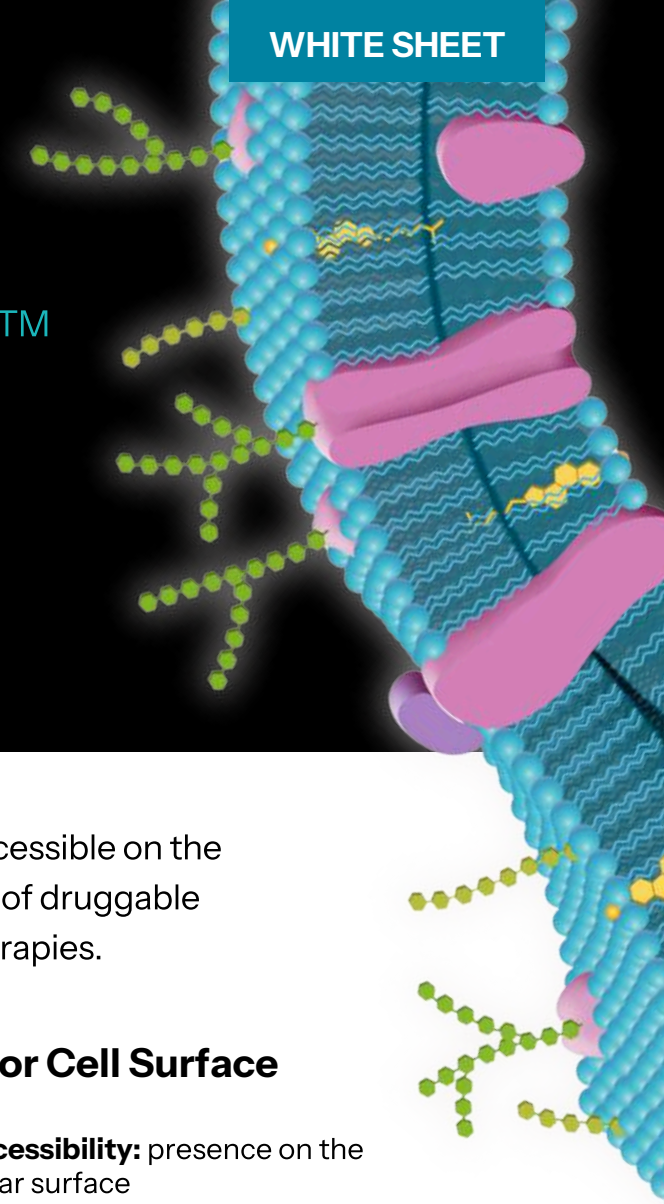
WHITE SHEET

SAPIENT

SurfaceSeek™

Mapping the druggable tumor cell surface proteome



SurfaceSeek directly measures the proteins truly accessible on the tumor cell surface, enabling confident identification of druggable targets for ADC, T-cell engager, and radioligand therapies.

Identifying Druggable Proteins at the Tumor Cell Surface

Advances in antibody engineering have fundamentally reshaped cancer drug development, now allowing oncology therapeutics to engage an increasingly diverse set of cell surface proteins. As a result, **drug success is now determined not only by the drug platform itself but also by the biological quality of the target it engages.** For surface protein targets, several critical criteria must be satisfied:

- **Target accessibility:** presence on the extracellular surface
- **Target density:** abundance to support therapeutic engagement
- **Tumor selectivity:** differential expression relative to critical normal tissues
- **Proteoform & epitope relevance:** structural compatibility with antibody binding
- **Target turnover and internalization:** optimization for therapeutic modality

These essential properties, however, are rarely captured in human tumors by conventional discovery approaches.

SurfaceSeek addresses these needs by directly quantifying the druggable tumor cell surface proteome using a mass spectrometry-based workflow, enabling more confident target identification and validation.

Limitations of Traditional Surface Target Discovery

Despite significant advances in oncology therapeutics, many programs fail because surface target biology is poorly characterized during early discovery. Most discovery workflows rely on indirect measurements that do not accurately reflect surface accessibility.

Common Approach	Key Limitation
RNA expression profiling	Does not indicate whether a protein is translated & reaches the cell surface.
Bulk proteomics	Cannot distinguish intracellular proteins from surface proteins.
Immunohistochemistry (IHC)	Lacks quantitative precision, epitope specificity, and scale for discovery.

As a result, **targets often advance into development without clear evidence that the protein is truly accessible, sufficiently abundant, or structurally compatible** with therapeutic binding, contributing to frequent failures during target validation and clinical development.

