

# Image-Guided Nanotherapeutic Delivery

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A certain class of multifunctional nanomaterials serves as a delivery platform for controlled drug release under image guidance. They have shown significant therapeutic potential and broad applications whereas their design specifics remain a subject of continued interest primarily due to multifunctional factors involved, ranging from nanomaterial properties, imaging modalities, and therapeutic agents to activation strategies.

Image-Guided Nanotherapeutic Delivery

Activation Strategies

Therapeutic nanomaterials

Imaging Modality

Controlled Release

Photodynamic Therapy

Photothermal Activation

## 1. Introduction

Over recent decades, nanoscale therapeutic systems have shown a rapid growth and significant contribution in image-guided delivery <sup>[1]</sup>. These systems are designed utilizing an integrative approach that combines both imaging and delivery functions in a single nanoscale entity. Their design is composed of three complementary modules that include an imaging probe, a therapeutic component, and a nanomaterial platform. Their imaging function plays a fundamental role in detecting and tracking the nanotherapeutic system following its administration (Figure 1) <sup>[2]</sup>. This helps to identify whether it is selectively distributed at its targeted site from a pharmacokinetic perspective and thus to determine an optimal timing for its therapeutic activation. Its therapeutic module is achieved with many strategies collectively by drug release <sup>[3][4][5][6]</sup>, photothermal activation <sup>[7]</sup>, photodynamic activation <sup>[8][9]</sup>, or the combination of these. Nanomaterial platforms are more variable in the range of their structure and function as illustrated in dendrimer polymers <sup>[10][11][12]</sup>, upconversion nanocrystals (UCN) <sup>[13][14][15]</sup>, metal-organic frameworks <sup>[16]</sup>, magnetic nanoparticles <sup>[17]</sup>, and hollow nanostructures <sup>[18]</sup>. This modular approach employed in nanotherapeutic design offers a combinatorial convenience and broad applicability in various therapeutic areas and personalized medicine <sup>[1]</sup>.

**Figure 1.** A schematic for image-guided nanotherapeutic delivery in tumors. A therapeutic nanomaterial is taken up in a diseased tissue via passive infiltration through leaky blood vessels or active biomarker targeting, imaged and therapeutically activated by endogenous factors or external stimulation [2].

**Therapeutic Activation.** Effectiveness of therapeutic strategies employed in image-guided delivery is dependent on the types of activation mechanism. Such activation strategies involve stimulations by either endogenous factors (pH, glutathione) [19][20] or external stimuli including light [6][3][4][5], ultrasound (US) [21][22][23], alternating magnetic field [5][17], or electric field [24]. These stimuli provide various mechanisms applicable for therapeutic activation including drug release that occurs through linker cleavage, nanomaterial disassembly, or gate opening. These strategies are described along with design factors involved in the selection and integration of imaging probes, payloads, and linkers to nanomaterials. Of particular attention is their individual role in therapeutic activation that occurs via stimulus-controlled linker cleavage, nanomaterial degradation, or induction of porosity.

**Imaging Modality.** Another important aspect considered here relates to how therapeutic strategies are integrated with imaging modalities. For this purpose, delivery systems need to be designed for their imaging capability, which is achieved with ultrasound (US), magnetic resonance imaging (MRI), magnetic particle imaging (MPI), thermal imaging, photoacoustic imaging (PAI), X-ray computed tomography (CT), γ-ray positron emission tomography (PET), or single photon-emission computerized tomography (SPECT). It should be noted that these imaging methods have been described individually and comprehensively in several review articles [25][26][27][28][29][30][31], including those focused on optical [32], magnetic resonance [33], magnetic particle [34][35], photothermal [36], photoacoustic [37], and ultrasound [38].

Briefly, nanoscale systems are engineered for image-guided delivery through modular assembly. They are variable in modular principles, design characteristics, and activation strategies. Identifying a strategy for most optimal

therapeutic efficacy remains an objective of significant interest [39].

