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

Drugging Tissue Restricted E3 Ligases for TPD-based Precision Medicine

April 27th, 2022

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Outline

How We Select Therapeutic Targets

- Drugging all target classes with multiple E3 ligases
- Opportunities for tissue sparing E3 ligases

How We Select Tissue Sparing E3 Ligases

- Selection criteria for tissue restricted E3 ligases
- A novel E3 ligase with broad utility for solid tumors

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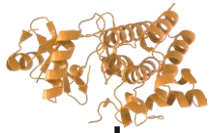
How We Select Our Targets

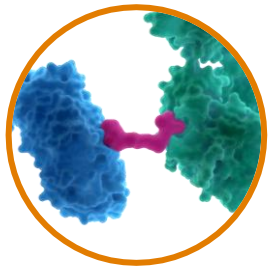
Expanding the Druggable Proteome with TPD

ID Drugged Targets with Clear Degrader Advantage

Small molecule binders exist but unable to drug target fully

e.g. IRAK4, MDM2…





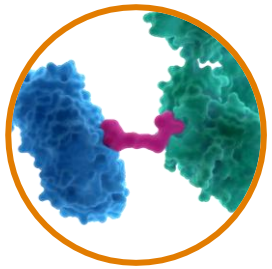
Heterobifunctional Degraders

UD Undrugged Targets

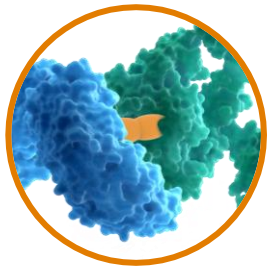
No other technology can drug

Ligandable Proteins
e.g. STAT3…

Un-ligandable Proteins
e.g. MYC, β-catenin…



Heterobifunctional Degraders

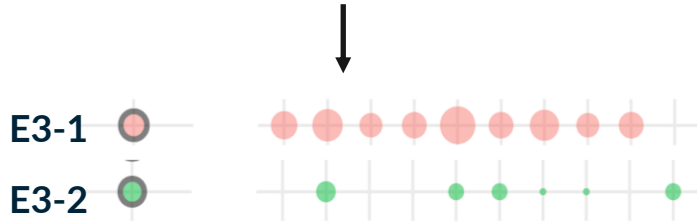


Molecular Glues

TR Clinically Validated Targets Unlocked by E3 Ligase Differential Expression

On target unwanted pharmacology limits clinical application

e.g. BH3, JAK's…



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

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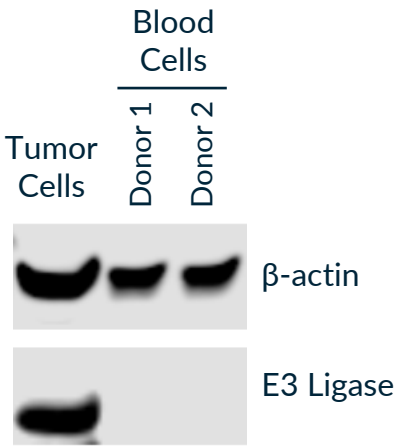
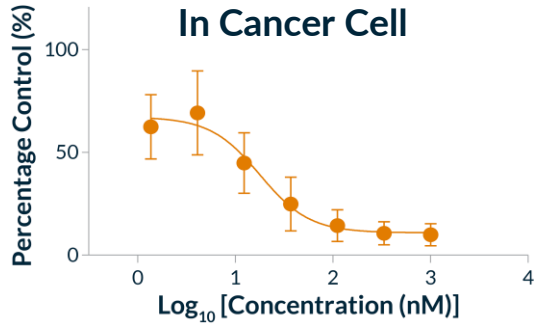
Unlocking a Clinically Validated Target by a Tissue Sparing E3

- Kymera has characterized an E3 ligase that is expressed broadly but NOT in ONE blood cell type
- A clinically validated oncology target has dose limiting toxicity driven by on-target pharmacology in the same blood cell type where this E3 ligase is absent/very low

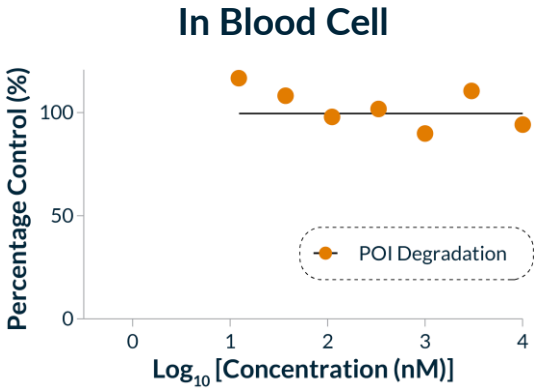
E3 Ligase is Almost Absent in One Blood Cell Type



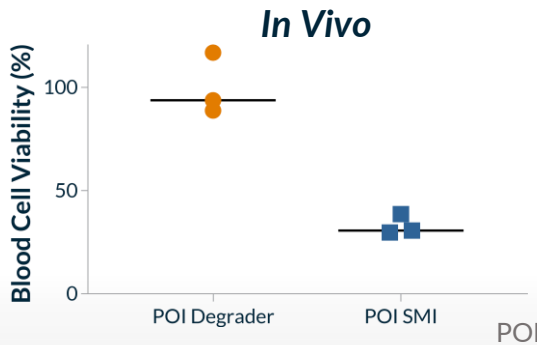
Optimization and Degrader Program



Kymera's degrader using this E3 ligase **degrades target in cancer cells**



Kymera's degrader using this E3 ligase **DOES NOT degrade target in one blood cell type**



In a pharmacologically active dose *in vivo* a **degrader allows blood cells to survive** while SMI leads to substantial cell death

- This program is projected to nominate a development candidate in 2022

POI = protein target of interest

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New Opportunities for Clinically Validated Targets

Ubiquitously Expressed Protein Targets

- There are many therapeutic proteins where a systemic blockade of their biology is **not tolerated**
- TPD with tissue restricted E3 ligases can help advance these classes of targets

