Abstract: Photodynamic therapy (PDT) is a promising cancer treatment which involves a photosensitizer (PS), light at a specific wavelength for PS activation and oxygen, which combine to elicit cell death. While the illumination required to activate a PS imparts a certain amount of selectivity to PDT treatments, poor tumor accumulation and cell internalization are still inherent properties of most intravenously administered PSs. As a result, common consequences of PDT include skin photosensitivity. To overcome the mentioned issues, PSs may be tailored to specifically target overexpressed biomarkers of tumors. This active targeting can be achieved by direct conjugation of the PS to a ligand with enhanced affinity for a target overexpressed on cancer cells and/or other cells of the tumor microenvironment. Alternatively, PSs may be incorporated into ligand-targeting nanocarriers, which may also encompass multi-functionalities, including diagnosis and therapy. In this review, we highlight the major advances in active targeting of PSs, either by means of ligand-derived bioconjugates or by exploiting ligand-targeting nanocarriers.

Keywords: photodynamic therapy; cancer; drug delivery; active targeting; nanocarriers

1. Introduction

A critical limiting factor of cancer treatment’s success is the lack of specificity associated with many traditional cancer therapeutics. Moreover, most anti-cancer drugs accumulate in normal and cancer tissues indiscriminately. Damage is instigated in proportion to the sensitivity of the tissue exposed [1]. This not only leads to significant, often debilitating side effects, but also to a decreased therapeutic efficacy [2]. Due to these obstacles, intense research is focused on the development of strategies to deliver effective therapeutic concentrations of anti-cancer agents specifically to the tumor, thereby increasing their therapeutic efficacy while reducing toxicity [3,4].

Targeted drug delivery in the context of cancer is mainly achieved by two approaches: passive and active targeting. The first is highly dependent on the physicochemical properties of drugs/nanocarriers and the pathophysiological features of the tumors [5]. It is proposed that the leaky and discontinuous tumor endothelium, in conjunction with poor tumor lymphatic drainage, naturally favors the accumulation of drugs/nanocarriers in tumors, a phenomenon known as the enhanced permeability and retention (EPR) effect [6]. In contrast, active targeting refers to the specific interactions, at a molecular
level, between a drug or its delivery system and the target cells (e.g., cancer cells), usually due to specific ligand–receptor interactions [7]. Extensive genome sequencing and proteomic exploration have caused a large number of biomarkers overexpressed in cancer cells to be discovered as suitable receptors for active targeting [8]. Active targeting intends not only to enhance tumor accumulation but also to increase intracellular delivery of the drugs through exploitation of receptor mediated endocytosis [9]. Although major improvements for the internalization of drugs or their delivery systems (e.g., nanocarriers) by cancer cells have been shown in vitro by means of different targeting moieties, limited success has been observed with in vivo cancer mouse models. Some studies have shown that upon systemic administration, targeted and non-targeted drugs/nanocarriers unexpectedly exhibited similar tumor accumulation. This clearly indicates that tumor accumulation of both targeted and non-targeted drugs/nanocarriers is highly dependent on the tumor pathophysiology, and therefore, on the EPR effect, rather than solely the presence of a ligand targeting the cancer cells [10,11]. Even targeted radiotherapy which utilizes high binding affinity antibody ligands only achieves below 0.01% of dose administered localized in the tumor [12,13]. Nevertheless, at the tumor level, the presence of the targeting ligand is crucial to enhance drug/nanocarrier internalization by the cancer cells. This is expected to correlate with improved therapeutic outcomes when compared with the non-targeted controls [10,11]. In addition, other cell populations of the tumor microenvironment (TME) rather than cancer cells have received great attention. For instance, targeting tumor endothelial cells is becoming popular, as they are considered important for angiogenesis, subsequent tumor growth and metastasis formation. Additionally, endothelial cells are readily accessible to any drug/nanocarriers injected in the vascular compartment, while cancer cell targeting is dependent on the drug extravasation from tumor vasculature [14].

Photodynamic therapy (PDT) is a promising and non-invasive anti-cancer treatment that may be potentiated by ligand-targeted strategies [15]. It relies on the interaction between light, a photosensitizer (PS) pro-drug and ground state molecular oxygen, which combine to provide a therapeutic effect mediated by singlet oxygen and/or other reactive oxygen species (ROS) [16,17]. Photodynamic action may proceed via two known principal paths of reaction, both very dependent on the oxygen content present in cells [18]. Absorption of a photon by the PS at a specific wavelength causes activation from the ground state to a short-lived excited state. The excited PS may decay—emitting fluorescence—and return to the ground state, or it can undergo intersystem crossing to form a relatively long-lived triplet state. The triplet state may also decay radiatively, emitting phosphorescence. This is a spin forbidden process, and thus, occurs slowly. Crucially, however, it may interact with molecular oxygen in a type I reaction to transfer an electron to surrounding biomolecules to produce ROS [15,19]. Alternatively, in a type II reaction, energy of the excited PS may be directly transferred to ground-state molecular oxygen, producing singlet oxygen, $^1$O$_2$ [15,16,18,19].

An ideal PS for the treatment of solid tumors should absorb light, with a high molar absorptivity, at a wavelength between 650 and 850 nm. high light penetration through human tissues is achieved while activation of biomolecules, for example, hemoglobin, is avoided. At the clinical level, most PSs are administered systemically. Following a certain interval of time, the drug to light interval (DLI), the tumor is illuminated, causing the photo-activation of the PS accumulated in the tumor microenvironment [19]. Tumor destruction is attained via a number of downstream targets, including cancer cells, tumor vasculature and the immune host system [20]. The primary site of damage is generally considered to coincide with the site of PS accumulation due to the short lifetime of ROS [21,22]. The accumulation of the PS in the tumor is highly dependent on the DLI. Prolonged DLI aims for the optimal distribution of the compound in cellular compartments (cellular-PDT), while the tumor vasculature tends to be targeted by PDT using shorter DLI (vascular PDT) [19]. In addition to irreversible damage to the cancer cells and tumor microvasculature, PDT may also activate the immune system against tumor antigens, which can lead to the induction of anti-tumor immunity [22,23].

Despite extensive research, PDT has yet to gain clinical acceptance as a first line anti-cancer therapy [20]. Porfimer sodium (Photofrin, “haematoporphyrin derivative”), temoporfin
Despite extensive research, PDT has yet to gain clinical acceptance as a first line anti-cancer treatment [24]. Formulation problems and difficulties in planning and monitoring the clinical administration have been significant challenges [19,25].

PDT treatments already offer some tumor selectivity and specificity as a function of the illumination region. Additionally, PSs (namely amphiphilic and lipophilic PSs) are known to have preferential accumulation at tumor sites due to their interaction with low density lipoproteins (LDL), which have overexpressed receptors on cancer cells [26]. Despite this, significant improvements for PDT treatment might be achieved by means of ligand-targeted strategies. Higher and more specific PS tumor accumulation is expected to enhance tumor destruction while avoiding skin photosensitivity [19,25,27] (Figure 1).

(Foscan, 5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin), 5-aminolevulinic acid (5-ALA) and talaporfin (Laserphyrin, “mono-L-aspartyl chlorin e6”) are the PSs already in clinical practice for cancer treatment [24].

In this review, the major advances regarding active targeting delivery of PSs, either by means of ligand-derived PS bioconjugates or by taking advantage of ligand-targeting nanocarriers, will be discussed in the context of cellular-PDT for cancer treatment.

Upon intravenous administration, a ligand-targeted PS is expected to be in circulation for adequate time to allow extravasation through endothelial fenestrations of the angiogenic tumor blood vessels into the tumor mass. Upon tumor accumulation, the targeting moiety attached to the PS is recognized by receptors overexpressed on the surfaces of cancer or other stromal cells, leading to endocytosis-mediated internalization of the PS. When the targeting-ligand and/or drug delivery carrier exhibits fusogenic properties that can destabilize the endocytic vesicles, the PS is released into the cell cytosol with further accumulation in different organelles. However, the PS may remain entrapped at the endocytic compartment until the illumination time. After a certain time (drug-to-light interval, DLI) which typically corresponds to the time that allows the highest tumor accumulation, illumination of tumors is performed with a laser at an appropriate wavelength. Photons are then absorbed by the PS which interact with molecular oxygen in type I and/or II reactions. Local generation of singlet oxygen, $^1O_2$, and/or different reactive oxygen species (ROS) oxidizes biomolecules in their vicinity. Finally, the generated oxidative stress and associated damage culminate in cancer cell death via different mechanisms.

Figure 1. Ligand-targeted strategies may ensure effective delivery of IV-administered photosensitizers (PSs) to cells of the tumor microenvironment. Upon intravenous administration, a ligand-targeted PS is expected to be in circulation for adequate time to allow extravasation through endothelial fenestrations of the angiogenic tumor blood vessels into the tumor mass. Upon tumor accumulation, the targeting moiety attached to the PS is recognized by receptors overexpressed on the surfaces of cancer or other stromal cells, leading to endocytosis-mediated internalization of the PS. When the targeting-ligand and/or drug delivery carrier exhibits fusogenic properties that can destabilize the endocytic vesicles, the PS is released into the cell cytosol with further accumulation in different organelles. However, the PS may remain entrapped at the endocytic compartment until the illumination time. After a certain time (drug-to-light interval, DLI) which typically corresponds to the time that allows the highest tumor accumulation, illumination of tumors is performed with a laser at an appropriate wavelength. Photons are then absorbed by the PS which interact with molecular oxygen in type I and/or II reactions. Local generation of singlet oxygen, $^1O_2$, and/or different reactive oxygen species (ROS) oxidizes biomolecules in their vicinity. Finally, the generated oxidative stress and associated damage culminate in cancer cell death via different mechanisms.
In this review, the major advances regarding active targeting delivery of PSs, either by means of ligand-derived PS bioconjugates or by taking advantage of ligand-targeting nanocarriers, will be discussed in the context of cellular-PDT for cancer treatment.

2. Targeting Approaches in the Context of Cancer

2.1. Targeting Different Populations of the Tumor Microenvironment

A tumor is not only a group of cancer cells proliferating in an uncontrolled manner but rather a complex tissue composed of different types of cells. These cells include cancer cells, cancer stem cells, endothelial cells, pericytes, cancer-associated fibroblasts and different types of immune infiltrating cells [28]. Collaborative interactions between cancer cells, associated stroma cells and the extracellular matrix form the tumor microenvironment, which governs disease initiation, progression and metastasis formation [29]. An awareness of the complexity of the tumor microenvironment is gaining acceptance as a necessary consideration for the design of novel cancer therapies. Indeed, a successful therapeutic approach should take into consideration the tumor microenvironment dynamics, and potentially, strategies that target different tumor cell populations may enhance therapeutic outcomes [29].

2.1.1. Targeting Cancer Cells and Cancer Stem Cells (CSCs)

The majority of the targeting approaches investigated to date are aimed at targeting cancer cells. Cancer cells express a large number of cell-surface receptors, often overexpressed, to fulfill the needs of tumor growth, migration, invasion and metastasis. Hence, these receptors can serve as suitable candidates for ligand-targeted cancer therapy.

Growth factor receptors, such as folate (FA) and transferrin (Tf) receptors, are regularly probed cancer cell targets owing to their overexpression in cancers of different histological origin. Different isoforms of the FA receptor (FR) exist with the α form present in several types of cancer cells, while the β form is mainly found on tumor-associated macrophages and monocytes [30]. FRα confers advantages for tumor growth, even in microenvironments with limited folate availability [31]. Similarly, the human Tf receptor 1 (TfR1) is an example of a transmembrane glycoprotein receptor often overexpressed on the surfaces of cancer cells [32], which ensures iron uptake by cancer cells, thereby playing a crucial role in cell growth [33]. FA and Tf targeting have proved to significantly enhance internalization in cancer cells. However, a certain degree of non-specificity may arise, as expression of those receptors in healthy tissues also occurs. Moreover, folate from diet can also be found in significant levels in body fluids, which will compete with the targeting therapy [34].

Other approaches based on the recent advances in antibody engineering and phage-display technology have been used to achieve targeting strategies with higher selectivity and specificity. For instance, monoclonal antibodies (mAbs), antibody fragments and nanobodies have been used to target cancer cell receptors with higher specificity. In this regard, the epidermal growth factor receptor (EGFR) is one of the most studied. EGFR is a receptor tyrosine kinase (RTK) expressed on normal human cells; however, significantly higher levels of expression are correlated with malignancy in a variety of epithelial cancers [35,36]. Its activation stimulates key processes for tumor growth, such as proliferation, angiogenesis, invasion and metastasis formation [36]. Targeting of EGFR has been achieved successfully with the mAb cetuximab [35] and by means of different peptides, such as the GE11 peptide [37–40]. Human epidermal receptor-2 (HER-2), another RTK, also represents a relevant therapeutic target as it is the most common overexpressed receptor in breast cancers, while it is minimally expressed in normal tissues [35,40]. Targeted therapy using clinically approved, anti-HER-2 mAb trastuzumab is widely used for the treatment of HER-2 breast cancer [41].

