Near-Infrared Fluorescence Imaging in Biomedicine

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Editor's note: Near-infrared (NIR) light (700-1700 nm) is beneficial in biomedical research for deep tissue imaging and therapy, with minimal scattering and phototoxicity. Advances in nanomaterials enable localized therapeutic effects, but many technologies are still in pre-clinical stages due to challenges like immune interactions. This review by Pothal et al. covers NIR principles, materials designs, applications in cancer theranostics, neuroregeneration, and biosensing, and strategies for improved safety in NIR nanomedicine.

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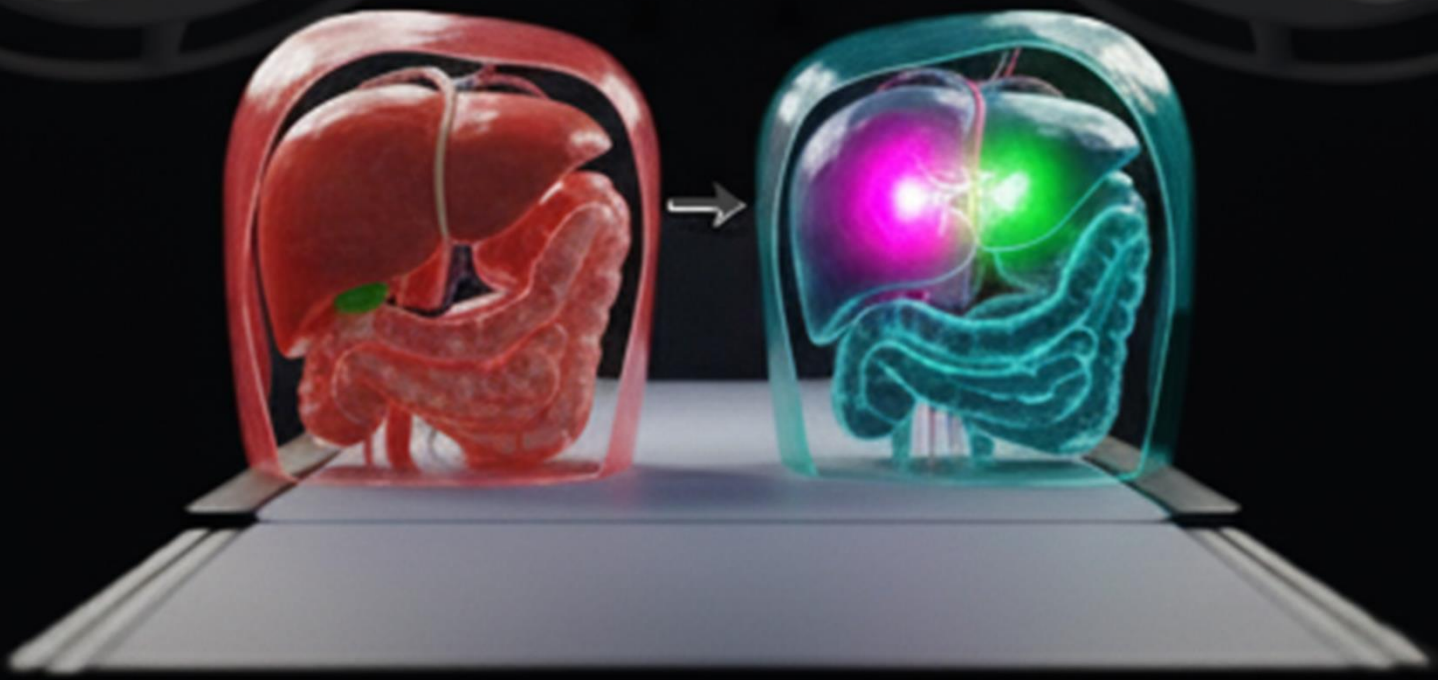

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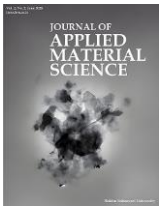

Review

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Abstract

Near-infrared (NIR) light, spanning 700-1700 nm, has attracted increasing attention in biomedical research because of its reduced photon scattering, lower tissue absorption, and minimal autofluorescence. As a result, NIR illumination enables deeper tissue penetration while maintaining low phototoxicity, making it particularly suitable for non-invasive imaging, biosensing, and remotely triggered therapeutic interventions. However, the practical use of these optical advantages depends powerfully on how efficiently light-matter interactions can be translated into controlled biological responses. In this regard, advances in nanomaterials have played a central role. Recent developments in polymeric nanocarriers, hybrid nanoparticles, and light-responsive soft materials have enabled NIR stimulation to be converted into localized thermal effects, chemical reactions, or imaging signals. Importantly, materials design at the nanoscale governs key parameters such as stability, drug release behavior, targeting efficiency, and biological compatibility. Consequently, material choice and engineering strategies have become decisive factors in determining system performance. Despite supporting progress, numerous NIR-based nanoplatforms remain limited to pre-clinical demonstrations. Challenges interlinked to immune interactions, biodistribution, material degradation, and scalable fabrication continue to restrict broader implementation. In this review, we present a materials-focused perspective on NIR-responsive nanotechnology. We first discuss the basic photophysical principles underlying NIR activation, then analyze polymer-based carrier designs and stimulus-controlled release mechanisms. Current applications in cancer theranostics, neuroregeneration, and biosensing are critically evaluated, with attention given to both advantages and limitations. Finally, emerging design strategies aimed at improving precision, safety, and translational feasibility are highlighted, providing realistic guidance for the future development of application-ready NIR nanomedicine.

Keywords: NIR-triggered drug delivery; NIR-II fluorescence imaging; NIR-guided biosensing; Deep-tissue bioimaging; Photocleavable linkers.

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1. Introduction

NIR illumination is gaining significance in modern biomedicine for its unique interactions with biological tissues at these wavelengths. The NIR spectrum is typically classified into NIR-I (700- 950 nm) and NIR-II (1000-1700 nm), where there is low absorption of NIR light by water, hemoglobin, and other endogenous chromophores. Also, both photon scattering and tissue autofluorescence are substantially lower in these regions. In combination, these characteristics allow NIR light to penetrate tissues more easily than visible or UV light while causing less phototoxicity [1-3]. Consequently, researchers are increasingly using NIR illumination in a growing number of applications, including non-invasive imaging, biosensing, and externally controlled therapeutic treatments. While NIR has favorable optical properties, NIR light alone does not enable a controlled biological effect. Subsequently, a medium is required to absorb the NIR light to create an area of localized thermal, chemical, or optical activity for which biomedical effects can be measured. The coupling of NIR photonics with nanotechnology has enabled the development of NIR-responsive nanomaterials that couple NIR light and biological systems with great precision at the nanoscale, as well as providing spatial and temporal precision for diagnostic and therapeutic procedures.

