Exploiting the Nanoparticle–Protein Corona for Advanced Biomedical Applications

Emma Cooper[1], James C. Reynolds[1] and Amanda Kate Pearce[1]*

[1]Department of Chemistry, Loughborough University, Loughborough, LE11 3TU

Email: a.pearce@lboro.ac.uk

Impact Statement

Nanoparticles have significant potential to improve medicines, diagnostics and other healthcare technologies, but their behaviour in the body can differ substantially from how they are designed or perform in the laboratory. This is largely because proteins from biological fluids rapidly attach to nanoparticle surfaces, forming a protein corona that changes how the nanoparticles interact with cells, tissues and the immune system. Understanding and controlling this process is therefore important for translating nanomaterials into effective and reliable biomedical technologies.

This Review highlights a shift in how the protein corona can be viewed: rather than being an unavoidable barrier to nanoparticle performance, it can potentially be used as a functional biological interface. We examine how nanoparticle properties can influence corona formation and how the resulting protein layer can be characterised, exploited and deliberately engineered for applications including targeted drug delivery, disease diagnosis, biosensing, molecular recognition and nanotoxicology. This approach could enable nanoparticles with improved therapeutic efficacy, more accurate diagnostics, and enhanced safety.

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI.

10.1017/S2978170126000051

This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is unaltered and is properly cited. The written permission of Cambridge University Press must be obtained for commercial re-use or in order to create a derivative work.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Realising these benefits at scale will require greater standardisation of protein-corona analysis, reproducible manufacturing and characterisation of nanoparticles, and improved understanding of how coronas evolve across different biological environments and between individuals. Integration of advanced analytical methods, computational modelling and rational materials design will be important for translating laboratory findings into robust and clinically relevant technologies. By bringing together emerging approaches to understand and engineer the nanoparticle–protein interface, this Review highlights opportunities to develop more predictable, effective and biologically informed nanomaterials for future healthcare applications.

Abstract

Over the past decades, nanoparticles (NPs) have emerged as powerful tools for a broad range of biomedical applications. However, upon exposure to biological fluids, the adsorption of biomolecules, particularly proteins, rapidly generates a protein corona (PC), creating a new biological identity that governs NP behaviour and performance in vivo. As PC formation is inevitable, research has increasingly moved beyond mitigating its effects, towards understanding how NP-PC complexes can be harnessed for biomedical advantage. Applications spanning biosensing, molecular recognition, nanotoxicity and drug delivery demonstrate the potential of the PC to actively enhance NP functionality rather than simply impede it. Although the formation, composition, and biological consequences of the PC, as well as the challenges of NP-PC characterisation and clinical translation, have been extensively reviewed over the past decade, the deliberate exploitation of the PC as a functional design element remains relatively underexplored. This review addresses this gap by examining the emerging biomedical applications of NP-PC complexes and highlighting how engineering NPs to direct PC formation can unlock new opportunities for improved performance and targeted functionality.

Keywords: nanoparticles; protein corona; nanomedicine; protein-nanoparticle interactions; surface engineering

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

1. Introduction

1.1 Nanoparticles in biomedicine

The rapid development of nanotechnology over recent decades has enabled exciting advances across multiple disciplines, particularly in medicine, where nanoscale materials have driven innovations in targeted drug delivery, diagnostic imaging, biosensing, and regenerative therapies. Within these applications, NPs offer several unique advantages including high surface-area-to-volume ratios, tuneable physicochemical properties, and readily functionalisable surfaces, allowing precise control over biological interactions and cargo delivery.[1] These features facilitate efficient cellular uptake via endocytic pathways, and improved penetration across tissues and biological barriers, overcoming limitations of conventional delivery methods.[2] Their high surface area-to-volume ratio improves drug loading capacity and enables dense surface functionalisation with targeting ligands or stealth coatings for increased biocompatibility and bioavailability.[3] In addition, the diversity of NP morphology, chemical composition, size, hydrophobicity, surface chemistry and electrostatic charge provides versatile platforms for designing tailored solutions to complex biomedical challenges.[4,5]

NPs can be broadly classified into three major categories:[6] organic NPs, including polymeric and lipid-based systems; inorganic NPs, such as metallic and quantum dots; and carbon-based NPs, including single-walled carbon nanotubes (SWCNTs). Owing to their highly tuneable physicochemical properties, these nanomaterials can be rationally engineered to meet the specific requirements of diverse biomedical applications.[7] Table 1 presents selected literature examples illustrating the diversity of nanoparticle materials investigated for biomedical applications, spanning organic, polymeric, inorganic and carbon-based systems. These examples were chosen to highlight the broad range of biological functions that nanoparticles can support, from drug delivery and disease diagnostics to antimicrobial activity, cancer therapy and biosensing. demonstrating the wide range of nanomaterial classes used in medicine, and their varied biomedical applications including diagnosis and treatment.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Table 1: Overview of NP types and examples of biomedical applications.

Nanomaterial Classification	Material	Biological activity	Biomedical application
Organic NPs	Liposomal Irinotecan	Drug delivery	Acute Lymphoblastic Leukaemia [8]
Organic NPs	PEGylated antibody fragment	Drug delivery	Crohn's disease, Rheumatoid Arthritis, Psoriatic Arthiritis[8]
Polymeric NPs	Poly(styrene)-block-poly(acrylic acid)	Disease diagnosis via computed tomography	Diagnosis of myocardial infarction[9]
Inorganic NPs	Silver	Antibacterial and antibiotic	Antimicrobial agent against *E.coli* and *S. Aureus*[10]
Inorganic NPs	Zinc oxide	Generate RSO and oxidative stress	Ovarian cancer[4]
Carbon-based NPs	Gd- doped graphene quantum dots	Radiotherapy and cancer therapy	T1 contrast agent and radiosensitisers[11]
Carbon-based NPs	SWCNT	Biosensing and imaging	Reversible mediator-free NIR glucose monitor[12]

1.2 Protein corona

Upon exposure to biological fluids, NPs rapidly interact with surrounding biomolecules, particularly circulating proteins, owing their high surface energy.[13–15] The surrounding proteins form a PC via electrostatic, hydrophobic, hydrogen-bonding, and π-π stacking interactions. This process impacts the NPs physicochemical properties, biological presentation, and ultimately their efficacy towards their target application.[16–18]

The formation of the protein corona is governed by both kinetics (which determine the rates of protein adsorption and exchange), and thermodynamics (which influence the energetic favourability of protein binding). Protein-NP association can be considered through two complementary approaches: physical association and colloidal association. Physical association describes the molecular interactions driving protein adsorption, including electrostatic, Van Der Waals, and hydrophobic interactions. In contrast, colloidal association describes the resulting changes in NP properties, such as surface potential hydrodynamic size, that arise from corona formation.[19] Initially, abundant proteins rapidly and reversibly adsorb to the NP surface, forming the 'soft

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

corona' (SC), whose composition is largely influenced by adsorption kinetics. Over time, these proteins are dynamically displaced by less abundant proteins with higher binding affinities, resulting in the formation of the more stable 'hard corona' (HC), which comprises more tightly bound proteins and is increasingly influenced by thermodynamic factors. The more abundant low affinity proteins form a more diffuse outer soft corona layer, see Figure 1.[20] Proteins within the HC often undergo conformational changes upon adsorption, whereas proteins associated with the SC generally retain their native structure.[21] The PC comprises of a complex network of proteins directly bound to the NP surface, alongside protein-protein interactions within the corona layer.[22] Owing to its greater stability under dynamic biological conditions, the HC is typically regarded as the dominant determinant of NP biological identity and is consequently the primary focus of NP-PC characterisation studies.[23]

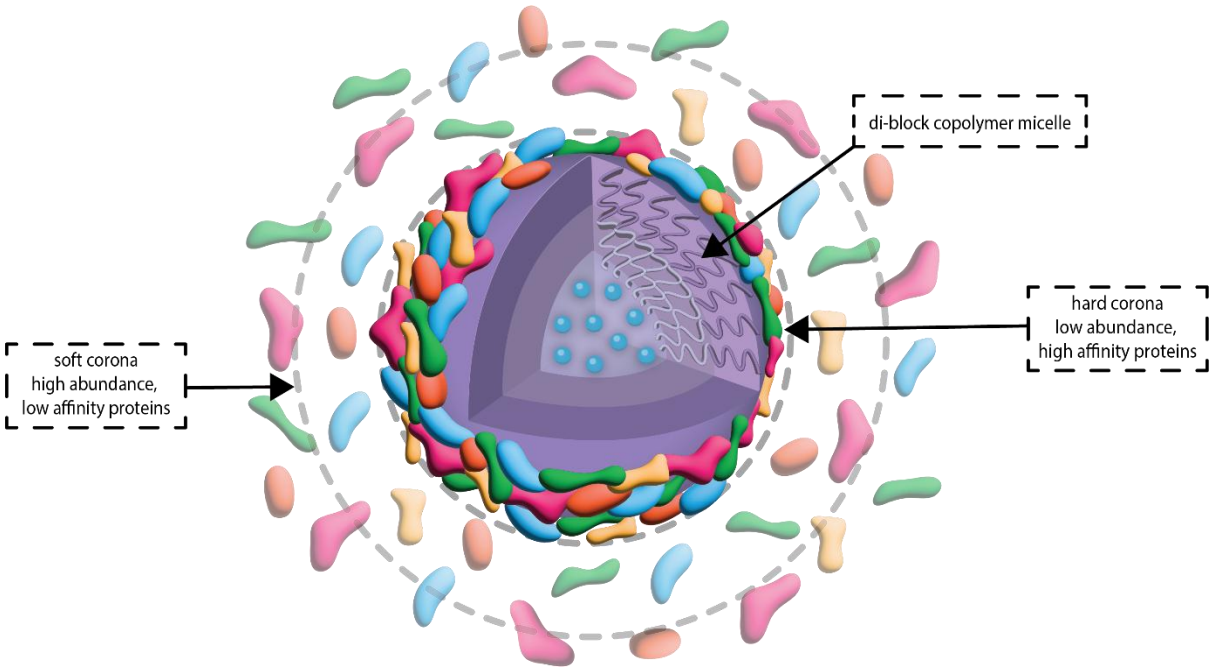


Figure 1. Schematic representation of a typical NP-PC complex, highlighting the differences in affinities between the proteins within the soft and hard corona, and non-associated surrounding proteins.

Although reports describing the use of NPs in diagnostic imaging, biosensing, drug delivery, molecular recognition and other biomedical applications have grown exponentially over recent decades, their clinical translation has remained comparatively slow.[24,25] A major challenge is the discrepancy between the engineered physicochemical properties of NPs and their biological identity following PC formation in vivo.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Consequently, understanding the factors that govern PC formation and composition is increasingly recognised as essential for the rational design of safer, more effective nanomedicines with improved translation potential.[26,27]

Over the past decade, approximately 100 reviews have examined the relationships between NP physicochemical properties, PC composition, and corona formation kinetics. Selected highly cited reviews of particular relevance to this work are highlighted elsewhere.[27–30] Collectively, these studies emphasise the critical role of the PC in dictating NP behaviour within biological environments and its influence on therapeutic performance.[31] However, the existing literature has predominantly viewed the PC as a barrier to be characterised, controlled, or mitigated. Comparatively little attention has been given to the deliberate exploitation of NP–PC complexes as functional entities that can enhance biomedical performance or enable entirely new therapeutic applications.

This review addresses this emerging opportunity by critically examining biomedical applications in which PC formation is not merely tolerated but is paramount to achieving application efficacy. We first discuss the challenges associated with characterising NP-PC composition and behaviour, before exploring how engineered NP-PC complexes are being leveraged in areas such as biosensing, molecular recognition, targeted drug delivery and nanotoxicity. By consolidating these developments, we aim to provide a more positive and application-focused perspective on the PC, highlighting how its rational characterisation and engineering may unlock new opportunities for targeted and clinically relevant nanomedicines.

2.1 NP physicochemical properties affect PC formation

NP physicochemical properties, including size, shape, composition, surface chemistry and charge, play a central role in determining protein adsorption and, consequently will influence the composition of the PC (Figure 2).[32] For comprehensive discussions of how NP properties influence PC formation, readers are referred to the reviews by Park *et al.* and Bilardo et *al.*[28] Here, we provide a brief overview of the key relationships between NP chemistry and PC composition, as understanding how NP design governs PC formation if critical for improving the predictive value of *in vitro* studies and bridging the translational gap to *in vivo* systems.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

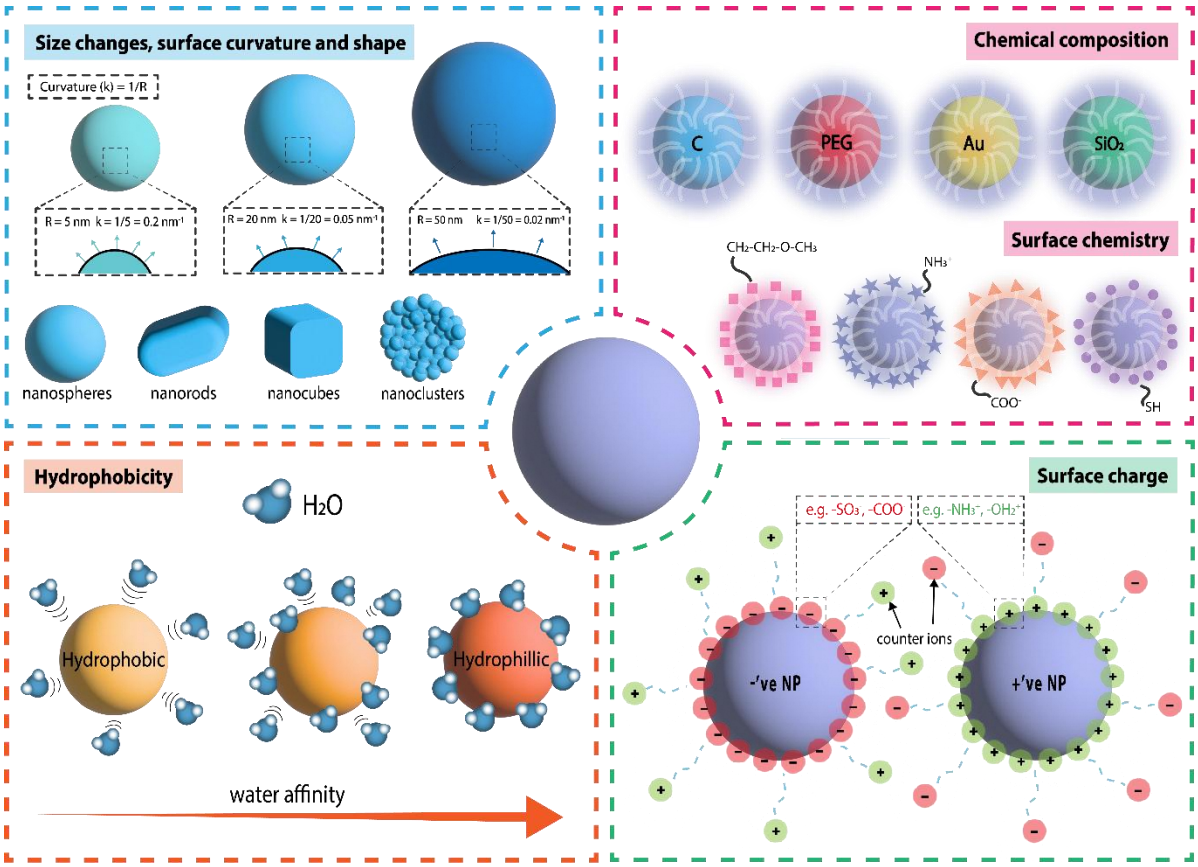


Figure 2. Schematic of the various physiochemical properties of NP that can influence the composition and formation of the PC.