Within tumors, CSCs are a small subpopulation of cells which are capable of self-renewal and differentiation into multiple cell types. CSC are highly tumorigenic and are also referred to as tumor-initiating cells. For instance, as few as 100 CSCs (isolated and identified as CD44+ CD24-) were able to induce tumor growth in non-obese diabetic/severe combined immuno-deficient (NOD/SCID)
mice [42], while in a humanized mouse model (NSG\textsuperscript{TM}), injection of 1000 melanoma CD71\textsuperscript{+} cells resulted in successful tumor induction [43]. The CSC tumor subpopulation is very challenging to eliminate, as they are often resistant to therapies, including chemotherapy and radiotherapy [44]. Despite this, CSC targeting presents an opportunity to fight cancer at the root by avoiding tumor relapse and metastasis formation [45].

The most common CSCs surface markers include CD44, CD133, ALDH1A1, CD34, CD24 and epithelial cell adhesion molecule (EpCAM). Among them, CD44 and CD133 are found overexpressed in different types of cancer. They are transmembrane glycoproteins with different functions that promote tumorigenesis. Targeting of CD44 may be achieved through the use of its endogenous ligand, hyaluronic acid (HA) [46], and by means of antibodies [46,47]. Other prominent markers of CSCs may be also targeted by monoclonal antibodies [48].

2.1.2. Targeting Endothelial Cells from Tumor Angiogenic Blood Vessels

The tumor microenvironment offers alternative targets for tumor delivery, including endothelial cells of the tumor blood and lymphatic vessels [49]. Cancer growth relies on an ability to induce the formation of new capillaries from pre-existing vessels, a process termed angiogenesis [12]. Thus, vascular endothelial cells are an important target for cancer treatment, as impeding angiogenesis is expected to cause tumor cell death due to reduced oxygen and nutrient supply [36]. Inhibition of angiogenesis may itself be a selective process. It occurs with a limited number of physiological processes, including wound healing, ovulation and pregnancy [50]. From a practical perspective, vascular endothelial cells are more directly accessible following systemic administration, and therefore, long circulation half-lives of the targeting therapeutics might not be necessary. Slower mutation rate and reduced risk of acquired drug resistance are additional advantages of targeting endothelial cells [14,51].

The unique features of the tumor vasculature have allowed the identification of several molecular targets that can be exploited to deliver therapeutics to the vasculature. The vascular endothelial growth factor receptors (VEGFR) are a family of glycoprotein receptors with vital functions for tumor vessel angiogenesis and neovascularization. VEGF overexpression has been associated with advanced tumor progression. Thus, the VEGF/VEGFR signaling blockade is of great interest as a targeted therapy. This may be achieved through mAbs (e.g., ramacirumab and tanibirumab) for colorectal, breast and lung cancers [52].

Integrins serve as another potential target of the tumor endothelial cells. Integrins are a family of cell surface transmembrane receptors that mediate interactions between the cell cytoskeleton and the extracellular microenvironment [53]. For instance, the $\alpha_v\beta_3$ integrin is highly expressed on neovascular endothelial cells and tumor cells, while lower expression is found in resting endothelial cells and most healthy tissues [36]. With regard to targeting $\alpha_v\beta_3$ integrins, cyclic or linear derivatives of RGD (Arg–Gly–Asp) oligopeptides have been the most studied ligands [36]. Other ligands have included mAbs such as abituzumab, an anti-$\alpha_v$ class integrin inhibitor [54]. Abituzumab has presented a typical profile of integrin-targeting therapeutic development with promising preclinical in vivo results that demonstrated tumor growth blockade. However, late phase clinical trial outcomes were very disappointing [53,55]. In a phase 1/2 trial, combination of abituzumab with standard therapy of cetuximab plus irinotecan for the treatment of wild-type metastatic colorectal cancer compared to standard therapy alone demonstrated a lack of improvement [56]. The lack of success of integrin targeted therapies may be attributed to the potential drawback of animal models as misleading guides [57].

Vascular cell adhesion molecule-1 (VCAM-1) is a transmembrane immunoglobulin found expressed on the surfaces of tumor endothelial cells [58]. It is an optimal target due to its virtual absence from normal human vasculature [59]. VCAM-1 expression is induced by several inflammatory cytokines and plays a significant role in leukocyte recruitment to sites of tissue inflammation [60]. Additionally, during tumor migration and angiogenesis, integrins on the surfaces of tumor endothelial cells bind
to VCAM-1 [59]. This binding promotes cell-to-cell adhesion and potentially extravasation of cancer cells, and therefore, metastasis formation. VCAM-1 is aberrantly expressed in breast, gastric, renal, melanoma, ovarian and colorectal cancers [58,61]. VCAM-1 may be targeted in drug delivery through the use of anti-VCAM-1 mAbs, which have been shown to enhance vascular tumor accumulation [14].

Finally, matrix metalloproteinases (MMP) are also promising targets of the tumor microenvironment. MMPs are a family of zinc-dependent endopeptidases mainly responsible for the turnover and degradation of the extracellular matrix [59]. MMPs are present in nearly all human cancer cells and their expression is correlated with metastatic potential and patient prognosis [62,63]. As an example, the MMP aminopeptidase N (APN), also known as CD13, is overexpressed on the endothelial cell surfaces of almost all major tumor forms. It has important roles in angiogenesis and tumor cell invasion. It is the receptor of the NGR peptide (Asp-Gly-Arg) and of its cyclic form. Both are widely used to target drugs towards tumor vessels [62,64].

2.1.3. Simultaneous Targeting of Different Cell Populations of the Tumor Microenvironment

The targeting of a marker present on multiple tumor cell types may offer the possibility of simultaneously targeting different cells that contribute to tumor progression (Table 1).

Significant progress was achieved with the discovery of the Lyp-1 peptide by Laakkonen et al. [65], which specifically binds to p32 receptors. These are overexpressed on tumor cells, tumor-associated macrophages and tumor associated lymphatics [66]. Targeting of tumor lymphatics vessels, in addition to cancer cells, could improve significantly therapeutic effects. This is due to metastasis formation often occurring upon cancer cells’ migration through the tumor lymphatic vessels [67,68]. Lyp-1 is a cyclic, 9-amino acid peptide that co-localizes with three different lymphatic endothelial cell markers, including lymphatic vessel endothelial hyaluronic acid receptor-1 (LYVE-1), podoplanin and VEGFR3. Importantly, it does not colocalize with lymphatic vessels of normal tissue. In addition to its targeting abilities, Lyp-1 has been demonstrated to have intrinsic therapeutic activity with inhibition of breast tumor growth in vivo [69]. Based on the success obtained with Lyp-1, the p32 receptor continues to be used as part of the screening process for ligands capable of lymphatic targeting [70].

Nucleolin is an intracellular protein overexpressed on both tumor endothelial cells and cancer cells of different histological origin [71]. Recently, it was also shown as a marker of breast CSCs [72]. Thus, nucleolin targeting enables simultaneous tackling of different tumor cell populations, which is expected to bring important therapeutic benefits. Major achievements have been revealed with the F3 peptide, a synthetic 31 amino acid peptide, which is a specific ligand for nucleolin [72–76].

In addition to enhanced cellular internalization, both the F3 and the Lyp-1 peptides can act as tumor-penetrating peptides due to the presence of “C-end rule” (CendR) motifs within their sequences [77]. Peptides with one arginine (R) (or rarely a lysine (K)) in the C terminus with the sequence R/K/XXR/K can be recognized and internalized by neuropilin-1, which is overexpressed on tumor endothelial and cancer cells. This activates a trans-tissue transport pathway which is mediated by endocytosis and exocytosis of the targeting therapeutics through endothelial and cancer cells, thereby allowing vascular extravasation and penetration across the tumor mass. F3 and Lyp-1 peptides are expected to be cleaved by endogenous proteases, exposing their internal CendR at the C-terminus, which improves tumor penetration [78]. Other examples of peptides with multi-targeting abilities are presented in Table 1.
Table 1. Examples of peptides for simultaneous targeting.

| Peptide | Receptor | Target Cells of TME                                                                 | Ref.       |
|---------|----------|------------------------------------------------------------------------------------|------------|
| Lyp-1   | p32, NRP | Cancer cells, tumor lymphatic endothelial cells and tumor associated macrophages    | [65,79]    |
| F3      | Nucleolin| Cancer cells, CSCs and tumor endothelial cells                                      | [71–73,80,81]|
| iRGD   | $\alpha_v\beta_3$, $\alpha_v\beta_5$ NRP | Cancer cells and tumor endothelial cells                                           | [77,82]    |
| T1      | p32, NRP | Cancer cells, tumor lymphatic endothelial cells and tumor associated macrophages    | [70,83]    |
| FS6     | VEGFR1   | Cancer cells, tumor endothelial cells, fibroblasts and tumor associated macrophages | [84]       |

2.2. Ligands for Active Targeting

Specific delivery of anti-cancer drugs to solid tumors, at relevant therapeutic doses, is still an unmet goal. One promising strategy to overcome this problem relies on the use of targeting ligands that are specifically recognized and internalized by cancer cells and/or other cells of the tumor microenvironment while avoiding healthy cells. Ligands of diverse nature (proteins, peptides, antibodies, nanobodies, etc.) have been used. Advantages and disadvantages of different classes of ligands are presented in Table 2.
Table 2. Ligands for active targeting.

| Ligand Type | Examples | Characteristics | Advantages | Disadvantages | Ref. |
|-------------|----------|-----------------|------------|---------------|------|
| Proteins    | Transferrin | Glycoprotein  | High affinity/specificity of TfR1 interaction | Potential off-target toxicity with high doses | [33,34,85–88] |
|             |          | Aids iron transport via TfR1 | | Potential competitive binding to malignant cell receptors | |
| Peptides    | RGD, Lyp-1, GE11, F3 | Low molecular weight Typically <50 aas | High target receptor affinity/specificity Enhanced tumor diffusion Biocompatibility Low manufacture costs Ease of conjugation | Slow receptor identification Low stability in vivo which may be improved by chemical modifications. | [27,89–95] |
| Antibodies  | Trastuzumab, Cetuximab | Y shaped macromolecules | High receptor target affinity/specificity Stability in vivo | Potential immunogenicity Heterogenous tumor antigen expression High cost/resource intensive production Large size limits tumor penetration | [7,30,96–100] |
| Nanobodies  | 7D12, 7D12-9G8 | Small/fully functional antibody fragment | High receptor target affinity/specificity High tissue penetration High thermal and chemical stability Reduced immunogenicity relative to mAbs | Small size can lead to unfavorably high blood clearance rate which may be avoided by chemical modification | [97,101–105] |
| Non-protein | Folate, Polysaccharides–Hyaluronic acid (HA) Bile acids (BAs) | Folate is used for purine and pyrimidine biosynthesis HA is a component of the extracellular matrix BAs facilitate targeting of apical sodium dependent bile acid transporter (ASB) | High affinity Minimal immunogenicity | Folate conjugates may undergo slow release HA may cause off-target effects | [35,106–111] |
| Ligand Type | Examples | Characteristics | Advantages | Disadvantages | Ref. |
|-------------|----------|----------------|------------|---------------|------|
| Aptamers    | A10 PSMA AS1411 | ss-DNA/RNA, Fold into distinct secondary/tertiary structures. | High target receptor affinity, Minimal immunogenicity, Low manufacturing cost, Suitable for large scale production, High thermal and chemical stability | Off-target effects may result in toxicity, Susceptible to nuclease degradation in vivo if unmodified | [112–115] |
2.3. Strategies to Identify New Ligands

The identification of new targeting moieties with higher specificity for tumors is still required for the development of targeting strategies with minimal normal tissue interaction. In the context of PDT, improved specificity is expected to significantly reduce skin sensitivity. This sensitivity is still one of the most limiting PDT side effects. Additionally, new ligands with multi-targeting abilities are also highly desirable in order to tackle the complexity and aggressiveness of the tumor microenvironment.

