OPEN ACCESS

Nano Biomed Eng

ISSN 2150-5578 http://nanobe.org

Review

Nanoparticles in Photodynamic Therapy

Thomas Nann*
Ian Wark Research Institute, University of South Australia, Adelaide, SA 5095, Australia
* Corresponding author: thomas.nann@unisa.edu.au

Abstract

This article contains a critical review on the application of different types of nanoparticles in photodynamic therapy (PDT). Passive carrier particles like photosensitiser-"doped" silica nanoparticles are discussed as well as luminescent and noble metal nanocrystals in conjunction with molecular photosensitisers. Recent achievements are highlighted and the fundamental limitations of these systems are discussed. The article is concluded by an outlook on potential improvements and the possibility for practical applications of nanoparticle-based PDT.

Keywords: Photodynamic Therapy, Oncology, Photosensitisers, Nanoparticles, Quantum Dots

Citation: Thomas Nann. Nanoparticles in Photodynamic Therapy. Nano Biomed. Eng. 2011, 3(2), 137-143. DOI: 10.5101/nbe.v3i2.p137-143

A chemist by training, Thomas Nann's career began at the University of Freiburg, Germany, where he completed his PhD in electrochemistry. He then commenced his independent work on the synthesis, characterisation and functionalisation of nanomaterials at Freiburg, where he was awarded his habilitation in 2004. In 2006 he accepted an appointment to the Chair of Nanosciences at the University of East Anglia (UEA), UK which he held for almost four years. Since June 2010, Thomas has been a Research Professor at the Ian Wark Research Institute at UniSA. In 2011 he was awarded one of the prestigious ARC Future Fellowships.

Thomas' current research interests are focussed on the synthesis and characterisation of functional nanomaterials and their application in the areas of energy and health. He has a track record of fundamental research on these topics which is documented by numerous publications in high ranking journals. Furthermore, he has successfully concluded many industrial collaborative projects, holds several patents and is a member on editorial boards of scientific journals.

Introduction

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 ($^1O_2$) [1-3]. The ROS is generated by a photosensitiser, which has to be brought in close proximity to the tumour cells and is usually administered systemically. The major advantages of PDT are that it is relatively inexpensive, non-invasive, can be applied locally and cumulative toxicity is not observed. However, limitations of the method are primarily connected with the systemic distribution of the photosensitiser and the local irradiation of tissue. Advanced disseminated diseases cannot be cured, because irradiation of the whole body with appropriate doses is impossible. Moreover, irradiation of "deep" tissue proves to be difficult with visible light since such wavelengths do not penetrate sufficiently into tissue.

The advent of nanosciences opened up new possibilities for PDT [4, 5], where nanoparticles were used as highly sophisticated, multi-functional medicines. More specifically, nanoparticles were employed as

- photosensitisers
- carriers of photosensitising molecules
- light antennas for photosensitising molecules (up- and down-converters)
- 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). Thus, although administered systemically, the nanoparticles are expected to concentrate at the target site. This would have several advantages: first, tissue does not necessarily have to be irradiated locally – viz. the patients would be able to expose themselves to sunlight. Second, the concentration of photosensitisers at the site of interest would be increased, which would lead to a higher concentration or ROS where required.

Furthermore, nanoparticles might act as photosensitisers directly, which would be beneficial due to their large absorption cross section [6, 7]. 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.

Finally, nanoparticles have been used as luminescence up- and down-converters, whereas their excited energy has been transferred to surface-bound photosensitisers. In case of down-converting nanoparticles, the motivation was primarily to exploit the large absorption cross-section of nanoparticles in conjunction with a classical photosensitiser. In case of up-converting nanoparticles, the prime motivation was to use infra-red light for irradiation, which penetrates deeper into tissue than ultraviolet or visible light. So far, several systems that realised combinations of these principles have been published.

This review article is targeted at readers with a medical background and readers from neighbouring areas of research who want to obtain an overview of current developments in PDT. We will discuss the current state of the art critically by focussing on the four main approaches to nanoparticle supported PDT mentioned above. Eventually, we will discuss the research results and highlight promising approaches.

Photosensitisers

PDT is based on the light-induced, local generation of a toxic species, which destroys the surrounding tissue, e.g. tumour cells. In the simplest case, this toxic species is singlet oxygen – the diamagnetic form of molecular oxygen. Unlike oxygen in its triplet ground state, singlet oxygen is highly reactive and short-lived. The energy of the singlet state lies approximately 7882 cm^{-1}, 1268 nm or 0.98 eV above the ground state [8]. Oxygen can be excited into its first singlet state (the $^1\Delta_g$ state) by direct absorption of radiation of appropriate energy (this effect plays probably a key role in the photochemical air pollution). However, the generation of $^1O_2$ by transfer of energy from an excited dye molecule (photosensitiser) is more effective (in the context of PDT, this is called a type II mechanism).

