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Nano drug delivery systems in photo dynamic therapy

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Abstract
Photodynamic therapy is an alternative therapeutic procedure for the treatment of cancerous and neurological diseases. It is a minimally invasive procedure where the photochemical reaction between light wave, photosensitizer (PS) and ground state oxygen produces toxic singlet oxygen ($^1O_2$). The highly reactive singlet oxygen destroys target cells by direct cellular damage, vasculature shutdown and an immune response against the target cell. The effectiveness of PDT depends on the $^1O_2$ generation capacity of the PS, accumulation of the PS and availability of ground state oxygen at the target site. A model PS for PDT should be a nontoxic pure compound of known composition with high singlet oxygen generation capacity. Accumulation of PS at the diseased cells at therapeutic concentration is essential for effective PDT. A vast range of potential PS exists with high singlet oxygen quantum yield but very poor accumulation at the target site. These limitations can be eliminated by conjugating the PS to a nanocarrier system for more efficient drug delivery at the target site. The unique physiochemical properties of diverse nanoparticles make it a versatile platform for developing targeted drug delivery systems. PS conjugation to nanocarrier systems can greatly improve its bio distribution and pharmacokinetics.

Keywords: Photodynamic therapy, Targeted Drug Delivery, Nanoparticles.

Introduction
PDT is a minimally invasive procedure with fewer side effects compared to conventional therapeutic procedures. In recent years photodynamic therapy has gained acceptance as an alternative treatment for cancerous and neurological diseases. In the past decades the efficiency of PDT has been greatly improved by the incorporation of nanotechnology. Selective accumulation of PS at the target site is one of the major requirements for effective PDT. The large impact of selective PS accumulation on PDT efficiency has generated the latest approach of TPDT (targeted photodynamic therapy). In this approach the PS molecules are conjugated to a nanocarrier system for more efficient drug delivery to the target site. In recent years many nanoparticle (NP) have been studied as nanocarriers for drug delivery systems. Nanoparticles have exceptional physiochemical properties for application as carriers in drug PS delivery systems. NPs have a stable structure with high specific surface area. In addition to high surface area for drug loading the surface chemistry of NPs allows it to be easily functionalized. These characteristics have established NPs as carriers for a wide range of drug delivery applications.

Photodynamic Therapy
Photodynamic therapy has garnered acceptance worldwide as an alternative therapeutic procedure. It is a minimal invasive procedure with reduced side effects compared to conventional therapeutics. Over the last couple of decades it has been approved for the treatment of cancer, macular degeneration and bacterial infections [1]. It is a medical procedure where photochemical reaction is used to destroy diseased cells. It is a minimally invasive method combining photosensitizer (PS), light irradiation and oxygen to produce in situ toxic reactive oxygen species. It is a two-step process, upon administration of the drug photosensitizers are selectively accumulated in the tumor area by the enhanced permeability and retention effect (EPR). After sufficient time for drug accumulation the photosensitizers are activated by light irradiation. The photo chemical reaction of PS produces reactive singlet oxygen from ground state oxygen molecules. The highly reactive singlet oxygen causes cell death through direct cellular damage, vascular shutdown and activation of immune response against target cell [2].

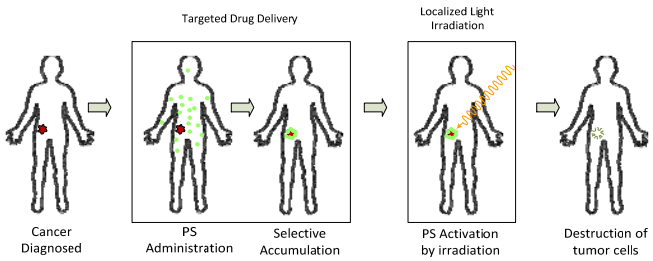

Fig 1: Targeted photodynamic therapy for selective destruction of cancerous cell.

In contrast to conventional therapeutics it offers high efficiency and minimal side effects due to the localized treatment in the target area. The high selectivity of the procedure is ensured by dual localization technique. First, photosensitizers are accumulated in the tumor area by a targeted drug delivery system. Then, a photochemical reaction is initiated at the target area through localized light irradiation. Moreover, as the generated toxic singlet oxygen has a small life time, the effect of the treatment is confined within a small area.

