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Leveraging nanoparticle protein corona to advance plasma proteome profiling

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The blood plasma proteome is a rich reservoir of potential biomarkers, yet its analysis is hindered by a protein concentration dynamic range exceeding ten orders of magnitude. Traditional fractionation and enrichment methods often present limitations in detecting rare proteins masked by the presence of abundant proteins. A promising frontier technology has emerged to overcome such limitations: leveraging nanoparticle protein coronas to enrich low-abundance plasma proteins and unveil previously inaccessible layers of the proteome. This *Perspective* highlights the capabilities of the protein corona technology in enhancing proteome coverage, addresses its current limitations and outlines future directions in proteoform analysis and causal inference.

Blood plasma proteins contain valuable information about the physiological condition of an individual[1,2]. The detailed analysis of these proteins offers potential for early disease detection, therapeutic discovery, and treatment monitoring, ultimately contributing to enhance both lifespan and quality of life[3]. Nonetheless, fully leveraging the benefits of an in-depth plasma protein analysis has been hindered by a trade-off between coverage depth and sample throughput due to the vast dynamic range of protein concentrations in the plasma proteome[4].

To address this issue, various strategies have been developed, including depleting highly abundant proteins (with demonstrated partial success) to enhance the depth of plasma proteome analysis[5]. Among these approaches, the protein corona—a coating of plasma proteins that spontaneously forms on nanoparticle surfaces[6]—has emerged as a powerful tool to improve proteome scavenging[5,7]. Its ability to rebalance protein abundance facilitates the identification of low-concentration proteins[6,8–10]. While, initially abundant proteins may interact at a higher propensity with nanoparticles, they are often replaced over time by proteins with a higher surface affinity, irrespective of their concentration in the bulk fluid. The protein corona composition is shaped by nanoparticle properties, such as size, charge, and surface chemistry, enabling the enrichment of specific proteome subsets for untargeted or targeted biomarker discovery exercises (Fig. 1)[6–12]. For instance, engineered nanoparticles can be used to uncover early-stage cancer markers or subtle changes in neurodegenerative disease progression[13]—applications where low-abundance proteins often carry the most diagnostic value[14–17].

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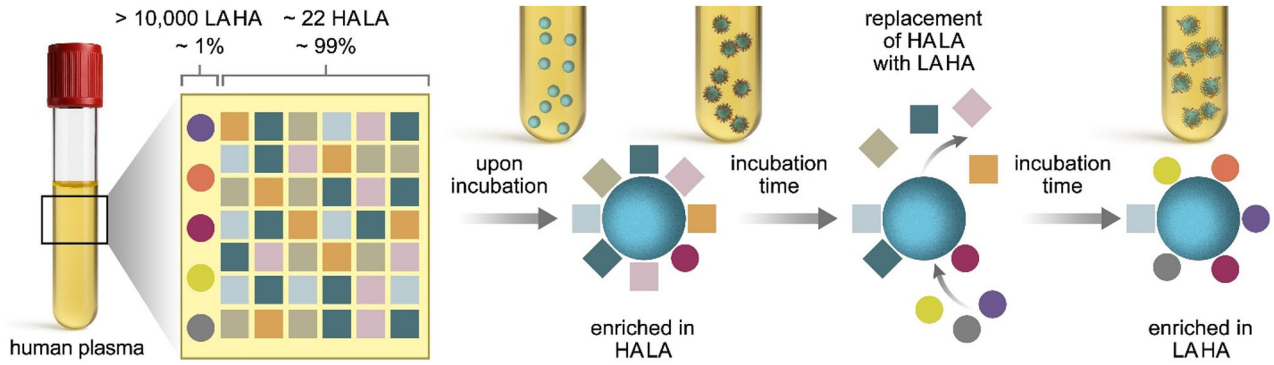

Fig. 1 | Ability of the protein corona to balance concentration disparities among plasma proteins. Upon interaction with human plasma, nanoparticles predominantly attract high-abundance, low-affinity plasma proteins (HALA), leading to a protein corona primarily composed of these proteins. During the early incubation period—which typically lasts several minutes—dynamic exchange occurs, wherein HALA are gradually replaced by low-abundance, high-affinity (LAHA) plasma proteins at the nanoparticle surface. Over the course of approximately 1 h (a timeframe which may vary depending on the physicochemical properties of the nanoparticles), the protein corona reaches its capacity to enrich LAHA plasma proteins while simultaneously depleting the HALA plasma proteins. This process highlights the key role of the protein corona in reshaping the local plasma proteome around nanoparticles and highlights its potential to enhance the depth of plasma proteome coverage.