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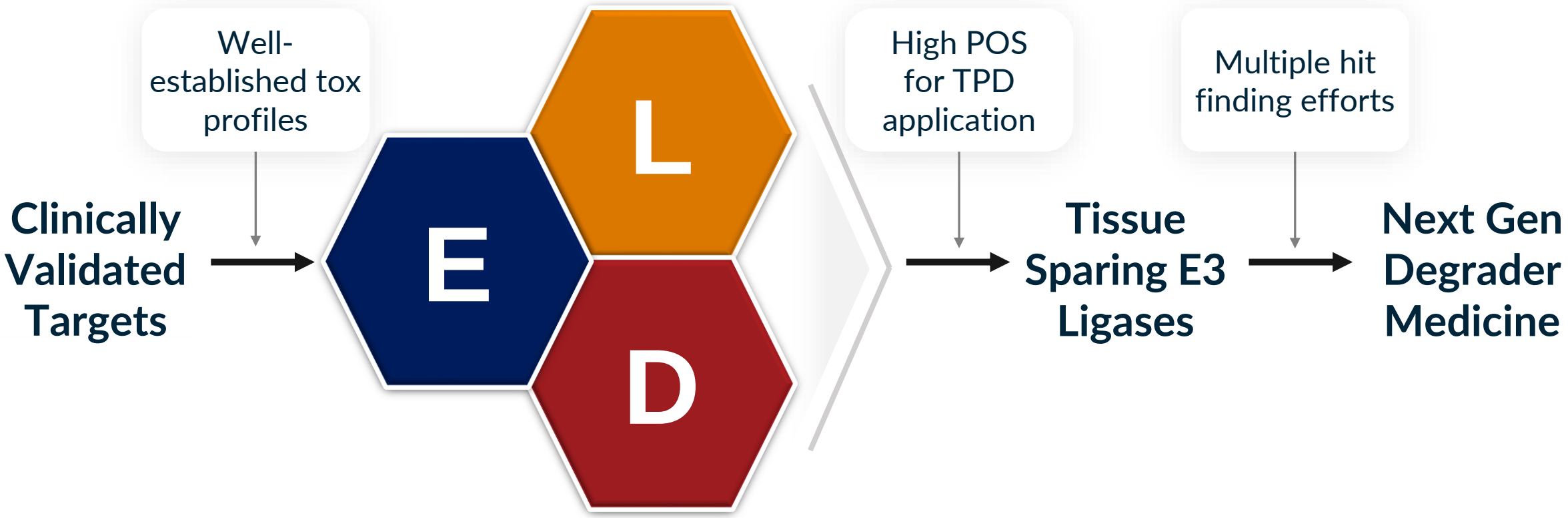
How We Select Tissue Sparing E3 Ligases

L.E.D Criteria Serve to Identify Matching E3 Ligases



Ligandability; **E**xpression; **D**egradation

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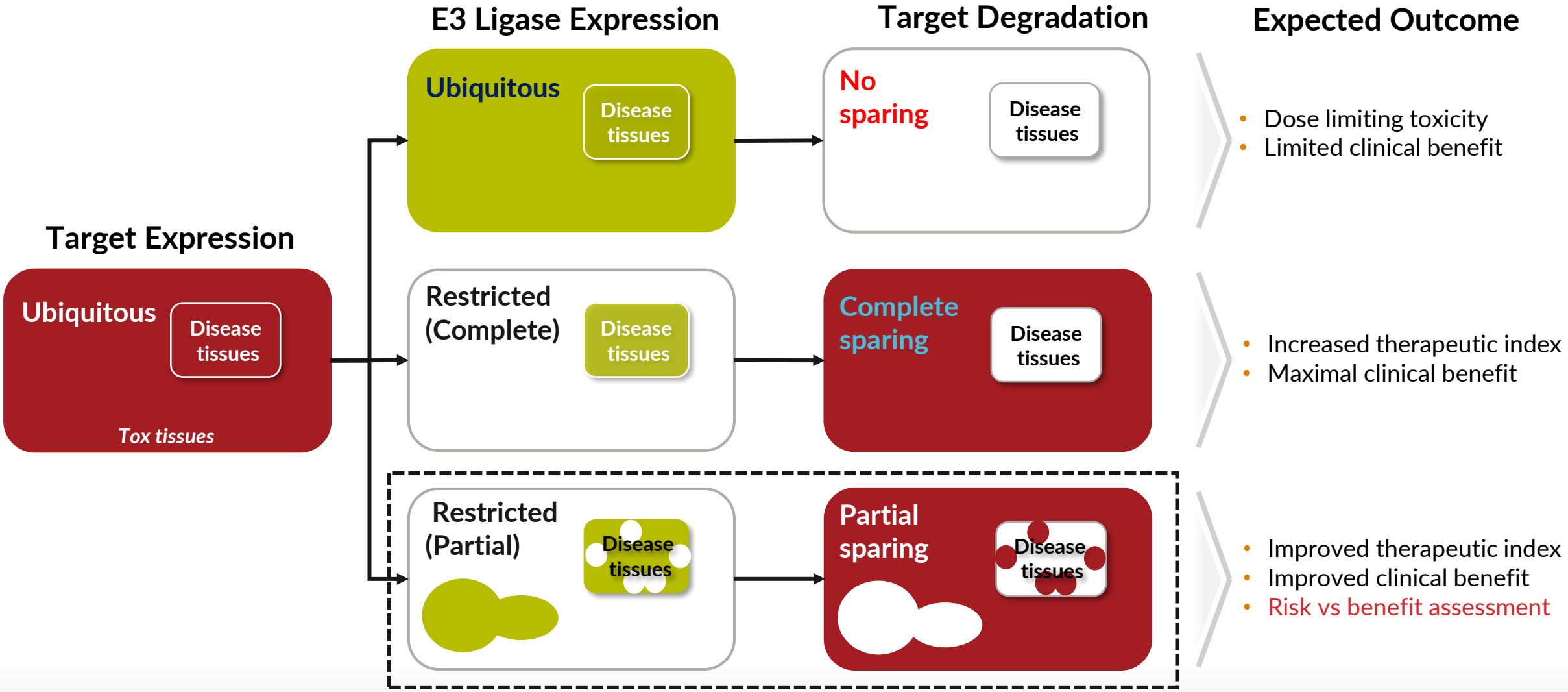
Desired Outcome for Tissue Sparing E3 Ligases

Increase of Therapeutic Index



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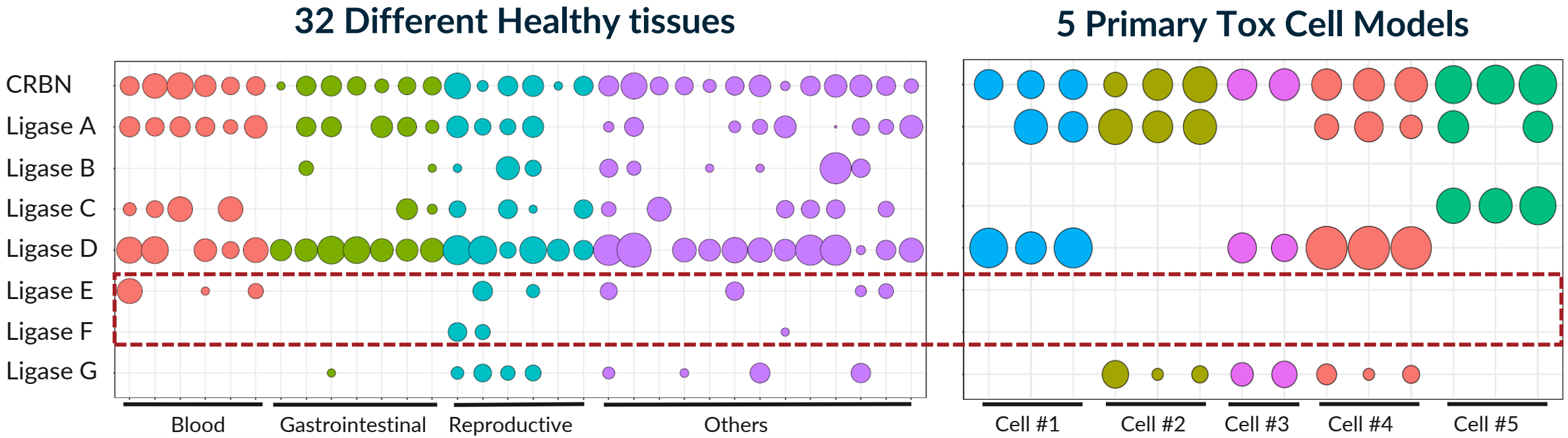
Example: Protein Expression of Select E3s in Healthy Tissues