Phage display technology is an effective means of identifying new antibodies and peptides that can target a certain receptor. It was developed in 1985 and regained popularity with the award of half of the 2018 Nobel Prize in Chemistry to Smith and Sir Gregory Winter [116,117]. This method takes advantage of bacteriophage (viruses that infect bacteria) machinery to synthesize and display different sequences of foreign peptides or antibodies at their surfaces. Phage display screenings can be performed in situ (e.g., with a recombinant form of the target receptor), in vitro using whole cells and even in vivo. In situ phage display studies include what was reported by Li et al. over a decade ago and allowed the discovery of the GE11 peptide (YHWYGYTPQNVI) [39], still largely used to target EGFR [118–120]. The EGFR mimotopes, P26 (VPGWSQAFMALA) and P19 (DTDWVRMRDSAR), were also recently identified [121]. Other examples include the LS-7 (LQNAPRS) peptide which targets the CSC-associated marker CD133 [122] and the new nanobody VUN100 for targeting the G-protein coupled receptor homolog US28 that is found to be overexpressed in glioblastoma [123]. Antibodies with inhibitory activity towards integrin α11/β1 were also identified in situ [124]. Recently, in vitro phage display using gastric cancer cells allowed the identification of DE532 (VETSQYFRGTLS) and GP-5 (IHDKKNAPSLVP) peptides, and specific antibodies to target gastric cancer [125]. The RKOpep (CPKSNNNGVC) peptide was selected for colorectal cancer targeting [126]. In vivo phage display was first described by Ruoslahti and co-workers in 1996 principally to identify new peptides to target brain blood vessels [127]. Later, the same group discovered the tumor-homing peptides F3 (KDEPQRRSARLSAKPAPPKPEPKKKAPAKK) [73], LyP-1 (cCGNKRTRC) [65] and TT1 (AKRGARSTA) [83], which have multi-targeting abilities. Lately, the CSP-GD (GDALFSVPLEVY) and CSP-KQ (KQNLAEG) peptides have also been recognized by in vivo phage display as potential ligands to target human cervical cancer [128].

Additionally, computer-aided drug discovery (CADD) methods have become important tools, as they permit the simulation and/or prediction of drug-target binding, by structure or ligand-based strategies [129]. When the structure of a certain cancer target/receptor is readily available, structure-based techniques can predict possible interactions between the target and different known ligands using data-mining. On the other hand, if there is no available information on the structure of the cancer target/receptor, new ligands can be designed using available ligands as references for that target.

The work of Hidayat et al. is an example of structure-based identification of new ligands [130]. With the aim of targeting the integrin αvβ3 receptor, complexes of integrin αvβ3 receptor-peptidomimetic (RGD) were used to reveal the structure of the integrin binding site. Three pharmacophores were identified, which further guided the design of a new ligand. Molecular docking confirmed the interaction of the new ligand with the integrin αvβ3 receptor, and molecular dynamics studies predicted a good stability of the new ligand when bound to the integrin αvβ3 receptor and a good inhibitory activity. However, this ligand was never validated with in vitro or in vivo studies.

3. Ligand-Targeted Photosensitizers

The covalent binding of PSs to ligands, specifically recognized and internalized by cancer cells and/or other cells from the tumor microenvironment, is an approach that has been explored to enhance the selectivity and efficacy of PDT [131]. The following section highlights some of the most promising targeted PS bioconjugates.
3.1. Folate and Transferrin-Targeted PS

FA and Tf are among the most often used targeting ligands, included in PDT. Although more frequently explored in nanocarriers for the targeted delivery of PSs, a few works have reported the synthesis of bioconjugates with improved selectivity for cancer cells [132]. Condensation of a carboxyl group with an amino group was used by Stallivieri et al. [133] and Suvorov et al. [134] for the conjugation of different PSs (e.g., 5,10,15,20-tetraphenylporphyrin (TPP), protoporphyrin IX (Pp IX), 5,10,15,20-tetraphenylchlorin (TPC), chlorin e₆, pheophorbide-a and zinc(II) phthalocyanines) to FA. Although lacking studies which demonstrate enhanced internalization by cancer cells, this work can serve as guideline for the synthesis of novel FA-targeted PS conjugates. Yang et al. [108] reported the conjugation of FA to a platinum porphyrin complex through an ethylenediamine linker. The activation of carboxylic acids from both FA and the platinum porphyrin complex allowed the formation of amide bonds with the linker (first the FA, followed by the PS), yielding a new FA-targeted PS selective for FRα-positive cell lines (HeLa cells). Confocal microscopy studies confirmed the endocytosis of the targeted-PS by HeLa cells, as opposed to the FRα-negative cell line (A549 cells). Phototoxicity assays showed further evidence of the PS’s selectivity, with a decrease of 78% of the viability of the FRα-positive cell line when compared to 25% of the FRα-negative line. Similarly, FA-targeted π-extended diketopyrrolopyrrole-porphyrin was also shown to be selective for FRα-positive HeLa cells [135]. The work of Liu et al. provides an important validation of the in vivo benefits of FA-targeting [136]. In a mouse model of nasopharyngeal epidermoid carcinoma, the conjugation of pyropheophorbide a with FA, using a 1 kDa polyethylene glycol (PEG) spacer, showed superior tumor accumulation and PDT efficacy when compared with the free or the non-targeted controls. Improvements were also noted when directly compared with the targeted-PS without the spacer PEG, highlighting the importance of the long blood circulation times needed to take advantage of the EPR effect. The PEGylated FA-targeted PS was able to eradicate subcutaneous KB tumors in BALB/c nude mice, at a considerably reduced dose (i.e., 60 nmol/mouse, DLI = 4 h, DL = 180 J/cm² at 670 nm). No recurrence occurred in the 90 days following treatment, unlike the non-targeted PS and the non-PEGylated targeted PS cases [136].

In 1994, Hamblin and Newman [137] were the first to report the conjugation of Tf to a PS, namely, hematoporphyrin. Their studies showed improved internalization of Tf-targeted hematoporphyrin by cancer cells (HT29 cells) and normal fibroblast (3T3), which increased the phototoxicity of hematoporphyrin. However, the uptake was only improved in an iron-deficient environment (which upregulates Tf receptors) and in medium supplemented with polycations (to increase binding to cell membranes). With this knowledge, it was anticipated that the in vivo translation of this targeting approach would be challenged by competition with the native form of Tf. Later, Cavanaugh [86] renewed attention on TfR1 as a PDT target and developed a method for the conjugation of chlorin e₆ to Tf, which involved the preliminary binding of the protein to quaternary amino ethyl-sephadex. After saturating the sephadex with Tf, the solution of chlorin e₆ with its activated carboxylic acid, was added. The Tf-targeted chlorin e₆ had the ability to kill in vitro breast cancer cells at concentrations 10–40-fold lower than the ones used with the free chlorin e₆. More recently, Kaspler et al. [138] reported the conjugation of a ruthenium (II)-based photosensitizer (Ru(II)(4,4′-dimethyl-2,2′-bipyridine(dmb))₂(2-(2′,2′′′:5′′′,2′′′-terthiophene)-imidazol[4,5-f]-[1,10] phenanthroline))Cl₂, known as TLD1433) with Tf. The Tf-targeted conjugate was associated with enhanced internalization and phototoxicity in rat bladder cancer cells when compared with the non-targeted counterpart. In vivo studies with mice bearing the highly immunogenic CT26.CL25 tumors revealed approximately 70% of overall survival with the Tf-targeted conjugate (50 mg/kg, 600 J/cm² at 808 nm), whereas only ≈30% was attained with the ruthenium complex alone [139–141].

3.2. Antibody and Nanobody-Targeted PSs

Antibodies and their fragments constitute another class of moieties commonly used for PS delivery which has increased in popularity with the progression of personalized medicine. Conjugation
through lysine (amide and isothiocyanate conjugation) or cysteine (maleimide conjugation), SNAP-Tag conjugation and “click” chemistry (copper-catalyzed alkyne-azide cycloaddition and copper-free strain-promoted alkyne-azole cycloaddition) are the most common synthetic strategies for the development of tetrapyrrole-based antibody-PS conjugates. This has been recently discussed in great detail by Sandland and Boyle [99].

One of the most promising examples of antibody-targeted PS relies on the water-soluble silica phthalocyanine-based PS IRDye700DX (IR700), which has been conjugated to different mAbs. Initially, studies performed with trastuzumab or panitumumab (anti-EGFR mAb)-targeted IR700 showed a preferential accumulation of the PS at the A31 cell membrane, inducing necrotic cell death upon illumination at 690 nm. In vivo specific A431 (epidermoid) and 3T3/HER2 (breast) tumor accumulation and shrinkage were initially reported (300 µg/mouse, DL1 = 24 h, DL = 30 J/cm²) [142]. This strategy was further investigated for bladder cancer treatment, either in monotherapy with panitumumab-targeted IR700 [143] or upon combination of the latter with trastuzumab (anti-HER2)-targeted IR700 [144]. Additional works have demonstrated that this strategy can be effective for tumors of different histological origin by using antibodies against relevant targets. Examples include prostate cancer (prostate-specific membrane antigen, known as PSMA) [145,146]; oral cancer (CD44); lung cancer (delta-like protein 3) [147,148]; glioblastoma (CD133) [149]; and melanoma (CD146) [150].

Overall, mAb-IR700 has the ability to induce specific cell death of cancer cells while sparing adjacent healthy tissue, tumor vessels and infiltrating-immune cells [142–150]. The mechanism triggering necrotic cell death was recently highlighted by Sato et al. [151]. By using trastuzumab, panitumumab or cetuximab-targeted IR700, the authors showed that a light-induced ligand-release reaction occurs upon illumination at 690 nm. The latter affects the physical properties of the conjugate, inducing physical stress, which, in turn, leads to the disruption of the cell membrane, cell swelling and blebbing followed by bursting of the membrane. Importantly, this enables the release of the intracellular content (including danger associated molecular patterns, DAMPS), thereby triggering the activation of the host immune system. This systemic response contributes to the long-term control of the disease and further therapeutic improvements can be achieved through inhibition of immune checkpoint blockers. For instance, combination of cetuximab-targeted IR700 with blockade of the PD1/PLL1 axis was shown. This resulted in complete rejection of MC38 tumors and inhibition of distant (and not illuminated) metastasis [152]. Phase 1/2 clinical trials (NCT02422979) of cetuximab-IR700 (RM1929) in patients with recurrent and advanced head and neck squamous cell cancer demonstrated encouraging results with several cases of partial remissions and others of complete remission [153,154]. Currently, the phase 3 clinical trial (NCT03769506) is ongoing [155].

Work continues to explore antibody-IR700 conjugates, such as the case-study reported by Isobe et al., wherein this PS was conjugated with an antibody targeting delta-like protein 3 (a specific biomarker of small-cell lung cancer) [148]. PDT resulted in reduced growth in tumor size of small cell lung cancer (i.e., SBC3 and SBC5 cell lines) xenografts in mice. Other examples of antibody-targeted PS are revealed in the works of Aung et al. and Darwish et al. using 1849-indocyanine green and a phthalocyaninato zinc(II) (ZnPc), respectively [156,157]. Aung et al. conjugated the PS with an antibody targeting tissue factor (TF) which is overexpressed in pancreatic cells [156]. Selectivity for pancreatic tumors in vitro and in vivo, and reduced tumor growth in xenografts, were shown. Darwish et al. targeted the CD38 glycoprotein which is overexpressed in myeloma and confirmed their hypothesis of increased selectivity and phototoxicity in vivo with their novel conjugate [157].

IR700 has also been successfully targeted to different types of cancer cells by means of nanobodies. Nanobodies are small but fully-functional fragments of the classical antibodies, each consisting of only a single variable heavy chain. The single domain structure leads to not only reduced immunogenicity in targeting but enhanced tumor diffusion and a more homogenous tissue distribution in comparison to intact mAbs. Driel et al. demonstrated that EGFR nanobody-IR700 conjugate selectively accumulated, at a time point as short as 1 h, in orthotopic OSC head and neck tumors, leading to ≈90% tumor necrosis while sparing adjacent healthy tissues [105]. Heukers et al. recently published the use of a nanobody to
target IR700 to cancer cells overexpressing c-Met, a receptor tyrosine kinase also known as hepatocyte growth factor receptor [158]. The nanobody-PS conjugate specifically killed gastric MK45N cancer cells in the nanomolar range. De Groof et al. reported a nanobody-IR700 conjugate to target cells expressing US28, a viral G protein-coupled receptor (GPCR) that has an oncomodulatory effect in the progression of glioblastoma [123]. The nanobody-targeted IR700 selectively destroyed glioblastoma cells in 2D and 3D in vitro cultures, showing potential for in vivo PDT. Notably, better tumor penetration and faster clearance was achieved in comparison to an anti-US28 antibody-targeted IR700 conjugate. This demonstrated the binding superiority of the nanobody in comparison to previously reported antibody [159].

Lastly, affibodies are another interesting class of targeting moieties. Affibodies are synthesized peptide mimetics of antibodies that have high specificity towards specific proteins. Owing to their small size (6–7 kDa), they exhibit better tissue penetration. Yamaguchi et al. reported the conjugation of IR700 to an affibody targeting HER2 [160]. The results pointed to a clear selectivity of the conjugate for HER2-overexpressing breast cancer cells, and a strong phototoxic effect mirrored in the low cell viability measured. The cell death mechanism observed with this affibody-PS conjugate was similar to the one proposed by Sato et al. [151].

3.3. Peptides-Targeted PS

The use of small peptides for the delivery of PS generally improves solubility in aqueous solutions, leading to higher phototoxicity and therapeutic efficacy [161]. Solution- or solid-phase strategies, involving carboxylic acid activations, Michael additions and Huisgen cycloadditions, have been used for conjugation of peptides to PSs and are discussed in detail by Williams et al. [162].

