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The gold nanoparticle–lipid membrane synergy for nanomedical applications

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The integration of gold nanoparticles (AuNPs) with lipid bilayers gives rise to powerful synergistic effects arising from nanoscale interactions. Precise control over these interactions enables the rational design of hybrid AuNP–lipid membrane multifunctional composites, unlocking advanced analytical tools and cutting-edge biomedical applications. From a materials design standpoint, functionalizing AuNPs with lipid membranes reduces cytotoxicity and enhances stability in complex biological environments. This biomimetic strategy also enables precise modulation of interactions at biological interfaces, opening new avenues to endow AuNPs with selective recognition and targeting abilities. Importantly, the combination leads to emergent collective behaviors. For instance, the self-assembly of AuNPs on lipid membranes creates plasmonic 'hot spots' that amplify Raman signals for ultrasensitive SERS-based diagnostics. Membrane-embedded AuNPs can also act as nanoscale heaters, enabling spatiotemporally controlled drug release through light-triggered lipid phase transitions or nanomechanical disruption of the lipid carriers. Furthermore, membrane-mediated AuNP clustering enhances magnetic, catalytic, and optical responses, contributing to the development of smart nanomotors and multifunctional therapeutic platforms. These synergistic functionalities arise specifically from the interplay between AuNPs and lipid architectures and cannot be replicated by either system alone. This review critically explores the functional synergy between AuNPs and lipid membranes, highlights recent key advancements, addresses current challenges, and outlines innovative applications in nanomedicine, including targeted drug delivery, photothermal therapy, and biomolecular sensing.

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1. Outline

1.1 AuNPs and lipid membranes: from interaction fundamentals to nanomedical applications

The combination of gold nanoparticles (AuNPs) with lipid membranes has long been explored in nanotechnology, driven by the unique and synergistic properties that emerge from their interplay.

AuNPs are among the most versatile nanomaterials for biomedical applications, primarily due to their remarkable ability to absorb and manipulate visible light, through a phenomenon known as localized surface plasmon resonance (LSPR).[1] Localized surface plasmon resonance (LSPR) refers to the collective and coherent oscillation of surface conduction electrons in response to incident electromagnetic radiation, occurring in gold and other noble metal nanoparticles. This

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Debora Berti

Our first contribution to Nanoscale Horizons dates back to 2021 with a communication that laid the conceptual groundwork for this invited review. In this contribution, we explore the rich synergy between gold nanoparticles and lipid membranes, highlighting how their integration enables advanced analytical tools and innovative nanomedical applications. We are honoured to be part of the 10th anniversary collection of a journal that continues to be a unique platform for interdisciplinary research in nanoscience and soft matter. We look forward to continuing this inspiring scientific dialogue in the years to come.

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resonance results in strong absorption and scattering of light at specific wavelengths, typically within the visible to near-infrared range. This optical effect is extremely sensitive to the physicochemical features of AuNP (*e.g.*, particle size, shape, and surface functionalization) and the surrounding chemical environment. Additionally, when individual AuNPs come into proximity, their plasmonic fields can couple, leading to measurable changes in optical properties. This sensitivity makes AuNPs versatile tools in biomedical sensing, enabling applications from colorimetric assays for disease diagnosis[2,3] to surface-enhanced Raman spectroscopy (SERS) for molecular detection.[4] Moreover, the light absorbed by AuNPs can be efficiently converted into heat or enhance the generation of reactive oxygen species, enabling, for instance, effective ablation of cancer cells.[5] These properties position AuNPs as ideal agents for photothermal and photodynamic therapies, both in cancer treatment and antimicrobial applications. Compared to other inorganic NPs, AuNPs offer superior chemical stability, tunable surface chemistry and precise control over size, shape and aggregation state. Additionally, they can be readily functionalized with targeting moieties making them ideal carriers for targeted drug delivery.

Despite these advantages, a major challenge is still represented by the gap between nanomaterial design and their effective clinical translation. This issue extends beyond AuNPs and is common across nanomaterials of all compositions, representing one of the main hurdles in modern nanomedicine.[6] A key factor contributing to this translational gap is the need for a deeper understanding NP behaviour and fate in biological environments. Once they are introduced in biological environments, NPs encounter diverse biological components and barriers.[7] The colloidal forces and dynamic interactions occurring at the nano-bio interface largely define the biological activity of nanomaterials. Recognizing the need for standardized materials to support the investigation of the nano-bio interface, in 2007 the National Institute of Standards and Technology (NIST) released citrate capped AuNPs as the first nanoscale reference standard to support biomedical research into biological effects of nanoparticles.[8] Since then, AuNPs have become the 'gold standard' for studying how key physicochemical parameters—such as size, shape, surface charge and surface functionalization—affect interactions with biological environments, offering broadly applicable insights across the field of nanomaterials.

Among the many biological structures occurring in the heterogeneous environment of living systems, lipid membranes stand out as key biological barriers encountered by nanomaterials. Lipids, as amphiphilic biomolecules, spontaneously assemble in water into a variety of structures, depending on their molecular composition and the surrounding medium. Among these assemblies, planar lipid bilayers form the structural backbone of cell membranes. For nanoparticles to reach their biological target and exert their medical functions, they must interact with these membranes—either by adhering to or penetrating them—*via* a range of specific and non-specific physicochemical interactions. To separate the physicochemical factors governing nanoparticle–membrane interactions from biological variables, synthetic lipid membranes—such as supported lipid bilayers (SLBs),[9] unilamellar vesicles (liposomes),[10] and giant unilamellar vesicles (GUVs)[11]—can be conveniently employed alongside natural membranes. These systems provide simplified yet robust models for studying NP–membrane interactions under controlled conditions. Over the past decade, these systems have been extensively used to investigate the behaviour of AuNP at the membrane nano-bio interface, often in parallel with *in vitro* and *in vivo* experiments. These studies highlighted that the surface chemistry of AuNP is a key factor in determining AuNP–membrane interactions. For instance, cationic AuNP surfaces are typically associated to enhanced cytotoxicity compared to neutral or anionic counterparts, while the presence of polyethylene glycol (PEG) coatings or protein–corona layers generally reduces AuNP–membrane interactions and cell uptake. Additionally, the absence of covalent graftings or strongly bound stabilizers on AuNPs facilitates AuNP aggregation on lipid membranes, as in the case of citrate-coated AuNPs.[12] Mechanistic studies, suggest that the citrate ligands are displaced upon membrane contact, leading to electrostatic de-stabilization and AuNP aggregation.[13–18] In addition to surface chemistry, the size of AuNPs size determines their fate upon contact with lipid membranes, where adsorption, internalization and aggregation are governed by membrane bending energy and tension.[19] Likewise, particle shape influences the available contact area with the membrane, modulating both adhesion forces and AuNP self-assembly at the lipid interface.[20]

On the membrane side, physicochemical properties such as lipid phase and curvature play essential roles. Fluid-state membranes generally enhance AuNP adsorption and clustering at the membrane surface, while ordered gel-phase bilayers limit these processes.[13,21–23] Another key player in AuNP–membrane interactions is the membrane interfacial curvature, that can assume positive or negative (*i.e.*, non-zero) values under selective cell conditions. Membrane-curvature effects have been recently investigated employing advanced model platforms, *i.e.*, non-lamellar lipid films with a bicontinuous internal structure adsorbed onto a solid support. Such systems were shown to exhibit greater structural resilience against disruption induced by cationic AuNPs, compared to compositionally analogous lamellar systems.[20]

Taken together, these investigations highlight the intricate interplay between AuNP physicochemical properties and lipid membrane characteristics, which governs AuNP behavior at the nano-bio interface. The fundamental insights gained from these investigations into the mechanisms governing AuNP–membrane interactions have informed the rational design of nanomedicines with enhanced biocompatibility and therapeutic efficacy. Moreover, these investigations have highlighted the synergistic effects emerging from the combination of AuNPs with lipid membranes, promoting their integration in nanotechnology, and laying the foundation for advanced biomedical applications discussed in the following sections.

