E3 Ligase Whole Body Atlas

A Large-Scale Absolute Abundance Map Enabling Next-Generation Tissue Selective Degraders

August 16th, 2022

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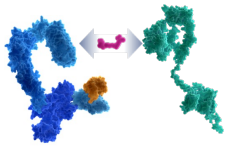
Outline



TPD & a need for tissue restricted E3 ligases

MaxQuantAtlas

MQAtlas: A novel algorithm for creating E3 Atlas

PEGASUS
E3 Ligase Whole Body Atlas

E3 Atlas and Insights for TPD

Application in developing tissue restricted degrader drugs

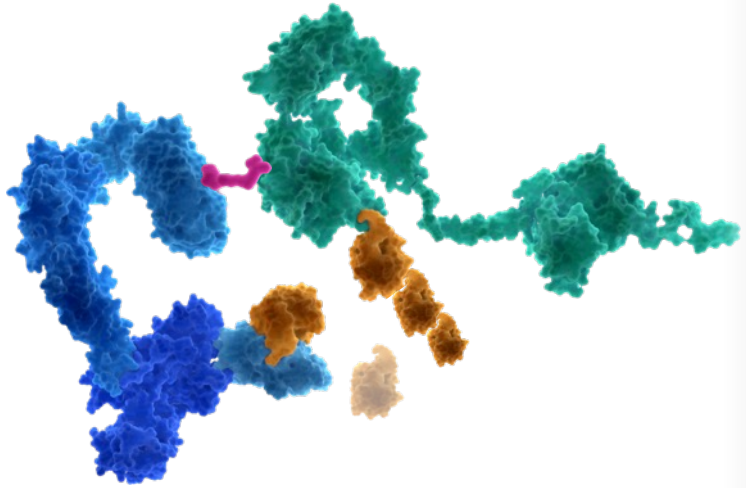
TPD and a need for E3 Atlas

KYMERA

Expanding the Druggable Proteome with TPD

Proteome Editing with TPD

Small molecule binds to E3 & disease-causing target protein to **induce its degradation**



Medical knock down strategy with **flexibility of a small molecule drug** (oral & systemic)

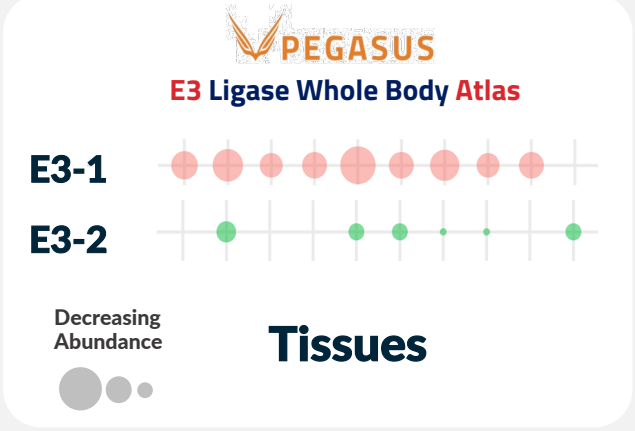
Target Types

ID — **Inadequately Drugged Targets with Clear Degrader Advantage**
e.g. IRAK4*, MDM2

UD — **Undrugged Targets by any other technology**
e.g. STAT3*

TR — **Clinically Validated Targets Enabled by E3 Ligase Tissue Restricted Expression**

Tissue restricted degradation **via restrictively expressed E3s eliminates unwanted on-target toxicity** in certain heathy tissues



Tissue sparing or selective E3 ligases allow **full clinical potential**

* Kymera Degraders **in Clinic**

The 'Why', 'What' and 'How' of E3 Atlas

Why?	**Tissue Restricted**	**Differentiated investment in high value E3 Ligases**
What?	**Human E3 Ligase Whole-Body Atlas**	**Determine expression profiles of ~600 unique E3 ligases (+ drug targets) in both health and disease**
How?	**Desired Features**	**Determine the ideal approach**

Approach: Proteomics + Novel Algorithm

- **Speed @ Budget:** *no* upfront reagent build cost ✓
- **Reliable:** protein level directly (+ QC) ✓
- **Deep Coverage:** all E3 ligases (& POIs) ✓
- **Scope:** human, whole body in health & disease ✓
- **Absolute abundance & stoichiometry** ✓

Introducing MaxQuantAtlas

A Novel Algorithm for Creating E3 Atlas

Development of a Human Whole Body Protein Expression Atlas

Strong Industry-Academia Collaboration

KYMERA

MAX PLANCK INSTITUTE OF BIOCHEMISTRY

Jürgen Cox Lab

Breakthroughs

- Algorithm for global concentration profiles
- Can tackle very heterogeneous quantitative proteomics data
- Computational scalability and feasibility
- Consolidated Atlas clusters globally by biology, not by technology

>4,000 Proteomes Integrated

>460 acquired @ Kymera
>3,400 published, e.g.

- **>40 Healthy Tissues**
- **>560 Primary Tumor Samples (CPTAC)**
- **>15+ Cell Types Relevant for Tox**
  (GI organoids, cardiomyocytes, hepatocytes…)
- **250 CCLE Cancer Cell Lines**
- **Skin Layers and Cell Types**
- **Immune and Structural Cell Types**
  (T cells, B cells, keratinocytes, fibroblasts …)

>16.5k unique gene IDs in Atlas

Introducing MaxQuantAtlas – A Novel Algorithm

A Scalable Workflow for Deep, Precise and Global Expression Maps

Heterogenous Proteomics Data

Public Repository Data

Kymera Internal Data

Multiple
MS Instruments

Multiple Repositories

Panorama
JPOST
PRIDE
iProX
MassIVE
PeptideAtlas

Multi-MS Technologies

- LFQ
- MS1 labeling
- TMT MS2
- TMT MS3
- DIA-LFQ
- Multiplexed DIA

Consolidation to an Atlas

MQAtlas

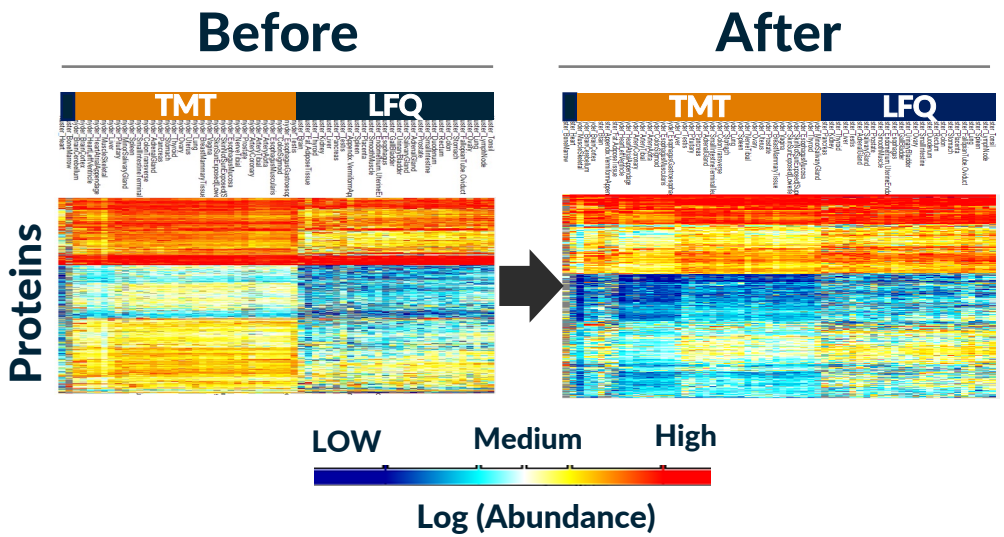
MQ Evidence Files Only → MaxQuant Consolidator → Automated Analysis + QC → Atlas Database & Web Server

