

Quantum Dots in Biomedical: Introduction, Synthesis, and Applications

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Abstract. Quantum dots have brought unlimited potential in biomedical applications with their fluorescence, light-induced catalyze, light-heat conversion, and photoacoustic capability. However, there are very limited reviews regarding current progress in quantum dots research and their application in the biomedical field, such as biosensing, bioimaging, and tumor therapy. In this article, a systematic review is done in two aspects: synthesis and application of quantum dots in biomedical applications. The functionalization of quantum dots is also mentioned and reviewed in this article.

Keywords: Quantum Dots, Synthesis, Biomedical.

1. Introduction

Since their very first discovery by Russian physicist Alexey Ekimov in 1981, quantum dots have brought unlimited potential in biomedical applications [1]. Quantum dots have attracted the attention from biomedical researchers owing to their fluorescence property [2], light-induced formation of reactive oxygen species (ROS) [3], and light-heat conversion property [4], and photoacoustic conversion [5]. They are often described as zero-dimensional materials made from either transition metal or nonmetal material. Although a variation in the product size of the quantum dots is reported in different articles, researchers commonly believe that less than 100nm in thickness and 100nm in diameter can be considered as quantum dots. Such dimensional properties make them possess a high surface-to-volume ratio, high stability, and extraordinary biocompatibility, which are suitable for constructing biosensing and curing platforms. As for their fluorescence property, quantum dots present several incomparable advantages compared to conventional organic fluorescent probes, such as low toxicity to life forms and low photo-bleaching effect [6]. Furthermore, their broad absorption spectra endow them with the ability of different quantum dots with distinct emission spectrums to be excited by one single wavelength of laser simultaneously. Several experiments observed that quantum dots possess a narrow, symmetrical, yet tunable emission spectra that would allow for a higher resolution in the detection of the specific target. Moreover, the adjustments of bandwidth of quantum dots can be achieved by controlling size in the synthesis process, which can be precisely controlled by reaction time [7].

The diagnosis and treatment of pathological changes in organs that lead to carcinogenesis or organic dysfunction is calling for more and more attention and efforts from scientists. According to World Health Organization, more than 18.0 million cancer cases were reported, among which more than 10.0 caused fatality [8]. A typical procedure to diagnose pathological changes involves histopathological biopsy in living conditions and molecular markers in which patients often experiences pain. The test result is often difficult to distinguish due to cancers' various genotypes and phenotypes from different origins [9]. To address this problem, fluorescence in quantum dots caused by excitation can be used to indicate the presence of tumor cells after being functionalized by cancer probes [10]. The ability to convert photons into acoustic signals brought by quantum dots is also used to image organ dysfunctions such as kidney dysfunction [5]. Quantum dots also provide a new thread in curing cancers, apart from their unlimited potential use in biosensing and *in-vivo* bioimaging. Currently, cancer treatment involves chemotherapy that will cause vast toxicity to cells in the whole body while therapies using quantum dots provide a safer, less toxic way against cancer. Reactive oxygen species are generated after the quantum dot with a specific bandwidth is excited by light, which can cause tumor cells to be eliminated. This is known as the light-induced catalytic

compatibility for quantum dots, and the therapies result from this property are called photodynamic therapy [3]. Temperature-sensitive cancer cells can also be eliminated by a kind of therapy in which quantum dots convert light into heat and specifically kills the tumor cell. These therapies are also known as photothermal therapies [11].

Currently, both transition metal quantum dots involving Cd, Te, Ag, and nonmetal quantum dots involving graphene and phosphorus are under scientists' research. However, their focus has shifted from transition metal material to carbon-based quantum dots due to their incomparable biocompatibility, as their decoration is relatively simple due to the presence of the π bond. Although there is plenty of research regarding quantum dots in different applications such as medication, environmental monitoring, and light-emitting materials using both nonmetal and transition metal materials, but a systematic review on the research progress of its application in biomedical remained few. As a result, the current progress of the applying quantum dots in the biomedical field, such as biosensing, bioimaging, and disease therapy is reviewed in this article.

2. Synthesis

The synthesis of quantum dots has undergone a long period of development. In most cases, quantum dots need to be functionalized by either loaded with a drug or a specific antibody to incorporate with designated cells rather than acting directly on the target. In this chapter, the synthesis of quantum dots will be discussed and introduce the means to functionalize quantum dots.