Singlet oxygen generation

The ground state photosensitizers when activated by light irradiation of appropriate wavelength are converted to a short lived excited state. The excited state photosensitizers decay to their ground state emitting fluorescence which generates radicals. The excited singlet state can take another path by intersystem crossing to a more stable excited triplet state. The energy transfer produces highly reactive singlet oxygen ($^1O_2$) species from molecular oxygen [3].

The production of singlet oxygen is the main key to cell destruction. The exact mechanism of how singlet oxygen induces cell death has been studied extensively, cell death by singlet oxygen occurs in two paths necrosis and apoptosis. High concentration of $^1O_2$ produces drastic changes in cell morphology such as cell membrane disruption causing cell death by necrosis. In apoptic cell destruction low level of $^1O_2$ initiates a series of events resulting in systematic shutdown of cell function [4].

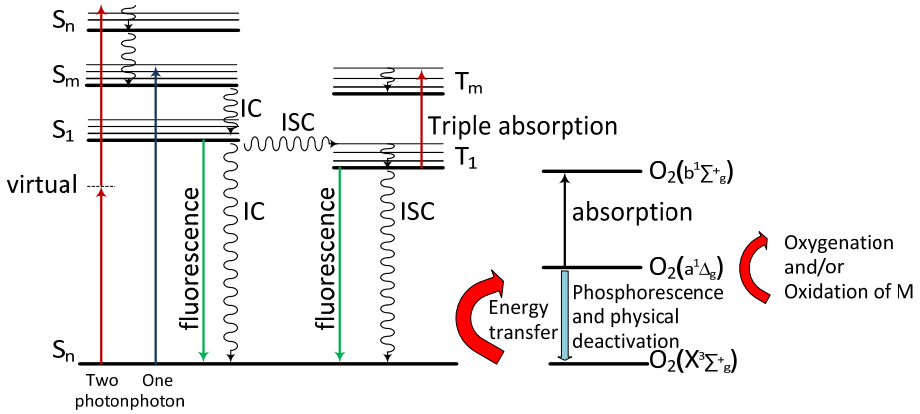

Fig 2: Jablonski diagram illustrating the mechanism of singlet oxygen generation by photo sensitizer upon light irradiation. Internal conversion and inter system crossing is denoted by IC and IRS, respectively.

Photosensitizer

Photosensitizers produce highly toxic reactive oxygen species from ground state oxygen molecules upon irradiation by light of a specific wavelength. An ideal photosensitizer should possess maximum absorbance in the therapeutic window of 650nm-850nm and high singlet oxygen quantum yield [5].The PS should be a stable compound soluble in water and not form aggregates. It should be able to preferentially retain at the target tissue and be rapidly removed from the body for low systematic toxicity. An ideal PS should also be non-toxic and have no dark toxicity in the absence of light.

A vast number of photosensitizers for PDT have been reported with high quantum yield for singlet oxygen production and a few of them have been approved by the FDA for clinical use. Photofrin® was the first PS approved for clinical use in 1993[5]. 5, 10, 15, 20-tetrakis (m-hydroxyphenyl) chlorine a second generation PS with high quantum yield and maximum absorbance at 652 nm was approved in 2002 [5]. ALA, porphycenes, phthalocyanines, chlorophil derivatives, unsymmetrical porphyrins, conformationaly designed porphyrins are few of the existing PS used for PDT [6].

Targeted Photodynamic Therapy

Targeted photodynamic therapy is a new approach where regression or inhibition of disease process is attained by destroying well defined target cells or biological pathways [7].The recent approach towards improvement of PDT is aimed at designing drug delivery systems for improved selective accumulation of the photosensitizers at the target site. The delivery mechanism is governed by the physiochemical properties of the photosensitizers and the pathological factors of the diseased organism. Due to the rapid growth through angiogenesis tumors exhibit distinctly different microenvironment than normal cells [1].In comparison to healthy tissues tumors possesses defective vasculature with leaky membranes enabling transfer of PS molecules into cells. This combined with poor lymphatic drainage system causes enhanced permeation retention (EPR) effect [8].Due to the EPR effect and unique microenvironment PS selectively accumulate at the tumor cells minimizing damage to the healthy tissues.

