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PERSPECTIVE

Bioinspired Nanoarchitectonics as Emerging Drug Delivery Systems

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We propose an important paradigm shift in preparation of functional materials with well-designed nanostructures, from the nanotechnological to the nanoarchitectonic approach. Nanoarchitectonics is a methodology for arranging nanoscale structural units in the required configurations for new functional materials by the sophisticated combination and harmonization of several processes including atom/molecule manipulation, chemical nanomanipulation, field-induced materials control and controlled supramolecular self-assembly. In particular, nanoarchitectonics bears features of nanoscale phenomena including their flexibility and uncertainty of structure due to the unavoidable influence of thermal fluctuation. It shares characteristics with structural constructions in biological systems and could become a powerful bioinspired approach for materials science. Here, we focus on examples involving drug delivery functions due to these promising applications of bioinspired materials research. We commence with a discussion of recent developments involving assemblies of small amphiphilic molecules, polymer micelles and molecular conjugates and follow this with examples of challenging concepts including inorganic nanostructure design for drug delivery and mechanically controlled drug release. The new concept of bioinspired nanoarchitectonics could significantly expand the possibilities of systems design for drug delivery.

1. Introduction

The importance of the development of materials' synthesis with nanoscale precision is well appreciated.[1] Innovation of functionality can be created by deliberate fabrication of materials where improvement of fabrication precision might result in advances regarding their accuracy, specificity and efficient creation of new functions. Precision in materials' fabrication is approaching the nanometre-scale with the associated technology becoming known as nanotechnology. The initial development of nanotechnology relied heavily on so-called top-down methods including various micro- and nano-fabrication techniques.[2] Subsequently, the counterpart concept of the bottom-up approach has become more popular for construction of functional materials and systems by using supramolecular interactions[3] and self-assembly processes.[4] Allied techniques for preparing structured assemblies such as self-assembled monolayer methods,[5] Langmuir-Blodgett techniques[6] and layer-by-layer assembly[7] have consequently also received increasing attention.

A new paradigm shift in nanomaterials science has now become necessary. Individual techniques of nanofabrication require careful combination for construction of functional materials and structures. However, only simple tools have been used to date to fabricate nanostructured materials for nanotechnology, despite a perceived requirement that we need to design and synthesize more sophisticated materials and structures. Thus, the central concept is now changing from nanotechnology to nanoarchitectonics.[8] The new concept of nanoarchitectonics was originally proposed by Aono.[9] It is a technological system for arranging nanoscale structural units into a required configuration. Sophisticated assembly, combination and harmonization of several processes make up nanoarchitectonics. It includes atom/molecule manipulation, chemical nanomanipulation, field-induced material control and controlled self-assembly and organization, leading to rational production of nanomaterials,[10] fabrication of nanosystem and nanostructures[11] and their application in environmentally-friendly science[12] and biological fields.[13]

However, nanoarchitectonics is not as simple as the already well-established microfabrication techniques. Devices based on physicochemical phenomena operating at the micrometre scale are essentially simply miniaturized versions of their macroscopic prototypes. This highlights the benefits of the top-down approach where macroscopic systems are simply miniaturized leading to high density and high efficiency for the microscopic systems. However, further reductions in size may lead to unexpected operation/activity at the nanoscopic scale, due to, for instance, quantum effects.[14] Certain phenomena possess degrees of uncertainty related to the probabilities of the occurrence of that process under the influence of thermal fluctuations. Because of this source of vagueness in operation, functional systems prepared by nanoarchitectonics may not obey simple input/output logic. However, nanoarchitectonic systems may be simultaneously addressable by multiple stimuli. This aspect of nanoarchitectonics is similar to that observed in some biological

systems. Actually, if materials' development based on nanoarchitectonics would share some characteristics with biological systems. Then it could become a powerful methodology in biomimetic[15] and/or bioinspired[16] approaches in materials science.

With the abovementioned points in mind, we will here discuss bioinspired nanoarchitectonics. The term 'bioinspired' is used in this review instead of 'biomimetic'. Although these two concepts share many common features, 'biomimetic' conveys a close analogy with some biological system while 'bioinspired' applies just to conceptual aspects of biological processes. Because current nanoarchitectonics is not closely related to biology, use of 'bioinspired' as a bridging term is more appropriate in this case than biomimetics. In order to highlight specific topics, we have focused on examples involving drug delivery functions because drug delivery is undoubtedly a promising application for bio-related materials research.

We will commence with a discussion of recent developments of assemblies of small amphiphilic molecules, polymer micelles and molecular conjugates. In the latter parts, examples involving challenging concepts are summarized. In these examples, inorganic nanostructure design for drug delivery and mechanically controlled drug release are described. We also consider how these challenging concepts have been inspired by biological processes. We hope that a new concept, bioinspired nanoarchitectonics, can significantly expand the possibilities for systems for drug delivery functions.

2. Advances Based on Traditional Material Design.

In order to demonstrate the new concept of bioinspired nanoarchitectonics in an understandable way, we will first introduce research developments of the more traditional materials' designs. For example, Drug delivery concepts involving assemblies of small amphiphilic molecules, polymer micelles and molecular conjugates are summarized in the following sections.

2.1. Assemblies of Low-molecular-weight Amphiphilic Molecules

Various types of molecular assemblies including biological membranes can be found in nature, where amphiphilic molecules play an important role in their spontaneous formation. Liposomes, spherical vesicles mainly composed of phospholipids and cholesterol, were originally developed as a model of biological cell structures. Recent advances have enabled production of DNA loaded vesicles possessing self-reproduction capabilities.[17] Liposomes have favourable characteristics for drug delivery, including biocompatibility, biodegradability, ease of surface decoration, and the ability to incorporate either hydrophilic or lipophilic drugs. Binding of poly(ethylene glycol) (PEG) chains on the surface enables extended periods of circulation in blood due to the prevention of adsorption of serum proteins.[18] The ability of PEG groups to enhance circulation times of the vehicle depends both on the amount of grafted PEG and the length of the polymer.[19] Examples of liposomal products already on the market include AmBisome® (for fungal infection), Doxil® (for Kaposi's sacroma), and Visudyne® (for age-related macular degeneration and choroidal neovascularization).[20] Such DDS products allow reduced invasiveness of drug treatments.