An efficient photosensitiser has to meet several pre-requisites: first, the excited state of the photosensitiser has to have an energy of more than 0.98 eV, otherwise it won't be able to transfer an oxygen molecule into its excited state (excited states above 2.23 eV are detrimental as well, because of insufficient overlap of the wave functions (Franck-Condon principle) [9]). Second, the excited states of the photosensitisers should have a relatively long lifetime, to allow the photosensitiser molecules to collide with oxygen molecules and transfer their excited energy. Even though there are exceptions of these rules of thumb, the majority of practically relevant photosensitisers comply with these conditions.

Molecular photosensitisers

The vast majority of nanoparticle based endeavours to PDT use "classical" molecular photosensitisers. This approach is favourable, because the ability of a substance to generate singlet oxygen is not sufficient to make it a successful therapeutic agent. In practise, aspects such as hypoxia (inadequate oxygen supply of cells and tissues), hydrophobicity and others have to be taken into account [10]. Even though many molecular photosensitisers such as rose bengal, rhodamines, anthraquinones and others have been reported to generate singlet oxygen by a type II mechanism, the vast majority of commercial PDT products is based on porphyrin, chlorin and phthalocyanine motifs (cf. Fig. 1) [11].

An interesting exception is 5-aminolevulinic acid (ALA), which is a precursor in the heme biosynthetic

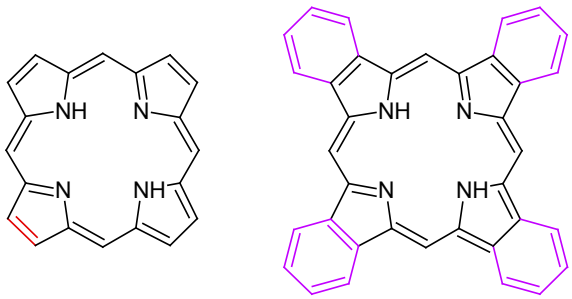

Fig. 1 Left basic structure of porphyrins (red double bond) and chlorins. Right: basic structure of phthalocyanines.

pathway [12]. On administration, ALA is fed into the protoporphyrin IX biosynthesis, which is a potent natural photosensitiser. To best of our knowledge, nanoparticle-supported local administration of ALA has not been realised yet.

Direct photosensitisation by nanoparticles

Although several types of nanoparticles have been discussed as potential candidates for PDTphotosensitising, only semiconductor nanocrystals (or Quantum Dots, QDs) did demonstrably generate singlet oxygen [13]. QDs have attracted an extraordinary amount of attention during the past decade, because they are a unique nanomaterial with size-tuneable optical properties: the luminescence of QDs shifts to the blue with decreasing nanocrystal size as depicted in Fig. 2. Furthermore, QDs can be manufactured with a relatively narrow luminescence line-width and excited broadly by wavelengths below their

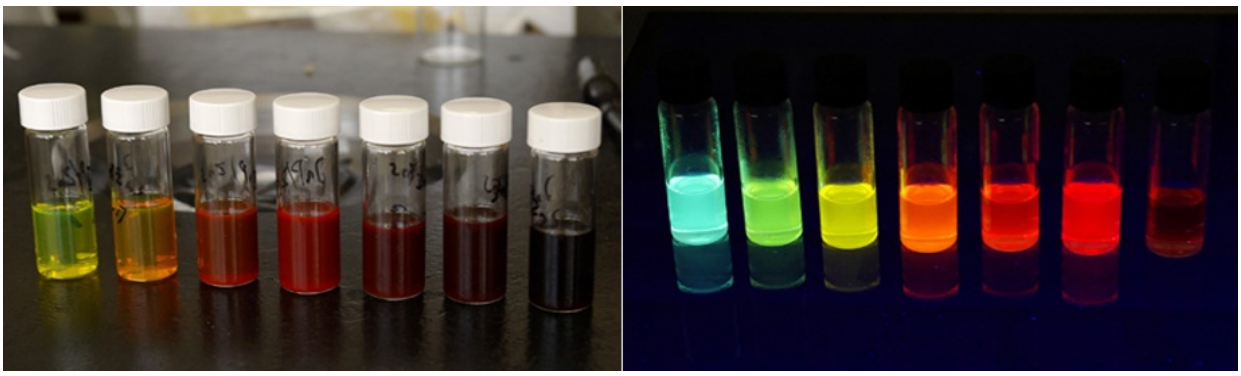

Fig. 2 Differently sized InP Quantum Dots. Left: photographic image; right: luminescence [17] – Reproduced by permission of The Royal Society of Chemistry.

first excited state. These optical properties make them interesting luminophores for bioimaging and other bio/medical applications [14]. The detrimental effect of the highly toxic cadmium [15] – which is a component of the widely used CdSe QDs – might be avoided by using alternative materials such as InP [16-18].

The direct generation of singlet oxygen by CdSe QDs has been first studied by Burda et al. in 2003 [13]. The authors found that the quantum yield of singlet oxygen production by CdSe QDs was approximately 5%. The first excited state of these QDs is a triplet state [19] and should be well suited for the photosensitisation of oxygen. We speculate that the low quantum efficiency observed is primarily due to a low Franck-Condon factor [20]. Later, Chen et al. observed a quantum yield of about 1% for the direct generation of singlet oxygen by CdTe QDs [21]. The same group published an article in 2010, where the same type of QDs was used for PDT by generation of another reactive oxygen species; by a so called type I mechanism [22]. Quantum yields of the ROS generation have not been measured.