## 2. Critical Aspects in Image-Guided Nanotherapeutic Delivery

As to nanotherapeutic systems developed for image-guided delivery, some of their mechanisms in therapeutic activation are attributed to cellular and pathophysiological factors, primarily low pH conditions [40][33][41] or elevated glutathione (GSH) levels [42]. Other mechanisms involve external stimulations which are more actively controlled via light-triggered linker cleavage [43][44][45][46][12], disassembly [47][48][49][50][51][52][53][54][55], pore gating [56][57][58], photothermal activation [36][59][60], photodynamic activation [61][62][63], US-mediated disassembly [64][65][66], hyperthermia [67], electroporation [68], and magnetic thermal activation [69]. Developing these activation strategies is making a significant impact on advancing knowledge and creating a new capability in nanotherapeutic delivery systems.

It is also worth noting current limitations associated with activation strategies. The degree of spatial resolution conferred by each activation strategy is variable as it is defined by the perimeter of its stimulus. Some strategies characterized by US, electromagnetic field, or thermal stimulation show relatively lower precision in spatiotemporal control compared to light activation. On the other hand, light shows a lower level of tissue penetration compared to US or electromagnetic stimulation [70]. This light limitation is currently addressed using an optical technique that allows tissue bypassing in which laser irradiation is delivered through a catheter inserted in a needle injected in tissue [71].

Another critical aspect which is of broad interest involves how to achieve specific nanomaterial uptake and localization in targeted cells only. Many systems discussed here are designed for tumor uptake via enhanced permeation and retention (EPR) [72], a passive targeting strategy that facilitates particle infiltration through leaky vessels in tumors (Figure 1). However, this passive targeting is not applicable for distinguishing specific tumor biomarkers or targeted binding and uptake at specific biomarker-overexpressing tumor cells. This lack of specificity is achieved otherwise by an active targeting strategy [73][74][4] in which a drug-loaded nanomaterial is functionalized through multivalent conjugation with a target-specific ligand or antibody. This active targeting has been applied to a few tumor biomarkers that include folate receptor (FAR) [60][65][41],  $\alpha_v\beta_3$  integrin [75][76][77][78], IGF1 receptor [79], epidermal growth factor receptor (EGFR) [80], CD105 [81], CCR5 [82], and nucleolin [40]. It would be equally applicable to other promising but less explored biomarkers that include prostate-specific membrane antigen (PSMA) receptors [83], Her2 [84], riboflavin receptors [85][86], and transferrin receptors [87] for brain delivery. In brief, multivalent ligand conjugation serves as an important strategy in the design of actively targeted systems.

Finally, clinical translation of nanotherapeutic agents is associated with significant challenges due to their multifunctional design, difficulty in synthetic scalability, and paucity of efficient clinical devices needed for their optimal activation. Nevertheless, they show a growing potential as evident with numerous types of nanotherapeutic agents either approved or advanced to clinical studies [88]. Of those, release control by endogenous factors is most often engaged as shown in poly(lactic acid-co-glycolic acid) (PLGA) nanoparticles (NPs) encapsulated with leuprolide (Eligard®) [89], albumin NPs bound with paclitaxel (Abraxane®) [90], and liposomes encapsulated with

doxorubicin (Doxil®) [91], mifamurtide (Mepact®) [92], vincristine (Marqibo®) [93], or irinotecan (Onivyde®) [94]. Thermal control of drug release is also successfully applied in heat-sensitive liposomes loaded with doxorubicin (ThermoDox®) [95]. Clinical development of photoactivated nanotherapeutics has been relatively slower but was already demonstrated by photodynamic therapy (PDT)-based verteporfin liposome (Visudyne®), which is approved for age-related macular degeneration and is currently being investigated for locally advanced pancreatic cancer [96] [97]. This strategy is also applicable in topical and superficial treatments as illustrated with PDT nanoemulsion (BF-200) [98], a topical agent investigated for treating actinic keratosis. In summary, nanotherapeutic activation strategies are currently being evaluated for their clinical translation [88][39].

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