BIOINSPIRED APPROACHES TO BUILDING NANOSCALE DEVICES

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1. INTRODUCTION

In 1959, Richard Feynman gave a speech called "There's plenty of room at the bottom," where he challenged scientists to construct atomic-scale devices. Since 1959, the dream of building nanoscale devices (~ 1 x 10^{-9} m) is slowly becoming a reality. The expected impact of nanodevices is immense. Nanodevices are comparable in size to most biological systems (e.g., viruses, organelles, proteins, DNA) and therefore, it has been suggested that nanodevices can be engineered to diagnose and treat malfunctions in cells. This can lead to a new generation of treatment strategies for cancer, AIDS, or Alzheimer. Future advances in the computer chip industry may also depend on nanotechnology – the ability to design atomic-scale chips may provide hard drives with greater memory capabilities or faster electronics. Assembled nanosystems are also expected to impact the aerospace program – where lightweight, high tear-resistant fabric (made with nanostructures) with embedded nanosensors may be designed for astronauts. To meet the challenges and rewards of nanotechnology, research institutions around the world have built infrastructures to study, manipulate, and design nanometer-sized materials (generally, < 100 nm) for building atomic-scale devices.

In the last couple of centuries, we have perfected the art of building macroscale devices such as clocks, calculators, computer chips, and cars. The building process generally involves the manufacturing of precursor components and the assembling of these components into a functional unit. The entire process can be automated using man-made machines. However, there is extreme difficulty in building similar devices with nanometer-dimensions. This is mainly due to the inability to assemble atoms or nanometer-sized components in a coordinated fashion. Top-down approaches, generally associated with photolithography and etching techniques, have been instrumental in advances in microscale technologies. However, a top-down approach has found limited

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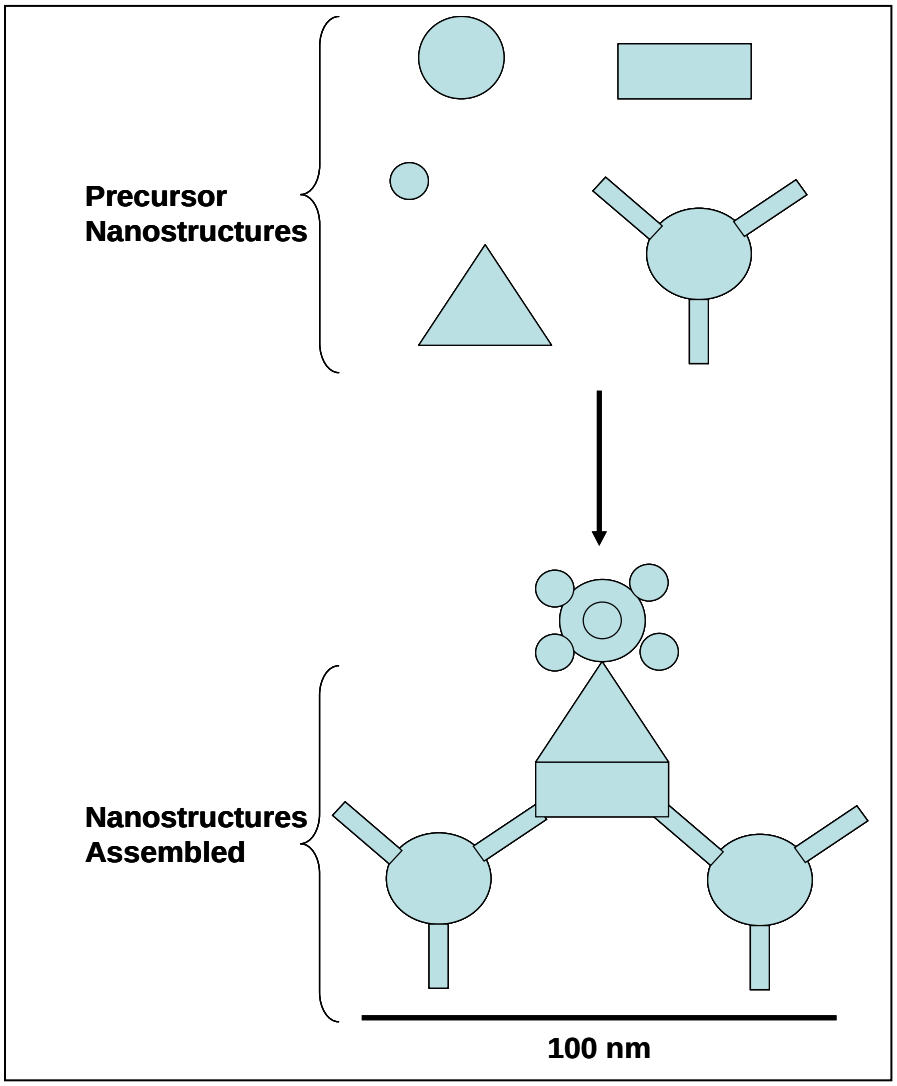