Over the decade, many different types of NIR-responsive nanomaterials, including nanocarriers, have been explored. Polymeric systems can be engineered with NIR absorbers, photothermal materials, or light-sensitive linkers so that upon NIR exposure, they release therapeutic agents in a controlled manner or produce imaging signals [4, 5]. Inorganic nanomaterials, including rare-earth-doped nanoparticles, quantum dots (QDs), and plasmonic nanostructures, offer excellent optical stability and unique photophysical properties, making them well-suited for imaging and sensing applications. However, there are still significant concerns associated with the long-term biocompatibility, clearance, and toxicity of these materials. In spite of the growing number of reports on NIR-responsive systems, very few have been converted to practical biomedical applications. Significant challenges remain in the way of progress, including differences in NIR radiation penetration across tissues, nonuniform heat production during photothermal activation, and unpredictable interactions with the immune system [6-8].

Many nanoplatforms show excellent results under controlled laboratory conditions but have difficulty when tested in complex, heterogeneous biological environments. These challenges highlight the critical role of material design, including particle size, surface chemistry, degradation characteristics, and mechanical stability, in shaping the biological performance of nanomaterials. Moreover, recent research has focused on developing multi-responsive, logic-controlled nanoplatforms to improve precision and safety. In such systems, NIR light serves as the primary external trigger, while internal biological cues, such as pH changes, enzyme activity, or redox conditions, provide additional control. This multi-trigger approach helps ensure that therapeutic activation occurs only at the specific site, thereby decreasing off-target effects and systemic toxicity. Importantly, surface functionalization with targeting ligands, such as antibodies, peptides, or small molecules, promotes specific accumulation in diseased tissues and enhances cellular uptake [9, 10].

Integrating diagnostic and therapeutic functionalities into a single platform is another key element of NIR-responsive nanotechnology. By integrating imaging agents with therapeutic materials, real-time tracking of biodistribution, treatment progress, and therapeutic results is possible. Feedback systems are necessary for optimizing treatment parameters and improving reproducibility. However, achieving this degree of multifunctionality through material engineering requires balancing optical performance, structural integrity, and biological compatibility, which can be challenging. With the rapid evolution of NIR-based nanotechnology, there is a clear need for a comprehensive review that addresses materials-based design principles, limitations, and operational considerations for this technology. Most existing reviews focus primarily on applications or optical performance, while giving little attention to material durability, scalability, or translation feasibility.

These issues must be considered if we are to guide future research towards systems that are not only scientifically novel but also practical. This review will provide a materials-oriented perspective on NIR-responsive nanotechnology. In this, we have discussed the fundamental principles of NIR light matter interaction, key material engineering strategies, and the role of polymeric and hybrid nanocarriers in controlled biomedical applications. Current advances in biosensing, bioimaging, cancer theranostics, and

neuroregeneration are critically examined, along with the challenges that limit clinical translation. Finally, we outline coming trends and realistic future directions to advance NIR-responsive nanomaterials toward application-ready, clinically relevant nanomedicine [11, 12].

2. Engineering and physics of NIR-responsive nanotechnology

The effectiveness of NIR nanotechnology for biomedical applications is primarily determined by how light interacts with matter and biological tissue. The NIR spectral region is particularly advantageous because NIR light (NIR-I: 700 - 950 nm, NIR-II: 1000 - 1700 nm) has lower absorption due to lower absorption by endogenous chromophores such as haemoglobin and water, and less scattering than visible light [2, 13, 14]. Figure 1 provides an overview of the optical properties, nanomaterial design, and the processes by which nanomaterials respond to NIR light, allowing NIR photons to easily penetrate deep into biological tissues and enabling non-invasive imaging and therapeutic process activation.