The peptide GE11 [39], discovered through phage display against EGFR, has attracted the interest of several researchers. Yu et al. reported the synthesis, characterization and in vitro phototoxicity of a GE11-targeted 1,4-bis(triethylene glycol)-substituted carboxyl ZnPc [161]. Enhanced internalization and phototoxicity of the GE11-PS conjugate was observed in EGFR-positive cells (A431 cells) but not in low-EGFR-expressing cells (MCF7). Biodistribution studies through in vivo fluorescence imaging revealed enhanced accumulation of the GE11-PS conjugate in A431 tumors in comparison to the PS attached to a control peptide. However, PDT efficacy in a cancer mouse model was not investigated. More recently, Kim et al. have also reported a GE11-chlorin(e4) conjugate (RedoxT) for theranostics [163,164]. The in vitro assays using HCC70 cells showed specific EGFR-mediated uptake and enhanced phototoxic effect of the conjugate [163]. Triple-negative breast cancer cells overexpressing EGFR (e.g., MDA-MB-231 and MDA-MB-468 cells) also benefited from this targeting approach, which was shown to be useful for in vivo near infrared (NIR) fluorescence imaging on xenograft mouse models [164]. With the aim of targeting sex-hormone-dependent tumors (namely breast cancers), a mono-substituted β-carboxyl ZnPc was targeted to gonadotropin-releasing hormone receptors (GnRHRs) upon conjugation with two GnRH peptide analogues. This included a native GnRH peptide which was directly conjugated to the PS, and an optimized form with a D-Lys as an anchoring point for the lysosomally cleavable hexapeptidic spacer (GGGFLG) which connects to the ZnPc. For the two conjugates, the selectivity and phototoxicity was higher in comparison to the free ZnPc, both in vitro and in vivo, in breast cancer models. Of note, the optimized analogue inhibits the blood–brain barrier crossing which is typically observed in GnRHR targeting. It also exhibited less skin accumulation. Thus, it might constitute a valuable targeting approach for breast cancer [165]. A correlation between higher GnRHRs expression and worse prognosis for head and neck squamous cell carcinoma (HNSSC) was also recently established, suggesting GnRHRs as potential targets for this type of cancer. In accordance, the conjugation of GnRH peptides to protoporphyrin IX was shown to effectively inhibit the viability of Detroit-562 pharyngeal carcinoma cells when compared to the free PS [166].

Recently, Zhang et al. developed an approach which envisages the targeting of the cell membrane of cancer cells without promoting cellular internalization [167]. To achieve this goal, the authors
attached Pp IX to the K-Ras-derived peptide, KKKKKSSKTKC-OMe, which has the ability to target the plasma membrane. The bioconjugate was able to destroy the cellular membrane of 4T1 cells at low concentrations, allowing a fast release of DAMPs, and therefore, immunogenic cell death. Both in vitro (4T1 cell line) and in vivo (4T1 tumor-bearing mice) assays showed an increased anti-tumoral effect of the bioconjugate when compared with the non-targeted counterpart. The triggered anti-tumor immunity was strong enough to inhibit the growth of contra-lateral (and non-illuminated) tumors and was potentiated upon combination with programmed cell death receptor 1 (PD1) blockade [167].

3.4. Other Targeting Strategies

While the abovementioned targeting strategies are the most used, additional approaches have been investigated for the development of targeted-PS conjugates (Table 3). Along with FA and Trf, other endogenous ligands have been investigated for anticancer targeted-PDT. For instance, biotin receptors have been shown to be more overexpressed than FRα in several cancer cell lines of different histological origin (e.g., colon, breast, renal, lung and leukemia) [168]. Biotin-targeted PSs were demonstrated to promote specific and enhanced accumulation in cancer cells, which was correlated with improved phototoxicity compared to what was obtained with free forms [168–171]. The synthesis of steroid-targeted PS is also a relatively common strategy, especially when targeting hormone-dependent tumors such as breast or ovarian cancers [172–174].

The metabolic changes of tumors may be explored as another approach to develop targeting strategies for cancer. Due to the high demand for glucose (Warburg effect) and cholesterol by the cancer cells, conjugation of PS with sugar molecules or lipoproteins (LDL, HDL) is being successfully used to improve the selectivity and phototoxicity of PDT [131,175,176]. Lastly, aptamer-targeted strategies have shown specificity similar to that obtained with the antibodies [114,177,178]. The low immunogenicity, longer shelf-life and low production costs constitute important advantages over antibodies.
Table 3. Examples of ligand-targeted tetrapyrrole PSs.

| Strategy          | PS                        | Ligand                              | Target                     | Application                                      | Ref.    |
|-------------------|---------------------------|-------------------------------------|----------------------------|--------------------------------------------------|---------|
| Endogenous ligand | Chlorin derivatives       | Biotin                              | Biotin receptor            | In vitro: CT26 cells                              | [168]   |
| Endogenous ligand | (Phthalocyaninato)zinc(II) | Biotin                              | Biotin receptor            | In vitro: HeLa and HuH-7 cells                    | [169]   |
| Endogenous ligand | Ruthenium (II) polypyridyl complex | Biotin                              | Biotin receptor            | In vitro: A549R cells                             | [170]   |
| Endogenous ligand | Silicon (IV) phthalocyanine | Biotin                              | Biotin receptor            | In vivo: mice bearing HeLa tumors                 | [171]   |
| Endogenous ligand | Pyropheophorbide a         | 17-substituted testosterone and epitestosterone | Androgen receptor         | In vitro: LNCaP and PC-3 cells                    | [174]   |
| Carbohydrate      | H₂TFPC (chlorin)          | d-glucose                           | Glucose transporter        | In vitro: MKN28, MKN45, HT29 and HCT116 cells; In vivo: mice bearing HT29 or HCT116 tumors | [175]   |
| Carbohydrate      | H₂TFPC (chlorin)          | d-mannose                           | CD206 (mannose receptor)   | In vitro: MKN28, MKN45, HT29, HCT116 and M1- and M2-polarized THP-1 macrophages; In vivo: mice bearing CT26 tumors In vitro: BaF3/gp130/IL6R/TNF cells expressing interleukin-6 receptor | [179]   |
| Aptamer           | Chlorin e₆ free acid      | AIR-3A (RNA aptamer)                | Interleukin-6 receptor     | In vitro: MCF-7, HCT 116 and SKOV-3 cells; Ex vivo: MCF-7 and HCT 116 tumours | [177]   |
| Aptamer           | Chlorin e₆ free acid      | AS1411 (DNA aptamer)                | Nucleolin                  |                                                   | [114]   |
4. Ligand-Targeted Nanocarriers for the Delivery of Photosensitizers

The development of delivery formulations that enable the systemic administration of a hydrophobic PS is an important aspect for its clinical translation. One promising strategy relies on the use of nanotechnology to create new drug delivery strategies [180]. The use of nanocarriers in the PDT field might not only improve PS solubility but also allow better pharmacokinetic and pharmacodynamic profiles, which would be expected to result in higher PS accumulations in tumors (either by passive or active targeting) while avoiding healthy tissues [181]. Overall, NPs have become increasingly popular within cancer PDT therapy as an effective means for PS delivery. Moreover, nanoparticles (NPs) can be prepared with different degrees of sophistication, allowing multifunctionality in a single system. In this regard, nanoplatforms which combine different therapeutic modalities (e.g., PDT + chemotherapy) or permit simultaneous diagnostic imaging and therapy functions (known as theranostics) have become very common.

The attachment of targeting moieties to the NPs’ surfaces is a strategy widely used to enhance tumor accumulation and the treatment specificity. However, with regard to tumor accumulation, the success of a targeted system is not straightforward, as many factors come into play. Indeed, the nanocarrier’s physicochemical properties (size, shape, charge, etc.), the type of ligand (proteins, peptides, antibodies, nanobodies, etc.), the target receptor (level of expression and ability to be internalized) and the pathophysiology of tumor (namely the blood and lymphatic vessels network) strongly impact tumor accumulation and cellular internalization [7]. For instance, Shmidt et al. developed a mechanistic model which suggests that active targeting of nanoparticles ≥50 nm does not improve tumor accumulation when compared with the non-targeted controls [182]. In accordance, a few works have demonstrated that targeted nanoparticles do not necessarily increase tumor accumulation, but instead cellular internalization [10,11].

To date, many types of organic and inorganic nanoplatforms have been developed for delivery of PSs (Figure 2). Typically, organic NPs are composed of lipids or polymers with the advantages of high biocompatibility and increased PS solubility. Inorganic NPs are metallic, metal oxide and metal salt in composition and have favorable optical properties that might enhance PDT properties. In the next section, ligand-targeted NPs aimed at systemic delivery of PSs (principally tetrapyrrole PSs) for cancer treatment will be briefly discussed.

Figure 2. Types of nanoparticles (NPs) that have been used to improve PS (depicted by green) solubility, bioavailability and tumor targeting: (A) lipid-based NPs (liposomes and solid lipid NPs), (B) polymer-based NPs (hydrogel and PNP), (C) cyclodextrin NPs, (D) inorganic NPs (Au, Fe and Si-NPs), (E) carbon nanomaterials (carbon nanotubes and fullerene) and (F) metal organic frameworks.
4.1. Ligand-Targeted Lipid-Based NPs

Lipids offer significant potential as natural and biocompatible materials for drug delivery [183]. Due to the hydrophobic nature of several PSs, lipid-based formulations have been considered as ideal carriers, which can be confirmed by the clinically approved liposomal formulation of verteporfin (known as Visudyne®) which is used for the treatment of age-related macular degeneration [184,185].

Liposomes are currently the most promising lipid-based NPs. Due to the development of liposomes by Bangham in 1965 [186] and thanks to evaluations of their biochemical properties over decades, liposomes have become a pioneer’s choice for drug delivery. Liposomes are typically composed of phospholipids but may also include other lipids, such as cholesterol. Typically, they can be defined as spherical vesicles having at least one (unilamellar lipid vehicles, SUV) or more (multilamellar lipid vehicles, MLV) lipid bilayers. Their structure contains two regions—hydrophilic, composed of the aqueous core, and hydrophobic, composed of lipids chains, meaning that they can be used as a drug carries for lipophilic or hydrophilic molecules [187]. Further improvements can be mediated by the functionalization of their surfaces through the chemical conjugation of targeting ligands. This is often attained via amide, disulphide or thioether bonds [188]. A variety of molecules, including mAbs (cetuximab [189], anti-HER2 [190]), peptides (cRGD [93], APRPG [191]), vitamins (biotin [192], FA [193]) and polymers (HA [194]) (Table 4) have been explored to improve liposome selectivity and cellular internalization. For instance, Kato et al. attached FA moieties to the porphyrin-conjugated lipid NPs (known as porphysomes) [195–197]. The presence of FA has improved the targeting ability of the formulation, resulting in enhanced cell death of lung cancer cells when compared with the non-targeted control (72% vs. 17% and 76% vs. 1% cell death in A549 and SBC5 cells, respectively). Moreover, in vivo fluorescence imaging showed specific accumulation of the Fa-targeted liposomes in A549 tumors. This correlated with a reduction of the tumor growth, a decrease of the Ki-67 cell proliferation index and enhanced cell apoptosis.

Nanocarriers offer the possibility of combining multiple therapeutic agents (PSs, chemotherapy, etc.) and other functions (ligand-targeting, imaging-mediated diagnosis, etc.) within the same system, which helps to tackle different aspects related to cancer treatment. For instance, liposomes composed of thermosensitive lipids were used to simultaneously encapsulate the chemotherapeutic drug doxorubicin (DOX) and the near-infrared photothermal (PTT) and PDT agent indocyanine green (ICG). FA and gadolinium chelates were further attached to the liposomal surface. The developed multifunctional liposomes allowed in vivo imaging by fluorescence, photoacoustic spectroscopy and magnetic resonance while tumor eradication was mediated by the combination of chemotherapy, PTT and PDT. Indeed, the FA-targeted nanoplatform caused effective phototoxicity in vitro against HeLa cells and site-specific accumulation of the FA-targeted formulation in HeLa tumors after systemic administration, which was correlated with tumor eradication for at least 2 weeks following tumor illumination [198].

