KYMERA

IRAK4 Degraders for MYD88 Mutant Lymphoma

Kymera Therapeutics

ICML, Lugano

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15-ICML

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Conflict of Interest Disclosure – Duncan Walker, Presentation Nr. 083

- Employment or leadership position: Kymera Therapeutics

- Consultant or advisory role: N/A

- Stock ownership: Kymera Therapeutics

- Honoraria: N/A

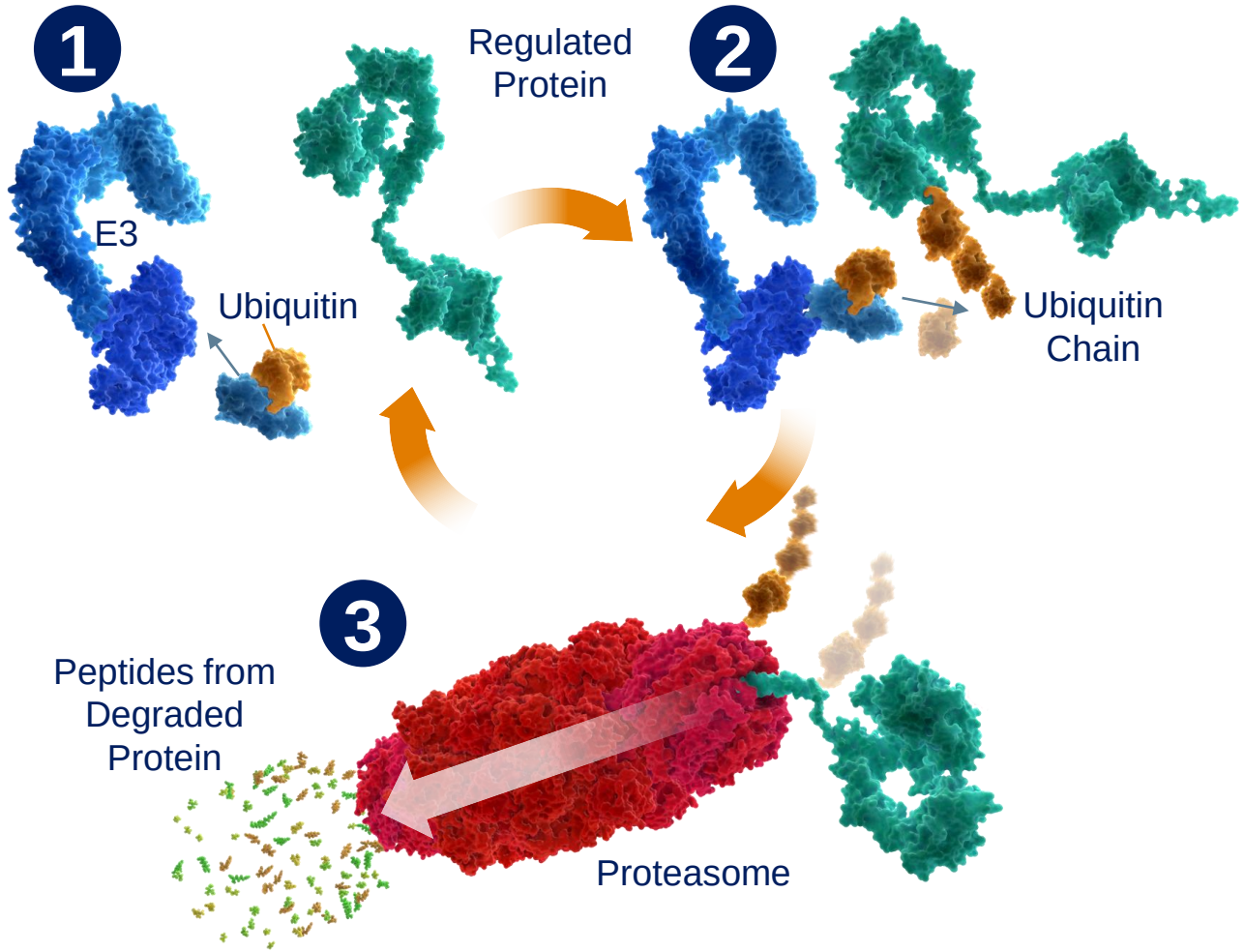
- Research funding: Kymera Therapeutics

- Other remuneration: N/A

Biology of Protein Degradation

The Ubiquitin Proteasome System – A Naturally Occurring Process to Regulate Protein Levels

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



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Targeted Protein Degradation Hijacks the UPS to Degrade Therapeutic Targets