The surface curvature and size of NPs influence both protein adsorption behaviour and the properties of the resultant corona.[33] Highly curved spherical NPs impose steric constraints that favour the adsorption of smaller proteins, while also reducing protein-protein interactions and limiting protein conformational changes relative to flatter surfaces. This behaviour is attributed to the reduced NP-protein contact area associated with increased curvature, which restricts protein adsorption and packing at the NP surface.[22,34]

NP size can further influence protein binding affinity and corona organisation. Lacerda *et al.* demonstrated that both the binding affinity (K) and degree of cooperativity (Hill coefficient, *n*) of protein adsorption depend on NP size and the identity of the protein, with larger gold NPs generally exhibiting higher protein binding affinities.[35] While *n* was found to be protein-dependent, several proteins exhibited reduced cooperativity on larger NPs, reflecting changes in protein–protein interactions at the NP surface. Furthermore, for gold NPs smaller than 50 nm, the thickness of the PC increased as NP

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

size increased, suggesting that reduced surface curvature facilitates greater protein accumulation at the NP interface. Marichal *et al.* similarly observed an increase in PC thickness with decreasing NP curvature for silicon NPs, however, unlike studies using simplified protein systems, they found that NP size had little effect on the overall corona composition in complex biological media.[36] These findings suggest that curvature may primarily influence the structural organisation and thickness of the corona, whereas its composition is additionally governed by competitive protein adsorption within the surrounding biological environment.

However, the relationship between NP curvature and protein adsorption is not always straightforward. Lin *et al.* reported that 80 nm polystyrene NPs adsorbed significantly more protein than 26 nm and 200 nm NPs, suggesting that protein adsorption reflects a balance between multiple size- and curvature-dependent factors rather than a simple size-dependent trend.[37] This complexity is further demonstrated *in vivo* by Garcia-Alvarez *et al.,* who found that 40 nm gold nanostars adsorbed approximately nine-fold less protein than 70 nm nanostars, yet displayed substantially greater corona diversity, containing 88.8% more distinct proteins.[38] Similarly, Hu *et al* showed that Fe_3O_4 NPs of different sizes (30, 200 and 400nm) generated distinct PC compositions and abundances, further demonstrating the size-dependent nature of NP-protein interactions.[39] Collectively, these studies demonstrate that NP size and surface curvature influence both the quantity and organisation of the PC, but their effects on corona composition are highly context- and protein-dependent.

NP surface charge is also a key determinant of PC composition and abundance. Positively charged NPs generally adsorb higher levels of proteins due to favourable electrostatic interactions with circulatory proteins, which typically carry an overall negative zeta-potential (ZP). In contrast, negatively charged NPs often exhibit reduced protein adsorption due to electrostatic repulsion.[40,41] However, in biological media, these interactions can be shielded by ionic screening and competitive adsorption, meaning that a simple clear correlation between ZP and protein binding isn't always observed. Consequently, both positively and negatively charged NPs can form substantial coronas depending on the biological environment.[42] Importantly, positively charged NPs are more frequently associated with enhanced adsorption of opsonins, including

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

immunoglobulins and complement proteins, leading to increased immune recognition and accelerated clearance.[43] Thus, although surface charge can strongly influence the quantity and identity of adsorbed proteins, its effects are highly dependent on the surrounding biological environment and should be considered alongside other NP surface properties.

NP surface chemistry, particularly their degree of hydrophobicity, is another important factor governing PC formation by influencing both protein abundance and composition. In general, more hydrophobic surfaces tend to promote greater protein adsorption due to stronger hydrophobic interactions with serum proteins.[44] For example, Yu *et al*. demonstrated that NPs functionalised with an undecane hydrophobic ligand adsorbed 2.1–fold more proteins than those coated with a tri-ethylene glycol hydrophilic ligand.[45] However, hydrophobicity alone is not a universal predictor of PC formation. In contrast, Monopoli *et al*. reported greater protein absorption on hydrophilic silica NPs than on hydrophobic polystyrene NPs, suggesting that additional factors, including surface charge, chemistry, and protein competition within complex biological media, can outweigh hydrophobic effects.[46] Hydrophobicity therefore represents an important, but highly context-dependent, driver of PC formation.

Specific surface functional groups can further direct the adsorption of individual protein classes.[47] Strongly basic groups that become positively charged at physiological pH, such as $–NH_2$, can promote adsorption of proteins with isoelectric points greater than 5.5, such as IgG.[48] For example, Gerasimovich *et al* demonstrated that functionalising polystyrene NPs with $–NH_2$ or $–SO_3$ groups resulted in distinct corona profiles, with apolipoproteins and complement factors among the predominant adsorbed proteins.[49] These findings demonstrate that surface functionalisation can provide a route towards deliberately directing PC composition rather than simply altering the overall quantity of protein adsorption.

Other physicochemical properties, including NP shape and surface roughness, can also influence PC formation by altering protein accessibility, adsorption kinetics and interfacial organisation. Collectively, these studies demonstrate that PC formation arises from the interplay of multiple NP physicochemical properties rather than any single

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

dominant parameter, highlighting the need to consider NP design as an integrated strategy for controlling corona composition and, ultimately, biological function.

2.2 PC impact on NP application efficiency

Protein adsorption fundamentally alters NP properties, creating a new biological identity that can obscure the behaviour originally defined by their engineered physicochemical characteristics. As a result, predicting NP performance *in vivo* becomes increasingly challenging, with significant implications for application efficiency and clinical translation. Changes in key properties such as size, surface chemistry, and charge following PC formation can compromise circulation time, reduce targeting specificity, and trigger unintended immune recognition. These effects can subsequently alter NP biodistribution, cellular uptake, toxicity and clearance, ultimately influencing therapeutic outcomes and biological responses.[17,20] The highly dynamic and complex nature of the PC further complicates its prediction, making it difficult to reliably anticipate NP behaviour across different biological environments.

Cytotoxicity

PC formation is frequently associated with reduced NP cytotoxicity by shielding the underlying NP surface and limiting direct interactions with cellular membranes.[50,51] For example, Ge et al. demonstrated that single-walled carbon nanotubes (SWCNTs) coated with multiple layers of bovine fibrinogen (BFG) exhibited significantly lower *in vivo* toxicity compared with uncoated SWCNTs, as the protein coating masked the nanotube surface and reduced adverse cell interactions.[52] Similarly, adsorption of serum proteins onto cationic gold NPs (AuNPs) markedly reduced toxicity towards HeLa cells by screening the positively charged NP surface, thereby decreasing membrane damage and improving biocompatibility.[53] . Coreas *et al*. reported that reduced graphene oxide (rGO) dispersed in sodium cholate (4 mg/mL) (c-RGO) formed a distinct human serum PC that induced greater mitochondrial dysfunction and cytotoxicity than particles dispersed at lower surfactant concentrations (2 mg/mL) (Figure 3) demonstrating that protein absorption does not universally mitigate NP toxicity.[54] These findings demonstrate that the biological consequences of PC formation are governed not only by the quantity of adsorbed proteins, but also by their composition and the resulting NP–protein interface.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

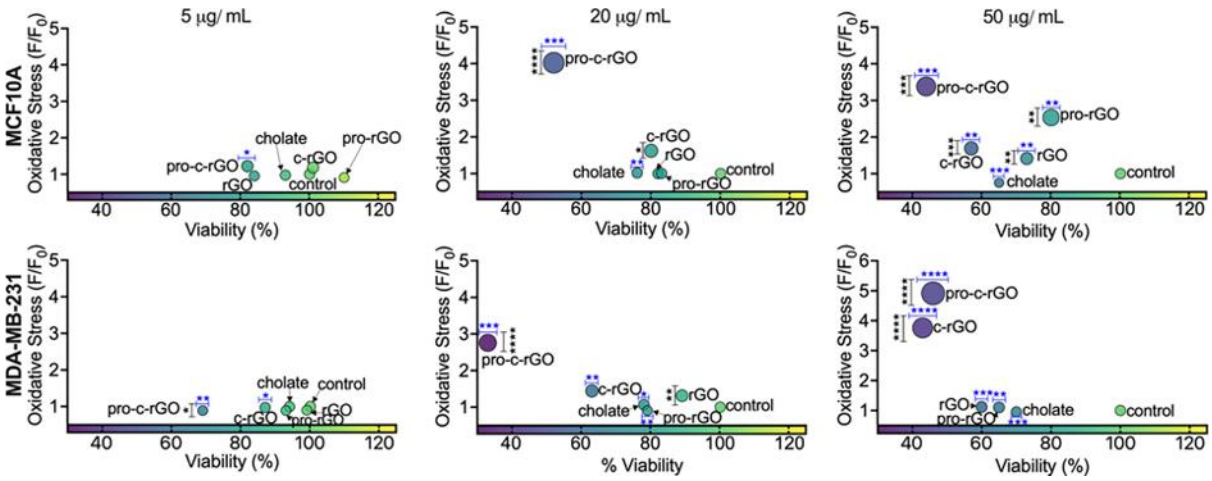


Figure 3. Cell viability and oxidative stress measured in MCF10A (top row) and MDA-MB-231 (bottom row) when exposed to 5, 20, or 50 μg/mL of rGO, protein-rGO, c-rGO or protein-c-rGO for 1 h. Each dot represents the mean of biological triplicates; the color of each dot represents percent viability; increasing size of the dot signifies larger induction of ROS. Reproduced with permission from [54], Copyright (2022) American Chemical Society.

Immune response, clearance and circulation

PC formation can profoundly alter NP interactions with immune cells by modifying cellular uptake pathways, immune recognition, and circulation time. Consequently, the composition of the PC plays a central role in determining NP biodistribution and clearance.[51] Coronas enriched with opsonins, including immunoglobulins and complement proteins, promote macrophage recognition through receptor-mediated phagocytosis, resulting in accelerated blood clearance and reduced therapeutic efficiency.[55] In contrast, enrichment of dysopsonins or other proteins that reduce immune recognition can prolong NP circulation and improve bioavailability.[56,56,57]

PEGylation involves the covalent attachment of polyethylene glycol (PEG) chains to the surface of NPs, creating a hydrophilic steric barrier that can reduce protein adsorption and immune recognition.[57] PEGylation remains the most widely adopted strategy for minimising protein adsorption and immune recognition, with this 'stealth' effect reducing macrophage uptake, prolonging circulation time, and improving pharmacokinetic performance.[58] Accordingly, numerous studies, including those employing poly(lactic-co-glycolic acid) (PLGA) NPs, have demonstrated enhanced *in vivo* circulation and target accumulation following PEGylation as a result of reduced opsonisation and nonspecific protein adsorption.[59] However, repeated administration of PEGylated NPs can stimulate the production of anti-PEG antibodies, reducing their stealth properties and promoting

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

accelerated blood clearance. *In vivo,* this can lead to the enrichment of anti-PEG IgG and IgM in the PCs of PEGylated particles, causing enhanced macrophage and immune system uptake (Figure 4).[60–62] More broadly, concerns regarding PEG accumulation and the generation of potentially toxic oxidative degradation products, together with concerns regarding immunogenicity, have highlighted the need for alternative surface chemistries.[63,64] Consequently, considerable effort has been devoted to developing alternative antifouling materials such as poly(glycerols), poly(N-vinylpyrrolidone), and poly(oxazolines). Although these materials can reduce nonspecific protein adsorption, concerns regarding immunogenicity and long-term biocompatibility remain, highlighting the need for next-generation surface chemistries that can either minimise unwanted protein adsorption or deliberately exploit PC formation to enhance NP performance.[58,61,65,66]

