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Research Progress and Application of Rare Earth Luminescent Materials in Biomedicine

Abstract: - Rare earth luminescence stands out as a key function of rare earth compounds. The variation in the number of 4f orbital electrons across rare earth elements results in a complex energy level structure, leading to a multitude of absorption and emission bands for rare earth ions. This distinctive feature allows these ions to emit light across a spectrum ranging from the near-infrared to the ultraviolet. Over recent years, rare earth luminescent materials, with their unique optical, electrical, and magnetic properties, have demonstrated significant potential in applications such as solar cell sensitization, catalysis, sensing, and

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particularly in the realms of bioluminescence imaging and medical diagnostics and treatment. The drive to enhance the efficiency of biomedical diagnostics and therapeutics has spurred ongoing research into the synthesis and properties of rare earth nanomaterials. In recent years, researchers have leveraged the small size and rich surface chemistry of rare earth nanomaterials, combining these with their unique optical, electrical, and magnetic characteristics to create composite functional nanomaterials. These materials have shown promising applications in biofluorescent labeling, biosensing, and disease diagnosis and treatment. This article delves into the advancements of rare earth luminescent materials in biomedicine, covering applications such as X-ray imaging, drug delivery and photodynamic therapy, and offers insights and future perspectives for research in this area.

Keywords: Rare earth compounds; Luminescent materials; Biomedicine; Photoluminescence

1.Introduction

Rare earth luminescent materials are a significant class of rare earth functional materials, predominantly utilized in energy-efficient lighting, flat panel displays, and scintillation crystals. They have emerged as a focal point of research within the realms of next-generation lighting, information display, and photoelectric detection, significantly contributing to the advancement of human society and scientific progress.

The advent of rare earth luminescent materials has marked a pivotal transformation in the evolution of luminescent materials, with several landmark discoveries. For instance, in 1908, Becquerel first identified the distinct absorption spectrum of rare earths. In 1959, the exploration of Yb^{3+} as a sensitizer and Er^{3+}, Ho^{3+}, Tm^{3+} as activators paved the way for the development of upconversion materials. The discovery of rare earth trichromatic luminescent materials such as $BaMgAl_{10}O_{17}$: Eu^{2+} in 1973, along with $MgAl_{11}O_{19}$: Ce^{3+}, Tb^{3+}, and Y_2O_3: Eu^{3+}, significantly enhanced the performance of electric light sources. At the dawn of the 21st century, the white light-emitting diode (WLED), which has been extensively researched, has catalyzed the development of a new generation of lighting technology based on luminescent materials.

Abundant rare earth resources in the world make rare earth luminescent materials a crucial avenue for maximizing the value of these resources. Consequently, the exploration of the design, synthesis, and application of novel rare earth luminescent materials holds substantial scientific and practical importance. This article delves into the progress of rare earth luminescent materials in the biomedical field, covering applications such as X-ray imaging, drug delivery and photodynamic therapy, and offers an analysis and outlook for future research in this domain.

2. Luminous materials

i) Light and electromagnetic radiation

Light is actually a form of energy. Its transmission mode is very unique; it can be transmitted between objects without the assistance of any medium, a form of energy transfer we call radiation. Radiation, as the name suggests, means that energy from a source travel in a straight line in all directions, of course, changing its direction as it passes through matter.[1] Initially, light was mistaken for a beam of particles, but later it was found that the properties of light were more closely related to the nature of waves, and it was eventually proved to be an electromagnetic wave.[2] As we all know, within the electromagnetic spectrum, which covers a very wide range of wavelengths, the proportion of light waves can be said to be very small. The accepted wavelength range of visible light (Figure 1) is from 400 nm to 780 nm.[2] Different colors of visible light correspond to different wavelength ranges, from purple to red, which the human eye can distinguish. From a biological point of view, the human eye's ability to observe and distinguish visible light depends on the function of the visual area of the human brain and the visual characteristics of the human eye. We should be familiar with the primary contributors to the recognition of visible light, namely rods and cones,[3] which have different roles and can be said to perform their own duties.[4] Rod cells are responsible for detecting weak light and are relatively sensitive, while cone cells are slightly fewer than rod cells and less sensitive, mainly used to process strong light and distinguish the color of light. The two work together to transmit the signals received to the brain, which processes them, allowing us to observe the colorful

world. The earliest strict definition of monochromatic light refers to light composed of a single wavelength, but in fact, a single wavelength of light is difficult to exist in isolation, more or less accounting for a certain band.[5] The electromagnetic waves on both sides of the violet and red wavelengths are considered ultraviolet and infrared radiation, respectively. Although the human eye cannot observe these, if the radiation reaches a certain intensity, it can also have a significant harmful effect on biological tissue.

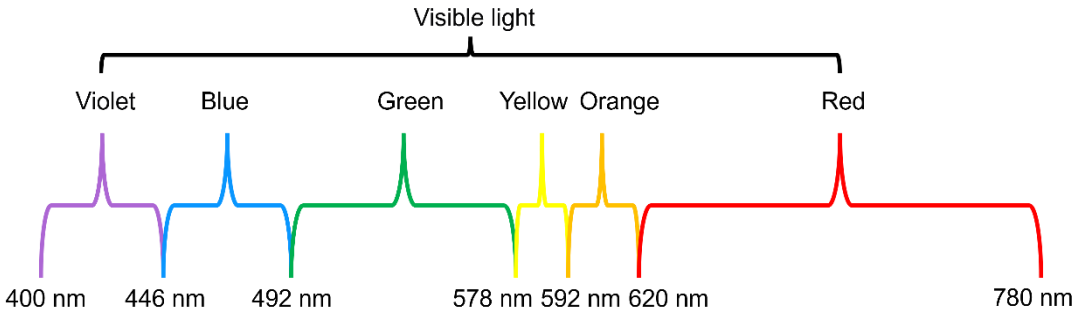

Figure 1. The wavelength range corresponding to different colors of visible light.

ii) The nature and process of luminescence

The essence of luminescence is actually a process involving absorption, transformation, and release. It begins by absorbing energy, then converts that energy into light radiation, and finally releases it into the environment. However, in a stricter sense, the concept of light radiation is broader, with luminescence being just one component. It is well known that optical radiation encompasses both equilibrium and non-equilibrium types. Equilibrium radiation, also known as thermal radiation, is typically the light emitted by hot objects. The sole determinant of thermal radiation is the object's temperature; radiation occurs under this condition as long as the temperature is sufficient. Non-equilibrium radiation, on the other hand, results from external forces. If, during the transition from a non-equilibrium to an equilibrium state, the residual energy is emitted as light radiation, this phenomenon is termed luminescence. Ultimately, luminescence is categorized as a type of non-equilibrium radiation, which, in fact, requires a background of thermal radiation as a prerequisite.[6]

