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Recent advances in UCNPs fluorescent nanomaterials as platforms for biological applications

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Abstract: *Upconversion nanoparticles (UCNPs) have a wide range of applications in biomedicine due to their unique optical properties, such as resistance to autofluorescence, deep tissue penetration ability, good biocompatibility, multifunctional integration ability, and low toxicity. The applications of UCNPs in biology cover a wide range of fields from diagnostics to therapy. compared with traditional fluorescent materials, UCNPs show unique advantages and great potential in biosensing, bioimaging, drug delivery, PTT/PDT, multimodal diagnostics, cell labeling, and molecular probes. With the further development in this field, the applications prospects of UCNPs in biomedicine will be even broader. This article reviews the applications and cutting-edge technologies of UCNPs in current popular biological fields such as biosensing, bioimaging, and drug delivery, and summarizes the prospects and challenges of UCNPs in the future of biomedicine.*

Keywords: *UCNPs, Biological application, Bioimaging, Drug delivery, Disease treatment*

1. Introduction

Since the beginning of the 21st century, the research on upconversion nanoparticles (UCNPs) has been rapidly developed in both theoretical and applied fields[1].Compared with traditional luminescent materials, upconversion luminescent (UCL) materials have become an important development in modern biomedical research by virtue of their unique nonlinear optical properties and their many advantages in terms of penetrability, low background signals, anti-photo-bleaching, color tunability, low excitation light demand, and biocompatibility[2-3].With the advances in nanotechnology for the preparation of small, high-quality and bright nanoparticles, upconverted nanomaterials have made significant contributions to the field of biology and biomedical research[4].UCNPs are widely employed in a variety of advanced biological applications, extending from background-noise-free biosensing, precision nanomedicine, and deep-tissue imaging to cellular biology, visual neurophysiology, and optogenetics[5-6]. For example luminescent probes are used for protein localization and monitoring biological processes[7].

The UCL mechanism takes place due to the interaction of low-energy incident photons and long-lived intermediate states of luminescent entity. The material is excited to a higher energy level through energy transfer, excited-state absorption and triplet-state annihilation, and subsequently emits a high-energy photon[8]. The upconversion efficiency can be achieved by co-doping sensitizer ions with activator ions having closely matched intermediate excited states[9]. Under near-infrared (NIR) laser irradiation, typical lanthanide-doped UCNPs exhibit anti-Stokes-shifted visible and UV emission, while the autofluorescence background is minimal, and the light scattering of biological tissues is greatly reduced. This reduction in light scattering due to NIR excitation will make the penetration depth of biological tissues far greater than the penetration depth under ultraviolet or visible light excitation, which makes UCNPs have great potential in biological applications[10], including tissues imaging[11], bioassay[12], photodynamic therapy, and other biomedical fields[13].

This article begins with an overview of the upconversion mechanism and its advantages, then focuses on the research progress of UCNPs in bioimaging, biosensing, drug delivery, photodynamic therapy (PDT), photothermal therapy(PTT), cell labeling, and molecular probes, and finally concludes with a summary of the challenges and prospects of upconverting nanomaterials for biological applications.

2. Upconversion luminescence

The study of the upconversion luminescence (UCL) phenomenon of rare earth ions began in the early

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1950s[14].In 1966, it was reported that the study of ytterbium tungstate sodium glass accidentally found that, when the matrix material is doped with Er^{3+}, Ho^{3+}, and Tm^{3+}, under infrared excitation, the visible light emission is increased by close to two orders of magnitude, accordingly, it was proposed that the anti-Stokes effect of rare earth ions, and the concept of "UCL" was formally put forward soon after, which aroused people's keen attention to the UCL, and began related research. 1960s ~ 70s, Auzel's group and Wright's group systematically studied the upconversion properties and mechanisms of rare-earth ions doped, and proposed that the UCL caused by the absorption of the excited state, the energy transfer, and cooperative sensitization. sensitization-induced UCL, and substable excitation is a prerequisite for upconversion phenomena[15]. During this period, the upconversion material was developed as a material that can effectively convert near-infrared (NIR) into visible light and reached a usable level.

