Nanomedicine and Small Molecule Modulation of Plasma for Deep Proteomics in Cardiovascular Disease Patients

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide[1]. Early detection is essential for timely interventions that can minimize heart tissue damage and improve patient outcomes. However, current blood-based biomarkers lack the sensitivity and specificity needed for early-stage detection, primarily due to the complexity of plasma proteins, where concentration differences span over ten orders of magnitude. This makes it difficult to identify low-abundance proteins[2].

Our study has two primary objectives: first, to significantly enhance plasma proteome coverage by integrating small-molecule and nanomedicine technologies that leverage the protein corona property. Second, to utilize machine learning and causal inference techniques for biomarker discovery through in-depth plasma proteome analysis with our innovative approach. These strategies aim to improve early CVD detection and enable more accurate, reliable diagnostic tools.

How effective is nanomedicine-based detection of low-abundance proteins in CVD, and what novel biomarkers can this method identify to improve diagnostics in patient care?

Methods

What is Protein Corona?

When nanoparticles enter biological fluids, they are rapidly coated by a dynamic layer of biomolecules known as the protein corona[3]. This corona is largely composed of proteins and defines the nanoparticle's 'biological identity,' dictating its biological interactions. The corona composition reflects the surrounding proteome, and its analysis can reveal disease-specific protein signatures with high-resolution.

Plasma Nanoparticle Detection

Plasma samples of over 1000 patients with cardiovascular conditions (including heart failure, myocardial infarction, and stroke) were treated with phosphatidylcholine to selectively attenuate highly abundant plasma proteins such as albumin. This modulation reduced nonspecific adsorption, enabling polystyrene nanoparticles to preferentially form a protein corona enriched with low-abundance plasma proteins. The nanoparticle-bound protein corona was analyzed to identify proteins differentially expressed across CVD phenotypes.

Results

Improved Detection Capacity and Proteome Coverage

Our innovative approach resulted in a nine-fold increase in plasma proteome depth.

- Many of these proteins were not detectable in traditional proteomics analyses without nanoparticle enrichment and small molecule modulation[4].
- These findings reveal a new and improved method in uncovering previously elusive biomarkers, many of which could serve as early indicators of disease or targets for treatment of CVD.

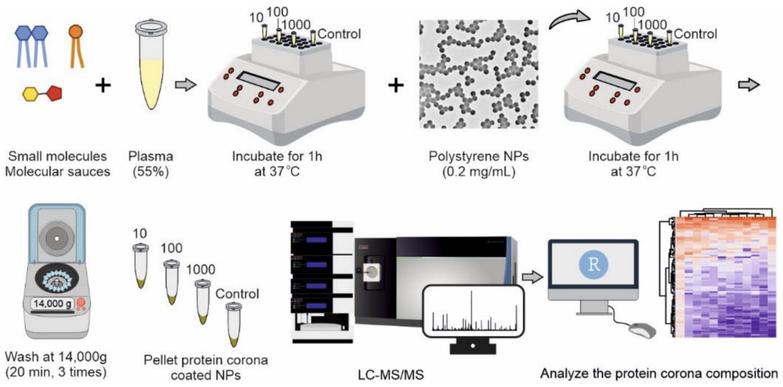
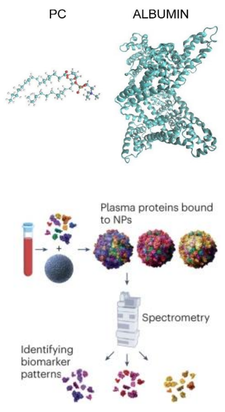


Figure 1. Experimental Workflow. *Plasma samples were exposed to phosphatidylcholine followed by polystyrene nanoparticles. The nanoparticles are then purified and isolated for analysis of their protein corona composition using mass spectrometry.*

Identification of Novel Biomarkers in CVD

Incubation of polystyrene nanoparticles with human plasma led to the detection of over 2000 proteins, including over 100 proteins known to vary in expression in cardiovascular disease patients.

- This includes the precise detection of conventional inflammatory markers, immune system modulators, coagulation factors, and mediators of cholesterol metabolism.
- Up to 600 proteins detected are low-abundance and are not well characterized by the Human Protein Atlas and existing literature[5].



Conclusions

This study demonstrates that combining nanomedicine-based protein corona formation with small-molecule plasma modulation significantly improves the depth and resolution of plasma proteomic profiling. This innovative approach enables the detection of a broader range of differentially expressed low-abundance proteins, many of which are poorly understood in the context of CVD pathogenesis. By expanding the detectable proteome, this method provides a powerful platform for biomarker discovery, offering the potential to advance early diagnosis and enable personalized treatment strategies in CVD management.

Our ongoing research focuses on developing AI-driven causality models of the identified proteins using our nanomedicine technology, aiming to pinpoint causal biomarkers specific to various CVD subtypes[6]. Initial analyses in patients with CVD and prostate cancer have identified a cardio-oncology biomarker: thromboxane A synthase 1, highlighting the potential of this approach for cross-disease biomarker discovery and targeted therapeutic development. Future studies should continue to implement novel techniques to amplify detection of low-abundance biomarkers specific to subtypes of cardiovascular disease, their pathogenesis, and prognosis.

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