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Perfluorocarbon nanomaterials for photodynamic therapy

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Abstract

Photodynamic therapy (PDT) is a treatment modality in which a photosensitizer is irradiated with light, producing reactive oxygen species, often via energy transfer with oxygen. As it is common for tumors to be hypoxic, methods to deliver photosensitizer and oxygen are desirable. One such approach is the use of perfluorocarbons, molecules in which all C–H bonds are replaced with C–F bonds, to co-deliver oxygen because of the high solubility of gases in perfluorocarbons. This review highlights the benefits and limitations of several fluorinated nanomaterial architectures for use in PDT.

Keywords

Perfluorocarbon; Fluorous; Photodynamic therapy; Singlet oxygen; Nanoemulsion; Micelle

Introduction

The harsh, chaotic, and hypoxic environments of solid tumors continue to be a difficult target for classic small molecule therapeutics. Traditional chemotherapeutics often clear rapidly and have significant off-target effects. To combat these limitations, nanomaterials have been designed to solubilize and mask insoluble cargoes, increase the serum half-lives of drugs, allow for stimuli-induced release of therapeutics, and facilitate tumor uptake through the addition of active targeting groups [1]. In addition, nanomedicine boasts many scaffolds that can be tuned to a specific target or cargo based on the desired application.

A complementary approach to limiting off-target effects is to apply external stimulus that triggers a therapeutic effect only at the tumor site. A member of this class of therapies is photodynamic therapy (PDT), the use of light to induce cell death. PDT requires three components: (1) light, (2) photosensitizer (PS), and (3) oxygen, the latter of which gets transformed into cytotoxic reactive oxygen species (ROS; Figure 1a) [2]. The first Food and Drug Administration (FDA)-approved iteration of PDT used Photofrin™ (**1**), a systemically administered oligomeric PS, which has been used to treat bladder, esophageal, lung, and endobronchial cancers [3]. A limitation of Photofrin™ is that, similar to other

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Declaration of competing interest

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small molecule chemotherapeutics, it undergoes broad biodistribution and accumulates in the skin and reticuloendothelial system, in addition to the tumor. When patients are exposed to sunlight, the PS is activated, resulting in side effects. To minimize the light sensitivity during PDT, the benefits of nanomaterials—originally studied for classic chemotherapeutics—are being leveraged to help selectively deliver the PS to the tumor. This approach provides two layers of targeting to increase specificity-targeting via the nanomaterial and the external stimuli.

Nanoparticles for PDT traditionally contain hydrophobic PSs (Figure 1b), such as cyanine dyes (**2**), phthalocyanines (**3**), chlorins (**4**), or porphyrins (**5**) [4]. Ideal PSs for PDT absorb near-infrared light with high absorption coefficients (ε) and efficiently convert the majority of the absorbed light into ROS, which is most commonly classified by the singlet oxygen quantum yield ($\mathbf{\Phi_\Delta}$). Cyanine dyes, phthalocyanines, and chlorins have excellent absorption properties, whereas phthalocyanines, chlorins, and porphyrins have the highest $\mathbf{\Phi_\Delta}$. One limitation of these hydrophobic PSs is they are prone to self-aggregation, decreasing the efficiency of the PS by reducing the absorption coefficient (ε) and/or singlet oxygen quantum yield ($\mathbf{\Phi_\Delta}$). Aggregation is evident by the broadening and blue shifting of the absorbance of the PS. Multiple strategies are highlighted in this review to maximize PDT efficiency by preventing PS aggregation.

A particularly promising nanomaterial scaffold for PDT are those that contain perfluorocarbons (PFCs). PFCs are molecules in which all C–H bonds have been replaced with C–F bonds (such as hexanes (**6**) versus perfluorohexanes (PFH, **7**)). PFCs form a separate, extremely hydrophobic and lipophobic phase termed the “fluorous phase” (Figure 1c). PFC nanomaterials are advantageous for PDT because the fluorous phase boasts up to 20-fold higher dissolved gas concentrations compared with aqueous phases (Figure 1d), allowing oxygen, one of the three essential components for PDT, to be delivered alongside the PS. The high gas solubility in the fluorous phase is due to the weak van der Waals interactions between PFC chains [5–8]. Indeed, the high oxygen solubility in PFCs has been used clinically in the 1980s and 1990s when PFC nanoemulsions were employed as blood substitutes [5,9].

In addition, fluorous nanomaterials are an attractive scaffold for PDT because of the extremely long singlet oxygen lifetimes in PFCs. The strength of the C–F bond renders it stable to highly reactive singlet oxygen, leading to half-lives 1000 times longer than in water (Figure 1d) [10]. The increased lifetime of the singlet oxygen provides a higher probability that singlet oxygen will diffuse into the water where it can react with surrounding biomolecules [11,12].

In this review, we will highlight recent advances in fluorous PDT, focusing on the various ways to deliver oxygen via perfluorinated architectures. We will cover three main architectures: lipid-stabilized nanoemulsions, macromolecule-stabilized nanoemulsions, and fluorous micelles (Figure 1e, Table 1).

