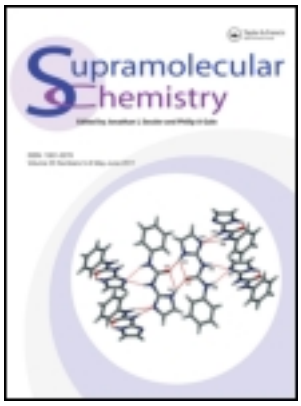

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Supramolecular approach for target transport of photodynamic anticancer agents

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Photodynamic therapy (PDT) is one of the most modern methods for cancer therapy. Various types of advanced photosensitisers (PSs) have been developed for effective application in PDT. Current research has started to demonstrate the high importance of targeted PS transport and subcellular localisation for the effective destruction of tumours. Another possible approach for the improvement of PDT is the use of synergic PS for combination anticancer therapy. The implementation of a supramolecular approach is necessary for their effective design. This can be achieved through the use of PS as non-covalent complexes with suitable carriers such as human serum albumin, lectins, cyclodextrins, polysaccharides, lipoproteins, liposomes, intravenous immunoglobulins and polymeric micelles. In addition, some of these carriers have their own anticancer activity. An alternative approach can be the use of PS for the transport of other anticancer agents. Therefore, this minireview focuses on describing these supramolecular PS systems for targeted transport and combination therapy.

Keywords: photodynamic therapy; photosensitisers, targeted transport; combination therapy; cancer

1. Introduction

According to the World Health Organization, 8 million deaths worldwide per year (around 13% of all deaths) are caused by cancer. Currently, 12 million new cases of cancer are diagnosed every year and approximately 27 million new cancer cases and 11.5 million deaths are expected in the next 20 years. Unfortunately, a significant number of cancer disease states lack effective therapeutic options and new anticancer agents as well as novel approaches to cancer treatment are still required.

Current treatment methods for cancer include chemotherapy, immunotherapy, radiotherapy, boron neutron capture therapy and surgical excision of the tumour; however, these have a range of drawbacks including the high toxicity of chemotherapeutic agents and the potentially severe side effects of radiotherapy amongst others. Therefore, new methods for the application of these treatments are being intensively studied and one of the most promising methods is photodynamic therapy (PDT). It is an effective method for the treatment of skin, eye, oral, head, neck and breast cancer as well as that of targetable internal organs such as the stomach, intestine, prostate and brain (*1*). PDT is carried out using specific anticancer agents called photosensitisers (PSs).

PSs are an extensively studied group of anticancer agents with high therapeutic potential and considerable selectivity for cancer cells (*2*). Their anticancer effect is based on their activation by light of a specific wavelength, resulting in a sequence of photochemical and photobiological processes that cause irreversible photodamage of tumour tissue. Cancer cell death is caused by oxidative stress because the photoactivation of the PS results in the production of singlet oxygen, which subsequently generates free reactive oxygen species, thereby destroying the cell structures (*3*) (Figure 1). The photodynamic effect is based mainly on an acute stress response involving mitochondrial damage, cytochrome *c* release and the activation of a caspase apoptotic sequence. One key feature of the medicinal application of PS is the absorption of light in the visible range of the spectrum. The wavelength clinically used for the excitation of PS is necessarily a compromise between the low absorption of light by living tissue and the requirement for sufficient light energy for PDT application (*4*). The body absorbs light up to a wavelength of 580 nm. At wavelengths higher than 900 nm, the photons may not have sufficient energy to initiate photochemical reactions. Therefore, the wavelength range between 600 and 800 nm is known as the 'spectral window' for *in vivo* photodynamic applications. Optimal spectral properties are observed in highly conjugated compounds; therefore, the structures of current PS are based on pyrrolic macrocycles, cyanine dyes, azines, triarylmethanes, xanthenes and natural compounds (*1*), examples are shown in Figure 2.

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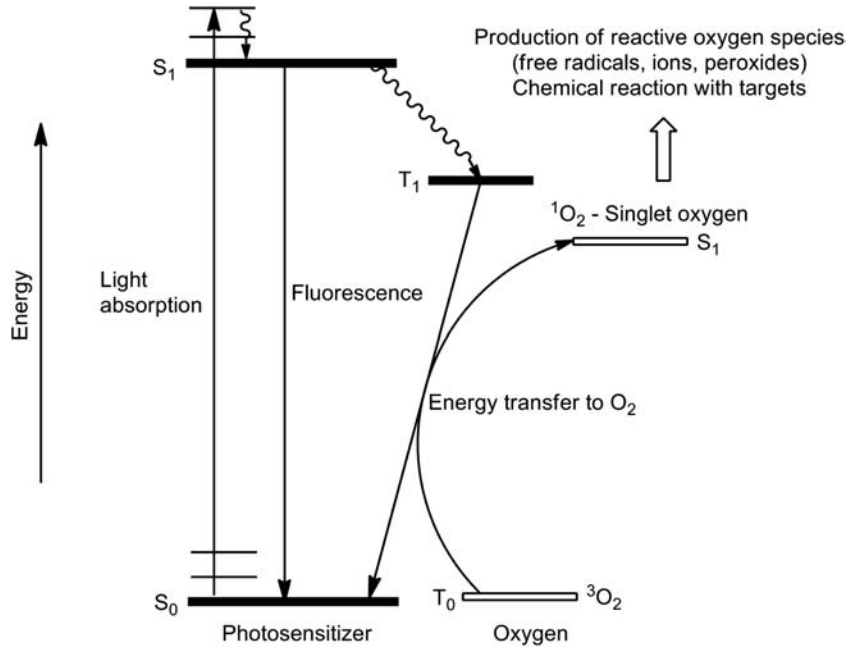

Figure 1. Jablonski diagram of singlet oxygen formation.

