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## Photodynamic therapy and its evolving innovation

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The use of light for the treatment of ailments has a long history with recordings of its use going back as far as ancient times. The continued study of this application for therapy has led to the development of photodynamic therapy (PDT), where photosensitizers can be excited and generate reactive oxygen species for a range of treatments with the most popular currently being its use in the treatment of cancer. In this work, we detail the history of PDT development and showcase the innovative design and progress of PDT with particular attention to the implementation and use of porous materials like metal–organic frameworks, covalent–organic frameworks, and nanoscale porous polymers which have been instrumental to its recent success while also providing an outlook of what may come for the technique. Together, this review aims at providing readers with a broad view of PDT as an application, its history of innovation and its derivative functions to give readers a foundational understanding and view of its future potential.

### Introduction

The application of light for the treatment and prevention of disease has been implemented across many areas of both the food and healthcare sectors. It silently facilitates the cessation of cellular replication and death of viral pathogens or bacteria and ironically often goes unseen. Regardless, its implementation has

been a bulwark of modern science to prevent pathogenic infections and treat many diseases while bypassing the need for harmful chemicals that, when introduced, may lead to deteriorated food quality or adverse side effects among patients.

The presence of negative side effects and complications due to drugs are often observed in oncology during chemotherapy for those suffering from cancer. The treatment options for cancer vary widely depending on the type of cancerous cell, location of the disease within the body, and the degree to which the cancerous cells have metastasized. These treatments typically include surgery, chemotherapy, radiation,

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immunotherapy, hormone therapy, stem cell transplants, or chemotherapy with the most common treatment options being surgery and chemotherapy. The administration of these harmful drugs is viewed as a necessary compromise to treat the disease and is usually paired with other treatment options like surgery, radiation, immunotherapy, hormone therapy and others to synergistically seize the growth of tumors and combat cancerous cells. However, despite years of effort and much progress, cancer remains the scourge of modern medicine, and a decisive treatment that is both effective and precise has remained elusive. Additionally, the number of cases is expected to increase in future years with projections in the rate of occurrence expected to increase to over 35 million per year by the year 2050 according to the World Health Organization.<sup>1</sup> This is an increase from approximately 20 million cases per year, with 9.7 million deaths per year reported in 2022 by the Agency for Research on Cancer.<sup>2</sup> Together, these factors create a major need for alternative treatments that can safely select

and eliminate cancer cells across a range of cancer variations, localities, and stages of severity.

Recent progress in research has allowed photodynamic therapy (PDT) to emerge as a promising technique to satisfy these goals in many cases. This method typically includes 3 key components: first, photosensitizers, which are porphyrins or structurally related compounds; second is an irradiation source, typically in the near-infrared range of 600–900 nm; and third, oxygen, which is prevalent within the body.

Early PDT methods leveraged the innate targeting of porphyrins to infiltrate photosensitizers within the cancerous tissue. Once inside, these light absorbing compounds can then be activated by specific wavelengths of light to create reactive oxygen species (ROS) which inhibit cellular replication and cause cell death. The advantages of this treatment over other methods arise from its high specificity and efficiency. Unlike many chemotherapy drugs, these compounds naturally accumulate in cancerous tissues and have low uptake in healthy cells. This creates a localized high concentration of photosensitizers which can be activated by irradiation to eliminate cancerous cells while having limited effects on healthy tissue. This leads to a very high kill rate for cancerous tissue while minimizing the undesirable side effects and complications that may accompany other treatment routes. However, PDT does face some challenges in limitations and areas that need improvement. Primary limitations include dependency on light penetration, which is usually 5–10 nm, lower efficiency in ROS production in hypoxic environments such as in large tumors, and traditionally poor photosensitizers in terms of selectivity toward target cells or ROS conversion. Chief among these is the limitation that comes with using light as an excitation source. This is an issue when trying to treat cancer found internally, particularly in areas that cannot be accessed using endoscopes or in areas that are difficult or dangerous to access such as the brain. Recent progress has pushed the boundaries in each of



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these areas, however, and even incorporated PS elements within porous structures as building blocks within porous materials like covalent-organic frameworks (COFs), nanoscale coordination polymers (NCPs), and metal-organic frameworks (MOFs) which have recently been recognized by the Nobel committee who awarded scientists Omar Yaghi, Richard Robson, and Susumu Kitagawa with the 2025 Nobel Prize in Chemistry for their pioneering contributions to the field.<sup>3</sup> The incorporation of these materials with PDT has allowed an increased concentration of PS at the desired location, providing binding sites for the conjugation of targeting groups on the exterior of these materials, and a vacant space within the pores of these materials can be utilized for drug storage and delivery. Together, this creates powerful drug delivery vehicles that can target, facilitate PDT, and deliver chemotherapy drugs all in one package.

Another significant use of PDT comes in the form of aPDT or antimicrobial photodynamic therapy, previously known as photodynamic inactivation (PDI). This process was originally discovered before PDT and led to its development for cancer treatment. Similar to PDT, aPDT uses either naturally occurring PSs within pathogens or administered PSs to infiltrate the cell before light activation to produce ROS and cause cell death. While it had its own merits, PDT overshadowed this method until recently where it has gained significant importance and popularity due to the rise of antimicrobial resistant drugs. This has caused aPDT to become an aspect of PDT with great significance that should not be overlooked.

Together, these forms of PDT offer critical solutions to medical professionals and patients suffering from cancer or antimicrobial resistance bacteria. In this work, we offer a thorough background of PDT, where it comes from, its mechanism, and advantages and disadvantages before expanding upon recent breakthroughs such as the adoption of advanced materials (*i.e.* MOFs/COFs/NCPs) that have expanded the application of PDT in an effort to improve patient outcomes. These achievements and future expectations create a balanced perspective and outlook as this field continues to develop and innovate.

## Historical context of light therapy

Before the idea of photodynamic therapy was formally proposed, ancient inhabitants began to use this concept to treat diseases.<sup>4</sup> In fact, the occurrence of light-based therapy to treat ailments such as vitiligo, alopecia, psoriasis, melancholy (depression) and other conditions can be found across the ancient world from Rome to India, Greece, China, and Egypt, demonstrating transmission of early medicinal practices between civilizations. The earliest example of these practices comes from Egypt in 1550 BC. The traditional Chinese medicine classic “Compendium of Materia Medica” that was compiled in 1578 records that plant psoralen can be used to treat vitiligo, alopecia areata, and other diseases.<sup>5</sup> This treatment is discussed by Parrish who describes the historical origins of PUVA (psoralen coupled with ultraviolet A). The origins of this technique, which is still used to this day, can be traced back to

ancient Egypt and India with the use of *Ammi majus*, an Apiaceae plant containing psoralen which is spread across the body before being exposed to sunlight.<sup>6</sup> These methods were preserved and continued throughout early history and through the Middle Ages. New developments in light therapy began in the 1890s when Danish researcher Niels Ryburg Finsen demonstrated that his carbon arc lamps (Finsen lamps) used filters and lenses to concentrate narrow ranges of light. Leveraging this, Finsen used UV light from 300 to 400 nm and showcased its bactericidal effects in treating conditions like Lupus, laying the foundation for modern phototherapy, for which he later received his Nobel prize in 1903.

### Developments leading to PDT

In 1900, the early research into “photodynamic action” began. This term was conceptualized and introduced by German scientists Tappeiner and his student Oscar Raab when they observed that the combination of acridine and light produced a strong toxicity to paramecia when they were exposed to both acridine and light, in contrast to acridine alone.<sup>7</sup> This phenomenon was then explored over the next few years by Herman von Tappeiner, expanding to a range of other fluorescent dyes, reporting on the effects on protozoa and enzymes, gathering support for their original theory and confirming its mechanism with its three essential components: (1) a photosensitizer, (2) a light source, and (3) oxygen. Although rudimentary from a modern perspective, the mechanism was described by the action of the PS absorbing the emitted light, causing it to become excited. This PS then reacts with a surrounding substrate, often oxygen, to create a cytotoxic effect.<sup>8</sup>

In 1904, Tappeiner formally proposed the concept of photodynamic action while he collaborated with Albert Jesionek, a local dermatologist. The group demonstrated the effect again in a clinical setting to treat basal cell carcinomas and lupus vulgaris by applying erythrosine to the affected areas followed by exposure to light, yielding meaningful results. Upon observing its success, it was subsequently applied to several other skin conditions, with variations in photosensitisers also being examined.<sup>9,10</sup>

In 1924, Albert Policard observed that when rat sarcomas were exposed to light, they shined with red fluorescence. He attributed this to porphyrins accumulating within tumors by bacterial infection sites.<sup>11</sup> However, this was later refined by Korbler and further investigated by other researchers who demonstrated that the affinity of porphyrins for tumors was in fact responsible for this activity and not the presence of any bacteria.<sup>12–14</sup> Through these investigations, identifying and treating metastasized tumors were improved. Research waned, however, during the war years, with the next major advancement in 1942 by Helmuth Auler and Georg Banzer. Here, the authors demonstrated that in contrast to Policard’s porphyrins, which were endogenous or naturally occurring within the specimen, exogenous porphyrins, specifically hematoporphyrin, could be injected and selectively localized among tumors, thus marking a major milestone for the first use of exogenous porphyrin for the selective identification of

tumors.<sup>15</sup> This finding was corroborated by published works starting in 1948 after the resolution of the worldwide conflict by Francis Figge and his colleagues where the group confirmed, expanded, and popularized related findings.<sup>16</sup> These contributions included the expansion of exogenous porphyrin use, demonstrating selectivity across tumor types, the introduction of quantitative tracking *via* radiolabelled porphyrin, as well as the first clinical demonstration of exogenous porphyrin used in human cancers.<sup>17,18</sup>