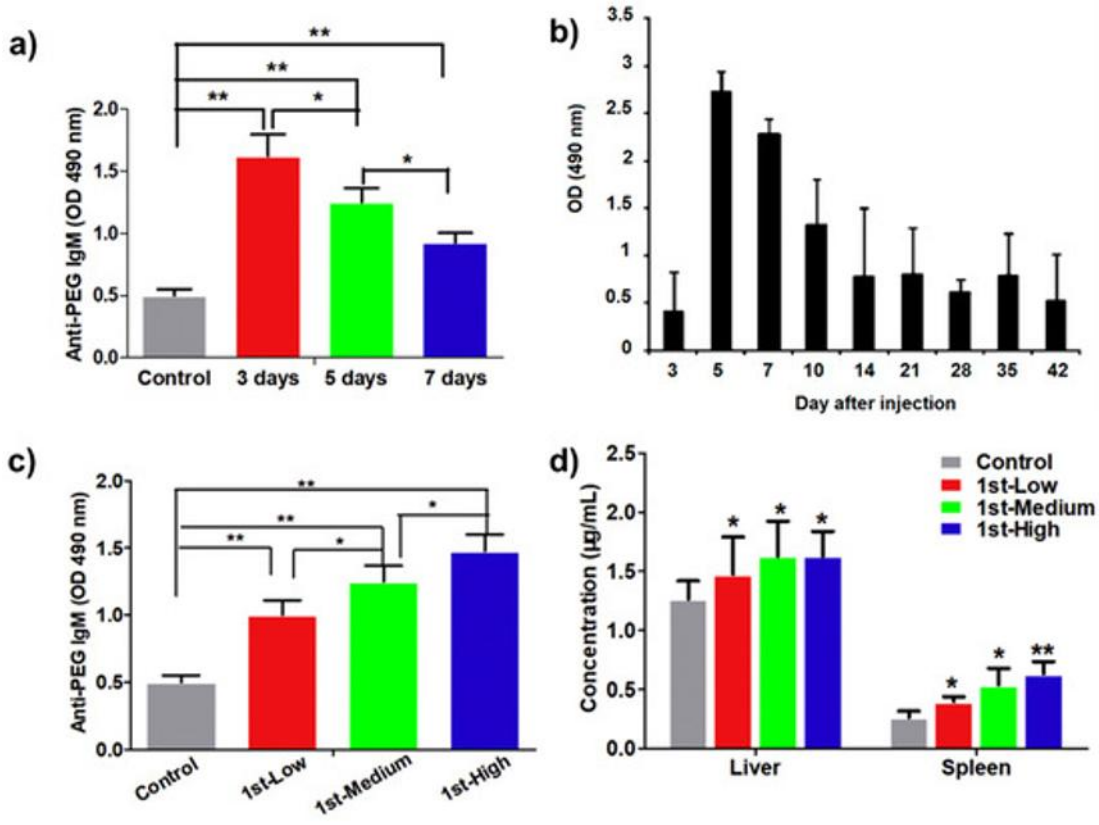


Figure 4. ***a)*** *Anti-PEG IgM production as a function of time tested in sera of rats intravenously injected with PEGylated liposomal gambogenic acid (PEG-GEA-L) at 1.5 mg/kg.* ***b)*** *Production of anti-PEG IgM in mouse sera determined as a function of time after treatment with PEGylated liposomes at 1 μmol/kg.* ***c)*** *The effect of PEG-GEA-L doses on anti-PEG IgM production recorded on the fifth day after the first injection. Rats were treated with low (1.125 mg/kg), medium (1.500 mg/kg), and high (1.875 mg/kg) dosages.* ***d)*** *Anti-PEG IgM in organ tissues of rats intravenously injected with various PEG-GEA-L doses. Reproduced with permission from Royal Society of Chemistry,* [62]*, licensed under CC BY 4.0.*

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Targeting ability

PC formation can significantly influence the targeting ability of NPs by masking surface ligands or altering their orientation, thereby reducing receptor-specific binding.[67] For example, Wang *et al*. demonstrated that PC formation of both PEGylated and transferrin-modified polystyrene NPs in cerebrospinal fluid (CSF) significantly reduced active targeting towards bEnd.3 and C6 cells.[68] Similarly, disease-specific PCs can modulate NP targeting. In a model of non-small cell lung cancer (NSCLC), transferrin-functionalised PEGylated NPs acquired distinct coronas when incubated in plasma from healthy donors and patients with NSCLC. The patient-derived corona significantly reduced transferrin receptor-mediated uptake, demonstrating that disease-dependent variations in PC composition can directly influence targeting efficacy.[69] Conversely, selective enrichment of dysopsonins within the PC can prolong circulation time and reduce immune clearance, increasingly the likelihood of NPs reaching their intended target, which will be discussed further below.[67,70]

Collectively, these studies demonstrate that the PC is a key determinant of NP targeting, with its composition capable of either impairing or enhancing therapeutic performance depending on the biological environment. Advancing this field will therefore require standardised approaches for PC characterisation and a greater understanding of how specific protein signatures influence NP behaviour *in vivo*, enabling the rational engineering of coronas for targeted biomedical applications.

2.3 Current methods of PC analysis

2.3.1 PC isolation techniques

Comprehensive characterisation of the PC, including its composition, biological identity, morphology, and protein binding affinities, is essential for understanding NP behaviour and guiding the rational design of PC-enabled biomedical applications.[71] The HC, comprising proteins that bind strongly and persist on the NP surface, is generally considered the dominant determinant of NP biological identity. In contrast, proteins within the SC interact more weakly and reversibly and have therefore traditionally been regarded as less influential in mediating *in vivo* cellular interactions.[72] Consequently, most analytical approaches remove the SC prior to *ex situ* characterisation, focusing primarily on the HC.[72] A variety of isolation techniques have been developed to recover

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

NP-PC complexes from protein-rich biological media while minimising protein loss, however no universally accepted standard currently exists.[73] *Table 2* summarises the most widely used PC isolation methods. Although these techniques effectively recover strongly bound proteins, many disrupt the dynamic SC and may alter the native structure and composition of the PC, limiting their ability to accurately represent the biological corona formed *in vivo*.[74]

Table 2: Summary of NP-PC isolation methods and their advantages and disadvantages[75,76]

Technique	Advantages	Disadvantages
Centrifugation	○ Rapid and cost effective ○ Suitable for isolating hard NPs with sufficient density ○ Simple and widely available using standard laboratory equipment	○ Poor recovery of low-density or soft NPs e.g. liposomes polymers ○ Protein contamination from incomplete separation ○ High centrifugal forces may induce NP aggregation or protein rearrangement, potentially altering the native corona
Magnetic separation	○ Rapid and straightforward separation ○ Minimised aggregation associated with high centrifugal forces ○ Can better preserve native NP-PC interactions	○ Limited to magnetic NPs or magnetically labelled systems ○ Not applicable to most NP formulations without modification ○ Magnetic interactions may promote aggregation in some systems
Size Exclusion Chromatography (SEC)	○ Gentle separation that better preserves native PC structure ○ Can separate free proteins from NP–PC complexes ○ Can be coupled with downstream analytical techniques	○ Relatively low throughput ○ Potential interactions with the stationary phase may change the PC ○ Limited resolution for similarly sized species
Flow-Field-Flow Fractionation (AF4)	○ Gentle, label-free separation with minimal disruption of the PC ○ Suitable for complex biological samples ○ Compatible with multiple detectors (MALS, DLS,	○ Time-consuming method optimisation ○ Requires specialised instrumentation and expertise ○ Limited accessibility in many laboratories

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

	ICP-MS, UV) for comprehensive characterisation	
Bio-layer interferometry (BLI)	○ Real-time monitoring of protein adsorption ○ No centrifugation required ○ Can distinguish soft and hard corona formation	○ Limited validation in complex biological fluids ○ Mainly demonstrated with model proteins ○ Lower throughput for proteomic analysis

Increasing evidence suggests that these weakly associated proteins play a more important biological role than previously appreciated. The dynamic exchange of proteins within the SC can influence HC formation and, in some cases, directly mediate NP interactions with the surrounding biological environment, thereby affecting cellular uptake, biodistribution, and overall NP behaviour.[76] Consequently, analytical approaches relying solely on *ex situ* isolation may provide an incomplete representation of the native PC.

To overcome these limitations, increasing attention has shifted towards *in situ* techniques capable of monitoring corona formation under biologically relevant conditions. Although challenging because of the transient nature of protein adsorption, methods such as cryo-transmission electron microscopy (cryo-TEM) combined with circular dichroism (CD) have shown promise for probing real-time protein exchange and adsorption-induced confirmational changes.[72,77,78] More recently, Baimanov *et al*. developed a bio-layer interferometry (BLI)-based "fishing strategy" that enables real-time monitoring of NP–protein interactions by measuring wavelength shifts associated with changes in bio-layer thickness during protein adsorption (Figure 5).[79] Subsequent washing steps allow sequential isolation of both the SC and HC, providing greater insight into corona evolution. However, this technique has thus far been demonstrated only with model proteins such as IgG, and requires validation using more complex biological fluids and a broader range of NP-binding proteins before its wider applicability can be established.[80]

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

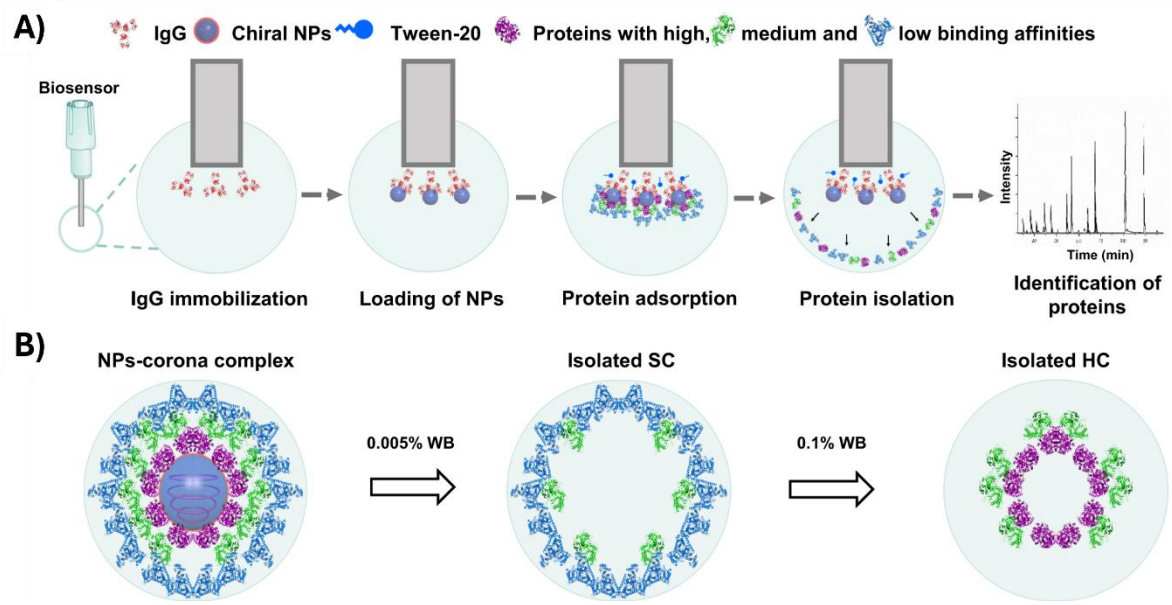


Figure 5. A) Schematic illustration of the BLI-based Fishing strategy including PC formation on the chiral NPs, the isolation of corona in situ, and identification of protein composition and abundance. B) Schemes demonstrating the isolation of soft corona (SC) and the hard corona (HC) in two steps by washing buffer (WB). All data are shown as mean values and standard deviations for triplicate biological samples (n = 3). Reproduced from [79] with permission from Nature Communications.

2.3.2 PC analysis and identification techniques

Comprehensive characterisation of the of the PC, including its composition, binding kinetics, morphology, structural evolution, and physicochemical properties, is essential for understanding how NP-PC complexes interact with biological systems and ultimately influence biomedical performance.[81] No single analytical technique can fully characterise the complexity of the PC, and consequently complementary methods are typically employed to investigate different aspects of corona formation. Broadly, these approaches either identify and quantify adsorbed proteins directly, or monitor changes in NP properties following protein adsorption. Table 3 and Figure 6 summarise the principal techniques used for PC characterisation together with their strengths and limitations.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Table 3: Summary of PC characterisation techniques.[80]

Measurement	Technique	Information obtained	Advantage	Disadvantage
Composition	Liquid Chromatography – Mass Spectrometry (LC-MS)	Protein identity, abundance and relative quantification of proteins	○ High throughput proteomic analysis ○ High specificity and sensitivity[82] ○ Can develop searchable NP-PC databases	○ Low abundance proteins may be masked (bias data)[83] ○ Requires prior PC isolation
Size	Dynamic Light Scattering (DLS)	Hydrodynamic diameter and aggregation state	○ Compact and affordable instrumentation ○ Non-invasive ○ Minimal sample preparation[84]	○ Highly sensitive to polydispersity ○ Unsuitable for complex or highly scattering biological fluids[84]
	Fluorescence correlation spectroscopy (FCS)	Changes in diffusion coefficient and size	○ Avoids additional separation steps to remove unbound proteins[85] ○ Real-time measurements in biological media	○ Requires fluorescent-labelled NPs/proteins (may cause changes in PC composition)[77]
Morphology	Transmission Electron Microscopy (TEM)	NP morphology and corona thickness	○ Direct visualisation of the PC	○ Sample drying and staining may alter native PC structure
	Scanning Electron Microscopy (SEM)	Surface morphology and corona thickness	○ Comprehensive 3D surface morphology image ○ High spatial resolution[86]	○ Difficult to produce a clear image of NP and PC ○ Require pre-treatment steps for sample preparation [87]

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Kinetics	Surface Plasmon Resonance (SPR)	Binding affinity, association/dissociation kinetics	○ Label-free approach ○ Measures accurate real-time changes in optical parameters[88]	○ High cost ○ Need to tailor sensors to individual NPs
	Microscale Thermophoresis (MST)	Binding affinity and interaction strength	○ Good for proteins with low binding affinities	○ Potential for biased data by NP agglomerates[89] ○ Requires fluorescence labelling (may change protein structure) [80]
	Bio-layer interferometry (BLI)	Binding kinetics and corona formation in real time	○ Label-free, real-time monitoring, distinguishes HC and SC	○ Limited validation in complex biological fluids
	Small- Angle X-ray Scattering (SAXS)	Changes in protein-NP association and binding kinetics and cooperativity	○ Label-free, non destructive and provides ensemble-averaged structural information	○ Limited structural resolution and potentially difficult interpretation in complex, heterogeneous systems[90]
Conformation changes	Circular Dichroism (CD)	Protein secondary structure	○ Provides detail on conformation of target proteins in complex environments	○ Not feasible with complex protein mixtures[91]
	DOSY-NMR (Diffusion order NMR spectroscopy)	Molecular diffusion coefficients and NP–protein interactions	○ Label-free analysis of NP–protein complexes in solution	○ Complex sample preparation and time consuming ○ Difficult to interpret for complex protein mixtures or high-molecular-weight species
	Small- Angle Neutron Scattering (SANS)	Protein conformational and structural changes upon NP binding	○ Contrast variation can distinguish components within complex systems, and low sample damage	○ Requires relatively large sample volumes and can involves long acquisition times[90]

