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Synergistic effects of combining phototherapeutics with traditional treatment modalities in oncology

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Phototherapeutic methods like photodynamic therapy (PDT), photothermal therapy (PTT) and photodecaging have emerged as promising modalities for cancer treatment. Phototherapeutics are activated by light and thereby generate reactive oxygen species (ROS), heat, or release a caged, toxic carry-on. Their distinct advantages of spatial and temporal control preserve healthy tissue while promising a minimal invasive alternative to traditional therapeutic approaches. When combined with each other or with other treatment modalities like chemotherapy, immunotherapy, *etc.*, they can exert a synergistic effect that enhances their overall efficacy by improving targeting and destroying cancer cells. Given the rapid expansion of combination therapies that incorporate phototherapeutic elements, it is crucial to gain an understanding of the most important phototherapeutic methods and their synergistic effects when used in combination. This review provides a comprehensive overview of these combinations, focusing on the benefits such as overcoming drug resistance, improving targeting, and minimizing side effects, while also addressing the current challenges that must be overcome. The clinical translation of these combination therapies is also explored, with particular attention to the regulatory hurdles and advancements required to bring these promising treatment modalities into clinical practice.

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1. Introduction

1.1. Overview of cancer therapy

Cancer remains to be one of the leading causes of death worldwide, making it crucial to keep advancing therapeutic strategies to improve patient outcomes.[1,2] Traditional cancer treatments like surgery, chemotherapy, and radiation therapy

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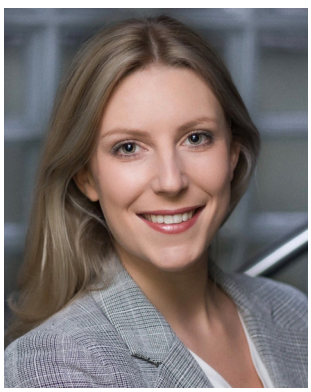

Flavia Kradolfer

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have been the mainstay for many years. However, these methods often have significant drawbacks, such as invasiveness, severe side effects, and the potential for tumors to develop resistance.[3–7]

Surgery has been a primary approach for removing solid tumors for a long time. While it can cure localized cancers, its effectiveness is limited when tumors are not well-defined or have spread. Additionally, surgery is invasive and can lead to long recovery times and loss of function.[7–9]

Chemotherapy uses cytotoxic drugs that interfere with cellular processes essential for division and survival. These drugs often target the DNA replication machinery, disrupt microtubule function or interfere with metabolic pathways unique to rapidly dividing cells. Despite its widespread use, chemotherapy often lacks specificity, which means it also destroys healthy, rapidly dividing cells. This leads to side effects like hair loss, nausea, and immunosuppression. Furthermore, cancer cells can develop resistance to these drugs, reducing their effectiveness over time.[10–12]

Radiation therapy uses high-energy particles or waves, such as X-rays, gamma rays, or electron beams, to damage the DNA within cancer cells. This damage, primarily in the form of DNA double-strand breaks, inhibits the cancer cells' ability to repair themselves and divide, ultimately leading to cell death. While it can effectively reduce tumor size and alleviate symptoms, it also affects nearby healthy tissues. This can cause side effects like skin irritation, fatigue, and an increased risk of secondary cancers.[13–15]

To address these limitations, the field of oncology has shifted towards more targeted and less invasive treatments. Targeted therapy aims to interfere not only with specific molecules involved in cancer growth and progression, but also with cancer marker, allowing a more precise attack on cancer cells while sparing normal tissues.[5,16–19] Examples include immunotherapy,[20,21] which target specific antigens on cancer cells or inhibitors,[22,23] that target cancer-related enzymes. Additionally, light induced therapies such as photodynamic therapy (PDT),[24] photothermal therapy (PTT),[25] and photouncaging[26] have opened new avenues in cancer treatment. These therapies use the unique properties of light to achieve precise, localized treatment, minimizing damage to surrounding healthy tissues. PDT utilizes light-activated photosensitizers to generate reactive oxygen species (ROS) that may selectively destroy cancer cells.[24] PTT employs photothermal agents that convert light into heat, causing localized hyperthermia and subsequent cancer cell death.[25] Photocages are light-responsive compounds that release therapeutic agents in a controlled manner upon exposure to specific wavelengths of light.[26]

Moreover, combination therapies are being increasingly explored to boost therapeutic efficacy (Fig. 1). By combining different modalities, like PDT or PTT with chemotherapy or immunotherapy, researchers aim to exploit synergistic effects, improve response rates, targeting, and overcome resistance.[24,27,28]

As the field of photoinduced cancer therapy continues to progress at a fast pace, it is crucial to understand the fundamental mechanisms and current challenges. This article will review the fundamental principles of PDT, PTT and photodecaging, addressing limitations and opportunities with a focus on their multimodal application in cancer therapy. Detailed information on different phototherapeutics (such as specific photosensitizers, photothermal agents, *etc.*) will not be discussed in the scope of this work. For this information, please refer to the excellent review of Tarrant, Lawrence and co-workers.[29]

1.2. Historical perspective on light-induced cancer therapy

The origins of light-induced therapy can be traced back to various ancient civilizations, where heliotherapy, the use of sunlight for therapeutic purposes, was practiced to treat a variety of skin diseases, infections, and bone diseases.[30–33] A significant milestone of this field was honored in 1903 when the Nobel Prize in Physiology and Medicine was awarded to the Danish physician Niels Finsen, who demonstrated the efficacy of ultraviolet light in treating *Lupus vulgaris*.[34] During the early 20th century, scientific pioneers of photochemotherapy like Raab and Von Tappeiner, started to combine drug administration with light irradiation. This was followed by the work of Daniell and Hill. Their work showed that hematoporphyrin could selectively accumulate in certain tissues and, when exposed to light, generate ROS that damaged targeted cells.[39] Further advancements were made by Dougherty in the 1980s through clinical studies, leading to the approval by the U.S. Food and Drug Administration (FDA) of Photofrin, the first photodynamic drug.[40,41] In 1909, the German scientist Ehrlich introduced the concept of the magic bullet, a drug that specifically targets the diseased site without harming surrounding healthy tissue. His work and ideas laid the groundwork for modern drug discovery.[42] Light-induced therapies embody this magic bullet concept by allowing selective irradiation at the diseased site, thereby minimizing damage to healthy tissues. Additionally, various strategies to enhance targeting are discussed in this review.

The exploration of synergistic agents in cancer therapy has evolved over decades, revolutionizing the treatment landscape. By combining different therapeutic agents enhanced efficacy, reduced resistance and minimized side effects can be achieved.[43,44] One of the pioneers of combinational treatment

Bernhard Spingler

Prof. Bernhard Spingler received his PhD degree (1998, summa cum laude) under the supervision of Prof. Margareta Zehnder from the University of Basel, Switzerland. After his postdoctoral stay with Prof. Stephen J. Lippard at MIT, USA, he returned to Switzerland to the University of Zurich. His research focuses on the development of novel BODIPY derivatives for medicinal applications on the one hand and on the improvement of crystallization procedures for small molecules on the other hand.