Figure 1. Schematic of assembling nanostructures in a controlled fashion.

use in building nanoscale devices mainly due to high costs of instruments and diffraction limit. A bottom-up strategy, where atoms are precisely assembled in the molecular scale, is one of the most promising strategies for building atomic-scale devices (see figure 1). Material scientists and chemists have spent the last thirty years perfecting the synthesis of nanoscale objects, that may one day become precursors for building nanoscale devices.[1-6] Semiconductor, metallic, non-metallic, and alloyed nanoparticles have been successfully synthesized and characterized. The precision of synthesis is so great that researchers can selectively and reproducibly grow protrusions on the surface of spherical quantum dots[7] or modify the dimensions of metallic nanoparticles using solution-based approaches[8, 9]. Simple monofunctional hybrid organic/inorganic nanostructures have demonstrated a plethora of applications in biomedical detection. Yet, the current challenge of nanotechnologists is to mix-and-match different types of nanostructures in a coordinated fashion to produce a functional device the size of a virus (< 100 nm).

Integrating organic molecules with inorganic nanostructures have produced exciting results in the field of nanodevice building. Organic molecules have been utilized as surface coatings to prevent unwanted nanoparticle aggregation, as molecules to direct nanoparticle assembly, and as homing devices to target nanostructures to specific biological sites. Furthermore, organic molecules have embarked greater functional capabilities into inorganic nanostructures. For example, Mirkin and coworkers used oligonucleotides to assemble and de-assemble metallic nanostructures[10, 11]. Montemagno and coworkers programmed rotational motion in nickel nanoparticles[12, 13] while Ruoslahti and coworkers directed quantum dots to tumour sites using homing peptides *in vivo*[14]. At the current state of research in this field, there is a wide-array of precursor nanostructures and organic molecules available to build nanodevices. However, the key challenge is to develop novel approaches to assemble them into a functional unit. In this chapter, we will describe some of the precursors available for device building and describe some of the recent strategies that utilize biological systems or biomimetic systems to assemble nanostructures.

2. NANOSTRUCTURES AS CORE COMPONENTS FOR BUILDING DEVICES

In the last thirty years, great efforts in the synthesis of nanoscale materials have provided researchers with a large set of building blocks for constructing nanoscale devices. Materials in this size-regime possess unique optical, electronic, and magnetic properties that can be tuned by altering the particle's size, shape, or composition. Metallic nanostructures have the ability to produce heat, quench luminescence, scatter light, and create surface plasmon upon optical excitation. Semiconductor nanostructures have the ability to emit light and are conductive upon optical or electrical excitation. Rod-shaped semiconductor nanostructures can polarize light while spherical shaped nanostructures cannot. Carbon nanotubes have unique electrical and mechanical properties, and are lightweight. Fullerenes are hollow in the core while dendrimers are highly porous. These are examples of some of the properties of nanostructures that may find use in nanoscale device building.

