APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

Machine Learning-Guided Photoresponsive Behavior of Metal Nanoclusters for Biomedical Diagnosis and Therapy: Mechanisms, Applications, and Emerging Perspectives

Haijing Wah Wu[1*]

[1] Cixi Institute of Biomedical Engineering, International Cooperation Base of Biomedical Materials Technology and Application, Chinese Academy of Science (CAS) Key Laboratory of Magnetic Materials and Devices & Zhejiang Engineering Research Center for Biomedical Materials, Ningbo Institute of Materials Technology and Engineering, CAS, 1219 ZhongGuan West Road, Ningbo 315201, China; Advanced Energy Science and Technology Guangdong Laboratory, Huizhou 516000, China, e-mail: haijing.wah@nimte.ac.cn

* Corresponding Author: Haijing Wah Wu, haijing.wah@nimte.ac.cn

DOI: https://doi.org/10.64440/IJAS/IJAS1005

ARTICLE INFO

Article history
Received Mar 09, 2026
Revised Mar 10, 2026
Accepted May 12, 2026

Keywords
metal nanoclusters;
machine learning;
photoresponsive behavior;
photoluminescence;
biosensing;
bioimaging;
photodynamic therapy;
photothermal therapy;
theranostics;
near-infrared imaging.

ABSTRACT

Metal nanoclusters (MNCs), typically composed of several to hundreds of metal atoms with dimensions below approximately 3 nm, have emerged as a distinctive class of nanomaterials for biomedical diagnosis and therapy. Their ultrasmall dimensions, atomically precise structures, discrete electronic states, tunable surface chemistry, and favorable photophysical properties enable optical responses that differ fundamentally from those of conventional metal nanoparticles. Upon photoexcitation, MNCs may undergo radiative recombination, charge trapping, energy or electron transfer, and nonradiative relaxation, thereby generating photoluminescence, reactive oxygen species, or localized heat. These processes provide the mechanistic basis for biosensing, bioimaging, photodynamic therapy, photothermal therapy, and integrated theranostic applications. Recent advances have further demonstrated that ligand engineering, core alloying, heteroatom doping, aggregation-induced emission, supramolecular assembly, and biomolecular templating can substantially regulate the optical and biological behavior of MNCs. More recently, machine learning (ML) has emerged as an additional design variable capable of accelerating the prediction of nanocluster structures, optical properties, ligand effects, fluorescence behavior, and biological responses. ML-assisted analysis can integrate multidimensional structural, spectroscopic, and biological datasets and thereby facilitate rational rather than trial-and-error design of MNC-based probes. This review systematically discusses the photoresponsive mechanisms of metal nanoclusters, their applications in biomedical sensing, imaging, photodynamic therapy, and photothermal therapy, and the emerging integration of ML with nanocluster engineering. Particular attention is given to structure–photophysics–biological function relationships, near-infrared and second near-infrared optical windows, multimodal theranostics, adaptive sensor design, and data-driven optimization. Finally, current challenges concerning quantum yield, photostability, biological stability, toxicity, model interpretability, data standardization, and clinical translation are discussed. The integration of atomically precise nanochemistry with artificial intelligence may provide a new framework for the development of more predictable, adaptive, and clinically relevant nanotheranostic platforms.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

INTRODUCTION

Nanomedicine has progressively transformed the interface between materials science, biology, and clinical medicine by enabling the manipulation of biological processes at molecular and nanoscale dimensions. Among the diverse nanomaterials investigated for biomedical applications, metal nanoclusters (MNCs) have attracted particular attention because they occupy an unusual size regime between individual metal atoms or molecular complexes and conventional plasmonic nanoparticles. Their dimensions are generally below 3 nm, and many atomically precise clusters contain only several to hundreds of metal atoms. At this scale, the continuous electronic bands characteristic of bulk metals disappear and are replaced by discrete, molecule-like electronic states. This transition gives rise to optical and electronic properties that are highly sensitive to cluster size, atomic composition, geometric structure, electron count, oxidation state, and surface ligands [1–4]. Recent perspectives continue to identify these characteristics as major reasons for the growing interest in MNCs as bioimaging and therapeutic platforms.

The biological importance of MNCs is closely associated with their combination of ultrasmall dimensions, surface functionalizability, and tunable optical properties. Gold (Au), silver (Ag), copper (Cu), and alloyed clusters can be stabilized by thiols, peptides, proteins, DNA, polymers, and other biomolecular ligands. These surface components not only prevent uncontrolled aggregation but can also determine cellular uptake, target recognition, circulation behavior, intracellular localization, and photophysical properties [5–8]. Protein-protected MNCs, for example, have been extensively investigated as fluorescent probes and as components of therapeutic systems involving imaging, drug delivery, photodynamic therapy (PDT), and photothermal therapy (PTT).

The photoresponsive behavior of MNCs is particularly important for biomedical applications. When incident photons possess energies compatible with the electronic transitions of a cluster, photoexcitation promotes electrons from the ground state to higher-energy states. The excited state can subsequently relax through several competing pathways. Radiative relaxation produces fluorescence or phosphorescence; charge trapping and electron transfer can generate reactive intermediates; energy transfer to molecular oxygen can produce singlet oxygen and other reactive oxygen species (ROS); and nonradiative relaxation converts absorbed optical energy into heat. Consequently, a single nanocluster platform may potentially function as a fluorescent sensor, imaging probe, photosensitizer, or photothermal agent depending on its structure and environment [9–12].

The relationship between MNC structure and optical response is therefore central to biomedical nanotechnology. Ligand engineering can alter surface states and excited-state lifetimes, while metal alloying or core doping can modify electronic structures and emission wavelengths. Aggregation-induced emission (AIE), assembly-induced emission, host–guest interactions, and protein or DNA templating provide additional approaches for controlling photophysical behavior [13–16]. Fluorescent MNCs have consequently been explored for the detection of biomarkers, ions, enzymes, pH, temperature, pathogens, and other biologically relevant analytes.

Despite these advances, substantial challenges remain. Many MNCs exhibit relatively low quantum yields, limited stability in complex biological environments, and excitation or emission wavelengths that do not optimally match the biological optical windows. In addition, the relationship between atomic structure, ligand configuration, excited-state dynamics, and biological function is highly nonlinear. The enormous chemical design space makes experimental optimization through conventional trial-and-error approaches inefficient.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Machine learning (ML) offers a potential solution to this problem. By learning relationships between experimentally measured or computationally generated descriptors and target properties, ML models can predict optical responses and guide the selection of promising nanocluster compositions and ligand environments. Recent work has already demonstrated the integration of ML with metal-nanocluster optical-property prediction and high-throughput screening. In particular, ML has been applied to predict fluorescence characteristics and identify structure–property relationships in thiolate-protected metal clusters. More recent work has also demonstrated automated ML-assisted analysis of fluorescence fingerprints generated by silver nanoclusters for multiplexed ion detection.

Therefore, integrating machine learning with the photoresponsive behavior of MNCs represents an emerging research direction in nanomedicine. Rather than treating ML as an independent computational tool, it can be incorporated into the entire design cycle, from cluster composition and ligand selection to optical prediction, biological targeting, therapeutic optimization, and post-treatment analysis.

This review therefore examines the photoresponsive behavior of MNCs and its biomedical implications, while introducing ML-guided nanocluster engineering as a new analytical and design dimension. The discussion focuses on four major biomedical applications: **biosensing, bioimaging, photodynamic therapy, and photothermal therapy**, followed by an analysis of the integration of ML with these systems and future prospects for intelligent theranostic platforms.

---

2. Photoresponsive Behavior of Metal Nanoclusters

The optical behavior of MNCs originates from their discrete electronic structures. Unlike larger metal nanoparticles, which commonly exhibit collective surface plasmon resonance, ultrasmall clusters display molecule-like transitions between discrete electronic states. Their optical absorption and emission therefore depend strongly on the number of metal atoms, electron count, geometric configuration, oxidation state, and ligand environment [1,3,17].

When a nanocluster absorbs a photon, an electron is promoted from a ground state to an excited state. The subsequent relaxation process can proceed through several competing pathways:

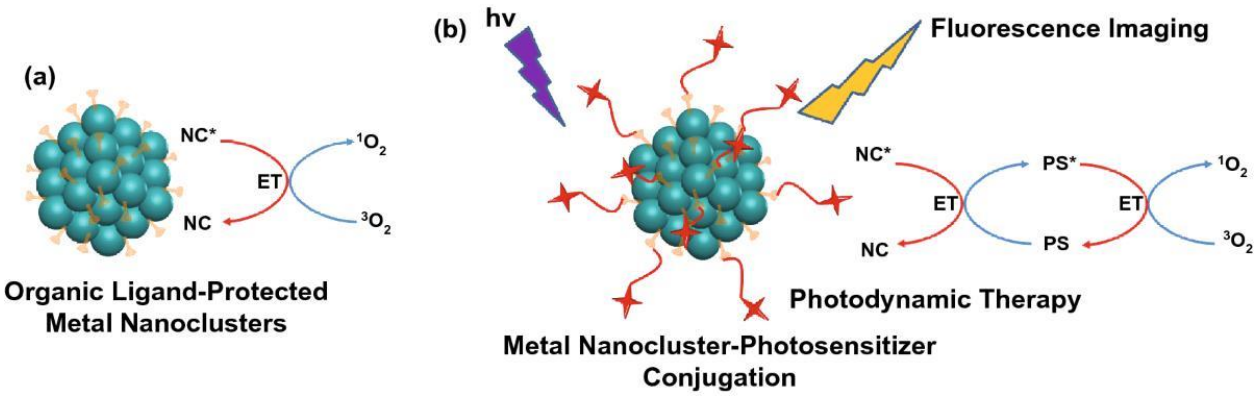
1. **Radiative relaxation**, producing fluorescence or phosphorescence;
2. **Charge trapping and electron transfer**, potentially generating reactive intermediates;
3. **Energy transfer**, particularly to molecular oxygen, producing singlet oxygen and other ROS;
4. **Nonradiative relaxation**, converting excitation energy into heat.

