Use Of Nano Particles And Nanocrystals In Drug Discovery

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Abstract

Because of their unique properties Nanocrystals (quantum dots) and other nanoparticles (gold colloids, nanobars, dendrimers and nanoshells) have been receiving a lot of attention for potential use in Therapeutics, Bioengineering and therapeutics drug discovery. In this review potential use of these Nanocrystals and Nanoparticles in drug discovery has been discussed. Special properties of these nanoparticles may offer new advancement in drug discovery.

INTRODUCTION

Nanobiotechnology is that branch of nanotechnology that deals with biological and biochemical applications or uses. Nanobiotechnology often studies existing elements of living organisms and nature to fabricate new nano-devices. Generally, nanobiotechnology refers to the use of nanotechnology to further the goals of biotechnology.

The potential uses and benefits of nanotechnology are enormous. We are promised everything from the mundane things like better paints, self-cleaning windows to the bizarre tiny submarines that will glide through our veins destroying pathogens and parasites. Nano- systems in biology, the most complex and highly functional nano-scale materials and machines have been invented by nature. Proteins and nucleic acids, and other naturally occurring molecules (polymers) regulate and control biological systems with incredible precision. Ultra-strong or other clever materials are commonplace – from muscle glue, through spider's silk, to water-repelling lotus leaves. Many nanotechnologists are in fact drawing inspiration from biology to device new materials and devices.

The approaches that are being used currently for drug discovery suffers from problems associated with selection of target and chemistry problems associated with leads [$_{12}$]. Nanoparticles and Nanocrystals have turned out to be a silver lining for all these problems

NANO CRYSTALS (QUANTUM DOTS)

A quantum dot is a semiconductor whose excitons are confined in all three spatial dimensions. As a result, they have properties that are between those of bulk semiconductors and those of discrete molecules.[$_{345}$] They were discovered by Louis E. Brus, who was then at Bell Labs. The term "Quantum Dot" was coined by Mark Reed.

Researchers have studied quantum dots in transistors, solar cells, LEDs and diode lasers. They have also investigated quantum dots as agents for medical imaging and hope to use them as qubits.

They are neither atomic nor bulk semiconductors. Their properties originate from their physical size, which ranges from 10–100 Å in radius. Due to their bright fluorescence, narrow emission, broad UV excitation and high photostability [$_{67}$], QDs have been adopted for in vitro bioimaging by many researchers as an alternative to organic based fluorophores [$_{689101112}$]. Most recently, in vivo applications of these QDs have also been reported [$_{131415}$].

Semiconducting QDs are spherical in shape, mostly direct-band-gap materials, and hold hundreds or thousands of atoms depending on their final size. Their radii varies from anywhere between 10–100 Å, which is known to be smaller than the bulk Bohr excitation radius (for CdSe dots, it is 50Å) [$_{1617}$]. When the radius of the QDs is smaller than the bulk Bohr excitation radius, it is reasonable to refer to energy levels rather than energy bands under the quantum confinement. QDs reveal unique electrical and optical properties coupled with the atomic structures of the dots cubic (zinc blende) or hexagonal (wurtzite) and due to quantum confinement.

VIRAL ASSEMBLY

Lee et al. (2002) reported using genetically engineered M13

bacteriophage viruses to create quantum dot biocomposite structures.[18] As a background to this work, it has previously been shown that genetically engineered viruses can recognize specific semiconductor surfaces through the method of selection by combinatorial phage display.[19] Additionally, it is known that liquid crystalline structures of wild-type viruses (Fd, M13, and TMV) are adjustable by controlling the solution concentrations, solution ionic strength, and the external magnetic field applied to the solutions. Consequently, the specific recognition properties of the virus can be used to organize inorganic nanocrystals, forming ordered arrays over the length scale defined by liquid crystal formation. Using this information, Lee et al. (2000) were able to create self-assembled, highly oriented, self-supporting films from a phage and ZnS precursor solution. This system allowed them to vary both the length of bacteriophage and the type of inorganic material through genetic modification and selection.

