Cosmos Multidisciplinary Research E-Journal
Online Available at www.cmrj.in
Recognized International Peer Reviewed Journal
Impact Factor 5.69
ISSN No. 2456-1665

Fundamental Physical and Biophysical Constraints on the Clinical Translation of Persistent Luminescence Nanoparticles: A Theoretical Perspective

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Abstract
Persistent luminescence nanoparticles (PLNPs) have emerged as promising optical nanoprobes for biomedical imaging and therapeutic applications because of their ability to emit long-lasting afterglow after the removal of the excitation source. Despite significant advances in material development and encouraging preclinical studies, their clinical translation remains limited. This review presents a theoretical analysis of the major physical and biophysical constraints that hinder clinical implementation, including the difficulty of achieving nanoscale particle size together with strong persistent luminescence, surface-related quenching effects, unresolved concerns regarding biodistribution, biodegradability, toxicity, and immune responses, as well as challenges associated with large-scale manufacturing and regulatory approval. Potential strategies such as surface passivation, defect engineering, biocompatible host materials, and near-infrared rechargeable systems are discussed as possible approaches to overcome these limitations. The analysis provides a conceptual framework for understanding the key barriers to clinical translation and offers guidance for the rational design of next-generation persistent luminescence nanomaterials.

Keywords: *Persistent luminescence, nanoparticles, electron traps, bioimaging, clinical translation, surface quenching, biosafety, theranostics.*

1. Introduction

Advances in biomedical imaging have transformed disease diagnosis, therapeutic monitoring, and precision medicine by enabling the visualization of biological processes with high spatial and temporal resolution. Among the available imaging modalities, optical imaging has gained widespread attention because of its high sensitivity, real-time imaging capability, relatively low cost, and non-invasive nature. Conventional fluorescence imaging, based on organic dyes, quantum dots, and fluorescent nanoparticles, has been extensively employed in tumor diagnosis, image-guided surgery, drug delivery, and biosensing. However, these fluorescent probes require continuous external excitation, which often leads to tissue autofluorescence, photobleaching, and a reduced signal-to-background ratio, thereby limiting imaging sensitivity, particularly for long-term in vivo applications.

Persistent luminescence nanoparticles (PLNPs) have emerged as an attractive alternative because they continue to emit light long after the excitation source has been removed. This unique afterglow phenomenon originates from defect-related trap states within the crystal lattice that store excitation energy and gradually release it through radiative recombination at luminescent centers. The temporal separation between excitation and emission effectively suppresses tissue autofluorescence and significantly enhances imaging contrast. Furthermore, depending on the host lattice, activator ions, and trap characteristics, PLNPs can be re-excited using ultraviolet, visible, near-infrared (NIR), or X-ray irradiation, making them versatile platforms for biomedical imaging and therapy.

Over the past decade, substantial progress has been achieved in the development of PLNPs through defect engineering, host lattice optimization, surface functionalization, and the design

of NIR-rechargeable systems. These advances have significantly improved persistent luminescence intensity, afterglow duration, and multifunctionality, leading to successful demonstrations in bioimaging, biosensing, drug delivery, photodynamic therapy, and image-guided diagnosis. Numerous preclinical studies have confirmed the excellent optical performance of PLNPs in small-animal models, highlighting their considerable potential as next-generation optical nanoprobes. Nevertheless, despite these achievements, no PLNP-based system has yet reached routine clinical application.

The absence of clinically approved PLNPs suggests that superior optical performance alone is insufficient for successful clinical translation. Unlike conventional luminescent materials, biomedical nanoplatforms must simultaneously satisfy multiple and often conflicting requirements, including high luminescence efficiency, nanoscale dimensions, colloidal stability, biocompatibility, biodegradability, reproducible large-scale synthesis, and regulatory compliance. These requirements are strongly interdependent. For example, high-temperature calcination improves crystallinity and defect formation, thereby enhancing persistent luminescence, whereas biomedical applications require small, well-dispersed nanoparticles with stable surface chemistry. Similarly, reducing particle size increases the surface-to-volume ratio, introducing surface defects that promote non-radiative recombination and diminish afterglow efficiency. In addition, long-term biodistribution, immune interactions, biodegradability, potential toxicity, manufacturing reproducibility, and the absence of standardized regulatory pathways continue to represent major obstacles to clinical implementation.

Although numerous reviews have comprehensively summarized the synthesis, luminescence mechanisms, and biomedical applications of PLNPs, comparatively little attention has been devoted to understanding the fundamental reasons underlying their limited clinical translation. Most existing studies emphasize improvements in material performance or application-specific demonstrations, whereas the interconnected physical, biological, and translational constraints governing clinical feasibility remain dispersed throughout the literature and have rarely been examined within a unified conceptual framework.

