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Review

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Nanomaterial-Based Immunosensors: Conjugation Strategies and Biomedical Applications of 0D Nanosensors

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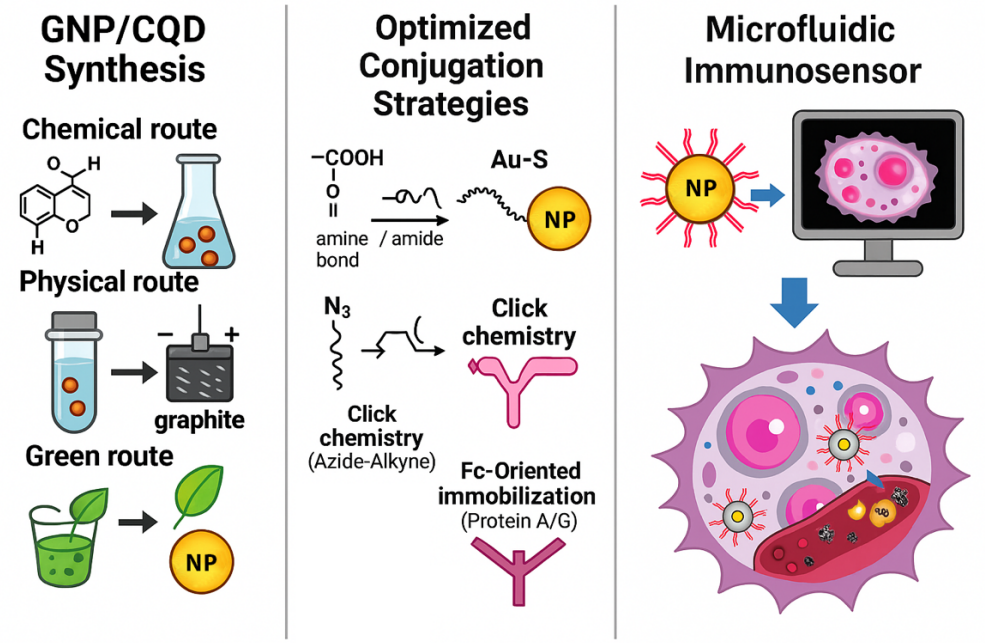
Graphical Abstract



Abstract

Gold nanoparticles (GNPs) and carbon quantum dots (CQDs) are widely used in immunosensing due to their tunable optical/electronic properties and flexible surface chemistry. However, inconsistent synthesis, complex and poorly controlled nano-bio interactions, and non-standardized bioconjugation hinder reproducibility and clinical translation. This critical review synthesizes recent advances (2015–2025) in surface functionalization and conjugation strategies for GNP- and CQD-based immunosensors, with emphasis on practical, reproducible workflows that support translational diagnostics. While this review primarily focuses on covalent bioconjugation strategies to improve stability and reproducibility, non-covalent interactions also play a critical, complementary role in nano-bio systems. Reversible interactions, such as antibody–antigen and ligand–receptor binding, provide dynamic, tunable interfaces that can be exploited for controlled binding, competitive displacement, and enhanced assay versatility. We conducted a focused, structured literature review across major databases to identify high-impact, translationally relevant studies. Emphasis was placed on mechanistic insights, quality control metrics,

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and conjugation methods that preserve biomolecule function in complex biological matrices. Optimized chemical and physical syntheses (including microfluidic and plasma routes) improve batch consistency; CQD bottom-up methods yield high quantum yields for fluorescence assays; and site-specific conjugation approaches (site-directed thiol–gold chemistry, click chemistry, and Fc-oriented immobilization) substantially enhance antibody orientation and assay reproducibility. Antifouling strategies (PEGylation, zwitterionic coatings) and hybrid GNP-CQD designs enable dual-mode sensing and improved stability. We distill best-practice recommendations (GMP-aware synthesis, rigorous QC: size/PDI/ligand density, validated conjugation protocols) and outline key translational barriers-protein corona effects, steric hindrance, scale-up, and regulatory constraints. The practical workflows and QC checklists provided here aim to accelerate the clinical readiness of nanomaterial immunosensors. With standardized synthesis, validated site-specific bioconjugation, and comprehensive in vivo evaluation, GNPs and CQDs hold strong potential for precision diagnostics and point-of-care theranostics.

Keywords:

Gold nanoparticles; Carbon quantum dots; Immunosensors; Bioconjugation; Precision nanomedicine; Nano-bio interface; Cancer biomarkers; Point-of-care diagnostics.

Rationale, Purpose, and Limitations

Nanomaterial-based immunosensors have demonstrated significant potential to improve diagnostic sensitivity and specificity; however, challenges related to reproducibility, nano-bio interactions, and clinical translation remain unresolved. The purpose of this review is to critically evaluate recent advances in the synthesis, surface functionalization, and bioconjugation of GNPs and CQDs, with a focus on practical, reproducible approaches for translational applications. This review aims to provide a structured framework linking physicochemical properties to immunosensor performance and to highlight key design considerations for clinical implementation. Limitations of this work include reliance on published studies with heterogeneous experimental conditions and the lack of standardized reporting across the literature, which may affect the direct comparability of data.