The main problems for cancer-destroying agents are their high toxicity towards healthy tissue and their low selectivity for cancer cells. In contrast to radiation therapy and chemotherapy, PDT has fewer adverse effects and higher selectivity (*5*). Suitably designed PS can have a high selectivity for cancer cells, usually based on higher accumulation of lipophilic compounds such as some PSs (*6*, *7*) in cancer tissue in comparison with healthy cells. The selectivity of PS for cancer cells can be markedly improved by suitable derivatisation with ligands used as cancer markers. PS conjugated with specific ligands including bile acid (*8*), folic acid (*9*), galactose (*10*), lactose (*11*) and oestradiol (*12*) amongst others were prepared and tested for this purpose (Figure 3). Another method is the use of specific drug delivery systems (DDS) with the ability to passively and actively transport anticancer agents into the tumour tissue. This method can usually be employed through the preparation of covalent PS conjugates with polymers (*13*), biopolymers including proteins such as antibodies (*14*), lectins (*15*), serum albumin (*16*), lipoproteins (*17*), polysaccharides (*18*), antisense oligonucleotides (*19*) or nanoparticles (*20*). Another possible method can be a supramolecular approach based on the application of PS as complexes with carriers such as proteins, saccharides, liposomes, polymeric micelles and oligonucleotides. In addition to their role as carriers, some of these supramolecular systems may also possess anticancer activity.

PDT can be used as a single therapy or in combination therapy with other therapeutic methods. The major advantage of combination therapy is its higher therapeutic effects in comparison to single therapy approaches. Appropriately designed combination therapy can also be used for the reduction in undesirable effects or to improve the effectiveness of other therapies. For example, the most effective use of PDT requires the monomeric form of the PS. Polyaromatic PS structures, which are necessary for high light absorption (*1*), tend to aggregate and hence lose their effectiveness in the aqueous environment. This problem can be solved through modification of the PS core by hydrophilic groups (*21*, *22*) (Figure 4) or by bonding of the PS to high molecular weight hydrophilic carriers such as proteins (*23*) or antibodies with anticancer activity. Another drawback of chemotherapy is the development of multidrug resistance some cancer cells, which can be reduced by the concurrent use of PDT (*24*). Several synergic porphyrin PSs that can integrate PDT and the second therapy (chemo-, radio- and immunotherapy) have been developed based on this principle, for example porphyrin-producing nitric oxide (*25*), porphyrins for the alkylation of DNA (*26*), conjugates of texaphyrin with dihydrofolate reductase inhibitors (*27*), conjugates of porphyrins with carboranes for boron neutron capture therapy (*28–30*) or oligonucleotide transport (*31*) (Figure 5). Effective methods can be based on the use of PS metallocomplexes with radioactive (*32*) or toxic (*33–38*) metals (Figure 6). The other method is based on the combination of PS with therapeutic proteins (monoclonal anticancer antibodies or chemotoxic lectins) with selectivity for cancer cells.