In this review, we present a theoretical framework to analyze the principal barriers preventing the clinical translation of persistent luminescence nanoparticles. Rather than considering individual challenges independently, we examine how materials physics, nanoscale optical behavior, biological interactions, manufacturing requirements, and regulatory considerations collectively determine the clinical feasibility of PLNPs. Four interconnected constraints are discussed: (i) the challenge of simultaneously achieving nanoscale dimensions, high crystallinity, and efficient persistent luminescence; (ii) luminescence degradation arising from surface-related quenching; (iii) biological limitations associated with biodistribution, biodegradability, toxicity, and immune responses; and (iv) manufacturing and regulatory challenges that hinder clinical implementation. By integrating these multidisciplinary factors into a single theoretical framework, this review provides a conceptual roadmap for the rational design and future clinical translation of persistent luminescence nanomaterials.

2. Fundamentals of Persistent Luminescence

Persistent luminescence is a unique optical phenomenon in which a material continues to emit light for a prolonged period after the excitation source has been removed. Unlike conventional fluorescence, where emission ceases immediately after excitation, persistent luminescence originates from the storage of excitation energy in defect-related trap centers within the crystal lattice. The stored energy is gradually released through thermal activation, producing delayed emission known as afterglow. This property enables temporal separation between excitation and emission, which significantly reduces background autofluorescence and improves imaging sensitivity in biological systems.

The persistent luminescence behavior of PLNPs is governed by the combined effects of the host lattice, activator ions, defect centers, and trap distribution. The host lattice provides structural stability, whereas activator ions act as luminescent centers responsible for photon emission. Intrinsic and extrinsic defects create trapping centers that capture charge carriers during excitation and release them gradually after the excitation source is removed. Therefore, persistent luminescence is not determined by a single component but results from the interaction among crystal chemistry, defect structure, and charge transport.

2.1 Persistent Luminescence Mechanism

The mechanism of persistent luminescence is generally explained by the trap-controlled luminescence model. Under external excitation, electrons are promoted to higher energy states or to the conduction band, leaving corresponding holes in the valence band. While some charge carriers recombine immediately to produce prompt luminescence, others are captured by defect-related trapping centers located within the forbidden energy gap. After excitation ceases, thermal energy gradually releases these trapped carriers, allowing them to migrate through the crystal lattice and recombine at luminescent activator ions. This delayed radiative recombination produces the characteristic afterglow of persistent luminescence.

The efficiency of this process depends strongly on trap depth and trap concentration. Shallow traps release charge carriers rapidly, resulting in high initial intensity but short afterglow duration. Conversely, excessively deep traps retain charge carriers for prolonged periods, limiting thermal release under physiological conditions. Therefore, an optimum trap distribution is essential for obtaining both high luminescence intensity and long-lasting afterglow. Crystal defects generated during synthesis, together with suitable activator and co-dopant ions, play an important role in controlling these trapping characteristics. A schematic representation of the persistent luminescence mechanism is shown in Figure 2.

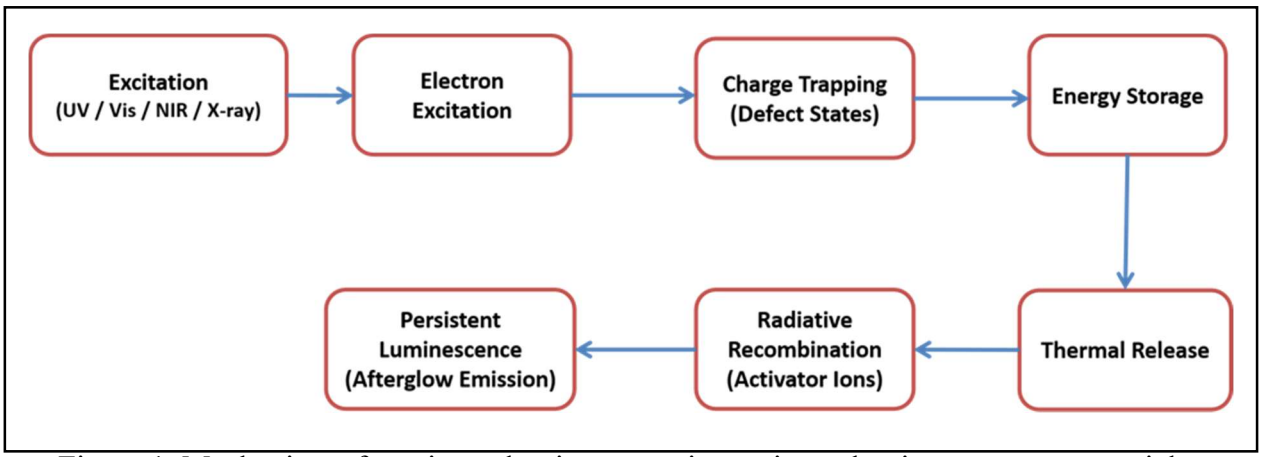

Figure 1. Mechanism of persistent luminescence in persistent luminescence nanoparticles (PLNPs).