Automatic / Scalable / Feasible

Core Concepts

How We Made the Data Comparable

MaxQuant consolidator

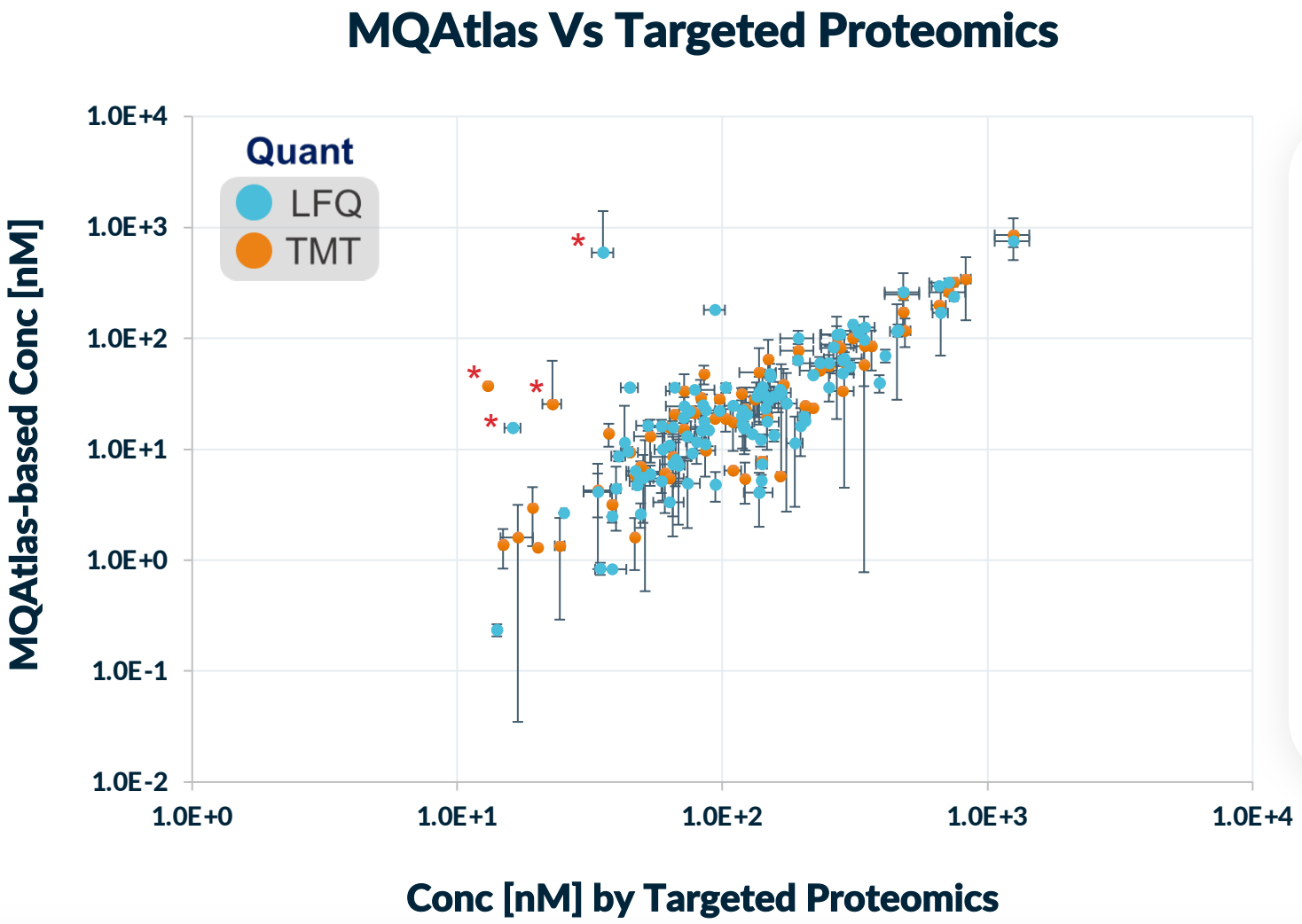


Comparable abundances across quant approaches AFTER MQAtlas Consolidation

- **Reconstructed protein intensities** in isobaric labeling data from MS1 precursor and MS2 reporter intensities
- **Optimized decompression** of TMT reporter intensities
- **Common protein grouping** over the entire atlas; comparability
- **Absolute calibration** by proteomic ruler or total protein concentration (Wiśniewski et al, *MCP*, 2014)
- **Dynamic range imputation** Novel imputation technique developed for big heterogeneous data.

- Does our Atlas provide reliable abundance estimates - technically?
- Does it capture the biology of sampled proteomes?

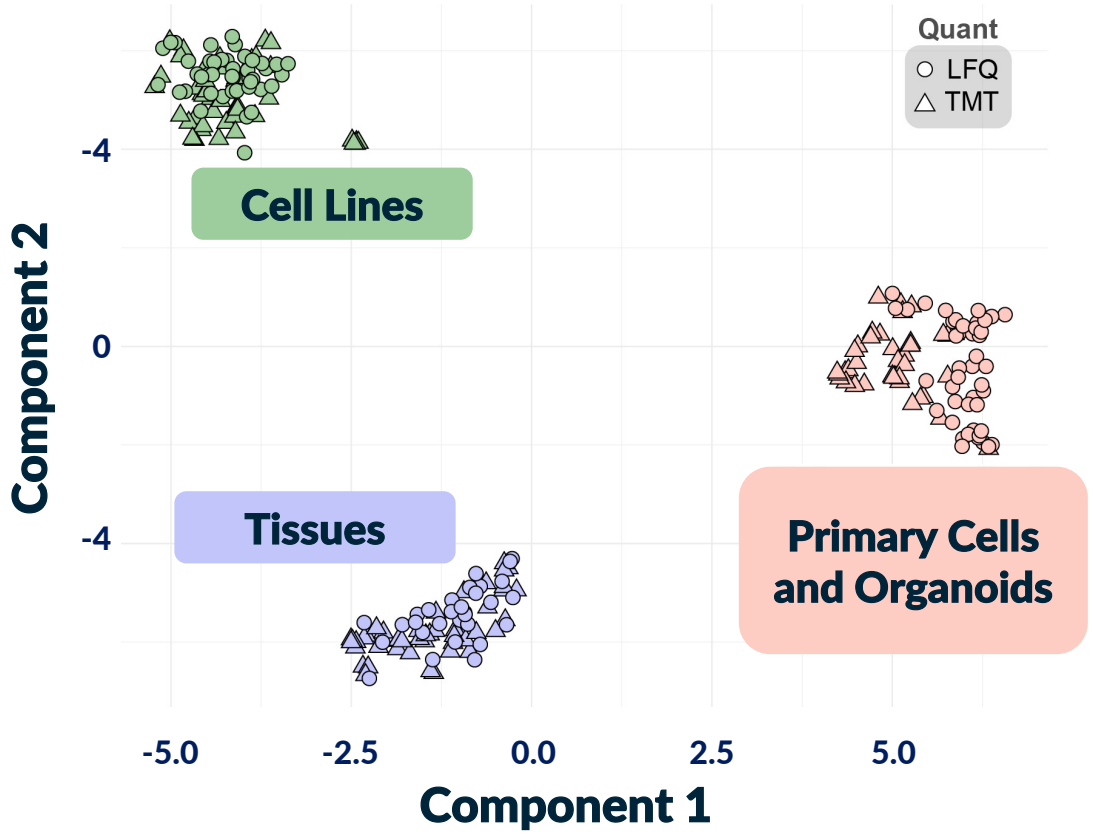
MQAtlas Absolute Abundance Estimations Correlate Well with Precise Spike-in Targeted Quantifications



- MQAtlas offers a surprisingly **high level of accuracy in abundance estimates** across multiple MS-technologies
- **25** E3 ligases & target proteins differentially expressed in seven different cell lines

*Probable false positive peptide identifications in E3 Atlas datasets

Consolidated Protein Atlas Clusters Globally by Biology, Not by Technology

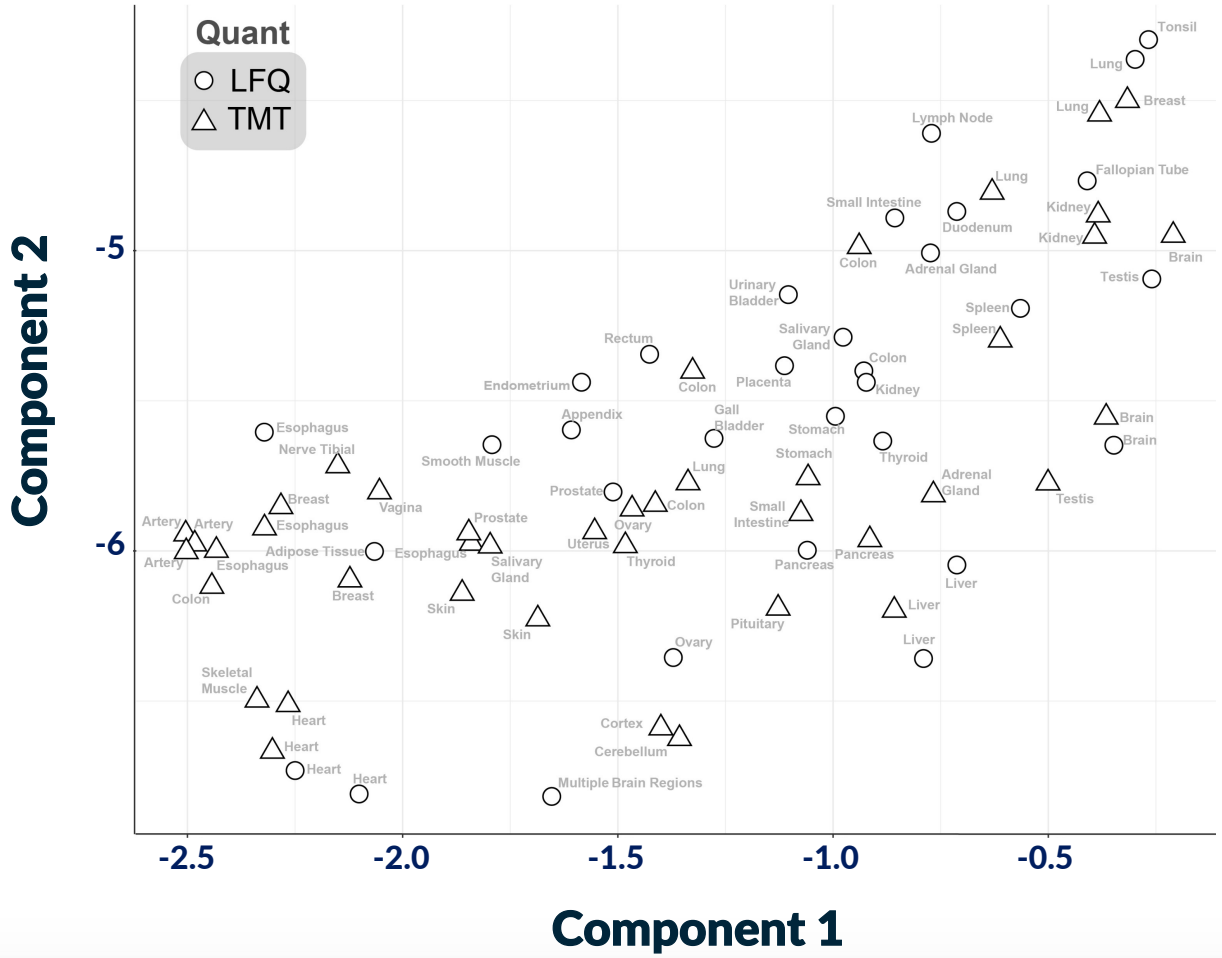


- **>60 proteomes** representing heterogenous data from multiple labs
- **Three major clusters** based on biology of samples completely independent of technical proteomic approach
- **Cancer cell lines cluster separate from tissues**
  - Non cancer cells in primary tumors
  - Difference in cultured lines vs primary tumors

