

Review



In Vivo Assembly and Disassembly of Nanoparticles: Recent Advances for Tumor Imaging and Treatment

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Abstract: Nanoparticles have been extensively employed for early cancer diagnosis and treatment due to their favorable optical, magnetic, and radioactive properties. As carriers, they can also attain targeted delivery and controlled drug release, thus improving therapeutic efficacy. However, simultaneously reconciling tumor-targeting enrichment efficiency, tunable collective properties, and metabolic clearance remains a formidable challenge in tumor imaging and therapy. Recently, responsive assembly and disassembly strategies that exploit characteristics of the tumor microenvironment have opened new avenues to address this challenge. On the one hand, *in vivo* assembly and disassembly of nanoparticles can optimize their biodistribution and metabolism, sequentially promoting tumor-targeted accumulation and systemic clearance. On the other hand, the physicochemical properties of nanoparticles are precisely modulated by changes in size and structure during the assembly and disassembly process, thus improving tumor theranostic performance. Although several reviews on size-tunable nanomaterials were published, they mainly focused on how size variations of nanomaterials influence their biological effects, such as enhanced penetration, increased retention, and accelerated elimination. Little attention has been paid to the size-dependent changes in the intrinsic properties (e.g., optical, magnetic, and radioactive properties) of nanomaterials, particularly inorganic nanomaterials, and the biological application of such changes. In this work, we review the *in vivo* assembly and disassembly of several types of inorganic nanoparticles and their applications in tumor imaging and treatment.

Keywords: nanoparticles; assembly; disassembly; tumor imaging; tumor therapy

1. Introduction

Cancer, a malignant neoplasm, is a devastating disease that severely threatens human health and substantially diminishes patients' quality of life. In recent years, the rapid progress of nanotechnology has driven the advance of functional nanoparticles, which—owing to their exceptional physicochemical properties, including tunable sizes, facile surface modification, passive tumor-targeting capability, and excellent optical, electrical, and magnetic characteristics—have demonstrated remarkable advantages in tumor-targeted delivery, *in situ* imaging, and precision therapy [1]. Current studies show that nanocarrier systems can efficiently deliver drugs, genes, and contrast agents through passive targeting. To date, the US Food and Drug Administration (FDA) has approved several nanomedicines for clinical cancer therapy [2]. Moreover, inorganic nanoparticles with outstanding



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photophysical properties (e.g., near-infrared absorption, efficient photothermal conversion, and photoluminescence) have further promoted the advancement of imaging and therapeutic modalities such as photoacoustic imaging, fluorescence imaging, photodynamic therapy, and photothermal therapy [3]. Despite these attractive features, the clinical translation of such nanoreagents still faces two major scientific challenges. First, tumor-targeting efficiency remains critically low: systemically administered nanoparticles typically achieve an intratumoral accumulation efficiency of only 0.7% [4,5], resulting in insufficient therapeutic doses and inadequate imaging signal-to-noise ratios, which severely compromise diagnostic and therapeutic efficacy. Second, the biocompatibility of nanomaterials poses a significant bottleneck for clinical translation, as potential long-term *in vivo* retention may cause metabolic disturbances and toxicity risks.

Therefore, researchers have systematically explored a range of strategies, including size regulation, morphological design, surface functionalization, and optimization of nanoparticle mechanical properties. Among these, the size effect—one of the most critical attributes of nanoparticles—governs their *in vivo* fate through multiple size-dependent processes: systemic circulation kinetics, organ biodistribution, tumor tissue penetration, cellular uptake efficiency, subcellular localization, and degradation and metabolic rates [6]. Recent studies have revealed that the compact extracellular matrix, aberrant vasculature, high interstitial fluid pressure, phagocytic cell uptake, and renal clearance within the tumor microenvironment collectively form a complex biological barrier system [5]. These pathological features give rise to a central dilemma in the field of nano-delivery. On one hand, larger nanoparticles (>50 nm) are easily sequestered by the reticuloendothelial system and struggle to penetrate deep into tumor tissues; however, their prolonged retention in tumors and other tissues increases tumor accumulation while also raising biosafety hazards. On the other hand, smaller nanoparticles (<10 nm), despite their extended circulation time and superior tissue penetration, suffer from insufficient intratumoral retention due to factors such as interstitial fluid washout, thereby compromising their accumulation efficacy. This “penetration–retention” paradox, dictated by the nanoparticle size effect, severely limits the diagnostic and therapeutic performance of conventional nanosystems.

Recently, *in vivo* assembly and disassembly strategies based on tumor microenvironment (TME) characteristics have opened new avenues to address this challenge [7–9]. Here, *in vivo* assembly refers to the process by which systemically administered nanoparticles spontaneously or stimulus-responsively organize into higher-order particulate structures (typically 50–1000 nm) within the physiological environment of a living organism (i.e., in the bloodstream, tumor tissue, or other tissue compartments), while *in vivo* disassembly of nanoparticles is the reverse process: pre-formed nanoparticles by assembly of small-sized nanoparticles administered systemically dissociate into primary building blocks in a living organism, triggered by physiological or pathological cues. The core design rationale comprises two key aspects. First, tumor-specific *in situ* assembly: utilizing exogenous physical stimuli (e.g., light and ultrasound) or endogenous TME cues (e.g., acidity, disease-associated enzymes, microRNAs, and redox species) to trigger the assembly of ligand-engineered small-sized nanoparticles (such as gold nanoparticles [10–12], CuS [13], and gold nanoclusters (AuNCs) [14–16]), thereby achieving a transition from small particles to larger aggregates. This strategy fully exploits the superior tumor-penetrating capability of small monodisperse nanoparticles and the enhanced retention of large aggregates, thereby improving intratumoral accumulation and retention for augmented theranostic efficacy. From a physicochemical perspective, the aggregation effect can synergistically amplify photothermal, photoacoustic, or luminescence signals, further improving theranostic outcomes. Second, controlled disassembly in the tumor region: triggered by external stimuli or internal biomarkers, the nanoaggregates dissociate into small-sized nanoparticles that can either enhance imaging signals or be rapidly eliminated from the body. Notably, the kidneys are crucial excretory organs, with glomerular basement membrane filtration pores measuring 4–6 nm. Theoretical calculations and experimental studies have confirmed that nanoparticles with hydrodynamic diameters below 6 nm undergo rapid glomerular filtration (clearance half-life < 24 h), substantially reducing systemic toxicity risks [17–20].

In this review, we summarize assembly, disassembly, and assembly–disassembly cascade strategies of various inorganic nanoparticles for tumor imaging and treatment. The discussion is organized by nanoparticle type, including gold nanoparticles, CuS nanoparticles, metal nanoclusters, iron oxide nanoparticles (IONPs), lanthanide-doped nanoparticles, and carbon-based nanoparticles, among others, and the underlying biochemical mechanisms are examined. Besides enhanced penetration and retention, we place special emphasis on tunable collective properties. Assembly strategies can be employed to enhance tumor retention and theranostic performance (e.g., photoacoustic imaging (PA), photothermal therapy (PTT), surface-enhanced Raman scattering, radiation therapy, magnetic resonance imaging (MRI), and fluorescence), while disassembly strategies offer distinct advantages in nuclear uptake, deep penetration, rapid elimination, enhanced MRI, and enhanced fluorescence (Figure 1). We then highlight key challenges that *in vivo* assembly and disassembly strategies currently face, and finally provide perspectives and future directions for enhancing the efficiency of tumor imaging and treatment.

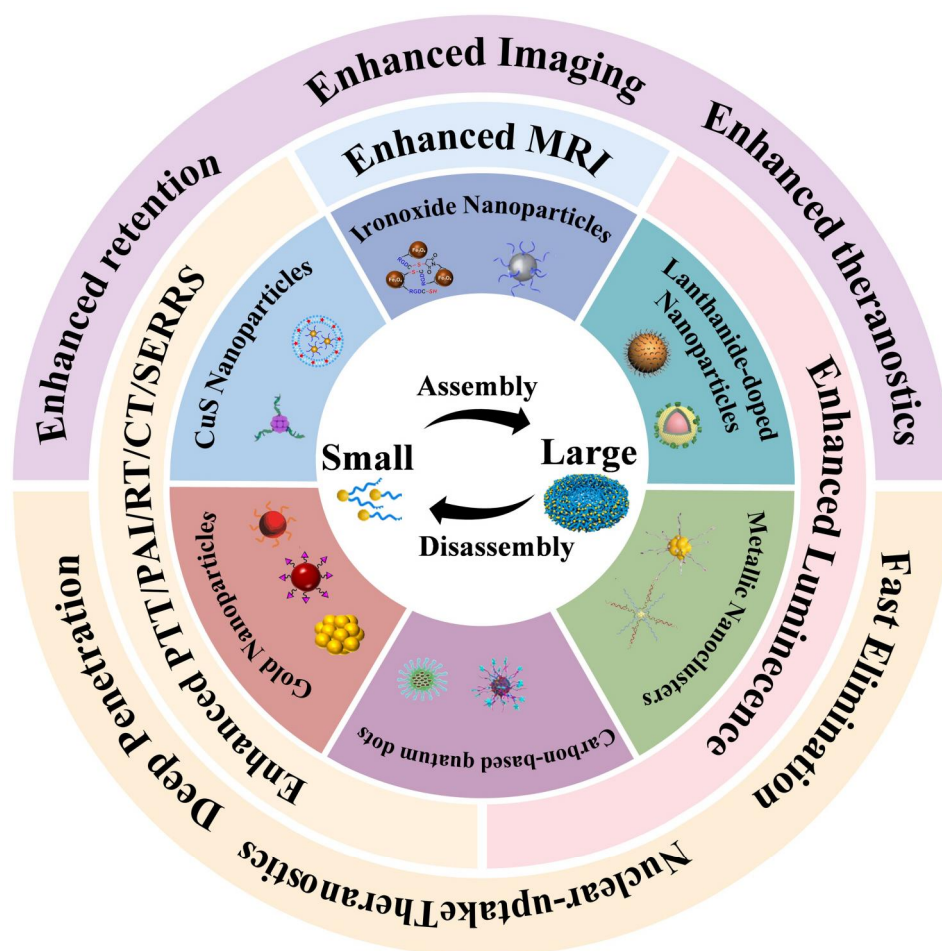


Figure 1. Scheme of nanoparticle assembly and disassembly strategy for tumor theranostics.

2. Tunable Collective Properties of Inorganic Nanoparticles

The structural and size modulation of inorganic nanomaterials not only profoundly influences their interactions with biological systems, but also directly dictates their tunable collective properties. Taking noble metal and semiconductor nanomaterials as examples, their optical performance and theranostic efficacy are intrinsically governed by particle size and aggregation state. For instance, the localized surface plasmon resonance (LSPR) of gold nanoparticles (AuNPs) in the first near-infrared (NIR I) region (750–900 nm) exhibits pronounced size dependence: when the particle size is below 50 nm, limited NIR absorption constrains photothermal conversion efficiency. However, tumor microenvironment-induced aggregation not only redshifts and intensifies the LSPR absorption peak but also improves tumor retention, synergistically enhancing both PTT and PAI [10–12]. Compared with NIR-I nanomaterials, CuS nanoparticles have attracted extensive attention due to their wide absorption in the second near-infrared (NIR-II) window (900–1350 nm). NIR-II lasers afford deeper tissue penetration (up to 3 cm) and a higher maximum acceptable exposure (1.0 W/cm²). Nevertheless, the NIR-II absorption of CuS nanoparticles is also size-limited. Experimental results show that reducing the particle size to 5 nm causes a 60% decline in the absorption cross-section. The *in-situ* assembly strategy simultaneously enhances intratumoral accumulation and retention and boosts NIR-II photothermal conversion capability, offering a promising approach for the diagnosis and therapy of deep-seated tumors [13]. Even smaller gold species, such as gold nanoclusters (AuNCs) with diameters below 2 nm, hold unique advantages for near-infrared fluorescence imaging owing to their molecule-like optical properties [14]. Nevertheless, their practical application as NIR-I or NIR-II fluorescence contrast agents is hindered by relatively low fluorescence quantum yields and rapid metabolic clearance. To overcome this bottleneck, self-assembly aggregation strategies provide a straightforward and versatile solution—amplifying fluorescence emission through the aggregation-induced emission (AIE) effect while optimizing biodistribution via size modulation [15]. As illustrated above, the tunable collective properties vary significantly among different types of inorganic nanoparticles. Accordingly, this review focuses on six representative classes: gold nanoparticles, CuS nanoparticles, metal nanoclusters, iron oxide nanoparticles (IONPs), lanthanide-doped nanoparticles, and carbon-based nanoparticles.

