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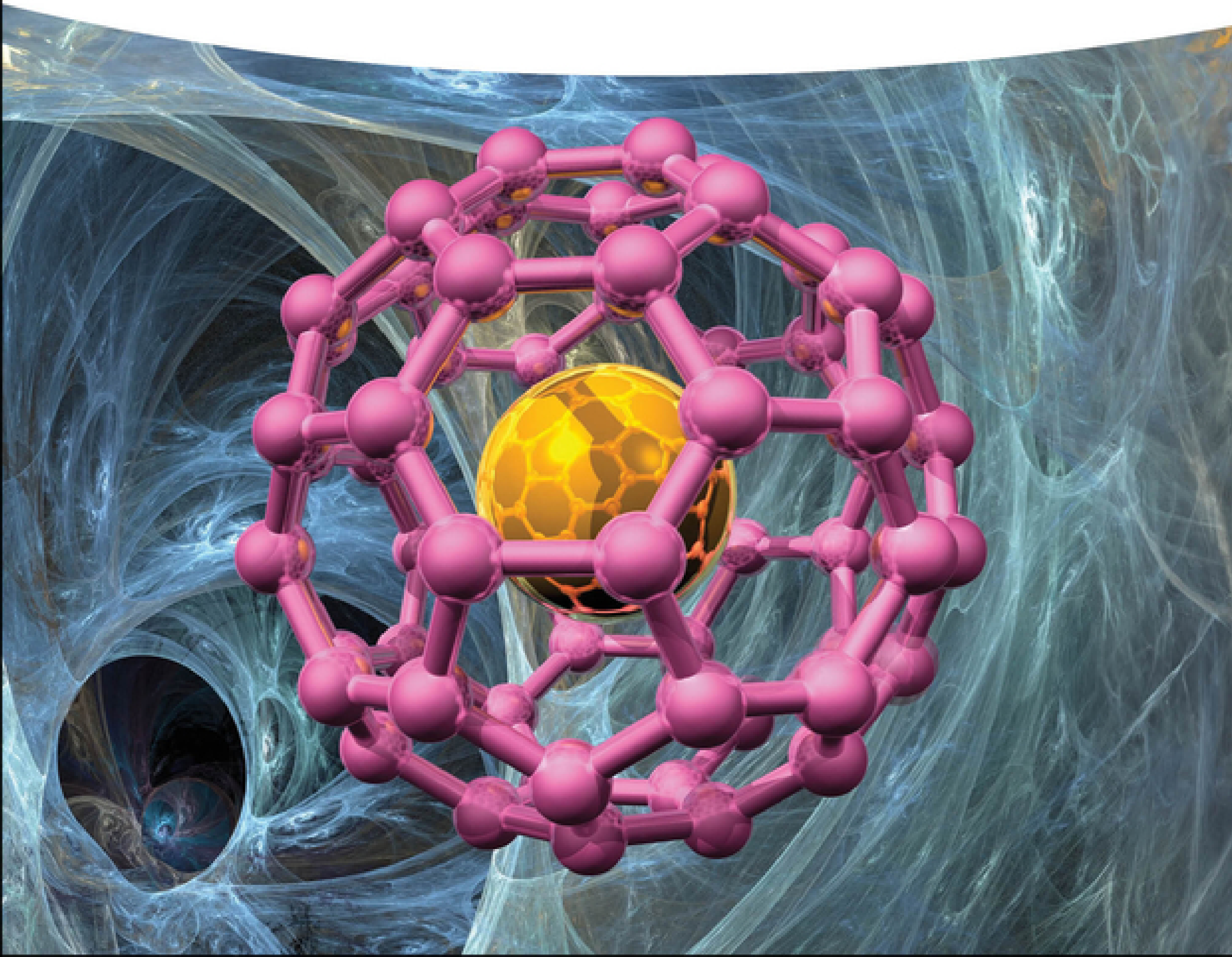
Photofunctional Nanomaterials for Biomedical Applications