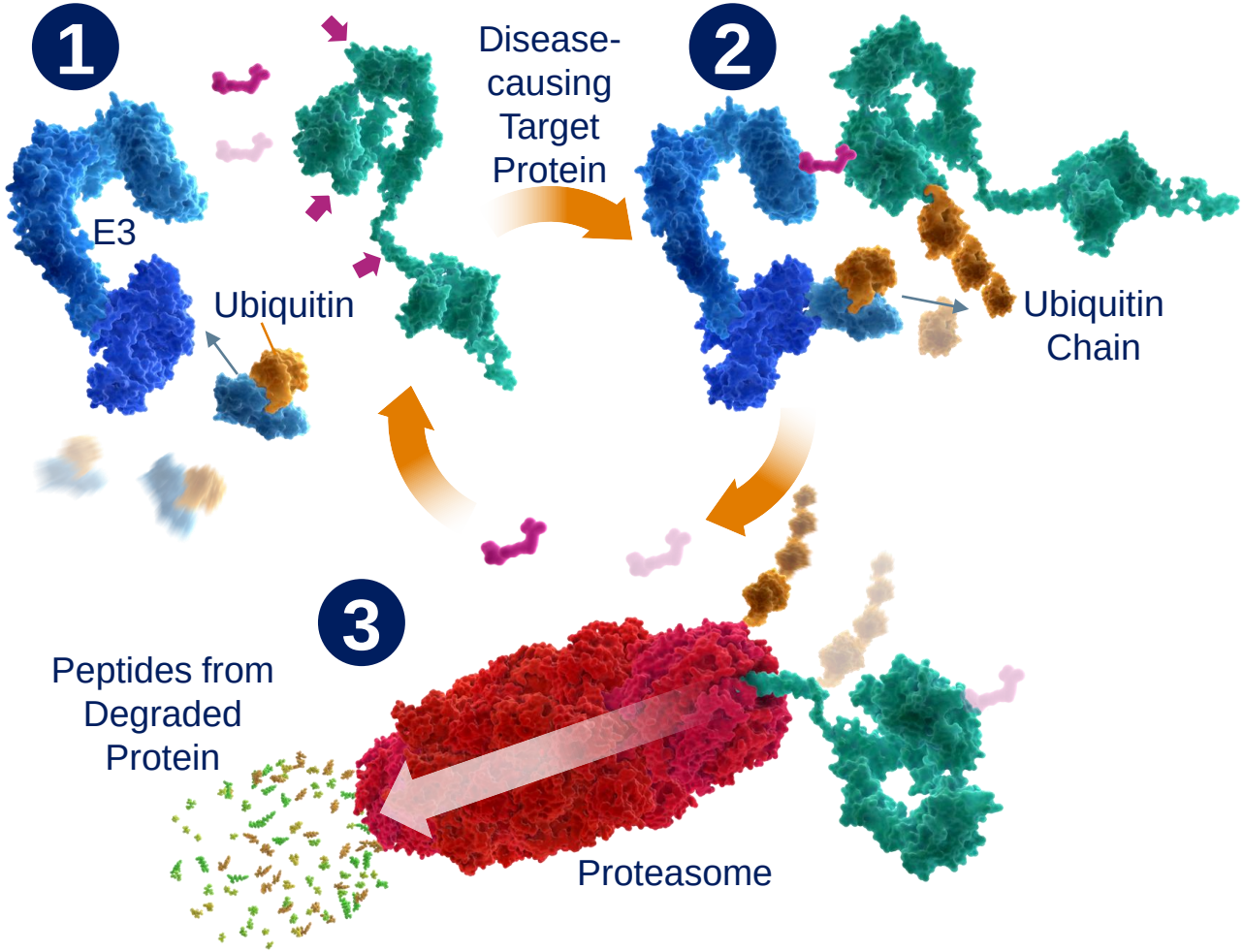
Our heterobifunctional drugs

BROAD OPPORTUNITY
Only Binding Site Required

EFFICIENT
Catalytic

PROLONGED IMPACT
Target Protein Degradation

HITCHING A RIDE
UPS Intact & Functional



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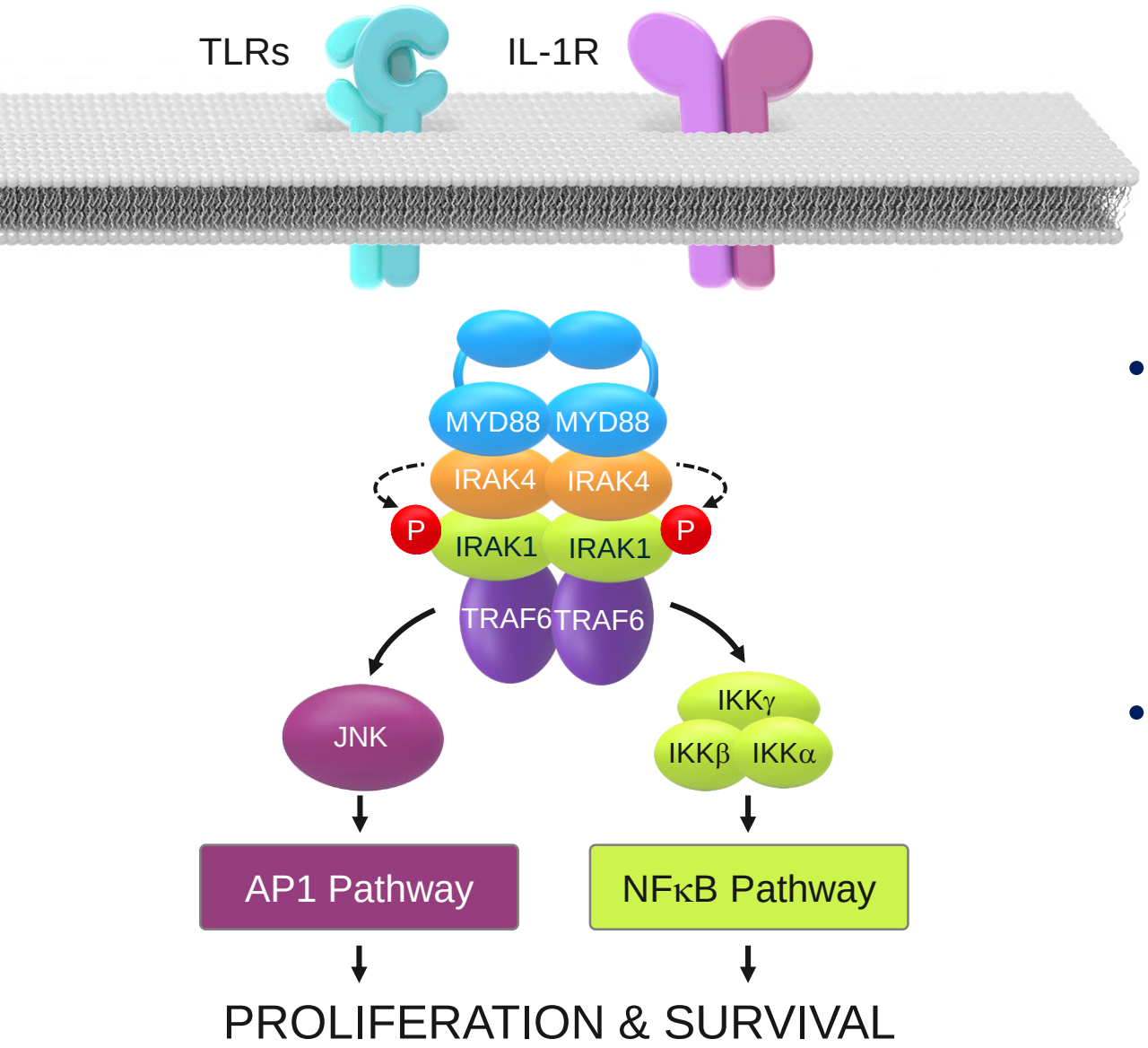
MYD88 Mutations: An Oncogenic Driver in Lymphoma



MYD88 Mutations

- 30-70% Primary CNS lymphoma
- 45-75% Primary extranodal lymphomas
- >90% Waldenström macroglobulinemia