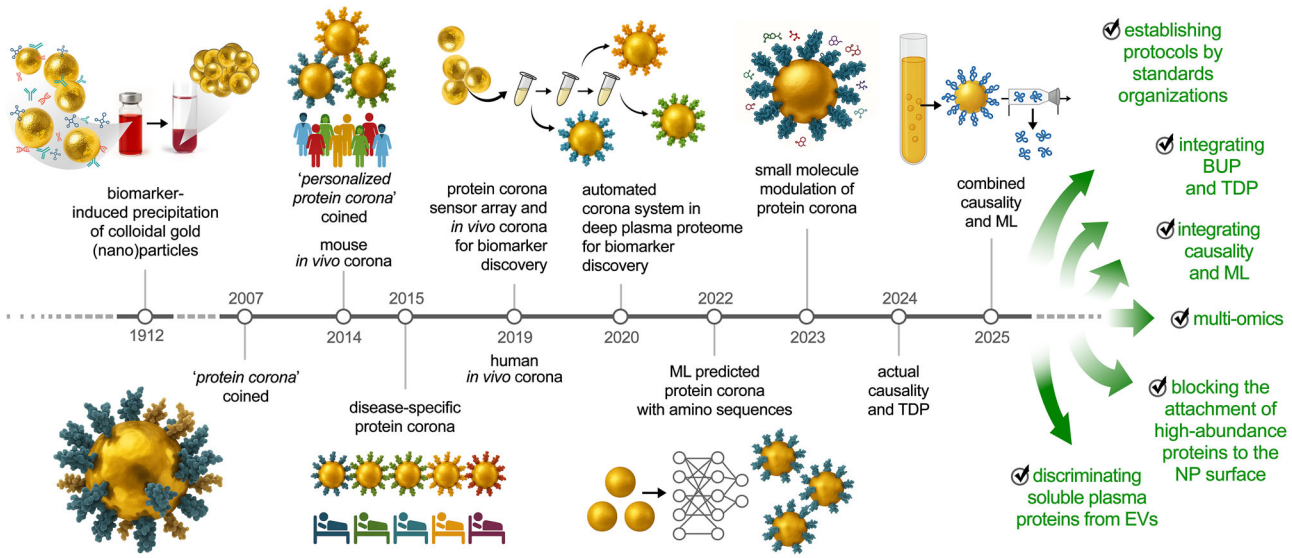

Fig. 2 | Evolution of protein corona research in plasma biomarker discovery and future directions. SA (sensor array), ML (machine learning), TDP (top-down proteomics), BUP (bottom-up proteomics), EVs (extracellular vesicles).

The utility of the protein corona in expanding proteomic depth extends far beyond blood plasma. This phenomenon serves as a powerful enrichment tool for a wide range of biological fluids where a disproportionate concentration of highly abundant proteins creates a significant challenge in dynamic range, effectively masking low-abundance biomarkers, which are often of high clinical relevance. This approach is particularly transformative for fluids characterized by specific dominant proteins, including: (i) cerebrospinal fluid, where albumin and IgG can obscure rare neurological markers[18]; (ii) urine, where uromodulin and albumin dominate the protein profile[19]; (iii) interstitial fluid/muscle lysates, where structural proteins like titin or myosin hinder the detection of signaling molecules[20]; (iv) synovial fluid, where high levels of albumin and hyaluronic acid-binding proteins complicate the study of joint inflammation[21]; and (v) saliva, where amylase and mucins comprise the bulk of the proteome[22].

Historical evolution of corona-based profiling

Figure 2 illustrates a timeline of key milestones in protein corona research for biomarker discovery. The first report, published in 1912—95 years before the term "protein corona" was coined—was by Carl Lange[23], who observed that diseased cerebrospinal fluid precipitated colloidal gold particles. Cerebrospinal fluid from healthy individuals did not cause precipitation, whereas the fluid from individuals presenting certain central nervous system conditions, including syphilis, consistently led to precipitation. The colloidal gold test has proved valuable for diagnosing these conditions[23].

