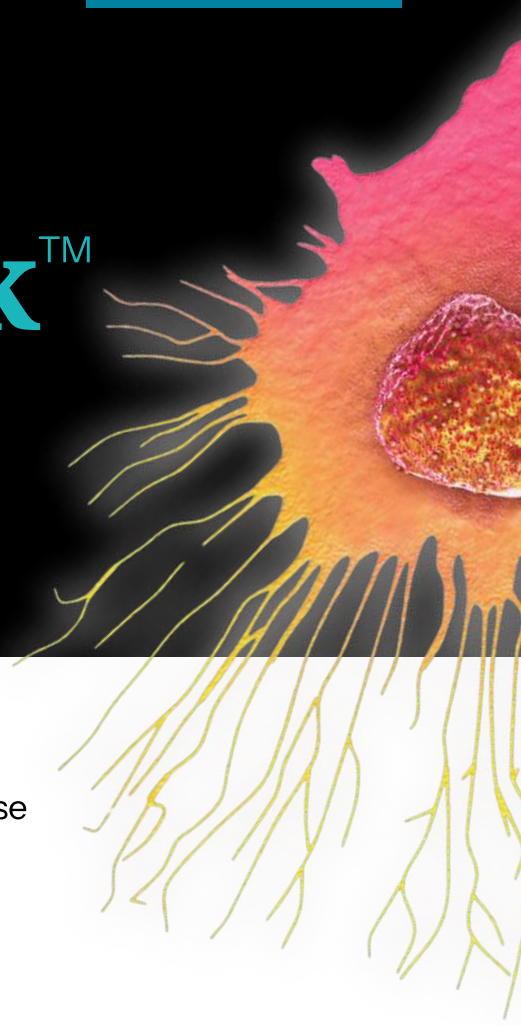
WHITE SHEET

SAPIENT

ResistanceSeek™

Quantifying **cellular resistance pathways** in human tumors



ResistanceSeek directly measures the protein networks that drive therapeutic resistance in human tumors, enabling precise identification of resistance mechanisms across ADC, T-cell engager, radioligand, and targeted oncology therapies.

Mapping the Functional Resistance Proteome

Oncology drug development rarely fails because a target lacks biological relevance. More often, it **stems from incomplete understanding or indirect measurement of resistance biology.** Across modern therapeutic modalities, including kinase inhibitors, ADCs, T-cell engagers, radioligand therapies, and immuno-oncology agents, tumors adapt through coordinated resistance programs that restore survival under therapeutic pressure.

For resistance to be effectively addressed, several key biological dimensions must be understood:

- **Pathway reactivation and bypass signaling**
- **Survival and anti-apoptotic protein upregulation**
- **Target modulation and antigen loss**
- **DNA damage response and repair activation**
- **Immune evasion and tumor microenvironment adaptation**

These critical resistance mechanisms are driven at the protein level and therefore rarely captured by conventional genomic approaches.

ResistanceSeek addresses this challenge by directly quantifying resistance-associated protein networks in human tumors using a mass spectrometry-based proteomics workflow.

Why Resistance Biology Is Frequently Missed

Despite exciting advances in cancer therapeutic modalities, resistance remains one of the primary causes of therapeutic failure. A central issue is that most development strategies rely on genomic or transcriptomic data that **do not fully reveal functional resistance states.**

Common Approach	Key Limitation
DNA sequencing	Captures mutations but not pathway activation or adaptation.
RNA expression profiling	Does not reflect protein activity or signaling dynamics.
Cellular & preclinical models	Often fail to capture human tumor resistance biology.

As a result, resistance is often inferred rather than directly measured, which means it is often recognized only after clinical failure and therefore **remains poorly integrated into biomarker strategy.**

The Power of the ResistanceSeek Approach

ResistanceSeek addresses this gap by **directly measuring the protein pathways that define resistance in human tumors.** The workflow applies deep discovery proteomics to comprehensively profile and map resistance biology across multiple dimensions.