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

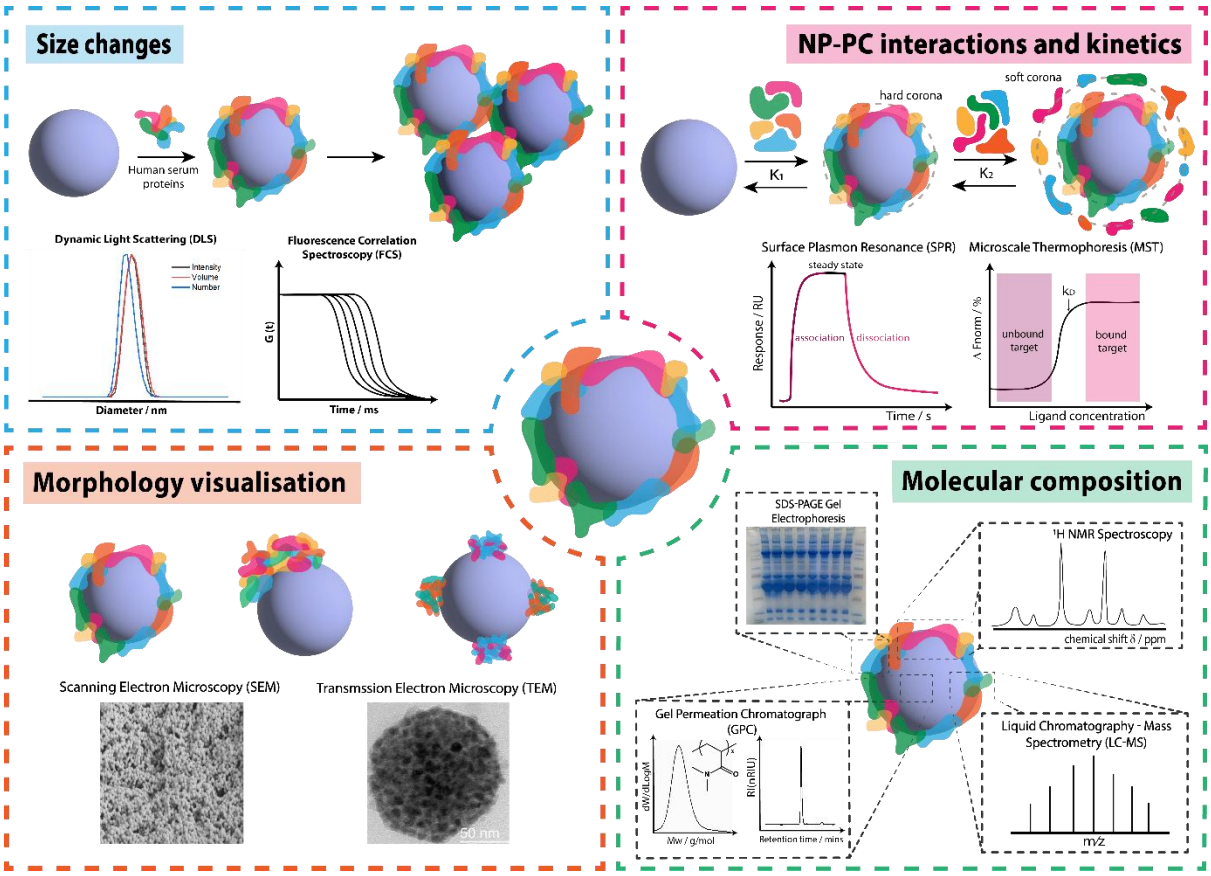


Figure 6. Schematic of common techniques used to characterise NPs and their subsequent PCs, categorised by property analysed.

Traditional analytical approaches generally rely on *ex situ* isolation of NP-PC complexes before characterisation. While highly informative, these methods will inevitably disrupt the dynamic nature of the PC and bias measurements towards the HC. In contrast, *in situ* techniques, such as DLS and FCS, enable analysis within biological media without prior isolation, reducing experimental artefacts and providing greater insights into the evolution of corona formation.[92] For a comprehensive overview of *in situ* PC characterisation approaches, readers are referred to the review by Fu *et al*.[76]

Conventional analytical methods such as LC-MS remain indispensable for determining protein composition, but provide only static insights of an inherently dynamic system such as the PC, which can lead to incomplete or misleading interpretations of its behaviour. Consequently, combining proteomic, structural, and kinetic techniques is increasingly recognised as essential for accurately predicting NP behaviour *in* vivo.[93]

To address these limitations, recent advances have focused on real-time three-dimensional *in situ* analysis of NP-PC complexes.[71] One promising example is nanoflow

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

cytometry (NanoFCM), which enables analysis of individual NP-PC complexes directly within a biological fluid.[94] Niu *et al.* integrated NanoFCM with dual fluorescence quantification to monitor protein adsorption in real time, simultaneously measuring size evolution, adsorption kinetics, NP aggregation, and the adsorption of key serum proteins such as human serum albumin (HSA) and transferrin (Figure 7).[95] The approach measures light scattering from individual NPs to determine size and fluorescence from labelled adsorbed proteins to quantify corona formation, with the absence of fluorescence from bare NPs providing a direct background control; notably, the authors quantified approximately 600 HSA molecules per NP and found that nearly 50% of serum proteins adsorbed within the first minute, reaching approximately 90% within 30 min. Such approaches provide a more comprehensive picture of the dynamic biological identity of NPs and represent an important step towards improving the predictive power of *in vitro* PC characterisation.

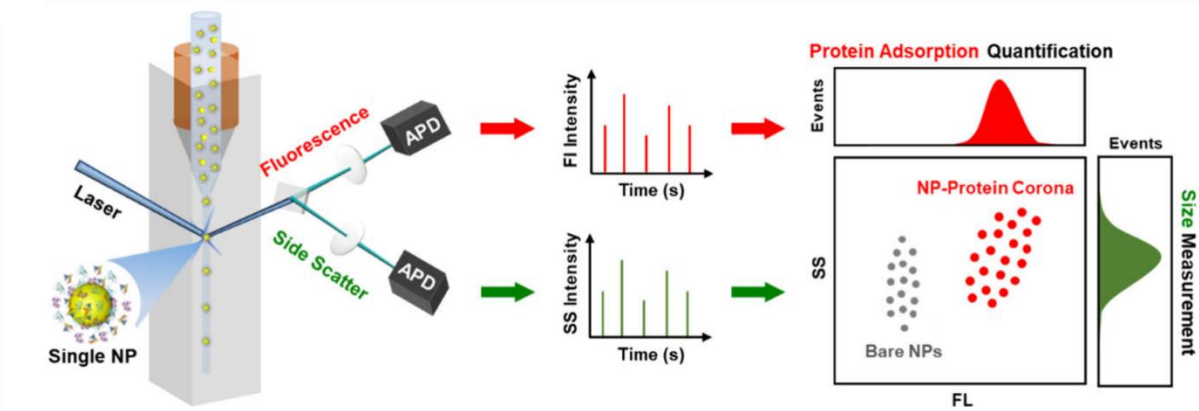


Figure 7. In-situ Characterization Technique for Detecting Nanoparticle–Blood Protein Interactions at Single-Nanoparticle Resolution Using NanoFCM. Reproduced from [95] with permission from the American Chemical Society, licensed under CC by 4.0.

3 Applications of NPs and their subsequent NP-PC complexes

Traditionally, PC formation has been viewed as a major barrier to the successful biomedical application of NPs. However, growing evidence suggests that, when appropriately understood and engineered, the PC can instead be exploited to enhance NP performance across a diverse range of biomedical applications.[96]

3.1 Drug delivery

NPs have become established as versatile drug delivery platforms owing to their tuneable physiochemical properties, high drug-loading capacity, and ability to selectively target

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

diseased tissues, thereby improving therapeutic efficacy while reducing systemic toxicity. Several NP-based therapeutics have now received regulatory approval, from Doxil, a landmark liposomal doxorubicin formulation used to treat ovarian cancer, to the more recent lipid nanoparticle-based mRNA vaccines against COVID-19 developed by Pfizer-BioNTech and Moderna, which demonstrated vaccine efficacy rates of approximately 95% and 94% respectively.[97,98] Nevertheless, biological barriers encountered *in vivo* continue to limit their clinical translation and therapeutic performance.

PC formation is a major contributor to these challenges, as the acquired biological identity governs NP biodistribution, circulation time, cellular uptake, and drug release. Rather than viewing the PC solely as an obstacle, increasing attention has shifted towards engineering NP surfaces to direct corona formation and improve delivery efficacy.[93] As discussed above, dysopsonin enrichment can prolong circulation and reduce immune clearance. Surface engineering can promote the endogenous adsorption of dysopsonins such as albumin and clusterin without deliberate protein precoating, potentially reducing macrophage recognition.[99] For example, Schöttler *et al*. showed that PEG- and poly(phosphoester)-modified polystyrene NPs exposed to plasma developed a corona enriched in clusterin (apolipoprotein J), with clusterin adsorption reducing nonspecific cellular uptake.[100] Similarly, Vincent *et al*. demonstrated that surface chemistry could control the conformation of endogenous albumin adsorbed onto polymeric nanocarriers, with surfaces that preserved albumin structure promoting immune evasion, whereas those inducing albumin denaturation enhanced macrophage recognition and clearance.[101] Conversely, selective enrichment of endogenous ApoE could potentially be exploited to enhance tissue targeting through receptor-mediated interactions, although relatively few studies have demonstrated deliberate control of specific corona components through NP surface chemistry alone.[102] This highlights an important opportunity to engineer the NP surface to direct endogenous PC formation towards prolonged circulation or tissue-specific targeting.

While this review focuses primarily on such deliberate engineering of NP properties to control the *in situ* PC, an alternative approach is to precoat NPs with selected biomolecules to manipulate subsequent corona formation.[103] Although distinct from

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

engineering the NP to direct endogenous protein adsorption, this approach provides proof of concept that deliberate control of the PC can alter NP–protein interactions and biological behaviour. For example, Li *et al*. used molecular dynamics simulations to show that pre-adsorption of HSA onto hydrophilic and hydrophobic gold NPs reduced subsequent complement C3b adsorption and weakened NP-membrane interactions, demonstrating the potential to modulate the PC to reduce immune recognition and influence NP transport.[104]

More recently, Miao et al. engineered lipid nanovesicles with glycosylated polyhydroxy polymers featuring tailored amino/hydroxyl ratios to dynamically regulate PC composition throughout circulation.[105] The optimised nanovesicles suppressed immunoglobulin adsorption in blood thereby prolonging circulation, before selectively enriching tumour-associated proteins, including CD44 and osteopontin (OPN), within the tumour microenvironment to enhance receptor-mediated cellular uptake and antitumour efficacy (Figure 8).

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

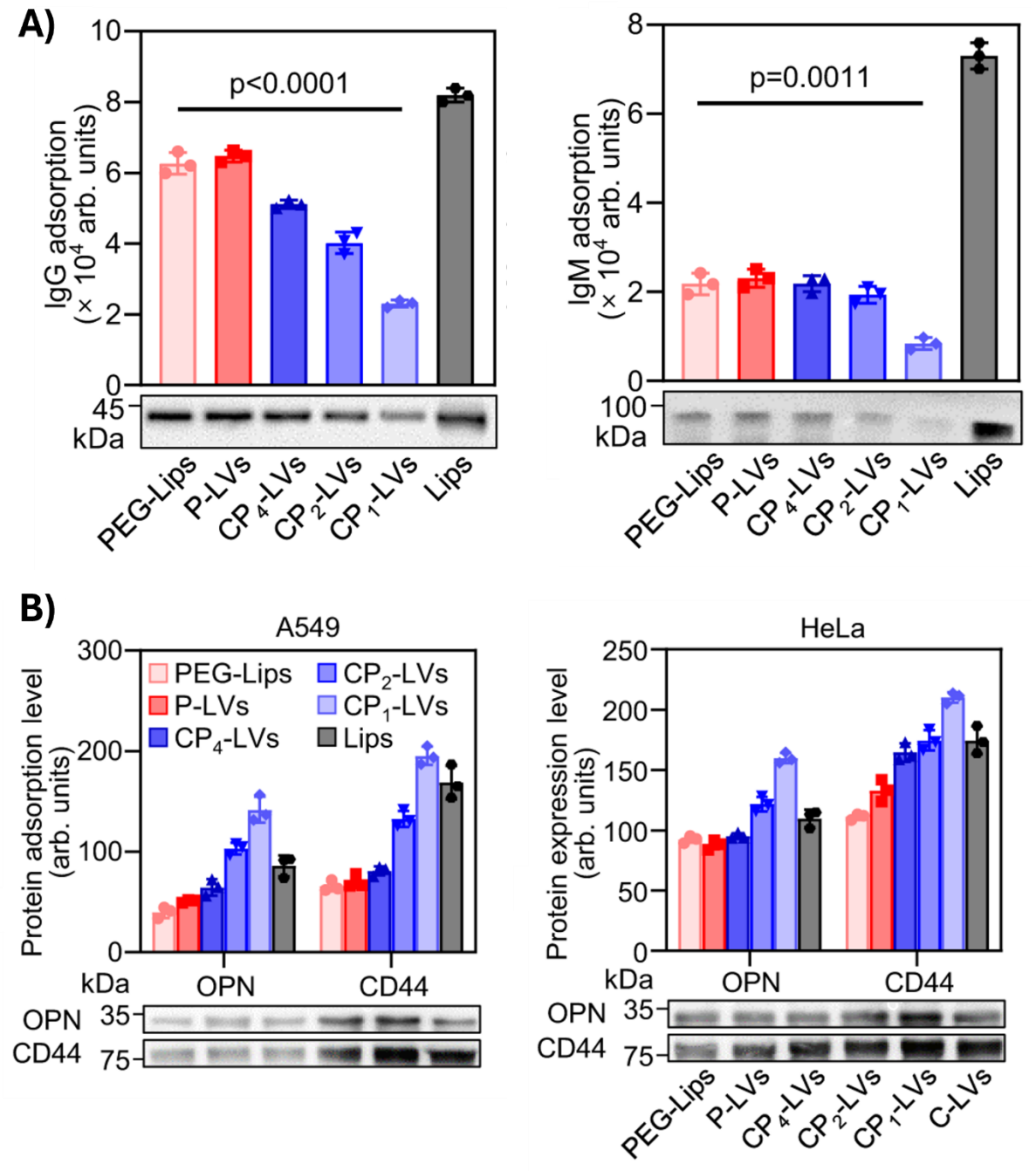


Figure 8. A) Western blot assay of IgG and f IgM adsorbed in the PC of the nanovesicles. The data are displayed as the mean ± SD (n = 3 independent samples). B) Osteopontin (OPN) and CD44 bound to nanovesicles as determined by Western blotting assay. The data are displayed as the mean ± SD (n = 3 independent samples). Reproduced from [105] with permission from Nature Communications, licensed under CC by 4.0.