- MYD88 constitutive activation drives proliferation and survival in B-cell malignancies through activating the NFkB and AP1 pathways
- IRAK4 is an integral component of MYD88 signaling
  - Both kinase activity and scaffolding function required for downstream signaling

Adapted from Yang et al. (2012) Cancer Cell 21, 6, pp723-737

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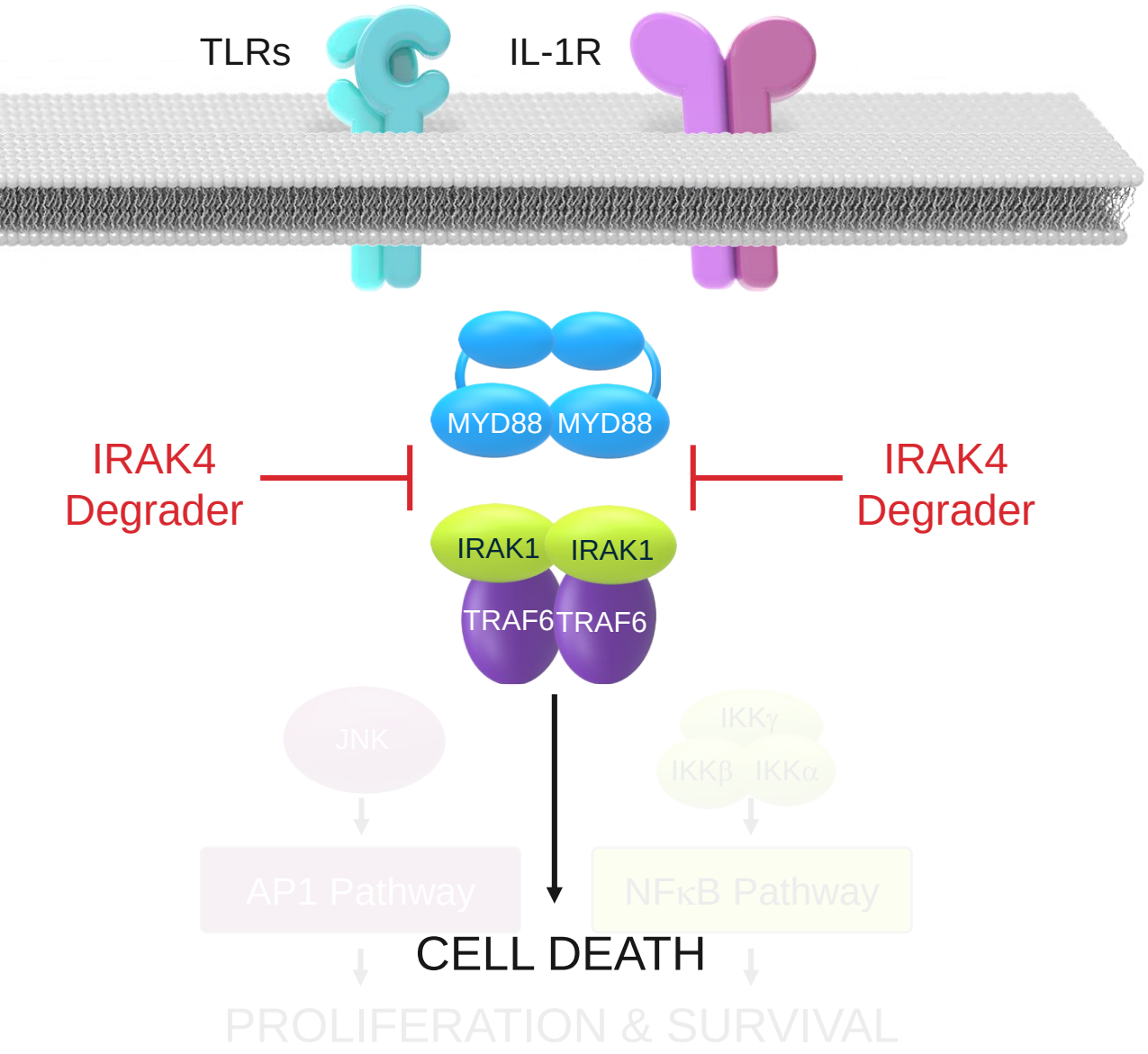
Degrading IRAK4 Will Disrupt MYD88-Dependent Survival Signals