The general luminous process can be illustrated in Figure 2. After absorbing energy (or becoming excited), the luminescent center A transitions from its ground state to the excited state A*, and then releases the energy through a radiative transition R (optical radiation), returning to the ground state. Of course, the energy may also be converted into lattice vibrations and released through non-radiative transitions (NR).[7] Consequently, much research focuses on suppressing non-radiative transitions to achieve higher luminous efficiency. However, if the luminescent center fails to absorb energy for some reason or if the absorbed energy is insufficient, a sensitizer acts as an aid. It forms an energy transfer chain with the luminescent center, absorbing energy and then transferring it to the luminescent center. Figure 3 depicts the schematic diagram of the luminescence process involving a sensitizer. The sensitizer first absorbs and transfers the energy, which the luminescent center A then receives, converts, and releases as light radiation.[8]

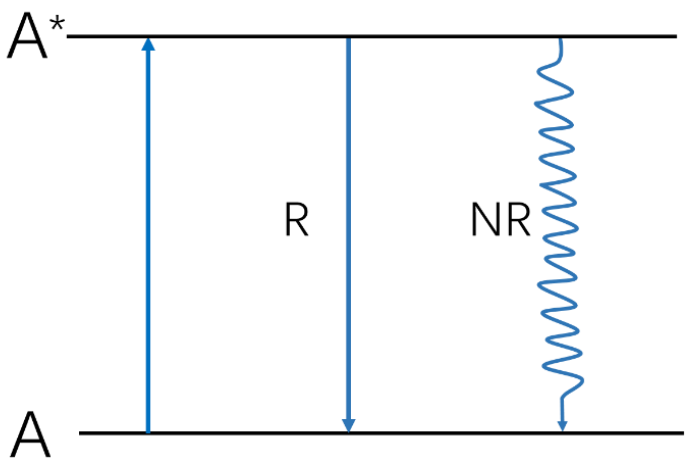

Figure 2. The schematic diagram of the luminescence process.

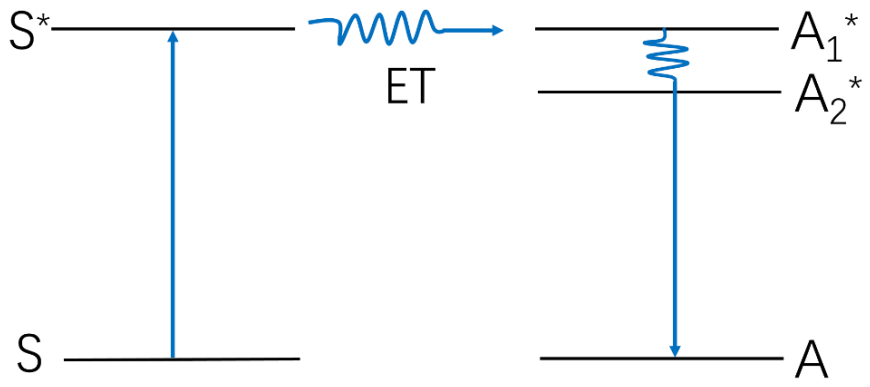

Figure 3. The schematic diagram of the luminescence process with the sensitizer.

2.1 History of luminescence phenomenon

Understanding the principle and process of luminescence allows us to better grasp the definition of luminescent materials. These materials are a class of functional substances capable of absorbing external energy and converting it into non-equilibrium light radiation, also referred to as luminous bodies. The existence of luminous materials in nature was discovered by humans at a very early stage. However, the systematic study of these materials dates back to the 17th century. The history of luminescence is well-documented as seen in Figure 4. As early as 1852, Stokes formulated the fundamental concept of Stokes' shift.[9] In 1867, Becquerel provided a detailed analysis of the spectral properties of rubies.[10] In 1878, Crookes conducted a systematic investigation of vacuum discharges that induce luminescence, thereby solidifying the research foundation for cathode-ray luminescence. At the end of the 19th century, two groundbreaking discoveries profoundly impacted the scientific community and clarified its direction, guiding those who were previously uncertain. These discoveries were X-rays[11] and natural radioactivity,[12] with Roentgen and Becquerel being the principal discoverers, respectively. In 1905, Einstein innovatively applied the concept of photons to a detailed examination of Stokes' theory,[13] leading to a deeper comprehension of optics. In 1913, Bohr's seminal quantum theory of the atom established a robust foundation for fundamental optical physics.[14]

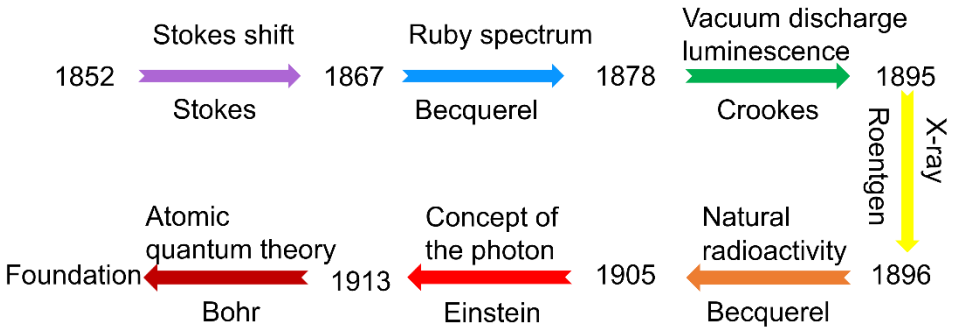

Figure 4. The historical research process of luminescence phenomenon.

2.2 Types and applications of luminous materials

As shown in Figure 5, The classification of luminous materials is diverse, and they are categorized based on their excitation modes. The main excitation modes include light excitation, cathode ray excitation, electrical excitation, thermal excitation, radiation excitation, acoustic excitation, and force excitation, among others.[15-23] Currently, luminous materials have seamlessly integrated into our lives, becoming an integral part of our daily experiences, illuminating every corner with vibrant light. They are ubiquitous, found in medical X-rays, fluorescent lamps, electronic device displays, and more. One of the earliest practical applications of luminous materials involved using the optical properties of $CaWO_4$ to locate tungsten ores.[24] With the rapid advancement of science and technology, the leading light-emitting materials are now predominantly found in the realms of fluorescent lamps and electronic display devices.[25-27] Additionally, luminous materials are utilized in the manufacture of oscilloscopes, photoelectric converters, and radar fluorescence screens.[28] They can also be crafted into optical coatings for decorative purposes and as light-emitting indicators.