Direct Measurement of Resistance Pathways

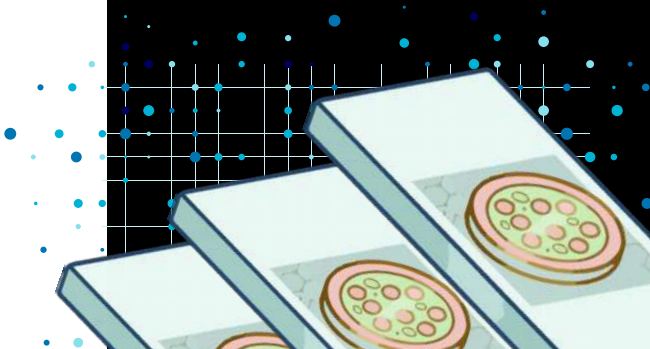
ResistanceSeek directly quantifies coordinated protein networks through which resistance mechanisms are executed, including:

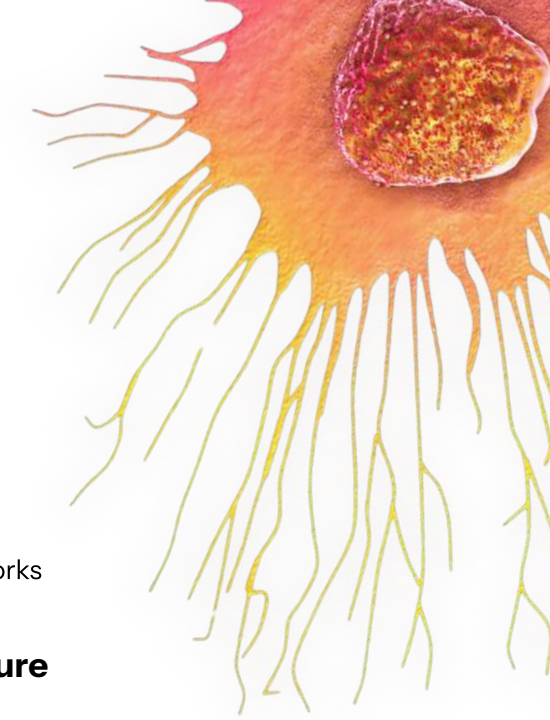
- **MAPK and PI3K/AKT/mTOR** pathway reactivation
- Upregulation of **anti-apoptotic proteins**
- Activation of **DNA repair pathways**
- Activation of **receptor tyrosine kinase signaling**
- Initiation of **immune evasion programs**
- Upregulation of **epithelial–mesenchymal transition (EMT) and lineage plasticity programs**
- Downregulation of **antigen target proteins and drug internalization programs**

ResistanceSeek is **optimized for both fresh-frozen and FFPE human tumor samples,** enabling:

- **Identificaton** of resistance-associated protein signatures
- **Determination of** responder vs. non-responder biology
- **Clarification** of follow-on trial design or asset repositioning

*This unlocks the ability to measure resistance biology in both **prospective studies and archived clinical samples.***





Modality-Specific Resistance Insights

ResistanceSeek enables systematic profiling of resistance mechanisms most relevant to different oncology therapeutic classes, including:

- **Kinase inhibitors:** pathway reactivation, bypass signaling, EMT
- **ADCs:** antigen downregulation, trafficking changes, payload resistance
- **TCEs:** antigen loss, interferon pathway defects, apoptosis resistance
- **RLTs:** DNA repair activation, hypoxia-driven survival
- **Immunotherapies:** antigen presentation loss, immune suppression networks

From Retrospective Interpretation to Prospective Measure

Historically, resistance has been treated as a retrospective explanation for therapeutic failure, identified only after tumors have already adapted. Modern oncology development requires **resistance to be defined as a measurable, functional state** – one that can be quantified, compared, and acted upon.

By directly profiling the protein networks that execute resistance programs, ResistanceSeek enables prospective insight into how tumors evade therapeutic pressure, supporting **mechanism-driven trial design, rational combination strategies, and improved patient stratification.**

How ResistanceSeek Guides Development Decisions

ResistanceSeek **generates quantitative data** that informs key decisions in oncology development.