In 2007, Dawson, Linse and colleagues coined the term "protein corona"[24]. The following year, Dawson's group discovered that the physicochemical properties of nanoparticles influence the composition of the protein corona on the nanoparticle surface[9]. Further research showed that both the concentration and composition of proteins within the protein corona do not align with the protein

profiles observed in serum or plasma ex vivo and in blood in vivo for mouse[25], rats[26], and humans[27], forming the basis for the protein corona's role in enhancing the depth of plasma proteome coverage[6]. In 2014, a study found that the protein coronas formed on identical nanoparticles differed significantly when incubated in plasma from individuals with different disease profiles[28]. Developed through this concept known as the "personalized protein corona", nanoparticles can be designed safer and more effective by taking the health profiles of individuals into account[29]; additionally, the idea that nanoparticles can be used as diagnostic tools to assess the health profiles of individuals was developed[14,16].

It is crucial to note that even though interspecies variation significantly affects the protein corona formation, the principle is consistent among species. Studies have shown significant differences between human and mouse coronas, such as 60-fold donor-dependent variance in immune cell association with liposomes and distinct pharmacokinetics in murine models compared to humans[29–31]. This highlights that preclinical animal models may not accurately predict human biomarker performance, necessitating the use of human samples early in development.

Strategies for deeper proteome scavenging

Although nanoparticles can concentrate low-abundance proteins on their surfaces, a significant challenge to further enhance plasma proteome scavenging is the limited number of proteins that can attach to each nanoparticle. A meta-analysis of protein corona studies involving 1702 nanoparticle systems shows the variability in protein identification across different materials; notably, silica and gold nanoparticles, often cited in literature, show strikingly different binding capacities compared to liposomes or polystyrene particles, emphasizing the need for material-specific optimization[5,32,33]. The complexity of protein corona analysis stems from a highly interconnected set of variables that influence the final proteomic output[32]. The number of identified proteins is primarily dictated by the physicochemical properties of the nanoparticle, such as its size, surface charge, and curvature, which determine the initial "synthetic identity."[6,34] However, this is further modulated by the biological source and its pre-analytical history, including processing methods, storage duration, and the specific anticoagulants used such as heparin, EDTA or citrate[35]. Beyond the sample itself, the incubation dynamics, including temperature and duration, govern the competitive adsorption of proteins, while the rigor of isolation and purification techniques determines the boundary between the pure corona and protein aggregates/contamination[36]. Current isolation techniques are largely limited to centrifugal or magnetic forces; however, alternative separation techniques such as size-exclusion chromatography, asymmetric flow field-flow fractionation (AF4), or affinity-based capture offer potential avenues to improve purity and coverage[37,38]. As extensively discussed in our prior publications, optimizing these protein corona collection methods and standardizing comprehensive workflows are critical steps toward achieving reproducible and insightful results[15,36,37,39,40]. Finally, the depth of the identified proteome is heavily dependent on the analytical pipeline, specifically the sensitivity of the mass spectrometry hardware and the specific bioinformatic software and algorithms used to process raw data and assign protein identities. Thus, the protein corona is not a fixed entity but a variable fingerprint shaped by the entire experimental workflow[36].

To increase plasma scavenging, three major strategies have been developed. The first approach is multi-nanoparticle arrays which uses diverse nanoparticles (called 'sensor arrays') with distinct physicochemical properties[5,41]. Each engineered nanoparticle type, designed with distinct characteristics, leads to different sets of plasma proteins adsorbed onto the nanoparticles. This strategy allows for the capture of a more diverse range of proteins. Therefore, the use of a protein corona formed on diverse engineered nanoparticles in plasma proteomics has advanced the field, enabling the quantification of several thousands of proteins[33,42].

The second approach is environmental modulation where, in addition to employing various types of nanoparticles, variations in temperature[43,44] and pH[45] can influence the composition of the protein corona, providing another avenue for enhancing plasma proteome coverage. This is primarily because changes in temperature or pH can alter the conformation of plasma proteins, thereby affecting their interactions with nanoparticles. For instance, studies examining the effect of temperature exposure, ranging from 5 to 45 °C, on the formation of protein coronas on magnetic nanoparticles have demonstrated significant compositional changes[46]. These variations can be strategically manipulated to form a protein corona sensor array, further improving the depth and breadth of protein capture.