An analogous approach was evaluated for a liposomal formulation combining chlorin e6 as PS, ICG as a PTT agent, and the hypoxia activated prodrug tirapazamine (TPZ) as a cytotoxic agent. Surface modification was employed with cRGD and conjugation of gadolinium chelates. The targeting ability of the formulation to the αvβ3 integrin receptor was confirmed via intracellular fluorescence of the chlorin e6. Measurements confirmed enhanced cRGD-mediated endocytosis and distribution of the targeted-PS in the cytoplasm; no fluorescence signal was detected for the ligand-free formulation. Phototoxicity studies carried out in A549 lung cancer cells resulted in 97% cell death after illumination at 808/660 nm (PTT and PDT effects), and only 75% cell death was caused by illumination specifically at 808 nm (exclusively PTT effect). Further studies in A549 tumor-bearing mice revealed 5.63-fold enhanced tumor accumulation of the cRGD-targeted PS in comparison with the non-targeted control 8 h post-injection. No tumor was observed for at least 2 weeks post-treatment with the cRGD-targeted formulation and the dual-illumination at 808/660 nm, and tumor regrowth was observed for single illuminations at 808 nm. In addition, the combination of chlorin e6, gadolinium and ICG permitted a theranostic use of the formulation, by allowing in vivo fluorescence/photoacoustic/MRI imaging [93]. HA-targeted
liposomes were also used for the encapsulation of ICG aimed at treated glioblastoma cancer. In vitro studies using U-87MG cells showed 65% of cancer cell death after laser radiation at 808 nm. Additional studies using nude mice bearing U-87MG tumors confirmed site-specific accumulation of the developed HA-targeted liposomes treatment was correlated with effective inhibition of tumor growth (to just 12.7% of the control group tumor size) and a decrease of the cell proliferation marker Ki-67 [199]. Despite promise, this study lacks the non-targeted control which is important to address the real impact of the HA-targeting strategy used herein. Multifunctional platforms, including those just mentioned, are attracting increasing attention, although, it is expected that this high level of sophistication may cause their clinical translation to be more challenging.

Although liposomes are the best-known lipid-based NPs, new delivery strategies based on lipids other than phospholipids have emerged in recent years. Solid lipid NPs (SLNs) are usually composed of a crystal lipophilic core (triglycerides, glyceride or waxes) which is solid at room and physiological temperatures, in which hydrophobic drugs can be encapsulated. The lipid matrix is composed of physiological lipids. Their preparation does not require the use of organic solvents and is easily scaled-up. As drug mobility decreases in the solid lipid state, drug release can be tuned by the adjustment of the composition of the solid matrix, allowing sustained release [197]. Improvements of the SLNs led to the development of nanostructured lipid carriers (NLCs), which unlike their predecessors, are formed by mixing solid and liquid lipids (oils). This results in an imperfect crystal lipid matrix that enables enhanced drug loading capacity [200]. Only a limited number of studies describing SLN/NLCs for the targeted delivery of PSs have been published. Ding et al. developed a multifunctional FA-targeted PEGylated NLC platform for chemo-PDT by combining paclitaxel (PTX) and ICG [201]. In vitro studies in human liver carcinoma cancer cells (HepG2) exhibited dose-dependent synergistic effect of PDT and chemotherapy reaching nearly 80% cell death for the highest drug concentration (2 µg/mL), while not exceeding 60% cell death for the individual ICG and PTX treatments. Treatment of HepG2 spheroids with FA-targeted formulation containing both ICG and PTX impaired their growth (<200 nm) better than NPs containing only ICG or PTX (spheroids > 300 nm). In vivo studies revealed site-specific tumor accumulation just 2 h after systemic administration. FA-targeted PEGylated NLC enabled 28.48-fold higher ICG tumor accumulation when compared to its free form and optimal ICG tumor accumulation was observed at 12 h post-injection. Other recent studies using targeted lipid-based NPs for the delivery of PSs are summarized in Table 4.
Table 4. Examples of ligand-targeted lipid-based NPs for photodynamic therapy (PDT).

| Nanocomposition | PS                  | Ligand            | Target            | Extra Features | Application                                                                 | Ref. |
|-----------------|---------------------|-------------------|-------------------|----------------|-----------------------------------------------------------------------------|------|
| Liposomes       | Erythrosine-decyl ester | Biotin            | Biotin receptor   |                | In vitro: ATCC® CCL1.3™ cells                                               | [192]|
| Liposomes       | ICG                 | FA                | FR                | DOX, Gadolinium (III) | In vivo: mice bearing HeLa tumors                                            | [198]|
| Liposomes       | Pyropheophorbide a-lipid | FA                | FR                |                | In vitro: A549, H647, H460, SBC5 and DFC1024 cell lines; In vivo: mice bearing A549 tumors | [196]|
| Liposomes       | (5,10,15,20-Tetraporphyrinato)zinc(II) | FA          | FR                |                | In vivo: HeLa cells                                                        | [202]|
| Liposomes       | Temoporfin          | FA                | FR                | PEG            | In vitro: A549, KB and HeLa cells                                           | [193]|
| Liposomes       | Verteporfin         | Anti-EGFR antibody (Cetuximab) | EGFR            |                | In vitro: Ovcar-5, CAMA-1 and A431 cells                                   | [189]|
| Liposomes       | Verteporfin         | Anti-EGFR antibody (Cetuximab) | EGFR            | Irinotecan      | In vitro: OVCAR-5, U87 and J774 cells                                      | [203]|
| Liposomes       | Pheophorbide a derivative | Anti-EGFR antibody (Cetuximab) | EGFR            | DOX            | In vitro: A-431 SK-BR-3 cells; In vivo: A-431 tumors                      | [204]|
| Liposomes       | Hydrophobically modified ICG with octadecylamine (ODA) | Anti-Her2 antibodies | Her2             | DOX            | In vitro: MCF7, SKOV3, A549 and S180 cells; In vivo: mice bearing SKOV3, A549 and MCF7 tumors | [190]|
| Liposomes       | Chlorin e₆ free acid | cRGD              | αᵥβ₃ integrin receptor | TPZ, Gadolinium (III), ICG | In vitro: A549 cells; In vivo: mice bearing A549 tumors                      | [93]|
| Liposomes       | Verteporfin         | Factor VII (FVII) protein | VEGFR            |                | In vitro: CHO-K1, EMT6, HEK 293, MDA-MB-231 and HUVEC cells; In vivo: mice bearing EMT6 tumors | [205]|

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| Nanocomposition | PS      | Ligand | Target | Extra Features | Application                  | Ref.          |
|-----------------|---------|--------|--------|----------------|------------------------------|---------------|
| Liposomes       | ICG     | HA     | CD44   | PEG            | In vitro: U-87MG; In vivo: mice bearing U87MG tumors | [199]         |
| Liposomes       | 5,10,15,20-tetrakis(4-aminophenyl) porphyrin, 5, 10,15,20-tetrakis(4-hydroxyphenyl) porphyrin, 5, 10,15,20-tetraphenyl porphyrin | HA     | CD44   | Rhodamine       | In vitro: MDA-MB-231 cells | [194]         |
| NLC             | ICG     | FA     | FR     | Paclitaxel, PEG | In vitro: HepG2 and NIH3T3 cells; In vivo: mice bearing HepG2 tumors | [201]         |
| NLC             | 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecfluoro-29H,31H-phthalocyanine | FA     | FR     |                | In vitro: MCF-7 cells          | [206]         |
4.2. Ligand-Targeted Polymer-Based NPs and Hydrogels

Polymeric NPs can be prepared from naturally occurring (HA [207]) or synthetic (poly lactic-co-glycolic acid (PLGA) [208], PEG [209]) polymers that exhibit good biocompatibility profiles. In polymeric NPs, depending on the preparation method, the drug can be linked to the structure in various ways, such as encapsulation, adsorption, dispersion or covalent attachment. Numerous ligand-targeted NPs of different types have been developed to improve PDT for cancer treatment and are summarized in Table 5. The most promising works with in vivo validations are discussed further herein.

PLGA is a co-polymer thermo-responsive polyester used in approved therapeutic devices and widely explored in NPs for drug delivery. It is synthesized upon ring-opening copolymerization of lactic acid (LA) and glycolic acid (GA). This has been the most popular, widely studied and most improved method for NP production over the past few decades. It allows control over the polymerization process while special attention is paid to the LA/GA ratio. The latter has a tuning impact on the hydrophobic properties of the formulation, thereby controlling the drug release kinetics [210]. Many attempts have been made to modify the surfaces of PLGA-based particles with targeting moieties to increase their specificity for cancer cells or other cells from the tumor microenvironment. Recently, two very promising approaches were reported in the literature, emphasizing their application in the field of PDT. Zhang et al. developed PLGA-based NPs that simultaneously incorporated chlorin e6 and DOX [211]. The Ns surface was modified with methoxy-PEG and red-blood cell (RBC) membranes to avoid immune responses, while FA was added to increase the specificity towards cancer cells. This multifunctional system resulted in 25% more HepG2 tumor accumulation and 1.3-fold higher apoptotic rates in comparison with the non-targeted formulation. Treatments with the targeted NP enabled effective suppression of tumor growth, achieving a tumor weight that was 0.51 ± 0.17 g lower when compared with tumors treated with the non-targeted approach. Of note, no pathological changes in the surrounding tissues were observed.

Chen et al. proposed cRGDfK-targeted PLGA-based NPs, aiming specifically at targeting glioblastoma cells [212]. In order to overcome the hypoxic conditions often found in the tumor site, a H2O2-activatable catalase was incorporated in the NPs. Cellular selectivity of the formulation toward αvβ3 integrin was tested by comparing cellular uptake of the targeted and non-targeted formulation on αvβ3 integrin overexpressed U87-MG cells. After 3 h of incubation, strong fluorescence was detected, but only for the targeted formulation, while remaining low for the control group. Phototoxicity experiments resulted in 98% cancer cell death, while only 15% was reached with the catalase-free NPs. The benefit of the cRGDfK moieties was demonstrated in mice bearing U87-MG tumors. Higher tumor accumulation and complete inhibition of tumor growth was observed for the catalase and targeting moiety containing formulation, while other approaches led to tumor growth within 8 days post-treatment.

Another promising example relies on the use of GE11-targeted PEG-polycaprolactone (PCL) NPs containing HOSiPcOSei(CH3)2-(CH2)2N(CH3)2, (Pc4, silicon phthalocyanine 4). The GE11-targeted NPs exhibited 15% more internalization in SCC-15 human squamous cell carcinoma cells compared to the non-targeted control. Phototoxicity in the range of 95% and reduced clonogenicity were attained with low doses of the PS (400 nM). It is important to point out that the in vivo study carried out with SCC-15 tumor bearing mice resulted in comparable tumor regression within the first 30 days of treatment for both approaches. However, unlike the GE11-targeted formulation, after that time tumor regrowth was observed in the non-targeted nanoplatform treated group [213].

Recently, hydrogels, cross-linked three-dimensional scaffolds of hydrophilic polymers with the ability to swell in aqueous media, have been gaining attention in pharmaceutical engineering [214]. Common hydrogel formulations used for drug delivery can be composed of natural (chitosan, agarose, alginates, hyaluronic acid) or synthetic (PEG, poly(N-isopropylacrylamide)) polymers. Hydrogels, due to their ability to swell in aqueous media, have been used in the PDT field to overcome the low solubility of PSs in polar media, while preventing the premature release of the PS without affecting
its photophysical properties [215]. Moreover, depending on their composition, type of cross-linking and route of administration, hydrogels can tune the pharmacokinetic profile and biodistribution of the PS. However, it is important to note that the distinction between hydrogels and nanogels is not uniform and clearly defined. Very often the term nanogel is used to define nanosized hydrophilic polymeric materials, referring mainly to their ability to exhibit the EPR effect. Extensive research led to the development of site-specific smart gels that can be tuned to respond to physiological fluctuations (e.g., thermoresponsive hydrogels) [216] or actively target overexpressed receptors on cancer cells due to the attachment of specific ligands, such as polysaccharides [217] and antibodies [218], to the polymer surface. In the context of PDT, most of the developed hydrogels are intended for local administration followed by sustained released of the PS, which might allow one to perform multi-illumination procedures. Only a few examples of hydrogel-based NPs with proper features for systemic administration have been published.

