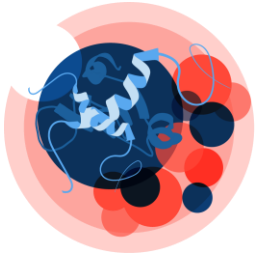

2nd Annual
Ligase Targeting Drug Development
Hijacking E3 Ligases to Mediate Degradation or Modulation of Undrugged Targets

Chemically Harnessing Novel E3 Ligase Biology for Next-generation TPD Therapeutics

Lewis D. Pennington, Ph.D.
Senior Director, Head of Platform Chemistry

KYMERA

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

April 26th, 2022

Forward-looking Statements

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Outline of Presentation

- Kymera's pipeline and platform
- Identifying a small molecule ligand for a novel E3 ligase
- Developing a heterobifunctional degrader for a POC POI*
- Evaluating pharmacology for cellular POC efforts
- Summary and Outlook

Founded 2016

KYMERA

Recognition

FIERCE FierceBiotech 2019 WINNER

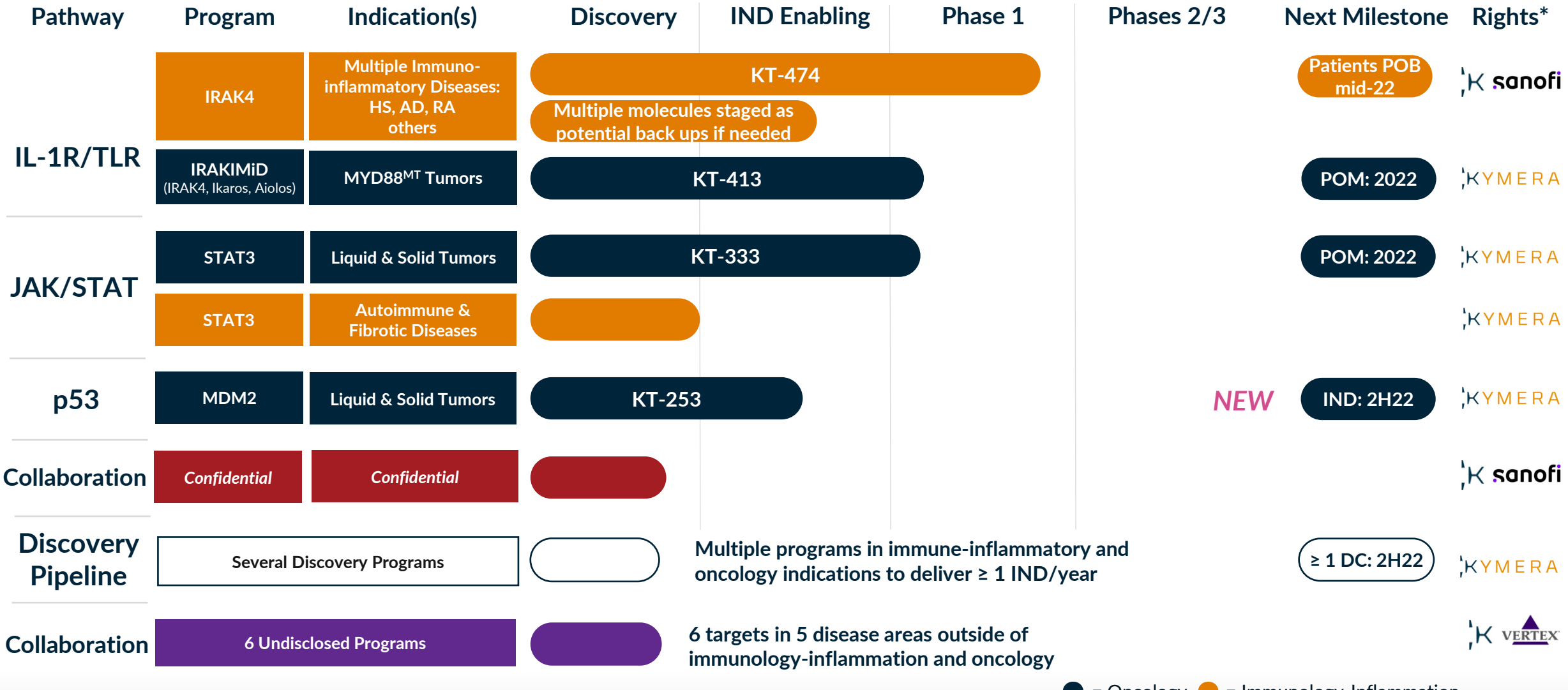
BOSTON BUSINESS JOURNAL 2021 BEST PLACES TO WORK Small Businesses Kymera Therapeutics

Partnerships

sanofi VERTEX gsk

* POC, proof-of-concept; POI, protein-of-interest

Kymera's Pipeline of Novel Protein Degraders



*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US

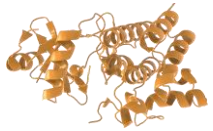
We Want to Drug All Target Classes

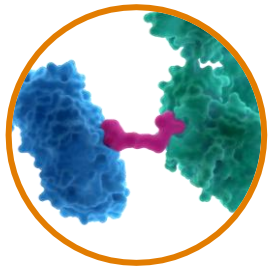
Expanding the Druggable Proteome with TPD

ID Inadequately Drugged Targets with Clear Degrader Advantage

Small molecule binders exist but unable to drug target fully

e.g., IRAK4, MDM2…



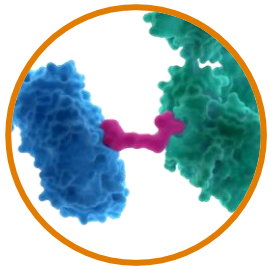


Heterobifunctional Degraders

UD Undrugged Targets

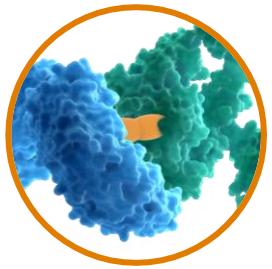
No other technology can drug

Ligandable Proteins
e.g., STAT3…



Heterobifunctional Degraders

Un-ligandable Proteins
e.g., other transcription factors



Molecular Glues

TR Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression

On-target unwanted pharmacology limits clinical application

Tissue sparing or selective E3 ligases eliminate unwanted toxicity and allow full clinical potential

