Quantitative Proteomics of Antibody-Drug Conjugates and Chemotherapy Targets in Prostate Cancer

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BACKGROUND

- Prostate cancer (PC) is a major cause of morbidity and mortality for men worldwide. In 2020[1], over 1.4 million men were diagnosed with PC, and approximately 375,000 men died from the disease.
- Prostate cancer treatment involves the use of androgen deprivation therapy, chemotherapy, targeted therapy, and immunotherapy.
- Despite significant advances in systemic therapy for PC over the past two decades, acquired resistance remains a significant obstacle preventing durable remissions and cures for metastatic disease patients.
- Mass spectrometry-based proteomics can identify multiple biomarkers from limited FFPE tissue.

METHODS

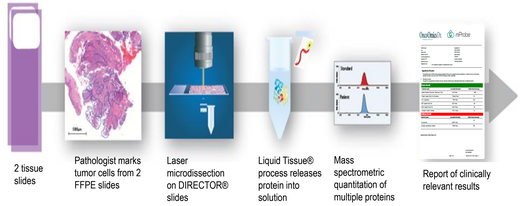

Figure 1. FFPE tumor tissues from 87 clinical prostate cancer patients were laser-microdissected and solubilized for mass spectrometry-based targeted proteomic analysis. These tests were run in a CLIA certified CAP accredited laboratory.

Multiplexed proteomic panel

Targeted chemotherapy panel:
TOPO1, TOPO2A, hENT1, ERCC1, MGMT, ALDH1A1, TUBB3

ADC panel:

Antibody Targets:
EGFR, HER2, HER3, TROP2, PSMA, Nectin-4, B7H3, CD166, STEAP1, EPCAM

Payload biomarkers:
TOPO1 and TUBB3

Neuroendocrine panel:
CD56, CHGA, SYP

RESULTS

Multiplexed Quantitative Proteomics Allows Parallel Analysis of multiple ADC Markers and Payload Targets of Sensitivity (TOPO1) or Resistant (TUBB3) in Prostate Cancer

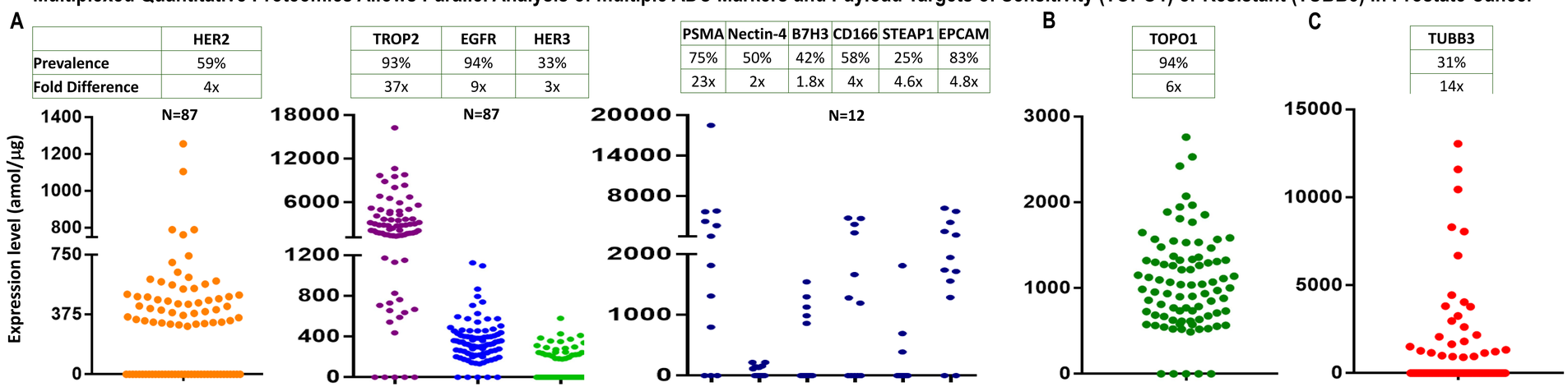

Figure 2. Expression distribution of receptor targets of ADCs in prostate cancer. (A) HER2, TROP2, EGFR, HER3, PSMA, Nectin-4, B7H3, CD166, STEAP1, and EPCAM expression distribution. HER2 was expressed in 59% of prostate cancer patients (n=87) and overexpressed (>750 amol/µg) in 5.7% (5/87) of cases. (B) TOPO1 (payload sensitivity biomarker for tecan derivatives, etoposide) expression. (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 Hormone Therapy and Chemotherapy Sensitivity/Resistance Markers

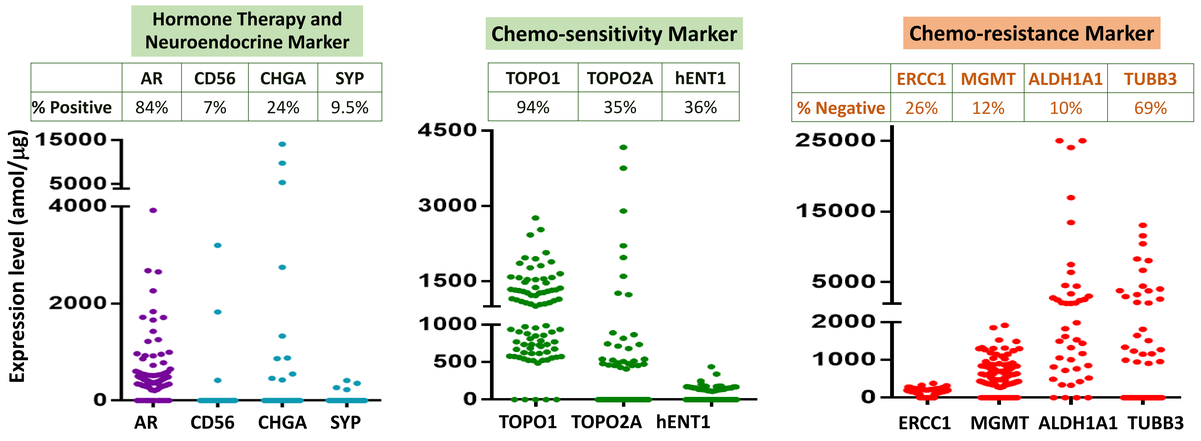

Figure 3. Prostate cancer tissue expression for each of the biomarkers as a multiplex analysis. AR (androgen receptor inhibitors marker).CD56, CHGA and SYP are markers for neuroendocrine differentiation. TOPO1, TOPO2A and hENT1 are sensitivity markers for irinotecan/etoposide, doxorubicin and gemcitabine, respectively. ERCC1, MGMT, ALDH1A1, and TUBB3 are resistance markers for platinum-based chemotherapy, temozolomide, cyclophosphamide, and taxanes, respectively.

CONCLUSIONS

- Although there is currently no approved ADC for prostate cancer, there are multiple approved and investigational ADC therapies in other cancer types. Quantitative proteomics detected varying expression levels of antibody-targets: HER2(59%), TROP2(93%), EGFR(94%), HER3(33%), PSMA(75%), Nectin-4(50%), B7H3(42%), CD166 (58%), STEAP1(25%), and EPCAM(83%).
- HER2 was detected in 59% of the cases with a range of expression from 301-1255 amol/µg, including a significant population of low HER2 (84%, <750 amol/µg) cases among the detected samples.
- MGMT and ALDH1A1 protein expression is absent in 12% and 10% of prostate cancers, respectively; temozolomide and cyclophosphamide may be considered as novel chemotherapy for some prostate cancers.
- 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.

Reference: 1. CA Cancer J Clin 71:209-249, 2021