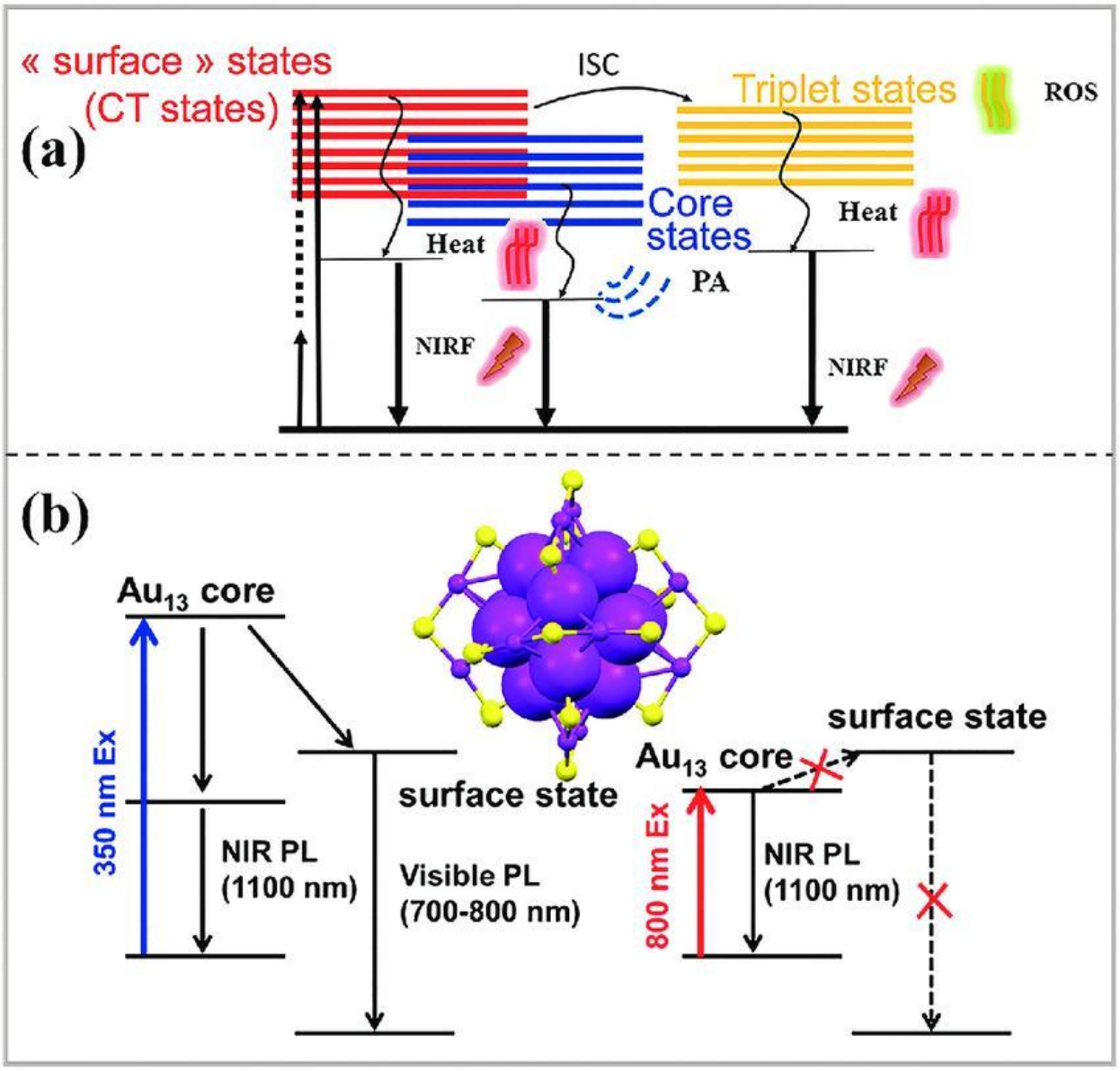
These pathways determine the ultimate biomedical function of a particular MNC.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

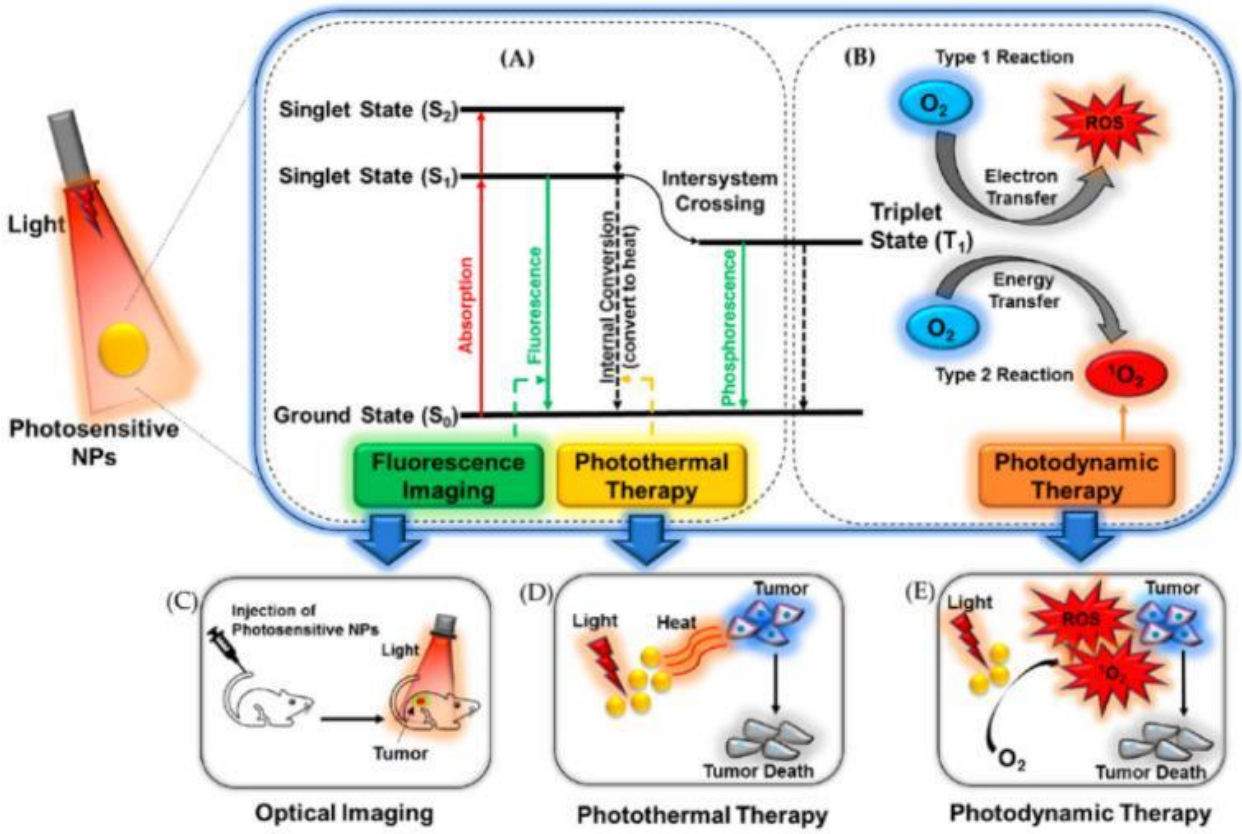
https://international-journal-of-applied-sciences.jo





APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo



4

Figure 1. Schematic representation of the photoresponsive behavior of metal nanoclusters and its relationship to biomedical sensing, imaging, photodynamic therapy, and photothermal therapy.

The relative contribution of each pathway can be controlled through structural and environmental engineering. Ligands may introduce new electronic states, restrict molecular motion, alter charge-transfer pathways, and modify the accessibility of the cluster surface. Metal doping may shift energy levels and change electron density, while aggregation or supramolecular confinement may suppress nonradiative losses and enhance emission.

This structure–property relationship is one of the defining features of MNCs. Because a small modification at the atomic or ligand level can substantially change optical behavior, MNCs offer a particularly attractive platform for precision nanomedicine [18–20].

Recent research has increasingly emphasized that the photophysical properties of MNCs should not be considered independently from their biological environment. pH, ionic strength, proteins, oxygen concentration, temperature, redox conditions, and cellular compartments may all influence excited-state behavior. Consequently, the same cluster can display substantially different optical responses in aqueous solution, serum, intracellular environments, or tumor tissues.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

This environmental sensitivity is advantageous for responsive biosensing but represents a challenge for quantitative imaging and therapy. The development of predictive models capable of incorporating both molecular descriptors and biological environmental variables is therefore an important area in which ML can provide significant value.

3. Luminescent Behavior of Metal Nanoclusters in Biomedical Sensing

The strong and tunable photoluminescence of MNCs has made them attractive candidates for optical biosensing. Their fluorescence can be modified by changes in ligand configuration, aggregation state, metal composition, oxidation state, analyte binding, electron transfer, and local environmental conditions.

Metal nanoclusters have been extensively investigated for the detection of biomarkers and biologically relevant molecules because they can combine recognition elements with intrinsic fluorescence. Reviews of fluorescent MNC biosensors have documented applications involving disease biomarkers, infectious agents, inflammatory indicators, and tumor-associated targets.

