2953 Targeted Degradation of IRAK4 Protein Via Heterobifunctional Small Molecules for Treatment of MYD88 Mutant Lymphoma

Joseph F. Kelleher, Veronica Campbell, Jesse Chen, Jared Gollob, Nan Ji, Hari Kamadurai, Christine Klaus, Henry Li, Christine Loh, Alice McDonald, Haojing Rong, Scott Rusin, Kirti Sharma, Dominico Vigil, Matt Weiss, Karen Yuan, Yi Zhang, Laurent Audoly and Nello Mainolfi, Kymera Therapeutics, Inc. 300 Technology Square, Cambridge, MA 02139. Contact: joe@kymeratx.com

Abstract Summary. See 2953 for full Abstract.

- Recurrent mutations in MYD88 drive 30-40% of ABC-DLBCL; MYD88 L265P is most prevalent mutation
- 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 KYM-001
- Key properties of KYM-001 *in vitro*:
  - Selective degradation of IRAK4 vs >10,000 other detected proteins in MYD88 mutant ABC-DLBCL line OCI-LY10
  - Induction of cell cycle effects and apoptosis within 48 - 72 h in OCI-LY10
  - Cytotoxicity in MYD88 mutant lymphoma cell lines
- Key properties of KYM-001 *in vivo*:
  - Exposure-dependent degradation of IRAK4 in OCI-LY10 xenograft with subcutaneous and oral dosing
  - Dose- and degradation-dependent inhibition of OCI-LY10 growth
  - Single agent tumor regression in MYD88 L265P mutant ABC-DLBCL xenograft model OCI-LY10
  - Strong activity in MYD88 L265P mutant ABC-DLBCL xenograft model TMD8
  - Targeted degradation of IRAK4 represents a promising new therapeutic opportunity for MYD88-driven lymphoma

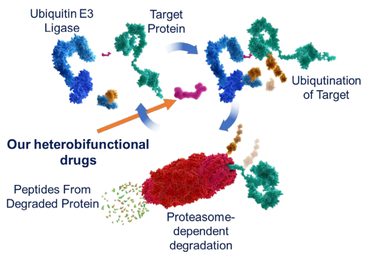
Overview of targeted protein degradation

BROAD OPPORTUNITY
ONLY BINDING SITE REQUIRED

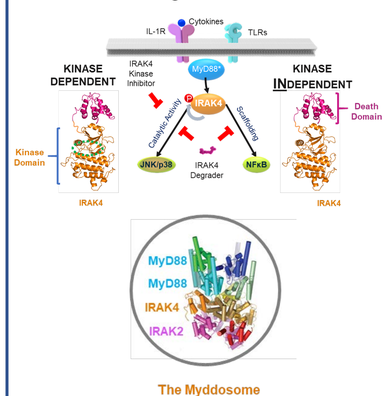
EFFICIENT
CATALYTIC

PROLONGED IMPACT
TARGET PROTEIN DEGRADATION

HITCHING A RIDE
UPS INTACT & FUNCTIONAL

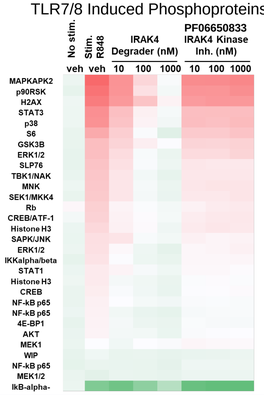


IRAK4 degradation is differentiated from kinase inhibition



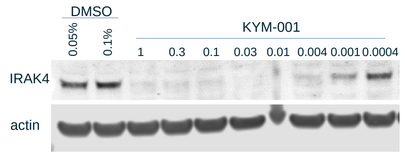
The Myddosome

TLR7/8 Induced Phosphoproteins

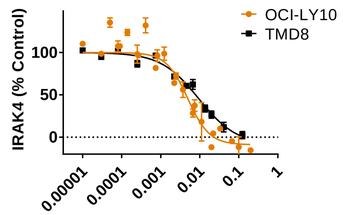


KYM-001 causes potent depletion of IRAK4 in MYD88 mutant lymphoma cell lines and is highly selective for IRAK4 vs >10,000 other proteins in OCI-LY10

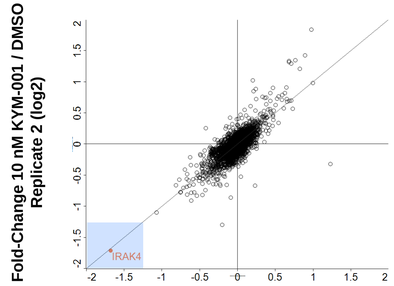
Immunoblot in OCI-LY10 at 24 h



IRAK4 in DLBCL Cell Lines MSD Assay at 4 h



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

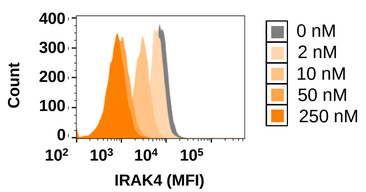
***In Vitro* Degradation (DC_{90}, μM)**

