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Light-triggered nanocarriers for nucleic acid delivery

Baihao Huang[a,b], Stefaan C. De Smedt[a], Winnok H. De Vos[b] and Kevin Braeckmans[a]

[a]Laboratory of General Biochemistry and Physical Pharmacy, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium; [b]Laboratory of Cell Biology and Histology, Department of Veterinary Sciences, University of Antwerp, Antwerp, Belgium

ABSTRACT

Gene therapy has evolved into a clinically viable strategy, with several approved products demonstrating its therapeutic potential for genetic disorders, cancer, and infectious diseases, and it has ample applications in regenerative medicine. Its success depends on the ability to efficiently and specifically deliver therapeutic nucleic acids (NAs) into target cells. Although viral or chemical carriers have been used in pioneering applications, safety concerns, and variable delivery efficiencies have prompted the search for alternative delivery vehicles. Light-mediated strategies have gained particular interest due to their biocompatibility and ability to improve the intracellular delivery efficiency. In this review, we focus on recent advancements in the development of light-triggered NA delivery carriers and discuss how they can be designed to overcome specific intracellular barriers. Additionally, we discuss notable therapeutic applications and highlight challenges and opportunities for translating this technology to a clinical setting.

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1. Introduction

Nucleic acids (NAs) are among the most crucial biomolecules, as they encode and regulate the functional information of living organisms. Not surprisingly, researchers have developed strategies to alter the expression of disease-related genes through the administration of exogenous NAs to produce a therapeutic effect (Ma et al. 2020). These mainly include messenger RNA (mRNA), small interfering RNA (siRNA), and microRNA (miRNA) having their target in the cytoplasm, while plasmid DNA (pDNA) and gene-editing systems like clustered regularly interspaced short palindromic repeat-associated 9 (CRISPR–Cas9) often require nuclear delivery to exert their function. A recent success is the mRNA vaccines that were developed to combat the COVID-19 pandemic. However, to enable more widespread use of gene therapy, improvements are needed in delivering NAs to their target sites, which is related to the various extra- and intracellular barriers that NAs must cross to reach their destination (Dowdy 2017; Durymanov and Reineke 2018).

Due to NAs being large, negatively charged, hydrophilic, unstable against nucleases, and immunogenic, it is notoriously difficult for naked NAs to overcome those barriers. For instance, negatively charged NAs not only face interactions with positively charged serum proteins, leading to aggregation and clearance even before reaching the target cells, but also have difficulty crossing the plasma and endosomal membranes once they do. One solution is to package NAs in carriers, such as viral vectors, lipid-based carriers, polymers, and inorganic nanoparticles, to shield them from nuclease degradation and immune recognition (Mendes et al. 2022). Additionally, as illustrated in Figure 1, nanocarriers are designed to interact with the cell membrane and be internalized, usually through endocytosis. Once inside the cell, they become trapped in endosomes, which gradually mature into endo-lysosomes, exposing the carriers and NAs to degradative hydrolytic enzymes. Therefore, nanocarriers are engineered to escape from endosomes and release their NA cargo into the cytosol. In the case of plasmids or gene-editing nucleases, such as the CRISPR–Cas9 system, an additional translocation to the nucleus is necessary to access the genome and transcriptional machinery.

One intriguing approach to enhance the intracellular efficacy of nanocarriers is to make them responsive to external stimuli, such as light, ultrasound, and magnetic fields. This stimuli-responsive design not only improves the specificity of the nanocarriers by activating them at the disease site but also reduces unwanted side effects (Do et al. 2019). Light is a particularly attractive stimulus for a range of therapeutic applications as it enables localized activation with precise spatiotemporal control (Tao Y et al. 2020; Rapp and DeForest 2021). Light-sensitive moieties can be incorporated into carriers to provide the capacity to generate heat, reactive oxygen species (ROS), and even mechanical forces. As we will discuss in more detail in this review, these features can enhance their effectiveness in crossing (intra-)cellular barriers and improving the transfection efficiency. Specifically, we will

CONTACT Kevin Braeckmans kevin.braeckmans@ugent.be Laboratory of General Biochemistry and Physical Pharmacy, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, Ghent 9000, Belgium