3. Gold Nanoparticles (AuNPs)

3.1. *In Vivo* Assembly of AuNPs for Enhanced Tumor Theranostics

Gold nanoparticles (AuNPs) have been widely investigated as contrast agents for various biomedical imaging modalities—including PAI, computed tomography (CT), and surface-enhanced resonance Raman scattering (SERRS) imaging—and as therapeutic agents for PTT and radiotherapy (RT), owing to their exceptional physicochemical properties, biocompatibility, and surface modifiability. Importantly, these photophysical characteristics and theranostic efficiency are directly governed by particle size and aggregation state. A variety of internal stimuli (e.g., acidity, enzymes, reactive oxygen species, and microRNAs) and external stimuli (e.g., ultrasound and light) can be harnessed to trigger the *in vivo* assembly of AuNPs. This assembly not only enhances the accumulation and retention of the nanoparticles, but also modulates their collective properties, thereby improving tumor theranostic outcomes (Table 1).

Table 1. A summary of *in vivo* assembly and disassembly strategies for gold nanoparticles (AuNPs).

Approaches	Property Changes	Stimuli	Key Enhanced Functions	References
Assembly	Size increasing	Legumain	Enhanced penetration and retention	[21,22]
		Furin	Enhanced penetration and retention	[23]
	Enhanced NIR absorption and photothermal conversion capability	Furin	Enhanced PTT	[13]
		MMP	Enhanced PTT	[24]
		GSH	Enhanced PTT	[25]
		miRNAs	Enhanced PTT	[12,26,27]
		Cathepsin B	Enhanced PTT	[28]
		Ultrasound	Enhanced PAI	[29]
		Light	Enhanced PAI and PTT	[10]
		Furin and low pH	Enhanced PAI and PTT	[30]
		HOCl	Enhanced PAI and PTT	[31]
		low pH	Enhanced PAI and PTT	[32]
		H ₂ O ₂	Enhanced PAI and PTT	[11]
	Increased X-ray attenuation	low pH	Enhanced CT	[33]
	Enhanced radiosensitization effect	low pH	Enhanced RT	[34,35]
	Enhanced local electromagnetic field	low pH	Enhanced SERRS	[36]
Disassembly	Size decreasing	Light	Enhanced nuclear-uptake	[37]
		low pH	Enhanced renal clearance and rapid excretion	[18–20,38,39]

3.1.1. *In Vivo* Assembly of AuNPs for Enhanced Accumulation and Retention

The stimuli-responsive assembly strategy for AuNPs can be leveraged to improve the accumulation and retention of nanomedicines within tumor tissues. Ruan et al. developed a legumain-responsive strategy to improve AuNP accumulation and retention in brain tumors [21]. The designed nanoplatfrom, AuNPs-A&C, comprises AuNPs-AK modified with the AK peptide (Ala-Ala-Asn-Cys-Lys) and AuNPs-CABT functionalized with 2-cyano-6-aminobenzothiazole (CABT). Upon exposure to the tumor-associated legumain, the AK peptide on the AuNPs-AK is cleaved by legumain and thus expose 1,2-thiolamino groups. These groups subsequently undergo a click cycloaddition with the cyano groups on neighboring AuNPs-CABT, driving the *in-situ* formation of AuNP aggregates. This aggregation effectively blocks nanoparticle exocytosis and minimizes backflow into the bloodstream, leading to significantly enhanced retention in mouse brain tumors. In order to further enhance the targeting ability, Ruan et al. modified the nanoplatfrom with an R8-RGD ligand, yielding AuNP-A&C-R [22]. The R8-RGD ligand facilitates receptor-mediated transcytosis through the blood–brain barrier and enables specific targeting of glioblastoma (GBM) cells via integrin $\alpha v \beta 3$. By integrating ligand-mediated active targeting with enzyme-directed *in situ* aggregation, the AuNP-A&C-R nanoplatfrom overcomes key delivery barriers in GBM treatment, achieving 1.72-fold and 2.66-fold higher GBM accumulation than AuNP-A&C and AuNP-R, respectively. Based on this bio-orthogonal click cycloaddition between the CABT cyano group and the 1,2-thiolamino group, Xie et al. further constructed a furin-responsive aggregating AuNP nanoplatfrom (AuNPs-D&H-R&C) that co-delivers doxorubicin and hydroxychloroquine to overcome chemoresistance in breast cancer [23].

3.1.2. *In Vivo* Assembly of AuNPs for Enhanced PTT

PTT is a cancer treatment modality that converts luminous energy into heat to elevate local tumor temperature [3]. Generally, the LSPR of AuNPs in the NIR region exhibits pronounced size dependence: when the particle size is below 50 nm, limited NIR absorption constrains photothermal conversion efficiency. By

increasing particle size or modifying nanostructure, the absorption peak can be red-shifted into the NIR-I region through the LSPR effect. Consequently, aggregation strategies can effectively enhance the PTT performance of gold nanomaterials [40,41]. As displayed in Figure 2A, Chen et al. developed a furin-instructed intracellular aggregation strategy [13]. They functionalized ~5 nm gold nanoparticles with a probe integrating a furin-cleavable RVRP peptide, a disulfide-caged cysteine, and a 2-cyanobenzothiazole moiety. Upon uptake by MDA-MB-468 cells, intracellular glutathione reduction and furin cleavage jointly trigger CBT-Cys click condensation, covalently crosslinking the particles into Golgi-localized aggregates. This aggregation markedly boosted near-infrared absorption and photothermal efficiency, achieving a temperature increase of 29.4 °C and an IC_{50} of 85.9 $\mu\text{g mL}^{-1}$ under NIR laser irradiation—far outperforming the non-aggregating control.

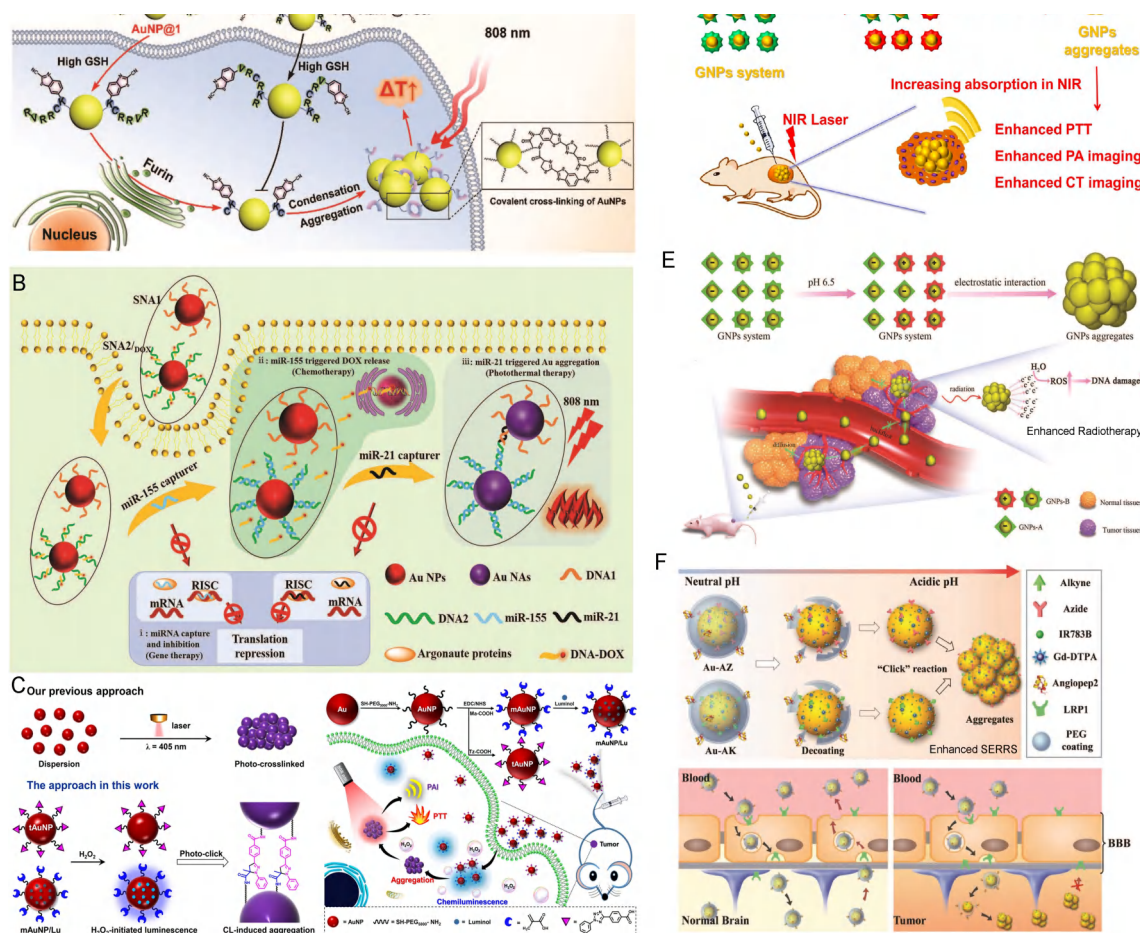


Figure 2. *In vivo* assembly of AuNPs for improved tumor theranostics. (A) Enzyme-triggered assembly of AuNPs for enhanced PTT. [13] Copyright 2020, John Wiley and Sons. (B) MicroRNA-triggered assembly of AuNPs for enhanced PTT. [12] Copyright 2022, John Wiley and Sons. (C) Light- and ROS-triggered assembly of AuNPs for enhanced PAI and PTT. [11] Copyright 2021, John Wiley and Sons. (D) Acid-triggered assembly of AuNPs for enhanced CT, PAI, and PTT. [33] Copyright 2015, American Chemical Society. (E) Acid-triggered assembly of AuNPs for enhanced RT. [34] Copyright 2019, John Wiley and Sons. (F) Acid-triggered assembly of AuNPs for enhanced SERRS. [36] Copyright 2017, John Wiley and Sons.

In addition to peptide ligands, deoxyribonucleic acid (DNA) has emerged as an ideal molecular engineering platform for constructing precisely controllable assembly systems in living organisms, owing to its unique advantages, including sequence programmability, precise molecular recognition, and the structural predictability of self-assembled nanostructures [42]. Through specific hydrogen bonding between A–T and G–C base pairs, single-stranded DNA molecules can undergo precise complementary pairing, enabling their self-assembly into nanostructures with well-defined spatial configurations. By rationally designing DNA sequences and modulating their conformations, synergistic responsiveness to multiple stimuli—including exogenous light and heat, or endogenous acidic pH, disease-associated enzymes, microRNAs, and redox signals—can be achieved [43–46]. By integrating programmable DNA with AuNPs, the nanoparticles can be assembled into superstructures via DNA hybridization in response to various biomarkers such as matrix metalloproteinase [24], glutathione [25], miRNAs [12,26,27], and cathepsin B [28]. For instance, Wang et al. engineered an intelligent spherical nucleic acid (SNA) nanosystem that

exploits endogenous oncogenic miRNAs for tumor-specific multimodal therapy [12]. As shown in Figure 2B, two types of SNAs were fabricated by conjugating AuNPs with different antisense oligonucleotides against oncogenic miR-155 and miR-21, with doxorubicin hybridized to the oligonucleotide shell of one SNA. Upon tumor accumulation, the system captures overexpressed miR-155 and miR-21, simultaneously inhibiting the oncogenic miRNAs for gene therapy, releasing doxorubicin for chemotherapy, and triggering AuNP aggregation to generate photothermal agents for *in situ* photothermal therapy.