The ability to assemble nanostructures requires precise control of the particle's surface chemistry, where molecules can be coated onto the surface to direct the assembly process. Strategies have been developed to readily permit the modification of a nanoparticle's surface chemistry[15-19] . The easiest types of nanoparticles to coat with

recognition biomolecules are metallic nanostructures such as gold or silver colloids. In preparing for coating, the surface of metallic nanoparticles is generally stabilized with a weak ligand that can be easily desorbed from the surface. For example, proteins such as bovine serum albumin and transferrin can be adsorbed onto the surface of citrate stabilized gold nanoparticles through ionic and hydrophobic interactions as well as dative binding. For other types of nanoparticles where the surface coating with biomolecules may be more difficult, extra processing steps are needed to create a surface with reactive functional groups (-COOH, -SH, or $–NH_2$). For example, semiconductor quantum dots do not readily adsorb proteins. In order to coat the surface of quantum dots with proteins, a layer of amphipolic polymer can be used to render the surface of the quantum dots with -COOH functional groups[20]. Primary $–NH_2$ group from biomolecules can then be cross-linked to the surface of the amphipolic polymer through a carbodiimide-assisted reaction, forming an amide bond linkage between the quantum dot and biomolecule. Specialized techniques have been developed for functionalizing carbon nanotubes, magnetic nanoparticles, and fullerenes for cross-linking to biomolecules.

3. BIOLOGY AS MODEL SYSTEM FOR BUILDING NANOSCALE DEVICES

A key challenge in building nanoscale devices is the ability to assemble components in a controlled fashion. How can one build a nanometer-sized RC-circuit? How can one build a detection and drug storage and delivery system the size of a standard virus (~50 to 150 nm)? Researchers have recently looked toward biology as a guide to assemble nanostructures into functional devices. One interesting fact about bioassembly in living cells and tissues is that only a small amount of subunits are required to produce a rich and diverse group of functional systems that regulate and maintain the viability of cells, tissues, organs, and the organism. The information in DNA, the blueprint of a cell, is encoded using only four distinct bases. Proteins, the functional units of a cell, are only composed of 20-amino acids. Yet, a cell has developed the capability to assemble 4-bases into a complete genetic code and 20-different amino acids into thousands of functional proteins.

The molecular inner-workings of a cell can be equated to a highly efficient assembly line that produces many types of biological nanomachines. For example, in the translation of ribonucleic acid (RNA) to proteins, individual protein-units are assembled together into a ~ 30-nm sized functional system called a ribosome. The ribosome interacts with RNA and translates the RNA-sequence into an amino acid sequence. This amino acid sequence then interacts with other biological systems to fold into an active protein. Eukaryotic ribosomes contain up to 82 proteins that assemble in a precise fashion to form this RNA-translational machine. This is just one example. Other sample systems include the proteins involved in the transcription process, RNAsomes that are involved in splicing activities, or protein-systems involved in extracellular signalling. Although we have not reached or even come close to such sophistication in designing nanoscale-devices, biological machineries provide design guidelines and inspirations for building nanoscale devices.

Mimicking biological systems for designing nanoscale-devices may be a powerful strategy. The controlling factors in coordinating the 20-amino acids and 4-bases into functional units are non-covalent interactions. These interactions include hydrophobic-hydrophobic interactions, van der Waals forces, hydrogen bonding, and molecular

stacking. Nanoparticles, in general, are extremely dependent on molecular forces to assist them in maintaining their monodispersity. The ability to coordinate the molecular forces, similar to the ability of proteins to properly fold into a functional unit, on the surface of nanoparticles is difficult to do at this particular point since protein folding mechanisms remain somewhat unclear. A simpler and first step toward the use of biology to mediate nanoparticle assembly is the use of recognition biomolecules (RBs). RBs can be coated onto the surface of nanoparticles and be used to direct the formation of nanoparticle aggregates.

