Application of Nanotechnology in Medical Science for Photodynamic Therapy

[1]Mihir Narayan Mohanty, [2]Manas Ranjan Senapati
[1]ITER, SOA University, Bhubaneswar, Odisha, India
[2]TAT, Bhubaneswar, Odisha, India

Abstract
Nanotechnology applications in biomedical science consists of drug eluting interfaces for implantable devices, vascular stents, orthopedic implants, dental implants, and cancer therapy. Photodynamic therapy represents an alternative treatment with great potential in some types of cancer and premalignant conditions. In the quest to improve this therapy, potential new non-tetrapyrrole photosensitizers are currently under research. Photodynamic therapy (PDT) is based on the administration of a photosensitizing agent (also known as a photosensitizer, PS), which is further activated by external irradiation with light. This therapy results in a sequence of photochemical and photo-biological processes that trigger irreversible damage to the irradiated tissues. Photodynamic therapy has emerged as an alternative to chemotherapy and radiotherapy for cancer treatment. Nanoparticles have recently been proposed as effective carriers for photosensitizers. Depending on their chemical composition, these can be used for diagnosis and therapy due to the selective accumulation of the photosensitizer in cancer cells. The safety aspects in the applications of nanotechnology to biomedical issues are also examined.

Keywords
Nanotechnology, Medical Application, Cancer Therapy, Photodynamic Therapy, Nanoparticls.

I. Introduction

Nanotechnology is the general term for designing and making anything whose use depends on specific structure at the nanoscale – generally taken as being 100 nanometres (100 millionths of a millimetre or 100 billionths of a metre) or less. A nanometer is one billionth of a meter or three orders of magnitude smaller then a micron, roughly the size scale of a molecule itself. The potential impact of nanotechnology stems directly from the spatial and temporal scales being considered: materials and devices engineered at the nanometer scale imply controlled manipulation of individual constituent molecules and atoms in how they are arranged to form the bulk macroscopic substrate. They may be in the form of particles, tubes, rods or fibres. The nanomaterials that have the same composition as known materials in bulk form may have different physico-chemical properties than the same materials in bulk form, and may behave differently if they enter the body. They may thus pose different potential hazards.

Nanotechnology and nanoengineering stand to produce significant scientific and technological advances in diverse fields including medicine and physiology. It is an interdisciplinary field that holds promise for the development of better diagnostic methods and treatments for different diseases, including cancer. Given the optical, magnetic and structural properties of nanoparticles (NP), their use has been proposed in the development of non-conventional treatments against cancer, such as photodynamic therapy (PDT). Newer and improved methods of cancer detection based on nanoparticles are being developed. They are used as contrast agents, fluorescent materials, molecular research tools and drugs with targeting antibodies. Paramagnetic nanoparticles, quantum dots, nanoshells and nanosomes are few of the nanoparticles used for diagnostic purposes. Drugs with high toxic potential like cancer chemotherapeutic drugs can be given with a better safety profile with the utility of nanotechnology. These can be made to act specifically at the target tissue by active as well as passive means. These nanotechnology-based techniques can be applied widely in the management of different malignant diseases.

Over the last few years, photodynamic therapy (PDT) has emerged as an alternative to chemotherapy and radiotherapy for the treatment of various diseases including cancer. It involves the use of light, photosensitizers (PS) and oxygen. The excitation of photosensitizers (PSs) with light of an appropriate wavelength leads to energy or electron transfer to neighboring oxygen or substrate molecules. Reactive Oxygen Species (ROS) and singlet oxygen (1O2) which are commonly accepted to be the main cytotoxic species are formed and lead to the destruction of cancer cells by both apoptosis and necrosis. The efficacy of PDT depends on the photosensitizer's ability to produce ROS and 1O2, oxygen availability, light dose and photosensitizer concentration in the treated area. [1-4].