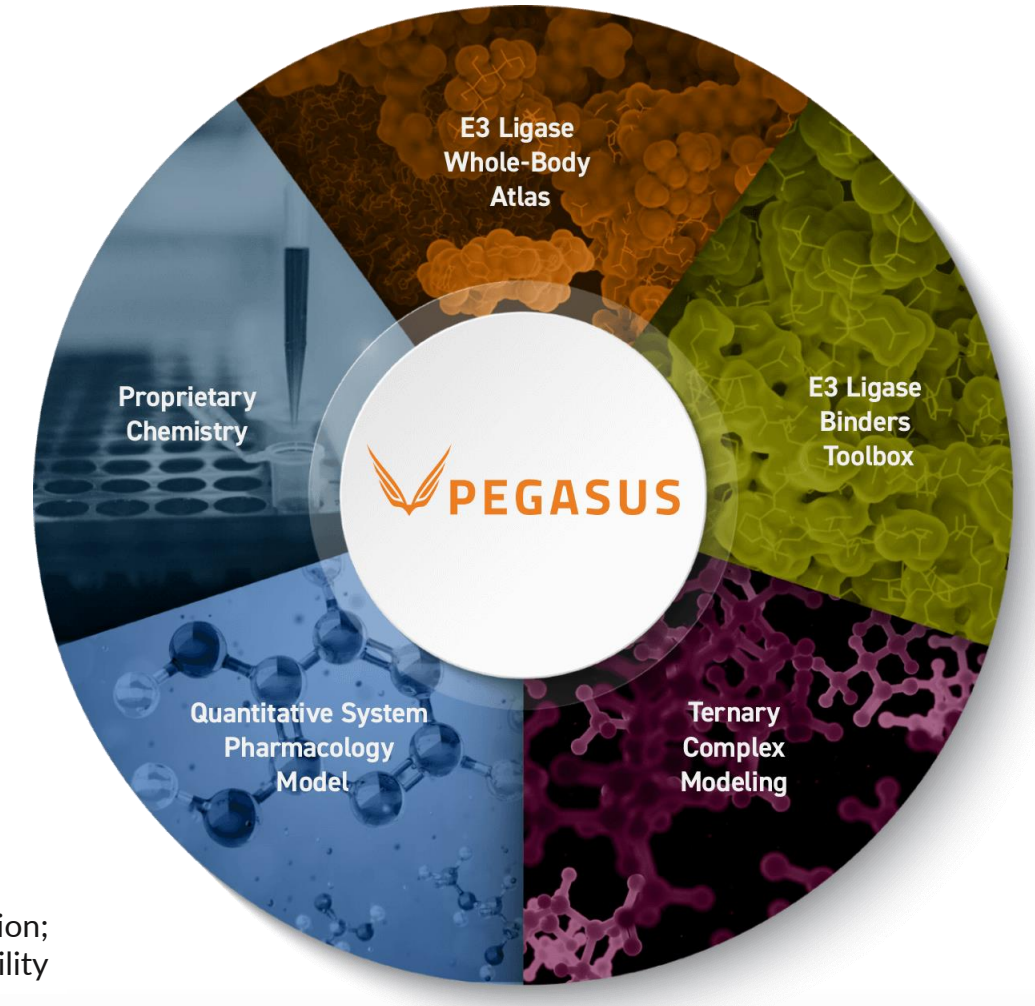
Platform for Harnessing Novel E3 Ligase Biology

E3 Ligase Whole-body Atlas

- RNA & protein expression profiles of ~ 600 E3s
- Disease & healthy tissues & cells (tissue distribution, absolute abundance, & subcellular localization)
- Novel E3 & POI pairing based on expression & biology

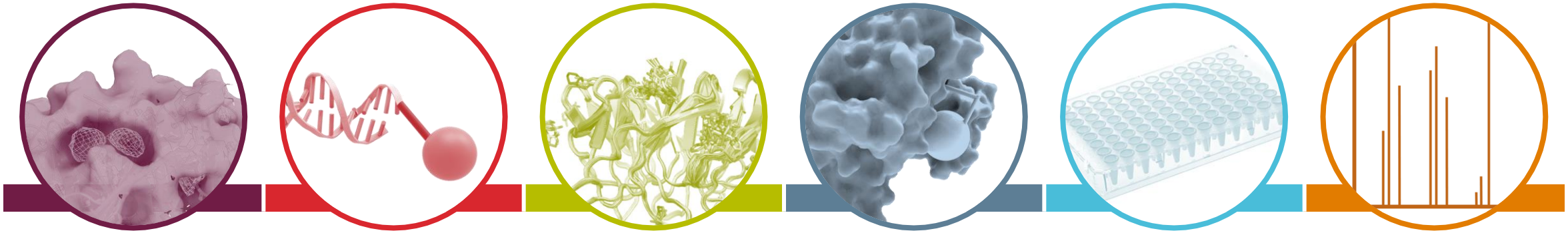
Proprietary Chemistry

- High-quality ligands for novel E3s
- Innovative degraders for new therapeutic opportunities
- Advanced molecular design principles for improved drug properties (e.g., DC_{50}, D_{max}, S_{H_2O}, P_{app}, & F_{oral})*



* DC_{50}, concentration at half-maximum degradation; D_{max}, maximum degradation; S_{H_2O}, aqueous solubility; P_{app}, cell permeability; F_{oral}, oral bioavailability

Comprehensive Hit Finding Toolbox



Virtual Screen

Criteria
- Availability of structure or homology model

Approaches
- DB ~8 million purchasable cpds
- Cloud enables screen < 24hrs
- AI to improve enrichment

DEL

Criteria
- High quality protein
- Ideal QC profile (single-species by SEC; <5% aggregation by DLS)

Fragment-Based Screen

Criteria
- Availability of high quality (crystallization-grade) protein
- Robust crystallization system

Approaches
- SPR, NMR
- X-ray
- LC/MS (covalent)

Cysteine Covalent Screening

Criteria
- Proteins have reactive cysteines

Approaches
- Covalent fragment screening on recombinant protein
- Whole cell covalent fragment screening