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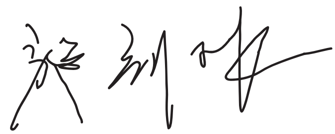
Foreword

According to the data by the International Agency for Research on Cancer of the World Health Organization, the global incidence rate of cancer can potentially escalate to 29.5 million by 2040. Even in the present era, cancer continues to persist as a prominent contributor to the deaths of humans worldwide. Tumor metastasis, as the leading factor, accounts for approximately 90% of cancer-related fatalities. In fact, metastasis may occur even at the time of cancer diagnosis for a number of patients. Importantly, plenty of individuals afflicted with lung cancer exhibit metastatic disease, as evidenced by an over 80% diagnosis rate. Furthermore, recent research have revealed the presence of diverse bacteria within the majority of solid tumors, which has been evidenced to be responsible for tumor metastasis and colonization. The current prevailing treatment modalities, such as chemotherapy, hormonal therapy, and radiation therapy, have achieved significant progress in treating metastatic cancer and prolonging the survival of patients to certain extents; unfortunately, the overall therapeutic efficacy remains unsatisfactory.

The advancements in nanotechnology have aroused significant progress or even breakthroughs in the biomedical fields. Photofunctional nanomaterials, being a novel class of light-responsive materials, have gained extensive attention and utilization. For example, they as carriers can achieve targeted drug delivery and controlled release, resulting in the enhanced efficacy of medications. After ingenious modifications with functional molecules, such as photosensitizers, photothermal agents, chemotherapeutic drugs, and gene composites, photofunctional nanomaterials exhibit great potential for advancing various therapeutic modalities such as photodynamic therapy, photothermal therapy, chemotherapy, antibacterial therapy, gene therapy, and biosensing. Moreover, these nanomaterials also enable simultaneous image-guided multi-modal therapy. Therefore, photofunctional nanomaterials hold immense promise in the biomedical fields.

Based on this, in this book, Professor Chunxia Li, Professor Jun Lin, and their collaborators have reviewed and summarized recent research progress on photofunctional nanomaterials for biomedical fields in a comprehensive and well-organized manner. Impressively, the authors have elucidated the underlying functioning mechanisms of these nanomaterials in depth and extensively discussed the challenges encountered by photofunctional nanomaterials along with their future development prospects. This book offers researchers in the nanomedicine field a highly methodical and professional compendium and reference summarizing the application of photofunctional nanomaterials in a broad spectrum.

Finally, it is anticipated that this publication will greatly benefit further advancements in the research and applications of photofunctional nanomaterials and establish a robust groundwork for the future clinical translation.



January 30, 2024

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Preface

In recent years, morbidity and mortality of cancer have obviously increased; therefore, cancer has become a serious threat to human health. Thus, how to provide new clues to prewarning and early diagnosis and therapy of cancer is highly demanded. To achieve this goal, the new material chemistry is essential because the nanoparticles have to be uniform and tunable in terms of physical properties such as size, shape, and surface. Photofunctional nanomaterials are light-driven functional materials that can effectively convert and utilize light energy, an inexhaustible source of clean and renewable energy. Especially, near-infrared (NIR) light is a highly accurate non-physical and non-invasive external stimulation method that has the unique advantages of high penetration depth and low fluorescence background interference, achieving synchronous control of time and space. Therefore, the light can be utilized to achieve controllable chemotherapy or photodynamic therapy (PDT). Photothermal nanomaterials can convert light energy into heat energy, resulting in local overheating and tumor ablation (photothermal therapy, PTT). Therefore, the design and applications of photofunctional nanocomposites are an important branch of biomedical functional materials and have become the frontier research direction in interdisciplinary fields.

This book will focus on providing researchers and graduate/undergraduate students in interdisciplinary fields including chemistry, materials science, and biomedicine, highlighting their full potential in biomedical applications including tumor diagnosis and therapy, photogenetically engineered bacteria, optical information storage, and biosensing.

Chapter 1 demonstrates a basic introduction and classification of photofunctional nanomaterials as well as their applications in biomedical fields.

