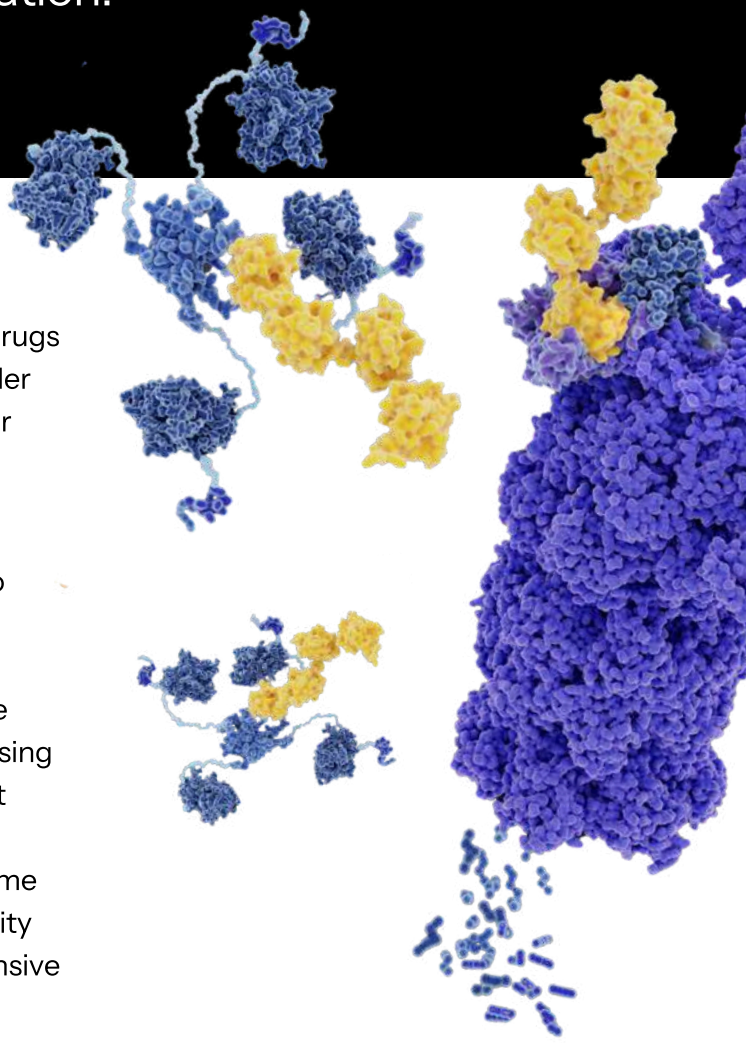
WHITE SHEET

SAPIENT

# Protein Degrader Proteomics

Measuring **degradation, selectivity, and mechanism for PROTACs and molecular glues,** from high-throughput screening to clinical target quantitation.



Targeted protein degraders, including PROTACs and molecular glues, can reach proteins that conventional drugs cannot. Instead of blocking a protein's activity, a degrader binds the protein and recruits an E3 ligase, marking it for destruction by the cell's ubiquitin-proteasome system. **This opens up targets long considered undruggable.**

The challenge is ensuring **selectivity.** A degrader has to remove its intended target without degrading other proteins, and it has to keep working as tumors adapt. A small change in chemistry can send a degrader after the wrong protein or push it to recruit the wrong ligase, causing effects that can ripple across the whole proteome. Most programs, however, still rely on Western blots and antibody-based assays that measure one protein at a time and rarely work in patient tissue. Problems with selectivity and safety then surface late in development, after extensive time and cost has already been invested.

**Sapient's Protein Degrader Proteomics measures what a degrader actually does to the proteome, directly and quantitatively, at every stage of development:** from screening large compound libraries, to deep profiling of selectivity and mechanism, to targeted assays in patient samples for clinical trials.

## Limitations of Traditional Degrader Characterization

Most degrader assays track only one or a few proteins at a time, making it impossible to see whether a degrader is truly selective since off-target degradation can happen anywhere in the proteome.

| Common Approach | Key Limitation |
|---|---|
| **Western blot / antibody assays** | Measure one predefined target at a time; miss off-target degradation and depend on reagent availability. |
| **RNA expression profiling** | Degraders act post-translationally; mRNA levels do not reflect protein degradation. |
| **Reporter and activity assays** | Report a proxy signal, not the actual proteome changes; cannot reveal unintended degradation. |
| **Targeted antibody panels (IHC)** | Predefined and low-plex; not discovery-capable and limited in patient tissue. |

## From Screen to Clinic: An End-to-End Workflow

Mass spectrometry measures thousands of proteins at once, without antibodies and without choosing targets in advance. **Sapient uses a single platform across three stages,** so results stay directly comparable from the first screen through the clinic.