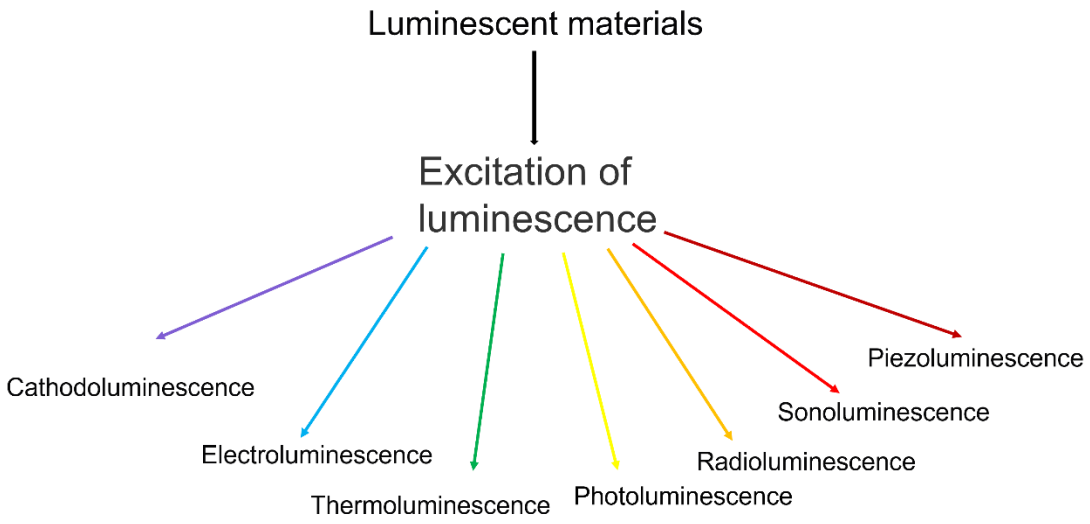

Figure 5. The classification of luminescent materials according to excitation method.

Photoluminescent materials are those that emit light upon excitation by external light sources, such as ultraviolet, visible, and infrared light. The process is primarily divided into three stages: light absorption, energy transfer, and light emission.[29] The luminous center and matrix of a material are crucial for absorbing external energy. When the luminous center absorbs energy, it transitions to a higher energy level and then returns to a lower level by emitting radiation. If the energy is absorbed by the material's substrate, the process changes, and optical radiation results from the recombination of electron-hole pairs. Photoluminescent materials are extremely common in everyday life, with typical representatives including fluorescent lamp materials, long afterglow materials, LED optical materials, and upconversion luminescent materials, among others.[30-43] For cathodoluminescent materials, the excitation light source is relatively unique, as it is excited by an electron beam. The luminescence center, once excited by the electron beam, releases energy through a radiation transition. This process is primarily utilized in the field of television imaging.[44] Electroluminescence involves using an external electric field to convert electrical energy into light energy, without the accompaniment of thermal radiation. Two typical examples of electroluminescence are diode luminescence and high-field electroluminescence. Diode luminescence represents injection luminescence, which is the light radiation phenomenon caused by the combination of electrons and holes due to

external energy. High-field electroluminescence, also known as intrinsic luminescence, involves optical radiation that results from the collision of high-energy particles.[45] There is a unique class of luminous materials that are excited at low temperatures, emitting light instantly. When the excitation ceases, the luminescence stops, and as the temperature rises, the luminescence is enhanced. These materials are called thermoluminescent materials.[46-48] Fundamentally, this phenomenon occurs because holes in the ground state become trapped by defect traps. If a hole is deeply bound, additional external energy, such as heat, is required to release the hole so that it can combine with returning electrons to produce light radiation. It should be noted that returning electrons preferentially combine with free holes, while other electrons wait for the arrival of external energy to release the bound holes and then combine with them. Photoluminescent materials share the same luminescence mechanism. The primary excitation sources are infrared light and specific wavelength light sources. In this case, the holes are in a waiting state, and the energy release frees the trapped electrons, leading to the combination and luminescence. These materials are primarily used in infrared detection and memory storage.[49] The excitation sources for radioluminescent materials, sonoluminescent materials, and stress luminescent materials are high-energy photons or particles, sound fields, and mechanical forces, respectively.[50,51] Energy is transferred from the outside world via an external source, leading to a radiative transition. These types of luminous materials warrant further in-depth research.

3. Rare earth luminescent materials

If we liken luminescent materials to a vast treasure trove, then rare earth luminescent materials are like the jewels within, shining brightly and dazzlingly. These rare earth luminescent materials stand out among a multitude of luminescent materials, not only due to the production advantage of rare earth resources[52] but also because of the in-depth exploration of the unique structure and excellent optical properties of rare earth elements. Rare earth luminescent materials are the mainstay in the fields of display and lighting, which in turn accelerates economic development and expands the application value of rare earth products.

3.1 Optical properties of rare earth elements

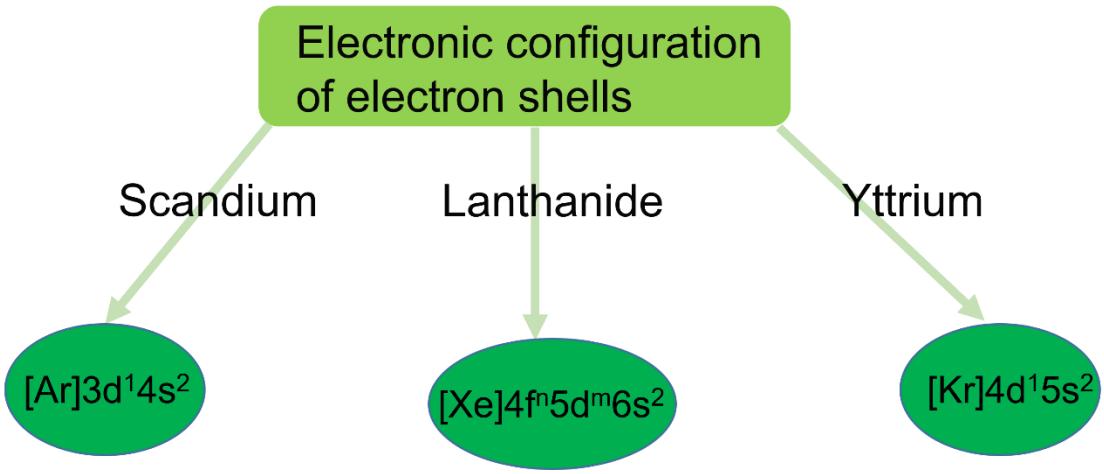

Figure 6. The electronic configurations of rare earth elements.