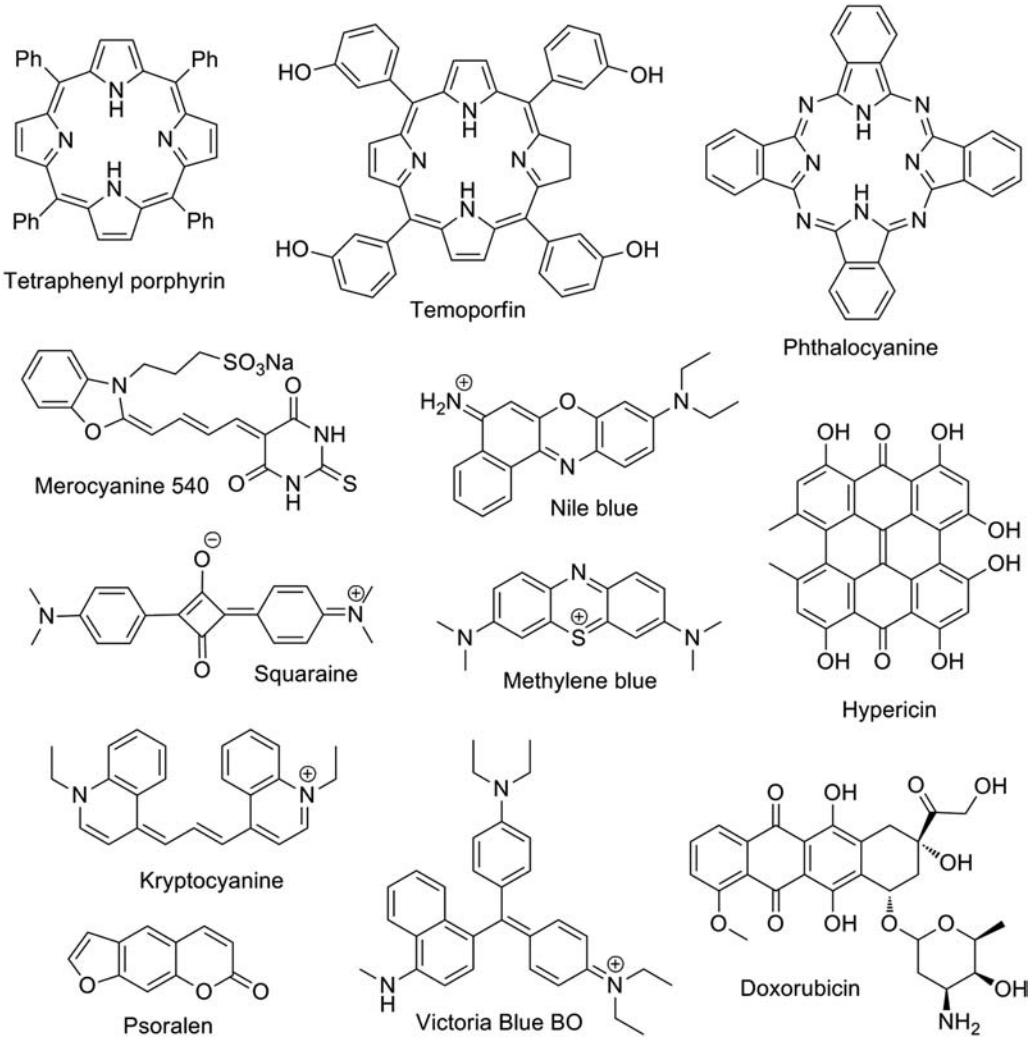

Figure 2. Examples of commonly used PSs.

2. Supramolecular approaches for target transport of PS

Studies focused on the use of PS combined with transport systems showed an improvement in anticancer efficacy. DDSs can be based on active or passive transport mechanisms. Passive transport can be used in the case of solid tumours for DDS with a suitable molecular weight. In the case of protein carriers (*39*), this phenomenon was observed for systems with molecular weights in the range of 12–150 kDa. Macromolecules with molecular weights higher than 40 kDa cannot be removed from the tumour and therefore become concentrated. There is a correlation between the half-life in plasma, the renal clearance and the accumulation in the tumour of the respective macromolecules. Passive transport can also be based on the lower pH of a tumour and cancer cells, an outer magnetic field and other methods of non-specific tumour or cancer cell recognition. DDS with active transport abilities have selectivity for specific cancer surface receptors (proteins and saccharides), for example lectins, antibodies and some polysaccharides such as hyaluronan. Unlike many covalent systems intended for the targeted transport of drugs, which usually suffer from being very rigid and unable to meet current requirements for flexibility, the supramolecular approach is based on the specific and effective binding of PS by non-covalent interactions. Transport systems based on proteins (lipoproteins, lectins, intravenous immunoglobulins and human serum albumin (HSA)) and saccharides (polysaccharides and cyclodextrins) can be developed for this application. Another advantage of this method is the frequently lower cost of clinical studies. Examples of systems developed for the delivery of photodynamic drugs are as follows.

2.1 Lectins

Lectins are intensively studied as protein-type carrier of PS, mainly for porphyrin. Lectins are multivalent proteins

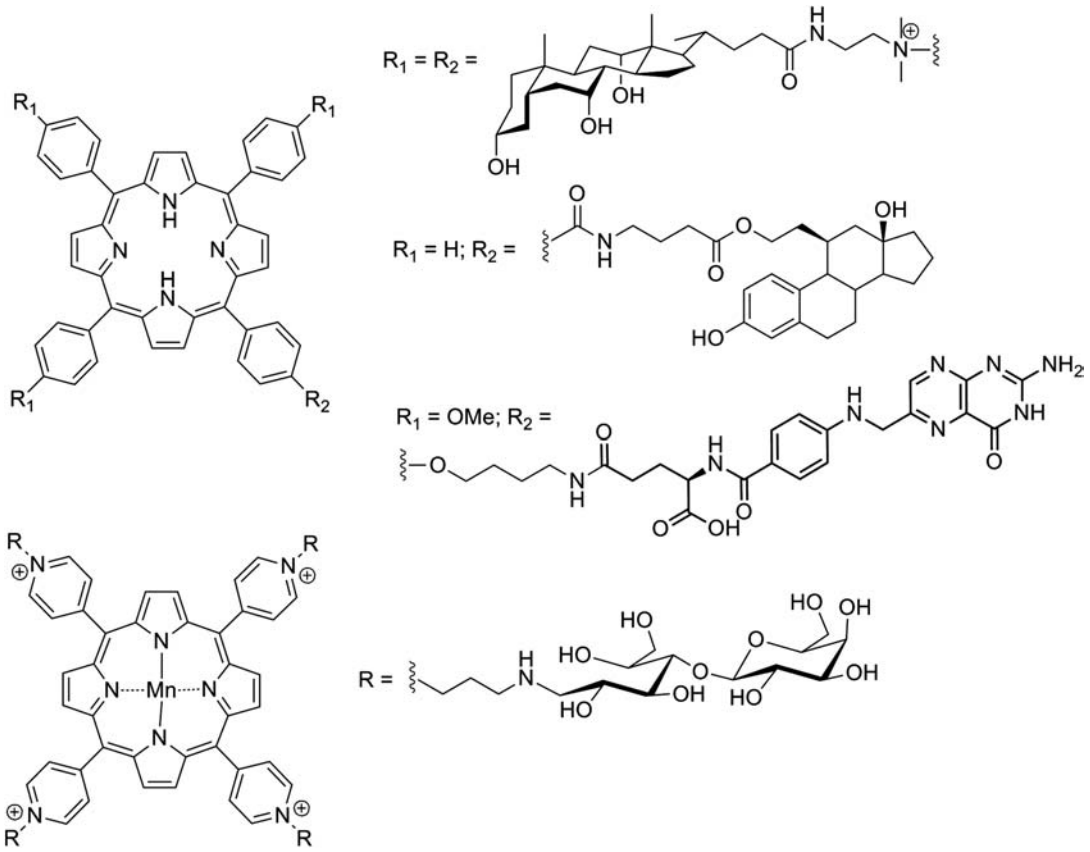

Figure 3. Porphyrin conjugates with enhanced selectivity towards cancer cells.

