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Nanoarchitectonics for Biomedical Research: Post-Nanotechnology Materials Approach for Bio-Active Application

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Nanoarchitectonics, as a post-nanotechnology concept, represents a methodology for the construction of functional materials employing atoms, molecules, and nanomaterials as essential components. The overarching objective of nanoarchitectonics is to develop functional systems comprising multiple functional units assembled in a hierarchical manner, as observed in biological systems. Nevertheless, the construction of such functional systems is a challenging endeavor. It would be prudent, therefore, to initially focus on the development of functional materials that interact with the complex functional structures of living organisms. Accordingly, this review article addresses the topic of nanoarchitecture as it pertains to biomedical applications. This article examines the current trends in research and presents examples of studies that support the concept of nanoarchitectonics and its applications in biomedical fields. The examples presented are as follows: i) molecular nanoarchitectonics developments, which are mainly based on molecular design and assembly; ii) material nanoarchitectonics examples, which are mainly based on material design using nanomaterials as components; and iii) biomedical applications with porous materials, which will be summarized under the heading of pore-engineered nanoarchitectonics due to their special structure. Finally, the review provides an overview of these examples and discusses future prospects.

1. Introduction

The human race is confronted with a multitude of challenges, which it addresses through the application of scientific and technological knowledge. In particular, the development of functional materials and problem-solving methods is of great significance. To address the energy problems facing humanity, a range of energy-related material systems have been developed, including solar cells,[1] fuel cells,[2] various batteries,[3] supercapacitors,[4] and other energy-related problems solutions.[5] In the field of environmental science, significant advancements have been made in the areas of sensing,[6] pollutant removal,[7] and carbon neutrality.[8] Similarly, in the biomedical sector, material science has made substantial contributions to biosensing,[9] drug delivery,[10] and cell engineering.[11] It is reasonable to assert that the advancement of material science has been a pivotal support to human society.

The development of materials technology has occurred in parallel with the evolution of human history. Initially, humans obtained materials from the natural environment and subsequently subjected them to a rudimentary processing technique. Subsequently, with the advancement of diverse scientific and technological disciplines during the 20th century, the capacity to synthesize novel materials was made possible. Even in modern science, organic chemistry,[12] inorganic chemistry,[13] polymer chemistry,[14] supramolecular chemistry,[15] coordination chemistry,[16] materials chemistry,[17] and biochemistry[18] play a major role in the development of new materials. It has also become clear that not only the material but also its nanostructure plays an important role.[19] For example, importance of nanostructures can be seen in reactive oxygen species (ROS)-responsive nanoparticles based on nonlinear optical properties, and relevant biomedical applications.[19d–19f] This is largely due to the progress of nanotechnology, which has been developing since the middle of the 20th century. Nanotechnology and related physics and physical chemistry have made it possible to directly observe and manipulate atoms and molecules,[20] and to analyze extremely small phenomena at the nano level.[21] It has been established that the development of functional materials with the desired physical properties hinges on the creation of materials based on an in-depth understanding of the nano-level structures that underpin their behavior.

It is evident that the subsequent phase is indispensable for the advancement of science and technology, which can facilitate the

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development of functional materials. This entails the fusion of basic science with nanotechnology for the creation of nano-based materials. In other words, it is the establishment of a paradigm for the creation of materials from the nanoscale. This function will be fulfilled by nanoarchitectonics, a concept that emerges from the field of post-nanotechnology (**Figure 1**).[22] Just as Richard Feynman proposed nanotechnology in the mid-20th century,[23] nanoarchitectonics was founded by Masakazu Aono on the eve of the 21st century.[24] This is a method of building functional materials by freely utilizing various scientific phenomena, processing technologies, and biological processes, using atoms, molecules, and nanomaterials as components.[25] This also includes conventional methods for similar purposes, such as self-assembly in supramolecular chemistry,[26] metal-organic frameworks (MOFs) in coordination chemistry,[27] covalent organic frameworks (COFs) in polymer chemistry,[28] template synthesis in materials chemistry,[29] self-assembled monolayers,[30] the Langmuir–Blodgett method,[31] and layer-by-layer (LbL) assembly[32] in interface science.

The term "nanoarchitectonics" is a very general and vague methodology that does not have any specific restrictions. Consequently, the concept of nanoarchitectonics can be employed to facilitate the creation of a multitude of materials and the advancement of their applications. The range of potential applications is considerable, even when considering articles published in recent years that include the term "nanoarchitectonics" in their title. It covers a wide range of topics, including material synthesis,[33] structural control,[34] elucidation of basic physical phenomena,[35] basic biochemistry,[36] general catalysts,[37] photocatalysts,[38] electrocatalysts,[39] solar cells,[40] fuel cells,[41] supercapacitors,[42] batteries,[43] other energy materials and devices,[44] environmental purification,[45] sensors,[46] devices,[47] drug delivery,[48] biosensors,[49] cell engineering,[50] and medical applications.[51] Originally, all materials are composed of atoms and molecules, so the methodology of nanoarchitectonics, which creates materials by building atoms and molecules, can be applied to all materials. In analogy with the theory of everything,[52] which is the ultimate goal of physics, nanoarchitectonics can be said to be a method for everything in material chemistry.[53] These statements imply a direction and definition of nanoarchitectonics. Nanoarchitectonics is a methodology that enables the creation of functional materials and systems from nanounits (atoms, molecules, and nanomaterials) through the combination of nanotechnology and other materials science with related technologies. This methodology could be applied to all materials.

Nanoarchitectonics techniques permit the combination of diverse processes, irrespective of whether they are equilibrium- or nonequilibrium-based. As a result, asymmetric and hierarchical structures can be readily produced.[54] In light of this background, the ultimate objective of nanoarchitectonics is the development of functional systems in which multiple functional units are hierarchically assembled, as observed in biological systems.[55] Indeed, one might argue that biological functional systems represent the pinnacle of nanoarchitectonics. Nevertheless, the construction of such functional systems presents a significant challenge. It would be prudent, therefore, to set the initial goal of nanoarchitectonics as the development of functional materials that interact with the complex functional structures of living organisms. In this context, this review article, entitled "Nanoarchitectonics for Biomedical Research", considers the role of nanoarchitectonics in the development of biomedical applications.

The field of biomedical applications is inherently complex, as it involves the manipulation of intricate biological material systems. The materials that act on them must be multifunctional. It is necessary to utilize materials systems that are capable of constructing and assembling a variety of functional elements. The development technologies in question are well aligned with the principles of nanoarchitectonics. This article examines the prevailing trends by presenting illustrative examples of research that endorse the concept of nanoarchitectonics and related instances in biomedical applications. The following examples are introduced: i) molecular nanoarchitectonics, which is based mainly on molecular designs and assembly; and ii) materials nanoarchitectonics, which is based mainly on material design using nanomaterials as components. Furthermore, due to their distinctive structure, biomedical applications utilizing porous materials are categorized as iii) pore-engineered nanoarchitectonics. In conclusion, the review will provide an overview of the aforementioned examples and discuss future prospects. The objective of this review is to present a selection of recent examples and to examine the potential impact of nanoarchitectonics in the biomedical field, while also identifying future research needs.

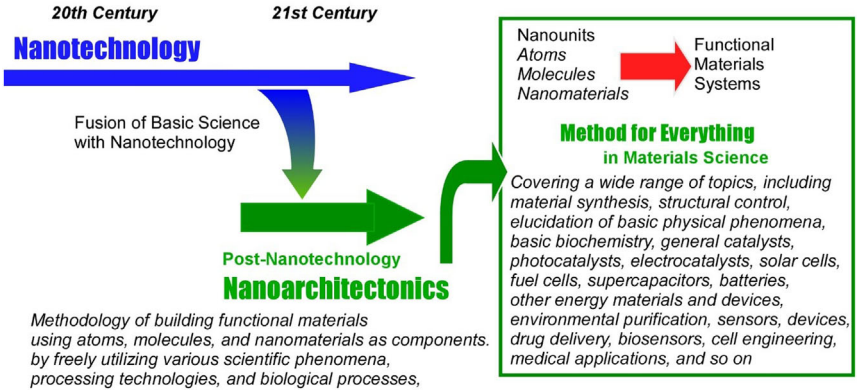

Figure 1. Conceptual outline and application fields of nanoarchitectonics.

2. Molecular Nanoarchitectonics

The functionality of biological systems is contingent upon a multitude of specificities. It is therefore reasonable to conclude that the control of vital functions through the devising of molecular structures represents a viable approach. The design of molecular structures and their incorporation into materials is a common undertaking in the field of biomedical research. This is regarded as a field of research based on the principles of molecular nanoarchitectonics. The application of intelligent molecular design has resulted in the creation of highly functionalized materials. Furthermore, nanoarchitectonics molecules can, on occasion, form supramolecular assemblies with highly efficacious biological functions. The following examples illustrate research that can be classified within this category.

Macrophages play diverse functions in innate immunity. Monocytes, the precursors of macrophages, adopt phenotypes that promote inflammatory or tissue repair functions. In this way, they respond to changes in the microenvironment. Imbalances between macrophage subtypes are characteristic of various pathologies, including rheumatoid arthritis, asthma, and age-related macular degeneration. It is important to control macrophage polarization in a spatiotemporal manner. This represents a new approach for treatment with fewer abnormalities. For this target, Hafezi-Moghadam et al. reported an approach called nanoarchitectonics for photo-controlled intracellular drug release in immune modulation (**Figure 2**).[56] As molecular nanoarchitectonics, fasudil, a small molecule Rho-associated kinase inhibitor, was conjugated to a photoresponsive group and a short polyethylene glycol chain. This novel amphiphilic prodrug spontaneously formed micelles. Fasudil was rapidly released when the prodrug nanoparticles were irradiated with ultraviolet light. Following UV irradiation, the photoactive probe molecule will be liberated from the caging agent by photolysis, thereby initiating a strong fluorescence response. This mechanism activates the fluorescence emission of the reporter molecule, thereby providing a quantitative means for cargo liberation. Cytokine stimulation induces differentiation of monocytes into macrophages. In contrast, UV irradiation prevented the polarization of monocytes loaded with prodrug nanoparticles. For example, current treatments for age-related macular degeneration cannot stop the progression of the disease in the long term. The above-mentioned method of preventing macrophage polarization is effective in that it targets the mechanistic root of the disease.

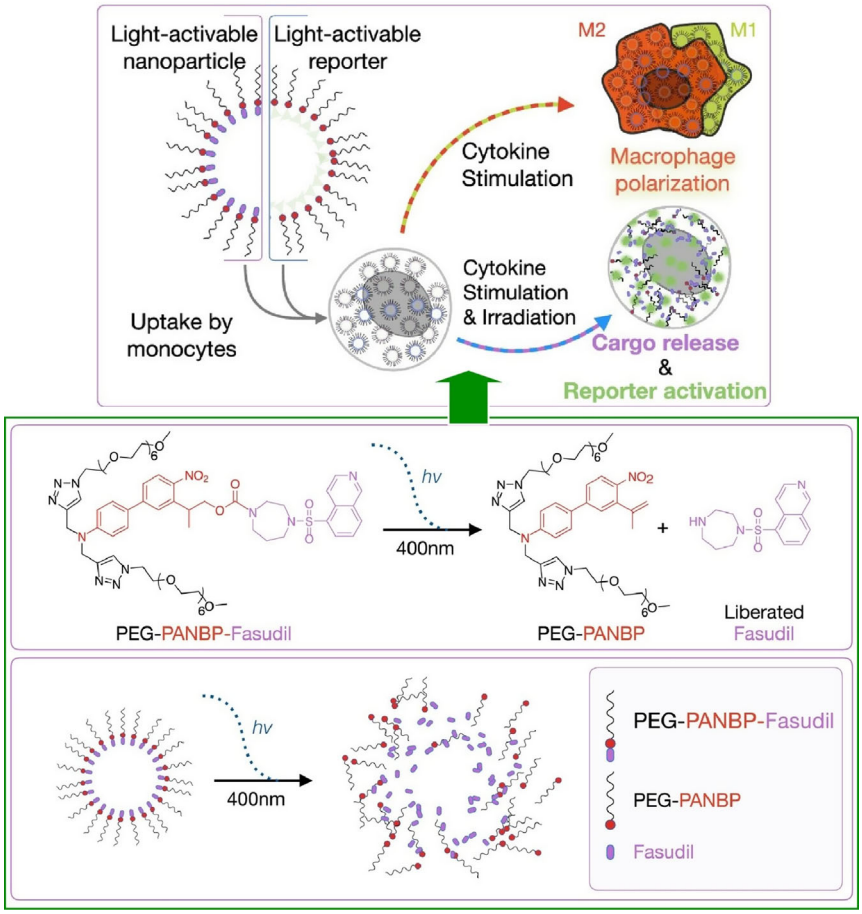

Figure 2. Nanoarchitectonics for photo-controlled intracellular drug release in immune modulation where fasudil, a small molecule Rho-associated kinase inhibitor, is conjugated to a photoresponsive group and a short polyethylene glycol chain, and is then rapidly released upon irradiated with ultraviolet light. Reproduced with permission.[56] Copyright 2022, American Chemical Society.