Liposomes have also been investigated as promising non-virus carriers for gene delivery.[21] Use of viral carriers is regarded as very effective in this field although there exist problems involving toxicity and immunogenicity. Because of the similarities in structure between liposomes and the envelopes of viruses, they are expected to exhibit similar functions. In many cases, liposome vectors appear to be taken up by cells through endocytosis, which is one of the major mechanisms of infection by viruses.

Micelles are nano-structured carriers composed of surfactants that can entrap lipophilic drugs at their interiors.[22] Although surfactants are common excipients in pharmaceutical products, the amount used in formulations is usually not sufficient to induce solubilisation since side effects including hemolysis and anaphylactic shock may result. Taxol® is one example where a large amount of surfactant (Cremophor EL) is required to dissolve the poorly soluble drug, paclitaxel.

Micelles can also accommodate oil components at their interiors. The resultant molecular assemblies are known as swollen micelles or microemulsions. Similar architectures can be found in the body and include bile salt micelles or high/low density lipoproteins. Mixtures of drug, oil and surfactant, designed to form a (micro)emulsion under mild agitation in the stomach or small intestine after oral administration, are called self-(micro)emulsifying drug delivery systems (Figure 1).[23] Oral absorption of poorly soluble drugs (including its reproducibility) can be improved by eliminating the dissolution process and by offering a wide oil-water interfacial area. Microemulsion droplets formed during the drug absorption process can be regarded as artificial bile salt micelles. The best example of a self-microemulsifying formulation is given by Neoral®, an immunosuppressant drug, which made great contributions to improvements in the success of transplantation operations.[24]

2.2. Polymer Micelles

Polymer micelles composed of block copolymers possess many advantages over surfactant micelles as a drug carrier, and clinical studies are in progress for various drugs.[25] Their size is sufficiently large to avoid renal excretion, but small enough to bypass filtration by interendothelial cell slits in the spleen. They

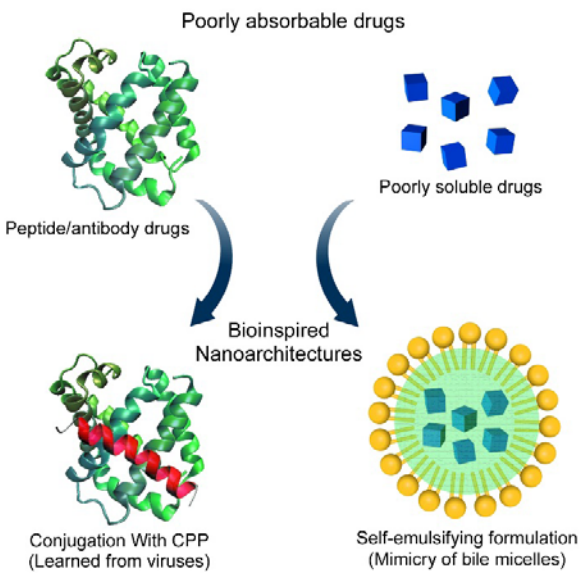

Figure 1. Bioinspired nanoarchitectures for improving oral bioavailability of poorly absorbable drugs.

can escape from the reticuloendothelial system (RES) and accumulate in solid tumour tissues through enhanced permeability and retention (EPR) effects.[26] Furthermore, polymer micelles are usually more stable with a remarkably low critical micelle concentration relative to small molecule surfactants. Drug molecules are enclosed in the core region by various mechanisms including chemical, physical or electrostatic interactions.

Typical polymer micelles are assemblies of amphiphilic block copolymers that form aggregates through hydrophobic interactions, while other mechanisms have also been utilized for improving efficacy of the polymer micelles. Harada and Kataoka found that mixtures of two types of charged block copolymers (poly(ethylene glycol)-*b*-poly(α,β-aspartic acid) and poly(ethylene glycol)-*b*-poly(L-lysine)) led to a micellar formation known as polyion complex (PIC) micelles. Interestingly, the block copolymers formed a fine-micelle structure to a molecular recognition process, and it was also possible to prepare a vesicles using the PIC system.[27] Kotsuchibashi et al. have developed a series of double-responsive block copolymers composed of two polymers with different lower critical solution temperatures (LCSTs).[28] The block copolymers were designed to be dissolved in water below the LCSTs (LCST1 and LCST2) of both constituent polymers (LCST1 < room temperature and LCST2 > normal body temperature). By a simple mixing of polymer solution with the required drug at room temperature, micellar structures with the drug molecules in their cores were spontaneously formed. Upon heating above body temperature, the micelles aggregated and the drug was released in a perfectly reversible process. Temperature responsive micellar aggregation has also been used for fabrication of 3-dimensional gel structures, which can also be used for drug delivery applications. Woodcock et al. prepared temperature responsive ABA type triblock copolymers. The LCST of A blocks could be enzymatically modified resulting in their deprotection. The micellar gels could thus be controlled by varying two factors *i.e.* temperature and concentration of enzyme,[29] which suggests use of both temperature and enzyme processes in the body for controlled release of drug molecules.

Table 1 Examples of CPP

CPP	Sequences
From RNA binding proteins	
HIV-1 Tat (48-60)	GRKKRRQRRRPPQ
HIV-1 Rev (34-50)	TRQARRNRRRRWRERQR
FHV Coat	RRRRNRTRRNRRRVR
HTLV-II Rex	TRRQRTRRARRNR
BMV Gag	KMTRAQRRAAARRNRWTAR
P22N	NAKTRRHERRRKLAIER
From DNA binding proteins	
Penetratin	RQIKIWFQNRRMKWKK
Protamine 1	PRRRRSSSRPVRRRRRPRVSRRRRRRGGRRRR
Islet-1	RVIRVWFQNKRCKDKK
PDX-1	RHIKIWFQNRRMKWKK
From viral proteins	
Erns	RQGAARVTSWLGRQLRIAGKRLEGRSK
Ribotoxin2 L3 loop	KLIKGRTPIKFGKADCDRPPKHSQNGMGK
From antimicrobial proteins	
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ
Magainin 2	GIGKWLHSAKKFGKAFVGEIMNS
Human lactoferrin (19-40)	KCFQWQRNMRKVRGPPVSCIKR
Crotamine	YKQCHKKGGKKGSG
From natural proteins	
pVEC	LLIILRRRIRKQAHAHSK
hCT (18-32)	KFHTFPQTAIGVGAP
Designed CPP	
Oligoarginine	R8 to R12
Pep-1	KETWWETWWTEWSQPKKRKV
MPG	GLAFLGFLGAAGSTMGAWSQPKKKRKV
Transpotan	GWTLNSAGYLLGKINLKALAALAKKIL

