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Light-based technologies in immunotherapy: advances, mechanisms and applications

Davide Frumento [a] and Ştefan Ţălu [b]

[a]Department of Pharmacy, University of Genoa, Genoa, Italy; [b]The Directorate of Research, Development and Innovation Management (DMCDI), The Technical University of Cluj-Napoca, Cluj-Napoca, Romania

ABSTRACT

Light-based immunotherapy uses specific wavelengths of light to activate or modulate immune responses. It primarily employs two mechanisms: direct activation of immune cells and indirect modulation of the tumor microenvironment (TME). Several light-based technologies are under investigation or clinical use in immunotherapy, including photodynamic immunotherapy (PDIT) and photothermal therapy (PTT). Optogenetic tools have the potential to precisely control T-cell receptor activation, cytokine release, or the activity of other immune effector cells. Light-based technologies present innovative opportunities within the realm of immunotherapy. The ability to precisely regulate immune cell activation via optogenetics, alongside the improved targeting of cancer cells through photoimmunotherapy, signifies a transformative shift in our strategies for immune modulation. Although many of these technologies remain in the experimental stage for various applications, initial findings are encouraging, especially concerning cancer treatment and immune modulation. Continued research and clinical trials are essential to fully harness the capabilities of light technology in the context of immune cell therapy.

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1. Introduction

Immunotherapy has emerged as a groundbreaking therapeutic approach that leverages the body's own immune system to fight diseases, particularly cancer, autoimmunity, and infectious diseases [1]. Unlike traditional therapies that directly target the disease-causing agents, immunotherapy modulates the immune system to enhance its ability to recognize and eliminate abnormal or foreign cells. In recent years, the integration of light-based technologies with immunotherapy has significantly enhanced the precision and efficacy of these treatments. This novel approach, often referred to as light-based immunotherapy or photomedicine, utilizes specific wavelengths of light to activate or modulate immune responses, offering a promising frontier in personalized medicine [2].

The application of light for therapeutic reasons, referred to as phototherapy (PT), has a long history, with documentation indicating its use in the treatment of skin conditions like psoriasis and vitiligo for many centuries [3]. The progress in our comprehension of photobiology, coupled with the emergence of advanced light sources such as lasers and light-emitting diodes (LEDs), has significantly broadened the application of light in the medical field, extending its influence from dermatology to encompass disciplines such as oncology and immunology [4]. The advancement of photodynamic therapy (PDT) in the 1970s represents a particularly important milestone in medical treatment. This innovative approach employs photosensitizing agents that, when exposed to light, generate reactive oxygen species (ROS). The resultant ROS are instrumental in inducing cell death in both cancerous cells and infected tissues [5].

Light-based immunotherapies utilize two main mechanisms: the direct activation of immune cells and the indirect alteration of the tumor microenvironment (TME). Direct activation entails the application of light-sensitive agents or compounds that, upon exposure to particular wavelengths, can either eliminate target cells or activate immune cells, including dendritic cells, macrophages, and T-cells. This focused immune response reduces harm to adjacent healthy tissues, presenting a notable benefit compared to traditional therapeutic approaches [6].

Indirect modulation refers to the modification of the tumor microenvironment (TME), which frequently exhibits immunosuppressive characteristics that enable tumors to escape immune surveillance. The application of light-based technologies can facilitate the reprogramming of this immunosuppressive milieu, thereby promoting the infiltration of immune cells that can target and eliminate malignant tissues [7]. Numerous light-based technologies are currently being explored or utilized in the realm of immunotherapy. Photodynamic Immunotherapy (PDIT) represents an advancement of traditional photodynamic therapy, as it incorporates immune modulation alongside the tumor-eradicating properties of PDT.