This molecular nanoarchitectonics-based design is useful for the development of new therapeutic approaches. In particular, the noninvasive and spatiotemporally precise drug release opens new possibilities for precise spatiotemporal immune cell modulation. This technology will facilitate the study of basic immune cell functions and the development of new innovative therapeutic approaches.

Osteoarthritis is a common cartilage degenerative disease. However, it seriously affects the quality of life of patients. Damage to articular cartilage and degradation of cartilage extracellular matrix, which is mainly composed of collagen II and proteoglycans, are involved in osteoarthritis progression. It induces the impairment of anti-inflammatory and proinflammatory pathways. Artificial joint replacement surgery, which is widely recommended in clinical practice, is a heavy burden on patients. Development of other control methods is desired. Luo, Chen, and co-workers reported nanoarchitectonics of cartilage-targeting hydrogel microspheres.[57] In this method, microfluidic and photopolymerization methods are combined (**Figure 3**). Cartilage-targeting peptides and ROS-responsive nanoparticles are accumulated in the hydrogel matrix. This allows nanoarchitectonics of cartilage-targeting hydrogel microspheres with ROS-responsive properties. Specifically, dexamethasone and cartilage-responsive copolymers are electrostatically adsorbed to form ROS-responsive nanoparticles. Monodisperse, uniform in size, and injectable hydrogel microspheres are then prepared. By using microfluidic technology, the ROS-responsive nanoparticles and collagen II targeting peptides were immobilized in the hydrogel matrix. Finally, photopolymerization was performed under ultraviolet light. The hydrogel microspheres with cartilage-targeting properties were retained in the joint cavity and promoted cellular uptake of the nanoparticles. The ROS-responsive nanoparticles react with osteoarthritis-induced intracellular ROS, which results in depolymerization of the nanoparticles. This change not only removes excess ROS and suppresses inflammation, but also promotes the release of kartogenin and dexamethasone in situ. Relatively, it realizes effective osteoarthritis treatment. The dual inhibitory action of the nanoparticles and

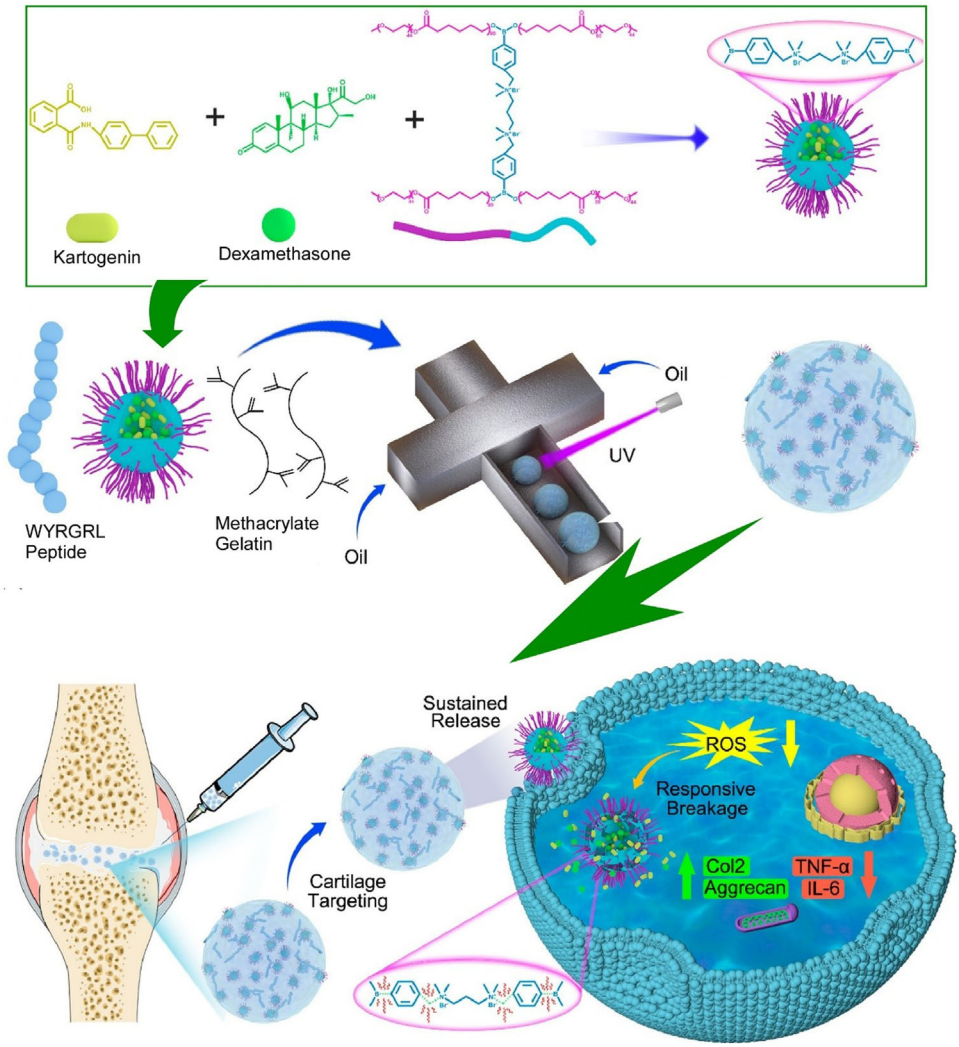

Figure 3. Nanoarchitectonics of cartilage-targeting hydrogel microspheres with schematic illustration of nanoparticle assembly, hybrid hydrogel microspheres fabrication, and osteoarthritis therapy. Reproduced with permission.[57] Copyright 2022, American Chemical Society.

hydrogel network achieves sustained release of the drug from the hydrogel microspheres. Local and long-term therapeutic effects after injection were obtained. Good ROS responsiveness was obtained in vitro. It was shown to promote cartilage differentiation and downregulate inflammatory factors. It was possible to effectively target and repair cartilage in an osteoarthritis model. In addition, the nanoarchitectonics method via microfluidic methods is expected to have a wide range of applications.

Mortality from infectious diseases has decreased thanks to various drugs and medical treatments. However, global health is still threatened by infectious diseases. New methods for rapid and accurate bacterial detection are attracting attention. Such technologies can effectively address bacterial threats such as bioterrorism, food poisoning, and hospital-acquired infections. Highly sensitive, rapid, and accurate detection of pathogenic bacteria is essential for treatment decisions. Watanabe et al. demonstrated a method that can highly selectively detect *Staphylococcus aureus* even in the presence of *E. coli* and the closely related *S. aureus, S. pseudintermedius*.[58] Surface modification and bioconjugation techniques of fluorescent nanoemulsions were developed (**Figure 4**). Specifically, a highly bright fluorescent nanoemulsion was combined with a bacteria-specific phage to produce a phage/fluorescent nanoemulsion. The phage/fluorescent nanoemulsion recognized the target bacteria highly selectively at the species level and achieved high affinity binding. Compared with phages stained with common organic dyes, the phage/fluorescent nanoemulsion enabled the fluorescent detection of bacteria with higher accuracy and reliability. Thus, the developed method can be used with a variety of phages and may be applicable to selective, sensitive, and rapid detection of any bacteria.

As a noninvasive clinical treatment, photodynamic therapy has been widely used to treat superficial cancers due to its unique selectivity and excellent tumor ablation properties. During the photodynamic therapy, ROS formed induce apoptosis of tumor cells. For effective treatment, strategies to increase the light penetration depth are required. Dual-photon photodynamic therapy has been attracting attention as a candidate because of its deep light penetration depth, high spatial selectivity, and low toxicity to normal tissues. To achieve this, it is a challenge to obtain highly efficient two-photon excited photosensitizers that are easily available. In the study titled emodin-based nanoarchitectonics with giant two-photon absorption, Zhao, Yang, Li, et al. showed that emodin, a natural anthraquinone derivative, could be a promising two-photon excited photosensitizer.[59] It has a large two-photon absorption cross-section and high singlet oxygen quantum yield. For this purpose, it was coassembled with human serum albumin (**Figure 5**). The time-dependent density functional calculation results show that the intersystem crossing rate is enhanced. As a result, more singlet oxygen is generated. The formed emodin/human serum albumin nanoparticles exhibited outstanding two-photon excitation photodynamic therapy properties against cancer cells. In vitro experiments show that emodin/human serum albumin nanoparticles significantly enhance the anticancer effect against MCF-7 cells via two-photon excitation photodynamic therapy. Ultra-efficient two-photon excitation photodynamic therapy with ultra-low drug dosage can be realized under femtosecond pulse laser irradiation. They show that molecular nanoarchitectonics based on natural anthraquinones is useful for efficient chemophototherapy for combined treatment of cancer.

Two-photon absorption fluorescence imaging has unparalleled spatiotemporal resolution. Accordingly, it has great potential in diagnostics and biomedicine. However, it remains a major challenge due to the limited photoluminescence in vivo. In their study titled two-photon nanoprobes based on bioorganic nanoarchitectonics, Xing, Yan, et al. fabricated self-assembled near-infrared (NIR) cyanine dye-based nanoprobes (**Figure 6**).[60] The two-photon absorption fluorescence imaging capability of the nanoprobes was significantly improved. Singlet oxygen generated during photooxidation enables the dimerization of the chromophores. The formation of two-photon absorption intermediates enhances the two-photon absorption fluorescence emission. The cyanine dye nanoprobes showed enhanced two-photon absorption fluorescence in the aggregated state. This facilitated the real-time visualization of blood circulation and tumor accumulation, as well as the application in cell imaging in vivo. The nanoprobes emitted strong fluorescence during

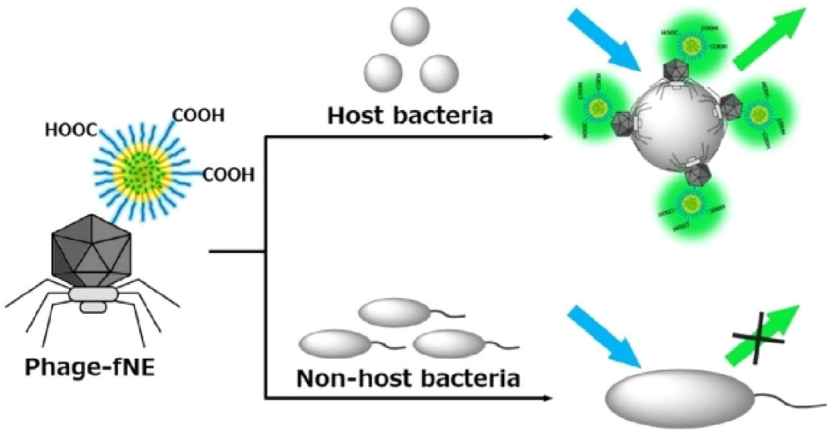

Figure 4. Schematic illustration of bacterial detection with the fluorescent dye-loading nanoemulsions, functionalized with bacteriophages that is used as a nanoarchitectonics method that can highly selectively detect *Staphylococcus aureus* even in the presence of *E. coli*. Reproduced with permission.[58] Copyright 2023, Oxford University Press.