3.1.3. *In Vivo* Assembly of AuNPs for Enhanced PAI

Besides converting absorbed NIR optical energy into heat for PTT, AuNPs can also transform optical energy into ultrasound for PAI. By leveraging optical contrast and ultrasonic resolution, PAI emerges as a compelling modality capable of providing distinctive structural and functional insights with a penetration depth reaching 5 cm [36]. Since the photoacoustic performance of contrast agents is also size-dependent, larger AuNPs or AuNP aggregates offer superior PAI performance compared to smaller ones [47]. Cheng et al. addressed the conflict between prolonged blood circulation and strong NIR absorption of AuNPs by designing photolabile AuNPs with diazirine-modified PEG ligands [10]. Upon 405 nm laser irradiation, the diazirine groups generate carbenes that covalently cross-link the small AuNPs (20.5 nm) into larger aggregates directly at the tumor site. This spatiotemporally controlled assembly shifts the plasmon resonance into the NIR region, endowing the aggregates with markedly enhanced photoacoustic signals and a photothermal conversion efficiency of 78.8%, thereby bridging a key gap in nanoparticle-based tumor theranostics.

To bypass the limited tissue penetration of external light, various endogenous stimuli-responsive assembly strategies for AuNP-based PAI have been developed. Cheng et al. engineered a gold nanoprobe, Au-RVRR, whose aggregation is exclusively driven by the cooperative effect of furin and low pH, enabling switch-on PAI and PTT of tumors [30]. Liu et al. designed a HOCl-activated aggregation strategy based on AuNPs co-functionalized with a polyethylene glycol ligand and an HOCl-responsive probe for combined PTT–PDT tumor treatment under PAI guidance [31]. Zhang et al. constructed zwitterionic AuNPs with mixed surface charges, harnessing the low pH of tumors to induce *in vivo* self-assembly for improved PAI and PTT outcomes. Zhang et al. developed mixed-charge zwitterionic surface-modified AuNPs that undergo pH-triggered *in vivo* self-assembly to enhance PAI and PTT [32]. Recently, Mao et al. exploited H₂O₂-initiated chemiluminescence to drive the aggregation of small-sized AuNPs, activating their theranostic properties [11]. As shown in Figure 2C, two types of AuNPs were constructed: tAuNP functionalized with 2,5-diphenyltetrazole, and mAuNP/Lu, in which luminol is adsorbed onto methacrylic acid-modified AuNPs. In the H₂O₂-overexpressing tumor microenvironment, mAuNP/Lu reacts with H₂O₂ to generate strong chemiluminescence, which locally triggers tetrazole-alkene cycloaddition between the two nanoparticles, leading to their covalent cross-linking and aggregation. This process enhances intratumoral retention and shifts the plasmon absorption into the NIR region, enabling activated PAI and effective PTT. This work harnesses tumor-endogenous H₂O₂ to produce an internal light stimulus that replaces external irradiation for nanoparticle assembly, offering a spatially selective and deep-tissue-feasible strategy for tumor theranostics.

3.1.4. *In Vivo* Assembly of AuNPs for Enhanced CT or RT

Gold's strong X-ray attenuation has inspired the development of various AuNP platforms as computed tomography (CT) contrast agents or radiosensitizers. Notably, particle aggregation further prolongs intratumoral retention and simultaneously boosts performance in both CT imaging and radiotherapy (RT). As illustrated in Figure 2D, Zhang et al. reported a pH-triggered assembly strategy based on two complementary peptide-conjugated AuNPs: one bearing negatively charged pentapeptides, and the other modified with a 2,3-dimethylmaleic anhydride-grafted peptide [33]. Once exposure to the acidic TME, the latter undergoes charge reversal from negative to positive, driving electrostatic crosslinking with the former and forming large aggregates that shift the plasmon absorption into the near-infrared region. This tumor-specific aggregation activates photothermal conversion and simultaneously enhances the contrast of CT, photoacoustic, and photothermal imaging, enabling effective photothermal tumor ablation with minimal off-target damage. Aggregate formation can also produce more ROS under gamma irradiation, thereby boosting RT efficacy. As shown in Figure 2E, this aggregation of AuNPs markedly amplifies the radiosensitization effect, achieving a sensitizer enhancement ratio of 1.730—far exceeding that of non-aggregating controls (~1.16) [34]. Luan et al. further designed a pH-triggered AuNP aggregation system (AuNPs-D-P-DA) for radiosensitization and synergistic chemoradiotherapy of esophageal cancer [35].

3.1.5. *In Vivo* Assembly of AuNPs for Enhanced SERRS

SERRS imaging has emerged as an attractive modality for precisely delineating tumors [48,49]. Particle aggregation generates a multitude of interparticle “hotspots”—nanogaps between neighboring AuNPs—which dramatically strengthen the local electromagnetic field and amplify the SERRS signal. Since larger aggregates harbor more hotspots, the degree of SERRS enhancement scales accordingly. Gao et al. developed a pair of blood–brain barrier-permeable gold nanoprobe that undergo acid-triggered self-assembly within the TME to activate SERRS signals for guiding brain-tumor surgery [36]. As shown in Figure 2F, the pair of nanoprobe, Au-AZ (functionalized with azide) and Au-AK (functionalized with alkyne), were both loaded with Raman reporters (IR783B) and shielded with a polyethylene glycol corona via acid-labile hydrazone bonds. In the acidic TME (pH 6.5), the hydrazone linkages are cut, shedding the PEG shielding layer and exposing the click functionalities, thereby promoting cycloaddition between the alkyne and azide groups and driving the formation of spherical nanoclusters with diameters up to ~200 nm. This acid-triggered aggregation generates numerous interparticle plasmonic hotspots that amplify the SERRS signal by up to ~20-fold.

3.2. Disassembly of AuNPs

3.2.1. Disassembly of AuNPs for Enhanced Nuclear Uptake

The nucleus houses genetic information and orchestrates cellular activities, making it central to tumor cell proliferation. Transporting drugs into this organelle is essential, as most therapeutic agents act specifically on intranuclear targets. Furthermore, nuclear delivery can effectively circumvent drug-resistance pathways, thereby overcoming multidrug resistance. Yet the nuclear envelope poses a formidable challenge, given that its pore complexes typically allow passage only below ~9 nm. Therefore, the most straightforward and potent strategy is to restrict nanoparticle size to under 9 nm, albeit at the potential cost of compromised systemic circulation and organ distribution. To address this contradiction, Huo et al. developed DNA-induced self-assembled gold–DNA “nanosunflowers” (~200 nm) that enable NIR-triggered disassembly into ultrasmall (~2 nm) gold nanoparticles for controlled oncogene silencing [37]. As illustrated in Figure 3A, the sunflower-like nanostructures are constructed by hybridizing 2-nm gold nanoparticles functionalized with a triple oligonucleotide (POY2T) targeting the c-myc oncogene with a complementary blocking strand (CA). This assembly yields strong NIR-I absorption centered at 767 nm and efficient photothermal conversion. Upon irradiation with a NIR laser, the local temperature rises above the DNA melting temperature (~41 °C), inducing the nanostructures to disassemble and release the 2-nm Au-POY2T nanoparticles, which can directly reach the nucleus and bind to the P2 promoter of c-myc to suppress its transcription (Figure 3B). Fluorescence imaging (Figure 3C) and bio-TEM images (Figure 3D) confirmed that light-triggered disassembly promotes nuclear uptake in MCF-7 cells. By controlling the preincubation time before 808-nm irradiation, both *in vitro* and *in vivo*, the extent of nanostructure internalization and, consequently, the gene-silencing efficacy can be precisely tuned, yielding c-myc mRNA suppression levels ranging from moderate (38.0% remaining) to profound (12.6% remaining) with correspondingly graduated antitumor effects.

3.2.2. Disassembly of AuNPs for Excretion

AuNPs possess multifunctional properties that suit a variety of biomedical imaging and therapeutic modalities, yet no gold-based agent has received U.S. Food and Drug Administration (FDA) clearance—partly due to unresolved questions surrounding excretion. FDA guidance stipulates that injected products, particularly diagnostic imaging agents, should be eliminated from the body within a reasonable period to prevent long-term retention. From a biological elimination standpoint, the kidneys function as the primary excretory route; the glomerular basement membrane harbors filtration pores of 4–6 nm, which inform the design criteria for nanoparticle size. Both theoretical analyses and experimental data have established that particles with hydrodynamic diameters under 6 nm undergo swift renal clearance (half-life < 24 h), markedly lowering the likelihood of systemic toxicity [50,51]. On the other hand, NIR absorbance and field enhancement scale with the dimensions of metallic nanoparticles. Consequently, most AuNP systems constructed for nanomedicine fall well above 50 nm, greatly exceeding the 6 nm limit for renal filtration. Large AuNPs are further favored for their extended blood residence and superior accumulation at diseased sites. Although such sizable particles typically show little or negligible acute toxicity upon systemic injection, they are sequestered within the reticuloendothelial compartments of the spleen and liver for months, generating hurdles for FDA acceptance and clinical adoption. Moreover, prolonged tissue retention of contrast agents can compromise follow-up imaging examinations. For greater translational promise, the mean particle diameter should remain below 6 nm to facilitate rapid renal

elimination and urinary excretion. Nevertheless, these ultrasmall particles often display poor tumor enrichment and unsatisfactory optical performance.

To address the above trade-off, stimuli-responsive disassembly methods have lately been designed to better harmonize nanoparticles' *in vivo* behaviors [52]. Generally, the small AuNPs (<5.5 nm, kidney-filterable) pre-assemble into large AuNP clusters (>50 nm) *in vitro* through biodegradable plasmonic liposomes [19], responsive polymers [20,38], or biodegradable silica matrices [53], followed by injection as a stable particle and systemic dissociation into primary building blocks in response to physiological or pathological cues. For instance, Yu et al. reported highly excretable gold supraclusters that resolve the long-standing trade-off between strong Raman scattering and efficient body clearance for *in vivo* Raman imaging [18]. As displayed in Figure 3E, the supraclusters are assembled from renally clearable 2.7 nm gold nanocluster building blocks through controlled cross-linking and conjugation of NIR resonant Raman dyes, achieving ultrahigh dye loading ($\sim 10^6$ dyes per particle) with fluorescence quenching by the metallic substrate. Despite moderate electromagnetic enhancement, their Raman brightness matches or exceeds that of conventional 60 nm Au-based SERS nanotags. pH-responsive stability enables the supraclusters to remain intact and active in acidic tumor microenvironments while dissociating into sub-5 nm nanoclusters under physiological conditions. As a result, the Raman signal at the tumor site is much stronger than in normal tissue (Figure 3F,G). Moreover, more than 73% of the gold is excreted within four months via hepatobiliary and renal pathways (Figure 3H–J), supporting the outstanding biocompatibility of this contrast agent.