This review will cover innovations enabled by the AuNP–membrane combination, of relevance in the field of nanomedicine (see Fig. 1). Particular interest will be devoted to the

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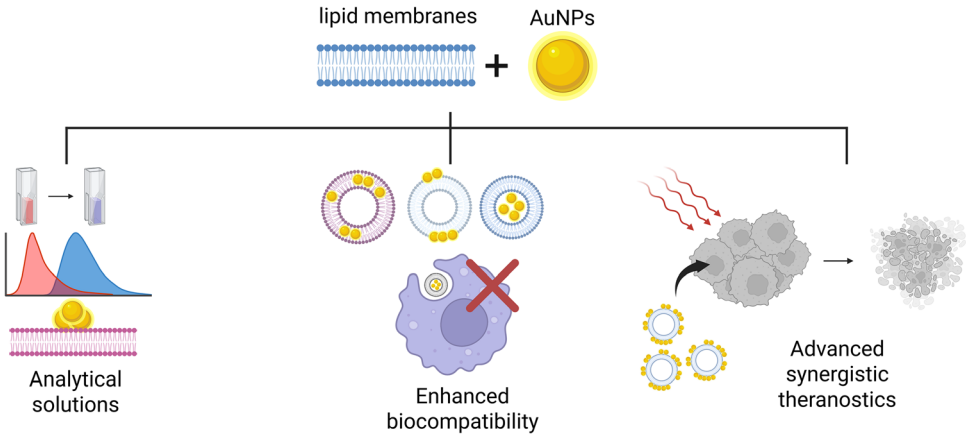

Fig. 1 Synergistic applications of AuNPs and lipid membranes. AuNPs serve as powerful probes in analytical assays to sense membrane properties, including physicochemical properties and composition. Also, lipid membranes can enhance the biocompatibility and stability of AuNPs in biological environments, altering AuNP biological fate and performances and contributing to the development of enhanced biomedical applications. The combination of AuNPs and lipid membrane also allow to create hybrid structures enabling for advanced theranostics strategies, combining for instance targeted diagnostic capabilities with programmed and localized delivery of active compounds and activation of the hybrid material. Created in BioRender. Zendrini, A. (2025) https://BioRender.com/dt6n1aa.

interaction between AuNPs and lipid membranes to develop hybrid nanomaterials, where lipid membranes enhance the biocompatibility of AuNPs, which are exogenous to living organisms and suffer of macrophage recognition, limited circulation time, and poor specificity (Section 2). Moreover, we will discuss how AuNPs can be used as versatile optical probes to characterize membrane properties, including stiffness, integrity, and composition (Section 3). Finally, Section 4 will present recent studies where the combination of lipids with AuNPs has led to new classes of nanomaterials with unique functional properties, arising from AuNP–membrane synergy. The application of these materials in nanomedicine has the potential to improve current therapeutic strategies and enable novel biomedical solutions.

2 Lipid membrane coatings to enhance AuNP performance in biomedical applications

In this section, we will discuss how lipid membranes can enhance the performance of AuNPs in biologically relevant media. Inorganic NPs are exogenous to biological organisms, and their use in medical practice faces challenges such as cytotoxicity, low accumulation at the target site, limited colloidal stability in biological fluids and rapid clearance by the immune system.[24]

Coating NPs with synthetic and natural membranes, or embedding them in a lipid bilayer, has emerged as an effective strategy to overcome such limitations, providing biocompatibility, immune escape ability and longer circulation time. Functionalization of AuNPs with artificial lipid bilayers, particularly those composed of zwitterionic phosphatidylcholine phospholipids, is widely employed to enhance the biocompatibility of AuNPs, preventing non-specific biological interactions at the NP surface.[25,26] Additionally, lipid bilayers composed of mixed zwitterionic and charged phospholipids can enhance the colloidal stability of AuNPs in aqueous media through electrostatic repulsion, while the incorporation of PEGylated phospholipids can provide steric stabilization.[26,27] Traditional strategies to produce bilayer-coated AuNPs include growing pre-synthetized Au seeds in the presence of lipids[28] or exploiting the interaction of pre-formed AuNPs in aqueous media with dry lipid films or vesicle dispersions (Fig. 2A and B).[29] Alongside traditional protocols, new preparation procedures have emerged, enabling seed-free, scalable aqueous synthesis of lipid bilayer-coated AuNPs, using sodium oleate as reducing and capping agent,[30] or single-step production of AuNP-bilayer embedded liquid–crystalline lipid mesophases (Fig. 2C and D).[31]

Furthermore, lipid membrane coatings offer an effective platform for AuNP functionalization, enabling integration of moieties for specific molecular recognition and cell targeting. In this context, the surface camouflaging of AuNPs with natural membranes, *e.g.*, derived from cells or extracellular vesicles (EVs), represents the latest frontier, where hybrid materials are typically formed through membrane fusion, aided by extrusion, ultrasounds and electroporation (Fig. 2E).[32–34] Upon coating with these biological membranes, AuNPs acquire superior biosafety and circulation lifetimes *in vivo*, but also unique properties such as tumour targeting or immunomodulation, arising from membrane-embedded functional molecules, that enable selective recognition of specific receptors on immune or cancer cells.[35–37] In this context, one major advantage of natural membrane coatings over synthetic ones is their ability to simultaneously target multiple antigens, rather than individual antigens as in conventional targeting approaches, enabling more efficient recognition by target cells.[32] For instance, white blood cell membrane-coated AuNPs inherit the self-recognition mechanisms of their source cells to evade phagocytosis, as well as specific surface ligands to target receptors at disease sites.[38,39] Similarly, AuNPs coated with

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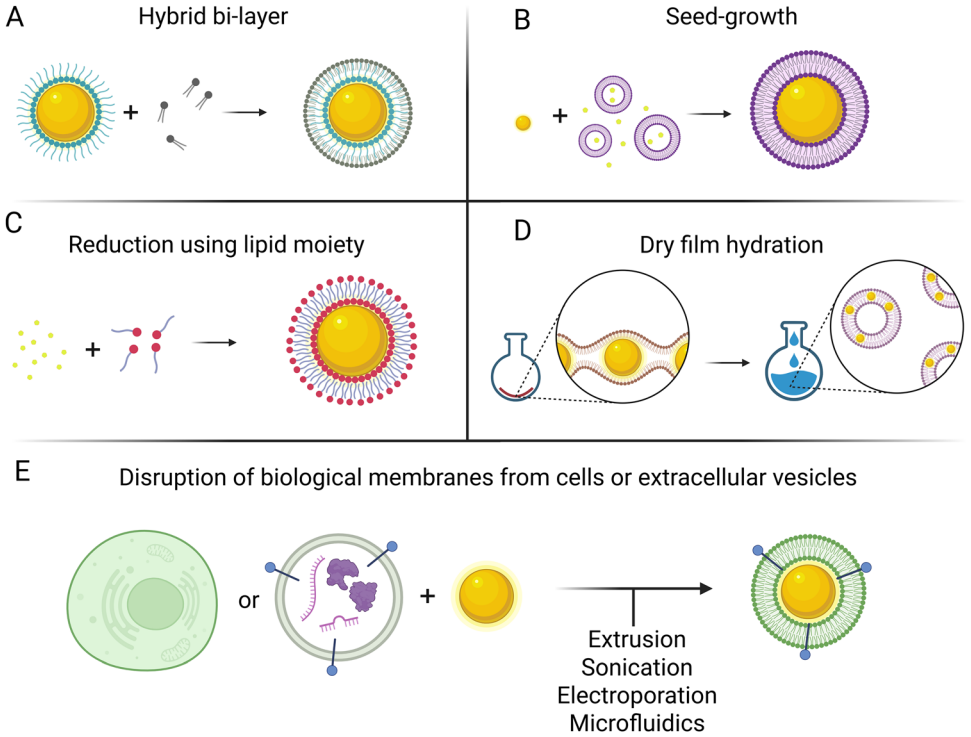