2.2 Biomedical Advantages of PLNPs

The unique optical properties of PLNPs provide several advantages over conventional fluorescent probes. Since afterglow emission is detected after the excitation source has been switched off, interference from tissue autofluorescence and scattered excitation light is significantly reduced, leading to a higher signal-to-background ratio. In addition, PLNPs exhibit excellent photostability and maintain their optical performance during prolonged observation, making them suitable for long-term biological imaging.

Another important advantage is their structural versatility. The emission wavelength, excitation pathway, and afterglow duration can be tailored by selecting appropriate host materials, activator ions, co-dopants, and surface modification strategies. Surface functionalization with

polymers, antibodies, peptides, or therapeutic molecules further enables targeted imaging, biosensing, drug delivery, and image-guided therapy. Recent developments in near-infrared-excitable PLNPs have also improved tissue penetration and expanded their potential for deep-tissue imaging. Despite these advantages, the translation of PLNPs from laboratory research to clinical practice remains limited. The same material properties responsible for persistent luminescence also introduce several physical and biological challenges when particle dimensions are reduced to the nanoscale. These limitations are discussed in the following sections from the perspective of physical, biophysical, and translational constraints.

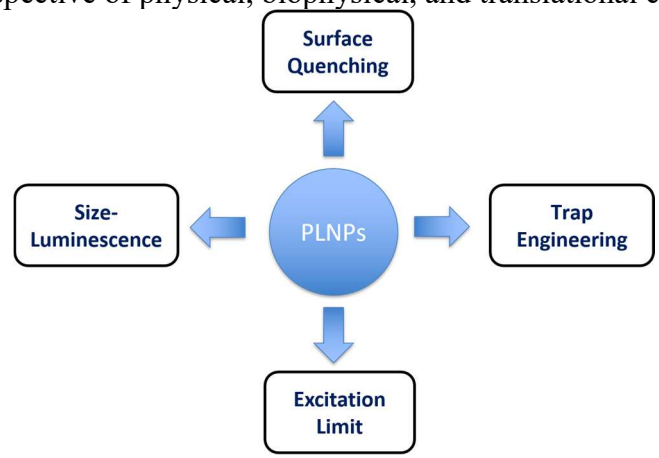

Figure 2. Biomedical advantages of persistent luminescence nanoparticles for bioimaging and theranostic applications.

3. Fundamental Physical Constraints

Persistent luminescence nanoparticles have demonstrated excellent optical performance in laboratory studies; however, several fundamental physical limitations restrict their clinical application. These limitations originate from the intrinsic relationship between crystal structure, particle size, defect chemistry, and charge transport. Unlike bulk phosphors, nanoparticles require simultaneous optimization of luminescence efficiency, particle size, colloidal stability, and surface properties for biomedical applications. Improving one parameter often affects another, making material design considerably more challenging. Therefore, understanding these physical constraints is essential for developing clinically translatable PLNPs.

3.1 Size–Luminescence Trade-off

Particle size is one of the most important factors controlling the luminescence performance of PLNPs. Biomedical applications generally require nanoparticles smaller than 100 nm because they exhibit improved dispersion, longer blood circulation, efficient cellular uptake, and better tissue penetration. In contrast, persistent luminescence is usually strongest in highly crystalline bulk phosphors prepared at elevated temperatures. This creates a fundamental conflict between optical performance and biological requirements.

Reducing particle size significantly increases the surface-to-volume ratio, exposing a larger fraction of atoms to the particle surface. Consequently, surface defects, dangling bonds, and structural disorder become more prominent. These defects introduce non-radiative recombination pathways that compete with radiative emission, resulting in a decrease in afterglow intensity and emission lifetime. At the same time, the reduction in crystal size may alter the distribution of trapping centers responsible for charge storage, further reducing persistent luminescence efficiency.

The synthesis conditions required to obtain strong afterglow present another challenge. High-temperature calcination promotes crystal growth, improves crystallinity, and generates efficient trapping centers, but it also produces larger particles and severe agglomeration. Conversely, low-temperature synthesis methods produce smaller nanoparticles with improved biological

compatibility but often exhibit lower crystallinity and weaker persistent luminescence. Therefore, obtaining sub-100 nm PLNPs with high afterglow intensity remains one of the most difficult challenges in persistent luminescence research.