### Stage 1: High-Throughput Degrader Screening

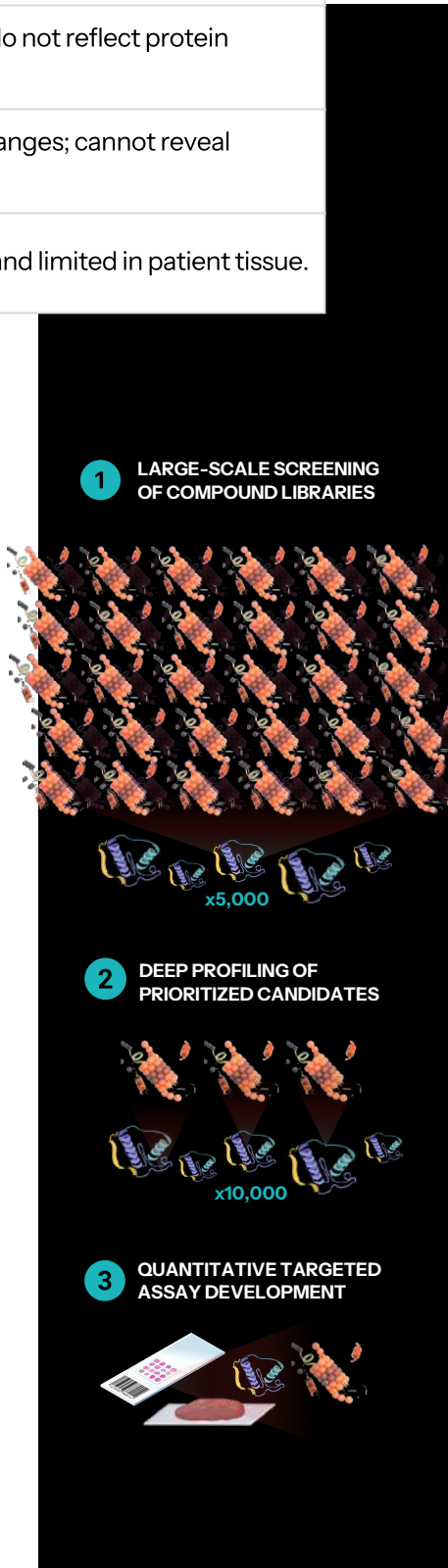
Sapient's sub five-minute method measures **more than 5,000 proteins per sample and runs thousands of samples a day.** Teams can screen large compound libraries, see how selectively each degrader hits its target, and move the strongest candidates forward.

### Stage 2: Deep Selectivity and Mechanism Profiling

For lead candidates, Sapient's deep profiling method measures **more than 10,000 proteins from as little as 20 µg of sample across cell lines, doses, and time points.** It confirms the target is degraded, shows which E3 ligase is recruited, and reveals any off-target degradation. SILAC labeling additionally reveals how fast the protein is degraded and replaced, and repeated sampling shows how the proteome shifts as resistance or toxicity develops.

### Stage 3: Targeted Assays for the Clinic

Sapient builds **targeted, fully quantitative, antibody-free assays for the proteins that matter most and runs them in both fresh-frozen and FFPE patient samples.** This measures target levels, target engagement, drug distribution, and pharmacodynamic response directly in clinical trial.

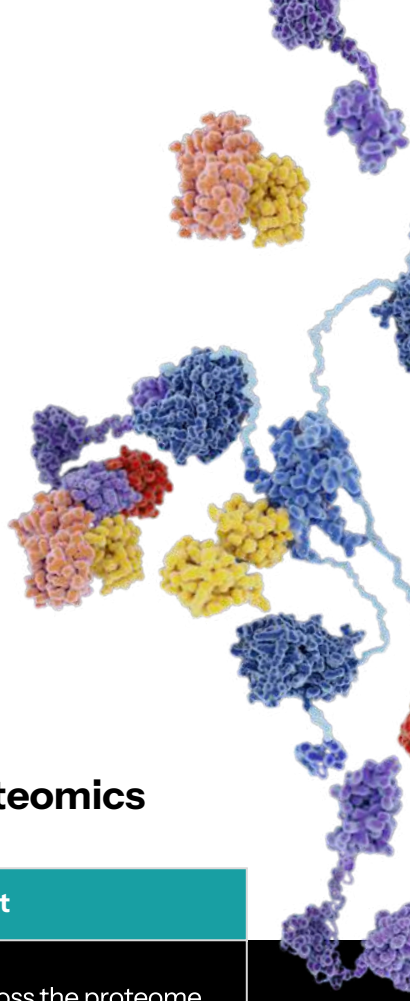


## E3 Ligase Profiling Across Normal Tissues and Tumors

A degrader can only work where its E3 ligase is present. Most degraders depend on just two ligases, CRBN and VHL, even though the human genome encodes more than 600. These ligases vary widely from tissue to tissue, so where one is expressed shapes both where a degrader works and where it may cause harm.

Sapient has **comprehensively profiled E3 ligase levels across a broad set of normal human tissues and tumors.** Teams can use this to:

- **Choose a ligase** that is present in the target tumor
- **Predict on-target, off-tumor toxicity** by comparing tumor and normal tissue
- **Design more selective degraders** around ligases enriched in tumors



## Key Questions Answered by Protein Degrader Proteomics

| Development Question | Sapient Insight |
|---|---|
| **Is the degrader selective for the intended target?** | HT screening ranks selectivity across the proteome |
| **What off-target proteins are being degraded?** | Deep proteome-wide profiling of on- and off-target effects |
| **Which E3 ligase is recruited, and is it expressed in the tumor?** | E3 ligase identification and expression atlas across tissues and tumors |
| **How fast is the target degraded and resynthesized?** | SILAC-based turnover and resynthesis kinetics |
| **Is the target engaged and degraded in patients?** | Targeted quantitative assays in fresh-frozen and FFPE tissue |
| **Why is resistance emerging?** | Longitudinal proteome monitoring over time |

See how Protein Degrader Proteomics can help you **discover targets and prioritize degrader candidates.** To learn more or request a study, visit **sapient.bio** or contact **discover@sapient.bio**.

**Discover more today.**

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