Fig. 2 Overview of the methods used to coat AuNPs with lipid membranes. The tested approaches include (A) Mixing pre-formed AuNPs, capped with thiolated molecules (*e.g.*, alkanethiols), with a solution containing the lipids of interest to form a hybrid bilayer. (B) Seed-mediated growth of AuNPs in aqueous solution in the presence of an Au precursor and lipids, which act as templates for controlled nanoparticle growth. (C) Direct reduction of Au^{3+} using a mixture of fatty acids and their salts (*e.g.*, oleic acid–sodium oleate) as capping agents. (D) Hydration of dry lipid films with AuNPs dispersed within, leading to the formation of membrane-embedded nanoparticles. The composition of the lipid film influences the resulting morphology (*e.g.*, vesicles, cubic mesophases). (E) Disruption of cells or extracellular vesicles *via* electrical or mechanical stimuli, followed by grafting of the biological membranes onto AuNPs. This method preserves some native biomembrane features—such as membrane-bound proteins—potentially conferring desirable capabilities (*e.g.* targeting, immune-evasion, *etc.*) to the AuNPs. Created in BioRender. Zendrini, A. (2025) **https://BioRender.com/dt6n1aa**.

cancer cell membranes are ideal for tumour-targeting, due to the presence of surface markers enhancing NP uptake due to homotypic binding processes.[40,41] Beyond cell membrane coatings, EV-based natural coatings offer a promising alternative, enabling the regulation of nanoparticle–cell interactions to enhance tissue-selective AuNP targeting. A recent investigation pioneered the combination of AuNPs with bacteriophages, developing hybrid systems endowed with natural recognition and targeting capabilities, effective even under conditions of biomolecular crowding.[32]

These and many other properties offered by biomimetic and biological coatings can dramatically enhance the performance of AuNPs *in vivo*, enabling superior targeted-delivery, bioimaging and sensing, therapy and immunomodulation (Fig. 3). In this regard, achieving a high level of coating integrity and homogeneity on the surface of AuNPs is key to ensure high internalization efficiency and targeting specificity. Conversely, non-uniform membrane coatings may lead to cargo leakage, unwanted adsorption of biomolecules in physiological fluids, heterogeneity in surface mechanical properties, and reduced affinity for biological interfaces.[42] A recent study highlighted that standard protocols for producing cell membrane-coated nanoparticles often result in low coating efficiencies, with approximately 60% of the nanoparticles exhibiting a coating degree below 20%. These findings underscore that current membrane-coating technologies still have significant room for improvement—advancements that could enhance the rational design of biomimetic AuNPs and contribute to more effective nanomedicine strategies.

Additionally, it must be considered that while membrane coatings substantially improve the biological performance of AuNPs by enhancing colloidal stability, prolonging circulation time, and enabling immune evasion, current biomimetic strategies primarily address "acute" interactions with the biological milieu and do not inherently guarantee long-term biocompatibility or safer clearance. Biomimetic coatings, particularly those derived from cellular membranes, effectively mask AuNPs from immune surveillance, thereby reducing rapid clearance by macrophages and other immune cells. However, due to the non-biodegradable nature of gold cores under physiological conditions, the potential long-term accumulation in organs such as the liver, spleen, and kidneys remains a critical concern.[43] The distinction must therefore be emphasized, as prolonged retention of AuNPs could still cause chronic toxicity or interfere with body homeostasis over time.[44]

2.1 Membrane-coated AuNPs for tumour targeting

The prolonged circulation time of AuNPs provided by membrane coatings can be conveniently used for non-specific

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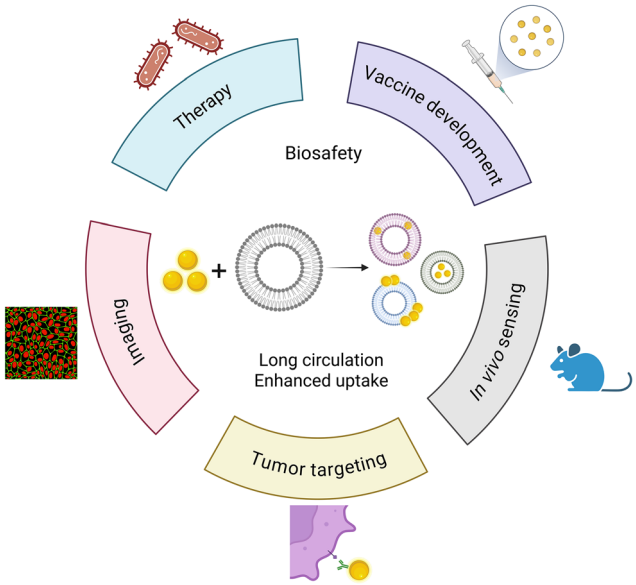

Fig. 3 Lipid membranes to improve properties of AuNPs in nanomedical applications. AuNPs can be combined with lipid membranes in various ways. Hydrophilic AuNPs are either coated by lipid membranes or tethered on the membrane surface, while hydrophobic AuNPs can be embedded within the bilayer. The lipid component enhances biocompatibility, promotes immune evasion, and prolongs blood circulation time while retaining AuNP optical properties. This strategy leads to hybrid systems with superior potential compared to bare AuNPs, enabling applications in imaging, therapy, targeting, sensing, and vaccine development. Created in BioRender. Zendrini, A. (2025) https://BioRender.com/dt6n1aa.

tumour accumulation. In this context, red blood cell (RBC) membranes provide an exceptionally long circulation half-life, owing to the presence of the membrane protein CD47, which acts as a 'don't eat me' signal by interacting with signal-regulatory protein α (SIRPα) on phagocytic cells, thereby inhibiting phagocytosis. Zou *et al.* recently demonstrated that tumour accumulation *via* enhanced retention and permeation (EPR) effect can be further enhanced by employing micro sized cellular platelet ''ghosts'', transporting hollow gold nanoparticles. The prolonged circulation time of such systems, combined with their large size, effectively reduced off-target accumulation in healthy tissues—occurring through vascular endothelial gaps—further improving tumor-targeting efficiency.[45] Such an increase in circulation time enhances the chances of membrane-coated AuNPs to permeate tumoral tissues, leading to their accumulation at tumour site. Beyond non-specific tumour accumulation, membrane-coatings on AuNPs also offer possibilities for specific tumour targeting, leveraging homotypic binding. This mechanism is used by cancer cells to adhere to each other through specific adhesion domains, prompting the growth of tumoral masses. Exploiting this very same principle, AuNPs coated by tumoral cell membranes can selectively accumulate and be taken up by homotypic cancer cells.[46] In this context, Xie *et al.* recently demonstrated that coating AuNPs with cancer cell membranes leads to a seven-fold increase in homotypic cell delivery, identifying the $\alpha_v\beta_3$ integrin—a cell surface receptor overexpressed on tumour cells—as the key driver of selective recognition.[47] Similarly, coating with mesenchymal stem cell or macrophage membranes can lead to preferential accumulation of AuNPs in cancer cells,[48] by leveraging the same integrin–ICAM and integrin–VCAM interactions that guide the recruitment of their parental cells to tumour sites. Additionally, molecular ligands (*e.g.*, peptides, antigens and aptamers) can be easily embedded within the membrane through non-covalent interactions, further enhancing AuNP tumour targeting properties. In this context, Srivastava *et al.* recently demonstrated that a tumor-targeting peptide—cyclic RGD—can be effectively incorporated into the RBC membrane coating of AuNPs to target $\alpha_v\beta_3$ integrin receptors expressed on cancer cells.[49]