- Complete absence across different tox cell types (e.g. Ligase B, E, F) could be due to detection limit. In these E3 cases, it is important to confirm by the bulk tissue RNAseq data (e.g. GTEX) as well as scRNAseq studies for a specific tissue
- E3 ligases with very restricted expression in normal tissues (e.g. ligase F) may have little clinical utility, unless expression is seen to be upregulated in the disease settings

Proteomics Team Data: Heathy Tissue E3 Atlas incorporating internal and published (Wang et al., *Mol Syst Biol*, 2019) deep label-free proteomics datasets.

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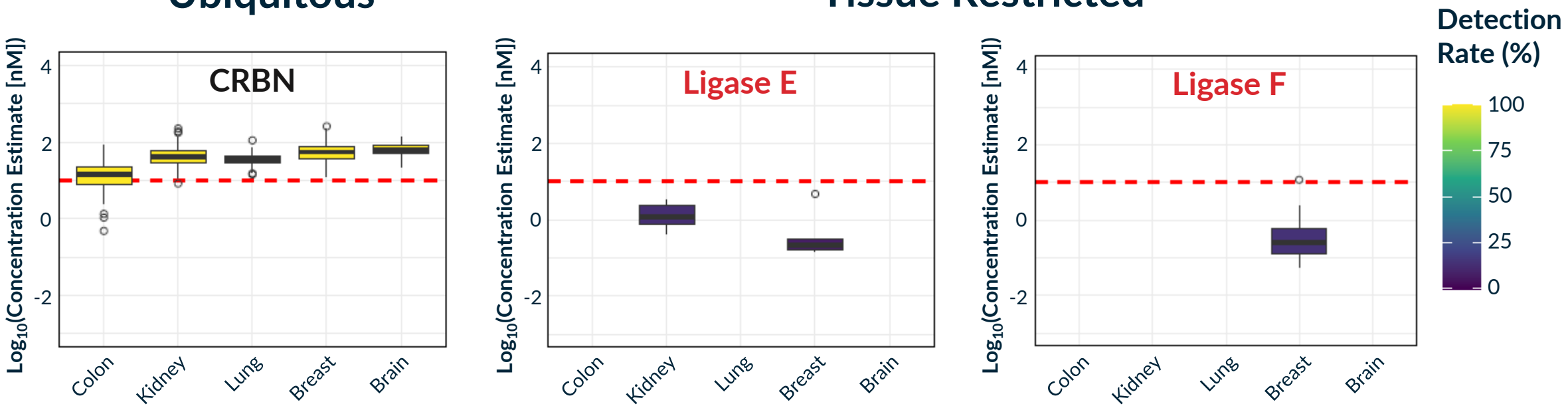
Example: Limited Utility for Highly Restricted E3 Ligases

Ubiquitous

Tissue Restricted



Data: Selected datasets from the Clinical Proteomics Tumor Analysis Consortium (CPTAC) and Cancer Genome Atlas Program (TCGA) reprocessed in E3 Atlas.

- For expression in the actual cancer cells (vs surrounding stroma), we evaluate protein and RNA data from CCLE and scRNAseq data from tumor samples.
- Highly restricted E3 ligases tend to have more heterogenous expression within the same tumor type

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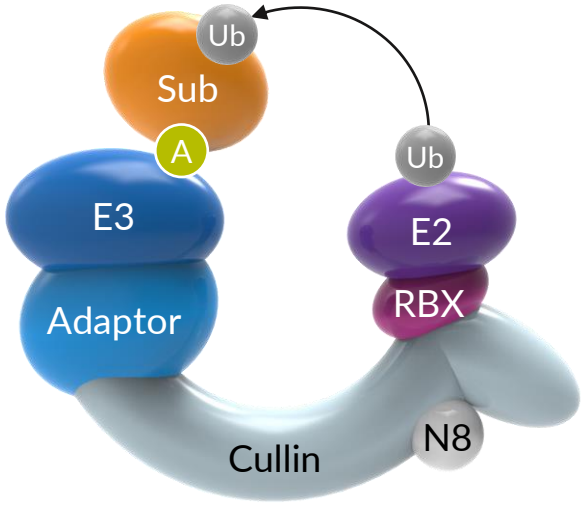
What Makes an E3 Ligandable and Druggable at Kymera?

- **Ligandability**: *likelihood* of identifying a small-molecule binder with affinity < 1 uM
- **Druggability**: *likelihood* of converting the ligand into a degrader with therapeutic potential

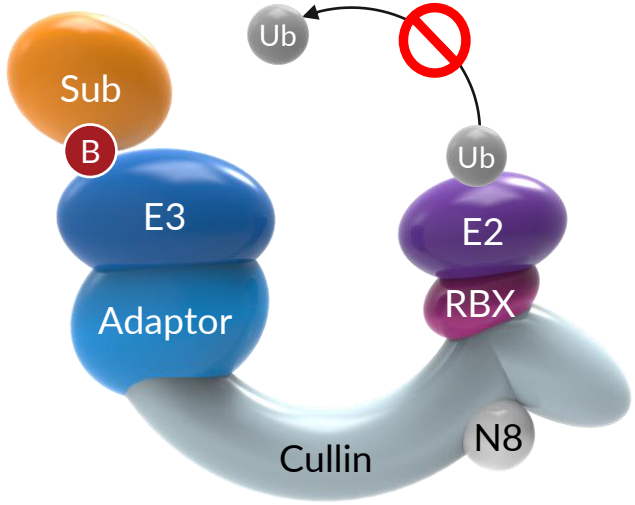
Site A

Ligandable; MORE Druggable



Site B

Ligandable; LESS Druggable



- Ligands that bind to either site A or B can lead to TCF but **only site A binders** could be converted to efficient degraders
- Validation of "**degrader competent**" site(s) by identifying **degron(s)** is desired to assess "**ligandability**" and "**druggability**"