CONTACT Davide Frumento davide.frumento@edu.unige.it Department of Pharmacy, University of Genoa, Viale Benedetto XV 7, Genoa 16132, Italy; Ştefan Ţălu stefan_ta@yahoo.com; stefan.talu@auto.utcluj.ro The Directorate of Research, Development and Innovation Management (DMCDI), The Technical University of Cluj-Napoca, Constantin Daicoviciu Street., No. 15, Cluj County, Cluj-Napoca 400020, Romania

Article highlights

- Light-based immunotherapy utilizes specific wavelengths to activate or modulate immune responses.
- Photodynamic immunotherapy (PDIT) and photothermal therapy (PTT) are key light-based technologies used in immunotherapy.
- Optogenetics offers precise control over immune processes.
- Current light-based therapies are mostly experimental, but early results are promising, especially for cancer treatment.
- Ongoing research and clinical trials are crucial to unlocking the full potential of light-based immunotherapies.

This combined approach not only effectively eliminates cancer cells but also stimulates dendritic cells, thereby triggering a vigorous anti-tumor immune response. Recent research has highlighted PDIT's capacity to induce immunogenic cell death (ICD), which significantly improves the effectiveness of checkpoint inhibitors frequently employed in cancer immunotherapy [8]. For the sake of clarity, Figure 1 depicts PDIT and PDT mechanisms. Photothermal Therapy (PTT) involves the use of nanoparticles that absorb near-infrared (NIR) light and convert it into heat, leading to localized hyperthermia that kills tumor cells. The subsequent release of tumor antigens can stimulate an immune response. PTT is often used in combination with immune checkpoint blockade to enhance the immune system's ability to target residual cancer cells [9]. Optogenetics, a field that originated in neuroscience, involves the genetic modification of cells to express light-sensitive ion channels. These channels can be activated by specific wavelengths of light, allowing precise control over immune cell activation. In the context of immunotherapy, optogenetic tools have the potential to precisely control T-cell receptor activation, cytokine release, or the activity of other immune effector cells. This precision reduces the risks of overactivation, which could lead to autoimmune complications [10]. LLLT, also known as photo biomodulation, utilizes low-intensity light, particularly in the red to near-infrared spectrum, to stimulate immune cells and promote tissue repair. Though traditionally used in wound healing and pain management, recent research suggests that LLLT can modulate immune responses by promoting macrophage polarization, dendritic cell activation, and T-cell recruitment, which are essential for effective immunotherapy [4].

Classic immunotherapy strategies are summarized in Table 1.

2. Optogenetics for immune modulation

Optogenetics is a method utilized to regulate or observe neural activity through the application of light, accomplished by the genetic incorporation of proteins that are sensitive to light [11,12]. Optogenetic tools such as channel rhodopsin (ChR), halorhodopsin, and archaerhodopsin (Arch) facilitate the modulation of neuronal activity, while the assessment of neuronal function can be achieved through genetically encoded sensors that detect ions, such as calcium, or measure membrane voltage. The primary effector in this framework is light, which offers the benefits of high spatial and temporal resolution across various wavelengths and sites [13]. It is fair to cite the pioneering work done by Prof. Zhuo-Hua Pan and his team [14], whom investigated the potential of transforming inner retinal neurons into photosensitive cells as a viable approach to confer light sensitivity in retinas devoid of rods and cones. Through the use of an adeno-associated viral vector for delivery, their findings indicate that sustained expression of a microbial-type rhodopsin, specifically channelrhodopsin-2 (ChR2), can be successfully established in the inner retinal neurons of rodents in vivo. Additionally, they provided evidence that the