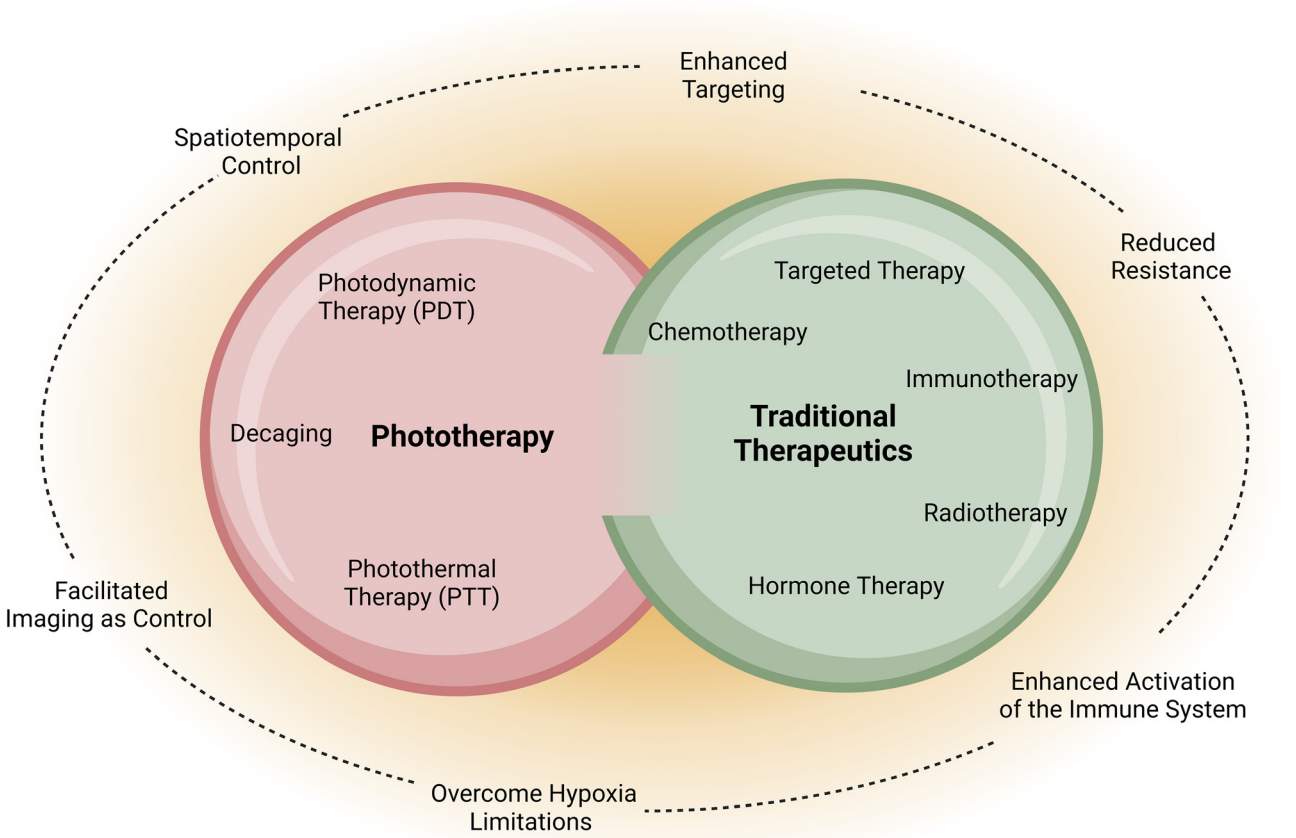

Fig. 1 Schematic representation of the synergistic effects achieved by combining phototherapies with conventional therapy methods. Fig. 1 was created using https://BioRender.com.

modalities was Vincent T. DeVita Jr. His work on the MOPP regimen to treat Hodgkin's lymphoma demonstrated the power of multi-drug regimens to cure cancers that were once considered fatal.[45] Photoinduced therapies, including PDT, PTT and photouncaging have become significant components of this approach.[46–48]

2. Fundamental mechanisms and challenges

2.1. Photodynamic therapy (PDT)

PDT represents a treatment modality that employs a photosensitizer activated by light in the presence of oxygen. A photosensitizer populates the singlet state S_1, after being excited. From there, intersystem crossing can occur which results in the population of the triplet state T_1. From this state two reaction pathways may occur. In a type-1 reaction, the excited photosensitizer reacts with water to generate hydroxyl radicals, peroxides, and superoxide species. In a type-2 reaction, ambient triplet oxygen is excited to form singlet oxygen. The outcome of both reaction types are reactive oxygen species (ROS) which are cytotoxic, leading to the destruction of the affected cell. The fundamental mechanisms of PDT are depicted in Fig. 2, highlighted in the Jablonski diagram. For effective tissue penetration the excitation wavelength must exceed 650 nm, due to light-absorbing biomolecules, but remain below 900 nm to ensure sufficient energy for singlet oxygen generation and avoid the absorption by water.[24,29,48–52] The absorption spectrum of hemoglobin, oxyhemoglobin and water is shown in Fig. 3, depicting the phototherapeutic window in which tissue penetration is most effective.[53] For a photosensitizer, its response to light at a suitable wavelength is also a crucial parameter for its suitability as a phototherapeutic. The light responsiveness describes the product of the extinction coefficient of the photosensitizer (ε) and its singlet oxygen quantum yield (Φ) at the given wavelength.[54,55] Ideal photosensitizers for light responsiveness in phototherapeutics typically have extinction coefficients in the range of 10^4 to 10^5 M^{-1} cm^{-1} and a singlet oxygen quantum yield above 50% when irradiated between 650 and 900 nm (phototherapeutic window).[54] However, PDT also comes with limitations. One notable limitation of PDT is the hypoxic nature of many solid tumors, which restricts its efficacy by impeding the production of singlet oxygen. Recent research endeavors aim to circumvent these limitations by either generating alternative ROS, other than singlet oxygen, or by co-producing oxygen at the targeted site, thereby enhancing the therapeutic potential of PDT under hypoxic conditions.[56–59] A different limitation states the rather poor cancer cell selectivity.[60]

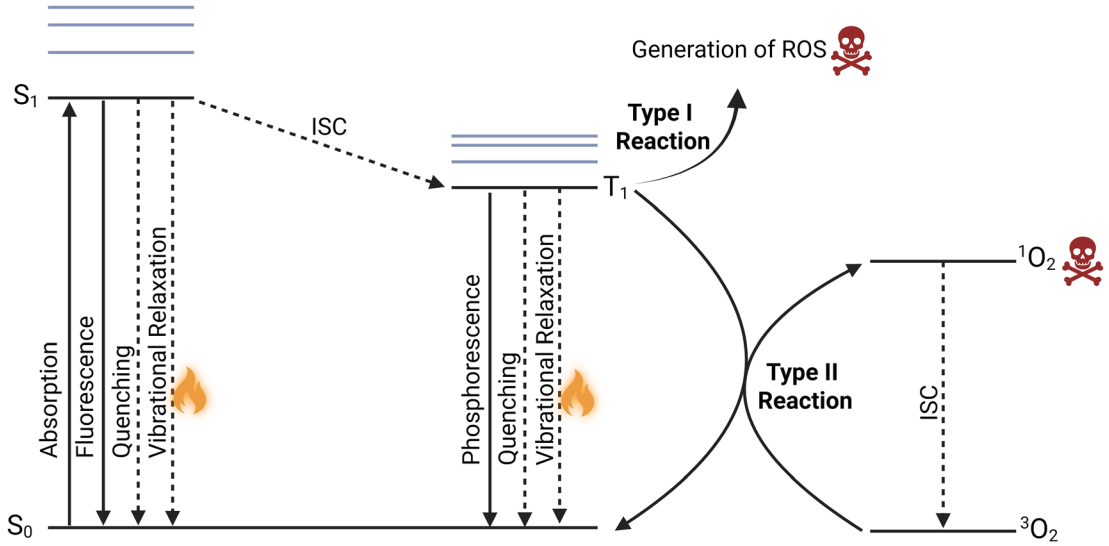

Fig. 2 Jablonski Diagram, highlighting the mechanisms of PDT (toxic products) and PTT (heat generation by non-radiative relaxation).[35–38]

