P04.14: Identification of Modality Agnostic Novel Anticancer Drug Targets on a Proteogenomic Platform

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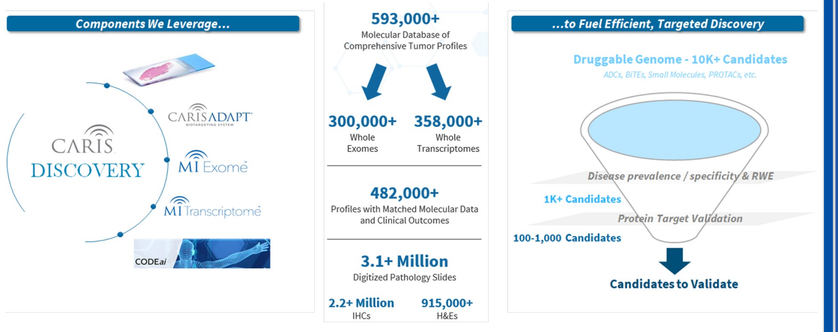
Purpose:

There is an unmet need for identifying novel and reliable molecular targets to address precise and individualized treatment decisions for cancer patients. Caris' target discovery platform provides comprehensive insights from real-world molecular and clinical outcomes generated from over 500,000 patients. Herein, we highlight our proteogenomic methods leveraging Caris' extensive molecular-profiling database and proteomic data generated using ADAPT™ [1,2], an aptamer-based platform that enriches cancer specific proteins from patient tissues. Our methodology results in identification of novel, clinically relevant, modality agnostic targets for cancer therapeutics development.

Tissue Derived Proprietary Datasets



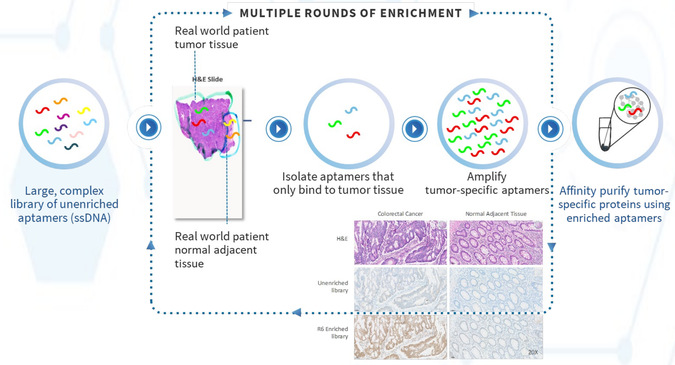
Validation Capabilities for Cell Surface (TCEs, ADC, DAC) & Intracellular (Degrader) Targets

Literature Analysis	Gene Expression Profiling	Tissue Expression/ Localization	Cancer Dependency	Cell Surface Validation	DAC/ADC Assays
Structure & Function	Normal & Cancer Tissue Expression Profile for Target and Isoforms*	Antibody Specificity IHC, WB, ELISA	DepMap**	Cell Surface Shaving	Internalization by confocal microscopy
Role in Cancer		IHC on Normal and Cancer TMAs	PICKLES***	Cell Surface Biotinylation	Cytotoxicity
Localization	Normal & Cancer Tissue Expression Profile for Family Members with >70% Protein Sequence Alignment	IHC on FFPE Slides from Cancer Cases	Caris Multimodal Data	Cell Surface Glycocapture	Correlation of E3 Ligase Expression & Degrader Target
Patent Landscape/ Clinical Trials		Cell Surface Proteomics/ whole Lysate Proteomics on FFPE tissues or cell lines	In-House Functional Screens (in development)	MS-Membrane Fraction Analysis	
				ICC and Flow Cytometry on Intact Cells	Correlation of Cell Surface Target and Degrader Target

*Normal tissue expression is downloaded from GTEx data (https://gtexportal.org) and compared to Cancer tissue expression generated by the Caris WTS pipeline.
**https://depmap.org/portal/download/all/?releasename=DepMap+Public+23Q4&filename=CRISPRGeneDependency.csv
***https://pickles.hart-lab.org/