Lipid-stabilized nanoemulsion

Lipid-stabilized PFC nanoemulsions are droplets of fluorous solvent stabilized by lipids, suspended in water (Figure 2a). These nanoemulsions are distinct from liposomes, which are composed of a lipid bilayer encapsulating an aqueous center. The lipid-stabilized PFC droplets are formulated primarily through a lipid film rehydration method in which a lipid film is first formed, and after the addition of buffer and fluorous solvent, energy is provided in the form of ultrasonication to form nanoemulsions ranging from 100 to 300 nm. These materials accumulate in the tumor via the enhanced permeability and retention (EPR) effect and are cleared through the liver. Common lipid surfactants can be seen in Figure 2b (**8**–**11**) along with common fluorous solvents for the formation of lipid-stabilized emulsions in Figure 2c. Perfluoro-15-crown-5-ether (PFCE, **12**) is often used for fluorine-19 magnetic resonance imaging (^{19}F-MRI) imaging. Perfluorodecalin (PFD, **13**), perfluorooctyl bromide (PFOB, **14**), PFH (**7**), perfluorotripropylamine (PFTPA, **15**), and perfluorotributylamine (PFTBA, **16**) are all PFCs used for oxygen delivery, with PFOB also being used for ^{19}F-MRI imaging and PFH for ultrasound imaging.

The first example of applying lipid-stabilized PFC nanoemulsions to deliver oxygen for use in PDT was reported in 1988 by Henderson and coworkers where they co-injected PFC nanoemulsions encapsulating PFD (**13**) and PFTPA (**15**) alongside nonencapsulated porphyrin PSs [13]. It took 25 years for this technology to be revisited and advanced with the inclusion of the PS in the PFC droplets. To date, three different PSs have been incorporated into the lipid tails stabilizing the water–PFC interface. These PSs are cyanine dyes IR780 (**2**) [11,14,15] and FDA-approved ICG [16], along with Ce6 (**4**) [12,17]. Aggregation of the PS is observed in each formulation; however, the fluorous nanomaterial does outperform the introduction of the PS alone.

The seminal paper combining a PS into a lipid-stabilized PFC nanoemulsion was published by Hu and coworkers in 2015 [11]. The specific nanomaterial, termed Oxy-PDT, included a mixture of DSPE-PEG$_{2000}$ (**8**), lecithin (**9**), and cholesterol (**10**) to stabilize PFH (**7**), with IR780 (**2**) incorporated in the surfactant layer. The implementation of PFH in lipid-stabilized droplets produced higher amounts of $^1O_2$, caused increased cell death *in cellulo* and shrunk tumors compared with controls without PFH via both intratumor and intravenous injection (Figure 2d). These nanoemulsions can also be used with good PDT efficiency (80–90% reduction in cellular viability upon irradiation) even under extreme hypoxic conditions because of the oxygen-carrying ability of the PFC droplets [11,14].

Following Hu's report, the benefits of lipid-stabilized PFC nanoemulsions for PDT were soon combined with the previously established ultrasound activity of PFCs. Ultrasound has been a useful, noninvasive imaging modality to monitor tumor regression following PDT treatment [18]. Song et al. used lipid-stabilized PFCs and external ultrasound stimuli to deliver bursts of oxygen to tumor sites for combined PDT and ultrasound imaging. Nanoemulsions were delivered to tumor-bearing mice via intravenous injection, and accumulated in the tumor via the EPR effect. When ultrasound was applied to the tumor site, a burst of oxygen was released because of the energy provided by the sound waves, rather than the slow diffusion of oxygen as seen without stimuli [17]. Yu et al. prepared

droplets that were designed to undergo pH-dependent coalesce upon ultrasound treatment. In this report, the lipid-stabilized droplets were able to accumulate in the acidic environment surrounding solid tumors through the EPR effect. The acidic pH protonated the lipids stabilizing the PFC nanoemulsions, promoting membrane fusion upon the introduction of ultrasonication. With sonication, the droplet size increased to ~1 μm and the droplets became trapped inside the tumor [12]. Both responsive materials displayed enhanced photodynamic efficiencies compared with nonresponsive controls.

Further combined responsive PFC nanoemulsions have been designed to enhance the photodynamic efficiency. In one example, glutathione (GSH) concentrations were decreased through the co-delivery of S-nitrosated human serum albumin (SNO-HSA) [15]. In the presence of GSH, which is upregulated in solid tumors, SNO-HSA was reduced to nitric oxide, which inhibits mitochondrial respiration, thereby increasing cellular oxygen. This, in addition to the oxygen delivered by the PFC droplets, enhanced the photodynamic efficiency (Figure 2e).

Overall, lipid-stabilized PFC nanoemulsions showcase the advantages of delivering PS and PFC simultaneously for PDT. In all cases, perfluorinated droplets outperformed oil or nonfluorinated controls *in cellulo* and *in vivo*. Furthermore, combination with ultrasound allows for further oxygen delivery, imaging, and controlled coalescence. Disadvantages of lipid-stabilized droplets include the need for lipid rehydration methods and limited opportunities for decreasing aggregation of the PS. More customizable macromolecule-stabilized PFC droplets have allowed some of these initial limitations to be overcome.

Macromolecule-stabilized nanoemulsions

Droplets of PFC can also be effectively stabilized in water by macromolecular amphiphiles (Figure 3a). Indeed, the FDA-approved PFC nanoemulsion, Fluosol-DA, used the 8 kDa triblock copolymer Pluronic F-68 (**17**) as a co-surfactant. PFC nanoemulsions stabilized with macromolecular amphiphiles are primarily formulated via ultrasonic emulsification of a biphasic solution producing nanoemulsions ranging from 100 to 400 nm in diameter. The serum half-lives of the nanoemulsions are related to their size, with smaller nanoemulsions having half-lives of a few days [19]. Macromolecular amphiphiles offer many opportunities to modify the surface chemistry of the nanoemulsions, which also allows for modulation of the serum half-lives and biodistribution [20]. Notably, both lipid and macromolecular stabilized nanoemulsions are kinetically stable and will not disassemble upon introduction to dilute environments (*e.g.* upon intravenous injection).