UCL is a photoluminescence phenomenon that mainly involves the conversion of low-energy photons into high-energy photons[16-17]. Generally, the luminescence processes and mechanisms can be mainly categorized into excited state absorption upconversion(ESA), energy transfer upconversion(ETU) and photon avalanche upconversion(PA), which is shown in Figure 1. Among them, PA depends on pump light energy and has a slow response to excitation; ETA has the lowest efficiency; ETU avoids the above shortcomings and has been widely used.

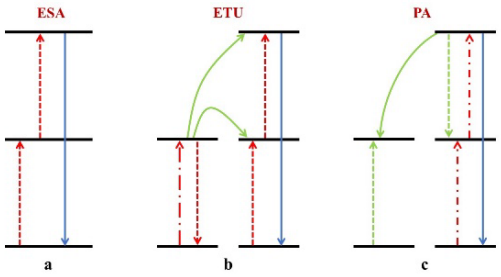

Figure 1: Main upconversion process (a) ESA,(b) ETU,(c) PA.

3. Biological application

Upconversion mechanisms offer significant advantages in biotechnology, including highly penetrating near-infrared light excitation that enables deep imaging and reduces background interference, resulting in improved imaging contrast. It supports real-time monitoring of dynamic biological processes, and many upconversion nanoparticles (UCNPs) have excellent biocompatibility for in vivo experiments. In addition, UCNPs can be used in combination with other imaging techniques, providing versatility and flexibility. Their high sensitivity enables the detection of very low concentrations of biomolecules, while the controllability provides greater options for experimental design. These advantages enable upconversion mechanisms to show potential for a wide range of applications in areas such as bioimaging, disease diagnosis and drug development.

3.1. Biosensing

The upconversion mechanism is highly sensitive in biosensing, capable of detecting very low concentrations of biomolecules and suitable for early disease diagnosis. Its high selectivity and low background interference significantly improve signal contrast. In addition, it supports real-time monitoring and multi-detection with good biocompatibility and low toxicity. These advantages give it the potential for a wide range of applications in disease diagnosis, environmental monitoring and food safety testing.

Carcinoembryonic antigen (CEA) is one of the most important tumor markers. Research by Wang et al. demonstrated the successful design of an ultrasensitive aptamer sensor based on FRET for detecting CEA[18]. CEA aptamer-modified UCNPs bind to the surface of graphene oxide (GO) via π-π stacking interactions. In this setup, energy is transferred from the UCNPs to GO, resulting in fluorescence quenching. When CEA is introduced, the CEA aptamer preferentially binds with CEA, forming a three-dimensional structure that separates the UCNPs-aptamer from GO and blocks the energy transfer process, thereby restoring the fluorescence of the UCNPs system. By combining UC-FRET and GO technologies, this sensor achieves high sensitivity and specificity in both aqueous solution and human serum, with a limit of detection (LOD) of 7.9 pg/ml and 10.7 pg/ml, respectively, which is at least an order of magnitude

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lower than those reported previously. Subsequently, Yu et al. developed a label-free fluorescent biosensor based on polydopamine-coated UCNPs (UCNPs@PDA), which consists of UCNPs@PDA and CEA aptamer-functionalized AuNPs (AuNPs-CEA aptamer)[19]. As illustrated in Figure 2, by coating the UCNPs surface with PDA, direct binding between DNA backbone phosphate groups and lanthanide ions is inhibited, preserving the aptamer's target recognition ability. The PDA-coated UCNPs allow AuNPs modified with CEA aptamers to adsorb onto the UCNPs@PDA surface via π-π stacking and hydrogen bonding interactions, thereby triggering energy transfer from UCNPs@PDA to AuNPs-CEA aptamer. In the presence of CEA, the high affinity of CEA to its aptamer causes the AuNPs-CEA aptamer to detach from UCNPs@PDA, leading to the recovery of upconversion fluorescence, which enables quantitative detection of CEA concentration. This biosensor provides a linear range of 0.1 to 100 ng/ml for CEA in aqueous solution, with a LOD of 0.031 ng/ml.

