Proteomic Profiling of Antibody-Drug Conjugate (ADC) Biomarkers in Pancreatic Cancer

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BACKGROUND

- Pancreatic cancer (PaC) is a highly fatal disease with a 5-year survival rate of 5-10%.
- Effective screening is not available, and most patients (50-55%) present with metastatic disease at diagnosis.
- For patients with advanced PaC, the standard chemotherapy combinations (FOLFIRINOX and/or gemcitabine/nab-paclitaxel) results in an overall survival of 7-11 months.
- The lack of effective therapies underscores the importance of exploring other agents including antibody drug conjugates (ADC).
- Mass spectrometry-based proteomics can identify multiple biomarkers from limited FFPE tissue.

METHODS

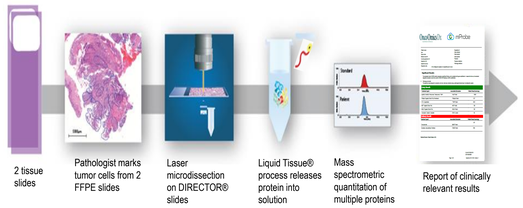


Figure 1. FFPE tumor tissues from 185 clinical PaC patients were microdissected and solubilized for mass spectrometry-based targeted proteomic analysis. These tests were run in a CLIA certified CAP accredited laboratory.

Multiplexed proteomic panel

Targeted chemotherapy panel:

MGMT, hENT1, RRM1, ERCC1, TOPO1, TOPO2A, and TUBB3

ADC panel:

Antibody Targets:

EGFR, HER2, FRalpha, mesothelin, Trop2, Nectin-4, ALCAM (CD166), CEACAM5

Payload biomarkers:

TOPO1 and TUBB3

RESULTS

Expression Distribution of HER2 and Payload Targets of Sensitivity (TOPO1) or Resistance (TUBB3) in Pancreatic Cancer

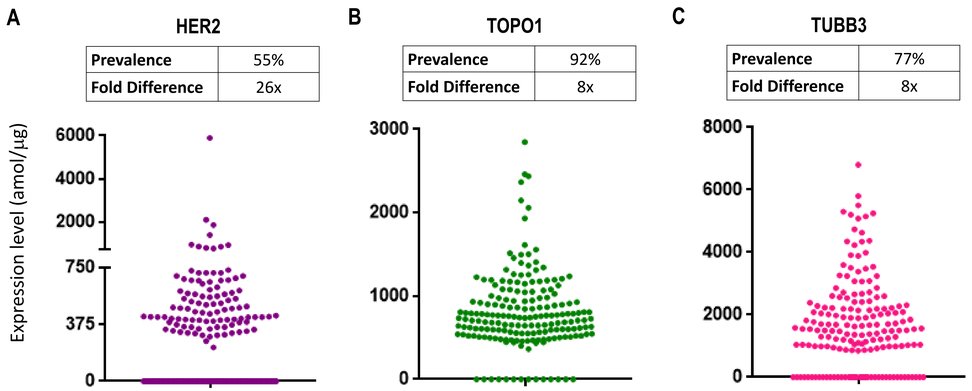


Figure 2. Expression distribution of antibody target (HER2) (A). HER2 expression was expressed in 55% of pancreatic cancer patients (n=185) and overexpressed (>750 amol/µg) in 5% (10/185) of cases. (B) TOPO1 (payload sensitivity biomarker for irinotecan and tecan derivatives) expression in pancreatic cancer. (C) TUBB3 (payload resistance biomarker for anti-tubulin inhibitors, e.g. docetaxel/taxane based derivatives) expression. Fold difference indicates the wide expression range of these biomarkers and is calculated by the highest detected / lowest detected value.