Introduction

Nanomaterial-enabled immunosensors are central to next-generation diagnostics and immunotherapy in oncology, infectious disease, and personalized medicine. GNPs and CQDs stand out because of their optical/electronic tunability, high surface area for bioconjugation, and amenability to multiplexed assays. GNPs provide localized surface plasmon resonance (LSPR) and surface-enhanced Raman spectroscopy (SERS) signal enhancement; CQDs supply bright, photostable fluorescence and facile surface functionalization. Despite strong preclinical results, translation to clinical diagnostics has been hampered by inconsistent synthesis protocols, inadequate QC, and insufficient control over nano-bio interfaces (e.g., protein corona). Notably, these interfacial interactions are not inherently detrimental; as non-covalent processes, they can also introduce dynamic and tunable binding mechanisms that may be harnessed to enhance sensor performance and design flexibility. This review synthesizes evidence (2015–2025) to provide practical, reproducible strategies for the synthesis, functionalization, and integration of GNPs and CQDs into clinically relevant immunosensors.

Advances in synthesis and characterization

Gold nanoparticles

Chemical methods

Chemical reductions (Turkevich citrate reduction, Brust–Schiffrin, seed-mediated growth) remain the most widely used methods for generating monodisperse spherical and anisotropic gold nanoparticles (GNPs) (10–200 nm) (1). Control of temperature, reagent stoichiometry, and capping ligand concentration enables tuning of size, shape, and LSPR (2) (3) (4) (5) (6). These methods are scalable and amenable to ligand exchange for downstream bioconjugation.

Physical methods

Laser ablation (LASiS) and plasma-assisted synthesis produce ligand-free, ultra-pure GNPs with minimal chemical contamination (7), important for sensitive biosensing and in vivo studies (8) (9) (10) (11). Limitations include lower throughput, broader size dispersion, and specialized equipment requirements. (12) (13)

Green chemistry

Biogenic approaches use plant extracts, microbes, or polysaccharides as reducing/capping agents, thereby improving biocompatibility and avoiding the use of toxic reagents (14) (15) (16) (17) (18). However, reproducibility and size

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control are major bottlenecks for clinical-grade production. (19)

Improving reproducibility

Strategies include strict control of reaction parameters, automation or microfluidic synthesis, thorough QC (UV–Vis, DLS, TEM, zeta potential), and well-documented SOPs to ensure batch consistency for clinical translation (20) (21) (22) (Table 1).

Table 1. Characteristics of chemical, physical, and green synthesis routes for GNPs and CQDs.

Synthesis Method	*Key Advantages*	*Key Limitations*	*Impact on Properties*	*Biomedical Suitability*
Chemical	Controlled size/shape; scalable; reproducible	Requires reducing agents; purification needed	Tunable morphology; stable surface chemistry	High (with proper purification)
Physical	High purity; no chemical residues	Low throughput; expensive equipment; broader size distribution	Clean surfaces; limited morphology control	Moderate (research-level)
Green	Biocompatible; eco-friendly; natural capping agents	Lower reproducibility; variable yields	Biocompatible coatings; reduced toxicity	High (promising for translation)

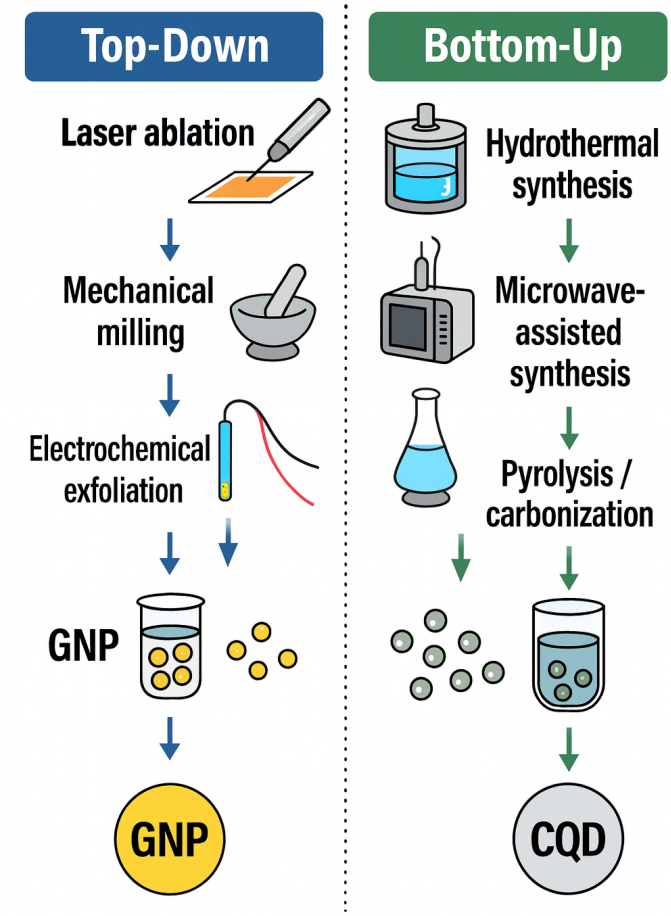

Figure 1. Overview of synthesis routes for gold nanoparticles (GNPs) and carbon quantum dots (CQDs). Top-down approaches include laser ablation, mechanical milling, and electrochemical exfoliation, whereas bottom-up methods involve hydrothermal synthesis, microwave-assisted synthesis, pyrolysis, and green

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chemistry routes. These fabrication strategies determine nanoparticle size, surface chemistry, optical properties, and reproducibility.