2.2 Membrane-coated AuNPs for tumor therapy

Leveraging their targeting abilities (Section 2.1), membrane-coated AuNPs can maximize their therapeutic efficacy at the target site and minimize side effects on other tissues. This property is widely exploited for photothermal-, chemo- and radiotherapy applications to treat tumours. To this purpose, natural membrane coatings derived from RBC, cancer cells, platelet, stem cells, and white blood cells (WBC) are the most employed. In this context, Xuan *et al.*, recently proposed macrophage cell membrane (MCM)-coated Au nanoshells as a new generation-photothermal conversion agents for *in vivo* photothermal cancer therapy.[50] These nanomaterials retained the original near-infrared absorption properties of AuNPs, while exhibiting membrane-induced recognition of the tumour endothelium. As a result, the authors reported efficient tumour growth suppression and selective ablation of cancer cells following near-infrared light (NIR) laser irradiation. Interestingly, MCM coatings proved more effective than RBC coatings in achieving active tumor targeting and accumulation. This enhanced performance was attributed to molecular recognition mechanisms toward cancer cells, mediated by specific proteins present on the leukocyte membrane. In another study, Kim *et al.* developed gold nanoroads coated with a synthetic lipid membrane for the treatment of primary breast cancer and the prevention of metastasis, combining phototherapy with immunotherapy.[51] The membrane coating enabled the incorporation of the immune stimulator α-GC to elicit immune response around the Au nanorods. The authors demonstrated that intra-tumoral injection of these materials in mice, followed by local NIR irradiation, effectively suppressed tumor growth through heat generation by the nanorods and prevented lung metastasis *via* immune-mediated mechanisms. Additionally, Sun *et al.* demonstrated the effective combination of chemotherapy and phototherapy for cancer treatment using doxorubicin-loaded gold nanocages camouflaged with 4T1 cancer cell membranes.[46] The cell membrane coating enabled highly specific homotypic tumor targeting, while the Au core triggered drug release through hyperthermia under NIR irradiation at the tumor site, resulting in effective breast cancer suppression *via* combined chemo-photothermal therapy. Other recent studies have explored neutrophil membrane-coated AuNPs for tumor inhibition through radiotherapy and alternative therapeutic strategies.[52] The study from Chen *et al.*

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represents a significant innovation in the field, where authors introduced a strategy to disrupt cancer cell redox balance using AuNPs as electron sinks, in combination with electroactive membrane coatings.[53] When coupled with AuNPs, these membranes promoted autonomous electron transfer from cancer cells, disrupting redox homeostasis and inducing cell death across multiple cancer types.

2.3 Membrane-coated AuNPs for *in vivo* sensing and imaging

Due to their long circulation, biosafety, and targeting selectivity, membrane coatings on AuNPs also offer advantages for *in vivo* imaging and sensing. In the field of bio-sensing membrane-coated AuNPs can be conveniently employed to detect bacterial infections. For instance, recently Chen *et al.* developed renal-clearable gold nanoclusters enclosed within bacterial toxin-responsive liposomes.[54] In these systems, exposure to *S. aureus* toxins triggers the rupture of liposomal membranes, resulting in the release of AuNPs. The colorimetric signal subsequently generated was proposed as a cost-effective diagnostic tool for *in vivo* urinary detection of implant-associated bacterial infections. Membrane-coated AuNPs also offer new avenues to detect other biological systems, *e.g.*, EVs, or investigate specific biological processes. In this context, Liu *et al.* employed cancer cell membrane-functionalized AuNPs as biomimetic probes for circulating EVs, which serve as biomarkers for cancer diagnosis.[55] By leveraging the selective binding of fibronectin 1—present in circulating EVs—to Tenascin-C, overexpressed in cancer cell membranes, they achieved efficient capture of EVs using AuNPs immobilized on a gold chip surface. This enabled ultra-sensitive surface plasmon resonance detection of circulating EVs, opening new avenues for non-invasive clinical cancer diagnosis. In another recent study, Hu *et al.* employed cell membrane-coated AuNPs for apoptosis imaging in living cells, based on detection of caspase-3—an enzyme overexpressed under apoptotic conditions.[56] In this study, a fluorophore-labeled polypeptide chain was anchored to the surface of AuNPs, with its fluorescence quenched upon attachment. Following cellular uptake, fluorescence is restored through cleavage by caspase-3, allowing efficient detection of apoptosis. The presence of a cell membrane coating enhances nanoparticle delivery and cellular penetration, resulting in a 1.8-fold increase in signal intensity compared to non-coated nanoparticles.

2.4 Membrane-coated AuNP for vaccine development

The presence of a cell membrane coating onto AuNPs enables precise control and programmability of their interactions with immune systems, enabling possibilities for activation and modulation of the innate immunity. In this respect, bacterial membrane coatings are appealing for the development of nanovaccines against infections, as they contain numerous immunogenic antigens with intrinsic adjuvant properties[57] and display various pathogen-associated molecular patterns that play a crucial role in stimulating innate immunity and promoting adaptive immune responses.[58] In a recent study, Gao *et al.* explored this possibility, by developing AuNPs coated by *E. coli* membranes, from bacterium-secreted bacterial outer membrane vesicles (OMVs).[59] These systems induced rapid activation of dendritic cells in the lymph nodes of vaccinated mice and generated durable antibody responses, with higher avidity than OMVs only. This highlights the synergistic effect between bacterial membranes and AuNPs in enhancing immune responses, underscoring their strong potential for antibacterial vaccine development. Additionally, cancer cell membrane-coated NPs, embedding membrane-related tumour antigens and specific functional proteins within the membrane, could be used to promote a tumour-specific immune response for anticancer vaccination. This strategy has proved to be effective for cancer cell membrane-coated polymeric NPs,[60] and could in principle be translated to AuNPs. RBC membrane coatings represent a promising alternative for the development of anticancer vaccines, as demonstrated by studies on polymeric membrane-coated nanoparticles[61]—an approach potentially translatable to AuNPs. Finally, WBC membrane coatings are particularly promising for both antibacterial and anticancer vaccination.[38] By mimicking native WBC–tumor interactions, they can modulate anticancer immune responses, and, by absorbing bacterial virulence factors, they can generate nanotoxoids that provide effective immune protection against bacterial infections. Although not yet tested with AuNPs, this strategy holds potential for the development of AuNP-based vaccines aimed at preventing cancer and infections.

3 Utilizing the optical properties AuNPs to study lipid membranes

This section explores how the unique spectroscopic properties of AuNPs can be exploited to probe fundamental physicochemical features of natural and synthetic lipid membranes and other lipid-based interfaces. Additionally, the use of AuNPs as plasmonic sensors for the detection of specific molecular components within lipid membranes are investigated (Fig. 4).

3.1 Detection through UV-vis spectroscopy

Traditionally, the measurement of physicochemical properties of lipid membranes often relies on specialized techniques that require complex, dedicated instrumentation. Lately, AuNPs are emerging as highly sensitive and robust probes for various lipid interfaces, including planar lipid membranes, as well as synthetic and natural membrane-bound nanoparticles such as liposomes, EVs, and lipoproteins. These applications primarily leverage the plasmon coupling effects that arise from the interactions between specific types of AuNPs (such as Turkevich-Frens AuNPs) and lipid membranes.