Atlas captures the biology of integrated diverse proteomes thereby providing reliable absolute abundance patterns in various models of human health and disease

Consolidated Protein Atlas Clusters Globally by Biology, Not by Technology

Tissue Specific Cluster

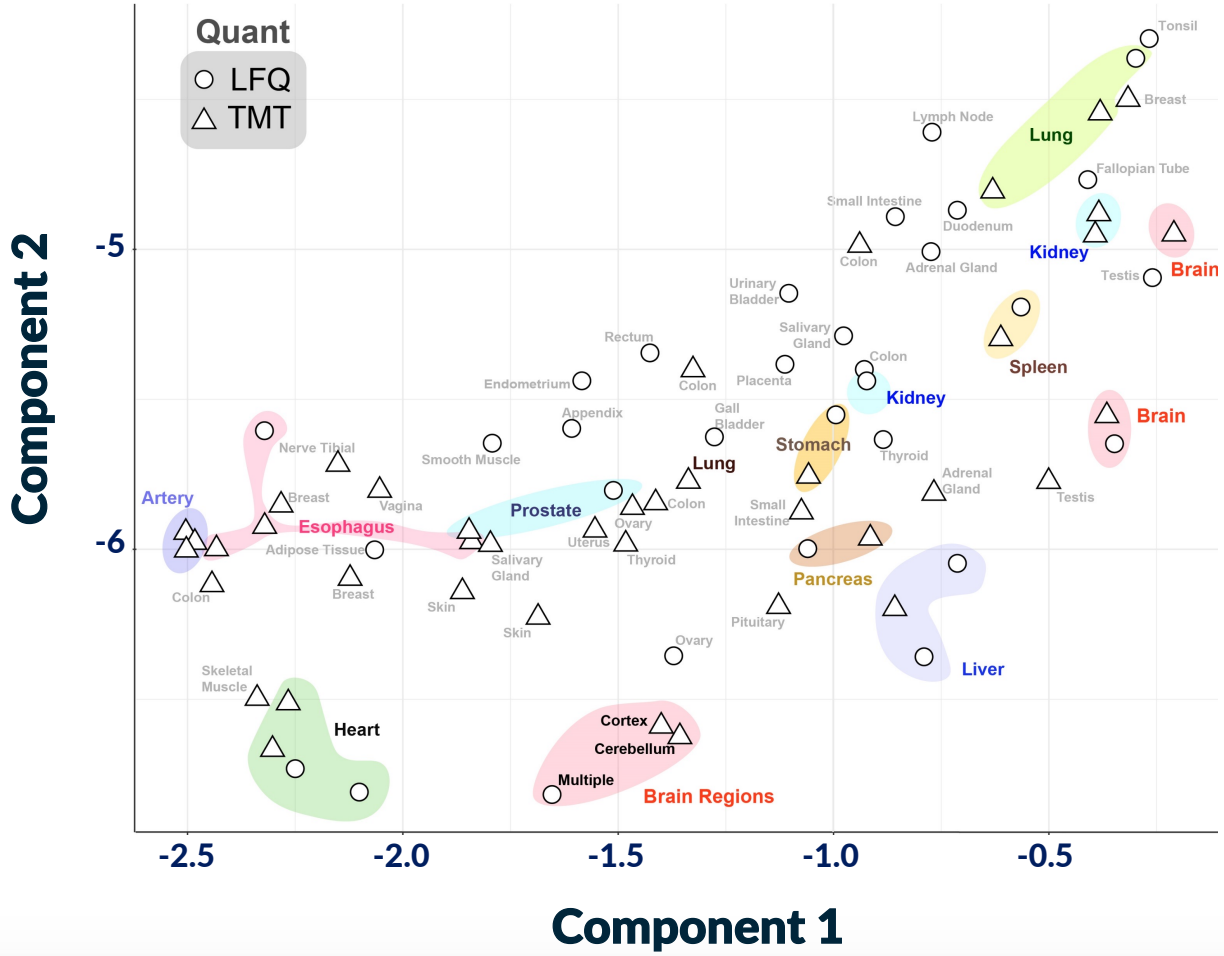


- Representative heterogenous data from multiple labs

UMAP analysis reveals data is NOT clustered by Quantification method

Consolidated Protein Atlas Clusters Globally by Biology, Not by Technology

Tissue Specific Cluster

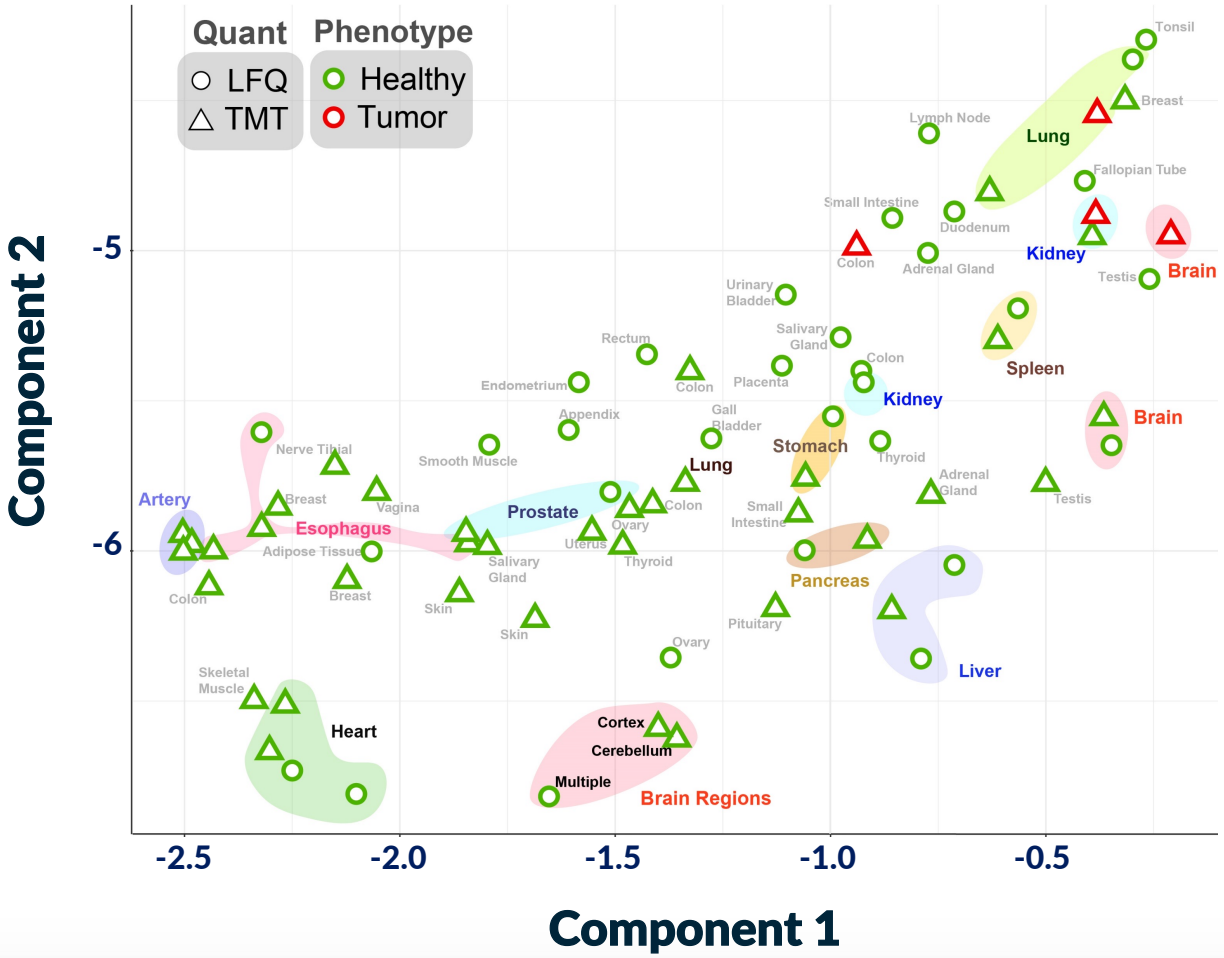


- Representative heterogenous data from multiple labs
- Clustering based on tissues → grouping diverse quant data of same tissue together

UMAP analysis reveals data is clustered by biology

Consolidated Protein Atlas Clusters Globally by Biology, Not by Technology

Tissue Specific Cluster



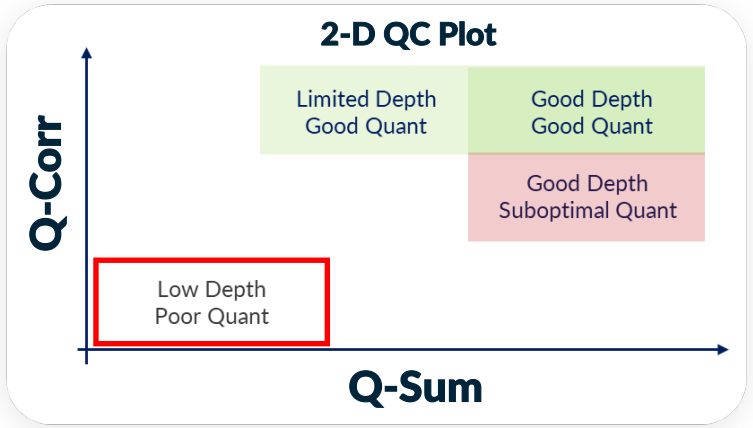
- Representative heterogenous data from multiple labs
- Clustering based on tissues
- Primary tumors group together
- Tumor and matching healthy tissues cluster together

Health and Disease Tissue Expression Map captures underlying biology providing reliable absolute abundance patterns

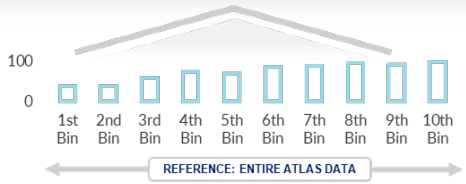
Improved Decisions with Quality Controlled Data Integration