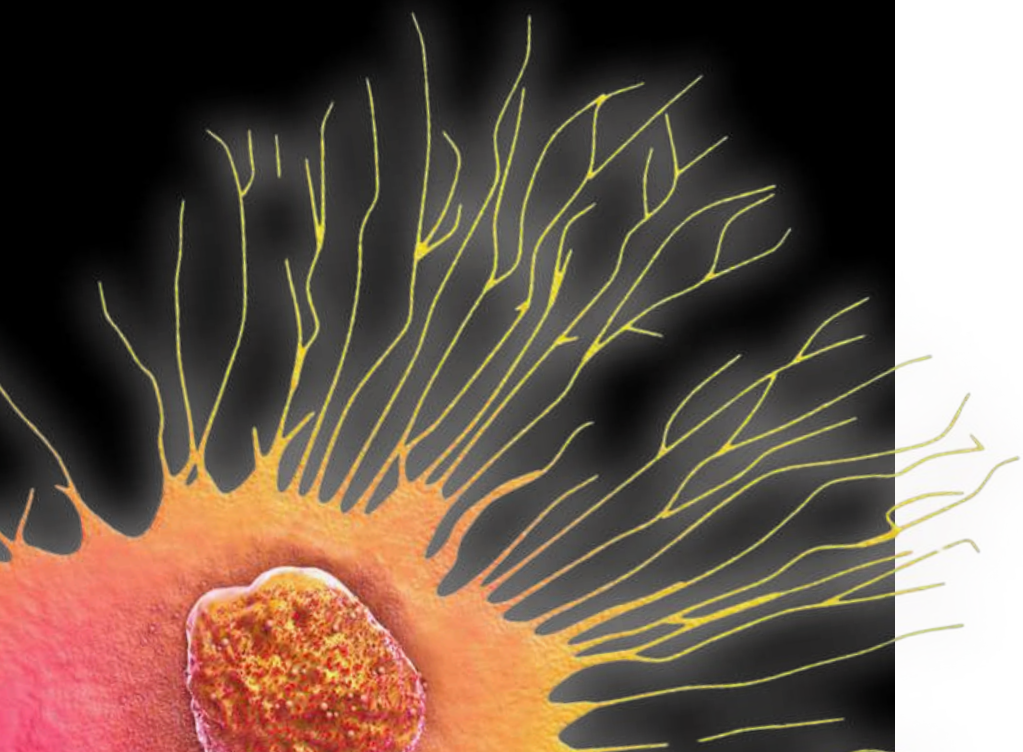
Development Question	ResistanceSeek Insight
Why are patients failing therapy despite target engagement?	Identification of activated resistance pathways
Which compensatory pathways are driving escape?	Quantitative pathway activation profiling
How should combination therapies be selected?	Identification of dominant resistance mechanisms
Can archived trials reveal responder subsets?	Proteomic profiling of FFPE cohorts
How can patient selection be improved?	Functional stratification based on resistance biology

ResistanceSeek:

From post-hoc analysis of resistance to **prospective insights**

Historically, resistance has been treated as a retrospective explanation for drug failure. In modern oncology development, resistance must be viewed as a **measurable and actionable variable.**

ResistanceSeek **shifts development from genomic inference to functional protein measurement** across the pathways that define resistance in human tumors – enabling mechanism-driven decision-making.



De-Risking Oncology Drug Development

For drug developers seeking to understand and overcome resistance, ResistanceSeek provides **direct biological insight into therapeutic failure and adaptation.** This workflow is particularly valuable in programs where teams are asking:

- Why are patients not responding despite target expression?
- What mechanisms are driving resistance to ADC, TCE, or IO therapies?
- Which pathways should be targeted in combination strategies?
- Can archived clinical trials reveal actionable resistance biology?
- Can patient populations be stratified based on functional response?

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

SAPIENT

Discover more today.

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