Belali et al. developed a FA-targeted and pH-sensitive chitosan-based hydrogel conjugated with 5,10,15,20-tetrakis(4-aminophenyl)porphyrin (NH$_2$-TPP) [219]. With the highest tested concentration, about 80% MCF7 human breast cancer cell death was attained, which represented an increase of two times when compared with the non-targeted formulation (40% cancer cell death). Hah et al. prepared polyacrylamide (PAA)-based hydrogel conjugated to methylene blue (MB) as the PS, and PEG chains aimed at prolonged NPs circulation in plasma [220]. The surface of the hydrogel was further decorated with the F3 peptide, which can selectively target tumor vasculature and cancer cells. Phototoxicity experiments carried out on MDA-MB-435 cells resulted in 90% cell death for the F3-targeted formulation, while the non-targeted particles only reached about 30% cell death. An analogous system was later studied using 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH) as a PS, expanding the possible application as a theragnostic tool in cancer treatment [221]. Chitosan/alginate-based hydrogel nanoparticles were developed to improve the uptake of 5,10,15,20-tetrakis(N-methyl-4-pyridyl)porphyrin tetratosylate (TMP), a highly hydrophilic PS with limited ability to be internalized by cells. Antibodies targeting the death receptor 5 (DR5), which is upregulated in several types of cancer, were conjugated onto the NPs’ surfaces. In vitro studies conducted in HCT116 colorectal carcinoma cells showed two-times more cellular uptake and phototoxicity than the non-targeted control [218]. Similarly to NPs, multifunctional and stimuli-responsive hydrogels have been developed. Enzymatic-responsive hydrogels, with synergistic photodynamic (ICG) and chemotherapeutic (DOX) mechanisms of action exhibiting enhanced activity, were recently reported for head and neck cancer. Nanoparticles containing ICG or DOX were incorporated in hyaluronic acid-acrylate-based hydrogels, which were further conjugated to MMP [222]. Mice bearing SCC-15 tumors submitted to intratumoral injection of the developed multifunctional hydrogel exhibited strong tumor regression that was significantly higher than the one attained with hydrogels containing only ICG or DOX. However, the real contribution of MMP targeting is difficult to assess, as MPP free hydrogels were not tested. Despite them being encouraging, most of the described research with hydrogels lacks in vivo study, which makes an assessment of their real potential as novel pharmaceutical formulations difficult.
Table 5. Examples of ligand-targeted polymer-based NPs for PDT.

| Nanocomposition                                                                 | PS                          | Ligand | Target | Extra Features                  | Application                                      | Ref.   |
|--------------------------------------------------------------------------------|-----------------------------|--------|--------|---------------------------------|--------------------------------------------------|--------|
| Methoxy-PEG-PLGA-based PNP                                                      | Chlorin e₆ free acid        | FA     | FR     | PEG, RBC membranes, DOX         | In vitro: HepG2 cells; In vivo: mice bearing HepG2 tumors | [211]  |
| PEGylated PLG-co-hydroxymethyl GA-based PNP                                    | meso-tetraphenylchlorine disulphonic acid disodium (TPCS₂₂₆) | anti-HER2 nanobody (11A4) | HER2 | PEG, Saporin                   | In vitro: SkBr3 (HER2+), MDA-MB-231 (HER2-) cells | [223]  |
| PLGA-based PNP                                                                 | Pheophorbide a              | FA     | FR     | PEG                             | In vitro: MKN28 cells; In vivo: mice bearing MKN28 tumors | [224]  |
| PLGA-based PNP                                                                 | Verteporfin                 | HA     | CD44   |                                 | In vitro: A549 cells                             | [225]  |
| HA-b-PLGA-based PNP                                                            | Hypocrellin A               | Tf     | Tf receptor |                                 | In vitro: A549, NIH-3T3 cells; In vivo: Mice bearing A549 tumors | [226]  |
| (PLGA) and carboxymethyl chitosan (CMC)-based PNP                              | meso-tetraphenylchlorine disulphonic acid disodium (TPCS₂₂₆) | HA        | CD44   | Docetaxel                       | In vitro: MCF-7 and MDA-MB-231 cells              | [208]  |
| PLGA-based PNP                                                                 | meso-tetraphenylchlorine disulphonic acid disodium (TPCS₂₂₆) | HA        | CD44   | Docetaxel                       | In vitro: MDA-MB-231 and HeLa cells               | [228]  |
| PEG-based PNP                                                                  | Coumarin chromophore        | Biotin | Biotin receptor | PEG                             | In vitro: HeLa cells                             | [208]  |
| 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(PEG-2000)]-based PNP | benzo[1,2-b:4,5-b’]dithiophene 1,1,5,5-tetraoxide | RGD-4R peptide | αᵥβ₃ integrin receptor | 4,4’-(2,2-diphenylmethene-1,1-diyl)bis(N,N-diphenylaniline) | In vitro: SKOV-3, HeLa, PC3 and MCF7 cells; In vivo: mice bearing SKOV-3 tumors | [229]  |
| PLGA-PNP                                                                      | MB                          | c(RGDfK) peptide | αᵥβ₃ integrin receptor | Catalase in the aqueous core, Black hole quencher-3 | In vitro: U87-MG, MCF-7, SKOV-3 and HaCaT cells; In vivo: mice bearing U87-MG tumors | [212]  |
| PLGA-PEG-based PNP                                                             | Verteporfin                 | hTf peptide | Tf receptor |                                 | In vitro: MDA-MB-231 cells                        | [139]  |
| PEG-PCL-based Polymeric micelles                                               | HOSiPcOiSi(CH₃)₂-(CH₂)₃N(CH₃)₂ PC 4 | GE-11 peptide | EGFR |                                 | In vitro: SCC-15 cells; In vivo: mice bearing SCC-15 tumors | [213]  |
| Nanocomposition                  | PS                              | Ligand                | Target          | Extra Features | Application                                         | Ref.   |
|---------------------------------|---------------------------------|-----------------------|-----------------|----------------|-----------------------------------------------------|--------|
| Chitosan-based hydrogel         | Tetrakis(4-aminophenyl)porphyrin| FA                    | FR              |                | In vitro: The MCF-7 (FR+) and HepG2 (FR−) cells     | [219]  |
| Chitosan/alginate-based hydrogel| meso-Tetra(N-methyl-4-pyridyl) porphine tetra tosylate (TMPyP) | Anti-DR5 antibody    | Death receptor 5 |                | In vitro: HCT116 cells                               | [218]  |
| HA-based hydrogel               | ICG                             | MMP-2                 | MMP-2 receptor  | DOX            | In vitro: SCC-15 cancer cells; In vivo: SCC-15 tumor bearing mice | [222]  |
| Polyacrylamide-based hydrogel   | MB                              | F3 peptide            | Nucleolin       | PEG            | In vitro: MDA-MB-435 and F98 cells                   | [220]  |
| Polyacrylamide-based hydrogel   | HPPH                            | F3 peptide            | Nucleolin       | PEG            | In vitro: MDA-MB-435 and 9L cells                    | [221]  |
4.3. Cyclodextrin (CDs)

CDs, natural cyclic oligosaccharides, are another example of materials used for the development of nanocarriers. Natural CDs are obtained mainly by enzymatic intramolecular transglycosylation of starch and are classified as alpha (α)-CD, beta (β)-CD or gamma (γ)-CD based on their number of linked D-glucopyranose units (6, 7 and 8 groups, respectively) [230]. CD’s applications in therapeutics are principally due to their ability to form host–guest complexes with a broad spectrum of drug molecules. This occurs predominantly through encapsulation, covalent conjugation or non-specific external binding [231]. The use of CD-based nanocarriers permits one to improve the solubility of several drugs, including PSs. [232]. Introduction of receptor targeting moieties enhancing the anti-cancer effects of PSs, delivered by means of CD, has also been extensively studied in recent years (Table 6).

β-CDs have been widely used for drug delivery owing to their ready availability and cavity size; however, low aqueous solubility might challenge their use in parenteral administration. Despite this limitation, several works using β-CD-based NPs for the delivery of PSs have been reported. As an example, HA-targeted β-CD-based NPs, containing adamantane-modified camptothecin prodrug (via a ROS-responsive thioketal linker) and adamantane-modified THPP, were recently described. This multi-functional formulation combines PDT with light-controlled chemotherapy. Significant internalization was observed in MDA-MB-231 breast cancer cells, which overexpress CD44 receptors, but not in cells with poor expression of CD44 receptors (MCF7), thereby indicating enhanced and specific uptake of the developed HA-targeted NPs. In vitro evaluation demonstrated low cytotoxicity in the dark while high phototoxicity was observed at low doses (50 µg/mL). Of note, in vivo experiments using mice bearing MDA-MB-231 tumors showed 3.7- and 2.2-fold higher tumor inhibition comparing to free THPP and camptothecin, respectively [233]. Similarly, Yao et al. developed β-CD-based NPs combining PDT with light activable release of camptothecin (via a nitrobenzene linker) [234]. The formulation was further decorated with lactobionic acid, which allows one to target asialoglycoprotein receptors-overexpressing tumor cells. The targeted formulation exhibited potent phototoxic effect against HepG2 cancer cells, both in vitro and in vivo, when compared with the non-targeted parent. Additionally, Zhang et al. developed mannose-targeted β-CDs-based NPs containing adamantane-modified BODIPY as the PS [235]. Receptor-specific internalization and anticancer activity were confirmed in MDA-MB-231 breast cancer cells, which overexpress mannose receptors. While the mannose-targeted NPs exhibited over 90% cell death, the ligand-free NPs only caused 11% cell death. In contrast, no significant differences were observed in the phototoxicity against MCF-10A cells lacking mannose-receptor overexpression. Treatment of mice bearing MDA-MB-231 tumors showed significant tumor growth inhibition in contrast to the non-targeted formulation. Importantly, no severe adverse reactions were noted during the treatment.
Table 6. Examples of ligand-targeted cyclodextrin-based NPs for PDT.

| Nanocomposition | PS                          | Ligand                                  | Target             | Extra Features                                      | Application                                                      | Ref. |
|-----------------|-----------------------------|-----------------------------------------|--------------------|-----------------------------------------------------|------------------------------------------------------------------|------|
| β-cyclodextrin  | Adamantane-modified 5,10,15,20-tetrakis(4-hydroxyphenyl)-21H,23H-porphine (THPP) | HA                                 | CD44 receptor     | Adamantane-modified camptothecin prodrug            | In vitro: MDA-MB-231 cells; In vivo: mice bearing MDA-MB-231 tumors | [233]|
| γ-cyclodextrin  | Fullerene C₆₀                 | FA                           | FR                 | GO                                  | In vitro: HeLa cells                                               | [236]|
| β-cyclodextrin  | Chlorin e₆ free acid         | Adamantine-CGKRK-GFLG-EE-HAIYPRH (T7) peptide | Tf receptor        | _                                                  | In vitro: MCF-7 cells                                              | [237]|
| β-cyclodextrin  | 1,8-dihydroxy-3-methylantraquinone (DHMA) | Lactobionic acid (LA) | Asialoglycoprotein receptors | PEG, camptothecin prodrug (NBCCPT), | In vitro: HepG2 cells; In vivo: mice bearing HepG2 tumors          | [234]|
| β-cyclodextrin  | Pheophorbide a                | FA                           | FR                 | Adamantane                                  | In vitro: MCF-7 and PC3 cells                                     | [238]|
| β-cyclodextrin  | Adamantane-modified BODIPY (BTA) | Mannose                        | Mannose receptor   | Adamantane                                 | In vitro: MDA-MB-231 and MCF-10A cells; In vivo: mice bearing MDA-MB-231 tumors | [235]|
| β-cyclodextrin  | Phenanthroline modified CD-Ruthenium complex | Tf                             | Tf receptor        | Adamantane                                  | In vitro: A549 cells 293T cells                                   | [239]|
| β-cyclodextrin  | GO                           | HA                           | CD44               | DOX, Fe₃O₄                                  | In vitro: BEL-7402 cells                                          | [240]|
| β-cyclodextrin  | (Phthalocyaninato)zinc(II)    | FA                           | FR                 | Camptothecin                                 | In vitro: HEP2 cells; In vivo: mice bearing HEP2 tumors           | [241]|
| β-cyclodextrin  | 5,10,15,20-Tetrakis(m-hydroxyphenyl)-21,23H-porphyrin (mTHPP) | Tamoxifen                     | Estrogen receptor  | –                                                  | In vitro: MCF7 and MDA-MB-231 cells                               | [242]|
| β-cyclodextrin  | Adamantane-modified 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin | FA                             | FR                 | DOX, GO                                      | In vitro: HeLa and OCT-1 cells; In vivo: mice bearing HeLa tumors | [243]|

Note: FA = folic acid; FR = folic receptor; GO = glucose oxide; DOX = doxorubicin; Tf = transferrin; HA = hyaluronic acid; CD44 = cell surface receptor for CD44; mTHPP = methyltetrahydroxyphenylporphyrin; THPP = tetrahydroxyphenylporphyrin; mTHPP = methyltetrahydroxyphenylporphyrin; HAIYPRH = histidine-arginine-lysine-yapheptide-repetitive peptide.
4.4. Carbon Nanomaterials (CNMs)

CNMs are low dimensional carbon-based constructs which were introduced for the first time in the mid-1980s. The largest applications of CNMs in medicine have been found for fullerenes, graphene oxide (GO), carbon nanotubes (CNTs) and carbon dots (CDs). CNMs can be classified based on their dimensionality. 0D carbon nanomaterials include CDs and fullerenes, which can be defined as hollow cages and quasi spherical NPs, respectively. The 1D group involves cylinder-shaped CNTs, whereas graphene is a 2D structure. CNMs contain carbon atoms in $sp^2$ (usually for fullerene, GO and CNTs) or $sp^3$ (mostly for CD) hybridization that are typically arranged in hexagonal lattices. CNMs have versatile electrochemical properties which have resulted in a wide range of applications, such as sensors for diverse materials (DNA, proteins, metals, etc.). Due to their small size (usually between 1 to 100 nm), large surface area and light absorption in the NIR region, CNMs have been explored for drug delivery, including in PDT [244]. Furthermore, their ability to absorb light in the NIR region makes CNMs promising candidates for PTT, hence their use in combination therapy. However, due to poor aqueous solubility as a result of the hydrophobic interactions and unspecific accumulation in soft tissues, the use of CNMs use is limited by their potential toxicity [245]. In recent years, many attempts focusing on CNMs surface modification have been investigated, with the goal of increasing their biocompatibility and tissue specificity [246]. Among them are the attachment of hydrophilic polymers (PEG, PEI, etc.) and targeting moieties as strategies which can modify their pharmacokinetic profile, tumor accumulation and cellular internalization [247].