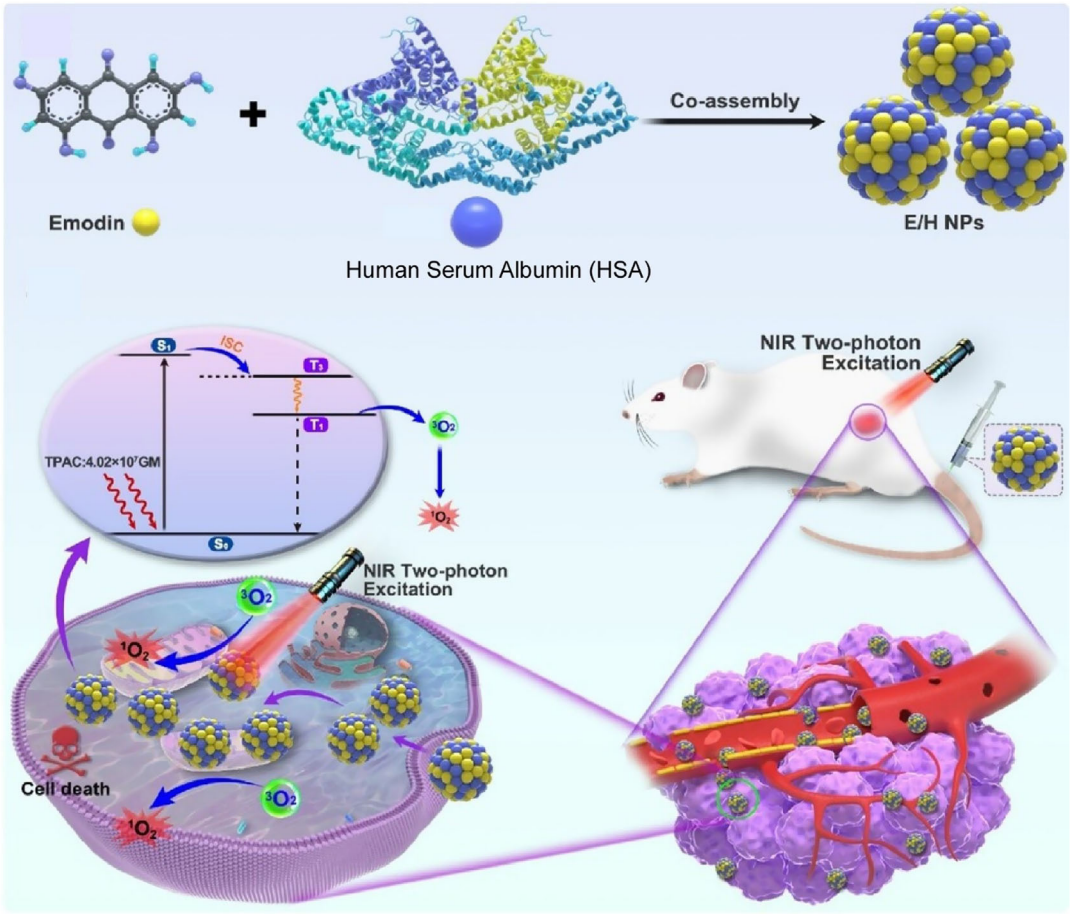

Figure 5. Emodin-based nanoarchitectonics with giant two-photon absorption: schematic illustration of the coassembly of emodin nanodrugs for efficient anticancer two-photo-excited photodynamic therapy. Reproduced with permission.[59] Copyright 2023, Wiley-VCH.

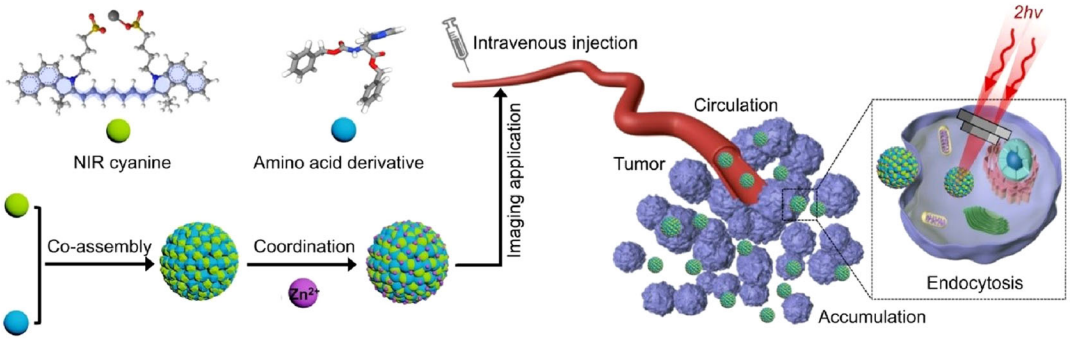

Figure 6. Two-photon nanoprobes based on bioorganic nanoarchitectonics with self-assembled near-infrared cyanine dye-based nanoprobes where two-photon absorption nanoparticles are applicable for tumor imaging and accumulation in tumor tissue and even single tumor cell endocytosis can be visualized. Reproduced under terms of the CC-BY license.[60] Copyright 2023, The Authors. Published by Springer-Nature.

light irradiation, achieving high imaging contrast. They showed excellent imaging performance both in vitro and in vivo. Moreover, nanoprobes starting from amino acid derivatives and widely used cyanine dyes have outstanding biosafety. NIR cyanine dye-based nanoarchitectonics formed by self-assembly with amino acid derivatives was demonstrated to yield versatile bioorganic two-photon absorbing nanoprobes based on the mechanism of photooxidation-enhanced luminescence. Existing two-photon absorbing probes suffer from potential biotoxicity and limited photoluminescence. The nanoarchitectonic nanoprobes here embrace the advantages of biosafety and unique photooxidation-enhanced luminescence properties. This will

pave the way for the design and development of more advanced two-photon absorbing fluorescent probes.

Liver fibrosis progresses to cirrhosis and liver failure. However, there is no effective clinical treatment. Therefore, antifibrotic drugs that suppress liver fibrosis are desired. Therapeutic peptides have attracted attention as candidates for antifibrotic drugs. However, therapeutic peptides are quickly degraded and accumulate in the liver insufficiently. Huang, Yan, Zou, et al. created nanomedicines from therapeutic peptides for the treatment of liver fibrosis in the project "supramolecular nanoarchitectonics based on antagonist peptide self-assembly".[61] Self-assembling antagonist peptides were rationally designed. Then, they were engineered into uniform peptide nanoparticles with well-defined nanostructures and uniform sizes (**Figure 7**). As molecular nanoarchitectonics, they created antifibrotic peptide nanoparticles based on self-assembly of antagonist peptides with hydrophobic dipeptides attached to the *N*-terminus. The peptide nanoparticles were promoted to accumulate in the liver and had limited distribution to other tissues. In vivo experiments confirmed that the peptide nanoparticles had significantly improved antifibrotic activity along with good biocompatibility. Our results demonstrate that supramolecular peptide nanoarchitectonics is a promising approach to enhance antifibrotic activity for the treatment of liver fibrosis. It provides a new perspective for the rational design of antifibrotic nanomedicines and promotes the clinical application of antifibrotic nanomedicines. It is not limited to this medical application, but is helpful for the rational design and clinical application of peptide-based therapeutic nanomedicines.

Cancer stem cells are a small cell population present in cancer tissues. They play a major role in metastasis, drug resistance, and recurrence. Cancer stem cells undergo self-renewal, differentiation, and tumorigenesis. They play a role in the recurrence of multiple cancer types. Targeting the cancer stem cell population is of great significance. Synthetic ligands that can recognize specific DNA sequences are promising for targeted disruption of transcription factor-DNA interactions. Pandian, Sugiyama, et al. synthesized cyclic pyrrole-imidazole polyamides that target Gli-mediated transcription and recognize eight base pairs of DNA (**Figure 8**).[62] These sequence-specific cyclic pyrrole-imidazole polyamides can inhibit the Hedgehog pathway, which is thought to play a major role in the proliferation of cancer stem cells. In vitro binding studies to the DNA showed that the cyclic polyamides were superior to the corresponding hairpin polyamides. It was shown that the cyclic pyrrole-imidazole polyamides have better binding affinity and specificity. The permeability of this cyclic pyrrole-imidazole polyamide into eukaryotic cells was evaluated and it was shown to be localized in the nucleus. Furthermore, it was confirmed that the cyclic pyrrole-imidazole polyamides inhibit the function of Gli. Combinatorial treatment of glioblastoma cells and brain cancer stem cells with cyclic pyrrole-imidazole polyamides and temozolomide increased cell death. A nanoarchitectonics approach based on transcriptionally targeted cyclic pyrrole-imidazole polyamides is a promising strategy to inhibit cancer stem cells.

In many pharmaceutical strategies, poly(ethylene glycol) is often conjugated to proteins or nanoparticles to improve therapeutic efficacy. However, poly(ethylene glycol) is immunogenic and can induce the production of antipoly(ethylene glycol) antibodies. To address these concerns, the binding properties of antipoly(ethylene glycol) antibodies must be analyzed. However, it is generally difficult to distinguish antipoly(ethylene glycol) antibodies. In the study titled nanoarchitectonics-based antibiotic cello-oligosaccharide platforms, Serizawa et al. proposed to utilize the structure of nanoarchitectonics-based 2D cello-oligosaccharide assemblies as a platform for enzyme-linked immunosorbent assay (**Figure 9**).[63] The aim is to identify antipoly(ethylene glycol) antibodies in a simple manner. To this end,

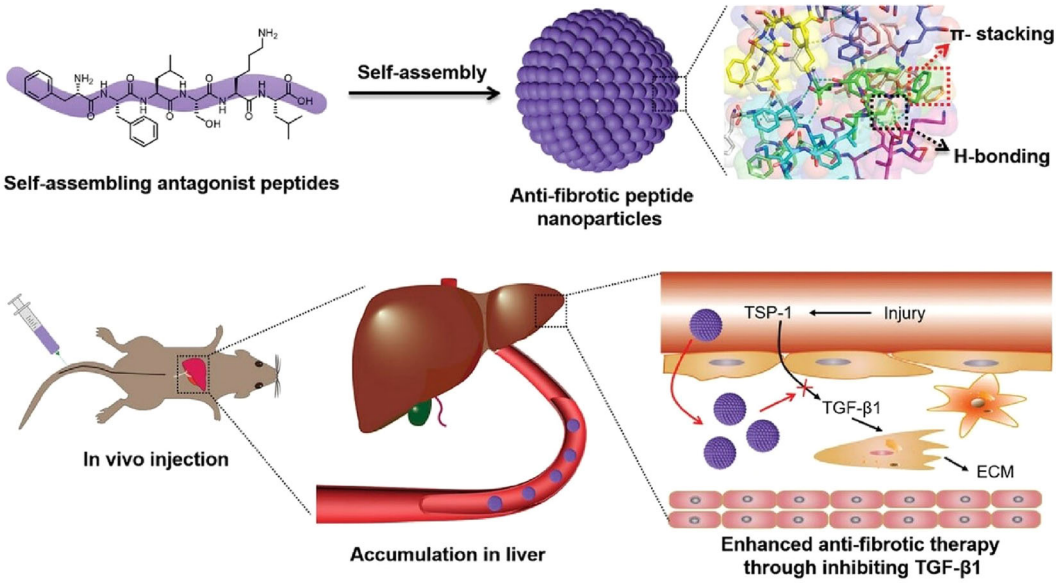

Figure 7. Supramolecular nanoarchitectonics based on antagonist peptide self-assembly: peptide nanoparticles fabricated from self-assembly of antagonist peptides for the treatment of liver fibrosis with selective accumulation of antifibrotic peptide nanoparticles in liver after in vivo injection and the enhanced antifibrotic therapy. Reproduced with permission.[61] Copyright 2023, Wiley-VCH.