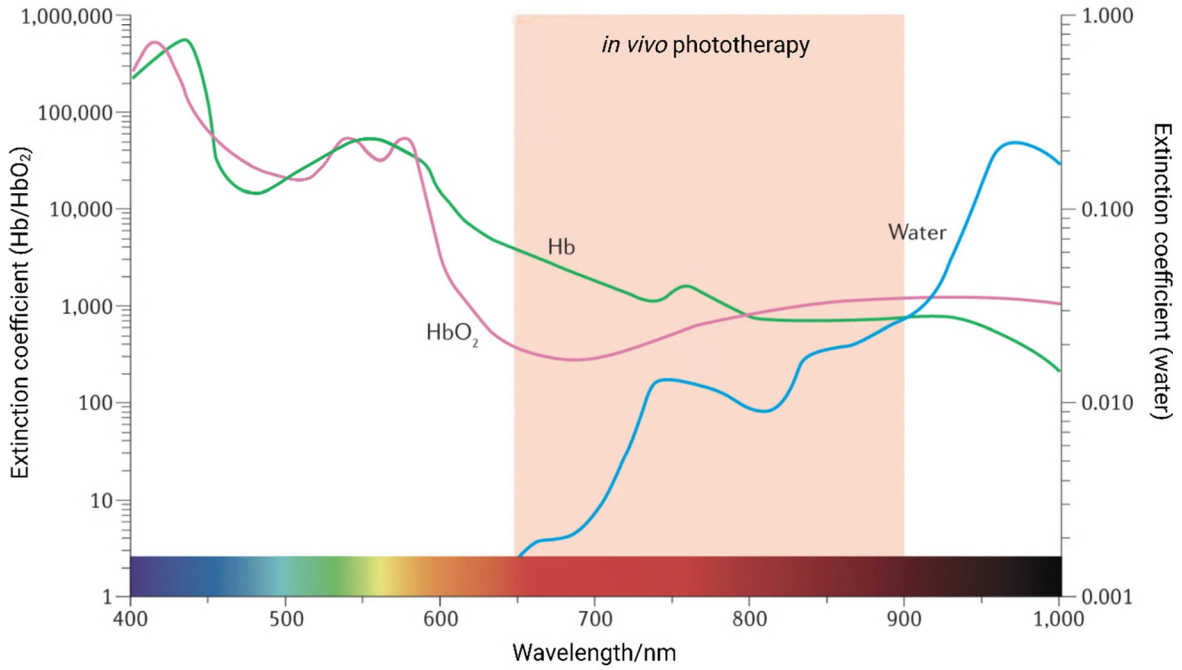

Fig. 3 Absorption spectrum of hemoglobin (Hb), oxyhemoglobin (HbO_2) and water. The graphic illustrates the wavelength region between 650 and 900 nm which can be used for phototherapeutic approaches, since biomolecules and water are less absorbent in this wavelength region. Figure adapted with permission from ref. 53. Copyright 2010 American Chemical Society.

An alternative form of photoinduced therapy, which is not restricted to the presence of oxygen, is PTT.

2.2. Photothermal therapy (PTT)

In PTT, light is utilized to excite a photothermal agent, which subsequently generates heat as it returns to its ground state in a non-radiative fashion, as indicated in Fig. 2. The generated heat damages the affected cells.[25] Dependent on the heat generated, hyperthermia is divided in three compartments. Mild hyperthermia takes place in the temperature range of about 40 to 45 °C. The elevated temperatures sensitize cancer cells to other therapies like radiation therapy, PDT and chemotherapy by increasing blood flow that results in an increased tumor oxygenation and transport of drugs into the tumor.[61] Moderate hyperthermia takes place at temperatures up to 50 °C. It causes time and temperature dependent apoptosis due to protein

denaturation that is enhanced by the tumor's microenvironment properties. During severe hyperthermia which is the case at temperature above 50 °C the mode of action changes and mainly necrosis and tissue coagulation take place.[62] For the excitation of the photothermal agent, the lower wavelength limitations are identical as in PDT. However, since the excitation of oxygen is not part of the mode of action, higher wavelengths are often applied. In PTT the administered photothermal agent is typically an organic aggregate or an inorganic nanomaterial.[63,64] Each type has unique advantages and disadvantages which influence their effectiveness and applicability in clinical settings.[65]

2.3. Photocages and photoswitches

Photocages are light-sensitive compounds that release a part of the molecule when exposed to the stimulus of light.[66] Photodecaging involves the light-induced removal of the photolabile protecting group (PPG) to release a biologically active molecule in controlled time and location.[67,68] The mechanism by which photodecaging takes place involves the absorption of a photon, promoting the photocage into an excited electronic state. From there, a series of bond rearrangements or cleavages can occur, ultimately leading to the release of the active compound. Depending on the chemical nature of the protecting group, heterolytic and homolytic cleavage can take place, resulting in either radicals or ions. Heterolytic cleavage is more prominent in medicinal applications, since the intermediates can be stabilized and yield in non-toxic byproducts and high quantum yields. A prime example is the *o*-nitrobenzyl group, where photoexcitation leads to intramolecular electron transfer and the formation of an *aci*-nitro tautomer intermediate, which then rearranges to release the cargo.[69] Photoswitches on the other hand can reversibly change their structure and thereby their properties in response to a specific wavelength of light. They have potential in targeted drug delivery where a drug is released only at the desired site, minimizing side effects and improving efficacy.[67,68] Like all photoinduced therapy forms, their efficiency is also dependent on the penetration of light into biological tissue, which means that the release or switch mechanism must be induced at wavelengths above 650 nm.[70,71] The low energy of the excitation wavelengths at which these photoinduced mechanisms must take place poses a fundamental challenge in this field.[26,72] A further challenge is their inherent lipophilicity due to aromatic structures, which limits their solubility in water.[73]

2.4. Light sources and their characteristics

Generally, photomediated therapies are promising cancer treatment methods, which use non-ionizing light to activate the drug. As already mentioned, a significant challenge in photomediated therapies is the limited light penetration through tissue when treating deep-seated tumors. The applied wavelength must exceed 650 nm, since biomolecules like hemoglobin and lipids but also water which is present in the tissue absorb rays of lower wavelengths (compare with Fig. 3) and lead to scattering.[53–55] Scattering dominates in most soft tissues and leads to diffusion of light, reducing penetration depth and making it difficult to maintain precise control over energy delivery. The scattering mean free path, typically on the order of 100 to 1000 microns, defines the scale at which light retains its directionality. Beyond this depth, wavefronts become distorted, and light effectively transitions from ballistic (direct) to diffuse transport. Absorption, while often less dominant than scattering, further limits the usable light dose in deep regions.[74] These propagation challenges are central to the design of effective phototherapies. Strategies such as using longer wavelengths (*e.g.*, near-infrared) or modifying tissue optical properties are often employed to enhance light penetration.[75] An understanding of wave propagation dynamics is therefore essential for optimizing light-based therapeutic efficacy and ensuring selective tissue interaction. There are various light sources which can be applied, among them Lasers and LEDs.[76] Both come with their respective benefits and limitations. Lasers are a coherent light source which offer high power and monochromatic light. They can be used for precise targeting of the desired tissue since they can be coupled with optical fibers. They are therefore also suitable for interstitial applications. LEDs are a non-coherent light source. They are more affordable but provide a broader illumination field. The targeting is therefore less precise; however, they are suitable for larger and better accessible tumors. A drawback of LEDs is their lower power and lower electrical-to optical conversion efficiency, leading to uncontrolled heating up of the tissue. The choice of light source depends on various factors, including the treatment site, cost and power requirements.[76–78]

2.5. Quantification methods in phototherapy research

The quantification of phototherapeutic success addresses the response of a cell culture or animal model to the applied therapy after irradiation and in the dark for control.[79]

Cell testing is performed to quantify the efficacy of phototherapeutics. Cell tests can be performed in traditional 2D cultures or in spheroid models. These 3D cell culture systems mimic the microenvironment of tumors more effectively than the 2D cultures. A crucial metric for phototherapy research thereby is the phototoxic index (PI). The PI describes the ratio of light to dark toxicity of the phototherapeutic, measured with assays that rely on the metabolic activity of the cells before and after treatment (viability assays). The PI is defined as the ratio of the concentration of phototherapeutic required to reduce the viability to 50% in the dark *versus* after irradiation.[48,79–88]

$$\mathrm{PI} = \frac{\mathrm{IC}_{50}^{\mathrm{dark}}}{\mathrm{IC}_{50}^{\mathrm{light}}}$$

A higher PI indicates greater efficacy.

Chorioallantoic membrane (CAM) is a thin, vascularized membrane, found in avian embryos, commonly fertilized chicken eggs. It serves as a respiratory organ and supports the exchange of gasses and nutrients. It is extensively used in cancer research, due to its possibility to grow tumors on the membrane, by applying cells on its surface.[89,90] The cancer cells will further stimulate angiogenesis, leading to vascularized

tumors. Phototherapeutics can then be injected into the blood vessels and accumulate in the tumor. There are many benefits of using CAM. First and foremost, CAM experiments are a simple, rapid and cost-effective alternative to common *in vivo* experiments, but still allow researchers to study processes like tumor growth, angiogenesis and drug delivery, which is not possible in cell culture testing.[91] Furthermore, the thin nature of CAM allows for easy real-time monitoring, due to its transparency.[92] CAM models are also valuable to investigate the combined effects of PDT and PTT. Studies have demonstrated a synergistic effect on vascular damage when using both therapies together, providing insights into potential clinical applications.[93]

In vivo models are essential in phototherapy research for evaluating the efficacy and safety of treatments before clinical trials. Common animal models in cancer research include mice, rats and zebrafish.[92,94–97] For phototherapy, tumor-bearing mice are often employed due their well-established role in experimental settings.[97,98] Their widespread use offers the advantage that many well-established experimental tools and resources are being commercially available. The treatment efficacy is assessed through tumor growth inhibition which is correlated to the volume of the tumor, survival rate and histological analysis.[99,100] Safety assessments usually include monitoring the body weight, behavior and examination of the major organs to detect potential toxicity.[101]

There are many different mouse models used in cancer research, which provide crucial insights into cancer development, progression and treatment efficacy. Selecting the right model is essential, as different models provide unique perspectives and data depending on the research focus. The mouse models can be categorized into two main groups, immunocompetent mice and immunodeficient mice.