Carbon quantum dots

Top-down fabrication

Laser ablation, electrochemical oxidation, and chemical oxidation yield crystalline carbon quantum dots (CQDs) (23) with tunable defect states but generally yield lower amounts and require purification (24) (25) (26) (27).

Bottom-up fabrication

Hydrothermal, microwave-assisted, and pyrolytic methods enable control over doping and passivation (28), producing CQDs with high quantum yields, critical for fluorescence immunoassays (29) (30) (31) (32). Bottom-up routes offer superior scalability and tunability for biosensing applications. (33)

Plasma-based CQD synthesis

Plasma methods provide rapid, solvent-free CQD production with minimal purification, though parameter optimization (power, gas composition) is essential (34) (35).

Key characterization tools

A robust characterization toolkit is essential: TEM/SEM for morphology; DLS and zeta potential for colloidal stability; UV–Vis and PL for optical signatures; FTIR/XPS for surface chemistry (36); XRD and Raman for structural insights; and TGA/DSC for thermal stability. These measurements feed QC acceptance criteria for clinical translation. (37)

Bioconjugation and nano-bio interface engineering

Mechanistic role of conjugation strategy

The conjugation method dictates antibody orientation, ligand density, steric accessibility, and assay reproducibility. Random EDC/NHS coupling produces heterogeneous orientations (38); click chemistry and site-specific thiol–maleimide or Fc-directed immobilization deliver improved orientation and consistent stoichiometry (39) (40) (41) (42) (43) (44) (45) (46).

Common conjugation approaches and optimization

EDC/NHS (carboxyl → amine): Widely used covalent method; requires optimization to minimize crosslinking and preserve antibody activity. (47) Thiol–gold (Au–S): Direct, strong bond for GNPs; high density of thiols can cause overpacking and steric hindrance (48)—control with mixed SAMs recommended. (49)

Click chemistry (azide–alkyne): Bio-orthogonal, stoichiometric, preserves protein function—excellent for multiplexing. (50) (51)

Affinity/Fc-oriented immobilization: Protein A/G or Fc-binding strategies orient antibodies to maximize antigen recognition. (52) (46)

Optimization parameters: ligand density (53), spacer length (PEG linkers) (54), pH (55), ionic strength (56), and blocking/passivation steps. (57)

Antifouling and stability

Key antifouling strategies include PEGylation, zwitterionic coatings, polysaccharide-based layers, and protein–polymer hybrid interfaces, all of which have demonstrated measurable reductions in protein adsorption and improved nano-bio interface stability. PEGylation remains one of the most widely used approaches due to its ability to form a dense hydration layer through hydrogen bonding, effectively suppressing nonspecific protein adsorption and prolonging circulation time. For example, PEG-modified gold nanoparticles with monodisperse PEG chains exhibit significantly lower and more stable protein adsorption compared to polydisperse coatings, resulting in improved pharmacokinetics and reduced protein corona formation. (58) Zwitterionic coatings, including sulfobetaines and carboxybetaines, generally provide enhanced antifouling performance compared to many conventional hydrophilic polymers. No single strategy can be considered universally optimal. These materials have been reported to reduce protein adsorption to ultralow levels (typically <5 ng cm^{-2}), significantly outperforming conventional hydrophilic polymers. (59) (60) In addition, polymeric antifouling coatings with tailored wettability (e.g., superhydrophilic surfaces) further inhibit biofouling by minimizing protein–surface interactions and reducing bacterial adhesion in biomedical environments. (60) (61)

Biopolymer-based coatings such as dextran and chitosan also contribute to antifouling by improving surface biocompatibility and modulating interactions at the tissue–material interface, thereby reducing immune responses and biofouling-related degradation of device performance. (61) Furthermore, hybrid protein–polymer systems, such as hydrophobin-based self-

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assembled monolayers followed by PEG grafting, have demonstrated significantly reduced nonspecific adsorption as confirmed by QCM-D measurements, highlighting their effectiveness in creating low-fouling biosensor surfaces.