It has to be noted that some wide band-gap semicoductor QDs such as ZnO [23] and TiO_2 [24, 25] have been tested as direct photosensitisers too, however, no systematic studies as to the quantum yields and nature of the ROS have been performed yet. A principal limitation of wide band-gap QDs is that they have to be excited with UV light, which does not penetrate deep into tissue and may cause radiation damage.

It is reasonable to conclude that QDs in itself are no match for molecular photosensitisers. The quantum efficiencies for singlet oxygen generation measured so far are far below figures interesting for clinical applications. However, the fact that QDs have a very high light absorption cross section makes them still interesting as light antennas for molecular photosensitisers [6, 7] – if one ignores the possibility that the patients might suffer from a subsequent heavy-metal poisoning.

Nanoparticular systems for PDT

Having established that nanoparticles in itself are not suitable for PDT, it has to be noted that they have a potential to enhance the performance of molecular photosensitisers. This principle has been tested with various types of nanoparticles, including passive carriers, noble metals, Quantum Dots, luminescence up-converters and others. Some nanoparticle systems have been rendered multi-functional by attaching targeting moieties (e.g. carbon hydrates) to their surfaces.

Passive nanoparticular carriers

Perhaps the most straightforward realisation of a nanosystem for PDT is to "dope" mesoporous (silica) nanoparticles with molecular photosensitisers. First systems of this type have been synthesised and tested by Kopelman et al. in 2003 [26] and recently reviewed by Durand et al. [27]. The delivery of photosensitisers by mesoporous silica nanoparticles has several advantages: first, basically any type of photosensitiser can be used as long as it can be embedded in a silica matrix. Second, if delivered locally, the concentration of photosensitiser can be increased, and third, the silica surface and particle body offer the possibility for further functionalisation. A wealth of photosensitising molecules has been embedded into silica nanoparticles, and some researchers were able to demonstrate an increased PDT efficacy compared to free photosensitisers [28, 29] (see Durand's review for a comprehensive list of articles on this nanosystem [27]).

The administration of drugs that are embedded in biodegradable polymer nanoparticles, is a rapidly emerging field. This variation of drug delivery is based on the principle that the drug is released as the polymer particles degrade. By far the most popular polymer for this purpose is poly(lactic-co-glycolic acid) (PLGA) [39]. This method falls – strictly speaking – more under the remit of general drug delivery than nano-sciences, because the nanoparticles serve the sole function of transporting the photosensitiser molecules to their destination. Therefore, we will not go into further detail here.

Multi-functional nanoparticular carriers

Even though many authors mention the potential possibility of attaching suitable targeting molecules against tumour cells onto the silica surfaces, there is only one publication where this has actually been done: Brevet

et al. have attached mannose to the surface of their silica nanoparticles [30]. Thus, the authors were able to demonstrate an improved PDT efficacy in vitro. An interesting, similar approach was realised by Cui et al. who "loaded" graphene oxide sheets (strictly speaking not a nanoparticular system) with photosensitisers and folic acid (a targeting moiety) [31]. The authors were able to demonstrate cellular uptake and photocytotoxcity of their system.

Besides nanoparticles with the ability to recognise tumour cells, there were several efforts being undertaken to create multi-functional PDT nanoparticles. The most popular one has been to co-embed magnetic nanoparticles into the silica matrix [32-35]. This allows for the simultaneous imaging of the tissue by magnetic resonance imaging (MRI) and/or magnetic direction of the particles. Similarly, magnetic nanoparticles were co-embedded into chitosan particles [36], or photosensitisers were direcly grafted onto magnetic nanoparticles [37]. Other possibilities for multi-functionality include the derivatisation with luminescent moieties [38], "exotic" photosensitisers such as C60 [39], and the simultaneous sensing of oxygen [40-41].

Down-converting nanoparticle/photosensitiser systems

Luminescence up- and down-conversion constitutes the process of converting incident light to shorter, longer wavelengths respectively. In this sense, every fluorescent dye is a down-converter, because it emits light of wavelengths longer than its excitation wavelength. This process may be exploited for PDT, when molecular photosensitisers are excited by up- or down-converters with a broad excitation characteristic (light antennas) or favourable wavelength (for example infra-red to visible up-conversion).

Above, we have discussed the possibility that Quantum Dots might directly act as photosensitisers. Even though it was found that they are not suitable for this purpose, they might be useful to enhance the efficiency of molecular dyes. The underlying idea is that QDs absorb light, and then transfer the energy to nearby molecular photosensitisers by means of Förster Resonance Energy Transfer. Fig. 3 shows a simplified scheme of luminescence down-conversion. The expected advantage is based on the large absorption cross-section, broad absorption characteristics (QDs absorb light of wavelength smaller than their band gap) and large particle surface, which allows to attach many photosensitiser molecules. Burda et al. have published the first example, where molecular photosensitisers were coupled onto QDs [13, 42]. These authors did not publish quantum yields for the generation of $^1O_2$ with their system, but established the principal feasibility.