3.1 Enzyme and biomarker sensing

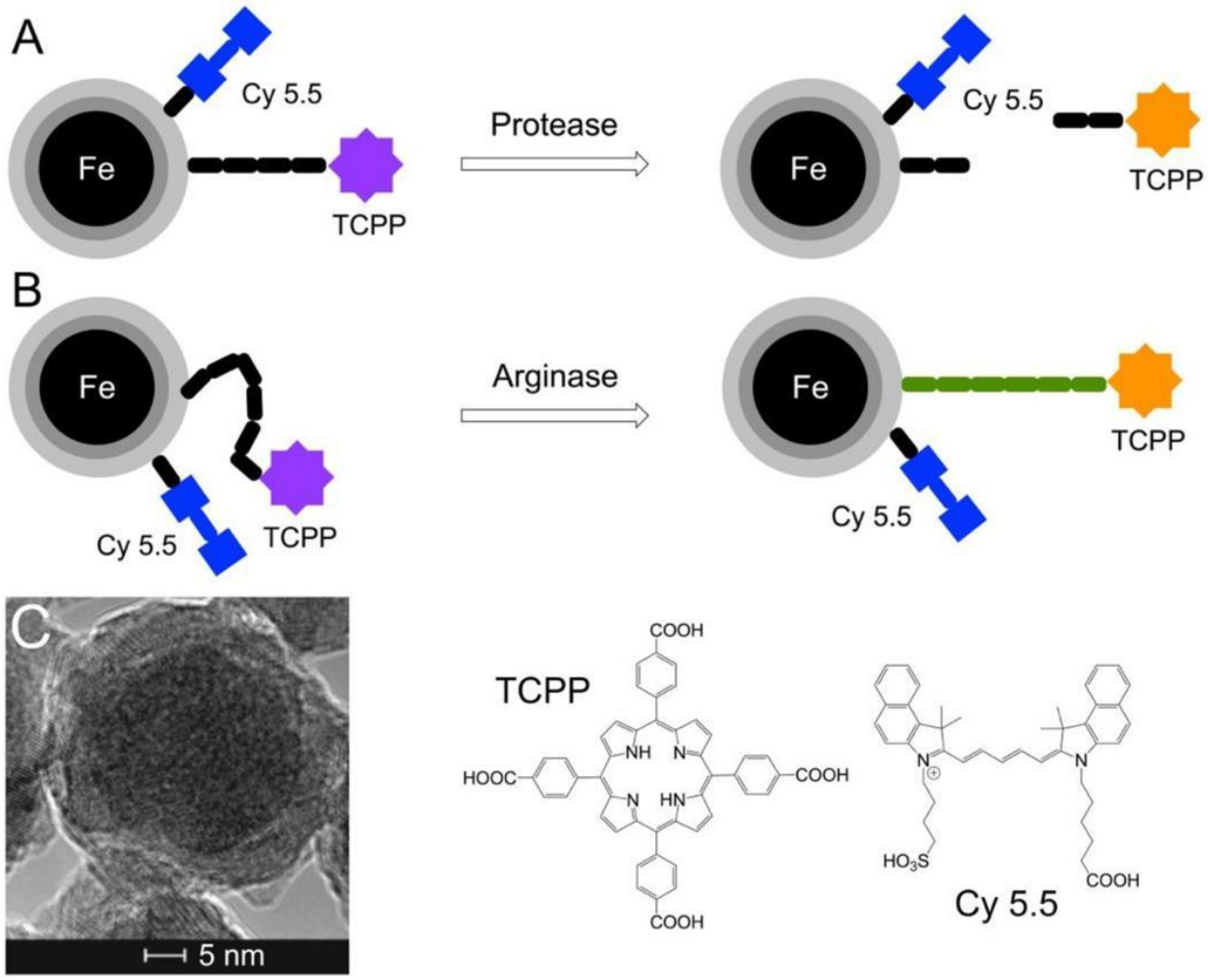
Ligand engineering is one of the most effective strategies for modifying MNC fluorescence. Functional ligands can provide selective binding sites for target biomolecules and simultaneously regulate the excited-state dynamics of the metal core.

For example, amino-acid-containing ligands, peptides, proteins, and nucleic acids can act as both stabilizing agents and recognition elements. Binding of the target molecule may alter the rigidity, electronic coupling, or charge-transfer characteristics of the ligand shell, resulting in fluorescence enhancement or quenching.

Such mechanisms can produce sensitive assays for enzymes and other disease-related biomarkers.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo



APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

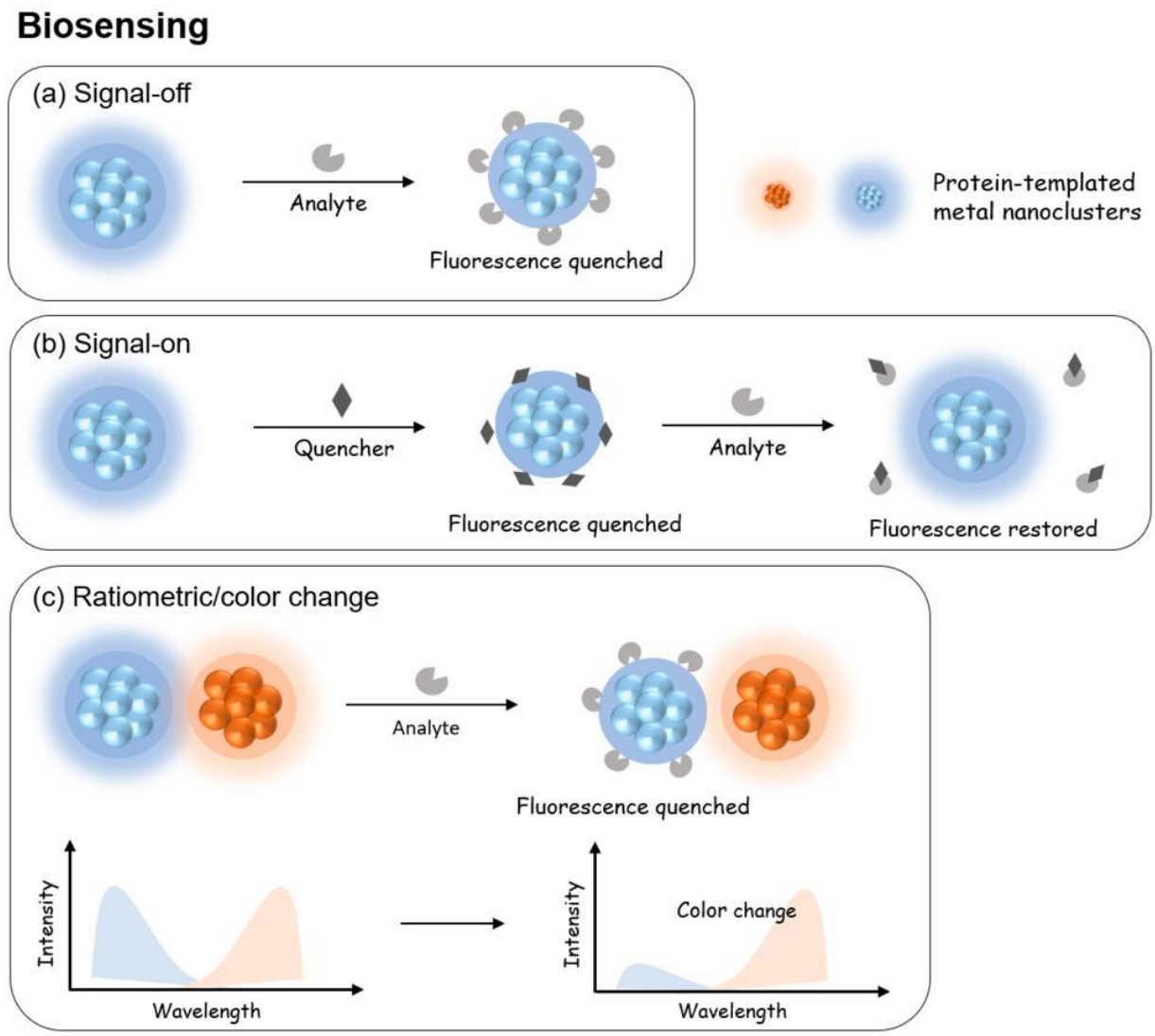


Figure 2. Representative mechanism of ligand-engineered metal nanoclusters for fluorescent biosensing and enzyme detection.

Aggregation-induced emission provides another important mechanism. In conventional fluorophores, aggregation may reduce fluorescence because of aggregation-caused quenching. In appropriately engineered MNC systems, however, aggregation can restrict molecular motion and suppress nonradiative relaxation, resulting in enhanced emission. This principle has enabled the development of highly sensitive sensors for proteins, metabolites, ions, and other analytes.

The emergence of ML further expands this capability. Instead of relying on a single fluorescence intensity value, ML can analyze multidimensional spectral fingerprints containing emission wavelength, intensity, lifetime, excitation dependence, and response patterns. Such approaches are particularly valuable for multiplexed detection in which different analytes produce partially overlapping spectral responses.

A recent 2026 study demonstrated an automated ML framework using multiple silver nanoclusters to generate fluorescence fingerprints for identifying and quantifying several heavy-metal ions, illustrating how nanocluster arrays and ML can be combined for multiplexed analytical detection.

3.2 Ion, pH, and temperature sensing

MNC fluorescence is also highly sensitive to changes in the local chemical environment. This property has enabled the detection of metal ions, pH, temperature, reactive species, and other physiological variables.

pH-sensitive MNCs are particularly relevant because intracellular and extracellular pH changes are associated with numerous pathological conditions. Tumor microenvironments, lysosomal compartments, inflammatory tissues, and bacterial biofilms may possess distinct pH characteristics. A fluorescent cluster capable of responding reversibly to these changes can therefore serve as a molecular-scale environmental probe.

Temperature-responsive clusters represent another promising application. Because temperature can alter ligand dynamics, excited-state relaxation, and nonradiative energy dissipation, MNC fluorescence may provide a convenient optical method for monitoring local temperature.

3.3 Machine learning-enhanced biosensing

The integration of ML represents a significant evolution from conventional single-analyte fluorescence assays.

A conventional sensor may depend on a simple relationship:

where is fluorescence intensity and is analyte concentration.

In an ML-assisted platform, however, the input can become a multidimensional feature vector:

where represents wavelength-dependent fluorescence intensity, represents the emission maximum, is fluorescence lifetime, and additional variables describe spectral or environmental characteristics.

The ML model can then estimate:

where may represent analyte identity, concentration, disease state, or biological condition.