Based on these advancements, Thomas Dougherty's group systematically screened hematoporphyrin and hematoporphyrin derivatives (HpD) to study their accumulation and phototoxicity with mouse tumor models.<sup>19</sup> This led to the first use of HpD + illumination applied in clinical patients in 1978 and has since been promoted for the treatment of many types of cancers such as skin cancer, esophageal cancer, lung cancer, *etc.* with a high local tumor control rate.<sup>20,21</sup> To activate Photofrin, a light source of a specific wavelength is required. With a study finding that red light at 630 nm was best for activating Photofrin, some corresponding laser devices were developed.<sup>22</sup> These laser devices typically feature diode lasers capable of delivering light at a stable wavelength of 630 nm. Next, advanced fiber optic transmission systems include flexible and rigid fiber diffusers capable of precise navigation in complex anatomical structures and precise delivery of light to the target area.<sup>23</sup>

The definition of PDT is extended to a treatment in which photosensitizers are selectively enriched in the lesion and reactive oxygen species are produced after specific light excitation, leading to the selective death of lesion cells. Since the 1990s, more porphyrin derivatives, ALA (5-aminolevulinic acid), phenyl porphyrins, red photosensitizers, *etc.*, have been developed and utilized for research and in practice.<sup>24,25</sup> Since then, clinical exploration studies of second-generation photosensitizers, such as *meta*-tetra(hydroxyphenyl)chlorin and *m*-THPC commonly known as

Foscan or benzoporphyrin derivative monoacid ring A or BPD-MA, common name Verteporfin, *etc.*, have reported their improved photosensitivity and tissue selectivity and reduced photosensitivity period and the expanded clinical scope of PDT.<sup>26,27</sup> Since 2000, many developments of three generations of photosensitizers, the expansion of laser types, and the combination of nanotechnology and targeting technology with PT have brought new development potential and opportunities to PDT.<sup>28,29</sup>

The research and application of PDT have been extended to many fields. According to the U.S. Food and Drug Administration (FDA), PDT is an approved method for the treatment of skin diseases. In addition, the range of cancer treatment *via* PDT has also been expanded to other cancers, like bladder, pancreatic, bile duct, and even brain, vascular diseases, and infectious diseases.

## Elements of PDT and their advancements

Photodynamic therapy has evolved over the years through many combined efforts. Recent advances have incorporated delivery vehicles and targeting moieties which when combined can improve efficacy and reduce off-site effects. Here, we aim to provide a detailed description of the mechanism of PDT and factors that influence its application below.

### Mechanism

The process of PDT typically includes three basic components: irradiation (often light), a photosensitizer, and a substrate. PDT is initiated by the administration of PSs to the desired area of effect. After this, the area is irradiated, causing photons of light to be absorbed by the extended conjugated  $\pi$  electron system created by the macrocycles within the PS (Fig. 1).

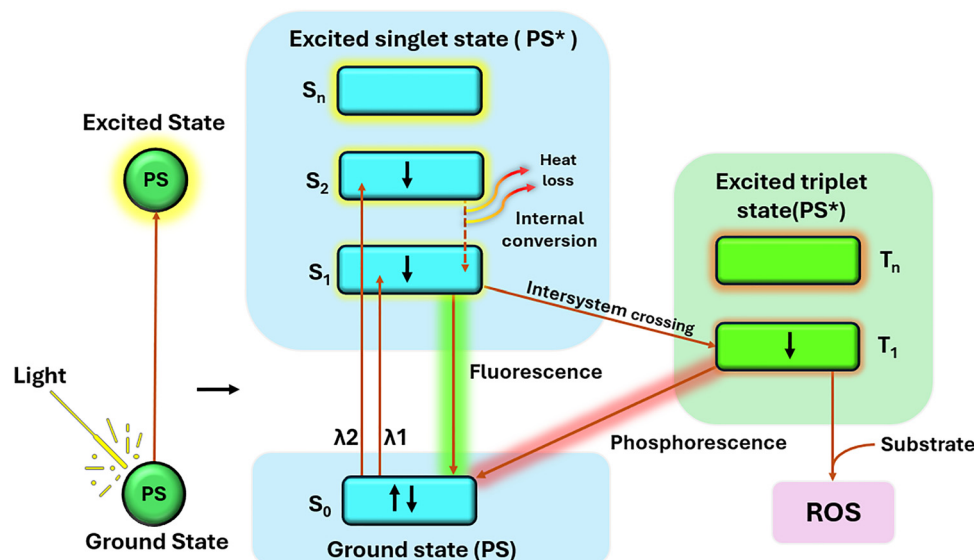


Fig. 1 Jablonski diagram depicting the process of PS excitation, energy transitions, and energy transfer to the substrate to create ROS.

This absorbed energy excites an electron within the PS, moving it from the highest occupied molecular orbital (HOMO) in its ground state ( $S_0$ ) to the lowest unoccupied molecular orbital (LUMO) in a state referred to as the singlet state ( $S_1$ ).<sup>30</sup> This electron exists in this state for a very short amount of time (femtoseconds) due to its instability before undergoing relaxation. From here, the electron may transition through one of the three ways. Due to its instability, the excited electron in the  $S_1$  state relaxes predominantly by returning to the ground state, losing its energy *via* fluorescence.<sup>31</sup> The second route occurs when the excited electron goes through a process known as intersystem crossing (ISC). During this phenomenon, the excited electron moves *via* non-radiative transition from the singlet state to the triplet state ( $T_1$ ). Other energy states can exist depending on the amount of energy absorbed (*i.e.*  $S_2$ ,  $T_2$ , *etc.*); however, these do not exist long and are not predominant. In the  $T_1$  state, the electron may then undergo relaxation *via* phosphorescence or, because the triplet state is long-lived (micro-milliseconds), the PS can transfer energy or an electron/hydrogen atom to surrounding molecules, especially ground state  $^3O_2$  or other substrates creating ROS or other radicals.<sup>32</sup> This exchange represents the therapeutically relevant state of the PS during PDT. The final form of relaxation comes in the form of vibrational relaxation. This is a non-radiative form of decay and may arise from either excited state,  $S_1$  or  $T_1$ , and undergoes relaxation through the release of energy in the form of heat.

The routes of creation for reactive species as a result of PDT are classified into three categories, simply described as Type 1, Type 2, and Type 3 mechanisms (Fig. 2). Each of these mechanisms create their therapeutic effects by either direct killing of

the cell (apoptosis, necrosis, autophagy, or necroptosis), vascular shutdown, or an anti-tumor response. In Type 1, the excited triplet state PS abstracts an excited electron or hydrogen from nearby reducing substrates. These include NADH/NADPH, glutathione, cysteine, ascorbic acid, guanine, or unsaturated lipids. This allows the PS to form a radical cation ( $PS^{\bullet+}$ ) and a substrate radical. Alternatively, the PS may accept an electron to form  $PS^{\bullet-}$  which rapidly transfers the electron to ground state oxygen ( $^3O_2$ ), even at very low concentrations of oxygen (<5 mmHg). This creates a superoxide anion radical ( $O_2^{\bullet-}$ ) which then reacts with water to form  $H_2O_2$ . This hydroxide then undergoes a Fenton reaction with trace  $Fe_2^+/Cu^+$  to generate a hydroxyl radical ( $\bullet OH$ ). While this mechanism is oxygen dependent, it tolerates low oxygen environments well and is the predominant pathway within hypoxic environments like that within large tumors. This mechanism can be characterized by the irreversible oxidation of the PS due to the nearby radicals causing PS bleaching.<sup>33</sup>

In contrast to type 1, the type 2 mechanism is characterized by a high singlet oxygen quantum yield, a strong increase in cytotoxicity within  $D_2O$ , and minimal bleaching of the PS. This mechanism represents the dominant pathway for most clinically approved PSs under well oxygenated conditions. In this mechanism, there is a transfer of energy from the  $T_1$  PS to nearby ground state oxygen, exciting it to the singlet oxygen state. In this state, oxygen becomes highly reactive with a short lifetime, thus constricting its damage to its locality only. While type 2 is the predominant mechanistic route of PDT, unlike in type 1, its dependence on oxygen (>15 mmHg  $O_2$ ) makes it struggle in hypoxic environments.<sup>34</sup>

Finally, Type 3 is an emerging proposed mechanism that has recently been described and has not yet been widely accepted. This method is oxygen independent and involves direct energy transfer to surrounding cellular targets including RNA, proteins, *etc.* without an ROS intermediate. Here, the PS binds and photoinduces a cleavage or cross-linking to the substrate.<sup>35</sup> While this method is still in its early stages and has not been widely recognized, it has shown potential as an alternative to the traditional mechanisms with its ability to treat larger tumors.