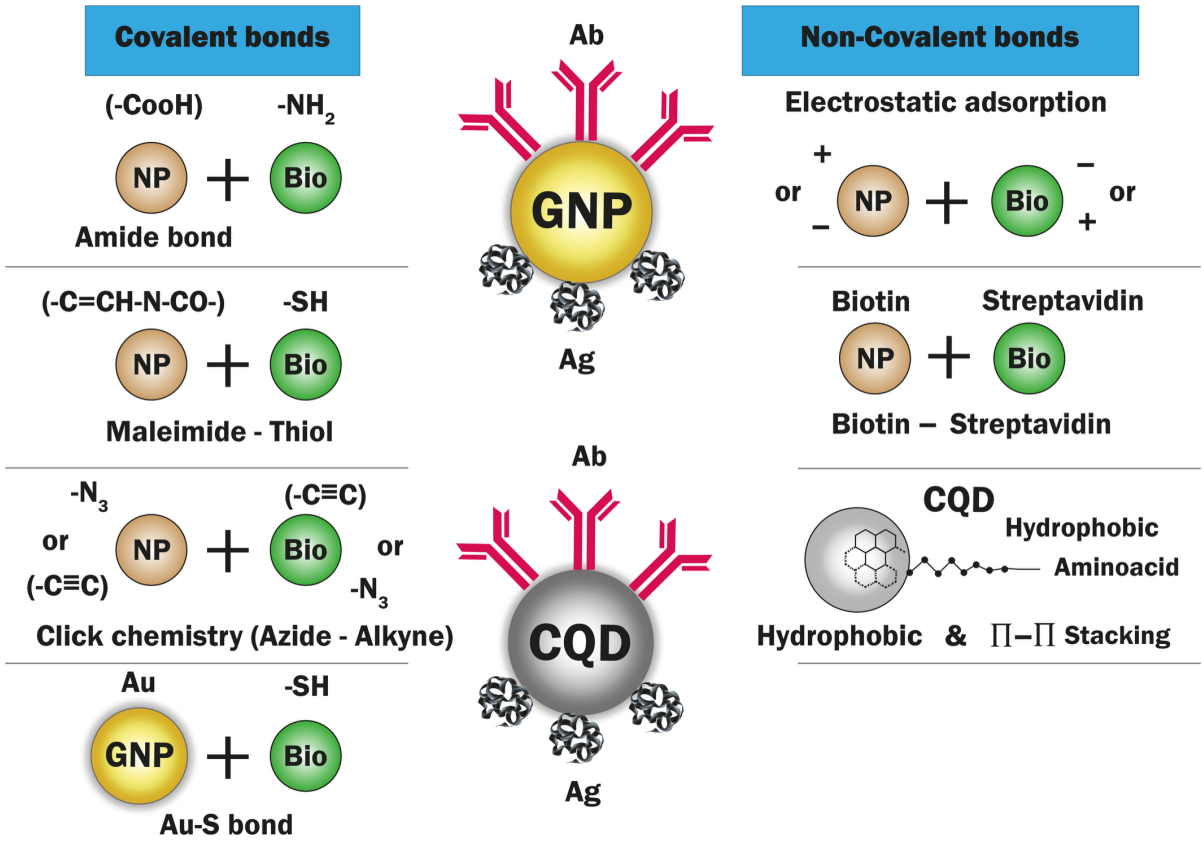

Figure 2. Comparison of covalent and non-covalent conjugation strategies for bioconjugating GNPs and CQDs. Covalent methods include amide coupling, maleimide–thiol linkages, click chemistry, and Au–S bonding, whereas non-covalent methods rely on electrostatic interactions, biotin–streptavidin affinity, hydrophobic forces, and π–π stacking.

At the molecular level, protein adsorption onto unmodified surfaces leads to the formation of a dynamic protein corona, consisting of both strongly bound ("hard") and weakly associated ("soft") protein layers, which can alter nanoparticle bio-reactivity, cellular uptake, and targeting efficiency. Experimental QCM studies further show that protein adsorption often occurs in multilayer structures with distinct viscoelastic properties, indicating structural rearrangements upon surface binding. Importantly, surface chemistry—including charge, hydrophobicity, and morphology—plays a dominant role in determining corona composition and stability, thereby directly influencing nanoparticle behavior in biological systems. In biosensing, antifouling surface engineering is critical to maintaining analytical accuracy. For instance, optimization of surface modification and antibody immobilization strategies has been shown to increase the fraction of active antibodies from 20–30% to up to 85–98%, while simultaneously reducing nonspecific binding and improving signal sensitivity and stability. (62) Moreover, uncontrolled protein adsorption can lead to conformational changes in proteins and loss of biological function, further emphasizing the necessity of effective surface passivation. (63) (64)

A comparative analysis of antifouling strategies suggests that while PEGylation remains the most established and versatile approach, its performance can be limited by immunogenicity and structural heterogeneity, particularly in long-term or repeated-use applications. In contrast, zwitterionic coatings consistently exhibit superior resistance to protein adsorption, owing to their strong hydration capacity and charge

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neutrality, making them highly effective at minimizing protein corona formation under complex biological conditions. However, their integration into multifunctional biosensing platforms can be synthetically more challenging. Biopolymer-based coatings offer enhanced biocompatibility and ease of functionalization but generally exhibit moderate antifouling performance compared to synthetic polymers. Hybrid systems that combine biological self-assembly (e.g., protein-based interfaces) with synthetic antifouling layers appear to offer a promising balance among stability, functionality, and antifouling efficiency. From a design perspective, no single strategy appears to be universally optimal; instead, the choice of antifouling approach should be application-specific. For high-sensitivity immunosensors operating in complex biofluids, zwitterionic or hybrid coatings may offer superior performance by maintaining low background signals. Conversely, PEG-based systems remain advantageous for applications requiring scalability and well-established surface chemistry. Overall, the most effective next-generation immunosensors are likely to emerge from integrated surface-engineering strategies that combine antifouling properties with controlled biofunctionalization, rather than relying on a single-material approach. (60) (61) (65) (66) (67)

Table 2. Comparison of functional properties and sensing capabilities of GNPs, CQDs, and GNP-CQD hybrid nanomaterials.