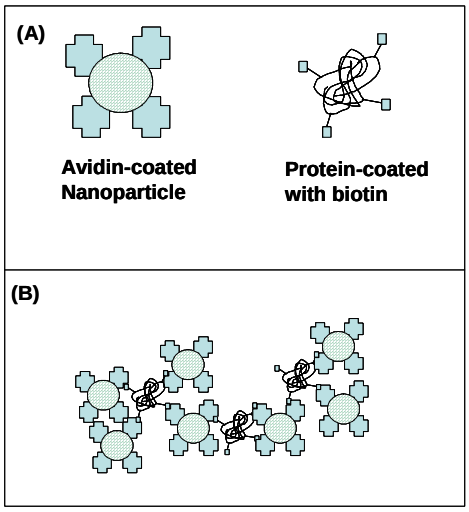

FIGURE 2. Schematic of proteins directing the assembly of nanoparticles. Avidin, a protein that binds to the vitamin biotin, is coated onto the surface of the nanoparticle. The addition of biotin-conjugated protein (e.g., albumin) to a solution of avidin-coated nanoparticle leads to aggregation due to the interactions between biotin and avidin.

The simple mixing of antibody-coated nanoparticles with their matching antigen in aqueous solution can lead to rapid aggregation of nanoparticles[16]. The ordering of nanoparticles within the aggregate network can be coordinated by the RBs. For example, proteins such as avidin have four binding sites to the small organic molecule biotin (see figure 2); antibodies are inhomogeneous in structure and have three binding sites. These two protein systems will yield nanoparticle-aggregates of different shape, size, and nanoparticle spacing. For nanoparticle assembly, proteins may one day act as "molecular glue" to join nanoparticles but will unlikely be used for building nanodevices that require dynamic assembly since protein-induced aggregation may be irreversible. Beyond network formation, the conjugation of proteins to the surface of nanoparticles provides nanoparticles with greater functional capabilities. Montemagno and coworkers proposed the powering of inorganic nanodevices with biomolecular motor[12, 21]. They demonstrated that biomolecular motors such as F_1-adenosine triphosphate synthase and myosin provide enough force to propel inorganic nanoparticles in solution. Vogel and coworkers proposed the use of motor proteins with microtubule track systems to construct molecular conveyer belts to build nanoscale devices[22, 23]. They are mimicking the biological process of vesicle transport inside cells.

Oligonucleotides, another biomolecule, provide great versatility in the assembly process (see figure 3). Oligonucleotides are short-fragments of DNA or RNA that can be easily synthesized using a machine. Similar to a zipper, single-stranded oligonucleotide sequences can hybridize, or pair-up, with a matching sequence through hydrogen-bonding interactions. They dehybridize simply by heating. In 1996, Alivisatos and coworkers[24]and Mirkin and coworkers[25] were two of the first groups to describe the use of oligonucleotides to assemble nanoparticles. Alivisatos and coworkers demonstrated the selective spacing of gold nanoparticles on surfaces while Mirkin and coworkers demonstrated the reversible aggregation of gold nanoparticles in solution.

Thiolated-oligonucleotides (e.g., HS-ATGGCCA where A, T, G, C refers to the nucleic acid bases adenine, thymine, guanine, cytosine) are directly adsorbed onto the surface of gold nanoparticles and excess oligonucleotides are removed from solution using ultracentrifugation. A solution of ATGGCCA-coated gold nanoparticles can aggregate in the presence of the palindrome sequence TACCGGTTGGCCAT due to the formation of an ATGGCCA-TACCGGT duplex. Upon formation of the duplex structure, the solution changes colour from ruby red to blue. This indicates the assembly of gold nanoparticles into an aggregate. Heating of the solution beyond the melting temperature induces the dehybridization of the ATGGCCA-TACCGGT duplex, returning the solution colour back to red.