2.3. Molecular Conjugates

Performance of drug molecules in the body may be improved by forming physical/chemical conjugates with other molecules. For this purpose, albumin is one of the most convenient molecular carriers for physical conjugation.[30] It has already been utilized in commercial formulations of paclitaxel (Abraxane®) for overcoming the low solubility of the drug. Drug molecules can also be chemically bound to carriers. Maeda *et al.* conjugated neocarzinostatin with poly(styrene-co-maleic acid) to extend its plasma half-life (1.8 min) by more than an order of magnitude.[31] This principle is now being widely exploited in pharmaceutical development. Also of note is the covalent attachment of poly(ethylene glycol) (PEG) to drug molecules since it is one of the most common modifications often being referred to as PEGylation.[32] It has been shown to improve safety and efficiency without loss of biological function, and it has great potential for reducing invasiveness of drug treatment protocols by reducing the frequency of administration. From this point-of-view, insulin is an excellent example of a therapeutic agent whose pharmacokinetic properties were significantly improved through PEGylation. In addition, immunogenicity, allergenicity, and antigenicity caused by aggregation of insulin were also eliminated since PEGylation precludes its aggregation.[33] This technology can also be used as a means to improve pharmacokinetics of viral vectors[34] or to silence the antigenic response of red blood cells towards the development of universal blood transfusion.[35]

Dendrimers are highly branched globular macromolecules with sizes on the order of nanometers, which can physically/chemically capture drug molecules to improve their solubilities and permeabilities.[36] Of the known dendrimers, polyamidoamine (PAMAM) and peptide-based dendrimers are the most representative that have been investigated for drug delivery use. Introduction of poly(ethylene oxide) chains is also effective for dendrimers because it can extend release rates of drugs, increase drug-loading capacity, enhance retention in the circulation, and reduce hemolytic toxicity.[37]

Another molecular fragment that has great potential in the drug delivery field is cell-penetrating peptide (CPP), which was first discovered during studies of human immunodeficiency virus (HIV).[38] Because CPP possesses the ability to permeate

biological membranes, it has been utilized to enhance membrane permeation of large molecules such as peptides and oligonucleotides (Figure 1). Table 1 shows representative CPPs together with their respective origins.[39] Various amino acid sequences have been identified that can be used promote permeation across biological membranes. Most CPPs are cationic since it promotes attractive interactions with biological membranes. Positive charges are usually due to the presence of arginine residues. CPPs can be attached to large molecules either by physical or chemical means but their high charges usually allow complex formation by simple mixing. Short interfering RNA (siRNA) is regarded as a promising molecule for silencing gene expression and its delivery technology is still under development. CPP was found to form complexes with siRNA by simple mixing, and effective intracellular delivery was achieved.[40] Oral delivery of biopharmaceuticals is also a challenging issue in drug development. However, the simple mixing of peptide drugs and CPP can be used to address this problem since it could significantly improve oral bioavailability of, for example, insulin.[41]

3. Emerging Challenge 1: Inorganic Nanoarchitectonics.

In order to create more highly innovative methodologies, we need to expand the concept of bioinspired nanoarchitectonics to include non-biological and non-organic materials. Living systems, with the exceptions of bone, teeth and some other materials, are essentially composed of organic compounds.. These compounds are made up from a limited number of elements, mostly carbon (C), hydrogen (H), oxygen (O) and nitrogen (N). Despite such an extremely limited selection of elements, biological systems can create surprisingly high-level functional systems albeit depending on the presence of some less common elements. If we construct similar systems by introducing different elements, we may be able to create highly functional systems that have not been so far attained by natural systems. Extension of bioinspired nanoarchitectonics to inorganic materials could become a powerful new challenge in materials development.

3.1. Mesoporous Motifs

In considering applications of inorganic nanostructured materials, one of the most successful examples is controlled drug release from inorganic mesoporous materials.[42] According to IUPAC classification, mesoporous materials are defined as substances containing pores of diameters in the range 2.0 – 50.0 nm. In the late 1980s and early 1990s, several research groups including those of Kunitake,[43] Kuroda[44] and Mobil[45] initiated pioneering concepts to synthesize mesoscale controlled spaces using template structures of molecular assemblies, as can be seen in the most famous example of mesoporous silica synthesis, which led to MCM-41.This synthetic strategy expanded rapidly to include preparation of variously structured mesoporous silica,[46] mesoporous carbon,[47] mesoporous metal oxides,[48] mesoporous metals,[49] periodic mesoporous organosilicate,[50] other mesoporous inorganic materials[51] and fibrous inorganic tubes.[52] These materials can be modified with organic groups to add further functionality. An example of innovative functionality lies in the introduction of gating properties at the inlets of mesopore channels, which has enable the design of mesoporous materials

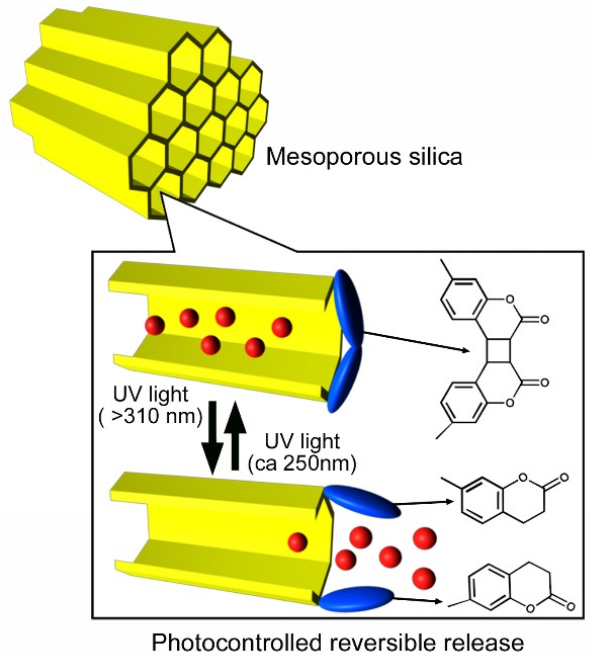

Figure 2. Regulation of drug storage and release from mesoporous silica by photonic stimuli.

with controlled functions for drug storage and release upon application of an external stimuli.