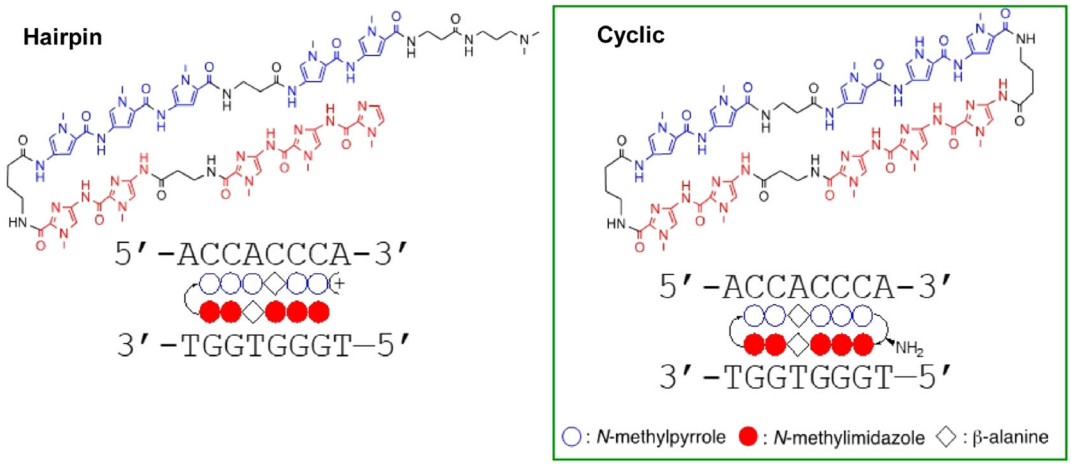

Figure 8. Cyclic pyrrole-imidazole polyamides recognizing eight base pairs of DNA where in vitro binding studies to the DNA showed that the cyclic polyamides are superior to the corresponding hairpin polyamides. Reproduced with permission.[62] Copyright 2022, Oxford University Press.

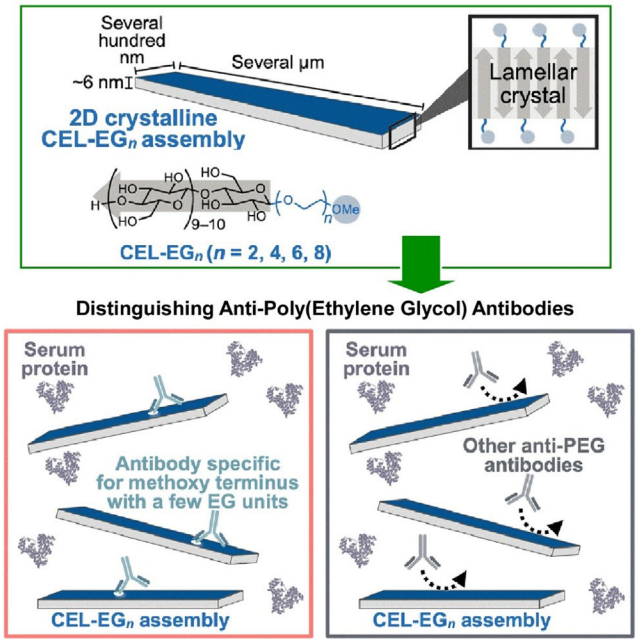

Figure 9. Nanoarchitectonics-based antibiotic cello-oligosaccharide platforms with distinguishing antipoly(ethylene glycol) antibodies by the assemblies. Reproduced with permission.[63] Copyright 2024, Royal Society of Chemistry.

they developed antibiofouling cello-oligosaccharide assemblies with one-terminal methoxy oligo(ethylene glycol) ligands. The two-dimensional crystalline cello-oligosaccharide assemblies were stably dispersed in buffer solutions. They had antibiofouling properties against nonspecific protein adsorption. As a result, it became possible to easily perform an enzyme-linked immunosorbent assay by centrifugation/redispersion cycles of the aqueous dispersion of the aggregates. Quantitative detection of antibodies was also possible with high sensitivity even in the presence of serum. These results pave the way for analyzing the binding properties of antipoly(ethylene glycol) antibodies in biological samples. This will enable reliable and simple investigation of the immunogenicity of poly(ethylene glycol)-modified therapeutics in use or under development, which will contribute to the design and development of improved therapeutics.

Immunogenic cell death can be a promising treatment for tumor regression. Ferroptasis, characterized by excessive lipid peroxidation, induces immunogenic cell death. It has gained attention as a potential strategy to activate antitumor immune responses. Shen et al. demonstrated a method to synergistically promote ferroptosis in an approach called biomimetic nanoarchitectonics with chitosan nanogels (**Figure 10**).[64] This method utilizes functionalized chitosan-ferrocene-sodium alginate crosslinked nanogels. It is a novel approach to modify pravastatin with M1 macrophage membrane. First, chitosan-ferrocene polymer was synthesized by amidation reaction. It was crosslinked with sodium alginate to form sodium alginate nanogel. Then, pravastatin was encapsulated within the nanogel. M1 macrophage membrane was coated on its surface. Ferrocene in the nanogel inhibited the glutathione peroxidase 4/glutathione pathway through ROS production and glutathione depletion. Pravastatin reduced the production of CoQ10 and suppressed the antioxidant function of ferroptosis suppressor protein 1. The synergistic inhibition of the two pathways resulted in significant lipid peroxidation accumulation and efficient ferroptosis. Both in vitro and in vivo experiments demonstrated excellent efficacy in tumor resection in ferroptosis-mediated cancer therapy. By pursuing nanoarchitectonics methods, it is also expected to develop immune-ferroptosis-mediated synergistic therapy for other types of solid cancer.

The mechanisms of life and the biomedical methods based on them are highly diverse. In contrast to a single function or action, multiple processes occur concurrently. It is anticipated that materials capable of withstanding these conditions will simultaneously perform a range of functions. To achieve this, it is necessary to design a variety of molecules and assemble them to create biomedical materials. The elucidation of general rules of molecular nanoarchitectonics for biomedical applications is not a straightforward process. Nevertheless, certain tendencies

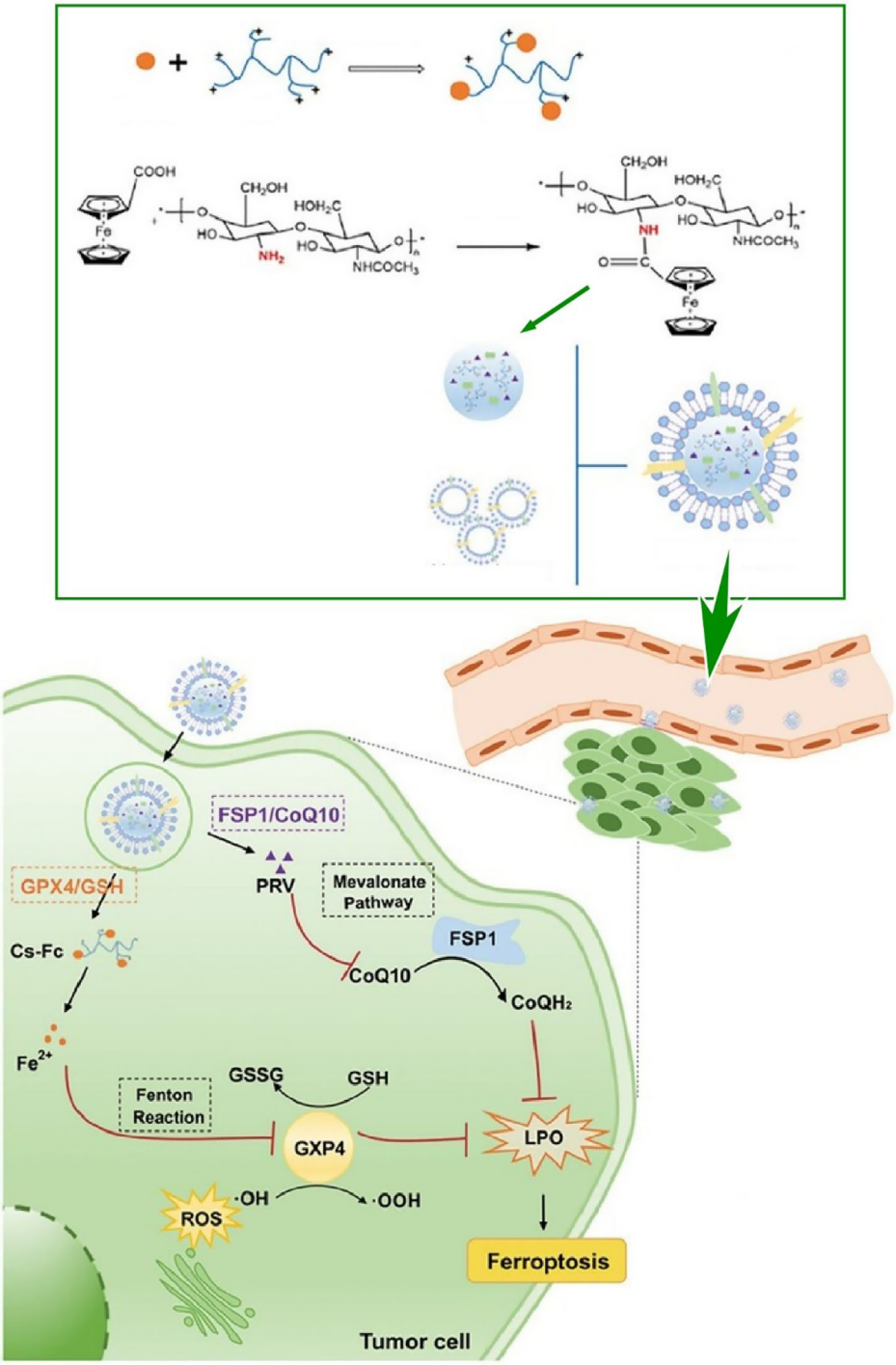

Figure 10. A method to synergistically promote ferroptosis in an approach called biomimetic nanoarchitectonics with chitosan nanogels for ferroptosis-antitumor therapy and immune activation. Reproduced with permission.[64] Copyright 2023, Wiley-VCH.

may be discerned. In addition to the requisite functionalities for the desired medical characteristics, the molecular designs for biocompatibility and stimuli-responsiveness appear to be significant structural factors. The field of molecular nanoarchitectonics, which involves the assembly of functional molecules into materials, has made a significant contribution to this area of research. The aforementioned effects are exemplified by the various cases presented above. The multifunctionality and complexity of materials required in the biomedical field will exceed those required in physics and chemistry. Nanoarchitectonics is a key area of focus in these disciplines. This assertion is corroborated by the aforementioned examples.

3. Materials Nanoarchitectonics

The preceding section addressed the advancement of biomedical materials through molecular designs and their supramolecular assemblies. These examples are presented as a summary of the molecular nanoarchitectonics approach. The following section will present examples of the development of biomedical materials utilizing a range of nanomaterials as functional components. These will be referred to as "materials nanoarchitectonics approaches". It is challenging to delineate these two forms of nanoarchitectonics with absolute precision; however, for the sake of clarity, they will be addressed in distinct sections.