New QC Parameters Developed

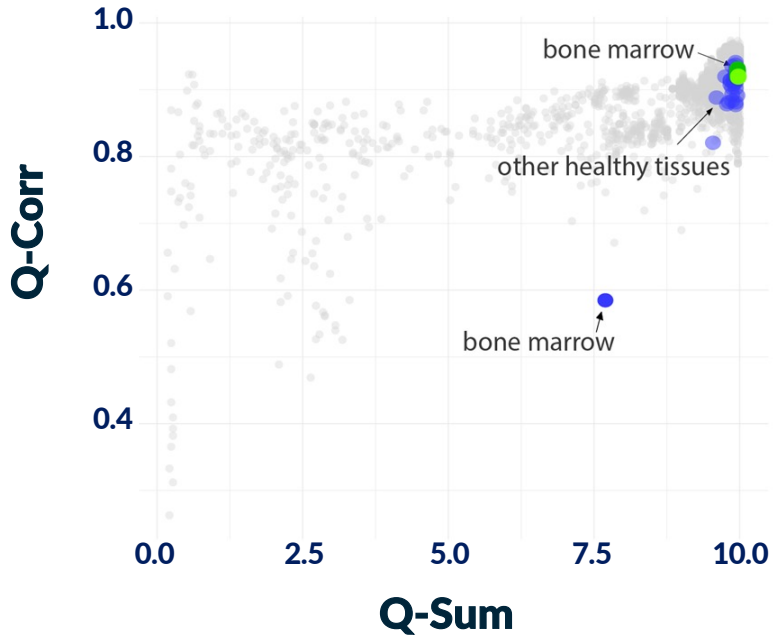
Comparable Quantitation?
Quantitative correlation
relative to reference proteome



Comparable Depth?
the sum of the quantiles
Protein detection across abundance bins



Atlas Data Resolved on 2D QC



QC'ed data correctly assigns CRBN as ubiquitous E3

QC'ed failed data incorrectly assigns CRBN as BM-sparing E3

- healthy tissues_published
- bone marrow_tmt_kymera
- bone marrow_lfq_kymera

Internal high-quality proteomes address data gaps

- Our **quality-controlled** expression atlas provides **reliable protein expression profiles**
- Kymera addresses data gaps with internal high-quality proteomes

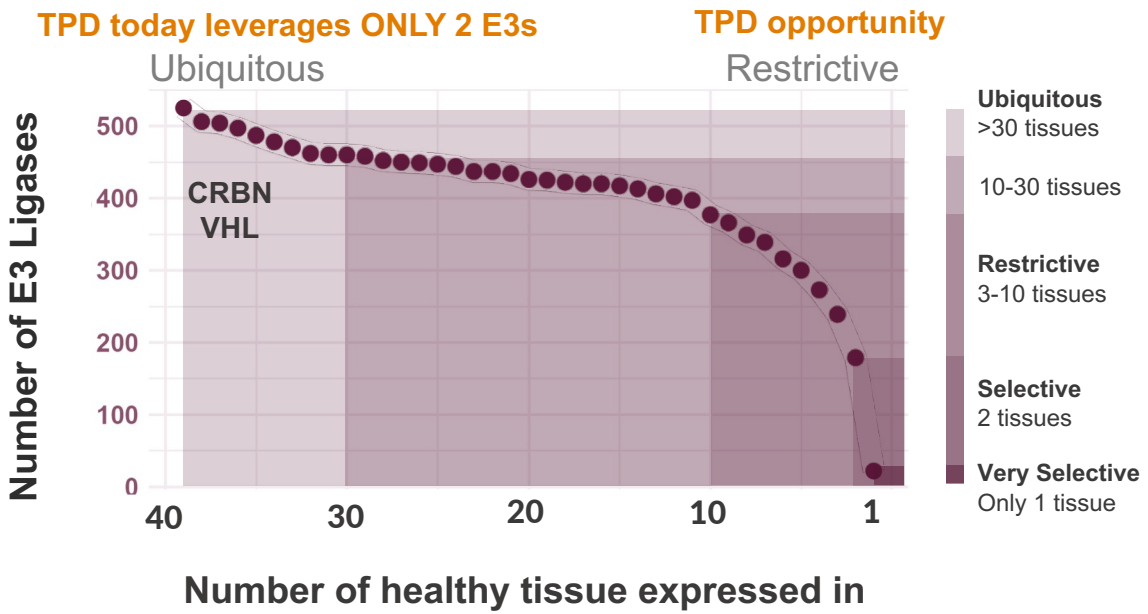
Learnings from E3 Whole Body Human Atlas

Implications for TPD

KYMERA

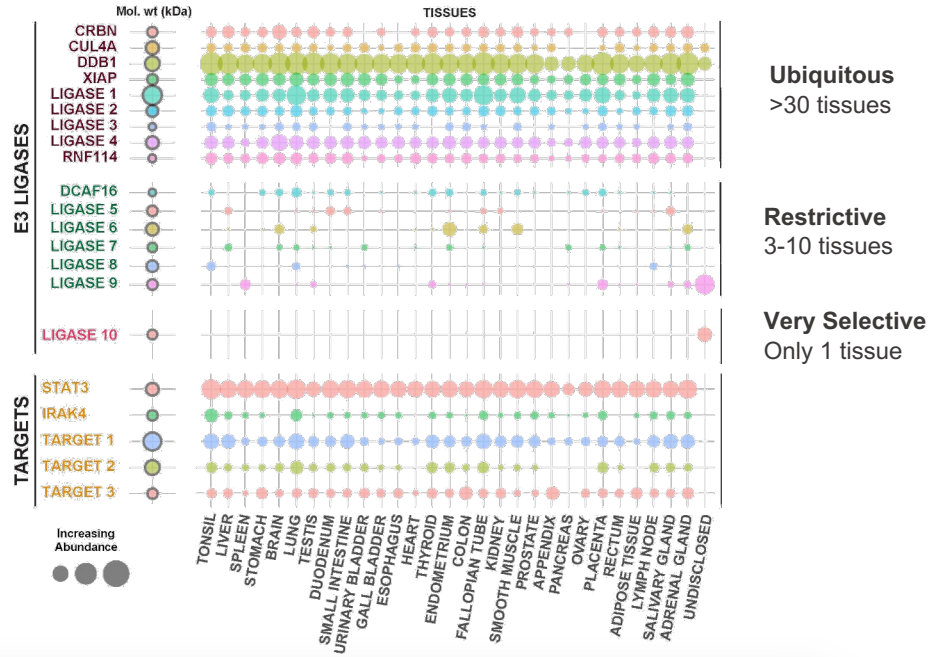
Novel E3 Ligases to Drug a New Generation of Targets

A Third of E3 Ligases are Selectively Detected in 1-2 Tissues



PEGASUS
E3 Ligase Whole Body Atlas

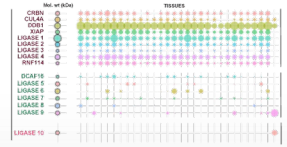
578 E3 Ligases
(Unique Gene IDs)



- Determined 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 via a machine learning algorithm
- Vision to develop tissue-selective or tissue-restricted degraders to enable novel therapeutic opportunities