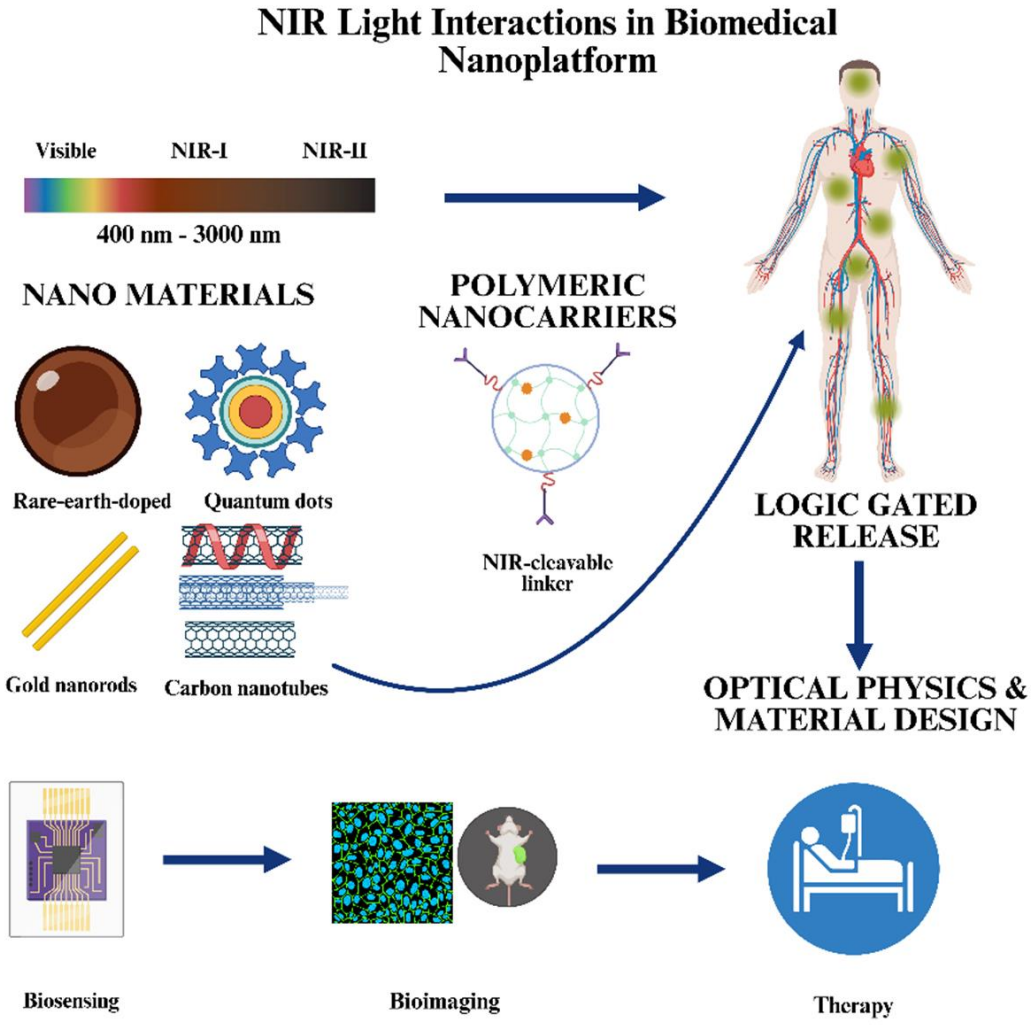

Figure 1. Schematic representation of NIR light interactions in biomedical nanoplatforms. The illustration outlines the NIR spectral windows (NIR-I: 700-950 nm and NIR-II: 1000-1700 nm) and highlights various nanomaterials, such as rare-earth-doped particles, QDs, gold nanorods, and carbon nanotubes, used in polymeric nanocarriers. These carriers are equipped with NIR-cleavable linkers for logic-gated drug or gene release upon photonic activation. Through engineered optical physics and material design, these systems enable deep-tissue biosensing, real-time bioimaging, and controlled therapeutic intervention, offering a promising strategy for minimally invasive, precision nanomedicine.

The improvement of NIR-responsive materials through well-structured, engineered nanomaterials plays a special role in reconfiguring the optical properties of NIR light for therapeutic applications *via* photothermal, photochemical, and fluorescent responses [15, 16]. Additionally, QDs exhibit bright, tunable fluorescence upon infrared excitation. However, proper surface modification is necessary before QDs can be used for therapeutic applications. In parallel, organic and polymer-based NIR absorbers have attracted increasing attention due to their favorable safety profiles and structural flexibility.

Materials such as indocyanine green, polydopamine, and conjugated polymers efficiently convert NIR light into localized heat, supporting photothermal and photoacoustic applications. Inorganic nanostructures, including gold nanorods and carbon-based materials, also exhibit strong photothermal conversion, enabling localized temperature elevation for tumor ablation or heat-triggered drug release. Therefore, selecting the right material is extremely important; optical performance must be balanced with biocompatibility/degradation behavior and long-term stability [17, 18]. New methods for precise control of therapeutic activation have been developed in recent years, with photothermal and fluorescent responses now used as components of more complex systems. Such methods include using NIR-cleavable chemical linkers or utilizing light-responsive polymer architectures to trigger the release of a drug or gene only upon exposure to the appropriate optical stimulus.

More advanced systems include the integration of multiple functions within one nanoplatform; this allows for the incorporation of both optical responses and biological triggers (such as pH shifts or cleavage enzymes), thus creating more logical systems with an additional layer of selectivity that enhances the safety of the system by ensuring activation occurs only when appropriate, thereby reducing potential off-target effects [19]. NIR-responsive nanomaterials also face practical limitations, including heat loss, inefficient heat transfer, light-intensity thresholds, and limited spatial resolution within biological tissues. The use of high-intensity or unevenly distributed light sources may lead to localized overheating, while tissue heterogeneity can further compromise therapeutic precision. Therefore, optimizing particle size, absorption efficiency, and material composition is essential to achieve reliable outcomes across diverse NIR nanoplatforms.

Establishing standardized and reproducible approaches for the fabrication and application of these platforms is equally important. Such standardization requires a comprehensive understanding of how physical principles, engineering design, and material structure collectively influence biological performance and biocompatibility. Consequently, the successful clinical translation of NIR nanotechnology will depend on the development and adherence to well-defined guidelines and regulatory standards [20, 21].

3. Polymeric nanocarriers with NIR-activated platforms

Nanocarriers of polymers have emerged as a versatile and clinically significant class of materials for controlled drug delivery, owing to their structural versatility, capacity, and biocompatibility, enabling precise and accurate molecular engineering. By using NIR light to activate the elements that make up these systems, they can provide high-level control over when and where to administer drugs, tailored to the patient's needs. There are many advantages to using NIR light; some examples include the ability to penetrate deep into the body while minimizing damage to surrounding tissue, as well as its safety as a safe alternative for performing certain procedures using light-based therapies [22, 23]. Therefore, polymer nanocarriers activated by NIR will play an important role in developing innovative ways to deliver therapeutic agents that were previously impossible to deliver.

There is significant research underway to develop these drug delivery systems by combining polymer chemistry and light-based technologies to improve the patient experience. Predominantly, NIR-responsive polymeric nanocarriers are fabricated from biocompatible polymers such as polyethene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), or amphiphilic block copolymers, which self-assemble into nanoscale structures including micelles, nanogels, or nanoparticles. These polymeric matrices deliver structural stability, extend systemic circulation time, and safeguard therapeutic payloads during systemic transport.

NIR responsiveness is achieved by integrating photothermal agents, photosensitizers, or upconversion

elements, which act as transducers, transforming optical energy into localized thermal or chemical stimuli that subsequently trigger controlled drug release [24-27]. Among the various activation strategies, photothermal-triggered drug release is the most widely investigated. In this design, NIR-absorbing agents, including indocyanine green (ICG), conjugated polymers, IR780, or polydopamine, are incorporated into the polymer matrix. In response to NIR irradiation, these agents readily convert photon energy into heat, elevating local temperature. The resulting thermal stimulus promotes polymer chain relaxation, weakens hydrophobic interactions, or induces a phase transition in heat-sensitive polymers, thereby facilitating accelerated drug diffusion and controlled drug release from the carrier. Notably, the localized nature of photothermal heating enables drug release at the irradiated sites, substantially minimizing off-target toxicity and improving therapeutic precision [28, 29].