PDT is an alternative treatment approach to cancer treatment. Photodynamic therapy (PDT) has been adopted as a minimally invasive approach for the localized treatment of superficial tumors, representing an improvement in the care of cancer patients. Photodynamic therapy (PDT), sometimes called photochemotherapy, is a form of phototherapy involving light and a photosensitizing chemical substance, used in conjunction with molecular oxygen to elicit cell death (phototoxicity). PDT has proven ability to kill microbial cells, including bacteria, fungi and viruses [5]. PDT is popularly used in treating acne. It is used clinically to treat a wide range of medical conditions, including wet age-related macular degeneration, psoriasis, atherosclerosis and has shown some efficacy in anti-viral treatments, including herpes. It also treats malignant cancers [6] including head and neck, lung, bladder and particular skin. The technology has also been tested for treatment of prostate cancer, both in a dog model [7] and in prostate cancer patients [8].

It is recognised as a treatment strategy that is both minimally invasive and minimally toxic. Other light-based and laser therapies such as laser wound healing and rejuvenation, or intense pulsed light hair removal do not require a photosensitizer [9]. Photosensitisers have been employed to sterilise blood plasma and water in order to remove blood-borne viruses and microbes and have been considered for agricultural uses, including herbicides and insecticides. Photodynamic therapy's advantages lessen the need for delicate surgery and lengthy recuperation and minimal formation of scar tissue and disfigurement. A side effect is the associated photosensitisation of skin tissue.

PDT applications involve three components:[2] a photosensitizer, a light source and tissue oxygen. The wavelength of the light

source needs to be appropriate for exciting the photosensitizer to produce radicals and/or reactive oxygen species. These are free radicals (Type I) generated through electron abstraction or transfer from a substrate molecule and highly reactive state of oxygen known as singlet oxygen (Type II).

PDT is a multi-stage process. First a photosensitiser with negligible dark toxicity is administered, either systemically or topically, in the absence of light. When a sufficient amount of photosensitiser appears in diseased tissue, the photosensitiser is activated by exposure to light for a specified period. The light dose supplies sufficient energy to stimulate the photosensitiser, but not enough to damage neighbouring healthy tissue. The reactive oxygen kills the target cells [9].

II. State of Art

The progress of nanotechnology applications have been grown since few years ago. Still many researchers in multidisplenary fields have approached in many ways. Since nanomaterials possessing analogous dimensions to those of functional aggregates organized from biomolecules they are believed to be a promising candidate interface owing to their enhanced interaction with biological entities at the nano scale (Whitesides, 2003). For this reason, nanocrystals with advanced magnetic or optical properties have been actively pursued for potential biomedical applications, including integrated imaging, diagnosis, drug delivery and therapy (Lewin et al., 2000; Hirsch et. al., 2003; Alivisatos, 2004; Kim et. al., 2004; Liao and Hafner, 2005). The development of novel biomedical technologies involving in vivo use of nanoparticles present multidisciplinary attempts to overcome the major chemotherapeutic drawback related to its spatial nonspecificity. For example, in most biomedical and magnetofluidic applications, magnetic nanoparticles of fairly uniform size and Curie temperature above room temperature are required. On the other hand, as the major advantage of nanotubes, the inner surface and outer surface of nanotubes can be modified differently due to their multifunctionalization. While the inner surface was tailored for better encapsulation of proper drugs, the outer surface can be adjusted for targeted accessing. On the other hand, the strong magnetic behavior made maghemite nanotubes easier controlled by a magnetic field, especially compared with hematite nanotubes. Mainly due to their tubular structure and magnetism, magnetic nanotubes are among the most promising candidates of multifunctional nanomaterials for clinical diagnostic and therapeutic applications. The tubular structure of magnetic nanotubes provides an obvious advantage as their distinctive inner and outer surfaces can be differently functionalized, and the magnetic properties of magnetic nanotubes can be used to facilitate and enhance the bio-interactions between the magnetic nanotubes and their biological targets (Son et. al., 2009; Liu et. al., 2009). One application paradigm of magnetic nanotubes is drug and gene delivery (Plank et. al., 2003).