Immunocompetent mice have a fully functional immune system and therefore possess a normal and complete immune response.[102] They can mount an immune reaction against tumors and transplanted tissue. Immunocompetent mice are therefore used when studying the interaction between tumors and the immune system, making them ideal for research in cancer immunotherapies and therapies that rely on the immune system interactions. This is the case for combination therapies of phototherapies with immune-modulating agents.[103] The disadvantage of immunocompetent mice models is that only syngenetic tumors can be used but no human cancer cell lines or patient derived xenografts.

Immunodeficient mice on the other hand have an impaired or absent immune system. This prevents them from mounting a typical immune response. They are often used to grow human tumors because of their lack of immune response that prevents the rejection of foreign tissue. Common immunodeficient mouse strains include nude mice (absence of T-cells) and SCID (severe combined immunodeficient) mice (absence of B- and T-cells). These models are valuable for studying human cancer cells *in vivo* and testing therapies directly on human tissue without the interference from the mouse's immune system.[92,104] Immunodeficient mice can be categorized into two mouse models: Xenograft models and humanized mouse models. Xenograft models are widely used due to their simplicity and rapid tumor growth. They are ideal for studying the efficacy of combination therapies such as phototherapy and chemotherapy or phototherapy and targeted therapies. By using patient-derived xenografts, meaning the implantation of cancer from a human patient, the patient's response to a treatment can be predicted.[103] Humanized mouse models are immunodeficient mice engrafted with human immune cells. This allows for studying the interactions between human tumors and the human immune system. These models are highly beneficial for immunotherapy research.[102,105]

Imaging modalities play a vital role in monitoring the progression and efficacy of phototherapies. They provide real-time and simultaneously non-invasive insights.[106] Fluorescence imaging utilizes the emission to visualize and quantify photosensitizer distributions and accumulations in tissue.[107] Photoacoustic imaging offers high-resolution deep tissue imaging. It provides detailed information on the vascularization and oxygenation status of tumors, which is important for evaluating the phototherapy efficacy.[108] Thermal imaging measures temperature changes induced by PTT. It is used to control the temperature to help prevent tissue from overheating.[109,110]

3. Multimodal approach

3.1. The principle of a multimodal approach

A multimodal approach describes the combination of more than one type of cancer treatment. Studies have shown that not only severe problems of common cancer therapies like hypoxia or insufficient targeting could be tackled this way, but that a multimodal approach could lead to a synergistic effect.[37,111–114] Photoinduced therapies are often a component of multimodal approaches due to their unique advantages, like their low invasiveness and their selective activation with an unproblematic activation-source - light.[18,59] There are many treatment combinations, most of them in the form of conjugates or single compounds which are able to undergo multiple processes at once.[48,67,115,116] Additionally there are metal complexes used for chemotherapy, which carry a photosensitizer as ligand.[117] Photoinduced therapy forms can either be combined with each other, when for example a photosensitizer produces heat and ROS simultaneously, or they can be combined with conventional treatment forms like immunotherapy, chemotherapy *etc.*[118–124]

3.2. Strategies to combine treatment modalities

Different methodologies are used in combining therapies, the ones which are most often used when combined with phototherapeutics, are discussed in this subchapter.

Conjugation involves the chemical linkage of different therapeutic agents to create a single multifunctional molecule. This approach allows for simultaneous delivery of multiple therapeutic agents, a targeting and a therapeutic agent or of a therapeutic and an imaging agent. Photosensitizers are often conjugated with chemotherapeutics to enhance treatment efficacy, targeting ligands such as inhibitors or antibodies or other therapeutic agents which ensure the precise delivery to the tumor cells. Thereby toxicity is reduced, and the therapeutic outcome enhanced.[125–127]

Conjugation can either be fixed or cleavable. Cleavable conjugation involves linking therapeutic agents with bonds that can be cleaved under specific conditions such as enzymes or light irradiation. This strategy allows for controlled release of therapeutic agents at the site of interest. Enzyme-cleavable conjugates utilize bonds that can be cleaved by enzymes only expressed or overexpressed in the tumor microenvironment. These conjugates usually contain peptide linkers.[128,129] Light-cleavable conjugates follow the principle of photocages where both molecules, the cage and the carry-on are therapeutics. This allows for spatial and temporal control over drug release.[130,131] This method is particularly advantageous with phototherapeutics, where the light used for activation simultaneously triggers the phototherapeutic effect.

Aggregation refers to the process where the therapeutic agent aggregates by itself or, in the case of coaggregation, with other therapeutic agents. Aggregates have properties different from their dissolved counterparts. Conventional fluorescent molecules usually undergo aggregation caused quenching (ACQ) when they form aggregates.[48,132] However, organic molecules can be modified to exhibit enhanced emission in their aggregated state. This concept is called aggregation induced emission (AIE).[133] For PTT both phenomena can be beneficial. ACQ enhances the relaxation over non-radiative processes, leading to a greater heat generation.[134] AIE on the other hand opens the possibility for the phototherapeutic to combine therapy with bioimaging.[135]

Even though PTT can occur without aggregation, it often plays a significant role in the photoinduced charge transfer (PCT), which further plays a crucial role in PTT. PCT mechanisms are used to improve the photothermal conversion efficiency of agents, making PTT more effective.[136,137] Aggregates often combine PDT and PTT since the photothermal properties are only achieved when the photosensitizer aggregates. This leads to synergistic effects, since the photosensitizer typically still keeps its ability to generate ROS.[48,135] Aggregation can take place in a controlled or a random manner. When molecules aggregate in a controlled manner, they either form J-aggregates or H-aggregates. J-aggregates form when molecules align in a head-to-tail fashion, resulting in a red-shifted absorption spectrum and enhanced photostability.[139,140] In the context of phototherapeutics, J-aggregates are preferred since their absorption is shifted to wavelengths which more likely penetrate the skin.[141,142] However, their reduced HOMO–LUMO bandgap results in a lower heat generation during relaxation. H-aggregates form when molecules align face-to-face. This leads to a larger HOMO–LUMO bandgap. The bigger bandgap further induces a blue-shift in absorption and a higher heat-generation upon light absorption and following relaxation.[140]

Encapsulation in nanocarrier systems is a method, where multiple therapeutic agents are encapsulated in carriers such as liposomes, micelles and dendrimers. Thereby the therapeutic agents are protected from degradation and the delivery to the tumor site can be enhanced. Further advantages are the possibility to deliver very hydrophilic and hydrophobic drugs, which would otherwise not be possible.[143,144] These carriers can be designed with an attached targeting unit or to respond to specific stimuli in the tumor microenvironment, such as pH, temperature, or redox gradients to release their payloads in a controlled manner.[145] This strategy is particularly beneficial for metal complexes, which often suffer from poor solubility, limited selectivity, or premature deactivation in biological environments. Encapsulation not only stabilizes these photoactive or chemotherapeutic complexes but also enables their integration into multimodal treatment platforms, combining, for instance, photodynamic, photothermal, and chemotherapeutic effects.[117,146]

Polymer–drug conjugates form macromolecular prodrugs which can improve the pharmacokinetic properties of the carrier-drugs by increasing their circulation time. Additionally, the conjugates larger molecular size enhances accumulation in the tumor through enhanced permeability and retention (EPR) effect.[147,148] The EPR-effect is a phenomenon observed in solid tumors. The enhanced permeability originates from irregular, disorganized blood vessels, which show larger gaps between endothelial cells compared to blood vessels in healthy tissue. This allows nanoparticles and larger molecules to pass. The increased retention comes from the impaired lymphatic drainage which prevents the efficient removal of larger particles. As a result, nanoparticles or macromolecular drugs such as polymer–drug conjugates accumulate within the tumor tissue.[149,150] Using these principles and methodologies, enhanced therapeutic platforms can be developed, which combine the strengths of different treatment modalities. The synergy achieved with these combinations has the potential to improve patient outcomes and advance the field of phototherapy in oncology.