Several approaches, including optimized synthesis conditions, surface passivation, and core–shell nanostructures, have been developed to improve luminescence without significantly increasing particle size. Although these strategies have produced encouraging results, a complete solution to the size–luminescence trade-off has not yet been achieved. The relationship between particle size, crystallinity, surface defects, and luminescence performance is illustrated in **Figure 3**.

3.2 Defect and Trap Engineering

Persistent luminescence is fundamentally controlled by the trapping and release of charge carriers. Consequently, the formation of suitable trapping centers is one of the most important requirements for obtaining efficient afterglow emission. These trapping centers originate from intrinsic crystal defects or from defects introduced through activator and co-dopant ions during material synthesis. Trap depth and trap concentration directly influence persistent luminescence performance. Shallow traps release charge carriers rapidly, producing strong initial emission but a short afterglow. In contrast, excessively deep traps retain charge carriers for long periods and reduce thermal release at physiological temperatures. Therefore, an optimum trap distribution is required to achieve both high brightness and prolonged emission.

The formation of trapping centers depends strongly on crystal structure, synthesis conditions, and dopant composition. Small variations in calcination temperature, reaction atmosphere, precursor purity, or dopant concentration may significantly alter the defect structure and trap distribution. Consequently, PLNPs with similar chemical compositions often exhibit different persistent luminescence properties because of differences in defect chemistry.

Recent advances in defect engineering have demonstrated that appropriate co-doping strategies can improve charge storage and afterglow performance by modifying the trap distribution. Nevertheless, the relationship between defect structure and persistent luminescence remains highly material dependent, and universal design principles have not yet been established. This lack of predictive control remains an important physical limitation for the rational design of PLNPs.

3.3 Excitation Limitations

The excitation characteristics of PLNPs also influence their suitability for biomedical applications. Most conventional persistent phosphors require ultraviolet excitation to generate sufficient charge carriers for persistent luminescence. Although UV irradiation efficiently excites many host materials, its limited tissue penetration and potential phototoxicity restrict its application for deep-tissue imaging.

To overcome these limitations, considerable efforts have been devoted to developing visible-light-, near-infrared-, and X-ray-excitable PLNPs. Among these approaches, near-infrared excitation is considered particularly attractive because of its deeper tissue penetration and reduced biological damage. However, efficient near-infrared excitation generally requires complex energy-transfer pathways involving sensitizer ions and carefully controlled defect structures. Similarly, X-ray excitation provides excellent penetration depth but introduces concerns regarding radiation exposure and excitation efficiency.

In addition to excitation wavelength, efficient energy transfer between the host lattice, trapping centers, and activator ions is necessary for obtaining strong persistent luminescence. Energy losses caused by defect-related quenching, impurity phases, or concentration quenching reduce the number of charge carriers available for radiative recombination, thereby decreasing afterglow intensity. Consequently, the development of PLNPs suitable for clinical imaging requires simultaneous optimization of excitation efficiency, energy transfer, and trap engineering. Overall, the physical performance of PLNPs is governed by a complex

relationship among particle size, crystal quality, defect chemistry, trap distribution, and excitation characteristics. Although substantial progress has been achieved in materials engineering, these physical limitations continue to restrict the development of persistent luminescence nanoparticles suitable for clinical applications. These challenges, together with the major strategies proposed to overcome them, are summarized in **Figure 3** and **Table 1**.