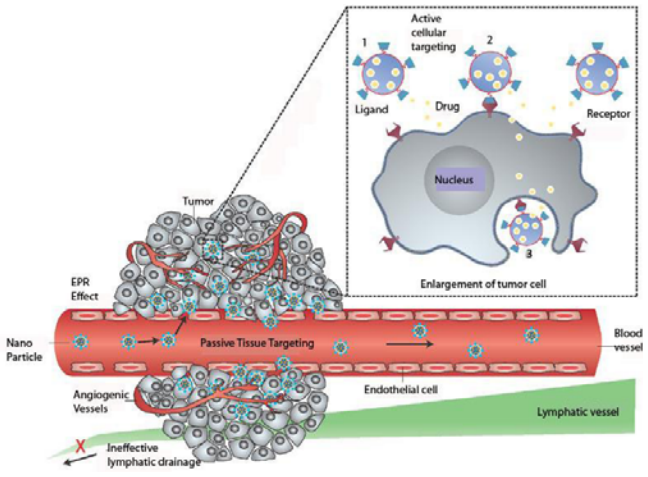

Fig 3: Illustration of the mechanism of selective accumulation of PS using targeted delivery. Selectivity is enhanced by active cellular targeting.

Recent research has further improved the selectivity by incorporating the concept of molecular recognition. This approach utilizes the unique microenvironment of the tumor cells. Tumors have high metabolic rate and the supply of oxygen and nutrients are not sufficient to maintain growth. This causes tumor cells to use glycolysis for extra energy resulting in an acidic microenvironment. Compared to healthy cells, the tumor cells over express certain [9].These over

expressed enzymes are characteristic of the tumor type but some enzymes are overexpressed in a wide range of tumors. Therefore these enzymes can be used as distinct receptors for targeting the exact tumors of interest. The PS is conjugated with ligands which have an affinity towards the enzymes overexpressed by the tumor cells and are responsive to the tumor micro environment.

It has been reported that the most common over expressed receptors by the tumor vasculature and cells are VEGF (vasculature endothelial growth factor), TF (tissue factor), EGFR (human epidermal growth factor) [1]. These receptors can easily be targeted for receptor mediated endocytosis by incorporating a number of ligands such aspeptides [10], anti-bodies [11], aptamers [12], folic acids [13] etc. Chaleix *et al.* demonstrated receptor targeting by conjugating αvβ3 integrin ligand RGD tripeptide to porphyrin derivatives for the photodynamic therapy of leukemia [1].

Another generation of photosensitizers have been developed which are only activated by the stimuli's present in the tumor microenvironment. Due to the rapid growth of tumor cells the temperature and pH of the tumor microenvironment is different from healthy cells. A pH or temperature sensitive delivery system will maintain the inactive state of the PS until the pH or temperature of the tumor microenvironment triggers PS activation. Mesoporous silica nanotubes conjugated to pH responsive polyelectrolyte for controlled drug release has been demonstrated by Yang *et al.* [14].Environmental PS activation is a promising field for enhancement of treatment selectivity. Combination of photo-induced electron transfer quencher to PS molecules has been studied for environmental activation. For further increase of selectivity the PS activation can be controlled by two distinct stimuli's of the microenvironment. In this case not only one but both of the stimuli's have to be present for the PS to be active [15].

An alternative method for increased selectivity has been proposed where the delivery system is composed of a PS, quencher and a disease specific linker. The concept is that the linker keeps the PS and the quencher in close proximity so that the PS remains inactive. But when the linker binds to the targeted tumor site the PS and quencher are separated activating the PS. This concept was demonstrated in the study by Clo *et al.* [16].They developed a molecular beacon comprising of a PS linked to an oligonucleotide sequence and another oligonucleotide sequence conjugated to a quencher. The two strands hybridized bringing the PS and quencher close resulting in inactivation of the PS. When the beacon interacts with the target nucleic acid the PS containing strand is displaced and the PS is activated.