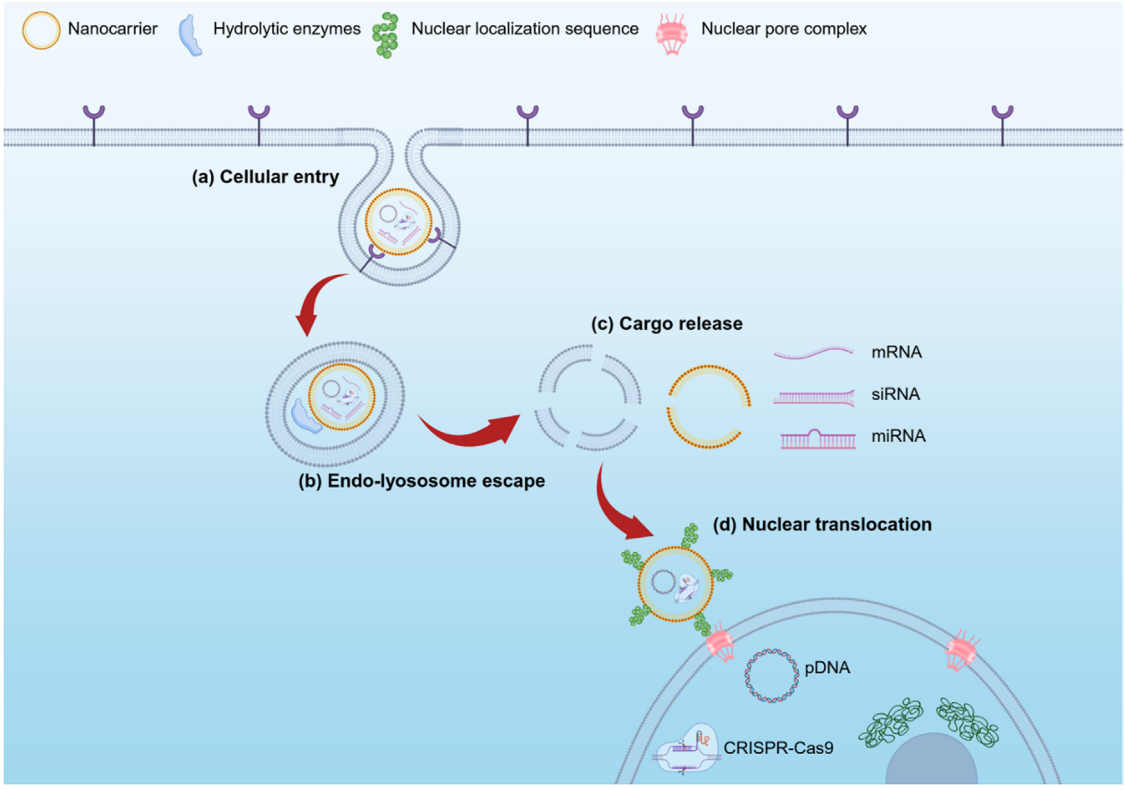

Figure 1. Schematic overview of (intra-)cellular barriers to NA delivery systems. (a) When NA therapeutics reach their target cells, they are typically internalized via endocytosis. (b) Once inside, they are inside endosomes which eventually mature into endo-lysosomes where the NAs may become degraded by hydrolytic enzymes. (c) To exert a therapeutic effect, the nanocarriers must release their NA cargo, such as mRNA, siRNA, or miRNA, from the endosomes into the cytoplasm. (d) For gene editing or pDNA-based therapies, additional nuclear translocation is required to access the genome and transcriptional machinery. Created by the authors with BioRender.

discuss how light can be used to enable better intracellular processing of carriers, including their uptake by cells (Section 2) and overcoming intracellular barriers, including release from endosomes (Section 3), enhanced nuclear translocation (Section 4), and more efficient release of NAs from the carriers (Section 5). Next, we consider the importance of using near-infrared (NIR) light for *in vivo* applications (Section 6), before we conclude with a discussion on notable applications of light-triggered NA delivery systems and considering what is needed to facilitate clinical translation (Section 7).

2. Cellular entry

Having reached the target cells, the first barrier that NA carriers must cross is the plasma membrane, a lipid bilayer with a multitude of embedded and associated proteins, carrying an overall negative charge. To enhance uptake by the cells, light has been used to either facilitate the direct translocation of NA carriers across the plasma membrane or to allow them to bind to the plasma membrane for subsequent endocytic uptake (Figure 2(A)) (Wrobel and Collins 1995; Ferreira et al. 2024). Direct translocation has been achieved using photothermal agents like gold nanoparticles (AuNPs), carbon nanotubes (CNTs), and polydopamine. Such photothermal nanocarriers can convert light into heat, which can increase membrane fluidity or even induce pore formation. These temporary structural changes in the plasma membrane have been shown to enable nanocarriers to translocate into the cell. One study used CNT-doped poly(dimethylsiloxane) modified with polyelectrolyte multilayers, onto which poly(ethyleneimine) (PEI)/pDNA complexes were bound by electrostatic interactions (Zhang Y et al. 2024). Heating of CNTs upon NIR irradiation resulted in the translocation of complexes into the cells, leading to a transfection efficiency of at least 95% in both adherent and suspension cells. Another study presented the use of a polydopamine-coated microporous spongy film loaded with PEI/DNA polyplexes. The photothermal properties of polydopamine were used to enhance the membrane permeability and polyplex internalization into the cells. Upon NIR irradiation, 85% of the treated human umbilical vein endothelial cells became transfected (Wang, Ren, et al. 2019; Wang, Thomas, et al. 2019).

Light can also be used to adapt the surface composition of nanocarriers, allowing control over their ability to bind to the plasma membrane and facilitate their endocytic uptake. For example, Zhang et al. described a nanocarrier for siRNA, composed of a gold nanorod core functionalized with biopolymers terminated with polyethylene glycol (PEG) and terpolymers conjugated with arginylglycylaspartic acid (RGD) peptides (Figure 2(B)) (Zhang P et al. 2016). Heating by NIR irradiation led to the shrinkage of the protective PEG corona and the exposure of RGD motifs, resulting in specific binding to integrin receptors on HeLa cells, followed by receptor-mediated endocytosis. The authors demonstrated high delivery efficiency of siRNA in target cells and the inhibition of tumor growth in a mouse model.