Two pioneering examples of drug delivery systems involving mesoporous materials are now briefly introduced. As shown in Figure 2, regulation of drug storage and release from mesoporous silica by photonic stimuli was reported by Fujiwara and co-workers through modification of mesoporous silica MCM-41 with photo-active coumarin residues.[53] These functional groups are respectively dimerized and de-dimerized upon irradiation with UV light at > 310 nm and ~250 nm. These photochemical processes induce pore closing and opening, resulting in drug being held within mesopores or being released from mesopores. In another pioneering example, Lin and co-workers synthesized a controlled drug release system using mesoporous silica with colloid capping.[54] Their mesoporous silica sphere was modified with 2-(propyldisulfanyl)ethylamine functional groups that covalently trap the water-soluble mercaptoacetic acid-carrying CdS nanocrystals. Cleavage of the resulting disulfide linkages by various reducing agents such as dithiothreitol or mercaptoethanol allowed stimuli-responsive release of drug molecules from the mesopore channels. Escellent examples on gate-contrlled delivery systems has been extensively researched.[55]

Significant processes in controlled drug delivery can be seen in recent examples. Zhang, Zhao and co-workers developed dendritic mesoporous silica nanospheres with hierarchic pore structures (Figure 3).[56] This mesoporous material was synthesized using a heterogeneous oil-water biphasic reaction system, where surfactant molecules self-assemble to induce continuous interfacial growth of silica nanostructures. Pore size at each growth step was regulated from 2.8 to 13 nm by varying the hydrophobic solvent (the oil phase) and the concentration of the silica source in the oil phase. This hierarchic structure is advantageous for protein loading and release. For example, the maximum loading capacity of bovine β-lactoglobulin is more

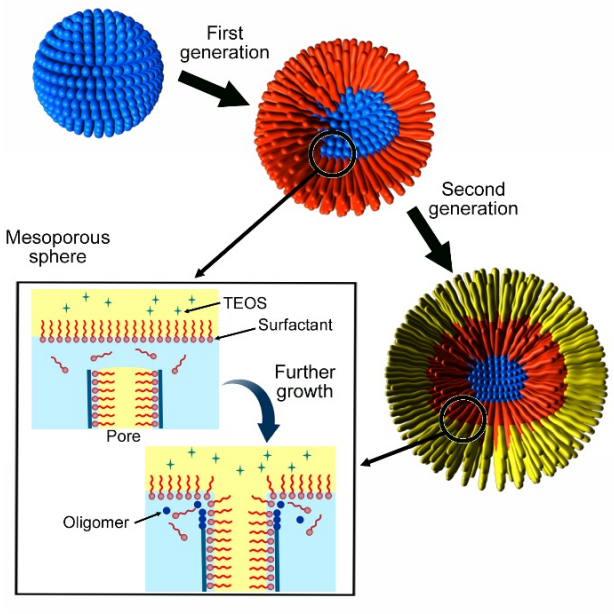

Figure 3. Dendritic mesoporous silica nanospheres with hierarchic pore structures.

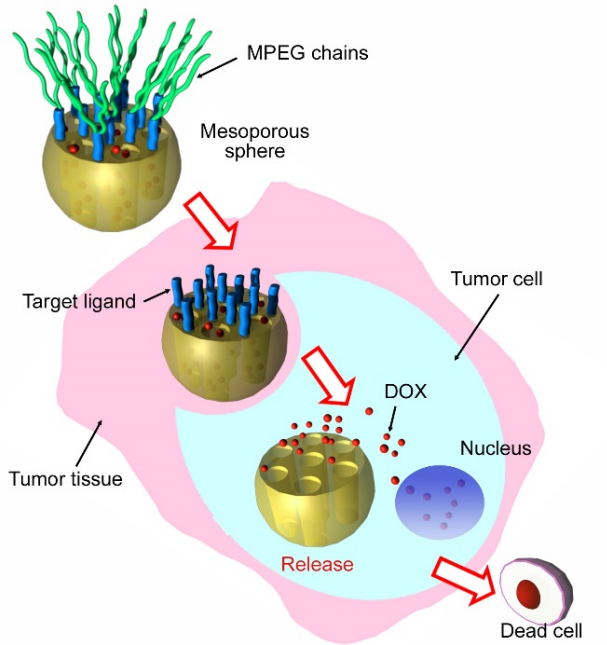

Figure 4. Dual responsive system of gate-modified mesoporous silica nanoparticles for rational delivery of antitumor drugs (MPEG: monomethoxypolyethylene glycol).

than 60% and release of the entrapped protein process can be regulated between 24 and 96 hours.

Tang and co-workers synthesized mesoporous silica materials with gates of single-stranded DNA that could be reversibly controlled by temperature variation.[57] Carboxyl modified single-stranded DNA gates were covalently attached to amino groups at the surface of mesoporous silica spheres. Negatively charged DNA strands adhered to the positive surface of the amine-modified silica surface resulting in closure of mesopores. Elevation of temperature weakens the interaction between DNA strands and silica surface so that pores were opened accompanied by release of drugs from the interior of the mesoporous silica materials. Upon depression of temperature, the DNA "gates" become re-adsorbed at the silica surface thus capping the pores. Interestingly, the critical temperature of the drug release could be tuned by varying the length of single-stranded DNA.

Zhang and co-workers developed a dual responsive system involving gate-modified mesoporous silica nanoparticles for rational delivery of antitumor drugs (Figure 4).[58] In their drug delivery system design, peptide fragments with the sequence RGDFFFFC was attached through redox-active disulfide bonds and monomethoxypolyethylene glycol was further immobilized through pH-sensitive benzoic-imine bonds. When the modified mesoporous silica nanoparticles approached the vicinity of a tumour, the acidic tumour extracellular environment induced cleavage of the monomethoxypolyethylene glycol tails to expose the RGD cell recognition fragment. Upon internalization of the nanoparticles into tumour cells, subsequent cleavage of disulfide bonds by reducing agents in the tumour cells resulted in release of antitumor drugs from the mesopores. In addition, in vitro cytotoxicity evaluations confirmed selective elimination of tumour cells by this system.

Apart from these drug delivery studies, controlled release systems from mesoporous silica materials have also been investigated from the viewpoints of their detailed mechanisms by using global gene expression analysis[59] or imaging for in vivo/in situ tracking of cancer chemotherapy.[60] These rapid developments can be understood by considering the conceptual similarity between biosystems and the designs of the respective mesoporous materials. The processes occurring in mesoporous drug delivery systems are reminiscent of the release of signal molecules and ions through membrane channels upon specific interactions at the cell surface. Therefore, drug delivery systems of gate-controlled mesoporous materials can be regarded as bioinspired nanosystems in materials science.