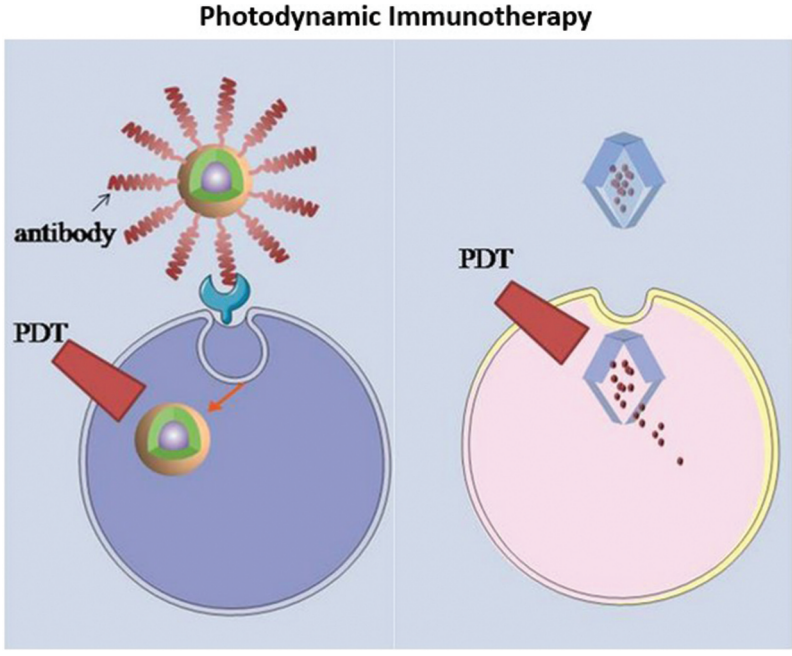

Figure 1. PDT (Photodynamic Therapy) and PDIT (Photodynamic Immunotherapy) functioning mechanisms.

Table 1. Classic immunotherapy strategies (reproduced with permission from [85]).

Oncological treatments	Methods	Targets
Immune Checkpoint Blockade	Immune checkpoints, including PD-1/PD-L1 and CTLA-4, play a vital role in the negative regulation of immune activation. Immune checkpoint blockade (ICB) functions by inhibiting the inhibitory receptors present on cytotoxic T lymphocytes (CTLs).	T cells
Adoptive cell therapy	Adoptive cell therapy encompasses the process of isolating a patient's own immune cells, cultivating them in a laboratory setting, and subsequently reinfusing them into the patient to bolster their ability to combat cancer. This therapeutic approach is particularly effective for non-solid tumors and can be categorized into two main types based on their specificity.	T cells, Natural killer cells, Tumor-infiltrating lymphocytes, Chimeric antigen receptor, Engineered T cell receptors
Cancer vaccines	Tumor-specific vaccines represent a category of active immunotherapy that focuses on tumor antigens. By administering particular antigens, these vaccines aim to boost immunogenicity and stimulate the patient's immune response. They can be formulated using various components, including cells, DNA, mRNA, peptides, and dendritic cells.	Antigen release/presentation
Non-specific immune modulation	Non-specific immune modulation refers to the application of immunomodulators aimed at augmenting the immune system's functionality in a generalized way. Notable examples of such agents include Bacille Calmette-Guérin (BCG), polysaccharides derived from mushrooms, and cytokines like interleukin-2 (IL-2).	Natural killer cells, Macrophages and Cytotoxic T Lymphocytes
Gene therapy	Gene therapy encompasses the identification of fundamental pathological mechanisms through genomic analysis. Additionally, it may include the introduction of exogenous target genes using vectors to rectify the activation of oncogenes or to stimulate the expression of tumor suppressor genes, as exemplified by oncolytic virus therapy.	Specific gene modifications
Immunosuppressive cells downregulation	Addressing the imbalanced levels of immunosuppressive cells within the immune microenvironment is crucial. For instance, the CXCR1/2 inhibitor SX-682 has the capability to impede the trafficking of myeloid-derived suppressor cells (MDSCs), while inhibitors of histone demethylases can effectively suppress regulatory T cells (Tregs).	MDSCs M2 macrophages, Tregs
Small molecules	Immunomodulatory small molecule inhibitors are designed to target intracellular pathways, including pattern recognition receptors, oncogenic signaling, and metabolic processes, thereby offering potential as complementary or alternative therapeutic options. An illustrative example is pexidartinib, a small molecule that specifically targets the KIT pathway while exhibiting immunomodulatory effects.	Immune checkpoints,PPR-related pathways, chemokines, cytokines, retinoic acid receptor-related orphan receptor gt, metabolic/oncogenic pathways, immuno-related kinases