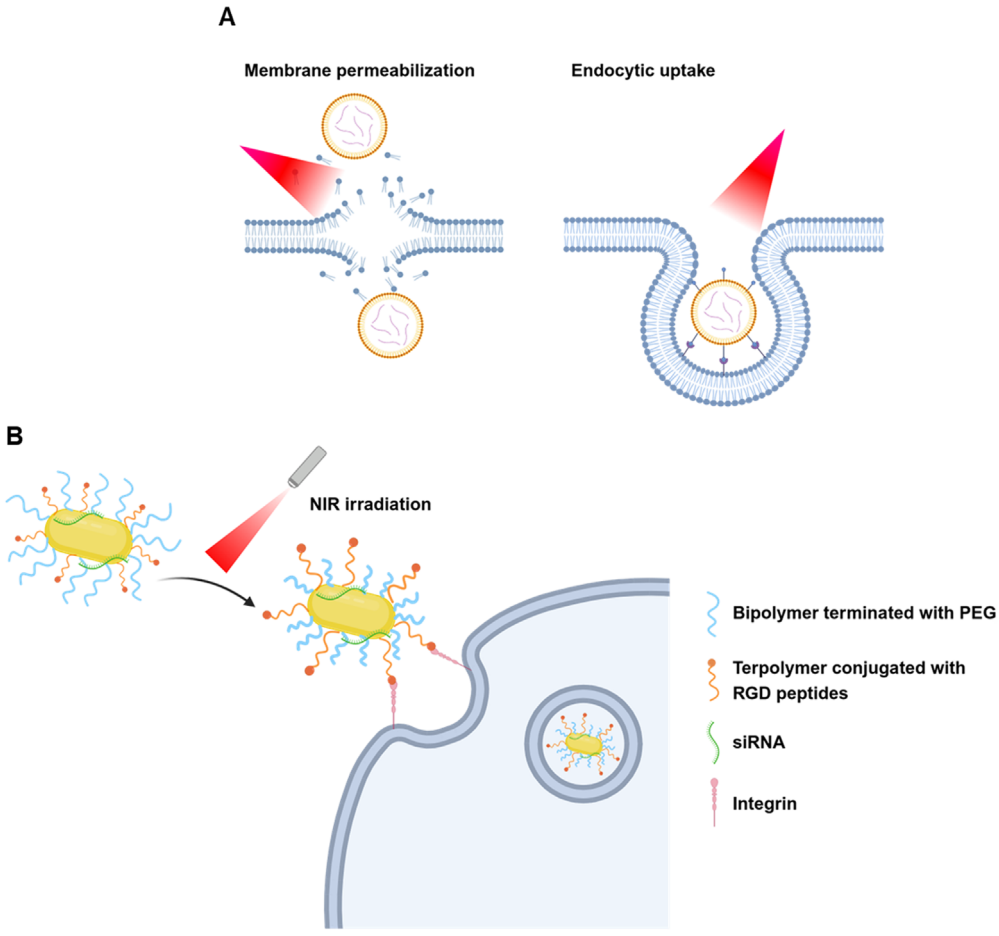

Figure 2. Light-mediated cellular entry of NA nanocarriers. (A) Light triggers have been used to facilitate direct translocation of NA carriers across the plasma membrane or to let them bind to the cell membrane for subsequent endocytic uptake. Created by the authors with BioRender. (B) NIR responsive gold nanorods were used as a nanocarrier for siRNA. Photothermal heating caused shrinkage of the PEG corona and the exposure of RGD peptides, facilitating binding to integrin and subsequent endocytic uptake. Adapted from Zhang P et al. (2016) with permission from the American Chemical Society.

3. Endo-lysosomal escape

After endocytic internalization, which is typical for most carrier-mediated delivery strategies, the NA-carriers will eventually end up in endosomes, which mature into late endosome and finally into lysosomes (Stewart et al. 2016). If they are not released from this compartment, the NAs are likely to be degraded enzymatically and by the low pH. Therefore, allowing the NAs to escape from the endo-lysosomal compartments is an important requirement for the success of gene therapies (Gilleron et al. 2013). Light can prove useful in enhancing endo-lysosomal escape through several effects, including photochemical, photothermal, and photomechanical effects.

Photochemical strategies rely on the formation of chemical species, such as ROS and carbon dioxide (CO_2), that oxidize lipids and proteins, increase membrane permeability or induce osmotic swelling, ultimately destabilizing the endosomal membrane (Wang H et al. 2015; Soe et al. 2020). One strategy is photochemical internalization (PCI), which destabilizes the endo-lysosomal membrane through the localized generation of a non-lethal dose of ROS produced by photosensitizers (Ji et al. 2019; Zhou J et al. 2020). For example, Chen et al. reported a liposomal carrier for antisense oligonucleotides (ASOs) loaded with the photosensitizer verteporfin (Chen W et al. 2017). Ultraviolet (UV) light activated verteporfin to generate ROS, destabilizing the endo-lysosomal membrane and facilitating the release of ASOs into the cytosol. After light-activated release, ASOs reduced the target mRNA levels (PAC1R and PACAP) and hindered the downstream differentiation of PC12 cells. With advancements in photosensitizer design, PCI has evolved from a purely *in vitro* tool into an *in vivo* therapeutic strategy (Nomoto et al. 2014). Mo et al. incorporated porphyrin-lipid conjugates into a clinically approved lipid nanoparticle (LNP) formulation, in which NIR irradiation leads to ROS generation by porphyrin (Mo et al. 2023). NIR-stimulated porphyrin-LNPs doubled the siRNA endosomal escape efficiency and enhanced gene silencing fourfold without increasing cytotoxicity in PC-3M-luc-C6 cells. Additionally, enhanced cargo release was achieved in prostate tumors *in vivo*.

Membrane destabilization by photothermal heating has also been explored to facilitate endo-lysosomal escape, as localized heating can cause membrane fluidization, phase transition and pore formation (Urban et al. 2009). For example, siRNAs targeting the heat shock protein 70 (Hsp70) gene were embedded in nanogels composed of DNA-grafted polycaprolactone via NA hybridization, and a photothermal polydopamine layer was coated on the nanogels (Ding et al. 2020). With continuous wave laser irradiation, the study

demonstrated thermally triggered endo-lysosomal escape and efficient gene silencing, resulting in significant tumor suppression in a HeLa tumor-bearing mouse model.

Light can also be used as a trigger to induce mechanical forces. Specifically, if the temperature of a photothermal nanoparticle in suspension reaches a critical threshold, the surrounding liquid will evaporate, forming an expanding vapor bubble that collapses when the nanoparticle's thermal energy is consumed (Ramon et al. 2021). The expansion and collapse of these vapor bubbles induce pressure waves that can be used to disrupt nearby barriers, such as the endosomal membrane. Fraire et al. developed a photothermal nanocarrier for siRNA delivery, using functionalized AuNPs to load siRNA by electrostatic interactions. In cancer cell lines, the authors performed a comparative study to determine whether photothermal heating or vapor bubble formation is the better approach to facilitate endosomal escape. They found vapor bubble-mediated endosomal escape was more consistent across cell types and led to higher siRNA transfection efficiency (~50–60%) compared to heat-mediated escape (~20–50%) (Fraire et al. 2020). The same group also tried a similar approach using carriers composed of cationic polymer JetPEI, pDNA, and anionic 10 nm AuNPs (Vermeulen et al. 2018). They found photothermal heating was insufficient to release pDNA from the endosomes, presumably because the pores were too small for pDNA, while vapor bubbles caused the pDNA molecules to be destroyed. This indicates that further work is needed on nanocarrier design to make this strategy viable for large NAs such as pDNA.