Significant advances in the field have been made in the last few years (Table 7). Multifunctional platforms that combine PDT with PTT, targeted delivery towards specific tumor cellular populations and other functionalities have become common. For instance, Shi et al. developed HA-targeted NCTs loaded with hematoporphyrin monomethyl ether (HMME), which combined PDT and PTT activities [248]. B16F10 cells treated with these NPs, and illumination at both 532 and 808 nm, resulted in around 90% cell death, which was significantly higher that the effect obtained with the free HMME, non-targeted NCTs or HA-targeted NCTs illuminated with a single wavelength. In contrast, no cytotoxic effect was observed in dark conditions. Treatment of B16F10 tumor-bearing mice demonstrated strong suppression of tumor growth (only 15% of the tumor volume of the control group) without systemic toxicity.

Another interesting study was provided by Zheng et al. [249]. The authors developed CD-decorated with carbon nitrite, coupled with Pp IX, PEG and the RGD peptide. Carbon nitrite was included in the formulation in order to trigger water splitting, and therefore, increased the oxygen concentration. This is of high importance, as hypoxic regions are commonly observed in solid tumors, which often compromise PDT efficacy. In vitro studies conducted in 4T1 cells demonstrated that 50% of cell death was attained with this nanoplatform in hypoxic conditions, while no photoactivity of the free PS was observed in the same conditions. In vivo biodistribution studies carried out on 4T1-tumor bearing mice showed specific tumor accumulation of the RGD-targeted CDs which was proved by monitoring increased fluorescence of the formulation in the solid tumor in comparison with other organs. This later was correlated with over 3-times stronger inhibition of tumor growth upon tumor illumination at 630 nm in comparison with free Pp IX and carbon nitride-free CD NPs, within 12 days of the experiment. Of note, anti-tumor immunity with significant impairment of distant (and not illuminated) metastasis was reported [249].

DOX loaded fullerene NPs, containing polymeric shell with tumor targeting NGR peptide were also tested against 4T1 breast cancer cells. The fullerene-based nanoplatfrom, with switch on/off properties, allowed for burst chemotherapeutic release after 532 nm laser irradiation. In vitro studies confirmed the impact of the peptide for enhanced targeting, resulting in 42% cell death after laser irradiation in comparison with only 20% obtained with the non-targeted counterpart. Moreover, after systemic administration, NP accumulation in the tumor area was 7.4-fold higher than that obtained with the non-targeted CDs. Reduced accumulation in heart and kidneys and decreased side effects were observed [250].
Table 7. Examples of ligand-targeted carbon nanomaterials for PDT.

| Nanocomposition | PS               | Ligand | Target | Extra Features | Application                       | Ref.       |
|-----------------|------------------|--------|--------|----------------|-----------------------------------|-----------|
| CNT             | ICG              | FA     | FR     | PTT            | In vitro: HeLa cells; In vivo: mice bearing HeLa tumors | [251]     |
| CD              | ICG              | FA     | FR     | Polydopamine   | In vitro: HeLa cells              | [252]     |
| CNT             | Organoselenium compound (PSeD) | AE105 polypeptide (uPAR) | Urokinase-type plasminogen activator receptor (uPAR) | pH-responsive triblock polymer composed of PEG-COOH, polyethyleneimine (PEI) and 3,4,5,6-tetrahydrophthalic anhydride (TA) (PPTA) | In vitro: MDA-MB-231 and L02 cells | [253]     |
| CNT             | (2-amino-phthalocyaninato)zinc(II) | FA     | FR     |                | In vitro: A375 cells              | [254]     |
| CNT             | HMME             | HA     | CD44   |                | In vitro: B16F10 cells; In vivo: Mice bearing B16F10 tumors | [248]     |
| CNT             | ICG              | HA     | CD44   |                | In vitro: SCC7; In vivo: mice bearing SCC7 tumors | [255]     |
| GO              | ICG              | Anti-epithelial cell adhesion molecule (EpCAM) antibody and A9-aptamer | PSMA |                | In vitro: LNCaP cells              | [256]     |
| GO              | Chlorin e₆ free acid | HA     | CD44   |                | In vitro: A549 cells              | [257]     |
| GO              | Chlorin e₆ free acid | RGD4C peptide | αvβ₃ integrin receptor | Polyvinylpyrrolidone (PVP) | In vitro: MGC803 cells | [258]     |
| GO              | Chlorin e₆ free acid | FA     | FR     |                | In vitro: MGC803 cell line        | [259]     |
| GO              | Chlorin e₆ free acid | HA     | CD44   |                | In vitro: HeLa and NIH3T3 cells    | [260]     |
| Nanocomposition | PS | Ligand | Target | Extra Features | Application | Ref. |
|-----------------|----|--------|--------|---------------|-------------|-----|
| GO              | MB | FA     | FR     | DOX           | In vitro: HeLa and MCF-7 cells | [261] |
| GO              | Verteporfin | c(RGDfK) peptide | αvβ3 integrin receptor | Banoxantrone dihydrochloride (AQ4N), and HIF-1α siRNA (siHIF-1α) | In vitro: Human PC-3 prostate cancer cell line; In vivo: mice bearing PC-3 tumor | [262] |
| GO              | 3-[1-hydroxyethyl]-3-devinyl-13\(^1\)-β,β-dicyanomethylene-13\(^1\)-deoxopyropheophorbide \(a\) | FA | FR | DOX | In vitro: Hep-G2 cells | [263] |
| GO              | Chlorin \(e_6\) free acid | FA | FR | 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-PEG2000 | In vitro: KB, A549, HeLa, HaCaT cells; In vivo: mice bearing HeLa tumors | [264] |
| GO              | Pyropheophorbide \(a\) | Anti-integrin αvβ3 antibody | αvβ3 integrin receptor | – | In vitro: MCF-7, U87-MG cells | [265] |
| GO              | Tetrakis(4-carboxyphenyl)porphyrin (TCPP) | FA | FR | – | In vitro: HeLa cells | [266] |
| GO              | HPPH | HK peptide | αvβ3 integrin receptor | PEG | In vitro: 4T1 cells; In vivo: mice bearing 4T1 tumors | [267] |
| Fullerene       | Fullerene (C\(_{60}\)) | FA | FR | DOX | In vitro: HeLa (FR+) and A549 and L929 (FR-) cells | [268] |
| Fullerene       | Fullerene (C\(_{60}\)) | FA | FR | – | In vitro: HeLa cells | [269] |
| Fullerene       | Fullerene (C\(_{60}\)) | HA | CD44 | – | In vitro: HCT-116 cells; In vivo: mice bearing HCT-116 tumors | [270] |
| Fullerene       | Fullerene (C\(_{60}\)) | Pullulan | Asialoglycoprotein receptors (ASGPR) | – | In vitro: HepG2 cell lines; In vivo: mice bearing tumors | [271, 272] |
| Nanocomposition | PS                      | Ligand                  | Target                  | Extra Features                                                                 | Application                                      | Ref.   |
|------------------|-------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--------|
| Fullerene        | Fullerene (C\textsubscript{70}) | R13 Aptamer             | EGFR                    | —                                                                              | In vitro: A549 cells                              | [273]  |
| Fullerene        | Fullerene (C\textsubscript{60}) | D-glucosamine           | GLUT-1 receptor         | —                                                                              | In vitro: PANC1 and PSC cells                     | [274]  |
| Fullerene        | Fullerene (C\textsubscript{60}) | NGR peptide             | CD13/aminopeptidase N receptor | DOX, 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-PEG | In vitro: 4T1 cells; In vivo: mice-bearing 4T1 tumors | [250]  |
| Fullerene        | Diadduct malonic acid-fullerene (C\textsubscript{60}) | NGR peptide             | CD13/aminopeptidase N receptor | 2-methoxyestradiol (2ME)                                                     | In vitro: MCF-7 cells                             | [275]  |
| Fullerene        | Fullerene (C\textsubscript{60}) | Tf                      | Tf receptor             | HA, Artesunate                                                                | In vitro: MCF-7 cells; In vivo: mice bearing S180 tumors | [276]  |
| CD               | Pp IX                   | FA                      | FR                      |                                                                                 | In vitro: HeLa and HT-29 cells                    | [277]  |
| CD               | CD                      | Heavy-chain ferritin     | Tf receptor             | DOX                                                                            | In vitro: MCF-7 cells; In vivo: mice bearing S180 tumors | [278]  |
| CD               | Pp IX                   | RGD peptide             | α\textsubscript{v}β\textsubscript{3} integrin receptor | Carbon nitride                                                                | In vitro: MCF-7 and 4T1 cells; In vivo: mice bearing 4T1 tumors | [249]  |
4.5. Inorganic NPs

Metals and metal oxides have been introduced to the field of medicine as potential composites for electron microscopy and drug delivery [279]. The history of their application goes back to ancient times, when the therapeutic property of gold was used in the treatment of various diseases, such as epilepsy or syphilis [280]. Today, classic examples of inorganic drugs used in clinical treatment are cisplatin (an FDA approved anticancer drug) [281] and iron oxide NPs used for the treatment of glioblastoma [282]. Inorganic NPs, due to their well-defined shape and easily modified surfaces, have also been applied in the field of PDT. Silica (SiNPs), iron oxide (IONPs) and gold (AuNPs) NPs are one of the most extensively studied delivery platforms for PS [283,284]. Many efforts to improve the tumor targeting ability of inorganic NPs, while enhancing the PDT effect, were investigated (Table 8). One advantage of such NPs is their ability to encompass multiple abilities, creating multifunctional platforms. For instance, Wang et al. designed a SiNPs formulation containing the chemotherapeutic drug, DOX, and the photosensitizer, MB, which was further decorated at the surface with a nuclear localization signal peptide (KKKRK) [285]. In vitro experiments performed using a human malignant glioma cell line (U87MG) confirmed the desired targeting activity of the formulation at the highest PS concentration (500 µg/mL), showing about 70% cell death for the targeted formulation in comparison with free DOX which only exhibited 35% cell death. Moreover, in vivo studies showed site specific U87MG tumor accumulation after systemic administration of the targeted SiNPs. This was associated with five times stronger tumor ablation when compared with free DOX, and importantly, an absence of systemic toxicity [285]. In another study, multifunctional nanosystems combining 5-aminolevulinic acid (5-ALA)-PDT, PTT (AuNPs) and imaging (dye Cy7.5) properties were developed for the treatment of breast cancer. Anti-HER2 antibody and HA conjugated to the particle surface mediated an enhanced targeting ability, resulting in 2.6 times higher uptake of the SiNPs into MCF7 cells than the non-targeted approach. Furthermore, animal studies confirmed enhanced accumulation in the tumor site (12.8% accumulation ratio after systemic administration). Although high NPs accumulation was observed in other organs, such as the liver, toxicity studies did not show any signs of pathological changes or systemic inflammation [286]. IONPs are also employed in PDT. As an example, IONPs specifically designed to trigger the Fenton reaction, and decorated on their surfaces with ICG and HA, exhibited promising results for the treatment of colon cancer. In vitro studies using HCT116 and A2780 cells revealed an effective IONP internalization which was correlated with PDT/PTT-mediated cell death upon illumination at 808 nm. Total remission of HCT116 tumors was achieved with the HA-targeted IONPs upon illumination at 808 nm, which was in contrast with free ICG, empty IONPs and non-illuminated IONP-ICG-HA. In addition, these multifunctional NPs allowed in vivo photoacoustic and fluorescence imaging, which revealed the highest tumor accumulation at 6 h post injection [287].