HTS

Criteria
- Available high-throughput assay format

Approaches
- Focused library
- Diversity set

ASMS

Criteria
- Availability of high-quality protein

Guiding Principles

Value-added Portfolio

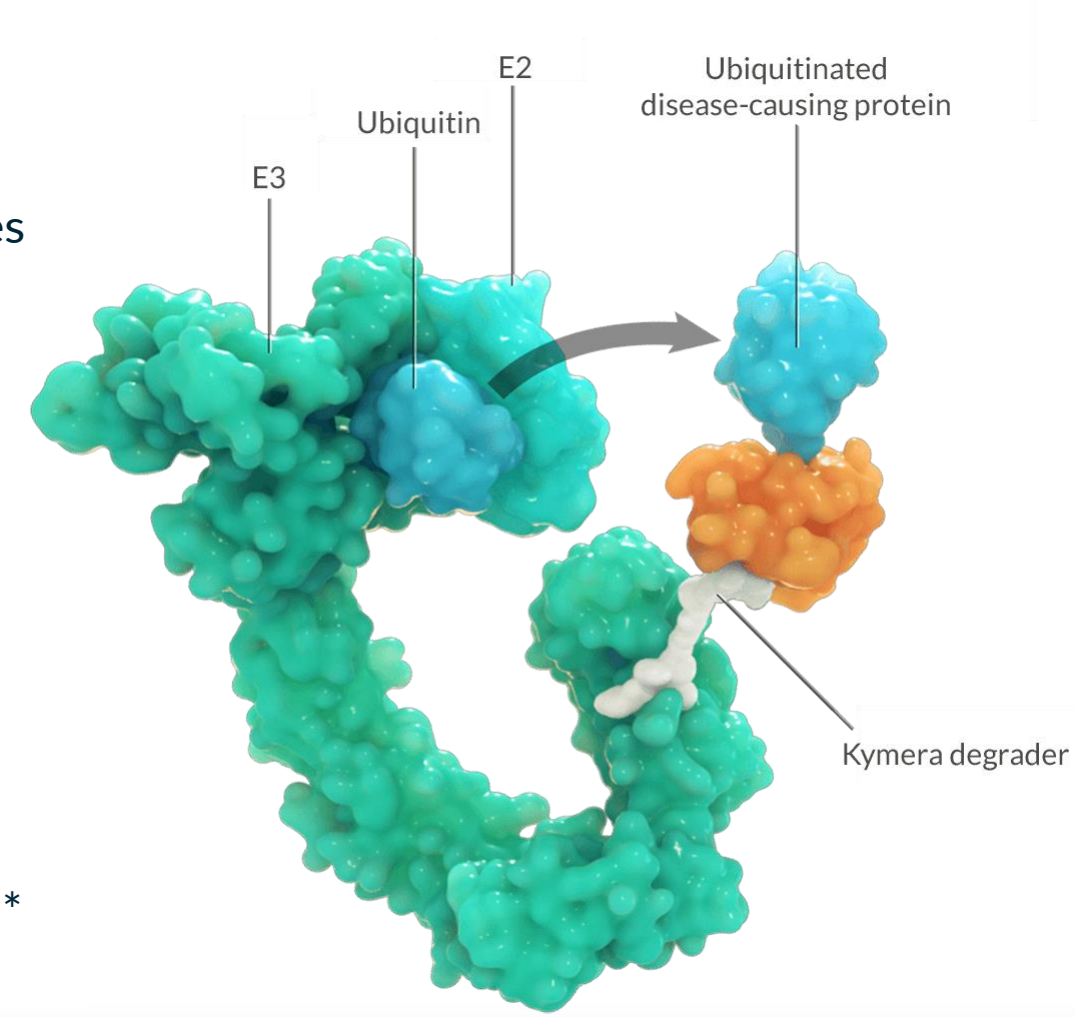
- Strategic pairing of novel E3s & POIs for targeted diseases
- Judicious balancing of biology & chemistry risks

Qualified Biology

- Holistic assessment of novel E3s (“LED” qualification)
- LED: ligandability, expression profile, & degradative activity

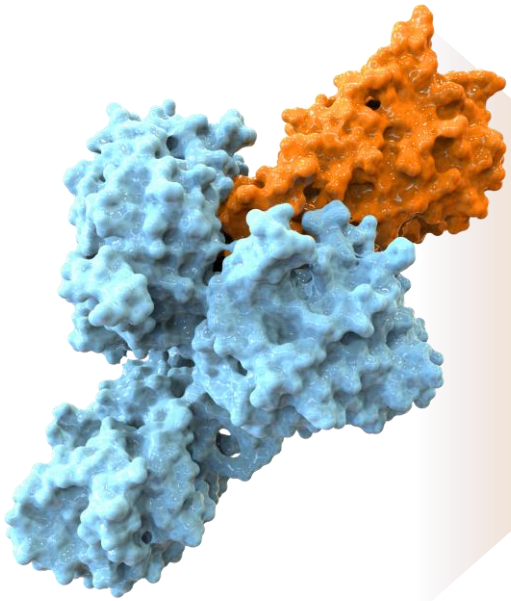
Enabled Chemistry

- Strategic tailoring of hit-finding: binding sites & ligand types
- X-ray crystal structures: ligandability, hit finding, & SBDD*



* SBDD, structure-based drug design

Kymera–GSK Partnership

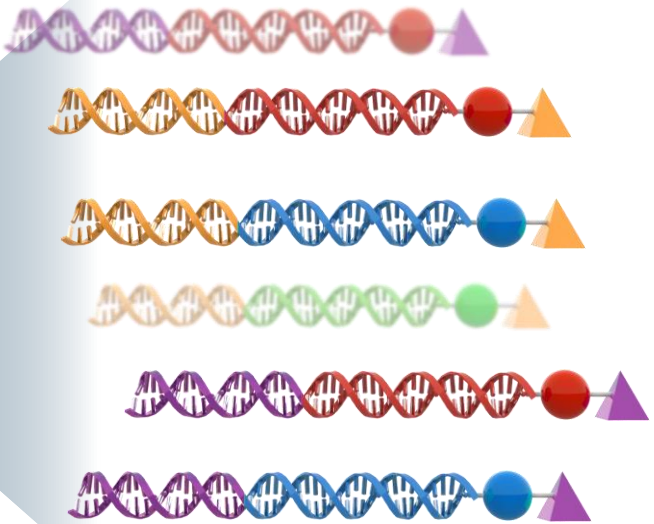


KYMERA

E3 Ligase Expertise

gsk

DEL Selection Expertise*



>80

E3s Evaluated

E3 Selection → E3 Qualification → DEL Selection → Ligand Optimization → Degrader Generation → Degrader Cell POC