This approach can improve selectivity in complex samples and enable simultaneous identification of several analytes. Recent developments in ML-guided metal-nanocluster research indicate that optical-property prediction and fluorescence engineering are becoming increasingly integrated with computational methods.

Nevertheless, successful clinical translation requires large, standardized, and biologically representative datasets. Variations in synthesis protocols, ligand purity, cluster size distributions, instrumentation, excitation wavelength, and sample matrices can introduce systematic biases into ML models. Thus, data standardization is as important as algorithmic sophistication.

---

4. Bioimaging Based on Photoresponsive Metal Nanoclusters

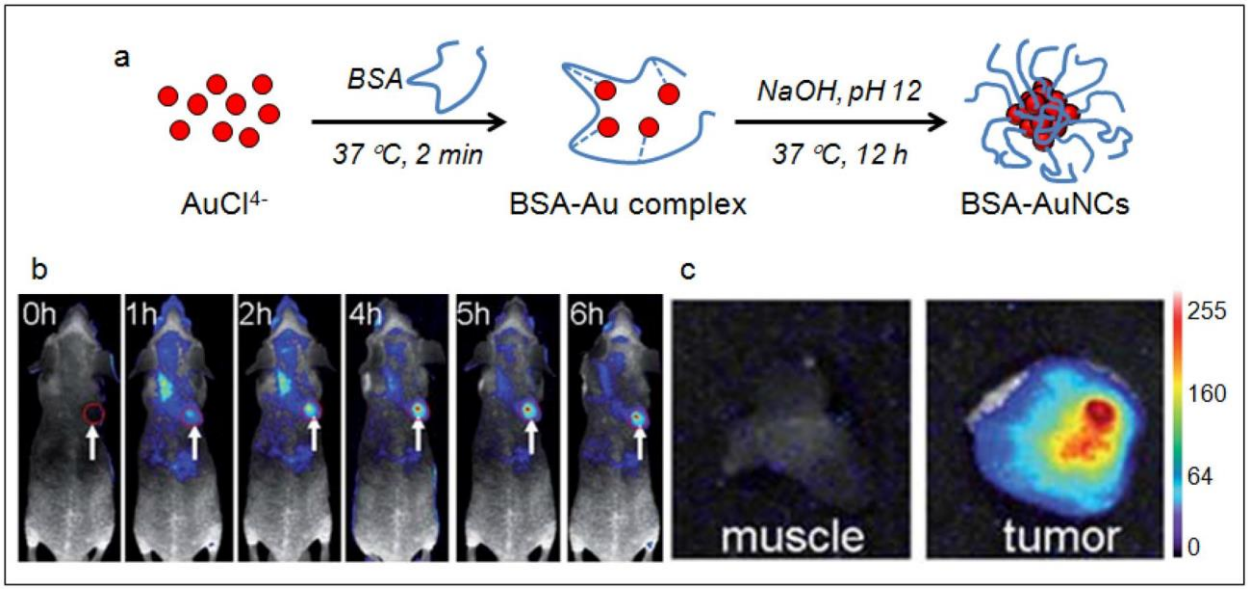
Bioimaging plays a central role in understanding biological structure and function and in enabling early disease detection. Fluorescent MNCs offer several potential advantages over conventional

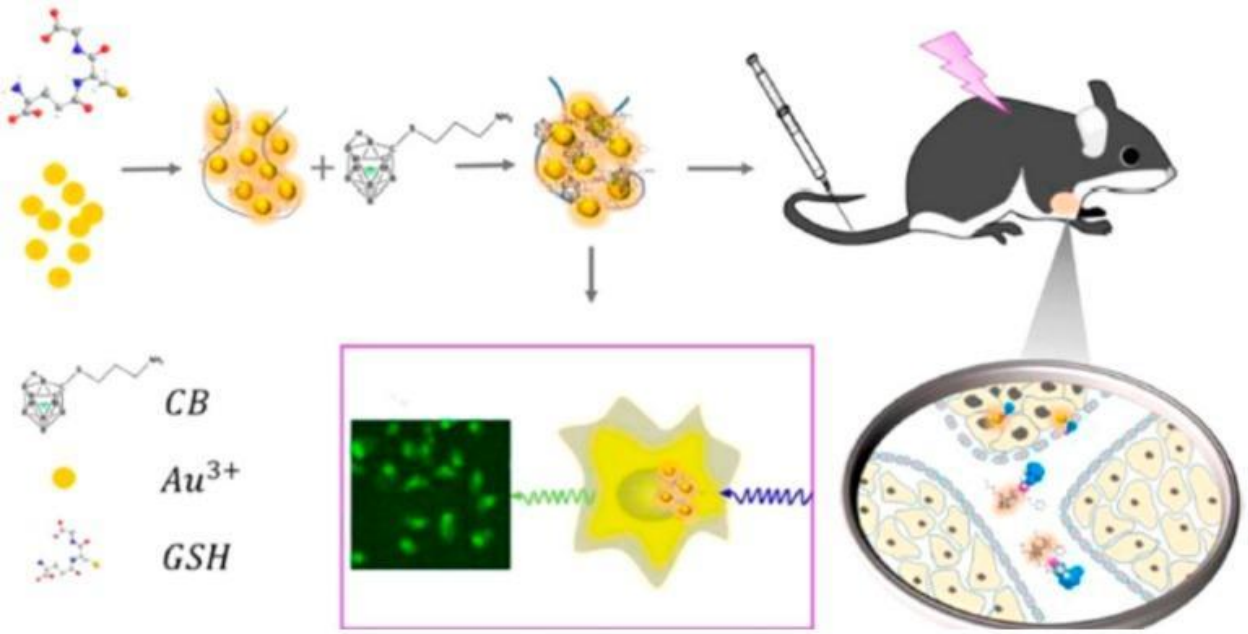
APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

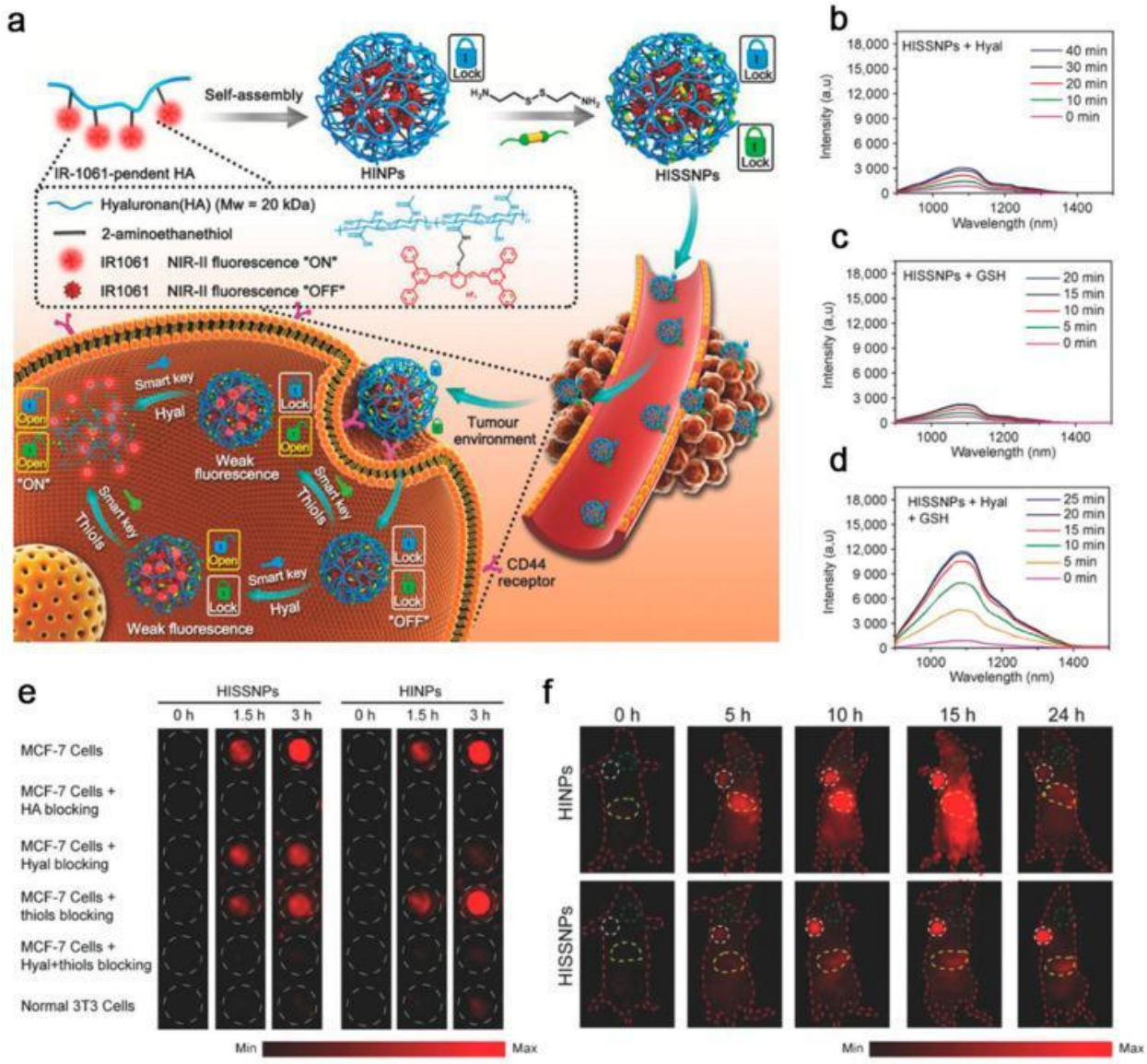
organic dyes and some semiconductor quantum dots, including ultrasmall size, tunable emission, high surface functionalizability, and favorable photostability.





APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo



4

Figure 3. Application of photoresponsive metal nanoclusters in cellular and in vivo bioimaging and imaging-guided therapy.

4.1 Cellular imaging

Functionalized MNCs can be engineered to recognize specific cellular compartments or biomolecular targets. Ligand selection is particularly important because the ligand shell determines interactions with cell membranes, intracellular proteins, organelles, and trafficking pathways.