4. Nuclear translocation

DNA such as plasmids, but also some regulatory NAs and donor templates for homology directed repair, require translocation to the nucleus. It has been reported that less than 0.1% naked DNA molecules directly injected into the cytoplasm are trafficked to the nucleus. Also when incorporated into carriers, only 1% is trafficked to the nucleus (Pollard et al. 1998). Not surprisingly, light has been considered as a tool to guide nanocarriers toward the nucleus. For example, Gomez et al. reported on the use of red light-switchable protein phytochrome B coupled to a nuclear localization sequence (NLS), to promote nuclear translocation of adeno-associated viral (AAV) vector (Gomez et al. 2016). To achieve this, the AAVs were engineered to contain the phytochrome interacting factor 6 (PIF6), to which phytochrome B tagged with NLS could bind upon light exposure, resulting in increased translocation of AAVs into nucleus (Figure 3). This way, gene delivery efficiency could be enhanced over sixfold as compared to non-engineered AAVs. Another work by Huo et al. conjugated 2 nm AuNPs with triplex-forming oligonucleotides (POY2T) to bind and downregulate the *c-Myc* oncogene (Huo et al. 2019). To enhance retention and reduce exocytosis, AuNPs self-assembled into sunflower-like nanostructures, which disassembled upon NIR irradiation, releasing ultrasmall AuNPs for efficient nuclear translocation. This light-triggered system effectively silenced the oncogene and inhibited tumor growth in an MCF-7 mouse model.

In addition to conventional NLS-mediated nuclear import, photomechanical forces have been explored as a strategy to transiently disrupt the nuclear envelope (NE), which restricts the passage of large molecules (>40 kDa, approximately 5 nm in diameter) without the assistance of an NLS. Houthaeve et al. demonstrated that photomechanical forces could induce NE rupture, allowing the influx of cytosolic cargo (Houthaeve et al. 2018). However, whether this strategy can be effectively and safely applied to NA delivery remains to be demonstrated.

5. NA release from carriers

Apart from crossing physical barriers as mentioned above, another crucial factor is to release the NAs from the nanocarriers. NAs are usually encapsulated or complexed with nanocarriers via chemical conjugation or other intermolecular interactions, such as electrostatic interaction, hydrophobic interaction, hydrogen bonding, and Van der Waals forces. While tight encapsulation with a carrier may be beneficial for protecting the NAs against degradation and facilitating uptake in cells, it may be detrimental to the efficient release of the NAs inside the cells. Therefore, light has also been considered as a trigger to facilitate NA release from their nanocarriers via photochemical or photothermal mechanisms.

5.1. Photochemically induced release

During the design of nanocarrier systems, light-sensitive covalent bonds and chemical functional groups can be integrated to enable light-responsive unpacking. Upon light

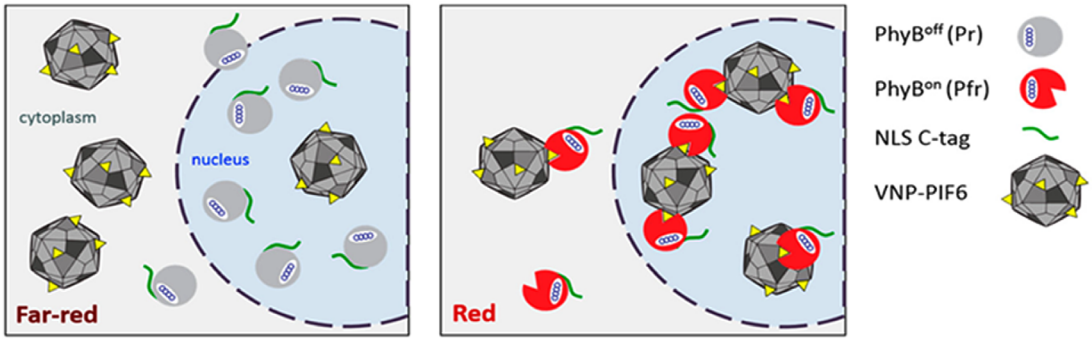

Figure 3. Schematic diagram of enhanced nuclear translocation of viral nanoparticles by light modulation. Left: phytochrome B tagged with NLS remained inactive under far-red light. Right: upon exposure to red light, phytochrome B-NLS bound to PIF6-modified AAVs, resulting in enhanced nuclear translocation. PhyB^{off} (Pr): inactivated phytochrome B. PhyB^{on} (Pr): activated phytochrome B. NLS C-tag: C-terminal His_6 tag nuclear localization sequence; VNP-PIF6: viral nanoparticles engineered to carry phytochrome interacting factor 6. Reprinted from Gomez et al. (2016) with permission from the American Chemical Society.

irradiation, cleavage of bonds, charge reversal, or isomerization of these structures alters or even disrupts the nanocarriers, accelerating the release of NAs (Figure 4) (Brown et al. 2013; Foster et al. 2015). Yang et al. prepared silica-coated upconversion nanoparticles (UCNPs) modified with cationic linkers for electrostatic siRNA loading, with the linkers being attached to the UCNP surface with photolabile *o*-nitrobenzyl ester groups (Yang et al. 2013). Upon NIR light irradiation, the linkers were cleaved by the upconverted UV light, liberating the siRNA from the nanoparticle surface. Another example is the release of miR-148b from silver nanoparticles in PAM212 cells, where 415 nm light irradiation induced the retro-Diels–Alder cleavage of the furan–maleimide linker (Liu et al. 2020). Fatieiev et al. instead used a light-triggered reversal in surface charge to release electrostatically loaded NAs (Fatieiev et al. 2015). *O*-nitrophenylene-ammonium moieties, which carry positive charges from their quaternary ammonium groups, were coupled to silsesquioxane nanoparticles. UV illumination converted these moieties into neutral nitrosophenylene-imine moieties, resulting in the release of DNA from the nanoparticle surface. Yet another option to destabilize the nanocarriers is the use of light-induced photoisomerization. Azobenzene derivatives, for instance, undergo *trans*-to-*cis* conformation upon UV light irradiation, lowering the affinity for NAs and thus promoting their release (Chaix et al. 2023).