Feature	*GNPs*	*CQDs*	*GNP-CQD Hybrids*
Optical Behavior	LSPR/SERS enhancement	Strong photoluminescence	Dual-mode (SPR + PL)
Surface Functionalization	Dense thiol-based conjugation	Carboxyl/amine-rich surfaces	Complementary binding chemistries
Signal Amplification	High plasmonic amplification	Fluorescence amplification	Synergistic amplification mechanisms
Biocompatibility	High (coating-dependent)	Low toxicity	Enhanced stability; reduced cytotoxicity
Detection Modes	Optical/electrochemical	Fluorescent	Multi-mode (optical + electrochemical)
Typical Applications	Cancer biomarkers; colorimetric assays	Fluorescence imaging; biosensing	Multiplex point-of-care testing; hybrid sensing

Steric hindrance & protein denaturation

High ligand packing density, small nanoparticle radius of curvature, and harsh conjugation conditions can denature proteins or shield binding sites (65). Practical solutions typically involve using Fc-directed, site-specific attachment strategies, incorporating flexible PEG linkers to allow sufficient mobility, keeping surface coverage at moderate levels to avoid steric crowding, and performing the conjugation under mild, near-physiological pH (~7.4) to preserve protein structure. (66) (54)

Electrochemical properties and hybrid strategies

GNPs enhance electron transfer in electrochemical sensors and provide plasmonic amplification, while CQDs provide electrochemical stability, abundant reactive groups, and bright fluorescence. Hybrids (GNP-CQD) leverage complementary benefits enabling dual-mode detection (optical + electrochemical) (67) (Table 2).

Diagnostic and therapeutic applications

Diagnostic applications

Cancer biomarkers

GNPs (SPR/SERS) and CQDs (fluorescence) detect PSA, HER2, CA-125, AFP, ctDNA, and exosomal miRNA at femtomolar to picomolar sensitivities in optimized assays (68) (69) (70) (71). GNP aggregation-based colorimetric assays enable simple, low-cost detection; SERS-active GNPs provide single-molecule sensitivity when properly functionalized. (72, 73)

Infectious diseases

GNPs dominate lateral flow assays (LFAs) due to strong visual readout and stability (74); CQDs enable multiplexed fluorescence readouts and real-time monitoring (75) (76) (77) (78) (79). Integration with electrochemical

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readouts and ML-based signal interpretation improves quantitative diagnostics. (80)

High-sensitivity bioassays

Plasmonic ELISA (pELISA) and CQD-enhanced electrochemical immunosensors achieve ultralow detection limits (fM) (81). Microfluidic integration reduces sample volumes, enhances binding kinetics, and enables multiplexing.

Therapeutic and drug delivery applications

GNPs: Carrier for drugs, photothermal agents (NIR absorption), imaging contrast agents (CT, PAI), and vaccine adjuvants (82) (83).

CQDs: Photosensitizers for PDT (ROS generation), rapid renal clearance advantages for safety, and carriers for redox-responsive drug release (83). Hybrid designs enable theranostics — simultaneous imaging, sensing, and therapy. (84)

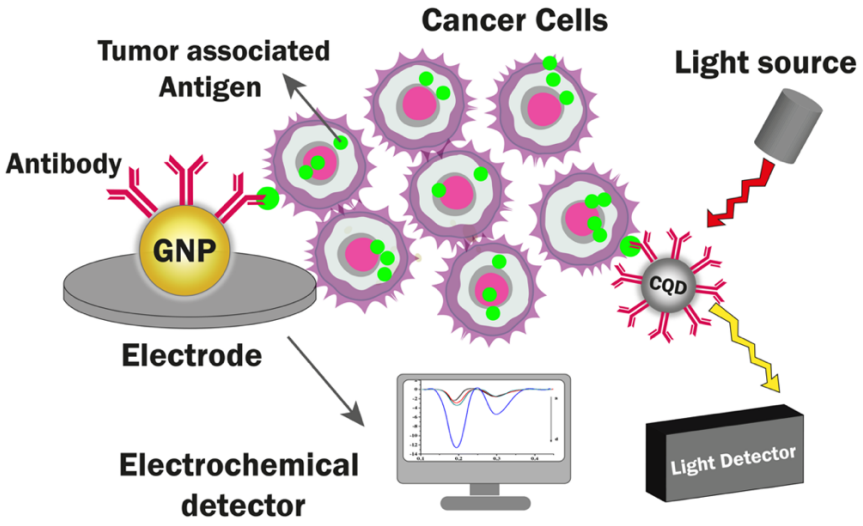

Figure 3. *Schematic of dual-mode GNP–CQD immunosensing for cancer biomarkers. GNP-labeled antibodies immobilized on electrodes enable electrochemical detection, while CQDs provide an optical readout upon illumination. Combined electrochemical/optical sensing enhances the accuracy and sensitivity of tumor-associated antigen detection.*

Comparative analyses and translational considerations

Comparison with other nanoplatforms

GNPs and CQDs exhibit distinct advantages over other nanoplatforms in optical and biosensing applications due to their intrinsic signal amplification properties. In contrast, lipid nanoparticles (LNPs), a class of biocompatible and biodegradable nanocarriers composed of phospholipids, cholesterol, and ionizable lipids, are primarily optimized for therapeutic delivery rather than sensing applications. (85) LNPs have demonstrated exceptional performance in the delivery of nucleic acids, including mRNA and siRNA, owing to their ability to protect cargo from degradation, facilitate cellular uptake, and enable endosomal escape. (86) This delivery efficiency has led to their widespread clinical translation, including applications in mRNA vaccines and gene therapy. (85) (86)