These studies demonstrate that the PC can be deliberately engineered to improve drug delivery, shifting its role from a barrier to an active mediator of therapeutic performance. Rather than simply minimising protein adsorption, rational control of corona composition represents a promising strategy for enhancing the clinical translation of NP-

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

based drug delivery systems. For a comprehensive discussion of PC-mediated effects on NP drug delivery, readers are directed to Wang *et al*.[99]

Although PC-mediated macrophage recognition is often considered detrimental as it accelerates NP clearance, it can be deliberately exploited in applications requiring targeted intracellular delivery to macrophages.[106] In these cases, engineering the PC to promote receptor-mediated phagocytosis offers an attractive strategy for enhancing therapeutic efficacy. For example, Tan *et al*. developed macrophage-targeted poly(lactic-co-glycolic acid) NPs for the delivery of germacrone in rheumatoid arthritis, demonstrating enhanced macrophage uptake and improved therapeutic outcomes through receptor-mediated internalisation.[107] Although this strategy relied on NP surface engineering rather than deliberate manipulation of the PC, it highlights the therapeutic potential of selectively promoting macrophage recognition. In this context, engineering the PC to direct receptor-mediated uptake represents an emerging alternative approach. For example, enriching the corona with opsonins, including complement proteins (C3b and C4b) and immunoglobulins, could promote interactions with macrophage surface receptors and facilitate phagocytosis, enabling efficient intracellular drug delivery.[103] However, immune recognition is governed by more than the presence of individual opsonins, with the overall PC composition, protein orientation, and accessibility of receptor-binding domains collectively determining macrophage interactions.[108]

Collectively, these studies demonstrate that the PC should not be viewed solely as a barrier to NP drug delivery, but also as a tuneable biological interface that can be engineered to either evade immune recognition or selectively enhance cellular uptake when therapeutically advantageous. A more comprehensive understanding of how specific corona compositions regulate receptor-mediated interactions will therefore be essential for the rational design of next-generation NP drug delivery systems.

3.2 Disease diagnostics

Rapid, sensitive, and accurate diagnostic techniques are fundamental for the early detection, monitoring, and management of disease. NP-based diagnostics have emerged as powerful alternatives to conventional methods by offering enhanced sensitivity, specificity, and multiplexing capabilities, while enabling the development of portable

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

biosensors and point-of-care testing platforms.[109] These advantages have been exploited across a broad range of applications, from infectious disease diagnosis to biomarker detection. For example, Au-NPs functionalised with DNA/RNA probes and antibodies enabled rapid detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the COVID-19 pandemic.[110] Similarly, Fe_3O_4-Ce-O_2 core-shell NPs were utilised for the detection of ROS-associated vascular disorders through ROS-responsive sensing mechanisms.[111]

Naturally occurring NPs, such as low-density lipoproteins (LDLs), may also offer opportunities for disease detection through their associated PCs. Ren *et al.* demonstrated that LDL-associated PCs were relatively depleted of highly abundant serum proteins, including albumin, a profile that has been attributed to their overall negative surface charge.[112,113] This enabled improved detection of lower-abundance proteins and proof-of-concept discrimination between healthy individuals and patients with melanoma, colon carcinoma, and liver cancer. Although the PC was not deliberately engineered for diagnostic purposes, these findings highlight the potential of PC proteomic profiles to reveal disease-associated changes and support biomarker discovery.

More broadly, increasing evidence indicates that disease-associated changes in the biological environment can alter PC composition, creating opportunities to exploit corona formation as a diagnostic tool.[114,115] Disease-associated alterations in the plasma proteome lead to distinct patterns of protein adsorption on NP surfaces, generating unique NP-PC signatures that can serve as biomarkers for the early detection of diseases including cancer and Alzheimer's Disease (AD).[116] These variations arise from pathological changes in the vascular system and plasma protein composition, which collectively reshape PC formation. These observations have led to the concept of the 'Personalised Protein Corona' (PPC), whereby each individual produces a characteristic corona that reflects their underlying physiological or pathological state.[117] By tailoring NP physicochemical properties to selectively enrich disease-associated proteins, PPC formation can be harnessed to develop highly sensitive, patient-specific diagnostic platforms.[118]

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

A seminal study by Hajipour et al. established the concept of the PPC using graphene oxide nanosheets as a NP platform.[114] By comparing the PCs formed from plasma collected from healthy individuals and patients with blood cancer, hypofibrinogenemia, diabetes, and hypercholesterolemia, the authors identified disease-specific corona signatures, demonstrating that pathological changes in the plasma proteome can be translated into distinct NP–PC fingerprints with diagnostic potential (Figure 9). Beyond disease classification, these personalised coronas also elicited markedly different biological responses, including changes in cellular uptake, cytotoxicity, apoptosis, oxidative stress, lipid peroxidation, and inflammatory signalling. These findings highlight that the PC not only represents a promising source of disease biomarkers but also reflects patient-specific biological variability that should be considered when designing NP-based diagnostic and therapeutic systems.

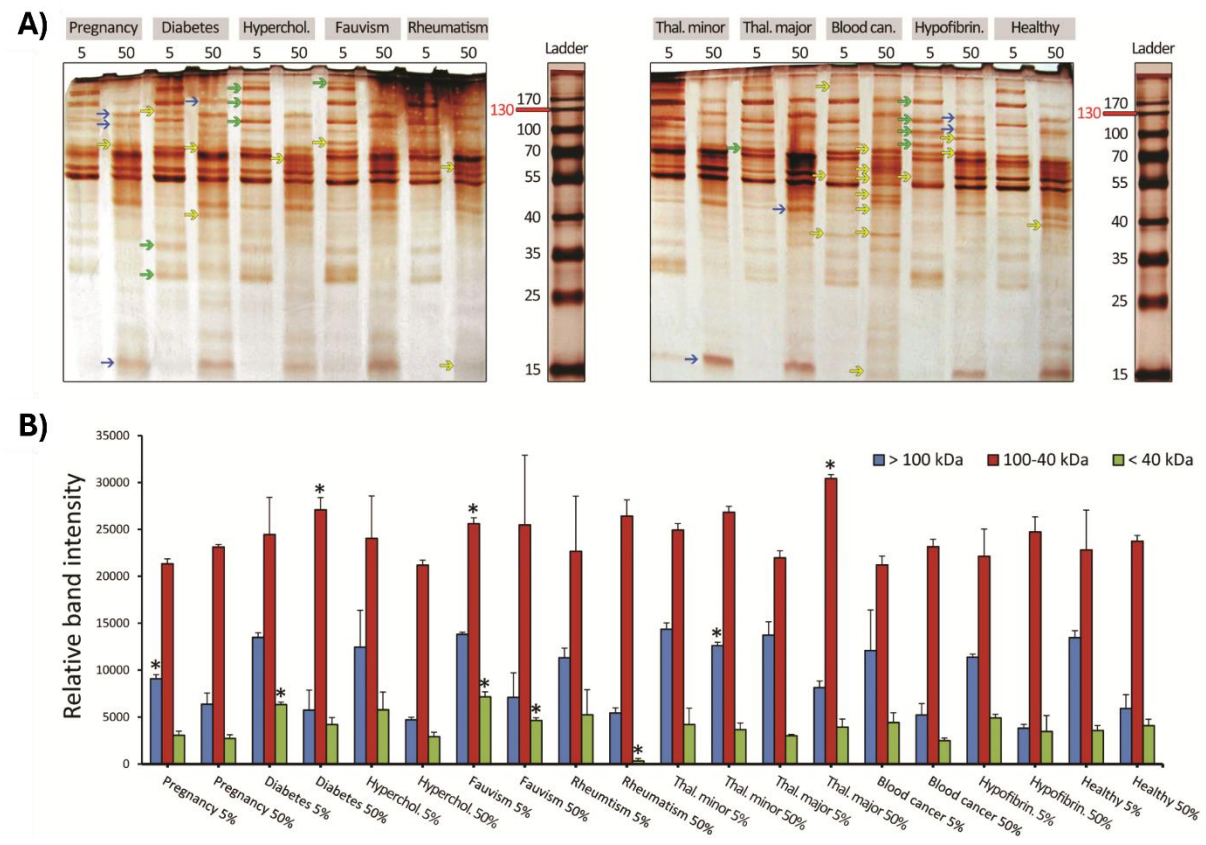


Figure 9. (A) SDS-PAGE gel (15%) of corona-coated graphene oxide (CCGO) obtained following incubation with 5% and 50% plasmas of different patients. The green and blue arrows mark the proteins that only appeared in the hard corona of 5% and 50% plasmas respectively. The yellow arrows mark the protein bands that specifically appeared/disappeared in the hard corona of a fraction of patients. (B) Relative amount of the proteins associated within the CCGO after incubation with 5% and 50% plasmas of different patients. Star (*) represents significant

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

differences ($P < 0.05$) compared to other patients. Reproduced with permission from [114], Copyright (2015) Nanomaterials.

Building on the concept of the PPC, Corbo *et al*. developed a multi-NP PC nanoplatform capable of distinguishing healthy individuals from patients with AD. [116] The platform comprised six NPs of comparable size (~100 nm) but differing in composition and surface chemistry, including plain, amino-, and carboxyl-functionalised polystyrene and silica NPs. Each NP generated a distinct yet complementary PC, which was characterised by LC-MS/MS to capture disease-dependent variations in protein adsorption. These proteomic datasets were subsequently integrated with machine learning algorithms to generate an AD-specific PC signature, which achieved 96% diagnostic accuracy when validated using blinded plasma samples. This work demonstrates how combining rational NP design with advanced data analysis can exploit subtle disease-specific differences in PC composition, offering a powerful strategy for the early diagnosis of complex diseases.

Digiacomo *et al*. further demonstrated the clinical potential of the PPC by developing a graphene-oxide NP-enabled blood (NEB) test for the diagnosis of pancreatic ductal adenocarcinoma (PDAC).[119] Analysis of the PPC formed from patient plasma revealed subtle but reproducible disease-specific differences, particularly within the 20–30 kDa protein fraction, including changes associated with apolipoprotein A-I. Importantly, combining the NEB test with the clinically established CA19-9 assay reduced false-negative diagnoses by 50% and increased overall classification accuracy to 92%, outperforming the conventional biomarker alone.

Collectively, these studies demonstrate that the PC can function as a highly sensitive molecular fingerprint of disease, capturing subtle pathological changes that may be overlooked by conventional diagnostic approaches. By integrating rational NP design with advanced proteomic analysis and machine learning, PC-based diagnostics have the potential to provide highly accurate, minimally invasive, and patient-specific diagnostic platforms, representing a promising step towards precision medicine.

3.3 Biosensing and molecular recognition

Nanoscale biosensors enable the highly sensitive and selective detection of biological analytes such as nucleic acids, viruses, proteins, and small biomolecules.[120] Compared

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

with conventional biosensors, NP-based platforms offer a high surface-area-to-volume ratio, tuneable surface chemistry, and enhanced signal transduction, enabling improved analytical sensitivity across a broad range of diagnostic applications. Gold NPs (AuNPs), in particular, have emerged as versatile sensing platforms owing to their unique optical and electronic properties.[121] For example, Gao *et al*. developed an AuNP-enhanced electrochemical biosensor capable of ultrasensitive detection of cardiac biomarkers, demonstrating the potential of nanostructured sensing interfaces for the early diagnosis of cardiovascular disease.[122]

Despite these advantages, maintaining high analytical performance in complex biological fluids remains a significant challenge as PC formation modifies the NP surface before target recognition can occur. Absorbed proteins can mask recognition elements, alter receptor orientation, and modify binding kinetics, ultimately reducing sensor sensitivity and specificity.[123] Tao *et al*. demonstrated this effect using AuNP-based sensors exposed to protein-containing media. Adsorption of abundant plasma proteins, including bovine serum albumin (BSA) and fibrinogen, reduced the detection signal by up to 80%, primarily through molecular crowding and steric shielding of receptor-binding sites, which impaired analyte access to the sensor surface.[124] These findings highlight the importance of considering PC formation during biosensor design, particularly for applications requiring direct operation in biological fluids.

Considerable effort has therefore focused on mitigating the detrimental effects of PC formation through antifouling surface modifications, including stealth polymers and tailored surface chemistries. While these strategies can reduce nonspecific protein adsorption and preserve receptor accessibility, they often introduce a trade-off between biofouling resistance and sensor performance.[123] For example, electrochemical sensors coated with polymers such as poly(N-2-hydroxypropyl)methacrylamide) (p(HPMA)) and polyacrylamide hydrogels demonstrated improved resistance to protein adsorption.[125] However, the insulating nature of these polymer coatings also attenuated electrochemical signal transduction, reducing overall sensitivity.[123,126] Consequently, the rational design of antifouling interfaces remains an important area of research, with the aim of balancing biofouling resistance with efficient analyte transport and signal generation.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Rather than simply mitigating PC formation, emerging strategies seek to exploit it as the functional recognition layer of the biosensor. By engineering NP physicochemical properties to direct the adsorption of disease-associated proteins, the PPC can serve as a biologically derived interface for selective molecular recognition.[122,127] For example, Zhang et al. developed polyhedral oligomeric silsesquioxane (POSS) polymer-caged AuNPs (PP-AuNPs), that exploited the PC-mediated modulation of NP catalytic activity for cancer biomarker detection. In this system, adsorption of plasma proteins altered the catalytic reduction of 4-nitrophenol, while competitive binding of metallothionein (a recognised tumour biomarker) produced a measurable change in catalytic response, enabling sensitive molecular detection.[128] Similarly, Quagliarini et al developed the Magnetic Levitation Nanoparticle-Enabled blood (MagLev NEB) test, which combines graphene oxide NPs with magnetic levitation to distinguish patients with pancreatic ductal adenocarcinoma (PDAC) based on differences in their PPCs. Figure 10 illustrates the MagLev fingerprints for breast cancer patients and PDAC patients, with the distribution of non-oncological patients (NOPs) superimposed as a reference where each dot represents a single donor. The minimal overlap of the MagLev fingerprints of NOPs and the cancer patients demonstrates high accuracy, sensitivity and specificity where the two groups are well-separated.[129,130]

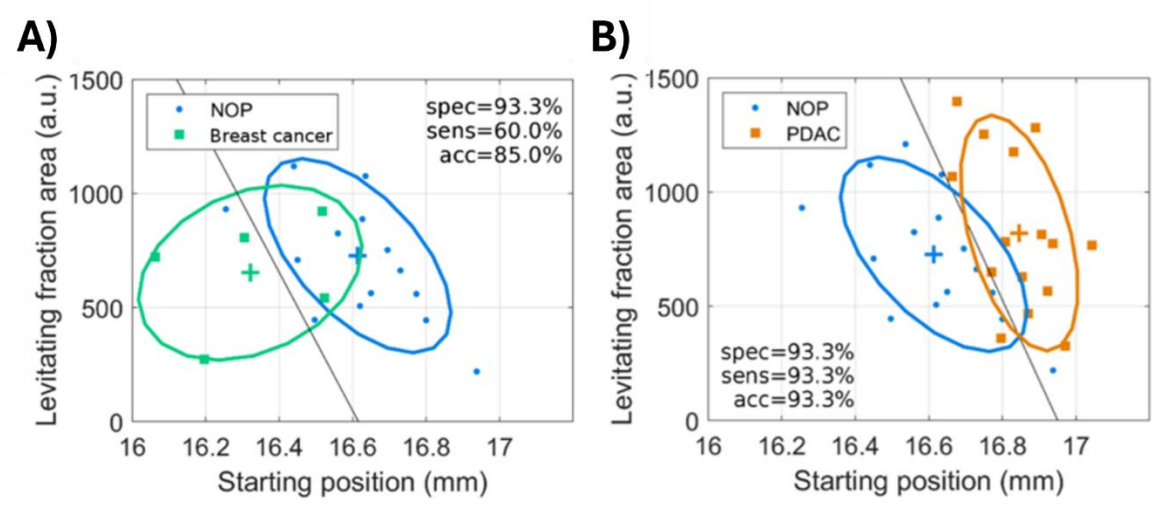


Figure 10. Scatterplots of detected MagLev fingerprints for (a) breast cancer and (d) PDAC, demonstrating distinct differences in the PPCs of non-oncological patients (NOPs) and cancer patients. NOP samples are superimposed as references in all the panels. Mean values are reported as crosses, multivariate distributions are depicted by ellipses. Outputs from linear discriminant analysis (LDA) are indicated by solid lines. Test specificity, sensitivity, and global

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

accuracy are listed in each panel. Reproduced with permission from [130], licensed under CC BY 4.0.

