PROTEOMIC PROFILING IDENTIFIES PROTEINS ASSOCIATED WITH THERAPEUTIC RESPONSE TO PD-1 IMMUNOTHERAPY

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BIOGNOSYS
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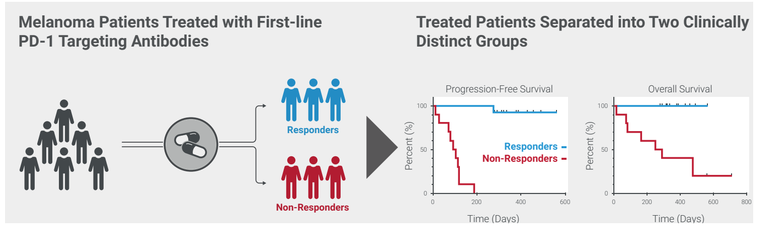
INTRODUCTION

Immune checkpoint inhibitors (ICI) have greatly improved the treatment options for patients with advanced stage melanoma, with improved clinical responses and overall survival compared to standard systemic therapies.

However, a large percentage of melanoma patients do not respond to ICIs, highlighting the need for a greater understanding of the tumor environment and host immune response.

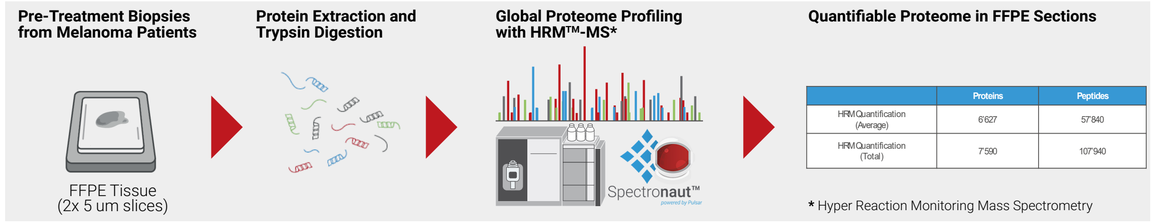
Here, we apply unbiased discovery proteomics, based on label-free data-independent acquisition (DIA) mass spectrometry, to deeply characterize global tumor proteomes to identify proteins and pathways that are associated with pretreatment response to anti-PD-1 immunotherapy.



CONCLUSIONS

- **Global proteomic analysis of FFPE specimens provides deep and unbiased quantification of tumor proteomes**
- **A set of 25 protein candidates were identified as a proteomic signature associated with response to PD-1 immunotherapy treatment in this initial discovery cohort**
- **A pathway level analysis showed increased metabolic processes associated with clinical response to ICI**
- **PLEKHA5 was strongly associated with non-responder status**
- **PLEKHA5 expression correlated with brain metastasis**

RESULTS



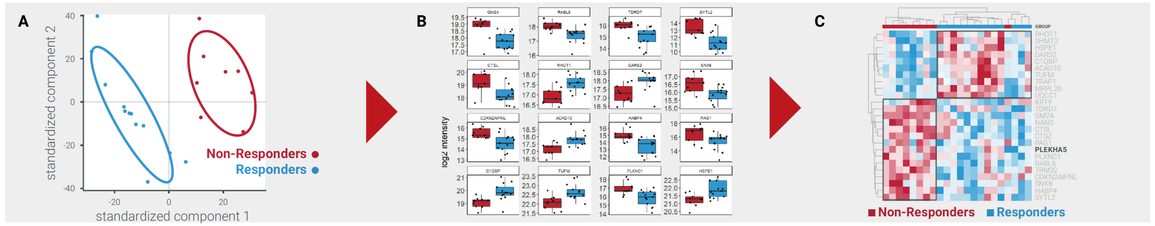


Figure 1: Discovery Proteomics Workflow Based on DIA Mass Spectrometry Quantified > 7,500 Proteins in FFPE Tissue. Proteins were extracted from FFPE samples and prepared for mass spectrometry to generate tryptic peptides. Samples were analyzed on high resolution mass spectrometry instruments and DIA data was extracted using Spectronaut™. Signals were extracted and proteins were quantified.

Figure 2: Global Proteome Analysis Reveals Immune System and Metabolic Processes (**A**) Partial Least Squares Discriminant Analysis (PLS-DA) identified a subset of proteins driving the difference between responders and non-responders. (**B**) Box plots of thetop 25 proteins highlight proteins both up and down regulated in the two groups. (**C**) The top 25 proteins form component 1 are sufficient to reconstruct the responder subgroups.

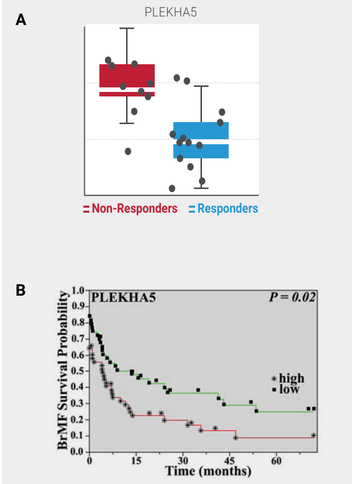


Figure 3: PLEKHA5 a Regulator of Brain Metastases Associate with Poor Response to PD-1 (**A**) PLEKHA5 was significantly up-regulated in the non-responder group. Prior studies by Jilaveanu et. al. (Clin Cancer Res; 21(9); 1978–80) had identified that overexpression of PLEKHA5 was associated with cerebrotropic tumors. (**B**) Brain metastasis free survival for a large cohort of melanoma subjects was stratified based on PLEKHA5 expression .