A variety of macromolecular surfactants, ranging from naturally occurring polymers and proteins such as hyaluronic acid and HSA to synthetic polymers, have successfully yielded PFC nanoemulsions (Figure 3b). Droplets stabilized by hyaluronic acid showed high targeting of solid tumors *in cellulo* and *in vivo* [21]. Those stabilized by albumin [22] and poloxamers [23,24] demonstrated biocompatibility and stability. Recently, we have focused on poly (2-oxazoline) amphiphiles (**18**) and found through varying the hydrophilic–lipophilic balance and architecture of polymer amphiphiles that the size, stability, cargo retention, and cellular uptake can be predicted and controlled [25].

One advantage of macromolecular surfactants has been decreasing aggregation of PSs, leading to increased PDT efficiency (Figure 3c) [22,26]. For example, the surface active protein albumin can act as a surfactant to stabilize PFC nanoemulsions [27] and also provide a hydrophobic binding pocket for the PS. In this case, the PFC core not only contributed to oxygen delivery but also helped decrease PS aggregation [22]. In other work, the PS was synthesized into an amphiphilic surfactant by the addition of a poly (ethylene glycol) chain and hydrocarbon to a heptamethine PS (**19**). The authors compared micelles of **19** to PFC droplets stabilized by **19** and, following the results similar to the albumin study, determined that the PFCs enhanced the PDT efficiency by both delivering oxygen and preventing aggregation [26]. A more advanced variant of a combined surfactant amphiphile is surfactant **20**, which is composed of hyaluronic acid with PS Ce6 (**4**) attached via disulfide linkages. Upon self-assembly and loading of PFH, droplets were formed that will disassemble to release free Ce6 after encountering high concentrations of GSH found in the tumor microenvironment [21].

An alternative approach to prevent aggregation is the solubilization of PSs in the fluorous phase through the use of PFC tags. In addition to decreasing aggregation, the tags also localize the PS in the highly oxygenated PFCs, promoting increased energy transfer to efficiently form cytotoxic ROS. This localization led to 140-fold more cell death compared with a hydrophobic PS incorporated in the surfactant layer of the PFC nanoemulsions (Figure 3d) [23,28].

Each of these materials produced ROS *in vitro*, *in cellulo*, and many were extended to tumor regression *in vivo*. By normalizing the tumor weight of saline-treated tumors to one and subtracting the weight of the treated tumors, we compared the overall tumor regression between systems (Figure 3e). In all cases, the materials containing PFCs outperformed the empty and oil controls, demonstrating the delivery of oxygen simultaneously with PSs is critical for enhanced photodynamic efficiency.

In contrast to the typical use of PFC nanoemulsions presented in this review, deoxygenated PFC nanoemulsions can also be used to further increase the hypoxia found in solid tumors to increase the efficacy of hypoxia-based agents such as Tirapazamine and Salmonella. By saturating PFC nanoemulsion containing IR780 with inert gases, the droplets absorb the little oxygen present in solid tumors. This oxygen is depleted by irradiating the droplets to produce ROS. The droplets are then able to absorb more oxygen, creating a cycle increasing tumor hypoxia (Figure 3f). This variation in PDT was quite effective at enhancing the efficacy of hypoxia-based agents to efficiently kill cells in culture and promote tumor regression [29].

In summary, PFC nanoemulsions stabilized by macromolecules are easily formulated via ultrasonication. Often the PSs are localized in the surfactant layer and aggregated. However, through clever design, the PSs can be forced into a monomeric state upon the addition of PFCs, the disassembly of the droplets, or solubilization within the fluorous phase with PFC tags. In all cases, the nonaggregated PSs outperformed aggregated PSs *in vitro*, *in cellulo*, and *in vivo*.

Micelles

Micelles are self-assembled architectures composed solely of polymer amphiphiles with hydrophobic payloads either covalently attached to the amphiphile or noncovalently associated with the hydrophobic center of the micelle (Figure 4a). A key difference between micelles and nanoemulsions is the quantity of PFC. Although fluorous solvents are not directly incorporated in the micelles as they are in lipid- and macromolecule-stabilized nanoemulsions, fluorous segments of polymer amphiphiles still have a high affinity for oxygen compared to water when saturated with oxygen (900 μM O_2 versus 600 μM O_2) [30]. Rodionov and coworkers systematically studied the oxygen-carrying ability of a range of fluorous polymers, varying the fluorous monomer (C_3F_7, C_6F_{13}, and C_8F_{17}) and the overall fluorous weight percent of the polymer (10, 12, or 15 wt%). Interestingly, they found the polymer composed of the shortest fluorous-containing monomer, but the highest wt% fluorine incorporation had the highest oxygen saturation (C_3F_7, 15 wt%) [30].

Fluorinated amphiphiles can be synthesized via living polymerizations or coupling reactions (designated with red versus orange dots in Figure 4b). PSs can be covalently attached to the polymer backbone or noncovalently associated with the hydrophobic center of the micelles to render fluorous micelles active agents for PDT (designated with gray versus black dots in Figure 4b, respectively). In addition, the polymers can be designed to incorporate mechanisms to decrease off-target effects through the addition of acid or esterase sensitive functional groups (designated with purple dot in Figure 4b). As with nanoemulsions, PSs can be prone to aggregation upon self-assembly (blue dot in Figure 4b), but careful amphiphile design can result in the PS remaining in the monomeric state (yellow dot in Figure 4b).