Recently, many biological applications of QDs have been reported.The usage of quantum dots for highly sensitive cellular imaging has seen major advances over the past decade. The improved photostability of quantum dots, for example, allows the acquisition of many consecutive focal-plane images that can be reconstructed into a high-resolution three-dimensional image. Another application that takes advantage of the extraordinary photostability of quantum dot probes is the real-time tracking of molecules and cells over extended periods of time [11]. Researchers were able to observe quantum dots in lymph nodes of mice for more than 4 months [20].

Semiconductor quantum dots have also been employed for in vitro imaging of pre-labeled cells. The ability to image single-cell migration in real time is expected to be important to several research areas such as embryogenesis, cancer metastasis, stem-cell therapeutics, and lymphocyte immunology.

Scientists have proven that quantum dots are dramatically better than existing methods for delivering a gene-silencing tool, known as siRNA, into cells.

First attempts have been made to use quantum dots for tumor targeting under in vivo conditions. There exist two basic targeting schemes: active targeting and passive targeting. In the case of active targeting, quantum dots are function with tumor-specific binding sites to selectively bind to tumor cells. Passive targeting utilizes the enhanced permeation and retention of tumor cells for the delivery of quantum dot probes. Fast-growing tumor cells typically have more permeable membranes than healthy cells, allowing the leakage of small nanoparticles into the cell body. Moreover, tumor cells lack an effective lymphatic drainage system, which leads to subsequent nanoparticle-accumulation.

BIOTOXICITY

As explained earlier, as a result of their superior optical properties, QDs have become more widely used for in vivo applications.This raises questions with respect to their biotoxicity. This question has been investigated by number of groups [21222324]. In these studies it has been reported that surface oxidation can occur under combine exposure to the aqueous/ UV-light excitation. This can lead to the release of cadmium ions in the case of CdSe-based QDs. The mechanisms for this were suggested as the tri-n-octylphosphine oxide- (TOPO-) mediated or UV-catalyzed surface oxidation. Toxicity of CdSe QDs in liver culture model is found to be dependent on processing conditions and nanoparticle dose. Under oxidized (30 min exposure to air) or long UV radiation (2–8 h) conditions, even QD concentrations of 0.0625 mg/mL are found to be highly toxic [22]. Before QDs are adopted for in vivo applications, a comprehensive study of shell type and thickness, as well as the relative diffusion rate of oxygen need to be well understood. As of today, this concern related to their toxic content being released under the given conditions effectively excludes the choice of QDs as drug delivery vehicles, even though they can offer a lot with additional surface functionalization capability, especially for targeted drug delivery.

OUTLINE OF OTHER NANOPARTICLE TECHNOLOGIES

Besides semiconducting QDs, other types of nanoparticles have been developed for biological applications. Below, are selected some of the nanoparticles that can also offer advancements in drug discovery.

COLLOIDAL GOLD

Colloidal gold, also known as “nanogold”, is a suspension (or colloid) of sub-micrometre-sized particles of gold in a fluid — usually water. The liquid is usually either an intense red colour (for particles less than 100 nm), or a dirty yellowish colour (for larger particles).The nanoparticles themselves can come in a variety of shapes. Spheres, rods, cubes, and caps are some of the more frequently observed ones.

In cancer research, colloidal gold can be used to target tumors and provide detection using SERS (Surface Enhanced Raman Spectroscopy) in vivo. These gold nanoparticles are surrounded with Raman reporters which provide light emission that is over 200 times brighter than quantum dots. It was found that the Raman reporters were stabilized when the nanoparticles were encapsulated with a thiol-modified polyethylene glycol coat. This allows for compatibility and circulation in vivo. To specifically target tumor cells, the pegylated gold particles are conjugated with an antibody (or an antibody fragment such as scFv), against e.g. Epidermal growth factor receptor, which is sometimes overexpressed in cells of certain cancer types. Using SERS, these pegylated gold nanoparticles can then detect the location of the tumor.[25]

Gold nanoparticles are being investigated as carriers for drugs such as Paclitaxel.[26]The administration of hydrophobic drugs require encapsulation and it is found that nanosized particles are particularly efficient in evading the reticuloendothelial system

NANOSHELL

Nanoshells are gold-layered dielectric nanoparticles with optical resonances that can be ‘tuned’ by the control of the relative size of their constituent layers.