MNCs have been investigated for imaging cellular organelles, cancer cells, proteins, and other biological structures. Their small dimensions may facilitate cellular uptake, while surface functionalization can increase specificity.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

Protein-protected MNCs have received considerable attention because proteins provide a biologically compatible scaffold while simultaneously influencing cluster formation and optical properties. Such systems have been explored for fluorescence imaging and molecular recognition.

4.2 Near-infrared imaging

A major limitation of conventional fluorescence imaging is tissue autofluorescence and light scattering. These problems become particularly significant when imaging deep tissues.

The near-infrared region provides improved tissue penetration and reduced background fluorescence compared with visible wavelengths. More recently, MNCs emitting in the second near-infrared window (NIR-II; approximately 1000–1700 nm) have emerged as promising candidates for deep-tissue imaging.

Atomically precise MNCs can be engineered to generate NIR emission, and recent literature emphasizes their potential for deep-tissue imaging because of their tunable electronic structures, photostability, and large Stokes shifts.

However, NIR-II MNCs remain subject to several limitations, including insufficient emission intensity, challenges in controlling emission wavelengths, biological stability, and the need to balance optical performance with renal clearance and long-term biosafety.

4.3 Imaging-guided theranostics

One of the most attractive characteristics of MNCs is their potential to combine diagnosis and therapy within a single platform.

A theranostic MNC may simultaneously:

- identify a pathological target;
- produce a fluorescence signal;
- deliver therapeutic molecules;
- generate ROS following photoexcitation;
- convert optical energy into heat;
- monitor therapeutic response.

This integration can reduce the need for separate diagnostic and therapeutic agents and may enable personalized treatment.

Recent perspectives describe ultrasmall coinage-metal MNCs as promising theranostic probes for bioimaging-directed diagnosis, photoinduced therapy, drug delivery, and optical urinalysis.

---

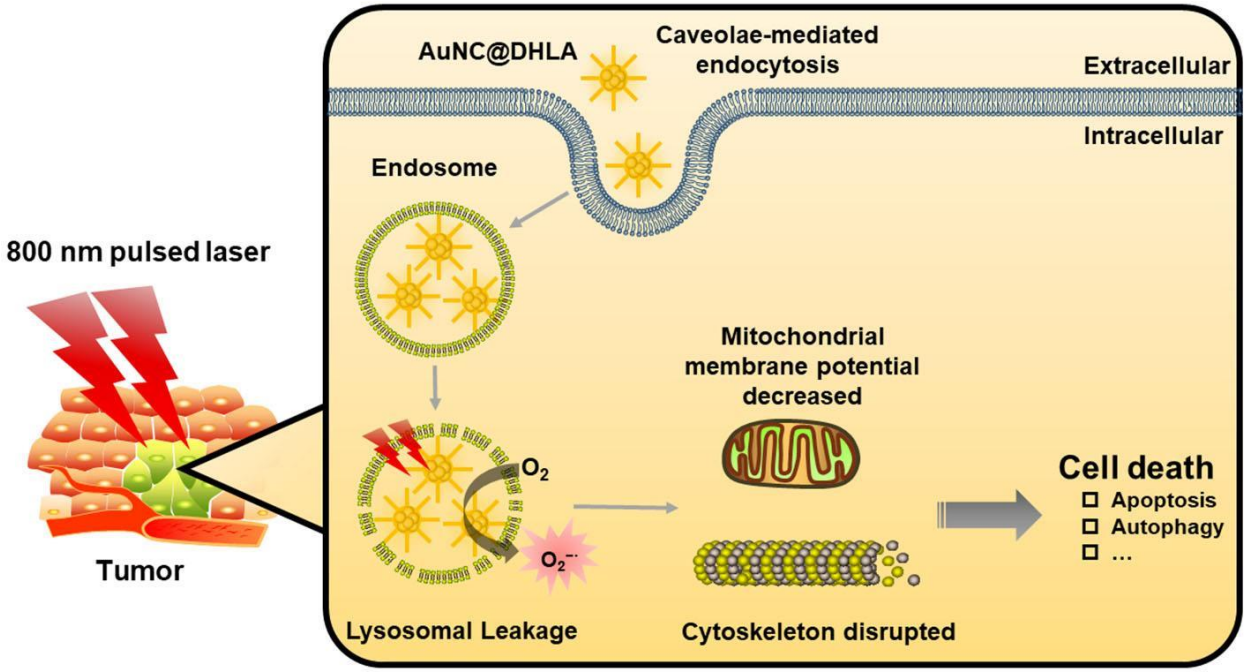
5. Excited-State Electron and Energy Transfer in Photodynamic Therapy

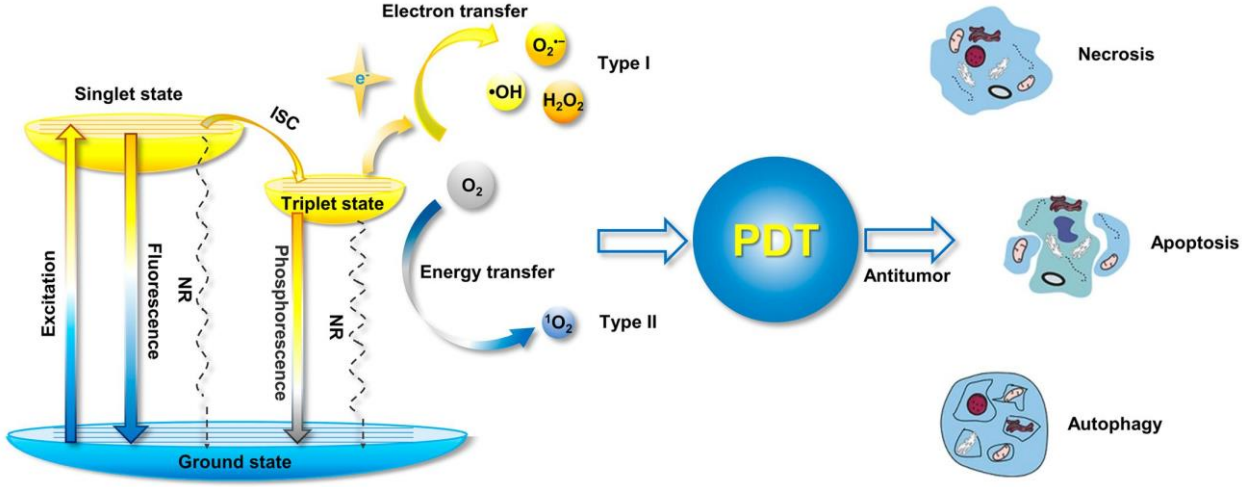
Photodynamic therapy is based on the interaction among a photosensitizer, molecular oxygen, and light. Following photoexcitation, the photosensitizer reaches an excited state and can transfer energy or electrons to surrounding molecules. In oxygen-rich environments, this process may generate reactive oxygen species capable of damaging cellular structures.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

MNCs can function as photosensitizing platforms because their discrete electronic states allow their excited-state pathways to be engineered.





APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

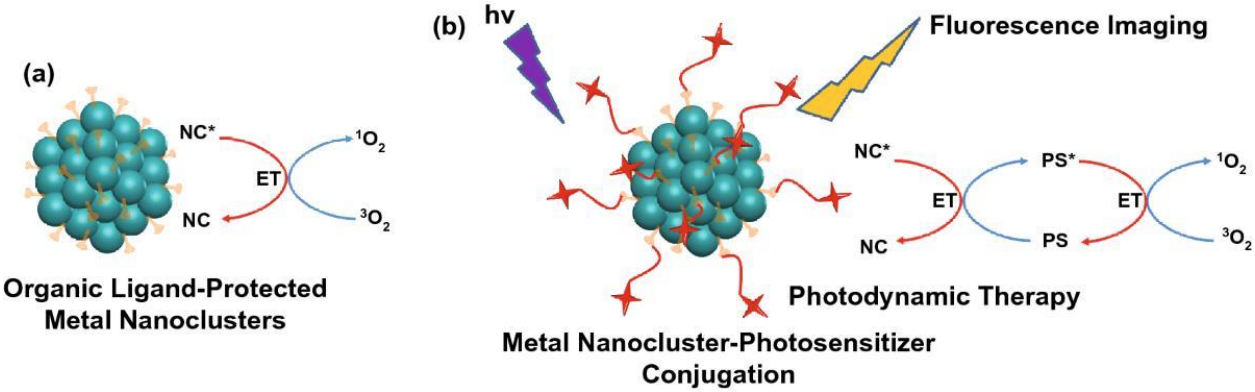


Figure 4. Photoinduced electron and energy transfer from metal nanoclusters to the biological microenvironment for reactive oxygen species generation and photodynamic therapy.

5.1 Reactive oxygen species generation

Following photoexcitation, MNCs may transfer energy to molecular oxygen and produce singlet oxygen , or participate in electron-transfer processes generating superoxide and hydroxyl radicals.

The resulting oxidative stress can induce:

- lipid peroxidation;
- protein oxidation;
- mitochondrial dysfunction;
- DNA damage;
- membrane disruption;
- apoptosis or other forms of regulated cell death.

This provides the fundamental basis for using photoresponsive MNCs in anticancer and antimicrobial applications.

5.2 Overcoming tumor hypoxia

One of the major limitations of conventional PDT is dependence on molecular oxygen. Solid tumors frequently contain hypoxic regions, which can reduce ROS generation and therapeutic efficacy.

An emerging strategy is to engineer MNCs with enzyme-like catalytic properties that alter the local tumor microenvironment. Catalase-like activity, for example, may convert hydrogen peroxide into oxygen and thereby partially alleviate hypoxia.

This approach transforms MNCs from passive photosensitizers into multifunctional catalytic nanoplatforms capable of modifying the biological environment in which photodynamic therapy occurs.