The third strategy is expanding plasma proteome coverage by rationally reprogramming the protein corona by spiking small molecules such as lipids, metabolites, vitamins, and synthetic drugs into the plasma prior to nanoparticle interaction[47,48]. In this approach, small molecules are selected or engineered to bind highly abundant plasma proteins, particularly human serum albumin, at defined functional domains such as fatty acid-binding pockets and Sudlow sites I and II. Binding of these small molecules can alter the physicochemical properties of the resulting protein/small molecule complex, including surface charge, hydrophobicity, conformation, and overall nanoparticle affinity. As a result, dominant plasma proteins such as albumin may exhibit reduced adsorption on the nanoparticle surface, decreasing their competitive binding of available sites. For example, compounds such as phosphatidylcholine can occupy hydrophobic pockets on albumin, modifying its interaction profile and attenuating its dominance in corona formation. This creates more availability of the nanoparticle surface for other plasma proteins, including lower-abundance species, thereby increasing proteomic depth[47]. A critical advantage of this strategy over traditional depletion methods is that it does not require physical removal of highly abundant proteins from the sample. Instead, it modulates how these proteins interact with nanoparticles during corona formation, preserving the overall plasma matrix while reducing the extent to which abundant proteins monopolize nanoparticle surfaces. This strategy is both highly tunable and scalable; by using a curated panel of diverse small molecules, researchers have successfully identified over 6500 proteins from a single human plasma sample, a gain of more than 2600 unique proteins, including FDA approved biomarkers, compared to enrichment with nanoparticles alone[48]. In addition to enhancing the depth of the plasma proteome, spiking small molecules based on their types and specific interactions with plasma proteins can selectively enrich particular protein subsets[48]. For example, adding cholesterol to plasma can increase the enrichment of apolipoproteins on nanoparticle surfaces[49,50]. Thus, both the identity and concentration of the small molecule should be optimized and tailored to the intended analytical application, with the goal of tuning high-abundance protein–nanoparticle interactions while expanding access to a broader and more informative plasma proteome.

Top-down proteomics

The advantages of utilizing the protein corona in plasma proteomics can be further amplified by adopting top-down proteomics (TDP) for proteoform-specific analysis[51–53]. Traditionally, most research in this area has centered on bottom-up proteomics (BUP), which analyzes peptides derived from enzymatic digestion of proteins. Although BUP allows for the sensitive detection of low-abundance proteins, it suffers from peptide-to-protein inference problems, lacking specific

information of the intact proteoforms arising from genetic variation, alternative splicing, and post-translational modifications (PTMs)[54]. However, starting in 2024, the field of protein corona-aided plasma proteomics began leveraging TDP, which focuses on proteoforms[55–59]. TDP enables the examination of full-length protein sequences and combinations of PTMs[51,54,60–63], providing a landscape of exact forms of protein molecules ("proteoforms") existing in the protein corona, advancing our understanding of nanoparticle-biosystem interactions, and enhancing biomarker discovery capabilities. TDP analysis of the protein corona revealed that one protein biomarker could have over 100 different proteoforms due to sequence variations and PTMs, whereas BUP can only offer the identification of protein groups[55,56,59]. TDP can provide unprecedented accuracy in defining the proteoforms in the protein corona proteome. The protein-corona-aided TDP outperformed the typical TDP approach regarding the measurement of proteoforms of relatively low-abundance proteins in human plasma, advancing disease biomarker discovery[57,59].

A critical consideration in corona proteomics is the potential for conformational artifacts. Nanoparticle binding can induce protein unfolding; for instance, cross-linking mass spectrometry has shown significant proteolyzable crosslinks, suggesting random coil conformations upon protein binding[64]. Careful controls are necessary to distinguish genuine PTMs and native proteoforms from adsorption-induced artifacts[36].