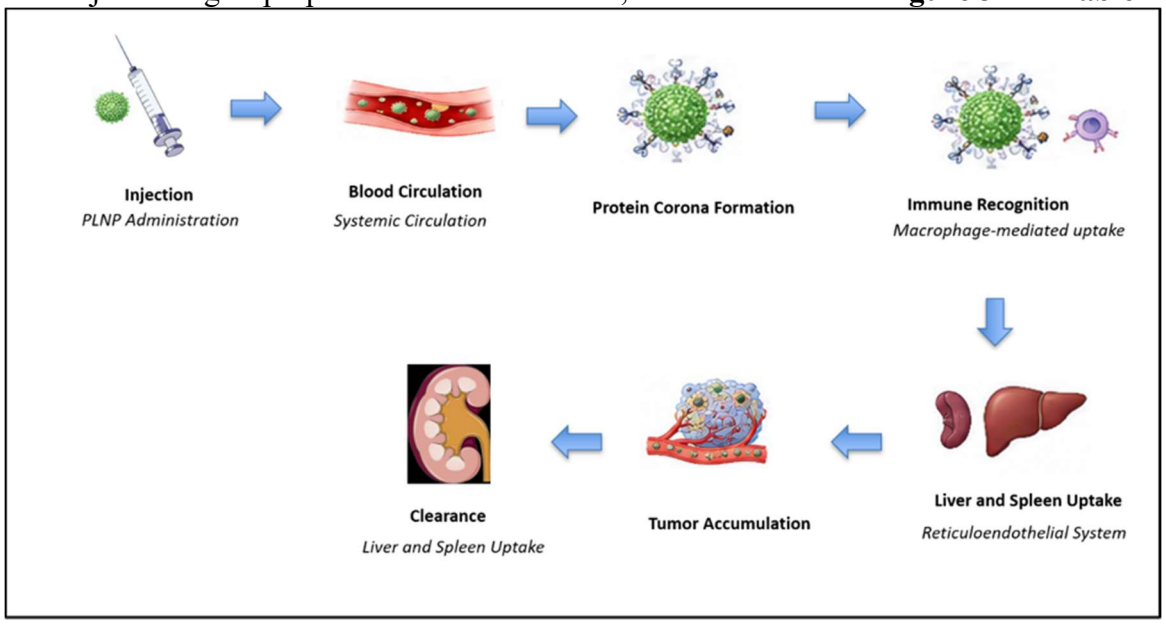

Figure 3. Fundamental physical and biophysical constraints limiting the clinical translation of persistent luminescence nanoparticles.

Table 1. Representative persistent luminescence nanoparticles reported for biomedical applications, their advantages, and current limitations.

Host Material	**Activator / Co-dopant**	**Excitation Source**	**Biomedical Application**	**Major Advantages**	**Current Limitations**	**Representative References**
$ZnGa_2O_4$	Cr^{3+}	UV, Visible, X-ray	Bioimaging	Strong NIR afterglow, high stability	Surface quenching, difficult nanoscale synthesis	Le Masne de Chermont et al.; Huang et al.; Wu et al.
$ZnGa_2O_4$	Cr^{3+}, Nd^{3+}	NIR	Deep-tissue imaging	Renewable NIR afterglow	Low excitation efficiency	Li et al.; Lin et al.
$LiGa_5O_8$	Cr^{3+}	X-ray	Tumor imaging	Deep penetration	Limited biocompatibility data	Shi et al.; Chen et al.
$ZnGa_2O_4$	Cr^{3+}, Pr^{3+}	NIR	Targeted bioimaging	Long afterglow	Complex synthesis	Abdukayum et al.
$ZnGa_2O_4$-based Core–Shell	Cr^{3+}	UV/NIR	Theranostics	Reduced surface quenching	Multi-step preparation	Huang et al.; Wang et al.
Metal–Organic Framework (MOF)-based PLNPs	Various	UV/NIR	Drug delivery & imaging	High drug loading	Limited long-term stability	Zhao et al.; Chen et al.

4. Fundamental Biophysical Constraints

Although significant progress has been achieved in improving the optical properties of persistent luminescence nanoparticles, their successful clinical application depends largely on their behavior in biological systems. Once administered into the body, PLNPs interact with blood components, biological fluids, cells, and tissues, resulting in changes to their physicochemical properties and biological performance. These interactions influence circulation time, biodistribution, cellular uptake, toxicity, and eventual clearance from the body. Therefore, the biological response to PLNPs must be considered together with their optical performance when evaluating their clinical potential.

4.1 Biological Fate of PLNPs

The biological fate of PLNPs begins immediately after administration. Upon contact with blood plasma, proteins rapidly adsorb onto the nanoparticle surface, forming a protein corona. This newly formed biological layer changes the original surface characteristics of the nanoparticles and influences their interactions with cells and tissues. As a result, the biological behavior of PLNPs is determined not only by their original physicochemical properties but also by the composition of the protein corona.

Following protein adsorption, PLNPs circulate through the vascular system and distribute to different organs depending on their particle size, surface charge, and surface chemistry. Nanoparticles with appropriate surface modification generally exhibit longer circulation times and improved accumulation at the target site. However, many PLNPs are rapidly recognized by macrophages of the mononuclear phagocyte system, resulting in preferential accumulation in the liver and spleen. This rapid clearance reduces the amount of nanoparticles reaching the diseased tissue and consequently decreases imaging sensitivity and therapeutic efficiency.

Particle size also plays an important role in determining biodistribution. Very small nanoparticles may be eliminated rapidly through renal filtration before sufficient target accumulation occurs, whereas larger particles are more likely to be retained by the liver and spleen. Therefore, selecting an appropriate particle size requires balancing prolonged circulation with efficient biological clearance.