In addition to thermally focused mechanisms, photo-oxidative and photochemical pathways provide a complementary pathway for NIR-activated polymer degradation and cargo liberation. In such systems, photosensitive agents generate reactive oxygen species (ROS) upon NIR excitation, which subsequently fragment ROS-sensitive linkers or polymer backbones. Polymeric carriers integrating boronic ester, thioketal, or sulfur-containing functionalities undergo controlled degradation in response to ROS, making light-triggered disassembly of nanocarriers and quick release of the drug at the target site [7]. This platform is highly advantageous because it effectively separates the drug release from temperature elevation, thereby reducing the risk of heat-driven damage to localized healthy tissues [30-34].

To enhance design flexibility, NIR activation approaches using upconversion nanoparticles or two-photon absorption mechanisms have been developed. In these systems, NIR photons are converted into higher-energy ultraviolet or visible photons, which subsequently fragment photolabile bonds within the polymer framework. This approach permits the use of well-established photocleavable chemistries while preserving the deep-tissue penetration benefits of NIR light. Such multiple-component systems highlight the importance of nanoscale engineering in regulating transfer of energy pathways and enabling efficient activation under clinically relevant irradiation parameters [35, 36].

The structural design, activation pathways, and therapeutic potential of NIR-responsive polymeric nanocarriers are summarized in Figure 2, which provides a consolidated view of polymeric nanocarriers designed for therapeutic activation using near-infrared light. These systems are commonly fabricated from biocompatible polymers such as PEG and PLGA and are engineered with responsive elements and cleavable linkers that maintain structural stability during circulation while enabling controlled release at the intended site. When exposed to NIR irradiation, incorporated transducing agents can generate heat, produce reactive oxygen species, or initiate photochemical processes through upconversion, thereby facilitating the release of the therapeutic payload. Such externally controlled activation allows treatment to be confined to the irradiated region, reducing the likelihood of affecting surrounding healthy tissue. Collectively, these platforms have demonstrated utility across several biomedical areas, including cancer treatment, site-specific drug delivery, theranostic imaging, and minimally invasive interventions, underscoring their growing importance in the development of precision-guided therapeutic strategies.

Regarding the structure of newly engineered NIR-responsive polymeric nanocarrier materials, many architectures have been developed, including block copolymer micelles, polymeric nanoparticles, nanogels, and fibrous scaffolds. Of these structures, amphiphilic block copolymer micelles are especially useful because they allow simultaneous delivery of both hydrophobic therapeutic agents and NIR-absorbing components within a single core; thereby providing the potential for integrated imaging and therapeutic functions. Additionally, polymeric nanofibers and injectable hydrogel systems can serve as localized delivery platforms, in which NIR irradiation softens the matrix or trigger-controlled degradation, resulting in site-specific drug release while minimizing systemic exposure. Together, these various structural architectures demonstrate how rational polymer design can be used to regulate both activation efficiency and overall therapeutic efficacy. Polymer prodrug/ nanocarrier systems are also becoming more widely used to control the release of drugs after administration [23, 37-39].

As part of this delivery system, therapeutic agents are attached to the polymer backbone *via* NIR- or ROS-sensitive linkers, yielding stable prodrugs at physiological temperatures. Once an NIR-sensitive

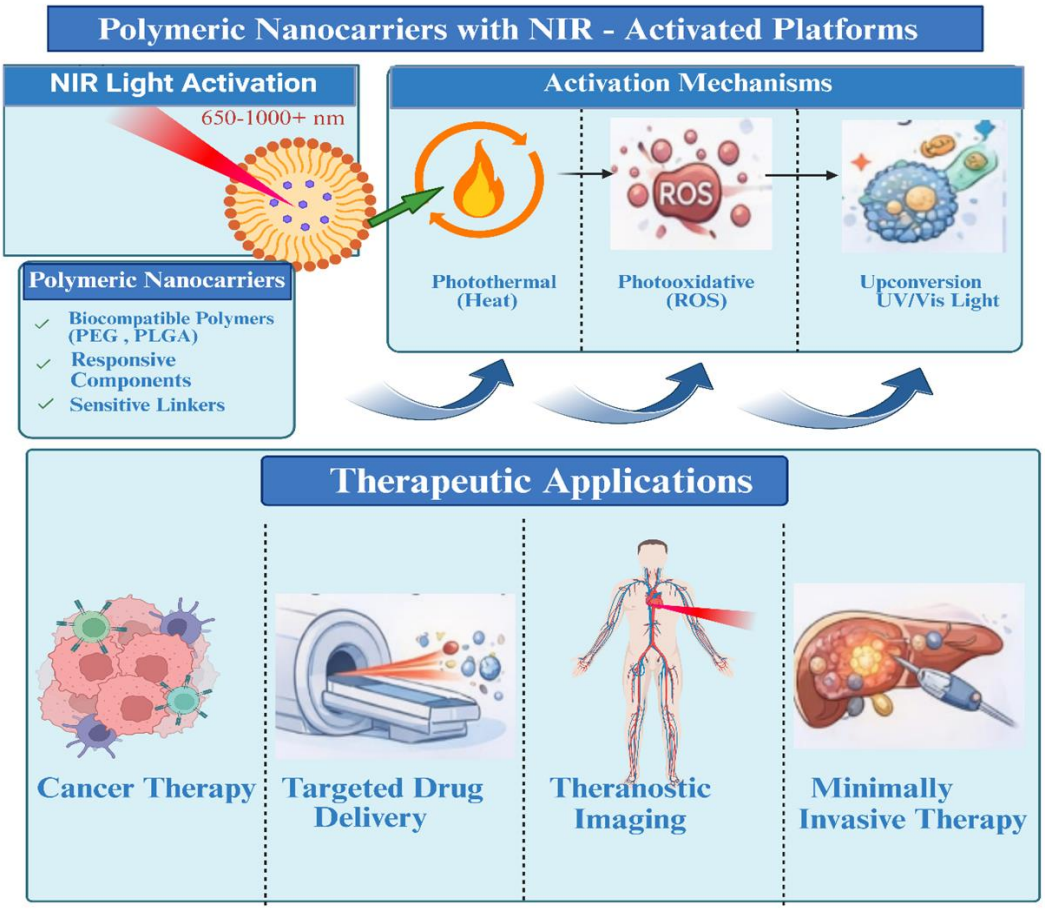

Figure 2. Schematic illustration depicting the design of polymeric nanocarriers fabricated from biocompatible materials and functionalized with responsive components that enable drug release following near-infrared (NIR) exposure. Incorporated photothermal agents, photosensitizers, or upconversion elements convert optical energy into localized thermal or chemical stimuli, thereby disrupting the carrier matrix or cleaving sensitive linkers. This controlled activation supports site-specific drug release while maintaining structural integrity during systemic transport. Representative biomedical applications, including cancer therapy, targeted drug delivery, theranostic imaging, and minimally invasive treatment approaches, are also highlighted, reflecting the expanding role of NIR-responsive polymer systems in advanced therapeutic design.

linker cleaves, an active drug is released in its native form, leading to minimal premature drug liberation and improved pharmacokinetic stability. The application of the above-described methods diminishes or eliminates the effect of molecular engineering on the drug-delivery process, thereby allowing the nanocarrier-prodrug combination to be developed using molecular engineering methodologies while remaining biologically responsive to an external stimulus. As a group, NIR-activated polymeric nanocarriers provide an effective means of delivering targeted therapy on an as-needed basis with high accuracy.