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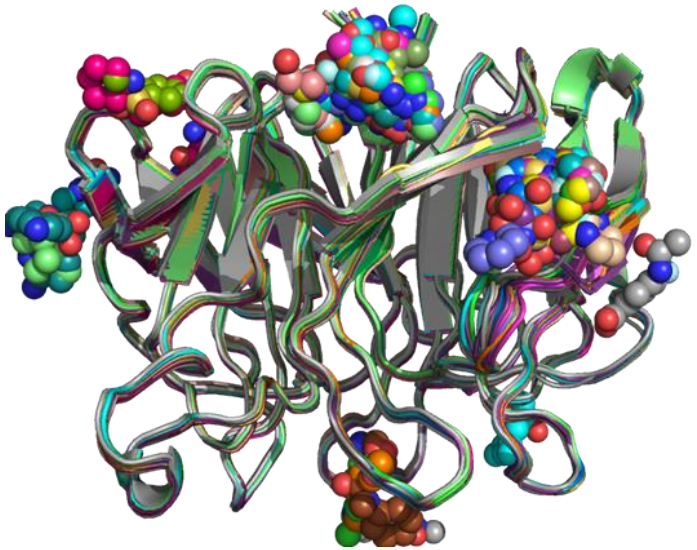
Ligandability Assessment by Pilot Screens

Fragment-Based Screen

Example of FBS by X-ray Crystal

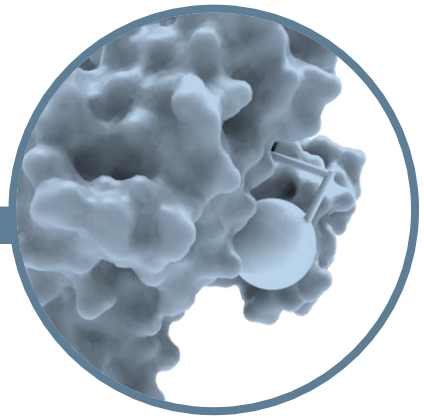


Criteria
- Availability of high quality protein with robust crystal system

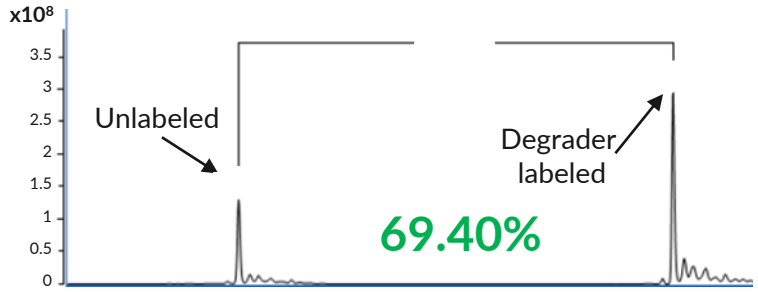
Approaches
- Orthogonal validation of hits by SPR and NMR by SBDD

Advantages
- Rapid evaluation of multiple potential ligandable sites

Cysteine Covalent Screening



Covalent Screen by Intact MS



Assessment of **functional competency** by *in vitro* ub and/or COFFEE assay with functionalized (degrader-labeled) E3 ligase

Criteria
- Surface exposed reactive cysteines

Approaches
- Covalent fragment screen on purified protein by intact MS

Advantages
- Early assessment of functionality of Cys sites by covalent degraders

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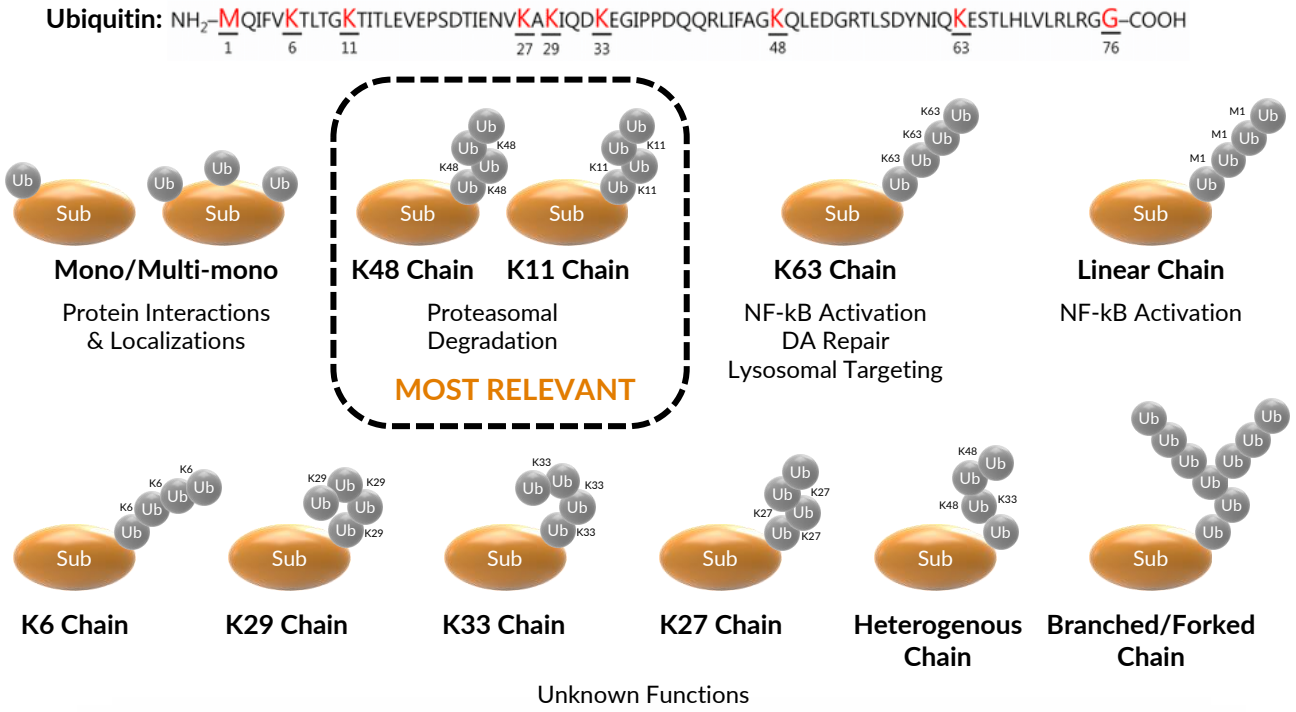
Why We Validate Degradative Activity of E3 Ligases