Interestingly, photochemical reactions can achieve two goals at once, i.e. liberating NAs while also promoting endo/lysosomal escape. Yuan et al. presented a polymeric DNA vector incorporating a photosensitizer with aggregation-induced emission characteristics and oligoethylenimine conjugated via a ROS-cleavable aminoacrylate linker (Yuan et al. 2015). Upon light irradiation, the generated ROS disrupted the endosomal membrane and cleaved the polymer, facilitating DNA unpacking for efficient gene delivery. Another study by Chen et al. developed nanoparticles comprising a hydrophilic siRNA shell, a hydrophobic core composed of ASOs and a NIR photosensitizer (Chen L et al. 2021). An $^1O_2$-cleavable linker between siRNA and ASO was utilized to control the disassembly of this nanosystem into free NAs under NIR light irradiation. The $^1O_2$ generated by photosensitizer additionally ruptured the lysosome and promoted the cytosolic release of siRNA and ASO.

5.2. Photothermally induced release

Next to photochemically induced release, also photothermal heating has been used for light-triggered release (Kong et al. 2016; Kontturi et al. 2019). Early studies made use of gold

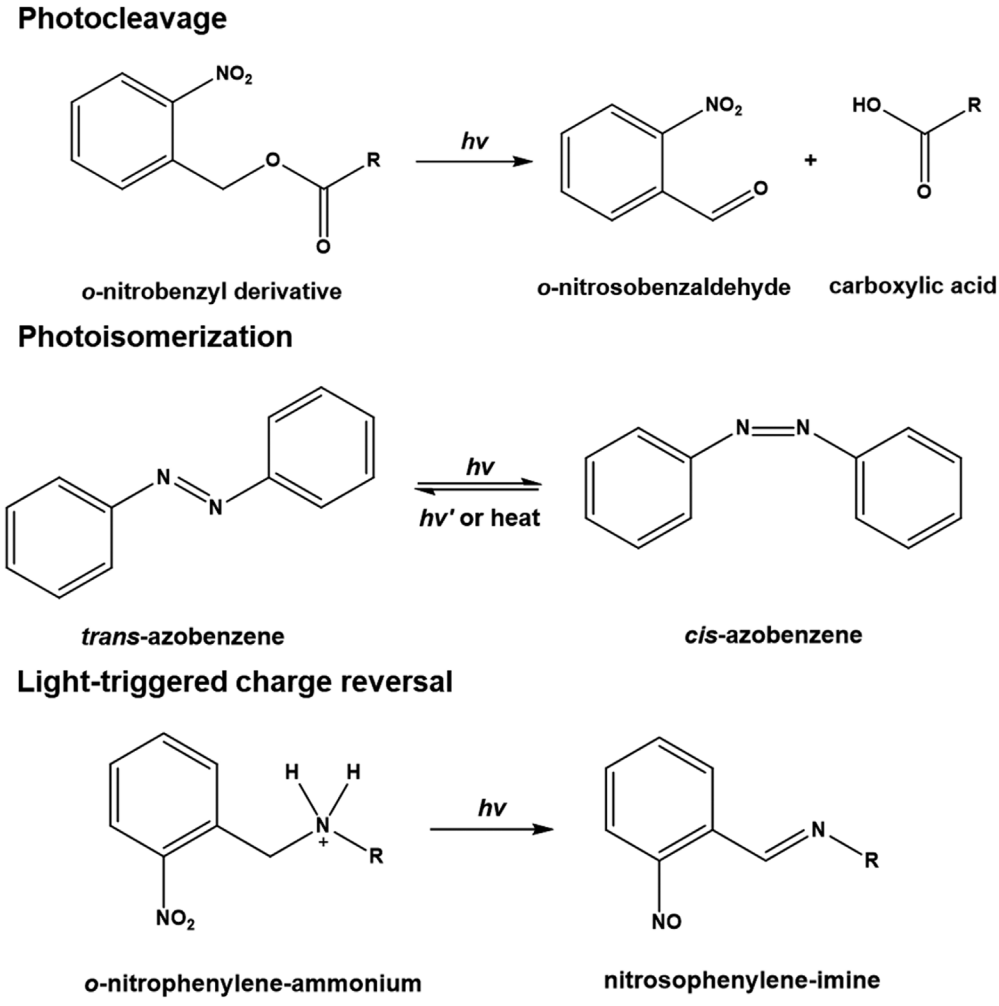

Figure 4. Examples of light-triggered NA release mechanisms via photocleavage, photoisomerization, and charge reversal. Created by the authors with ChemDraw.

nanorods onto which NAs were loaded via electrostatic interaction or gold–thiol bonds (Takahashi et al. 2005; Chen C-C et al. 2006; Wijaya et al. 2009). The melting and fusion of gold nanorods upon laser irradiation reshaped them into spheres and caused the NAs to be released. Alternatively, intermediary molecules can be attached to the surface of gold, which anchor NAs via noncovalent interactions and release them through a combination of photothermal heating and photon-induced hot electron transfer upon NIR light exposure (Huschka et al. 2011, 2012). The localized heating weakens electrostatic interactions between nanocarriers and NAs, while hot electron transfer modifies the charge of carrier molecules and further disrupts the binding. Expanding beyond gold-based systems, Roy et al. synthesized reduced graphene oxide (RGO) nanocomposites functionalized with quaternary ammonium-modified poly(allylamine hydrochloride) and a modified derivative, which enhanced DNA binding through increased positive charge (Roy and Jaiswal 2020). Upon NIR laser irradiation, the photothermal effect of RGO weakened the electrostatic interaction between DNA and the nanocomposite, facilitating DNA release. The use of NIR light allowed penetrating deeper into tissues compared to visible light, and the lack of cytotoxicity of these particles made them more attractive from a translational perspective.