- Degrading IRAK4 abrogates MYD88-signaling and drives cell death
  - Removes kinase-dependent signaling
  - Disrupts myddosome scaffolding function

Adapted from Yang et al. (2012) Cancer Cell 21, 6, pp723-737

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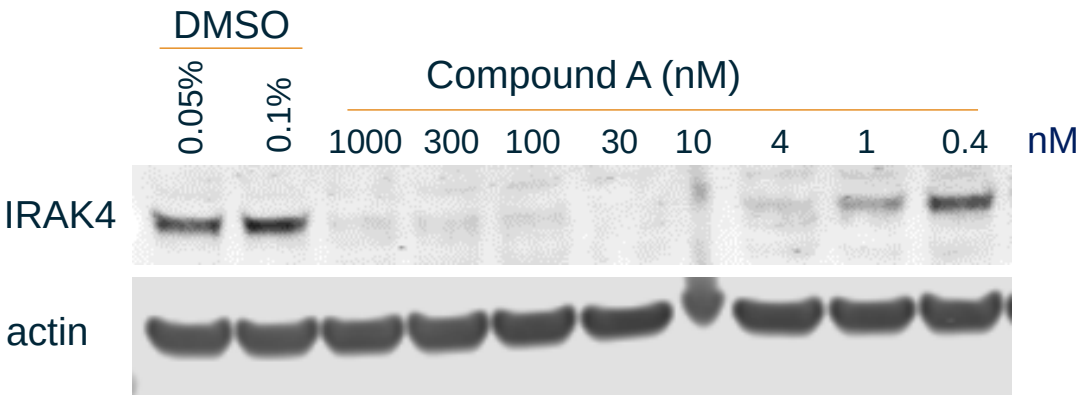
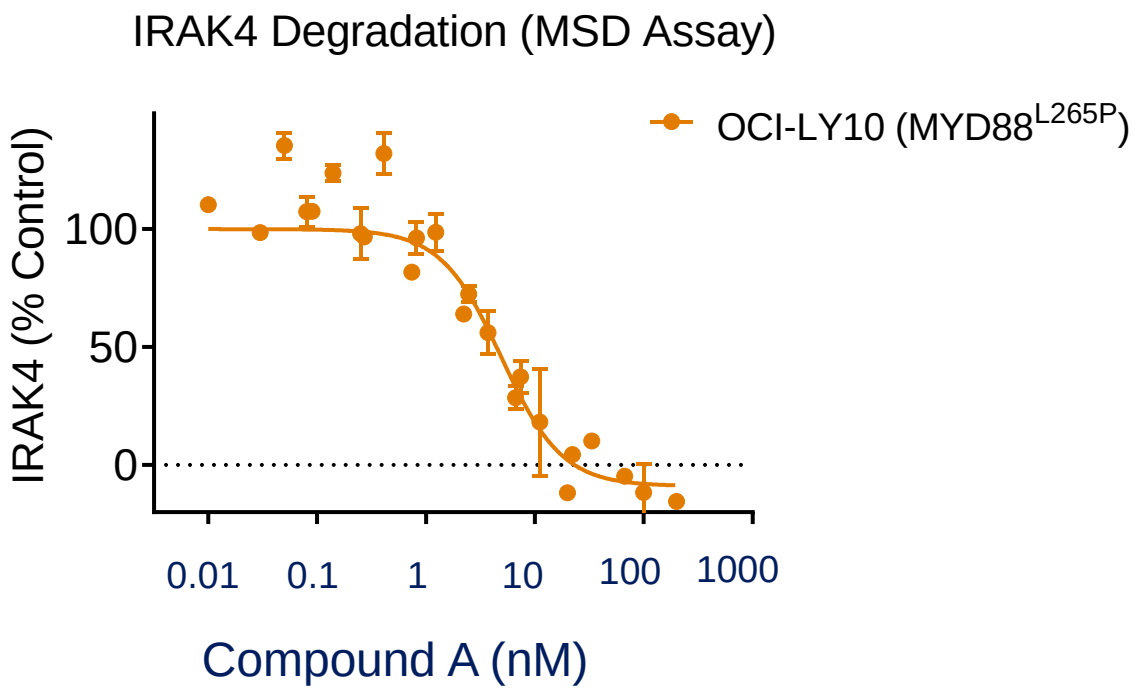
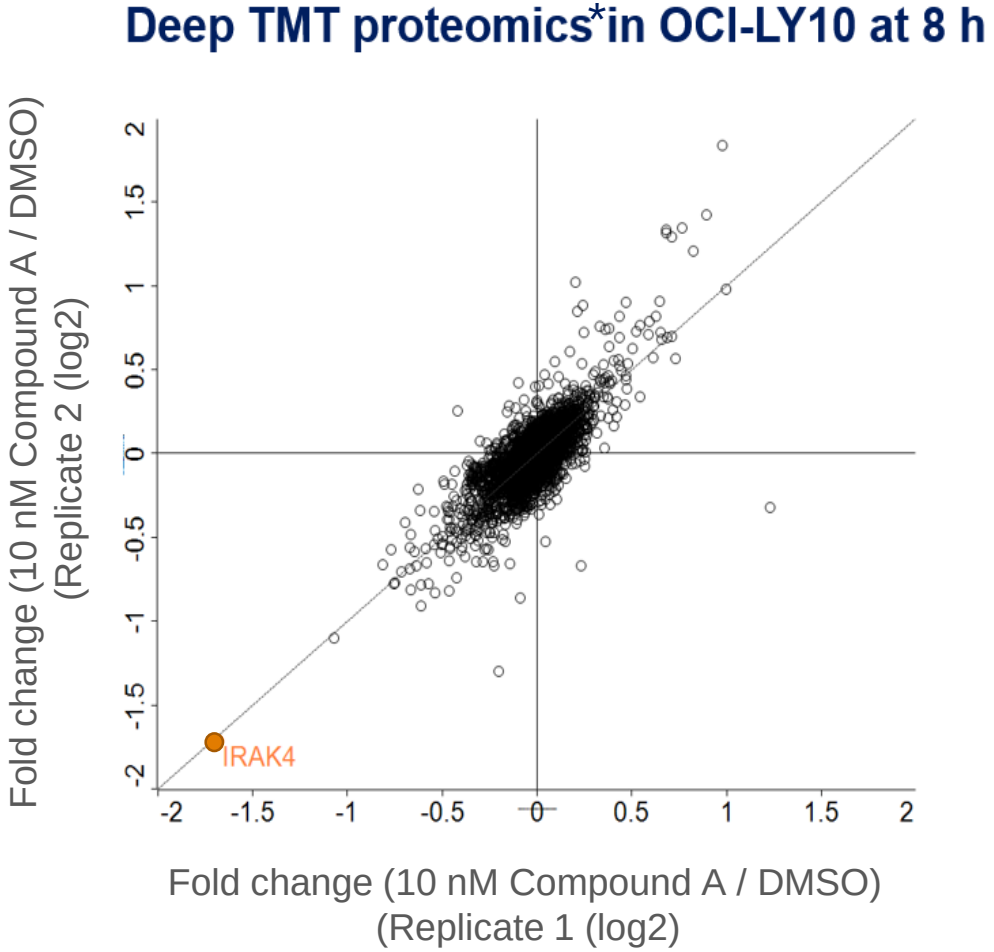
Kymera's IRAK4 Degraders are Potent and Selective







*10,000 proteins monitored

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IRAK4 Degraders Show Selective Activity in MYD88^{MUT} Lymphoma

Assay		Compound B	IRAK4 Kinase Inhibitor
Degradation	**IRAK4 OCI-LY10 DC_{50} (nM)**	28	**-**

	Cell Line	Subtype	MYD88 Status	Co-Mutations	Viability IC_{50} (nM)	
Viability*	OCI-LY10	ABC	L265P	CD79A, A20$^{+/-}$	13	>2000
	SUDHL-2	ABC	S222R	A20 $^{-/-}$	18	>2000
	U-2932	ABC	WT	A20$^{+/-}$	>2000	>2000
	Daudi	Burkitt	WT	-	1000	>2000