Once ROS and other radicals are created, they have short half-lives which limit their diffusion distance to roughly 20–200 nm from the PS.<sup>30,32</sup> This allows PDT to be innately selective in its local effects. This, along with the ability to strictly control its activation through on/off switching, makes PDT exceptionally site specific and biocompatible. The generation of ROS within the selected cells then begins a cascade of events that result in cell death. The primary recipients of ROS activity are listed here.<sup>36</sup> The first of these are unsaturated lipids among membranes. The oxidation of these lipids initiates a chain reaction within the membrane to form hydroperoxides that disrupt membrane integrity, increase permeability and cause leakage, resulting in vascular shutdown, hypoxia, and nutrient deprivation. When PSs are activated near the mitochondrial membrane, the leakage results in the loss of cytochrome *c* which neutralizes energy production within the

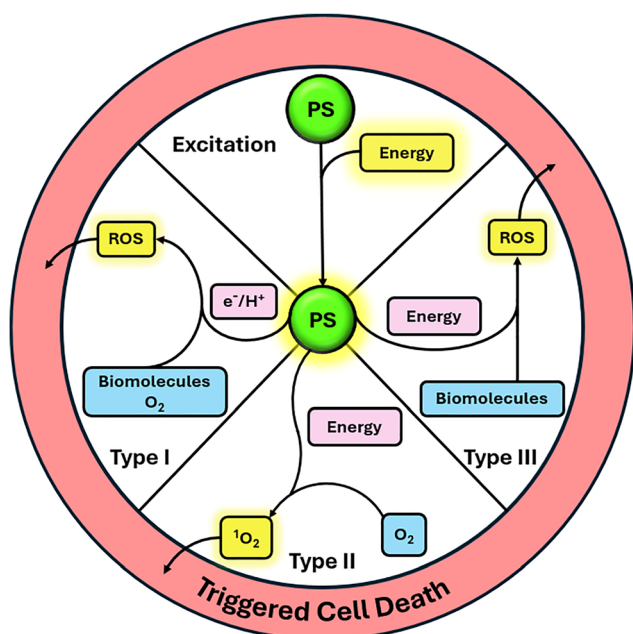


Fig. 2 Cartoon representation of PDT mechanism types with substrates in blue, PSs in green, how energy is transferred in pink, and energized components in yellow.

cell. Next are amino acids and proteins. The oxidation of these can cause the inactivation of enzymes and receptor proteins which disrupt cellular metabolism and signaling. Nucleic acids, DNA and RNA, may also be oxidized. This can cause strand breaks, cross-linking, or mutations, leading to a cessation of replication and transcription that can lead to activation of p53, upregulating pro-apoptotic genes. Other oxidized elements within the extracellular matrix include carbohydrates or cholesterol. Like ROS, these components act as oxidizers that go on to disrupt cellular functions, leading to cell death.

### Irradiation

The use of light in PDT is one of the major factors that allows this process to be minimally invasive and exceptionally site specific. While many light sources are viable for surface treatments, the use of lasers has made it possible to control the area exposed to irradiated light, thus allowing the treatment to be selectively initiated and localized.<sup>37,38</sup> This factor alone offers a significant advantage over conventional chemotherapy as it minimizes systemic side effects.

The process of irradiation for PDT is also not trivial and is reliant on several factors. First, not all wavelengths of light are functional in PDT. Among conventional PDT, the wavelength of light used is typically within the therapeutic window (650–900 nm, Fig. 3).<sup>39</sup> The reason for this use of a narrow range is to prevent the adsorption of the photons by surrounding endogenous chromophores like hemoglobin and water, which absorb below 600 nm and above 900 nm, respectively. Second, the wavelength of light must be paired with the associated absorption of the selected PS within this range. This is important as the energy of the photons being absorbed must be sufficient to excite the PS electrons to the singlet state. Third, the fluence of light (amount dosed) is a major factor that controls the extent to which the PS is activated and therefore the intensity at which PDT is administered. This dosing is a measure of the power density of irradiation in energy per area ( $\text{J cm}^{-2}$ ) over time (seconds) and is typically administered *via* LED light or lasers which can be irradiated on the surface of the body inserted through fiber optic cables to irradiate areas within the body. This leads us to our final consideration during irradiation which is the penetration depth required for treatment. This is the most consequential factor currently as it has created a significant challenge for researchers. This is because of the limitation of the therapeutic window constricting the amount of energy allowed to be applied to PSs and the inaccessibility of some tumors within the body. This is expressed in the Planck–Einstein relation where the energy of light is described ( $E=(hc)\lambda^{-1}$ ). This illustrates the inverse relationship between a photon of light's energy and its wavelength. Lower wavelengths of light do not adequately penetrate tissue, making PDT ineffective for large tumors and difficult to use in various organs and areas that are difficult to access. This has caused researchers to use lower wavelengths of light in an effort to maximize the penetration depth. However, this remains constricted by the therapeutic window and thus limits the possible amount of energy applied and resulting efficiency of

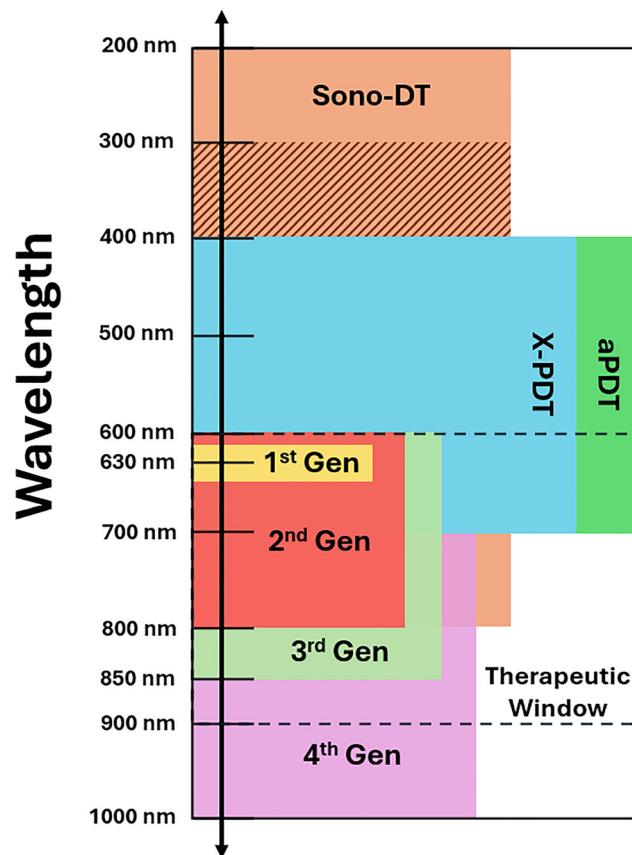


Fig. 3 Diagram depicting the wavelengths at which PSs become excited illustrating progress of PS excitation over time including 1st generation (excitation  $\sim 630$  nm), 2nd generation (600–800 nm), 3rd generation (600–850 nm), and 4th generation (700–1000 nm); Sono-DT absorbs over a broad band from 200 to 800 nm but peaks between 300 and 400 nm, and aPDT or X-ray PSs absorb from 400 to 700 nm.

PDT. This drawback has been a major hindrance to the advancement of PDT within clinical space as it effectively limits the degree and location of activity. New methods have been developed, however, to overcome this hurdle.

### Photosensitizers

Photosensitizers are a class of light-sensitive compounds, usually non-toxic or of low-toxicity, that can accept photons of energy to excite electrons, elevating them to a higher energy state. This is made possible due to the conjugated aromatic systems present among the PSs, allowing for light absorption and energy transfer. PSs typically include a tetrapyrrole macrocycle backbone which may include porphyrins, chlorins, phthalocyanines, bacterio-chlorins, or other similar moieties.<sup>32</sup> Notably, these molecules strongly absorb light within the therapeutic window and have high quantum yields for generating ROS, meaning that they have a propensity to convert energy toward the substrate to generate the ROS.<sup>30</sup> For reference, a high quantum yield for PDT would typically be between 0.5 and 0.9, where this represents 50–90% of energy conversion from light to the substrate. Other characteristics that lend them to operation within biological systems include good solubility, low

toxicity in the dark, and rapid clearance which can help to avoid prolonged photosensitivity. The backbone, substituents, and coordinated groups of these PSs can also be modified to improve therapeutic behavior. This may include the addition of peripheral substituents to improve solubility, amphiphilicity, biodistribution, or membrane affinity. Heavy metal ions such as Pd, Ru, and Sn may be added to the PS *via* coordination within the porphyrin's ring structure to enhance ISC by increasing the triplet state population and can aid in the prevention of quenching. This tunability of the PS has allowed for several improvements over traditional designs by improving key characteristics like quantum yield, ISC efficiency, and increased triplet lifetime.<sup>40</sup>

The development of PS has progressed at this point through stages, with three generations being identified. The first-generation photosensitizers, described in 1913 by Friedrich Meyer-Betz, are represented by the first injected PS, hematoporphyrin.<sup>41</sup> This earliest prototype of clinical application of PDT was comprehensively and systematically summarized by Dougherty's group with the application of HpD in early tumor treatment, laying the foundation for clinical PDT.<sup>20</sup> Beginning in the 1980s, the group standardized commercial controlled-doses production of Photofrin, a chemical-purified stable photosensitizer derived from hematoporphyrin that later became the first FDA-approved PDT photosensitizer (Fig. 4). This generation of PS suffered though from slow clearance, poor selectivity, and moderate quantum yield.<sup>32</sup>

The second-generation photosensitizers are represented by improved porphyrins such as Temoporfin, Foscan, phthalocyanine, and verteporfin which had more optimized chemical structures, better efficiency due to higher quantum yields, improved absorption at deeper penetration depths owing to

their molar absorptivity, and enhanced selectivity with better clearance. Detty reviewed the clinical progress of these photosensitizers and their advantages and limitations compared with first-generation photosensitizers.<sup>42</sup> Practically, Szeimies verified the effectiveness of PDT in combination with 5-ALA (5-ALA-PDT) in 1996 and since then, 5-ALA has remained one of the main treatments for skin disease.<sup>43</sup> This generation of PS is characterized by its ability to absorb a wider range of light, allowing for activity deeper within tissue, faster clearance, higher singlet oxygen yields due to improved ISC efficiency, enhanced targeting, and better solubility.