In the following years, a whole series of articles has been published, were different photosensitisers were coupled onto (mostly cadmium based) QDs. Selke et al. reported an overall quantum yield of 43% at 355 nm for

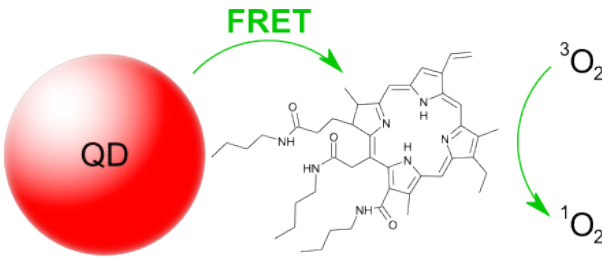

Fig. 3 Principle of luminescence down-conversion using a QD and a chlorin e6 based photosensitiser.

the generation of singlet oxygen with a meso-tetra(4-sulfonatophenyl)porphine dihydrochloride (TSPP)/QD system [43]. Several variations of this theme have been published, using chlorin e6 [44], toluidine blue O (TBO) [45], phthalocyanines [21, 46], methylene blue [47] and protophorphyrin IX [48]. Most of these authors did not publish any quantum yields for the singlet oxygen production, however, Nyokong et al.'s results indicate that these quantum yields are in the same order of magnitude like those of the photosensitisers, which were increased in the presence of QDs [46].

The use of cadmium based QDs for PDT is not acceptable, due to the toxicity of cadmium. Although, cadmium chalcogenide QDs may be replaced by less toxic alternatives (for example indium phosphide [16, 17]), it is questionable whether a small increase in singlet oxygen quantum yield compensates for the potential risks of QDs in general (for example nanotoxicity).

Up-converting nanoparticle/photosensitiser systems

Up-converting phosphors emit light of a wavelength shorter than their excitation. Infra-red (IR) to visible up-converters are the most common systems. The potential advantages of up-converting nanoparticles for PDT are obvious: infra-red light penetrates deeper into tissue than visible light. This would enable PDT in "deep" tissue. A side-effect would be that no natural dyes were excited and therefore less radiation damage was expected. The main disadvantage of up-converting nanoparticles is that their luminescence quantum yield is usually well below 1% [49] (to best of our knowledge, there are no measured figures published for nanoparticles yet). That means that if the same principles apply as observed with down-converters, the overall quantum yields for singlet oxygen production are expected to be very low.

The first article where up-converting nanoparticles were combined with a photosensitising molecule (merocyanine 540 in this case), was published in 2007 by Zhang et al. [50]. The authors were able to demonstrate that a ROS was produced on irradiation of the nanoparticles with IR light, which was toxic to cells. To date, there are only two other publications on up-converting nanoparticle based PDT therapeutics: the first one published by Chatterjee et al. in 2008 [51], and the second one by Zhang et al. in

2009 [52]. Both groups used zinc phthalocyanine (ZnPc) as photosensitiser and showed that their systems did produce a ROS and were capable of causing cell death on irradiation. Quantitative measurements of singlet oxygen production or individual quantum yields have not been measured yet.

Other nanoparticles systems

By far the the two most studied nanoparticle-based PDT systems are photosensitiser-"doped" silica nanoparticles and QD-based down-converting approaches. However, some more "exotic" experiments have been undertaken, such as the direct generation of a ROS by ZnO nanocrystals (which was successful in principal, however the use of ultraviolet (UV) irradiation limits the applicability of the method intrinsically as mentioned above) [23]. Another interesting, but rather adventurous approach tries to combine radiation cancer therapy with PDT by using nanoparticles that are capable of scintillation luminescence [53]. The authors claim to have shown the principal feasibility of their idea.

Several authors coupled molecular photosensitisers onto gold nanoparticles, as pioneered by Russell et al. in 2002 [54]. A definite increase in singlet oxygen quantum yield was observed, which can probably be attributed to an effect similar to metal enhanced fluorescence [55]. Again, different photosensitisers such as TBO [56], porphyrins [57], chlorins [58] and others have been tested. An attractive feature of this approach is that gold nanoparticles are non-toxic and already used in therapy. Therefore, it can be expected that clinical approval and eventually application of these therapeutics are much easier to be achieved as with more unconventional systems.

Table 1 shows an overview of the nanoparticle based PDT systems which were discussed in this review (the list is not comprehensive, but highlights the most important contributions).

Table 1. Nanoparticles for PDT. WARNING: This table is not comprehensive!

