Ligase Targeting Drug Development

Seize the Therapeutic Value of Ubiquitin Ligases

Drugging Tissue-Restricted E3 Ligases

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KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

May 25-27, 2021

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Outline

- Kymera introduction, platform and pipeline
- Drugging tissue-restricted E3 ligases – a Kymera case study
- Summary

Kymera: A Leading TPD Company

Fierce 15 WINNER FierceBiotech

BOSTON BUSINESS JOURNAL BPTW 2021 BEST PLACES TO WORK

Founded:	2016
Stage:	Clinical
NASDAQ:	KYMR
Employees:	~100
Cash balance at Q1'21*:	$435M

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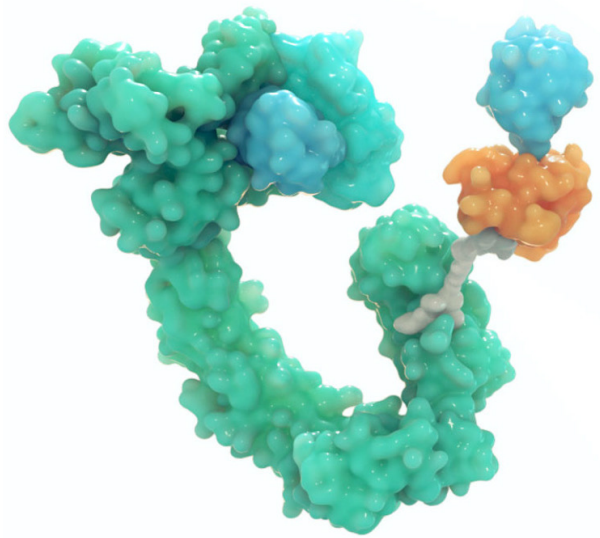


- Premier, **disease agnostic** protein degrader discovery platform
- Key **enabling partnerships**:

SANOFI VERTEX gsk

- Initial focus in **immune-inflammation (I/I) and oncology**
- First company set to dose degrader to **healthy volunteers and I/I patients**
- Expect **3 INDs** and clinical initiations by end of **2021**
- First proof-of-biology established in humans in **2021**

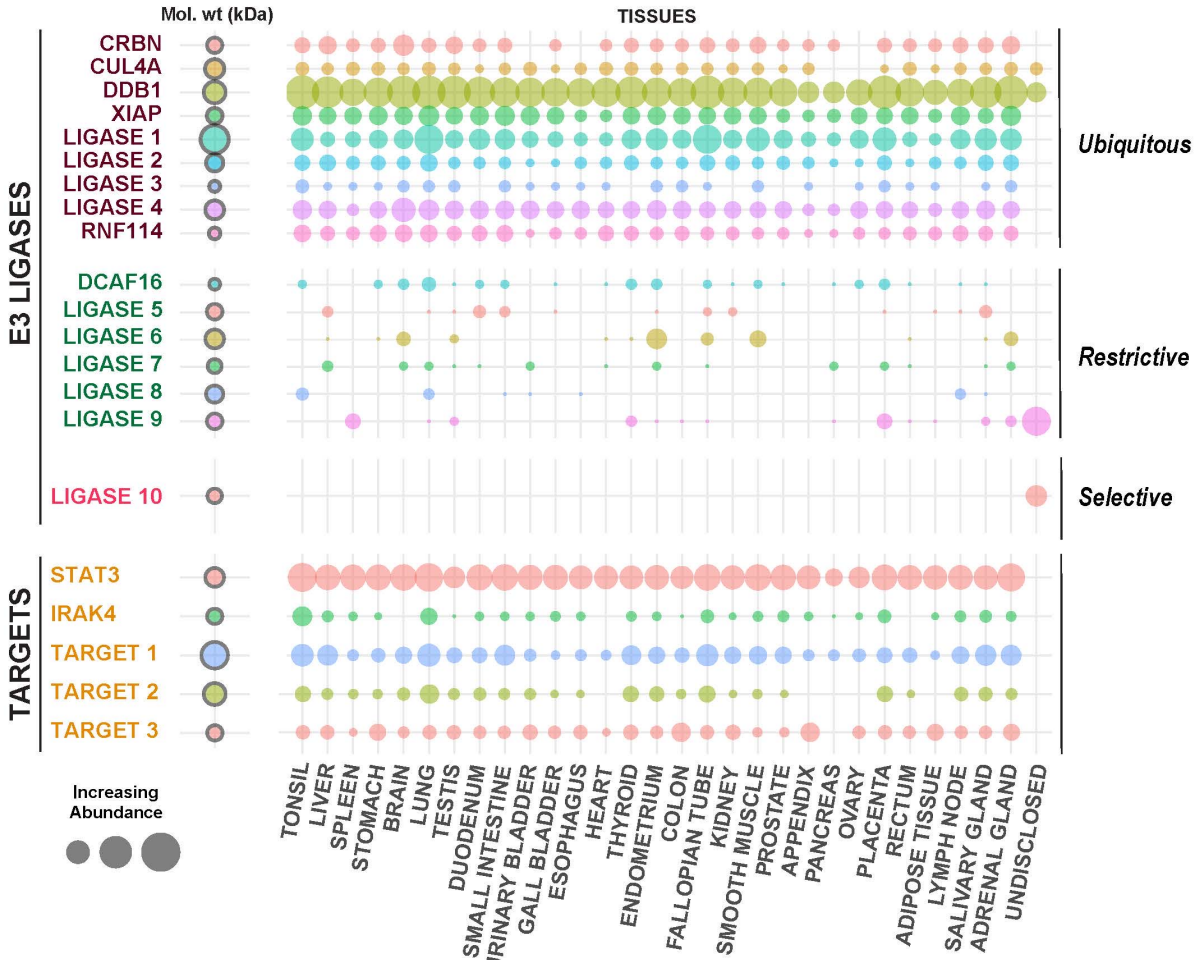
* Kymera expects that its cash, cash equivalents, and investments as of 3/31/2021, excluding any future potential milestones from collaborations, will enable the Company to fund its operational plans into 2025.