One of the promising applications concerns the biological field. In the research groups of Halas and West, these nanoparticles have been applied to number of biological applications such as detection of immunoglobulins in whole blood, and for thermal ablation of cancerous cells both in vitro and invivo [2728].Research is being performed to create nanoshells with high absorptions at biologically useful wavelengths by altering the thickness of the shells. Particularly, the Near Infra Red region, which corresponds with low absorption by tissue, may be useful.

In the literature, special attention is given to gold nanoshell with a dielectric core (gold sulfide,silicon dioxide,...). Gold is a biocompatible compound, making it a useful material for medical applications.

DENDRIMERS

Dendrimers are hyperbranched, tree-like structures and have compartmentalized chemical polymers. The first dendrimers were synthesized divergently by Vögtle in 1978[29], by Denkewalter and coworkers at Allied Corporation as polylysine dendrimers in 1981[30], by Tomalia at Dow Chemical in 1983[31] and in 1985[32], and by Newkome in 1985[33]. In 1990 a convergent synthesis was introduced by Fréchet[34]. Dendrimers then experienced an explosion of scientific interest because of their unique molecular architecture .

The properties of dendrimers are dominated by the functional groups on the molecular surface. Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics the structure of active sites in biomaterials because dendritic scaffolds separate internal and external functions.[353637]. For example, a dendrimer can be water-soluble when its end-group is a hydrophilic group, like a carboxyl group. It is theoretically possible to design a water-soluble dendrimer with internal hydrophobicity, which would allow it to carry a hydrophobic drug in its interior. Recently it has been shown that redox-active nanoparticles can be synthesized, placing the redox molecules between the nanoparticle core and the dendritic wedges; despite their isolation, some of the redox molecules (COOH in this case) remained uncoupled, and thus still reactive.

Another property is that the volume of a dendrimer increases when it has a positive charge. If this property can be applied, dendrimers can be used for drug delivery systems (DDS) that can give medication to the affected part inside a patient's body directly.

NANOBARCODES

Nie [38] et al. embedded QDs such as CdSe- and ZnS-capped dots in different colors with highly controlled ratios into polymer microbeads.This created a large spectrum of beads with different colors and intensities for multiplexed, HTS of DNA or proteins. This technique utilizes the advantages of QDs over organic dyes. The spectrum of QD-embedded microbeads was reported to be 10% narrower than the QDs alone, which further benefits the multiplexed imaging. In addition, the approximate pore separation on the surface of the polymer microbeads was given as ~30 nm within 1.2 m bead that contains 50,000 QDs. This eliminates the possibility of FRET between the two neighbouring QDs, as the distance between adjacent

pores (30nm) greatly exceeds the Förster radius (5–8nm). These promising microbeads were applied for DNA detection and hybridization of target sequences. They can withstand higher temperatures during the hybridization process than

QDs. The sensitivity to the low amount of target sequences

is currently under investigation.

CONCLUSION

In this review, different types of nanoparticles including QDs, gold colloids, magnetic tags, nanobarcodes, dendrimers and nanoshells are described for their potential use in drug discovery.However, as discussed earlier there are some limitations yet to be resolved for their use in the drug discovery studies, namely, toxicity, size variation, agglomeration, potential multiple drug attachment to a single QD and blinking. As long as the advantages and disadvantages for each nanoparticle are understood very well, the analysis of the experimental data and some ambiguities in the data can be ruled out in a better way. With the current extra effort being given in the nanotechnology area, some of the shortcomings of these particles should be understood and addressed in the near future. Perhaps the birth of a better nanoparticle can be expected.

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