that can recognise diverse cancer saccharide motifs (*40*) such as GD3 gangliosides (*41*). The selectivity of lectins is comparable with monoclonal antibodies, but their price is considerably lower than monoclonal antibodies. Cancer saccharide receptors are recognised by the lectins through their hydrophobic cavity. Some lectins (*42*) [concanavalin A (*43*), *Pisum sativum* lectins (*44*) and others] have other hydrophobic binding sites. These sites can also be used for the binding and transportation of hydrophobic compounds. Lectins are studied for use as transporters of various types of anionic, cationic and non-ionic porphyrins. Values of binding constants are generally between 3×10^3 and 1×10^5 mol/dm^3. The presence of lectin-specific saccharides has usually no significant influence on the expression of the lectin–porphyrin interaction. In addition, lectins can have anticancer effects through the activation of the caspase apoptotic pathway, inhibition of cancer signal pathways and blocking the cholesterol sulphate metalloprotease-7 binding site on the cell surface (*40*, *45*).

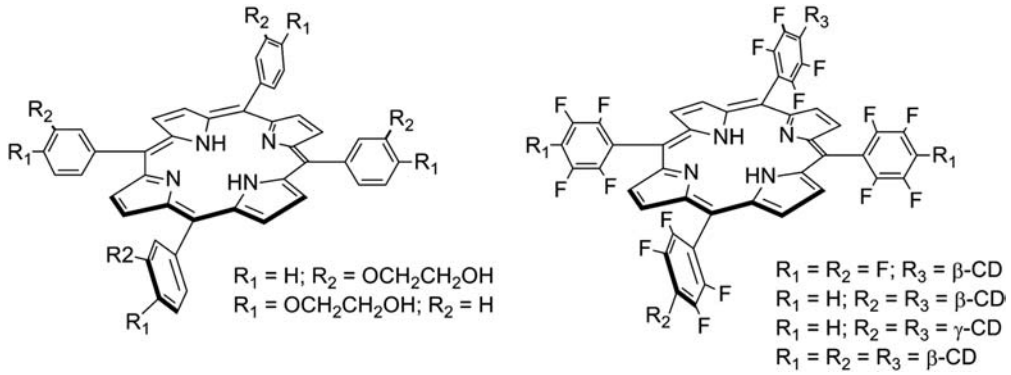

Figure 4. Porphyrin PSs with hydrophilic substitution.

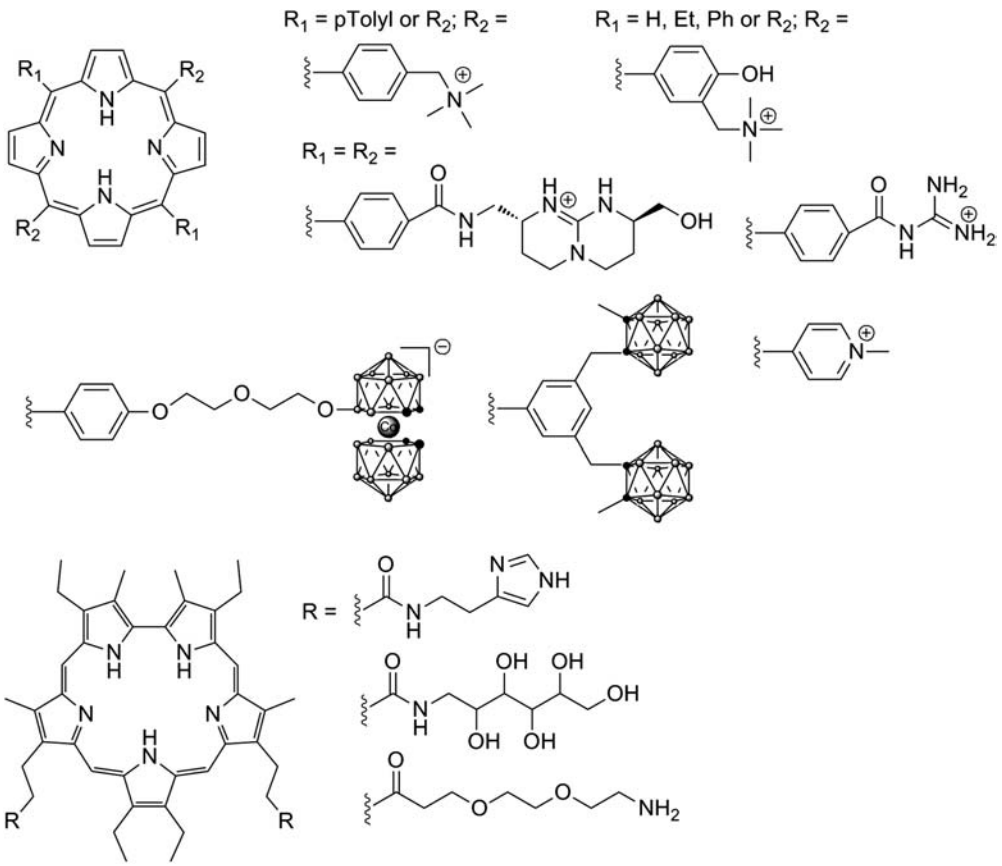

Figure 5. Conjugates for PDT with additional therapy.

