degrader that is suboptimal as single agent, supporting further exploration of combinations that target oncogenic NFκB signaling.
- These preclinical studies with IRAK4 Degraders provide guidance on tumor PK/PD projected to be effective in patients, and further support pre-clinical assessment and clinical development of KYM-001 Compound A, Compound B and related leads in MYD88-driven lymphomas via oral route.

Disclosures: Kelleher, Campbell, Chen, Gollob, Ji, Kamadurai, Klaus, Li, Loh, McDonald, Rong, Rusin, Sharma, Vigil, Walker, Weiss, Yuan, Zhang and Mainolfi: *Kymera Therapeutics:* Employment, Equity Ownership.
Audoly: *Kymera Therapeutics:* Employment, Equity Ownership, Membership on an entity's Board of Directors.