4. Combinational strategies and their synergistic effects

4.1. Combining photodynamic and photothermal therapy

4.1.1. Opportunities. PDT and PTT are combined, when photosensitizers aggregate and thereby form heat while not losing their capabilities to form ROS,[48] or when photosensitizers and photothermal agents are co-administered.[138,146,151] Some NIR light-responsive metal complexes, have shown to effectively support the synergistic action of ROS and heat in the absence of classical nanocarrier systems, showing an example for a single-agent dual-functionality.[152,153] While the efficacy of PDT suffers from the hypoxic microenvironment of solid tumors,[154] the combination with PTT can be an innovative solution for this obstacle.[117,146,155] The rise in temperature during moderate hyperthermia in PTT leads to denaturation of DNA and subsequent apoptosis.[25,156] Additionally, already moderate hyperthermia improves blood circulation to the tumor site, which delivers higher oxygen levels and drug-concentrations, thereby increasing the efficacy of PDT.[138,157] On the other hand, PTT suffers from upregulation of certain heat-shock proteins, that may prevent DNA-denaturation. ROS have shown to disrupt these heat-shock proteins, which elevates the efficacy of PTT.[158] The synergistic effect that is shown in the combination of PDT and PTT therefore results from the interplay of ROS and heat generation.[146,151,156]

Example: Nanoplatforms that combine PDT and PTT.

Several studies have focused on combining different phototherapeutics to achieve this synergistic effect. A noteworthy example comes from a recent study by Lim and colleagues, who introduced an innovative all-organic nanoplatform (Combi NP). By combining phthalocyanines for PTT with protoporphyrin IX (PPIX), the compounds showed enhanced cytotoxicity and the ability to induce apoptosis in hypoxic conditions. Phthalocyanines are known for their excellent photostability and near-infrared (NIR) absorption, allowing irradiation and excitation of the photosensitizer through tissue. The study emphasizes the importance of biocompatibility which is better in all-organic nanoplatforms rather than with integrated inorganic compounds. It therefore provides a safer and more effective alternative for clinical applications.[138] The mode of action of these nanoplatforms is depicted in Fig. 4.

Example: Dual modal photodynamic and photothermal agent.

BODIPY based photosensitizers can aggregate in cells, forming nanoparticles which simultaneously produce heat and ROS upon irradiation, as illustrated in Fig. 5. The study of Spingler and co-workers report about systems for which this effect leads to very high phototoxic indices in 2D as well as in 3D cell cultures, using an excitation wavelength of 630 nm. The reported BODIPY derivatives address the limitation of solid tumors, the hypoxic environment, by posing an oxygen-independent alternative mechanism of action.[48] BODIPYs are commonly employed compounds in combination therapy of PDT and PTT since they can be easily modified according to the desired properties. Additionally, they provide the possibility to act as photocages which opens the possibility to conjugate them with a targeting unit.[159,160]

4.1.2. Challenges. When combining a photosensitizer and a photothermal agent, their absorption wavelengths must overlap.[138] Is this not the case, treatment must be performed with two different wavelengths, which complicates the therapeutic process and poses more regulatory hurdles for clinical translation since both sources must be approved.[162] This is not the case for dual-modal photodynamic and photothermal agents which simultaneously generate heat and ROS.[48]

Nanoplatforms often pose a risk of potential systemic and organ-specific toxicity, especially when containing inorganic nanomaterials such as gold, iron, copper and tungsten.[163,164] Studies therefore should always consider toxicity and excretion studies *in vivo* while evaluating their anti-cancer ability.[158,161]

4.2. Combining phototherapy and chemotherapy

4.2.1. Opportunities. Combining phototherapeutics and chemotherapeutics can significantly improve the therapeutic

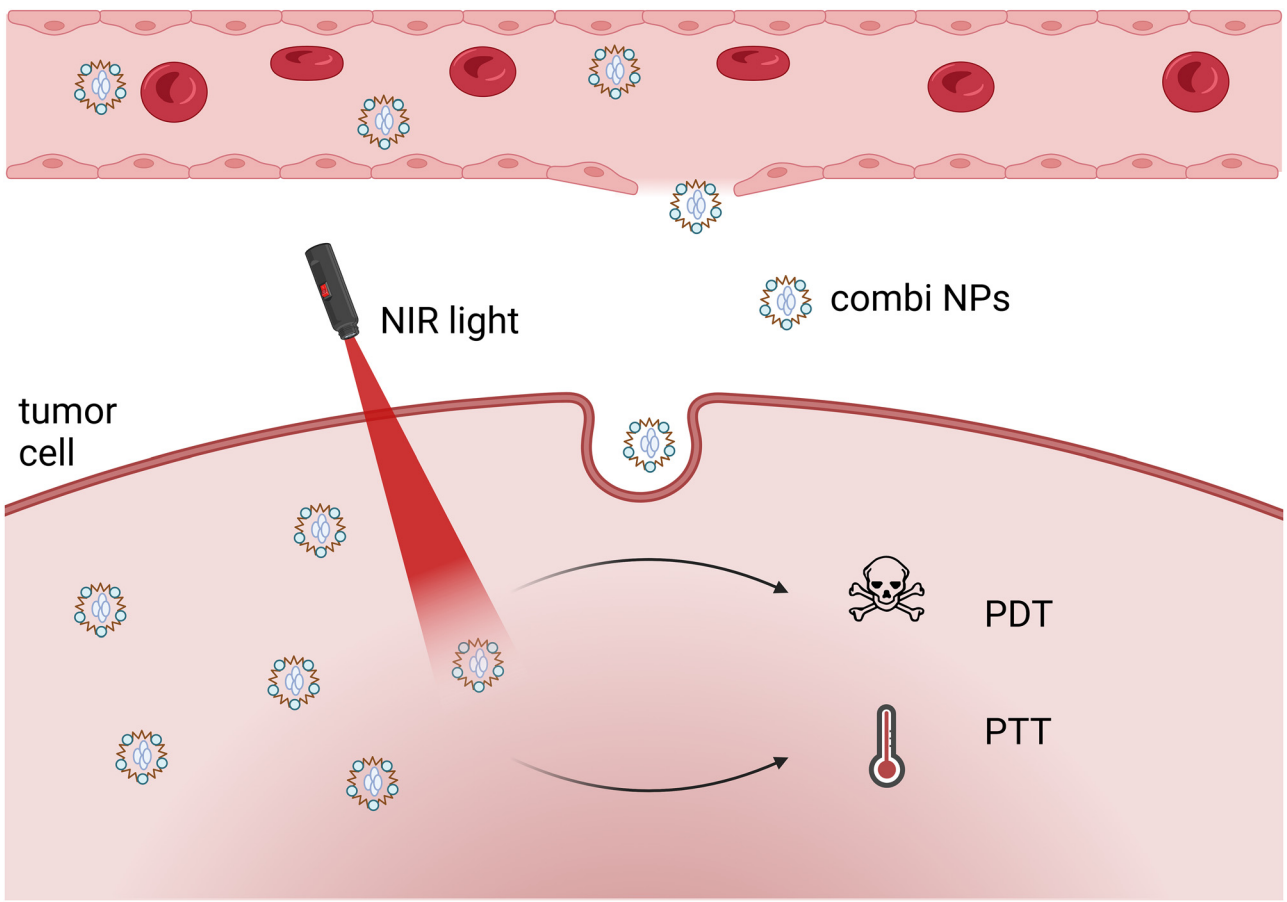

Fig. 4 Schematic representation, illustrating the operational mechanism in synergistic tumor therapy. Figure adapted from ref. 138. Fig. 4 was created using https://BioRender.com.