The Power of the SurfaceSeek Approach

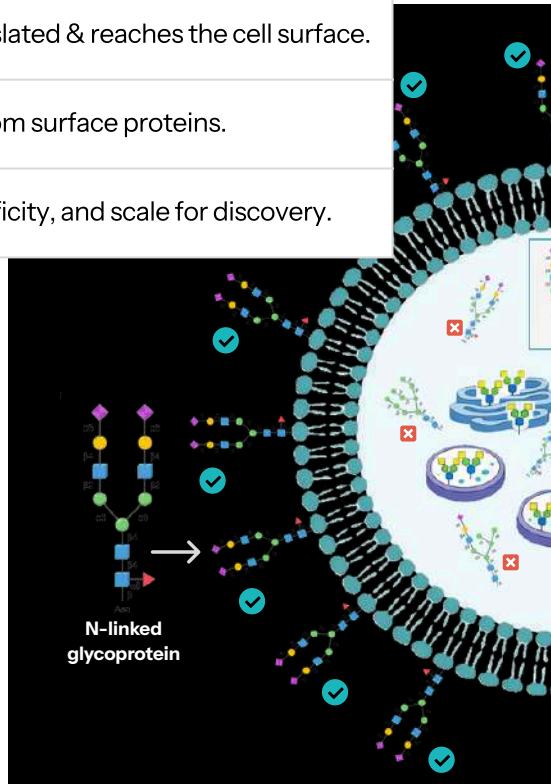
SurfaceSeek addresses this challenge by directly measuring proteins that are functionally deployed on the tumor cell surface.

Direct Measure of Surface-Accessible Proteins

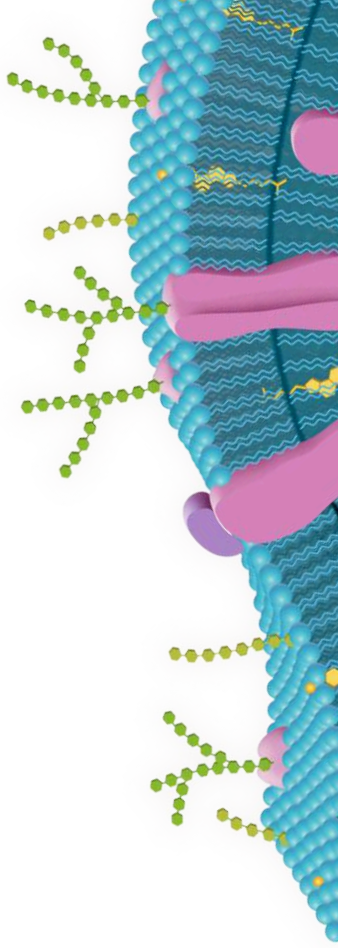
SurfaceSeek **combines selective enrichment with high-resolution mass spectrometry** to map the tumor cell surface proteome. This workflow provides multiple layers of biological insight critical for evaluating surface targets.

As membrane proteins are trafficked through the endoplasmic reticulum and Golgi apparatus, they undergo N-linked glycosylation as part of maturation. **Mature proteins that reach the extracellular surface contain fully processed N-linked glycans,** often including terminal sialic acid residues.

SurfaceSeek selectively enriches proteins bearing these charged N-linked glycans, **enabling preferential identification of proteins that have completed trafficking and are exposed on the cell surface.** Importantly, SurfaceSeek can be performed in **fresh-frozen and FFPE human tumor samples.** It further incorporates extracellular protein- and SILAC-based labeling strategies in cellular systems to **validate cell membrane localization and protein turnover / internalization kinetics –** transforming cell membrane protein measurements into dynamic biological insight.



- Identify proteins **functionally deployed** on the tumor cell surface
- **Reduce background** from intracellular trafficking intermediates
- Assay tumor cell surface proteins **directly in human tumor samples**



Quantitative Surface Protein Abundance

SurfaceSeek provides **quantitative measurements of surface protein abundance,** allowing comparison across tumor samples and normal tissues in patient studies.

These measurements help evaluate whether candidate targets are compatible with specific therapeutic modalities to guide target selection:

- **ADC targets** often require high abundance and efficient internalization
- **Radioligand therapy targets** benefit from high tumor selectivity
- **T-cell engager targets** require sufficient and consistent antigen density

Tumor Selectivity and Normal Tissue Risk

Target selectivity is essential to **minimize on-target, off-tumor toxicity.** SurfaceSeek can be **applied to both tumor and normal tissues,** enabling direct comparison of protein expression across tissue types.