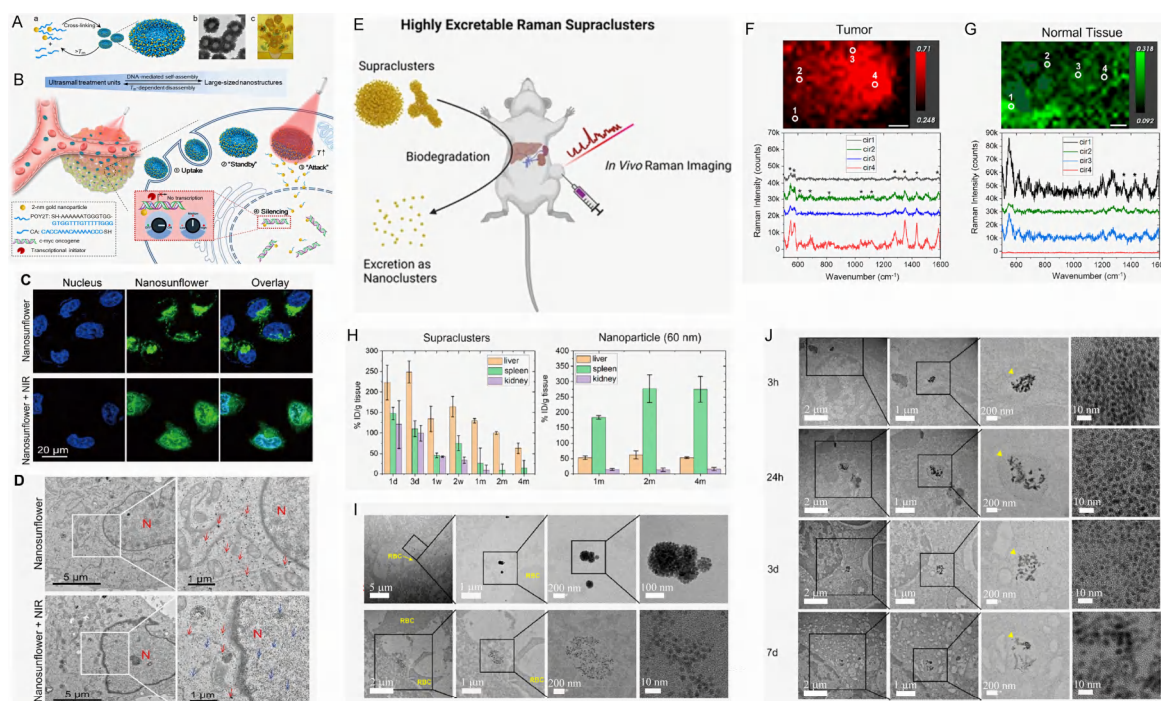


Figure 3. *In vivo* disassembly of AuNP assemblies for improved tumor theranostics. (A,B) Illustration of gold-DNA nanosunflowers undergoing disassembly to facilitate nuclear entry. (C) Confocal microscopy of FITC-labeled nanosunflowers (green) in MCF-7 cells before (upper) and after (lower) NIR irradiation; nuclei were counterstained with DAPI. (D) Bio-TEM micrographs showing the localization of large nanosunflowers (top, red arrow) in the cytoplasm and, after NIR exposure, the spread of liberated small NPs (bottom, blue arrow) into both cytoplasm and nucleus in MCF-7 cells. [37] Copyright, 2019, AAAS. (E) Depiction of spherical and branched gold supraclusters that degrade into excretable nanoclusters in the liver and spleen, enabling *in vivo* Raman tumor imaging. (F,G) *In vivo* Raman maps of supraclusters at the tumor site and in normal tissue (upper panels), together with representative Raman spectra taken from regions 1–4 (lower panels). * indicate the spectral peaks corresponding to the SQ740-Supracluster Raman spectrum. (H) Quantification of gold by ICP-OES, revealing the biodistribution of supraclusters (left) and nanoparticles in the liver, spleen, and kidneys (right). (I) TEM images of GSHE-Au supraclusters (upper row) and the dissociated nanoclusters (lower row) in the perivascular region of the liver. (J) TEM images of spleens harvested at 3 h, 24 h, 3 days, and 7 days after systemic injection of GSHDE-Au supraclusters, showing particle capture and evolution over time. [18] Copyright 2007, American Chemical Society.

4. Copper Sulfide (CuS) Nanoparticles

4.1. Disassembly of CuS for Enhanced Penetration

CuS nanoparticles have drawn considerable interest as candidates for PAI and PTT [39,54]. Their characteristic NIR absorption, centered near 1100 nm, arises from the LSPR of p-type carriers within vacancy-doped nanocrystals. Achieving deep tumor penetration is critical to improving therapeutic efficacy, yet the transport of nanomedicines into deep tumor regions is restricted by multiple biological obstacles, such as elevated interstitial fluid pressure and a compact extracellular matrix. In recent years, stimuli-responsive disassembly approaches have been exploited to increase nanoparticle penetration depth, taking advantage of the enhanced permeability of smaller particles [55–57]. For instance, Wang et al. developed an artificial base-directed topological single-stranded DNA encoding strategy for single-step, valence-controlled synthesis and programmable assembly of NIR-II molecular-like nanostructures for cancer theranostics [57]. As shown in Figure 4A, a chimeric DNA encoder (comprising a metal-binding template and a functional domain) enabled aqueous-phase synthesis of ultrasmall CuS nanoparticles with high NIR-II absorption via thymine–Cu²⁺ coordination. The incorporation of a “Y”-shaped artificial base allowed precise valence control (mono-/di-/trivalent), and the trivalent CuS nanodots were assembled into ~90 nm pH-responsive nanoaggregates (CuS-i) through i-motif linkers *in vitro*. These nanoaggregates remained stable at physiological pH but disassembled into ultrasmall nanodots in the acidic tumor microenvironment (Figure 4B,C,F). In contrast, the pH-nonresponsive control, CuS-n, remained intact under acidic conditions (Figure 4D,E,G). The CuS-i exhibited excellent photothermal conversion efficiency (Figure 4H). Moreover, CuS-i showed deeper penetration under acidic conditions (Figure 4I,J). In a 4T1-xenografted mouse model, CuS-i effectively accumulated at the tumor site (Figure 4K). Compared with CuS-n, CuS-i achieved deeper intratumoral penetration and generated higher temperatures under 1064 nm laser irradiation, owing to its pH-responsive disassembly (Figure 4L–P). This size switching conferred prolonged circulation, efficient tumor accumulation, and deep intratumoral penetration, enabling homogeneous photothermal heating and superior antitumor efficacy in 4T1 tumor models under 1064-nm irradiation.

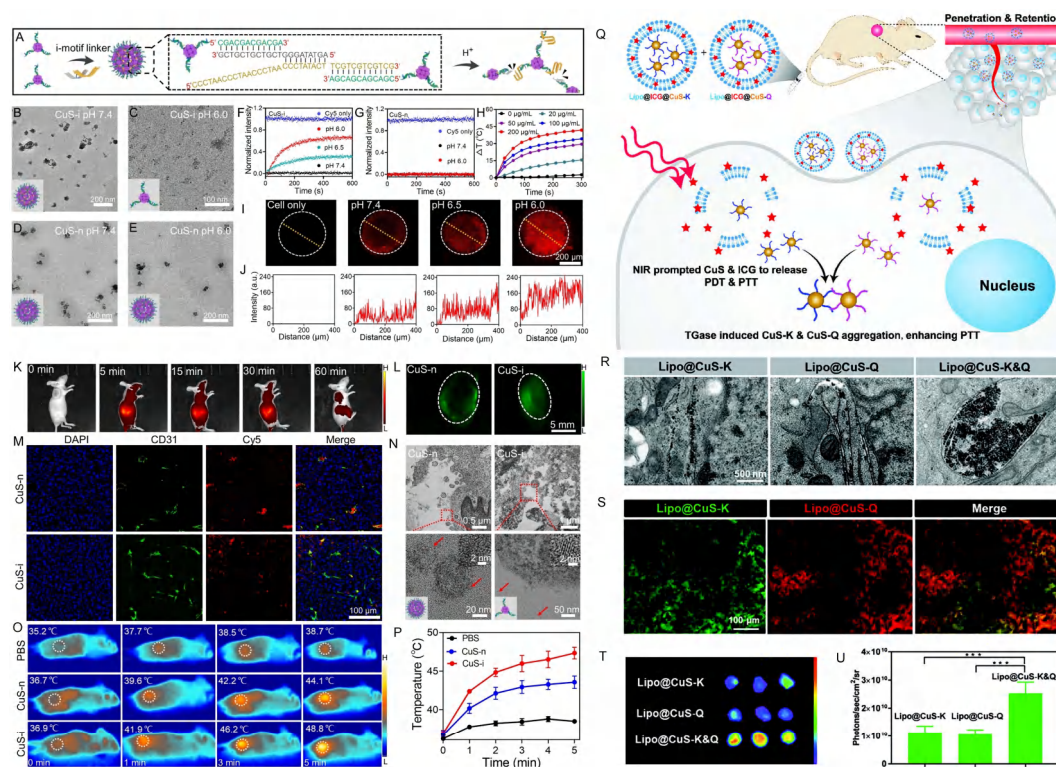


Figure 4. *In vivo* assembly and disassembly of CuS nanoparticles. (A) Schematic of the assembly and disassembly processes of DNA-encoded CuS NDs. (B,C) TEM images of CuS-i in PBS at pH 7.4 and 6.0, respectively. (D,E) TEM images of CuS-n in PBS at pH 7.4 and 6.0, respectively. (F,G) Disassembly kinetics of CuS-i and CuS-n across different pH values. (H) Temperature elevation of CuS-i at various concentrations under 1064 nm laser irradiation. (I) Confocal images showing the penetration of Cy5-labeled CuS-i in tumor spheroids at pH 7.4, 6.5, and 6.0. (J) Corresponding fluorescence intensity profiles from panel (I). (K) *In vivo* fluorescence imaging of a 4T1 tumor-bearing mouse at indicated time points after intravenous injection of Cy5-CuS-i. (L) PA images of 4T1 tumors excised from mice after intravenous injection of CuS-n and CuS-i. (M) Immunofluorescence staining of (N) CuS-n, (O) CuS-i, (P) Lipo@CuS-K, (Q) Lipo@CuS-Q, (R) Lipo@CuS-K&Q. (S) Confocal images of Lipo@CuS-K, Lipo@CuS-Q, and Merge. (T) Photothermal conversion efficiency of Lipo@CuS-K, Lipo@CuS-Q, and Lipo@CuS-K&Q. (U) Bar graph showing photothermal conversion efficiency for Lipo@CuS-K, Lipo@CuS-Q, and Lipo@CuS-K&Q.

tumor sections collected 1 h after intravenous injection of Cy5-CuS-n or Cy5-CuS-i. (N) TEM images of tumor tissues 1 h after intravenous injection of CuS-n and CuS-i. (O,P) Photographs and tumor temperature changes in mice injected with CuS-n or CuS-i, followed by 1064 nm irradiation for 5 min at 1 h post-injection. [57] Copyright 2024, John Wiley and Sons. (Q) Schematic of NIR- and TGase-triggered assembly/disassembly of CuS NPs for enhanced tumor penetration and retention. (R) TEM images of Lipo@CuS-K, Lipo@CuS-Q, and Lipo@CuS-K&Q NPs after incubation with A375 cells. (S) Co-localization of Lipo@CuS-K and Lipo@CuS-Q NPs in tumor tissues. (T,U) Representative images and quantitative analysis of aggregation and retention in tumor tissues after 808 nm irradiation at 24 h post-injection. *** indicates extremely significant difference between the two groups. [13] Copyright 2023, John Wiley and Sons.

4.2. Disassembly and Assembly Cascade of CuS Nanoparticles

By virtue of their broad NIR-II absorption (900–1350 nm), CuS nanoparticles have attracted significant interest over typical NIR-I materials. Lasers operating in this window enable tissue penetration depth up to 3 cm and tolerate a higher exposure limit (1.0 W/cm²). Yet, the NIR-II absorption capacity is compromised by size reduction; experimental evidence shows that decreasing the diameter to 5 nm results in a 60% attenuation of the absorption cross-section. Employing an *in situ* disassembly and assembly cascade not only improves penetration and retention within tumors but also restores and boosts photothermal conversion for PAI and PTT, providing a novel paradigm for tackling deeply located malignancies. For instance, Gao et al. developed a smart nanosystem that reconciles the conflict between deep tumor penetration and prolonged retention by combining near-infrared (NIR) light-triggered disassembly with transglutaminase (TGase)-mediated assembly [13]. As shown in Figure 4Q, ultrasmall CuS nanoparticles were functionalized with lysine-rich (CuS-K) or glutamine-rich (CuS-Q) peptides and co-encapsulated with indocyanine green (ICG) into thermosensitive liposomes. Upon irradiation with a NIR laser, the photothermal effect of CuS disintegrated the liposomes, releasing the tiny CuS NPs and ICG, which efficiently penetrated into deep tumor regions. Once internalized, CuS-K and CuS-Q were crosslinked by tumor-overexpressed TGase, forming larger aggregates through the enzyme-catalyzed reaction between the lysine and glutamine residues on the peptide shells. Bio-TEM imaging confirmed the effective assembly of CuS-K and CuS-Q in A375 cells. In an A375 melanoma model, CuS-K and CuS-Q effectively penetrated tumor tissue and were retained at the tumor site (Figure 4S–U). This light-triggered disassembly and enzyme-directed assembly not only enhanced tumor penetration, but also markedly amplified the photothermal conversion efficiency and improved intratumoral retention.