i) Internal structure of rare earth elements

Since Finnish scholar J.Gadolin first introduced rare earth elements to human knowledge in 1794, they have become inextricably intertwined with our lives. [53] Rare earth elements consist of all the lanthanides, along with scandium and yttrium, spanning from lanthanum to lutetium, totaling seventeen elements.[54] Their unique electronic layer structure is inherently designed to exhibit extraordinary physical and chemical properties. Figure 6 illustrates the three electronic configurations of rare earth elements. The figure reveals that although scandium and yttrium have low atomic numbers and lack a 4f electron layer, their outer electronic configuration of (n-1) d^1ns^2 closely resembles that of the lanthanides, indicating similar chemical properties. The electronic structures of the remaining fifteen lanthanides are not significantly different, showing a regular pattern: $[Xe]4f^n5d^m6s^2$ (where m=0 or 1, n=0-14). Each element has the same number of electrons in the 6s orbital, a similar number in the sub-outer orbital, and the number of electrons in the 4f orbital changes gradually with increasing atomic number. As the atomic number increases, electrons fill the 4f orbital according to established rules. However, the dispersion effect of the 4f electron cloud means that not all electrons are efficiently distributed to neutralize the increasing nuclear charge, causing outer electrons to be partially attracted by the nuclear charge. This gravitational effect increases with the atomic number, leading to a

gradual decrease in atomic or ionic radius. This regular phenomenon is known as “lanthanide contraction”.[55,56] The change in atomic number is the decisive factor driving the gradual change in lanthanide contraction, making it the key determinant of lanthanide element properties. For instance, the coordination ability of lanthanide metals with specific ligands increases as the radius decreases. Additionally, the metallic alkalinity of these elements decreases progressively from lanthanum to lutetium.

ii) Luminescence mechanism of rare earth elements

Rare earth elements exhibit distinctive optical properties due to their unique electronic transitions. These transitions are primarily categorized into three types: ① Transitions within the f-n electron configuration, known as f-f transitions; ② Transitions between different configurations, referred to as f-d transitions; ③ Transitions between ligands and metals, also known as charge transitions.

The f-f transition is the predominant form of electronic transition in rare earth ions. The 4f shell contains a multitude of energy levels, leading to a variety of electronic transitions that result in diverse absorption and emission spectra. Ions such as Sm^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, and Tm^{3+} are particularly notable for their strong, characteristic emissions, which are largely due to f-f transitions.[57] The f-f transition is characterized by several key features: (1) The absorption and emission spectra are linear and remarkably sharp; (2) The colors are pure, with a long lifespan and high luminous efficiency; (3) The transition is resistant to external interference, and temperature quenching is minimal; (4) The spectral line coverage is extensive, resulting in an extremely rich palette of colors.

In addition to f-f transitions, f-d electronic transitions also occur, primarily in certain low-valence rare earth ions. The typical ions are Eu^{2+}, Yb^{2+}, Sm^{2+}, etc.[58] This electronic transition is highly susceptible to lattice vibrations, resulting in a less sharp transition band that contributes to a broadband spectrum. The main characteristics include: (1) The emission spectrum takes the form of a broadband spectrum; (2) The color of the emission spectrum is influenced by different substrates; (3) Temperature significantly impacts the emission; (4)

Compared to f-f transitions, it exhibits strong emission intensity and a short fluorescence lifetime.

The last emission form is the electronic transition between the ligand and the metal ion.[59] Electrons in the ligand are transferred to the empty 4f orbitals of metal ions through a series of transitional processes, resulting in a broad emission band. This allowable transition significantly enhances the luminescence intensity and efficiency of rare earth ions. Representative ions include Sm^{3+}, Eu^{3+}, Tb^{3+}, and Tb^{4+}, which exhibit characteristic charge transfer bands in the near ultraviolet region. These charge transfer bands have the following characteristics: (1) The electronegativity of the ligand atom influences the position of the transfer band; (2) An increase in coordination number leads to a decrease in the energy of the charge transfer band; (3) The oxidation state of rare earth ions also significantly affects the position of the charge transfer band. The variety of electronic transition forms enriches the emission lines of rare earth ions, making rare earth luminescent materials an essential component in the industry.

4. The application of rare earth luminescent materials in biomedical field

Rare earth luminescent materials possess several outstanding characteristics, including excellent photostability, unique anti-Stokes shifts, sharp characteristic emission peaks, easily adjustable luminescence, and near-infrared excitation. These features make them widely applicable in the fields of optical displays and printed anti-counterfeiting.[60-62] Additionally, their high atomic number, low phonon energy, high X-ray absorption coefficient, long lifetime, and high long-term stability are extremely beneficial for the use of rare earth luminescent materials in X-ray imaging and X-ray medical treatments. Furthermore, their near-infrared excitation, deep penetration, low background noise, and low toxicity promote the development of rare earth luminescent materials in medical sensors and photodynamic therapy, among other medical technologies. This article primarily summarizes and introduces applications in X-ray imaging, drug sustained release and photodynamic therapy.

4.1 X-ray imaging

We understand that rare earth elements generally have high atomic numbers, which endows them with a strong ability to absorb X-rays. Given that rare earth nanophosphor materials possess high stability and significant X-ray absorption capabilities, utilizing these materials for X-ray imaging is a promising endeavor.[63,64] X-ray imaging: When an X-ray emitter irradiates an object, the degree of X-ray absorption varies due to the different elements, densities, and thicknesses of the materials. Consequently, the dose of X-rays transferred to the screen or film also varies, resulting in images with different contrasts on the screen or film.[65-68] The potential mechanism for X-ray scintillation imaging in rare earth nanophosphor materials involves the photons from X-rays first interacting with the atoms in the rare earth nanophosphor materials through the photoelectric effect and Compton scattering, releasing a large number of thermal electrons. These thermal electrons further thermalize to generate electron-hole pairs, ultimately causing the rare earth nanophosphor materials to emit fluorescence.