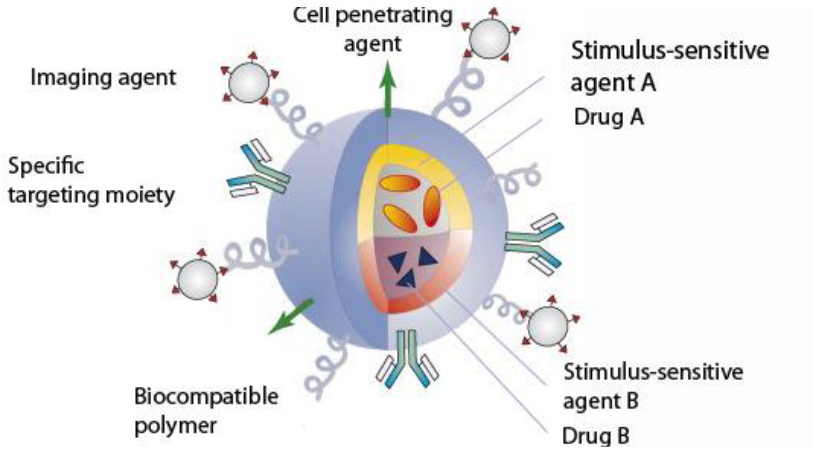

Fig 4: Multi-functional nano particle for therapeutic application. Stimuli responsive controlled drug release, active targeting, therapeutic drug and imaging combined in a nanoplatform for enhanced treatment.

The recent focus in PDT is developing multifunctional nanocomposites for combined therapeutics. Different approaches towards combining fluorescence imaging, therapeutics drugs, stimuli responsiveness and targeting modalities have been studied. A multifunctional nanoparticle combining imaging (iron oxide), tumor targeting (peptide) and PS (Photofrin) in poly acryl amide nanoparticle was reported by Reddy *et al.* [17]. Combination of therapeutic procedures for effective treatment is a recent strategy. The combination of photodynamic agents and photo thermal agents along with imaging agents can result in more effective treatment of tumor cells. Another approach is to introduce external stimuli guided drug delivery. External magnetic field can be used as stimuli for delivery systems containing magnetic nanoparticles. S. Giri *et al.* designed a drug delivery system using iron oxide nanoparticle as gate keeper for drugs loaded in the mesostructure of MSNP. The iron oxide nanoparticle responds to magnetic stimuli releasing the drug load to the target area [18].

Nanotechnology in Therapeutics

The infusion of nanotechnology to therapeutic is being used to manipulate the constraints and strengths of conventional therapeutics to push its limits.This field has been extensively studied and a number of highly effective nanotherapeutic procedures are widely practiced at present. The first study of nanomaterials for therapeutics was reported in the 1950 by Jatzkewitz, he studied a polymer- peptide-mescaline conjugate as potential drug delivery system [19].Since then numerous studies have been conducted aimed at improving existing methods or developing new strategies for therapy. The first nanotherapeutic agent approved by the US FDA (United States Food and Drug Administration) was a liposome based nanoconjugate for the treatment of Kaposi's sarcoma in 1995 [20]. Multifunctional particles with nanoscale dimensions similar to molecules in our body have been successfully used for therapeutic procedures. The nanosize of the particles imparts unique physiochemical properties compared to the bulk element. Moreover the nanosize of the particles itself is

an advantage for therapeutic applications. The physiochemical properties of Nanoparticles can be fine-tuned by manipulating the morphology, surface chemistry and chemical composition of the particles. This ensures that nanoparticles can be designed to fulfill a vast range of therapeutic requirements.

At present mainly two paths are being explored for achieving increased therapeutic efficiency through nanotechnology, One scheme is to design nanoparticles with such intrinsic properties that it is able to function as a therapeutic agent itself. The other is aimed at designing nanocarriers for drugs and treatment modalities. Nanoparticles as therapeutic agents have been studied extensively with admirable results. Quantum dots and up conversion nanocrystals have been applied as effective therapeutic agents for photodynamic therapy utilizing their unique response to optical stimuli [21].In recent studies magnetic nanoparticles and carbon nanotubes have been studied for photo thermal therapy and have shown promising results[19].