The properties of the oligonucleotide-induced aggregates can be easily manipulated. Changing the length of the oligonucleotide sequence can alter the length between nanoparticles in the aggregate network. Complex structures can also be developed – for example, Mucic et al. demonstrated the construction of binary nanoparticle networks where 8-nm gold nanoparticles were assembled onto the surface of a 31-nm gold nanoparticle (figure 3)[26]. Different types of nanoparticles can be introduced into the oligonucleotide aggregates. Enzymes that can cleave specific DNA sequences (e.g., EcoRI) may provide another tool for producing unique structures in the aggregate network[27, 28] . Oligonucleotides provide a versatile "molecular glue" to organize nanostructures for engineering nanoscale devices. However, there are still great difficulties in producing aggregate structures with controlled size (e.g., structures with only 2, 3, or 4 particles) or shape (e.g., 3-D cubical vs. spherical shaped aggregate) using oligonucleotide-based methodologies.

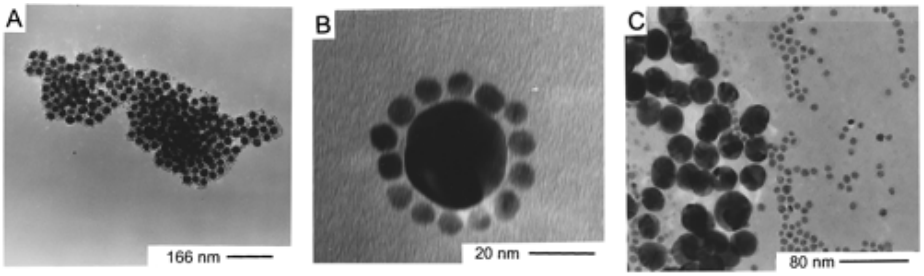

FIGURE 3. TEM images of nanoparticle assembly. 8-nm colloidal gold nanoparticles were coated with the sequence 3'$HS(CH_2)_3O(O)OPO$-ATG-CTC-AAC-TTC and 31-nm colloidal gold nanoparticles were coated with the sequence 3' TAG-GAC-TTA-CGC-$OP(O)(O)O(CH_2)_3SH$. (A) Upon addition of the linking sequence 5'TAC-GAG-TTG-AGA-ATC-CTG-AAT-GCG to a solution of the oligonucleotide-coated 8 and 31-nm gold nanoparticle, aggregation was observed. The 31-nm gold nanoparticles were covered with 8-nm gold nanoparticles. (B) By varying the ratio of 8-nm to 31-nm (in this example, it was 120:1), satellite structures can be formed. (C) When the linking sequence does not match either of the oligonucleotide sequences on the 8 or 31-nm gold nanoparticles, the nanoparticles do not aggregate. This figure is adapted from ref. 26 with permission.

Surface-based techniques have recently been employed to provide a second level of control for nanoparticle aggregate formation. In a recent study by Bashir and co-workers, biotinylated oligonucleotide sequences were placed onto the surface of a silicon substrate[29]. Avidin-coated nanoparticles were then incubated with the substrate and were attached onto the surface through an avidin-biotin interaction. The addition of excess avidin-coated nanoparticles produced a monolayer of nanoparticles that can be released

from the surface by dehybridizing the oligonucleotide sequence. Other surface-based approaches have utilized molecular templating as a strategy to organize nanoparticles. In one example, Stupps and coworkers developed nanometer-scaled ribbon structures out of polymers and then nucleated and grew semiconductor nanoparticles onto these ribbon structures[30]. Although the use of bio-inspired approaches toward nanoparticle assembly has provided a first level of control, this is nowhere near the level of complexity that cells have used to assemble their biomolecular machines. The next step in nanoscale-device building is to develop novel methods that can lead to a high level of control for nanoparticle assembly and that can integrate different-types of nanoparticles into a complex 3-D network, just like the ribosome. Once that has been achieved, we will be one-step closer to building smart and usable nanoscale devices.