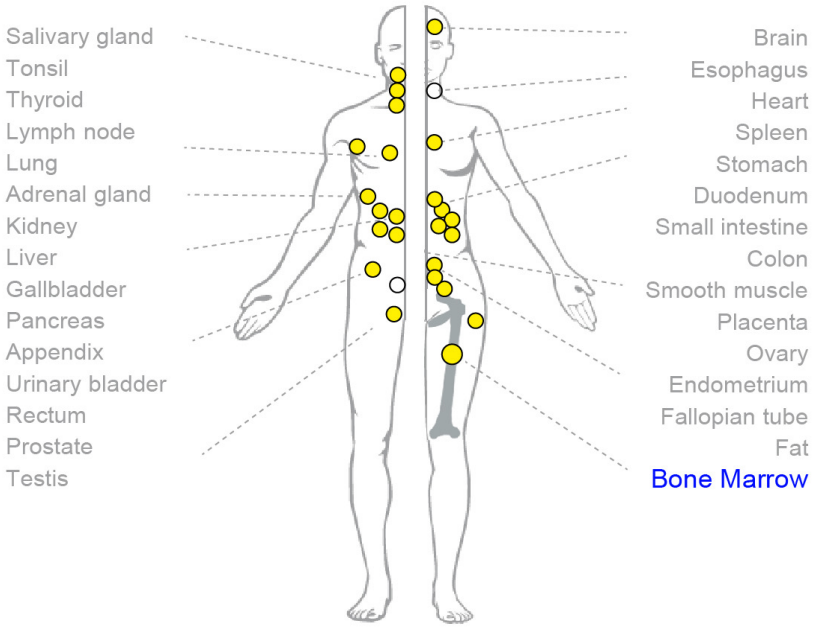
Towards Restrictive Degradation

Using Human E3 Atlas-based Expression Profiles of ALL Ligases

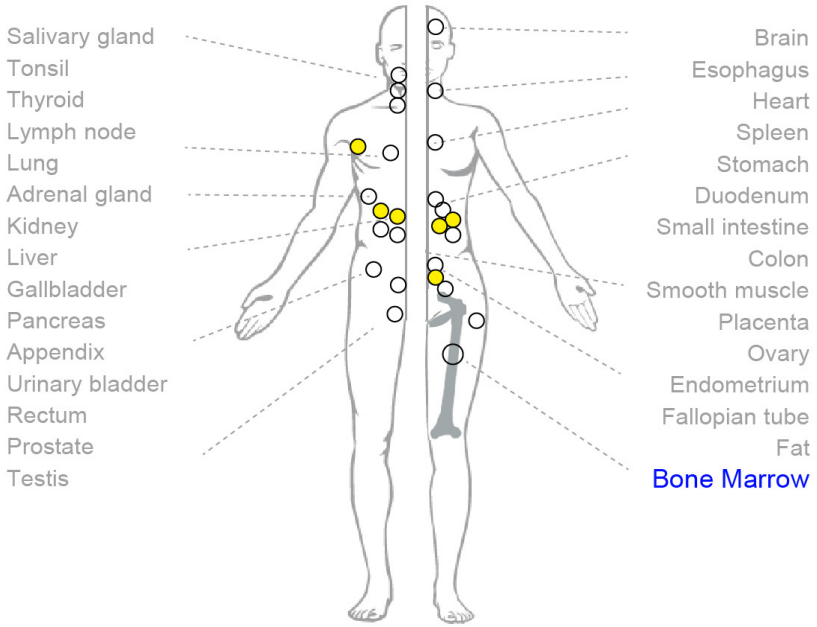


Example: Oncology / Selective Degradation / Tissue Sparing

● = Target Degradation

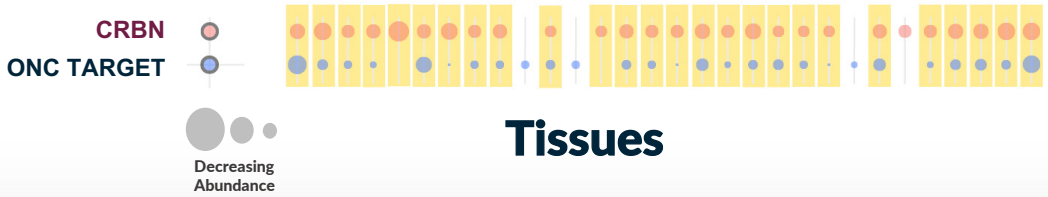


Undesired Degradation =Clinical Tox

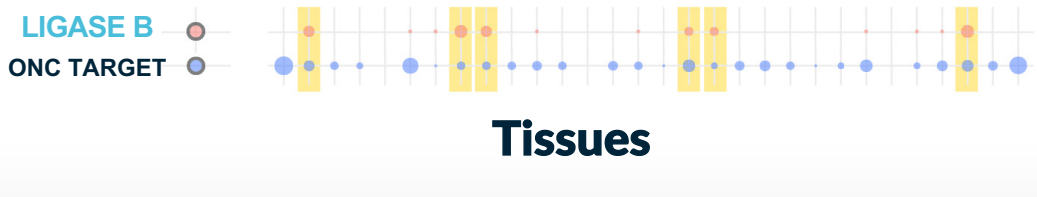


No Degradation =Safe

Ubiquitous Target Degradation



Restrictive Target Degradation



Lessons for TPD from E3 Atlas Mining Exercises

BENEFIT

Clinical utility
Candidate E3

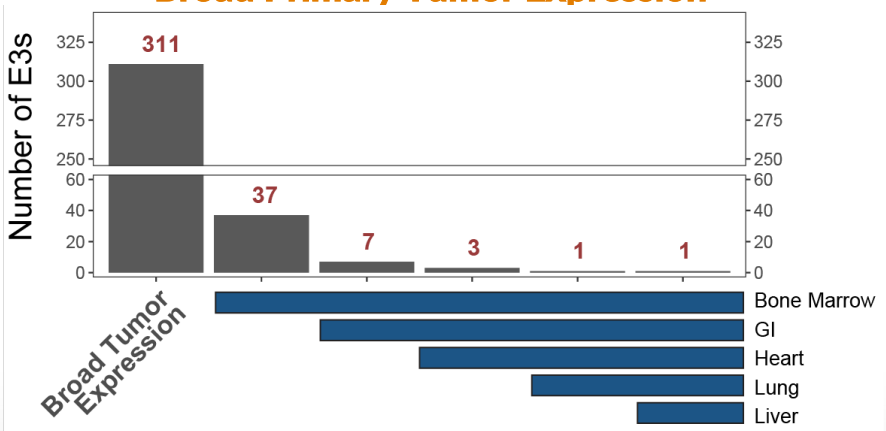
Safe Degraders

RISK

Clinical tox
De-risk all tissues

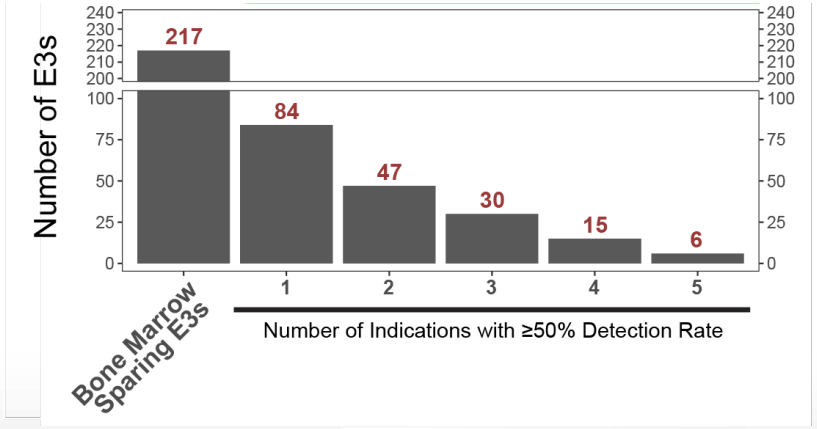
1 'Very' Restricted Expression Profiles Yield Rather Limited Candidate E3 Ligases for Drug Discovery

Tissue Sparing Potential of E3s with Broad Primary Tumor Expression



2 E3 Candidates Addressing 'all' Potential Toxicity Concerns May Have Little Clinical Utility

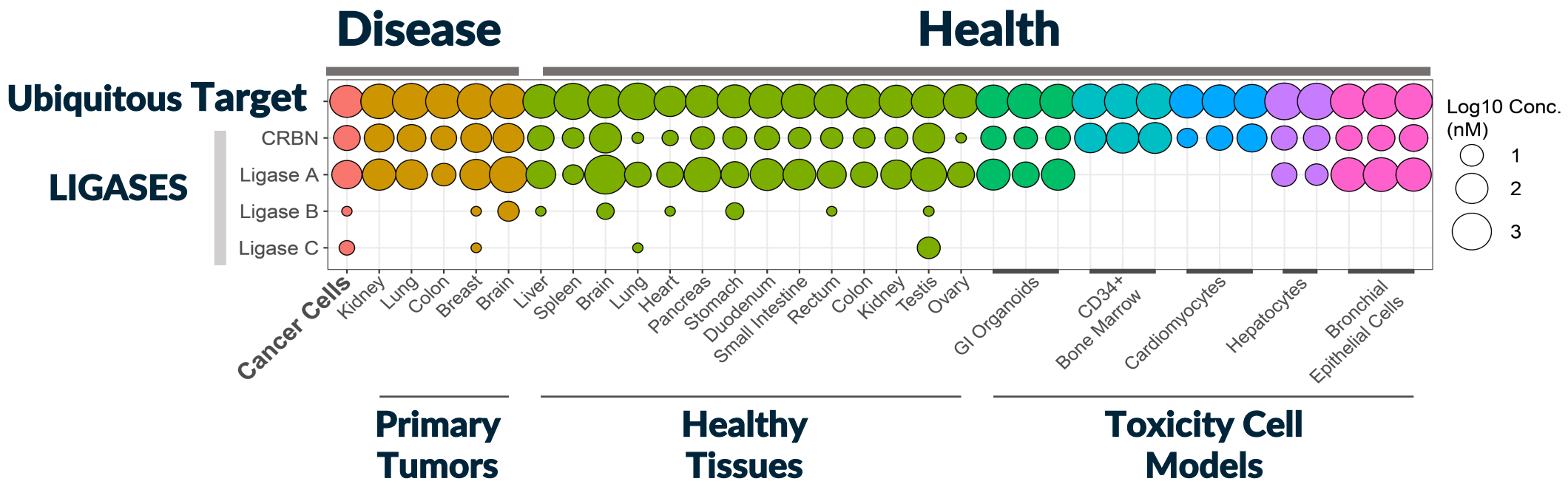
Clinical Utility of Bone Marrow Sparing E3s



Example - E3 Ligase Profiles

Varying De-risking vs Clinical Utility Balance

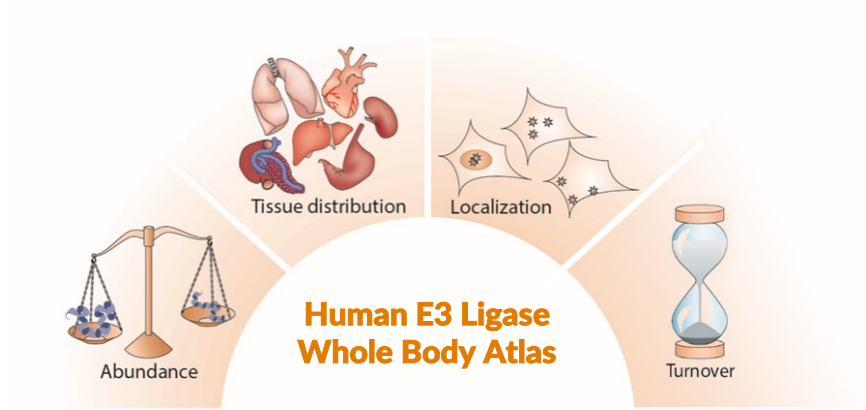
Representative Absolute Abundance Profiles in Healthy & Cancer Resolved to Tissues & Cells

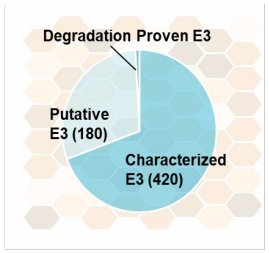


	Cancer Expression	Tox / Health Contexts Spared
LIGASE A	Broad	Few
LIGASE B/C	Restricted	Broad