The third generation of photosensitizers has improved on prior designs by gradually developing toward nanoformulation, targeting, and integration of diagnosis and treatment, which is detailed in the discussion of the mechanism of action and cell death pathway of the new photosensitizer by Zhang.<sup>44</sup> In particular, the strategy of these multifunctional photosensitizers is to become activated by external physical stimuli (*e.g.*, ultrasound, applied magnetic or electric fields, two-photon excitation) or by endogenous biological stimuli (*e.g.*, temperature, acidic pH, enzyme activity, high glutathione/redox levels, or hypoxia markers), thereby greatly improving the selectivity of PDT. This new and attractive development direction holds potential as an effective enhancement to traditional PSs. The progression beyond free PSs as the only delivery mechanism through conjugation with delivery vehicles has created several advantages over unbound PSs, leading to multi-functional systems with greater effectiveness and therapeutic outcomes.

Finally, an emerging fourth generation of PSs has recently been described. These are PSs that combine advanced functionalities like stimuli activation, bioorthogonal reactions, immunotherapy and the use of AI to address existing

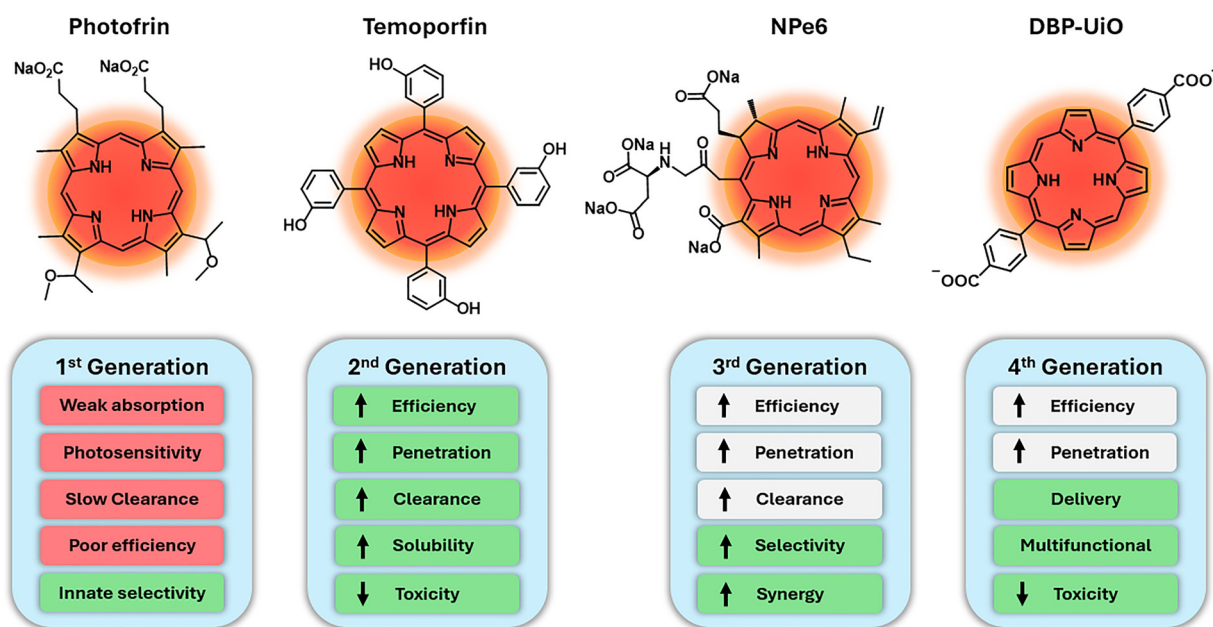


Fig. 4 Representative examples from each evolution of PSs used for PDT from the 1st to the emerging 4th generation with photoactive areas highlighted on the structures and advantages and disadvantages listed with new improvements from older generations highlighted in green.

limitations.<sup>45,46</sup> These innovations also include alternative methods for PS excitation such as using sound waves or X-rays which are described in greater detail below.

### Conventional delivery and targeting

The targeted delivery of PSs to cancer sites was not originally required due to what has become known as the enhanced permeability and retention (EPR) effect. This describes the accumulation of PSs within cancerous tissue that occurs naturally.<sup>47</sup> This is the result of a combination of the leaky blood vessels surrounding cancerous tissue, allowing for nanoparticles to diffuse into the interstitial space, and the increased retention within cancerous tissues due to impaired lymphatic drainage.<sup>40</sup> The accumulation is also a result of the high demand of low-density lipoprotein (LDL) from cancerous tissues needed for proliferation. This need is observed by the overexpression of LDL receptors on cell surfaces. PSs within the bloodstream bind to the LDLs and subsequently piggyback their way into cancerous cells by endocytosis using this up-regulated mechanism for (initially) unintended selective uptake.<sup>48</sup> While some PSs do find their way into normal cells, these are typically cleared quickly in 24–72 hours while poor clearance among cancerous cells allows PSs to be retained for weeks in some instances.<sup>49</sup> Although it would seem that this would lead to increased effectiveness, this can cause complications due to prolonged light sensitivity and collateral damage to the surrounding healthy tissue.

This propensity for the distribution of PSs in areas other than the site of interest leads to undesirable off-target side effects in 1st generation PSs. To overcome this issue, researchers utilize delivery vehicles to concentrate the loaded materials for stimuli responsive release. The use of these tools has several benefits listed here: (1) the targeted release of the loaded materials, localizing their effect; (2) improved solubility of drugs/PS, increasing bioavailability; (3) protection of the loaded material from premature decomposition and/or clearance; (4) the controlled release rate of the material; and (5) combination therapy.

Leaning into the propensity for cancer cell selectivity toward LDLs, researchers examined the use of lipid-based vehicles for PS delivery. These include liposomes, solid lipid nanoparticles, and emulsions, with the first reported use being in 1983 by Calzavara and coworkers.<sup>50</sup> Each showed promising results and had the added benefit of making a poorly soluble PS more bioavailable by solubilizing it with the lipid NP; however, there were some limitations arising from instability, lack of consistency, low drug encapsulation, and lack of sustained release. This has led researchers to develop modern liposomal formulations to address these challenges and the exploration of alternative tools for delivery and selective uptake.

To selectively target cancerous tissue, targeting substituents have been combined with PSs. These target groups focus on exploiting factors like the overexpression of receptors, angiogenesis markers, or the local hypoxic or acidic environment within and surrounding cancerous tissue. These targeting groups include biocompatible moieties including antibodies,

peptides, aptamers or nucleic acids, and other small molecules like folic acid. These could be bound to free PSs or incorporated into delivery vehicles like liposomes through surface modification.<sup>51</sup>

Polymers have also been explored for use as delivery vehicles.<sup>40</sup> Because of the ability to control their size, shape, and building units, researchers have been able to synthesize nanostructures and hydrogels from block polymers, cross-linked polymers, or dendrimers *via* synthetic routes that are relatively simple, making them easy to utilize. Instead of housing PSs within a spherical endosome as with liposomes, these structures are largely amorphous and leverage a sponge-like strategy for PS uptake and release of PS or loaded drugs for delivery.<sup>52</sup> The functionalization of these polymers allows for controlled release from their amorphous structures and random arrangement of polymer chains. The added benefit of being able to functionalize the exterior of these nanostructures allows for direct binding of targeting moieties onto the surface and the tuning of the polymers to facilitate control over release rates. The significant advantages that these materials offer make them excellent competitors to liposomal delivery; however, they continue to suffer, in some cases, due to issues with biocompatibility, variations in degradation rates, cost, or complex synthesis routes.<sup>53</sup>