Pegasus: E3 Ligase Whole-Body Atlas

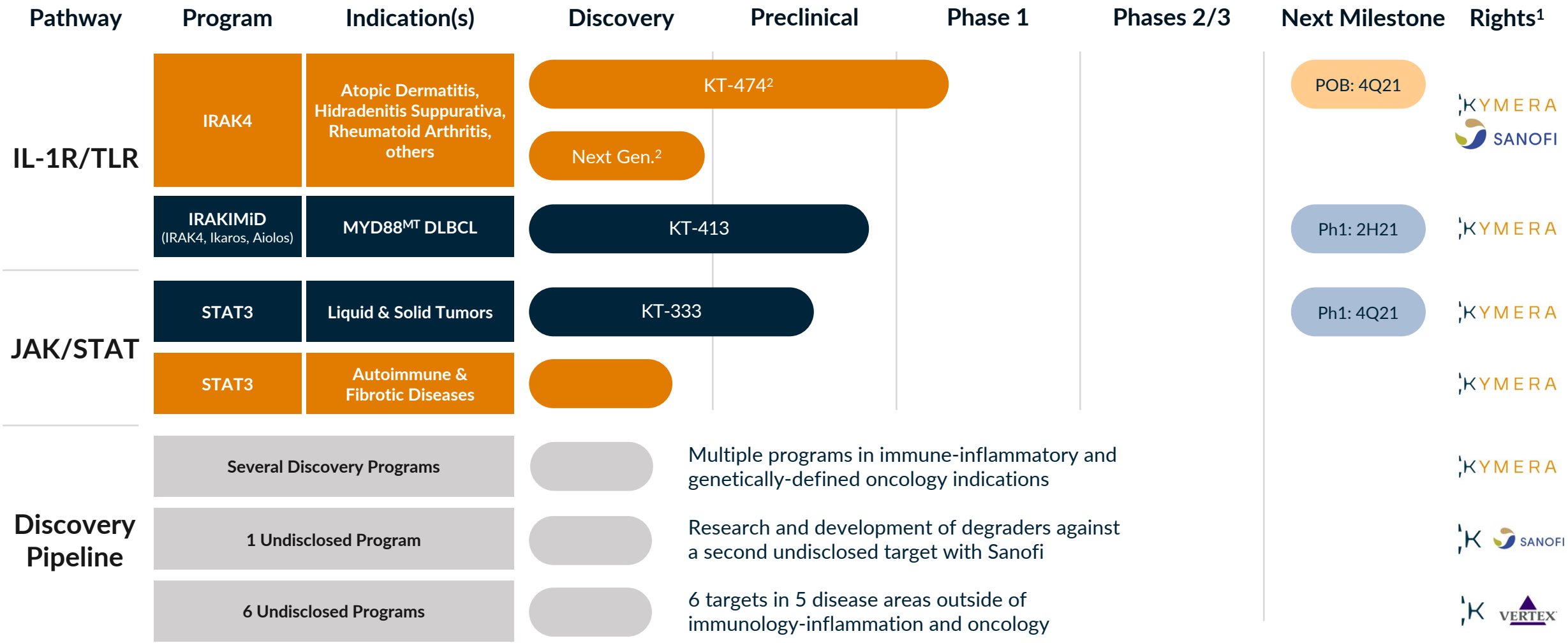
Different expression profiles of E3's provide opportunity for tissue selective/restricted degradation