Nanomaterials used as carriers for therapeutic agent offers better drug delivery system, enhanced drug efficiency and multimodal therapeutics. The Bio distribution and pharmacokinetics of drugs is largely dependent on its size. Particles with dimensions smaller than 150nm can easily move through tumor cells. On the other hand particles dimensions smaller than 5.5 nm are easily removed by the excretory system [22]. The drug circulation time in body fluid can be controlled by adjusting the size of the drug particles. After drug administration nanoparticles circulate through the blood stream and slowly accumulate in the affected site, a longer drug circulation time results in higher drug accumulation. Another important aspect of drug delivery systems is the selective accumulation of drug at the target site. Side effects by damage to healthy cells can be reduced by concentrating the drugs only at the target site.

Prominent nanoparticles used in therapeutics

Nanoparticles offer a vast range of physiochemical properties depending on its composition and morphology. In recent studies different nanoparticles have been studied for their potential use in therapeutics among them the most promising ones can be grouped as follows

Gold nanoparticle

Gold nanoparticles possess unique characteristics which are particularly suitable for therapeutics, they offer high biocompatibility, oxidation resistance and can be easily synthesized in desired size and shape. Most importantly they exhibit surface Plasmon resonance an optical property that allows the nanoparticles to convert light energy into thermal energy [19]. In Photo thermal therapy this surface property is exploited to destroy target cells by heat through external light stimulus. The surface chemistry of Gold nanoparticles can be easily modified for targeted drug delivery by simple ligand exchange procedure. The optical properties of gold nanoparticles are dependent on the size and morphology of the particles. Zhang and coworkers have shown the optical properties of gold nanoshell can be tuned by adjusting the shell thickness [23, 24, 25]. For accessing internal target sites deep penetration is necessary. NIR (Near Infra-Red) light waves have been reported to cause deep penetration. High NIR absorbance can be obtained by tuning the size and structure of gold nanoparticle. Recently Xia *et al.* have demonstrated a controlled drug delivery system using the Plasmon resonance property of gold nanorod to trigger drug release by NIR laser. A vast amount of study has been reported using different shapes of gold nanoparticles for thermal ablation, photo thermal therapy, controlled drug delivery and imaging [19].Yang *et al.* demonstrated a dual modal therapeutic procedure using gold nanoparticle, they combined chemotherapy and photo thermal therapy [19].Multifunctional gold nanorod for RNA (Ribonucleic acid) delivery has been reported by Chakravarthy *et al.* [26] and aptamer conjugated gold nanorod for targeted drug delivery was reported by tan and coworkers.

Magnetic nanoparticle

Magnetic nanoparticles offers yet another dimension to nanotherapeutic, external stimuli enhanced targeting. The combination of external magnetic field and receptor targeting surface ligand imparts dual modal targeting for better drug delivery. In addition the nanoparticles can function as imaging agents also. Lee *et al.* reported Fe_3O_4-silica nanoparticles for simultaneous drug delivery and MRI imaging [19]. Use of magnetic nanoparticles in diverse therapeutic procedures have been reported including magnetolytic therapy, MRI, hyperthermic therapy, gene transfer, drug delivery et [19].Recently Silva *et al.* studied the use of lanthanide doping to fine tune the magnetic properties of nanoparticles [19].Protection from oxidation and corrosion by biocompatible coating is very important to maintain the therapeutic efficiency of drugs. Sun *et al.* reported four types of PEG coated iron oxide nanoparticles with high aqueous dispersion [27].Sun *et al.* described Au- Fe_3O_4 nanoparticles modified with antibody and platin molecules for specific targeting [19].

Semiconductor quantum dots

Semiconductor quantum dots are 1-10 nm in size and possess tunable florescence spectra ranging from blue to the NIR [25]. They have been extensively studied for therapeutic and diagnostic imaging. Alvisatos *et al.* showed that quantum dots can be water soluble and attached to biological molecules. They have been studied for targeted drug delivery and imaging [28]. Quantum dots exhibit cytotoxic effect by generating reactive oxygen species under UV irradiation. In 2003 Samia *et al.* reported quantum dots as photodynamic therapy agent for direct cancer therapy [29]. Quantum dots can also act as cofactors for photosensitizers in PDT through Forster Resonance Energy Transfer. Hybrid photosensitizer-quantum dot systems of different combinations have been reported with very good results [19].

