Review

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A new classification method of nanotechnology for design integration in biomaterials

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Abstract: Currently, advanced biomaterial design solutions often have more than two kinds of nanotechnology design strategies, but there is no suitable classification to describe these designs systematically. Based on the material design ideas and the modes of implementing functions, this article exemplifies and proposes a new nanotechnology classification that includes physical properties, the chemical reactions that respond to the microenvironment and bio-inspired incorporation. If two or more nanotechnology designs in the same classification are to be integrated into the same biological material, it is necessary to analyze the integration conflict between the designs. With the development of big data, this classification method may help researchers and artificial intelligence to realize automated integration of multiple designs and provide new material nanotechnology design integration solutions.

Keywords: nanotechnology classification, design integration, biomaterials

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1 Introduction

Nanotechnology is defined as the "intentional design, characterization, production and application of materials, structures, devices and systems by controlling their size and shape in the nanoscale range (1–100 nm)" [1], and it has been widely applied in many fields [2,3]. For biomedicine, most of the diseases originate from the alterations in the physiological state at the molecular or nanoscale level, and in the course of disease treatment, biomolecules, biological agents, chemical medicine and bio-barriers are commonly in the nanometer level in size [1]. The past medical technology has limitations in the development of medicines because the objects of the biomaterial technology research are at a bigger size level compared with the biomolecules and biochemical reactions [4]. In principle, nanotechnology could be used to realize more powerful biomedicine regulation.

Nowadays, advanced biomaterials often contain more than two kinds of nanotechnology design strategies, but there is no suitable category to describe these designs systematically. There are big nanotechnology data originating from research articles; however, still there is a lack of systematic analysis between different function implementations of these designs. It is necessary to put forward a reasonable nanotechnology category for technology adoption and implementation. Currently, most classifications describe the application field [5] or the properties of materials [6], such as the origin (natural and anthropogenic), chemical composition (metals, metal alloys, metal oxides, semiconductors, carbon nano-objects, polymers and the category of nanomaterials including silicates and carbonates) and whether it is toxic [7]. These kinds of biomaterial data classifications can provide solutions, which have been tested by other articles. For automated, selective and innovative manufacturing and integration of new biomaterials, depending only on the cognitive scheme for data as mentioned above is not enough. Whether they are researchers or artificial intelligence (AI) replacing the job of creating new materials, in addition to choosing

raw materials and material processing (nanotechnology), they also need to think about technology integration. This requires a new classification framework to guide nanotechnology processing to realize new processing integration. Currently, the establishment of nanotechnology categories is still difficult [8], and few articles have tried to classify by function implementation. Here, we introduce several nanotechnology designs in the field of biomaterials and describe a classification method including physical properties, the chemical micro-environment responding through a chemical reaction and bio-inspired incorporation, which contains the design of biomimetic materials and the indirect use of parts of natural organisms to form composite materials. The parts of organisms in composite materials provide an expected biological effect, but the biological mechanism may not be clear or it is difficult to synthesize replacement currently. This paper reviews some examples related to pharmacokinetics, cellular growth regulation, interference with body recognition and biological detection to classify them from the new perspective of function implementation. This classification focuses on a quick understanding of the nanotechnology design, the interplay between different designs and predicting the design conflict in a material, which contains integration of more than two nanotechnology designs. It also may work as a category architecture for the automatic generation of design solutions by using big data and AI.

2 Physical properties

Nanotechnology could directly change the physical properties of materials and then alter the pharmacokinetics or biological response. As early as 2001, a three-dimensional environment was proposed to be closer to the actual growth environment of cells [16]. Technology development led to many facilitated methods for preparing three-dimensional physical structures as shown in Figure 1 [9]. In the solvent casting and particulate leaching method [10,11], a sacrificial porogen is evenly dispersed in a prepolymer solution and poured into a mold (Figure 1a and b). After the polymerization completes, the porogen leaches through the solvent or at high temperature to yield a porous material. The main disadvantage of this is the toxicity of the solvent remnants. In the traditional 3D printing technology for manufacturing stents, the fused deposition modeling technology requires the material to be printed out in fluid form, which is then solidified into different shapes (Figure 1c). A CAD model (Figure 1c-b) was formed by laser scanning (Figure 1c-a), followed by the creation of a specific porous scaffold (Figure 1c-c). MicroCT (Figure 1c-d) and SEM (Figure 1c-e) were used to show the morphology and microstructure. Figure 1d shows the technology of two-photon polymerization (TPP) using a laser to activate a photosensitizer such as Irgacure 2959 to make methacrylamide-modified gelatin partially insoluble in solution, which then cures to form a specific shape of the scaffold material [13]. Figure 1e shows the laser-assisted bioprinting (LAB) method, in which a layer of 1 wt% alginate is first coated on a glass slide, moistened with 0.1 M $CaCl_2$ solution, then the hydrogel containing cells is laser printed on the surface of the material and finally $CaCl_2$ solution is sprayed, and after waiting for some time, a gel is formed. The 3D technology can also produce materials that contain cells directly. The femtosecond pulsed laser method uses TPP technology to polymerize materials to wrap the cells (Figure 1f-a), and the MTT results show that the cell viability is not affected. Figure 1f-b and c displays the CAD model for fabrication and the corresponding cell image under a light microscope [15].

In addition to the structure design above, more studies may focus on the impact of physical properties on biological functions, such as delivery [17], cell growth, protein adsorption and biorecognition regulation.

Hyaluronic acid synthase type 2 (HAS2) is delivered into cells using mesoporous silica nanoparticles with a core–cone structure (MSN-CC), a size of 170 nm and 15–40 nm pores to promote the synthesis of hyaluronic acid [18]. Surgery results of Sprague Dawley (SD) rats indicated that it is effective in preventing synovial inflammation of osteoarthritis and bone defects (Figure 2).

For a material to be used as a scaffold or a template for bone repair, it often needs to have biocompatibility, biodegradability and holes suitable for cell growth. Figure 3a shows the preparation of the degradable material poly(lactic-co-glycolic acid)/hydroxyapatite after the processes of water ultrasonication, refrigeration and air-drying [19]. The morphology result showed that the average pore diameter was 50 mm, which is larger than the 10 mm required for cell infiltration as verified by cell experiments in vitro [21]. For cell adhesion as shown in Figure 3b, for surface pattern sizes ranging from 100 to 3,000 nm, increasing the nanopattern size may lead to cellular spreading by the vinculin tractive effort [20,22].