To deliver cancer drugs to tumors, they must be delivered by leaking from the surrounding blood vessels. However, tumor vasculature is not always leaky enough. Setyawati, Wang, Leong, et al. developed gold nanoparticles that can induce in vivo endothelial leakiness (nanoparticle-induced endothelial leakiness, NanoEL).[65] They developed a method to induce leakage of drugs from tumor vasculature using NanoEL. A systematic study showed that in vitro NanoEL induction is governed by the intrinsic particle density, size, and surface charge of the nanoparticles. This work produced a calibratable in vivo leakage effect using a library of gold nanoparticles with different sizes and roughness. NanoEL particles induce leakage of tumor vascular walls, improving infiltration into the interstitial space within tumors. The synergistic effect of NanoEL and the therapeutic effect of doxorubicin delivered from liposomes can be used. This approach resulted in complete regression of tumors despite minimal administration frequency. Pretreatment of tumor vasculature with nanoEL particles prior to therapeutic administration can result in complete cancer regression in animal models of both primary tumors and secondary micrometastases. Using the NanoEL concept, endothelial leakage in tumor vasculature can be induced in a tumor-independent manner, thereby opening a therapeutic window for nanomedicines and drugs to reach tumors. This approach to engineer tumor vascular leakage represents a new paradigm for enhancing intratumoral availability of anticancer drugs. This approach may potentially be applicable to other diseases closely linked to the vasculature. The utilization of NanoEL gaps facilitates the optimal exploitation of anticancer therapeutic benefits within the context of cancer therapeutics. Furthermore, the nanoarchitectonics strategy has the potential to integrate the observed effects of the materials into medical devices, thereby facilitating more practical applications.

Hollow spheres and capsules have been actively researched in the biomedical field as drug carriers.[66] Such capsules can be tuned in structure by external stimuli. By adjusting the pore size of the capsule shell, it is possible to obtain the function of releasing drugs over a long period of time. As a capsule construction material, silica is a nontoxic, highly biocompatible, and chemically stable material, making it suitable for biological applications. However, it is not always easy to adjust the structure of inorganic silica. Ji et al. used a dissolution-regrowth process to prepare silica microcapsules made of flake shells (**Figure 11**).[67] The flake shell is a structure formed by the assembly of silica nanosheets, and its structure is easy to control by external stimuli. Structurally flexible flake shell silica microcapsules could be prepared by a simple dissolution-regrowth process. The microcapsule dispersion can be stably stored for at least one week without precipitation. The flake shell is composed of an incomplete siloxane network. Therefore, the structure can be flexibly adjusted and fixed by processing under appropriate pH conditions. This method enabled long-term sustained drug delivery at a constant release rate. During encapsulation, the pores remain relatively large, allowing drugs to be loaded into the capsules. After pH treatment, the pores narrow, significantly slowing down the drug release rate from the capsules. This approach is promising for applications that require sustained release of long-term therapeutics, such as antiallergy drugs, steroids, and hormone replacement therapy, over a period of weeks to months.

Nanoarchitectonics can be introduced into cell surface engineering, for example, as a powerful tool to modify and enhance the properties of living cells.[68] Alternatively, cells can be used as sacrificial templates to create cell-mimetic materials. As one such example, Fakhrullin et al. reported an approach entitles as "nanoarchitectonics meets cell surface engineering".[69]

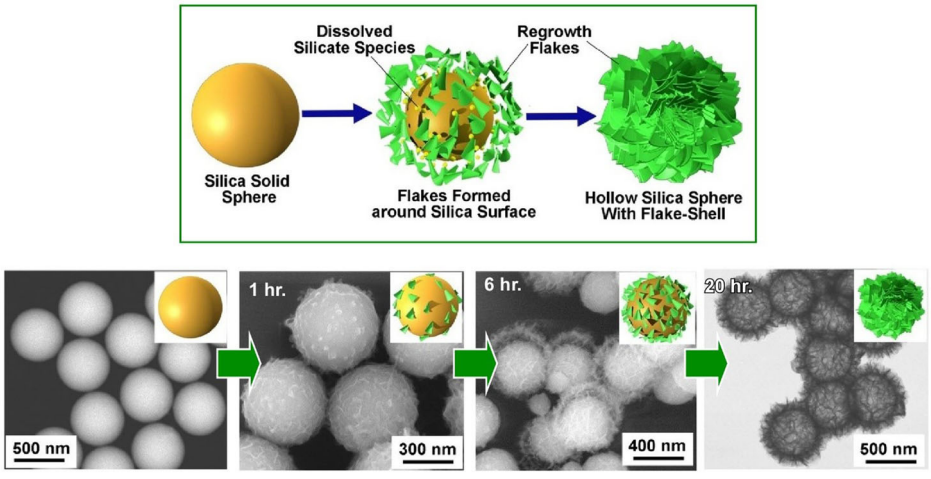

Figure 11. A dissolution-regrowth process to prepare silica microcapsules made of flake shells. Reproduced with permission.[67] Copyright 2012, Wiley-VCH.

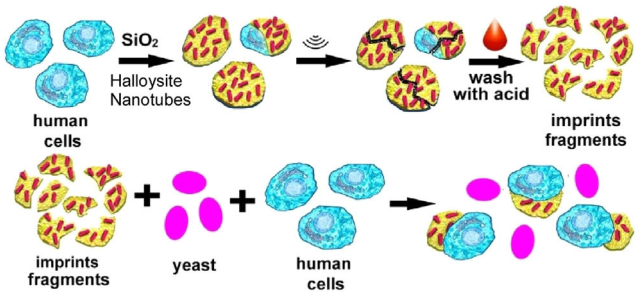

Figure 12. Nanoarchitectonics for cell surface engineering: production of silica/halloysite cell-mimicking imprints and recognition of human cells by the imprints in HeLa/yeast cells mixture and the imprints obtained by destruction of inorganic shells deposited on live cells. Reproduced under terms of the CC-BY license.[69] Copyright 2019, The Authors. Published by Beilstein Institut.

This is a cell-recognition silica imprinting method that can selectively detect human cells (**Figure 12**). This is a technique to create a nanoarchitectonics-based imprint for human cell recognition. HeLa cells were used as templates to create a silica inorganic shell doped with halloysite clay nanotubes. A polyelectrolyte nanolayer was used to create a silica/halloysite cell-mimetic imprint composite inorganic shell around human HeLa cells. The shell was then disrupted by sonication, and the cell debris was dissolved by acid washing. In the process, a polydisperse silica/halloysite cell imprint was created. Using this imprint, selective recognition of HeLa cells in cell growth medium supplemented with yeast cells was successfully achieved. There are differences in the surface properties of cancer cells and normal cells. Tumor cells have more microvilli than nondividing normal cells. By recognizing these differences, it is possible to nanoarchitectonically create materials that can selectively recognize normal and tumor cells.

Layered transition metal dichalcogenides have attracted attention as 2D materials. These materials are being explored for applications in catalysis, battery materials, sensors, and biomedical applications. Leong et al. reported the fabrication of MoS_2 superstructures using LbL nanoarchitectonics and the delivery of anticancer drugs (**Figure 13**).[70] The superstructures consist of MoS_2 nanosheets stacked in a planned manner with DNA oligonucleotides of a defined sequence. First, MoS_2 nanosheet nanostructures were modified with DNA oligonucleotides bearing thiol end groups. In this process, the property of DNA thiol groups binding to sulfur atom vacancies on the MoS_2 surface is utilized. Individual sheets were nanoarchitected into layers with complementary DNA oligonucleotides. The assembly into higher-order superstructures was performed by interlayer assembly using ATP aptamers as linkers. The higher-order superstructure was finally completed by adding the anticancer drug doxorubicin to this. The superstructured layered assemblies were delivered into cells through the process of endocytosis and trafficking to endosomes and lysosomes. These superstructures

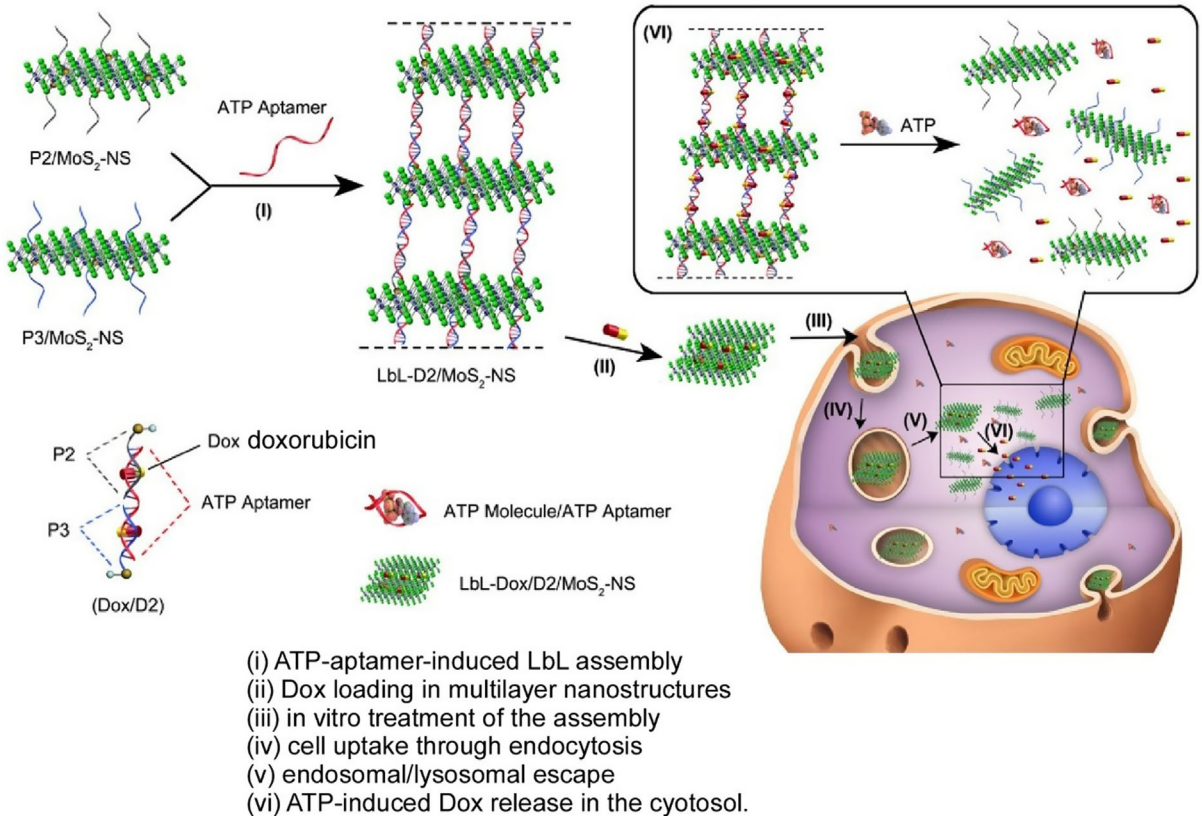

Figure 13. Fabrication of MoS_2/DNA superstructures using LbL nanoarchitectonics and the delivery of anticancer drugs, doxorubicin. Reproduced with permission.[70] Copyright 2017, American Chemical Society.

autonomously degrade in cancer cells with enhanced ATP metabolism. Once inside the cells, small ATP molecules entered the laminated nanosheets and bound to the ATP aptamer linker. The binding of the target ATP molecule to the aptamer linker eliminated the interlayer assembly force, and the multilayered superstructures disassembled. As the higher-order structures disassembled, doxorubicin was released. In the original superstructure, the MoS_2 nanosheets acted as a shield. This higher-order structure behaved like Testudo. It was even resistant to damaging intracellular DNA enzymes. Under ATP-rich conditions, the intracellular role of the drug-loaded nanotestudo rapidly shifted from a defensive state to an offensive state. It released anticancer drugs and induced highly efficient apoptosis of cancer cells. The synergistic effect of DNA specificity and the two-dimensional plane of MoS_2 nanosheets works effectively in this nanoarchitectonics. An autonomous stimuli-responsive drug delivery system has been designed and demonstrated, and this concept may have applications in many areas of nanomedicine.