Surface engineering has been widely employed to improve the biological behavior of PLNPs. Surface modification using polyethylene glycol, silica, phospholipids, and other biocompatible coatings reduces protein adsorption, improves colloidal stability, and prolongs blood circulation. Targeting ligands can further enhance selective accumulation in diseased tissues. Although these strategies improve biological performance, they cannot completely eliminate protein adsorption or immune recognition under physiological conditions.

The overall biological fate of PLNPs, from systemic administration to tissue accumulation and clearance, is summarized in **Figure 4**.

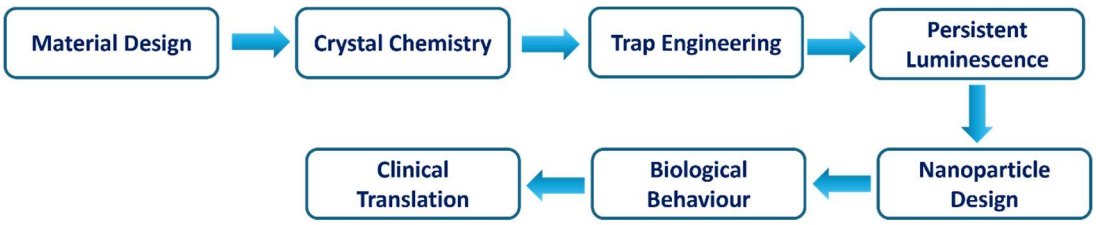

Figure 4. A theoretical framework for the clinical translation of persistent luminescence nanoparticles (PLNPs).

4.2 Biosafety and Long-Term Toxicity

Biosafety remains one of the major concerns limiting the clinical translation of persistent luminescence nanoparticles. Most PLNPs are composed of chemically stable inorganic materials containing rare-earth or transition-metal ions. Although these materials exhibit

excellent luminescence properties and acceptable short-term biocompatibility, their long-term biological effects remain insufficiently understood.

One important concern is the slow degradation of inorganic nanoparticles under physiological conditions. Persistent luminescent materials are generally designed to maintain high structural stability in order to preserve their optical properties. However, this stability may also result in prolonged retention within biological tissues after administration. Accumulation of nanoparticles in organs such as the liver, spleen, or kidneys following repeated exposure may increase the risk of long-term toxicity.

Another challenge is the possible release of constituent ions during degradation. Although rare-earth ions are widely used because of their favorable optical properties, their long-term metabolism and biological effects require further investigation. Similarly, host materials containing heavy metals should be carefully evaluated because of potential toxicity and environmental concerns. Consequently, both the host lattice and dopant composition should be selected by considering not only luminescence efficiency but also biological safety.

Surface properties also influence the biosafety of PLNPs. Poor colloidal stability may promote particle aggregation under physiological conditions, resulting in uneven tissue distribution and altered biological responses. In contrast, biocompatible surface coatings improve nanoparticle dispersion and reduce undesirable interactions with biological systems. Therefore, surface modification contributes not only to optical stability but also to improved biological compatibility.

Despite encouraging progress, systematic evaluation of long-term toxicity, biodegradation, immune response, and repeated-dose exposure remains limited. Standardized biosafety assessment protocols specific to persistent luminescence nanoparticles have not yet been established, making direct comparison among different studies difficult. Consequently, long-term biosafety continues to represent one of the major barriers preventing the clinical translation of PLNPs.

The principal biophysical barriers discussed in this section, including protein corona formation, biodistribution, immune recognition, biodegradation, and long-term toxicity, are summarized in **Figure 4** and **Table 2**. These biological limitations, together with the physical constraints described in the previous section, demonstrate that improving luminescence performance alone is insufficient for successful clinical translation. Additional challenges related to large-scale manufacturing, quality control, and regulatory approval are discussed in the following section.

Table 2. Fundamental barriers to the clinical translation of persistent luminescence nanoparticles and possible strategies for future development.

Barrier	**Underlying Cause**	**Impact on Clinical Translation**	**Current Strategies**	**Future Research Priority**
Size–luminescence trade-off	High-temperature calcination required for efficient traps	Difficult to obtain bright sub-100 nm PLNPs	Core–shell structures, optimized synthesis	Low-temperature synthesis with high crystallinity
Surface quenching	High surface-to-volume ratio	Reduced afterglow intensity	Surface passivation, silica/polymer coating	Novel surface engineering approaches
Defect engineering	Uncontrolled trap distribution	Poor reproducibility of persistent luminescence	Co-doping, crystal engineering	Predictive defect design using computational methods