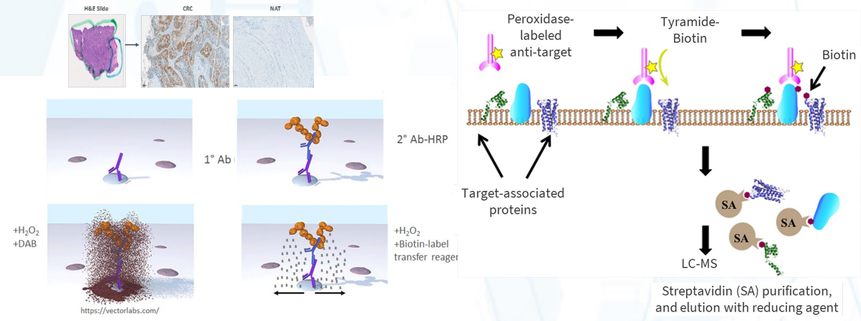
Methods:

ADAPT™ Biotargeting



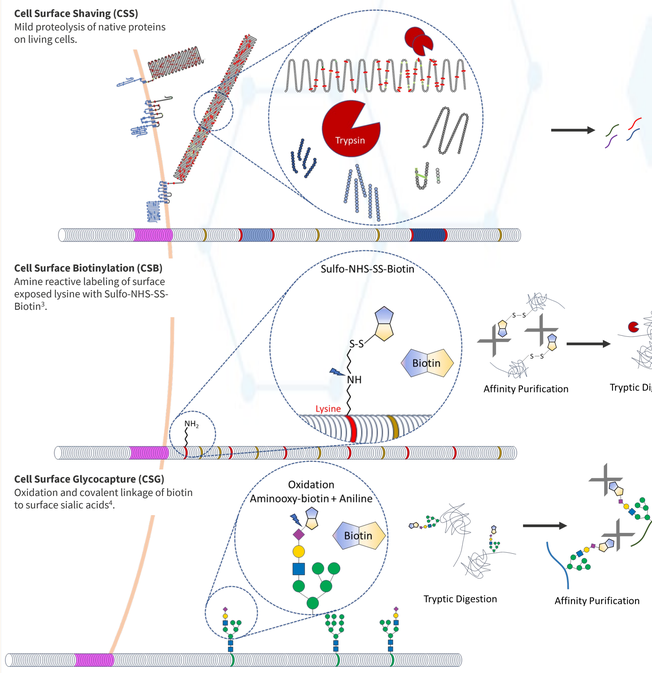
Identifies Clinically-Relevant Targets Inaccessible to Traditional Proteomics in Tissue

Proximity Labeling from Patient Samples

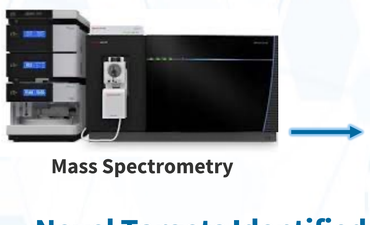


Mining for Cancer Specific Proteins & Protein Interaction Partners from Patient Samples

Caris Cancer Cell Surfaceome



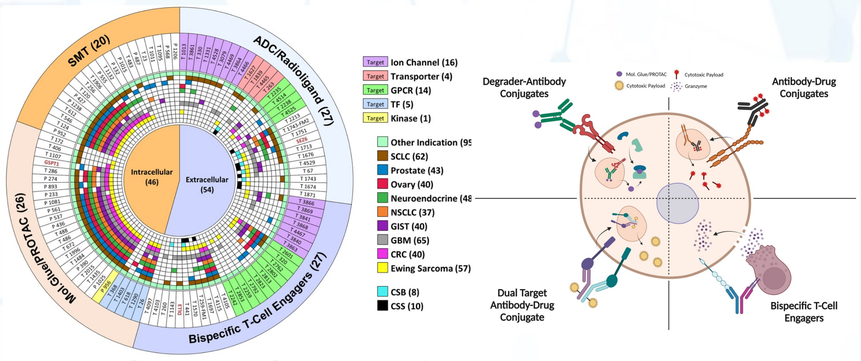
CSB/CSS - Triplicate samples from both adherent and suspended cells.
CSG – Triplicate samples of cells lifted non-enzymatically