3.2. Layered Motifs

A distinct characteristic of biosystems is the highly hierarchic nature of their structures as can be found in organelles, cells, tissues, and organs. Nanoarchitectonics inspired by hierarchic features of biological systems can be accomplished by a two-step process, (i) unit nanostructure formation and (ii) layering of these unit structures. So-called layer-by-layer (LbL) assembly is a powerful tool in this two-step process since LbL assembly is applicable to layered-type bioinspired nanoarchitectonics.[61] The LbL method has excellent versatility for the assembly of various kinds of substances including organic polymers, inorganic nanostructures, molecular assemblies, biomaterials, and even viruses.[62]

Prior to introducing drug delivery systems involving hierarchic LbL structures, several examples of hierarchic constructions of nanostructures will be briefly mentioned. Figure 5 shows organic-inorganic hybrid vesicles assembled in a layer-by-layer manner. Katagiri et al. introduced an inorganic silica-like framework to surfaces of lipid bilayer vesicles (so called cerasome) from alkoxysilane-bearing lipids (top in Figure 5).[63] Because silica supports at the surface significantly strengthened vesicular structures (middle in Figure 5), the cerasomes can be

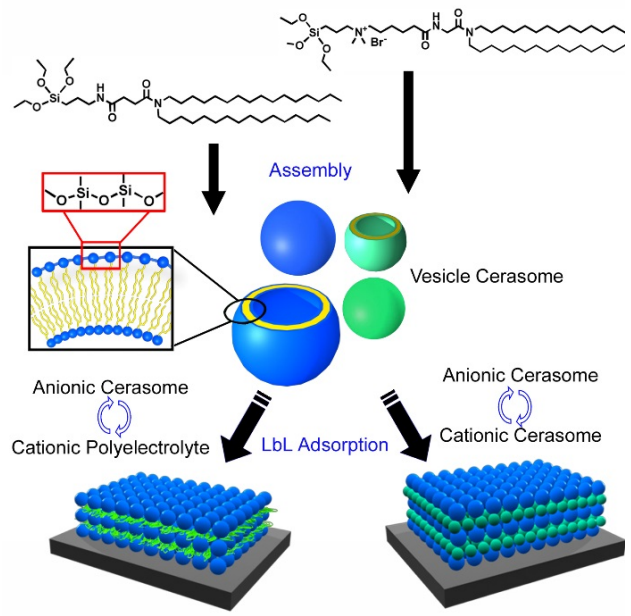

Figure 5. Organic-inorganic hybrid vesicles (cerasomes) and their layer-by-layer assemblies..

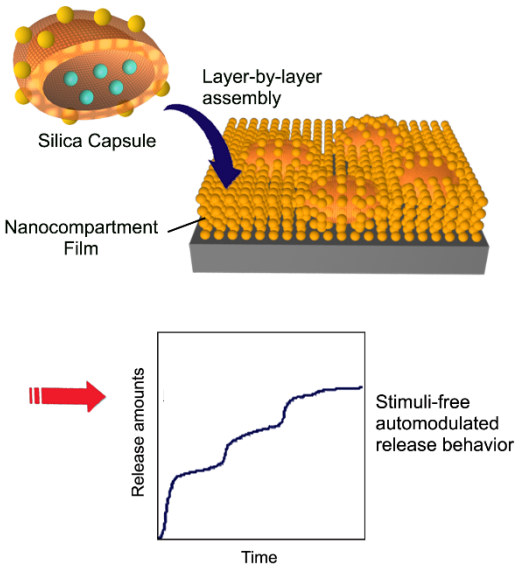

Figure 6.. Layer-by-layer film of mesoporous silica capsules and silica nanoparticles for auto-modulated materials release.

further assembled into layered hierarchic structures by using LbL assembly with cationic polyelectrolyte (poly(diallyldimethylammonium chloride), PDDA) (bottom left in Figure 5).[64] In addition, cerasomes with cationic surface charges were directly assembled by LbL technique without applying an interlayer polyelectrolyte. Two-types of cerasome of diameters 20 - 100 nm and 70 - 300 nm were alternately assembled into hierarchic assemblies as multi-cellular tissue mimics (bottom right in Figure 5).[65]

The same strategy can be applied for construction of layered assemblies of pre-structured nanomaterials into hierarchic structures. For example, Ji et al. reported LbL assembly of ionic liquids and graphene oxides that were reduced after the assembly process.[66] These structures provide fluidic interlayer structures sandwiched by highly π-electron-rich graphene nanosheets. Therefore, the assembled LbL films exhibited greater selectivity (more than 10 times) for benzene vapour over cyclohexane despite their similar molecular sizes, molecular weights, and vapour pressures. Similarly, hierarchic layer-by-layer structures were constructed from pre-synthesized mesoporous carbon CMK-3[67] and mesoporous carbon capsules.[68] In the case of LbL assembly of CMK-3, highly cooperative guest adsorptions resulted in discrimination of tea components such as tannic acid and catechin. This activity might be caused by promoted molecular interactions within carbon nanospaces. On the other hand, tuneable guest selectivity was demonstrated in the application of LbL films of mesoporous carbon capsules as a sensor of gas phase analytes. These functions originate from specific molecular interactions in confined nanospaces. This is also a fundamental characteristic that can beobserved in many biological processes and, therefore, the abovementioned examples can be regarded as bioinspired nanoarchitectonics.

Ji et al applied an LbL strategy for the preparation of an auto-modulated materials release system (Figure 6).[69] This resulted in a bioinspired nanoarchitectonic system because many biological processes operate using auto-modulation involving some feedback response. In the system reported, mesoporous hollow silica capsules containing hierarchical micro- and nanospaces with capsule interiors of 1000 x 700 x 300 nm and mesopores of average diameter 2.2 nm were assembled alternately with cationic polyelectrolyte performed with the aid of anionic silica nanoparticles as a co-adsorber (top in Figure 6). Quantitative analyses of water evaporation from the LbL films of mesoporous silica capsules revealed a stepwise profile even though no external stimulus was applied (bottom in Figure 6).