The integration of therapy, imaging, and controlled release within a single system also makes them among the most important components of current theranostic approaches [23, 40, 41]. However, numerous challenges remain, such as limited light penetration into deep tissues, prolonged polymer degradation, and large-scale reproducibility, which remain significant barriers to bringing these technologies to the clinic. To overcome these barriers, it will require continued advancements in polymer chemistry, the optimization of photothermal materials, and system-level engineering to ensure the safety, effectiveness, and feasibility of translating these materials for use as therapeutic modalities in patients.

4. Biological interfacing and biomedical applications

The overall biomedical benefits of NIR fluorescence imaging platforms depend on their ability to effectively interface with complex biological environments while preserving their optimal optical performance, target specificity, and/or biosafety. After systemic injection, NIR fluorescent probes and nanocarriers encounter numerous biological barriers before they can emit NIR fluorescence, including adsorption of serum proteins, recognition by the immune system, and rapid clearance from circulation mediated by cells of the mononuclear phagocyte system (MPS). Researchers have worked extensively to develop biologically adaptive interfaces that enhance circulation stability, reduce nonspecific interactions, and increase site-specific accumulation of probes or carriers in target tissues.

One of the most popular ways to enhance materials' ability to interface with living systems and improve their compatibility is through surface modification with hydrophilic polymers, specifically polyethene glycol (PEG) and zwitterionic coatings. These surface coatings will decrease opsonization and reduce macrophage uptake, thereby increasing the time the probes remain in the bloodstream before accumulating in the target tissue [42-44]. Surface chemistries also allow modular/orthogonal additional functionalization with targeting ligands, which can be very advantageous without compromising colloidal stability and/or optical properties, both of which are very important for *in vivo* fluorescence imaging studies.

Targeted biological interactions can be selectively metabolically activated (i.e., enhanced) by binding to or cellular entry into these molecules. NIR fluorescent nanoplatforms are routinely combined with 1 or more ligands such as: (i.e. RGD peptide; folic acid, transferrin; an antibody; an aptamer) that can bind to a receptor that is over-expressed on the surface of a cancer cell, inflamed endothelium; or vascularization of the brain and induce receptor-mediated internalization through the process of receptor-mediated endocytosis, thereby increasing the concentration of the imaging agent in the intracellular space and improving the contrast of the imaging at the diseased site through. NIR fluorescence enables these targeted systems to provide high-contrast visualization of tumors, metastatic lesions, and pathological tissues, with minimal background interference.

In addition to both passive and active targeting, there has also recently been the development of stimuli-responsive biological interfacing as an even greater design choice. Because of these developments, many NIR fluorescent platforms on the market have been developed to integrate endogenous biological cues (such as acidic pH, enzyme activity, or redox gradients) with exogenous NIR excitation within a single platform. This dual-responsiveness allows for the specific activation of probes, signal amplification and/or controlled release of therapeutic agents strictly within diseased microenvironments (e.g. by destabilizing the nanocarrier once the endogenous cue has been detected and then activating the fluorescent dye within the platform by means of NIR irradiation to enhance the fluorescent dye's emission intensity or exhibit photothermal or photodynamic effects), thus improving the accuracy of diagnosis and the precision of therapeutic effect [45-48].

The biological interfacing, targeting mechanisms, and NIR-triggered diagnostic and therapeutic functions of these nanoplatforms are illustrated in **Figure 3,** which depicts their interactions with biological systems following systemic administration. Surface modification with PEG or zwitterionic coatings enhances circulation stability and reduces immune clearance, while ligand-mediated targeting promotes accumulation at diseased sites. Upon exposure to NIR light, embedded fluorophores or photothermal agents generate optical or localized thermal responses that support real-time imaging and controlled therapeutic action. This coordinated integration of surface engineering, targeting capabilities, and optical responsiveness highlights the potential of these nanoplatforms for precise, minimally invasive biomedical interventions.

The use of advanced NIR fluorophores, along with the introduction of upconversion nanoparticles, has dramatically increased both resolution and imaging depth. The second near infrared window (NIR-II - 1000 - 1700 nm) provides lower photon scattering, almost no autofluorescence in tissue, and much better penetration of light than compared to either visible light or NIR-I, and therefore provides the first opportunity to obtain real-time images with high quality of deep tissue tumors, vascular networks, and organ structures within the body. Encapsulating NIR-II fluorophores in a polymer also improves their photostability, biocompatibility, and circulation time, enabling longitudinal *in vivo* evaluation of biodistribution and treatment effects.