Collectively, these studies demonstrate a paradigm shift in biosensor design, where the PC is no longer regarded solely as a source of biofouling but as a dynamic molecular recognition element that can enhance diagnostic performance. Continued advances in NP engineering, together with standardised approaches for PC characterisation, will be essential for translating these personalised biosensing platforms into clinical practice. For a comprehensive discussion of PC-mediated biosensing strategies, readers are directed to Cheeseman *et al*.[123]

3.4 Nanotoxicology

Minimising nanotoxicity is essential for the safe clinical translation of NP-based technologies. While the intrinsic physicochemical properties of NPs, including their high surface free energy and surface reactivity, can promote undesirable interactions with cells and biological membranes, PC formation fundamentally alters these interactions by redefining the NP's biological identity. Consequently, the PC can modulate cellular uptake, biodistribution, immune activation, and cytotoxicity, in some cases attenuating adverse biological responses by shielding the NP surface.[131] Although these effects have been widely characterised, comparatively few studies have deliberately engineered or exploited the PC as a strategy to improve the safety profile of nanomaterials. This emerging concept therefore represents a promising direction for the rational design of safer nanomedicines, and the following examples highlight its potential.

Silver NPs (AgNPs) possess unique antibacterial, optical, catalytic, and electronic properties, making them attractive for a wide range of biomedical applications, including biosensing, antimicrobial coatings, and drug delivery.[132] Batista *et al*. investigated how different polymer stabilisers, including polyethyleneimine (PEI), polyethylene oxide (PEO), and polyvinylpyrrolidone (PVP), influenced PC formation on AgNPs.[133] SDS-PAGE and LC-MS analyses revealed bovine serum albumin (BSA) as the predominant corona protein following exposure of NPs to FBS, although the extent of protein adsorption varied with the specific polymer coating. The resultant PCs substantially reduced AgNP cytotoxicity compared with the corresponding particles that had not had an FBS pre-coating step, while largely preserving their antimicrobial performance. These findings

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

demonstrate that PC formation can improve the biocompatibility of polymer-stabilised AgNPs without substantially compromising their antimicrobial function. Conversely, PC formation does not universally reduce nanotoxicity; in some systems it can increase cellular uptake and stimulate reactive oxidative species (ROS) production, leading to enhanced cytotoxicity.[54,134] These contrasting outcomes highlight that the biological consequences of the PC are highly system-dependent and reinforce the need to understand, rather than simply minimise, protein adsorption when designing safer nanomaterials.

Xiao *et al*. further demonstrated how PC formation can fundamentally alter NP-cell interactions using amino-functionalised PS micro- and nanoplastics as a model system.[135] In HER2-positive breast cancer cells, pristine PS-NH_2 NPs strongly adhered to the cell membrane, disrupting HER2-mediated signalling pathways associated with cell proliferation and survival. However, following incubation in human plasma, the NPs acquired a PC enriched in apolipoprotein A3 (APOA3), albumin, and apolipoprotein C2 (APOC2), which redirected cellular uptake towards endocytosis and subsequent lysosomal trafficking. By reducing direct membrane interactions, PC formation alleviated the adverse biological effects observed with pristine particles and improved cell viability (Figure 11). Although this study did not deliberately engineer the PC, it demonstrates how controlling corona composition could provide a powerful strategy for modulating NP–cell interactions and improving nanomaterial safety.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

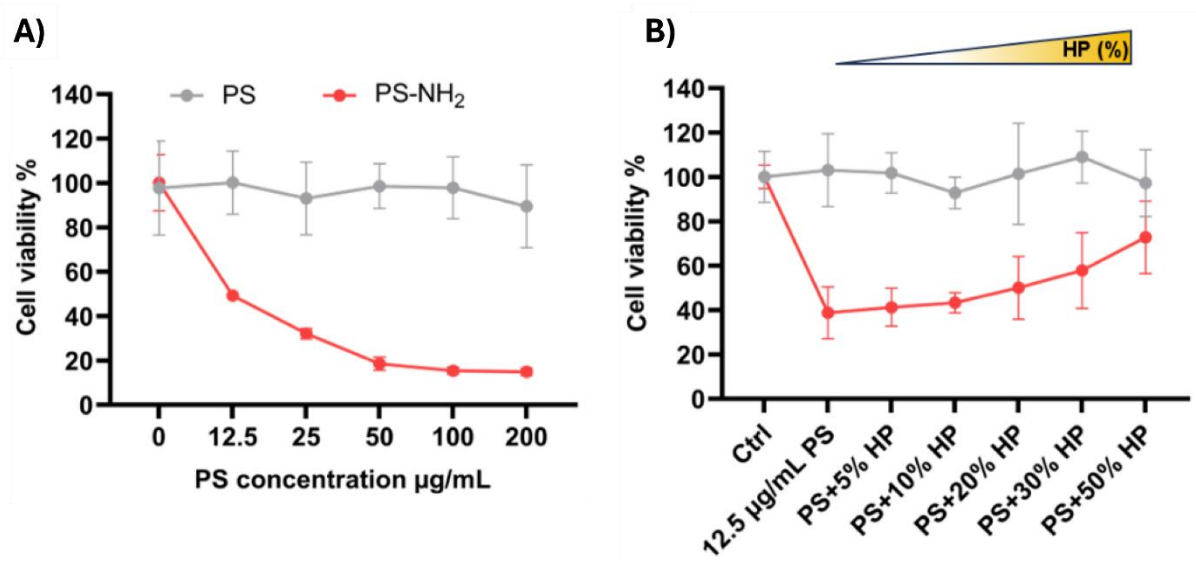


Figure 11. ***A)*** *Cell viability of SK-BR-3 cells upon incubation with PS NPs and PS-NH_2 NPs.* ***B)*** *Cell viability of SK-BR-3 cells upon incubation with coronated PS NPs and PS-NH_2 NPs. Results are expressed as the percentage of living cells to untreated cells. Data are reported as mean ± SD, n = 6. Reproduced with permission from [135], Copyright (2024) The Royal Society of Chemistry.*

As discussed previously, the PC is a dynamic and continuously evolving structure, with adsorbed proteins being exchanged as NPs encounter different biological environments throughout their *in vivo* journey. This continual remodelling can substantially alter NP-cell interactions and, consequently, their biological effects. Cai *et al*. demonstrated that, following cellular internalisation, blood-derived proteins within the corona of AuNPs were progressively displaced by intracellular proteins, including pyruvate kinase M2.[136] This intracellular protein exchange disrupted protein homeostasis, impaired glycolytic metabolism, and ultimately induced cell death, highlighting that PC evolution continues beyond circulation and into the intracellular environment.

Collectively, these studies demonstrate that nanotoxicity is governed not only by the initial composition of the PC but also by its dynamic evolution throughout biological transport and cellular processing. A more complete understanding of these spatiotemporal changes will therefore be essential for the rational engineering of PCs that minimise adverse biological effects while preserving NP functionality.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

4 Challenges and Outlook

4.1 Standardisation and reproducibility

Despite significant advances in PC characterisation, substantial challenges remain in generating reproducible and clinically relevant datasets. A major limitation arises from the lack of standardised protocols for PC isolation, sample preparation, proteomic analysis, and bioinformatic processing, resulting in considerable inter-study variability.[74] Mahmoudi *et al*. highlighted this issue by reporting that only 1.8% of proteins were consistently identified across 17 identical samples analysed by 17 independent proteomics laboratories in the United States.[137] The discrepancies were attributed to differences in sample preparation, LC–MS instrumentation, acquisition parameters, and data analysis workflows.[138,139] Encouragingly, subsequent multicentre work demonstrated that harmonising these analytical workflows can substantially improve reproducibility: applying a uniform database-search and data-processing pipeline increased the overlap in identified proteins from 1.8% to 16.2% across the top 11 facilities, while further standardisation of sample preparation and instrumentation increased overlap to 40%.[140] These findings highlight the substantial impact of methodological standardisation on PC characterisation and emphasise its importance for generating comparable datasets and accelerating clinical translation.

4.2 Dynamic PC evolution

Beyond analytical variability, the inherently dynamic nature of the PC continues to limit our understanding of NP behaviour *in vivo*. Protein adsorption and desorption occur continuously as NPs encounter different biological environments, resulting in progressive remodelling of corona composition throughout circulation and following cellular uptake. Although the total quantity of adsorbed protein often remains relatively constant, the identities of bound proteins evolve according to the surrounding biological milieu, consistent with the Vroman effect.[141] The rate and extent of this remodelling are strongly influenced by NP physicochemical properties.[142] For example, hydrophobic NPs generally form more stable protein interactions that slow corona exchange, whereas carboxylated polystyrene NPs (COOH-PS NPs) exhibit more rapid adsorption kinetics and faster protein exchange dynamics.[27,142143] Capturing these spatiotemporal changes remains a significant challenge, particularly as recent evidence suggests that HCs retain

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

a "molecular memory" of previous biological environments, providing insight into the NP's biological journey. [142] Recent work by Adumeau *et al.* has extended this concept beyond extracellular environments, demonstrating that following cellular internalisation, some NP-PC complexes can acquire additional cell-derived biomolecular layers termed 'condensate coronas'.[144] These hybrid complexes, comprising proteins, mRNAs and long RNAs, were shown to facilitate intracellular NP trafficking and the transfer of functional proteins and RNAs between cells. Understanding how NP-associated biomolecular layers evolve following cellular uptake, and how these changes influence NP fate and function, therefore represents an important direction for future research.

4.3 Computational approaches for PC prediction

Alongside experimental advances, artificial intelligence (AI), machine learning (ML) and molecular simulations are emerging as powerful tools for accelerating PC research.[145] These approaches can identify relationships between NP physicochemical properties and corona composition that would be difficult to resolve experimentally. For example, Fu *et al.* developed ML frameworks capable of predicting relative protein abundance (RPA) and adsorption patterns on NP surfaces, providing guidance for rational design of PCs in biomedical applications.[146] Similarly, Yan *et al.* integrated nanostructure imaging with multiple NP descriptors to predict nano-bio interactions and biological responses,[147] while Panigrahi *et al.* employed molecular simulations to investigate interactions between plasma proteins and carbon-based nanomaterials, informing the design of safer and more effective drug delivery systems.[148]

4.4 Analytical limitations

An additional challenge is ensuring that experimentally generated PCs accurately reflect those formed *in vivo*. Most studies continue to rely on simplified *in vitro* systems using isolated serum or plasma, which fail to reproduce the complexity of dynamic blood flow, sequential organ exposure, and patient-specific biological variability. Consequently, translating PC findings from laboratory studies to clinical settings remains difficult.[149] Future research should therefore prioritise physiologically relevant experimental models, patient-derived biological samples, and real-time *in situ* characterisation techniques capable of capturing corona evolution under clinically representative conditions.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Finally, the large dynamic range of protein concentrations in biological fluids presents a persistent analytical challenge. Highly abundant proteins, including albumin and immunoglobulins, can dominate the PC and mask the detection of low-abundance proteins that may play disproportionately important roles in NP targeting, immune recognition, or disease-specific molecular signatures.[142,150] Improvements in proteomic sensitivity and selective enrichment strategies will therefore be essential for revealing these functionally important low-abundance proteins.

Ultimately, the field is shifting from viewing the PC as an unavoidable biological barrier to recognising it as a tuneable biological interface. Future advances will therefore depend not only on improving our ability to characterise the PC, but on integrating predictive strategies to engineer their formation for specific biomedical applications. Combining standardised experimental workflows with AI, advanced proteomics, and rational NP design offers a realistic pathway towards personalised nanomedicines in which PC is deliberately harnessed to improve therapeutic efficacy, diagnostic accuracy, and safety.

5. Conclusion

As PC formation is effectively unavoidable following NP exposure to biological fluids, future research should increasingly focus on understanding and directing, rather than preventing its formation. By engineering NP physicochemical properties to control PC composition and evolution, the corona can be transformed from an obstacle to clinical translation, into a functional biological interface that enhances therapeutic efficacy, diagnostic accuracy, biosensing performance, and nanomaterial safety. Continued advances in PC characterisation, standardised analytical workflows, predictive computational modelling, and rational NP design will be essential for bridging the gap between *in vitro* and *in vivo* studies and accelerating the clinical translation of PC-enabled nanotechnologies. Ultimately, harnessing the PC offers a paradigm shift in nanomedicine, enabling the development of more effective, personalised, and biologically informed NP systems.