5. Iron Oxide Nanoparticles (IONPs)

5.1. Assembly of IONPs for Enhanced T₂

Iron oxide nanoparticles (IONPs) are extensively utilized in biosensing, imaging, drug delivery, and thermal therapy, thanks to their outstanding physicochemical traits and biocompatibility. In particular, they serve as potent T₂ contrast agents for MRI, a noninvasive technique that provides high spatial resolution and favorable penetration depth. Stimuli-responsive assembly can amplify imaging signals by enhancing tumor retention and capitalizing on size-dependent effects. Large IONPs (>10 nm) and their assemblies show pronounced T₂-weighted MRI performance, attributed to their high saturation magnetization and low specific surface area [58]. What's more, a larger size consistently reinforces the T₂ signal [59]. This relationship has spurred the development of various enzyme (caspase-3/7, matrix metalloproteinase-2, TGase, furin, and cathepsin B) or GSH-responsive assembly strategies for heightened T₂-weighted tumor MRI [60–65]. This activatable *in vivo* assembly strategy for IONPs has significantly improved the SNR of tumor MRI with several-fold enhanced T₂ signal.

Unlike large IONPs or IONP assemblies that produce T₂ MR signal, extremely small IONPs (ESIONPs, <5 nm) are appealing T₁ contrast agents—the abundant surface Fe ions efficiently accelerate T₁ relaxation of surrounding water protons, and well-dispersed ESIONPs generate feeble saturation magnetization with relatively slow T₂ relaxation. Wu et al. identified 3.6 nm as the optimal size for T₁-weighted imaging [66]. Accordingly, assembling ESIONPs can switch contrast from T₁ to T₂. Wang et al. harnessed acid-triggered self-assembly of sub-5 nm ultrafine iron oxide nanoparticles (uIONPs, ~3.5 nm) to exploit the EPR effect for enhanced tumor delivery with a T₁-to-T₂ MRI switch [67]. Zhang et al. engineered a GSH-responsive ultrasmall Fe₃O₄ nanoparticle probe that maps intratumoral GSH heterogeneity via interlocked longitudinal and transverse relaxation signals [68]. As shown in Figure 5A, ~3.9 nm Fe₃O₄ nanocrystals were functionalized with an asymmetric PEG ligand bearing a maleimide group, and a peptide containing RGD and angiopep-2 was tethered through a disulfide bond. In the tumor microenvironment, elevated GSH cleaves this bond, exposing thiols that undergo a click reaction with surface maleimide groups to trigger controlled aggregation. This GSH-driven aggregation has opposing effects on

MRI: R_1 decreases owing to reduced surface hydration, while R_2 increases due to stronger interparticle magnetic coupling, yielding an interlocked $\Delta R_2/\Delta R_1$ ratio strongly dependent on GSH concentration.

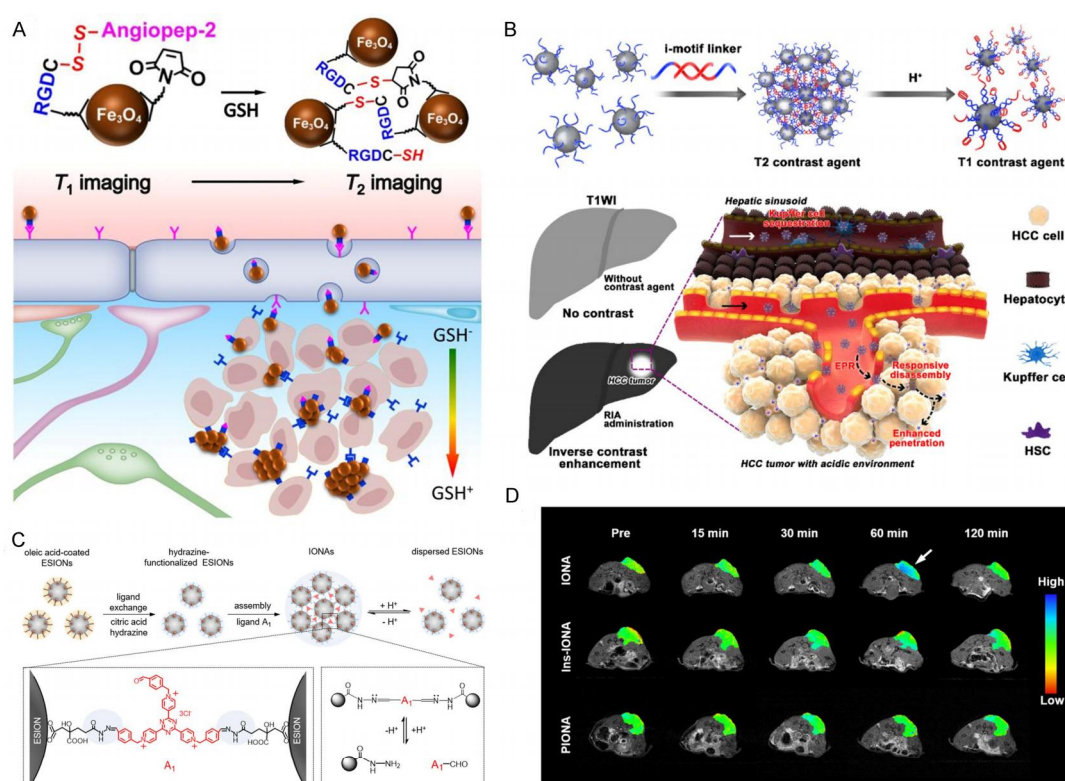


Figure 5. *In vivo* assembly and disassembly of IONPs. (A) Scheme of GSH-triggered assembly of IONPs for enhanced T₂. [68] Copyright 2021, John Wiley and Sons. (B) Scheme of acid-triggered disassembly of DNA-Fe₃O₄ nanoassembly for enhanced T₁. [69] Copyright 2018, American Chemical Society. (C) Scheme of IONA formation and its acid-responsive disassembly. (D) T1-weighted MR images pre- and post-i.v. injection of various IONA formulations in tumor-bearing mice. [70] Copyright 2019, American Chemical Society.

5.2. Assembly of IONPs for Enhanced PTT

In addition to serving as contrast agents for MRI, IONPs could also be employed as photothermal ablation agents. The photothermal effects of IONPs are attributed to phonon-mediated nonradiative transitions between different oxygen vacancy sites. Upon NIR laser irradiation, IONPs effectively convert luminous energy into heat, raising local temperature and improving drug penetration and accumulation near tumors. Wang et al. developed an enzyme-instructed self-assembly approach for ~10 nm IONPs functionalized with a furin-cleavable RVRR peptide, a disulfide-caged cysteine, and a 2-cyanobenzothiazole moiety [71]. Upon intracellular activation by furin and glutathione, an intermolecular CBT-Cys click condensation covalently crosslinks the nanoparticles into aggregates, substantially enhancing both the transverse relaxivity (r_2 from ~146 to 239 mM⁻¹s⁻¹) and photothermal conversion efficiency (from 41.3% to 56.5%). To further improve photothermal conversion, Wei et al. constructed smart Au-Fe₃O₄ Janus nanoparticles (~20 nm) co-functionalized with a weakly acidic and a strongly basic ligand, creating a near-neutral zwitterionic surface that remains stable at neutral pH (7.4) [72]. In the acidic TME, protonation of the carboxylate groups reduces electrostatic repulsion, triggering surface charge reversal and rapid aggregation (from ~28 nm to ~106 nm). This acid-induced aggregation simultaneously amplifies the T₂ relaxivity (r_2 from ~35 to 281 mM⁻¹s⁻¹), photoacoustic signal, and NIR absorption, yielding a photothermal conversion efficiency of 77.5%. It is foreseeable that *in situ* assembly of different nanoparticles in tumors can fully integrate the characteristics of each type of nanoparticle and achieve complementary advantages among different nanoparticles [73].

5.3. Disassembly of IONPs for Enhanced T₁

Given that ESIONPs (<5 nm) are appealing T₁-weighted contrast agents, the disassembly of ESIONP assemblies can also realize a T₂-to-T₁ switchable MRI. For instance, Lu et al. designed pH-activatable ESIONP assemblies (RIAs) based on i-motif DNA-assisted crosslinking for imaging of small hepatocellular carcinoma

(HCC) through an inverse MRI contrast enhancement strategy [69]. As shown in Figure 5B, ultrasmall iron oxide nanoclusters (USIONCs, ~3 nm core diameter) with T_1 contrast capability were crosslinked by pH-sensitive DNA linkers, consisting of i-motif sequences and their partially complementary strands, into nanoassemblies of approximately 120 nm at neutral pH 7.4. Upon exposure to the acidic TME, the i-motif DNA undergoes a rapid conformational switch to a quadruplex structure, causing linker dissociation and prompt disassembly of the RIAs into well-dispersed USIONCs within ~40 s ($t_{1/2} \approx 12$ s at pH 5.5), accompanied by a marked decrease in the r_2/r_1 ratio that converts the RIAs from a T_2 to a T_1 contrast agent. Recently, Li et al. developed pH-responsive IONP assemblies (IONAs) chemically cross-linked by small-molecule aldehyde derivative ligands through dynamic hydrazone bonds, enabling tumor acidity-triggered amplification of T_1 -weighted MRI (Figure 5C) [70]. Notably, the chemically cross-linked IONAs preserved structural integrity at neutral pH even under highly dilute conditions, overcoming the inherent instability of conventional polymer-based assemblies that dissociate below their critical aggregation concentration. T_1 -weighted MRI of tumor-bearing mice demonstrated that IONAs produced significantly higher tumor signal amplification compared with both pH-insensitive cross-linked controls and polymer-based assemblies, owing to the full hydrophilicity of the disassembled ESIONPs that maximizes water accessibility and second-sphere relaxivity (Figure 5D).

5.4. Assembly and Disassembly Cascade of IONPs

To simultaneously enhance imaging signals and reduce safety risks, Cheng et al. developed a programmed size-changeable nanotheranostic agent (AtkCPTNPs) that reconciles the inherent conflict between effective tumor retention and rapid post-therapy elimination through an assembly–disassembly cascade [74]. As shown in Figure 6A, the initial ~90 nm nanoparticles are assembled from pH-responsive PEG–PC7A, ROS-responsive polyprodrug-functionalized IONPs, and an AIE photosensitizer (MeOTTMN). In the acidic TME, PC7A protonation triggers shedding of the PEG shell and exposure of the hydrophobic polyprodrug–IONP core, inducing the formation of large IONP aggregates that substantially enhance tumor retention and T_2 -weighted MRI contrast. Under MRI-guided white-light irradiation, the photosensitizer generates ROS that simultaneously execute photodynamic therapy and cleave thioketal linkers to release camptothecin for chemotherapy, after which the aggregates re-disperse into small individual IONPs that are rapidly cleared, minimizing long-term toxicity. TEM images demonstrated the pH-triggered assembly and light-responsive disassembly (Figure 6B). Acid-triggered assembly led to enhanced T_2 -weighted MRI contrast (Figure 6C–E), and subsequent light-triggered disassembly resulted in more rapid elimination (Figure 6F). This work first demonstrated a “small–large–small” programmed size-change strategy that sequentially addresses accumulation, retention, combination therapy, and metabolic elimination, thereby achieving imaging-guided chemo/photodynamic therapy with both high antitumor efficacy and favorable biosafety.