First Human E3 (& POI) Absolute Expression Atlas in Health & Disease

Invest in E3s with Tissue Sparing Potential for Targets with Unmet Clinical Need





~600 E3 ligases

E3 Ligase Matching TA or Target Criteria

- Pan expressed
- Differentially expressed
- Disease-specific
- Tissue-specific
- Tissue-sparing

MaxQuantAtlas

Relative Abundance in Health and Disease

- Tissue sparing or Ubiquitous
- Expression in disease: Broad or restricted

Absolute Abundance

- Benchmarking expression of novel E3s vs CRBN/VHL
- E3: target stoichiometry to predict efficiency of ternary complex formation

Subcellular Localization

- Match E3 and POI subcellular location
- ID colocalized (interacting) partners for compartment specific degradation approaches

Half-Life

- E3 and POI(s): QSP modeling and covalent hit strategies

Advanced Wses: e.g. Targeted Delivery of Degraders

- Selected expression of differentially expressed surface expressed proteins

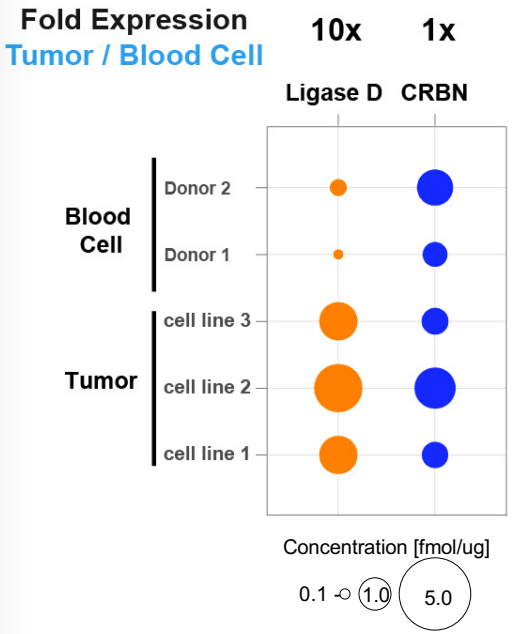
E3 Atlas-enabled Novel Precision Medicine Degrader Programs

KYMERA

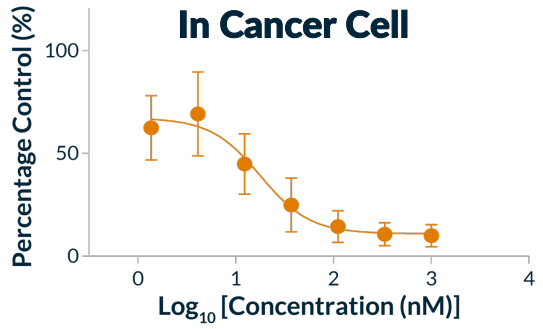
Unlocking a Clinically Validated Target by a Tissue Sparing E3

- 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

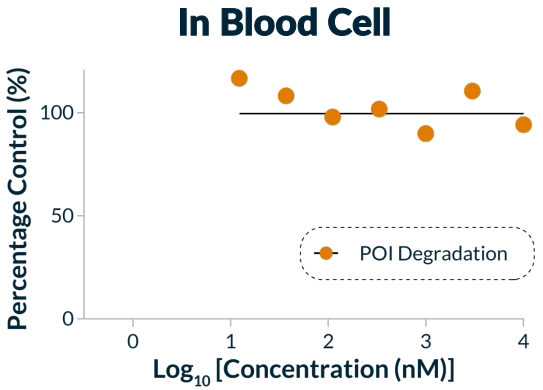
E3 Ligase is Almost Absent in One Blood Cell Type



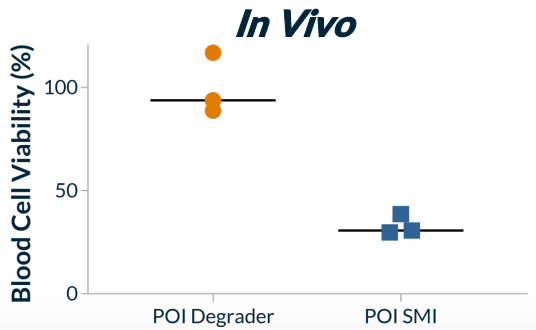
Optimization and Degrader Program



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**



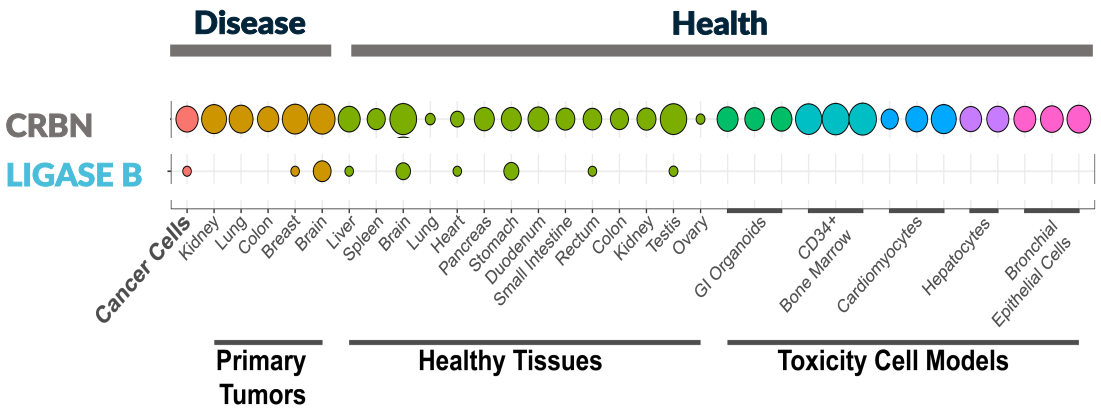
In a pharmacologically active dose *in vivo* a **degrader allows blood cells to survive** while SMI leads to substantial cell death

POI = protein target of interest

Chemically Harnessing a Novel Very Restrictive E3 Ligase

Ligase B :

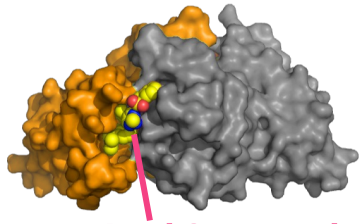
Favorable healthy & disease profile for tissue-selective degradation



Ligand Identification and Degrader

Small Molecule Ligand Bound to a Tissue-selective E3 Ligase

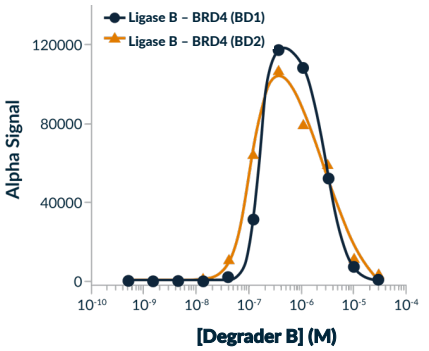
Ligase B, Ligand B



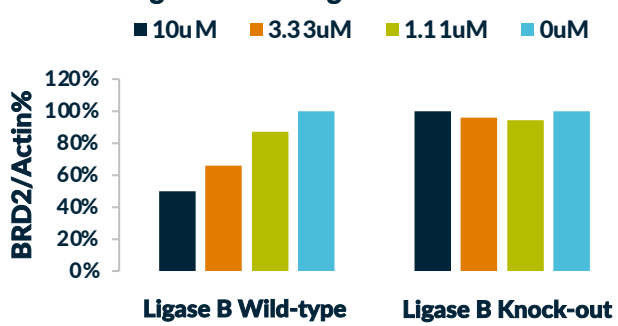
Lead Compound

Affinity K_D = < 0.2 uM

Leads to Ternary Complex Formation with a Protein of Interest



Cell-based Degradation by HiBiT

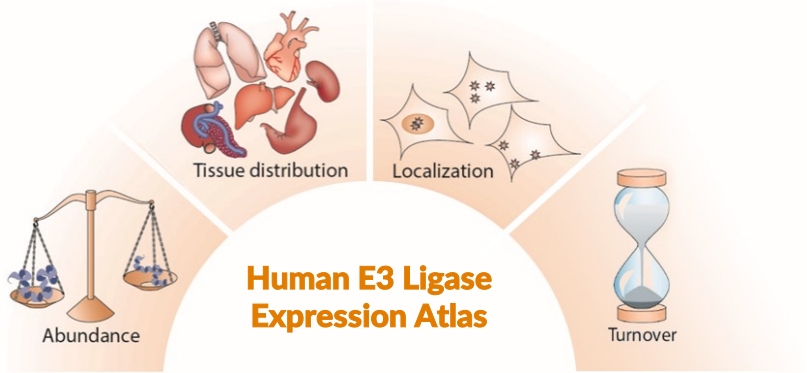


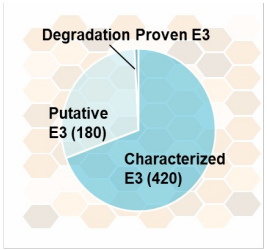
Summary

- Kymera's Mission is to develop tissue restricted drugs maximizing the therapeutic index of clinically well-validated targets by minimizing on-target toxicity
- Developed a Novel Algorithm (MQAtlas) for creating a large-scale protein concentration map of E3s in health and disease
- E3 Ligase Whole Body Atlas routinely used to identify tissue sparing E3 ligases in a disease agnostic manner
- Through **Pegasus Platform**, Kymera is able to chemically harness biology of identified novel tissue restricted E3 ligases

PEGASUS

E3 Ligase Whole Body Atlas





~600 E3 ligases

E3 Ligase Matching TA or Target Criteria

- Pan expressed
- Differentially expressed
- Disease-specific
- Tissue-specific
- Tissue-sparing

MaxQuantAtlas

Acknowledgements

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Christopher Browne
Scott Rusin