- **E3 Ligase Whole-Body Atlas**
- E3 Ligase Binders Toolbox
- Ternary Complex Modeling
- Quantitative System Pharmacology Model
- Proprietary Chemistry

- Focused on determining the expression profiles of ~600 unique E3 ligases
- Patterns mapped in both disease and healthy contexts
- Ability to match a target protein with appropriate E3 ligase based on expression and biology
- Vision to develop tissue-selective or tissue-restricted degraders to enable novel therapeutic opportunities



Kymera's Pipeline of Novel Protein Degraders



1. Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
2. Sanofi collaboration to develop IRAK4 degrader candidates, including KT-474 (SAR444656), outside of oncology and immuno-oncology fields.

Drugging Tissue-Restrictd E3 Ligases

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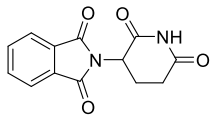
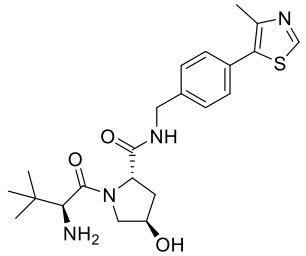
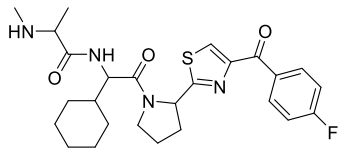
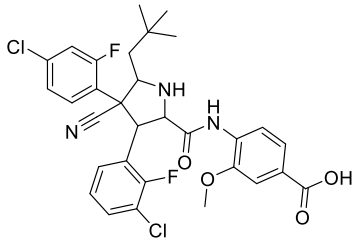
Current E3 Landscape Today and Limitations

E3 Ligase	Cereblon	VHL	IAP	MDM2
Compounds	Thal, Pom	VH032, VL285, and derivatives	LCL161, GDC-0152	Nutlins
				
	Thalidomide	**VH032**	**LCL161**	**Idasanutlin**
MW	**258**	**431**	**500**	**616**
LogP	**0.02**	**0.85**	**3.78**	**4.50**
PSA	**109**	**84**	**91**	**112**
Limitations	iMiD Biology; stability/ epimerization	Peptide-based renders oral BA challenging	Auto-ubiquitination/ NF-kB modulation; cytotoxicity making interpretation of results difficult	On-target biology

- Ubiquitous expression is both good and bad; can **increase risk** of off-target/adverse effects
- Desired properties for novel E3 ligands:
  - Low M_W/drug-like properties
  - No cytotoxicity/ neosubstrate effects
  - Spares normal protein homeostasis
  - Tissue sparing

Ligandability Assessment of E3 Ligases

"Targeted protein degradation can only be realized if the structure of the targeted E3 ligases features pockets or crevices with **geometrical** and **physicochemical properties** that allow the binding of a small-molecule ligand."

E3 Ligase Class	Examples	Ligandability Assessment
DCAF	**CRBN**, DCAF15, DCAF16, EED, DCAF1	WDR domains and related b-propeller structures found in many E3 ligase subfamilies contain pockets that are generally **deep** and **enclosed**
BTB	KEAP1, KLHL3, KLHL6, KLHL20, KLHL40, KCTD5	BTB-Kelch domain proteins most tractable for drug development, but **significant variation** in pocket shape and surface charge means differential ligandability
VHL-, SOCS-box	**VHL**, KLHDC2, KLHDC3, KLHDC10, SOCS6, ASB9	Kelch domain subfamily members have deep pockets (but may favor acidic ligands), while SH2 domain members **historically poor** ligandability (pTyr).
F-box	BTRC, FBXL3, FBXO44, FBXW7, SKP2	WDR subfamily (FBXW) has **good size/shape** for ligandability, whereas LRR domains don't provide well-defined pockets
IAP	**XIAP**, BIRC2, BIRC3, BIRC7, BIRC8	Lots of precedent for ligandability of BIR domains, but ***earlier degraders induced auto-ubiquitylation*** and degradation, reducing effect on targeted substrates
APC	CDC20, FZR1/Cdh1	WDR domains and D-box binding site provide good ligandability, but there are **concerns about hijacking** important cell-cycle regulator
HECT	HERC1, HERC2, ITCH, NEDD4	Compounds binding HECT domains will act as **catalytic inhibitors**, so focus should be on other domains like RCC1-like domain (RLD) which is related to WDR and Kelch domains, making them ligandable.
TRIM	TRIM2, TRIM3, TRIM21, TRIM24, TRIM58	PRY/SPRY domain has **variable ligandability** and bromodomain subfamily is highly ligandable.