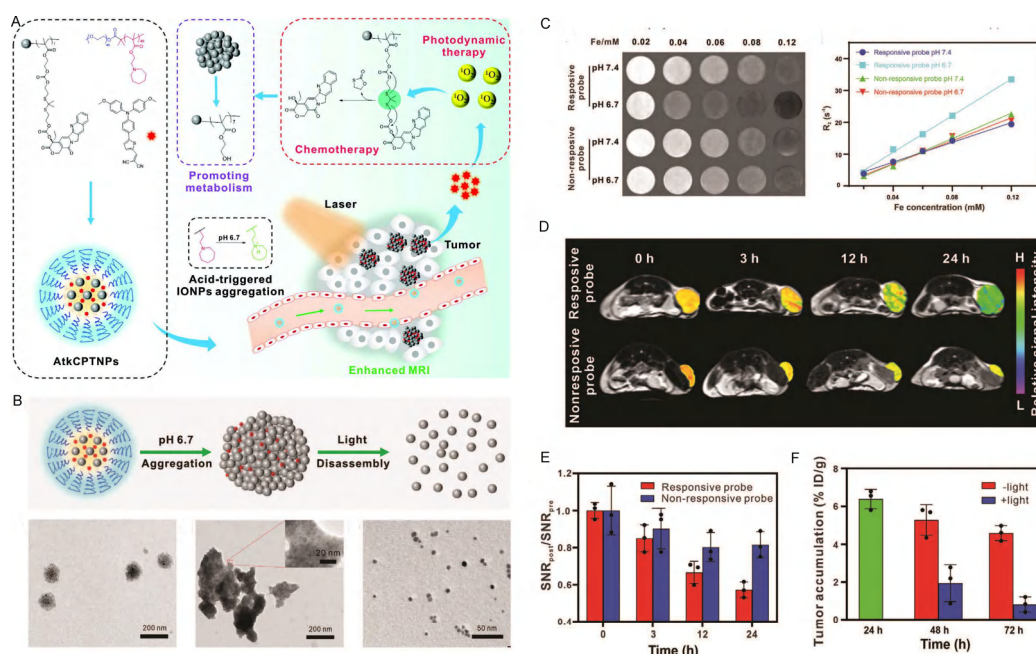


Figure 6. *In vivo* assembly and disassembly cascade of IONPs. (A) Schematic of acid-triggered assembly and light-triggered disassembly for improved MRI and clearance. (B) Schematic and TEM images of the assembly/disassembly process. (C) T_2 -weighted MR images of responsive and non-responsive probes at pH 7.4 and 6.7 (left); corresponding

transverse relaxation rates (right). (D,E) T₂-weighted MR images (D) and SNR changes (E) in CT26 tumor-bearing mice after intravenous injection of the nanotheranostic agents. (F) Tumor accumulation of AtkCPTNPs at different time points, with and without light irradiation. [74] Copyright 2021, John Wiley and Sons.

6. Lanthanide-Doped Nanoparticles

Lanthanide ions possess dense energy levels, yielding emissions that span from UV–visible to infrared. Several ions act as NIR-II emitters: Ho³⁺ (1185 nm), Nd³⁺ (1060 and 1310 nm), Er³⁺ (1525 nm), and Tm³⁺ (1450 nm). According to their luminescence mechanism, lanthanide-doped nanoparticles are categorized as upconversion nanoparticles (UCNPs) or downconversion nanoparticles (DCNPs).

6.1. UCNPs

UCNPs upconvert NIR excitation to visible emission [75–77] and are extensively applied in deep-tissue photodynamic therapy (PDT). Ai et al. devised an enzyme-responsive strategy that covalently cross-links peptide-functionalized UCNPs *in vivo* for tumor-selective accumulation and boosted PDT [78]. As depicted in Figure 7A, the UCNPs were equipped with cathepsin B (CtsB)-cleavable peptides and 2-cyanobenzothiazole (CBT) groups. Cleavage by tumor-overexpressed CtsB exposes cysteine residues that condense with CBT on neighboring particles, covalently assembling the UCNPs into larger structures exclusively at the tumor site (Figure 7B,C). This enzyme-driven aggregation amplifies upconversion luminescence under 808 nm excitation via enhanced light scattering (Figure 7D,E), which subsequently increases singlet oxygen production from the conjugated chlorin e6 (Ce6) and greatly elevates PDT efficacy. Conversely, Li et al. adopted a disassembly-based approach to improve PDT. Their pH-responsive nanoagents (PPNs) were formed by clustering UCNPs with pH-sensitive polymeric ligands conjugated to Ce6 [79]. At pH 7.4, the UCNPs form large assemblies (~120 nm, negatively charged) where Ce6 molecules are packed tightly, quenching both fluorescence and photoactivity. In the mildly acidic tumor milieu (pH ~6.5), imidazole protonation (pK_a ~6.8) reverses the surface charge from negative to positive, promoting cellular uptake. Upon reaching endo/lysosomal pH (~5.5), stronger electrostatic repulsion and weakened hydrophobic forces cause the PPNs to disassemble completely into individual UCNPs. This separation relieves Ce6 self-quenching and reactivates the photosensitizers. Under 980 nm irradiation, the UCNPs emit red light absorbed by Ce6, producing singlet oxygen.

6.2. DCNPs

DCNPs combine NIR excitation with narrow NIR-II emission and high photostability, positioning them as powerful NIR-II imaging tools for multiplexed sensing, time-gated detection, and image-guided interventions [80]. To simultaneously achieve rapid systemic clearance of ultra-small imaging nanoprobe and long-term tumor retention of assembled clusters, thereby overcoming the fundamental trade-off between efficient body elimination and sustained tumor contrast, Wang et al. developed an *in vivo* self-assembly approach for NIR-II fluorescent nanoprobe (NaGdF₄:5%Nd@NaGdF₄, ~7–12 nm) functionalized with complementary DNA strands and FSHβ targeting peptides [81]. As shown in Figure 7F, through a two-stage sequential intravenous injection (8 h interval), complementary DNA hybridization drove tumor-specific *in situ* assembly, forming aggregates that prolonged retention while unassembled nanoprobe were rapidly cleared via renal and hepatic routes. TEM images demonstrated the DNA-complementarity-induced assembly of DCNPs (Figure 7G), and the assembled structures maintained stable NIR-II fluorescence (Figure 7H). This *in vivo* assembly strategy yielded a stable tumor-to-normal tissue NIR-II signal ratio of ~12.5 and an optimal surgical window of approximately 6 h. Under NIR-II fluorescence guidance with ~8 mm penetration depth and superior photostability, large tumors and eye-invisible peritoneal metastases (≤ 1 mm) were completely excised.

To elegantly circumvent the long-standing challenge of high background signals from reticuloendothelial system accumulation while maintaining superior tumor imaging performance, Zhao et al. reported a NIR-controlled supramolecular approach that reversibly assembles and disassembles UCNPs and DCNPs *in vivo* for precision tumor imaging [82]. As shown in Figure 7I–K, azobenzene-modified UCNPs (UCNP@Azo) and β-cyclodextrin-modified NIR-II-emitting DCNPs (DCNP@β-CD) were sequentially injected with an optimized time interval, enabling spontaneous tumor-specific assembly through trans-azobenzene/β-cyclodextrin host–guest recognition, which enhanced tumor accumulation approximately fourfold and prolonged probe retention. Crucially, 980 nm NIR irradiation, upconverted by UCNPs into UV/blue light, triggered photoisomerization of azobenzene from the trans to cis form, driving disassembly specifically in the liver. The assembly and disassembly processes were characterized by TEM and DLS (Figure 7L). This remotely controlled disassembly reduced nonspecific

retention in the reticuloendothelial system, accelerated hepatobiliary and renal clearance, and substantially improved the signal-to-noise ratio (~15) and tumor-to-normal tissue contrast for image-guided surgery.

Although these NIR-II imaging systems have improved delivery efficiency at tumor tissues and rapid excretion at healthy organs by using *in vivo* nanoparticle self-assembly, unpredictable cross-linking in blood, RES, and normal tissues would also cause high background signal and possible long-term cytotoxicity. Thus, microenvironment-sensitive assembly systems are desirable for *in vivo* NIR-II tumor detection and bioimaging [83].

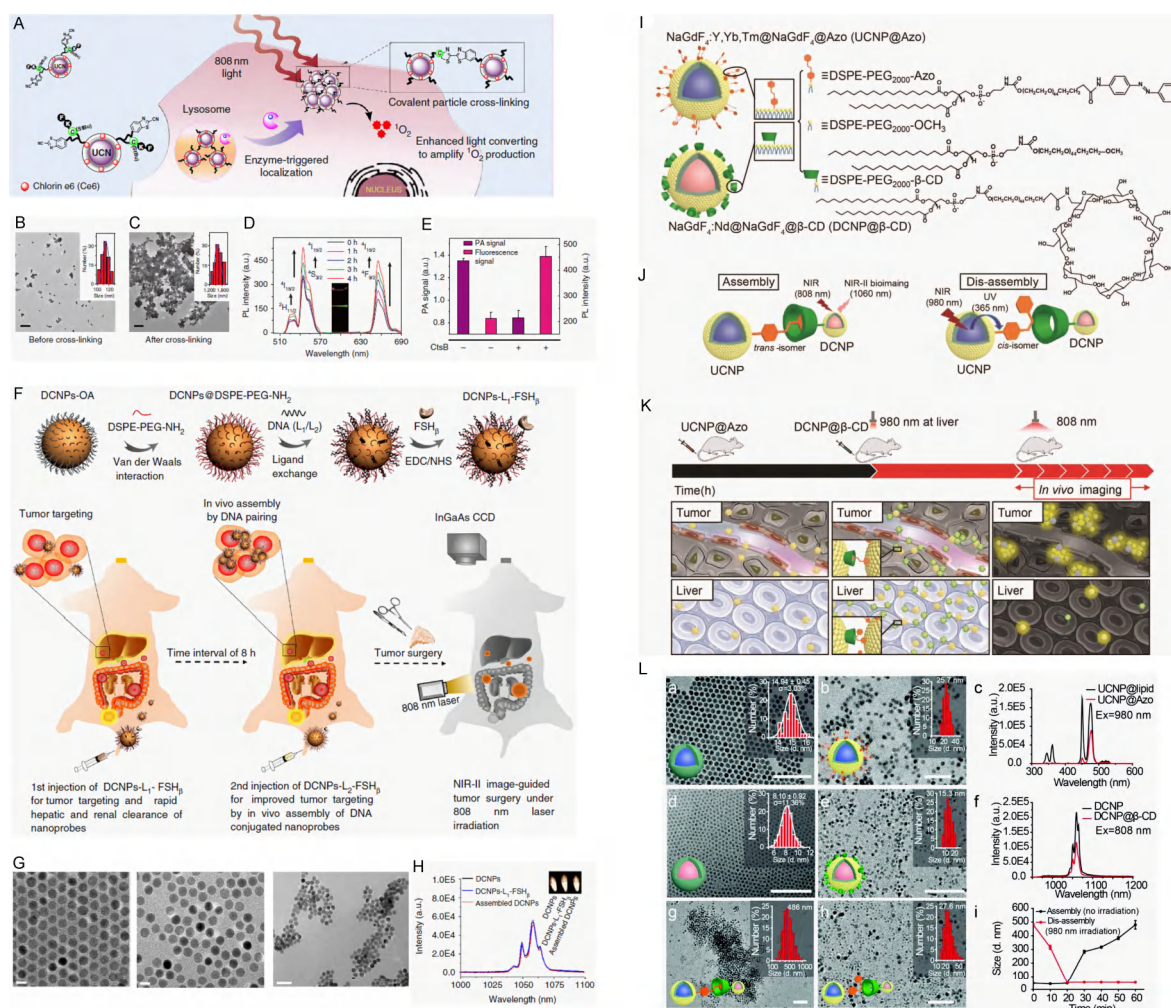


Figure 7. *In vivo* assembly and disassembly of lanthanide-doped nanoparticles. (A) CtsB-triggered UCN assembly for enhanced PDT. (B,C) TEM and DLS characterization of UCNPs before (B) and after (C) assembly. Scale bar, 200 nm. (D) Time-course luminescence spectra of CRUN with CtsB treatment. (E) PA images and UCL signal after 4 h incubation of CRUN with CtsB. [78] Copyright 2016, Springer-Nature. (F) Sequential *in vivo* assembly of DNA/FSH β -modified DCNPs: DCNPs-L1-FSH β (first injection) and DCNPs-L2-FSH β (second injection) hybridize through DNA complementarity, improving tumor targeting and enabling fast hepatic/renal clearance after two-stage injection. (G) TEM images of DCNPs, L1-modified DCNPs, and assembled DCNPs-L1-FSH β /DCNPs-L2-FSH β in PBS. (H) NIR-II fluorescence spectra and corresponding images (inset) of DCNPs, DCNPs-L1-FSH β , and self-assembled DCNPs. [79] Copyright 2018, Springer-Nature. (I-K) Assembly and NIR laser-regulated disassembly of nanoprobe for stable and accurate NIR-II imaging. (L) TEM (a,b; d,e; g,h), DLS (insets and panel i), and luminescence spectra (c,f) of nanoprobe during *in vitro* assembly and disassembly. [81] Copyright 2018, John Wiley and Sons.