2.2 *Human serum albumin*

Another protein with the ability to transport PS is HSA, which is found in high concentrations in the blood. Serum albumins have one or two specific and several non-specific binding sites for various porphyrins (*46*). Porphyrin molecules can be incorporated into the apolar central domains of protein matrices, values for the binding constants between 10^4 and 10^5 mol/dm^3 have been observed. They can also sorb onto the surface of protein globules and the values for the binding constants are found to be between 10^3 and 10^4 mol/dm^3. Porphyrin affinity for serum albumins can be increased by the use of porphyrins as metallocomplexes (*47*, *48*). This type of transport mechanism is mainly used for hydrophilic PS, hydrophobic

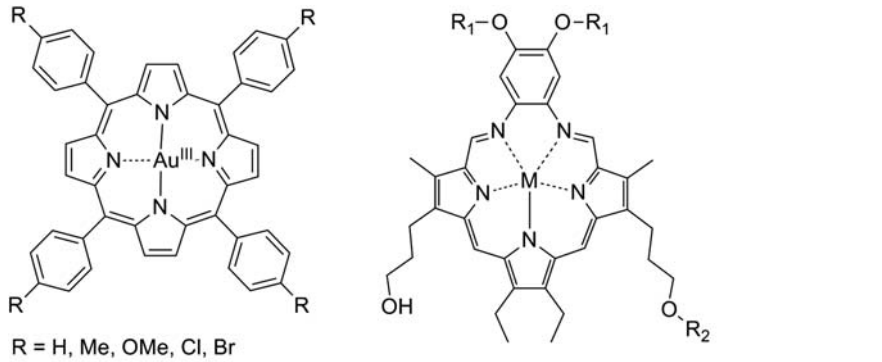

Figure 6. Metallocomplex-based PSs.

PS prefer lipoproteins as their transport system (*49*). In addition, plasma proteins such as HSA are required as nutrients by proliferating cancer cells to a greater extent than in normal tissues.

2.3 Lipoproteins

An important group of PS transport systems are carriers with hydrophobic cores: low-density lipoproteins (LDLs). LDLs are a heterogeneous population of water-soluble, macromolecular aggregates of lipids and proteins that are responsible for the transport of water-insoluble nutrients (*50*). LDL is the class of plasma lipoprotein particles which carries the majority of cholesterol and its esters in plasma. Hydrophobic core in LDL facilitates the incorporation of poorly soluble drugs. Many malignant tissues over express LDL receptors in comparison with normal tissues (*51*). A series of studies indicated that the LDL receptor is responsible for the accumulation of hydrophobic PS in tumour and cancer cells (*49*, *52*, *53*). LDL as a PS transport system has significantly higher and faster PS accumulation in tumour tissue compared to classical PS formulations. These facts demonstrate the high potential of LDL as an excellent vehicle for the delivery of hydrophobic anticancer agents including PSs.

2.4 Polymeric micelles

Polymeric micelles are formed in aqueous solutions from amphiphilic block or graft copolymers (*54*). Their size (10–100 nm) is suitable for passive transport into tumour tissues. They have hydrophobic core and hydrophilic corona on the surface of the micelle, which usually contains polyethylene glycol. This glycol is frequently used to inhibit non-specific interactions of DDS in order to extend their residence time in circulation. Hydrophobic drugs such as PS can be physically entrapped in the core of the micelles and thus be delivered to the tumour. Usually, physical entrapment can be based on hydrophobic and electrostatic interactions between the drug and polymer. Other methods include dialysis from an organic solvent or by oil-in-water emulsion procedures. Use of polymeric micelles as DDS has a positive influence on PS photodynamic effectiveness. For example, Zhang et al. (*55*) observed a lower IC_{50} for a combination of PS and polymeric micelles then for PS alone when an *in vitro* study was carried out on a Lewis lung carcinoma cell line. Polymeric micelles are a nearly ideal vehicle for the transport of dendrimeric PS. Their photodynamic efficacy can be markedly improved by the use of oppositely charged polymeric polyion micelles (*56*). An *in vitro* study carried out on Hela cells clearly showed a 1000-fold increase in efficiency for the use of third generation of dendrimeric PS and polymeric micelles than for the use of PS alone (*57*). This efficiency was 10 times higher than the efficiency of second generation PS and polymeric micelles. The efficiency of PSs alone was similar for all the studied generations (Figure 7). Liberation of the transported PS can be effected through adjusting the ionic strength or pH changes in a pH-responsive micelle [e.g. poly(*N*-isopropylacrylamide) or polyion complex micelles]. After the uptake of the micelle by a lysosome or endosome and its subsequent protonation and destabilisation, transported PS is liberated (*35*). It is well known that solid tumours have a lower extracellular pH than the pH of blood. This can be exploited for the selective liberation of transported PS in the extracellular surrounding of the tumour tissue. For example, Kim et al. designed and tested poly(β-amino ester) polymeric micelles for the transport of protoporphyrin IX (Figure 8) in a mouse model with squamous cell carcinoma (*58*). The authors observed a 10-fold increase in the uptake of the transported PS than the free porphyrin. This caused significantly higher photo-