Excitation limitation	Dependence on UV excitation	Limited tissue penetration	NIR- and X-ray-excitable PLNPs	Self-rechargeable and visible-light-responsive PLNPs
Protein corona formation	Adsorption of plasma proteins	Altered biodistribution and targeting	PEGylation, biomimetic coating	Dynamic protein corona control
Long-term biosafety	Non-biodegradable inorganic materials	Potential organ accumulation	Biocompatible coatings	Biodegradable persistent luminescent materials
Manufacturing reproducibility	Variation in synthesis conditions	Batch-to-batch inconsistency	Standardized synthesis protocols	Scalable GMP-compatible production
Regulatory challenges	Lack of specific guidelines	Delayed clinical approval	Standardized characterization	International regulatory framework for PLNPs

5. Translational Challenges

Although significant progress has been achieved in the synthesis and biomedical application of persistent luminescence nanoparticles, their transition from laboratory research to clinical practice remains limited. This gap is not solely due to material performance but also results from challenges related to manufacturing, quality control, regulatory approval, and commercialization. Therefore, successful clinical translation requires coordinated advances in both materials science and translational research.

One of the major challenges is the large-scale production of PLNPs with consistent physicochemical and optical properties. Most reported synthesis methods, including sol–gel, hydrothermal, combustion, and co-precipitation techniques, are optimized for laboratory-scale preparation. Scaling these methods to industrial production often introduces variations in particle size, crystal quality, defect concentration, and dopant distribution. Since persistent luminescence strongly depends on these structural characteristics, even small changes during synthesis may significantly influence afterglow intensity and optical reproducibility.

Batch-to-batch consistency is another important requirement for biomedical applications. Clinical-grade nanoparticles must exhibit reproducible particle size, surface chemistry, luminescence intensity, and colloidal stability. However, persistent luminescence is highly sensitive to synthesis parameters such as precursor purity, calcination temperature, reaction atmosphere, heating rate, and cooling conditions. Variations in these parameters may produce nanoparticles with different optical and biological characteristics, reducing manufacturing reliability.

Standardized quality control remains another limitation. Current studies often employ different methods to evaluate particle size, trap characteristics, luminescence intensity, and afterglow duration, making direct comparison among different PLNP systems difficult. In addition to structural characterization, future quality assessment should include standardized measurements of optical performance, colloidal stability, surface chemistry, sterility, and long-term storage stability. The establishment of internationally accepted characterization protocols would significantly improve reproducibility and facilitate comparison between independent studies.

Regulatory approval represents another major obstacle. Before clinical use, nanomaterials must demonstrate consistent manufacturing quality, comprehensive biosafety, predictable pharmacokinetics, and long-term stability. Although several nanomedicines have received regulatory approval, no persistent luminescence nanoparticle has yet progressed to routine

clinical application. One reason is the absence of regulatory guidelines specifically developed for persistent luminescent nanomaterials. Consequently, researchers must satisfy the broader safety and quality requirements established for nanomedicines while also addressing issues unique to PLNPs, including persistent optical performance, defect stability, and long-term retention in biological tissues.

Another challenge is the limited availability of clinically relevant studies. Most published investigations focus on material synthesis, optical characterization, and proof-of-concept demonstrations in small animal models. Comparatively few studies evaluate large-animal models, long-term toxicity, pharmacokinetics, manufacturing reproducibility, or clinical feasibility. As a result, the current literature provides extensive evidence of laboratory performance but relatively limited information regarding the practical requirements for clinical implementation.

Therefore, the successful translation of PLNPs requires a multidisciplinary approach that combines advances in materials engineering, nanomedicine, pharmaceutical manufacturing, toxicology, and regulatory science. Rather than optimizing a single material property, future research should focus on developing standardized, reproducible, and clinically relevant PLNP platforms that satisfy both scientific and regulatory requirements. The major physical, biophysical, and translational barriers discussed throughout this review are summarized in **Table 2**. Their interrelationship forms the basis of the theoretical framework proposed in the following section.

6. A Theoretical Framework for Clinical Translation

The discussion presented in the previous sections demonstrates that the clinical translation of persistent luminescence nanoparticles (PLNPs) is not limited by a single factor. Instead, it is governed by a series of interconnected physical, biophysical, and translational constraints. Most published studies have attempted to improve individual properties, such as afterglow intensity, particle size, or surface functionalization. Although these approaches have enhanced the performance of PLNPs in specific applications, they have not fully resolved the broader challenges associated with clinical implementation. Therefore, a more integrated strategy is required to guide the future development of clinically viable PLNPs.

Based on the analysis presented in this review, clinical translation can be viewed as a sequential optimization process rather than an isolated materials problem. In this perspective, the successful development of PLNPs depends on balancing five interconnected stages: materials design, physical performance, biological behavior, translational feasibility, and clinical applicability. These stages are closely interrelated, and progress in one stage often influences the performance of the others.