4.6. Metal Organic Frameworks (MOFs)

MOFs can be defined as hybrid and crystalline constructions of metal ions clusters coordinated by multifunctional organic ligands/linkers. Due to their versatile properties regarding size, morphology, biodegradation and chemical composition, MOFs have found a very broad spectrum of applications, such as for targeted drug delivery [288,289]. A few works have used ligand-targeted MOFs in the context of PDT (Table 8). A good example of this approach relies on HA-targeted MOF NPs containing zirconium (IV)-based 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin and α-cyano-4-hydroxycinnamate. The latter is an inhibitor of monocarboxylate transporter 1, which can be used to reduce lactate uptake by cancer cells, and therefore, aerobic respirations and oxygen consumption. In vitro experiments confirmed an enhanced phototoxicity of the formulation against CT26 colon adenocarcinoma cells, in both aerobic and anaerobic conditions (cell death > 80%), while no toxicity was observed on COS7 fibroblasts. Strong inhibition of CT26 tumor growth without signs of toxicity was observed [290].
Table 8. Examples of ligand-targeted inorganic nanoparticles (INPs) and metal organic frameworks (MOFs) for PDT.

| Nanocomposition | PS       | Ligand                                | Target                  | Extra Features | Application                                           | Ref.   |
|-----------------|----------|---------------------------------------|-------------------------|----------------|-------------------------------------------------------|--------|
| SiNPs           | MB       | Nuclear localization signal peptide (KKKRK) | Nuclear receptor        | DOX            | In vitro: U87MG cancer cells, In vivo: U87MG tumor bearing mice | [285]  |
| SiNPs           | (Phthalocyaninato)zinc(II) | FA | FR | - | In vitro: A431, SCC12, CAL27 and NHEKs cells | [291]  |
| SiNPs           | (5-[p-[3-(2′,5′-dioxo-2′,5′-dihydro-1H-pyrrol-1′-yl)-N-3-phenoxypropyl]propanamide]-phenyl]-10,15,20-tri-p-pyridyl-porphyrine derivative) | Dimannoside-carboxylate | Mannose 6-phosphate receptor | - | In vitro: LNCaP cells | [292]  |
| SiNPs           | Chlorin e6 free acid | FA | FR | FA polyethylene glycol-b-poly (asparaginyl-chidamide), DOX | In vitro: MCF-7/ADR cells | [293]  |
| SiNPs           | Chlorin e6 free acid | HA | CD44 | DOX | In vitro: SCC7 cells | [294]  |
| SiNPs           | 5,10,15,20-Tetrakis(N-methyl-4-pyridyl)porphyrin tetra tosylate (TMPyP4) | FA | FR | G-quadruplex DNA, DOX | In vitro: HepG2 and 3T3 cells | [295]  |
| SiNPs           | N-[3-(triethoxysilyl)propyl]-O-[4-(10,15,20-tri(3-hydroxyphenyl)-(2,3-dihydro)porphyrin-5-yl)phenyl]-carbamate | FA and Biotin; RGD and RAD; Cetuximab and Bovine Serum Albumin-conjugated nanoparticles | PEG | In vitro: A549, CCD-34Lu, KB cells, HeLa, A431 and HUVEC cells | [296]  |
| SiNPs           | 5-ALA | FA | FR | - | In vitro: B16F10 cells | [297]  |
| SiNPs           | 5-(4-carboxyphenyl)-10,15,20-triphenoxychlorin (TPC) | Neurupulin-1 (NRP-1) | VEGFR | Gadolinium | In vitro: MDA-MB-23 cells; In vivo: mice bearing U87 tumors | [298]  |
| Nanocomposition | PS | Ligand | Target | Extra Features | Application | Ref. |
|-----------------|----|--------|--------|---------------|-------------|-----|
| SiNPs | 5,10,15-Trisulphonatophenyl-20-(N-phenyl-N'-propyltriethoxysilanecarbamide) porphyrin | HA | CD44 | | In vitro: HCT-116 cells | [299] |
| SiNPs | 5,10,15-Trisulphonatophenyl-20-(N-phenyl-N'-propyltriethoxysilanecarbamide) porphyrin | Mannose, galactose | Mannose, galactose receptors | Camptothecin, fluorescein isothiocyanate | In vitro: Y-79 cells | [300] |
| SiNPs | (5,10,15,20-Tetraphenylporphyrinato) palladium(II) | cRGDyK peptides | $\alpha_v\beta_3$ integrin receptor | fluorescent contrast agent, ATTO647N | In vitro: MCF-7 and U87-MG cells | [301] |
| SiNPs | 5,10,15-Trisulphonatophenyl-20-(N-phenyl-N'-propyltriethoxysilanecarbamide) porphyrin | Galactose | Galactose receptor | Camptothecin | In vitro: HCT-116, Capan-1 and MDA-MB-231 cells | [302] |
| AuNPs | (5,10,15,20-Tetraphenylporphyrinato)zinc(II) | FA | FR | Thioglucose | In vitro: HeLa and MCF-7 cells | [303] |
| AuNPs | ICG | RGD peptide | $\alpha_v\beta_3$ integrin receptor | Doxycycline, Combrertatin A4 phosphate, PEG | In vitro: HUVEC and HT-1080 cells | [304] |
| AuNPs | Chlorin $e_6$ (Ce$e_6$-labeled aptamer sequence) | Nucleolin-targeting aptamer AS1411 | Nucleolin | DNA-programmed polymeric SNA, DOX | In vitro: HeLa cells | [305] |
| AuNPs | 5-ALA | Anti-HER2 antibody, HA | HER2, CD44 | PEG, Cy7.5 | In vitro: MCF-7 cells; In vivo: mice bearing MCF-7 tumors | [286] |
| AuNPs | Chlorin $e_6$ free acid | Anti-CD3 antibody | CIK-cells | | In vitro: MGC-803 and GES-1 cells; In vivo: mice bearing MGC-803 tumors | [306] |
| Nanocomposition | PS | Ligand | Target | Extra Features | Application | Ref. |
|-----------------|----|--------|--------|---------------|-------------|-----|
| AuNPs           | HOSiPcOSi(CH$_2$)$_2$-(CH$_2$)$_3$N(CH$_3$)$_2$, (Pc 4) | PSMA | PSMA receptor | PEG | In vitro: PC3pip (PSMA+) and PC3flu (PSMA−) cells; In vivo: mice bearing PC3pip or PC3flu tumors | [307] |
| AuNPs           | Chlorin e$_6$ free acid | α-lipoic acid-EGF | EGFR |  | In vitro: MDA-MB-468 cells | [308] |
| AuNPs           | (Phthalocyaninato)zinc(II) Lactose-containing thiol derivative | Galectin-1 receptor |  | CTSE-sensitive imaging agent, PEG | In vitro: SK-BR-3 and MDA-MB-231 cells | [309] |
| AuNPs           | 5-ALA | U11 peptide | Urokinase-type plasminogen activator receptor (uPAR) | Thiolated carboxyl terminated PEG | In vitro: PANC1-CSTE cells; In vivo: mice bearing PANC1-CSTE tumors | [310] |
| AuNPs           | (5-[4-(11-mercaptopoundecyloxy)phenyl]-10,15,20-triphenylporphyrin) Anti-erbB2 ICR55 antibody | ErbB2 |  | In vitro: SK-BR-3 cells | [311] |
| AuNPs           | 5-ALA | R8-PLGLAG-EK10 peptide | MMP-2 |  | In vitro: SCC-7 cells; In vivo: mice bearing SCC-7 tumors | [312] |
| AuNPs           | Verteporfin | FA | FR | PEG-P(Asp-Hyd)-DHLA block copolymer | In vitro: HeLa cells | [313] |
| AuNPs           | HOSiPcOSi(CH$_2$)$_2$-(CH$_2$)$_3$N(CH$_3$)$_2$, (Pc 4) | EGF, Tf | EGFR, Tf receptor |  | In vitro: U87MG and LN229 cells; In vivo: mice bearing U87-MG tumors | [314] |
| Au nanoclusters | Pp IX | FA | FR | Lipoic acid | In vitro: L929 and C6 cells; In vivo: mice bearing C6 tumors | [315] |
| AuNPs           | HOSiPcOSi(CH$_2$)$_2$-(CH$_2$)$_3$N(CH$_3$)$_2$, (Pc 4) | EGF | EGFR |  | In vitro: 9L.E29 cells; In vivo: mice bearing 9L.E29 tumors | [37] |
| Nanocomposition | PS                                      | Ligand                  | Target                | Extra Features                  | Application                                      | Ref. |
|-----------------|-----------------------------------------|-------------------------|-----------------------|---------------------------------|--------------------------------------------------|------|
| AuNPs           | HOSiPcOSi(CH<sub>3</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, (Pc 4) | Tf                      | Tf receptor           |                                 | In vitro: LN229 and U87 cells; In vivo: mice bearing U87 tumors | [140] |
| AuNPs           | (Phthalocyaninato)zinc(II)              | Jacalin (lectin)        | T antigen             | Thiol-functionalized PEG        | In vitro: HT-29 cells                             | [316]|
| IONPs           | ICG                                     | HA                      | CD44                  | amino PEG                      | In vitro: A2780 and HCT-116 cells; In vivo: mice bearing HCT-116 tumors | [287]|
| IONPs           | 5, 10, 15, 20-tetra(phenyl-4-N-met32hyl-4-pyridyl) porphyrin | AS1411 aptamer          | Nucleolin             | Daunomycin                      | In vitro: A549 and C26 cells                     | [317]|
| IONPs           | Chlorin e<sub>6</sub> free acid         | HA                      | CD44                  |                                 | In vitro: B16F1 cells                             | [318]|
| IONPs           | Hypericin                               | Lactose                 | Asialoglycoprotein receptors (ASGP-R) | Polydopamine                  | In vitro: HepG2 and MCF-7 cells                   | [319]|
| IONPs           | Pheophorbide a                          | FA                      | FR32                  | PEG, Caffeic Acid               | In vitro: MDA-MB-231 NIH3T3 and MCF-7 cells       | [320]|
| IONPs           | HOSiPcOSi(CH<sub>3</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, (Pc 4) | Fibronectin-mimetic peptide (Fmp) | Integrin β1              |                                 | In vitro: CT26, 4T1, HeLa, COS7, MCF-7 and HepG2 cells; In vivo: mice bearing M4E tumors | [321]|
| MOF             | Tetrakis(4-carboxyphenyl)porphyrin (TCCP) | HA                      | CD44                  | CHC                             | In vitro: H22 and NIH3T3 cells; In vivo: mice bearing H22 tumors | [291]|
| MOF             | TCPP                                    | HA                      | CD44                  | HIF signaling inhibitor (ACF), Zirconium ions | In vitro: H22 and NIH3T3 cells; In vivo: mice bearing H22 tumors | [322]|
| Nanocomposition | PS                        | Ligand                  | Target                        | Extra Features | Application                                      | Ref.      |
|-----------------|---------------------------|-------------------------|-------------------------------|----------------|-------------------------------------------------|----------|
| MOF             | (Phthalocyaninato)zinc(II)| FA                      | FR                            | DOX            | In vitro: HeLa cells                            | [323]    |
| MOF             | Al(III) phthalocyanine chloride tetrasulfonic acid (AlPcS4) | Catalase (CAT) protein molecules | Cancer cell membrane antigens | Cancer cell membrane | In vitro: HeLa, COS7; In vivo: mice bearing HeLa tumors | [324]    |
| MOF             | TCPP                      | FA                      | FR                            | TPP            | In vitro: SMMC-7721 cells                       | [325]    |
| MOF             | MB                        | cRGD                    | αᵥβ₃ integrin receptor         | –              | In vitro: A549 and HeLa cells                   | [326]    |
| MOF             | TCPP                      | Bovine Serum Albumin-sulfonamides (SAs) complexes | Carbonic anhydrase IX | –              | In vitro: 4T1 cells; In vivo: mice bearing 4T1 tumors | [327]    |
| MOF             | TCPP                      | Sulfadiazines           | Carbonic anhydrase IX         | Bovine serum albumin, MnO2 | In vitro: 4T1 cells; In vivo: mice bearing 4T1 tumors | [328]    |
| MOF             | TCPP                      | Aptamer of A549 lung cancer cells | A549 lung cancer cells        | DOX            | In vitro: A549, MCF-7 and LO2 cells              | [329]    |
5. Conclusions and Future Perspectives

Tumor selectivity is widely regarded as an essential consideration in the development of any new cancer treatment and PDT is no exception. Indeed, the clinical application of PDT is often limited by the PS’s inability to preferentially accumulate in the tumor. As a consequence, side effects, such as severe skin photosensitivity, may be developed, ultimately leading to reduced quality of life for the patient. As discussed in this review, targeting ligands that are recognized and internalized by receptors overexpressed on cancer cells and/or other cells of the tumor microenvironment are being used as an attempt to enhance tumor selectivity. Despite promising, this strategy often fails to meet full expectations. This is likely explained by the high dependence of active targeting (like passive targeting) on the EPR effect to effectively reach the tumor cells. Additionally, the use of standard 2D monolayer cell cultures for in vitro testing of active targeting strategies may provide a limited view of in vivo potential. Thus, 3D cell cultures that better mimic the tumor microenvironment complexity might be a valuable tool to be explored when bridging results from 2D cell culture and in vivo experiments [330]. In addition, the frequent use of strategies with increased complexity might complicate pharmaceutical development and scale-up, making the translation from bench top to bedside a daunting task.

Despite these limitations, active targeting continues to be a promising and advantageous approach to promote effective internalization of the PSs into the targeted tumors cells. Thus, to realize the full potential of active targeting, research efforts must continue towards the development of new and improved targeting ligands with multi-targeting abilities and trans-tissue transport abilities. Along with better formulations for systemic administration of PSs, such improvements are expected to promote specific and enhanced PS tumor accumulation accompanied with internalization by different cells of the tumor microenvironment.

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