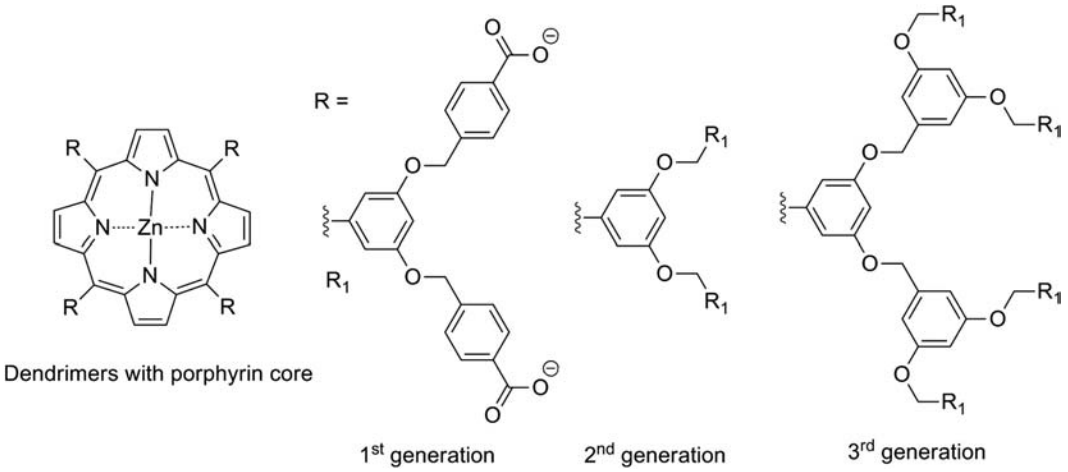

Figure 7. Dendrimeric PS.

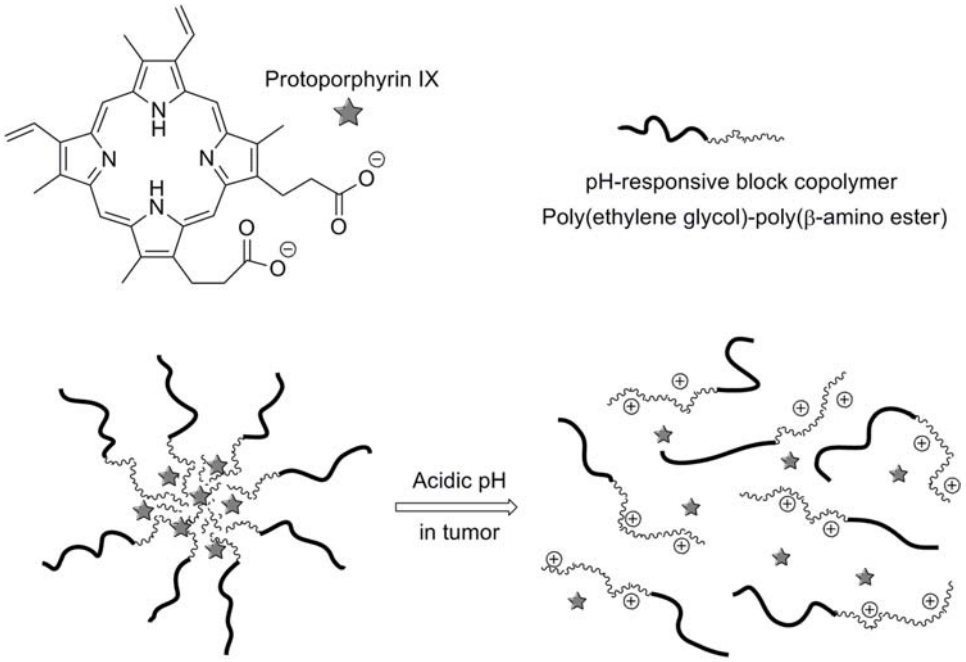

Figure 8. Protoporphyrin IX in pH-responsive micelle.

dynamic tumour reduction when using a transported PS in comparison to a free porphyrin.

Thermo-sensitive polymeric micelles can also be used for the transport of anticancer drugs, for example a poly(*N*-isopropylacrylamide) micelle (*59*). The correct drug release can be controlled by local heating or cooling during a particular time period. Other possible methods of polymeric micelle targeting can be simply based on an external magnetic field and the incorporation of magnetic nanoparticles into micelle (*60*, *61*).

2.5 Liposomes

Liposomes are spherical, self-closed structures containing lipid bilayers (mainly phospholipids) on the surface and an aqueous phase internally (*62*). Hydrophobic drugs are incorporated into their membranes. Advantages of this loading are very slow PS aggregation and its high photodynamic efficacy (*63*). The aqueous phase can contain various hydrophilic agents such as polysaccharides and hydrophilic drugs. For example, chitosan can be used to improve adsorption of anionic and cationic porphyrins by lipid layers (*64*). This fact could also be simply and effectively used for the preparation of liposomes with higher loading ability and the design of combination therapies (porphyrin PDT and chitosan induction of apoptotic signal pathway). Jang et al. prepared liposomes that incorporate PS and cisplatin for the use in combination therapy (*65*). In blood, liposomes are usually transported with the lipoprotein fraction. This is probably the cause of the higher and faster PS accumulation in tumour tissues when liposomes are used in the formulation (*66–69*). For the improvement of retention in blood, liposomes can be prepared as conjugates with polyethylene glycol, sialic acid (*70*) or polyethyleneimine (*71*). Similar to polymeric micelles, liposomes can be prepared to be pH (*72*), thermo-sensitive (*73*) or magneto-sensitive (*74*). Their selectivity for cancer cells can be improved by their conjugation with an anticancer monoclonal antibody (*75*), cancer selective polysaccharides such as hyaluronan (*76*) or small ligands with cancer specificity (e.g. folate (*77*), 3,5-dipentadecycloxybenzamidine (*78*) or cholesterol). These modifications have a significant influence on PS efficacy. For example, Diaz et al. observed (*77*) in an *in vitro* study carried out on Hela cells with high expression of folate receptors that there was a twofold increase in the accumulation of Zn-tetraphenylporphyrin in the cells for folated liposomes than for a normal PS liposomal formulation. Photodynamic cell mortality was 96% for folated lyposomes and 65% for normal liposomes.