Schapira, Crews et al Calabrese, Bullock & Crews *Nat Rev Drug Discov* (2019); Ishida & Ciulli, *SLAS Discov.* (2021)

What Makes an E3 Ligandable at Kymera?

Ligandability: *likelihood* of identifying a small-molecule binder with affinity < 1 uM

Druggability: *likelihood* of converting the ligand into a degrader with therapeutic potential

Ligandability assessment helps optimize resources towards **POC**

Qualifier

Precedence and Datamining

- ❑ Contains ligandable domains/protein family analysis
- ❑ Known substrate(s)
- ❑ Known and validated small-molecule

Structure-based Assessments

- ❑ Ligandability score
- ❑ Cryptic pocket available

Experimental/Biophysical

- ❑ Identified hits from pilot screens

Key Challenges

Precedence and Datamining

- Data reliability, clean-up/curation
- Data integration

Structure-based Assessments

- Requires structure of target protein or homology

Experimental/Biophysical

- Protein expression/stability

Applying *In silico* Ligandability Metrics to Rank E3s

E3 Ligase	SiteScore	P2Rank	Known Degrader	PDB Code
Ligase A	1.11	40.1		•
Ligase X	1.11	18.5		•
Ligase B	1.10	35.4		•
Ligase C	1.09	22.9		•
Ligase D	1.09	33.8		•
Ligase E	1.09	21.1		•
Ligase F	1.08	11.0		•
CRBN	1.06	23.7	•	6h0g
Ligase G	1.06	20.5		•
Ligase H	1.04	45.1	•	•
Ligase I	1.04	14.3	•	•
Ligase J	0.93	10.2		•
Ligase K	0.91	9.5		•
Ligase L	0.66	1.3	•	•

- *In silico* methods can help identify and characterize binding pockets to rank E3s with available structure
- There are E3s with better pocket scores than those with known degraders
- No single metric is ideal for ranking; best used in combination with information from other data sources

How We Leverage Lead Discovery Strategies to Identify E3 Ligands

	Virtual Screen	DEL	Fragment-Based Screen	Chemoproteomics	HTS	ASMS
Screening Strategies	**Criteria** • Availability of structure or homology model **Approaches** • DB ~8 million purchasable cpds • Cloud enables screen < 24hrs • AI to improve enrichment	**Criteria** • Not amenable to proteins with disordered regions or DNA binding • High quality protein • Ideal QC profile (single-species by SEC; <5% aggregation by DLS)	**Criteria** • Availability of high quality (crystallization-grade) protein • Robust crystallization system **Approaches** • SPR, NMR • X-ray • LC/MS (covalent)	**Criteria** • Proteins have reactive cysteines **Approaches** • Covalent fragment screening on recombinant protein • Whole cell covalent fragment screening	**Criteria** • Available high-throughput assay format **Approaches** • Focused library • diversity set	**Criteria** • Availability of high quality protein

Hit Validation and Optimization

- SPR
- DSF
- ASMS
- MST
- Radiolabeling
- NMR
- X-ray
- SBDD
- Chemistry

Degrader Validation

- Degrader design and synthesis across targets
- AlphaLISA; Cell-based degradation

Novel Cullin Ring E3 Ligase Characteristics and Ligandability Assessment

E3 Ligase Type:	Cullin-RING
Known Substrates:	Endogenous substrates
Function:	Confidential
Crystal Structures:	Structure solved
Expression:	Expressed in selected tissues; broadly expressed in cancer cells

Precedence and Datamining

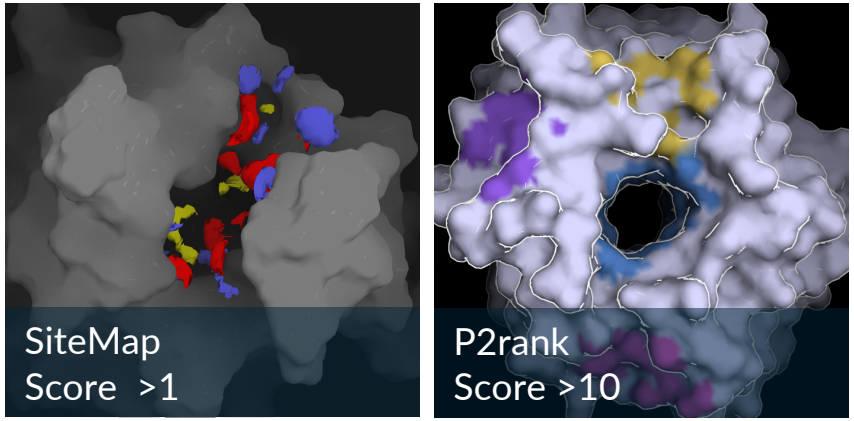
- ☑ Contains ligandable domains/protein family analysis
- ☑ Known substrate(s)
- ☐ Known and validated small-molecule