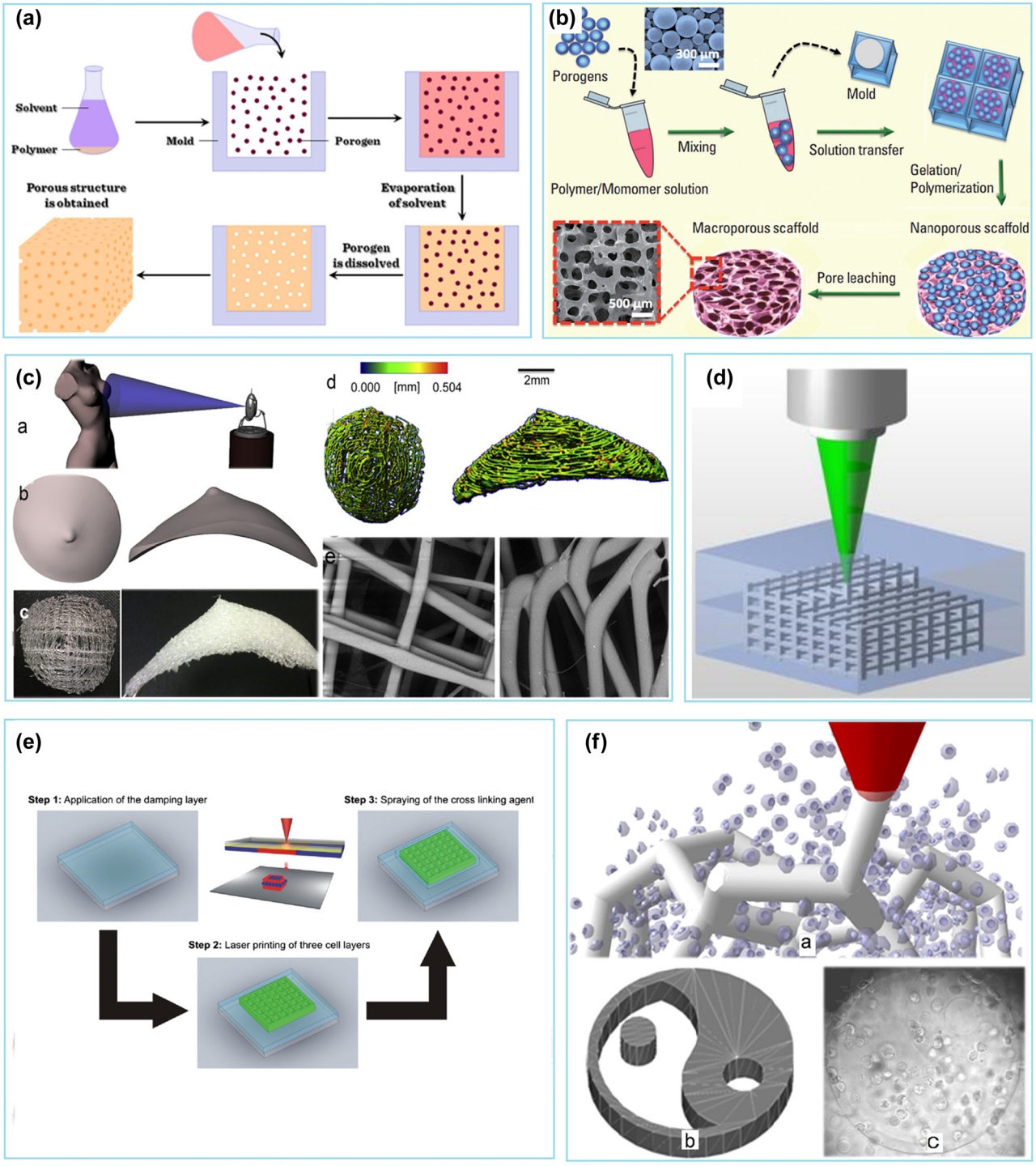


Figure 1: Different kinds of tissue engineering scaffold preparation methods [9]: (a) solvent casting [10], (b) particulate leaching [11], (c) laser scanning and fused deposition modeling [12], (d) principle of the TPP technique [13], (e) LAB method [14] and (f) laser-printed 3D tissue grafts consisting of cells [15].

Physical structure designs can also influence the application of materials in flowing environments. In intravenous injection applications, nanoparticles (NPs) as drug carriers possess the advantages of long-term existence in the blood circulation and high permeability and residence time [23–26]. As is known, NPs have the enhanced permeability and retention (EPR) effect [27]. However, there are still limitations, including the clearance by monocytes and low

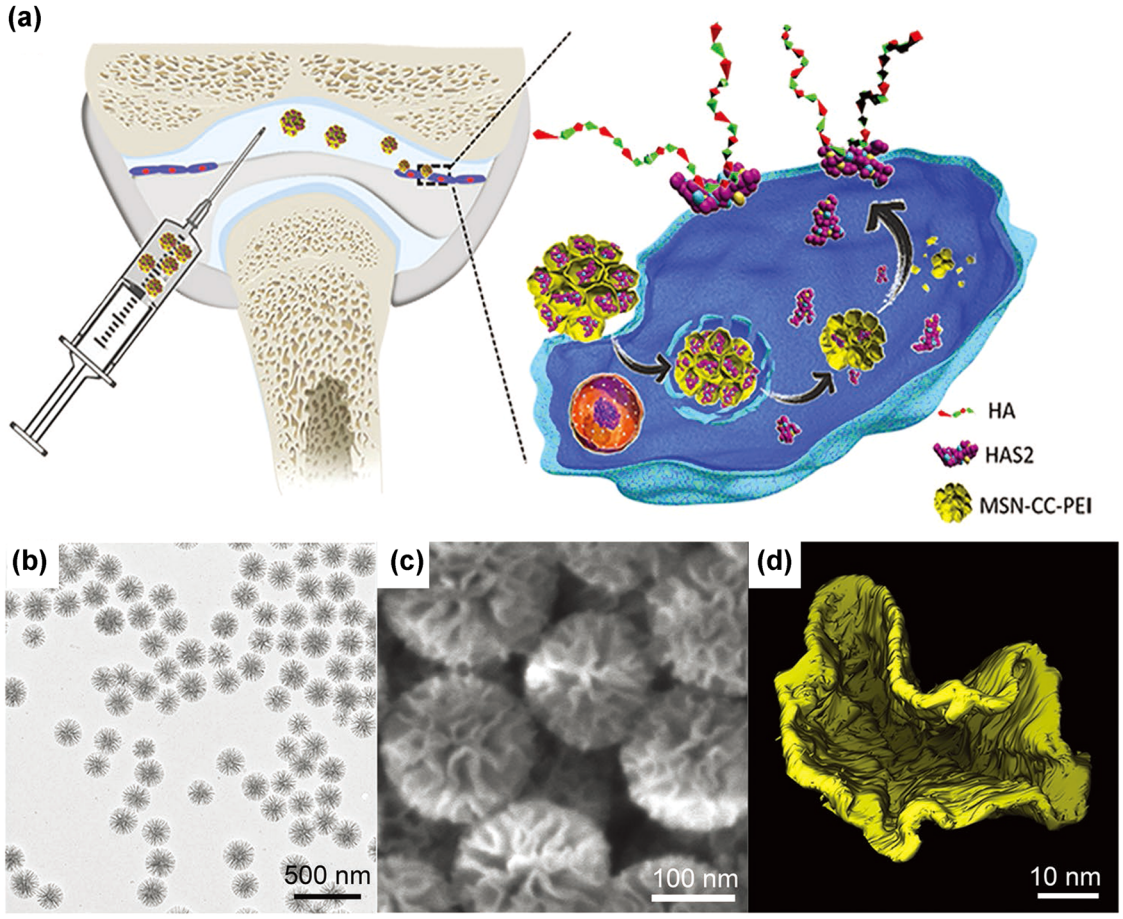


Figure 2: (a) HAS2 molecules are delivered using MSN-CC to synovial cells. The image results of (b) TEM, (c) SEM and (d) electron tomography technique for MSN-CC [18].

uptake by cancer cells, which currently are not ideal for human testing [28,29].

Figure 4 shows that the problem of the material being cleared by the monocyte system could be solved by a supramolecular pre-coated protein crown shielding system [30]. First, MSNs were modified with 3-(trimethoxysilyl) propyl acrylate, and then the GSH and alkenyl groups were connected by click chemistry. In the study, loading of doxorubicin (DOX), camptothecin, DiIC18 and DiD, respectively, has been tried. Finally, the recombinant fusion protein GST-HER2-Afb is attached to mesoporous silica through the supramolecular effect. Experimental results show that this protein shielding system could effectively reduce the adsorption of serum proteins while retaining targeting specificity.