Lanthanide doped up conversion particle

Lanthanide doped up conversion nanoparticles convert NIR excitation to the visible range by photon up conversion. This is a valuable property for use in therapeutic procedures and diagnostic imaging. Recent studies have shown that lanthanide doped up conversion particles offer high sensitivity assays, reliable single molecule tracking and can be used for in vivo imaging [19]. Up conversion nanoparticles can be combined with multi therapeutic modalities to achieve advanced therapeutics. Li *et al.* demonstrated a multimodal nanoparticle possessing radioactivity, magnetism and up conversion luminescence property [30]. Drug delivery systems using up conversion particles are mostly concentrated on a core-shell

system where the UC particle acts as the core and the drugs are absorbed in the shell structure. A number of studies have been reported on the controlled release of drugs by a core shell structure of UC nanoparticles [31, 32]. UC nanoparticles functionalized with photosensitizer are effective for PDT as it offers deep penetration through NIR excitation.

Carbon Nanomaterials

Considerable amount of study has been dedicated to utilize the unique physical and chemical properties of carbon nanoparticles. Mainly three forms of the carbon based nanoparticles; fullerenes, nanotubes and nanodiamond have been investigated. Fullerenes are efficient therapeutic agents for neurological disorders. Nanotube, nanodiamond and fullerenes have been shown to be excellent carriers for targeted drug delivery. Bhirde *et al.* demonstrated a targeted drug delivery system by modifying carbon nanotubes with epidermal growth factor [33]. Carbon nanotubes are able to absorb NIR irradiation and convert it to thermal energy, the use of carbon nanotubes in thermal ablation was reported by Marches *et al.* [34]. Nanodiamonds have excellent biocompatibility and unique luminescence spectra enabling them to be used in drug and gene delivery systems.

Mesoporous silica nanoparticles

Mesoporous silica particles were first reported in 1971 but the development of a series of ordered mesoporous materials in 1992 brought the unique physiochemical properties into limelight [18]. The mesoporous particles were synthesized in hexagonal (MCM41) cubic (MCM48) and lamellar (MCM50) Shape by liquid-crystal template method using cationic surfactant. The resulting particles had ordered mesoporous structure with high BET surface area and pore volume. Since then many synthesis methods have been reported for producing mesoporous silica with different structural properties. Using a tri-block copolymer as structure directing agent a mesoporous structure with larger pore size and thicker walls was reported as SBA 15 by G.D. Stucky and coworkers [35, 36].The SBA 15 particles had micro pores connecting the mesopores. Another series of mesoporous silica AMS-n was reported by Che *et al.* using anionic surfactant in combination with a co-structure directing agent. Presently many mesoporous silica particles have been established by varying the surfactants, reaction condition and the reactant composition. MSNP has unique surface characteristics and its size and morphology can be fine-tuned according to the requirements of the therapeutic procedures. The US FDA has approved silica as 'GRAS' (Generally Recognized as Safe) [37]. They are biocompatible at the effective dosage of therapy.

MSNP as a carrier system for the PS molecule can produce an effective targeted delivery system. Moreover MSNP are non-toxic and biocompatible so their incorporation to drugs does not produce any additional toxic effect. In recent years MSNP-PS conjugates has been explored to increase the PDT efficiency. Gu *et al.* demonstrated bacteria inactivation by PDT using PS grafted silica nanoparticles [38]. The target specificity of PDT has been further increased by conjugating a targeting moiety to MSNP-PS nanocomposite. The targeting ligand mediates active endocytosis where the ligand attracts the tumor cell and the nanocomposite is engulfed by the tumor cells. This improves the selective accumulation in tumor cell. Using mannose as the targeting agent, mannose functionalized MSNP was covalently attached to a PS. In another study a multifunctional nanocomposite was developed by Gary Bobo *et al.*, where an anticancer drug, PS and targeting agent galactose were conjugated to MSNP [39]. Use of MSNP in PDT is an emerging field and different strategies for further improvement are now being explored.

Conclusion

Photodynamic therapy is an emerging therapeutic procedure and has already been successfully applied in various fields of therapeutics. The probable applications of PDT covers a vast range of treatments but the requirement for selective accumulation in target site imposes some limitations. These limitations can be overcome by combining the unique physiochemical properties of nanoparticles to PDT. At present a large pool of nanoparticles are available for application in PDT, many have been studied with promising results. The recent trends in study show there is immense potential for nanoparticles in PDT.

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