2.1. Synthesis of quantum dots

The synthesis of quantum dots can be sorted into two genres, either known as bottom-up or known as top-down approaches which both categories can produce quantum dots of similar size with completely different starting points. Here-in, the synthesis of nonmetal graphene quantum dots will be discussed mainly since there has been sufficient research regarding on the synthesis of transition metal quantum dots.

2.2. Bottom-up approach

The bottom-up approach can be regarded as building larger material from small pieces, even though quantum dots are very small. Several bottom-up methods such as hydrothermal method, sol-gel method, precursor pyrolysis, and microwave-assisted synthesis are used to fabricate quantum dots from relatively small molecules.

Precursors involved in hydrothermal methods to fabricate graphene quantum dots typically include glucose and melamine. A novel solvothermal way to produce graphene quantum dots involving hydrogen peroxide and N, N-Dimethylformamide as solvent was proposed in 2016, which does not produce various impurities. Hydrogen peroxide will be completely consumed due to either reaction or decomposition, resulting in the only appeared impurity to be expanded graphite [12]. However, the hydrothermal process provides a low-cost yet simple approach. An experiment conducted by Shen et al. involves dispersing pure oxidized graphene in deionized water by ultrasonic at first. Later on, the product was transferred and heated in an autoclave, successfully synthesizing graphene quantum dots [13]. Furthermore, it has been reported that the crystallization of inorganic precursors from hydrothermal methods results in products whose size and shape can be controlled by adjusting either the reaction time or the temperature and pressure inside the autoclave. This result suggests a possible way to achieve size control in the hydrothermal method [14].

Sol-gel has been a common technique used in material sciences for a long period and has been successfully applied to manufacturing transition metal quantum dots. In general, when a metal precursor is introduced into an acidic or basic medium, a sol is prepared. After the sol is prepared, polymerization leads to gel formation [11, 14]. The sol-gel method is considered to be a low-cost method but with broad-distributed size and uncontrollable defect, which leads to the sol-gel method being seldomly used recently, especially when the research focus is on graphene quantum dots [15].

2.3. Top-down approach

The top-down approach refers to thinning a bulk material into smaller units that can reach a size comparable to quantum dots. Chemical exfoliation and electrochemical exfoliation are the two most common ways to produce quantum dots. Chemical exfoliation uses chemical reagents such as oxidants or reductants to break bonds between atoms. Among all, oxidative cleavage is the most frequently used approach to synthesize graphene quantum dots which often uses strong acids as oxidants since strong acids such as sulfuric acid or nitric acid are easy to access [7]. However, previous experiments also suggested that the removal of strong acid residue increases the overall effort, and the final photoluminescence emission spectrum is found to be pH-dependent, indicating the residue of acid or adding too much base will result in a shift in the emission spectrum [16].

Electrochemical cleavage is another top-down strategy to produce quantum dots from bulk material. More dimensional uniform products were reported in various research, regardless of whether their precursors were carbon nanotube, graphite, or graphene sheet [7].

The current research interest in synthesizing transition metal quantum dots via the top-down method includes enhancing size control through extra methods such as sonication. Sonication is a proposed method since it is a simple way with less equipment and low cost. In 2021, Borah et al. reported a top-down method with controllable crystalline phase and size of the MoO₃ quantum dots through sonication, revealing a new possible way to form highly crystalline transition metal quantum dots [17]. The workflow of this project was demonstrated in Figure 1, where the final sonication resulted in fine size control. Furthermore, as reported in another research conducted by Zhao et al., SnO and SnO₂ quantum dots are synthesized by ultrasonic-assisted method from the corresponding mesocrystals [18].