In order to avoid the formation of protein crowns affecting the targeting of NPs, Figure 5a displays a simple regulation of the surface protein crown formation by surface grafting PEG [31]. The erBB2-receptor binding flow cytometry statistical analysis of PEG with different molecular weights such as 1, 5 and 10 kDa was performed on SKBR3 and MCF7 cells. It was found that PEG with a small molecular weight could be backfilled to avoid the loss of the target regardless of

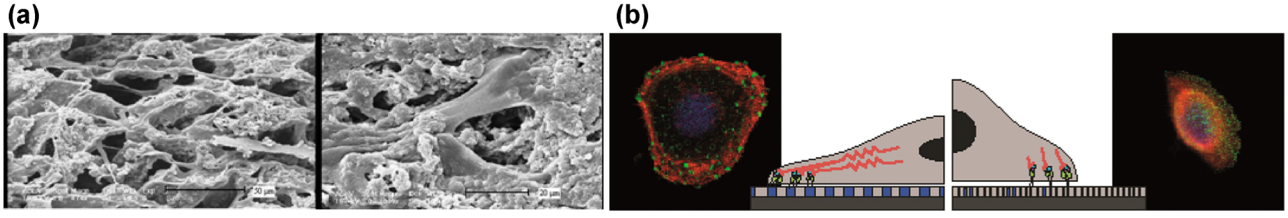


Figure 3: A scaffold for cell growth. (a) Scanning electron microscopy images showing the morphology of cells on the surface of a porous scaffold (left) and in-depth cells (right) after 3 days of cell seeding [19]. (b) The regulation of cell spreading by nanopatterns [20].

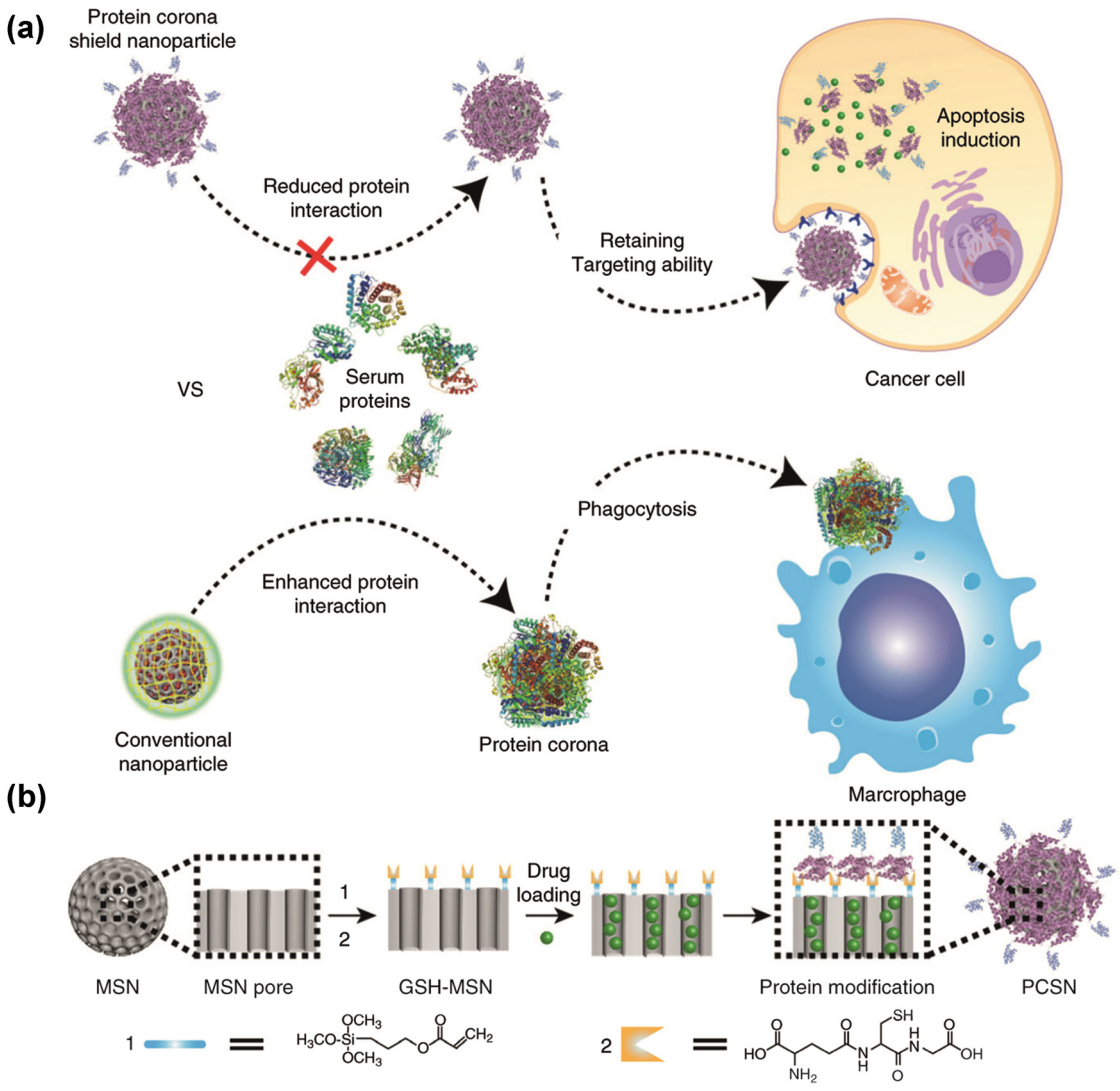


Figure 4: (a) Nanoparticles will lose the function of targeting peptides after the blood protein crown formation on them. Protein crown shielding system could avoid the blood protein crown formation to maintain the targeting and avoid the phagocytosis by macrophages. (b) Structure diagram of the protein corona shield system [30].

prior (Figure 5b) or post (Figure 5c) exposure to human serum.

Also, for other methods including photothermal therapy [32], magnetism [33], etc., which usually do not involve the production of new substances, the design of physical properties is straightforward and intuitive. Despite the convenience and simplicity of the methods in which materials' physical properties directly affect the micro behavior, there are still two limitations in this category: (1) the variety of physical property designs is limited, which makes the integration easier to conflict. For instance, a sphere with a diameter of 1.5 mm can reduce the body's foreign body response [34], but still, it is too large for the NP drug delivery system that needs to enter the cells [35]. (2) In theory, diseases always originate from the change of the physiological environment, while the obtained physical properties are always constant. So they are unfavorable to deal with specific changes of disease. Maybe other categories of nanotechnology could provide more help.

3 Chemical microenvironment response

In addition to chemical reactions used to generate new substances, the changes of the pathological environment are always the response conditions for intelligent