1

Discussed Today

* DEL, DNA-encoded library

Novel E3 Ligase X (E3LX): Value Proposition

Current E3 Ligases are Limited

- All are ubiquitous: cereblon, VHL, MDM2, IAP, etc.
- Each has chemistry, biology, or safety challenges

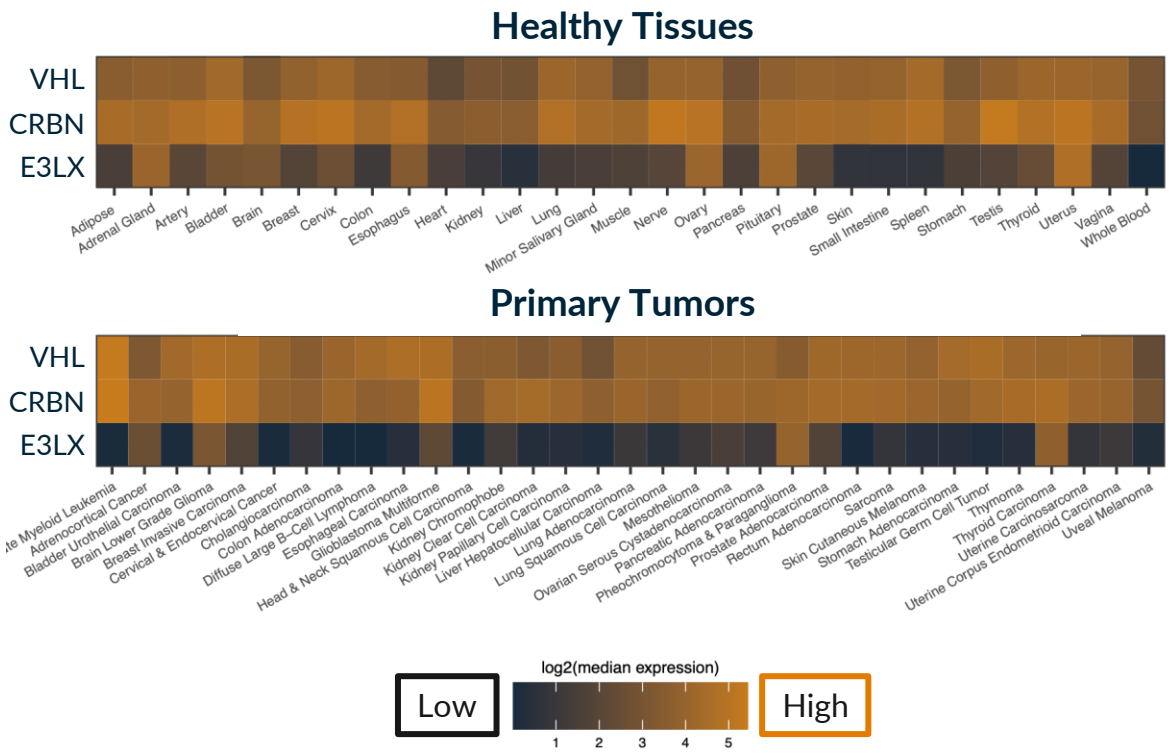
Improved Ubiquitous E3s Needed

- Novel E3-based degraders that allow improved oral bioavailability, increased neo-substrate scope, and fewer safety challenges

Tissue-selective E3s Most Valued*

- Including tissue-restricted or tissue-sparing
- Potential for improved efficacy and safety

E3LX Expression Profile by RNA-Seq#



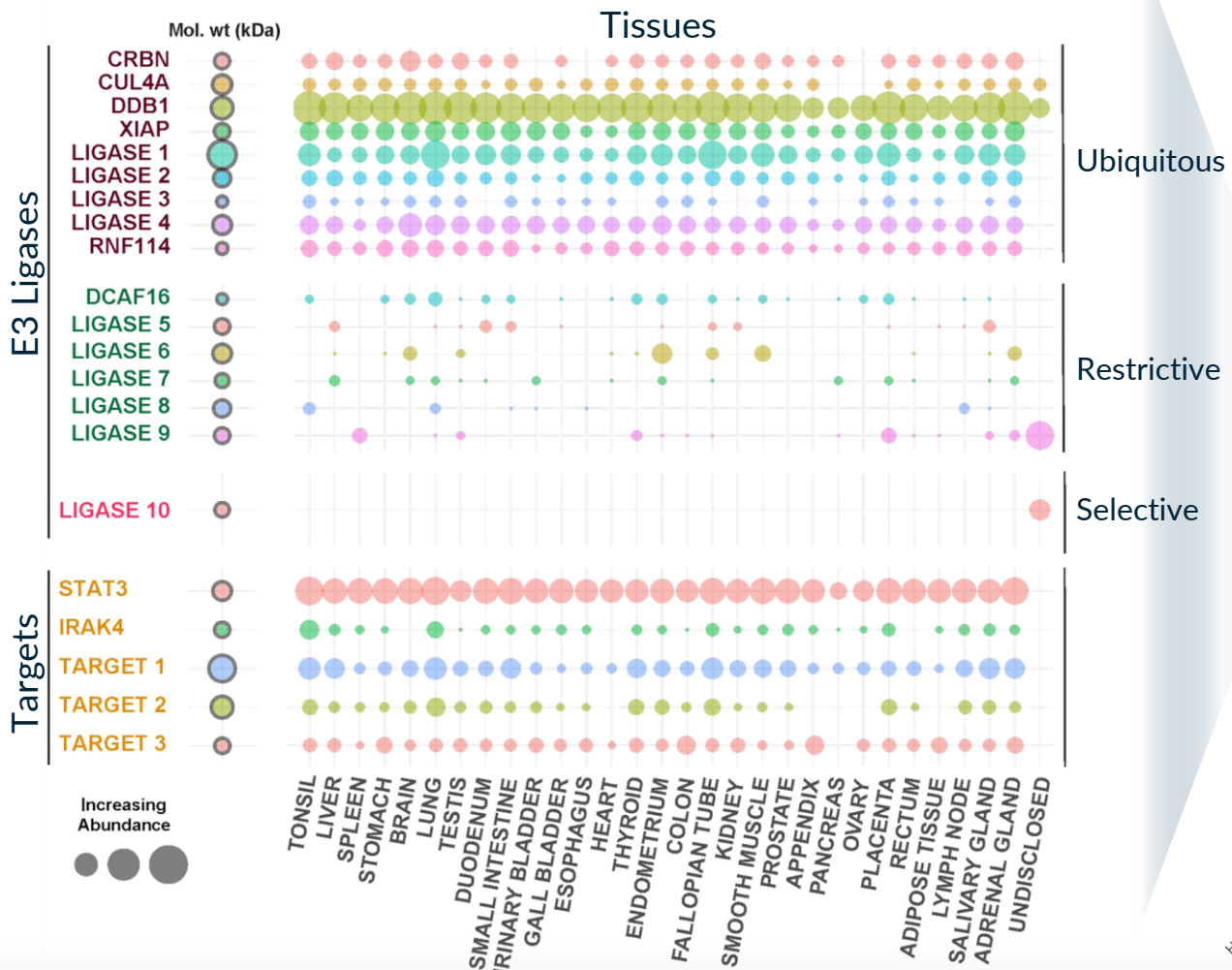
E3LX: low expression in most healthy tissues
E3LX: high expression in select primary tumors