To reduce the toxicity from prolonged irradiation and heating of photothermal materials, some groups have shown the benefit of pulsed laser illumination (Goodman et al. 2017; Riley et al. 2018). In this case, NA release is achieved using extremely short pulses of light (usually <10 ns), limiting the overall light dose and concomitant heating. Wang et al. used a femtosecond-pulsed NIR laser to trigger siRNA release with high precision from gold nanorods, where they introduced a dithiocarbamate anchoring strategy to load siRNA (Wang J, He, et al. 2018). Enhanced green fluorescent protein (EGFP) knockdown reached 70% efficiency in SKOV-3 cells upon laser treatment, while cell viability was unaffected. Fraire et al. also used pulsed laser irradiation to achieve both siRNA release from AuNP-based nanocarrier and efficient endosomal escape simultaneously (Fraire et al. 2020). By tuning the laser fluence, they triggered siRNA release via heating or vapor bubble formation, with vapor bubbles generating mechanical forces that ruptured endosomal membranes for enhanced cytosolic delivery.

6. Light penetration in biological tissues

The penetration of light through tissues is a crucial factor to consider when applying light-triggered NA delivery carriers *in vivo*. UV or visible light, although effective for photoactivation *in vitro*, are suboptimal for *in vivo* applications due to strong scattering and high absorption by biological tissues, next to potential phototoxicity (Juzenas et al. 2002; Tsang and Zhang 2024). While localized delivery systems such as gradient-index (GRIN) lenses or optical fibers can partially address these issues, broader, and less invasive *in vivo* applications benefit from the use of NIR light, offering improved tissue penetration and reduced phototoxicity (Figure 5(A)) (Smith et al. 2009; Hemmer et al. 2016).

Originally, the focus was primarily on light in the NIR-I window (700–900 nm), as many photothermal agents with established clinical safety profiles have strong absorption in the NIR-I region. As one example, Zhou et al. used ROS-responsive polymeric nanoparticles for the delivery of p53 mRNA using a clinically approved photosensitizer indocyanine green (ICG) (Zhou H et al. 2023). ROS generation via 808 nm light irradiation resulted in nanoparticle disassembly and p53 mRNA release. More recently, however, the NIR-II (1000–1700 nm) window also emerged as a suitable spectral window for *in vivo* applications (Yin et al. 2021; Zhao and Chen 2024). Compared to shorter wavelengths, NIR-II light suffers significantly less from scattering and absorption by biological tissues, enabling it to penetrate deeper into tissues (Figure 5(B)). In addition, reduced scattering of NIR-II light also improves the spatial resolution, which is important for precisely controllable NA delivery. For instance, Li et al. synthesized a lipid conjugated to a NIR-II polymethine dye, enabling light-to-heat conversion upon 1064 nm laser irradiation. This lipid–dye conjugate was incorporated in mRNA loaded LNPs (Li et al. 2023). Laser irradiation triggered endosomal escape, resulting in enhanced luciferase expression in the liver of mice. Another example is the study by Tao et al. who developed a nanocarrier composed of a gold 'nanooctopus' core and a mesoporous polydopamine shell loaded with CRISPR–Cas9 ribonucleoprotein (RNP) (Tao W et al. 2022). NIR-II irradiation significantly improved the release of CRISPR–Cas9 RNP due to the destabilization of non-covalent interactions. Furthermore, they demonstrated that the nanocarriers exhibited deeper tissue activation of the photothermal gold 'nanooctopus' core in the NIR-II window compared to NIR-I light, resulting in a higher tumor temperature upon NIR-II irradiation (Figure 5(C)).

7. Applications and preclinical translation

Intracellular delivery of NAs offers the opportunity to intervene at the very heart of pathogenic processes. It allows correcting genetic defects, modulating the expression of genes, or producing new gene products in a variety of disease settings. In this context, light-mediated delivery is rapidly gaining traction as a minimally invasive approach with translational potential (Table 1).

Topical tissues such as the skin, eyes, and ears, are attractive target tissues for light-triggered systems as they can be fairly easily treated with UV/visible light (Normand et al. 2005; Chang et al. 2019; Blersch et al. 2020). One study demonstrated light-activation of caged ASOs, which were chemically modified with 1-(2-nitrophenyl)ethyl photolabile groups, resulting in reduced miRNA-92a levels in the treated skin (Lucas et al. 2017). In a diabetic mouse model with delayed wound healing, light-activated ASOs accelerated wound closure, increased epithelial proliferation, and enhanced granulation tissue formation. In another case, NIR light induced the sequential release of two miRNAs from AuNPs, which were functionalized with DNA strands that sequestered the miRNAs through hybridization of complementary strands (Lino et al. 2018). The transfected human