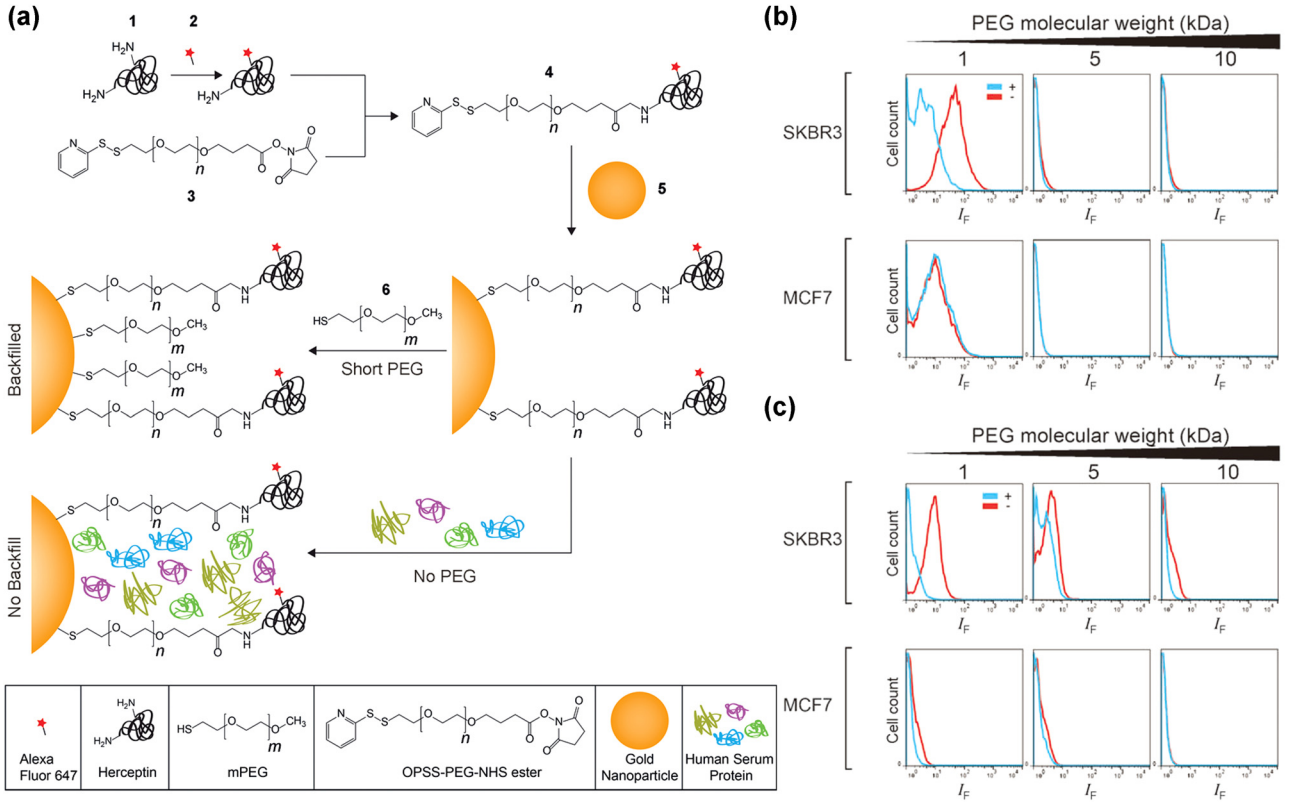


Figure 5: Serum–protein adsorption could reduce the binding specificity but this situation could be alleviated by PEG backfilling. (a) Herceptin (1) was initially conjugated to Alexa Fluor 647 (AF647; 2) through amine-reactive succinimidyl ester chemistry, followed by a second conjugation step with orthopyridyldisulfide polyethyleneglycol *N*-hydroxysuccinimide ester (OPSS-PEG-NHS ester; 3) to generate OPSS-PEG-Herceptin-AF647 (4). The surfaces of the 50 nm gold nanoparticles (5) were functionalized with (4) and backfilled with methoxy-polyethylene glycol (mPEG, 6) through thiol coordination. (b) The molecular weight of the PEG used for backfilling affects the binding specificity. Herceptin-conjugated gold nanoparticles with 1, 5 and 10 kDa PEG backfill were incubated with SKBR3 and MCF7 cells prior to (b) and post (c) exposure to human serum [31].

biomaterials [36]. The most typical application is the change of pH in the area of disease tissue.

Pei-Pei Yang introduced the material BP-FFVLK (-His6)-PEG, in which the protein–peptide structure contains a hydrophobic end and a hydrophilic end, and it can self-assemble in liquids to form NPs (Figure 6a). His6 is a pH-responsive motif. After the NPs are injected into tumor model mice, they accumulate in the tumor site through a passive targeting mechanism. Then, the NPs transform into nanofibers (NFs) due to changes in the hydrophilicity/lipophilicity balance under the acidic conditions of the tumor microenvironment and form a nested structure (Figure 6b). This nest-like structure can effectively result in material retention for a long time and help in sustained drug release [37].

For the treatment of cancer, Ya Jin et al. noted that the connective tissue fibers at the cancer site ranged in size from 40 to 80 nm [39], which was not conducive to the deep penetration of NPs into cancer tissues. So, a nanomicelle was designed by Xu et al. to dissolve the tissue fibers [38]. First, the micelle is formed by a self-assembly reaction between succinic anhydride-modified cisplatin-conjugated poly(ε-caprolactone)-*block*-poly(ethylene oxide)-triphenylphosphonium (CDDP-PCL-PEO-TPP) and maleimide-terminated poly (ethylene glycol)-*block*-poly(β-amino ester) (MAL-PEG-PBAE). Next, Col-TCPPB NPs are prepared through a click chemical combination of thiolated collagenase and maleimide groups on the TCPPB micelle. The acidic environment of cancer cells makes the hydrophobic PBAE segments hydrophilic. The NPs break down and release some collagenase-containing ingredients and digest collagen fibers, which enhances the permeability to NPs. At the same time, staying at the tumor site due to the enlargement of particles is also considered to be beneficial (Figure 7).

Not only the cancer environment but also the acidification in the intracellular compartment should be considered for drug release. In chronic pain, the substance P (SP) neurokinin 1 receptor (NK1R) will

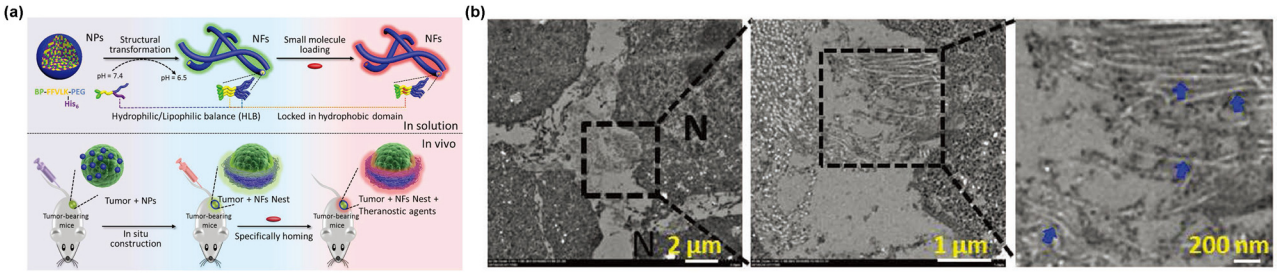


Figure 6: (a) In the acidic microenvironment of tumors, NPs transform to nanofibers to wrap tumor cells. (b) TEM images of the NFs around tumor tissue. The blue arrows indicate NFs [37].

accumulate in acidified endosomes, and it sends signals for maintaining pain [41–43]. NK1R in endosomes is an important target for pain relief. The author of this article designed diblock copolymers synthesized with the same hydrophilic shell of P(PEGMA-*co*-DMAEMA). pH-responsive NPs (DIPMA) were synthesized with the hydrophobic cores of P(DIPMA-*co*-DEGMA) or using the non-pH-responsive cores of PBMA to form BMA NPs (Figure 8a). An aprepitant drug was introduced by self-assembly and tested. From the experimental results it can be observed that it can quickly suppress the signal of SP and then realize a nonopioid treatment option for chronic pain (Figure 8b) [40].

In contrast to the physical property design of materials, the design of chemical microenvironment responses can respond to the biochemical environment or the biological substance that occur in diseases and make timely adjustments. However, there are still two kinds of limitations for this category: (1) the design is based on our full understanding of the disease, and for the unclear one, it is difficult to provide a design. (2) Similar biochemical changes in pathology may occur in different parts of the human body, such as the acidic environment in both the nucleus and tumor cells, which may interfere with the tumor targeted performance of antitumor materials. Although scholars have suggested that targeting both tumor cells and the tumor microenvironment will greatly increase the effectiveness of treatment [44,45], we still have doubts. In fact, in addition to the strategy of chemical microenvironment response, naturally derived targeting elements, such as antigens and antibodies, could provide more materials research ideas.