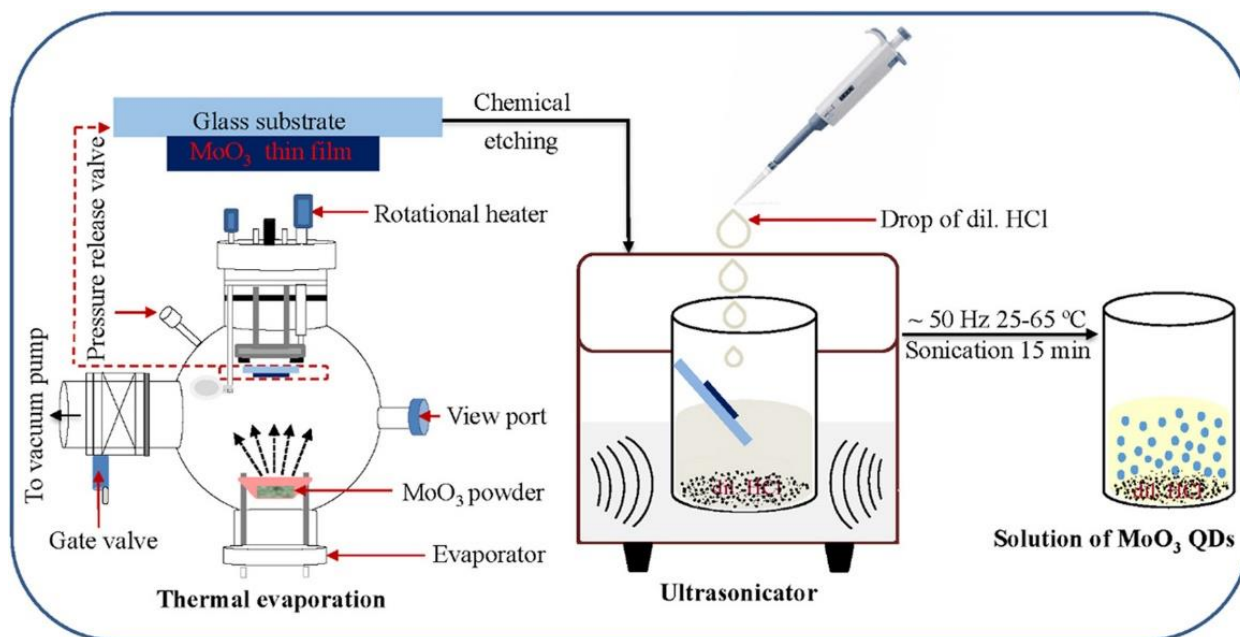


Figure 1. Illustration of sonication involved size-control [17]

2.4. Functionalizing quantum dots

Even though quantum dots provide a very bright future for many applications, however, they still need to be coated since their high surface energy can result in surface defects and undergo fluorescence quenching while excited [19]. The surface modification provides the quantum dot tunable functions since bare quantum dots cannot be applied to biomedical applications. The functional group that provides the quantum dots' specific function was loaded through different chemical or physical methods, including ultrasonic-assisted dispersion, formation of π - π stacking, and covalent functionalization.

Ultrasonic-assisted dispersion can disperse quantum dots into the vacant site of bigger molecules [11]. It had been reported before that a genetically engineered polypeptide was expressed in *E. coli* that had two kinds of sites-pentameric and tetrameric sites that would both fit the Ag_2S quantum dots inside. Compared to dodecanethiol-capped Ag_2S quantum dots, the quantum yields were still maintained at a 4.3% high level even after the loading [11]. The following figure illustrates the mechanism of ultrasonic-assisted dispersing of Ag_2S quantum dots into genetically engineered polypeptides PC_{10}A matrix.

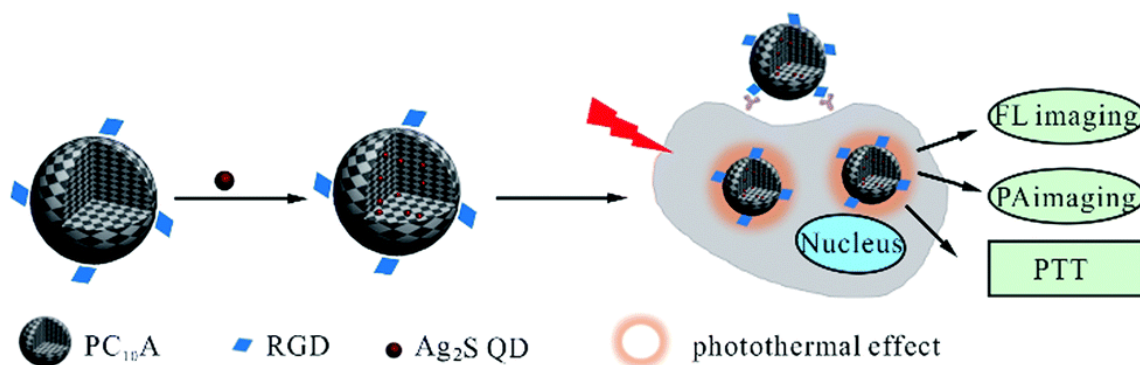


Figure 2. An example of ultrasonic dispersion modification [15]