7. Metallic Nanoclusters

7.1. Assembly of Metallic Nanoclusters

Metal nanoclusters of gold, silver, and copper consist of a few to hundreds of atoms, with diameters (typically 1–10 nm) comparable to the electron Fermi wavelength [84,85]. This quantum confinement yields high photostability, large Stokes shifts, and non-blinking emission. AuNCs under 2 nm are particularly attractive for NIR fluorescence imaging owing to their molecule-like optical characteristics [14]. Nevertheless, their practical

application as NIR-I/NIR-II probes is constrained by poor fluorescence quantum yield and fast clearance. *In vitro* assembly of AuNCs into monodisperse nanoassemblies such as nanoribbons, supraparticles, etc. has been demonstrated as an efficient strategy for significantly enhancing AuNCs' fluorescence through the AIE effect [86–89].

Leveraging the AIE effect to boost fluorescence quantum yield, *in vivo* self-assembly strategies have been harnessed for imaging tumor biomarkers. For example, Ran et al. constructed a nucleic acid-driven AIE probe from AuNCs to visualize telomerase activity in tumor cells and solid tumors [90]. Cluster formation restricts ligand motion and enhances ligand-to-metal charge transfer, yielding strong AIE emission at 570 nm. Systemic injection into HeLa tumor-bearing mice produced markedly higher fluorescence in tumors than in normal tissue, establishing the first *in vivo* demonstration of AIE-based telomerase imaging. Wang et al. further created a versatile DNA–AuNC nanomachine platform that coupled toehold-mediated strand displacement (TMSD) with AIE enhancement, enabling prolonged NIR-I fluorescence imaging of both microRNAs and proteases [16]. As depicted in Figure 8A, for TK1 mRNA imaging, an mRNA-responsive nanomachine (mDNA–AuNC) was built by co-immobilizing a three-component DNA hybrid and a fuel strand on AuNCs; target binding initiates cascaded TMSD reactions, driving amplified AuNC self-assembly, enhanced fluorescence, and extended tumor retention. For cathepsin B sensing, a DpAuNC nanomediator—mediator DNA electrostatically loaded on peptide-modified AuNCs—releases the mediator upon protease cleavage, activating a downstream DNA–AuNC nanomachine for TMSD-mediated aggregation. This biomarker-triggered *in situ* size conversion combines efficient small-size tumor penetration with the prolonged retention of large aggregates, enabling long-term fluorescence imaging of TK1 mRNA (up to 72 h) and cathepsin B in tumor cells and tumor-bearing mice.

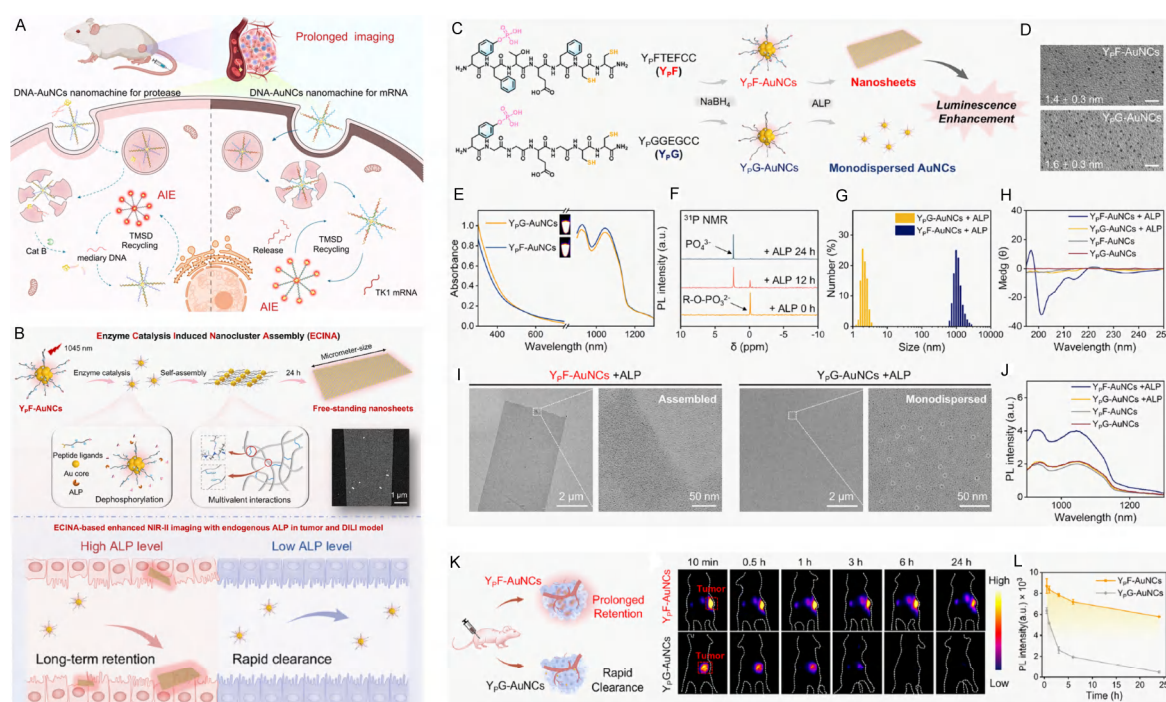


Figure 8. *In vivo* assembly of AuNCs. (A) Illustration of Cathepsin B- and microRNA-triggered assembly of NIR-I AuNCs for prolonged imaging. (B) ECINA-driven formation of freestanding monolayered nanosheets for enhanced NIR-II tumor imaging. (C) Synthesis and ALP-triggered assembly process of AuNCs. (D) TEM image of AuNCs. Scale bar, 10 nm. (E) Absorption and PL spectra of AuNCs in aqueous solution. Inset: NIR-II image. (F) ^{31}P NMR spectra of YPF-AuNCs after incubation with ALP for different times. (G) DLS size distributions before and after 24 h ALP treatment. (H) CD spectra with and without ALP incubation. (I) TEM images of two AuNCs before and after ALP treatment. (J) PL spectra before and after ALP incubation. (K) *In vivo* imaging protocol and NIR-II images of mice at indicated time points after intratumoral injection of YPF-AuNCs or YPG-AuNCs. (L) Quantitative NIR-II PL signals in tumors over time, from the images in (K). [16] Copyright 1879, American Chemical Society.

Since NIR-II imaging (1100–1700 nm) offers high spatial resolution and deep tissue penetration, it has attracted considerable interest in the development of fluorescence probes operating in this spectral window. AuNCs are attractive candidates for NIR-II fluorescence imaging [91]; however, their practical utility is limited by low fluorescence quantum yields and poor targeting specificity. Recent works have therefore aimed at boosting the photoluminescence quantum yields (PLQYs) of AuNCs [92,93], with AIE through nanoparticle assembly

emerging as one of the most effective routes to high PLQYs. For instance, Sun et al. developed a reverse emulsion-confined electrostatic assembly strategy that overcomes the uncontrolled diffusion and electrostatic repulsion typical of conventional aqueous assembly, enabling precise tuning of AuNC nanoassemblies for enhanced NIR-II fluorescence imaging [15]. Owing to the aggregation-induced ligand rigidification and the retention of Au(I)–S bond integrity, the resulting assemblies exhibited remarkable NIR-II fluorescence enhancement, with the PLQY increasing from 0.16% to 1.18%.

Thanks to the AIE-enhanced NIR-II fluorescence, *in vivo* stimuli-responsive assembly of NIR-II AuNCs has recently been applied to disease diagnosis [94]. For example, Xu et al. developed an enzyme catalysis-induced nanocluster assembly (ECINA) strategy to prepare freestanding, micrometer-scale monolayered nanosheets from peptide-capped AuNCs [95]. As shown in Figure 8B, ultrasmall YpF-AuNCs were synthesized by designing an alkaline phosphatase (ALP)-cleavable peptide ligand (YpFTEFCC) that integrates a hydrophobic self-assembly domain with terminal cysteine anchors. Upon ALP-mediated dephosphorylation, the peptide shell underwent a conformational shift into β -sheet structures, driving the directional, template-free organization of the nanoclusters into large-area single-layer sheets. As a control, YpG-AuNCs tethered with a peptide ligand (YpGGEGCC) lacking the hydrophobic self-assembly domain could not assemble into large-area single-layer sheets after ALP-mediated dephosphorylation (Figure 8C). TEM images and spectral analysis demonstrated the successful preparation of both YpF-AuNCs and YpG-AuNCs; upon dephosphorylation, the YpF-AuNCs self-assembled into single-layer sheets, whereas the YpG-AuNCs remained unchanged (Figure 8F–I). Moreover, this ordered assembly rigidified the ligand shell, suppressed nonradiative decay, and led to an around 2-fold enhancement of NIR-II emission at 1045 nm (Figure 8J), a phenomenon attributed to a nanoconfinement effect. Most notably, endogenously overexpressed ALP in tumor tissue triggered the *in-situ* assembly of the nanoclusters, resulting in prolonged lesion retention and high-contrast NIR-II imaging in a subcutaneous osteosarcoma model (Figure 8K,L). This work represents a pioneering conceptual advance, demonstrating that enzymatic catalysis can replace traditional templates to spatiotemporally program the hierarchical assembly of sub-nanometer clusters into functional two-dimensional nanostructures for advanced bioimaging and theranostics.

7.2. Disassembly of Metallic Nanoclusters

In addition to the AIE effect, some metallic nanoclusters exhibit aggregation-caused quenching (ACQ). Consequently, disassembly of these nanoclusters can restore their NIR-I or NIR-II fluorescence. Dai et al. reported self-quenched AuNCs (Sq-AuNCs) as a single-component fluorescent turn-on probe for intracellular glutathione imaging, eliminating the need for separate donor–acceptor pairs [96]. Bovine serum albumin-protected AuNCs were crosslinked via disulfide bonds, inducing aggregation that caused a 40 nm red-shift and quenched the NIR-I emission (quantum yield from ~6% to 0.69%). Upon exposure to intracellular GSH, the thiol groups cleaved the disulfide bridges, leading to disaggregation and restoration of the quantum yield to 5.08%. Recently, Zhou et al. reported a strategy for fabricating water-soluble nanoassemblies of NIR-II luminescent AuNCs that exhibit an unusual disassembly-induced emission enhancement (DIEE) [97]. As shown in Figure 9A, the AuNCs were co-functionalized with 3-mercaptopropyltrimethoxysilane (MPTMS), a cross-linkable silane ligand, and a hydrophilic PEG thiol. Upon phase transfer to water, the MPTMS ligands underwent hydrolysis and condensation to form a siloxane (Si–O–Si) network, driving the assembly of AuNCs into ~80–130 nm nanostructures (Figure 9B). The assembly was accompanied by a red-shift of the AuNC emission to ~1070 nm and a QY of 1.8%. Under mildly acidic conditions (pH 4.0), the interparticle T^3 cross-linking state gradually converted to intraparticle T^2 and T^1 states, leading to controlled disassembly into ~34 nm particles (Figure 9C). Simultaneously, a more than 6-fold emission enhancement was observed, with the quantum yield reaching 12%, accompanied by a ~115 nm blue-shift (Figure 9D). Mechanistic investigations revealed that the transformation from dominant interparticle cross-linking to intraparticle cross-linking intensified the ligand-to-metal charge transfer transitions and shifted the emission route from core-state to shell-state excitation, which was responsible for the unusual DIEE. Furthermore, disassembly into smaller particles facilitated efficient renal clearance and significantly reduced nonspecific retention in the liver and spleen (Figure 9E–H), with urinary excretion reaching 30.6% of the injected dose—nearly 2.2-fold higher than that of the assembled counterpart (Figure 9G). This work utilizes the conversion of siloxane cross-linking states to achieve an unprecedented DIEE effect, combined with the simultaneous realization of disassembly-promoted renal clearance, thereby establishing a novel concept for engineering highly emissive and renal-clearable nanostructures for *in vivo* bioimaging.