To assess the responsiveness of materials to X-rays, one typically considers several factors: the fluorescence/phosphorescence intensity, the stability of the material under X-ray excitation, the relationship between X-ray dose rate and the luminescence of the material, the light yield of the material under X-ray excitation, and the modulation transfer function (MTF) values of the material's scintillator film images under X-ray excitation.[69-71]

Firstly, the fluorescence/phosphorescence intensity of the material under X-ray excitation is crucial. As the term implies, a material's responsiveness to a particular excitation source must be characterized by the production of luminescence that is not weak when excited by that source. This ensures that the material has potential for subsequent applications. Secondly, stability is a vital criterion. Under the influence of the excitation source, the material must exhibit a certain level of stability, whether it be photostability, environmental stability, or chemical stability. Appropriate data must support its development for future use. The relationship between X-ray dose rate and the luminescence of materials is a mathematical value that requires identifying the lowest detectable dose rate of X-rays. If the material can still produce photoluminescence with sufficient intensity when excited by this minimum detectable dose rate, and if the safety of this dose rate meets human requirements, then this dose rate can

be defined as the lowest detectable dose rate for the material under the given excitation source. For inorganic scintillators used in X-ray diagnostics, the minimum dose is 5.50 μGy $_{air}S^{-1}$. If the tested and calculated minimum dose rate of the material is not higher than this minimum diagnostic dose, then the minimum dose rate of the material is suitable for applications such as detection and diagnosis in medical X-ray procedures.

The light yield of scintillator materials is defined as the number of visible photons produced per MeV of absorbed X-ray energy, indicating the efficiency of X-ray conversion.[72] Typically, a commercial LuAG:Ce scintillator with a known light yield of 22,000 photons/MeV is used as a reference, and then the light yield of the scintillator material is calculated. If the calculated light yield of the scintillator material is not significantly different from or much greater than that of the commercial LuAG:Ce scintillator, it indicates that the scintillator material has a certain response to X-rays. The spatial resolution of X-ray imaging of materials is generally calculated using the Modulation Transfer Function (MTF), which is the ability to distinguish adjacent details and their sharpness in a material.[73] Mathematically, spatial resolution can be determined by the pixel size in a matrix, and the pixel size parameter is measured using narrow slits, sharp objects, and line test patterns. For example, in X-ray spatial resolution testing, a standard X-ray resolution test pattern image is usually selected to directly test the spatial resolution of the material under X-ray excitation. The limit of clear lines is the preliminary spatial resolution of the material under X-ray excitation. The MTF of the material's scintillator film image is then calculated using the edge method and compared with the limit value (line pairs: lp) directly obtained from the X-ray resolution test pattern. If the calculated MTF value is not significantly different from the test value, the resolution value of the material's scintillator under X-ray excitation can be defined. Resolution is a simple concept to define the spatial resolution of an image, which is related to the physical/chemical properties of the material itself, but the imaging resolution can also be changed by adjusting the film thickness, film manufacturing process, and image capture device.[74] Interestingly, the dose of X-rays is irrelevant to the imaging resolution, meaning that the resolution of the image does not improve with an increase in the dose of X-rays, and is mainly related to the performance of the material

itself. Ma et al.[75] studied the high-resolution X-ray imaging of $NaGdF_4$:Ce/Tb nanomaterials (Figure 7), where the presence of Ce^{3+} and Gd^{3+} significantly reduces the number of electron-hole pairs produced by X-ray excitation of this rare earth luminescent material, and the photoluminescence afterglow is also greatly reduced, reducing light scattering and significantly improving the resolution of X-ray imaging, which is higher than most publicly known X-ray scintillator materials and commercial scintillator CsI(Ti).

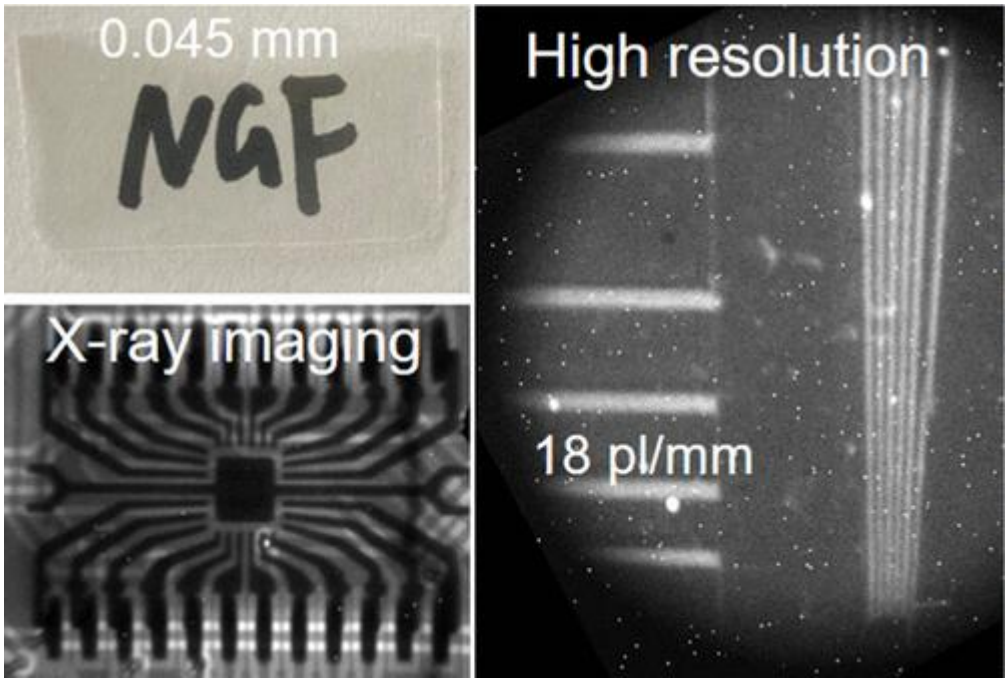

Figure 7. The high-resolution X-ray imaging of $NaGdF_4$:Ce/Tb nanomaterials. Adapted with permission.[75] Copyright 2021 American Chemical Society.