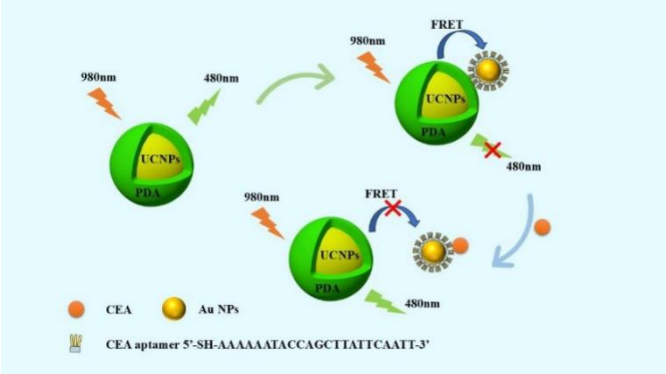

Figure 2: Principle of the biosensor based on UCNPs @ PDA and AuNPs.[19]

3.2. Bioimaging

UCNPs are one of the most promising nanomaterials for bioanalytical and biomedical applications[20]. UCNPs can effectively reduce autofluorescence and improve the signal-to-noise ratio. NIR light also has excellent tissue penetration capabilities, making it suitable for deep-tissue imaging. Compared to traditional materials, UCNPs exhibit strong photostability, long-lasting signal, and resistance to photobleaching. Their low-energy characteristics minimize tissue damage, making them ideal for non-invasive imaging. Furthermore, UCNPs can be combined with other imaging techniques to create a multimodal imaging platform, providing more comprehensive diagnostic information. These advantages make UCNPs show a wide range of application prospects in the fields of bioimaging and disease diagnosis.

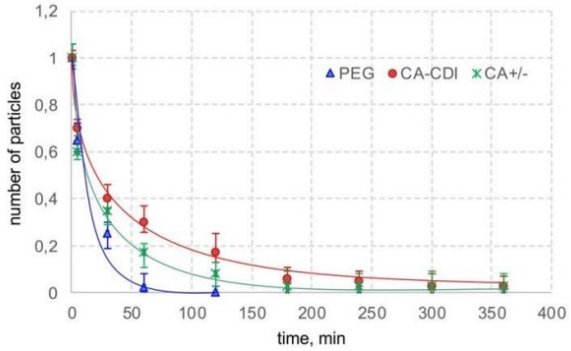

Figure 3: Normalized dependence of the UCNP amount modified with PMAO-PEG, CA by using carbodiimide activation and CA due to electrostatic interactions vs blood circulation time. The data was obtained from 15 mice (5 mice per curve).[22]

In invivo imaging, by functionalized modification of the surface of UCNPs, their targeted binding to specific cells or biomolecules can be achieved for precise molecular imaging and diagnosis. Li et al. constructed tumor-affinity peptide-modified $NaErF_4$:Yb@$NaGdF_4$:Yb core@shell UCNPs for active tumor-targeted UCL/MR dual-modality bioimaging[21]. Demina et al. prepared biocompatible colominic acid-modified UCNPs, which prevent the interaction of surrounding water molecules with cells and proteins, and can be used as carriers for the delivery of drugs and photosensitizers to sites of

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inflammation[22]. It was shown that the obtained UCNPs-CA nanocomplexes were highly hydrophilic, endogenous, non-toxic, and low non-specific hemoprotein adsorption. The UCNPs-CA nanocomplexes were hypo-absorbed by macrophages in vitro, and they played an active role in the inflammatory response. Also when injected intravenously, the circulation time of UCNPs-CA nanocomplexes in the bloodstream of small animals was prolonged up to 3 hours compared to polyethylene glycol coating as shown in Figure 3. This led to an efficient accumulation of UCNPs at the site of inflammation due to microvascular remodeling, accompanied by enhanced uptake and retention.

The DSPE-PEG-Glu coated core-shell structure UCNPs prepared by Sun et al. exhibit low cytotoxicity and can actively target GLUTs overexpressed on bladder cancer cells[23]. It was shown that with an increase in DSPE-PEG-Glu content in the coating, both the targeting efficiency and cellular uptake of these nanoparticles increase correspondingly. As shown in Figure 4, under 980 nm laser irradiation, glycosylated phospholipid-coated UCNPs exhibited a higher selective accumulation in cancer cells than in normal cells, enhancing the UCL of bladder cancer cells at 540 nm and 660 nm. Li et al. constructed a NIR-activatable P-DNA nanomachine for spatiotemporally controlled Zn^{2+} imaging in cancer cells[24]. UCNPs were modified with the energy harvester dyes FITC, photolocked DNAzyme, and BHQ1-labeled substrate strands. A portion of the UCNPs radiation at 450 nm was initially collected by the FITC and quenched by the BHQ1. Irradiation at 980 nm induces photocleavage of the PC linker, activating the DNAzyme catalytic reaction in the presence of Zn^{2+}, which restores FITC brightness at 540 nm. The amount of intracellular Zn^{2+} was imaged by quantitatively measuring the recovery intensity of FITC against the internal standard brightness of UCNPs at 450 nm.