Mass Spectrometry

Data Analysis Pipeline

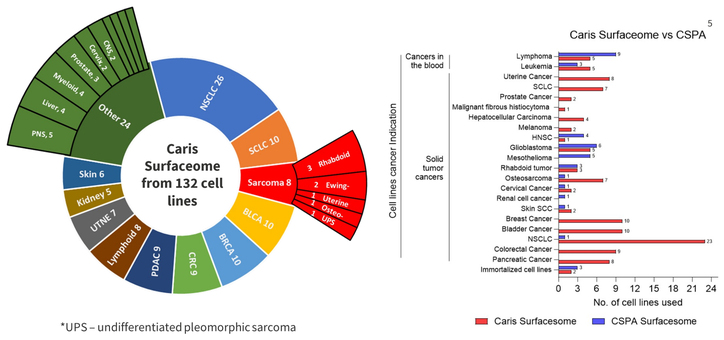
Novel Targets Identified Across Cancer Indications and Priority Target Modalities



- Most Targets in the Early Stages of Wet Lab Validation Pipeline
- Targets in red font are known drug targets for case studies/pipeline validation

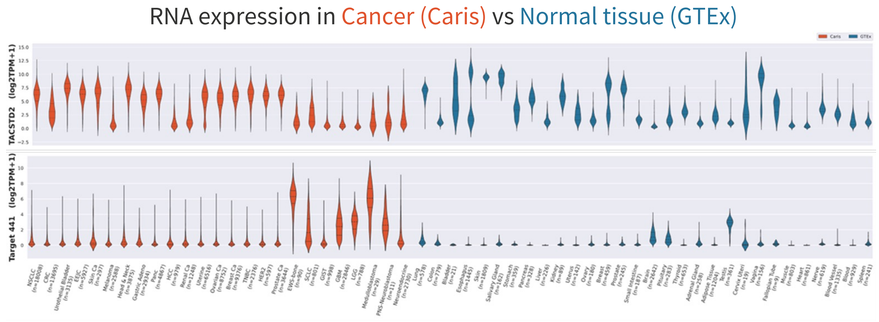
Results:

Caris Cell Surfaceome

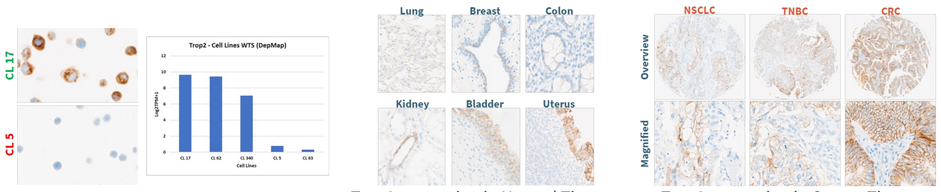


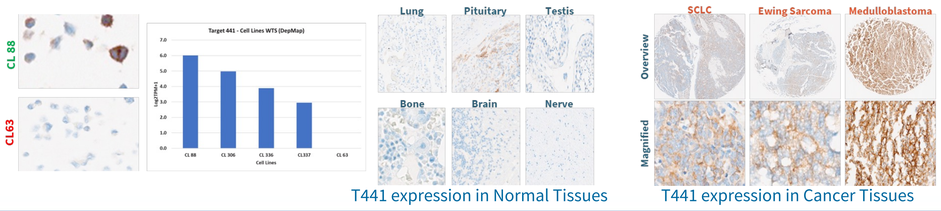
*UPS – undifferentiated pleomorphic sarcoma

