# Unlocking Untapped Potential:

## Addressing Current Challenges in Targeted Protein Degradation

## Preface

Targeted protein degradation (TPD) is an emerging therapeutic field with the potential to tackle disease-causing proteins that have traditionally been challenging to target with conventional small molecules. **Selecting the right E3 ligase is critical for TPD, as it determines drug efficiencies, target selectivities, and drug resistance profiles** in various cancer cells. Although there are over 600 E3 ligases in human cells, only a limited number—CRBN, VHL, IAP, and MDM2—have been utilized for PROTAC®/molecular glue technology. Most PROTAC®s developed so far have been restricted to CRBN or VHL, which are ubiquitously expressed in the human body. This ubiquity explains **the recent emergence of drug resistance in CRBN- or VHL-based degrader PROTAC®s**. Moreover, there is a lack of understanding about the many available E3 ligases, the exact mechanisms of PROTAC®/glue, the variability of ligand-substrate interactions, and the observed drug resistance and toxicity.

In conclusion, there is a **pressing need to identify new E3 ligases and delineate their mechanisms.**

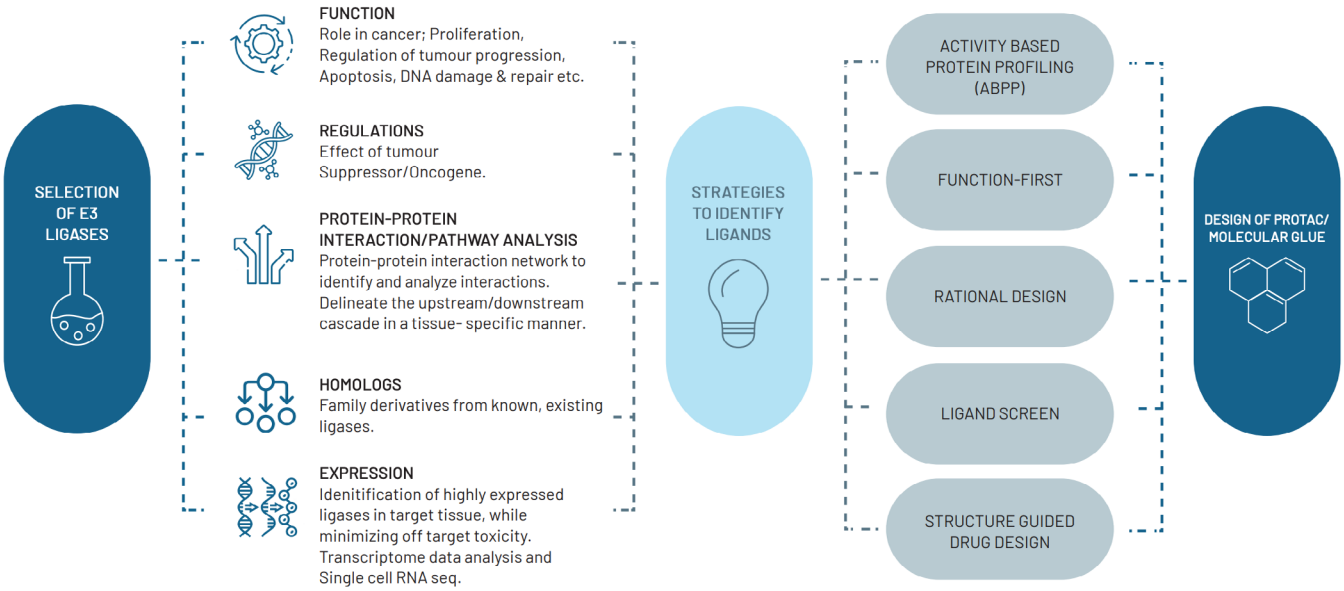
# Strand: Expertise in Curation and Bioinformatics Services to Enhance Your Discovery Process

Strand can streamline the process of selecting the right E3 ligase with our custom curation and bioinformatics services. We enhance your discovery platform in multiple ways by adding the following information:

## Curated evidence and dataset findings on:

1. The **function of the E3 ligase in cellular progression**, including proliferation, apoptosis,DNA damage repair, immunity, and metabolism.
2. The role in **regulating tumor progression in a tissue or cancer-specific manner**:
   - **Interaction with oncogenes/tumor suppressor** genes to be an efficient ligand for a target in that specific cancer.
3. **Protein-protein interaction** networks to analyze if two proteins physically interact or fall within the same pathway:
   - **Pathway** analysis on E3 ligases and their specific substrates to **delineate the upstream/ downstream cascade and identify the right target** in the cancer/tissue of interest.
4. **Expression patterns to classify E3 ligases and inform potential off-target toxicity**:
   - **E3 ligases overexpressed in specific cells or tissues** — for example, brain (FBXL16, KCTD8), pancreas (ASB9), skeletal muscle (KLHL40, KLHL41), testis (DCAF4L1), and fallopian tube (DCAF8L1).
   - E3 ligases **under-expressed in normal cells** to reduce the risk of on-target, off-tumor toxicity in undesired normal tissues.
   - E3 ligases that are **specifically overexpressed in tumors make ideal targets**. Studies have shown that certain E3 ligases are highly expressed in more than 15 cancer types, with some exhibiting pan-cancer expression while being absent in normal tissues.
   - Evidence of **high tumor expression of E3 ligases** as shown by proteomic analysis.
   - **Integration of both proteomic and transcriptomic data** to demonstrate high concordance of these highly expressed E3 ligases in tumors.
5. **Transcriptome dataset analysis** to screen a large number of tumors simultaneously and enable effective comparison with normal tissues.
6. **Single cell RNA seq data analysis** to understand the complexity of each tumor and identify exact expression profiles on a cellular level, given that tumors are heterogeneous.
7. Studies on **protein families** to facilitate E3 ligase ligand selection for efficient protein degradation:
   - **Ligandability and structure availability** from ChEMBL, Uniprot.
   - **Curation of literature and databases** like ProtacDB and E3Atlas for candidate selection.

The ideal E3 ligase will be one that has a functional implication in the tissue/cancer of interest, regulates important tumor-specific genes, and is highly expressed in tumors but sparingly in normal tissues.




***PROTAC® is a registered trademark of Arvinas Operations, Inc.**

**24+** YEARS OF EXPERIENCE

**80,000+** Genetic Tests Reported

**500+** Projects Executed for Genomics Majors Globally

Presence in **20+** Countries

strand


7th Floor, MSR North Tower, #144, Outer Ring Road, Nagavara, Bengaluru - 560045

+91 9980448044 hello@strandls.com strandls.com