π - π stacking is another common method used in modifying graphene quantum dots. Unlike the ultrasonic dispersion approach that requires a site for the insertion of quantum dots, π - π interaction requires the presence of π bonds, which is especially suitable in modifying graphene quantum dots. Under most circumstances, the more typically used functional group in research is aromatic rings since it ensures an area large enough for forming stable interaction. This process does not involve the formation of covalent bonds, so it is considered as a non-covalent functionalization which requires a simpler process and less selectivity towards reagents [20]. Due to the massive π -bonds in graphene quantum dots, the surface functionalization process involving graphene quantum dots is commonly related to π - π stacking.

In addition, forming covalent bonds between quantum dots and functional groups is yet another common technique in functionalizing oxygen-containing quantum dots. Oxygen-containing groups are commonly found in the majority of carbon quantum dots [21]. A covalent bond connected graphene quantum dot was synthesized as a cancer-curing platform. In this platform, the CD44 receptor-targeted hyaluronic acid unit was loaded through covalent bonds between carboxylic groups in hyaluronic acid and amine groups in nitrogen-doped graphene quantum dots. Meanwhile, cancer-curing oxidative drug ferrocene was linked to the hyaluronic acid through its -COOH group and the remaining -NH₂ group in hyaluronic acid. Researchers concluded that covalent bond provides a promising way to load different functional groups to quantum dots [22]. Covalent functionalizing could also be used in functionalizing transition metal quantum dots. In a work reported by Alberio et al., covalent functionalizing with bulk carbon molecules such as C₆₀ achieves improved efficiency in solar cells, providing a possible way to functionalize transition metal quantum dots [23]. This decoration was finished by a series of bond-forming processes demonstrated in Figure 3.

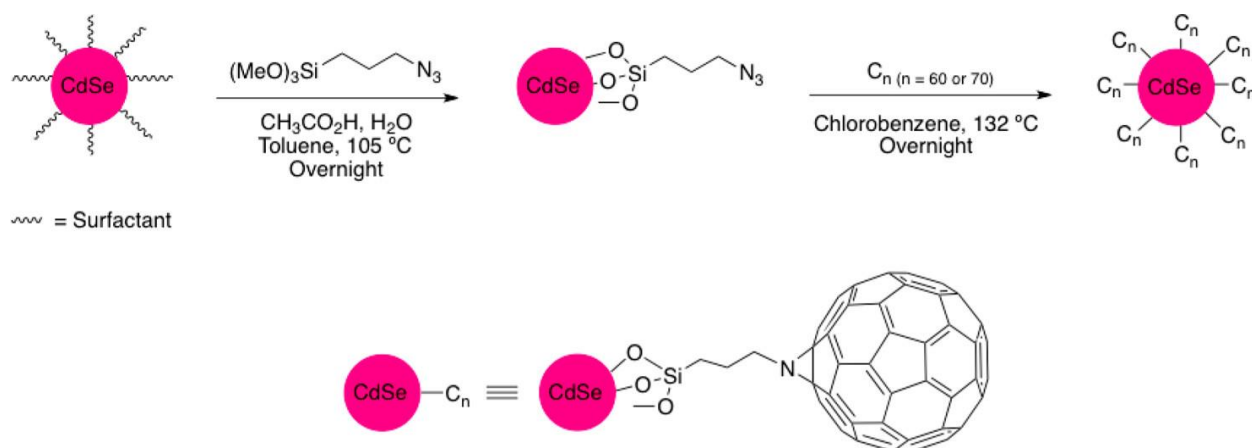


Figure 3. Procedure for linking C70-CdSe [23]

3. Application

After endowing specific functions to quantum dots, they possess unlimited capability with unique properties. Up to now, many attempts of researchers to apply quantum dots to the biological or medical realm have achieved very successful results. Among most of the applications, the used quantum dots are from graphene, which exhibits less toxicity towards organisms compared to some transition metals such as Cd and Pb. In this section, the discussion of quantum dots' application will be delivered from two aspects: biosensing and bioimaging and tumor therapy and drug delivery. As shown in Table 1, which briefly summarizes the different sizes, types, as well as applications of various quantum dots reported in previous research [3, 5, 13, 20, 24-27].