OCI-LY10 at 4 h:	0.18
TMD8 at 4 h:	0.044

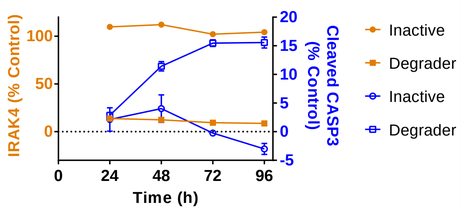
TMT = Tandem Mass Tag

KYM-001 treatment is cytotoxic and induces apoptosis in OCI-LY10 lymphoma line

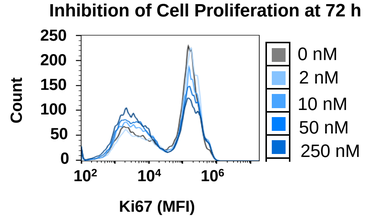
Decrease of IRAK4 at 24 h



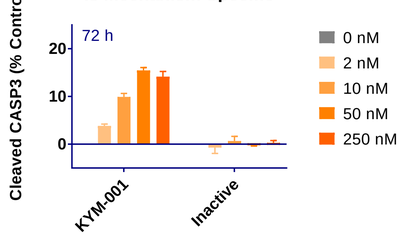
Time Dependent Induction of Apoptosis With 50 nM KYM-001



Inhibition of Cell Proliferation at 72 h



Induction of Apoptosis Is Mechanism Specific



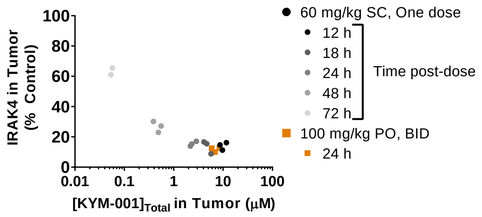
Cellular Viability (CTG; IC_{50}; μM)

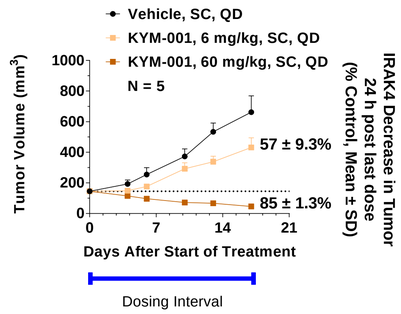
OCI-LY10 (MYD88 L265P):	0.19
TMD8 (MYD88 L265P):	0.33

Inactive = Analog of KYM-001 which does not bind E3

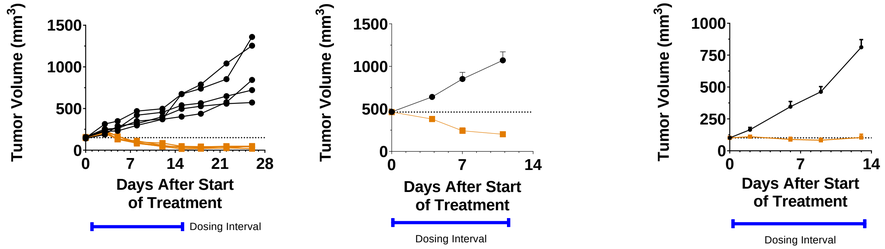
KYM-001 tumor PK/PD and relationship to anti-tumor effect in OCI-LY10

OCI-LY10 Tumor PK/PD: Terminal KYM-001 Exposure Correlates With IRAK4 Decrease





KYM-001 is highly active in two MYD88 mutant mouse xenograft models, OCI-LY10 and TMD8



Conclusions

- This is the first report of a potent, highly selective and efficacious IRAK4 degrader, KYM-001.
- KYM-001 is differentiated from other agents targeting the IL1R/TLR/ Myddosome signaling pathway and uniquely impacts the mechanism(s) driving MYD88 mutant lymphoma by degrading IRAK4.
- KYM-001 caused potent and specific degradation of IRAK4 in two MYD88-mutant ABC DLBCL cell lines, OCI-LY10 and TMD8, with DC_{90}'s of 180 and 44 nM, respectively.
- KYM-001 and other lead molecules exhibited selective cytotoxic effects on MYD88-mutant cells, with an anti-proliferative and apoptotic response triggered within 48 hours.
- KYM-001 causes exposure related IRAK4 degradation *in vivo* in OCI-LY10 mouse xenografts via SC and PO routes.
- *In vivo* OCI-LY10 mouse xenograft study using daily dosing of an IRAK4 degrader for 2 weeks demonstrated complete tumor regression associated with 85% IRAK4 lowering in tumor measured at 24 hours following last dose.
  - Activity *in vivo* also demonstrated against TMD8 ABC DLBCL tumors and large, established OCI-LY10 tumors.
- These preclinical studies with an IRAK4 degrader provide guidance on tumor PK/PD projected to be effective in patients, and further support clinical development of KYM-001 and related leads in MYD88-driven lymphomas via subcutaneous or oral routes.

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