The majority of fluorous amphiphiles used to formulate micelles are synthesized through RAFT polymerization (**21**–**24**) [31–34]. This controlled radical polymerization allows precise control of block lengths and has high functional group tolerance, which provides opportunities for postpolymerization attachment of PSs. Other amphiphiles used for micelles for PDT include the coupling of standard hydrophilic polymers (i.e. polyethyleneimine (**25**) [35] or hyaluronic acid (**26**)) [36] with fluorous carboxylic acids (Figure 4b). In all cases, the amphiphiles self-assemble into thermodynamically stable micelles (~15 nm) or aggregates (<200 nm) when placed in water. These small nanomaterials accumulate in the tumor via the EPR effect. Because of their small size, they can exhibit long serum half-lives; however, they are prone to disassembly when diluted below the critical micelle concentration (CMC).

Approaches to PS introduction vary based on the amphiphile. Hydrophobic PSs such as porphyrins [34], chlorins [35], and derivatives [36] have been incorporated via copolymerization with hydrophobic and fluorous-containing monomers (**22**, **24**, **26**). The covalent incorporation of PSs prevented the undesired or premature leakage of payloads, a major limitation of PFC nanoemulsions. In other instances, PSs were noncovalently sequestered into the interior of the polymer micelles (**21**, **23**, **25**) [31,33,35]. For both approaches, PS aggregation was observed. Even so, in all cases, the fluorinated analogs outperformed the hydrocarbon variants delivering more oxygen, thereby producing more ROS, leading to increased cell death *in cellulo* and *in vivo*. Polymer amphiphiles can

also be modified to have responsive behavior in the presence of cellular stimuli, such as the acidic microenvironment surrounding tumors and hyaluronic acid esterases. In the first example, an acrylate containing pentafluorophenyl porphyrin was copolymerized with diethylaminoethylmethacrylate and poly (ethylene glycol) to create an acid-sensitive amphiphile that self-assembles into micelles (**22**). When **22** is exposed to acidic environments, the diethlyamino side chains became protonated, facilitating a hydrophobic to hydrophilic transition, which substantially changed the CMC, leading to nanomaterial disassembly. This disassembly resulted in the deaggregation of PSs, increasing the fluorescence and the photodynamic efficiency *in vitro*, *in cellulo*, and *in vivo* [32]. In the second example, hyaluronic acid was esterified with perfluorooctanoic acid and the PS pyropheophorbide a (Ppa) (**26**). Upon self-assembly, polymer aggregates of approximately 150 nm were formed, displaying significant aggregation of Ppa. The fluorinated segments increased the photodynamic efficiency 3-fold compared to controls with no fluorination [36].

Overall, each self-assembled, fluorinated polymer outperformed the hydrocarbon variants both in cell culture and tumor regression studies. Under hypoxic cell culture conditions, the micelles and larger polymer aggregates are able to facilitate cell death upon irradiation, suggesting oxygen is indeed incorporated into the nanoparticles. In xenograft tumor models, the nanoparticles were all reported to reduce the tumor volume by 75–90% compared with the volume of the saline control (Figure 4c).

Other

The majority of approaches toward dual oxygen and PS delivery with fluorous nanomaterials involve nanoemulsions (both lipid stabilized and macromolecule stabilized) or micelles. With potential size and payload leaching limitations of emulsions and instability at low concentrations, an inherent problem for micellular systems, other architectures that accomplish combined delivery of oxygen and PS have started to be pursued. These include Mg–Al-layered double hydroxides (LDHs) with a PS and fluorous solvent cointercalated [37], covalent organic polymers [38], and superhydrophobic silica [39]. Each of these takes different approaches to deliver oxygen and PS simultaneously, but a unifying advantage is that their composition promotes the monomeric form of the PS, eliminating the challenges with PS aggregation that occur in droplets and micelles.

LDHs are synthetic clay materials composed of layers of positively charged metal hydroxides separated by layers of anions and water. Often, these materials are used as catalysts for chemical conversions [40]. Interestingly, LDHs can enter cells and release their interlayer anions either through ion exchange with cellular anions or dissolution in the acidic environment of the lysosome. LDHs with magnesium and aluminum cations were prepared, and protoporphyrin IX (ppIX) and perfluoroheptanoic acid (PFHA) were coupled to the surface. Notably, the protoporphyrin aggregated significantly with the addition of the PFHA compared with PS immobilized on LDH alone. However, this did not inhibit the photodynamic efficiency, as the fluorous-containing LDH-ppIX oxidized two substrates specific for reaction with singlet oxygen faster than nonfluorous containing LDH or PS alone (Figure 5a) [37].

The covalent organic polymer (COP) was cleverly designed with tetra (hydroxyphenyl)porphyrin vertices bridged with perfluorosebacic acid to create a cross-linked fluorous polyester. Because of the fluorinated linkages, PFCE could be loaded into the COP (Figure 5b). The fluorinated COP loaded with PFCE outperformed the fluorinated COP and a hydrophobic control COP in dissolved oxygen loading, singlet oxygen production, cellular toxicity, and tumor regression [38].

Superhydrophobic silica surfaces for biofilm reduction were formulated through coupling either a phthalocyanine or a combination of Ce6 and a silyl perfluorobutane to a glass slide. Both surfaces were effective at reducing biofilm formation through PDT; however, in this case, the phthalocyanine-decorated surface outperformed the Chlorin e6/perfluorobutane functionalized surface. The authors attributed this difference to increased loading of the phthalocyanine PS compared with Ce6 (4.1 versus 1.4 μmol/g). As biofilms are commonly hypoxic, one would expect optimization of the PS loading accompanied with fluorous chains, will in the future, be a superior material (Figure 5c).

