Nano-omics: nanotechnology-enabled harvesting of blood-circulating biomarkers

Marilena Hadjidemetriou

NanoOmics team, Nanomedicine Lab,
Faculty of Biology, Medicine & Health,
University of Manchester, UK

marilena.hadjidemetriou@manchester.ac.uk

Over the past decade, the development of 'simple' blood tests that enable disease screening, diagnosis or monitoring and facilitate the design of personalized therapies without the need for invasive tumour biopsy sampling has been a core ambition in cancer research.

Among liquid-biopsy analytes, proteins are the biological endpoints of cellular processes and the most clinically established biomarkers in molecular diagnostics. However, the discovery of novel protein biomarkers in blood remains notoriously difficult. This is largely due to the blood proteome analysis challenge, caused by the overwhelming masking effect of highly abundant proteins (e.g., albumin accounts for 50% of the total protein content). The extraction and mass spectrometry (MS) analysis of massively diluted amounts of disease-specific proteins in blood (at the pg/ml-ng/ml range), remain a major bottleneck for liquid biopsies to be embedded in clinical practice.

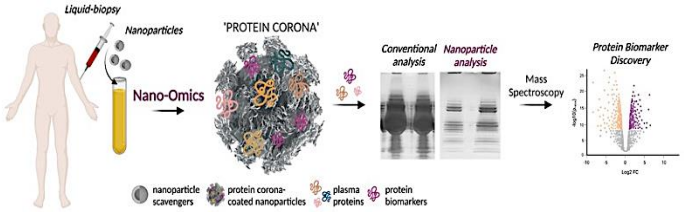
The quest for novel blood biomarkers has led to the development of nanotechnology-based blood analysis solutions. We have recently introduced the *'Nano-Omics'* paradigm,[1] to describe the nanotechnology-enabled enrichment and analysis of blood-circulating molecular biomarkers. Nano-Omics utilizes nanoparticles (NPs) as scavenging platforms to capture, enrich and isolate disease-associated analytes from biological fluids for downstream omics analyses.

Specifically for protein biomarker discovery, Nano-Omics exploits the spontaneous and untargeted adsorption of proteins onto the NP surface once in contact with biological fluids, known as *'protein corona'* formation (**Fig.1**).[2] Recovery and purification of corona-coated NPs from unbound proteins and subsequent analysis MS addresses the issue of albumin masking and offers substantial 'broadening' of the blood proteome coverage. This results in the identification of low molecular weight and low abundance proteins that cannot be directly detected by conventional proteomic analysis of blood.[3] Comprehensive comparison between *'healthy'* and *'diseased'* coronas by MS enables the identification of multiple previously unrecognized candidate biomarker proteins (**Fig.1**). Unlike other NP-based biosensing technologies designed to capture already-known disease-associated analytes, this 'blood-mining' approach has the potential to accelerate the discovery phase of the biomarker development. While the *ex vivo* corona formation (upon incubation of NPs with biofluids in a tube) has been exploited for the analysis of human clinical samples, the molecularly richer *in vivo* corona (forming upon intravenous administration of NPs and their subsequent recovery from blood) has been shown to enable the discovery of biomarkers in preclinical models.

During the past decade, we have learnt that a complex protein corona forms rapidly on the surfaces of all nanoscale materials to varying degrees, depending on their physicochemical properties and surface characteristics. More recently, the NP protein corona formation has conceptually morphed into the multi-molecular self-assembly of layers composed of proteins, lipids, polysaccharides and nucleic acids, termed the *'biomolecule corona'*. For example, we demonstrated the interaction of cfDNA with lipid-based NPs upon their incubation with human plasma samples.[4] The discovery of this additional omics dimension paves the way for further investigations of the potential exploitation of the NP biomolecule corona to enrich proteogenomic biomarkers in blood. The Nano-Omics platform technology could be deployable across a range of biomarker applications and pressing clinical challenges.

Figures

Figure 1. The Nano-Omics proteomics analysis workflow. The Nano-Omics technology relies on the non-specific adsorption of disease-associated proteins onto the nanoparticle surface, once in contact with blood (known as '*protein corona'* formation). Protein corona analysis by liquid chromatography-tandem mass spectrometry (LC: MS/MS) addresses the issue of albumin masking and enables an in-depth analysis of the blood proteome.



References

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