Scintillator materials that emit light upon X-ray excitation (XEL) exhibit varying luminescent effects under different X-ray radiation doses.[76] When these materials display high resolution and clear contrast under low-dose radiation, they have immense potential in security detection and medical treatment. Rare earth nano-luminescent materials also have the potential to become the next generation of X-ray scintillator materials. In recent years, with increasing attention, these materials have demonstrated excellent scintillation performance in the field of X-ray imaging.[77] The spatial resolution of scintillator materials is tested using the edge method,[78] which quantifies the imaging capability of the material with a numerical value (line pairs). Ma

et al.[75] investigated the X-ray imaging applications of $NaGdF_4$:Ce/Tb rare earth nano-scintillators, which can achieve a spatial resolution as high as 18.6 lp/mm under X-ray radiation. Lu et al. [79]found that under X-ray radiation, $LiLuF_4$ has a higher X-ray absorption capability compared to CdTe, CdZnTe, BaF_2, and $CsPbBr_3$. The $LiLuF_4$:15Tb rare earth nano-scintillator exhibits a minimum detection limit of 36.31 $nGy_{air}s^{-1}$, significantly lower than the commonly used X-ray diagnostic dose rate (5.50 $\mu Gy_{air}s^{-1}$), and its spatial resolution surpasses 20 lp mm^{-1}. Liu et al.[80] explored $NaLuF_4$:Tb@$NaYF_4$ rare earth nano-scintillators, which under X-ray radiation, demonstrate excellent long afterglow luminescence. Compared to the spatial resolution of traditional X-ray scintillator films (typically less than 5 lp mm^{-1}), this scintillator film's spatial resolution exceeds 20 lp mm^{-1}.

Zhao et al. [81] developed a novel nanohybrid material based on Bi_2Se_3-conjugated upconversion nanoparticles (UCNPs) using an in situ growth method. The synthesized UCNP-Bi_2Se_3 nanohybrid material exhibits excellent cell upconversion luminescence performance, good CT imaging, and cancer cell ablation capabilities, making it an ideal candidate for non-invasive multimodal imaging-guided photothermal therapy, suitable for precise cancer diagnosis and treatment. Nampi et al. [82] synthesized $NaYF_4$ (host lattice) doped with Yb^{3+} (sensitizer) and Er^{3+} (activator) using a hydrothermal method with the addition of polyethyleneimine (PEI). Preliminary research indicates that UCNPs have the potential to be applied in bioimaging and tissue imaging of cellular structures alongside multiphoton dyes. With appropriate surface modification and suitable biological conjugation procedures, UCNPs can be utilized for targeted imaging as well as sensing of biomolecules and proteins. Zhang et al. [83]designed an ultrasensitive photochemical sensor for hydrogen sulfide (H_2S). They prepared a complex probe with Tb^{3+} as the luminescent center, replacing the pyridine-2,6-dicarboxylic acid ligand with azide ($-N_3$), achieving the detection of trace amounts of H_2S in biological samples. This probe, which has high hydrophilicity, effectively eliminates the background fluorescence of biological samples by utilizing a delayed 0.1ms fluorescence collection, enabling precise quantitative analysis of H_2S levels in plasma.

4.2 Drug delivery

Drug delivery systems based on rare earth-doped nanomaterials combine the dual characteristics of luminescence and drug release. Since the location of drug delivery can be marked by fluorescence and the efficiency of drug release can also be detected, these rare earth-doped nanomaterials have tremendous potential application value in theragnostic. Doxorubicin hydrochloride (DOX) and Ibuprofen (IBU) are often used as drug models. Drug delivery systems can generally be divided into three categories: (1) drugs are placed in the mesoporous silica layer coated on the outer surface of nanomaterials; (2) drugs are placed in the hollow mesoporous lanthanum materials; (3) drugs are placed in hollow lanthanum nanospheres. Mesoporous silica has many unique properties, such as their ease of forming mesoporous structures, large specific surface area, abundant Si-OH groups, and excellent biocompatibility, making them considered a good drug carrier. Typically, silica spheres are synthesized using a templating method, which involves the preparation of a core and a shell layer, followed by the removal of the core template. To store drugs within the mesoporous silica spaces and prevent premature drug release before reaching the target location, we usually require a system with stimulus-responsive and controllable release properties. Temperature, pH, visible/near-infrared light, and magnetic fields are all responses that have been applied to drug release systems.

Liu et al. used a photo-switch to initiate drug release.[84] They synthesized mesoporous silica-coated $NaYF_4$:Yb, Tm@$NaYF_4$ nanoparticles and modified them with azobenzene, loading DOX into the pores. Under 980 nm excitation, the nanoparticles emit ultraviolet and visible light, which is immediately absorbed by the photo-sensitive nitrogen-containing molecules in the silica pores. Under ultraviolet light irradiation, the nitrogen-containing molecules isomerize from the trans to the cis configuration, and conversely, under visible light irradiation, the cis isomerizes back to the trans. The reversible photo-responsive process of the upconversion nanoparticles under ultraviolet and visible light excitation generates a continuous inversion conversion process, and the rotation of the nitrogen-containing molecules, front and back, forms a molecular turbine that drives the release of DOX. This method has been extended to release proteins, enzymes, hydrophobic coumarin 153, and Nile red, among others.

Combining rare earth-doped nanoparticles with a mesoporous silica layer typically requires

complex operational steps and post-treatment, and it is necessary to maintain a pore-forming medium throughout the synthesis process, followed by calcination to completely remove it after synthesis. Loading drugs into the hollow spheres of mesoporous rare earth layers is a more direct and simple drug delivery system. For example, $GdVO_4$:Dy (Figure 8),[85] Gd_2O_3:Eu,[86] $GdVO_4$:Yb, Er/Ho/Tm,[87] and $Yb(OH)CO_3$@$YbPO_4$:Er nano spheres[88] have all been widely studied.

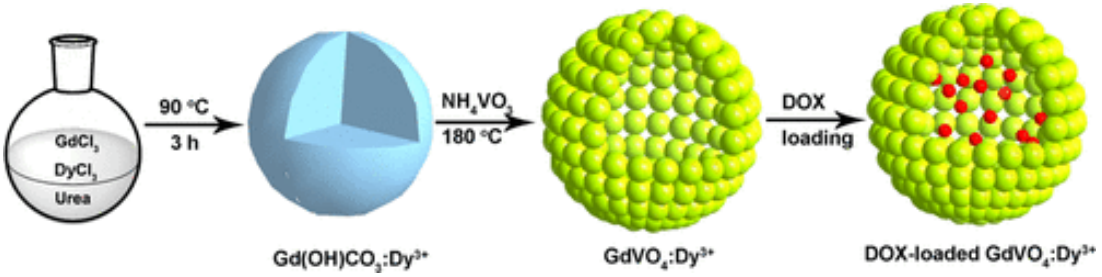

Figure 8. Scheme for the preparation process of $GdVO_4:Dy^{3+}$ and subsequent loading of anticancer drug (doxorubicin hydrochloride, DOX). Adapted with permission.[85] Copyright 2013 American Chemical Society.