4. MICROBIAL SYSTEMS FOR ASSEMBLING NANOSTRUCTURES.

The use of microbial systems is another promising approach toward building nanoscale devices. Microbial systems may be used as templates for organizing nanoparticles or be programmed to express a set of worker proteins that can organize nanoparticles into functional devices.

Viruses possess hundreds of unique sizes and shapes that may be useful as templates for organizing nanoparticles. Emory and coworkers are proposing the development of optical sensing surfaces by coordinating SERS-active nanoparticles (SERS, surface-enhanced raman spectroscopy) onto the surface of tobacco mosaic viruses (TMV) [31]. The surface of the TMV is chemically modified to attract nanoparticles. For example, primary thiol atoms can be introduced onto the surface of the virus using Traut's reagent (a.k.a. iminothiolane), which modifies the surface of the virus to attract metallic nanoparticles. Therefore, the overall structures of the nanoaggregate are similar in shape and dimension to the virus. Metallic nanoparticles have a high binding affinity toward primary thiols. Furthermore, the ability to mutate the protein coating of virus may be useful for tuning the spacing between nanoparticles as well as for mediating nanoparticle heterogeneity on the surface of viruses.

Viruses can also be genetically engineered to produce a set of recognition peptides that can selectively identify nanoparticles based on their composition and lattice structure (figure 4). This technique is known as phage-display, where specific or unknown substrates, are panned against a library of phage particles to identify recognition molecules. With this technique, genes are inserted into viral particles called phage, and expressed as peptides on the outer perimeter of the phage after replication in bacteria. These genes can be mutated or varied to create a diverse pool of phage that can be screened against nanoparticles. Although, phage-display has been traditionally used in molecular biology, Belcher and coworkers pioneered the use of phage-display for nanotechnology research [32, 33]. They demonstrated the ability to program phage-particles to selectively identify specific type of nanoparticles and to use the phage-as a means of organizing these nanoparticles into a 3-D layer. Phage-particles may one day be programmed to assist in the build-up of nanoscale devices.

Yeast cells also have the capability to build nanoscale devices. In 1989, Winge and coworkers discovered the ability of the yeast cells *Candida glabrata* or *Schizosacharomyces pombe* to synthesize semiconductor nanocrystals[34]. Feeding yeast with Cd^{2+}- atoms can lead to the expression of a family of proteins that assist in the