Each of these architectures displays the importance of co-delivery of PS and oxygen. When designing platforms distinct from the traditional emulsions and micelles, the most important factor is the biocompatibility of the platform used. From there, it has been shown that fluorous small molecules can be functionalized to the surface of materials or used as building blocks to further load additional fluorous solvent and oxygen.

Summary and outlook

PDT with fluorous materials is a promising approach to treat diseases through the co-delivery of oxygen and PSs. Although there are other methods to increase tumor oxygenation, including the reduction of hydrogen peroxide to oxygen *in situ* and hyperbaric oxygen inhalation [41–45], PFCs represent a simple, safe, and inert approach. In the past 5 years, the use of PFCs to deliver oxygen and improve photodynamic efficiencies has become an attractive method to propel PDT into the treatment of nonsurface-exposed cancers and diseases [4]. Future work will continue to improve PS properties, including reduction in aggregation, shifting the absorbance to the near-infrared region of the electromagnetic spectrum for enhanced tissue penetration, and increasing quantum yields of singlet oxygen generation [46]. Nanomaterial scaffolds will also continue to be optimized, providing means to increase PFC/oxygen content and monomeric PS. A particularly promising approach is the use of mesoporous silica nanoparticles, which have already shown individual use for PDT [47] and as molecular oxygen shuttles through the inclusion of fluorous solvents [48,49]. Self-assembled peptide–PS conjugates recently used for PDT also have the potential for PFC incorporation [50]. With continued optimization and building from the clinical precedence for PDT and PFCs for oxygen delivery, we expect the utility of fluorous nanomaterials for PDT to make rapid strides in the next decade.

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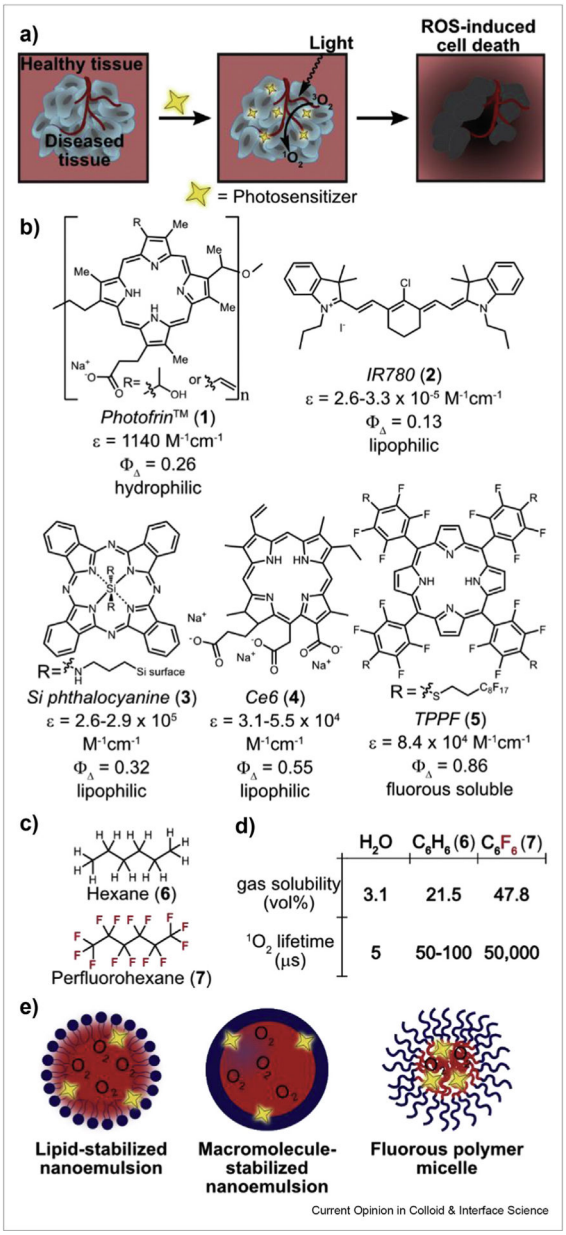

Figure 1.

(**a**) Photodynamic therapy (PDT) involves the introduction of a photosensitizer, which generates reactive oxygen species (ROS) upon irradiation with light to result in cell death. (**b**) Structures of common photosensitizers. (**c**) Molecular structures of hydrocarbon (hexane, **6**) and perfluorocarbon (perfluorohexane, **7**). (**d**) Table of gas solubilities and singlet oxygen lifetimes in water, hexanes (**6**), and perfluorohexanes (PFH, **7**). (**e**) Common perfluorocarbon nanomaterials for PDT discussed herein.