In a plausible mechanism for the observed auto-modulated water release, stepwise release is assumed to originate from the combination of two processes: (i) water evaporation from the pores and (ii) capillary penetration into the pores. The number of release steps is determined by the ratio of water volume to mesopore volume in the capsule wall. Water entrapped in mesopore channels initially evaporates to the exterior in the first step of water release. After most of the water has evaporated from the mesopores, penetration of water from the capsule interior into mesopores occurs probably through rapid capillary penetration. A similar step-wise release could be observed with the liquid drugs. This stimulus-free controlled release system would be of great utility for development of energy-less and clean drug release applications.

In most of the reported controlled release systems, application of an external stimulus is required to regulate release of materials. In contrast, many biological events do not always require external stimuli and operate according to feedback from internal signals. Therefore, we can say that the abovementioned LbL films of mesoporous silica capsules exhibit bio-like, and can be regarded as a bioinspired nanoarchitectonics material.

3.3. Self-Growth Carrier

A critical and impressive feature of living systems is that of repeated reproduction cycles which involves DNA/RNA replication processes, cell duplication and highly sophisticated assemblies of protein components. Although it is a difficult task to imitate this, it is a point that has stimulated research into the preparation of carriers of information required for duplication and is one of the attractive examples of bioinspired nanoarchitectonics.

Ji et al. prepared cell-like flake-shell capsules from simple silica nanoparticles (Figure 7).[70] Spontaneous formation of flake shell capsules occurred during a hydrothermal process applied to silica nanoparticles. Gradual dissolution of silica from the surface of the nanoparticles and precipitation as silica nanosheets in the vicinity of the parent particle converted the original nanoparticles into hollow spherical capsules consisting of assembled silica nanosheets (top in Figure 7), to which was applied the term flake-shell capsules. The capsules are simple assemblies of silica nanosheets, and therefore possess structural flexibility reminiscent of cells or other soft lipid assemblies. The capsules respectively expand or contract when heated or cooled and the size of the pores in the outer wall consequently vary since they are formed by spaces between the nanosheets. The dynamically structural flexibility of the flake-shell capsules was confirmed by scanning electron microscopy (SEM) observations. The diameter of a flake-shell capsule decreased from 560 to 440 nm upon heating through irradiation with the electron beam for 5 min.

The structural softness of the flake-shell capsules can be used for tuning of drug storage and delivery. For example, pH adjustment of surrounding media results in formation of both densely packed mesoporous shells and a loose flake-sheet network (bottom in Figure 7). The presence of macroholes in the loose shell is advantageous for encapsulation of larger quantities of drug molecules at the interiors of capsules. Narrowing of the pores after anappropriate post pH treatment led to slow release of the encapsulated drug. The appropriate combination of these pH treatments was used to effectively tune the DDS efficiency as demonstrated for the sustained release time of estradiol and the anticancer drug doxorubicin.

Organic capsules are flexible and structural adjustment is often possible although they have the drawback of low mechanical strengths. On the other hand, inorganic capsules have good mechanical properties while their structures cannot be easily adjusted. Thus, the flake-shell possesses the merits of both organic and inorganic capsules based on soft assembly of hard silica nanosheets. It is a typical example of inorganic bioinspired nanoarchitectonics. It was also demonstrated that flake-shell capsules are good media for accommodation of biofunctional molecules. Their hydrophilic surfaces provide great potential for their application in enzyme immobilization.[71] The flake-shell capsules facilitated uptake of enzymes of different sizes such as lysozyme, lipase, and chymotrypsin. The porous nature of the flake-shell capsules is advantageous for fast diffusion of small substrate molecules while enzymes are maintained intact. In particular, introduction of amine and dextran functionalities was used to control enzyme loading and activity. In addition, the flake-shell silica capsules exhibited slow degradation under physiological conditions and low cytotoxicity. Therefore, the flake-shell capsule systems have good potential for biocatalysis-triggered drug delivery.

Ji et al reported a method for substrate-mediated reverse gene transfection using a silica film composed of an upright-sheet network (Figure 8).[72] This structural feature is grown from a silicon wafer. The silica film composed of an upright nanosheet network was fabricated through a one-pot self-growth process. A 500 nm thick layer of silica was first sputtered onto a silicon wafer that was incubated in an aqueous $NaBH_4$ solution at 75 °C. SEM observations revealed long wrinkles and small bulges with 10 nm thickness accompanied by consumption of the silica surface layer (from top to middle in Figure 8).

For the solid phase gene transfection, DNA was fixed on the solid surface and then cells adsorbed onto the DNA-bearing surface. The silica film with the upright-sheet network exhibited a higher DNA immobilization capacity compared to flat silica

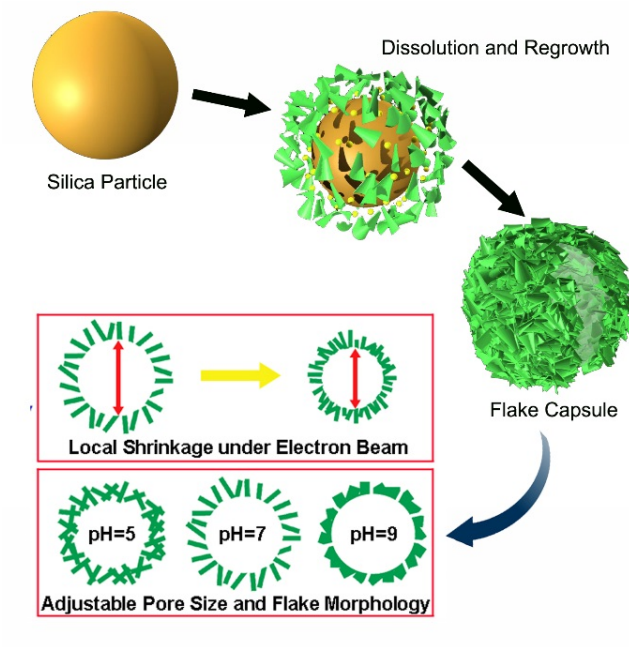

Figure 7. . Formation and morphology control of silica flake-shell capsules

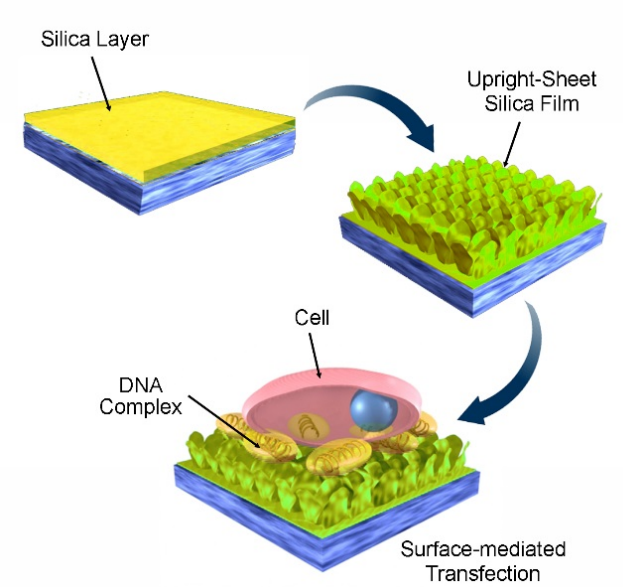

Figure 8. Reverse gene transfection using a silica film composed of an upright-sheet network.