From Chapters 2–7, the rare earth luminescence nanomaterials are systematically introduced, mainly shedding light on their luminescence mechanism, multiform luminescence modulation, construction of composites, and the corresponding applications in gene delivery as well as the biosafety evaluation.

Chapter 8 provides an overview of photosensitizers for PDT. The basic principles of PDT, classifications of various photosensitizers, and the mechanisms during treatment are outlined.

Chapter 9 introduces the persistent luminescent materials for optical information storage applications. And the design of ternary quantum dots and their application in tumor-related marker detection, imaging, and therapy are mentioned in Chapter 10.

Chapter 11 summarizes nanomaterial-induced pyroptosis and immunotherapy including pyroptosis pathways and the potential for immunotherapy, especially in activating effector T cells and promoting dendritic cell maturation.

Chapter 12 mainly highlights the latest developments of inorganic nanomaterials in PTT. The mechanism and application of nanomaterial-based PTT against cancer by photothermal immunotherapy are also expounded.

Chapter 13 begins by presenting an overview of the antibacterial mechanisms inherent in photofunctional antibacterial nanomaterials, focusing on the approaches developed to overcome resistance in multidrug-resistant (MDR) pathogens and the prominent challenges in the field of photofunctional antibacterial nanomaterials.

Chapter 15 describes the concept of X-ray-activated PDT, outlines the interaction mechanisms between X-rays and nanosystems, and introduces the application of X-ray-activated nanosystems in photodynamic therapy for deep-seated tumors.

And, the last chapter, Chapter 16, introduces the perspectives on the opportunities and potential benefits of photofunctional nanomaterials for biomedicine.

Finally, we greatly acknowledge the substantial contribution from Prof. Hongjie Zhang, Prof. Rongjun Xie, Prof. Yulei Chang, Prof. Ruichan Lv, Prof. Xiaoji Xie, Prof. Renren Deng, Prof. Tao Zhang, Prof. Guanying Chen, Prof. Jing Feng, Prof. Yixi Zhuang, Prof. Ziyong Cheng, Prof. Bingbing Ding, Prof. Ping'an Ma, Prof. Zhiyao Hou, Prof. Biao Dong, Prof. Lin Wang, Prof. Piaoping Yang, Prof. Jinliang Liu, and Dr. Qianqian Sun to this book.

26 January 2024
Qingdao, China

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1

General Introduction and Background of Photofunctional Nanomaterials in Biomedical Applications

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1.1 Introduction to Nanomaterials

From the perspective of human history, the history of human knowledge of the world is the history of the development of scale and materials. With the continuous development of science and technology, human cognition of the world has long exceeded the single macroscopic world, and the emergence of nanotechnology in 1984 has directly brought human beings into an infinite and mysterious "small size, big world." Therefore, as an important tool for human beings to explore the microscopic world, the research and application of nanomaterials have been widely valued by many disciplines in recent years [1].

Nanomaterials are materials that have at least one dimension in three-dimensional space in the nanoscale range (1–100 nm, 1 nm = 10^{-9} m) or are composed of them as basic units [2, 3] and are known as "the most promising materials of the 21st century." As research progresses, scientists are gradually discovering that materials with dimensions at the nanoscale can exhibit unique properties that are superior to those of conventional materials in terms of physics, chemistry, optics, thermodynamics, and magnetism [4–6]. This is because the ratio of the number of atoms on the surface of nanomaterials to the total number of atoms increases dramatically as the particle size decreases. The special properties of nanomaterials are as follows.

1.1.1 Surface and Interfacial Effects

When the size of a material is reduced to the nanoscale, the number of surface atoms, the surface area, and the surface energy increase dramatically, and at the same time, a large number of unsaturated bonds, dangling bonds, and active centers

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appear in nanomaterials, and the surface defects of the material also increase. These defects introduce many surface states in the energy barrier band gap, which become traps for electrons or holes, seriously affecting the optical, photoelectrochemical, and nonlinear optical properties of the materials [7–10]. Therefore, many new properties of nanomaterials are inextricably linked to their surface and interfacial effects.