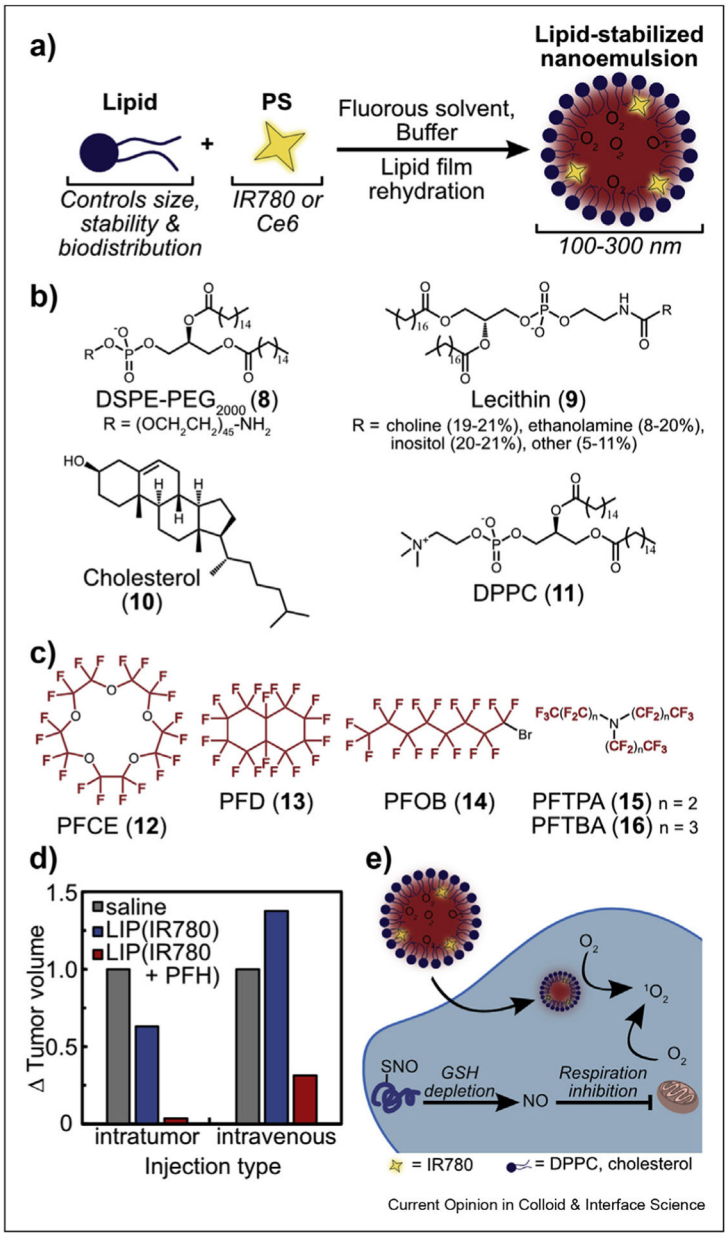

Figure 2.

Lipid-stabilized nanoemulsions for photodynamic therapy. (**a**) Formulation of lipid-stabilized nanoemulsions by lipid rehydration and subsequent sonication. (**b**) Panel of common lipids used to stabilize nanoemulsions. (**c**) Panel of common fluorous solvents for PDT. (**d**) Reduction in tumor volume when treated with lipid-stabilized nanomaterials containing IR780 without PFH (blue) or with PFH (red) compared with the saline control (gray). Data adapted from *Nat. Commun.* **2015**, *6*, 8785. (**e**) Schematic showing the increase in oxygenation through the delivery of lipid-stabilized PFC nanoemulsions and S-nitrosated human serum albumin (SNO-HSA).

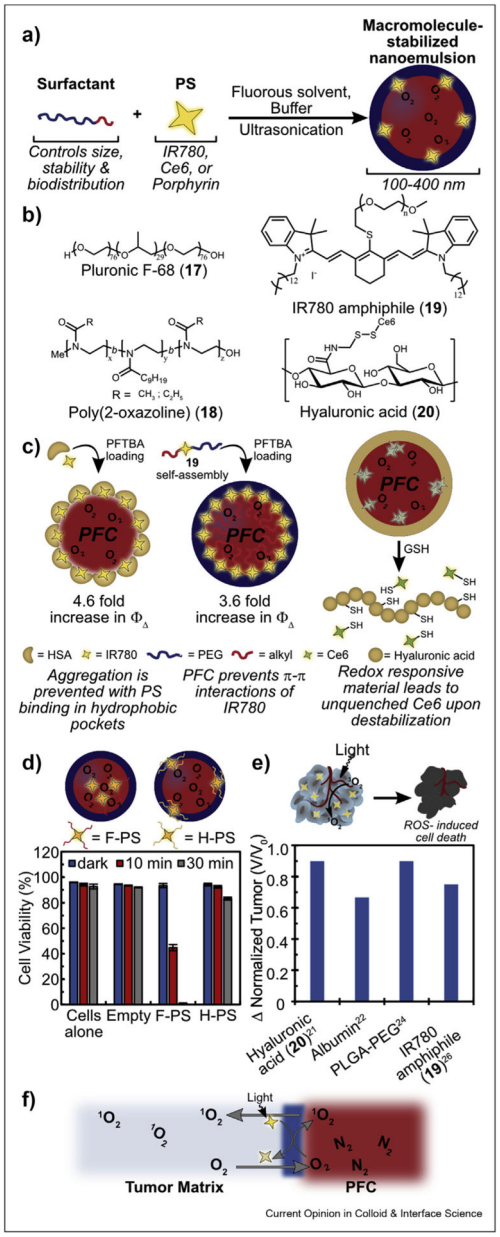

Figure 3.

Macromolecule-stabilized nanoemulsions for PDT. (**a**) One-step formulation of PFC nanoemulsions for PDT. (**b**) Selected polymeric surfactants for stabilizing PFC nanoemulsions. (**c**) Schematic of PFC promoting unquenched IR780 by forcing IR780 into hydrophobic pockets; Schematic of PFC promoting an unquenched IR780 through prevention of **π**–**π** interactions of the amphiphile-PS; Schematic of GSH responsive nanomaterial that becomes unquenched after disassembly. (**d**) Solubilization of PS in the fluorous phase increases ROS-induced cell death 140-fold compared with hydrophobic control. Data adapted from *Chem. Commun.* **2017**, *53*, 13043. (**e**) Compilation of tumor regression. Tumors treated with saline were normalized to 1, with change in tumor volume plotted (gray). Data are adapted from Refs. [15,16,18,20]. (**f**) Deoxygenated PFC

nanoemulsions increase tumor hypoxia by absorbing the minimal oxygen found in the tumor environment.