Two-dimensional MXenes with photothermal conversion ability are expected to have biomedical applications. Kankala et al. reported a study titled "transition metal oxide-decorated MXenes as drugless nanoarchitectonics" (**Figure 14**).[71] Ti_3C_2 MXene nanosheets were prepared and decorated with copper oxide. Using this material, drugless nanoarchitectonics for synergistic photothermal-chemodynamic therapeutic effects was demonstrated. Photothermal ablation under NIR-II laser irradiation provided photothermal therapeutic effects for Cu_2O-decorated MXene nanosheets. The reaction of Ti_3C_2 MXene nanosheets with H_2O_2 was utilized to release Cu_2O for generating ROS in tumors. In other words, it generates a large amount of lethal free radicals in an acidic environment. Mechanistically, these lethal free radicals unbalance glutathione levels in cells,

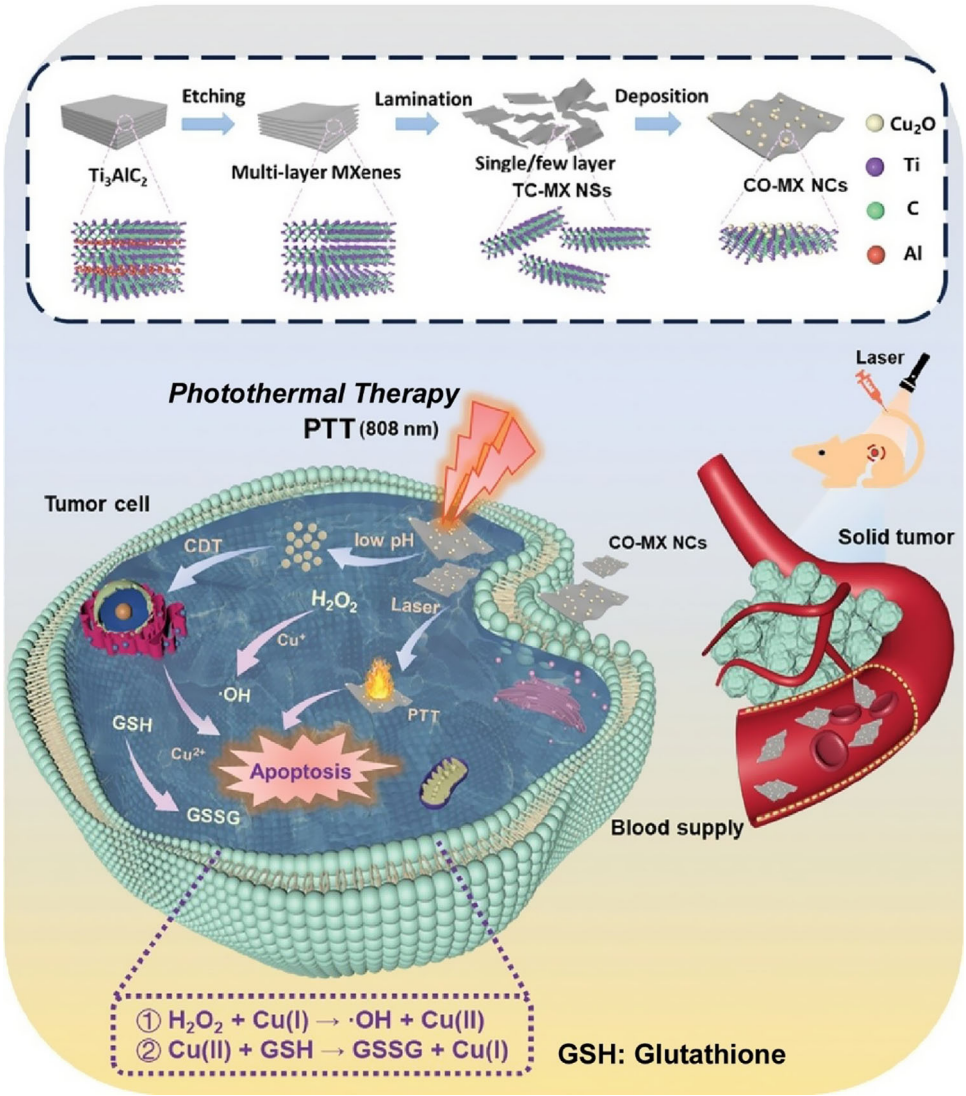

Figure 14. Transition metal oxide-decorated MXenes as drugless nanoarchitectonics: the design and fabrication progress of Cu_2O/MXene nanocomposites, as well as subsequent hyperthermia-enhanced tumor nanocatalytic therapy in mice in vivo, along with precise mechanistic roles. Reproduced with permission.[71] Copyright 2023, Wiley-VCH.

leading to mitochondrial dysfunction and inducing apoptosis in 4T1 cells. In addition, the release of Cu^{+} ions was promoted in the acidic microenvironment of cells. The chemodynamic and photothermal therapy effects were synergistically enhanced by the Fenton-like reaction. In vivo studies using mice showed excellent biodistribution of intravenously administered Cu_2O-modified MXene nanosheets. They showed good biocompatibility and no signs of toxicity. Thus, a drugless nanoplatform that exerts synergistic photothermal–chemodynamic therapy effects is constructed. Such drug-free nanoarchitectures are expected to provide a new method to substantially improve the therapeutic effects against various cancers.

The creation of composites consisting of various component materials is also an important methodology in materials-based nanoarchitectonics. Nishina et al. nanoarchitected a multicomponent composite hydrogel that exhibited antibacterial activity.[72] They synthesized a graphene oxide-based hydrogel consisting of magnesium oxide and povidone-iodine. In this composite design, the graphene oxide in the hydrogel plays two roles: as a gelling agent through self-assembly and as a carrier for magnesium oxide and povidone-iodine. Meanwhile, the magnesium oxide particles act as a cross-linking initiator and filler that enhances the cohesive and adhesive strength of the hydrogel. Magnesium oxide promotes antibacterial activity and controls cellular activity. Povidone-iodine slowly releases free iodine from the hydrogel, which shows bactericidal activity over time. The hydrogel showed antibacterial activity against *S. aureus*. The combination of graphene oxide, magnesium oxide, and povidone-iodine in this hybrid nanoarchitectonics also shows various other effects on physical properties. They exhibit improved physical properties, including electrical conductivity, fluid uptake capacity, water retention capacity, and water vapor transmission rate. These properties make them attractive for a variety of biomedical applications, including medical uses such as drug delivery, tissue engineering, tissue scaffolding, and wound coverage and healing.

As an example of composite nanoarchitectonics, Imae, Tsutsumiuchi, Kawai, et al. succeeded in synthesizing magnetite nanoparticles by coprecipitation and improving their dispersibility in aqueous media by carbon dot treatment (**Figure 15**).[73] Magnetite nanoparticles of 9 nm were synthesized by coprecipitation. They were hybridized with carbon dots by in situ hydrothermal treatment. They were further chemically bonded to acid-treated carbon nanohorns via carbon dots. Magnetite nanoparticles were precipitated in situ on acid-treated carbon nanohorns. The resulting composites were stable in aqueous media. The composites were useful for loading/releasing drugs such as doxorubicin and gemcitabine. For example, the carbon dots-immobilized composites showed photodynamic/photothermal effects under laser irradiation for the release of gemcitabine. The release of gemcitabine from the magnetite-bound composites was completed when the hyperthermia method was performed together with a magnet. These open-type carriers are convenient for injecting DDS directly into cancer cell domains, and are expected to be suitable for complex medical treatments and reduce the burden on patients.

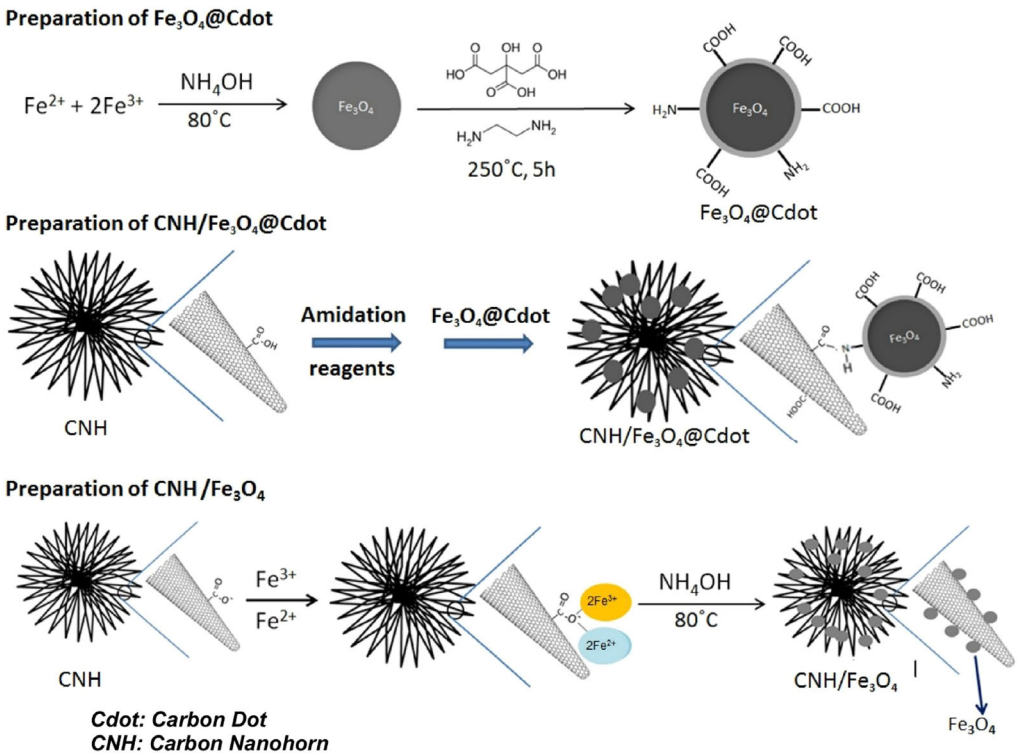

Figure 15. Syntheses of magnetite nanoparticles by coprecipitation and improving their dispersibility in aqueous media by carbon dot treatment: the preparation schemes of Fe_3O_4@carbon dot, carbon nanohorn/Fe_3O_4@carbon dot, and carbon nanohorn/Fe_3O_4. Reproduced with permission.[73] Copyright 2022, Oxford University Press.

Functional materials formed by materials nanoarchitectonics can also be integrated into medical devices. For example, mechanically flexible microsupercapacitors are important in the field of portable electronics. They can be considered as a complement to microbatteries, or even as a replacement, especially in the application of portable biomonitoring devices. Lightweight, flexible, and wearable microsupercapacitors are expected to be used for real-time biomonitoring of body conditions. However, compared to microbatteries, microsupercapacitors generally have a low energy density. To address this issue, Pumera et al. published an article titled nanoarchitectonics-based microsupercapacitor for health monitoring application.[74] In this work, they develop a high-energy density microsupercapacitor integrated with a force-sensing device for monitoring the radial artery pulse in humans (**Figure 16**). They nanoarchitectonicize functional device structures using temporally and spatially controlled picosecond pulse lasers. A single-step roll-to-roll fabrication technique creates laser-induced Ti/O-rich nanoparticles derived from MXene covalently bonded to graphene. A single-step tracing process is performed on MXene-coated polyimide sheets. When ablated with a Nd:YAG solid-state laser, the exfoliated MXene sheets absorb infrared energy, generating high temperatures on the PI polyimide sheets. Self-organization and ordering of C—C bonds creates 3D graphene nanostructures decorated with MXene. Although laser-induced graphene is hydrophobic, room-temperature oxygen plasma treatment is used to modify the wettability of the underlying surface, allowing for better electrode–electrolyte interactions. Laser-induced direct patterning enables roll-to-roll fabrication of active electrode materials. Applications include diverse ones such as energy storage devices, biomonitoring, and real-time biomonitoring of body conditions.

Nanomaterials with varying dimensionalities, structures, and compositions are employed in medical applications. While these materials possess distinctive characteristics, they are not inherently versatile. These are combined to address complex targets for biomedical applications. To achieve this, a rational materials architecture is required. In this regard, the field of materials nanoarchitectonics is of considerable utility.