Different proteoforms from the same gene can have divergent biological functions[60,61,65,66]. Proteoforms from the same gene due to RNA alternative splicing ("protein isoforms") have drastically different interactomes, indicating distinct biological functions[45]. Single mutation of the phosphatase and tensin homolog (PTEN) tumor suppressor protein creates different proteoforms, changing its function from suppressing tumors to driving tumors[67]. Histone proteoforms due to combinatorial PTMs modulate gene expression and disease progression[68,69]. A novel KRAS4b proteoform biomarker for human colorectal cancer (CRC) was discovered, and connections between a specific mutation (Gly13Asp) and the proteoform of KRAS4b were revealed[70]. CRC cells have a significant transformation in proteoform profiles (including well-known CRC-related pathways) after metastasis, and different proteoforms of the same gene show opposite expression profiles between metastatic and non-metastatic CRC cells[61]. Phosphorylated sarcomeric proteoforms were determined as novel biomarkers of hypertrophic cardiomyopathy[71]. Proteoforms can strongly influence the formation of the protein corona on the surface of nanoparticles and lead to significant changes in nanoparticle–cell interactions[72], signaling the importance of evaluating the protein corona in a proteoform-specific manner. Different proteoforms of human serum albumin (HSA) change the physiochemical properties of HSA and substantially influence its binding affinity to nanoparticles and the thickness of the protein corona, significantly impacting on nanoparticle-HeLa cell interactions and nanoparticle uptake[72]. However, proteins captured within the nanoparticle protein corona may still be too complex for TDP; thus, further development of protein separation techniques[51,55,73,74] is needed to bridge such a gap.

For the development of more robust and effective nanoparticle-based diagnostic systems, precise characterization of proteins and proteoforms within the protein corona is crucial—something that can be achieved through the combined use of BUP and TDP. In a recent study, the integration of TDP and BUP approaches was performed, for the first time, in protein corona research[75]. TDP analysis of the protein corona on polystyrene nanoparticles identified 3505 proteoforms spanning 344 genes in human plasma samples. Concurrently, BUP analysis revealed 4570 protein groups, 45,790 peptides, and 23,632 modified peptides from the same samples. The integration of these extensive datasets enhances proteoform characterization, with approximately 35% of identified proteoforms containing mass shifts being more accurately characterized, thereby producing a more detailed proteoform landscape of the protein corona. This combined approach surpasses the capabilities of individual techniques and significantly improves our understanding of proteoform diversity within the corona.

Moving beyond correlation: 'actual causality' in corona analysis

Recent advancements in machine learning and artificial intelligence (AI) have begun to permeate the field of protein corona research[7]. For example, machine learning has been used to predict protein corona profiles on the surfaces of nanomaterials based on amino acid sequences and DNA[76,77]. However, to date, the application of machine learning in plasma proteomics has focused on non-protein corona analysis[2,78–82]. Machine learning-based approaches for biomarker discovery primarily rely on correlation to interpret data and draw conclusions, identifying associations without establishing direct cause-and-effect relationships between variables. This emphasis on observation can lead to misleading connections, where co-occurrence does not imply causation[83].

To address this limitation, the concept of actual causality, introduced by Halpern and Pearl[84,85], has been used in the field of protein corona research[83], with its first application observed in cardio-oncology[86]. For example, AI analyses of protein corona profiles in patients with metastatic and non-metastatic prostate cancer, with or without cardiac atherosclerosis, identified 22 proteins strongly associated with either atherosclerosis or metastatic prostate cancer[86]. By combining AI with causal inference methods, only thromboxane A synthase 1 (TBXAS1) emerged as a primary causal factor linked to both conditions[86]. TBXAS1 plays a crucial role in promoting platelet aggregation, vascular smooth muscle cell proliferation, endothelial dysfunction, and thrombosis[87–89]. Remarkably, identifying TBXAS1 as a key factor in metastatic cancer using AI and causal analysis was validated by an independent large clinical study, which showed that aspirin—by inhibiting thromboxane A2 synthesis (TBXAS1's precursor)—reduces platelet-mediated thrombosis and prevents cancer metastasis[90].

While promising, implementing actual causality in protein corona studies presents practical challenges. This approach requires larger sample sizes than typical proteomics studies to power the causal algorithms, and necessitates rigorous validation of the "counterfactual" scenarios inherent in causal logic. Experimental designs must be adapted to not just identify biomarkers, but to perturb the system (e.g., using knockout models or specific inhibitors like aspirin in the TBXAS1 case) to validate the predicted causal links.