A common alternative approach for delivery in biological systems is the use of inorganic nanoparticles. These may include gold nanoparticles (AuNPs), upconversion nanoparticles (UCNPs), or mesoporous silica nanoparticles (MSNs). Beyond the previously mentioned functionalization common among delivery mechanisms, each of these rigid, non-degrading, and tunable structures offer stability and dual-purpose functions. The inherent characteristics of AuNPs bring with them optical, electronic, and chemical properties including their ability to take part in surface plasmon resonance (SPR). This allows for these AuNPs to absorb and scatter wavelengths of light in the visible and near-infrared regions which can be leveraged for energy transfer to conjugated PSs, resulting in an amplification of ROS generation. This is especially useful for extending the effectiveness of PDT at deeper tissue depths. Additionally, the reflection of this light can also be used for imaging, real-time analysis, and treatment.<sup>54</sup> UCNPs are core-shell nanoparticles doped with rare-earth atoms that endow the UCNPs with the same ability of AuNPs, to convert NIR to visible light to overcome penetration depth issues in PDT.<sup>55,56</sup> Unlike these two NPs with solid interiors, MSNs are porous and offer the ability to encapsulate drugs and PSs. Because this porosity is intrinsic and persists throughout the material, these MSNs exhibit high loading capacity. Additionally, the ease of functionalization makes these materials good candidates for combining targeting and delivery with the added benefit of performing selective and controlled release. For example, the functionalization of the pores of these materials can bestow gating by folic acid for selectively controlled release in the acidic environments of cancer cells. Additionally, the interactions within the pores of the material mitigate the release rate of loaded molecules, effectively

resulting in a sustained release profile. However, these silica-based NPs suffer from limitations similar to the other inorganic materials in that they exhibit slow clearance and have issues regarding cytotoxicity, though recent coated UCNPs have demonstrated a > 80% reduction in tumor size within hypoxic models with low toxicity, indicating clinical potential.<sup>56</sup>

Collectively, the development of each of these materials and ligands has shown potential in bringing new therapeutic options despite limitations with investigation, improvements, and development continuing and even producing several clinically approved PDT agents. However, the drawbacks like burst release, self-quenching by neighboring PSs, and cytotoxicity remain prohibitive. These drawbacks create a compelling need for next-generation delivery platforms to overcome these challenges.

### Advanced materials for delivery

The challenges faced by conventional delivery methods have led to the adoption of cooperative combinations of delivery methods and the development of new, advanced materials to overcome these setbacks. Together, these materials have been shown to effectively target and deliver drugs for treatment for a range of ailments. Examples of these advanced materials include porous materials like that of MOFs or COFs for PDT and other applications.<sup>57</sup> These materials have distinct characteristics that make them lucrative options for cooperative vehicles for drug delivery. MOFs specifically have received much attention and recognition recently with the presentation of the 2025 Nobel Prize in Chemistry awarded to pioneers who led the forefront of development for the introduction and first generations of MOF materials.<sup>3</sup> The segregation of these linkers in both MOFs and COFs allows for the functional groups or groups coordinated to the metal sites to isolate potential reactive centers. Additionally, the empty interior of these materials creates ample space for the passage of molecules. The addition of various functional groups into the pores of these materials creates excellent selective forces that have been implemented for separations and uptake or retention of specific elements like rare earth minerals which can improve PDT effectiveness.<sup>58</sup> While these materials have already made a name for themselves through applications of catalysis and separations, they have a very promising future for other tasks, specifically biomedical related applications.<sup>56</sup>

These materials are synthesized by joining metal nodes with organic compounds that link each node together through the coordination of negatively charged moieties to the positively charged metal node (Fig. 5, top). Depending on the symmetry of each node and linker, various geometries and shapes can be created in the products.<sup>59</sup> This characteristic is shared among COFs where instead of coordinating to node, linkers form covalent chemical bonds with one another from terminal groups to create a robust 2D sheet. Eclipsed stacking, the most common form of extension in COFs, occurs when 2-D COF sheets  $\pi$ - $\pi$  stack directly on top of one another, allowing for the extension of these materials into the 3rd dimension (Fig. 5, bottom). However, this leads to the interlayer distance between

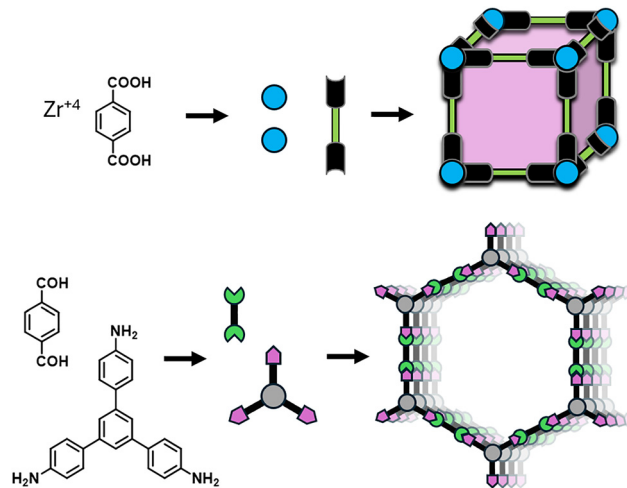


Fig. 5 Cartoon representation to illustrate the basic building blocks and final 3D structure via coordination in MOFs (top) and chemical bonds and stacking in COFs (bottom).

porphyrins to be small and the PS to be too close in proximity to one another for effective activation due to quenching. To solve this, new synthesis methods have been developed to create separation. For example, a recent publication by Sun and colleagues in 2023 demonstrated the use of an unconventional topology in COF-919 to improve PDT effectiveness in COF mediated PDT.<sup>60,61</sup> By mixing the orientations of the linkers, the authors were able to create separation between the PS, which increased its effectiveness.

Because of their naturally large vacant pores, these materials have a high uptake capacity, making them excellent candidates for the storage of materials like drugs, and can even house materials as large as proteins. This was first demonstrated in 2011, where the Ma group immobilized a microperoxidase within the Tb-mesoMOF and showed that not only could the enzyme be kept safe from environmental factors, but its catalytic activity could also be improved through immobilization within the pores.<sup>62</sup> In parallel during the same year, the Ma group published their first of many works that helped set the foundation and pioneer the use of porphyrin-based MOFs. Here, the group demonstrated a new series of MOFs incorporating porphyrins, the base unit of PS, which were used as linkers within this series of frameworks termed metal-metalloporphyrin frameworks or MMPFs.<sup>63</sup> The Ma group showed that the rigid structure of these porphyrins makes them excellent candidates for building blocks within these crystalline materials and their ability to absorb light permitted them to take part in photocatalytic reactions. In 2012, the Ma group published two following articles that demonstrated the versatility of the porphyrin-based framework with a new topology that increased the density of catalytic centers and set a new benchmark for surface area within a porphyrin-based MOF.<sup>64,65</sup> The group also demonstrated that the porphyrins within these MOFs could be functionalized *via* metal ion exchange to manipulate catalytic behavior.<sup>66-69</sup> The Ma group then published a novel porphyrin-based COF (CHF-1) in 2014 and demonstrated its ability to

Table 1 A comparative analysis of delivery vehicles used for PDT

| Vehicle       | Loading capacity | Circulation duration | Bio-compatibility          | Stability | Risk of PS self-quenching | Synthesis difficulty | ROS generation efficiency |
|---------------|------------------|----------------------|----------------------------|-----------|---------------------------|----------------------|---------------------------|
| Lipid NPs     | Moderate         | Short                | Very high                  | Moderate  | Moderate                  | Moderate             | Moderate                  |
| Polymer NPs   | High             | Moderate             | High                       | High      | Moderate                  | Moderate–complex     | High                      |
| Inorganic NPs | High             | Moderate–long        | Moderate <sup>a</sup>      | Very high | Low                       | Moderate             | High                      |
| MOFs          | Very high        | Moderate–long        | Moderate–high <sup>a</sup> | High      | Low                       | Complex              | Very high                 |
| COFs          | High             | Moderate             | Moderate                   | Very high | Low–moderate <sup>b</sup> | Complex              | High                      |
| NCPs          | Very high        | Moderate             | High                       | High      | Low                       | Moderate–complex     | Very high                 |

<sup>a</sup> Dependent on selection of components. <sup>b</sup> Recent designs have overcome this issue.

operate as a biomimetic enzyme.<sup>70</sup> The same year, the group contributed a review showcasing the advancements in porphyrin MOFs including the diverse porphyrin-based species used as linkers and highlighted the potential and current underutilization they had for biological applications.<sup>71</sup> Lin and coworkers also published in 2014 demonstrating the first use of MOFs for PDT.<sup>72</sup> The following year in 2015, Lin and coworkers pushed the boundaries of the field by filing the first patent for the application of PDT using a MOF with porphyrin linkers.<sup>73</sup> In 2020, the Ma group introduced a custom-designed Corrole-based COF with a desymmetrized hcb topology.<sup>74</sup> This yielded a unique pore with staggered AB stacking with an elliptical shape instead of the common pore shapes observed in many other COFs.