Chemotherapy in cancer treatment is often accompanied by side effects, since intravenously applied cytotoxic drugs do not only accumulate in tumor tissues but distribute within the whole body. Adverse reactions of common chemotherapeutic agents, for instance, comprise vomiting, nausea, cardiotoxicity, and immune suppression. To restrict cytotoxic effects to the tumor region, a more targeted approach would be desirable. Thus, the targeting of active toxic substances to the tumor region or activation of initially inactive substances in the tumor region might be a solution to overcome this problem.

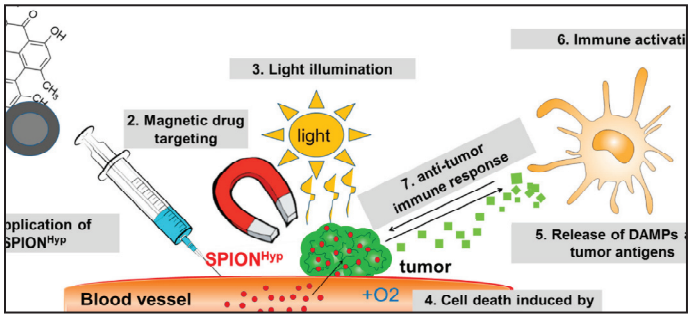

Fig. 1: Combination of Magnetic Drug Targeting (MDT) and Photodynamic Therapy (PDT).

III. Nanotechnology Application Issues in PDT

The phototoxic effect of hypericin can be utilized for Photodynamic Therapy (PDT) of cancer. After intravenous application and systemic distribution of the drug in the patient's body, the tumor site is exposed to light. Subsequently, toxic reactive oxygen species (ROS) are generated, inducing tumor cell death. To prevent unwanted activation of the drug in other regions of the body, patients have to avoid light during and after the treatment cycles, consequently impairing quality of life. Furthermore, nanoparticles might act as photosensitisers directly, which would be beneficial due to their large absorption cross section. A similar approach uses transparent nanoparticles (silica) which are "doped" with photosensitising molecules. These approaches aim to increase the efficiency of PDT by increasing the quantum yield of conversion of light to ROS.

Photodynamic therapy (PDT) is a relatively new method for cancer treatment, where tumour cells are destroyed by light-induced, local production of a reactive oxygen species (ROS), such as singlet oxygen (1O2). The advent of nanosciences opened up new possibilities for PDT, where nanoparticles were used as highly sophisticated, multi-functional medicines. More specifically, nanoparticles were employed as (i) photosensitisers (ii) carriers of photosensitising molecules (iii) light antennas for photosensitising molecules (up- and down-converters) (iv) carriers of multiple functions, for example targeting moieties or magnetic nanoparticles Theoretically, nanoparticles have the potential to improve PDT beyond its current limitations. Nanoparticle surfaces can be modified with different functional moieties such as photosensitisers and/or targeting molecules (for example antibodies against certain types of cancer cells).

The development of nanoparticles-based photosensitizers can overcome most of the shortcomings of classic photosensitizers such as liver accumulation. Polymeric nanoparticles that can be made biodegradable by an appropriate choice of composition and structure. They have the following features.

1. Produced in an optically transparent form. Therefore, light activation and optical probing can readily be accomplished.
2. Polymeric nanoparticles provide three different structural platforms for diagnosis and therapy namely:

- An interior volume in which various probes and therapeutic agents can be encapsulated;
- A surface which can be functionalized to attach targeting groups to carry the nanoparticles to cells or biological sites expressing appropriate receptors. and
- Pores in the nanoparticles, which can be tailored to be of specific sizes to allow selective intake or release of biologically active molecules or to activate therapeutic agents. They can be used for different therapies. Different materials used in this field are summarized below.