5.3 NIR and NIR-II photodynamic therapy

Visible light has limited penetration depth in biological tissue. Consequently, NIR excitation is highly desirable for deep-tissue PDT.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

The development of NIR- and NIR-II-responsive MNCs can potentially improve treatment of tumors located below the tissue surface. In addition, two-photon excitation offers another approach for increasing effective penetration depth while providing improved spatial selectivity.

The combination of NIR-II fluorescence imaging and PDT is particularly attractive because the same excitation source may facilitate both visualization and treatment.

5.4 Low-intensity and accessible photodynamic systems

An important emerging concept is the development of photodynamic systems that operate under relatively low optical intensities. Such systems could potentially simplify equipment requirements and expand the accessibility of photodynamic treatment.

However, claims concerning low-power or smartphone-based activation should be interpreted cautiously. Translation from proof-of-concept experiments to clinical treatment requires systematic assessment of tissue penetration, delivered dose, exposure uniformity, toxicity, and reproducibility.

---

6. Nonradiative Relaxation and Photothermal Therapy

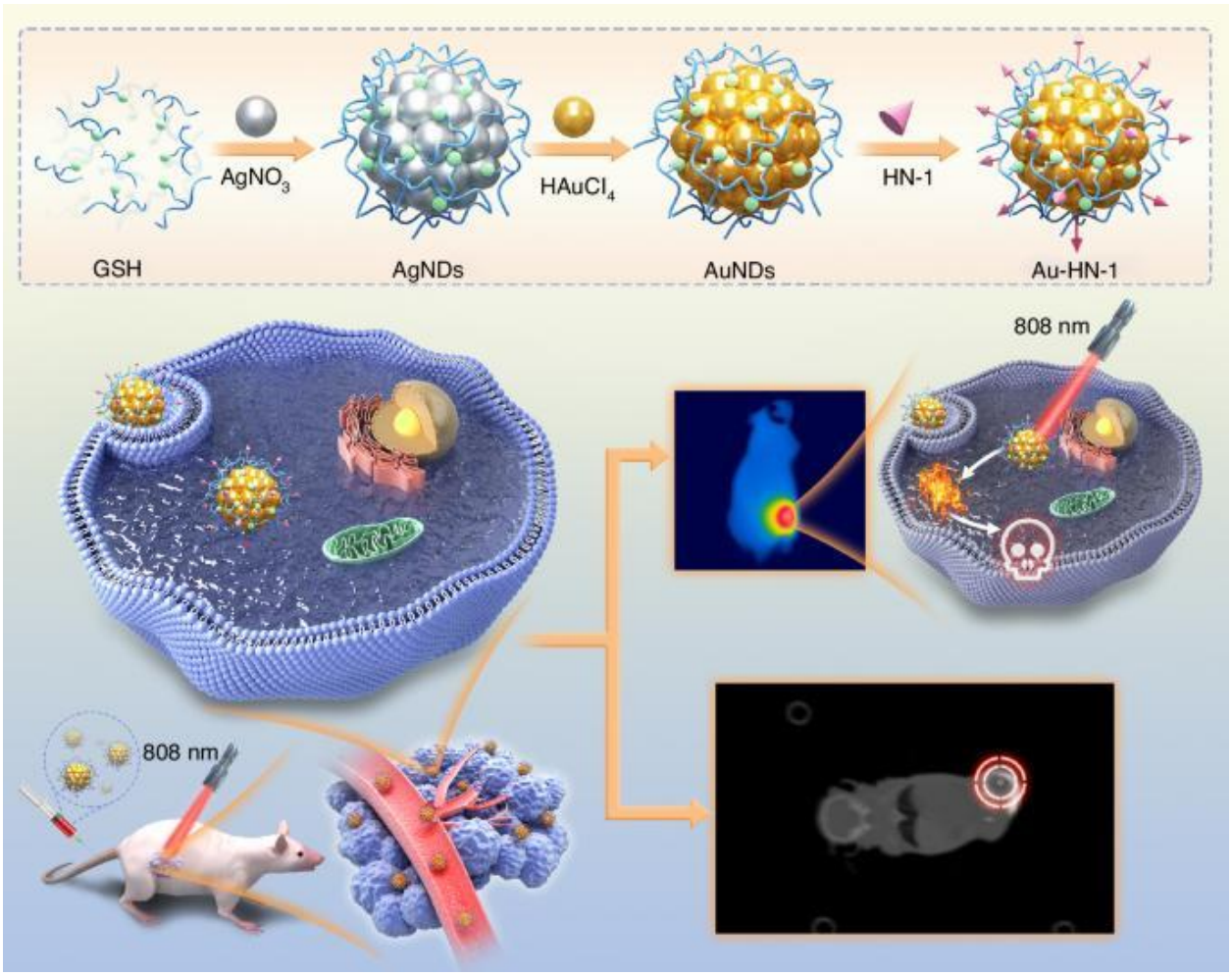
In contrast to fluorescence, nonradiative relaxation converts absorbed optical energy into thermal energy. This process can be exploited for photothermal therapy, in which localized heating damages pathological cells.

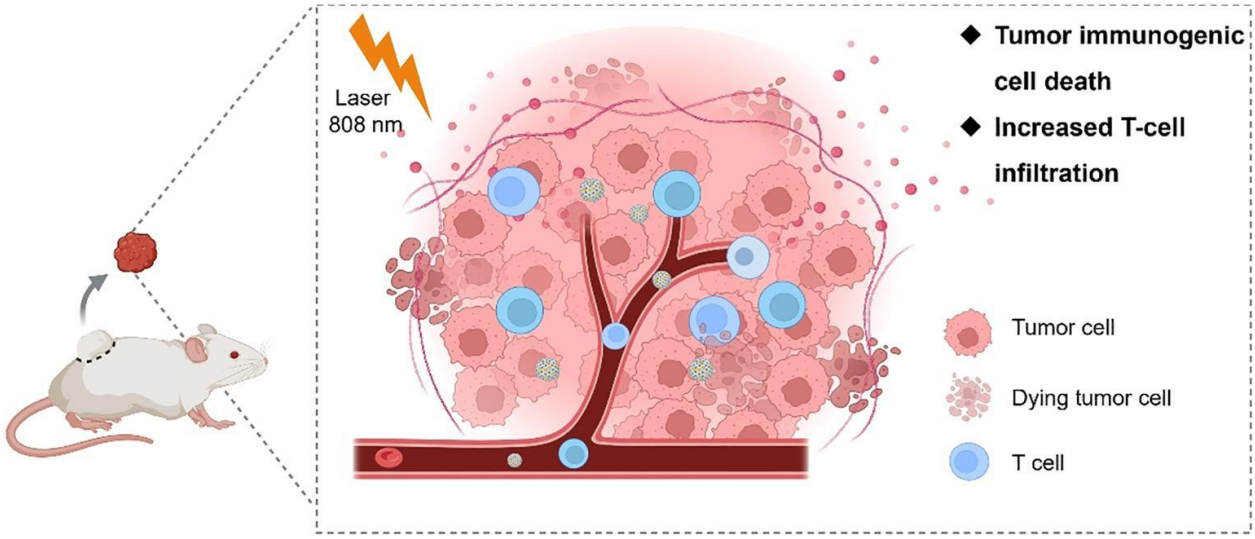
Photothermal conversion is particularly attractive for cancer treatment because it can be spatially controlled through targeted delivery and external light irradiation.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo





The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Figure 5. Nonradiative relaxation and photothermal conversion of metal nanoclusters for imaging-guided photothermal therapy.

6.1 Photothermal conversion mechanisms

The photothermal performance of a metal nanomaterial depends on its absorption characteristics and the efficiency with which absorbed energy is converted into heat.

For conventional plasmonic nanoparticles, photothermal conversion is strongly associated with collective electronic oscillations. At the nanocluster scale, however, the mechanism is governed by discrete electronic transitions, excited-state relaxation, charge-transfer processes, and interactions among neighboring clusters.

This distinction is important because isolated atomically precise clusters may have relatively limited photothermal conversion compared with larger plasmonic assemblies.

6.2 Cluster assembly and photothermal enhancement

One strategy for overcoming this limitation involves assembling MNCs into larger architectures. Controlled aggregation can modify electronic coupling and create collective optical responses.

The resulting structures may exhibit stronger NIR absorption and improved photothermal conversion while retaining some of the functional advantages of the individual clusters.

Such hierarchical design represents an important bridge between molecular nanoclusters and conventional plasmonic nanomaterials.

6.3 Combined photothermal imaging and therapy

The integration of fluorescence imaging and photothermal therapy provides a particularly attractive theranostic strategy.

A single platform can potentially:

1. accumulate preferentially in the tumor;
2. generate an optical imaging signal;
3. identify the tumor location;
4. receive external NIR irradiation;
5. convert optical energy into heat;
6. induce tumor-cell damage;
7. enable subsequent monitoring of treatment.

This approach can improve treatment localization and reduce unnecessary irradiation of healthy tissue.

6.4 Combination therapy

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935

https://international-journal-of-applied-sciences.jo

Photothermal therapy can also be combined with PDT, chemotherapy, immunotherapy, or controlled drug delivery.

Heat generated by MNCs can enhance drug release, increase membrane permeability, modify tumor perfusion, and potentially improve immune responses. Meanwhile, ROS generated during PDT can provide an independent cytotoxic mechanism.

Consequently, multifunctional MNC platforms may provide synergistic rather than merely additive therapeutic effects.

---

7. Machine Learning-Guided Engineering of Photoresponsive Metal Nanoclusters

The enormous chemical and structural design space of MNCs represents both an opportunity and a challenge. A cluster can vary in:

- metal composition;
- number of metal atoms;
- oxidation state;
- electron count;
- geometric structure;
- ligand identity;
- ligand density;
- ligand conformation;
- surface charge;
- heteroatom doping;
- aggregation state;
- biomolecular environment.

Each parameter may influence absorption, emission wavelength, quantum yield, lifetime, ROS generation, photothermal conversion, stability, cellular uptake, and toxicity.

Traditional experimental optimization cannot efficiently explore this multidimensional space.

Machine learning provides an alternative.