Structure-based Assessments

- ☑ Ligandability score
- ☐ Cryptic pocket available

Experimental/Biophysical

- ☑ Identified hits from pilot screens

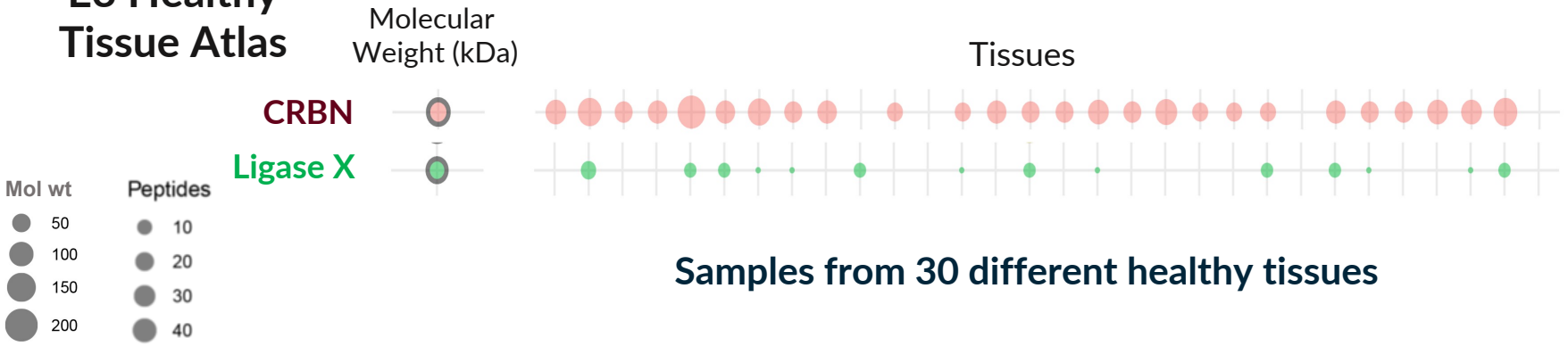


2 orthogonal *in silico* methods suggest pocket is ligandable

SBDD/Hit-finding activities initiated based on **ligandability** assessment and X-ray system established

E3 Ligase X is a Low Abundant and Tissue-Restricted Protein, Broadly Expressed in Multiple Cancer Cell Lines