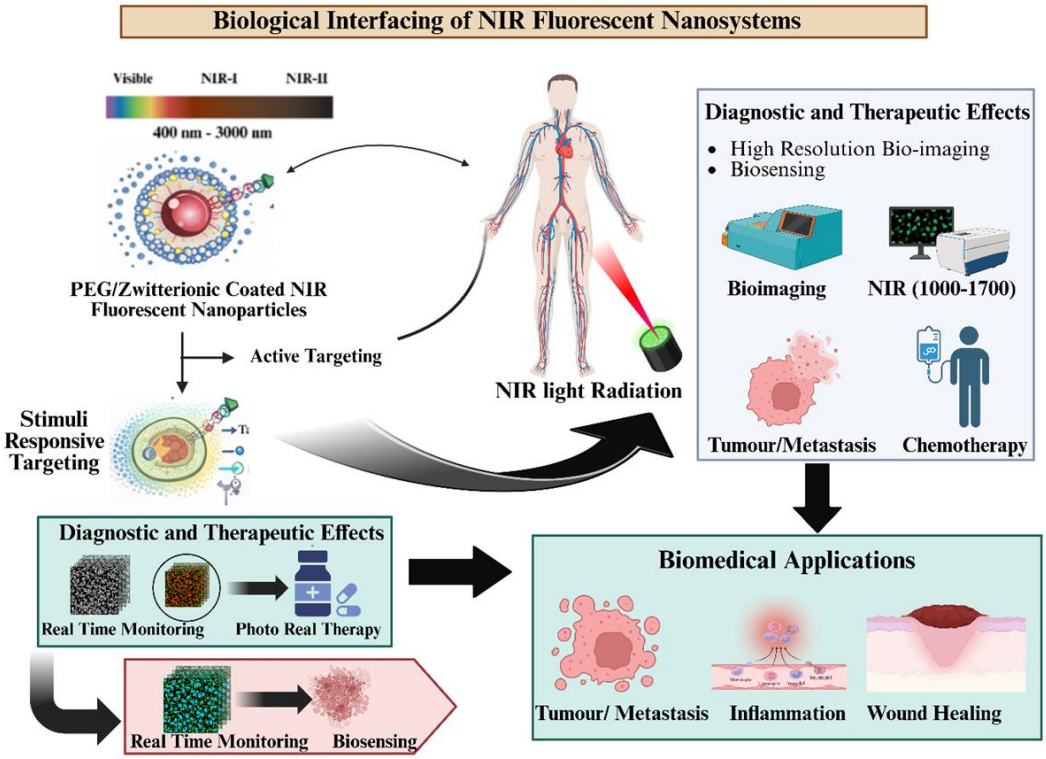

Figure 3. Schematic illustration depicting PEG- or zwitterionic-coated NIR fluorescent nanoparticles engineered for improved circulation stability and reduced immune recognition. Surface functionalization supports ligand-mediated targeting and promotes accumulation within diseased tissues. Upon near-infrared (NIR) irradiation, embedded fluorophores or photothermal agents generate optical or localized thermal responses, enabling high-contrast imaging, biosensing, and site-specific therapeutic activation. These features collectively demonstrate the applicability of NIR nanoplatforms in tumor visualization, inflammation monitoring, wound assessment, and image-guided treatment.

NIR fluorescence imaging has made a massive difference in how oncologists find and treat tumors, allowing them to see where the tumor begins and ends so they can perform proper surgery if needed. There are new types of nanotechnology platforms that can be detected by NIR light that will allow clinicians to use multiple modalities for imaging and therapy (PTT, PDT, and chemotherapy) and use that platform for delivering drugs as well as tracking how well the drugs are working and figuring out when to deliver the next infusion. NIR offers an additional option for an "NIR-identified" tumor that has been treated and how this will synergize with immunotherapy (i.e., by using NIR light for phototherapy to induce immunogenic cell death and enhance immune responses directed toward the tumor, potentially creating a synergistic effect with immune checkpoint inhibitors).

NIR fluorescence imaging has significant potential for use in areas such as neurology, inflammation, and regeneration beyond cancer. NIR fluorescent probes that can cross the blood-brain barrier have been designed to help visualize both brain tumors and the neuroinflammation associated with them. Light-activated delivery systems have enabled spatiotemporal control of the release of neurotrophic factors for neural repair. NIR-responsive systems used for the visualization or treatment of wounds/inflammation allow localized treatment, reducing systemic exposure and, in turn, accelerating tissue regeneration [1, 49, 50].

NIR fluorescence biosensors have made rapid and highly sensitive detection of pathogens and disease biomarkers available as an immediate diagnostic tool in two environments - clinical and point of care. For example, NIR imaging used to guide the surgeon during surgery (intraoperatively) is now an important part of surgical navigation, lymphatic mapping, and vascular visualization, thereby increasing surgical accuracy and improving patient outcomes. Overall, when intelligent

biological interfacing is combined with NIR fluorescence imaging, both diagnostic and therapeutic approaches are being fundamentally transformed throughout biomedicine. Collectively, these new technologies demonstrate the tremendous potential of NIR-responsive platforms to provide precise, image-guided, patient-centered solutions in healthcare, positioning them as leaders in the future of biomedical imaging and nanomedicine [51-54].

5. Prospective paths, obstacles, and perspectives

While there have been significant improvements in NIR fluorescence imaging technology, many barriers remain that prevent its broad clinical use. Addressing these hurdles and taking advantage of new opportunities will determine how NIR fluorescence imaging evolves in biomedicine. Optimizing performance with second near-infrared (NIR-II) emissive fluorophores remains a challenge, even as technology has advanced to enable greater design accuracy for optimized-performance compounds. The majority of currently available compound candidates are limited by low emission light intensity or quantum yield, low photostability, or concerns about biocompatibility and long-term clearance after use [55-58]. Importantly, although NIR-II imaging has demonstrated penetration depths approaching several millimeters to centimeters in small animal models, direct translation of these results to human tissues remains challenging. Human anatomical structures are thicker and exhibit greater optical heterogeneity, increased lipid content, and more complex vascular networks, all of which enhance photon scattering and absorption. Consequently, clinically achievable imaging depth may be more restricted than that observed in murine models, often confining NIR applications to intraoperative or superficial imaging contexts. Addressing this translational gap requires optimization of fluorophore brightness, detector sensitivity, and photon management strategies.

Quantum dots and rare-earth mineral fluorophores both exhibit excellent optical properties; however, they raise important safety concerns. Quantum dots containing cadmium or lead cores may pose risks of heavy metal ion leakage, particularly under oxidative or lysosomal degradation conditions. Preclinical studies have reported long-term accumulation in organs such as the liver and spleen, raising concerns regarding chronic toxicity and delayed clearance. Similarly, rare-earth nanoparticles often demonstrate limited biodegradability and prolonged biological retention, which may contribute to inflammatory responses or incomplete systemic elimination. Organic fluorophores generally exhibit lower toxicity than inorganic systems, but must still be assessed for improved stability, brightness, and long-term safety before clinical application.

To gain regulatory approval and be used successfully in human biology, manufacturers must account for both physical performance characteristics and biological effects related to potential toxicity when designing fluorescent agents. The second substantial barrier comprises non-standardized imaging instruments and quantitative imaging protocols. Current NIR imaging systems differ widely in excitation sources, detector sensitivity, spectral filters, and image processing algorithms, creating inconsistencies in how data are obtained or interpreted across different clinical trials [59-62]. These variances make it difficult to directly compare results and ultimately establish uniform performance standards. To ensure reliability and reproducibility, especially as NIR fluorescent imaging approaches become more common, there is a clear need to establish standardized calibration procedures, validated reference materials, and quantitative imaging frameworks.