Different Types of Ubiquitin Linkages

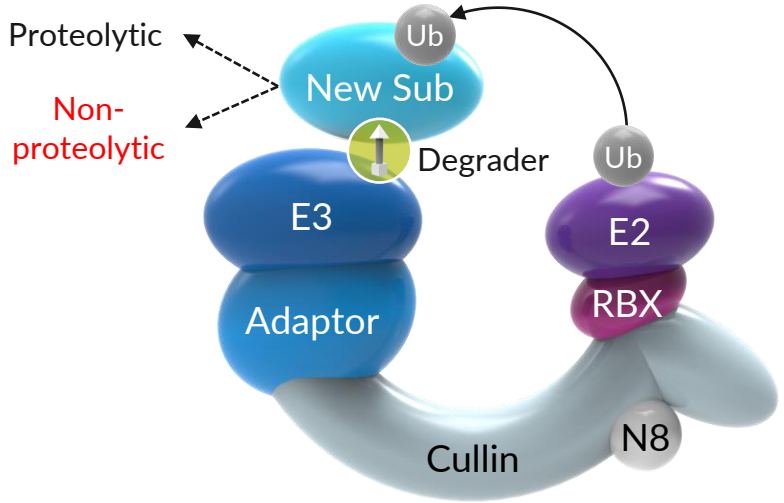
- >600 known E3 ligases in human



- The vast majority (>95%) of human E3 ligases are RING domain based which **do not** specify ubiquitin chain linkage

Unknown Risks for Novel E3 Ligases

- Not all E3 ligases are suitable for TPD application



- Validation of intrinsic **degradative activity** is a must-have mitigation strategy

Adapted from: Park CW at al. *BMB Rep.* 2014

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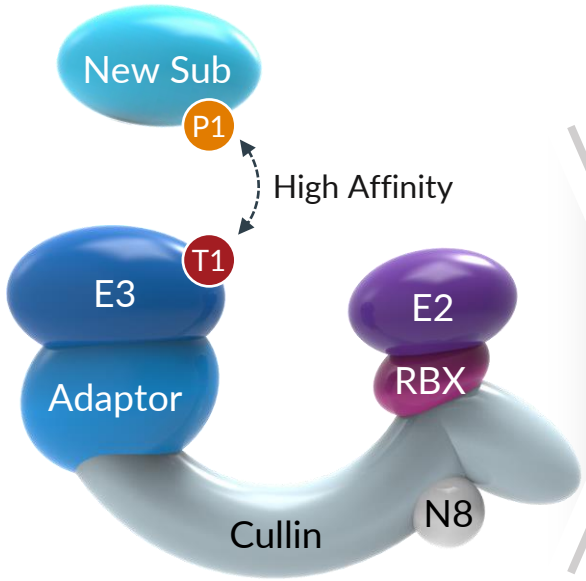
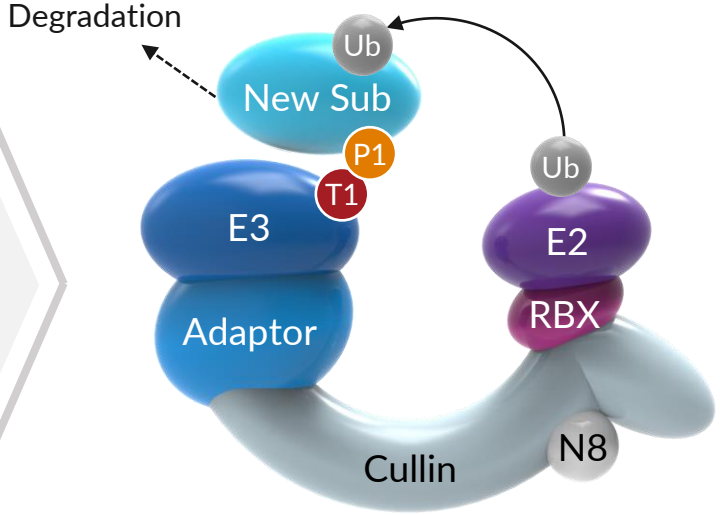
How We Validate Degradative Activity of E3 Ligases

New Proximity Assay Based on High Affinity Peptide-protein Pair

Leveraging Peptide-Protein Pair



Forced E3-Sub Interaction



PoC of New Proximity System

Example with Ligase D

- Not all neo subs are equally degradable!
- Ubiquitination is likely to happen on subs

- Leveraging a **high affinity interaction** between peptide (T1) and protein (P1) to enable a forced proximity of E3 and substrates
- Enable early assessment of **intrinsic degradative activity** of novel E3 ligases in both cellular and cell-free contexts
- Small peptide size (~15a.a.) allows for assessment of "D" with **a minimal perturbation** of the natural conformation E3 ligases
- Affinity between T1-P1 could be "**tunable**" by T1 variants; Scalable and quantitative with readily degradable reporter proteins

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A Novel Tissue Sparing E3 Ligase with Broad Cancer Utility

High Level Background

Ligase Type:	RING domain-based
Known Substrates:	Multiple degradative substrates identified
Function:	Confidential Information
Crystal Structures:	Structure solved by internal effort
Value Proposition:	• Broad utility in cancer • Highly expressed in multiple cancer types • Low to no expression in key tox cell types. • Compelling biology for UPS involvement.

Tractability Assessment

Precedence and Datamining

- ☑ Contains ligandable domains/protein family analysis
- ☑ Known degrons/substrates
- ☐ Known and validated small-molecule

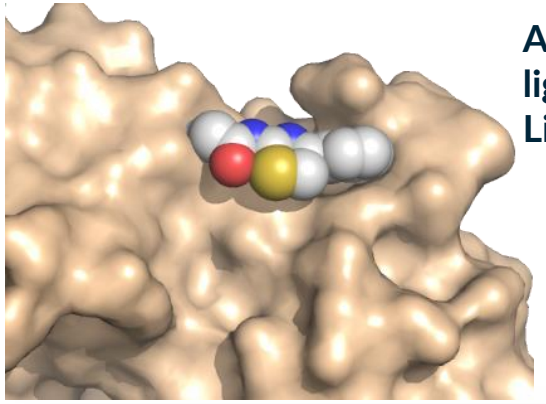
Structure-based Assessments

- ☑ Ligandability score
- ☐ Cryptic pocket available

Experimental/Biophysical

- ☑ Identified hits from pilot screens

Progress on Chemical Matter



An example of ligand-bound Ligase D

Protein Sciences & Lead Discovery

- **FBS by X-ray crystal**: multiple hits binding to 3 sites, including a known degron binding site; one with Cys
- **Cysteine covalent screen**: multiple single-labeling hits with confirmation by co-crystals
- **DEL screen**: (+/-) competitors to identify more "drug-like" molecules