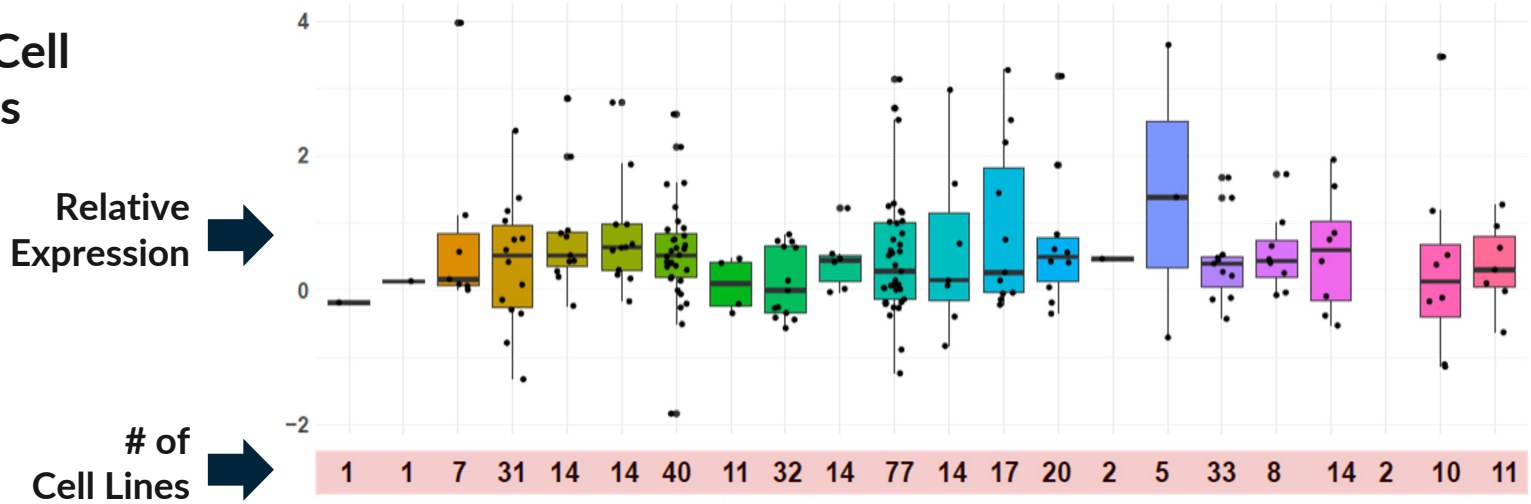
E3 Healthy Tissue Atlas



Samples from 30 different healthy tissues

E3 Healthy tissues atlas confirms ubiquitous expression of CRBN and restrictive expression for **Ligase X**

CCLE Cell Lines



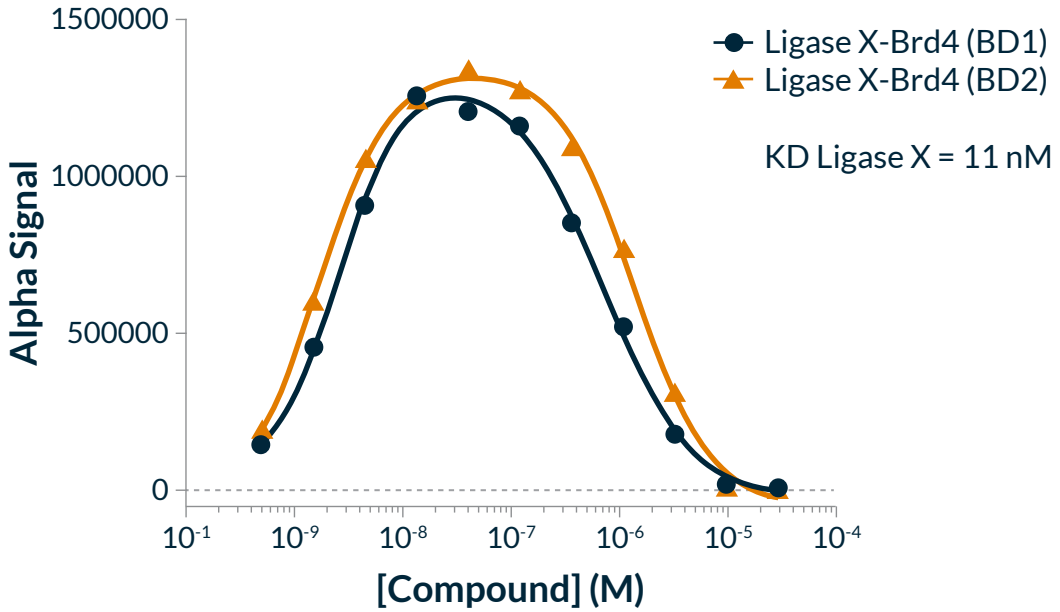
Cancer lines originated from 22 different tissues

Ligase X is expressed in majority of CCLE cancer cell lines at low levels

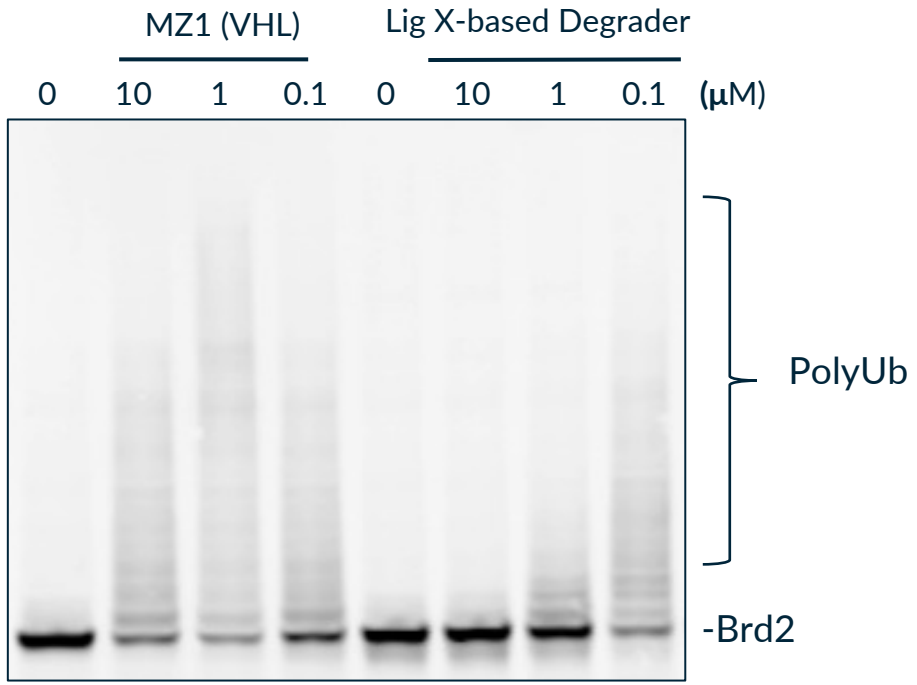
Ligase X Peptidomimetic Degrader Promotes Ternary Complex Formation and Brd2 Ubiquitination *In vitro*