From a biological perspective, achieving in vivo delivery efficacy and target specificity remains difficult. While modifications in surface and active targeting strategies have improved tissue accumulation, heterogeneous biological barriers such as dense extracellular matrices, tumor vascular irregularities, and immune clearance mechanisms still inhibit probe penetration and uniform distribution. Moreover, off-target accumulation in organs such as the liver and spleen can reduce imaging contrast and raise safety concerns. Future efforts are expected to focus on adaptive and biomimetic delivery strategies, including cell membrane-coated probes, endogenous ligand mimicry, and stimuli-responsive systems that dynamically respond to disease microenvironments. Furthermore, spatial precision during NIR-guided imaging and therapy may be compromised in dynamic biological environments.

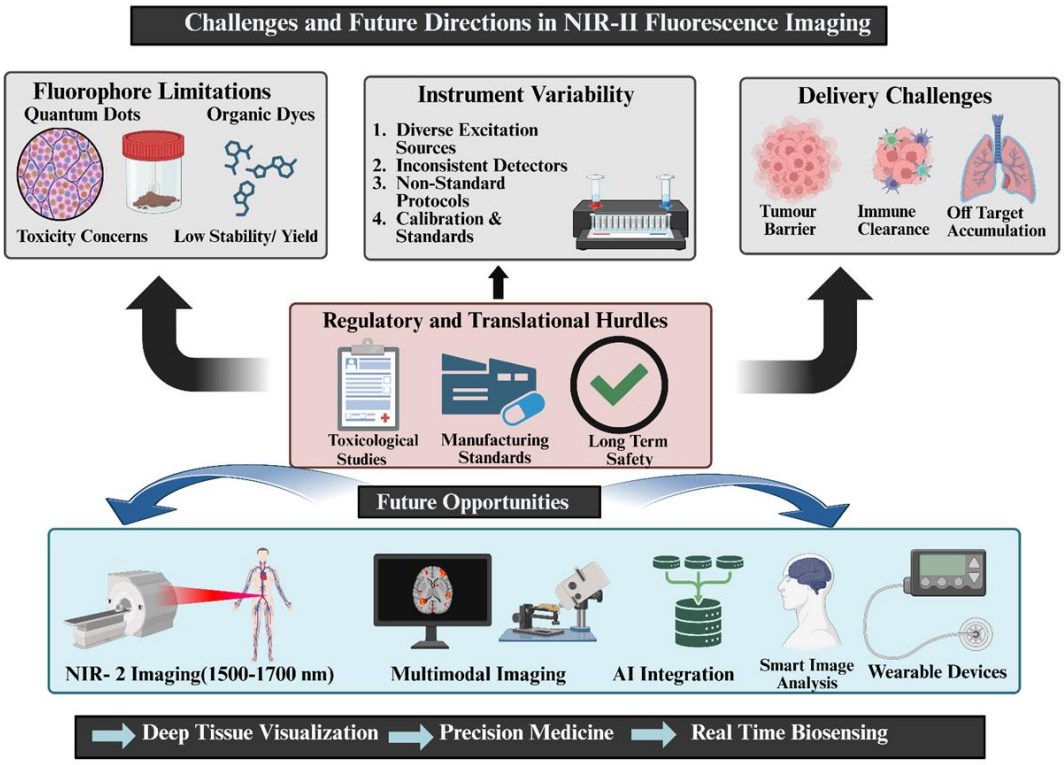

Figure 4. Schematic overview highlighting the principal factors influencing the clinical translation of NIR-II imaging technologies. Key limitations include fluorophore-related concerns such as stability, emission efficiency, and biocompatibility, along with variability in imaging instrumentation arising from differences in excitation sources, detector sensitivity, and calibration practices. Biological barriers, including immune clearance, tumor heterogeneity, and off-target accumulation, further affect delivery efficiency and imaging reliability. The figure also summarizes key regulatory considerations, including toxicological assessment, manufacturing consistency, and long-term safety requirements. Concurrently, advances in extended NIR-II imaging windows, multimodal imaging platforms, artificial intelligence-assisted analysis, smart image processing, and wearable optical devices are expected to improve diagnostic accuracy and support the progression of precision medicine and real-time biosensing.

Physiological motion, including respiratory movement and cardiac pulsation, can introduce motion artifacts that affect imaging resolution and targeting accuracy. During photothermal activation, thermal diffusion beyond the irradiated region may reduce spatial selectivity, particularly in highly perfused tissues. These challenges highlight the importance of real-time feedback systems, motion-compensated imaging platforms, and artificial intelligence-assisted reconstruction algorithms to enhance precision under clinically relevant conditions. There are numerous regulatory and translational challenges restricting the use of NIR dyes. NIR fluorescence dyes require a rigorous clinical development program, including toxicological evaluation, reproducible large-scale manufacturing, and long-term safety studies. From a regulatory standpoint, compliance with Good Manufacturing Practice (GMP) standards and validation of batch-to-batch reproducibility are essential. In the United States, translation typically involves submission of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA), followed by phased clinical trials assessing safety, dosage optimization, and efficacy.

Very few NIR dyes (e.g., indocyanine green) have been accepted in clinical practice, and current applications are largely driven by their established safety records [44, 63, 64]. To facilitate the transition from pre-clinical phases to clinical application, the development of NIR fluorescence imaging systems will require collaboration among material scientists, pharmacologists, regulatory scientists, and clinical stakeholders. The major technological, biological, and regulatory challenges, together with emerging future

Table 1. Comparative analysis of NIR-responsive platforms and translational challenges

Platform Type	Emission Window	Clinical Penetration Depth	Biocompatibility	Clearance	Regulatory Status	Major Limitations	Ref.
Organic Fluorophores	NIR-I / NIR-II	Moderate (intraoperative / superficial in humans)	Generally favorable	Metabolic clearance possible	Limited approvals (e.g., ICG)	Lower brightness, photobleaching	[65]
Quantum Dots	NIR-I / NIR-II	High preclinical depth	Potential heavy metal toxicity	Slow organ clearance	Not clinically approved	Heavy metal ion leakage, long-term safety	[8]
Rare-Earth Nanoparticles	NIR-II	High preclinical depth	Limited biodegradability	Prolonged retention	Preclinical stage	Chronic retention, inflammatory risk	[66, 67]
Polymeric Nanocarriers	NIR-triggered systems	Dependent on embedded dye	Generally biocompatible	Tunable degradation	Mostly preclinical	Scale-up reproducibility challenges	[23, 68]
Hybrid Nanoplatforms	Multimodal	Enhanced functionality	Variable	Complex pharmacokinetics	Experimental	Manufacturing complexity, regulatory burden	[69-71]
Organic Fluorophores	NIR-I / NIR-II	Moderate (intraoperative / superficial in humans)	Generally favorable	Metabolic clearance possible	Limited approvals (e.g., ICG)	Lower brightness, photobleaching	[65]

directions in NIR-II fluorescence imaging, are summarized in Figure 4. In addition, a comparative analysis of representative NIR-responsive platforms, highlighting their translational status, biocompatibility considerations, and major limitations, is presented in Table 1 to provide a structured overview of the current landscape.