Co-mutations in CD79A and A20 do not impact cell activity

* Viability measured by CTG at 4 days

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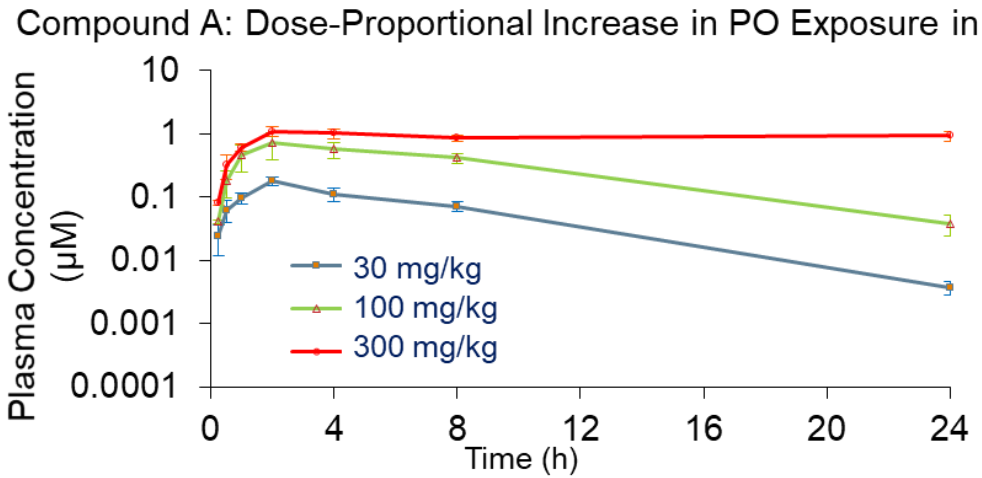
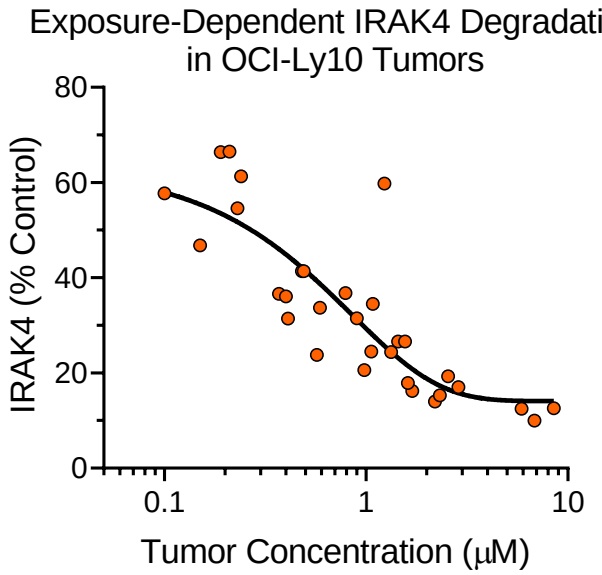
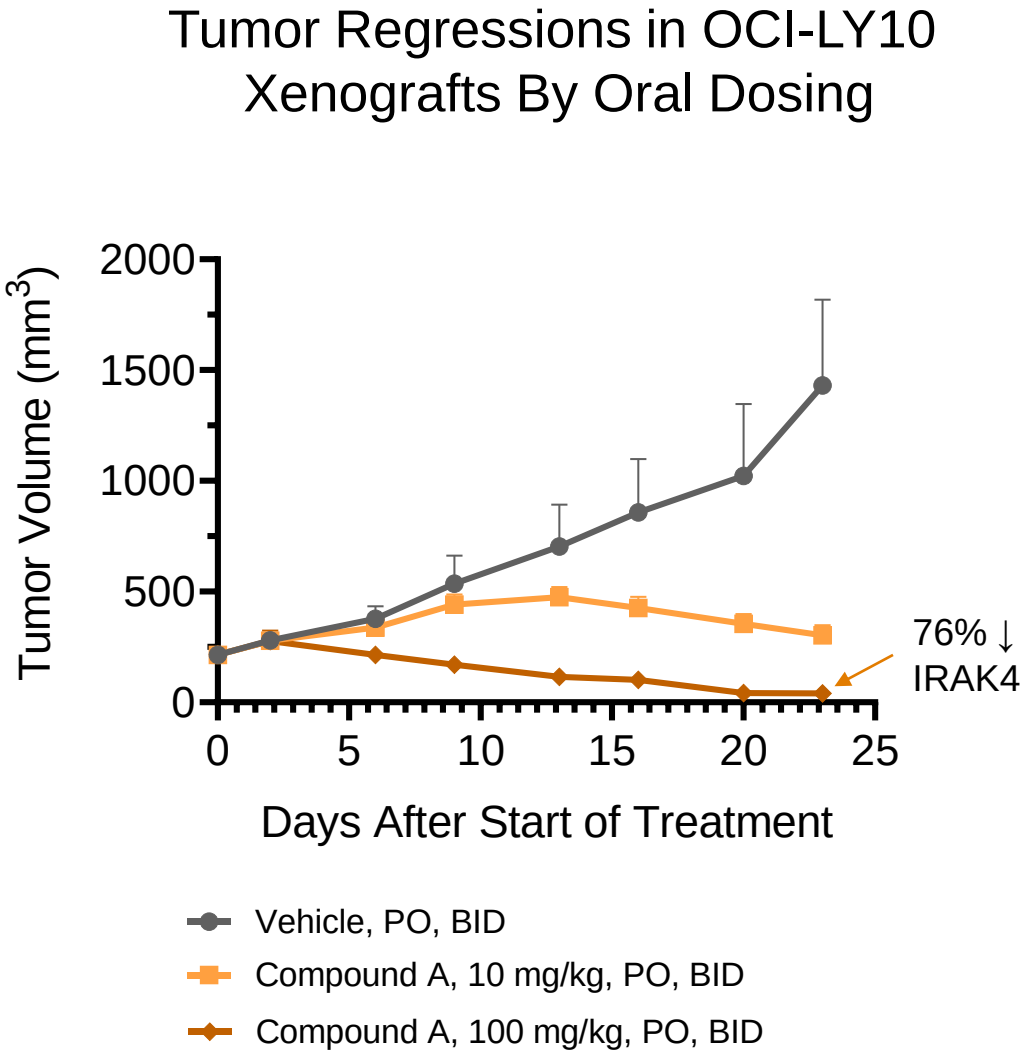
Lead Degraders Achieve Tumor Regression With Daily Oral Doses