1.1.2 Small Size Effect

When the size of the material is comparable to or smaller than physical quantities, such as the wavelength of light waves (less than 100 nm), the radius of exciton bands of De Broglie wavelengths (1–10 nm), or the coherence length of superconductivity, the periodic boundary conditions of the internal crystals will be disrupted, and the density of atoms near the surface layer of the particles of amorphous nanoparticles will be reduced. This will lead to significant changes in the macroscopic physical and chemical properties (such as sound, light, electricity, magnetism, heat, and mechanics) of the nanomaterials [11–14].

1.1.3 Quantum Size Effect

When the size of the material is reduced to the nanometer scale, the electronic energy levels near the metallic Fermi energy level change from continuous to discrete, and the continuous energy band, valence band, and conduction band of semiconductors become discrete energy level structures, and the bandgap broadening phenomenon is called the quantum size effect [15–18]. When the energy level spacing is greater than the thermal, magnetic, electrostatic, photonic, or superconducting condensation energy, nanomaterials will exhibit a range of properties that are very different from those of bulk materials.

1.1.4 Macroscopic Quantum Tunneling Effects

When the scale of a material enters the nanometer range, certain macroscopic quantities of nanoparticles (such as particle magnetization intensity, magnetic flux in quantum coherent devices, and electric charge) exhibit tunneling effects that can cross the potential barriers of the macroscopic system and produce changes, known as macroscopic quantum tunneling effect [19–22]. Macroscopic quantum tunneling is the theoretical basis for future microelectronic and optoelectronic devices.

Because of the special properties mentioned above, nanomaterials have many more excellent physicochemical properties than macroscopic materials. Physically, nanomaterials have good electrical conductivity, dielectricity, magnetism, and mechanical properties. From a chemical point of view, nanomaterials are highly active on the surface and are particularly prone to adsorbing other atoms or chemically reacting with other atoms, which greatly improves the catalytic ability of the reaction. As a result, nanomaterials have broad application prospects in many fields such as optoelectronics, environmental science, and biomedicine.

1.2 Introduction and Classification of Photofunctional Nanomaterials

The development and application of materials are a sign of the progress of time and human civilization. The history of materials is as long as the history of mankind. Mankind has gone through a long period of Stone Age, Bronze Age, and Iron Age. Nowadays, with the continuous improvement of nanomaterial synthesis technology, research on nanomaterials has gradually shifted to refinement and functionalization. At the same time, with the growing demand for material functions in science and technology and living standards, as well as the cross-fertilization of the frontiers of various disciplines, a wide range of functionalized nanomaterials have emerged.

Functionalized nanomaterials are diverse and wide-ranging, and there are many ways to classify them. Functional nanomaterials can be classified into electrical nanomaterials, magnetic nanomaterials, optical nanomaterials, thermal nanomaterials, acoustic nanomaterials, chemical nanomaterials, invisible nanomaterials, and so on according to their performance, which is spectacular, and a large number of new functional nanomaterials have been introduced every year. Among them, a series of nanomaterials with unique optical properties (light-functional nanomaterials) have been successfully prepared [23–28], which has become one of the hotspots in the field of functionalized nanomaterials in recent years and has been widely applied in many fields, such as bioanalysis and sensing, illumination and display, environmental monitoring and purification, energy conversion and storage, biomedicine, anticounterfeiting, and information.

In fact, the understanding of optical phenomena in nature has a long history, and it can be said that human beings have progressed along with the knowledge of optical phenomena in nature. For example, fire is man's first perception of light, without which human society would not have survived. The propagation and absorption of light profoundly affect all aspects of nature, and without the phenomena of selective absorption, scattering, transmission, and reflection of light by matter, there would be no colors, no heat, no energy transformed by light, and no production of all biomass in nature. Photofunctional nanomaterials are light-driven functional materials that can effectively convert and utilize light energy, an inexhaustible source of clean and renewable energy. To date, the applications of photofunctional nanomaterials are very diverse, but essentially, the same physical and chemical processes take place and follow similar laws, including photon capture, photon absorption and utilization (conversion), and physicochemical processes at the surface interface [29].