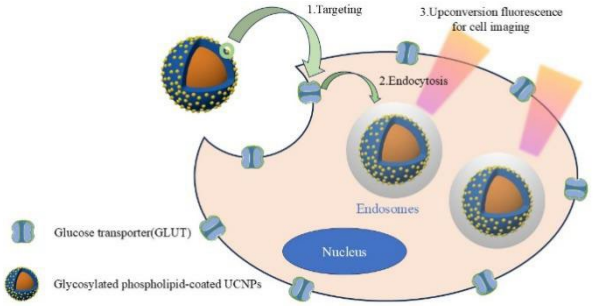

Figure 4: Schematic illustration of glycosylated phospholipid coating that promotes uptake of UCNPs by cancer cells and UCL emitted from UCNPs under NIR (980 nm) laser irradiation for cancer cell imaging.[23]

3.3. Drug delivery and therapy

Currently, research on Upconversion technology (UT) for drug delivery and therapeutics is undergoing rapid development. Researchers have developed a variety of upconverting nanomaterials capable of converting near-infrared light to visible light to enable precise regulation of drug release and enhance targeting and biocompatibility. These materials optimize drug loading and release by modulating structural and surface modifications for temporal and spatial control, thereby improving therapeutic efficacy. In addition, the researchers optimized the composition and structure of the material to improve the efficiency of photothermal conversion, combined with photodynamic therapy(PDT) and photothermal therapy(PTT) to achieve synergistic treatment and enhance the anti-tumor effect, while combining with drug delivery to improve the overall therapeutic efficiency. These advantages make UT show great potential in modern medicine.

Fedoryshin et al. conducted a study of photocleavage on the surface of UCNPs to release the chemotherapeutic 5-fluorouracil (5FU)[25]. The therapeutic drug was attached by ONB photoactivated linker and UCNPs were used as photocaging nanocarriers. Free 5-FU was released for treatment and quantified after NIR irradiation which upconverts within the UV range. Compared to direct UV irradiation triggered photolysis, excitation of modified UCNPs with NIR radiation released up to 77% of the drug in 10-15 min. kim et al. prepared posAuNP@UCNPs nanocomposites by coating 30 nm UCNPs on 80 nm AuNPs via DOPA-PEI and then exposed the nanocomposites with 980 nm NIR light irradiation to facilitate its intracellular delivery, which was shown to be effective in a three-dimensional osteoarthritis model for the treatment of osteoarthritis with baricitinib[26]. The therapeutic effects of UCPPin and PassT for intracellular delivery of baricitinib in an in vitro 3D model of OA were also

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compared. UCPPin with posAuNP@ UCNP nanocomposites was found to have better substance delivery than PassT. Tam et al. designed a thin LBMS shell coated with UCNPs alone, which was able to release a small hydrophobic drug at low laser power (1 W/cm^2), with a 2.1-fold increase in drug release upon NIR irradiation[27]. It was found that a thinner shell increased the rate of NIR-induced LBMS shell degradation and subsequent drug release, leading to shorter lag times in achieving drug release comparable to that of UV-activated systems, as shown in Figure 5.