Critical challenges: the issue of protein aggregates and extracellular vesicle contamination

A pressing challenge in plasma proteomics is the risk of protein contamination. A source of such contamination arises from protein aggregates[91], extracellular vesicles (EVs)[92,93] and cells present in plasma prior to their interaction with nanoparticles. Magnetic nanoparticles, widely used in industrial plasma proteomics, facilitate efficient extraction and washing through external magnetic fields, which enables automation. However, magnetic separation can inadvertently contribute to contamination[91]. The aggregation of magnetic particles under magnetic fields can trap non-specific proteins, including those not genuinely associated with the protein corona, leading to impurities that skew proteomic results. Addressing these contamination issues is essential to improve the accuracy, specificity, and reproducibility of proteomic analyses[94]. Particularly in biomarker discovery, distinguishing between soluble plasma proteins and those derived from EVs is vital. The extensive molecular and structural heterogeneity of EVs presents significant opportunities for fundamental biological insights and therapeutic advancements, yet this same complexity introduces substantial challenges throughout the EV research pipeline[95].

Superparamagnetic nanoparticle-based separation methods are particularly prone to co-isolating a broad spectrum of EVs, because strong magnetic forces that promote the formation of magnetic aggregates are also capable of entrapping EVs.

Recent literature highlights the complexity of distinguishing EV-associated proteins from soluble biomarkers[95,96]. While some studies suggest high overlap, caution is needed when inferring EV enrichment based solely on databases that aggregate data from diverse cell types[95,96]. However, empirical evidence specifically in plasma contexts suggests that background contaminants—such as EVs and platelets—can inflate protein identifications in nanoparticle-based workflows. A recent study also supported this hypothesis by comprehensively comparing the number of identified proteins, their quantity, and protein groups across neat plasma, EV-enriched plasma (through centrifugation), and plasma processed with three advanced proteomic workflows—Proteograph (Seer), Mag-Net (ReSynBio), and ENRICHplus (PreOmics)[97]. The selectivity of each method for enriching EV protein cargos was also evaluated. Among the identified proteins in each plasma sample, 1200 protein groups were common to all enrichment methods as well as EV-enriched plasma. Data analysis shows that neat plasma shared 97% similarity with the enriched samples. Notably, of 12 EV-derived proteins examined, 10, 7, and 8 markers were identified by Proteograph, ENRICHplus, and Mag-Net, respectively. This supports the premise that nanoparticle-based enrichment, particularly using magnetic beads, may unintentionally co-isolate EV populations.

Our recent cryo-transmission electron microscopy analysis exposed a significant confounding factor in standard isolation techniques: both centrifugation and magnetic separation extensively co-isolate EVs along with the nanoparticle protein corona[96]. We quantified this by comparing proteomic outcomes from polystyrene nanoparticles and superparamagnetic beads incubated in standard human plasma versus plasma depleted of EVs using a 37-epitope immunoaffinity panel. The data were striking: EV depletion caused a threefold drop in identified proteins for polystyrene nanoparticles (from ~4500 to ~1600) and a twofold drop for magnetic beads (from ~1700 to ~900)[96].

Beyond mere quantification, the composition of the corona shifted fundamentally. In standard plasma, the top-ranked proteins were intracellular cytoskeletal components, consistent with EV contamination. Conversely, in EV-depleted plasma, the profile accurately reflected genuine soluble plasma adsorbates, such as apolipoproteins and complement factors[96]. This distinction is critical because soluble plasma proteins and EV-encapsulated cargo represent fundamentally different biological information. Soluble proteins typically reflect systemic physiological states and liver function, whereas EV proteins offer a snapshot of the intracellular processes from their specific tissue of origin[95]. Conflating these distinct pools obscures the true origin of a biomarker, potentially leading to misinterpretations of disease mechanisms and hindering the development of targeted therapeutics[95].

These findings reveal a notable trend: proteomic strategies employing superparamagnetic separation systems tend to include a higher proportion of EV-derived proteins. This conflation of soluble and vesicular fractions can obscure the origins of biomarker signals, confounding data interpretation and compromising the accuracy of identification.