Peptidomimetic ligand of Ligase X based degrader provided **validation** but not suitable start point for hit finding

Ternary Complex Formation - AlphaLISA



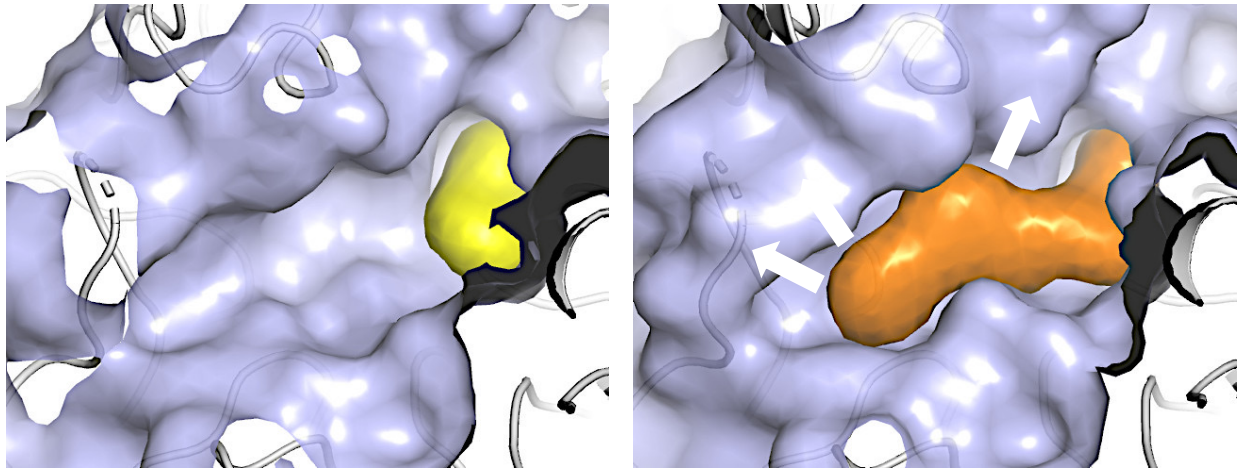
Cell-free Brd2 Ubiquitination (OCI-LY10)



An Early Fragment X-ray Structure Solved along with Virtual Library Evaluation Led to Very Potent Binders of this Target

	HTRF
Fragment bound X-ray structure	IC_{50} > 1 mM
Rational design to explore SAR	IC_{50} < 30 µM
In silico library evaluation and synthesis	IC_{50} < 5 µM
3x	
Rational design to optimize library hits	IC_{50} = < 0.1 µM MW <400; clogP 0.7

Total # of virtual compounds evaluated	40K
Total # of crystal structures	18
Total # of compounds made	195