LNPs lack intrinsic optical or electronic signal amplification, limiting their direct applicability in biosensing platforms. (87) Polymeric nanoparticles offer complementary advantages, particularly in terms of structural versatility, tunable degradation profiles, and controlled drug release. Their physicochemical properties can be engineered to improve drug bioavailability, targeting efficiency, and sustained release kinetics. However, these systems generally lack inherent signal-generating capabilities, making them less suitable for label-free or signal-enhanced biosensing applications. (88) Similarly, silica-based nanoparticles provide high surface area, chemical stability, and ease of functionalization, enabling efficient drug loading and multifunctional design. Nevertheless, their optical response is typically indirect and requires additional functional components. (87) Table 3 summarizes platform tradeoffs.

Advantages & limitations of GNP vs. CQD immunosensors

GNPs offer strong plasmonic signal amplification, well-established surface functionalization via Au–S chemistry, and compatibility with

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multimodal imaging platforms, making them highly suitable for optical and electrochemical immunosensing applications. (89)

Table 3. Comparison of major nanomaterial platforms, highlighting their functional advantages, limitations, and application-specific roles in biosensing and drug delivery.

Nanomaterial	*Primary Advantages*	*Major Limitations*	*Best Application Areas*
GNPs	Strong plasmonic signal amplification; high stability; facile surface conjugation	Cost; aggregation; potential accumulation/toxicity	Imaging; plasmonic biosensing; targeted diagnostics
CQDs	Bright and stable fluorescence; low toxicity; tunable emission; easy functionalization	Limited drug loading; batch-to-batch variability	Fluorescence biosensing; real-time imaging
LNPs (lipid nanoparticles)	High encapsulation efficiency; excellent for nucleic acid delivery (mRNA, siRNA); efficient cellular uptake and endosomal escape	Limited intrinsic optical properties; stability and storage constraints	Gene delivery; mRNA vaccines; nucleic acid therapeutics
Silica NPs	High surface area; tunable porosity; multifunctional loading capacity; good chemical stability	Potential toxicity; immune activation; complex degradation behavior	Drug delivery; imaging; theranostics; controlled release
Polymeric NPs	Controlled release; biodegradability; high structural versatility; tunable degradation kinetics	Limited intrinsic signal generation; slower degradation in some systems	Drug delivery; targeted therapies; sustained release systems

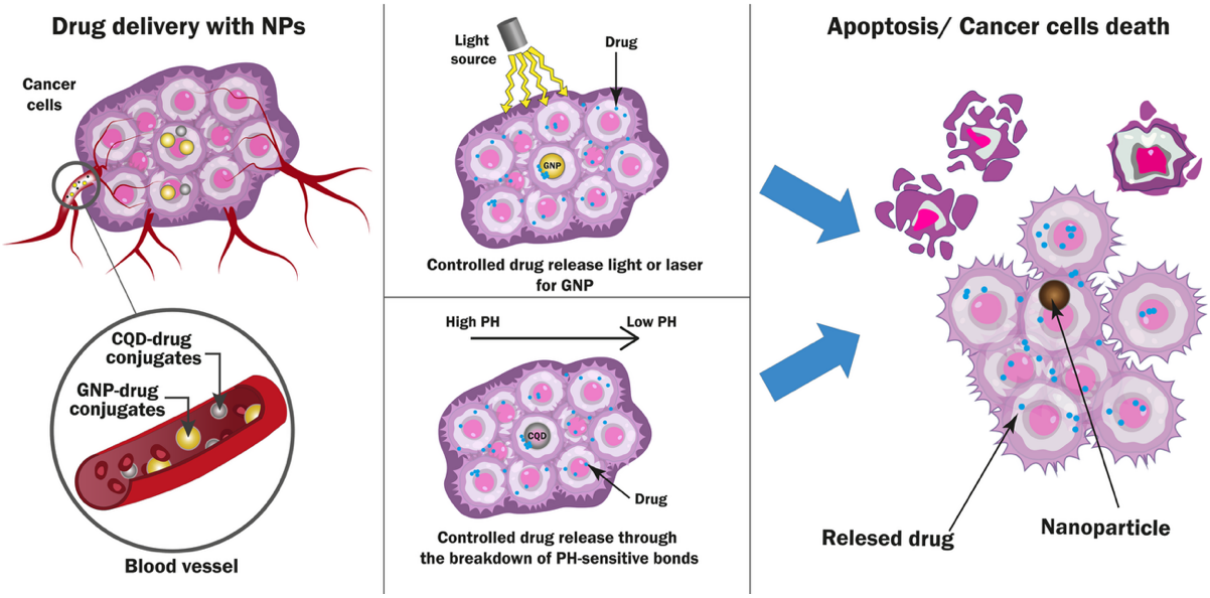

Figure 4. Nanoparticle-mediated drug delivery and controlled release mechanisms using GNPs and CQDs. GNPs offer photothermal or light-triggered drug release, while CQDs provide pH-responsive payload delivery. These mechanisms induce apoptosis in cancer cells and increase therapeutic precision.