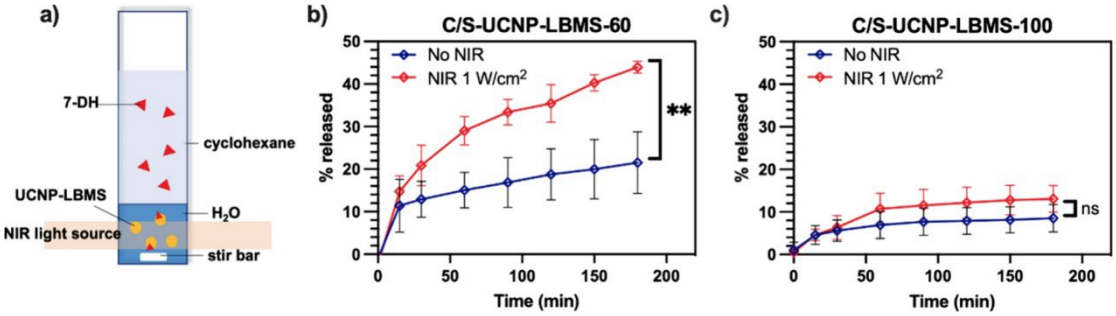

Figure 5: (a) Schematic of the drug release experimental setup. Release of 7-DH from (b) C/S-UCNP-LBMS-60 and (c) C/S-UCNP-LBMS-100 with and without 980 nm NIR irradiation at 1 W/cm^2 . The 7-DH release was monitored using the variation of the absorbance at λ = 281 nm.[27]

Wang et al. developed an effective noninvasive phototherapy based on the dual-site FRET route for three-component NIR braintargeted nanotherapy of glioma[28]. As shown in Figure 6, the system addresses the issues of spectral mismatch and poor single-point FRET photoenergy utilization in traditional UCNP-based therapies through multiple optimizations. The Precise adjustment of the Tm doping ratio significantly improved the emission of UCNPs at 475 nm. The aggregates effectively enhanced the absorption of ZnTPP at 475 nm, both together driving the spectral matching and maximized the utilization of the emission at 475 nm, resulting in effective PDT via the FRET route. The NIR radiation at 800 nm is efficiently utilized and converted into heat of CuS NPs for PTT.

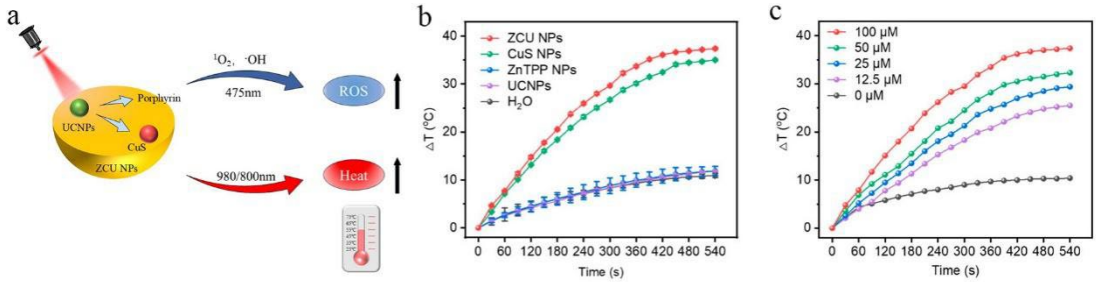

Figure 6: (a) Illustration of dual-site FRET route. (b) and (c) were the photothermal plots of various samples and different concentrations of ZCU NP solutions.[28]

3.4. In vivo tracking and cell labeling

UT, which utilizes UCNPs to convert low-energy light into high-energy light, has shown great potential in recent years for in vivo tracking and cell labeling. Due to their high sensitivity, low background signal and their excellent biocompatibility and low toxicity, UCNPs are able to efficiently label cells and monitor them in real time in living organisms. This technology is particularly suitable for deep tissue imaging, overcoming the limitations of conventional fluorescent labeling, such as light scattering and phototoxicity.

Sun et al. synthesized radioactive 153Sm-labeled UCNPs using a cation-exchange post-labeling method[29] and performed dynamic quantitative study of biodistribution in vivo without compromising the excellent UCL ability of the nanophosphors. Ma et al. successfully synthesized and utilized $NaYF_4$:Yb^{3+}, Er^{3+} UCNPs in the labeling and tracking of rabbit bone marrow mesenchymal stem cells during osteogenic differentiation in vitro[30]. And positively charged modified $NaYF_4$:Yb^{3+}, Er^{3+} UCNPs (i.e., PAH-PAA-UCNPs) were synthesized using PAA and PAH, which enhanced their biocompatibility and cellular uptake, and improved the cell labeling efficiency. yang et al. developed a LRET-based UCL nanosensor using UCNPs as donors and dual-organic dyes as acceptors[31]. In this structure, the UCNPs cintain emitted ions in the shell , which shortens the distance between donor and acceptor, thus providing