1.2.1 Capture of Photons

Light has a fluctuating and particle duality (wave-particle duality), and when considering the energy conversion between light and electrons, light is treated as a particle called a photon. The trapping of photons is the first step in the process of light conversion and utilization by photofunctional nanomaterials, and the more photons that are trapped, the greater the chance that they will be absorbed. It can also be assumed that the photon trapping ability of a material determines the upper limit of its light conversion efficiency. In general, the photon trapping capability of photofunctional nanomaterials can be increased in three directions: broadening the absorption spectral range of the material, reducing the loss of light after it has passed through the material, and increasing the optical range of light in the material.

1.2.2 Absorption and Conversion of Photons

In addition to trapping as many photons as possible, photofunctional nanomaterials must have the ability to absorb and convert the trapped photons into phonon vibrations, photogenerated electron-hole pairs, or other energies. When light is shone on a material, various physicochemical effects such as photothermal effect, photoluminescence, photoelectric effect, and photochemical effect, are produced due to electromagnetic vibrations of electromagnetic waves or inelastic collisions of photons.

Among them, the photothermal effect refers to the fact that photothermal materials, after absorbing the energy of light radiation, do not directly cause a change in the internal electronic state but convert the absorbed light energy into the vibration of the crystal point structure (which means the production of phonons), thus causing a temperature rise and the generation of thermal energy [30]. As the research progressed, it was found that the photothermal effect of photofunctional nanomaterials depends not only on the incident light but also on the absorption spectrum of the material itself. Materials are dense systems consisting of a large number of atoms and molecules, and thermal energy is the average kinetic energy of the irregular motion of these particles. In other words, the accelerated motion of atoms and molecules at the microscopic level corresponds exactly to the increased temperature of the material at the macroscopic level (known as heating). The characteristic frequencies of the continuous relative vibrations and rotations of the atoms and molecules in the material are similar to those of infrared light, so they can resonate with external infrared light. Therefore, when a material is irradiated with infrared light, the motion of the atoms and molecules of the material will be enhanced, and a large amount of heat will be emitted. In contrast, the material absorbs less blue-violet light, resulting in less heat generation and a poorer thermal effect.

Photoluminescence is the process by which a material absorbs photons and then re-radiates them [31]. When the material is irradiated with light of a certain wavelength, the electrons in the ground state of the material (mainly π electrons and f and d electrons) are excited to a high-energy state, and when the external light stops, the electrons in the excited state will jump back to the ground state. In the process of the electron jump, some of the energy is emitted in the form of photons to accomplish the purpose of the light. Photoluminescence can be divided into two categories according to the delay time: fluorescence and phosphorescence [32]. Fluorescence is the emission of photons immediately after the substance is excited, and the luminescence time is $\leq 10^{-8}$ seconds. Phosphorescence can continue to emit light for a long time, and usually, the luminescence time is $\geq 10^{-8}$ seconds. According to light excitation and emission, photoluminescent nanomaterials can be classified into upconversion luminescence or downconversion luminescence nanomaterials according to the nature of their light emission. Among them, upconversion luminescence is a photoluminescence phenomenon that violates Stokes' law, which is manifested by the conversion of several low-energy (long-wavelength) photons into one high-energy (short-wavelength) photon [33]. Downconversion luminescence is a photoluminescence phenomenon that obeys Stokes' law and is manifested by the conversion of a high-energy photon into one or more low-energy photons [34]. When one low-energy photon is emitted, it is commonly referred to as luminescence, and when two or more low-energy photons are emitted, it is referred to as quantum clipping of luminescence.

Photoelectric effect, which is the electrical effect of light, refers to the material in the light of the phenomenon of emission of electrons, the essence of photon excitation material to produce electrons and hole pairs; electrons migrate into the external circuit to do work, manifested as electrical energy [35]. Photochemical effect is the chemical effect of light, which refers to the material used in the photon excitation to produce electrons and hole pairs. They were with the reactant redox reaction, stored as chemical energy phenomenon [36].