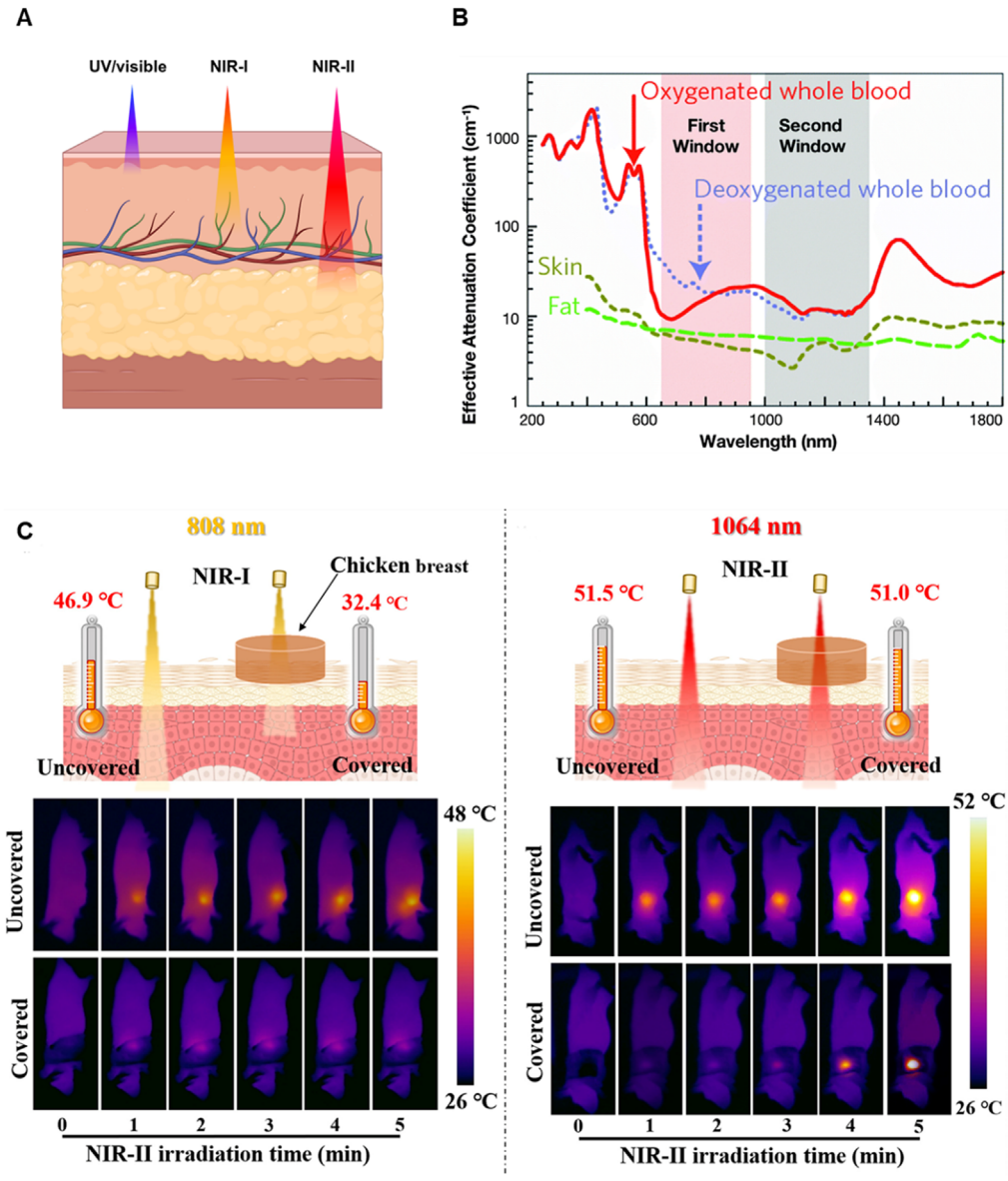

Figure 5. Comparison of tissue penetration under different light irradiation wavelengths. (A) Schematic illustration of the relative penetration depths of UV/visible, NIR-I, and NIR-II light through the tissue layers. Created by the authors with BioRender. (B) Optical NIR windows in biological tissues, showing the effective attenuation coefficient reflecting the absorption and scattering by oxygenated blood, deoxygenated blood, skin, and fatty tissue. Reprinted from Hemmer et al. (2016) with permission from the Royal Society of Chemistry. (C) *In vivo* comparison of the photothermal effects induced by NIR-I (808 nm) and NIR-II (1064 nm) laser irradiation, evaluated both without and with a biological barrier (chicken breast tissue). Reprinted from Tao W et al. (2022) with permission from Elsevier.

outgrowth endothelial cells improved the healing rates after being transplanted in a wound healing mouse model. In the context of eye treatment, several studies have confirmed that laser photocoagulation improved AAV vector-mediated gene delivery to retinal cells, which facilitated AAV uptake in multiple retinal layers (Lee et al. 2014, 2015).

Light-triggered NA delivery systems have also been developed for cancer therapy (Wang Z et al. 2017; Zhang Y et al. 2018; Zhang Z et al. 2019; Shi et al. 2020). For instance, in the study of Zhang et al., a NIR laser was used to regulate the surface composition of nanocarriers, thereby enhancing their uptake in irradiated tumor cells while minimizing uptake in non-irradiated healthy tissue (Zhang P et al. 2016). This selective uptake maximized the gene silencing efficiency of siRNA while minimizing side effects, enabling targeted therapy with high spatial precision. In another study, light-triggered gene editing was achieved by loading CRISPR–Cas9 plasmids onto AuNPs and releasing them into the cytosol via localized heating (Wang P, Zhang, et al. 2018). The *Plk-1* gene was successfully knocked out, leading to tumor growth inhibition in a mouse melanoma model. In another study, short-term light irradiation produced a non-lethal ROS dose that was sufficient to promote the endosomal escape of a plasmid expressing the p53 protein, which could induce the apoptosis of tumor cells. Subsequent longer light irradiation produced a lethal amount of ROS, providing a dual strategy to kill cancer cells (Han et al. 2015; Wang J, He, et al. 2018). Others have also developed nanocarriers containing both therapeutic NAs and classical chemotherapeutics. The team of Wu et al. elegantly showed that the effectiveness of doxorubicin (DOX) treatment could be enhanced by light-mediated delivery of short-hairpin RNA (shRNA) to reduce drug efflux by downregulating

Table 1. Preclinical trials of light mediated NA delivery.