To ensure data integrity, it is essential to also develop workflows that discriminate between plasma solutes and vesicular components. This is not merely a task of "cleaning" the sample; EV-based biomarkers are already in clinical trials, and thus, there is potential synergy in analyzing both fractions. However, realizing this potential requires the methodological capacity to either purposefully integrate or strictly separate these signals to avoid data conflation. Several mitigation strategies have been proposed to achieve this: ultracentrifugation serves to pre-clear plasma by pelleting EVs prior to nanoparticle incubation[98]; immuno-adsorption utilizes EV-specific magnetic beads to remove vesicles during pre-processing[96]; and asymmetric flow field-flow fractionation (AF4) offers a high-resolution approach to isolate EVs from soluble proteins based on their distinct hydrodynamic sizes before any nanoparticle interaction occurs[99].

Industrial progress and future outlook

The capacity of protein corona technology to enhance plasma proteome coverage has catalyzed significant industrial translation and commercial interest. Driven by the critical demand for deeper proteomic analysis, the industry has prioritized the development of automated, scalable workflow, that standardize the interaction between plasma and nanoparticles[5,33]. These innovations are crucial for transitioning proteomics from small-scale academic studies to large-cohort clinical applications, where reduced preparation time and high reproducibility are critical. Continued innovation is needed in the selection and design of nanoparticle systems for automated workflows. Choosing and engineering nanoparticles involves balancing throughput, depth of coverage, and signal purity. Ultimately, although commercial magnetic platforms provide an accessible "turn-key" option for large-scale studies, the optimal solution is context dependent and requires trade-offs between the desired discovery depth and the specific biological fraction under investigation.

This technological maturation aligns with broader market dynamics; the proteomics sector is projected to exceed US$130 billion by 2035[100]. Currently, growth is anchored in the consumables and reagents segment, fueled by the uptake of automated systems, specialized affinity reagents, and protein-capturing nanoparticles. However, the expansion of plasma proteomics now permeates the entire value chain—spanning instrumentation, bioinformatics startups, and pharmaceutical companies integrating these tools into drug target discovery pipelines.

The future of protein corona research in plasma proteomics is expected to focus on six key strategies (Fig. 3): (i) establishing standardized proteomics workflow protocols through collaboration with standardization organizations; (ii) developing strategies to further inhibit the attachment of highly abundant proteins to the surfaces of nanoparticles while releasing their "passenger" proteins; (iii) discriminating soluble plasma proteins from those derived from EVs and other vesicular components; (iv) developing sample processing workflows that offer simultaneous multi-omic scavenging of biological samples[101], resulting in more powerful multi-dimensional (e.g., different combinations of proteo-geno-lipido-metobolo-mic) analyses; (v) integrating TDP and BUP to enhance the identification of proteins and proteoform biomarkers[75]; and (vi) incorporating a combination of AI and causality principles to improve the accuracy and robustness of proteomics analyses and biomarker discovery[86].

In summary, protein corona methodologies represent a transformative leap in our ability to mine the "deep proteome" for low-abundance biomarkers. By coupling these material science innovations with advanced analytical techniques like TDP and BUP, the field is poised to overcome historical bottlenecks in sensitivity and specificity. Ultimately, the convergence of standardized automation, nanoparticle engineering, and AI-driven analysis brings us closer to a "universal," mass spectrometry-based blood test[102,103]. Such a tool—capable of continuous, cost-effective health monitoring—would fundamentally reshape healthcare, enabling a shift from reactive treatment to proactive, personalized medicine for conditions ranging from early-stage oncology to neurodegenerative disease. However, significant hurdles remain for clinical translation. Most biomarkers fail validation. Rigorous orthogonal confirmation, inter-species validation, and success in independent cohorts are pre-