4 Bio-inspired incorporation

For design requirements for which there is no clue or that exceed our cognition, a long natural derivative

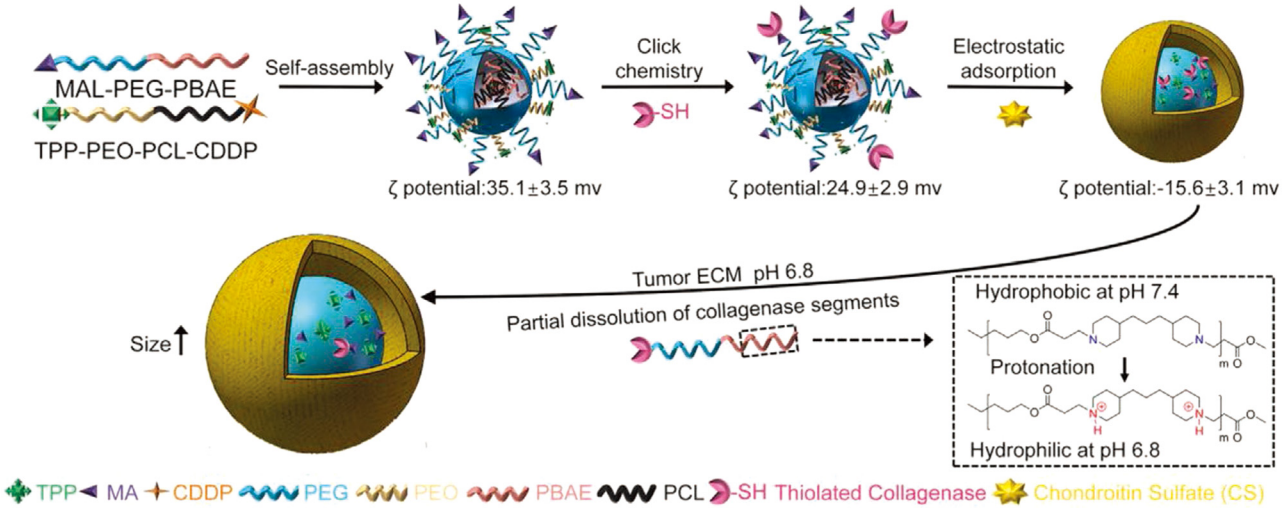


Figure 7: Schematic diagram of the size-changeable multifunctional nanoparticles [38].

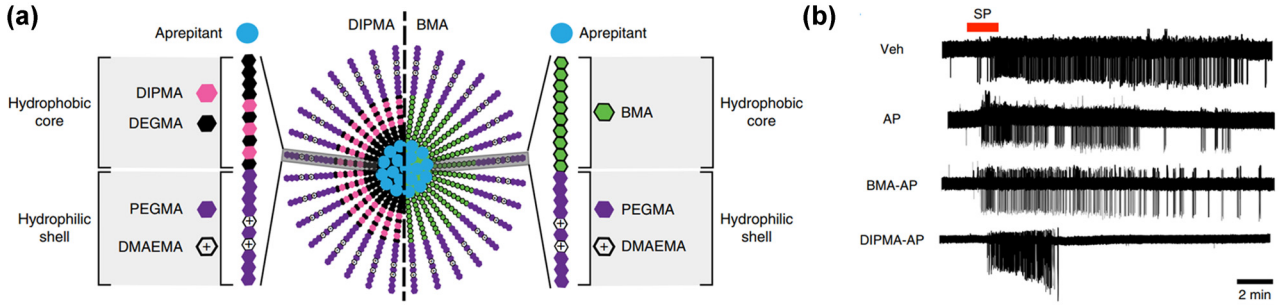


Figure 8: (a) Structure diagrams of pH-responsive (DIPMA) and pH-non-responsive (BMA) nanoparticles. (b) Cell-attached patch-clamp to record the potential changes of the neurons with stimulation [40].

could inspire us a lot. A natural substance such as DNA molecules with a diameter of 20 nm and the cellular membrane could be utilized or simulated to achieve some biological reactions [7]. The main aspect of bio-inspired incorporation is that we don't know or understand many processes in organisms, while we have observed some of the biological materials' superior performance, e.g., antigen–antibody-specific binding involving site binding domains is a targeted binding. This technology design provides new approaches for the biofunction implementation and at the same time, materials in this design is considered to reduce the complex level of rejection reactions research than artificially synthesized materials. Extraction and separation by bioengineering by taking a biological component as a material skips the problem of manufacturing difficulties [46].

In the natural human body, the membrane of M1 macrophages affects delaying of the phagocytosis of NPs and their movement towards the tumor site. According to these characteristics, the M1 macrophage membrane was isolated and utilized to pre-encapsulate NPs (Figure 9) [47]. After the particles are targeted and enriched in the tumor tissue, under laser irradiation of 650 nm, the bilirubin–PEG core undergoes hydrophobic conversion and cleavage to release DOX from small-sized NPs [BA (D)] and the photosensitizer Ce6 irradiated with laser light produces reactive oxygen species, killing tumor cells in a dual way. The article did not design artificial chemical synthesis of M1 macrophage membranes, but the author directly used a component of the biological body through biological separation to achieve the target effect that has been observed in nature.

Biological base complementary pairing and melting curve analysis are the core of gene chip detection. In a study, the DNA of an extracted biological sample is amplified in an enclosed chamber by the polymerase chain reaction (PCR) method. After the amplified DNA is hybridized with DNA probes fixed in different regions of interest (ROI), differences of the melting curves between mutant type and wild type are detected, and then quickly and massively the mutation is analyzed [48]. Specific biological reactions lead to the accuracy, and the integration of miniaturized biochip leads to the testing rapidity. Currently, it is difficult for the human race to create other physical and chemical reactions to achieve the same detection performance.

In response to the sudden global health crisis, rapid testing and screening of clinical samples could obtain information in a short time. A solid-phase oligonucleotide DNA array with addressable pixels, each one containing sequences complementary to specific parts of PCR amplicons, is used. Multiple PCRs are performed on the nucleotide sequences extracted from the samples, and then the PCR product is detected (Figure 10a and b). DNA–DNA hybridization events are detected at every pixel throughout the multiplex PCR sequence identification through probe–amplicon solid-phase melting-curve analysis (Figure 10c). This platform is fabricated using sub-micron complementary metal-oxide semiconductor (CMOS) processes [23] and includes independent DNA biosensors with thermocycling capabilities.

In another field such as cardiovascular disease treatment, there are many studies on biological factors. In our previous work [49,50], anticoagulation function is realized by the heparin agent extracted from porcine. Heparin-based NPs were formed by an electrostatic reaction after mixing poly-L-lysine solvent and heparin solvent. Surface modification with NPs still maintains the anticoagulation function and can selectively regulate cell behavior, which may have promising application in the field of intravascular stents. Tissue plasminogen activator has also been widely studied as a thrombolytic agent, using different materials such as polymers, micelles and microbubbles to achieve drug targeting, protection and release to the lesion location [51]. With