* Békés, M.; Langley, D. R.; Crews, C. M. *Nat. Rev. Drug Discov*. **2022**, *21*, 181-200.

RNA-Seq, RNA sequencing; GTEx, TCGA data

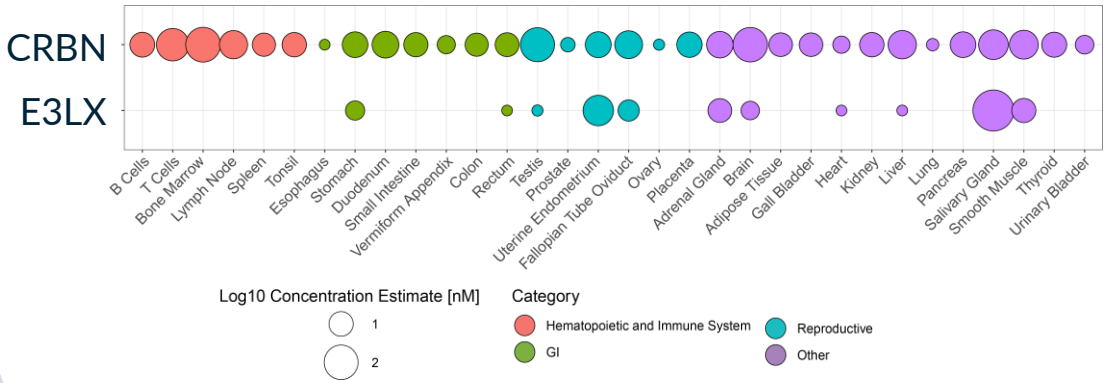
E3LX Expression Profile Substantiated by Proteomics

E3 Ligase Whole-body Atlas

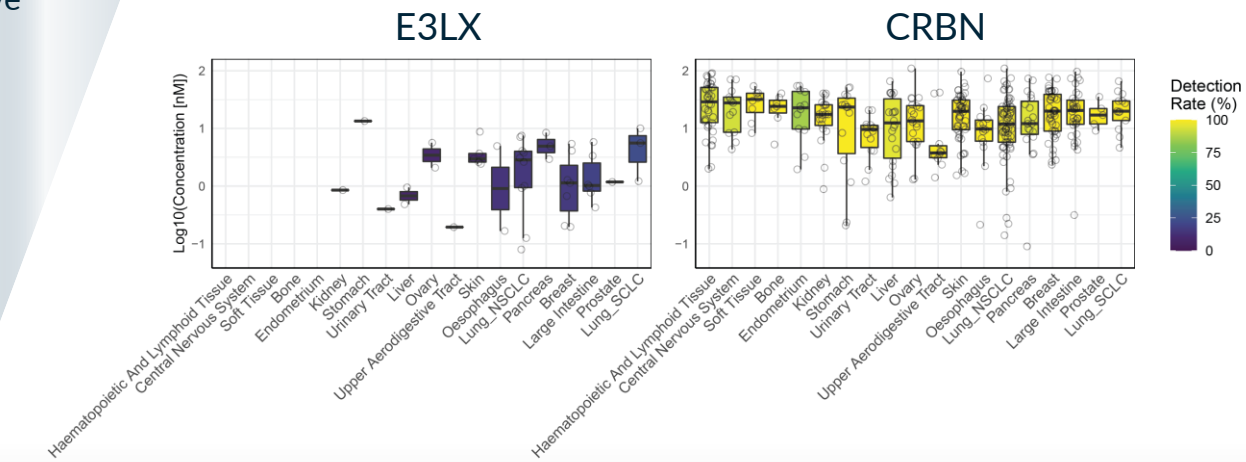


E3LX Protein Expression Profile

HEALTHY Tissues**



CANCER Cell Lines***



** Wang et al., Mol Syst Biol 2019, reprocessed and supplemented with internally acquired data.
*** Nusinov et al., Cell 2020, reprocessed

E3LX: Qualified Biology

Expression Profile

- RNA & protein show favorable healthy & disease profile for tissue-selective degradation; cytosolic & nuclear localization of protein