A. Silver Nanoparticles

Silver nanoparticles (NPs), or nanosilver (NS), are clusters of silver atoms that range in diameter from 1 to 100 nm and are attracting interest as antibacterial and antimicrobial agents for applications in medicine. Nanosilver (NS), comprising silver nanoparticles, is attracting interest for a range of biomedical applications owing to its potent antibacterial activity. It has recently been demonstrated that NS has useful anti-inflammatory effects and improves wound healing, which could be exploited in developing better dressings for wounds and burns. The key to its broad-acting and potent antibacterial activity is the multifaceted mechanism by which NS acts on microbes. This is utilized in antibacterial coatings on medical devices to reduce nosocomial infection rates. Many new synthesis methods have emerged and are being evaluated for NS production for medical applications. NS toxicity is also critically discussed to reflect on potential concerns before widespread application in the medical field [10-14].

B. Magnetic Nanoparticles

Magnetic nanoparticles are used extensively in the field of biomagnetics for a broad range of applications, such as drug delivery, cell labelling and sorting, magnetic resonance imaging, sensing as well as therapeutic applications such as an AC magnetic field-assisted cancer therapy, i.e. hyperthermia, PDT. Luminescent magnetic particles are also attractive tools for life science applications such as multimodal imaging, analyte monitoring, nanotherapeutics, and combinations thereof. [15-18].

C. Quantum dots

Quantum dots have emerged as an important class of material that offers great promise to a diverse range of applications ranging from energy conversion to biomedicine. Here, we review the potential of using quantum dots and quantum dot conjugates as sensitizers for photodynamic therapy (PDT). The photophysics of singlet oxygen generation in relation to quantum dot-based energy transfer is discussed and the possibility of using quantum dots as photosensitizer in PDT is assessed, including their current limitations to applications in biological systems. The biggest advantage of quantum dots over molecular photosensitizers that comes into perspective is their tunable optical properties and surface chemistries. Recent developments in the preparation and photophysical characterization of quantum dot energy transfer processes are also presented in this review, to provide insights on the future direction of quantum dot-based photosensitization studies from the viewpoint of our ongoing research. Photodynamic therapy is thereby a newer application that lends itself for the exploration of quantum dots as photosensitizers [19–26].

D. Gold Nanoparticles

Among all the metal nanoparticles, gold NPs (AuNPs) are receiving the greatest attention mainly due to a combination of unique properties that lend themselves to multiple applications such as labeling, delivery, heating and sensing. Moreover, due to localized surface plasmon resonances, it has been recently demonstrated that the field enhancement of the incident light around gold nanoparticles could be used to increase the excitation efficacy of the photosensitizer. Gold nanoshells can serve as excellent multi-functional theranostic agents (fluorescence imaging þ NmPDT þ NmPTT) upon single photon NIR light excitation under ultra-low laser doses.Gold nanoparticles (AuNPs) of different size and shape are widely used as photosensitizers for cancer diagnostics and plasmonic photothermal (PPT)/photodynamic (PDT) therapy, as nanocarriers for drug delivery and laser-mediated pathogen killing, even the underlying mechanisms of treatment effects remain poorly understood. There is a need in analyzing and improving the ways to increase accumulation of AuNP in tumors and other crucial steps in interaction of AuNPs with laser light and tissues. In this review, we summarize our recent theoretical, experimental, and pre-clinical results on light activated interaction of AuNPs with tissues and cells [27-34].

E. Silica Nanoparticles

Among the variety of nanoparticles, silica-based nanomaterials have very recently emerged as promising vectors for PDT applications. Silica nanoparticles are indeed chemically inert and the silica matrix porosity is not susceptible to swell or change with a varying pH. A variety of precursors and methods are available for their synthesis allowing flexibility and thus meaning numerous PDT drugs can be encapsulated. Furthermore, particles size, shape, porosity and mono-dispersibility can be easily controlled during their preparation. Moreover silica nanoparticles are especially suitable for PDT since they do not release the photosensitizer but allow O_2 and $1O_2$ to diffuse in and out through the shell of silica nanovehicles, reducing the risk of toxicity and vascular clogging caused by free PSs aggregate into clusters in blood [35-39].