expression of ChR2 in the remaining inner retinal neurons of a mouse model exhibiting photoreceptor degeneration can restore the retina's capacity to encode light signals and relay these signals to the visual cortex [14]. A significant milestone in the advancement of optogenetic technology occurred in 1971 when Oesterhelt and Stoeckenius [15] discovered bacteriorhodopsin, a protein resembling rhodopsin found in the purple membrane of Halobacterium halobium, which functions to pump protons when exposed to light. This foundational discovery paved the way for the subsequent identification of other opsin family members, including halorhodopsin, which was characterized in 1984 by Sugiyama and Mukohata [16], and channelrhodopsin, identified in 2002 by Nagel et al. [17] Additional early methodologies were formulated and implemented by the research teams led by Boris Zemelman and Gero Miesenböck at the Sloan-Kettering Cancer Center in New York City [18], as well as by Dirk Trauner, Richard Kramer, and Ehud Isacoff at the University of California [18], Berkeley, among other collaborative groups. A significant advancement in the field was the finding that the mere introduction of a microbial opsin gene, in the absence of any supplementary elements, rendered neurons sensitive to light [19]. Initially developed within the field of neuroscience, optogenetics has emerged as a revolutionary technology that facilitates the optical control of specific cells across a range of intricate tissues. This is accomplished through the introduction of either naturally occurring or engineered proteins that possess a photoreceptive domain linked to a biological function. Despite the presence of certain limitations in traditional optogenetic proteins, such as challenges in expression within mammalian cells and suboptimal light sensitivity, there has been considerable advancement in the diversification of the optogenetic toolkit over recent years. This progress has led to enhancements in protein characteristics essential for the restoration of vision through optogenetics. A key component of this toolkit is "opsins," which are a family of light-sensitive proteins characterized by their retinal-binding and seven-transmembrane structure, encoded by specific opsin genes. Opsins serve as light-activated ion pumps or sensory receptors and are found across a wide array of organisms, encompassing both eukaryotes and bacteria [20]. Opsin genes can be categorized into two primary families: microbial opsins (type I), which are located in prokaryotes, algae, and fungi, and are generally responsible for encoding proteins that utilize retinal in its all-trans form, and animal opsins (type II), which are exclusive to higher eukaryotes and primarily facilitate vision. The latter encode G protein-coupled receptors (GPCRs) and, in the absence of light, bind retinal in the 11-cis configuration.

Microbial opsins are proteins that harness light energy to facilitate the active transport of ions across excitable cells membranes [21] or to permit the passive movement of ions

through open channels. When introduced into cells that do not naturally respond to light, these opsins provide a means for precise optical modulation of various cellular functions. They enable rapid activation and inhibition of neural activity in the mammalian brain without the need for chemical agents. The primary microbial opsins utilized in the field of optogenetics include channelrhodopsins (ChRs) and light-driven ion pumps, such as halorhodopsin and Arch proteins. ChRs, which are activated by blue light, function as nonspecific cation channels derived from green algae. The first identified channelrhodopsin, known as channelrhodopsin-1 (ChR1), was discovered in the organism Chlamydomonas reinhardtii. Subsequently, a second channelrhodopsin, designated as ChR2, was identified from the same organism [22]. Both categories of channelrhodopsins exhibit swift kinetic properties and enable the targeted depolarization of genetically defined cells upon exposure to light [23]. Halorhodopsins are light-activated chloride pumps derived from archaeal organisms. When these proteins are expressed in specific cells and exposed to yellow light, they facilitate the transport of chloride ions from the external environment into the cell, resulting in hyperpolarization and subsequent inhibition of the target cell's activity. The halorhodopsin from the archaeon Natronomonas pharaonis (NpHR) was the first to be utilized in neuronal applications [24]. ChR2 exhibits peak responsiveness to light at a wavelength of 470 nm, while NpHR is most effectively activated by light at 580 nm [24]. Due to their distinct activation maxima, these elements can be co-expressed within the same cell, allowing for the independent modulation of cellular activity, characterized by millisecond precision and swift reversibility [25,26]. Arch proteins, such as Arch-3, are light-activated proton pumps derived from Halorubrum sodomense. When these proteins are expressed in neuronal cells and exposed to yellow or green light, they facilitate the efflux of positive charges, resulting in hyperpolarization of the neurons. A novel variant, ArchT, which exhibits enhanced light sensitivity, has recently been developed and applied for the purpose of silencing extensive areas of the brain. The peak excitation wavelengths for both Arch and ArchT are around 566 nm [27,28].