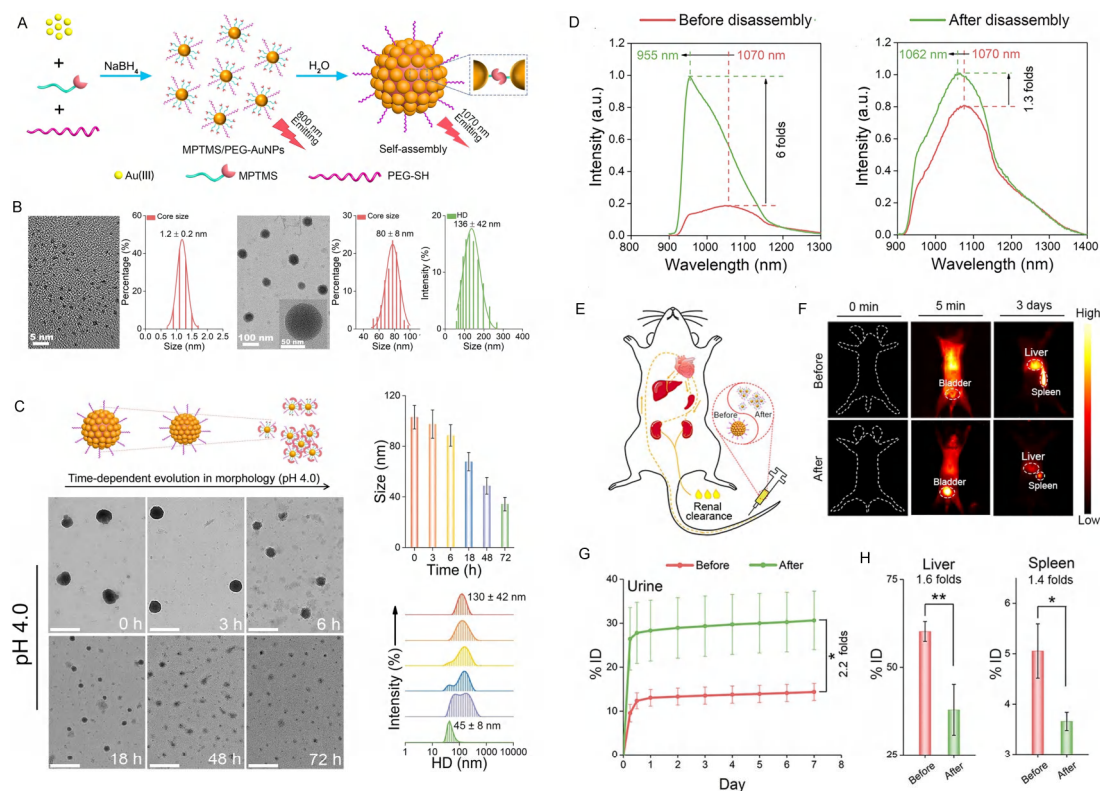


Figure 9. *In vivo* disassembly of AuNC assemblies. (A) Synthetic route of MPTMS/PEG-AuNPs. (B) TEM images and size distributions/HDs before and after assembly. (C) Morphological evolution scheme (upper) and TEM images (lower) of assembled particles during degradation at pH 4.0, with corresponding core size distributions and HDs. Scale bar, 200 nm. (D) Fluorescence spectra of the assemblies before and after disassembly at pH 4.0. (E) Clearance pathway. (F–H) *In vivo* fluorescence imaging (F), renal clearance over 7 days (G), and liver/spleen biodistribution at 7 days post-injection (H) of MPTMS/PEG-AuNPs before and after disassembly. [97] Copyright 2022, John Wiley and Sons.

8. Carbon-Based Quantum Dots

Carbon-based quantum dots, such as carbon dots (CDs) and graphene quantum dots (GQDs), have been widely applied in tumor theranostics due to their exceptional optical properties and low toxicity [98,99]. The *in vivo* disassembly strategies for carbon-based quantum dots could be used to promote drug delivery and controlled release. For example, Hou et al. developed tumor-associated fibroblast (CAF)-responsive honeycomb-like CD nanoassemblies for spatially programmed multi-drug delivery to enhance chemoimmunotherapy against desmoplastic tumors [100] (Figure 10A,B). Ultrasmall CDs (~10 nm) were surface-loaded with doxorubicin (DOX) and Fe³⁺ ions, and then crosslinked by fibroblast activation protein- α (FAP- α)-cleavable peptides into mesoporous assemblies (~106 nm) encapsulating losartan (Figure 10C). Upon tumor accumulation, FAP- α overexpressed on perivascular CAFs cleaved the peptides, triggering disassembly and biphasic drug release (Figure 10D–F). To further enhance the retention and penetration of drug molecules, Su et al. developed a size-changeable GQD nanoaircraft (SCNA) that achieves hierarchically accumulated and deep-penetrating drug delivery via a sequential pH- and NIR-responsive size transformation [101]. As shown in Figure 10G, the SCNA consists of ultrasmall GQDs (< 5 nm) loaded with DOX through π - π stacking and encapsulated within a pH-sensitive amphiphilic polymer (HTPGS) to form ~150 nm nanoparticles. At low pH, protonation of the N-acetylhistidine moieties reduces electrostatic repulsion, triggering interparticle aggregation that enhances tumor accumulation and retention. Upon subsequent irradiation with a NIR laser, the photothermal effect of the GQDs loosens the hydrophobic and π - π interactions, disassembling the aggregates back into 5 nm DOX/GQD units that penetrate deep into tumor tissue. The work couples a pH-driven aggregation step for enhanced accumulation with an NIR-activated disassembly step that generates tissue-penetrating nanoscopic drug carriers, thereby elegantly reconciling the conflicting size requirements for prolonged tumor retention and deep intratumoral penetration.

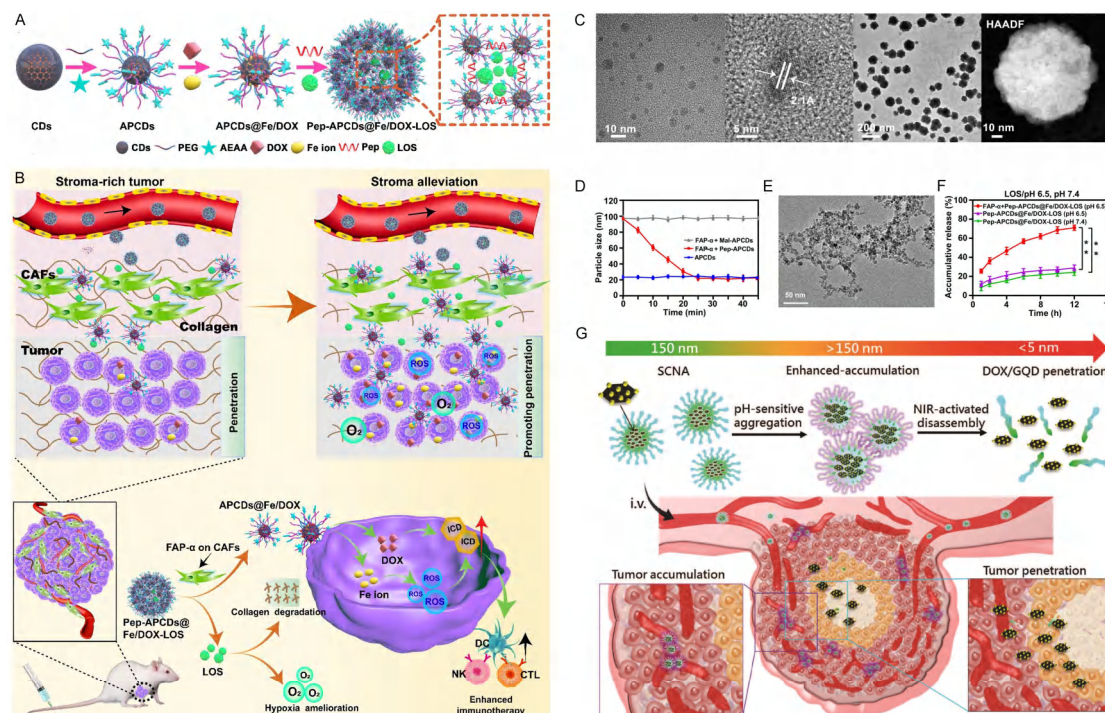


Figure 10. *In vivo* assembly and disassembly of carbon-based quantum dots. (A) Preparation of drug-loaded CD nanoassemblies. (B) CAF-responsive disassembly of CD nanoassemblies to promote antitumor immunity. (C) TEM and HAADF-STEM images of APCDs (first two panels) and Pep-APCDs@Fe/DOX-LOS (last two panels). (D,E) FAP- α -triggered size change measured by DLS (D) and TEM (E). (F) LOS release profiles under different conditions. [100] Copyright 2021, John Wiley and Sons. (G) Acid-driven assembly of SCNAs for enhanced tumor accumulation and NIR-driven disassembly into DOX/GQDs to facilitate deep tumor penetration. [101] Copyright 2017, John Wiley and Sons.

In addition to drug delivery, disassembly strategies have also been exploited to enhance the imaging performance of carbon dots. Liu et al. developed Gd^{3+} -induced self-assembly of carbon dots (C-dots) into ~98 nm spherical assemblies (A-C-dots), which were further loaded with the photosensitizer Ce6 to construct a FRET-based imaging system (A-C-dots@Ce6) [102]. In this system, the assembled C-dots (A-C-dots) served as the energy donor (blue emission at 450 nm under 405 nm excitation), while Ce6 acted as the energy acceptor (red emission at 655 nm). Upon assembly, the close proximity between A-C-dots and Ce6 enabled efficient FRET, producing significantly enhanced red fluorescence compared to free Ce6, which substantially improved imaging sensitivity. In the acidic tumor microenvironment, the A-C-dots disassembled into ultrasmall discrete C-dots (~3 nm) due to the weakened Gd^{3+} -carboxylate coordination, which released Ce6 and disrupted the FRET process. This FRET disruption could be monitored in real time through the decrease of red fluorescence and the concurrent recovery of blue fluorescence, allowing dynamic tracking of drug release. In addition to the FRET effect, Xing et al. developed fluorescence-switchable iron-doped carbon dot assemblies (FCDDs) based on the ACQ effect [103]. FCDDs were prepared by covalently crosslinking amino-rich Fe-doped carbon dots using DSP (dithio-bis(succinimidyl propionate)) as a crosslinker through amidation chemistry. In the assembled state, the close proximity of FCDs leads to aggregation-caused quenching. In the presence of GSH, the disulfide bonds within the DSP crosslinkers were broken, and the FCDDs rapidly disintegrated into ultrasmall FCDs (~12 nm). The consequent relief of the ACQ effect switches the fluorescence “on”, enabling tumor-specific fluorescence imaging with high signal-to-background contrast.

Besides, *in vitro* pre-assembly of carbon-based quantum dots was demonstrated to enhance their NIR-II imaging performance through the EPR effect [104]. Therefore, there's reason to believe that *in vivo* assembly of carbon-based quantum dots may facilitate their penetration and retention as well as rapid excretion for enhanced fluorescence imaging with high signal-to-background contrast.

9. Summary and Outlook

Identifying tumor markers can allow cancer to be diagnosed months or even years ahead of clinical symptoms, substantially widening the critical window for intervention. In addition, a number of these markers double as key therapeutic targets. In recent years, nanoparticle assembly and disassembly strategies have sharpened

the precision and sensitivity of tumor diagnosis and therapy. As such strategies continue to emerge, they will spur the design of next-generation nanoplatforams for tumor imaging and treatment, helping to refine existing therapeutic paradigms.

Despite the significant advantages of assembly and disassembly strategies in enhancing tumor accumulation efficiency and improving nanoparticle biosafety, two major bottlenecks remain. First, numerous studies have focused only on a single process (i.e., either assembly or disassembly), and reports on complete assembly–disassembly cascades, especially those involving renally clearable nanoparticles, are extremely rare. Consequently, it remains difficult to simultaneously enhance tumor accumulation efficiency and reduce toxicity risks [105–108]. Second, owing to the lack of precise control over the assembly process *in situ*, most assemblies form amorphous aggregates, making it challenging to establish quantitative structure–property relationships between the structural parameters of the aggregates (e.g., size, morphology) and their optical performance (e.g., absorption/emission wavelength, photothermal conversion efficiency, quantum yield). This, in turn, hinders the precise modulation of the optical properties of the assemblies. Therefore, how to precisely regulate the assembly–disassembly cascade and control the structure and optical properties of the assemblies within complex physiological environments remains a key scientific challenge that urgently needs to be addressed in future research.

Author Contributions

Q.L.: writing—original draft preparation, visualization; H.W.: writing—original draft preparation; J.P.: visualization, investigation; Z.L.: software, validation; Y.L.: software, validation; W.X.: software, validation; J.G.: software, validation; W.X.: supervision; H.Y.: writing—reviewing and editing; F.Z.: supervision, writing—original draft preparation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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