1.2.3 Physical-chemical Processes at the Surface Interface

The physical processes at the surface interface of photofunctional nanomaterials mainly involve thermal radiation dissipation and relaxation quenching of photogenerated photons. In photothermal materials, by controlling the composition and structure of the nanomaterials, the radiation angle coefficients of the materials can be effectively reduced, thereby reducing the dissipation of thermal energy and improving the utilization of photothermal conversion energy. In luminescent materials, photons generated by photoluminescence can be recaptured by the material and achieve relaxation by nonradiative bonding, thus reducing the luminescence effect. In semiconductor nanomaterials, photoelectrons migrate to the surface of the material and return to the interior of the material to recombine with holes after work is done by the external circuit, achieving the conversion of light energy into electrical energy.

Surface interface chemical reactions of photofunctional nanomaterials usually occur during photocatalysis of the materials. Photogenerated electrons and holes migrate to the surface or interface of the material and combine with electron acceptors or donors adsorbed on the surface of the photocatalytic material to undergo a redox reaction, storing the energy in the chemical bonds of the products and realizing the conversion of light energy into chemical energy. The detailed process of the chemical reaction at the surface interface roughly involves the following processes. First, the reactants must diffuse around the material and pass through the Helmholtz layer to be adsorbed onto the active sites of the material. Next, the reactants undergo structural rearrangement at the active site and undergo redox reactions with photogenerated electron holes. Finally, the reaction products desorb from the surface of the material and return to the reaction solution. In the whole process, a series of elementary reactions such as adsorption of reactants, charge exchange, and desorption of products together constitute the whole interfacial reaction process.

1.3 Introduction to Nanobiomedicine

In recent years, nanomaterials have been gradually integrated with biology and medicine in the development process, gradually forming a new discipline, namely "nanobiomedicine" (Figure 1.1) [38, 39]. Some people call the cooperation between nanomaterials and biomedicine "a great change" because it not only opens the door for nanobiology and nanomedicine but also brings new opportunities for biomedical research and clinical application. Governments around the world have increased the investment of funds and personnel in nanomedicine research, and nanobiomedicine has rapidly become a frontier and hot topic in the development of the biotechnology field in various countries, attracting more and more attention and expectations.

To be more precise, nanobiomedicine is an emerging discipline that applies nanomaterials to biomedical field, which involves materials science, physics, chemistry, biology, medicine, quantum science, and many other fields, and has very distinctive multidisciplinary cross characteristics. The research directions of nanobiomedicine include but are not limited to drug delivery and release [40–42], bioimaging [43], diagnosis and treatment of diseases (especially tumors) [44, 45], biosensing [46, 47], tissue engineering, and so on [48–50].

1.3.1 Nano-drug Delivery Systems

Through the design and preparation of nanocarriers such as nanoparticles, nanocapsules, nanofibers, and drugs are encapsulated in nanoscale structures to achieve precise drug delivery and release. Such nano-drug delivery systems can improve drug bioavailability, reduce side effects, and enable targeted therapy.

1.3.2 Nano-imaging Technology

High-resolution nano-imaging technology has been developed by exploiting the special optical, magnetic, and acoustic properties of nanomaterials. For example, nanoparticles can be used as contrast agents for fluorescence imaging, magnetic resonance imaging (MRI), and photoacoustic imaging (PAI) to achieve accurate imaging of biological tissues and lesions.

1.3.3 Nano-diagnostic Technologies

By exploiting the special properties of nanomaterials, nano-diagnostic technologies have been developed for biomarker detection, early diagnosis of diseases, and prognostic assessment. For example, nanoprobes can be used to detect the presence and activity state of specific molecules, enabling highly sensitive and selective diagnosis.