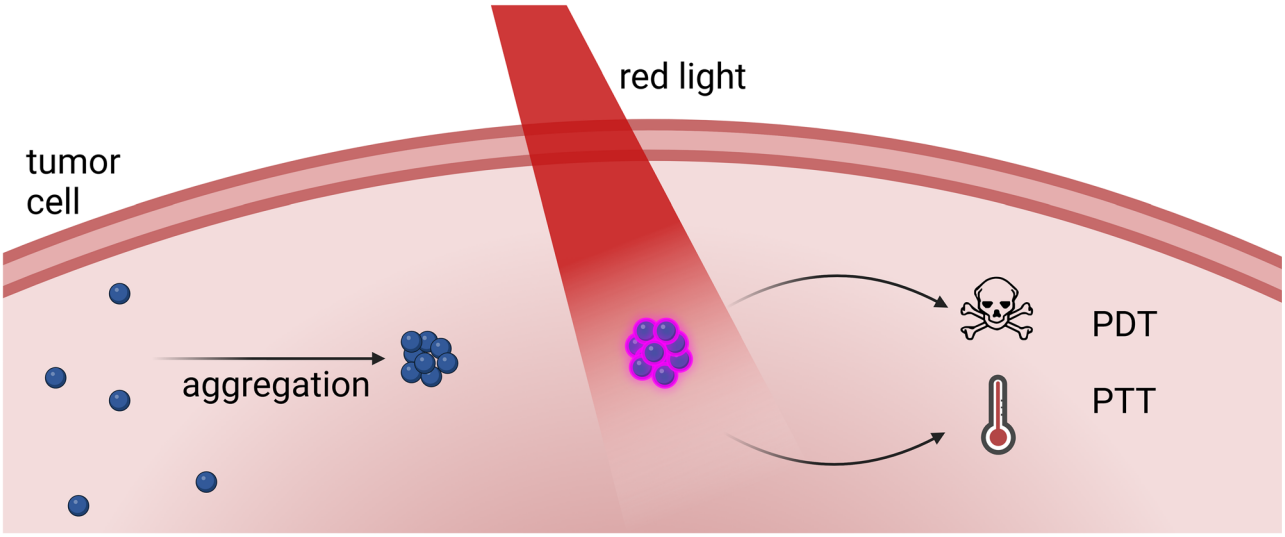

Fig. 5 Illustration of the aggregation and excitation of BODIPY photosensitizers for simultaneous PDT and PTT.[48] Fig. 5 was created using https://BioRender.com.

outcome of cancer treatments by leveraging the synergistic effects of both modalities. The combination enhances the therapeutic efficacy by helping to overcome drug resistance through oxidative stress in the cells generated by ROS or hyperthemic weakening of the tumor's defenses.[161,165] Further, the combination can be used for targeted treatment by enabling light- or singlet oxygen-controlled release of caged chemotherapeutics.[130,166] It also has the capability to induce immunogenic cell death.[167–169]

Example: Hypoxia-activated chemotherapy against tumor drug resistance enhanced with heat.

Tumor drug resistance poses a significant challenge in cancer therapy. Chen, Wang and co-workers discovered the novel nanoplatform AMPG to overcome tumor drug resistance. The platform combines PTT, chemodynamic therapy (CDT) and hypoxia-activated chemotherapy for enhanced treatment efficacy of the hypoxic environment within tumors. CDT uses the tumor's microenvironment, such as high H_2O_2 levels and acidity, to trigger chemical reactions that produce ROS. The proposed mechanism of action consists of laser irradiation which induces the generation of heat (42.8 °C) by the AMPG nanoplatform. Simultaneously, the conversion of the hypoxia-activated part of the nanoplatform, AQ4N to its chemotherapeutic form, AQ4, is enhanced. The elevated temperature furthermore enhances the efficiency of CDT through accelerated release of Mn^{2+} and improved efficiency of hydroxyl radical formation. The mode of action is illustrated in Fig. 6. The nanoplatform additionally offers real-time monitoring of the blood oxygen saturation, using photoacoustic imaging.[161] This reflects the hypoxic status of the tumor during treatment. The study demonstrated on mouse models, that the synergistic treatment induced apoptosis in otherwise drug-resistant tumors, which shows the potential of AMPG nanoplatforms.

4.2.2. Challenges. The combination of phototherapeutics and chemotherapeutics requires careful coordination of treatment protocols. This complexity can complicate treatment planning, potentially limiting clinical application. When one of the therapeutics is already approved for clinical use, the combination of both therapeutics is facilitated for further approvement.[27] Further, the effects of both therapies can lead to increased toxicity through heightened oxidative stress and inflammation.

4.3. Combining phototherapy with immunotherapy or targeting antibodies

4.3.1. Opportunities. The combination of phototherapeutics with immunotherapy offers great potential for enhancing cancer treatment efficacy. There are several opportunities how this combination can lead to synergistic effects. Antibody–drug conjugates (ADC) can enhance tumor targeting of phototherapeutics by the targeting unit, the antibody. This minimizes off-target effects and enhances delivery of the phototherapeutic to the tumor site.[119,170] Further, phototherapeutics can induce immunogenic cell death, leading to the release of damage-associated molecular patterns (DAMPs), which subsequently activate the immune system through initiation of inflammation, recruitment of immune cells and stimulation of the adaptive immune response. This cascade changes the tumor from immunosuppressive to immunostimulatory.[168,171–173] A different approach is the combined administration of a phototherapeutic with pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) to promote the immune response.[174] The combined approach has shown promising results in preclinical models, leading to enhanced tumor regression, reduced metastasis and improved survival rates.[174,175] By tailoring the combination of phototherapeutics with immunotherapy or antibodies to individual patients, treatments can be personalized.[172,176]

Example: Immune activation for enhanced photodynamic immunotherapy.

Limitations of traditional methods for tumor immunotherapy include low immunogenicity of the tumor environment. Wang, Di and co-workers designed the novel photodynamic

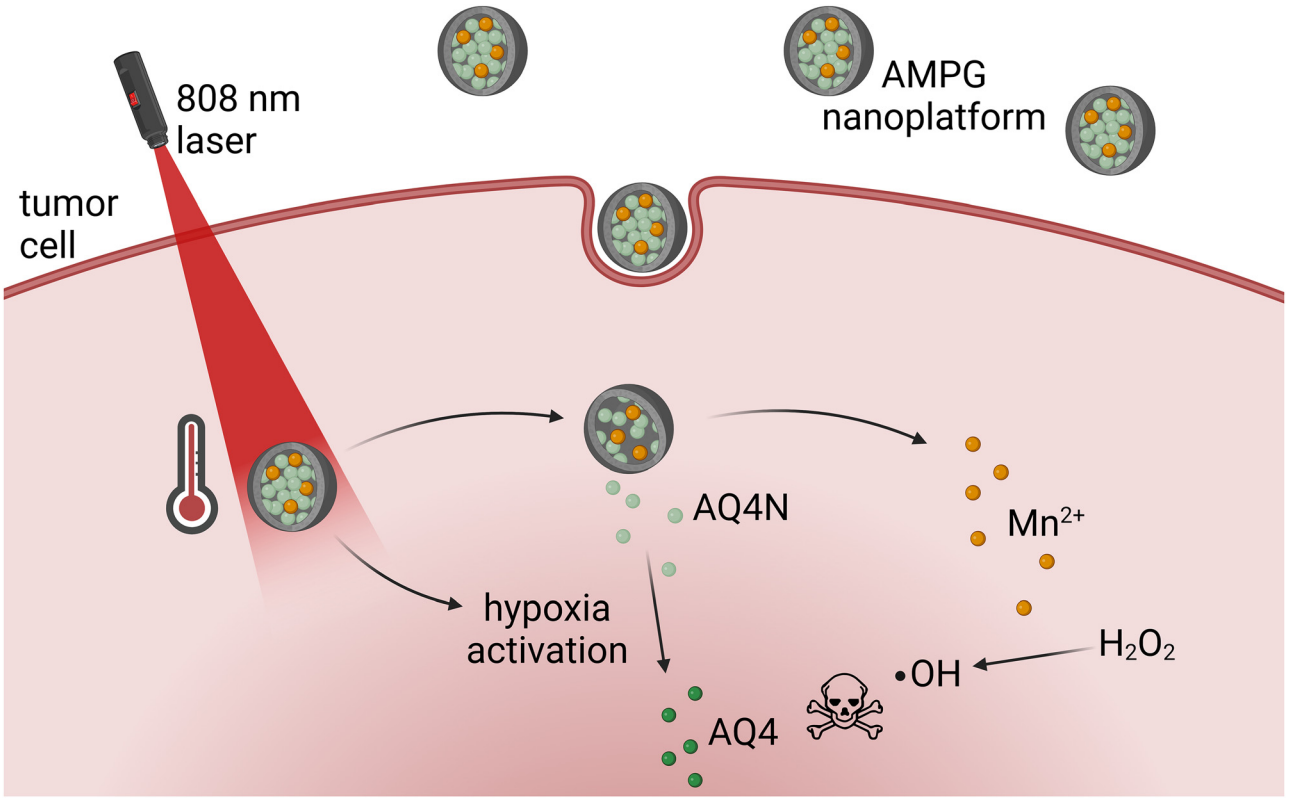

Fig. 6 Schematic illustration of AMPG nanoplatforms and high -temperature PTT dual-enhanced hypoxia-activated chemotherapy and CDT. Figure adapted from ref. 161. Fig. 6 was created using https://BioRender.com.