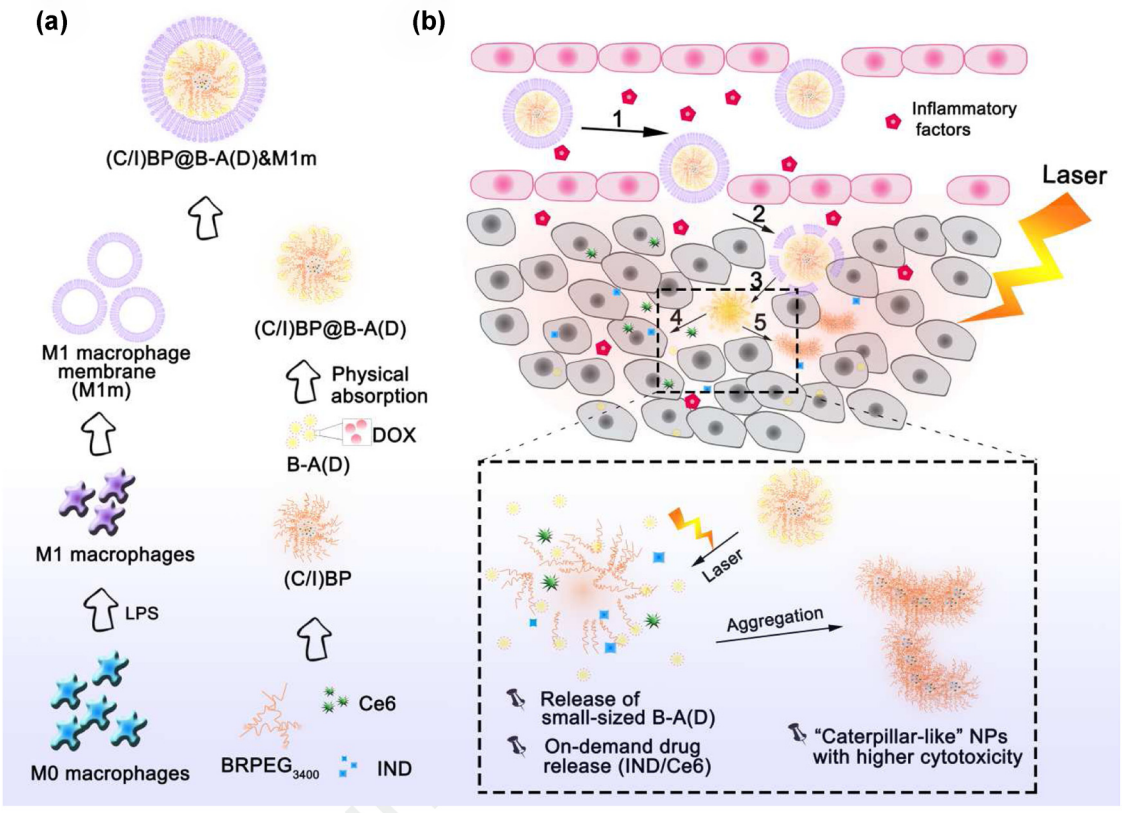


Figure 9: Schematic diagram of nanoparticle structure and functions. (a) The preparation of (C/I)BP@B-A(D)&M1m particles. (b) Targeting and therapeutic effects of nanoparticles. (1) The M1 macrophage membrane wraps the particles to reduce the clearance by the mononuclear phagocyte system; (2) EPR effect on the tumor; (3) M1 macrophage membrane separates in an acidic environment; (4) the toxic hydrophobic chlorin e6 (Ce6) and IND are released by laser irradiation; and (5) the aggregated "caterpillar-like" structure is also toxic to tumor cells [47].

the aim of sustained neovascularization, Chiappini et al. delivered the VEGF-165 gene into cells by using biodegradable silicon nanoneedles [52]. These are the design integrations between the physical properties of carrier delivery functions and biological incorporation of biomolecular functions.

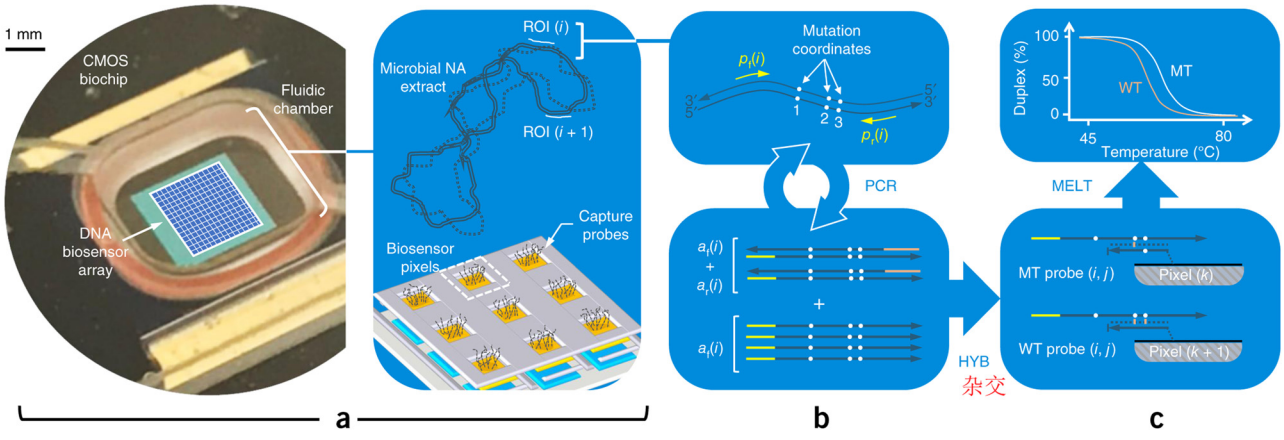


Figure 10: Nucleic acid amplification test platform. (a) Schematic diagram of the platform structure. (b) Multiple amplification of SSDNA in different ROI. (c) After multiplex amplification, the melting curve of the double-stranded DNA combined with the probe in the ROI area could show the mutation signal. [48]

Table 1: Different categories of nanotechnology design with examples

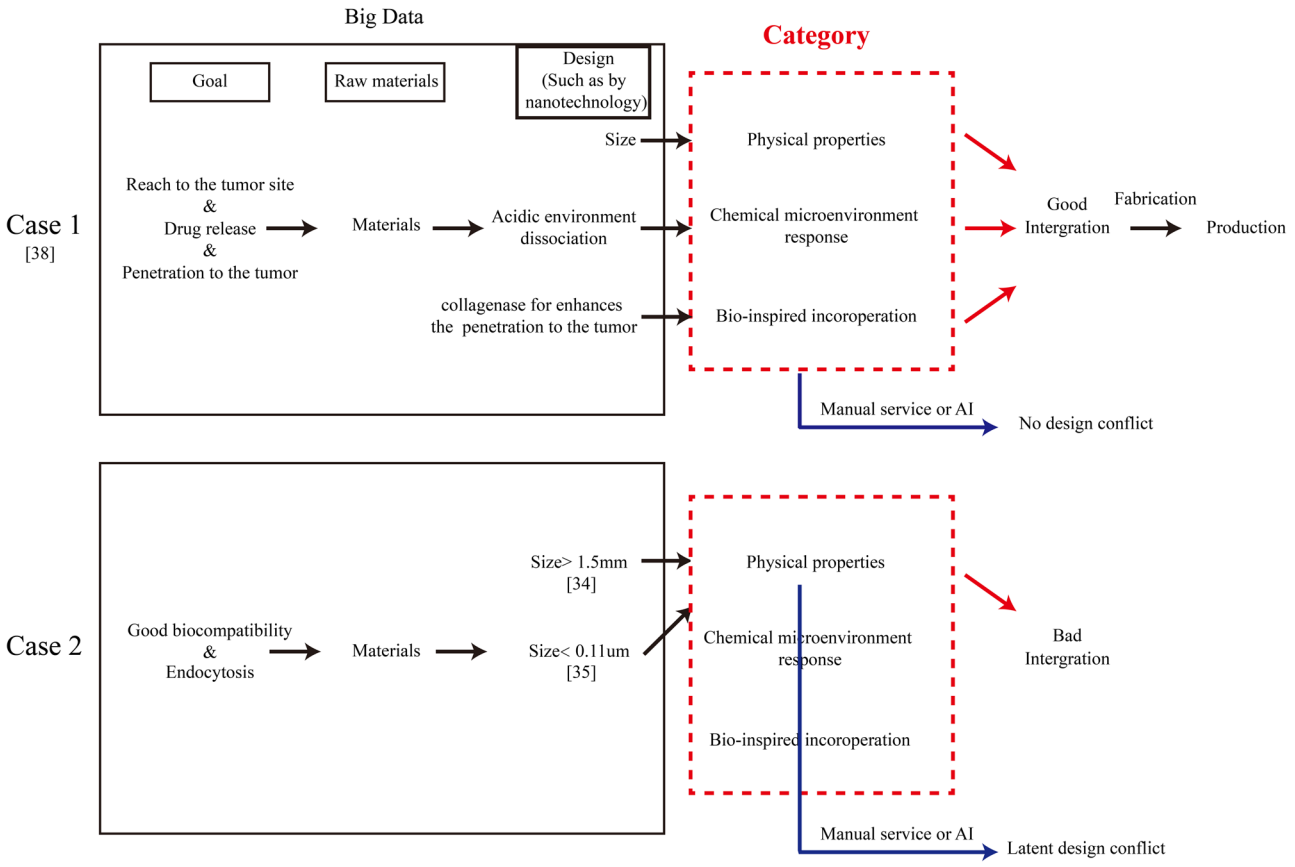
Categories	Nanotechnology design	Function	Materials
Physical properties	Core–cone structure	Delivery	MSNs [18]
	Nanopatterns	Cell spread regulation	Gold regions with fibronectin and surrounded by protein- and cell-resistant polymer brushes [20]
	Mesoporous nanoparticles	Delivery	MSNs modified by 3-(trimethoxysilyl) propyl acrylate and click chemistry with GSH and alkenyl groups [30]
	Polyethylene glycol backfilling	Inhibits the protein corona formation to maintain targeting function	OPSS-PEG-Herceptin-AF647-mPEG [31]
Chemical microenvironment response	His6 is a pH-responsive motif	Targeting tumors; transformation of NPs to NFs to construct a nest-like host of tumors	BP-FFVLK(-His6)-PEG [37]
	PBAE segments undergo a transition from being hydrophobic to hydrophilic with the protonation of the tertiary amino group in the acidic microenvironment	Release collagenase	CS/Col-TCPPB NPs [38]
	DIPMA pH-responsive	Targeting the acidification of the intracellular compartment	DIPMA [40]
Bio-inspired incorporation	The membrane of M1 macrophages encapsulates nanoparticles	Delaying phagocytosis; tumor targeting	(C/I)BP@B-A(D)&M1m [47]
	DNA–DNA hybridization	Comprehensive mutation analysis	Semiconductor biochip [48]
	Modification by heparin	Anticoagulation; inhibits smooth muscle cell proliferation (the mechanism is unclear)	Heparin/poly-L-lysine nanoparticles [50]