Turkevich-Frens AuNPs are Au nanospheres typically ranging from 10 to 40 nm, capped with citrate anions (AuNPs@citrate). This type of AuNP exhibits a strong affinity for lipid interfaces due to the absence of steric stabilizers.

The binding of AuNPs@citrate to lipid membranes has been extensively studied, and several mechanisms have been proposed to explain this phenomenon. Upon binding to lipid membranes, AuNPs@citrate lead to local membrane remodelling, including

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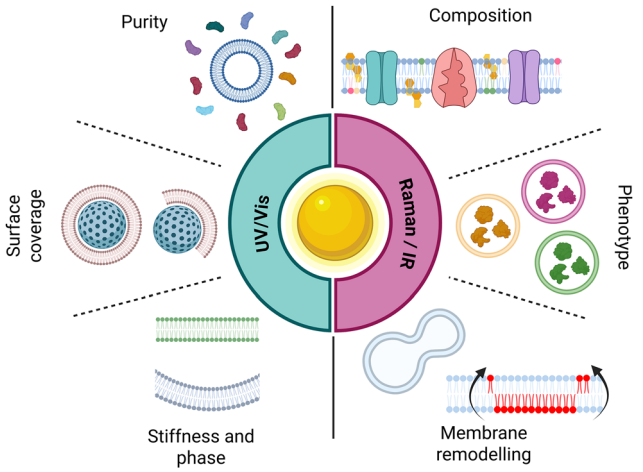

Fig. 4 AuNPs as analytical multifunctional probes for lipid membrane characterization. Spectrophotometry and SERS/SEIRS allow for highly sensitive and spatially resolved analysis of lipid membranes through AuNPs, starting from simple synthetic systems up to the complexity of cell plasma membranes. The spectroscopic properties of AuNPs enable the detection of diverse physico-chemical membrane features, including but not limited to structural organization, stiffness, phase behavior, and composition, also opening for fast QC of synthetic nanomaterial coverage. Created in BioRender. Zendrini, A. (2025) **https://BioRender.com/dt6n1aa**.

bending, thinning, wrapping, or pore formation.[62] Additionally, the interaction with lipid membranes often causes a partial desorption of citrate ions from the AuNP surface, destabilizing the particles and promoting membrane-templated clustering. This clustering, in turn, is accompanied by a visible spectral shift and a corresponding color change.[22]

This colorimetric response has been used to develop simple yet effective assays for characterizing lipid membrane properties. For instance, we recently demonstrated that LSPR is highly sensitive to the mechanical properties of phospholipid membranes.[63] This assay is based on the principle that AuNP clustering is connected to membrane softness—the softer the membrane, the larger the clustering and associated plasmonic shift. According to our hypothesized mechanisms, AuNPs@citrate aggregate more extensively on soft lipid vesicles because fluid-phase membranes—typically composed of unsaturated lipids like DOPC—are more deformable and dynamic, allowing for easier reorganization of lipids around adsorbed nanoparticles. This membrane fluidity facilitates membrane wrapping or partial embedding of the nanoparticles, promoting citrate release and thereby favoring AuNP clustering. In contrast, stiffer membranes—such as those in the gel phase formed from saturated lipids like DPPC—exhibit reduced lipid mobility and resistance to deformation, which inhibits these cooperative effects and limits nanoparticle aggregation on the membrane surface.

In this work, by pinching liposome standards through atomic force spectroscopy (AFM), a "plasmonic shift *vs.* mechanical stiffness" calibration was established, which was subsequently used to measure the rigidity of synthetic and natural vesicles with unknown compositions, based on AuNP aggregation on their surfaces.

Feizpour and colleagues have also leveraged the relationship between membrane rigidity and AuNP aggregation to develop a microscopy-based method for studying the fluidity of viral envelopes.[64] Their approach examined how AuNP clustering on the viral membrane influenced light polarization. Interestingly, the observed trend remained consistent: the greater the membrane fluidity, the larger the AuNP aggregation, resulting in a more pronounced induced light polarization.

Beyond stiffness and fluidity, AuNP@citrate were also utilized to develop an assay to grade EV preparation purity from soluble proteins. This application is based on the observation that their clustering at lipid interfaces is significantly reduced in the presence of free proteins forming a protein corona on NP surface. This causes a noticeable reduction in the plasmonic shift, offering a convenient way to distinguish pure EV preparations from free protein-contaminated ones. Maiolo and colleagues used this phenomenon for the rapid detection of soluble protein contaminants in EV preparations.[65] In their study, they first validated the concept using synthetic vesicle dispersion intentionally contaminated with bovine serum albumin, then benchmarked the assay on real EV samples. One key advantage of this assay is that if a sample is confirmed to be "pure," the plasmonic shift can also serve as an indicator of vesicle concentration, providing a fast and efficient method to estimate vesicle content. The assay was further refined[66,67] and optimized to work with minimal sample volumes and adopted for clinically relevant applications[68,69] and fundamental research.[70–74]

Another example of the analytical use of AuNP@citrate involves the determination of the extent of coverage of synthetic nanoparticles with a phospholipid membrane during the fabrication of hybrid synthetic-organic nanomaterials.[75] As discussed in Section 2, coating synthetic nanoparticles with lipid membranes is a strategy used to camouflage them, altering their uptake, clearance, toxicity, and biodistribution. Until now, verifying membrane coverage has relied primarily on advanced microscopy techniques. In this study, membrane-coated silica nanoparticles (SiNPs) were synthesized by inducing liposome rupture *via* osmotic shock. The degree of membrane coverage of SiNPs, effectively verified through cryo-electron microscopy (cryo-EM), was proportional to the number of liposomes used. Remarkably, when the samples were mixed with AuNPs@citrate, a linear correlation was observed between plasmonic variations and the degree of membrane coverage upon the SiNPs. This finding provides a convenient "quality control" method for assessing membrane coverage, a crucial parameter for optimizing the production of homogeneous lipid-coated hybrid nanomaterials and ensuring their effective application.

Interestingly, AuNPs@citrate also respond to non-bilayer phospholipid interfaces, such as those found in lipoproteins, natural nanoparticles responsible for transporting lipids through the bloodstream to various tissues. As we have recently shown, AuNPs@citrate are able to quantify and distinguish between the five different classes of lipoproteins in solution.[76] Lipoproteins are classified into five main types (plus subclasses) and, unlike liposomes, consist of a single phospholipid leaflet surrounding a hydrophobic core of triacylglycerols and

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cholesterol. The differences between the five classes of lipoproteins were distinguished based on the distinct plasmonic shifts observed when fixed amounts of lipoproteins were exposed to AuNPs@citrate. Moreover, we identified AuNPs@citrate as a promising tool for studying high-density lipoproteins (HDL), whose mesoscale analysis presents significant challenges even for advanced microscopy techniques such as cryo-EM, liquid-AFM, and ultramicroscopy.

3.2 Detection through vibrational spectroscopies

Colorimetric readouts are not the only way AuNPs can provide insights into lipid membranes. Techniques such as surface-enhanced Raman scattering (SERS) exploit the LSPR of AuNPs to amplify molecular signals, enabling the characterization of events occurring at the lipid interfaces (*e.g.* interactions between molecules and membranes) down to single-molecule detection. In SERS, the Raman signal of molecules adsorbed onto or near AuNPs is enhanced both through electromagnetic and chemical mechanisms. For this reason, SERS has been applied in several studies to explore lipid membrane properties, including membrane morphology and membrane composition.[77] For instance, Stepanenko and co-workers used gold nanoparticle-assisted SERS to characterize the composition of cell membranes and lipid microvesicles.[78] In their study, they performed both SERS and tip-enhanced Raman spectroscopy (TERS) on red blood cells and red blood cell-derived microvesicles, comparing the resulting Raman fingerprints with those of standard lipid solutions. The authors were able to detect the chemical signatures of specific lipids in red blood cell membranes, such as cholesterol, ceramide, sphingomyelin, and various phospholipids. Their findings aligned well with results obtained through conventional Raman spectroscopy, with the added benefit of enhanced sensitivity provided by SERS. In addition to lipids, they were also able to detect specific protein structures, such as histidine residues and aromatic side chains.