Together, these works demonstrate why porous materials like MOFs or COFs offer significant advantages for PDT. First, the separation created by using PSs as linkers prevents the PS from interacting with one another, effectively eliminating the occurrences of self-quenching. This coupled with the increased density of PS as a result of taking part in the extended framework means that there is a dramatic increase in catalytic efficiency compared to free PSs. The vacant interiors of these porous materials also allow for bifunctional attack of cancerous tissue through both PDT and chemotherapy routes in what is referred to as a “combination therapy” where two forms of therapy are used in concert to defeat the target. The ability to functionalize the interior of MOFs/COFs allows researchers an additional way to tune the release profiles of these drugs or prevent the escape of other encapsulated groups.<sup>75</sup> As an example of their use, in 2023, Lin and colleagues demonstrated a nanoscale MOF that was used to confine PSs within the pore of the crystal instead of including them in the MOF structure as linkers.<sup>76</sup> This strategy prevented PS aggregation/quenching and offered a novel route for the administration of poorly soluble PSs.

Another advanced material is represented by nanoscale coordination polymers or NCPs. These were first introduced in 2008 by Lin and colleagues, with the term expanding nomenclature to encompass both crystalline (MOFs) and non-crystalline polymers.<sup>77</sup> Instead of only materials that form a unit cell and extend to create a repeatable structure, this term

includes materials that may be amorphous with similar characteristics and capabilities.

Because of the ease with which the surfaces of these materials can be functionalized, the addition of polymers like FA can selectively release the loaded drugs within the environment of cancerous cells. The same mechanism allows for the conjugation of other selective targeting groups like antibodies and aptamers bestowing the materials with active targeting rather than simple passive targeting that may lead to a higher occurrence of offsite effects.<sup>78</sup> Also, because of the customization of linkers or nodes within synthesis, components can be selected for their biocompatibility. This along with their stability makes these materials exceptionally amenable toward biological applications like PDT. Recently, however, more focus has been on the implementation of COFs which have allowed researchers to utilize organic only materials to promote higher biocompatibility and any potential risk of toxicity from degradation. This is demonstrated again by Lin and colleagues who have published works expanding the frontier of this field in recent years.<sup>79,80</sup> To compare each of these materials, we provide an analysis of each and compare their features in Table 1.

## Recent advancements and innovations

Due to the diverse composition of modern PDT therapies, there are many facets of PDT that continue to undergo improvements. This has led to the development of “smart materials” which combine drug delivery, targeting, and ROS generation in an all-in-one package and alternative methods for PS activation.<sup>81</sup> The main thrust of these endeavors centers around overcoming the challenges of (1) the limitation of light penetration depth, (2) increasing the effectiveness of PSs administered, (3) improving targeting selectivity, and (4) reducing off-site collateral effects. Here, we identify and discuss several significant innovations that have been developed to overcome these roadblocks, particularly in the context of advanced materials. These innovations have led to valuable treatment routes that can combine and synergize with conventional techniques to enhance effectiveness and combat cancer deep within tissue with minimal side effects.

## Immunotherapy and PDT

The programmed activation or evasion of the immune system by delivery vehicles allows for treatments to selectively elicit a cooperative immune response or prevent the system from initiating a response. Evasion can be achieved by using neutral or zwitterionic groups attached to the surface of the vehicle that create areas of high hydration, low charge, and/or steric repulsion which prevent attachment and recognition by immunoglobulins or immune cells. Polyethylene glycol or PEG is a prime example of this as it is commonly used in drug formulations as a coating to increase the circulation time and evade immune responses using its long carbon chains for steric repulsion. Alternatively, a more elaborate mechanism for vehicle stealth is represented by the decoration of “self” signaling peptides such as CD47 peptides or the coating of vehicles in the patients' own cell membranes. These effectively allow the vehicle to be recognized by the immune system, preventing a response.

In contrast, triggering an immune system response can have several benefits that make it worthwhile. Groups that activate the immune response are characterized by being charged, being hydrophobic, or having agonists that trigger an antigen response. By eliciting an immune response, treatments can enhance treatment efficacy by promoting local recognition and clearance of pathogens or tumors. Additionally, this improved response can lower the required number of doses required for full treatment.<sup>82,83</sup>

Recently, it has been shown that effects of PDT treatment can lead to immune responses within the body. This was demonstrated by groups led by both Sun and Dai in 2022 who showed that when PDT initiates enough lipid peroxidation, a cooperative acute inflammatory response is produced, leading to antitumor immune activity.<sup>84,85</sup> In 2023, Sun and colleagues' work (mentioned previously) also showed that increased pyroptosis also promoted T-cell infiltration, boosting T-cell mediated immune responses which helped inhibit metastasis and recurrence.<sup>60</sup>

While this is the result innate to PDT, other routes of immune activation have also been demonstrated by incorporating PDT with immunotherapeutic agents. For example, Lin and colleagues have reported on this topic several times and demonstrated the delivery of an immunotherapeutic agent (resiquimod) by conjugating it to a hafnium based MOF (Hf-DBP-QP, Fig. 6).<sup>86</sup> The activation of the PDT active MOF led to the triggered release of this agent which acts as a TLR agonist and activated nearby antigen-presenting cells, stimulating an immune response. These methods of coordination between PDT and immunotherapy represent a significant advancement in development and a bright frontier for the technique.

## Theranostic PDT

The natural release of energy in the form of fluorescence after PS excitation has allowed researchers to use some PS for imaging; however, this can lead to ROS generation and off-target effects. In 2000, Babbar and colleagues were inspired to

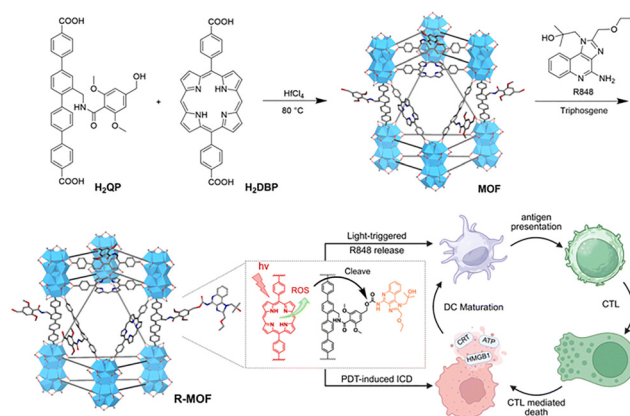
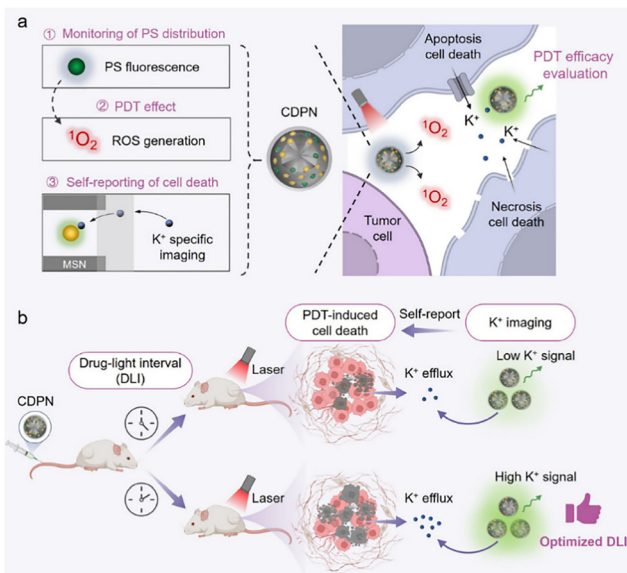


Fig. 6 Synthesis of Hf-DBP-QP (MOF) and its covalent conjugation with R848 via a ROS-cleavable linker to yield the R-MOF, a dual-function platform that mediates PDT and immune activation. Upon light irradiation, the R-MOF induces ICD and locally releases R848, promoting dendritic cell maturation and T cell infiltration within the TME. Reproduced from ref. 86 with permission from the Royal Society of Chemistry, copyright 2025.

incorporate a radio label (<sup>99m</sup>Tc) with a PS called photosan-3. In doing so, the authors used SPECT imaging (single-photon emission computed tomography) to demonstrate the first dual-use PS for diagnostic imaging to identify tumors and tandem PDT.<sup>87</sup> Theranostics is not only limited to radiolabeling, however, as other methods have utilized PSs to absorb ultrasonic waves for 3D tumor mapping or dosing of PSs with gadolinium or iodine for MRI and CT, respectively, for visualization in deep tissue.<sup>88–90</sup> A recent example of progress within PDT theranostics was demonstrated by Ling and colleagues in 2025.<sup>91</sup> In this work, the authors showcased a novel cell death self-reporting photodynamic theranostic agent or CDPN (Fig. 7). By leveraging dyshomeostasis in K<sup>+</sup> as a biomarker, the accurate *in situ* evaluation of treatment efficacy could be monitored and optimized. This technique represents a major step forward for real-time monitoring of treatment and illustrates the impact that such advancements may have on oncology. This combination of empowering healthcare professionals with the ability to manage not only the location of treatment but also the extent to which treatment is applied allows patient outcomes to be dramatically improved.