Acknowledgements

The authors thank Loughborough University for funding.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

Author Contributions

E.C. – Writing – Original Draft Preparation, Visualization; J.C.R – Writing – Review and Editing; A.K.P – Conceptualization, Supervision, Writing – Review and Editing.

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

This study did not involve the novel creation, generation, or analysis of primary research materials. All relevant literature is cited in the References.

References

1 I. Zainab, Z. Naseem, S. R. Batool, F. Pierini, S. Kizilel and M. A. Nazeer, *Beilstein Journal of Nanotechnology*, 2025, **16**, 1499.

2 E. Blanco, H. Shen and M. Ferrari, *Nat. Biotechnol.*, 2015, **33**, 941–51.

3 P.-D. Ly, K.-N. Ly, H.-L. Phan, H. H. T. Nguyen, V.-A. Duong and H. V. Nguyen, *Frontiers in Nanotechnology*, 2024, **6**, 1456939.

4 G. De Crozals, R. Bonnet, C. Farre and C. Chaix, *Nano Today*, 2016, **11**, 435–463.

5 A. K. Pearce and R. K. O'Reilly, *Biomacromolecules*, 2021, **22**, 4459–4469.

6 S. Anu Mary Ealia and M. P. Saravanakumar, *IOP Conf. Ser. Mater. Sci. Eng.*, 2017, **263**, 032019.

7 M. Nikzamir, A. Akbarzadeh and Y. Panahi, *J. Drug Deliv. Sci. Technol.*, 2021, **61**, 102316.

8 D. Bobo, K. J. Robinson, J. Islam, K. J. Thurecht and S. R. Corrie, *Pharmaceutical Research 2016 33:10*, 2016, **33**, 2373–2387.

9 M. Karam, D. Fahs, B. Maatouk, B. Safi, A. A. Jaffa and R. Mhanna, *Mater. Today Bio*, 2022, **14**, 100249.

10 T. Bruna, F. Maldonado-Bravo, P. Jara and N. Caro, *Int. J. Mol. Sci.*, 2021, **22**, 7202.

11 F. Du, M. Zhang, A. Gong, Y. Tan, J. Miao, Y. Gong, S. Zou, L. Zhang, L. Zhang, C. Wu, M. Sun and H. Ju, *Biomaterials*, 2017, **121**, 109–120.

12 V. Zubkovs, N. Schuergers, B. Lambert, E. Ahunbay and A. A. Boghossian, *Small*, 2017, **13**, 1701654.

13 Y. Sun, Y. Zhou, M. Rehman, Y. F. Wang and S. Guo, *Chem & Bio Engineering*, 2024, **1**, 757–772.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

14 T. Kopac, *Int. J. Biol. Macromol.*, 2021, **169**, 290–301.

15 T. Cedervall, I. Lynch, S. Lindman, T. Berggård, E. Thulin, H. Nilsson, K. A. Dawson and S. Linse, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 2050–2055.

16 C. Corbo, R. Molinaro, A. Parodi, N. E. Toledano Furman, F. Salvatore and E. Tasciotti, *Nanomedicine*, 2016, **11**, 81.

17 H. Li, Y. Wang, Q. Tang, D. Yin, C. Tang, E. He, L. Zou and Q. Peng, *Acta Biomater.*, 2021, **129**, 57–72.

18 W. C. Chou and Z. Lin, *Curr. Opin. Biotechnol.*, 2024, **85**, 103046.

19 K. Nienhaus and G. U. Nienhaus, *Small*, 2023, **19**, 2301663.

20 C. K. Elechalawar, M. N. Hossen, L. McNally, R. Bhattacharya and P. Mukherjee, *J. Control. Release*, 2020, **322**, 122.

21 S. Panico, S. Capolla, S. Bozzer, G. Toffoli, M. Dal Bo and P. Macor, *Pharmaceutics 2022, Vol. 14, Page 2605*, 2022, **14**, 2605.

22 P. Foroozandeh and A. A. Aziz, *Nanoscale Research Letters 2015 10:1*, 2015, **10**, 221-.

23 A. M. Villacorta, A. Mielcarek, M. G. Martinez, H. Jorge, A. Henschke, E. Coy, V. Gomez-Vallejo, J. Llop and S. E. Moya, *Small*, 2024, **20**, e2309616.

24 J. M. Metselaar and T. Lammers, *Drug Deliv. Transl. Res.*, 2020, **10**, 721–725.

25 E. Gultepe, R. Valluru, N. B. Brown and S. Sridhar, *Nano Today*, 2026, **66**, 102898.

26 M. H. Akhter, H. Khalilullah, M. Gupta, M. A. Alfaleh, N. A. Alhakamy, Y. Riadi and S. Md, *Biomedicines*, 2021, **9**, 1496.

27 G. Bashiri, M. S. Padilla, K. L. Swingle, S. J. Shepherd, M. J. Mitchell and K. Wang, *Lab Chip*, 2023, **23**, 1432–1466.

28 S. J. Park, *Int. J. Nanomedicine*, 2020, **15**, 5783.

29 W. Richtering, I. Alberg and R. Zentel, *Small*, 2020, **16**, 2002162.

30 M. P. Monopoli, C. Åberg, A. Salvati and K. A. Dawson, *Nat. Nanotechnol.*, 2012, **7**, 779–786.

31 L. Böhmert, L. Voß, V. Stock, A. Braeuning, A. Lampen and H. Sieg, *Nanoscale Adv.*, 2020, **2**, 563–582.

32 B. Xiao, Y. Liu, I. Chandrasiri, C. Overby and D. S. W. Benoit, *ACS Appl. Mater. Interfaces*, 2023, **15**, 13993.

33 I. Rouse and V. Lobaskin, *Biophys. J.*, 2021, **120**, 4457–4471.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

34 M. Mahmoudi, I. Lynch, M. R. Ejtehadi, M. P. Monopoli, F. B. Bombelli and S. Laurent, *Chem. Rev.*, 2011, **111**, 5610–5637.

35 S. H. D. P. Lacerda, J. J. Park, C. Meuse, D. Pristinski, M. L. Becker, A. Karim and J. F. Douglas, *ACS Nano*, 2010, **4**, 365–79.

36 L. Marichal, G. Klein, J. Armengaud, Y. Boulard, S. Chédin, J. Labarre, S. Pin, J. P. Renault and J. C. Aude, *Nanomaterials 2020, Vol. 10, Page 240*, 2020, **10**, 240.

37 Y.-W. Yin, Y.-Q. Ma and H.-M. Ding, *Langmuir*, 2024, **40**, 15205–15213.

38 R. García-Álvarez, M. Hadjidemetriou, A. Sánchez-Iglesias, L. M. Liz-Marzán and K. Kostarelos, *Nanoscale*, 2018, **10**, 1256–1264.

39 Z. Hu, H. Zhang, Y. Zhang, R. Wu and H. Zou, *Colloids Surf. B Biointerfaces*, 2014, **121**, 354–361.

40 W. Huang, G. Xiao, Y. Zhang and W. Min, *Biomedicine & Pharmacotherapy*, 2021, **139**, 111541.

41 C. C. Fleischer and C. K. Payne, *J. Phys. Chem. B*, 2012, **116**, 8901–7.

42 R. Bilardo, F. Traldi, A. Vdovchenko and M. Resmini, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, 2022, **14**, e1788.

43 E. Papini, R. Tavano and F. Mancin, *Front. Immunol.*, 2020, **11**, 567365.

44 R. M. Visalakshan, M. N. MacGregor, S. Sasidharan, A. Ghazaryan, A. M. Mierczynska-Vasilev, S. Morsbach, V. Mailänder, K. Landfester, J. D. Hayball and K. Vasilev, *ACS Appl. Mater. Interfaces*, 2019, **11**, 27615–27623.

45 Q. Yu, L. Zhao, C. Guo, B. Yan and G. Su, *Front. Bioeng. Biotechnol.*, 2020, **8**, 522931.

46 M. P. Monopoli, D. Walczyk, A. Campbell, G. Elia, I. Lynch, F. Baldelli Bombelli and K. A. Dawson, *J. Am. Chem. Soc.*, 2011, **133**, 2525–2534.

47 A. Gessner, A. Lieske, B. R. Paulke and R. H. Müller, *J. Biomed. Mater. Res. A*, 2003, **65**, 319–326.

48 B. Kharazian, N. L. Hadipour and M. R. Ejtehadi, *Int. J. Biochem. Cell Biol.*, 2016, **75**, 162–174.

49 E. Gerasimovich, A. Karaulov, I. Nabiev and A. Sukhanova, *Nanomaterials*, 2025, **15**, 1013.

50 R. M. Sarimov, E. A. Molkova, A. V Simakin, A. S. Dorokhov and S. V Gudkov, *Int. J. Mol. Sci.*, 2025, **26**, 9771.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

51 Y. K. Lee, E.-J. Choi, T. J. Webster, S.-H. Kim and D. Khang, *Int. J. Nanomedicine*, 2015, **10**, 97–113.

52 C. Ge, J. Du, L. Zhao, L. Wang, Y. Liu, D. Li, Y. Yang, R. Zhou, Y. Zhao, Z. Chai and C. Chen, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 16968–16973.

53 M. Wen, Y. Li, W. Zhong, Q. Li, L. Cao, L. li Tan and L. Shang, *J. Colloid Interface Sci.*, 2022, **610**, 116–125.

54 R. Coreas, C. Castillo, Z. Li, D. Yan, Z. Gao, J. Chen, D. Bitounis, D. Parviz, M. S. Strano, P. Demokritou and W. Zhong, *Chem. Res. Toxicol.*, 2022, **35**, 1244–1256.

55 L. Digiacomo, D. Pozzi, S. Palchetti, A. Zingoni and G. Caracciolo, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, 2020, **12**, e1615.

56 E. Papini, R. Tavano and F. Mancin, *Front. Immunol.*, 2020, **11**, 567365.

57 K. Partikel, R. Korte, N. C. Stein, D. Mulac, F. C. Herrmann, H. U. Humpf and K. Langer, *European Journal of Pharmaceutics and Biopharmaceutics*, 2019, **141**, 70–80.

58 *Nature Nanotechnology 2025 20:5*, 2025, **20**, 575–575.

59 P. Kesharwani, V. Kumar, K. W. Goh, G. Gupta, A. Alsayari, S. Wahab and A. Sahebkar, *Mol. Cancer*, 2025, **24**, 205.

60 K. Shiraishi and M. Yokoyama, *Sci. Technol. Adv. Mater.*, 2019, **20**, 324.

61 T. T. H. Thi, E. H. Pilkington, D. H. Nguyen, J. S. Lee, K. D. Park and N. P. Truong, *Polymers (Basel).*, 2020, **12**, 298.

62 M. F. S. Deuker, V. Mailänder, S. Morsbach and K. Landfester, *Nanoscale Horiz.*, 2023, **8**, 1377–1385.

63 G. Bashiri, M. S. Padilla, K. L. Swingle, S. J. Shepherd, M. J. Mitchell and K. Wang, *Lab Chip*, 2023, **23**, 1432–1466.

64 S. Schöttler, K. Landfester and V. Mailänder, *Angew. Chem. Int. Ed.*, 2016, **55**, 8806–8815.

65 N. M. Gulati, P. L. Stewart and N. F. Steinmetz, *Mol. Pharm.*, 2018, **15**, 2900.

66 J. Humphries, N. M. Warne, O. M. Feeney, K. J. Thurecht and K. Kempe, *Journal of Controlled Release*, 2026, **394**, 114838.

67 W. Xu, M. Xu, Y. Xiao, L. Yu, H. Xie, X. Jiang, M. Chen, H. Gao and L. Wang, *Asian J. Pharm. Sci.*, 2022, **17**, 401–411.

68 Y. Wang, H. Zhang, W. Xiao, Y. Liu, Y. Zhou, X. He, X. Xia, T. Gong, L. Wang and H. Gao, *J. Control. Release*, 2021, **333**, 352–361.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

69 L. Yu, M. Xu, W. Xu, W. Xiao, X. H. Jiang, L. Wang and H. Gao, *Nano Lett.*, 2020, **20**, 8903–8911.

70 H. Gao and Q. He, *Expert Opin. Drug Deliv.*, 2014, **11**, 409–420.

71 W. He, W. Wu, Y. Li, Q. Liu, P. Ren, H. Liu and F. Chen, *Nanomedicine*, 2025, **20**, 769–771.

72 O. Vilanova, A. Martinez-Serra, M. P. Monopoli and G. Franzese, *Frontiers in Nanotechnology*, 2024, **6**, 1531039.

73 L. Böhmert, L. Voß, V. Stock, A. Braeuning, A. Lampen and H. Sieg, *Nanoscale Adv.*, 2020, **2**, 563.

74 N. M. Mayordomo, A. Zatarain-Beraza, F. Valerio, V. Álvarez-Méndez, P. Turegano, L. Herranz-García, A. López de Aguileta, N. Cattani, A. Álvarez-Alonso and M. L. Fanarraga, *Biomimetics*, 2025, **10**, 276.

75 M. J. Hajipour, R. Safavi-Sohi, S. Sharifi, N. Mahmoud, A. A. Ashkarran, E. Voke, V. Serpooshan, M. Ramezankhani, A. S. Milani, M. P. Landry and M. Mahmoudi, *Small*, 2023, **19**, 2301838.

76 F. Fu, D. Crespy, K. Landfester and S. Jiang, *Chem. Soc. Rev.*, 2024, **53**, 10827–10851.

77 Y. Sun, Y. Zhou, M. Rehman, Y. F. Wang and S. Guo, *Chem & Bio Engineering*, 2024, **1**, 757–772.

78 D. Sanchez-Guzman, G. Giraudon-Colas, L. Marichal, Y. Boulard, F. Wien, J. Degrouard, A. Baeza-Squiban, S. Pin, J. P. Renault and S. Devineau, *ACS Nano*, 2020, **14**, 9073–9088.

79 D. Baimanov, J. Wang, J. Zhang, K. Liu, Y. Cong, X. Shi, X. Zhang, Y. Li, X. Li, R. Qiao, Y. Zhao, Y. Zhou, L. Wang and C. Chen, *Nature Communications 2022 13:1*, 2022, **13**, 5389-.