films. The DNA reverse transfection capability was evaluated through in vitro transfection experiments on the human embryonic kidney mammalian cell line using green fluorescent protein reporter genes (bottom in Figure 8). The silica film containing a dense upright-sheet network exhibited approximately double the transgene expression efficiency of solution-based transfection.

Solid-mediated transfection has attracted attention due to the higher delivery efficiency of DNA over liquid phase transfection methods. The proposed method using structured non-toxic silica film can be used to avoid contamination that is usually problematic when using conventional substrates from animal sources. In addition, it is possible to arrange different types of DNA on a solid surface and introduce it to cells. This technology is also effective for systematic analysis and profiling of the effects of genes.

4. Emerging Challenge 2: Control by Hand Operation

Innovative challenges regarding the mechanisms of drug delivery should be made based on bioinspired nanoarchitectonics. Although we use machines involving mechanical action in our daily life, advanced micro- and nano-machines are driven mostly by the other stimuli such as electric, photonic and chemical inputs. Control of mechanical motion is rather difficult in artificial machines. In contrast, many biological systems use mechanical motion for operation of functional systems. Therefore, mechanical-control of artificial systems could be an important target in bioispired nanoarchitectonics. Exploration on simple-to-administer drug delivery systems is useful in developing countries and/or under disaster and emergency situations. Mechanical manipulation of drug entrapment and release using simple manual action such as hand motion would have a wide range of opportunities for practical application. Hand manipulation for drug delivery for use in any situation will create various possibilities in many medical opportunities.[73]

4.1. Mechanical Regulation of Drug Release

Kawakami and co-workers developed a gel material envisioning a new drug administration method in which the drug is released when the patient applies manual pressure to the gel (Figure 9).[74] The gel used was synthesized from alginate and cyclodextrin in which the drug ondansetron had been entrapped. Mechanical compression of the gel upon application of one-time compressions up to 50 % strain and five-cycle compressions up to 50 % strain induced drug release, *i.e.*, the drug was released when stimulus mimicking finger-pressure by the patient was applied. It was found that this effect was maintained for at least 3 days. While the binding constants were not significantly altered upon application of 30 % strain, the constant decreased dramatically under strains above 50 %. Molecular dynamics simulations revealed that the release of ondansetron should be promoted even with only small restriction and deformation of the cyclodextrin molecule.

Oral administration of drugs is difficult for patients experiencing nausea during cancer chemotherapy. Even in such cases, the proposed material can provide drug release simply by pressing or rubbing it. This system could be useful in cases of natural disasters, since the developed materials do not require special devices and electricity in their use. Patients can administer their drugs under any environment at their own convenience. Thus, this material offers an extremely convenient new dosing strategy.

Although mechanical control of drug delivery by applying rational supramolecular design has not been well explored, some pioneering examples have been reported. For example, Schaaf, Lavalle and coworkers demonstrated mechanically responsive drug-releasing LbL films with a drug-reservoir layer of biodegradable polyelectrolytes and a mechano-sensitive LbL barrier.[75]Degradation of the reservoir layer by trypsin could be initiated by stretching of the films, resulting in the release into solution of the anticancer drug paclitaxel. Apart from this example, LbL structures have been widely used in the field of drug delivery. Introduction of the mechanical control concept to LbL film techniques could be used to create many possibilities in simple-to-administer drug delivery systems.

4.2. Mechanical Operation of Molecular Machines

An advanced strategy for drug delivery would be the use of molecular machines as drug carriers. Although control of molecular machines by various stimuli such as electric, photonic, thermal and chemical inputs has been intensively investigated,[76] mechanical control of molecular machines is not well explored. This is due to the fact that we cannot mechanically access molecular machines although other external stimuli such as light irradiation or addition of chemicals can be easily applied. For mechanical control of molecular machines, we have to couple two kinds of motions over very different length scales. That is, coupling must be made from meter or centimetre-size mechanical motions to nanometre-scale molecular motions. While direct coupling of these motions is almost impossible, they can be rationally combined in a two-dimensional medium. Within two-dimensional media such as molecular films, in-plane directions possess macroscopically visible dimensions while their thicknesses are maintained in the nanometre regime. Therefore, large visible macroscopic motions can be connected

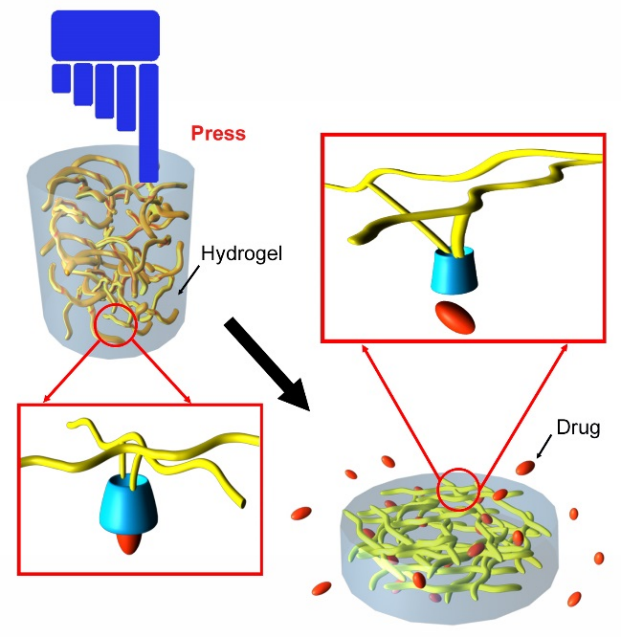

Figure 9. Gel material consisting of alginate and cyclodextrin and its drug release by mechanical compression.