4. Pore-Engineered Nanoarchitectonics

In the previous two sections, molecular nanoarchitectonics and materials nanoarchitectonics have been shown to be useful for creating functional materials for biomedical applications. These discussions are based on a general materials perspective. The following section will discuss materials with specific structural features. These are materials with controlled pore structures. Porous structures include MOFs,[75] COFs,[76] mesoporous materials,[77] and nanoporous materials,[78] that are used in a wide range of applications. Nanometer-sized pore structures provide valuable opportunities for drug uptake and release, as well as other biointeractions. In the following section, entitled pore-engineered nanoarchitectonics, this section will provide an overview of some examples of the synthesis and biomedical applications of controlled pore structures.

One of strategies to overcome cisplatin resistance and side effects is the conversion of cisplatin platinum(II) to platinum(IV) complexes. This involves functionalization of the axial position of cisplatin. This can be done with bioactive ligands to target specific cancer cell types. This modification leads to targeted therapy and thus severe side effects can be reduced.

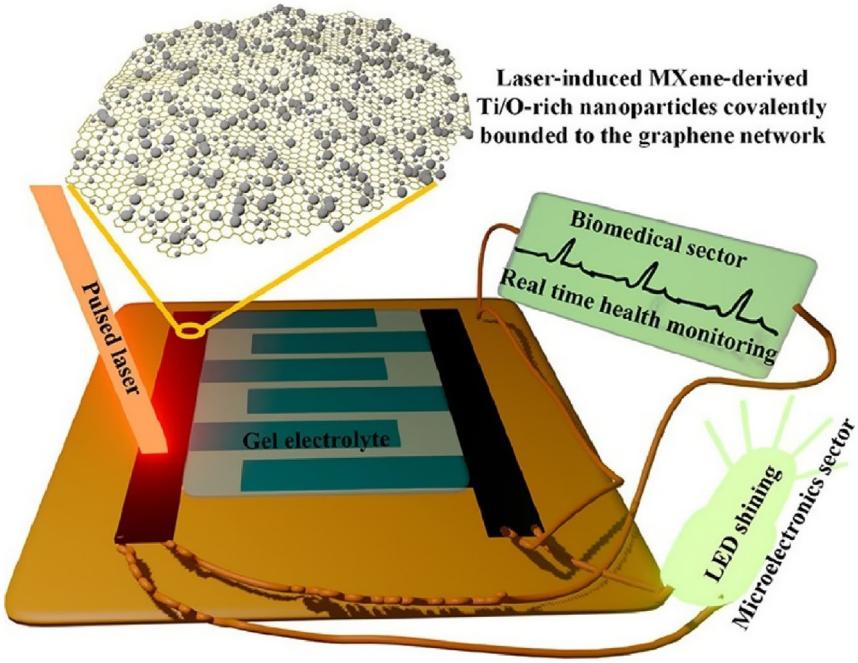

Figure 16. A high-energy density microsupercapacitor integrated with a force-sensing device for monitoring the radial artery pulse in humans by nanoarchitectonics fabrications using temporally and spatially controlled picosecond pulse lasers. Reproduced under terms of the CC-BY license.[74] Copyright 2023, The Authors. Published by American Chemical Society.

Such molecular modifications can be advanced to overcome cisplatin resistance by enhancing its uptake into cancer cells. An interesting approach has been reported to be the immobilization of dual-acting prodrugs on self-assembled hybrid porous MOFs. In their review article, Lestari et al. described the development of several prodrug-modified cisplatin and their anticancer activity in several cancer cell lines.[79] The involvement of cisplatin derivatives in MOFs is summarized (**Figure 17**). The sustained release, controlled and targeted delivery, and anticancer activity of the drug are discussed. Several nanoarchitectonic structural requirements need to be considered for the use of MOFs as drug carriers. These include tunable pore size to meet the desired loading capacity, particle size suitable for biocompatibility of MOFs, stability of MOFs themselves, and desirable interactions with drugs through MOF modification. For stimuli-responsive drug delivery, it is also important to design to utilize the differences in microenvironment between healthy cells and cancer cells. Available environmental conditions include pH, glutathione, ATP, and enzymes. In the direct assembly method for loading prodrugs into MOFs, prodrugs are directly used as organic ligands through coordination bonds. Meanwhile, in the postsynthesis strategy, prodrugs are covalently bound to metal centers or organic ligands. Compared with conventional encapsulation, these strategies prevent premature release. They result in continuous drug delivery to the target. For immobilization of cisplatin-based platinum(IV) prodrugs into MOFs, biologically active axial ligands such as other anticancer drugs, microtubule disrupting agents, nonsteroidal anti-inflammatory drugs, and enzyme inhibitors can also be incorporated as additional elements. This dual-acting strategy has been shown to be a promising approach to address the development of resistance to cisplatin and the severe side effects associated with its use in cancer treatment. Moreover, triple-acting is also a possibility for MOF-based platinum(IV) prodrugs.

3D bioprinting is a technique that allows the precise fabrication of customized tissues and organs. Hydrogel materials that can be embedded with living cells are called bioinks. They have many advantages, including printability, LbL repeated processing, structural stability, and biological properties. Hsu et al. evaluated the reinforcing effect of MOF zeolite imidazolate framework-8 (ZIF-8) in polyurethane-gelatin hydrogel bioink (**Figure 18**).[80] ZIF-8 crystals, a porous material, were synthesized by a solvothermal method. ZIF-8 crystals were added to polyurethane-gelatin hydrogel bioink. The printability, layerability, and thermal responsiveness of polyurethane-gelatin and ZIF-8 composite hydrogels as well as their mechanical properties such as shear thinning behavior were evaluated. Even with the addition of a relatively small amount of ZIF-8, the composite bioink with polyurethane-gelatin hydrogel was observed to have a significantly improved structural stability and elastic modulus. In addition, mesenchymal stem cells were able to survive and proliferate in the bioink for a long period of time (7 days). In the future, new functions such as drug loading, sensing, and supercapacitance may be introduced into bioinks by utilizing the properties of MOFs as porous materials. The strong reinforcing effect of ZIF-8 and the drug loading/sensing properties of MOFs will open up new possibilities for 3D bioprinting.

Mesoporous silica nanoparticles, which have high porosity, have been investigated as excellent nanocarriers for drug delivery.[81] In practical applications, it is important to deliver drugs to the target site by bypassing clinical barriers. Improvements in cellular uptake by material designs are required. For example, lipid coating of mesoporous silica nanoparticles has significantly reduced many of the drawbacks and enhanced their

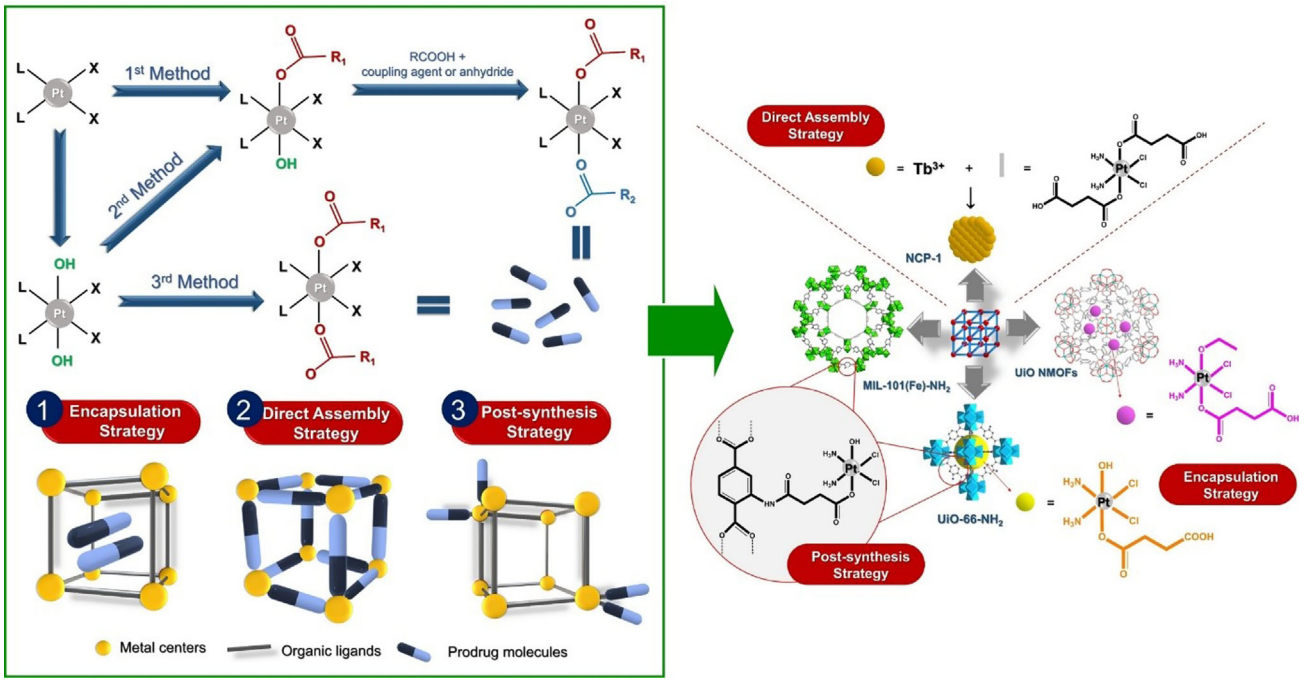

Figure 17. Synthesis (left) and prodrug delivery (right) in several MOFs: encapsulation strategy, direct assembly strategy, and postsynthesis strategy. Reproduced with permission.[79] Copyright 2022, Oxford University Press.

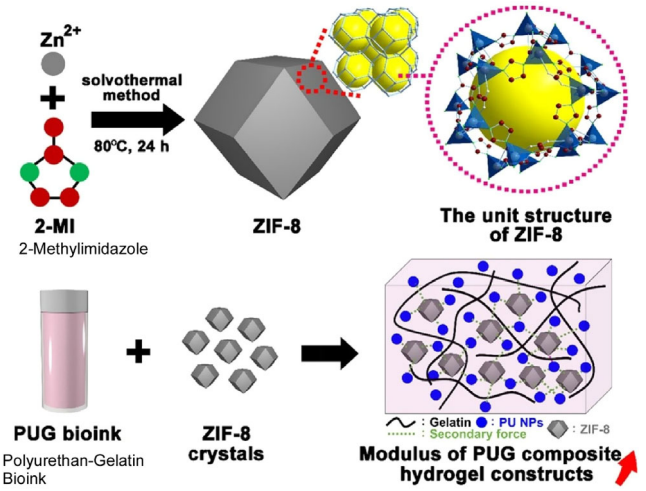

Figure 18. Reinforcing effect of MOF zeolite imidazolate framework-8 (ZIF-8) in polyurethane-gelatin hydrogel bioink, where modulus of the bioink can be enhanced by mixing with ZIF-8 crystals in different amounts. Reproduced with permission.[80] Copyright 2021, American Chemical Society.

compatibility. Vinu et al. demonstrated a dual-protection drug delivery approach using lipid-coated core-shell mesoporous silica nanoparticles with hexagonal morphology and conjugated with cabazitaxel drug.[82] Cabazitaxel-conjugated lipid-coated core-shell mesoporous silica nanoparticles showed superior physical properties in factors such as drug release, cellular uptake, and cytotoxicity. It was actually demonstrated to be suitable for prostate cancer (PC-3) cell line. The core-shell mesoporous silica nanoparticles were coated with a lipid layer by liposome fusion method. Lipid coating showed excellent biocompatibility and better cellular uptake. Cytotoxicity in PC-3 cancer cells was enhanced. Anticancer drug cabazitaxel was conjugated to β-lactam via a hydrazone linker that was only cleavable at acidic pH. This dual-protected core-shell mesoporous silica nanoparticle system showed a significant increase in drug release at pH 5.4 compared to pH 7.4. This nanoarchitectonic approach of core-shell mesoporous silica nanoparticles combined with stimuli-responsive system and lipid coating may improve therapeutic delivery and treatment difficulties in many other cell lines and diseases. Further modifications could be used for many other cell lines and diseases by enhancing site-specific drug delivery. In general, the lipid coating of mesoporous silica nanoparticles allows for the combination of the advantages inherent to each nanoarchitectonics component. The coating of mesoporous silica nanoparticles with lipid bilayers allows the advantages of liposomes to be combined, including low toxicity, low immune response, prolonged circulation time, and low clearance. Furthermore, the advantageous features of mesoporous silica nanoparticles, including high drug loading, surface area, solid nature, pore volume, pore diameter, and functionalization, are also included.