In a similar way, the composition of endothelial cell plasma membrane was probed,[79] as well as those of several model liposomes.[80] EVs are also extensively analysed through SERS, with reports about the characterization of mesenchymal stromal cell-derived EVs.[81] A noteworthy recent study by Bebesi and colleagues firstly demonstrated the enhancement of the infrared signature of liposome and EVs (as opposed to the Raman signal) using AuNP assisted surface-enhanced infrared spectroscopy (SEIRS).[82] This approach enables more precise and sensitive characterization of EVs through attenuated total reflection infrared spectroscopy (ATR-IR), which typically suffers from a poor signal-to-noise ratio, particularly when performed directly on biological fluids. A clever application of SERS in the field of EVs is given by Caponnetto *et al.*, who explored its potential in monitoring drug loading efficiency in EVs for targeted delivery applications.[83] By functionalizing EVs with SERS-active nanoparticles, the authors demonstrate a non-destructive and highly sensitive approach to detect and quantify encapsulated drug molecules. This technique allows for real-time assessment of the drug-EV interaction, providing valuable molecular-level insights without compromising the structural integrity of the delivery vehicles.

SERS has also shown great promise for label-free vesicle detection in the context of cancer diagnostics. Stremersch *et al.* pioneered a label-free SERS method to identify EVs from healthy and cancerous cells by coating them with a ''shell'' of cationic AuNPs.[84] Since then, this approach has evolved to enhance EV capture using specific antibodies or aptamers, combined with Raman reporters for precise identification. For instance, Wang and colleagues reported the use of DNA aptamers and multiple SERS probes to target specific EV subpopulations.[85,86] Further advancements were made by Tian *et al.*,[87] who developed an ultrasensitive immunoaffinity assay combining magnetic bead capture with Raman-active Au nanostars functionalized with cholesterol-labeled DNA anchors, enabling the detection of just a few dozen EVs. Similar approaches have been successfully applied to detect EVs in diluted plasma samples and to develop integrated platforms for the simultaneous separation, SERS-based detection, and typing of EVs from various cell sources, including multiple cancer types,[88–91] towards possible clinical applications.[92,93] Label-free SERS detection has also improved significantly, particularly by exploiting hybrid gold-based nanostructures composed of different materials,[94–96] enhancing data analysis through advanced statistical models[97,98] and machine learning algorithms,[99–102] and implementing rapid enrichment protocols to facilitate AuNP–EV interaction.[103]

Aside for detection purposes, AuNP-assisted SERS proves also useful for fundamental studies at the molecular level, providing information regarding the orientation of moieties within lipid bilayers,[104] and the events occurring at the lipid interface (*e.g.*, transfer of material between lipid interfaces, *etc.*). As a proof of concept, Suga and colleagues developed a membrane SERS (MSERS) system to probe phospholipid layer dynamics.[105] They functionalized AuNPs with decanethiol (AuNP@PL) and grafted different phospholipid layers onto them. When AuNP@PL self-assembled into small clusters, plasmon coupling transformed them into Raman antennas, amplifying the local Raman signal by two orders of magnitude and enabling analysis of layer thickness and hydrocarbon chain dynamics, phase state, and phase transitions. Similarly, Taylor *et al.* developed a SERS-assisted method to study lipid membrane dynamics, such as the bending of aliphatic chains and rotation of phospholipid headgroups, using a gold-coated lipid membrane where AuNPs were stably co-assembled in an ''AuNP-on-mirror'' geometry.[106] This sandwich configuration allowed for the detection of vibrational shifts and fluctuations in the Raman peaks associated with specific chemical bonds, providing qualitative insights into lipid diffusion, bending, and flexing at the single-molecule level.

Lipid membranes are highly dynamic structures, where fusion and transfer events between lipid interfaces, as well as lipid flipping between bilayer leaflets, frequently occur. AuNP-assisted SERS offers an efficient way to study these phenomena. For example, in 2009, Kundu *et al.* developed a method to monitor lipid transfer between vesicles and supported lipid monolayers in real time using hollow gold nanoshells as SERS-active surfaces.[107] More recently, Qi and colleagues brought lipid dynamics detection directly to the cell surface by using

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metal–organic hybrid constructs composed of zeolitic imidazole and AuNPs. Their approach enabled the SERS-based sensing of phosphatidylserine externalization, a hallmark of membrane damage and cell apoptosis.[108]

The remarkable versatility of AuNPs in lipid membrane studies highlight their potential as powerful analytical tools for probing several properties of lipid-based interfaces.

4 The functional synergy of AuNP–lipid membrane hybrid nanomaterials

In this section, we will explore how the integration of AuNPs with lipid membranes unlocks new frontiers in the development of nanomaterials for bio-nanomedicine applications. Previously, we examined how lipid membranes can stabilize AuNPs through coating, confer biological specificity, and extend their circulation time while preserving the AuNPs intrinsic properties, and conversely, how AuNPs can be used to probe physicochemical properties of lipid membranes. In this third section, we shift our focus to the emerging synergistic properties that arise uniquely from their combination that neither component can exhibit alone. Both AuNPs and lipid membranes exhibit responsiveness to external stimuli such as light, pH, and temperature, which can be mutually elicited to produce hybrid multifunctional systems. Such composite materials display novel, emergent behaviors that are of particular interest for innovative applications ranging from light-triggered drug delivery to ultrasensitive SERS-based theranostics (Fig. 5).

4.1 Crowding of AuNPs onto lipid membranes

A compelling example of this synergy is the use of lipid membranes as a template to control the clustering of AuNPs onto their surface, rather than simply using them as scaffold to encapsulate targeting moieties or enhance AuNP biocompatibility. This localized crowding of AuNPs can give rise to emergent properties not present in the individual components, such as modulation and enhancement of their plasmonic behavior—features of particular interest for sensing and therapeutic applications. However, potential changes in cytotoxicity associated with such aggregation must be carefully evaluated on a case-by-case basis.