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high LRET efficiency. In addition, the use of dual dyes as acceptors not only afford flexible modification and thermodynamic stability of the system, but also provide higher bursting efficiency than a single dye as an acceptor, as shown in Figure 7. Polikarpov et al. demonstrated the production of targeted upconversion photoluminescent nanocouples UCNP@SiO_2-LPG-MIL-38 for the photodynamic diagnosis of bladder cancer cells, and evaluated their effect on the selectivity and molecular specificity towards Glypican-1-positive uroepithelial carcinoma cells T24[32]. These nanoconjugates specifically labeled the target cells and made them observable under NIR laser excitation. Chen et al. proposed that a synergistic identification method based on Wright's staining (cytomorphology) and $NaYF_4$:Yb, Er UCNPs-CD38 immunofluorescent probe labeling (immunophenotyping) could be used for leukemia cell imaging and clinical diagnosis[33]. In this approach, both cell morphology and immunolabeling can be determined visually. Compared with other leukemia diagnostic methods, this integrated approach offers the advantages of simplicity, rapidity, low cost, and high sensitivity, providing an alternative to the traditional bone marrow smear method for the early diagnosis of leukemia.

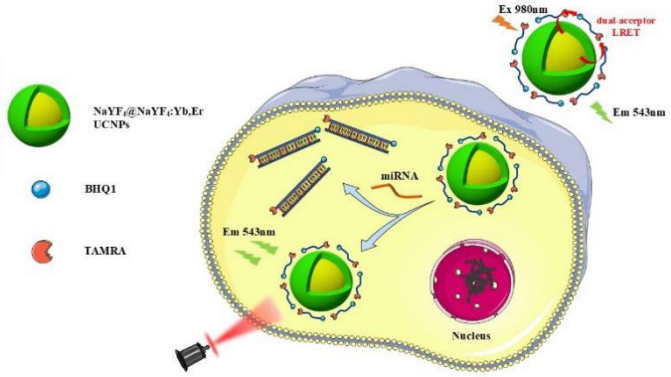

Figure 7: Schematics of the Dual-Acceptor-Based UCL Nanosensor for in Situ Imaging of miRNA in Living Cells.[31]

3.5. Molecular probes

Molecular probes are tools used to detect and recognize specific molecules or biological structures, usually some molecules or nanomaterials with specific recognition capabilities. UT utilize rare-earth ion-doped nanomaterials that produce high-energy visible or UV light emission upon excitation by NIR. This UCL phenomenon provides new opportunities for molecular probe applications. The better tissue penetration, low phototoxicity and small scattering of near-infrared light make upconversion probes outstanding in deep tissue imaging and non-invasive diagnosis, overcoming the shortcomings of conventional probes.

Fang et al. designed a novel probe based on cancer cell membrane-coated UCNPs (CCm-UCNPs)[34]. In this probe, natural cell membranes isolated from cancer cells were coated with UCNPs. The probe exhibited homologous targeting and immune escape capabilities. Combining the luminescence of UCNPs, the paramagnetism of Gd^{3+}, and click chemistry with surface-modified label 18F, CCm-UCNPs were used for ultrasensitive in vivo UCL/MRI/PET multimodal precise imaging of TNBC and differentiation of the MDA-MB-231 and MCF-7 tumor-bearing mice models in vivo. Zhang et al. constructed an HOCL-activatable and blood-brain barrier permeable UCNPs for real-time visualization of NI in vivo[35]. The probe has the advantages of good sensing performance toward HOCl, excellent blood-brain barrier permeability, deep penetration depth, and good biocompatibility, which can be used for the diagnosis of brain inflammation in the LPS-induced NI model and the monitoring the occurrence of stroke-related NI. To the best of our knowledge, this is a "NIR-in,NIR-out" fluorescent probe for real-time, noninvasive observation of NI. Shida et al. developed a type of UCNPs with several hours of photostability at the single-particle level, which enables long-term multicolor SPT[36]. Zhao et al. constructed a fluorescence FRET system based on a novel fluorescent probe and graphene oxide (GO) for the detection of H5N1 IAV hemagglutinin (HA)[37]. When HA is present, the aptamer undergoes a conformational change and moves away from the GO surface, as shown in Figure 8. The fluorescence signals showed a linear relationship for HA quantification in the range of 0.1 ~ 15 ng ml^{-1} with a LOD of 60.9 pg ml^{-1}. The sensor is also suitable for human serum samples with a linear range of 0.2 ~ 12 ng ml^{-1} and a LOD of 114.7 pg ml^{-1}.