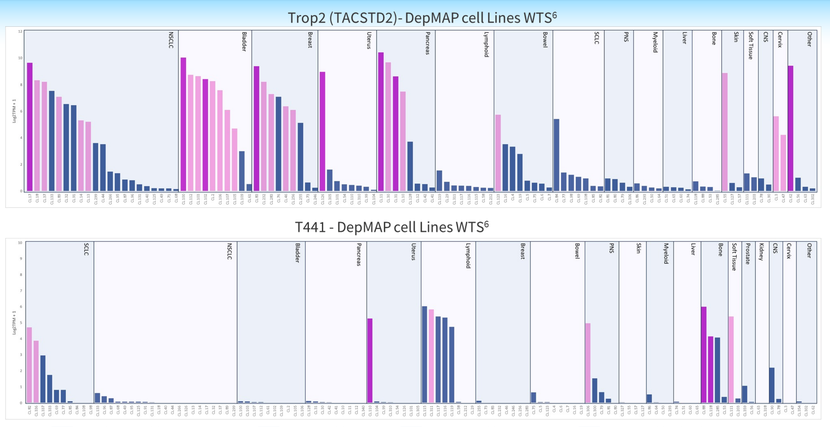
RNA expression in Cancer (Caris) vs Normal tissue (GTEx)

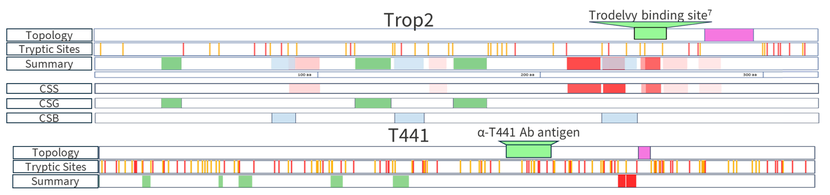


Example of Trop2, known drug target, with high expression in normal tissues vs Caris' candidate that passed selection

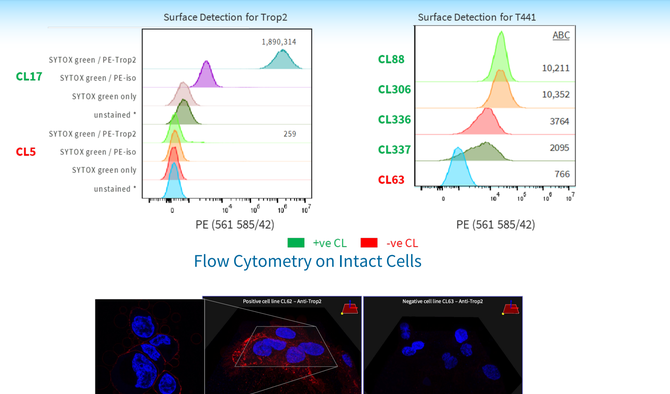


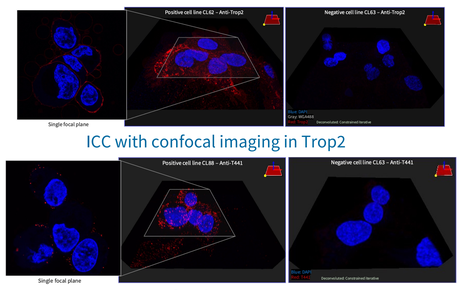






Peptide regions detected by CSS (red), CSG (green) or CSB (blue)





- Clear distinction is observed between positive and negative cell lines for both Trop2 and T441 in Immunocytochemistry **(ICC)** performed on in-tact cells.
- Single focal plane is consistent with membrane localization.

Conclusions:

- We have identified and shortlisted several novel candidates that are enriched in a particular cancer indication using RNA-expression and protein localization by IHC on patient tissue. These targets were stratified into surface or intracellular targets based on their detection by cell-surface proteomics, ICC and flow cytometry.
- Caris cell surfaceome provides a strong foundation for discovery of novel surface targets exploiting three mass spectrometry approaches from >100 cancer cell lines and providing peptide level data focusing on ECD and transmembrane domain for the identification of novel cell surface targets that covers an array of indications.
- Our approach identifies modality-agnostic targets directly from patient tissue that are validated for presence, localization, protein expression, and dependency. Clinically actionable targets are evaluated to provide informed strategies for drug development across therapeutic modalities from biologics to small molecules.

References:

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6. WTS data for cell lines from DepMap (Expression public 23Q2), Depmap.org
7. Olivier, Timothee, and Vinay Prasad. "Sacituzumab govitecan in metastatic triple negative breast cancer (TNBC): Four design features in the ASCENT trial potentially favored the experimental arm." *Translational oncology* vol. 15,1 (2022): 101248. doi:10.1016/j.tranon.2021.101248