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Webserver Implementation
Kevin Dushney
Anthony Phillips

Kymera Platform Team
Biology
Chemistry
Lead Discovery

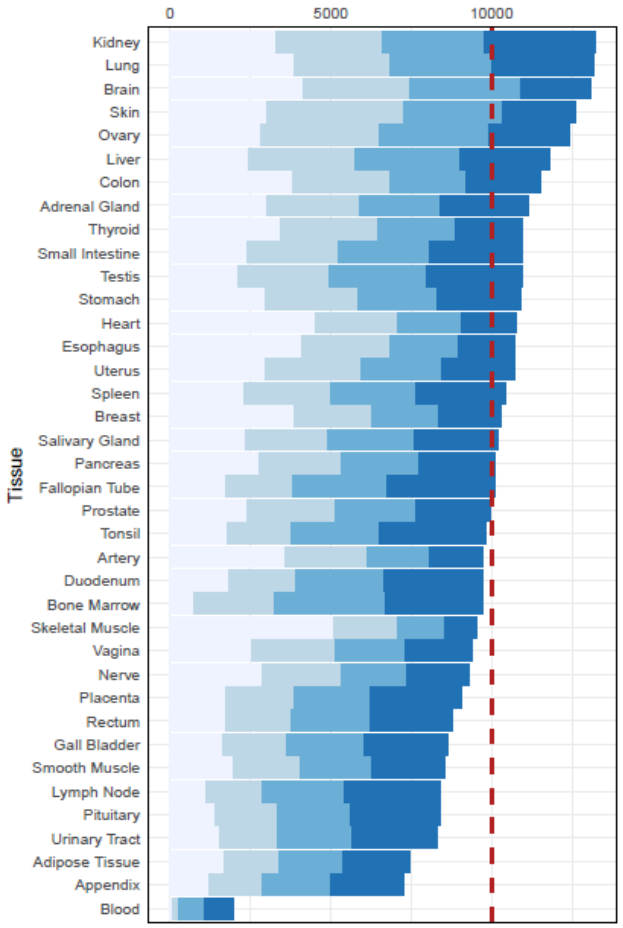
Kymera Oncology Team

Backup

KYMERA

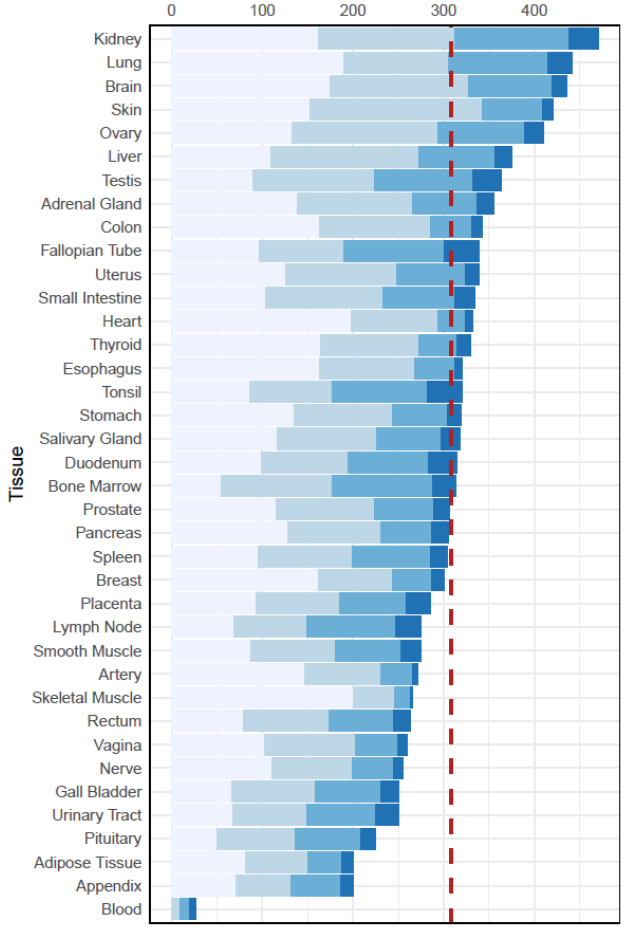
Abundance of E3s and Transcription Factors

Total Proteome



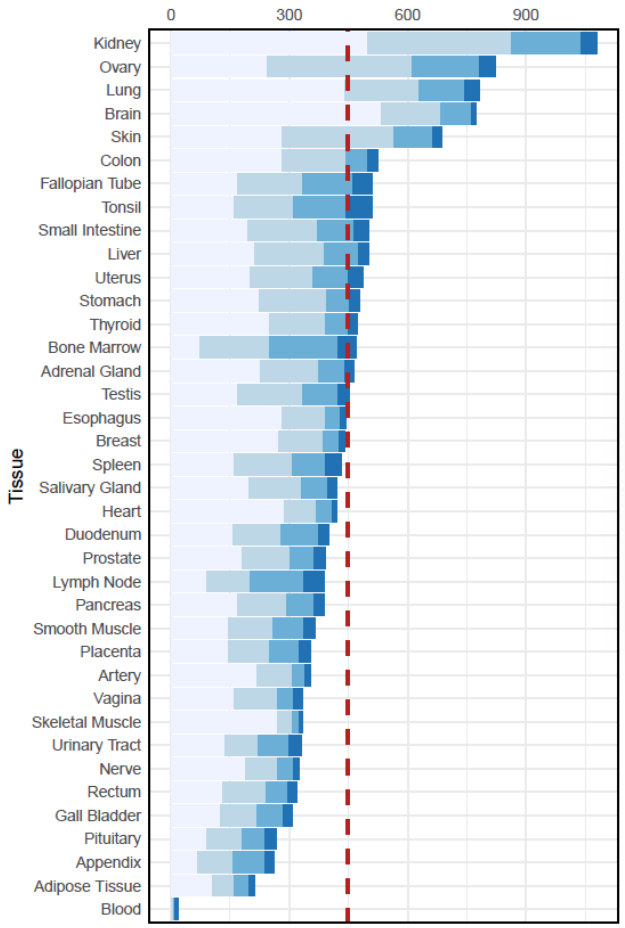
Average ≈ 10,000

E3 Ligases



Average ≈ 300

Transcription Factors*



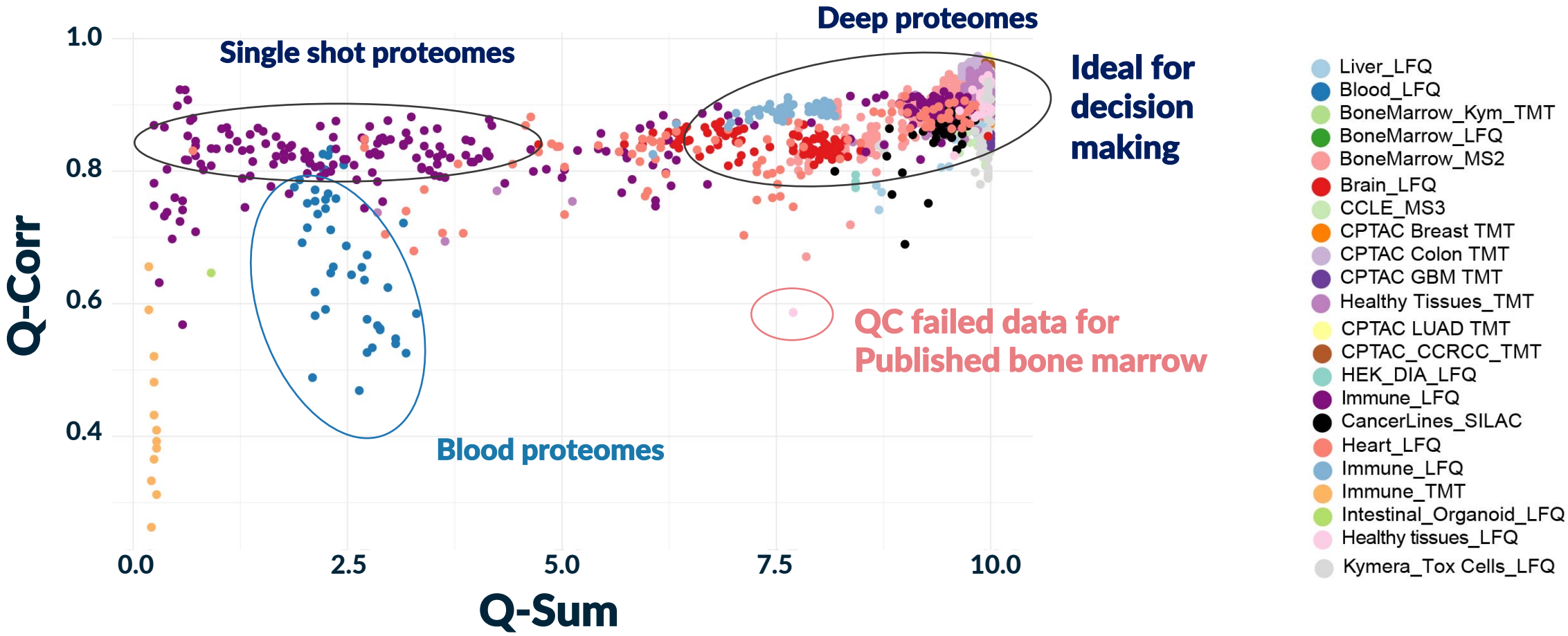
Average ≈ 450

- **E3s are generally a lower abundant protein class but expressed at higher levels than transcription factors**