Type	Function of NP	Photosensitiser	Reference(s)
Silica	Passive carrier	m-THPC	[26]
		Pc4	[28]
		HPPH	[29]
		C60 + various	[39]
	Carrier and oxygen sensing	HPPH	[40]
	Carrier and targeting molecule	Porphyrin	[30]
	Carrier and luminescent	HP	[38]
Silica + Fe_3O_4	Carrier and magnetic	ZnPc	[32]
		PHPP	[33]
		Ir complex	[34]
	Carrier, magnetic, luminescent	MB	[35]
Chitosan + Fe_3O_4	Carrier and magnetic	PHPP	[36]
Fe_3O_4	Magnetic carrier	Chlorin e6	[37]
Quantum Dots	Photosensitiser	QDs	[13,42]
	Generates ROS	QDs	[22]
	FRET donor for photosensitiser	phthalocyanines	[21,46]
		TSPP	[43]
		Chlorin e6	[44]
		TBO	[45]
		MB	[47]
		PpIX	[48]
Up-converters	FRET donor for photosensitiser	M-540	[50]
		ZnPc	[51,52]
ZnO	Photosensitiser	ZnO	[23]
Scintillators, QDs	FRET donor for photosensitiser	TOAP	[53]
Au	Metal enhanced fluorescence?	ZnHMPc	[54]
		TBO	[56]
		porphyrins	[57]
		Sn chlorin e6	[58]

Summary and perspective

At the end of this review article, we have to ask whether nanoparticles in PDT live up to their promises. From what was discussed above it is clear that there is no general answer to this question. It has been shown that Quantum Dots (including wide band-gap QDs like ZnO, TiO_2 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. Quantum Dot/photosensitiser conjugates showed very promising results. The main drawback here is the intrinsic toxicity of the cadmium-based QDs. This problem might be solved in the future by using less toxic base materials such as InP or $CuInS_2$. Finally, the two most promising approaches were

photosensitiser-doped silica nanoparticles and gold nanoparticle/photosensitiser conjugates. Both systems showed very promising results and the underlying nanoparticles have already clinical approval for other applications. A secondary conclusion of the published work is that molecular photosensitisers cannot be replaced by nanoparticular systems. 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. Similarly, an approach that combines the proven concept of ALA therapy with a nanoparticle system has not been studied yet. We anticipate that the future direction in this research area will concentrate on the most promising nano-systems and improve them by adding multi-functionality (e.g. targeted drug delivery).

Abbreviations

ALA	5-aminolevulinic acid
FRET	Förster resonance energy transfer
HP	Hematoporphyrin
HPPH	2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide
IR	infra-red
M-540	Merocyanine 540
m-THPC	Meta-tetra(hydroxyphenyl)-chlorin
MB	Methylene blue
1O2	Singlet oxygen
Pc	Phthalocyanine
Pc4	Silicon phthalocyanine 4
PDT	Photodynamic therapy
PHPP	2,7,12,18-Tetramethyl-3,8-di-(-1propoxyethy 1)(-13,17-bis-(3-hydroxypropyl)porphyrin
PLGA	Poly (lactic-co-glycolic acid)
PpIX	protoporphyrin IX
QDs	Quantum Dots
ROS	Reactive oxygen species
TBO	toluidine blue O
TOAP	tetrakis (o-aminophenyl) porphyrin
TSPP	meso-tetra (4-sulfonatophenyl) porphine dihydrochloride
ZnHMPc	1,4,8,11,15,18-Hexahexyl-22-methyl-25-(11-mercaptoundecyl) phthalocyaninato zinc