Table 1. Comparison between different quantum dots size

Material	Average size	Size variation	Application	Reference
Graphene	32.20	20-60	Photodynamic Therapy	[3]
Black Phosphorous	1.74	1.51-1.97	Photoacoustic Imaging	[5]
Graphene	2.27	2.02-2.52	Metabolites Measurement	[24]
Carbon	3.35	2.75-4.25	Bioimaging	[25]
Graphene	-	1.5-4.0	Bioimaging	[20]
Graphene	3.7	1.5-6.5	Bioimaging	[26]
MoS ₂	5	-	Bioimaging	[27]

3.1. Biosensing and bioimaging

In environmental appliances, quantum dots bring a promising future in biosensing through their fluorescence ability. With quantum dots, the detection of soluble particles can be achieved with ultra-low limits and ultra-high sensitivity. For example, researchers previously used quantum dots to detect the presence of ClO⁻ in water solution, which had a linear response range from 0.1 to 50 μmol/L. Meanwhile, this biosensor had a sensitivity as high as 0.03 μmol/L. These nitrogen-doped also turn out to be highly stable under various pH conditions, as well as changing ionic strength conditions. Although popular analytical methods such as coulometry, iodometric titration, etc., have a mature workflow and have been applied widely in both industrial and scientific fields, such methods still face problems brought by their cumbersome operations and relatively low sensitivity when compared to quantum dots related analytical methods. In addition to quantum dots, nonmetal heteroatom doping provides the most effective way of promoting specific chemical and optical properties and will ultimately enhance the quantum yield [28]. In monitoring cell activity, quantum dots could also play an important role. Xu et al. reported a novel quantum dot-based on MoS₂ for monitoring the pH in

mitochondrial without interrupting normal cell metabolism. This research used LA-TPP and LA-RhB as indicators that will reflect pH change by monitoring the ratio of red and blue light in the emitted fluorescence light. In addition, the TPP and RhB are attached to the quantum dots by forming Mo-S covalent bonds with the surface defect site of the quantum dots. Test results indicated a specifically targeted probe towards mitochondria and a linear response range from 5.5 to 8.0 [27].

Cancer research is a hot spot in the modern medical field and the research for either detecting or curing cancer has lasted for decades. Due to the rapid spread of cancer cells, early detecting and locating of cancer cells is critical for prevention and therapies. *In-vivo* and *in-vitro* tests have been carried out prior to examine the feasibility and detect possible toxicity during the application of quantum dots. A graphene quantum dots decorated motif-designed peptide nanofibers were synthesized and applied to *in-vivo* locating and imaging of tumor cells. Compared to bare graphene quantum dots, PNF-modified graphene quantum dots showed similar cell internalization levels but a fivefold stronger fluorescence intensity, suggesting more PNF-modified graphene quantum dots were delivered into the cells. Researchers concluded this as a result of stronger interactions between positively charged peptide nanofibers and cell membranes which is negatively charged, facilitating the cellular internalization of modified quantum dots. In addition, test results also revealed that only weak fluorescence was observed in COS-7 cells while a seven times stronger signal was observed in HeLa cells. This result indicated the PNF-modified quantum dots exhibit specific targeting of HeLa cells, suggesting the modification was successful [20]. Apart from organic quantum dots, inorganic quantum dots such as CdTe was also synthesized to detect the presence of zebrafish cells *in-vitro*. This research proposed a mathematical assisted process derivation to design a microreactor that will accomplish ultra-fine size control with minimized size discrepancy. Researchers concluded afterward that the conducted final particle size dimensionless formula is involved with physical variables namely temperature, flow rate, and Cd/Te ratio. As a result, a more intensive fluorescence was observed in the microreactor group. In comparison with the control group which no fluorescence was observed, the result revealed that a monodispersed size of quantum dots will result in a significantly improved cell internalization [29].

Magnetic resonance imaging is a widely applied imaging technique without invasive procedure and ionizing radiation but suffered from a long detection time and low sensitivity [30]. This widely applied technic could also be improved by introducing contrast agents to which quantum dots can be applied. For example, Yang et al. reported a contrast agent involving graphene quantum dots which showed 16 times longer relaxation time than conventional nano contrast agents [31].