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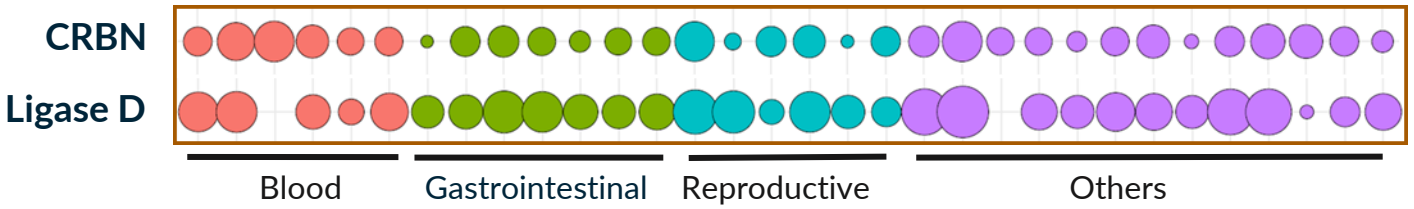
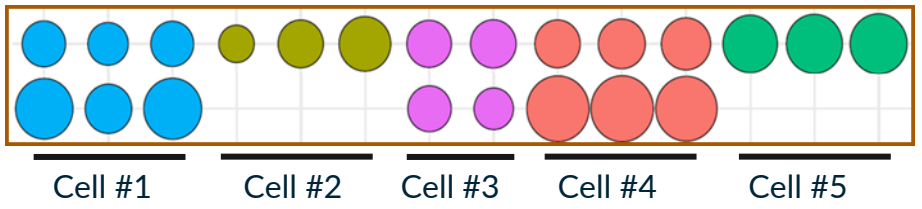
Protein Expression of Ligase D in Healthy and Cancer Tissues

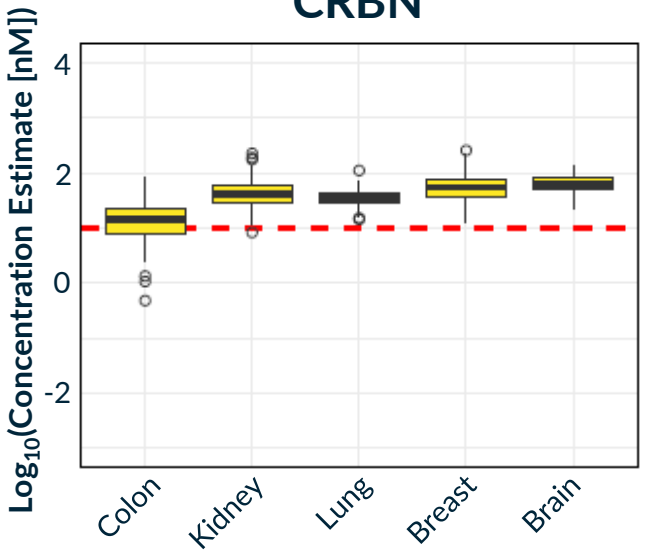
32 Different Healthy Tissues



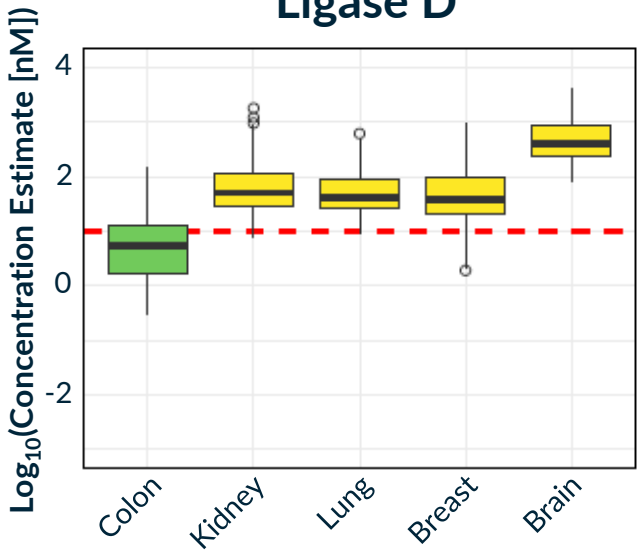
5 Primary Tox Cell Models



CRBN



Ligase D



- Highly expressed in multiple cancer types (i.e. comparable to CRBN)
- Very low to no expression in key tox cells, especially in blood progenitors
- Tissue-sparing potential is suitable for multiple solid tumor indications

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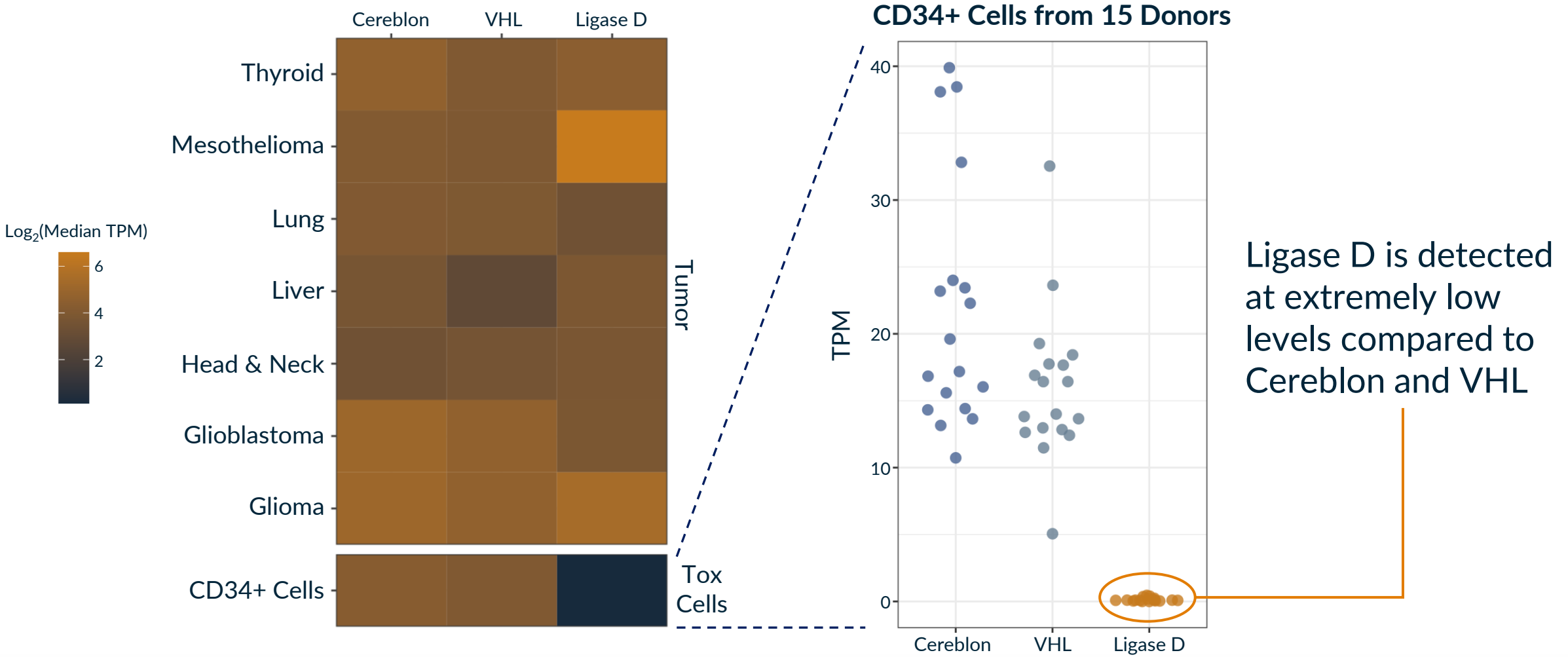
Ligase D is Not Expressed in Blood Lineage Progenitors