In this framework, we have recently shown how this synergy is instrumental in the fabrication of SERS tags for ultrasensitive imaging and diagnostic.[109] Typically, SERS tags consist of metallic NPs functionalized with Raman active molecules (Raman Reporters, RRs), *i.e.* molecules with intense signals in the Raman spectrum.[110,111] However, direct functionalization of AuNPs with RRs often compromises colloidal stability, leading to uncontrolled aggregation.[4,112,113] Overcoming this synthetic challenge involves complex synthetic procedures, including tedious solvent exchange steps and precise optimization of stabilizers and RR concentration. Moreover, the exposure of RRs to the external environment often results in degradation or desorption and forces protocol re-optimization when RR molecular structure is changed. We addressed these limitations by exploiting the self-assembly of citrate stabilized AuNPs on the surface of liposomes with hydrophobic RRs embedded within the lipid bilayer.[109] Beside effectively protecting RRs from degradation and avoiding time-consuming synthetic procedures to graft RRs directly on the AuNP surface, this approach also enables controlled, spontaneous clustering of AuNPs on the membrane. This clustering creates multiple plasmonic "hot-spots" on the liposome membrane at nanoparticle junctions, *i.e.*, regions of highly intensified electromagnetic fields.[114] With this structural configuration, we hypothesized that small hydrophobic RRs laterally diffuse within the lipid bilayer, a behavior well-documented for similar

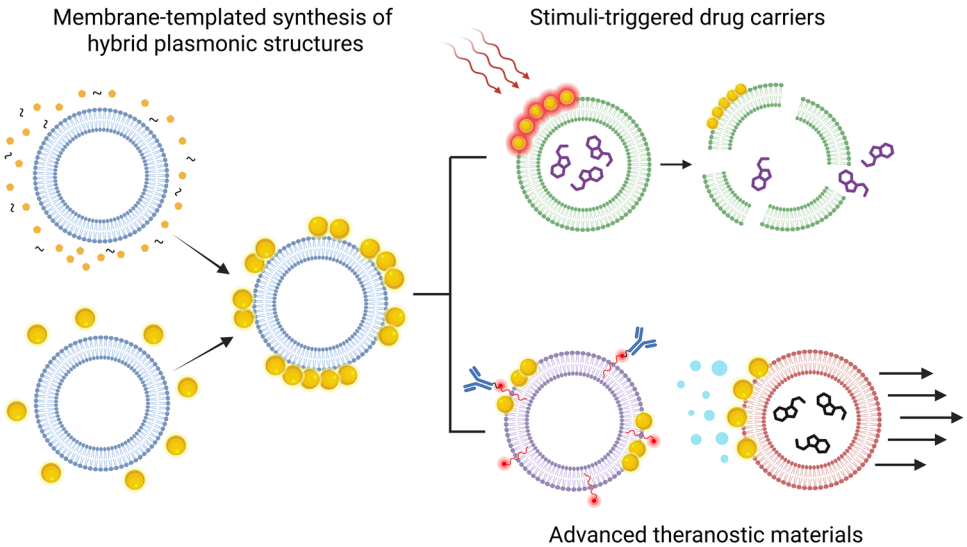

Fig. 5 Key examples of advanced synergistic applications of AuNP–lipid membrane hybrid systems. Lipid membranes act as templates and main constituents for the synthesis of hybrid AuNP–lipid membrane nanomedicines. These materials show great promise in the biomedical field, with potential uses as advanced theranostics and precise triggerable drug delivery systems. Created in BioRender. Zendrini, A. (2025) https://BioRender.com/dt6n1aa.

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molecules such as organic dyes. This mobility allows RRs to reach and covalently bind the surface of the AuNPs *via* their thiolated moieties, positioning them within regions of intense electromagnetic fields and enabling Raman signal amplification of several orders of magnitude. As a further advantage of this technology, the lipid membrane offers an easy means to embed targeting moieties such as antibodies, enabling molecular specificity. The efficacy of such systems has been demonstrated *in vitro* for the detection of GM1 gangliosidosis, where they outperformed traditional fluorescence-based assays in sensitivity.

Beyond diagnostics, AuNP clustering on membranes has also proven valuable for nanomotor design. Wang *et al.* reported a nanomotor system obtained by the self-assembly of gold core–platinum shell nanoparticles (Au@Pt) on liposomes.[115] In this case, the motion is generated by the structural asymmetry of the particle assembly, combined with catalytic decomposition of exogenous or endogenous hydrogen peroxide (H_2O_2), driving autonomous motion. The authors showed that Au@Pt aggregates on fluid-phase liposomes retain high catalase-like activity, decomposing H_2O_2 to propel the liposomal nanomotors toward cancer cells. Similarly, we demonstrated that also magnetoplasmonic nanoparticles (Au@Fe_3O_4) can cluster on liposomes in a controllable manner, by varying liposome composition and concentration.[116] This aggregation results in hybrid nanostructures where the high number of NPs on the lipid membrane results in enhanced magnetic and plasmonic properties, including increased magnetic responsiveness, further underlying the critical role of lipid membranes in driving NP crowding and function.

Alternatively, Troutman *et al.* demonstrated *in situ* AuNP synthesis templated by liposome surfaces.[117] In this method, ascorbic acid reduces chloroauric acid in liposome suspensions, initiating nanoparticle nucleation templated by the lipid bilayer. Liposomes surface served as the spherical template, leading to the formation of AuNPs–lipid complexes. When assembled on the liposome surface, the AuNP crust produces plasmonic properties resembling those of a solid gold shell, yielding a new class of biodegradable plasmon resonant nanocapsules. Camacho *et al.* further investigated the influence of bilayer phase state on *in situ* AuNP synthesis.[118] Using dipalmitoylphosphatidylcholine (DPPC) liposomes at various temperatures, they show that stable AuNPs@DPPC nanohybrids with good photothermal conversion efficiency can be successfully prepared. When synthesized with the gel phase liposomes, AuNPs form quasi-fractal clusters with red-shifted plasmon bands, while the aggregation is inhibited on fluid phase liposomes. These hybrids preserved the structural integrity of the liposomes, with only a minor shift in melting temperature within the hyperthermia therapeutic window. The authors demonstrated that the hybrids could efficiently generate heat when exposed to NIR light, positioning them as versatile candidates for photothermal induced drug delivery capacity.

4.2 Near-infrared light triggered drug release

A critical challenge in liposomal drug delivery is achieving controlled release of encapsulated drugs from the aqueous core precisely at the target site. 'Golden liposomes,' hybrid systems incorporating AuNPs within or around lipid bilayers, have emerged as a promising solution by combining the selective optical and photothermal properties of AuNPs with the drug loading capacity of liposomes.[119–122] Various past strategic approaches have evolved to optimize triggered drug release, including embedding AuNPs directly within the bilayer[123,124] and creating AuNP shells that can selectively degrade the hybrid structures upon stimulation.[125] Notably, as mentioned above, approaches enabling the formation of AuNP clusters within the bilayer present significant advantages.

In this context, Zhigaltsev *et al.* reported an intriguing approach to exploit AuNP–lipid membrane synergy to form light responsive systems.[126] The authors developed a microfluidic strategy for loading 5 nm tannic-acid capped AuNPs into lipid nanoparticles (LNPs) containing ionizable cationic lipids *via* rapid ethanol mixing. This resulted in multilamellar LPNs capable of hosting up to 20 AuNPs per LNP. The authors suggested that AuNPs are complexed by ionizable lipids and located at the intersection of the lamellae. In a follow-up study, Utzel *et al.* demonstrated that, under pulsed laser irradiation, *in situ* synthesized AuNP clusters embedded in LNPs ''explode'' the lipid layers, releasing encapsulated doxorubicin (DOX) with high precision.[127] This method significantly enhanced drug accumulation in target cells, up to 11-fold compared to conventional DOX-LNPs, and achieved efficient cancer cell killing. Simulations indicated that the release mechanism is driven by localized nanothermal effects, ensuring DOX remains intact post-irradiation.

The development of targeted drug delivery systems that can be activated within neural tissue represents a critical advancement for treating neurological disorders. Xiong *et al.* expanded on this synthetic approach by forming gold shells on mechanoresponsive liposomes that remain stable under ambient conditions and only release their cargo upon mechanical stimulation.[128] This was achieved *via* ultrashort laser pulse excitation of plasmonic nanoparticles that were stereotaxically injected at 2 mm and 4 mm depths into the striatum with near-infrared (NIR) light. This generates nanomechanical effects that stress and rupture the lipid membrane. Since this innovative photorelease system could be activated even in deep brain regions of mice, it offers a highly controlled and minimally invasive therapeutic strategy.