Core-shell mesoporous silica nanoparticles can carry a large amount of various kinds of drugs. Furthermore, a mechanism that responds to stimuli can be introduced. It is expected to be a promising drug delivery system. However, there is still room for development in the synthesis of mesoporous silica nanoparticles themselves. Vinu and co-workers have recently reported the synthesis of core-shell mesoporous silica nanoparticles using a triple surfactant-assisted soft template method.[83] A trisurfactant system with cetyltrimethylammonium bromide, Pluronic F-127, and fluorocarbon-4 surfactant as templates is investigated. This combination results in the synthesis of core-shell mesoporous silica with the highest specific surface area, large specific pore volume, and well-ordered porous structure. The surface charge distribution and packing parameters of these surfactant aggregates can be well controlled, and the resulting texture parameters can be adjusted accordingly. In particular, the size and texture properties of the core-shell structure is able to be easily modified by controlling the amount of fluorocarbon-4 surfactant. The optimized core-shell mesoporous silica nanoparticles showed a very large surface area and could be loaded with high concentrations of the drugs doxorubicin and docetaxel. The administration of doxorubicin-loaded core-shell mesoporous silica nanoparticles to LNCaP and PC-3 cells showed higher cytotoxicity compared to free doxorubicin. The new core-shell mesoporous silica nanoparticles prepared using a tri-surfactant method are promising carriers for drug delivery systems. The drug delivery system developed here will be useful as a versatile platform for loading and delivery of various types of chemotherapeutic drugs.

Modification of the device surface with hydrogels provides nonfouling, excellent biocompatibility, etc. Integrating these devise properties into a mesoporous platform provides a favorable structure for biomolecule adsorption or hybridization with capture agents. Masud, Hossain, Kaneti, et al. developed a κ-carrageenan hydrogel-coated mesoporous gold electrode (**Figure 19**),[84] which can be used for chronocoulometric detection of microRNA (miRNA). The κ-carrageenan gel forms a three-dimensional porous network on the gold electrode surface. In the presence of the redox molecule ruthenium hexaammine(III) chloride, high adsorption of the target miRNA occurs. The mesoporous structure with high surface area promotes the adsorption of the analyte. The 3D network of double helices in the κ-carrageenan gel further enhances the accessibility of the miRNA through the porous network. This is followed by chronocoulometric intercalation of the adsorbed miRNA. By attaching miRNA to the mesoporous gold electrode/gel surface, the assay showed a better electrochemical signal. The concentration of the target miRNA can be quantified from the signal intensity. Thus, the mesoporous gold electrode/gel system for miRNA detection has potential clinical applications. It is expected that it can be used to detect RNA biomarkers for the diagnosis of chronic and infectious diseases.

The above examples illustrate the utilization of porous structures in a variety of contexts. The creation of an ordered porous structure results in an increase in the volume that can accommodate drugs, as well as an expansion of the contact area for signal transmission. These characteristics render the structure advantageous for drug delivery to living organisms and for sensitive sensing of biological materials. Furthermore, nanoarchitectonics will facilitate the incorporation of additional functional sites, thereby enabling the development of porous materials with even more advanced biomedical applications. There are numerous methodologies for developing porous materials, and it can be

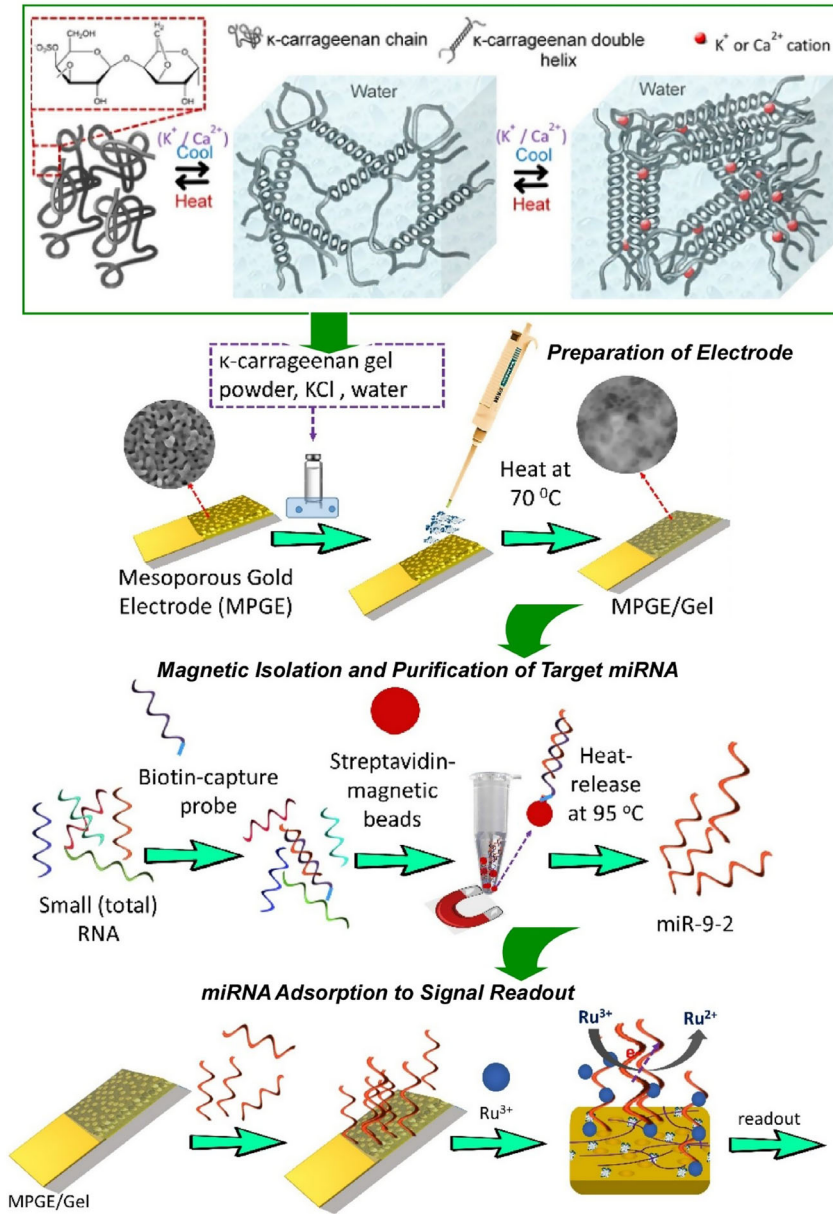

Figure 19. A κ-carrageenan hydrogel-coated mesoporous gold electrode which can be used for chronocoulometric detection of miRNA. Reproduced with permission.[84] Copyright 2022, Oxford University Press.

anticipated that a diverse range of functional materials will be created from them.

5. Conclusion and Future Perspectives

As illustrated in the preceding section, this review has presented examples of functional materials that are utilized in medical applications from the vantage points of molecular nanoarchitectonics, materials nanoarchitectonics, and pore-engineered nanoarchitectonics. It should be noted that the examples provided are not exhaustive and do not necessarily represent the most advanced or exemplary work in the field. However, there is no doubt as to the diversity and direction of these developments. The application of molecular design principles has resulted in the development of highly functional materials. The utilization of molecular nanoarchitectural methodologies will facilitate the generation of supramolecular assemblies with exceptional biological functionality, which can be employed in biomedical applications. It can be stated that the contribution of molecular nanoarchitectonics, which assembles functional molecules as basic materials, is significant. Furthermore, the development of biomedical materials utilizing a range of nanomaterials as functional components was also demonstrated. Nanomaterials

of varying dimensions, architectures, and compositions are employed in medical applications. The properties of each component material are specific, yet versatility is not a universal attribute. Such combinations can be used for advanced biomedical applications. As an illustration of a particular structural configuration, porous materials were previously discussed. The creation of a regular porous structure allows for an increase in the volume that can accommodate drugs, while simultaneously enhancing the contact area for signal transmission. A multitude of pore-engineered nanoarchitectural techniques exist, which can be employed to create a diverse array of functional materials.

As evidenced by the aforementioned examples, a diverse array of materials are employed as components, contingent upon the specific objectives of medical and biological applications. This characteristic differs from that observed in the design of materials for energy or environmental applications. The materials employed for these applications tend to be somewhat fixed. It is not uncommon for carbon materials, nanoparticles, two-dimensional materials, and so forth to be employed in this context. The strategy is frequently to combine these components with the objective of maximizing surface area or enhancing catalytic activity. The design of materials is rational and relatively uniform. In contrast, materials employed in biomedical applications are highly specific and possess distinct properties, necessitating a case-by-case approach. It is challenging to present a unified concept that encompasses the numerous examples. The aforementioned examples demonstrate the characteristics of materials employed in biomedical applications. This exemplifies the challenge inherent to the development of biomedical materials.

Nevertheless, it is in this area that nanoarchitectonics can demonstrate its greatest potential. The objective of nanoarchitectonics is to utilize a range of nanomaterials and associated methodologies for the construction of functional materials. It is essential to consider the diverse purposes of biomedical applications when applying this scheme. Presently, such endeavors are being undertaken on an individual basis for each specific purpose and subject area. Rather than a unified methodology, these approaches are based on the researcher's own experience and ideas. To facilitate future development, it is essential to overcome these limitations. Fortunately, humans have developed a means, namely, artificial intelligence, that is capable of handling a very large amount of information. Materials informatics and machine learning have been employed to develop materials and comprehend chemical processes.[85] The creation of materials suitable for biomedical applications will be facilitated through the collaboration of nanoarchitectonics and materials informatics. This represents a crucial step toward a significant advancement in this field. For instance, the potential for nanoarchitectonics and materials informatics to work in concert has been demonstrated in the context of functional porous materials.[86] Similarly, the integration of these two fields is of paramount importance in the development of biomedical materials, which are inherently complex and diverse.

A further crucial aspect of development is the manner in which these approaches can be developed from their fundamental scientific basis to a point where they can be applied in an industrial context. In this regard, biomedical applications are in a more advantageous position than those in the energy and environmental fields. The suitability of functional materials constructed with nanoscale structural precision for mass production is not guaranteed. The cost-effectiveness of nanoarchitectonics may be called into question when treating large quantities of pollutants or designing energy plants. Conversely, in the context of biomedical applications, the utilization of small structures and quantities is advantageous for a multitude of applications. Furthermore, the threat of competition from inexpensive materials is minimal. It appears that the biomedical field is an appropriate setting for the precision synthesis of nanoarchitectonics. It is therefore anticipated that examples of industrial applications will emerge from the field of biomedical research that will benefit the wider industrial world. The potential for significant financial gain will undoubtedly stimulate further advancement in this field. As previously stated in the Introduction, the open challenge in nanoarchitectonics is the establishment of methods to create all the functional materials. Consequently, the open challenge of nanoarchitectonics in biomedical engineering would be the production of materials applicable for all the biomedical opportunities.

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Conflict of Interest

The author declares no conflict of interest.

Author Contributions

Katsuhiko Ariga: Conceptualization (lead); Funding acquisition (lead); Methodology (lead); Project administration (lead); Resources (lead); Visualization (lead); Writing—original draft (lead); Writing—review and editing (lead).

Data Availability Statement

Research data are not shared.

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