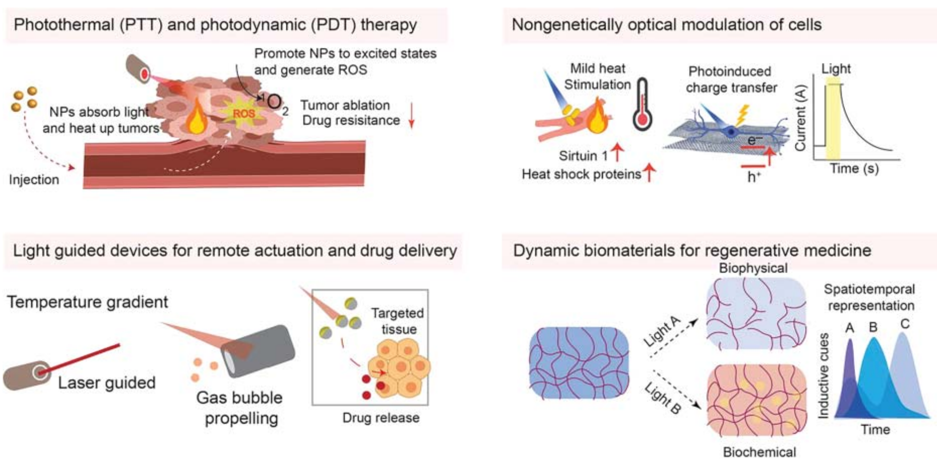

Figure 1.1 Inorganic light-responsive nanomaterials have been widely applied to four main research fields of light-responsive biomaterials, which consist of PTT and PDT, light-guided devices for remote actuation and drug delivery, nongenetically optical modulation of cells, and dynamic biomaterials for regenerative medicine. Source: [51]/John Wiley & Sons/CC by 4.0.

1.3.4 Nanotherapeutic Technology

Using the special properties of nanomaterials, therapeutic methods have been developed for thermotherapy, phototherapy, drug release, and other therapeutic methods. For example, thermal therapy for tumors can be achieved by absorbing light energy from nanomaterials to produce thermal effects or by using nanoparticles with specific responsiveness to achieve targeted drug release.

1.3.5 Nano-biosensors

Using the special properties of nanomaterials and biorecognition molecules, nano-biosensors have been developed to monitor biomolecules, cellular activities, and biological processes. These sensors can monitor physiological and pathological changes in organisms in real time and provide timely diagnostic and therapeutic feedback.

1.3.6 Tissue Engineering

Nanotechnology can be used to create materials such as scaffolds, nanoparticles, and nanofibers with nanoscale structures to support and guide cell growth and differentiation. These nanomaterials can mimic the microstructure of human tissues and provide a suitable physical and chemical environment to promote cell adhesion, proliferation, and differentiation. In addition, nanotechnology can be used to prepare nanocarriers with controlled drug release to enhance the therapeutic efficacy of tissue-engineered constructs.

At present, nanobiomedicine has become an important direction in the development of nanotechnology, and its booming momentum will continue to provide new technologies and methods for modern biomedical research, open up new horizons for important biomedical problems at the nanoscale, and reveal the relevant new principles and possible practical applications.

In the biomedical field, the choice of light has unique requirements. As a common external stimulus with the advantages of noninvasiveness, high spatial and temporal resolution, and spatial and temporal controllability (including controllable light intensity and wavelength), light sources play an important role in biology and medicine [37, 51] and can induce organisms to perform or regulate many specific biological processes at a given site, such as gene transfection, cell function, signaling, ion channel opening, protein activity, molecular isolation, and tissue regeneration (Figure 1.2) [52]. However, most current photosensitive components respond only to ultraviolet or visible light, so the use of light as an excitation source for biomedical applications is subject to certain dilemmas that jeopardize its potential applications; for example, ultraviolet or visible light is readily absorbed and scattered in living tissues and has a very shallow tissue penetration depth [53, 54]. In addition, ultraviolet is phototoxic and is likely to damage biomolecules such as nucleic acids, proteins, and lipids. These issues need to be addressed from two perspectives. On the one hand, since biological tissues cannot efficiently absorb near-infrared (NIR) light