As these hybrid AuNP–liposome systems can be loaded with multiple cargoes, they have also been used to co-deliver therapeutic agents with photothermal agents, where the local hyperthermia provided by the AuNP resulted in both the release of the therapeutic agent (zinc phthalocyanine) and the creation of reactive oxygen species, enhancing the destruction of breast tumor-bearing female Sprague–Dawley (SD) in rats.[129]

In addition to explosive release, controlled release can be achieved through triggering phase transitions between lipid mesophases.[130] Different mesophases have different diffusion-controlled release rates dependent on their nanostructures. Of particular interest to drug delivery are the bicontinuous cubic phases and inverse hexagonal phases. The cubic phases are highly ordered, three-dimensional networks of continuous,

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curved lipid bilayers, twisted into interconnected, open ended water channels. Lipids are known to form three different cubic phase symmetries – *Im*3*m*, *Pn*3*m* and *Ia*3*d*; the difference in their structures lies in how the lipid bilayers are arranged to form these channels. The inverse hexagonal phase is formed by lipid molecules where the polar head groups face inwards, thus creating a water channel – the hydrophobic hydrocarbon chains are on the outside, surrounding the aqueous core. As there is only symmetry in two dimensions compared to the three dimensions of the bicontinuous cubic phases, the inverse hexagonal phase offers a more restrictive diffusion pathway, leading to a slower release. Exceptional control over drug release rate can be easily done through changes in environmental factors such as temperature. When AuNP are embedded into non-lamellar lipid mesophases, they act as nanoscale heaters which can trigger phase transitions within fractions of a second, resulting in alterations in drug release with exceptional precise modulations.[131]

5 Conclusions and future perspectives

Over the past decade, the synergy between AuNPs and lipid membranes has played a pivotal role in advancing both our fundamental understanding of nano-bio interactions and the development of innovative analytical and nanomedical technologies. From an application perspective, AuNPs have emerged as powerful and versatile tools for probing the physicochemical properties of lipid membranes. Their unique spectral characteristics and high sensitivity make them ideal candidates for detecting subtle membrane features that are often difficult to access using traditional probes or without sophisticated instrumentation. However, the same sensitivity that makes AuNPs attractive for analytical applications also poses a significant challenge: their optical response is influenced by multiple parameters simultaneously. Lipid concentration, membrane stiffness, surface charge, and the presence of associated biomolecules can each modulate AuNP–membrane interactions. However, these properties are often interdependent and tend to vary simultaneously in complex systems. As a result, interpreting experimental outcomes becomes challenging, as it is difficult to isolate the effect of individual parameters. To fully exploit the potential of AuNP-based assays and translate them into robust, reliable tools, it is therefore essential to deconvolute the contributions of individual membrane properties (*e.g.*, composition, stiffness, charge, protein content). Achieving this remains an open challenge, but it is crucial for ensuring the accuracy, reproducibility, and broad applicability of AuNP–membrane technologies across diverse biomedical and biological contexts. In this direction, we recently introduced the concept of nanoplasmonic isosbestic points as a promising analytical tool to probe the relationship between AuNP aggregation and membrane properties.[132] Specifically, by using lipid vesicles as soft templates for AuNP clustering, we demonstrated that nanoplasmonic isosbestic wavelengths emerge over specific AuNP-to-vesicle number ratios and serves as unique optical fingerprints for distinct AuNP–AuNP spacings within the clusters. Importantly, we found that these isosbestic points shift systematically with membrane stiffness, offering a simple and sensitive colorimetric approach to infer mechanical properties of the membrane of samples with unknown concentration. This strategy illustrates how nanoplasmonic isosbestics can support the deconvolution of individual membrane contributions—such as stiffness and concentration—opening for new quantitative, label-free assays on complex soft matter systems.

In the field of nanomedical therapies, this review highlights how hybrid AuNP–lipid assemblies offer significant advantages across multiple biomedical areas, indicating their potential clinical translation both as innovative diagnostic and in therapeutic tools.[133–135] However, despite promising pre-clinical outcomes and encouraging results from multiple early-phase clinical trials, the translation of AuNP–lipid hybrids from bench-to-bedside must face several challenges. A critical hurdle in nanomedicine clinical translation lies in bridging the gap between laboratory efficacy and patient safety.[133] Rigorous validation of preclinical findings through well-designed clinical studies is essential to establish both therapeutic efficacy and long-term safety profiles in humans. Furthermore, the complexity of hybrid nanostructures necessitates robust control over their physicochemical properties during synthesis, requiring standardized formulations and reporting protocols to ensure batch-to-batch reproducibility.[136] The scale-up of manufacturing processes must also be addressed, ensuring that these nanomedicine products can be produced in large quantities while maintaining strict quality control and compliance with regulatory standards.[137,138] Quality assurance measures must encompass not only the chemical and physical attributes but also biological functionality, such as therapeutic efficiency[139] and immunogenicity.[140]

Yet, the unique properties emerging from AuNP–lipid combinations could broaden their applicability to research domains where the potential of AuNPs remain largely unexplored. One particularly promising unexplored field involves the use of AuNP–lipid assemblies as heterogeneous catalysts for optimising synthetic reactions. By hosting catalysts within the lipid phase, reagent access to the catalyst's surface is enhanced, resulting in improved reaction yield.[141] This approach aligns with creating ''on water'' conditions, an important strategy for developing environmental-friendly techniques in sustainable chemistry. Traditional surfactant-based approaches face sustainability challenges due to the environmental cost of surfactant synthesis[142] – a limitation that phospholipid-based systems could potentially overcome. Lipid bilayers offer unique properties that further enhance catalytic performance, where bilayer fluidity directly contributes to increased catalytic activity.[143] Additionally, by using non-lamellar mesophases, the high interfacial area and the tuneable dimensions of the lipid cubic phases control the diffusion of the reagents into the matrix and their interaction with the catalyst. For instance, Duss *et al.* synthesised palladium NP within the cubic phase and exploited their structural properties to control the Suzuki–Miyaura cross-coupling of

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5-iodo-2′-deoxyuridine and phenylboronic acid.[144] Given the broad catalytic versatility of AuNPs,[145] their incorporation into lipid membranes and non-lamellar mesophases may provide a unique opportunity to control the reaction of industrially important reactions.

From a broader perspective, future research should also explore how natural biological mechanisms can be exploited to further enhance the performance of hybrid nanomaterials in biological systems—particularly in terms of targeting efficiency, immune evasion, and toxicity control. A key example in this regard is the biomolecular corona. Often described as one of the most formidable challenges for nanomaterials, this layer of biomolecules adsorbed onto the surface of any nanoparticle exposed to biological fluids plays a crucial role in shaping the nanoparticle's biological identity, cellular uptake, and biodistribution, modifying the NPs synthetic design. However, recent studies have increasingly highlighted the potential ability to modulate and engineer the corona by rationally tuning the hybrid material composition.[146] Thus, defining the identity and function of nanomaterials by either promoting or inhibiting the recruitment of specific biomolecules—could be a game changer in nanoparticle-based biomedical applications. In this context, AuNP–lipid hybrids may offer a particularly versatile platform, as their combined physicochemical properties potentially allow for fine-tuning of corona formation.[147] Such control would enable researchers to fully take advantage of the remarkable properties these materials already exhibit.

Author contributions

Conceptualization: J. C., L. C., A. Z. Investigation: J. C., L. C., K. F., L. P., A. Z. Writing – original draft: J. C., L. C., K. F., A. Z. Writing – review & editing: all the authors. Supervision: D. B., P. B., C. M. Project administration: D. B., P. B., C. M. Visualization: A. Z. For more information about the CRediT taxonomy, please refer to **https://credit.niso.org**.

Conflicts of interest

There are no conflicts to declare.

Data availability

No new data were created or analyzed during this study.

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