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These properties make them attractive for fluorescence-based sensing and real-time bioimaging. Nevertheless, CQDs often suffer from batch-to-batch variability and require effective surface passivation to prevent fluorescence quenching and maintain signal stability in complex biological environments.

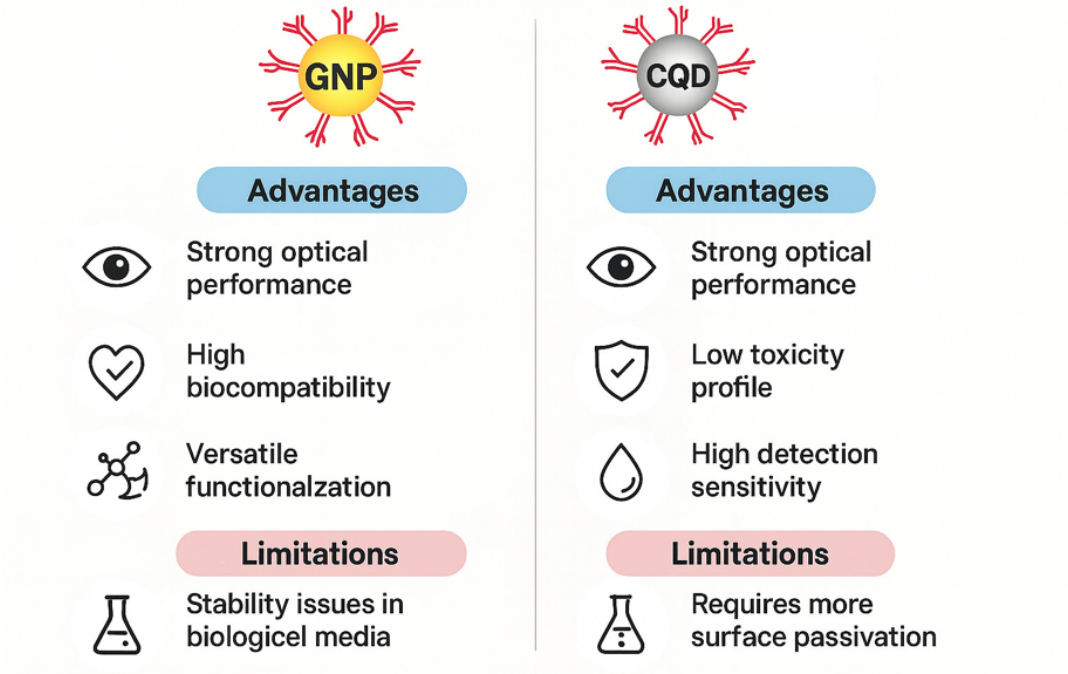

Figure 5. Comparative summary of the advantages and limitations of GNP- and CQD-based immunosensors. Parameters include optical performance, biocompatibility, surface functionalization versatility, stability in biological environments, detection sensitivity, toxicity profile, and translational barriers such as reproducibility and scale-up manufacturing

(37) Overall, GNPs are generally preferred for applications requiring strong signal amplification and multimodal detection, whereas CQDs are advantageous for low toxicity, fluorescence-based sensing platforms. (See Figure 5).

Scale-up, GMP, and regulatory pathways

Key translational bottlenecks: batch-to-batch reproducibility, robust surface functionalization at scale, endotoxin/sterility control, stability/shelf-life, and validated toxicology (92). Adoption of standardized descriptors (size ± SD, PDI, ligand density, endotoxin content) and early engagement with regulatory agencies is essential (93). Integration of production automation (microreactors) and in-process QC will accelerate clinical translation. (94)

Computational modeling & predictive design

Computational modeling has become a critical approach for elucidating nano-bio interactions and enabling the predictive design of nanomaterial-based immunosensors, particularly by bridging the gap between experimental observations and mechanistic understanding. Molecular dynamics (MD) simulations, as first-principles modeling approaches, allow detailed investigation of nanoparticle–biomolecule interactions at the atomistic level, providing insights into binding dynamics, conformational stability, and interaction pathways that govern nano-bio interfaces. These simulations are particularly valuable for understanding how surface properties, such as charge, size, and functionalization, influence particle–cell interactions and internalization. (95) Density functional theory (DFT) further complements MD by enabling quantum-level analysis of nanomaterials, including electronic structure, adsorption energies, and charge transfer phenomena. Such calculations are essential for predicting surface reactivity and stability of functionalized nanomaterials, as well as understanding ligand–surface interactions at the molecular level. (96) Importantly, DFT-based descriptors

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(e.g., band gap, adsorption energy) are frequently used as input features for predictive modeling frameworks, linking physicochemical properties to biological performance. (96) (97) Monte Carlo and multiscale modeling approaches provide an additional layer of insight by capturing stochastic adsorption processes and system-level behavior that cannot be resolved at purely atomistic scales. These methods are particularly relevant for modeling protein corona formation, nanoparticle aggregation, and adsorption equilibria under biologically relevant conditions, where competitive binding and dynamic exchange processes dominate nano-bio interactions. (97) (98) Molecular docking techniques are widely applied to predict binding affinity and preferred orientation of biomolecules on nanoparticle surfaces, enabling rational optimization of bio-recognition interfaces. These approaches are especially important for immunosensor design, where ligand orientation and accessibility directly influence binding efficiency and signal output. (95)