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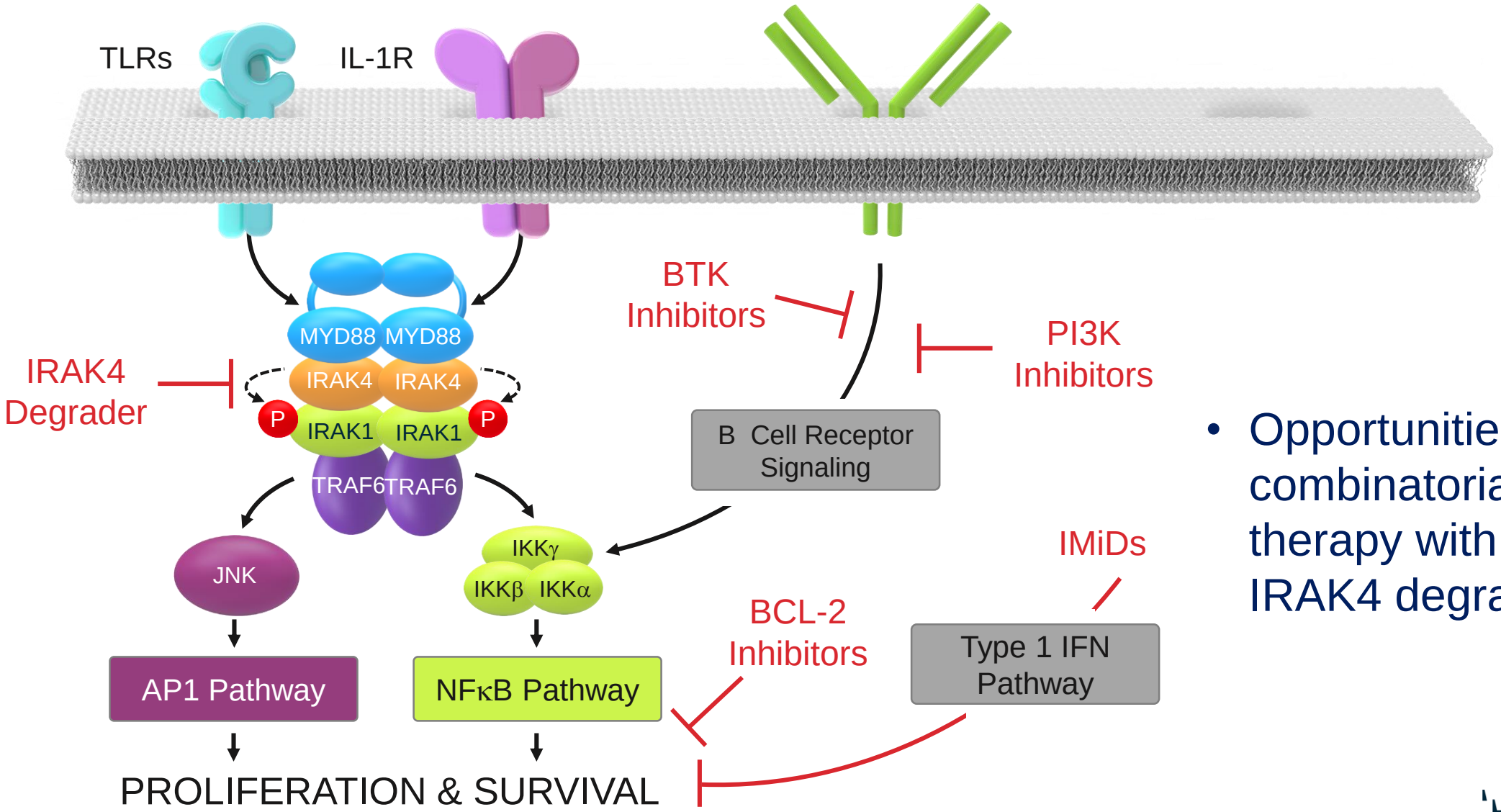
Targeting Convergent Pathway Signaling