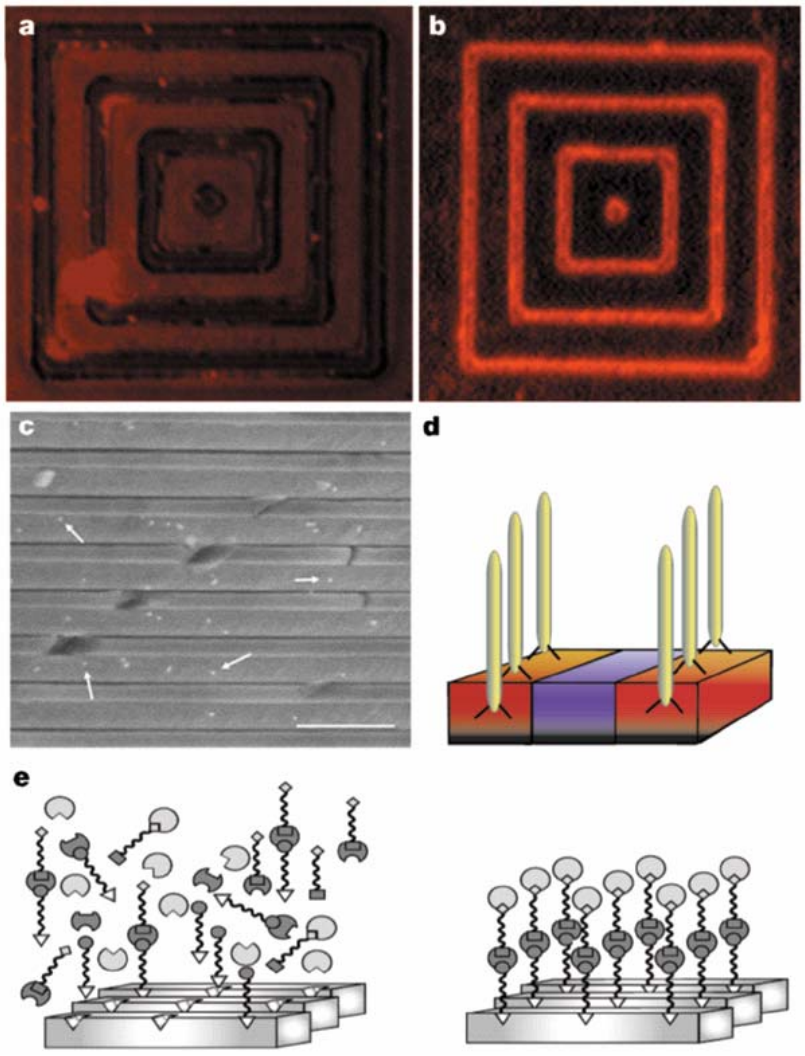

FIGURE 4. This figure depicts the use of phage-display screening to select for recognition molecules that can bind to inorganic targets. (A-B) An optical image of inorganic surface (1-μm GaAs and 4μm SiO_2). The autofluorescence of the SiO_2 was observed. Upon incubation with tetramethylrhodamine (TMR)-phage particles that recognized the GaAs surface, a high fluorescence emission was observed on the thinner lines. TMR is fluorophore and this indicated the direct binding of phage particles to targeted site. (C) To further verify the selective binding of phage particles, the phage-particles were tagged with gold nanoparticles. The surface consisted of GaAs and $Al_{0.98}Ga_{0.02}As$. As shown in panel B, a SEM image revealed gold nanoparticles were stationed only on the GaAs region of the surface (shown by the arrows). Scale bar is 500 nm. (D) Diagram of the selection and binding process. (E) Diagram showing the use multiple phage-particles to direct assembly. This figure is adapted from ref. 32 with permission.

construction of ~ 3.0 nm CdS-nanoparticles. Once, the desired size of the nanoparticles is reached, yeast produces a glutathione-like protein to coat the surface of the nanoparticles. This protein helps to stabilize the nanoparticle from aggregation inside the cell and to direct the nanoparticles out of the cell. Recent studies have demonstrated the synthesis of different-types and sizes of nanoparticles using yeast cells[35-37].

5. CURRENT STATE AND HIGHLIGHT OF BIOAPPLICATIONS OF NANOSTRUCTURES

Although the successful design of nanoscale devices is several decades away, nanoparticles have been integrated with biological molecules for numerous biomedical applications. These can be considered, in some manners, to be simple, monofunctional nanostructures that can manipulate the release of drug molecules or to detect biomolecules in solution.