TCGA RNAseq, reprocessed by Toil; CD34+ RNAseq from Yuan, *Blood*, 2021, reprocessed internally

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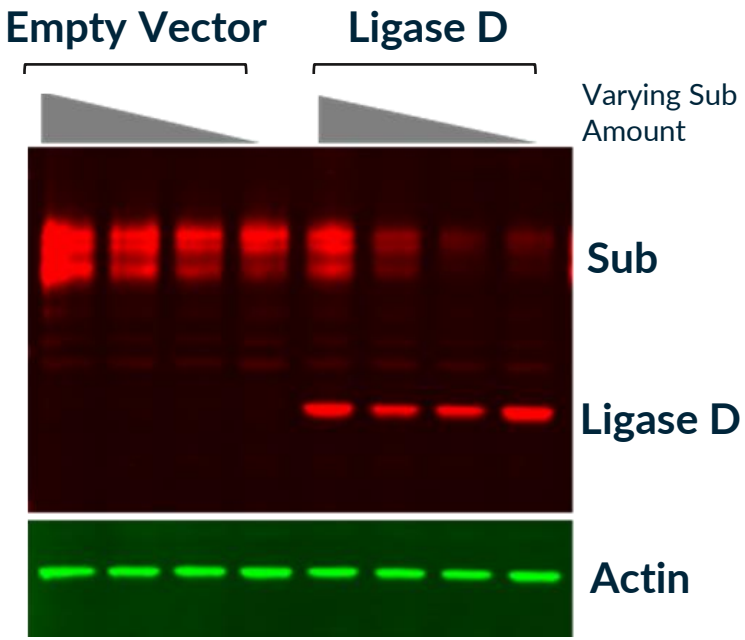
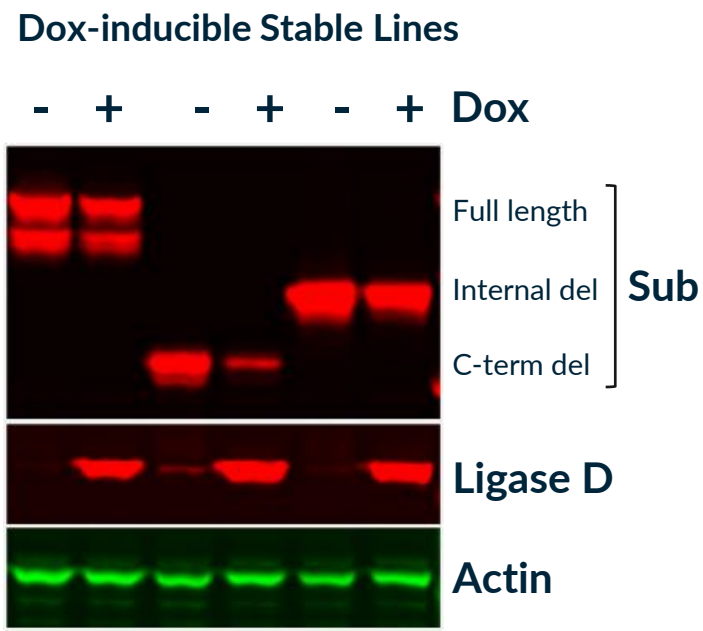
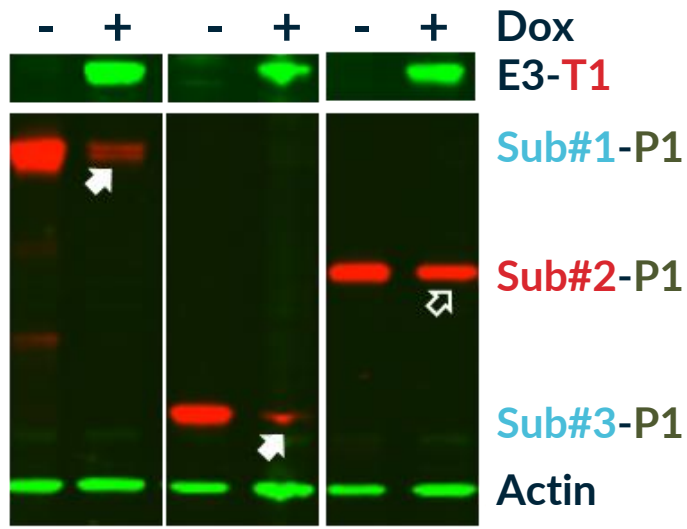
Robust "D" Toward Natural and Neo-substrates

Degradation of Endogenous Substrate





Degradation of Neo Substrates



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Validation of Druggability of Novel Site