Degradative Activity

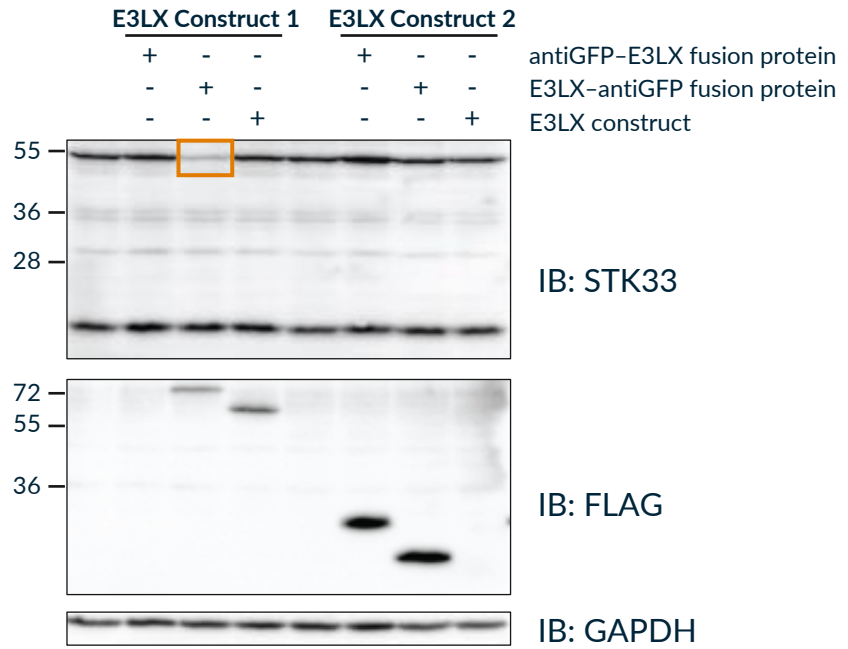
- Endogenous: no known substrate → no known degron
- Induced: STK33 is neo-substrate using AdPROM system

Ligandability

- RING E3 ligase (family includes MDM2, cIAP1, etc.)*
- No reported X-ray crystal structures or SM ligands

E3LX Degradative Activity by AdPROM#

A549 Cells Stably Expressing GFP–STK33 Fusion Protein



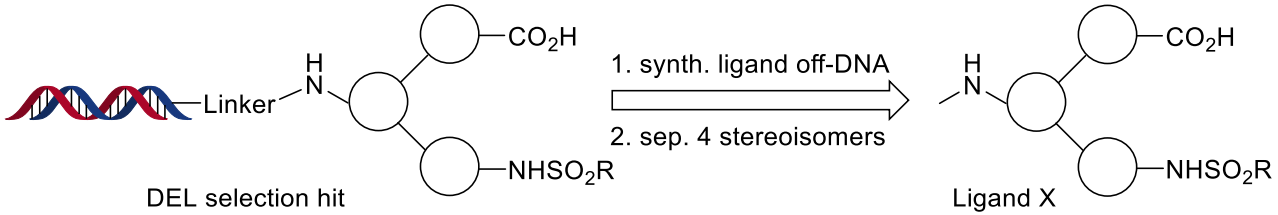
* Jevtić, P.; Haakonsen, D. L.; Rapé, M. *Cell Chem. Biol.* **2021**, *28*, 1000-1013.

AdPROM, affinity-directed PROtein Missile

E3LX: Enabled Chemistry

Hit Finding Strategy

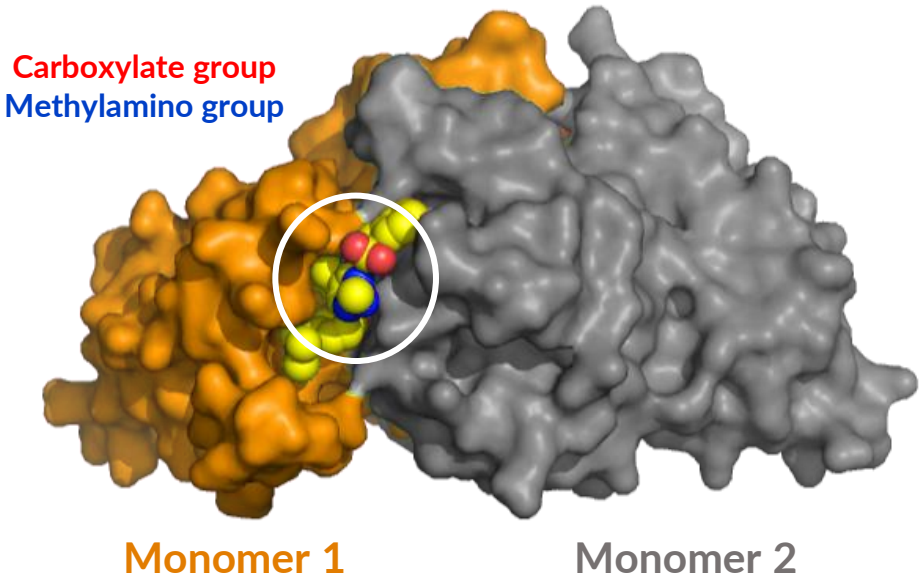
- Binding sites unknown at time of DEL selection
- DEL selection done at GSK (~ 100 unique DELs)
- Diverse, 2–4 cycle library; billions of compounds



X-ray Crystal Structure

- Ligandability validated (Ligand X K_d = 0.20 μM)
- Enables structure-based virtual screening
- Allows SBDD for binding affinity & exit vectors

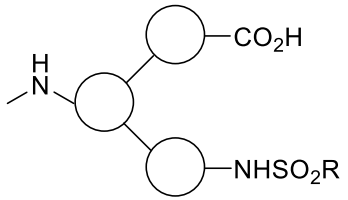
E3LX–Ligand X Complex Structure by X-ray Crystallography (3.3 Å)

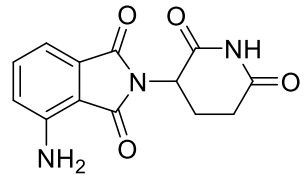


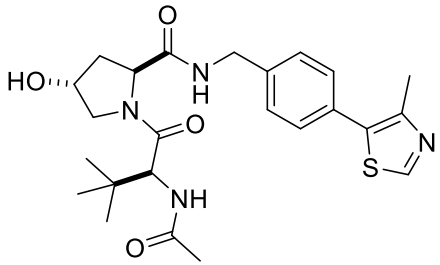
Ligand X binds at the interface of dimeric C-terminal domain of E3LX