Opsins found in animals, including rhodopsin and melanopsin, are part of the extensive family of naturally occurring light-sensitive G protein-coupled receptors (GPCRs), and they serve as significant resources for optogenetic research and applications. Unlike microbial opsins, animal opsins exhibit significantly greater light sensitivity due to the amplification of light signals through G-protein coupled signaling pathways. Research has demonstrated that vertebrate rhodopsins [29,30] and cone opsins [31] can serve as effective optogenetic tools for modulating neuronal excitability even under low light conditions.

3. Light switchable CAR-T cells

Nguyen and Huang et al. developed a light-responsive CAR T cell (LiCAR-T) system by leveraging the light-activated reassembly of the split-CAR architecture. This innovative system utilizes either a light-oxygen-voltage (LOV) domain-based optical dimerizer (LOV2-ssrA/sspB) or cryptochrome 2 paired with CRY-interacting basic helix-loop-helix N (CRY2/CIBN) as optogenetic dimerization mechanisms to modulate CAR T cell immunotherapy [32]. The researchers enhanced the design of the LiCAR-T system to tackle several technical issues, including insufficient targeting of the plasma membrane, unintended accumulation in the nucleus, and background activation under low-light conditions. To evaluate the spatiotemporal regulation of the tumor-eradicating functions of LiCAR-T cells, a series of in vitro co-culture experiments were performed using CD19-positive tumor cells. To address the limitations of blue light-responsive technologies regarding tissue penetration, Nguyen et al. employed upconversion nanoparticles (UCNPs) as nanotransducers to detect near-infrared (NIR, 700–1000 nm) light, which offers deeper tissue penetration and serves as a wireless stimulation source. UCNPs are unique luminescent nanomaterials that convert NIR excitation into visible light with shorter wavelengths. By utilizing the multiple metastable intermediate energy levels inherent in lanthanide ions, UCNPs create a ladder-like energy structure that enables electrons to ascend through various energy levels by absorbing multiple excitation photons. The researchers further refined the dopant composition and size of UCNPs, resulting in a 4.5-fold enhancement in NIR-to-blue upconverted light emission. This advancement allows for the use of NIR light as a wireless stimulus to activate the injected UCNPs, leading to efficient blue emission that drives the reassembly of the split-CAR [32].

The field of non-opsin-based optogenetics is witnessing remarkable progress in cell biology, attributed to its exceptional flexibility and accurate regulation of biochemical pathways in both spatial and temporal contexts [33]. In the past decade, there has been a significant increase in the development of genetically encoded photo-switchable modules that respond to light across various wavelengths. A key advancement in this area is the fusion of optogenetics with immunoengineering, a rapidly evolving discipline that requires interdisciplinary collaboration among engineers, nanomaterial chemists, immunologists, and cancer biologists. The approach termed "optoimmunoengineering" offers unique advantages that not only support but also enhance existing efforts to improve immunotherapies. Unlike traditional genetic modification methods such as knockout, knockdown, mutagenesis, or overexpression, which result in permanent changes to the spatiotemporal dynamics of signaling networks, genetically encoded light-switches allow for the reversible modulation of protein activity or gene expression in a timely manner, thus reducing the likelihood of long-term side effects. Furthermore, optogenetic techniques afford a high level of control over engineered cells, enabling remarkable precision in spatiotemporal manipulation [34–37]. The advancement of photoactivatable CAR-T cells presents a significant improvement over small molecule-gated CAR-T cells, which lack precise spatial control. This innovative approach allows for the targeted activation of these "living therapeutics" at designated tumor sites, thereby minimizing off-tumor cytotoxicity. Furthermore, when applied to investigate and enhance the cancer-immunity cycle, optogenetic techniques can enable immune cells to overcome the energy barriers imposed by the immunosuppressive tumor microenvironment (TME). This not only provides new insights into the mechanisms

underlying antitumor immunity but also sheds light on the resistance challenges faced in immunotherapy [38,39].