Identification of Covalent Ligands

Screen by Intact MS

Retest & Selectivity

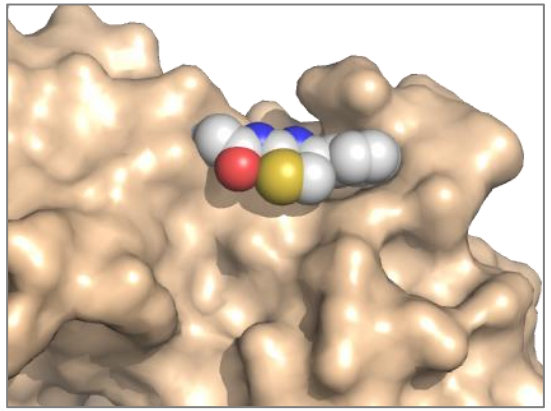
Workflow for covalent ligands screen

COFFEE

Labeling Optimization

Co-crystallization

Validated hits w/ co-xtals

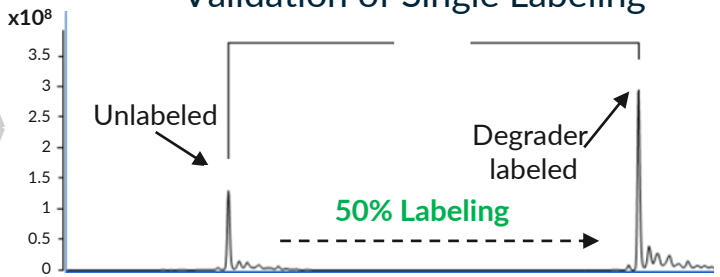


Confirming covalent and non-covalent interactions

Validation of Functional Competency

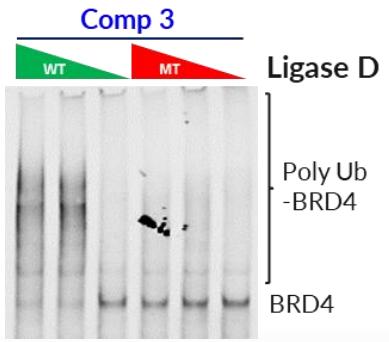
Functionalized E3

Ligase D

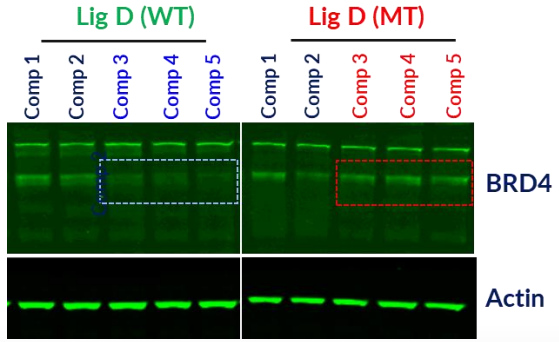


Testing Functional Competency

In vitro ub



In Cell by COFFEE



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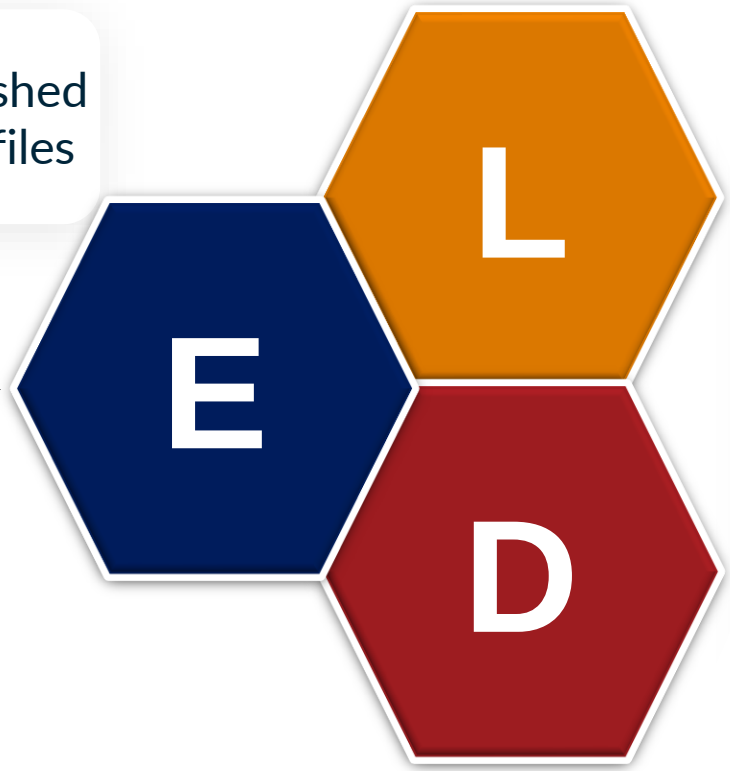
Developing Next Gen Degrader for Precision Medicine

Well-established BM tox profiles

Clinically Validated Targets



High POS for TPD application

Ligase D Sparing BM CD34+ Cells

Identified Multiple Ligands

Degrader for Precision Medicine

Work in Progress

Ligandability; Expression; Degradation

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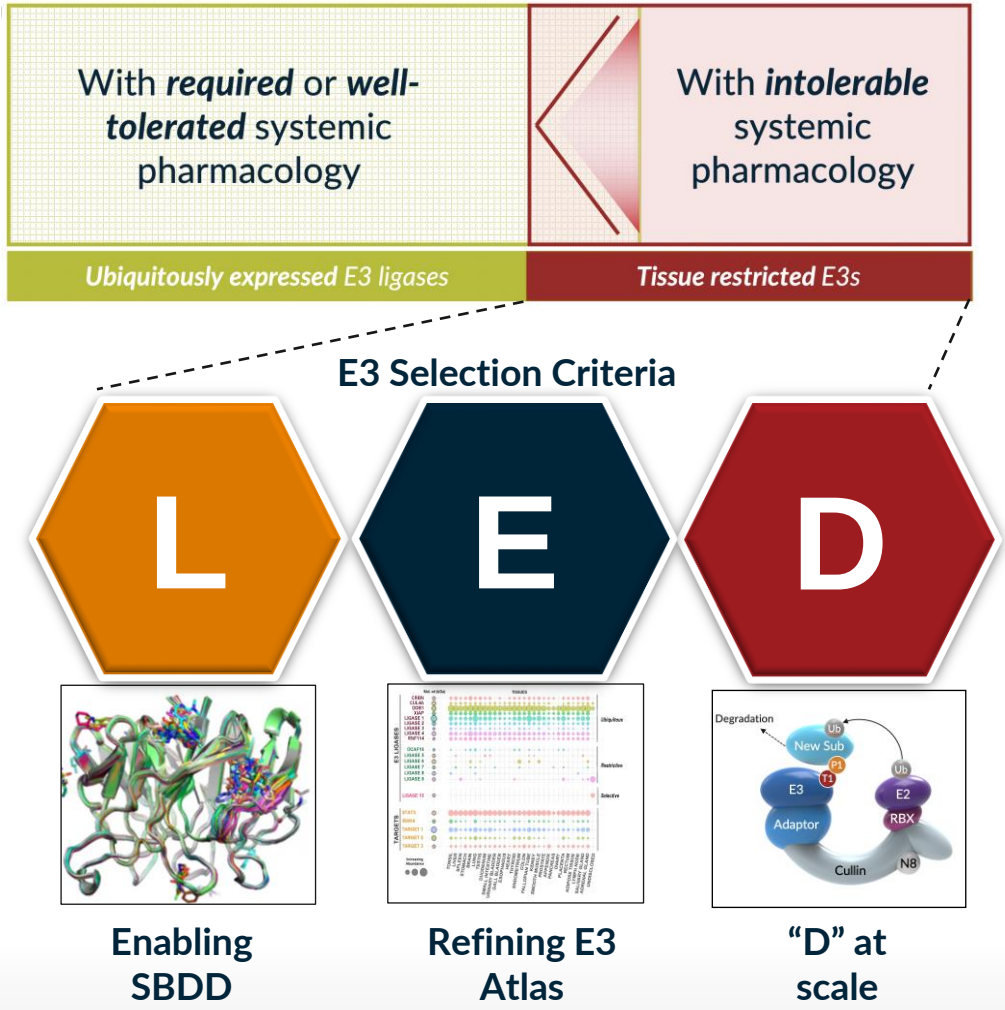
Summary and Future Ambition

- TPD with **tissue sparing E3 ligases** can help maximize the therapeutic index of clinically well-validated targets by minimizing on-target toxicity
- Tissue restricted degradation can enable new **therapeutic opportunities** for these classes of targets
- The E3 Ligase Whole-Body Atlas identified multiple E3 ligases with **restricted expression** across different healthy tissues and tox cell types
- Through Pegasus Platform combined with L.E.D selection criteria, we identified a novel tissue-sparing E3 with a broad utility in solid tumor indications

Enabling TPD-based Precision Medicine



Enabling SBDD | **Refining E3 Atlas** | **"D" at scale**

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Thank You

July 2021

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