4.3 Photodynamic therapy

Photodynamic therapy (PDT) involves the use of non-toxic dyes, known as photosensitizers, which, when activated by a light source, produce reactive oxygen species (ROS) in an oxygen-dependent reaction. These ROS, when specifically applied to biological cells, can lead to cell death and tissue destruction.[89,90] The photosensitizer (PS), light source, and oxygen all play crucial roles in PDT, and each of these components is non-toxic.[91] However, they can precisely and predictably treat cells or tissues, making PDT increasingly attractive, especially in cancer treatment. PDT is characterized by minimal side effects, low long-term toxicity, precise targeting, and the ability to trigger anti-tumor immune responses that can extend the survival of cancer patients.[90] These unique features make PDT a potentially ideal strategy for cancer treatment.

In the three critical aspects of PDT, finding suitable materials for photosensitizers is essential, the light source must have adequate penetration, and there is a need to overcome severe oxygen

dependency. Rare earth nano-luminescent materials can effectively address these issues. These materials can be excited by near-infrared light with strong penetration to produce photoluminescence.[92,93] Their fluorescence is non-blinking and non-bleaching, and the upconversion emission covers a wide range of areas (from the ultraviolet to the visible to the near-infrared regions), which gives rare earth nano-luminescent materials great potential in PDT. Not only can these materials be excited by near-infrared light to produce upconversion luminescence, but they are also easily surface-functionalized, allowing them to be combined with other materials to form multifunctional nano-composites, enhancing their precise targeting capabilities.

For PDT applications, rare earth nano-luminescent materials also require the selection of appropriate host matrices, sensitizers, and activators. Common host matrices include CaF_2 (Figure 9),[94] $NaYF_4$ (Figure 10),[95] $NaGdF_4$,[96,97] $NaLuF_4$,[98,99] and $BaYF_5$.[100,101] These matrices must be lattice-matched with the doped sensitizer and activator rare earth ions to ensure the successful preparation of the rare earth nano-luminescent materials and subsequent PDT. In terms of biological therapeutic applications, the sensitizers for rare earth nano-luminescent materials are not unique and still rely on Yb^{3+} and Nd^{3+} to transfer excitation energy. The activators are generally Er^{3+}, Ho^{3+}, and Tm^{3+}.[102,103] Tm^{3+}, when excited by near-infrared light, has multiple characteristic emission peaks, with the main peak located in the 800 nm near-infrared region, making Tm^{3+} particularly suitable for imaging in deep biological tissues.

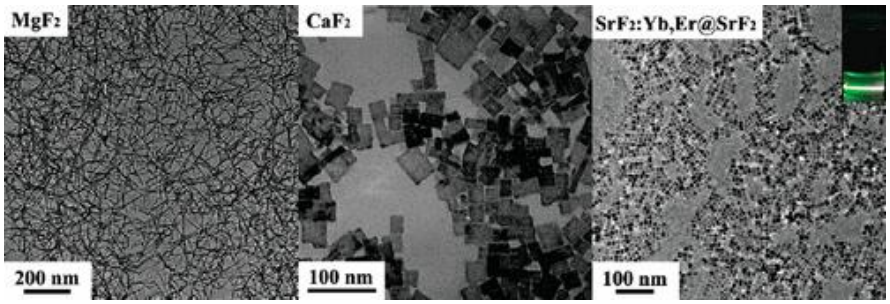

Figure 9. The TEM images of MgF_2 nanoneedle-constructed 3D networks, cubic CaF_2 nanoplates and core/shell SrF_2:Yb,Er@SrF_2 nanocrystals.

Adapted with permission.[94] Copyright 2009 American Chemical Society.

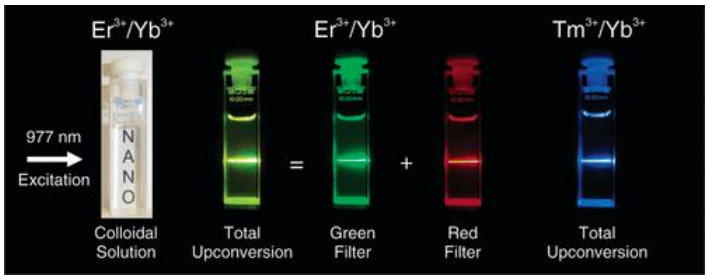

Figure 10. The colloidal solutions of $NaYF_4$ nanocrystals in dichloromethane excited at 977 nm demonstrating upconversion luminescence. Adapted with permission.[95] Copyright 2006 American Chemical Society.

Additionally, it has characteristic emission peaks at 479 nm, 450 nm, and 350 nm, and the photoluminescence produced can activate certain photosensitizers and semiconductors, such as ZnO and TiO_2 (Figure 11 and 12).[104-107] Rare earth nano-luminescent materials can be excited by various light sources, and near-infrared light is a good choice for PDT. Within the near-infrared region, 808 nm excitation is optimal, primarily because 808 nm has the lowest absorption by all biological molecules and is less likely to cause overheating effects among near-infrared excitation sources.[108] Therefore, rare earth nano-luminescent materials primarily doped with Nd^{3+} are typically used for PDT under 808 nm excitation.

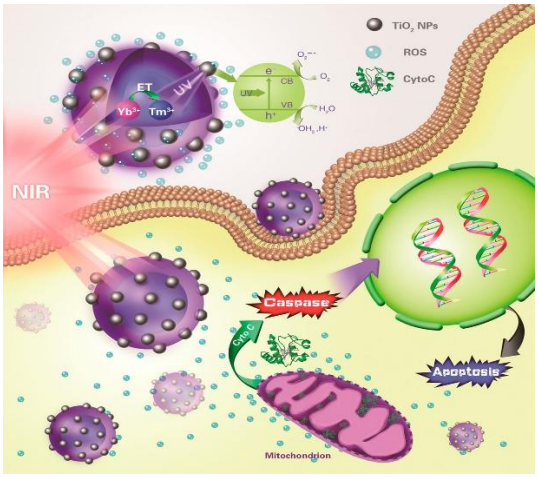

Figure 11. Plot for potential molecular mechanism of inducing apoptosis with UCNPs@TiO_2-based NIR light mediated PDT treatment. Adapted with permission.[104] Copyright 2015 American Chemical Society.