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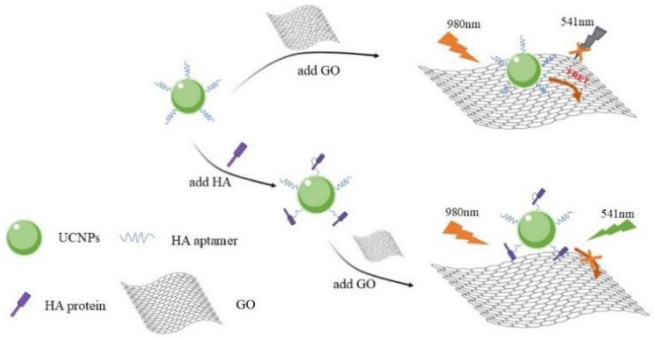

Figure 8: Schematic illustration to detect HA of influenza based on the FRET method.[37]

4. Conclusions and outlook

Upconversion Technology (UT) has received extensive attention and in-depth research in the field of biomedicine in recent years, and its core advantage lies in the use of upconversion nanoparticles (UCNPs) to convert low-energy near-infrared (NIR) light into high-energy visible or ultraviolet (UV) light. UCNPs are used to convert low energy NIR light into high energy visible or UV light. This technology has unique optical properties that give researchers new tools in diagnostic, therapeutic and basic biological research. It not only improves the resolution and sensitivity of biological imaging, but also provides new means for photodynamic therapy and targeted drug delivery, among others.

In this review, we present the current state-of-the-art of UCNPs in the biomedical field. UCNPs offer a number of significant advantages, such as background-free autofluorescence, minimal background tissue damage, and long penetration depths in biological tissues, that will keep UCNPs at the forefront of bioimaging and therapeutics for a long time. Their unique optical properties make them suitable for proper functionalization and can be designed for effective delivery and accurate drug release and control in response to specific stimuli. Several NIR excited UCNP-based biological imaging systems have been reported in the literature. Compared to traditional fluorescent imaging, the NIR excitation of UCNPs enables deeper penetration into biological tissues while reducing background fluorescence, significantly enhancing imaging contrast and sensitivity. This technology is suitable for non-invasive diagnosis of deep tissues and plays an important role in research on major diseases such as cancer, cardiovascular diseases, and neurological disorders. UT also finds applications in photodynamic (PDT) and photothermal (PTT) therapies, as it can convert NIR light into high-energy light to activate photosensitizers that produce reactive oxygen species, thus killing cancer cells or pathogens. Additionally, due to the low damage and excellent tissue penetration of NIR light, UT in photodynamic therapy results in less harm to healthy tissues, making it a potential approach for treating diseases such as cancer. Moreover, UT has garnered attention in targeted drug delivery. UCNPs can be modified on the surface to bind with drugs, allowing for controlled drug release via NIR light and precise targeting of specific sites, thereby enhancing therapeutic efficacy while reducing side effects on healthy tissues, ultimately improving the safety and effectiveness of treatment.

UT shows great potential in the biomedical field, especially in deep bioimaging, photodynamic therapy and drug delivery. UCNPs are capable of converting near-infrared light into visible or ultraviolet light, and have the advantages of high photostability, low background interference, and multispectral detection, which make them unique for precision medicine. In addition, through surface functionalization, these materials can also achieve multi-functional “diagnosis and treatment integration”, combining imaging and treatment. As technology continues to advance, UT will have broader application prospects in the biomedical field, promoting the development of new diagnostic and therapeutic tools and methods. However, the diffusion of this technology faces a number of challenges, including low luminescence efficiency, potential biotoxicity, complex synthesis processes, and in vivo stability. Despite the remarkable progress of UCNPs in the laboratory, challenges such as mass production, long-lasting safety and clinical validation still need to be addressed to realize clinical applications. With the continuous optimization of the technology, UT is expected to become an important tool in the biomedical field and promote the development of personalized medicine.

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