Unlike physical property design and chemical microenvironment response design, this is more based on the laws derived from a long life. In the methods including materials inspired by biology, such as liposome simulation [53] derived from the composition of the cellular membrane, DNA base complementary pairing detection derived from gene replication and antigen–antibody targeted binding derived from biorecognition, most of the raw materials are not obtained by chemical synthesis but through biochemical extraction and collection, which are then re-assembled and re-processed into new materials. The advantage of this category is that despite the mechanisms being not clear, the functions could still be obtained through biological extraction treatment. This method could avoid the difficulty in the synthesis of raw materials and increase the biocompatibility. The disadvantage is that the application is limited by biological cognition and bio-immunogenicity. However, there is no denying that bioinspired incorporation greatly broadens the research of materials and achieves a wider range of applications.

Based on the examples mentioned above, we make a classification summary of the studied nanotechnology, as shown in Table 1.

5 Conclusions and discussion

This study systematically classifies nanotechnology in the aspects of implementing functions and reviews the corresponding materials design, including the direct alteration of the physical properties of materials, chemical-reaction-related smart response system designs that are affected by the microenvironment and bio-inspired incorporation that includes biological principle inspiration or utilization of part of the biological substance. These categories are independent and could be used for inductive design methods, such as the physical properties of NPs, pH-responsive chemical reactions and biologically inspired cell membrane



Scheme 1: Schematic diagram of the role of nanotechnology categories in the integrated design of multifunctional biomaterials. Case 1: nanotechnology designs belonging to different categories could be successfully integrated. Case 2: two designs belonging to the same category may lead to integration conflict.

encapsulation. As medical requirements increase, current designs of biomaterials containing two or more design forms in different categories of design always will not conflict. In contrast, there may be design conflicts for the same category of nanotechnology design. For example, if hypothesis function A needs the material physical structure to be round while function B needs the material structure to be needle-shaped, it is hard to integrate the two kinds of function strategies. A new classification method is put forward to analyze this kind of problem, while it also has limitations. For example, spherical shape and small size also belong to the category of physical properties, but the design integration can also be realized. This misjudgment is because the range of classification is too large. With the development and refinement of classification, this misjudgment can be reduced.

In the future, reasonable technology classification may be important as an architecture of choice for biomedicine design integration (Scheme 1). With the development of big data and AI, new material design could be carried out by AI: First, analyzing the multiple functions required, then selecting reasonable materials and integrating nano designs that are non-conflicting. Finally, controlling the equipment to complete the material fabrication processing.

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References

[1] Kim BY, Rutka JT, Chan WC. Nanomedicine. N Engl J Med. 2010;363(25):2434–43.
[2] Xiong C, Li B, Liu H, Zhao W, Duan C, Wu H, et al. A smart porous wood-supported flower-like NiS/Ni conjunction with

vitrimer co-effect as a multifunctional material with reshaping, shape-memory, and self-healing properties for applications in high-performance supercapacitors, catalysts, and sensors. J Mater Chem A. 2020;8(21):10898–908.
[3] Liang Y, Qin H, Huang J, Huan S, Hui D. Mechanical properties of boron nitride sheet with randomly distributed vacancy defects. Nanotechnol Rev. 2019;8(1):210–7.
[4] Dobrovolskaia MA, Patri AK, Zheng J, Clogston JD, Ayub N, Aggarwal P, et al. Interaction of colloidal gold nanoparticles with human blood: effects on particle size and analysis of plasma protein binding profiles. Nanomedicine. 2009;5(2):106–17.
[5] Brydson RM, Hammond C. Generic for Nanotechnology: Classification and Fabrication Methodologies. New Jersey: John Wiley & Sons, Ltd; 2005. p. 1–55.
[6] Parida P, Behera A, Chandra Mishra S. Classification of biomaterials used in medicine. Int J Adv Appl Sci. 2012;1(3):31–5.
[7] Dolez PI. Nanomaterials definitions, classifications, and applications. Amsterdam: Elsevier B.V.; 2015. p. 3–40.
[8] https://libguides.lib.msu.edu/c.php?g=411870&p=4466012.
[9] Peng Z, Tang P, Zhao L, Wu L, Xu X, Lei H, et al. Advances in biomaterials for adipose tissue reconstruction in plastic surgery. Nanotechnol Rev. 2020;9(1):385–95.
[10] Pongracz DBJ. Three dimensional cultures and tissue engineering tissue, 1st edn. Hungary: University of Pécs Press, University of Pécs; 2011. p. 3–53.
[11] Bencherif SA, Braschler TM, Renaud P. Advances in the design of macroporous polymer scaffolds for potential applications in dentistry. J Periodont Implant Sci. 2013;43(6):251–61.
[12] Zhang B, Sun H, Wu L, Ma L, Xing F, Kong Q, et al. 3D printing of calcium phosphate bioceramic with tailored biodegradation rate for skull bone tissue reconstruction. Bio-Design Manuf. 2019;2(3):161–71.
[13] Ovsianikov A, Deiwick A, Van Vlierberghe S, Pflaum M, Wilhelmi M, Dubruel P, et al. Laser fabrication of 3D gelatin scaffolds for the generation of bioartificial tissues. Materials. 2011;4(1):288–99.
[14] Gruene M, Pflaum M, Deiwick A, Koch L, Schlie S, Unger C, et al. Adipogenic differentiation of laser-printed 3D tissue grafts consisting of human adipose-derived stem cells. Biofabrication. 2011;3(1):015005.
[15] Ovsianikov A, Muhleder S, Torgersen J, Li Z, Qin XH, Van Vlierberghe S, et al. Laser photofabrication of cell-containing hydrogel constructs. Langmuir. 2014;30(13):3787–94.
[16] Cukierman E, Pankov R, Stevens DR, Yamada KM. Taking cell-matrix adhesions to the third dimension. Science. 2001;294(5547):1708–12.
[17] Guo S, Fu D, Utupova A, Sun D, Zhou M, Jin Z, et al. Applications of polymer-based nanoparticles in vaccine field. Nanotechnol Rev. 2019;8(1):143–55.
[18] Li H, Guo H, Lei C, Liu L, Xu L, Feng Y, et al. Nanotherapy in joints: increasing endogenous hyaluronan production by delivering hyaluronan synthase 2. Adv Mater. 2019;31(46):e1904535.
[19] Nazarpak MH, Pourasgari F, Sarbolouki M. Preparation of a novel porous scaffold from poly(lactic-*co*-glycolic acid)/hydroxyapatite, Asian Biomed. 2011;5(4):513–8.
[20] Gautrot JE, Malmström J, Sundh M, Margadant C, Sonnenberg A, Sutherland DS. The nanoscale geometrical maturation of focal adhesions controls stem cell differentiation and mechanotransduction. Nano Lett. 2014;14(7):3945–52.
[21] Pham QP, Sharma U, Mikos AG. Electrospun poly(epsilon-caprolactone) microfiber and multilayer nanofiber/microfiber scaffolds: characterization of scaffolds and measurement of cellular infiltration. Biomacromolecules. 2006;7(10):2796–805.
[22] Yousefi AM, Oudadesse H, Akbarzadeh R, Wers E, Lucas-Girot A. Physical and biological characteristics of nanohydroxyapatite and bioactive glasses used for bone tissue engineering. Nanotechnol Rev. 2014;3(6):527–52.
[23] Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. J Control Rel. 2008;126(3):187–204.
[24] Horcajada P, Chalati T, Serre C, Gillet B, Sebrie C, Baati T, et al. Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. Nat Mater. 2010;9(2):172–8.
[25] Jeong K, Kang CS, Kim Y, Lee YD, Kwon IC, Kim S. Development of highly efficient nanocarrier-mediated delivery approaches for cancer therapy. Cancer Lett. 2016;374(1):31–43.
[26] Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013;12(11):991–1003.
[27] Maeda H, Nakamura H, Fang J. The EPR effect for macromolecular drug delivery to solid tumors: improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging *in vivo*. Adv Drug Delivery Rev. 2013;65(1):71–9.
[28] Hatakeyama H, Akita H, Harashima H. A multifunctional envelope type nano device (MEND) for gene delivery to tumours based on the EPR effect: a strategy for overcoming the PEG dilemma. Adv Drug Delivery Rev. 2011;63(3):152–60.
[29] Mahmoudi M, Bertrand N, Zope H, Farokhzad OC. Emerging understanding of the protein corona at the nano-bio interfaces. Nano Today. 2016;11(6):817–32.
[30] Oh JY, Kim HS, Palanikumar L, Go EM, Jana B, Park SA, et al. Cloaking nanoparticles with protein corona shield for targeted drug delivery. Nat Commun. 2018;9(1):4548.
[31] Dai Q, Walkey C, Chan WC. Polyethylene glycol backfilling mitigates the negative impact of the protein corona on nanoparticle cell targeting. Angew Chem Int Ed Engl. 2014;53(20):5093–6.
[32] Zhang H, Chen G, Yu B, Cong H. Emerging advanced nanomaterials for cancer photothermal therapy. Rev Adv Mater Sci. 2018;53(2):131–46.
[33] Pantic S, Skodric SR, Loncar Z, Pantic I. Zinc oxide nanoparticles: potential novel applications in cellular physiology, pathology, neurosciences and cancer research. Rev Adv Mater Sci. 2019;58(1):17–21.
[34] Veiseh O, Doloff JC, Ma M, Vegas AJ, Tam HH, Bader AR, et al. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. Nat Mater. 2015;14(6):643–51.
[35] Wang SH, Lee CW, Chiou A, Wei PK. Size-dependent endocytosis of gold nanoparticles studied by three-dimensional mapping of plasmonic scattering images. J Nanobiotechnology. 2010;8:33.
[36] Lan T, Guo Q. Phenylboronic acid-decorated polymeric nanomaterials for advanced bio-application. Nanotechnol Rev. 2019;8(1):548–61.

