Discovery of PTN as a serum-based biomarker of pro-metastatic prostate cancer

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Background

Prostate cancer is the most common cancer among men worldwide and the second and third leading cause of cancer-associated deaths in men in the United Kingdom and United States, respectively. A blood test for prostate-specific antigen (PSA) is commonly used as a screening tool for prostate cancer. Unfortunately, PSA is elevated with other conditions, such as benign prostatic hyperplasia (BPH), and cannot distinguish between low-risk and high-risk cancer (most likely to progress and become metastatic leading to patient death). This results in overtreatment of patients with low-risk prostate cancer and delayed or ineffective treatment of many patients with high-risk prostate cancer. One of the major clinical challenges in prostate cancer is distinguishing the patients who may benefit from surgery or radiotherapy from patients who should not be treated but rather managed with active surveillance. Thus, there is an urgent unmet need to define new minimally invasive biomarkers that can distinguish men with prostate cancer from those with benign diseases such as BPH, and differentiate clinically relevant cancers from indolent cancers at diagnosis. **The purpose of this study is to identify and validate new biomarkers for early stratification of high-risk and metastatic prostate cancer from low-risk prostate cancer.**

Identification of blood-based biomarkers through high-multiplex immunoassays

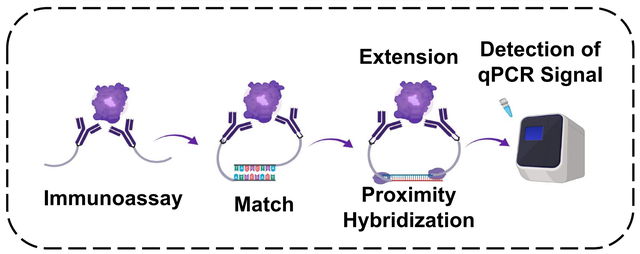


Figure 1. Olink Method.
A pair of oligonucleotide-labeled antibodies were used to recognize and bind to each target protein. Once the two antibodies bind to the protein target, the complementary oligonucleotides attached to each antibody hybridize and a DNA reporter sequence is formed. High throughput, real-time qPCR is used to quantify the DNA reporter sequences Figure generated via BioRender (https://biorender.com).

Identification of blood-based biomarkers for clinically significant prostate cancer