80 F. Fu, D. Crespy, K. Landfester and S. Jiang, *Chem. Soc. Rev.*, 2024, **53**, 10827–10851.

81 Y. Li and J. S. Lee, *Materials 2020, Vol. 13, Page 3093*, 2020, **13**, 3093.

82 B. Ranapangu, M. Sandhu and A. T. Paul, *Drug Discov. Today*, 2025, **30**, 104534.

83 Y. Meng, J. Chen, Y. Liu, Y. Zhu, Y. K. Wong, H. Lyu, Q. Shi, F. Xia, L. Gu, X. Zhang, P. Gao, H. Tang, Q. Guo, C. Qiu, C. Xu, X. He, J. Zhang and J. Wang, *J. Pharm. Anal.*, 2022, **12**, 879–888.

84 S. Bhattacharjee, *J. Control. Release*, 2016, **235**, 337–351.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

85 G. U. Nienhaus, P. Maffre and K. Nienhaus, *Methods Enzymol.*, 2013, **519**, 115–137.

86 M. Battaglini, M. Belenli Gümüş and G. Ciofani, *Adv. Mater. Technol.*, 2021, **6**, 2100660.

87 S. Yu, D. Baimanov, Z. Guo, Q. Gao, C. Chen, M. B. Cardoso and L. Wang, *Small Methods*, 2025, **9**, 2500348.

88 S. S. Atale, S. Dyawanapelly, D. D. Jagtap, R. Jain and P. Dandekar, *Int. J. Biol. Macromol.*, 2019, **123**, 97–107.

89 O. Vilanova, J. J. Mittag, P. M. Kelly, S. Milani, K. A. Dawson, J. O. Rädler and G. Franzese, *ACS Nano*, 2016, **10**, 10842–10850.

90 J. T. T. Carvalho, A. Malfatti-Gasperini, B. J. Boyd, L. Wang and M. B. Cardoso, *ACS Omega*, 2025, **10**, 46199–46209.

91 N. J. Greenfield, *Nature Protocols 2007 1:6*, 2007, **1**, 2876–2890.

92 K. Nienhaus and G. U. Nienhaus, *Small*, 2023, **19**, 2301663.

93 A. A. Ashkarran, *Nanomedicine*, 2025, **20**, 2709–2712.

94 L. Yang, S. Zhu, W. Hang, L. Wu and X. Yan, *Anal. Chem.*, 2009, **81**, 2555–63.

95 Y. Niu, Y. Yu, X. Shi, F. Fu, H. Yang, Q. Mu, D. Crespy, K. Landfester and S. Jiang, *Nano Lett.*, 2024, **24**, 9202–9211.

96 B. Önal Acet, D. Gül, R. H. Stauber, M. Odabaşı and Ö. Acet, *Nanomaterials*, 2024, **14**, 823.

97 A. Yusuf, A. R. Z. Almotairy, H. Henidi, O. Y. Alshehri and M. S. Aldughaim, *Polymers (Basel).*, 2023, **15**, 1596.

98 R. Shi, X. Liu, Y. Wang, M. Pan, S. Wang, L. Shi and B. Ni, *Hum. Vaccin. Immunother.*, 2024, **20**, 2342592.

99 Y. F. Wang, Y. Zhou, J. B. Sun, X. Wang, Y. Jia, K. Ge, Y. Yan, K. A. Dawson, S. Guo, J. Zhang and X. J. Liang, *Nano Research 2022 16:1*, 2022, **16**, 715–734.

100 S. Schöttler, G. Becker, S. Winzen, T. Steinbach, K. Mohr, K. Landfester, V. Mailänder and F. R. Wurm, *Nat. Nanotechnol.*, 2016, **11**, 372–377.

101 M. P. Vincent, S. Bobbala, N. B. Karabin, M. Frey, Y. Liu, J. O. Navidzadeh, T. Stack and E. A. Scott, *Nature Communications 2021 12:1*, 2021, **12**, 648-.

102 J. Kreuter, D. Shamenkov, V. Petrov, P. Ramge, K. Cychutek, C. Koch-Brandt and R. Alyautdin, *J. Drug Target.*, 2002, **10**, 317–325.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

103 H. Li, Y. Wang, Q. Tang, D. Yin, C. Tang, E. He, L. Zou and Q. Peng, *Acta Biomater.*, 2021, **129**, 57–72.

104 L. Li, Y. Yang, L. Wang, F. Xu, Y. Li and X. He, *J. Mol. Biol.*, 2023, **435**, 167771.

105 Y. Miao, L. Li, Y. Wang, J. Wang, Y. Zhou, L. Guo, Y. Zhao, D. Nie, Y. Zhang, X. Zhang and Y. Gan, *Nature Communications 2024 15:1*, 2024, **15**, 1159-.

106 D. Cai, W. Gao, Z. Li, Y. Zhang, L. Xiao and Y. Xiao, *Biomedicines*, 2022, **10**, 1203.

107 T. Tan, Q. Huang, W. Chu, B. Li, J. Wu, Q. Xia and X. Cao, *Drug Deliv.*, 2022, **29**, 692–701.

108 V. Mirshafiee, R. Kim, S. Park, M. Mahmoudi and M. L. Kraft, *Biomaterials*, 2016, **75**, 295–304.

109 L. N. Thwala, S. C. Ndlovu, K. T. Mpofu, M. Y. Lugongolo and P. Mthunzi-Kufa, *Nanomaterials*, 2023, **13**, 1247.

110 J. Wang, A. J. Drelich, C. M. Hopkins, S. Mecozzi, L. Li, G. Kwon and S. Hong, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, 2022, **14**, e1754.

111 Y. Wu, Y. Yang, W. Zhao, Z. P. Xu, P. J. Little, A. K. Whittaker, R. Zhang and H. T. Ta, *J. Mater. Chem. B*, 2018, **6**, 4937–4951.

112 D. Ren, L. Wei, S. Boutry, M. Özkan, E. Poliukhina, L. S. Riudalbas, K. Homicsko, D. E. Speiser, J. Fellay, Q. K. Ong and F. Stellacci, *ACS Cent. Sci.*, 2026, **12**, 1439–1450.

113 M. La Belle, P. J. Blanche and R. M. Krauss, *J. Lipid Res.*, 1997, **38**, 690–700.

114 M. J. Hajipour, J. Raheb, O. Akhavan, S. Arjmand, O. Mashinchian, M. Rahman, M. Abdolahad, V. Serpooshan, S. Laurent and M. Mahmoudi, *Nanoscale*, 2015, **7**, 8978–8994.

115 G. Caracciolo, D. Caputo, D. Pozzi, V. Colapicchioni and R. Coppola, *Colloids Surf. B Biointerfaces*, 2014, **123**, 673–678.

116 C. Corbo, A. A. Li, H. Poustchi, G. Y. Lee, S. Stacks, R. Molinaro, P. Ma, T. Platt, S. Behzadi, R. Langer, V. Farias and O. C. Farokhzad, *Adv. Healthc. Mater.*, 2021, **10**, 2000948.

117 E. P. Cisneros, B. A. Morse, A. Savk, K. Malik, N. A. Peppas and O. L. Lanier, *Journal of Nanobiotechnology 2024 22:1*, 2024, **22**, 714-.

118 E. P. Cisneros, B. A. Morse, A. Savk, K. Malik, N. A. Peppas and O. L. Lanier, *Journal of Nanobiotechnology 2024 22:1*, 2024, **22**, 714-.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

119 L. Digiacomo, D. Caputo, R. Cammarata, V. La Vaccara, R. Coppola, E. Quagliarini, M. Iacobini, S. Renzi, F. Giulimondi, D. Pozzi, G. Caracciolo and H. Amenitsch, *Nanoscale*, 2025, **17**, 7066–7075.

120 J. Yoon, M. Shin, T. Lee and J. W. Choi, *Materials 2020, Vol. 13, Page 299*, 2020, **13**, 299.

121 A. Karnwal, R. S. Kumar Sachan, I. Devgon, J. Devgon, G. Pant, M. Panchpuri, A. Ahmad, M. B. Alshammari, K. Hossain and G. Kumar, *ACS Omega*, 2024, **9**, 29966–29982.

122 R. Gao, Y. Mao, C. Ma, Y. Wang, H. Jia, X. Chen, Y. Lu, D. Zhang and L. Yu, *ACS Appl. Mater. Interfaces*, 2022, **14**, 55414–55422.

123 S. Cheeseman, P. Moazzam, N. Mahmoudi, M. Mahmoudi, F. Caruso, A. Tricoli and D. R. Nisbet, *Small*, 2025, **21**, e03820.

124 X. Tao, X. Chang, X. Wan, Y. Guo, Y. Zhang, Z. Liao, Y. Song and E. Song, *Anal. Chem.*, 2020, **92**, 14990–14998.

125 N. Alizadeh, A. Georgas, C. Argirusis, G. Sourkouni and N. Argirusis, *Coatings 2026, Vol. 16, Page 164*, 2026, **16**, 164.

126 J. J. Gooding and V. R. Gonçales, *Curr. Opin. Electrochem.*, 2017, **5**, 203–210.

127 S. Lee, J. Cha, S. Shin, M. Yoon, G. Sánchez-Velázquez, S. Yang, M. S. Strano and S. Y. Cho, *ACS Nano*, 2025, **19**, 24653–24668.

128 Y. Zhang, J. Hao, X. Xu, X. Chen and J. Wang, *Anal. Chem.*, 2020, **92**, 2080–2087.

129 E. Quagliarini, L. Digiacomo, D. Caputo, A. Coppola, H. Amenitsch, G. Caracciolo and D. Pozzi, *Nanomaterials*, 2022, **12**, 1397.

130 E. Quagliarini, D. Caputo, R. Cammarata, G. Caracciolo and D. Pozzi, *Cancer Nanotechnol.*, 2023, **14**, 16.

131 U. Havelikar, K. B. Ghorpade, A. Kumar, A. Patel, M. Singh, N. Banjare and P. N. Gupta, *Discover Nano 2024 19:1*, 2024, **19**, 165-.

132 P. J. Babu, A. Tirkey, A. A. Paul, K. Kristollari, J. Barman, K. Panda, N. Sinha, B. R. Babu and R. S. Marks, *Engineered Regeneration*, 2024, **5**, 326–341.

133 C. C. S. Batista, K. Panico, J. Trousil, O. Janoušková, C. E. de Castro, P. Štěpánek and F. C. Giacomelli, *Colloids Surf. B Biointerfaces*, 2022, **218**, 112778.

134 J. Wang, Y. Xu, Y. Zhou, J. Zhang, J. Jia, P. Jiao, Y. Liu and G. Su, *Science of The Total Environment*, 2024, **914**, 169590.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

135 S. Xiao, J. Wang, L. Digiacomo, A. Amici, V. De Lorenzi, L. A. Pugliese, F. Cardarelli, A. Cerrato, A. Laganà, L. Cui, M. Papi, G. Caracciolo, C. Marchini and D. Pozzi, *Nanoscale*, 2024, **16**, 16671–16683.

136 R. Cai, J. Ren, M. Guo, T. Wei, Y. Liu, C. Xie, P. Zhang, Z. Guo, A. J. Chetwynd, P. C. Ke, I. Lynch and C. Chen, *Proc. Natl. Acad. Sci. U. S. A.*, 2022, **119**, e2200363119.

137 A. A. Ashkarran, H. Gharibi, E. Voke, M. P. Landry, A. A. Saei and M. Mahmoudi, *Nature Communications 2022 13:1*, 2022, **13**, 1–11.

138 H. Gharibi, A. A. Ashkarran, M. Jafari, E. Voke, M. P. Landry, A. A. Saei and M. Mahmoudi, *Nature Communications 2024 15:1*, 2024, **15**, 342-.

139 F. Klont, L. Bras, J. C. Wolters, S. Ongay, R. Bischoff, G. B. Halmos and P. Horvatovich, *Anal. Chem.*, 2018, **90**, 5405–5413.

140 A. A. Ashkarran, H. Gharibi, S. M. Modaresi, A. A. Saei and M. Mahmoudi, *Nano Lett.*, 2024, **24**, 9874–9881.

141 P. Foroozandeh and A. A. Aziz, *Nanoscale Res. Lett.*, DOI:10.1186/S11671-015-0922-3.

142 N. M. Mayordomo, A. Zatarain-Beraza, F. Valerio, V. Álvarez-Méndez, P. Turegano, L. Herranz-García, A. López de Aguileta, N. Cattani, A. Álvarez-Alonso and M. L. Fanarraga, *Biomimetics*, 2025, **10**, 276.

143 E. Haghighi, S. S. Abolmaali, A. Dehshahri, S. A. Mousavi Shaegh, N. Azarpira and A. M. Tamaddon, *J. Nanobiotechnology*, 2024, **22**, 710.

144 L. Adumeau, Y. Lin, M. M. McCafferty, S. Vercellino, Y. F. Wang, X. Yang, W. Zhang, D. Garry, F. Bertoli, C. Gaffney, Y. L. Dee, L. Song, E. Canepa, X. Xiao, Y. Ye, G. Huang, Q. Wang, L. Liao, Z. Zhao, K. Evers, L. Cursi, V. Petseva, Z. Xie, A. Fleming, E. Sheridan, I. Morera, K. Liu, Y. Li, M. Saccomanno, A. Marcantognini, Y. Yan and K. A. Dawson, *Nature Materials 2026 25:6*, 2026, **25**, 1045–1057.

145 T. Kopac, *Bioengineering 2025, Vol. 12, Page 312*, 2025, **12**, 312.

146 X. Fu, C. Yang, Y. Su, C. Liu, H. Qiu, Y. Yu, G. Su, Q. Zhang, L. Wei, F. Cui, Q. Zou and Z. Zhang, *Research*, 2024, **7**, 0487.

147 X. Yan, J. Zhang, D. P. Russo, H. Zhu and B. Yan, *ACS Sustain. Chem. Eng.*, 2020, **8**, 19096–19104.

148 A. R. Panigrahi, A. Sahu, P. Yadav, S. K. Beura, J. Singh, K. Mondal and S. K. Singh, *Adv. Protein Chem. Struct. Biol.*, 2024, **139**, 263–288.

149 G. Caracciolo, O. C. Farokhzad and M. Mahmoudi, *Trends Biotechnol.*, 2017, **35**, 257–264.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.

150 M. Mahmoudi, *Nature Communications 2022 13:1*, 2022, **13**, 49-.

Downloaded from https://www.cambridge.org/core. 18 Nov 2026 at 04:41:57, subject to the Cambridge Core terms of use.