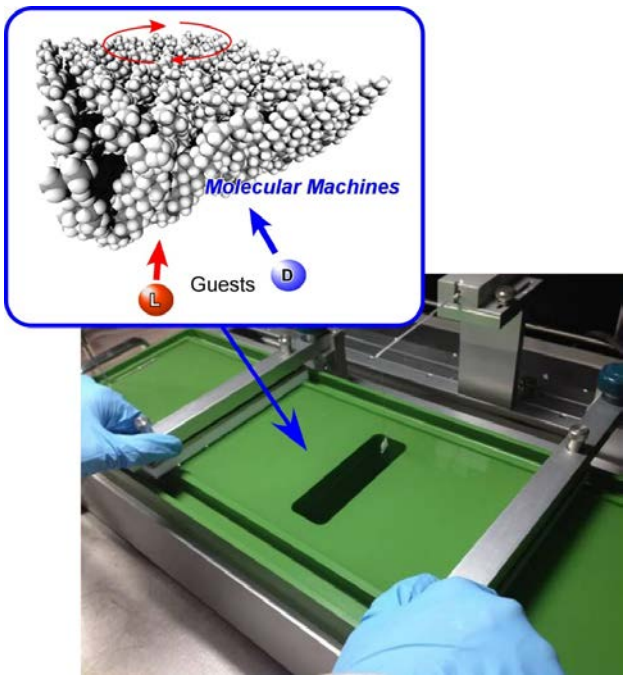

Figure 10. Chiral discrimination of amino acids by mechanical control of a polycholesteryl-substituted cyclen as a molecular machine component at the air-water interface.

with nanometre-scale molecular functions within two-dimensional media.[77]

This concept can be realized using a Langmuir monolayer at the air-water interface where the monolayer film can be flexibly deformed in the in-plane direction and functions at the nanometre-scale such as surface interactions occur in the film direction. Several examples of molecular detection and discrimination have been realized at a Langmuir monolayer by applying mechanical control. For example, chiral discrimination of amino acids was mechanically controlled using an octacoordinate sodium complex of a polycholesteryl-substituted cyclen as a molecular machine component at the air-water interface (Figure 10).[78] This molecular machine undergoes twisting behaviour with two possible quadruple helicate structures. Changes of relative stability of recognition complexes upon mechanical compression of the monolayer controls enantioselectivity of an amino acid dissolved in the water subphase. Detection selectivity converted from D- to L-form in the case of valine and, conversely, from L- to D-form in the case of phenylalanine upon mechanical compression. A similar concept was applied for sensitive discrimination between thymine and uracil using a cholesterol-armed triazacyclononane in its Langmuir monolayer.[79] A mechanically controllable fluorescent assay of D-glucose was also demonstrated through effective quenching of the fluorescence resonance energy transfer process as a novel concept of a mechanically-controlled indicator displacement assay.[80]

Capture and release of a target molecule through mechanical motions has also been demonstrated (Figure 11).[81] In that example, a steroid cyclophane molecule with a cyclic core consisting of a 1,6,20,25-tetraaza[6.1.6.1] paracyclophane connected to four steroid moieties (cholic acid) through a flexible L-lysine spacer was used as a deformable molecular machine. Because cholic acid has an amphiphilic nature with hydrophilic

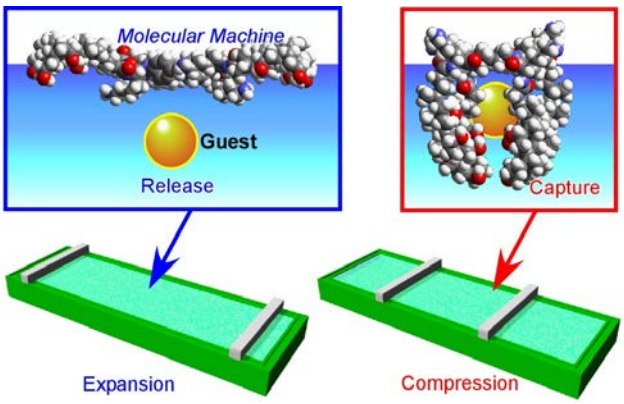

Figure 11. Capture and release of a target molecule through mechanically controlled motions of a steroid cyclophane.

and hydrophobic faces, the steroid moiety is oriented parallel to the water surface at low pressures, resulting in an open form of the molecular machine. Mechanical compression of the monolayer induces formation of a cavity conformation of the steroid cyclophane molecule, which has the capability to bind a guest molecule in the subphase. Capture of a guest molecule dissolved in the water subphase was demonstrated in situ. The capture and release of the guest molecule can be actually repeated by compression and expansion of the monolayer over the scale of tens of centimetres. This example demonstrates that use of a two-dimensional medium is appropriate for pressure-induced capture and release of drug molecules for mechanically driven drug delivery.

5. Conclusions

In this review, several examples of recent research on drug delivery are explained on the basis of the new concept of bioinspired nanoarchitectonics. These examples are roughly categorized into (i) recent advances in the traditional approaches including molecular assemblies, micelles and molecular conjugation and (ii) emerging challenges such as drug delivery with inorganic nanostructures and mechanical control of drug delivery. The former examples are well recognized and make reasonable extensions of existing technologies. On the other hand, the latter examples appear more innovative. We can say that the concept of bioinspired nanoarchitectonics covers a wide research area including both traditional aspects and exploration of novel avenues of research. This interesting feature originates from the rather ambiguous definitions of the key terms, bioinspired and nanoarchitectonics. These terms only require the limitations, (i) use of concepts and mechanisms found in biological systems and (ii) harmonized construction of functional materials from nanoscale units for materials design and synthesis. Such ambiguity and wide-applicability of the concept are indeed important when we seek out new paradigms and explore new fields. Not limited to drug delivery applications, bioinspired nanoarchitectonics can be utilized in many research fields and open tremendous possibilities.

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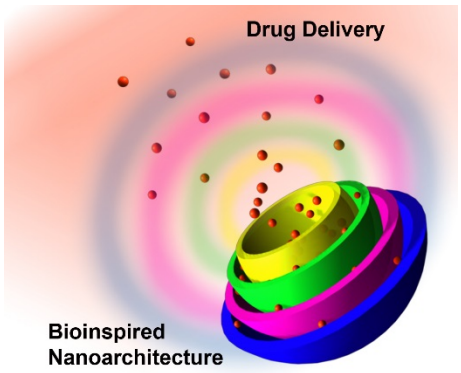

Bioinspired nanoarchitectonics opens a new era for designing of drug delivery systems

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