2.6 Polysaccharides

Polysaccharides can be used for the targeted transport of hydrophobic drugs. The binding of hydrophobic molecules such as PS to polysaccharides is based on the CH/π saccharide interaction. The utility of this type of complex can be improved by use of PS with suitable saccharide binding groups or complementary charges in the case of

charged polysaccharides (*79*). Current research is focused on the development of polysaccharide microcapsules (*80*) and nanoparticles (*81*) as non-covalent PS transport systems. Polysaccharides can also have various degrees of anticancer activity, especially saccharide cancer markers that can be used as immunostimulants and vaccines (*82*). Anionic polysaccharides such as hyaluronic acid and heparin are inhibitors of heparinase III and can be used for the inhibition of vascular endothelial growth factor receptors (*83*). Cationic polysaccharides such as chitosan can act as apoptosis inductors (caspases) (*84*, *85*). These phenomena can be coupled with the reduction of tumour metastasis, invasiveness, aggressiveness and angiogenesis. An *in vivo* study (*86*) focused on the combination of photofrin (mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units, Figure 9). PDT and β-glucan immunotherapy showed significantly higher necrosis than the sole use of photofrin or β-glucan. These facts indicate that the use of polysaccharides as PS supramolecular transport systems could have high therapeutic efficacy.

2.7 Cyclodextrins

A specific class of saccharide transport systems are cyclodextrins (cyclic oligoglucose compounds), which possess a relatively hydrophobic cavity and a hydrophilic surface (*87*). They are one of the best known and most extensively studied transport system for drugs. Three basic types of cyclodextrins (α, β, γ) with different numbers of glucose units are known. The ability of each cyclodextrin to form inclusion complexes with specific guests depends on the proper fit of the guest molecule into the hydrophobic cyclodextrin cavity, which is governed by steric effects and non-covalent binding interactions (*88*). The steric fit depends on the relative size of the cyclodextrin with respect to the size of the guest molecule. The complexation ability of basic cyclodextrin units is not usually enough for targeted transport as the value of the binding constants are in the range of $10^2 - 10^3$ mol/dm^3. This problem can be solved using cyclodextrin derivitisation or by the preparation of advanced cyclodextrin systems such as cyclodextrin dimers. For example (*89*), the value of the binding constants of inclusion complexes of β-cyclodextrin dimer with porphyrins are about 2×10^6 mol/dm^3.

2.8 Cyclodextrin–porphyrin conjugates

In the field of targeted transport, it is also possible to use porphyrins as carriers for anticancer agents. Our group designed and tested cyclodextrin–porphyrin conjugates (Figures 4 and 10) for the targeted transport of drugs and combination therapy with PDT and chemotherapy (*90–93*). The *in vitro* efficacy of our system was tested on mouse with mammary carcinoma 4T1 and human chronic myelogenous leukaemia K562 cells. The cell mortality of PS/drug complexes and porphyrin–CD–drug complexes in the dark (without PDT) corresponded in most cases to the mortality induced by the free drug. Only administration of PS complexes with hydrophobic drugs (taxanes) resulted in a 5–8% higher cell mortality in comparison to β-CD/drug complexes, thus indicating that PS is likely facilitate solubility and/or uptake of these drugs into cells. The combination of PDT with chemotherapy showed a significant synergic effect for the tested PSs with various drugs (paclitaxel, doxorubicin, thioguanine, lomustine, lapatinib, fluorouracil, etc.). An *in vivo* study carried out on nu/nu mice with 3T1 tumours for complexes of PS with paclitaxel or doxorubicin showed high tumour destruction in the combined therapy mode. For example, we observed a 10% and an 81% reduction in tumour volume for chemotherapy with transported doxorubicin