References

1. Brown SB, Brown EA, Walker I. The present and future role of photodynamic therapy in cancer treatment. *The Lancet Oncology.* 2004; 5(8):497-508. doi:10.1016/S1470-2045(04)01529-3.
2. Sharman WM, Allen CM, van Lier JE. Photodynamic therapeutics: basic principles and clinical applications. *Drug Discovery Today.* 1999; 4(11):507-517. doi:10.1016/S1359-6446(99)01412-9.
3. Dougherty H, Dougherty H, Gomer CJ, Jori G, Kessel D, Korbelik M, et al. Photodynamic Therapy. *J. Natl. Cancer Inst.* 1998; 90(12):889-905. doi:10.1093/jnci/90.12.889.
4. Liu C. Research and Development of Nanopharmaceuticals in China. *Nano Biomed. Eng.* 2009; 1(1):1-12. doi:10.5101/nbe.v1i1.p1-12.
5. Zhang Y. Relations between Size and Function of Substance Particles. *Nano Biomed. Eng.* 2011; 3(1):1-16. doi:10.5101/nbe.v3i1.p1-16.
6. Leatherdale CA, Woo W-K, Mikulec FV, Bawendi MG. On the Absorption Cross Section of CdSe Nanocrystal Quantum Dots. *J. Phys. Chem. B.* 2002; 106(31):7619-7622. doi:10.1021/jp025698c.
7. Osborne SW, Blood P, Smowton PM, Xin YC, Stintz A, Huffaker D, et al. Optical absorption cross section of quantum dots. *J. Phys.: Condens.Matter.* 2004; 16(35):S3749. doi:10.1088/0953-8984/16//35/016.
8. Schweitzer C, Schmidt R. Physical Mechanisms of Generation and Deactivation of Singlet Oxygen. *Chem.Rev.* 2003; 103(5):1685-1758. doi:10.1021/cr010371d.
9. Ochsner M. Photophysical and photobiological processes in the photodynamic therapy of tumours. *J. Photochem. Photobiol. B: Biol.* 1997; 39(1):1-18. doi:10.1016/S1011-1344(96)07428-3.
10. Allison RR, Sibata CH. Oncologic photodynamic therapy photosensitizers: A clinical review. Photodiagn. *Photodyn. Ther.* 2010; 7(2):61-75. doi:10.1016/j.pdpdt.2010.02.001.
11. Wainwright M. Photodynamic Therapy: The Development of New Photosensitisers. *Anti-Cancer Agents in Medicinal Chemistry.* 2008; 8(12):280-291. doi:10.2174/187152008783961888.
12. Peng Q, Warloe T, Berg K, Moan J, Kongshaug M, Giercksky K-E, et al. 5-Aminolevulinic acid-based photodynamic therapy. *Cancer.* 1997; 79(12):2282-2308. doi:10.1002/(SICI)1097-0142(19970615)79:12<2282::AID-CNCR2>3.0.CO;2-O.
13. Samia ACS, Chen X, Burda C. Semiconductor Quantum Dots for Photodynamic Therapy. *J. Am. Chem. Soc.* 2003; 125(51):15736-15737. doi:10.1021/ja0386905.
14. Rosenthal SJ, Chang JC, Kovtun O, McBride JR, Tomlinson ID. Biocompatible Quantum Dots for Biological Applications. *Chemistry & Biology.* 2011; 18(1):10-24. doi:10.1016/j.chembiol.2010.11.013.
15. Matović V, Buha A, Bulat Z, Đukić-Ćosić D. Cadmium Toxicity Focus on Oxidative Stress Induction and Interactions with Zinc and Magnesium. *Archives of Industrial Hygiene and Toxicology.* 2011; 62(1):65-76. doi:10.2478/10004-1254-62-2011-2075.
16. Xu S, Kumar S, Nann T. Rapid Synthesis of High-Quality InP Nanocrystals. *J. Am. Chem. Soc.* 2006; 128(4):1054-1055. doi:10.1021/ja057676k.
17 .Xu S, Ziegler J, Nann T. Rapid synthesis of highly luminescent InP and InP/ZnS nanocrystals. *J. Mater. Chem.* 2008; 18(23):2653-2656. doi:10.1039/B803263G.
18. Xu S, Klama F, Ueckermann H, Hoogewerff J, Clayden N, Nann T. Optical and Surface Characterisation of Capping Ligands in the Preparation of InP/ZnS Quantum Dots. *Sci. Adv.Mater.* 2009; 1(2):125-137. doi:10.1166/sam.2009.1035.
19. Nirmal M, Norris DJ, Kuno M, Bawendi MG, Efros AL, Rosen M. Observation of the "Dark Exciton" in CdSe Quantum Dots. *Phys. Rev. Lett.* 1995; 75(20):3728. doi:10.1103/PhysRevLett.75.3728.
20. Bawendi MG, Carroll PJ, Wilson WL, Brus LE.Luminescence properties of CdSe quantum crystallites:Resonance between interior and surface localized states. *J. Chem. Phys.* 1992; 96(2):946-954. doi:10.1063/1.462114.
21. Ma J, Chen J-Y, Idowu M, Nyokong T. Generation of Singlet Oxygen via the Composites of Water-Soluble Thiol-Capped CdTe Quantum Dots-Sulfonated Aluminum Phthalocyanines. *J. Phys. Chem. B.* 2008; 112(15):4465-4469. doi:10.1021/jp711537j.
22.Chen J-Y, Lee Y-M, Zhao D, Mak N-K, Wong RN-S, Chan W-H, et al. Quantum Dot-mediated Photoproduction of Reactive Oxygen Species for Cancer Cell Annihilation. *Photophys. Photobiol.* 2010; 86(2):431-437. doi:10.1111/j.1751-1097.2009.00652.x.
23. Li J, Guo D, Wang X, Wang H, Jiang H, Chen B. The Photodynamic Effect of Different Size ZnO Nanoparticles on Cancer Cell Proliferation In Vitro. *Nanoscale Research Letters.* 2010; 5(6):1063-1071. doi:10.1007/s11671-010-9603-4.
24. Cai R, Kubota Y, Shuin T, Sakai H, Hashimoto K,Fujishima A. Induction of Cytotoxicity by Photoexcited TiO_2 Particles. *Cancer Research.* 1992; 52(8):2346 -2348.
25. Yamaguchi S, Kobayashi H, Narita T, Kanehira K, Sonezaki S, Kubota Y, et al. Novel Photodynamic Therapy Using Water-dispersed TiO_2–Polyethylene Glycol Compound: Evaluation of Antitumor Effect on Glioma Cells and Spheroids In Vitro.*Photo-*