F. ZnO Nanoparticles

Because of its potential of non-toxicity, zinc oxide (ZnO) is also a candidate for the materials applicable for biomedicine. Furthermore, among the PDT agents, ZnO is a material of particular interest due to its unique optical and electronic properties and has been widely used for device applications including transducers, phosphors and variators. Although ZnO nanoparticles have been intensively used in the cosmetic industry for many years, they have only recently been explored as active cancer therapy drugs themselves. ZnO nanomaterials are considered to be relatively biocompatible, with bulk ZnO being recognized as a GRAS (generally recognized as safe) substance by the FDA. ZnO has traditionally been used for photocatalytic oxidation of organic pollutants. For nanoscale ZnO, large numbers of valence band holes and/or a conduction band are available to serve in redox reaction. The holes are powerful oxidants and can split water molecules into H^+ and OH^-. The conduction band electrons are good reducers and react with dissolved oxygen molecules to generate superoxide radical anions (O2-) which in turn react with H^+ to generate HO_2. radicals and others ROS. Based on the photodynamic therapy concept, the photoactivation of ZnO nanoparticles is predicted to lead to greater levels of ROS release [40-44].

G. Carbon Nanoparticles

Single (SWNTs) or multiwalled carbon nanotubes (MWNTs) can be used as delivery agents for PDT photosensitizers. Carbon nanotubes present several advantages. It has been shown that they are internalized by mammalian cells through endocytosis even if other mechanisms can occur, they are excreted from the body rapidly and present no significant cytotoxicity, they can be modified chemically but non covalent associations are also possible. Indeed, fullerene and its derivatives have been extensively studied in the biomedical field. Their biological activities towards various cell types have been reported, and previous results have highlighted their potential uses as photosensitizers in photodynamic therapy of tumor and photoinactivation of bacteria and viruses, antioxidative/cytoprotective reagents and carriers for drug delivery [45-48].

H. TiO_2 Nanoparticles

The application of TiO_2 nanoparticles in life science is attracting more and more attention since the first report of photocatalytic disinfection by Matsunaga et al. in 1985. In recent years, TiO2 nanoparticles were used in the field of phototherapy of malignant cells, and have been viewed as the potential photosensitizing agents for PDT due to their unique phototoxic effect upon the irradiation. In 2010, Tessy Lopez group investigated the possible synergy of zinc phthalocyanines (ZnPc), supported on TiO2 nanoparticles and probed their in vitro photoactivity using visible light, on cancer cells and Leishmania parasites. They studied the photosensitizing effect of ZnPc, nano-TiO2, and ZnPc-TiO2 conjugate, against a panel of tumor and normal mammalian cells and on promastigote forms of Leishmania parasites. As was expected, nano-TiO2 alone under visible light irradiation was not phototoxic for the cells; in contrast, ZnPc treatment at the same condition was photoactive for all the studied cells and parasites. The composite ZnPc-TiO2 was not found to be phototoxic; however, it was active against tumor and nontumor mammalian cells but less than the pure ZnPc PS, which may be due to their lower internalization by the cells as compared to ZnPc. ZnPc-TiO2 was internalized by the cells at a lower level than ZnPc. The localization of ZnPc-TiO2 and ZnPc was observed in mitochondrial molecules. No fluorescence signal was observed in human-derived fibroblasts exposed to ZnPc-TiO2 [49-54].