immunotherapy nanovaccine Dex-HDL/ALA-Fe_3O_4, which shows significant tumor site accumulation and lymph node homing. Upon laser irradiation, ROS are generated at the tumor site, leading to the release of tumor antigens and immunogenic cell death. At the same time, hydrogen peroxide is converted to oxygen by the Fe_3O_4 nanoenzyme part of the vaccine, which supports a stronger immune response in the tumor microenvironment. The nanovaccine showed tumor regression and inhibition of metastasis and tumor recurrence in preclinical cancer models. The study shows the potential of photodynamic therapy for effective immune activation to overcome the limitations of current cancer vaccines.[172]

4.3.2. Challenges. Developing ADC that effectively incorporate phototherapeutics require challenging design and formulation strategies.[119] The combination of different treatment modalities requires studying the pharmacokinetics and pharmacodynamics of each compound separately as well as the combined therapeutic, which complicates the ADC's translation into clinics.[177] Furthermore, the synergistic effect is suppressed if the tumor microenvironment hinders immune cell activity.[167,168,178]

4.4. Combining phototherapy with radiation therapy

4.4.1. Opportunities. Phototherapeutic approaches and radiation therapy (RT) are combined in different manners. While the introduction of phototherapeutic methods to RT can be conducted as a salvage treatment (after RT) or as a neoadjuvant treatment (before RT), they can also be combined concomitantly.[179] One of the primary advantages of combining phototherapy with RT is the synergistic effect that is achieved by addressing the tumor over two different destruction pathways. This dual assault showed great potential in several studies.[180–182] The synergy often allows for the use of lower doses of both therapies, which can significantly reduce side effects that are typically associated with high-dose radiation therapy.[180,181] The synergistic effect of PDT and RT is the overcoming of the wavelength limitation in PDT (refer to example below). In combination with a targeting unit, the effect of RT is more precisely limited to the tumor tissue which reduces off-target effects and therefore the overall toxicity of the treatment. When combining PTT and RT the synergistic effect is achieved by thermal radiosensitization of the cancer cells, which enhances the therapeutic efficacy.[183]

Example: RT-induced PDT with scintillating nanoparticles.

PDT suffers from limitations like the low penetration depth of light. To overcome this limitation scintillating nanoparticles (NPs) that convert ionizing radiation, like X-rays, into UV, visible, or infrared light to activate photosensitizers are developed. This approach, known as RT-induced PDT leverages NP constructs optimized for efficient energy transfer. Scintillating NPs absorb X-ray photons through mechanisms like the photoelectric effect and Compton scattering, producing light that can activate nearby photosensitizers. By maintaining a nanoscale separation (<10 nm) between the scintillator and the

photosensitizer, energy transfer *via* Förster resonance energy transfer (FRET) takes place.[179] In a recent study, Chen and co-workers demonstrated copper-iodine clusters in bovine serum albumin (Cu–I@BSA), which show strong radioluminescence. These NPs can be conjugated with a targeting unit (GA) and a photosensitizer (EB) to form a cluster (Cu–I@BSA-EBGA) for RT-induced PDT. *In vivo* studies show successful accumulation of the clusters in tumors. Through low-dose X-ray irradiation, ROS are generated, and effective tumor inhibition is achieved. The degradation of the cluster further leads to free copper and iodide ions which when reacted with H_2O_2 lead to cell death by damaging DNA, decreasing ATP generation, modulating mitochondrial functions and increasing oxidative stress in the cell.[185]

4.4.2. Challenges. The main drawback in combining PTT and PDT with RT is the management of thermal and oxidative stress. While the generation of ROS and heat respectively are the central mechanisms of PDT and PTT, their combination with RT, which also generates ROS, can exacerbate these effects.[183]

4.5. Combining phototherapy with targeted therapy

4.5.1. Opportunities. Phototherapeutics in combination with inhibitors are often used to enhance targeting or to induce a dual attack to overcome potential resistance mechanisms that develop against single therapies.[186,187] Targeted therapy involves drugs that specifically target cancer cells. It works by interfering with specific molecules involved in cancer growth and survival. Targeted therapy is often used for cancers with specific genetic mutations, such as breast cancer (HER2-positive), lung cancer (EGFR mutations), and chronic myeloid leukemia (BCR-ABL mutation).[186,188] Inhibitors used for targeting are often tyrosine kinase inhibitors (TKI), since they target those critical signaling pathways involved in tumor growth, angiogenesis and metastasis.[187,189–191] Since many of them are FDA approved, they are safe, and easily accessible as targeting units for combined therapy with other treatment methods like PDT and PTT.[187,189] The integration of light-activated drugs with TKIs can improve the efficacy by reducing systemic toxicity and enhancing drug delivery to the tumor site.[184] Also, the combination can be used to monitor the real time inhibition process, making it not only functional for therapy but also in diagnostics.[184] Furthermore, TKI can be photocaged. This combination provides spatiotemporal control over the drug action, allowing precise timing and localization over its release.[184,192,193] This is particularly beneficial in reducing off-target effects and improving patient outcomes.

Example: Photocaged kinase inhibitor for photo-controlled release and monitoring. Grøtli, Andréasson and co-workers recently presented an all-photonic kinase inhibitor, where light is used to control the release of a kinase inhibitor and monitor the inhibition process in real time through fluorescence. This dual functionality allows for precise spatiotemporal control, which offers significant potential for advanced cancer therapies. The discussed kinase inhibitors are inactive until activation by light irradiation. Only then, they bind to its target kinase. The inhibitors are designed with fluorescence caging groups, that quench their fluorescence when still bound to the inhibitor, so to the inactive form of the inhibitor. When the inhibitor is activated, the fluorescence is also restored, and it is possible to track its binding to the target (Fig. 7). While the study focuses on the lymphocyte-specific protein tyrosine kinase which is a key enzyme in T-cell and natural killer cell signaling, the authors suggest, that this all-photonic approach could be extended to other kinases and biorelevant targets, offering a broad application spectrum in theranostics.[184]

4.5.2. Challenges. As for all combinations that include phototherapeutics, one limitation states the light penetration through tissue.[192] When administering inhibitors in combination with phototherapeutics, determining the optimal dosing and timing is challenging due to the higher complexity. A thorough understanding of how the therapeutics interact and influence each other must be gained to maximize synergistic effects while minimizing adverse reactions.[189] Furthermore the combination may lead to unique side effects that are not observed with either therapy alone. To ensure patient safety and treatment efficacy, these side effects must be carefully monitored.[190]

4.6. Phototherapeutics to treat other diseases than cancer

4.6.1. Opportunities. While this review primarily addresses the application of phototherapeutics in cancer therapy, these agents are being explored across a much broader spectrum of medical conditions. Phototherapeutics show great potential in combating infectious diseases.[194] PDT and PTT have been explored for their ability to target and destroy pathogens like multidrug-resistant bacteria. Zhao, Xi, Meng and co-workers developed photosensitizers that effectively target and eradicate biofilms and resistant strains of *Helicobacter pylori*, which are significant contributors to gastric diseases and a major challenge in antibiotic treatments.[195,196] Biswas, Hussain and co-workers reported a dinuclear cobalt(II) complex that exhibits potent antibacterial activity upon red or near-infrared light irradiation. The complex generates reactive oxygen species that effectively disrupt bacterial membranes, showing significant photodynamic killing against both Gram-positive and Gram-negative strains. This light-triggered mechanism offers a promising strategy to combat antibiotic-resistant bacteria with minimal dark toxicity, positioning it as a potential candidate for photodynamic antimicrobial chemotherapy and surface disinfection applications.[152] Studies in the field of Alzheimer's disease research were conducted by Chao, Ran and co-workers, who developed a photolabile curcumin–diazirine analogue which induces changes in the structures and properties of amyloid beta. In combination with LED or molecular light irradiation, the accumulation of amyloid beta could be slowed down. This states a promising alternative to conventional treatments against Alzheimer's disease.[197]

4.6.2. Challenges. Despite these promising opportunities, several challenges remain to be addressed. A primary challenge is the need for targeted delivery systems that can ensure the precise localization of phototherapeutic agents to the diseased tissue.