chem. Photobiol. 2010; 86(4):964-971.doi:10.1111/j.1751-1097.2010.00742.x.
26. Yan F, Kopelman R. The Embedding of Meta-tetra(Hydroxyphenyl)-Chlorin into Silica Nanoparticle Platforms for Photodynamic Therapy and Their Singlet Oxygen Production and pH-dependent Optical Properties. *Photochem. Photobiol.* 2003; 78(6):587-591. doi:10.1562/0031-8655(2003)0780587TEOM.
27. Couleaud P, Morosini V, Frochot C, Richeter S, Raehm L, Durand J-O.Silica-based nanoparticles for photodynamic therapy applicatiao *Nanoscale*. 2010; 2(7):1083-1095. doi:10.1039/C0NR00096E.
28. Zhao B, Yin J-J, Bilski PJ, Chignell CF, Roberts JE, He Y-Y Enhanced photodynamic efficacy towards melanoma cells by encapsulation of Pc4 in silica nanoparticles. *Toxicol. Appl. Pharmacol.* 2009; 241(2):163-172. doi:10.1016/j.taap.2009.08.010.
29. Kim S, Ohulchanskyy TY, Bharali D, Chen Y, Pandey RK, Prasad PN. Organically Modified Silica Nanoparticles with Intraparticle Heavy-Atom Effect on the Encapsulated Photosensitizer for Enhanced Efficacy of Photodynamic Therapy. *J. Phys. Chem. C.* 2009; 113(29):12641-12644. doi:10.1021/jp900573s.
30. Brevet D, Gary-Bobo M, Raehm L, Richeter S, Hocine O, Amro K, et al. Mannose-targeted mesoporous silica nanoparticles for photodynamic therapy. *Chem. Commun.* 2009; (12):1475-1477. doi:10.1039/B900427K.
31. Huang P, Xu C, Lin J, Wang C, Wang X, Zhang C, et al. Folic Acid-conjugated Graphene Oxide loaded with Photosensitizers for Targeting Photodynamic Therapy. *Theranostics.* 2011; 1:240-250.
32. Kim H-J, Shin K-J, Han MK, An K, Lee J-K, Honma I, et al. One-pot synthesis of multifunctional mesoporous silica nanoparticle incorporated with zinc(II) phthalocyanine and iron oxide. *Scr. Mater.* 2009; 61(12):1137-1140. doi:10.1016/j.scriptamat.2009.09.001.
33. Chen Z-L, Sun Y, Huang P, Yang X-X, Zhou X-P. Studies on Preparation of Photosensitizer Loaded Magnetic Silica Nanoparticles and Their Anti-Tumor Effects for Targeting Photodynamic Therapy. *Nanoscale Res. Lett.* 2009; 4(5):400-408-408. doi:10.1007/s11671-009-9254-5.
34. Lai C-W, Wang Y-H, Lai C-H, Yang M-J, Chen C-Y, Chou P-T, et al. Iridium-Complex-Functionalized Fe_3O_4/SiO_2 Core/Shell Nanoparticles: A Facile Three-in-One System in Magnetic Resonance Imaging, Luminescence Imaging, and Photodynamic Therapy. *Small*. 2008; 4(2):218-224. doi:10.1002/smll.200700283.
35. Tada DB, Vono LLR, Duarte EL, Itri R, Kiyohara PK, Baptista MS, et al. Methylene Blue-Containing Silica-Coated Magnetic Particles: A Potential Magnetic Carrier for Photodynamic Therapy. *Langmuir.* 2007; 23(15):8194-8199. doi:10.1021/la700883y.
36. Yun Sun et al. Magnetic chitosan nanoparticles as a drug delivery system for targeting photodynamic therapy. *Nanotechnology*. 2009; 20(13):135102. doi:10.1088/0957-4484/20/13/135102.
37. Huang P, Li Z, Lin J, Yang D, Gao G, Xu C, et al. Photosensitizer-conjugated magnetic nanoparticles for in vivo simultaneous magnetofluorescent imaging and targeting therapy. *Biomaterials*. 2011; 32(13):3447-3458. doi:10.1016/j.biomaterials.2011.01.032.
38. Zhang R, Wu C, Tong L, Tang B, Xu Q-H. Multifunctional Core−Shell Nanoparticles as Highly Efficient Imaging and Photosensitizing Agents. *Langmuir.* 2009; 25(17):10153-10158. doi:10.1021/la902235d.
39. Davydenko MO, Radchenko EO, Yashchuk VM, Dmitruk IM, Prylutskyy YI, Matishevska OP, et al. Sensibilization of fullerene C60 immobilized at silica nanoparticles for cancer photodynamic therapy. *J. Mol. Liq.* 2006; 127(1-3):145-147. doi:10.1016/j.molliq.2006.03.046.
40. Cheng S-H, Lee C-H, Yang C-S, Tseng F-G, Mou C-Y, Lo L-W. Mesoporous silica nanoparticles functionalized with an oxygen-sensing probe for cell photodynamic therapy: potential cancer theranostics. *J. Mater. Chem.* 2009; 19(9):1252-1257. doi:10.1039/B816636F.
41. Bechet D, Couleaud P, Frochot C, Viriot M-L, Guillemin F, Barberi-Heyob M. Nanoparticles as vehicles for delivery of photodynamic therapy agents. *Trends in Biotechnology*.2008; 26(11):612-621. doi:10.1016/j.tibtech.2008.07.007.