IV. Proposed Nanomaterials for PDT

Altering the peripheral functionality of porphyrin-type chromophores can affect photodynamic activity. Diamino platinum porphyrins show high anti-tumour activity, demonstrating the combined effect of the cytotoxicity of the platinum complex and the photodynamic activity of the porphyrin species. Positively charged PC derivatives have been investigated. Cationic species are believed to selectively localise in the mitochondria.

Zinc and copper cationic derivatives have been investigated. The positively charged zinc complexed PC is less photodynamically active than its neutral counterpart in vitro against V-79 cells. Water-soluble cationic porphyrins bearing nitrophenyl, aminophenyl, hydroxyphenyl and/or pyridiniumyl functional groups exhibit varying cytotoxicity to cancer cells in vitro, depending on the nature of the metal ion (Mn, Fe, Zn, Ni) and on the number and type of functional groups. The manganese pyridiniumyl derivative has shown the highest photodynamic activity, while the nickel analogue is photoinactive. Another metallo-porphyrin complex, the iron chelate, is more photoactive (towards HIV and simian immunodeficiency virus in MT-4 cells) than the manganese complexes; the zinc derivative is photoinactive.

The hydrophilic sulphonated porphyrins and PCs (AlPorphyrin and AlPC) compounds were tested for photodynamic activity. The disulphonated analogues (with adjacent substituted sulphonated groups) exhibited greater photodynamic activity than their di-(symmetrical), mono-, tri- and tetra-sulphonated counterparts; tumour activity increased with increasing degree of sulphonation.

Photodynamic therapy represents an alternative treatment with great potential in some types of cancer and premalignant conditions. In the quest to improve this therapy, potential new nontetrapyrrole photosensitizers are currently under research. Combinations of cancer therapy modalities are attracting attention to improve the outcome of treatment, since single modality has not always been sufficiently effective. It offers a promising platform for early cancer detection and treatment and has applications in both in intracellular molecular imaging, molecular profiling, highly sensitive solution assays and in magnetic nanoparticles for magnetic resonance imaging (MRI), Qdots for optical imaging, Raman active nanoparticles for Raman spectroscopy etc..

V. FeCo nanoparticles

FeCo nanoparticles were synthesized by a coprecipitation method under Ar atmosphere from their chloride hydrate precursors. The FeCo nanopowders were dried in Ar gas, and were dispersed in 2-propanol solvent with 10 -2 M and sonicated for 1 hour followed by addition of TEOS and 25% ammonia solution of volume ration 3:1. The mixture was sonicated for 1 h to coat the SiO 2 onto the surface of FeCo nanoparticles. The solution containing suspended FeCo-SiO 2 nanoparticles was decanted and purified using methanol several times in order to remove unreacted Fe and organic materials from the surface. The coated nanopowders were naturally dried in air. The FeCo nanoparticles are spherical in shape with about 20 nm in size and well-dispersed. The size distribution is very uniform, indicating the high-quality of the nanoparticles. It is noted that the magnetization saturation moment increases when FeCo nanoparticles are synthesized at lower temperature (such as at ice temperature) due to controlled nucleation compared to as-grown nanoparticles. The magnetization of silica coated FeCo decreases, mainly due to the reduction in the demagnetization factor among nanoparticles through coupling, which is generally induced through direct exchange coupling and dipolar interaction. The magnetization reduction in coated FeCo is not significant, illustrating a strong dipolar exchange coupling. The effect of FeCo and silica-coated FeCo nanoparticles on rat LE cells suggests that they induce ROS in a dose dependent manner.

An extensive study of metallated texaphyrins focused on the lanthanide (III) metal ions, Y, In, Lu, Cd, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm and Yb found that when diamagnetic Lu (III) was complexed to texaphyrin, an effective photosensitiser (Lutex) was generated. However, using the paramagnetic Gd (III) ion for the Lu metal, exhibited no photodynamic activity. The study found a correlation between the excited-singlet and triplet state lifetimes and the rate of ISC of the diamagnetic texaphyrin complexes, Y(III), In (III) and Lu (III) and the atomic number of the cation.