More recently, machine learning (ML) and artificial intelligence (AI) approaches have emerged as powerful data-driven tools for predicting nano-bio interactions and accelerating nanomaterial discovery. ML models can identify complex structure–property relationships from large experimental and computational datasets, enabling the prediction of key parameters such as protein corona composition, nanoparticle toxicity, and cellular uptake. (97) (95) In particular, ML frameworks have been successfully applied to predict biomolecular corona formation based on nanoparticle physicochemical descriptors, overcoming limitations of purely experimental approaches. (97) In addition, hybrid approaches integrating DFT with ML have demonstrated significant potential in accelerating materials discovery by reducing computational cost while maintaining predictive accuracy. These models enable rapid prediction of properties such as adsorption energies, reaction pathways, and electronic characteristics, facilitating high-throughput screening of nanomaterials. (96)

Overall, computational modeling provides a multiscale framework in which physics-based simulations (MD, DFT), stochastic modeling (Monte Carlo), and data-driven approaches (ML/AI) collectively enable predictive design of nanomaterial interfaces. Such integrated strategies are essential for minimizing protein corona formation, optimizing ligand orientation, and ultimately improving the sensitivity, specificity, and reproducibility of immunosensors.

Future directions and outlook

Despite substantial advances in nanomaterial-based immunosensors, a persistent gap remains between laboratory-scale performance and reliable clinical implementation. A major underlying challenge is the lack of standardization in nanoparticle synthesis and characterization, which directly affects reproducibility across studies. Variations in size distribution, ligand density, and colloidal stability can lead to inconsistent biofunctionalization and unpredictable nano-bio interactions. Moving forward, the field must transition toward GMP-aligned production and standardized quality control frameworks that link physicochemical parameters to functional performance, enabling reproducible and clinically comparable results. Equally critical is the need to move beyond conventional conjugation strategies toward precisely controlled biointerfaces. Random immobilization of antibodies often results in partial loss of activity due to steric hindrance or unfavorable orientation. In contrast, site-specific conjugation strategies such as Fc-directed immobilization or bio-orthogonal click chemistry enable preservation of antigen-binding regions and improved signal consistency. However, their broader adoption will require scalable and robust implementation strategies compatible with real-world manufacturing constraints.

Another key limitation arises from the complexity of biological samples. While many sensing platforms demonstrate excellent performance in buffered conditions, their reliability often deteriorates in complex matrices such as whole blood or saliva due to protein corona formation and nonspecific adsorption. Addressing this challenge requires integrated solutions that combine antifouling surface engineering with microfluidic sample handling. Rather than treating these components separately, future systems should be designed holistically, with sample preprocessing, surface chemistry, and signal transduction co-optimized to maintain sensitivity under realistic conditions. From a materials perspective, the next generation of immunosensors is likely to rely on hybrid nanostructures that integrate complementary

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functionalities within a single platform. For example, combining gold nanoparticles with CQDs can enable simultaneous optical and electronic signal transduction, improving both sensitivity and robustness. The practical significance of such systems lies in their compatibility with miniaturized and portable devices, which are essential for point-of-care diagnostics. However, achieving this integration will require careful control over interfacial interactions to avoid signal interference and ensure stability.

A particularly transformative direction is the integration of AI into both assay development and system optimization. Rather than relying on empirical optimization, AI-driven approaches can identify non-obvious relationships between surface chemistry, biomolecular interactions, and sensing performance. For instance, ML models can be used to predict optimal ligand densities, anticipate protein corona formation under specific conditions, or dynamically adjust assay parameters based on real-time data. In this context, AI is not merely a tool for data analysis but a framework for adaptive, self-optimizing sensor systems.

The long-term clinical adoption of nanomaterial-based immunosensors will depend on a more comprehensive understanding of their in vivo behavior. While short-term biocompatibility is often demonstrated, long-term immunotoxicity, biodistribution, and clearance mechanisms remain insufficiently characterized. Addressing these questions is essential not only for regulatory approval but also for ensuring the safe integration of these technologies into clinical workflows. Taken together, future progress in this field will depend on shifting from isolated component-level optimization to integrated system-level design. The convergence of standardized manufacturing, controlled biointerfaces, hybrid nanomaterials, and data-driven optimization strategies is expected to define the next generation of robust, scalable, and clinically translatable immunosensing platforms.

Conclusion

GNPs and CQDs present complementary strengths for immunosensors: GNPs for plasmonic amplification and multimodal imaging, CQDs for bright, tunable fluorescence and favorable safety profiles. Translational success will depend on standardized synthesis and characterization, robust site-specific conjugation methods that preserve biomolecule function, effective antifouling strategies, and rigorous in vivo safety and manufacturing controls. Addressing these requirements will allow these nanomaterials to fulfill their potential for precision diagnostics and theranostics.

AI Use Statement

AI-assisted tools (ChatGPT) were used to improve language clarity and structure. The authors carefully reviewed and validated all content and take full responsibility for the manuscript.

Author Contributions: Conceptualization, M.S. and B.S.; literature review and data curation, M.S. and K.A.; figure design, graphical visualization, and illustration, M.S. and K.A.; writing; original draft preparation, M.S.; writing; review and editing, K.A., A.F., E.H., M.V., and B.S.; supervision, B.S. All authors have read and agreed to the published version of the manuscript.

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