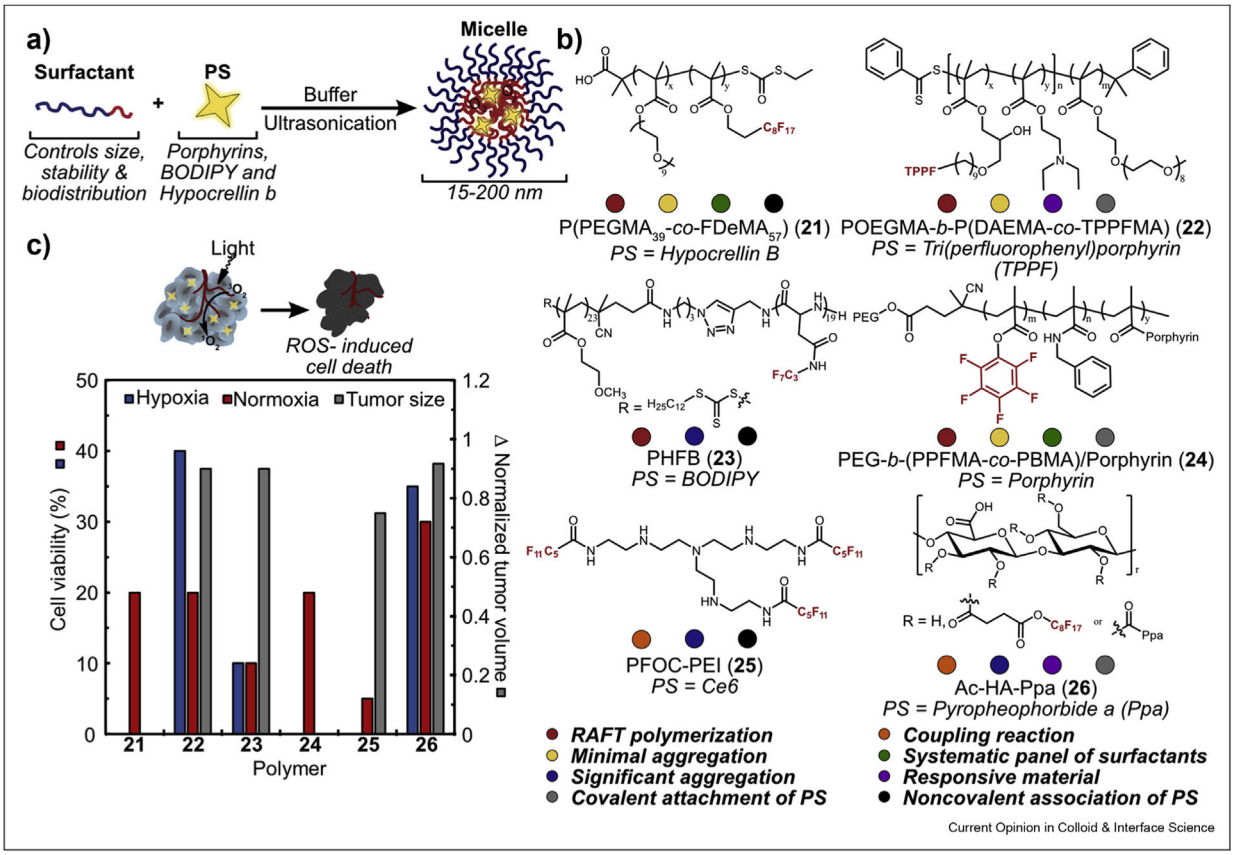

Figure 4.

Fluorous polymer micelles for photodynamic therapy. (**a**) One-step formulation of fluorine-containing micelles for PDT. (**b**) Panel of surfactants used for micelle formation. (**c**) Compilation of cell viability and tumor regression after PDT treatment. Cell viability was measured in hypoxia (blue) and normoxia (red) conditions. Tumors treated with saline were normalized to 1, with change in tumor volume plotted (gray). The data were adapted from Refs. [31–36].