42. Samia ACS, Dayal S, Burda C. Quantum Dot-based Energy Transfe: Perspectives and Potential for Applications in Photodynamic Therapy. *Photochemistry and Photobiology*. 2006; 82(3):617-625. doi:10.1562/2005-05-11-IR-525.
43. Shi L, Hernandez B, Selke M. Singlet Oxygen Generation from Water-Soluble Quantum Dot−Organic Dye Nanocomposites. *J. Am. Chem. Soc.* 2006; 128(19):6278-6279. doi:10.1021/ja057959c.
44. Tsay JM, Trzoss M, Shi L, Kong X, Selke M, Jung ME, et al. Singlet Oxygen Production by Peptide-Coated Quantum Dot−Photosensitizer Conjugates. *Journal of the American Chemical Society.* 2007; 129(21):6865-6871. doi:10.1021/ja070713i.
45. Narband N, Mubarak M, Ready D, Parkin IP, Nair SP, Green MA, et al. Quantum dots as enhancers of the efficacy of bacterial lethal photosensitization. *Nanotechnology*.2008; 19(44):445102.doi:10.1088/0957-4484/19/44/445102.
46. Moeno S, Antunes E, Nyokong T. The determination of the photosensitizing properties of mercapto substituted phthalocyanine derivatives in the presence of quantum dotscapped with mercapto-propionic acid. *Journal of Photochemistryand Photobiology A: Chemistry.* 2011; 218(1):101-110. doi:10.1016/j.jphotochem.2010.
47.Rakovich A, Savateeva D, Rakovich T, Donegan J, Rakovich Y, Kelly V, et al. CdTe Quantum Dot/Dye Hybrid System as Photosensitizer for Photodynamic Therapy. *Nanoscale Research Letters*. 2010; 5(4):753-760.
48. Duong HD, Rhee JI. Singlet oxygen production by fluorescence resonance energy transfer (FRET) from green and orange CdSe/ZnS QDs to protoporphyrin IX (PpIX). *Chemical Physics Letters.* 2011; 501(4-6):496-501. doi:10.1016/j.cplett.2010.11.021.
49. Vetrone F, Naccache R, Mahalingam V, Morgan CG, Capobianco J A. The Active-Core/Active-Shell Approach: A Strategy to Enhance the Upconversion Luminescence in Lanthanide-Doped Nanoparticles. *Adv. Funct. Mater.* 2009; 19(18):2924-2929. doi:10.1002/ adfm.200900234.12.009.
50. Zhang P, Steelant W, Kumar M, Scholfield M. Versatile Photosensitizers for Photodynamic Therapy at Infrared Excitation. *J. Am. Chem. Soc.* 2007; 129(15):4526-4527.doi:10.1021/ja0700707
51. Chatterjee DK, Yong Z. Upconverting nanoparticles as nanotransducers for photodynamic therapy in cancer cells. *Nanomedicine*. 2008; 3(1):73-82. doi:10.2217/17435889.3.1.73.
52. Qian HS, Guo HC, Ho PC-L, Mahendran R, Zhang Y. Mesoporous-Silica-Coated Up-Conversion Fluorescent Nanoparticles for Photodynamic Therapy. *Small.* 2009; 5(20):2285-2290.doi:10.1002/smll.200900692.
53. Chen W, Zhang J. Using Nanoparticles to Enable Simultaneous Radiation and Photodynamic Therapies for Cancer Treatment. *J. Nanosci. Nanotechnol.* 2006; 6:1159-1166(8). doi:10.1166/ jnn.
54. Hone DC, Walker PI, Evans-Gowing R, FitzGerald S, Beeby A, Chambrier I, et al. Generation of Cytotoxic Singlet Oxygen via Phthalocyanine-Stabilized Gold Nanoparticles: A Potential Delivery Vehicle for Photodynamic Therapy. *Langmuir.* 2002; 18(8):2985-2987. doi:10.1021/la0256230.2006.327.
55. Aslan K, Gryczynski I, Malicka J, Matveeva E, Lakowicz JR, Geddes CD. Metal-enhanced fluorescence: an emerging tool in biotechnology. *Current Opinion in Biotechnology*. 2005; 16(1):55-62.doi:10.1016/j.copbio.2005.01.001.
56. Gil-Tomás J, Tubby S, Parkin IP, Narband N, Dekker L, Nair SP, et al. Lethal photosensitisation of Staphylococcus aureus using a toluidine blue O-tiopronina-gold nanoparticle conjugate. *J. Mater. Chem*. 2007; 17(35):3739-3746. doi:10.1039/B706615E.
57. Zaruba K, Kralova J, Rezanka P, Pouckova P, Veverkova L, Kral V.Modified porphyrin-brucine conjugated to gold nanoparticles and their application in photodynamic therapy. *Org. Biomol. Chem.* 2010; 8(14):3202-3206. doi:10.1039/C002823A.
58. Gil-Tomas J, Dekker L, Narband N, Parkin IP, Nair SP, Street C, et al. Lethal photosensitisation of bacteria using a tin chlorin e6-glutathione-gold nanoparticle conjugate. *J. Mater. Chem*. 2011; 21(12):4189-4196. doi:10.1039/c0jm03555f.