Ligand X: Key Properties

Improved Properties Needed



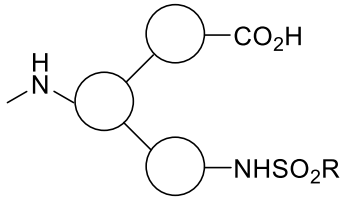


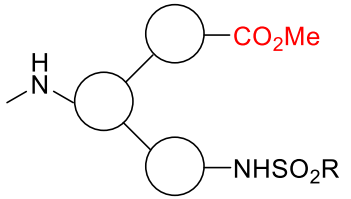


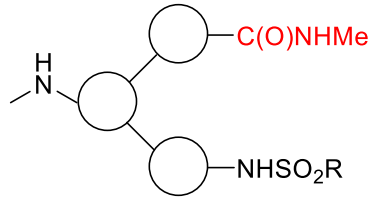
Molecular, Physicochemical, & Pharmacological Properties	E3LX, Ligand X	CRBN, Pomalidomide	VHL, VH032
Binding affinity, K_d (μM)	0.20	1.2	0.60
Molecular weight, MW (Da)	623	273	473
Topological polar surface area, TPSA (Å^2)	128	110	111
Lipophilicity, cLogP	3.8	–0.20	0.70
Kinetic aqueous solubility, PBS at pH 7.4 (μM)	15	258	284
Passive permeability, WT-MDCK P_{app} A→B (x 10^{-6} cm/s)	0.30	30	0.60

Ligand X: Exploratory Binding SAR

Carboxylic Acid is Important

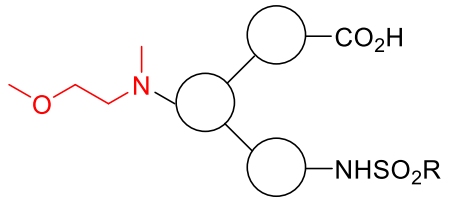


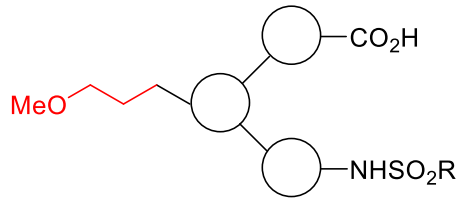




Binding Affinity	Ligand X	Analogue 1	Analogue 2
E3LX SPR K_d (μM)	0.20	9.5	46

DNA Exit Vector is Favorable

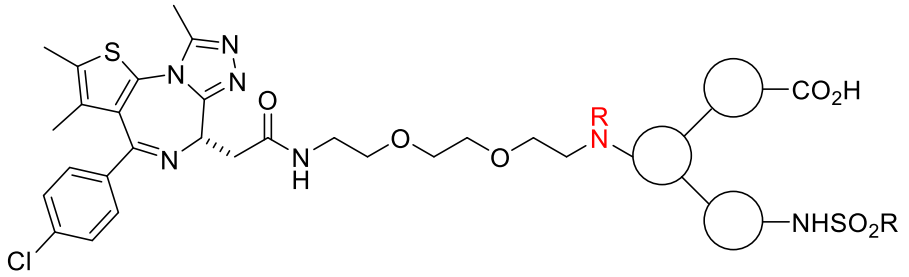




Binding Affinity	Analogue 3	Analogue 4
E3LX SPR K_d (μM)	0.16	0.14

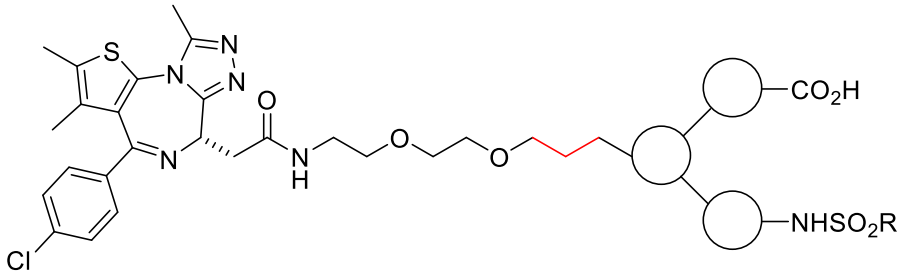
Degrader X: Exploratory Binding SAR

Degraders Have Lower Affinity



Binding Affinity	Degrader X (R = H) and Analogue 1 (R = Me)
E3LX SPR K_d (μM)	Degrader X = 1.6; Analogue 1 = 6.3