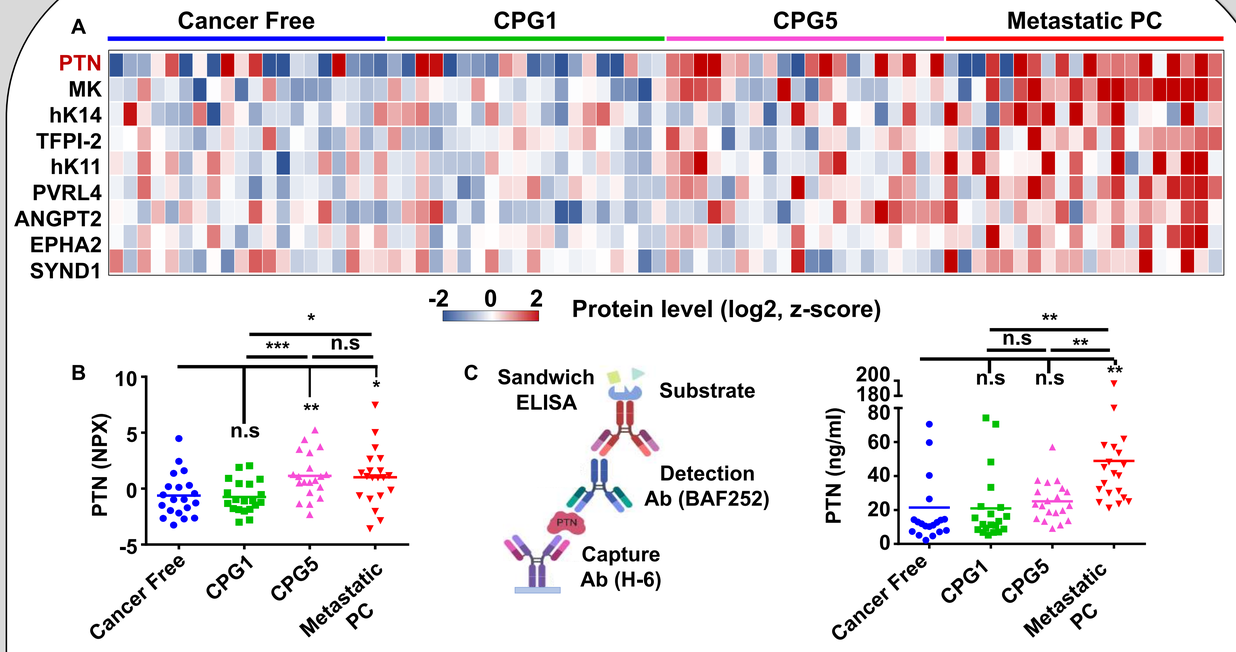
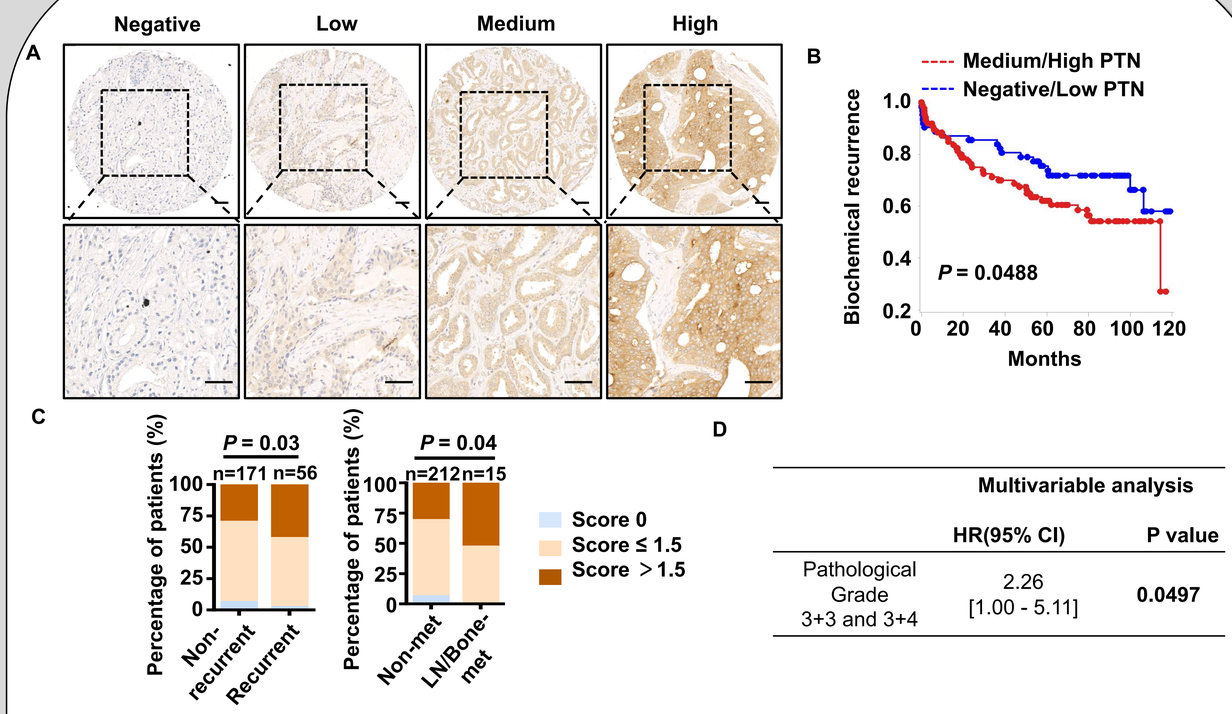


Figure 2. Identification of blood-based biomarkers for clinically significant prostate cancer.
A. Heatmap of nine proteins found to be elevated in at least on group in the proteomics. 80 serum samples from 4 different patient groups: 1) cancer free group, 2) the Cambridge Prognostic Group (CPG) 1 disease with 97% 10 year survival, 3) CPG5 disease with 50% 10 year survival, and 4) men who have presented with metastatic disease at diagnosis were analyzed using the Olink Multiplex panels Immuno oncology and Oncology II panel. Out of the 174 proteins tested, these 9 candidates demonstrated significant alterations in protein levels when compared across patient groups. B. Normalized protein expression (NPX) for PTN is plotted. **PTN**, pleiotrophin protein, exhibits the most cohesive increase in high-grade/metastatic disease. C. PTN levels in the 80 serum samples used for proteomics analysis were analyzed by Sandwich ELISA.

High tissue levels of PTN in prostate cancer are associated with poor prognosis



	Multivariable analysis	
	HR(95% CI)	P value
Pathological Grade 3+3 and 3+4	2.26 [1.00 - 5.11]	**0.0497**

Figure 3. High tissue levels of PTN in prostate cancer are associated with poor prognosis.
A. IHC staining of PTN on Stanford University tissue microarrays (TMAs). B. High PTN expression correlates with lower 10-year recurrence-free survival. P=0.049. C. Strong staining for PTN correlates with prostate cancer recurrence after prostatectomy (recurrent patients: n=56, and non-recurrent patients: n=171) (Right panel). High PTN levels correlate with prostate cancer metastasis (Left panel). D. Multivariate analysis of high levels of PTN as an independent predictor of biochemical recurrence in patients with pathological Gleason Grades 3+3 and 3+4. P<0.05.

Acknowledgement

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Conclusions

Our study provides strong evidence for the role of PTN as a serum-based biomarker for aggressive prostate cancer.

- **Serum PTN expression may be specific for the presence of poor prognosis local and metastatic disease.**
- **PTN may also serve as a predictor of disease progression.**
- **Our data justifies its further evaluation as a potential early detection biomarker of lethal disease**

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Conflicts of interest: None.