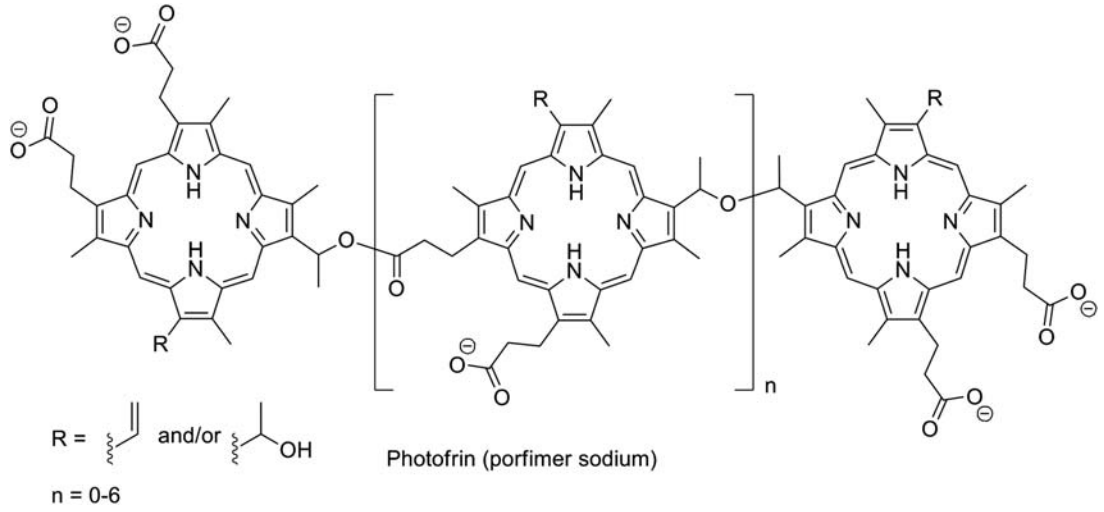

Figure 9. Photofrin.

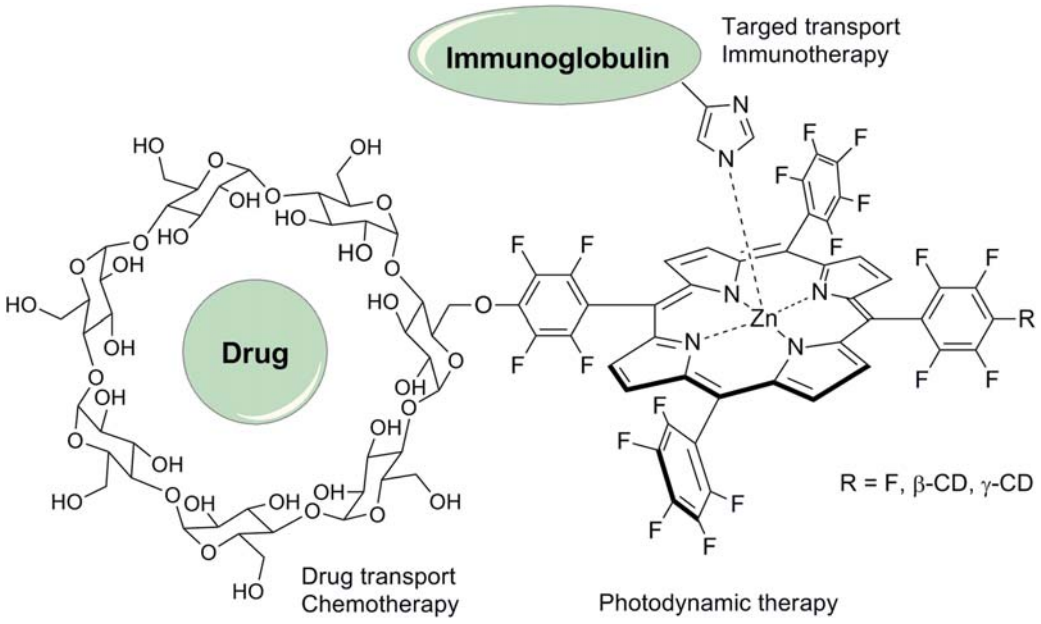

Figure 10. Multimodal therapeutic system.

alone and PS carrier alone, respectively. Their combination caused a 96% reduction in tumour volume. The synergic effect of the combination therapy *in vitro* and *in vivo* was confirmed by Student's *t*-test, ($P < 0.05$). These studies clearly demonstrated the high therapeutic efficacy and flexibility of this approach.

2.9 Immunoglobulins

Tumour selectivity and anticancer PS efficacy can be improved by application of an intravenous immunoglobulin as a suitable macromolecular carrier with another mode of anticancer activity. They can induce statistically significant inhibition of tumour growth, invasiveness, angiogenesis and prolongation of survival time (*94–96*). These phenomena are associated with the production of antitumour and antiangiogenic cytokines, inhibition of matrix metalloproteinase activity, downregulation of growth factor production and apoptotic effects. Their other important benefit is a favourable price, which allows the upgrade of the anticancer therapy without incurring a significant additional cost. Therefore, we designed and tested cyclodextrin–porphyrins as metallocomplexes in the form of complexes with intravenous immunoglobulins on a nu/nu mice model using human amelanotic melanoma C32 (Figure 10). In accordance with our previous results, we observed a significant effect of PDT, mainly with the use of another therapy, on tumour reduction. Using full three therapy modes strongly enhanced the anticancer efficacy of the tested system. For example, the number of mice cured was one per six treated for the combination of PDT with second therapy. With the use of the full three therapy, we found five cured mice per six treated. Our work (*97*) demonstrated a significant positive influence of immunoglobulin carrier on the anticancer efficacy of our system, mainly through the inhibition of tumour recurrence.

2.10 Oligonucleotides

Another type of advanced supramolecular system of interest is based on the use of complex cationic porphyrin derivates in combination with antisense oligonucleotides. *In vitro* studies showed that this type of structure is highly effective for oligonucleotide transport (*31*, *98*, *99*). The results demonstrated the potential of this approach for future use in the field of targeted transport and combination therapies with photodynamic and antisense oligonucleotide therapy.

3. Conclusion

The wide application of the supramolecular approach to anticancer PDT can motivate its substantial improvement. This minireview presented various types of supramolecular systems based on natural and synthetic molecules that can be used for the targeted transport of PS to cancer cells. This minireview also focused on the application of these systems in combination therapy.

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