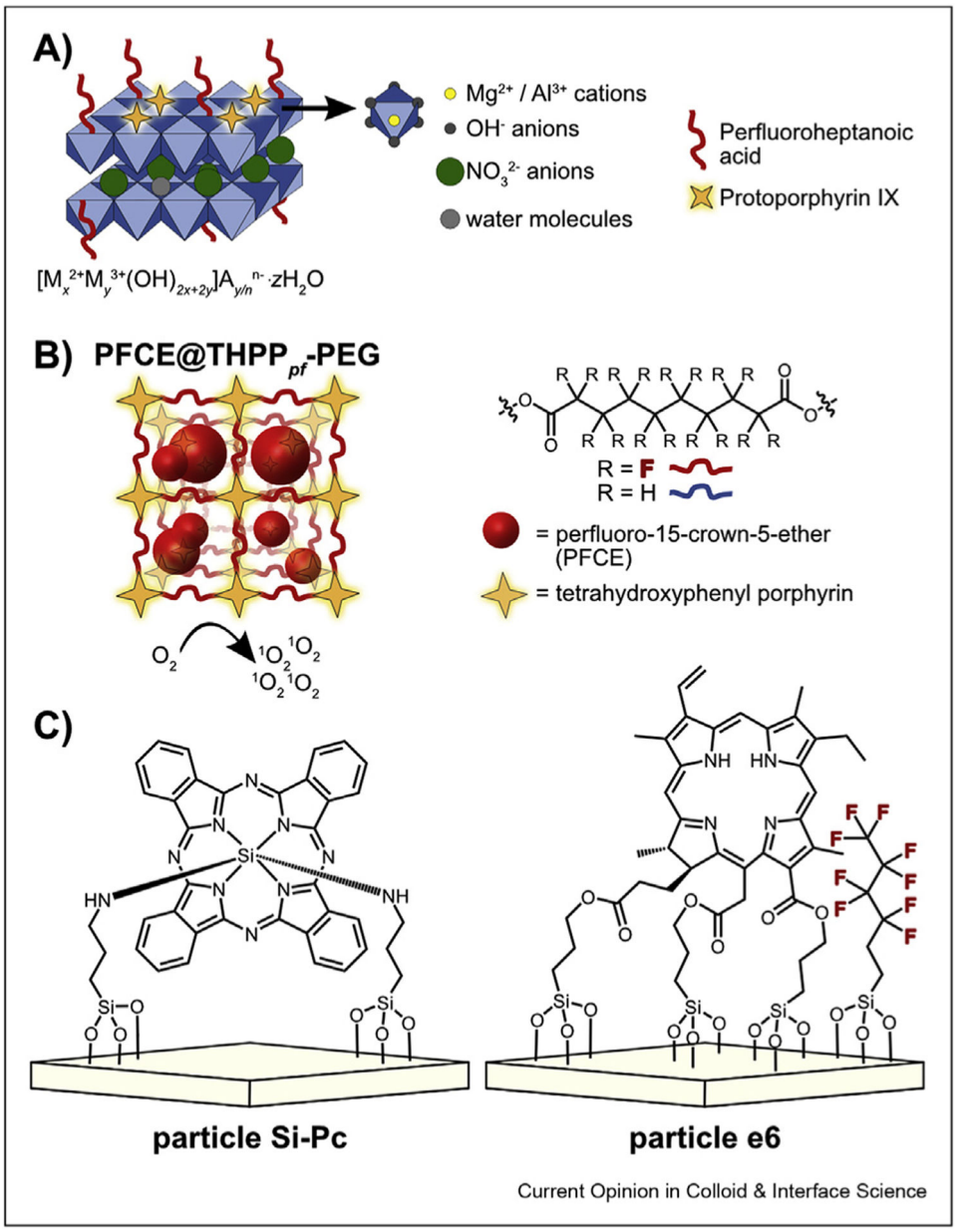

Figure 5.

Other fluorous nanomaterial scaffolds loaded with PS for photodynamic therapy. (**a**) Layered double hydroxides (LDHs) decorated with PS and fluorous chains. (**b**) Covalent organic polymer (COP) formulated with PS and fluorous linkers for the inclusion of PFCs to enhance PDT. (**c**) Superhydrophobic surfaces for the treatment of bacterial biofilms.

Table 1

Compilation of fluorous nano-PDT.

Nanomaterial architecture	Amphiphile	Fluorous solvent	PS	Size (nm)	Ref
Lipid-stabilized nanoemulsions	DSPE-PEG_{2000} (**8**), lecithin (**9**), and cholesterol (**10**)	PFH (**7**)	IR780 (**2**)	200	[11]
	DSPE-PEG_{2000} (**8**), lecithin (**9**), and cholesterol (**10**)	PFH (**7**)	Ce6 (**4**)	100	[12]
	DSPE-PEG_{2000} (**8**), lecithin (**9**), and cholesterol (**10**)	PFH (**7**)	IR780 (**2**)	250	[14]
	Cholesterol (**10**) and DPPC (**11**)	PFD (**13**)	IR780 (**2**)	250	[15]
	DSPE-PEG_{2000} (**8**), cholesterol (**10**), and DPPC (**11**)	PFOB (**14**)	ICG	320	[16]
	DSPE-PEG_{2000} (**8**), cholesterol (**10**), and DPPC (**11**)	PFCE (**12**)	Ce6 (**4**)	160	[17]
Macromolecule-stabilized nanoemulsions	Hyaluronic acid	PFH (**7**)	Ce6 (**4**)	240	[21]
	Albumin	PFTBA (**16**)	IR780 (**2**)	140	[22]
	PF68	PFD (**13**): PFTPA(**15**)	TPPF (**5**)	175	[23]
	PLGA-PEG	PFOB (**14**)	IR780 (**2**)	120	[24]
	IR780 amphiphile	PFTPA (**15**)	IR780 (**2**)	255	[26]
	HSA	PFTBA (**16**)	IR780 (**2**)	160	[29]
Micelles	Polymer **21**	-	Hypocrellin B	100	[31]
	Polymer **22**	-	TPPF (**5**)	160	[32]
	Polymer **23**	-	BODIPY	150	[33]
	Polymer **24**	-	Porphyrin	30	[34]
	Polymer **25**	-	Ce6 (**4**)	110	[35]
	Polymer **26**	-	PPA	150	[36]
Other	Layered double hydroxide	Perfluoroheptanoic acid	Protoporphyrin IX	-	[37]
	Covalent organic polymer	PFCE (**12**)	Porphyrin derivative	80	[38]
	Silica slides	Nonafluorosilane	SiPC (**3**) versus Ce6 (**4**)	-	[39]