Application	Cargo	Photosensitizer	Wavelength of light source	Functional barriers	Reference
Cancer therapy (HeLa xenograft model)	siRNA, ASO	Pheophorbide a	670 nm	Endo-lysosomal escape, cargo release	Chen L et al. (2021)
Cancer therapy (HeLa xenograft model)	siRNA	Polydopamine	808 nm	Endo-lysosomal escape	Ding et al. (2020)
Cancer therapy (SCC-7 xenograft model)	pDNA	Protoporphyrin IX	630 nm	Endo-lysosomal escape, cargo release	Han et al. (2015)
Cancer therapy (MCF-7 xenograft model)	DNA	AuNPs	808 nm	Cargo release, nuclear translocation	Huo et al. (2019)
Cancer therapy (MCF-7 xenograft model)	pDNA	CNTs	NIR	Cargo release	Kong et al. (2016)
Cancer therapy (cutaneous tumor model)	miRNA	Silver nanoparticles	415 nm	Cargo release	Liu et al. (2020)
Cancer therapy (HeLa xenograft model)	ASO	Aggregation-induced emission (AIE) polymer	White light	Endo-lysosomal escape	Shi et al. (2020)
Cancer therapy (Mia-paca-2 xenograft model)	CRISPR–Cas9 RNP	Gold 'nanooctopus'	1064 nm	Cargo release	Tao W et al. (2022)
Cancer therapy (prostate tumor xenograft model)	miRNA	ICG	NIR	Endo-lysosomal escape, cargo release	Wang H et al. (2015)
Cancer therapy (B16F10 xenograft model)	pDNA	Pheophytin a	661 nm	Endo-lysosomal escape, cargo release	Wang J, He, et al. (2018)
Cancer therapy (A375 xenograft model)	pDNA	AuNPs	514 nm	Endo-lysosomal escape, cargo release	Wang P, Zhang, et al. (2018)
Cancer therapy (U87MG xenograft model)	siRNA	Gold nanoshells	765 nm	Endo-lysosomal escape, cargo release	Wang Z et al. (2017)
Cancer therapy (HepG2/ADR xenograft model)	Short-hairpin RNA	–	405 nm	Cargo release	Wu et al. (2018)
Cancer therapy (Huh7 xenograft model)	CRISPR–Cas9 RNP	Silicene nanosheets	1064 nm	Endo-lysosomal escape, cargo release	Yin et al. (2021)
Cancer therapy (MCF-7 xenograft model)	ASO	PbS@CdS quantum dots	808 nm	Cargo release	Zhang P et al. (2023)
Cancer therapy (HeLa xenograft model)	siRNA	Gold nanorods	808 nm	Cellular uptake, endo-lysosomal escape	Zhang P et al. (2016)
Cancer therapy (HeLa xenograft model)	siRNA	UCNPs, hypocrellin A	980 nm	Endo-lysosomal escape, cargo release	Zhang Y et al. (2018)
Cancer therapy (Cal-27 xenograft model)	siRNA	UCNPs	980 and 808 nm	Endo-lysosomal escape, cargo release	Zhang Z et al. (2019)
Cancer therapy (H1299 xenograft model)	mRNA	ICG	808 nm	Cargo release	Zhou H et al. (2023)
Wound healing	siRNA, miRNA	–	365 nm	Cargo release	Blersch et al. (2020)
Wound healing	miRNA	Gold nanorods	780 nm	Endo-lysosomal escape, cargo release	Lino et al. (2018)
Wound healing	ASO	–	385 nm	Cargo release	Lucas et al. (2017)
Tissue regeneration	siRNA, miRNA	–	UV	Cargo release	Huynh et al. (2017)
Retinal	pDNA	–	532 nm	Uncertain	Lee et al. (2014, 2015)
Retinal	ASO	VP22 protein	532 nm	Cargo release	Normand et al. (2005)
Ear	DNA	–	808 nm	Uncertain	Chang et al. (2019)

P-glycoprotein (Wu et al. 2018). They developed a photoresponsive mesoporous silica nanoparticle system, which enabled sequential, wavelength-dependent release of shRNA and DOX using orthogonal light activation of 405 nm and 365 nm, respectively. In a subcutaneous HepG2/ADR xenograft model, sequential light-triggered release of shRNA and DOX led to significant tumor growth suppression.

8. Challenges and future directions

Despite remarkable progress in light-mediated NA delivery systems, they remain at a preclinical stage due to several challenges. First, many systems are still designed for stimulation by visible-to-NIR-I light, with limited tissue penetration due to significant scattering and absorption by water and chromophores like hemoglobin (Hong et al. 2017). Increasing the NIR-I light intensity can compensate this to some extent, but may cause undesirable tissue heating and related cytotoxic effects, including protein denaturation, membrane disruption, enzyme inactivation, and cell death via hyperthermia (Xu and Liang 2020). In addition, commonly used US Food and Drug Administration (FDA)-approved NIR fluorophores, such as ICG, suffer from poor photostability and are prone to degradation under irradiation, making them difficult for repeated irradiation and long-term storage. While light stimulation in the NIR-II window offers deeper tissue penetration, FDA-approved fluorophores for clinical applications are lacking. Further studies on the biodistribution and biocompatibility of NIR-II probes are warranted, with several studies currently underway (Li et al. 2020; Tang et al. 2025).

Another challenge to consider is the complexity and cost of producing light-triggered NA nanocarriers. Many of these

systems rely on intricate particle designs that may hinder scalability and clinical translation (Stavis et al. 2018). To achieve their intended functions, such nanocarriers often require precise control over size, shape, and functionalization, further increasing technical complexity. Moreover, the incorporation of rare or precious metals as photosensitizers significantly elevates production costs. Therefore, future research should prioritize the development of delivery platforms with simple designs that utilize biocompatible and cost-effective materials.

9. Conclusions

Light-triggered nanocarriers for NA delivery are set to enable more efficient and specific gene therapy due to their fine spatiotemporal control and tunability. They can enhance NA delivery at the intracellular level in various ways, including stimulating particle uptake, promoting endo-lysosomal escape, facilitating nuclear translocation, and enabling NA release. Ongoing research aims to further refine their selectivity, reduce off-target effects and combine multiple effects (such as release and uncoupling) simultaneously. A crucial bottleneck remains enhancing nuclear entry, but some pioneering results show promise. Clinical translation will require NIR-II light-responsive systems for deeper tissue penetration. Future work should also prioritize validating safety and scaling up the production of certified photothermal materials for *in vivo* applications. While much work remains to be done, light-triggered systems for NA delivery show great promise for effective and safe gene therapy.

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Author contributions

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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