This supports early identification of targets with **favorable tumor selectivity profiles.**

Proteoform and Isoform Resolution

Genes frequently produce multiple protein variants through alternative splicing, proteolytic processing, and post-translational modifications. **Only some of these forms may contain extracellular domains compatible with therapeutic binding.** Because SurfaceSeek analyzes proteins at the peptide level, it can resolve:

- **Protein isoforms**
- **Proteolytic cleavage products**
- **Post-translationally modified proteoforms**

This level of molecular resolution is particularly important when evaluating **antibody epitopes and therapeutic binding sites.**

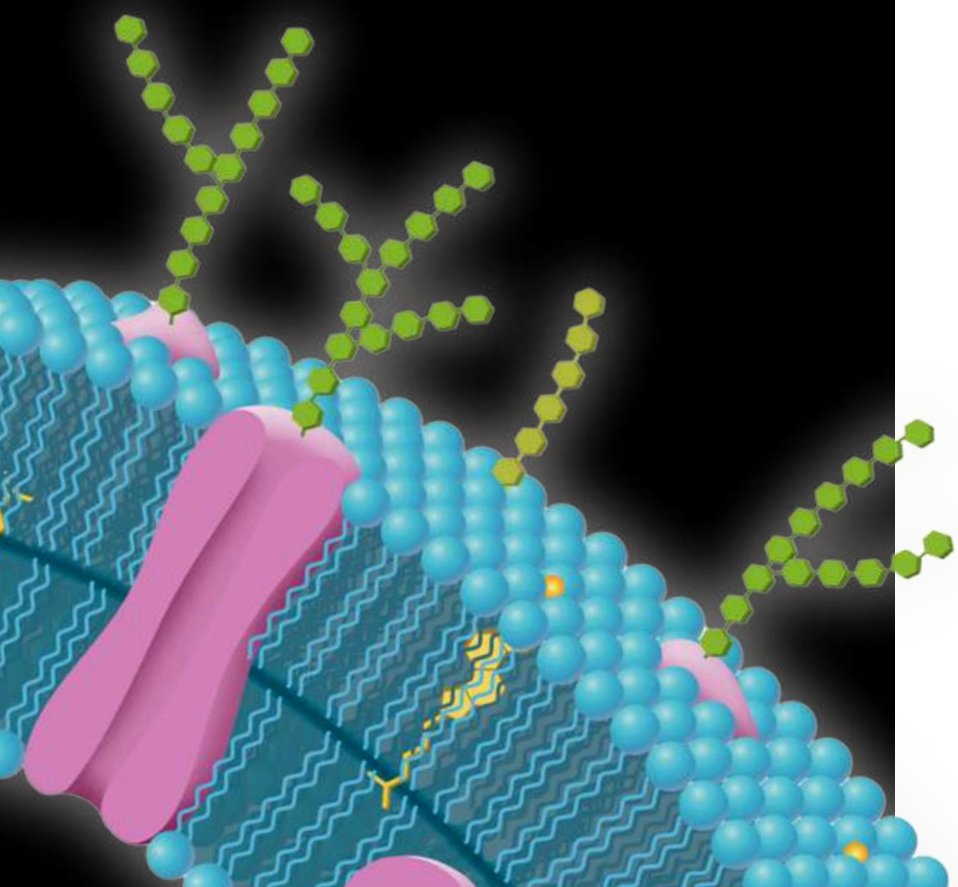
Development Question	SurfaceSeek Insight
Is the protein truly accessible on the tumor surface?	Detection of mature extracellular proteins
Which proteoforms contain therapeutically relevant epitopes?	Peptide-level isoform and proteoform resolution
Is the target tumor-selective?	Tumor vs. normal tissue expression comparison
Is the target compatible with a specific modality?	Surface abundance and trafficking insights

SurfaceSeek:

A **rigorous framework** to identify robust surface targets

Historically, oncology targets have often been advanced based on the question, “Is the protein expressed?”

SurfaceSeek **reframes target discovery from qualitative expression analysis to quantitative characterization,** aligning target selection with the mechanistic requirements of modern cancer therapeutics.



De-Risking Oncology Drug Development

Successful target development requires understanding surface accessibility, abundance, structural form, and tissue distribution. **SurfaceSeek generates quantitative biological data that informs critical decisions during target discovery and validation,** including:

- Is the protein functionally deployed on the tumor cell surface?
- Which surface targets have sufficient density to support ADC or T-cell engager therapies?
- How does tumor surface expression compare to normal tissues?
- Why has a clinically tested target shown inconsistent activity across patients?

To request a SurfaceSeek study, contact discover@sapient.bio.

SAPIENT

Discover more today.

+ sapient.bio
+ discover@sapient.bio
+ 858.290.7010