4. Photodynamic therapy (PDT) in immunomodulation

Traditional antitumor treatments such as surgical excision, chemotherapy, radiotherapy, and targeted molecular therapies are effective in managing early-stage tumors; however, they remain inadequate for advanced-stage malignancies [40]. Optimistically, cancer immunotherapy has the potential to inhibit cancer recurrence and extend the survival duration of patients in the advanced stages of the disease by stimulating the host's immune response [41]. To date, a variety of immune-based therapies have received approval for the treatment of cancer, including checkpoint blockade immunotherapy, adoptive cell therapy (ACT), and cancer vaccines [1,42–44]. Immune checkpoint therapy has notably transformed the landscape of clinical research among various therapeutic approaches. A prime illustration of this is the FDA's initial approval of the checkpoint inhibitor ipilimumab, a therapeutic antibody that targets cytotoxic T lymphocyte-associated protein 4 (CTLA-4), resulting in significant regression of metastatic melanoma [45]. Furthermore, the administration of PD-1 blocking antibodies, such as nivolumab, has been shown to markedly enhance the objective response rate in various advanced malignancies [46]. Notwithstanding the previously discussed advantages of immune checkpoint therapy, a significant proportion of patients with diverse cancer types exhibit insensitivity to immune checkpoint inhibitors, primarily attributable to the low immunogenicity of their tumors [47–49]. Upon the absorption of a photon by a photosensitizer (PS), three distinct outcomes may occur. Initially, the PS transitions from its ground state to a transient excited singlet state, which may subsequently return to the ground state through the emission of fluorescence. Alternatively, this transient excited singlet state can undergo intersystem crossing, resulting in the formation of a more stable triplet state. The triplet state of the excited PS has the potential to react with various endogenous substances, leading to the generation of free radicals such as hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\cdot-}$). Additionally, this relatively stable triplet state can directly engage with molecular oxygen, producing singlet oxygen ($^1O_2$). Typically, in photodynamic therapy (PDT), the reactive oxygen species (ROS) produced by the PS are primarily associated with the latter interaction [50,51]. Recently, photodynamic therapy (PDT) utilizing photosensitizers (PSs) activated by localized laser irradiation has been shown to selectively target and damage tumor tissue while sparing normal organs [52], [53–55]. In contrast to surgical procedures, photodynamic therapy (PDT) is characterized by its lower invasiveness. Furthermore, numerous studies have demonstrated that PDT effectively enhances the antitumor immune response via multiple mechanisms [56]. Calreticulin (CRT), which is situated on the endoplasmic reticulum (ER), translocates to the surface of the cell membrane during photodynamic therapy (PDT), thereby emitting an "eat me" signal that triggers an immune response [57]. The expression of the transcription factor NF-κB and the protein heat shock protein 70 is increased [58], or facilitating the release of cytokines such as IFN-γ and IFN-α [59]. Enhancing the homing capabilities of antigen presenting cells (APCs) and cytotoxic T lymphocytes (CTLs) through the promotion of mutations [60]. The process involves the recruitment of neutrophils to eliminate cancer cells, subsequently leading to the infiltration of macrophages [61,62]. PS-generated photodynamic therapy (PDT) is particularly effective in triggering immunogenic cell death (ICD), a widely employed approach for eliciting an immune response. As ICD progresses, tumor cells undergo a series of sequential transformations [62]. For example, calreticulin (CRT) and heat shock proteins (HSPs) are presented on the surfaces of cells undergoing apoptosis. Additionally, adenosine triphosphate (ATP) and high-mobility group box 1 protein (HMGB1) are released from these dying cells. The released ATP acts to attract antigen-presenting cells (APCs) into the tumor microenvironment. The presence of CRT enhances the ability of APCs to engulf and digest dead cells. Furthermore, HMGB1 facilitates the presentation of tumor-associated antigens (TAAs) to APCs. The expression of HSPs plays a crucial role in the maturation and migration of dendritic cells (DCs). Moreover, immunogenic cell death (ICD) can further enhance APC maturation through the secretion of proinflammatory cytokines. Consequently, ICD significantly promotes the activation of the immune response. Notably, ICD serves as a critical link between photodynamic therapy (PDT) and immunotherapy in the context of cancer treatment [62,63]. Nonetheless, various factors considerably hinder the effectiveness of photodynamic therapy (PDT), thereby diminishing its potential to elicit an immune response. Primarily, tumor hypoxia can impair the effectiveness of oxygen-dependent PDT, and the oxygen utilization during PDT can exacerbate tumor hypoxia, resulting in a detrimental cycle [64]. Despite its potential, several factors significantly impede the efficacy of photodynamic therapy (PDT), consequently reducing its ability to provoke an immune response. A key issue is tumor hypoxia, which can undermine the effectiveness of oxygen-dependent PDT. Furthermore, the consumption of oxygen during the PDT process can worsen tumor hypoxia, creating a harmful feedback loop [65]. The effectiveness of photodynamic therapy (PDT) is notably diminished in hypoxic tumor environments, as the process relies on the production of reactive oxygen species (ROS), which necessitates substantial oxygen consumption [66]. High concentrations of photosensitizers (PSs) are known to induce aggregation-caused quenching (ACQ), which significantly diminishes their optical properties. Furthermore, the systemic administration of PSs may lead to phototoxicity due to unintended distribution and accumulation in healthy tissues [67–69]. Fortunately, the advent of advanced nanomedicines has introduced innovative strategies to enhance the efficacy of photodynamic therapy (PDT), thereby improving the immune response [70]. These sophisticated nanomedicines address the issue of tumor hypoxia by integrating various self-oxygenation techniques. By utilizing novel nanocarriers, they can effectively regulate the in vivo distribution of PSs, ensuring targeted accumulation within tumors. Additionally, intelligent tumor microenvironment (TME)-responsive nanoplatforms not only mitigate phototoxicity by preventing the premature release of PSs into the bloodstream but also facilitate their