## X-PDT

A notable achievement by Jin Xie and colleagues in 2016 introduced X-ray activated PSs, inducing PDT without the need for visible light. This has become known as X-PDT and leverages the high energy X-rays that penetrate deep within tissues and become absorbed by scintillators. These scintillators then convert the energy to lower energy and release UV or visible light via luminescence which can excite nearby PSs and may even be used in challenging areas like the brain, thus overcoming a key limitation surrounding the penetration depth. In 2018, Lin and colleagues applied the concept to MOFs. In this PDT mechanism, high-energy X-rays are absorbed by rare-earth minerals which are used as the nodes.<sup>92</sup>



**Fig. 7** Designing cell death self-reporting theranostic nanoagents (CDPNs) facilitates real-time monitoring of tumor responses and enables dynamic optimization of therapeutic strategies. (a) CDPNs combine PDT effects with visualization of PS accumulation and self-reporting of cell death. The ROS generated by CDPNs trigger cell death, resulting in an increase in the extracellular  $K^+$  concentration. *In situ*, real-time monitoring of cell death through  $K^+$ -specific fluorescence imaging allows for timely evaluation of PDT efficacy. (b) CDPNs provide prompt feedback on PDT responses and guide the optimization of the drug-light interval, resulting in significantly improved antitumor efficacy. Reproduced from ref. 91 by Bian *et al.*, licensed under CC BY 4.0 by Wiley-VCH, copyright 2025.

Advances in this PS excitation technique are still being revealed. Recently, in 2025, Zeng and colleagues demonstrated the use of hafnium based silica nanoparticles to directly transfer high energy electrons to the triplet state of PSs (Fig. 8).<sup>93</sup> By bypassing the ISC route and the use of scintillators, the authors were able to enhance ROS generation efficiency even with low doses of X-ray radiation. The authors also showed that the treatment induced production of T cells to create an immunotherapeutic effect. Because the dose of radiation required is lower than that of traditional radiotherapy, X-PDT is a promising alternative to other cancer treatment methods. However, its use of rare-earth minerals and novelty mean that there is a consideration to be made in terms of cost and there is the same, although lower, risk of toxicity due to X-ray irradiation.

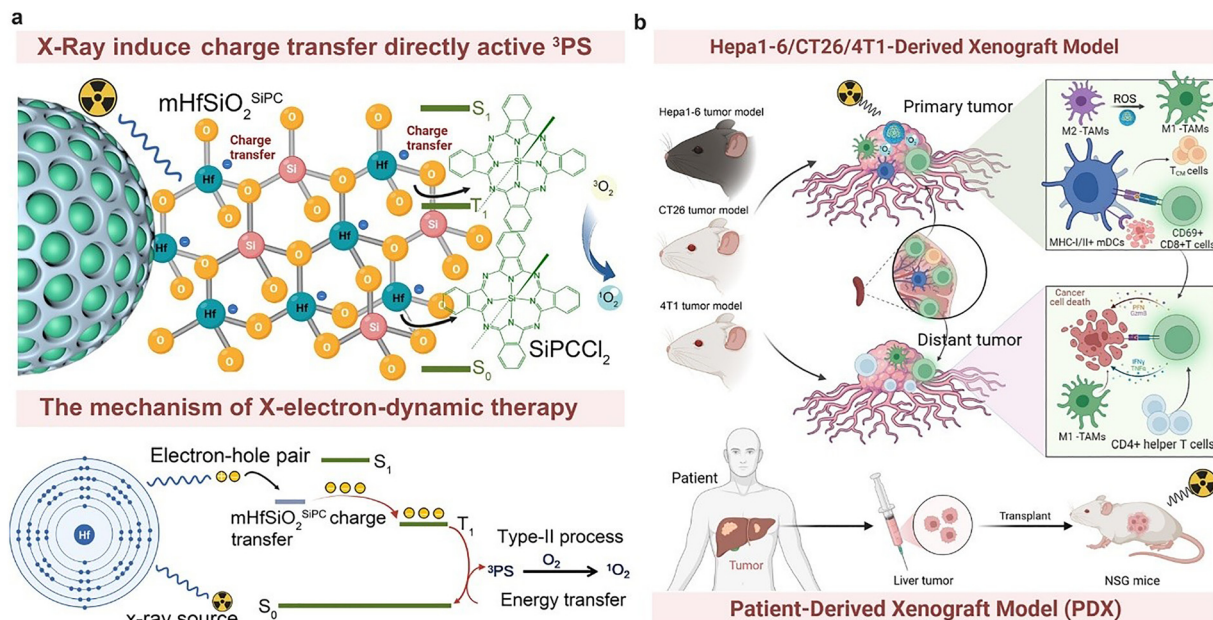
### Sonodynamic therapy

The use of sound waves has also been implemented as an alternative energy source to initiate SDT or sonodynamic therapy. Originally discovered in 1989 by Umemura and colleagues, SDT was first observed in hematoporphyrin where it could be sensitized by low-intensity ultrasound (US) for the treatment of tumors.<sup>94</sup> Instead of using energy from a light source to generate ROS, this route uses ultrasonic waves to induce cavitation in the local environment of the tumor where cancer

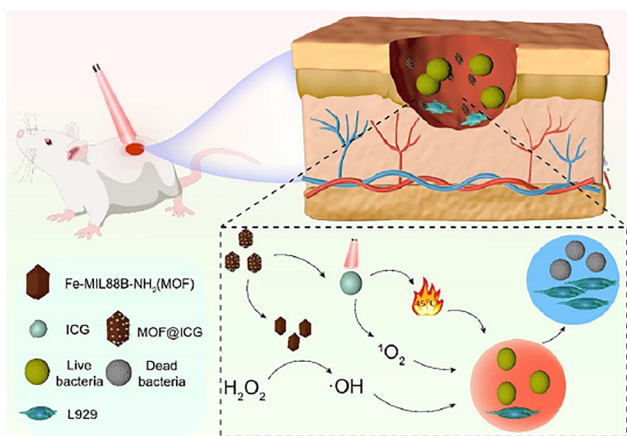
cells have a lower density compared to the surrounding healthy tissue. Cavitation then produces extreme conditions in the surrounding microenvironment, creating a high energy density.<sup>95</sup> This is observed to lead to the activation of the nearby PS by one of two routes. In the first mechanism, this high energy density leads to short bursts of light that are absorbed by the nearby PS, leading to the generation of ROS.<sup>96</sup> The second pathway occurs through direct energy transfer from the surroundings to the PS before ROS generation. Like X-PDT, SDT allows for deeper penetration, but may also be combined with PDT for a greater effect. Additionally, the administration of SDT can be applied effectively in hypoxic environments without the need for oxygen present causing cell death *via* the type 3 mechanism described above for PDT. However, the distribution of ultrasonic waves can lack precision, leading to some collateral effects in surrounding tissue. In 2024, Fan and colleagues demonstrated this concept adapted to the porphyrin MOF PCN-224 coated with  $CaO_2$  (Fig. 9).<sup>97</sup> This coating served a dual function by dissolving in the acidic environment of cancer cells and delivered  $Ca^{2+}$ , thus imparting selective activation and triggering calcium overload, respectively. The addition of the complex also creates an increased intensity of the local cavitation, greatly enhancing the effectiveness of the SDT. Together, this treatment offers a synergistic, biocompatible, and effective alternative to conventional treatments.

### Photothermal therapy

Another significant innovation has been the development of photothermal therapy or PTT. As the name suggests, this derivation from PDT uses energy in the form of heat for its effect. The mechanism for PTT is quite similar to PDT with the exception that its effect is only achieved through the non-radiative decay pathway. After irradiation with near IR light irradiation, PTAs (photothermal agents) instead of PSs convert absorbed light to thermal energy. These PTAs can be inorganic materials (*i.e.* gold nanoparticles) or organics like dyes. The absorbed energy is then dissipated to the surrounding microenvironment as heat, resulting in hyperthermia within the cancerous tissue. This leads to necrosis or apoptosis through local damage of protein, membranes, and nucleic acids.<sup>98,99</sup> A recent study by Yang and colleagues demonstrated a multifaceted approach combining, PDT, PTT, and enzyme delivery to effectively attack cancer cells.<sup>100</sup> The MOF was loaded with a photoactive dye (IR780) and glucose oxidase (GOx) which can eliminate the primary energy source for cancer cells and also makes the cells more susceptible to hyperthermia. Leveraging the MOF instability in acidic environments, the authors used a passive targeting approach to release the contents of the MOF within the cancer cells. This allowed glucose oxidase to begin starving the cells, while IR780 was triggered by light to generate both ROS and a hyperthermic local environment. This led to the synergistic combination of these treatments and the effective killing of cancer cells in both *in vitro* and *in vivo* settings while minimizing side effects.



**Fig. 8** Mechanism of X-eDT and its antitumor effect. (a) Schematic illustration depicts the concept of X-eDT using a hafnium-silica radiosensitizer compared to conventional X-PDT. X-eDT involves electron transfer from hafnium-silica nanoparticles by directly activating the lower-lying triplet states of photosensitizers upon X-ray exposure, leading to enhanced  $^1\text{O}_2$  production. The process depicted in (b) shows Lipid@mHfSiO<sub>2</sub>sipc as a radiosensitizer to generate ROS through X-eDT and induce immunogenic cell death (ICD) characterized by calreticulin (CRT) exposure, high mobility group box 1 (HMGB-1) release, as well as adenosine triphosphate (ATP) secretion in various tumor mouse models. Furthermore, this ICD promotes dendritic cell (DC) maturation via phagocytosis. Intravenously administered X-eDT enhanced M1 macrophages to tumors in both sides. Repolarized macrophages and mature DCs enhance antigen processing and presentation to CD8+ T cells, leading to their priming, proliferation, and infiltration into primary and distant tumors. Consequently, CD8+ T cells recognize and induce tumor cell death, releasing more tumor antigens and inducing a robust abscopal effect on distant tumors. Reproduced from ref. 93 with permission from the American Chemical Society, copyright 2025.