One of the most interesting concepts in functional nanoscale systems is the integration of thermosensitive hydrogels with colloidal nanoparticles for optically controlling drug release. Halas and West described the use of gold nanoshells for localized drug delivery[38]. These nanoshells are made from a silica dielectric core with a gold shell, and their plasmon resonance wavelength can be tuned by varying the size of the core and the shell. It has been well known that colloidal gold nanoparticles and more recently, colloidal nanoshells have large absorption cross-sections (e.g., 5-nm diameter gold particle has a cross-section 3 nm^2 at 514 nm). Because of this, colloidal gold nanoparticles and nanoshells possess a photothermal effect that is induced by non-radiative collisions between optically excited electrons with solvent molecules. Thermal-sensitive polymers such as the copolymer N-isopropylacrylamide and acrylamide can undergo a phase-change when the polymer is heated above their lower critical solution temperature (LCST). At a temperature > LCST, molecules trapped inside the polymer are released into the external environment due to the shrinking of the polymer. Essentially, molecules such as drug agents that are trapped in the core are squeezed out of the hydrogel when heated. The development of thermal-sensitive polymer matrices on the surface of gold nanoshells can be utilized for storage of drug agents while the gold nanoshells can act as an optical switch to control the release of drug agents. It is believed that one day nanoparticle/drug storing system can be directly targeted to lesions *in vivo*. The advantage is that the drug molecules are protected from the immune defence systems *in vivo*; and can be selectively released at sites of injury - which is expected to reduce side effects.

Recently, Ruoslahti and coworkers have demonstrated the successful targeting of nanoparticles to specific sites in living animals[14]. They discovered peptides that specifically target tumour vasculatures[39, 40]. Two of these peptides were conjugated onto the surface of two different-emitting quantum dots. These peptide-conjugated quantum dots were introduced into a mouse bearing xenograft tumours through injection into the tail vein. After 20 minutes, two distinct fluorescence signals were distinctly apparent on the tumour tissues upon optical excitation. Co-staining with markers showed the localization of red-emitting quantum dots in the blood vessels while green-emitting quantum dots localized in the lymphatic vessels. No significant quantum dot emission was apparent in other nearby tissues and organs. Targeting molecules have been identified for tumour vessels and normal vessels in the brain, kidney, lungs, skin,

pancreas, and other tissues[41]. The integration of targeting molecules with nanostructures should provide a means of delivering nanostructures to specific cells and tissues *in vivo* as well as nanoparticle-based contrast agents for ultrasensitive optical imaging.

Beyond *in vivo* applications of nanostructures, interfacing organic molecules with inorganic nanostructures have led to the development of a new generation of *in vitro* detection systems. Mirkin and coworkers harnessed the unique absorption characteristics of aggregated and non-aggregated gold nanoparticles for the detection of genetic mutations[42, 43]. Natan and coworkers developed a metallic-barcoding system that can analyze thousands of biomolecules simultaneously[44]. Colloidal metallic nanoparticles have also been utilized for genomic and proteomic screening. Dai and coworkers developed highly selective electronic biosensors by using protein-adsorbed carbon nanotubes[45]. Furthermore, there has been significant progress in the development of semiconductor quantum dots for biosensing and detection applications[46]. Other types of nanoparticles such as fullerenes and dendrimers have found applications in drug storage and delivery. Magnetic nanoparticles are utilized as contrast agents for enhancing MRI-imaging. In the future, we foresee the development of multifunctional nanostructures where onset and evolution of a disease can be sensed by the nanostructure. The sensing of the disease, then, causes the selective release of one type or a combination of drug agents. Nanostructures are rapidly advancing toward everyday use in research labs and the clinic and in the future, we can expect nanotechnologists to design of multifunctional nanostructures that can potentially diagnose and treat a disease.

6. CONCLUSIONS

The field of nanotechnology has great potential to change the world. There has been a tremendous focus in the last thirty years on developing and characterizing nanostructure materials. Nowadays, the goal is to utilize these materials as precursors to build nanoscale devices and to develop novel approaches to assemble these precursor nanostructurs into a functional device. Biology offers an excellent guide for assembling nanostructures since a cell can produce thousands of different functional units with only 20-different amino acid building blocks. Biomolecules such as proteins, oligonucleotides and microbial systems have been successfully applied toward organizing nanostructures into macrostructures. Although we have not built complex and functional nanostructures, there are numerous examples in the literature that demonstrate the utility of simple monofunctional nanostructures for biosensing and imaging applications, and drug storage/release systems. In the future, the ability to assemble nanostructures into complex functional units should produce novel systems that will have a broad and significant impact.

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