Constraints related to fluorophore performance, variability among imaging instruments, and ongoing difficulties in achieving efficient biological delivery collectively limit reproducibility and imaging precision. Regulatory expectations, particularly those related to toxicological evaluation, manufacturing reliability, and long-term safety, further complicate clinical implementation. Despite these obstacles, steady progress in extended NIR-II imaging windows, multimodal diagnostic platforms, artificial intelligence-assisted image analysis, and emerging wearable optical technologies points toward a promising future. These developments are expected to improve deep-tissue visualization and enable more accurate, image-guided therapeutic strategies. Taken together, the field appears to be moving toward greater technological maturity, where continued interdisciplinary collaboration will be essential for translating NIR fluorescence imaging from advanced research settings into routine clinical practice.

While various limitations exist, ample room exists for optimism regarding the future of NIR fluorescence imaging. With continuing advancements to the NIR-II regime, as well as the introduction of NIR-IIb (1500-1700 nm) imaging windows, anticipated improvements to both spatial resolution and imaging depth should allow for visualization of deeply-seated tissues within the body and for visualizing dynamic biological processes at levels of detail comparable to those which were previously unattainable. Continued development of detector technology, especially high-sensitivity InGaAs cameras coupled with enhanced optical filtering, will drive the conversion to ultra-deep tissue imaging at a greatly accelerated rate [72-75]. The diagnostic potential of NIR fluorescence imaging is expected to evolve through its integration with multimodal imaging and artificial intelligence (AI).

The ability of NIR imaging to provide complementary anatomical and physiological information when combined with modalities such as MRI, photoacoustic imaging, and CT further enhances diagnostic accuracy and supports multimodal clinical decision-making. To achieve even better signal extraction, automate feature recognition, and provide instantaneous decision-making support during surgical/therapeutic procedures, AI will enhance the capabilities of image reconstruction and analysis algorithms across all three modalities. Overall, the continued development and

implementation of these technologies will significantly increase the accuracy of diagnoses and improve the efficiency of clinical workflows.

Looking forward, NIR fluorescence imaging is poised to play an increasingly central role in precision medicine, particularly in image-guided surgery, immunotherapy monitoring, regenerative medicine, and real-time biosensing. Some upcoming uses include: developing a patient-specific probe design for a custom probe; using longitudinal follow-up to assess therapy response; and connecting to wearable or minimally invasive devices for optical imaging. As the fields continue to collaborate as they do now, this method of imaging will shift from a primarily research-focused approach to a necessary part of clinical practice. There remain many challenges regarding probe design, instrumentation, biological interface, and regulatory hurdles; however, new technologies and strategic collaborations across disciplines are rapidly redefining how we do NIR fluorescence imaging. These will be key components for fully leveraging NIR-based technologies and developing next-generation, image-based, patient-focused biomedical applications [42, 44, 76-78].

6. Conclusions

In the last decade, NIR fluorescence imaging has developed rapidly as a new tool in the life sciences, providing benefits including deep tissue penetration, minimal scattering of light, low levels of fluorescent materials within the living organism (autofluorescence), and the ability to visualize in real time. There have been many advances in fluorescent dye chemistry, nanoplatform design, and optical instrumentation, which have increased the potential of NIR imaging for diagnosis, image-guided therapy, and precision medicine. The transition from conventional NIR imaging (NIR-I) to imaging in the second NIR window (NIR-II) has dramatically improved the quality of images produced (spatially and in terms of depth) of complex biological anatomy and the ongoing changes that occur in living organisms.

This review illustrates how the rational design of NIR-responsive nanoplatforms, through the integration of optimized NIR-fluorophores, biocompatible polymers, and surface engineering, has facilitated effective biological targeting and expanded the range of biomedical applications for NIR fluorescence imaging. Some strategies that enhance performance include improving circulation time with PEG, using targeting ligands to increase the specificity of the materials, and developing "smart" systems that can activate NIR imaging agents precisely when required.

The use of NIR fluorescence imaging has also increased image contrast, thereby improving overall effectiveness in cancer treatment, regenerative medicine, inflammation reduction, and biosensor detection and measurement. By incorporating several treatment modalities, such as photothermal and photodynamic therapies, NIR fluorescence imaging has become a platform technology in theranostics, enabling diagnosis, monitoring, therapeutic targeting, and achieving accurate therapeutic outcomes.

Even with current advancements in this field, many hurdles remain before full integration with other advanced tools (e.g., two-photon microscopy and mass spectrometry). Continued innovation in organic (nuclear) and inorganic fluorophores; expanded imaging windows (NIR-IIb, etc.); and advanced detector technology will provide opportunities for NFI to enhance current imaging capabilities.

The integration of NIR fluorescence imaging with multiple modalities, alongside automated image interpretation via Artificial Intelligence, will drive significant advancements in clinical workflows for real-time decision support and personalized treatment planning. Increasing numbers of procedures are being performed using NIR fluorescence imaging for immunotherapy monitoring, regenerative medicine, wearable medical device diagnosis, and minimally invasive surgeries, further establishing the clinical relevance of NIR imaging technology.

In conclusion, NIR fluorescence imaging is leading the charge in the next wave of biomedical imaging technology by bridging the core disciplines of optical science and the applied discipline of translational medicine. Collaboration across all disciplines to address current technological and regulatory barriers will be essential to maximizing this technology's overall potential in the clinical setting. As probe design, biological interfacing, and imaging advances continue to evolve, NIR fluorescence imaging will ultimately provide patients with guidance for examination and treatment through new, precision, patient-centered imaging technologies.

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Conflict of Interest

The authors declare no conflict of interest.

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