VI. Cobalt

Cobalt is a Block D, Period 4 element. It is also an essential human nutrient as part of vitamin B12.The morphology of cobalt nanoparticles is spherical, and their appearance is a grey or black powder. Cobalt nanoparticles possess magnetic properties, which leads to applications in imaging, sensors, and many other areas. The following are the areas of application of cobalt nanoparticles:

1. Medical sensors
2. Biomedicine as a contrast enhancement agent for magnetic resonance imaging (MRI)
3. Site-specific drug delivery agents for cancer therapies
4. Coatings, plastics, nanofibers, nanowires, textiles, and high-performance magnetic recording materials
5. As a magnetic fluid - made of iron, cobalt, nickel and its alloy nanoparticles
6. Microwave-absorption material

More research is going on to explore their electrical, magnetic, optical, imaging, dielectric, catalytic, biomedical and bioscience properties for more applications.

- In the field of PDT, synthesis and characterization of molybdenum chlorophyllin (Mo- Chl) compounds associated

in a complex with magnetic nanoparticles (citrate-coated cobalt ferrite), the latter prepared as a biocompatible magnetic fluid (MF). This complex material can be developed for application as a synergic drug for cancer treatment using PDT and hyperthermia (HPT).

- To develop new multifunctional magnetic nanoparticles (MNPs) with good magnetic properties, biocompatibility, and anticancer activities by photodynamic therapy (PDT), synthesis of multifunctional cobalt ferrite (CoFe2O4) nanoparticles (CoFe2O4-HPs-FAs) by coating with hematoporphyrin (HP) is an alternate solution. By conjugating with folic acid (FA) for targeting cancer cells it can work dramatically.
- The characterization of water-soluble and biocompatible photosensitizer (PS)-conjugated magnetic nanoparticles composed of a cobalt ferrite (CoFe2O4) magnetic core coated with a biocompatible hematoporphyrin (HP) shell has been reported. The photo-functional cobalt ferrite magnetic nanoparticles (CoFe2O4@HP) were uniform in size, stable against PS leaching, and highly efficient in the photo-generation of cytotoxic singlet oxygen under visible light. With the CoFe2O4@HP, we acquired in vitro MR images of cancer cells (PC-3) and confirmed good biocompatibility of the CoFe2O4@HP in both normal and cancer cells. The potential of the CoFe2O4@HP as an agent for photodynamic therapy (PDT) applications.
- Synthesis of folic acid-(FA) and hematoporphyrin (HP)-conjugated multifunctional magnetic nanoparticles (CoFe2O4-HPs-FAs), which were characterized as effective anticancer reagents for PDT, and evaluated the influence of incubation time and light exposure time on the photodynamic anticancer activities of CoFe2O4-HPs-FAs in prostate cancer cells (PC-3 cells).

VII. Conclusion

Quantum Dots (including wide band-gap QDs like ZnO, TiO2 and similar types of nanoparticles) are capable of producing singlet oxygen and ROS, however, the overall quantum yields were poor and there is no prospect that they can be increased in the foreseeable future. Similarly, up-converter/photosensitiser nanosystems work in principal, but their very low quantum yield of singlet oxygen production makes them unlikely candidates for clinical applications. The main drawback here is the intrinsic toxicity of the cadmiumbased QDs. This problem might be solved in the future by using less toxic base materials such as InP or CuInS2. All "successful" approaches relied on successful photosensitisers and the nanoparticles were primarily means to increase their efficiency. One of the promises of nanoparticle-based PDT systems that can be found mentioned in almost any publication in the area is the potential to equip the nanoparticles with additional targeting moieties. However, this option was only studied very rarely. A nanoparticle drug-delivery system that combines two complementary types of anticancer treatment could improve outcomes for patients with pancreatic cancer and other highly treatment-resistant tumors while decreasing toxicity.

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