- Opportunities for combinatorial therapy with IRAK4 degraders

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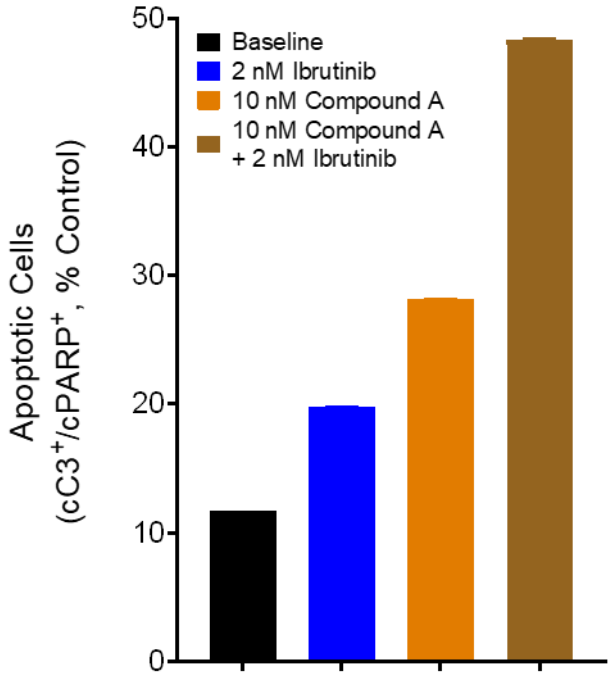
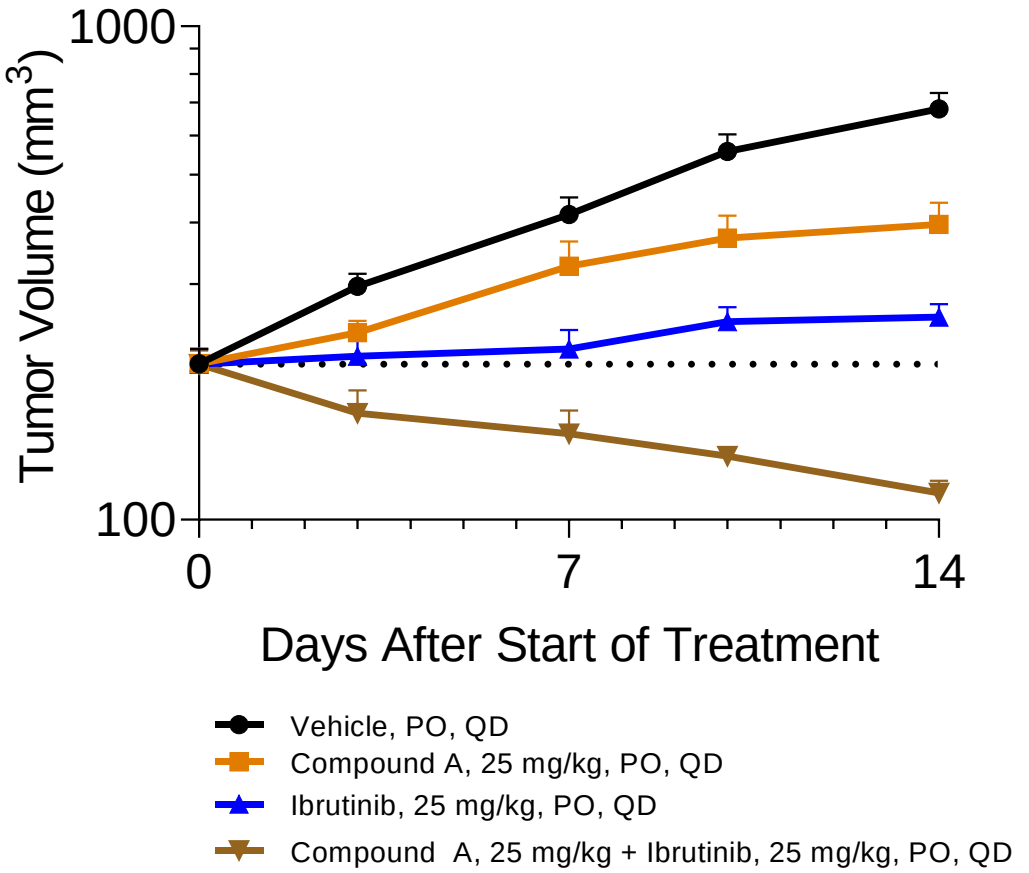
Sub-pharmacological Dose of IRAK4 Degrader Synergizes with BTK Inhibitor to Kill OCI-LY10 In Vitro and In Vivo

IRAK4 degradation + BTK inhibition increases apoptosis at 72 h in OCI-LY10 *in vitro*



Combination with BTK inhibition causes OCI-LY10 tumor xenograft regression at sub-pharmacologic dose of IRAK4 degrader



Synergy in antiproliferative assays was demonstrated using Chou-Talalay method (C.I. <0.1)

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Summary

- Kymera's degraders achieve potent and selective knockdown of IRAK4 with advantages over small molecule inhibition
- IRAK4 degraders selectively cause cell death in MYD88-mutant cell lines
  - Small molecule kinase inhibitor is not active – demonstrating advantage of IRAK4 protein knockdown
- Tumor regression in vivo obtained with orally dosed compounds and associated with ≥75% IRAK4 knockdown in tumors
- Several synergistic opportunities to explore clinically: Sub-pharmacological doses of IRAK4 degraders synergize with BTK inhibitor to kill OCI-LY10 in vitro and in vivo
- Data support advancement into clinic for treatment of MYD88-mutant lymphomas both as monotherapy and in combination with drugs targeting complimentary pathways

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Thank you

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