7.1 Structure–property prediction

ML models can be trained using experimentally measured or computationally calculated descriptors to predict optical properties.

A generalized workflow can be represented as:

Possible descriptors include:

- metal composition;

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

- atomic count;
- valence-electron number;
- cluster geometry;
- ligand descriptors;
- molecular orbital characteristics;
- surface charge;
- solvent parameters;
- calculated absorption features.

The output may include:

- absorption maximum;
- emission wavelength;
- fluorescence intensity;
- quantum yield;
- excited-state lifetime;
- photothermal conversion efficiency;
- ROS generation efficiency.

Recent work on ML applications for thiolate-protected metal nanoclusters specifically highlights the use of computational approaches for predicting and engineering optical properties and fluorescence behavior.

7.2 ML-assisted ligand engineering

Ligand selection is one of the most powerful methods for modifying MNC behavior.

Instead of experimentally testing hundreds or thousands of ligands, ML can identify molecular descriptors associated with desirable properties.

For example:

A model could therefore rank candidate ligands according to their predicted ability to:

- enhance fluorescence;
- shift emission toward NIR-II;
- increase quantum yield;
- improve aqueous stability;

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

- enhance target binding;
- reduce nonspecific cellular uptake.

This could substantially accelerate the discovery of next-generation MNC probes.

7.3 ML for fluorescence fingerprint analysis

The combination of multiple MNCs with ML can generate highly informative fluorescence fingerprints.

Instead of assigning a target based on a single intensity change, a sensor array may produce a multidimensional response:

where each represents the response of a different cluster or optical channel.

ML classification can then determine the identity of the analyte, while regression models can estimate its concentration.

This approach is particularly attractive for biological fluids containing multiple interfering compounds.

The recent application of automated ML to silver nanocluster fluorescence arrays demonstrates the feasibility of this strategy for multiplexed chemical detection.

7.4 ML-guided bioimaging

ML can also enhance image analysis after MNC-based imaging.

Deep-learning models can assist in:

- tumor segmentation;
- cell classification;
- organelle identification;
- fluorescence-background correction;
- image denoising;
- quantitative biodistribution analysis;
- treatment-response assessment.

Thus, ML does not merely help design the nanocluster; it can also analyze the biological information generated by the nanocluster.

This creates a closed-loop architecture:

Such an iterative framework could become an important foundation for intelligent nanomedicine.

7.5 ML-guided photodynamic and photothermal optimization

Therapeutic performance depends on several variables simultaneously, including:

- nanocluster concentration;

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

- excitation wavelength;
- irradiation power;
- irradiation duration;
- oxygen concentration;
- tumor microenvironment;
- cellular uptake;
- ROS production;
- temperature elevation.

ML can integrate these variables and identify combinations associated with improved therapeutic efficacy while minimizing toxicity.

The ultimate objective is not simply to maximize ROS or temperature. Instead, the optimization problem can be formulated as:

subject to:

This multi-objective optimization perspective is particularly relevant to personalized nanomedicine.

8. Integrated Intelligent Theranostic Platforms

The convergence of MNCs, optical stimulation, biomolecular engineering, and ML provides a foundation for a new generation of intelligent theranostic systems.

A future MNC platform could simultaneously perform:

Detection → Localization → Diagnosis → Treatment → Monitoring → Adaptive Optimization

Such a system would differ fundamentally from conventional nanomedicine, in which diagnosis and treatment are often implemented as independent stages.

8.1 Multimodal diagnosis

MNCs can potentially integrate:

- fluorescence imaging;
- NIR-II imaging;
- CT contrast;
- MRI-related functionality;
- photoacoustic imaging;
- molecular sensing.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Combining multiple modalities may compensate for the limitations of individual imaging techniques.

8.2 Adaptive therapy

The therapeutic component can also be made responsive to the biological environment.

For example, an MNC platform may be engineered to respond differently under:

- acidic pH;
- elevated ROS;
- high glutathione;
- hypoxia;
- specific enzymes;
- externally applied NIR irradiation.

ML can then help determine the relationship between these environmental conditions and therapeutic response.

8.3 Personalized nanomedicine

Different tumors and patients exhibit substantial biological heterogeneity. Consequently, a nanoplatform optimized for one tumor may not perform equally well in another.

An ML-enabled theranostic framework could incorporate patient-specific variables such as imaging characteristics, biomarker profiles, tumor microenvironment, and treatment response to select the most appropriate nanocluster design or irradiation protocol.

This concept remains largely preclinical, but it represents an important long-term direction for MNC-based medicine.

9. Challenges and Limitations

Despite rapid progress, several fundamental challenges must be resolved before MNC-based intelligent theranostics can achieve broad clinical translation.

9.1 Low and variable quantum yield

Many MNCs exhibit lower quantum yields than optimized organic fluorophores. Their emission can also vary substantially with solvent, pH, temperature, ligand structure, and aggregation state.

Improving quantum yield while preserving biological stability remains an important objective.

9.2 Photostability and biological stability

A material that is highly stable in buffer may behave differently in serum or intracellular environments. Protein adsorption, ligand exchange, oxidation, aggregation, and degradation can modify the optical properties of MNCs.

Therefore, future studies should evaluate stability under physiologically relevant conditions rather than relying exclusively on idealized laboratory media.

9.3 NIR-II emission

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Although NIR-II MNCs provide an attractive route toward deep-tissue imaging, strong and reproducible emission remains difficult to achieve.

The ideal probe should combine:

- strong NIR-II emission;
- high photostability;
- low toxicity;
- appropriate circulation time;
- effective targeting;
- predictable metabolism;
- efficient clearance.

Recent reviews identify NIR emission, photostability, and atomically precise structure as major advantages of MNCs, but the translation of these properties into robust biomedical probes remains an active research challenge.

9.4 Biosafety and pharmacokinetics

Ultrasmall size may facilitate renal clearance, which is advantageous for reducing long-term accumulation. However, clearance behavior depends strongly on hydrodynamic size, ligand chemistry, charge, protein corona formation, and cluster stability.

Therefore, comprehensive evaluation of:

- acute toxicity;
- chronic toxicity;
- immunogenicity;
- biodistribution;
- metabolism;
- renal clearance;
- degradation products

is essential.

9.5 Data limitations for machine learning

The effectiveness of ML depends on the quality and quantity of training data.

Current MNC datasets are fragmented across laboratories and often differ in:

- synthesis conditions;

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

- nomenclature;
- structural characterization;
- spectroscopy;
- biological models;
- irradiation parameters;
- measurement instruments.

Consequently, models trained on heterogeneous datasets may learn experimental artifacts rather than universal structure–property relationships.

Standardized reporting and interoperable databases are therefore essential.

9.6 Model interpretability

A highly accurate black-box model is not necessarily sufficient for nanomedicine.

Researchers need to understand **why** a particular ligand, atomic composition, or structural parameter improves a specific optical or biological property.

Interpretable ML and explainable artificial intelligence should therefore become integral components of future MNC research.

---

10. Future Perspectives

The future development of MNC-based biomedical systems is likely to involve the convergence of four major technological domains:

atomically precise nanochemistry + advanced photophysics + artificial intelligence + biomedical engineering.

First, the synthesis of atomically precise MNCs will increasingly be combined with computational screening. Rather than experimentally synthesizing large numbers of candidate clusters, researchers may first use ML models to identify promising compositions and ligands and then experimentally validate a smaller set.

Second, multimodal optical responses are likely to become increasingly important. Multi-emissive MNCs can generate more than one emission band, allowing ratiometric measurements that reduce environmental and instrumental interference. A 2026 review highlights multi-emissive MNCs as an emerging platform for biosensing, bioimaging, and therapeutic applications.

Third, artificial intelligence may increasingly be used to connect nanocluster structure with biological outcome. This could enable prediction not only of fluorescence but also of cellular uptake, biodistribution, toxicity, therapeutic efficacy, and treatment response.

Fourth, the development of autonomous or semi-autonomous nanomaterial discovery platforms may accelerate. Such platforms could follow an iterative process:

This closed-loop approach may dramatically reduce the time required to identify optimized MNC candidates.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Finally, the integration of AI-guided design with bioactive clusters is increasingly recognized as a future direction for rational construction and biomedical translation. Recent literature explicitly identifies AI-empowered rational design and activity programming as emerging opportunities for bioactive cluster systems.

11. Conclusion

Metal nanoclusters represent a distinctive and rapidly developing class of nanomaterials for biomedical diagnosis and therapy. Their ultrasmall dimensions, atomically precise structures, discrete electronic states, tunable surface chemistry, and diverse photoresponsive behaviors provide a powerful foundation for biosensing, bioimaging, photodynamic therapy, photothermal therapy, and integrated theranostics.

The central feature underlying these applications is the controllable behavior of photoexcited electrons. Radiative relaxation can generate fluorescence for sensing and imaging; energy and electron transfer can generate reactive oxygen species for photodynamic therapy; and nonradiative relaxation can convert optical energy into heat for photothermal therapy. Through ligand engineering, metal alloying, heteroatom doping, aggregation-induced emission, supramolecular assembly, and biomolecular templating, these pathways can be systematically modified.

The introduction of machine learning adds a new dimension to this field. Instead of relying primarily on empirical optimization, ML can analyze complex relationships among atomic composition, cluster structure, ligand chemistry, optical response, biological environment, and therapeutic outcome. ML-assisted fluorescence fingerprint analysis can improve multiplexed biosensing, while predictive models can accelerate the discovery of clusters with desired emission properties, NIR-II activity, photodynamic efficiency, and photothermal performance.

However, significant challenges remain, particularly concerning quantum yield, photostability, biological stability, NIR-II emission, toxicity, pharmacokinetics, data standardization, and ML interpretability. Addressing these limitations will require close collaboration among nanochemists, photophysicists, biologists, clinicians, data scientists, and computational researchers.