X-ray with Fragment | X-ray with Optimized Ligand

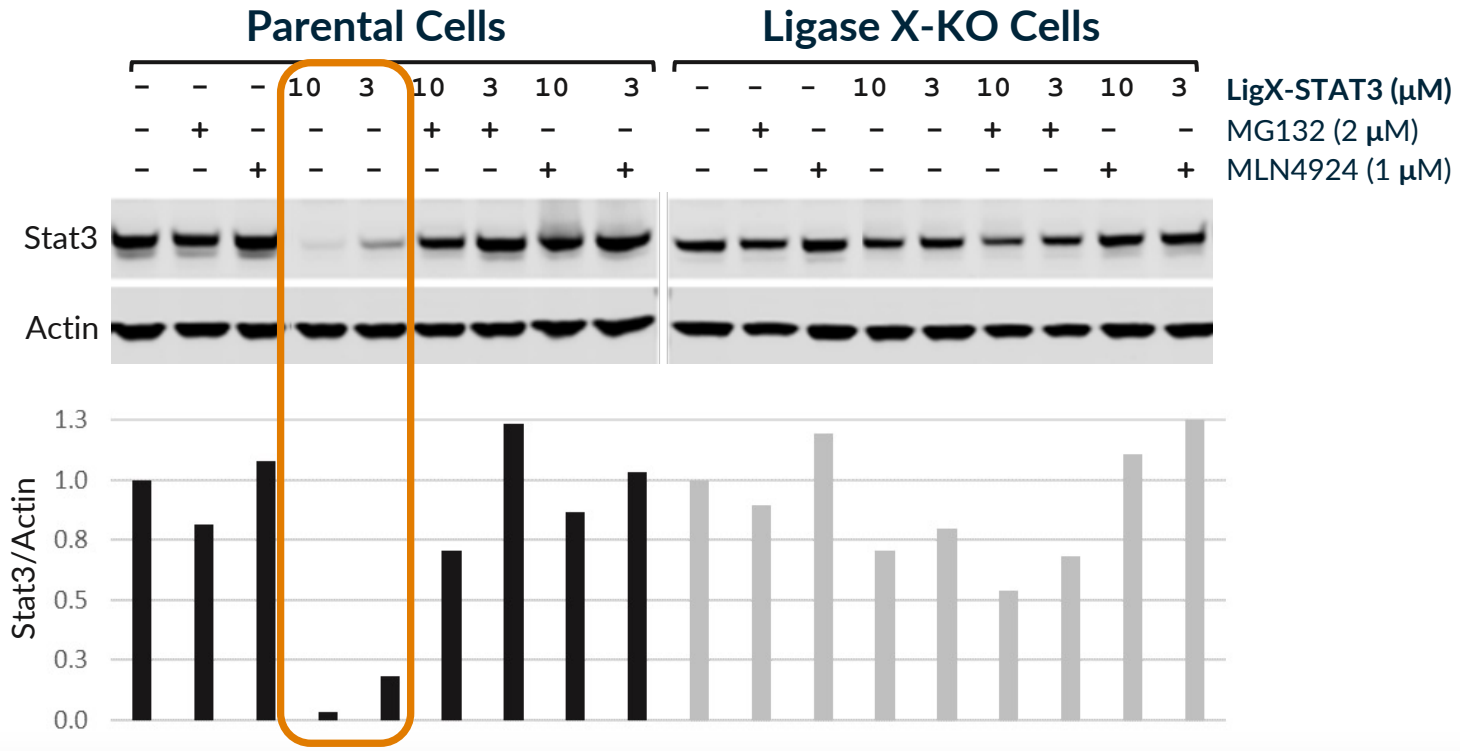
- Successfully applied SBDD to rapidly identify diverse E3 ligase ligands
- Multiple exit vectors identified and confirmed via chemistry, molecular modeling and X-ray
- Degraders synthesized for BRD4 + additional Kymera targets including STAT3 and IRAK4

Physical properties and in vitro ADME of representative Ligase X ligands

Physical and DMPK properties	Cpd 1	Cpd 2	Cpd 3
Ligase X HTRF IC_{50} (μM)	1.9	2.7	0.75
Mw	360	362	349
clogP	2.3	2.5	-0.2
Solubility at pH 7.4 (μM)	271	279	277
HLM Clint (μL/min/mg)	2	<1	2.7
MDCK AB/BA (P_{app}) / ER	0.6 / 0.9 / 1.6	0.6 / 1.2 / 2.1	0.8 / 1.2 / 1.6

Ligase X ligands have low Mw and excellent physical properties

STAT3 Degrader Based on Ligase X Demonstrates Broad Degradation Across Multiple Cancer Cell Types



Cells (Assay)	DC_{50} (μM)
A549 (HiBiT)	**0.20**
Su-DHL-1 (MSD)	**0.82**
Uveal Melanoma 92-1 (WB)	**<1**
OVCAR-3 (WB)	**0.6**
OVCAR-8 (WB)	**1.0**

- Degrader LigX-STAT3 demonstrated dose-dependent degradation of STAT3, achieving >50% STAT3 degradation at 1 μM.
- STAT3 degradation was rescued by proteasome inhibitor MG-132 or neddylation inhibitor MLN4924, indicating UPS mediated protein degradation
- Knockout of ligase X abolished STAT3 degradation, indicating the degradation is ligase X dependent.

Summary

- Kymera's powerful Pegasus platform has identified the expression profile of **600 unique E3 ligases**
- The E3 ligase Atlas is able to identify novel E3 ligases based on **expression**, **distribution**, and **intracellular localization**
- E3 Ligase X has restricted expression across **tissues** and **cell lines**
- An early fragment crystal structure and virtual library evaluation enabled an SBDD campaign to deliver **sub 1 uM lead**
- STAT3 degraders based on ligase X demonstrate degradation across **multiple cancer cell types**

Q & A

THANK YOU