**Fig. 9** Schematic diagram illustrating the use of MOF@ICG NPs for treating bacterial infections and repairing skin wounds by PTT/PDT/chemodynamic therapy. Reproduced from ref. 102 with permission from the Royal Society of Chemistry, copyright 2024.

### Antimicrobial PDT

While many forms of PDT and its related innovations focus on the treatment of cancer, another form of PDT traces its roots directly to the original discovery of PDT by Oscar Raab in 1900 and has seen a resurgence of interest recently with the increase in prevalence of drug-resistant bacteria.<sup>7</sup> This critical issue has

become a major concern in healthcare leading to a resurgence by researchers in the use of PDT to kill these bacteria or viral infections. This form of PDT is referred to as antimicrobial PDT (aPDT) that, while similar to PDT, instead selectively targets microbes (*i.e.* bacteria, fungi, or viruses) rather than cancer cells. PSs used in aPDT are non-toxic to animals/humans and include dyes or porphyrins like methylene blue or chlorin. These are distributed upon a surface and preferentially bind to microbial cells or biofilms, leading to endocytosis. After entering the cells, the PSs are activated by light, not between 650 and 900 nm as in PDT, but by a range typically between 600 and 700 nm.<sup>101</sup> The remaining aspects and mechanisms of aPDT do not deviate from those of PDT. Recently in 2024, Cai and colleagues reported the use of the MOF Fe-MIL-88B-NH<sub>2</sub> loaded with indocyanine green and evaluated its effectiveness as an antibacterial agent for wound cleaning (Fig. 10).<sup>102</sup> Upon irradiation, the material produced heat and singlet oxygen and also leveraged the Fenton reaction to create ROS, thus achieving a three-mode low-temperature therapeutic that killed bacteria and promoted wound healing.

Because of the biocompatibility, effectiveness, and speed at which aPDT operates, this method has been implemented in high-risk settings to treat infections and prevent complications with operations such as in organ transplants. Although highly effective, aPDT suffers in some of the same scenarios as PDT, especially with challenges related to light penetration.<sup>103</sup> A recent review by Wu and colleagues illustrates the significant

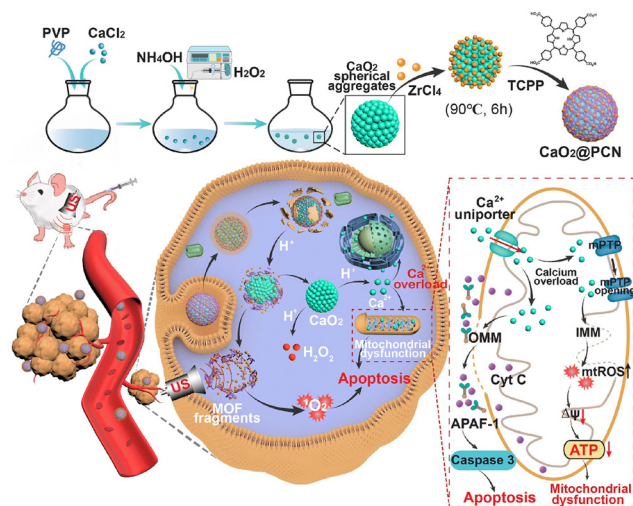


Fig. 10 Schematic mechanism of CaO<sub>2</sub>@PCN for acidity-responsive sequential degradation using SDT/IIT. Reproduced from ref. 97 with permission from the Royal Society of Chemistry, copyright 2024.

interest and recent progress made in this research area.<sup>61</sup> Here, the timeliness and innovation on display from many of the selected works highlight the degree of interest and rapid rate at which the field is advancing and expanding.

### Other PDT targets

While PDT has started as a treatment for skin conditions and recently has primarily been researched as an oncological treatment and for antimicrobial activity, its success and selectivity

have inspired others to adopt it for the treatment of other diseases. The areas include ophthalmology, dermatology, immunology, cardiology, and neurology.<sup>104–107</sup> This final area of research represents another major challenge where researchers are exploring PDT in order to create a novel treatment for the neuropathies of dementia and Alzheimer's disease.<sup>108</sup> Here, PDT is targeted towards the pathological tau aggregates and beta-amyloid plaques. Progress in this area has seen some success but has had difficulty in overcoming the same challenges observed in cancer treatment. Because of the focus on the brain, these particularly center around the issues of crossing the blood brain barrier and the penetration depth of applied irradiation.<sup>109–111</sup> Due to the extremely limited options available for treatment of these diseases, the significance and potential for development in this direction cannot be overstated.

## Outlook

Due to the many aspects that go into PDT and related innovations, there are many directions from which advancement for PDT may come. From the excitation source to the PS composition, delivery vehicle coating, vehicles themselves, conjugates, or targeting moieties, each of these facets have potential to be improved and further developed. This also means that advancements in many other related fields can have a significant impact on and drive opportunities for future innovation and exploration in research areas surrounding PDT (Fig. 11).

With the recent recognition of MOFs winning the 2025 Nobel Prize in Chemistry, we expect the implementation and acceptance of these and other porous materials like MOFs/COFs/NCPs to increase, becoming more commonplace among synthesis routes and treatments for medicinal purposes. In fact, these events are already on the horizon as demonstrated by Wenbin Lin and colleagues who have a nanoscale porous polymer in phase 2 of testing in clinical trials.<sup>112</sup> Other future progress that will break out and become hallmarks of cancer or related research fields will be those that demonstrate effective selectivity and treatment in sensitive or hard to reach areas like the brain or large tumors with minimal side effects, offering a significant advantage over conventional treatment routes.

## Conclusions

The long history and consistent innovation of PDT exemplify the effectiveness of the applied scientific process for research and development. These innovations have revealed PDT to be an effective treatment across a range of ailments and show a promising outlook in its development as a treatment option in oncology. Combination therapy has allowed PDT to leverage targeting, ROS generation, and drug delivery to combat cancerous tissue, even in hard-to-reach locations, with excellent selectivity and lasting results. This advancement is largely impacted by its adoption of porous materials like MOFs, COFs, or NCPs which allow for facile conjugation of targeting moieties

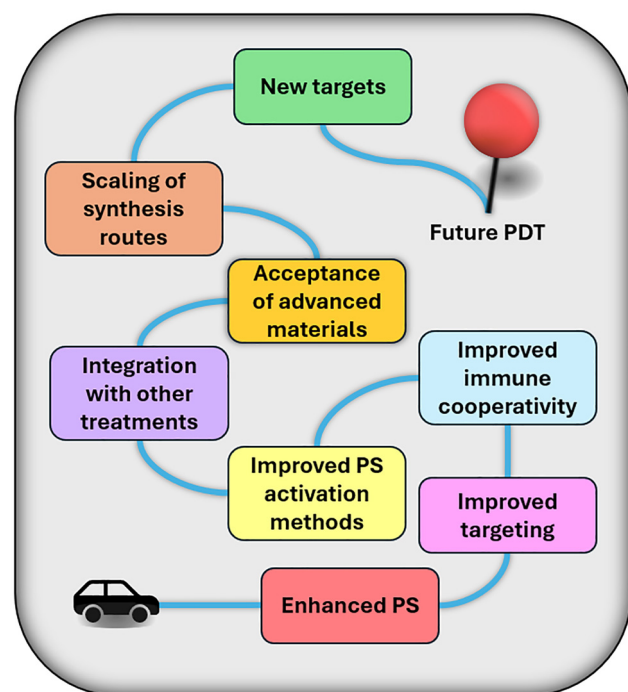


Fig. 11 A roadmap showcasing the many facets of PDT that will lead to future advancements and success in both academic and industry settings.

or polymer coatings, loading and delivery of chemotherapy drugs or immunotherapy agents, and the incorporation of PSs within the structure of the nanoparticle or encapsulated in its interior. This concentration of PS within porous materials prevents self-quenching by isolating PSs, amplifies ROS generation within cancerous cells, and allows for better targeting/selectivity, leading to improved treatment efficacy. While improved treatments using porous materials are on the horizon as they move through clinical trials, applications of PDT among other neuropathic diseases are also being investigated and may prove to be among the first effective treatments for Alzheimer's disease and dementia. Although PDT is highly popular, the success of advanced materials in PDT following these clinical trials is likely to ignite interest and propel research in surrounding areas and diseases, creating a new frontier in industry that has long been primed by academics.

## Author contributions

J. P. and S. M. were responsible for conceptualization; J. P., W. F., M. K., and D. H. were responsible for investigation and writing – original draft preparation; J. P. was responsible for project administration; J. P. and S. M. were responsible for writing – review and editing; S. M. was responsible for project supervision.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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