Overall, the combination of **atomically precise metal nanoclusters, photoresponsive nanomedicine, and machine learning** has the potential to transform the development of biomedical nanoplatforms from empirical material discovery toward predictive and data-driven engineering. Future MNC systems may therefore evolve from passive imaging probes and therapeutic agents into **intelligent, adaptive, multifunctional theranostic platforms** capable of detecting disease, guiding treatment, responding to biological conditions, and continuously optimizing therapeutic performance.

APPLIED SCIENCE

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Ethical Considerations

Not applicable. This study did not require ethical approval because it does not include human or animal subjects and does not involve any personal or sensitive data.

List of Abbrevations:

(MNCs): Metal nanoclusters; (ML): machine learning; (PDT): photodynamic therapy , (PTT): photothermal therapy; (Cu): copper , (Ag): silver, (Au): Gold, (AIE): Aggregation-induced emission.

Acknowledgment:

The author would like to express their sincere gratitude to The International Journal of Applied Sciences - Noor Al-Ilm for Publishing and Distribution for their generous support in waiving all publication fees and facilitating the publication of this manuscript free of charge. Their commitment to promoting scientific research and supporting researchers is highly appreciated.

Author Contribution:

All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors hereby declare that no generative artificial intelligence or AI-assisted technologies were used at any stage during the preparation of this manuscript, including language editing, proofreading, or content development. The authors take full responsibility for the originality and integrity of the work presented in this publication.

Funding:

This research received no external financial funding. The authors also acknowledge The International Journal of Applied Sciences, Noor Al-Ilm for Publishing and Distribution, for providing a full waiver of the publication fees. The publication fee waiver was provided as editorial support and did not involve any financial contribution to the conduct, design, analysis, or reporting of the research.

The International Journal of Applied Sciences.
Vol. 2, No. 1, 2026, pp. 139-171
ISSN 3104-8935
https://international-journal-of-applied-sciences.jo

Conflicts of Interest:

"The authors declare no conflict of interest."

References

1. Jin R. Atomically precise metal nanoclusters: stable sizes and optical properties. **Nanoscale**. 2015;7:1549–1565.
2. Zhang B, et al. Ultrasmall coinage metal nanoclusters as promising theranostic probes for biomedical applications. **J Am Chem Soc**. 2023. doi:10.1021/jacs.3c02880.
3. Su Y, Xue T, Liu Y, et al. Luminescent metal nanoclusters for biomedical applications. **Nano Research**. 2019;12:1251–1265. doi:10.1007/s12274-019-2314-y.
4. Zheng J, Nicovich PR, Dickson RM. Highly fluorescent noble-metal quantum dots. **Annu Rev Phys Chem**. 2007;58:409–431.
5. Romeo MV, López-Martínez E, Berganza-Granda J, Goñi-de-Cerio F, Cortajarena AL. Biomarker sensing platforms based on fluorescent metal nanoclusters. **Nanoscale Advances**. 2021;3:1331–1345. doi:10.1039/D0NA00796J.
6. Shang L, Dong S, Nienhaus GU. Ultra-small fluorescent metal nanoclusters: synthesis and biological applications. **Nano Today**. 2011;6:401–418. doi:10.1016/j.nantod.2011.06.004.
7. Zare I, Chevrier DM, Cifuentes-Rius A, et al. Protein-protected metal nanoclusters as diagnostic and therapeutic platforms for biomedical applications. **Materials Today**. 2023;66:159–193. doi:10.1016/j.mattod.2020.10.027.
8. Liu Y, et al. Synergistic integration of metal nanoclusters and biomolecules as hybrid systems for therapeutic applications. **Acta Pharmaceutica Sinica B**. 2021;11:1175–1199. doi:10.1016/j.apsb.2020.12.004.
9. Chen J-W, Lin S-Y, Yang Z-Q, Huang K-Y, Deng H-H, Chen W. Multi-emissive metal nanoclusters: luminescence origin, tailoring strategies, and biomedical applications. **Nanoscale**. 2026. doi:10.1039/D6NR01696K.
10. Xu J, Li L, Shang Y, et al. Automated machine learning assisted fluorescent sensor array based on silver nanoclusters for detection of multiple heavy metal ions. **Microchimica Acta**. 2026;193:509. doi:10.1007/s00604-026-08234-w.
11. Mo. Advances in machine learning applications for thiolate-protected metal nanoclusters with potential metallic core exploration. **Journal of Intelligent Medicine**. 2025.
12. Muhammad, Li X, Sun Z, et al. Luminescent metal nanoclusters: intrinsic features, photophysical mechanisms and emerging applications. **Coordination Chemistry Reviews**. 2026. doi:10.1016/j.ccr.2026.218180.
13. Wu Z, Jin R. Optical properties and applications of atomically precise metal nanoclusters. **Nano Today**.
14. Xie J, Zheng Y, Ying JY. Protein-directed synthesis of highly fluorescent gold nanoclusters. **J Am Chem Soc**. 2009;131:888–889.

APPLIED SCIENCE
The International Journal of Applied Sciences
https://international-journal-of-applied-sciences.jo
ISSN 3104-8935
Vol. 2, No. 1, 2025, pp. 1-8

15. Díez I, Ras RH. Fluorescent silver nanoclusters. **Nanoscale**. 2011;3:1963–1970.

16. Mathew A, Pradeep T. Noble metal clusters: applications in medicine. **Curr Opin Biomed Eng**.

17. Aikens CM. Origin of the optical properties of gold and silver nanoclusters. **J Phys Chem C**.

18. Kang X, Chong H, Zhu M. Au25(SR)18: the captain of the great nanocluster ship. **Nanoscale**.

19. Du Y, Sheng H, Astruc D, Zhu M. Atomically precise noble metal nanoclusters as efficient catalysts: a bridge between homogeneous and heterogeneous catalysis. **Chem Rev**.

20. Chakraborty I, Pradeep T. Atomically precise clusters of noble metals: emerging link between atoms and nanoparticles. **Chem Rev**.

21. Wang Y, et al. Metal nanoclusters for biosensing and biomedical imaging: advances in ligand engineering and optical regulation.

22. Luo Z, Zheng K, Xie J. Engineering ultrasmall water-soluble gold and silver nanoclusters for biomedical applications. **Chem Commun**.

23. Chen Y, et al. Gold nanoclusters: recent advances in synthesis, characterization, and biomedical applications.

24. Yeh YC, Creran B, Rotello VM. Gold nanoparticles: preparation, properties, and applications in bionanotechnology. **Nanoscale**. 2012;4:1871–1880.

25. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. **Chem Soc Rev**. 2012;41:2740–2779.

26. Riley RS, Day ES. Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. **Wiley Interdiscip Rev Nanomed Nanobiotechnol**. 2017;9:e1449.

27. Dolmans DEJGJ, Fukumura D, Jain RK. Photodynamic therapy for cancer. **Nat Rev Cancer**. 2003;3:380–387.

28. Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. **Chem Soc Rev**. 2015;44:2484–2517.

29. Master A, Livingston M, Sen Gupta A. Photodynamic nanomedicine in cancer treatment: state of the art. **Nano Today**. 2013;8:233–242.

30. Lovell JF, Liu TWB, Chen J, Zheng G. Activatable photosensitizers for imaging and therapy. **Chem Rev**. 2010;110:2839–2857.

31. Weissleder R. A clearer vision for in vivo imaging. **Nat Biotechnol**. 2001;19:316–317.

32. Smith AM, Mancini MC, Nie S. Second window for in vivo imaging. **Nat Nanotechnol**. 2009;4:710–711.

33. Hong G, Antaris AL, Dai H. Near-infrared fluorophores for biomedical imaging. **Nat Biomed Eng**. 2017;1:0010.

34. Dai H, Shen S, Zhang Y, et al. Near-infrared-II fluorescent nanomaterials for cancer imaging and therapy. **Adv Mater**.

35. Jiang Y, Pu K. Multimodal biophotonics imaging using semiconducting polymer nanoparticles. **Adv Biosyst**.

36. He X, Gao J, Gambhir SS, Cheng Z. Near-infrared fluorescent nanoprobes for cancer imaging: a review. **Curr Opin Chem Biol**.

37. Li C, et al. Atomically precise metal nanoclusters for bioimaging and therapy: progress and perspectives. **ACS Nano**. 2025.

38. Liu Y, et al. Design and biomedical applications of bioactive clusters: emerging opportunities for AI-guided rational design. **Chemistry – A European Journal**. 2026.

39. Zheng J, Zhang C, Dickson RM. Highly fluorescent, water-soluble, size-tunable gold quantum dots. **Phys Rev Lett**. 2004;93:077402.

40. Yu Y, New S-Y, Xie J, Su X, Tan YN. Gold nanoclusters: syntheses, structures, and applications. **Small**.

41. Yuan X, Luo Z, Zhang Q, et al. Synthesis of highly fluorescent metal nanoclusters by biomolecules and their biomedical applications.

42. Chen L, et al. Aggregation-induced emission of metal nanoclusters and applications in chemical and biological sensing.

43. Wang G, et al. Assembly-induced emission of metal nanoclusters for sensitive biosensing.

44. Kawasaki H, Kumar S, Li G, et al. Photodynamic properties of ligand-protected gold nanoclusters.

45. Han G, et al. Two-photon-activated photodynamic therapy using gold nanoclusters for deep-tissue cancer treatment.

46. Yang Y, et al. NIR-II fluorescence imaging-guided photodynamic therapy and photothermal therapy based on ultrasmall gold nanoclusters.

47. Park J, et al. Albumin-based gold nanocluster assemblies for fluorescence imaging and photothermal cancer therapy.

48. Chen J, et al. Photothermal conversion and therapeutic applications of metal nanocluster-based nanostructures.

49. Wang Y, et al. NIR-II-responsive nanocluster systems for multimodal imaging and synergistic cancer therapy.

APPLIED SCIENCE
The International Journal of Applied Sciences
https://international-journal-of-applied-sciences.jo
ISSN 3104-8935
Vol. 2, No. 1, 2025, pp. 1-8

50. Zare I, et al. Metal nanocluster-based nanomedicine: diagnostic, therapeutic and translational challenges.