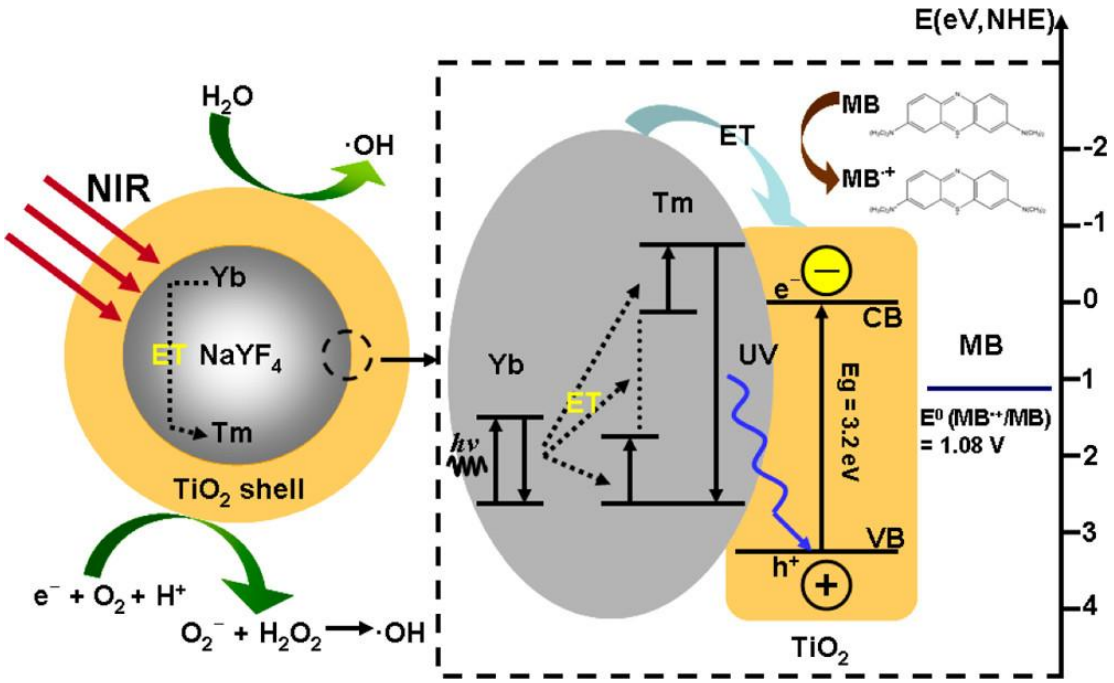

Figure 12. Illustrative Diagrams of Energy Transfer among Yb^{3+}, Tm^{3+}, and TiO_2. Adapted with permission.[107] Copyright 2013 American Chemical Society.

Zhang et al. synthesized a multifunctional material by loading the photosensitizer porphyrin 540 into silica-coated Y_2O_3:Yb, Er nanoparticles, which selectively killed cancer cells upon infrared excitation by generating singlet oxygen (Figure 13).[109] Wang et al. demonstrated for the first time the application of photodynamic therapy based on upconversion nanoparticles in vivo,[110] by non-covalently linking Ce6 to polyethylene glycol-modified upconversion nanoparticles. The resulting upconversion nanoparticle-Ce6 composite was able to enter cancer cells and cause cell death under 980 nm light irradiation. After 30 minutes of irradiation with an excitation light of 0.5 W/cm^2, 70 % of the tumor cells at the injection site of the upconversion particles-Ce6 were eliminated. Iris et al. developed a new method to enhance the effectiveness of photodynamic therapy,[92] by co-loading ZnPc and MC540 into the mesoporous silica layer of $NaYF_4$:Yb, Er nanoparticles. The two main emission peaks of $NaYF_4$:Yb, Er, green (~540 nm) and red (~660 nm), match the absorption of ZnPc and MC540, allowing for the simultaneous activation of both photosensitizers.

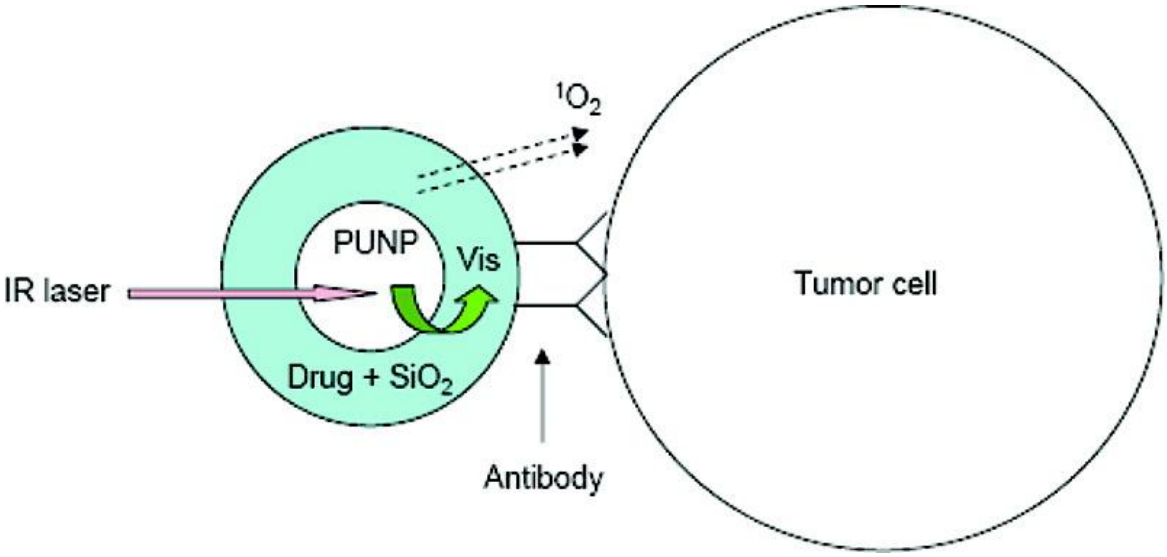

Figure 13. Schematic of the design of the versatile photosensitizer based on photon upconverting nanoparticles (PUNPs). Adapted with permission.[109] Copyright 2007 American Chemical Society.

CONCLUSIONS

In summary, with the continuous research and development of material chemistry, rare earth doped materials have attracted much attention due to their unique multifunctional properties, and they have gradually shown great application prospects in the field of X-ray imaging, drug delivery and photodynamic therapy. This has also prompted researchers to carry out extensive research on the synthesis, morphology control, property exploration and function exploration of materials. In the field of biomedicine, on the one hand, the size and morphology of materials not only affect their own properties but also affect their biological applicability. On the other hand, people are trying to realize the functions of diagnosis, targeting and treatment at the same time by designing multifunctional composite materials. Therefore, it is of great significance to control the size and shape of materials and design composite functional materials for further application of materials.

Conflicts of Interests

The authors declare no competing financial interest.

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