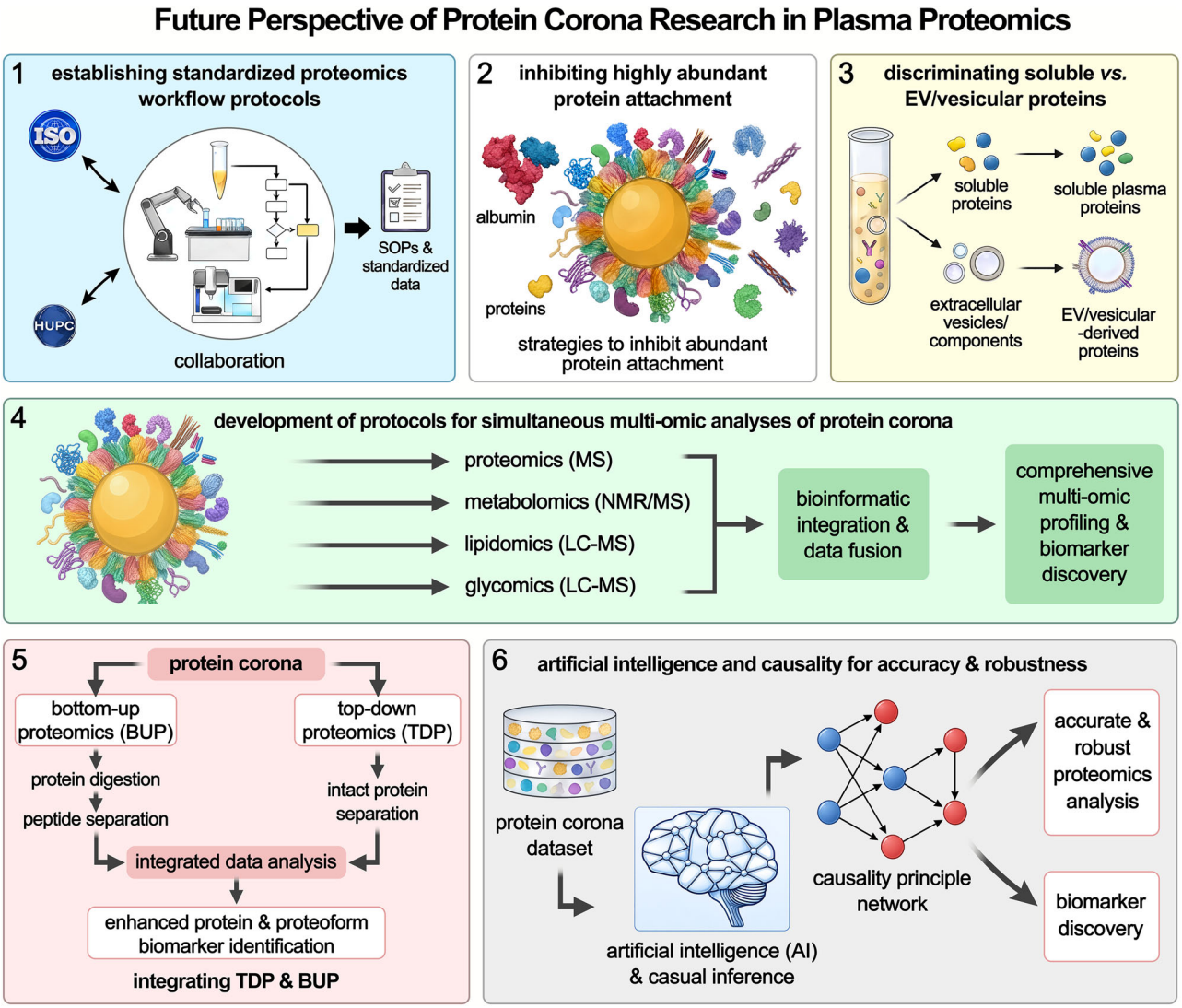

Fig. 3 | Future perspective of protein corona research in plasma proteomics. The six key strategies of improving the efficacy of the protein corona in improving the depth of plasma proteomics.

requisites before any corona-based diagnostic can receive regulatory approval.

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Author contributions

A.A.S., B.G., B.B., L.S., Y.G., D.R.N., V.S., K.K., B.B., C.J.M., F.C. and M.M. contributed to conceptualization, literature review, drafting the original manuscript, and reviewing the final version. FC and MM led the conceptualization and supervised the manuscript preparation. All authors reviewed and approved the final version of the manuscript.

Competing interests

M.M. is co-founder and director of the Academic Parity Movement www.paritymovement.org (a non-profit organization dedicated to addressing academic discrimination, violence and incivility) and co-founder of Targets Tip, AlbuDerm, and XProteome Inc., and receives royalties/honoraria for his published books, plenary lectures, and licensed patents. FC is co-founder of Messenger Bio Pty Ltd. A.A.S. and B.B. are co-founders of XProteome Inc. The authors declare no conflicts of interest.

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