Quantitation of ADC Targets in Pancreatic Cancer

	Trop2	EGFR	HER3	FR-α	Mesothelin
Prevalence	91%	88%	23%	10%	65%
Fold Difference	25x	11x	5x	17x	59x

Nectin-4	CD166
42%	42%
1.3x	3x

CEACAM5
92%
182x

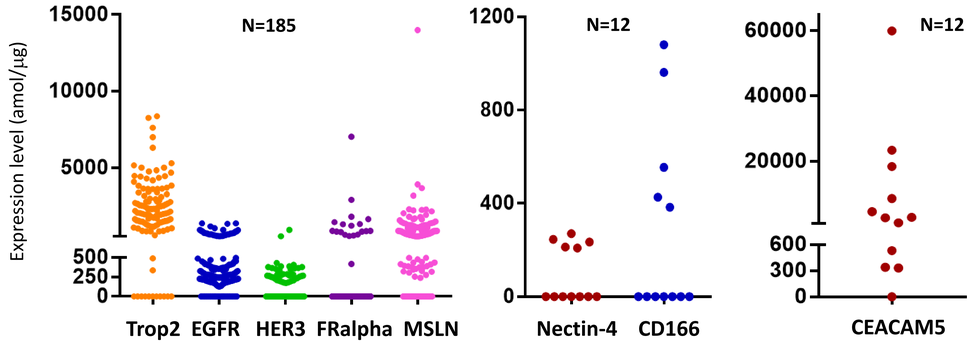
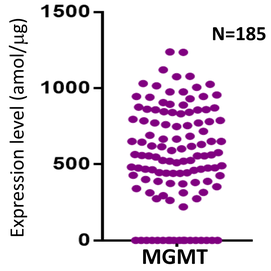


Figure 3. Expression distribution of receptor targets of ADCs in pancreatic cancer. Trop2, EGFR, HER3, Folate receptor-alpha (FR-α), Mesothelin (MSLN), Nectin-4, ALCAM (CD166), and CEACAM5 expression distribution.

"Targeted" Chemotherapy Protein Biomarkers

Novel Chemotherapy Marker



MGMT Expression Distribution

% Negative	15%

Figure 4. Expression of MGMT in pancreatic cancer. Cancers that do not express MGMT are likely responsive to temozolomide. MGMT expression is absent in 15% of pancreatic cancers suggesting that these patients may receive benefits from temozolomide treatment.

Conventional Chemotherapy Marker

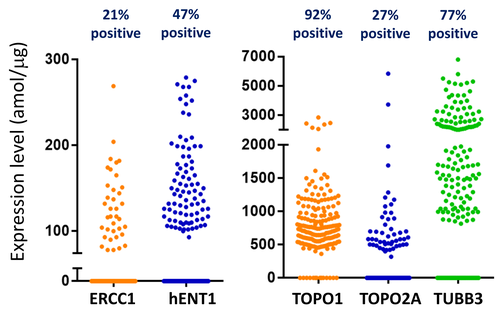


Figure 5. Pancreatic cancer tissue expression for each of the biomarkers as a multiplex analysis. ERCC1 (platinum-based chemo resistance marker). hENT1 (gemcitabine sensitivity marker). TUBB3 (taxanes resistance marker. TOPO1 (irinotecan and topotecan sensitivity marker). TOPO2A (doxorubicin sensitivity marker).

CONCLUSIONS

- Concurrent proteomic quantitation of HER2, TOPO1, and TUBB3 may improve patient selection for HER2 ADCs.
- Although there is currently no approved ADC for PaC, there are multiple approved and investigational ADC therapies in other cancer types. Quantitative proteomics detected varying expression levels of antibody-targets: Trop2(91%), EGFR(88%), HER2(55%), HER3(23%), Folate receptor –alpha (10%), Mesothelin (65%), Nectin-4(42%), CD166 (42%), and CEACAM5(92%)
- MGMT protein expression is absent in 15% of pancreatic cancers and temozolomide may be considered as a novel chemotherapy for PaC.
- The ability to multiplex 72 protein biomarkers from 2-3 FFPE sections provides immense actionable information on clinical treatment or for patient stratification for clinical trials.

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