The first stage involves rational materials design. Selection of the host lattice, activator ions, co-dopants, and synthesis conditions determines the crystal structure, defect chemistry, and trap distribution of PLNPs. These parameters directly influence the optical properties of the material, including excitation efficiency, persistent luminescence intensity, emission wavelength, and afterglow duration. Consequently, material design provides the foundation for all subsequent stages of development.

The second stage focuses on physical performance. An ideal PLNP should simultaneously exhibit strong afterglow, efficient charge trapping, high crystallinity, stable defect structures, and nanoscale particle dimensions. However, the size–luminescence trade-off, surface quenching, defect engineering, and excitation limitations discussed in Section 3 demonstrate that these properties are closely interconnected. Improving one parameter frequently influences another, requiring careful optimization rather than independent modification.

The third stage considers biological behavior after administration. Once PLNPs enter the biological environment, their performance is no longer determined solely by intrinsic optical properties. Protein corona formation, biodistribution, immune recognition, biodegradation, and

long-term biosafety collectively determine whether nanoparticles can successfully reach and remain at the target site. Therefore, biological compatibility should be regarded as an integral component of material design rather than a separate post-synthesis consideration.

The fourth stage addresses translational feasibility. Even when PLNPs demonstrate excellent optical performance and acceptable biosafety, their practical application depends on reproducible large-scale synthesis, standardized quality control, manufacturing consistency, and regulatory compliance. These requirements are essential for ensuring reliable clinical performance but are often overlooked during early-stage materials research.

The final stage is clinical applicability, where all previous requirements must be satisfied simultaneously. A clinically successful PLNP should combine efficient persistent luminescence, favorable biological behavior, scalable manufacturing, and regulatory acceptance within a single platform. Failure to satisfy any one of these stages may prevent successful clinical translation regardless of improvements achieved in other areas.

This conceptual framework highlights an important shift in the design philosophy of persistent luminescence nanoparticles. Rather than maximizing a single performance parameter, future research should emphasize balanced optimization across all stages of development. Such an approach may accelerate the transition of PLNPs from laboratory research to clinically useful nanoplatforms and provide a practical roadmap for future investigations.

The proposed framework is not intended to replace existing materials design strategies but to integrate them into a unified translational perspective. By establishing clear relationships among materials science, nanotechnology, biology, and clinical requirements, this framework provides a conceptual basis for the rational development of next-generation persistent luminescence nanoparticles.

7. Future Perspectives

Although persistent luminescence nanoparticles have shown significant potential for biomedical imaging and theranostic applications, several challenges must be overcome before they can achieve clinical translation. Future research should focus on balancing optical performance with biological safety rather than optimizing individual material properties.

The development of biodegradable host materials and biocompatible surface coatings is expected to reduce long-term toxicity and improve nanoparticle clearance. At the same time, advances in crystal chemistry and defect engineering should enable better control of trap distribution and afterglow efficiency without compromising nanoscale dimensions. The design of near-infrared-excitable and self-rerechargeable PLNPs may further improve deep-tissue imaging and reduce dependence on ultraviolet excitation.

Equally important is the establishment of standardized protocols for material characterization, biosafety evaluation, and quality control. Greater collaboration among materials scientists, biologists, clinicians, and regulatory agencies will be essential for translating laboratory-scale PLNPs into clinically reliable nanoplatforms.

Finally, future studies should adopt an integrated design strategy in which materials design, physical performance, biological behavior, and translational requirements are optimized simultaneously. Such an approach, as outlined in the theoretical framework proposed in this review, may accelerate the development of safe, efficient, and clinically translatable persistent luminescence nanoparticles.

8. Conclusions

Persistent luminescence nanoparticles have attracted considerable interest for biomedical imaging because of their unique afterglow emission, high signal-to-background ratio, and excellent photostability. However, despite significant advances in materials design and optical performance, their successful clinical translation remains limited.

This review demonstrates that the major barriers to clinical application arise from interconnected physical, biophysical, and translational constraints. The size–luminescence

trade-off, defect and trap engineering, excitation limitations, biological interactions, long-term biosafety, manufacturing reproducibility, and regulatory requirements must all be addressed to achieve clinically viable PLNPs.

To provide a broader perspective, this review proposes a theoretical framework that integrates materials design, physical performance, biological behavior, and translational feasibility into a unified strategy for PLNP development. We believe that this framework can serve as a practical guide for future research and contribute to the rational design of persistent luminescence nanoparticles with improved clinical potential. j

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