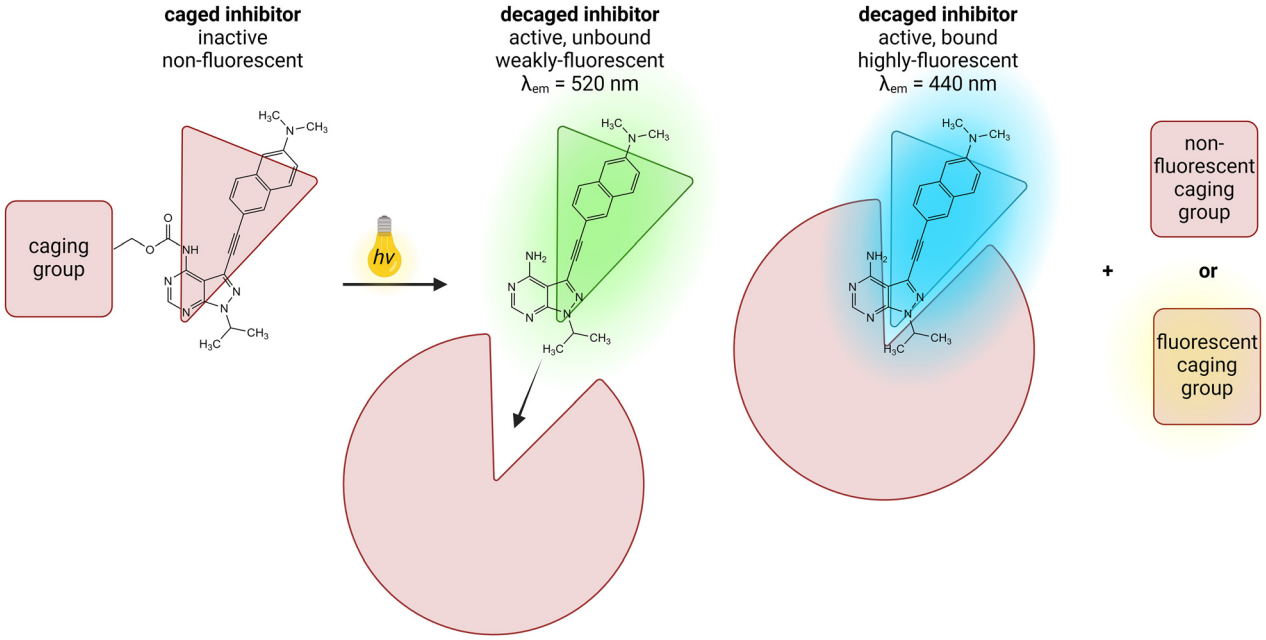

Fig. 7 Working principle of caged inhibitors. The biologically active inhibitor is released by means of light and only shows strong emission upon binding to the enzyme. Different caging groups, fluorescent and non-fluorescent are possible. Figure adapted from ref. 184. Fig. 7 was created using **https://BioRender.com**.

This would minimize off-target effects during and after treatment.[194,195,198] The development of resistance to phototherapeutic agents, although less common then with antibiotics is also a concern that needs to be addressed.[194,196] Various approaches to overcome challenges in this area of research are developed, including the development of multifunctional nanoplatforms that can enhance the targeting and efficacy of phototherapeutic agents, as well as the integration of phototherapy with other treatment modalities like common antibiotics to achieve synergistic effects.[196,199]

5. Clinical translation and regulations

Almost 30 years have passed since the first phototherapeutic drug, Photofrin was approved by the FDA.[40,41] As the field of phototherapeutics expands rapidly, it is surprising that as of now only a handful of phototherapeutic drugs are approved for clinical application and that photothermal therapy has not yet found its way into clinics. Even though, heat as a treatment modality in the form of laser ablation devices and hypothermia devices are already used.[200,201] The clinical translation of phototherapeutics faces numerous challenges, some of which are listed herein:

1. Immune clearance and *in vivo* stability: the rapid clearance of nanomaterials by the mononuclear phagocyte system (MPS) leads to reduced accumulation in tumors. Emerging strategies like cell membrane biomimetic coatings or stealth polymers help camouflage particles from immune surveillance and extend their half-life.[202]

2. Biocompatibility and safety concerns: many inorganic nanocarriers, though efficient in light absorption, may accumulate in organs or cause toxicity. Innovations like carrier-free nanomedicines and biodegradable platforms are being developed to address this, offering high drug-loading efficiency without unnecessary excipients.[203]

3. Complexity in light delivery and tissue penetration: PTT and PDT rely on precise light exposure, which is challenging for deep-seated tumors or large tissue volumes. While NIR light offers deeper penetration, factors like tissue scattering, absorption and heat diffusion remain limitations. Emerging technologies such as NIR II excitation and implantable light-delivery devices aim to overcome these depth and targeting issues.[204]

4. Tumor heterogenity and microenvironment: the variability in tumor microenvironments like hypoxia, pH and redox gradients, complicates therapeutic predictability. To address this, multifunctional platforms are being engineered to generate oxygen *in situ*, thereby restoring efficacy even in low-oxygen settings.[205]

5. Regulatory barriers: while common treatment modalities usually solely involve a drug, phototherapeutics work in combination with a light source. The therapy method therefore not only requires precise control over one component, but a minimum of two. If combinational methods are used, the number of components increases even further, which complicates the clinical translation. The European parliament of the council on advanced therapy regulates these combinations in two different categories. Products that include one active ingredient together with a medical device (like light) are regulated as combined medical products. Combinations which however use more than one active ingredient, are regulated as fixed

combinations medical products.[206] In the United States, the regulation of combination products falls under the jurisdiction of the FDA. The FDA has established a framework for regulating combination products, which can include combinations of drugs, biologics, and medical devices. The classification differs between five combinations, which are: 1. The combination of products that include two or more regulated components, such as a drug and a device, 2. The Single-Entity Combination Products, which are products that contain two or more active ingredients in a single dosage, 3. The Co-Packaged and Cross-Labeled Products, that include two or more separate products, packaged together, 4. Advanced therapies and combination products, these products include advanced therapies, such as gene therapy, cell therapy *etc.* and 5. Fixed-Dose Combination Products, which include multiple drugs that are combined in a single dosage form, such as a pill or and injection.[207] The regulation of these products focuses on ensuring that the combination of active ingredients is safe, effective, and provides a clear therapeutic advantage over the individual components used separately.

In clinical studies, consistent light dosimetry and controlled drug distribution is crucial.[114] Effective delivery of photother-apeutic agents to the tumor is also crucial. As discussed in previous chapters, nanocarriers and targeted delivery systems are being explored extensively to enhance the selective accumulation of the therapeutic agents in tumors. By improving selectivity, off-target effects and thereby reduced toxicity can be achieved.

The regulatory approval process for phototherapeutics is complex. However, the incorporation of real-time imaging and diagnostic technologies into treatment protocols may help to meet these regulatory requirements.[208] Despite these challenges, the future of phototherapeutics looks promising. Recent advancements like the integration of phototherapeutics with other treatment modalities are showing great potential in enhancing treatment efficacy and expanding the range of treatable conditions. Ongoing clinical trials continue to refine phototherapy and thereby bringing them closer to a broader clinical adoption, that would offer patients more effective and less invasive treatment options.[208]

6. Conclusion

The synergistic effect achieved by combining PDT, PTT and photocages with traditional treatment modalities represents a significant advancement in cancer treatment. By leveraging the strengths of those modalities, combinations not only enhance therapeutic efficacy but also address some of the limitations associated with each therapy when used independently. The ability to integrate these therapies with conventional treatment methods, such as chemotherapy, immunotherapy, radiotherapy and targeted therapy further amplifies their potential, offering an improved approach for cancer treatment. Since the clinical translation of these multimodal therapies requires overcoming significant regulatory and technical challenges, continued research and innovation in this field is essential to realize the full potential of these combined therapies. The integration of these treatment modalities into clinical application ultimately improves patient outcomes and expands the range of treatable conditions.

Author contributions

Flavia Kradolfer wrote the original draft. Caroline Maake and Bernhard Spingler revised the manuscript. All authors contributed to the final version of the manuscript. For this manuscript AI-based tools were used for literature research assistance and language style refinement.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

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

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