*Total: 1639 genes, Lambert et al., Cell 2018

Improved Decisions with Quality Controlled Data Integration

New QC Parameters Developed



Developing Next Gen Degrader for Precision Medicine

Well-established BM tox profiles

Clinically Validated Targets

L

E

D

High POS for TPD application

Identified Multiple Ligands

Ligases with varying Sparing potential

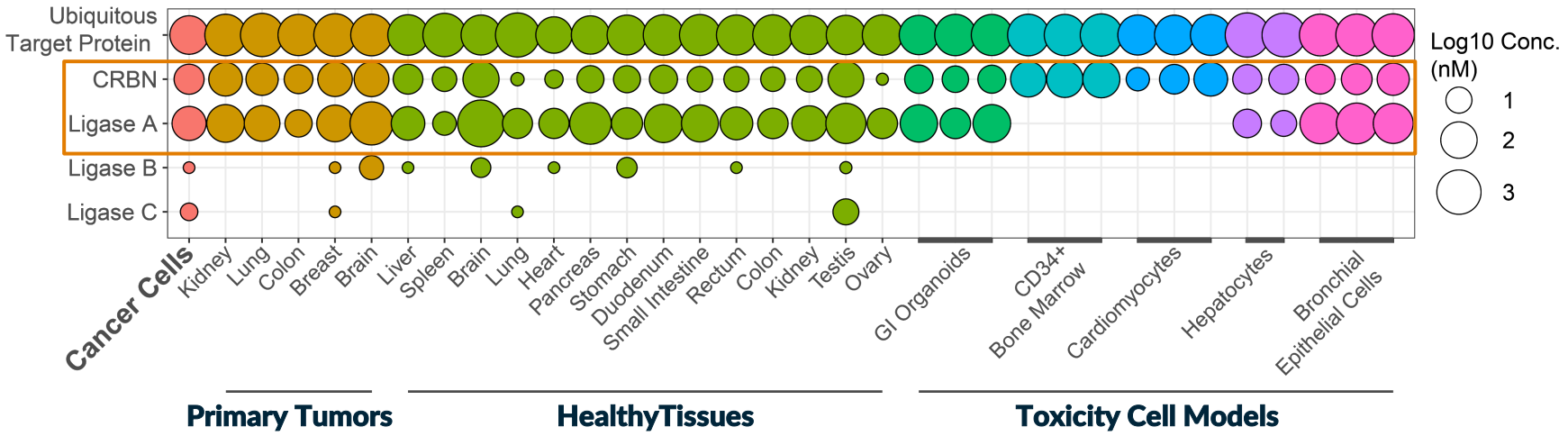
Degrader for Precision Medicine

Work in Progress

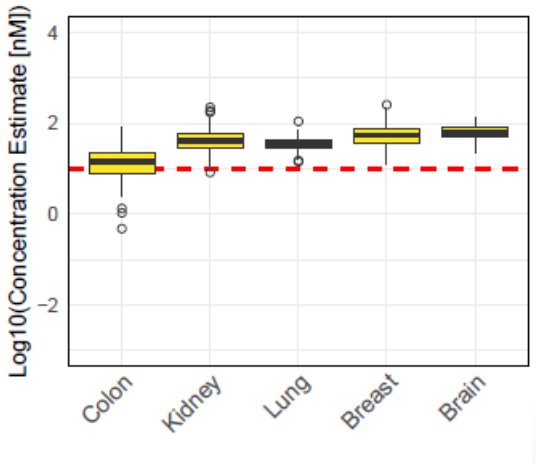
Ligandability; **E**xpression; **D**egradation

A Novel Tissue Sparing E3 Ligase with Broad Cancer Utility

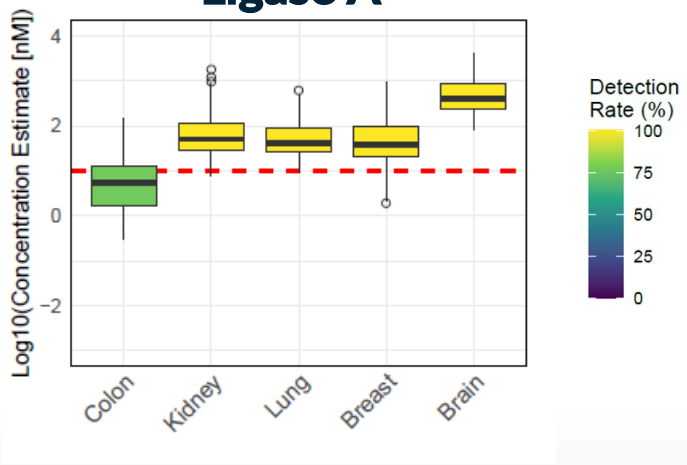
Protein Expression in Healthy and Cancer Tissues



CRBN



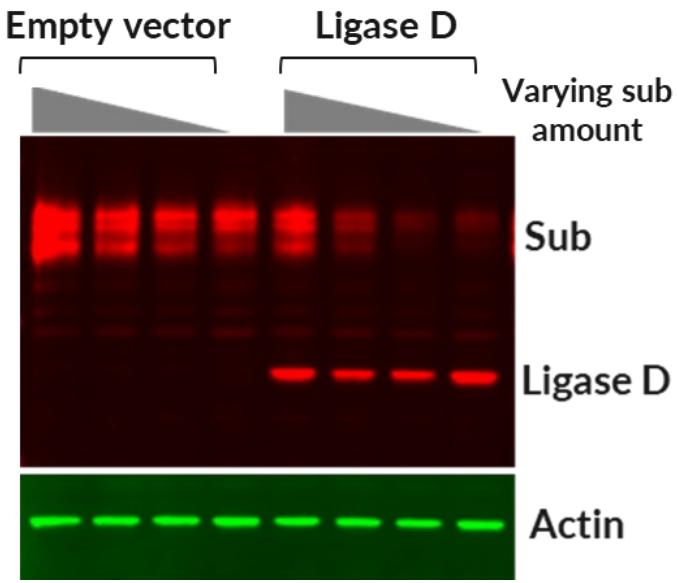
Ligase A



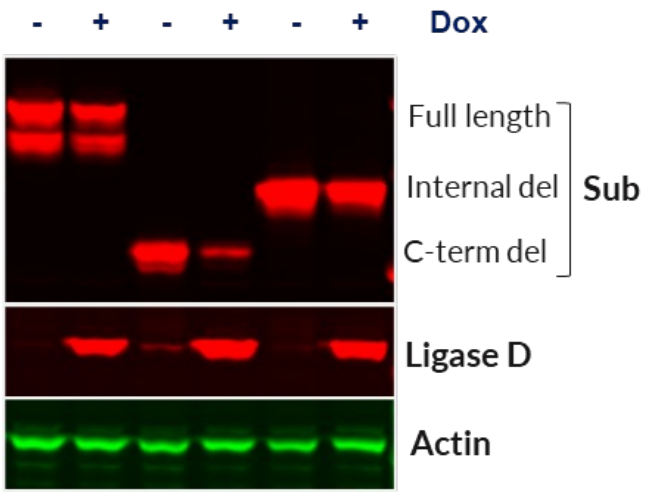
- Highly expressed in multiple cancer types (i.e. comparable to CRBN).
- Very low to no expression in key tox cells, especially in blood progenitors.
- Tissue-sparing potential is suitable for multiple solid tumor indications.

Robust "D" toward Natural and Neo-substrates

Degradation of Endogenous Substrate

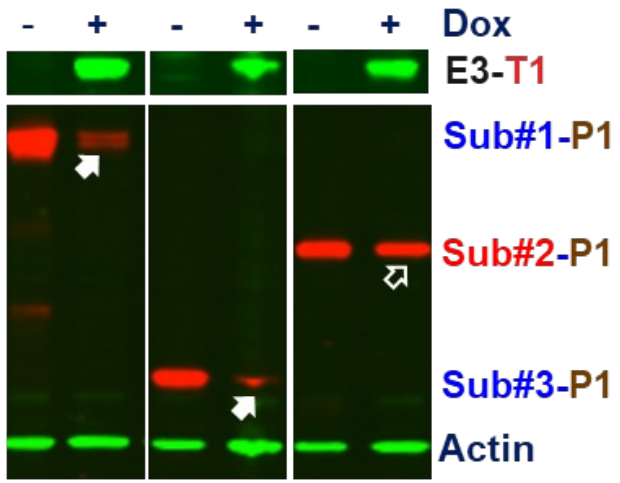


Dox-inducible stable lines



Degradation of Neo Substrates

PoC of New Proximity System



Validation of Druggability of Novel Site

Identification of Covalent Ligands

Screen by intact MS

Retest & Selectivity

COFFEE

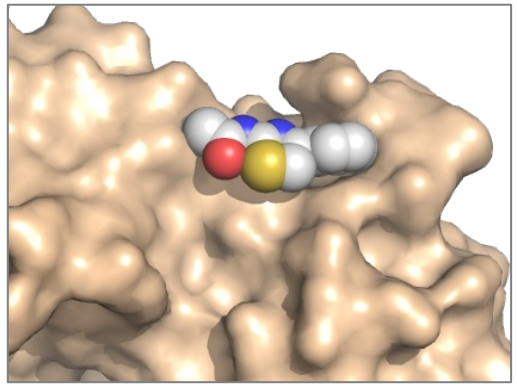
Labeling Optimization

Co-crystallization

Validated hits w/ co-xtals

Confirming covalent and non-covalent interactions

Workflow for covalent ligands screen

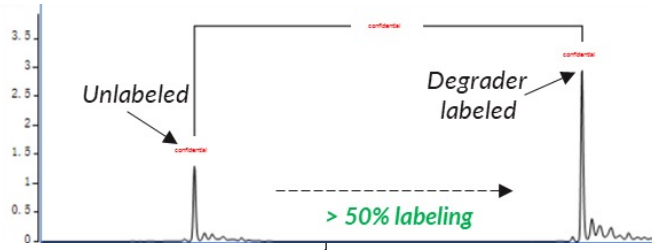


Validation of Functional Competency

Functionalized E3

Lig D

Validation of single labeling



Testing Functional Competency

In vitro ub

Comp 3

WT MT

Ligase D

Poly Ub -BRD4

BRD4

In Cell by COFFEE