3.2. Tumor Therapy and Drug Delivery

The search for an efficient way to prolong the life expectations of a cancer patient has never been stopped. Quantum dots can help to address the problem by becoming multipurpose drug delivery particles. In 2017, a novel theragnostic strategy combining quantum dots as an imaging agent and curcumin as the anti-cancer agent was synthesized. The aim of the research is to evaluate the feasibility of using these bifunctional nanoparticles as both drug delivery platform and bioimaging reagent. Starting from Poly-(D, L-lactic-co-glycolic) acid RG503H (PLGA) nanoparticles, they were first added with curcumin. Later on, the quantum dots were added to PLGA nanoparticles. However, according to the test results, quantum dots modification will result in a decreasing drug release profile compared to original PLGA nanoparticles. But in cell viability tests, the deduction will be insignificant, especially compared to the bare curcumin group. Hence, PLGA modification significantly increases the percentage of released curcumin, while the functionalized bioimaging quantum dots will slightly decrease the effect [32].

In addition to a multipurpose drug delivery platform, quantum dots can also serve as a therapeutic medicine using their unique property. Photodynamic therapy is considered to be a low-invasive therapy in treating cancers that typically only requires laser light of a specific wavelength to excite photosensitizer and generate reactive oxygen species that can erase tumor cells. In the latest work reported by Magaela et al., researchers doped folic acid nitrogen with graphene quantum dots,

successfully synthesized and conjugated with Zn tetra morpholine porphyrin through π - π stacking. Photodynamic therapy activity tests are performed on MCF-7 cancer cells. After being irradiated with 625nm lights for 30 mins. Compared to dark conditions at 40 $\mu\text{g}/\text{mL}$ concentration, the cell viability dropped significantly from nearly 100% to 31%. In addition, the quaternized derivative of zinc tetra morpholine porphyrin, which has a blue shift of 18nm was also studied to investigate its efficacy in antitumor medicine, which also exhibited an excellent anti-cancer effect [3].

The photon-heat conversion ability of quantum dots is regarded as a side effect that needs to be addressed since it lowers the quantum yield, resulting in a dimmed fluorescent light. However, this property can be used as a thermal therapy for temperature-sensitive tumor cells. Graphene quantum dots have exhibited extraordinary absorption rates in the near-infrared range (650-950nm) [4]. A novel type of nitrogen-doped quantum dots has been tested by Sheini et al. for their photothermal conversion efficiency. The photothermal performance was assessed by measuring the temperature change in the solution irradiated by an 808nm laser. After 600s irradiation, sample temperature rose significantly from 20 degrees Celsius to nearly 40 degrees Celsius in 125 $\mu\text{g}/\text{mL}$ group, while the blank control group only rose to 23 degrees Celsius.

Transition metal quantum dots could also play a role in photothermal therapy if no cytotoxicity is presented. A self-assembly platform based on Ag_2S was studied for its chemo-photothermal therapy and guided imaging recently. In this research, the cancer cell membrane was extracted, and modified Ag_2S quantum dots and chemotherapy medicine Te nanorods were captured in it. Induced by H_2O_2 inside the cell, the Te nanorods would turn into TeO_6^- which would lead to the dysfunction of the mitochondrion. In addition, light irradiation would result in fluorescence being turned on to illustrate the presence and location of tumor cells, and light irradiation would also result in a temperature rise, leading to cell death. *In-vivo* tumor treatments afterward suggested the size of the tumor volume is 3.9 folds lower after 808nm light irradiation [33].

4. Conclusions

Due to their unique properties, we expect quantum dots to serve more in bioimaging and biosensing applications. Moreover, after being loaded with a specific drug, it can be a powerful platform that can simultaneously detect and cure possible carcinogenesis *in-situ*. In the coming decades, the use of graphene quantum dots will be the trend, but transition metal quantum dots could still be applied after addressing the toxicity and synthesis cost concerns. Furthermore, more functionalization methods need to be proposed to adapt to the variation of loads. Nevertheless, graphene quantum dots still have several problems that need to be addressed, such as the low quantum yield and unknown metabolism pathway before being applied to actual use. To conclude, there is still plenty of room at the bottom, and with quantum dots boosting the modern medication, a giant leap forward could still be witnessed shortly.

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