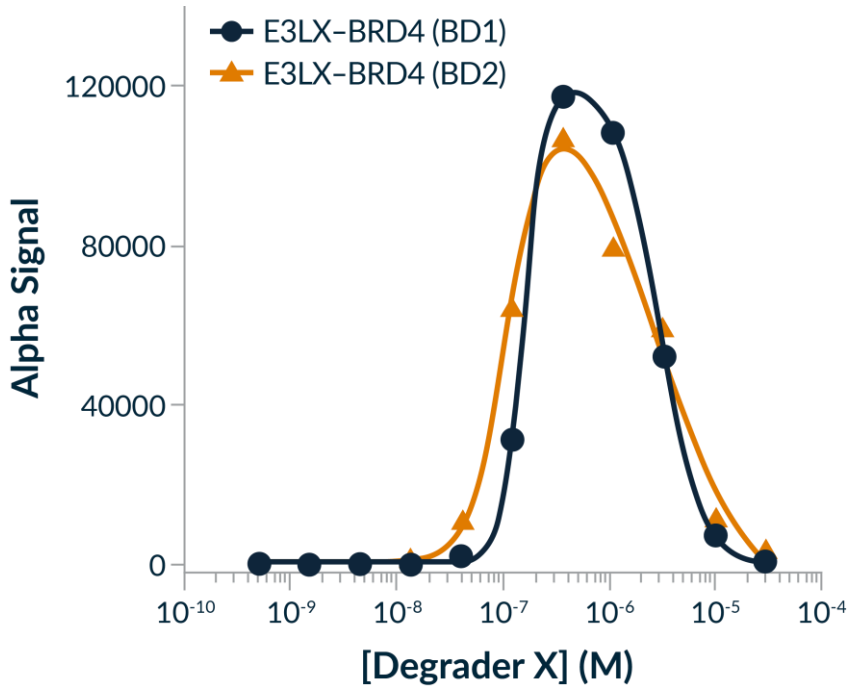
Methylene Linker Similar to Amine



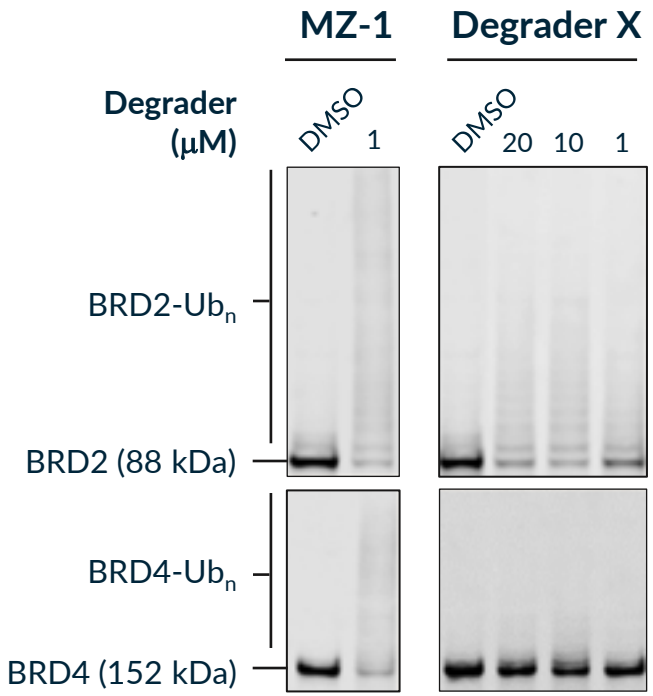
Binding Affinity	Analogue 2
E3LX SPR K_d (μM)	0.89

Degrader X: Exploratory Cell-free Assays Toward Rapidly Assessing Inducible Degradative Activity

Ternary Complex Formation by AlphaLISA



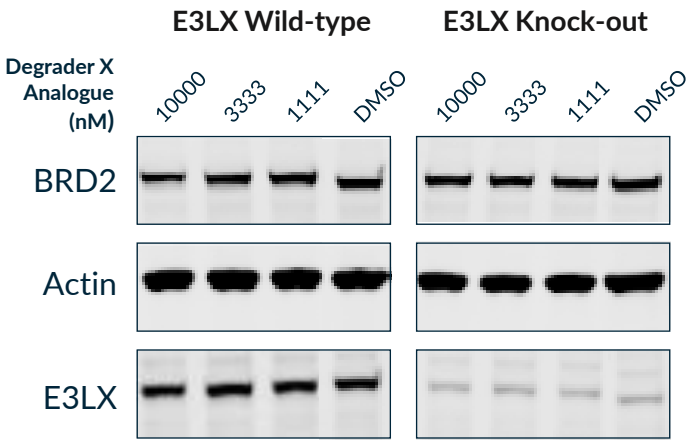
Cell-free Ubiquitination by Western Blot (WB)*



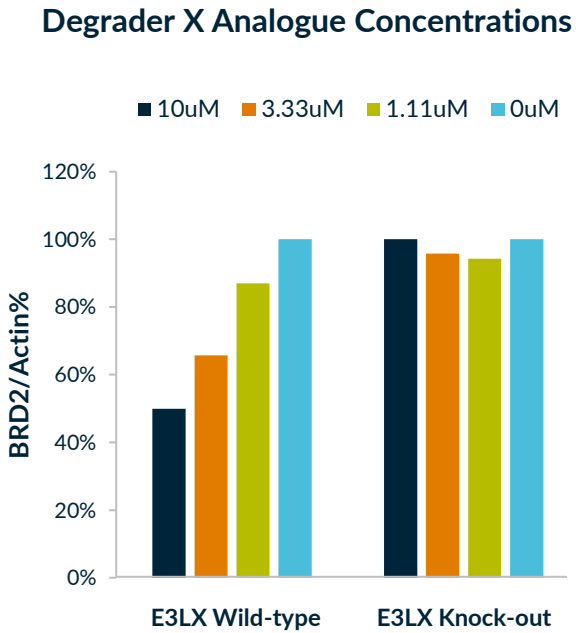
* Cell lysate derived from OCI-LY10 cells

Degrader X Analogue: Exploratory Cell-based Assays Toward Rapidly Assessing Inducible Degradative Activity

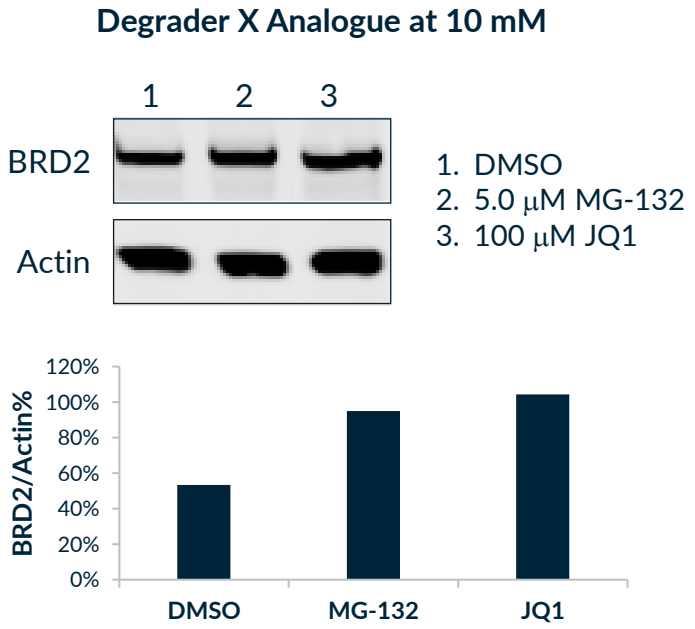
Cell-based Degradation by WB



Cell-based Degradation by HiBiT



Cell-based Degradation Rescue



HEK293 cells used throughout

Summary and Outlook

- **E3LX**: favorable tissue-selective expression profile was identified by the E3 ligase whole-body atlas at Kymera
- The first SM ligand for E3LX, Ligand X, was identified by DEL selection at GSK
- The first E3LX–Ligand X complex structure by X-ray solved at Kymera
- The first E3LX-based exploratory tool degraders exhibit UPS-mediated degradation
- Improvement of physicochemical and pharmacological properties of new E3LX ligands and E3LX-based degraders needed to further harness this novel E3 ligase

THANK YOU

Q & A