[37] Yang PP, Luo Q, Qi GB, Gao YJ, Li BN, Zhang JP, et al. Host materials transformable in tumor microenvironment for homing theranostics. Adv Mater. 2017;29(15):1605869.
[38] Xu F, Huang X, Wang Y, Zhou S. A size-changeable collagenase-modified nanoscavenger for increasing penetration and retention of nanomedicine in deep tumor tissue. Adv Mater. 2020;32(16):1906745.
[39] Jin Y, Wu Z, Li C, Zhou W, Shaw JP, Baguley BC, et al. Optimization of weight ratio for DSPE-PEG/TPGS hybrid micelles to improve drug retention and tumor penetration. Pharm Res. 2018;35(1):13.
[40] Ramírez-García PD, Retamal JS, Shenoy P, Imlach W, Sykes M, Truong N, et al. A pH-responsive nanoparticle targets the neurokinin 1 receptor in endosomes to prevent chronic pain. Nat Nanotechnol. 2019;14(12):1150–9.
[41] Jensen DD, Lieu T, Halls ML, Veldhuis NA, Imlach WL, Mai QN, et al. Neurokinin 1 receptor signaling in endosomes mediates sustained nociception and is a viable therapeutic target for prolonged pain relief. Sci Transl Med. 2017;9(392):eaal3447.
[42] Jimenez-Vargas NN, Pattison LA, Zhao P, Lieu T, Latorre R, Jensen DD, et al. Protease-activated receptor-2 in endosomes signals persistent pain of irritable bowel syndrome. Proc Natl Acad Sci U S A. 2018;115(31):E7438–E7447.
[43] Yarwood RE, Imlach WL, Lieu T, Veldhuis NA, Jensen DD, Klein Herenbrink C, et al. Endosomal signaling of the receptor for calcitonin gene-related peptide mediates pain transmission. Proc Natl Acad Sci U S A. 2017;114(46):12309–14.
[44] Sheeba CJ, Marslin G, Revina AM, Franklin G. Signaling pathways influencing tumor microenvironment and their exploitation for targeted drug delivery. Nanotechnol Rev. 2014;3(2):123–51.
[45] Swartz MA, Iida N, Roberts EW, Sangaletti S, Wong MH, Yull FE, et al. Tumor microenvironment complexity: emerging roles in cancer therapy. Cancer Res. 2012;72(10):2473–80.
[46] Muthukumar T, Sreekumar G, Sastry TP, Chamundeeswari M. Collagen as a potential biomaterial in biomedical applications. Rev Adv Mater Sci. 2018;53(1):29–39.
[47] Hu C, Lei T, Wang Y, Cao J, Yang X, Qin L, et al. Phagocyte-membrane-coated and laser-responsive nanoparticles control primary and metastatic cancer by inducing anti-tumor immunity. Biomaterials. 2020;255:120159.
[48] Hassibi A, Manickam A, Singh R, Bolouki S, Sinha R, Jirage KB, et al. Multiplexed identification, quantification and genotyping of infectious agents using a semiconductor biochip. Nat Biotechnol. 2018;36(8):738–45.
[49] Liu T, Liu Y, Chen Y, Liu S, Maitz MF, Wang X, et al. Immobilization of heparin/poly-(L)-lysine nanoparticles on dopamine-coated surface to create a heparin density gradient for selective direction of platelet and vascular cells behavior. Acta Biomater. 2014;10(5):1940–54.
[50] Liu T, Zeng Z, Liu Y, Wang J, Maitz MF, Wang Y, et al. Surface modification with dopamine and heparin/poly-*L*-lysine nanoparticles provides a favorable release behavior for the healing of vascular stent lesions. ACS Appl Mater Interfaces. 2014;6(11):8729–43.
[51] Huang D, Wu K, Zhang Y, Ni Z, Zhu X, Zhu C, et al. Recent advances in tissue plasminogen activator-based nanothrombolysis for ischemic stroke. Rev Adv Mater Sci. 2019;58(1):159–70.
[52] Chiappini C, De Rosa E, Martinez JO, Liu X, Steele J, Stevens MM, et al. Biodegradable silicon nanoneedles delivering nucleic acids intracellularly induce localized *in vivo* neovascularization. Nat Mater. 2015;14(5):532–9.
[53] Zangabad PS, Mirkiani S, Shahsavari S, Masoudi B, Masroor M, Hamed H, et al. Stimulus-responsive liposomes as smart nanoplatforms for drug delivery applications. Nanotechnol Rev. 2018;7(1):95–122.