release at the tumor site to counteract the ACQ phenomenon. Most importantly, these nanomedicines proficiently co-deliver PSs alongside immunomodulators to their intended targets, thereby optimizing cancer immunotherapy [71].

5. Photoimmunotherapy (PIT)

The practice of phototherapy (PT) can be traced back approximately 4,000 years to ancient Egypt, where it was employed to address Vitiligo through the boiling of a plant extract followed by exposure to sunlight. In contrast, contemporary phototherapy emerged in the 1970s, utilizing artificial light sources for treatment [72,73]. Phototherapy can be classified into two primary types: photodynamic therapy (PDT) and photothermal therapy (PTT). In the case of PDT, a photosensitizing agent is exposed to light, leading to the production of reactive oxygen species (ROS), which are highly cytotoxic and induce cell death. Conversely, PTT operates on the principle of elevating local temperatures, typically achieved through laser irradiation. Near-infrared (NIR) lasers, specifically those within the wavelength range of 650 to 1350 nm, are commonly employed in PTT due to their effective tumor penetration capabilities [74–78]. PTT is classified into two distinct categories. The first category, referred to as mild hyperthermia, involves temperature elevations ranging from 43 to 50°C. This increase results in heightened membrane permeability, enhanced cellular uptake, disruption of metabolic signaling, and impaired membrane transport. Tumor cells exhibit a limited ability to recover from these types of damage. The second category, known as photothermal ablation, occurs at temperatures exceeding 50°C, resulting in the destruction of the cellular membrane and subsequent necrotic cell death. PDT has received FDA approval for nearly four decades. Hematoporphyrin derivative (HPD) was the inaugural photosensitizer to obtain FDA approval. Currently, other FDA-approved photosensitizers include Foscan®, Levulan®, Radachlorin®, Metvix®, and Photofrin® [78]. Photothermal therapy (PT) induces immunogenic cell death (ICD), which results in the release of tumor-specific antigens (TSAs) and damage-associated molecular patterns (DAMPs), including calreticulin (CRT), high mobility group box 1 (HMGB-1), and adenosine triphosphate (ATP). This process enhances the immunogenicity of the tumor microenvironment, as DAMPs facilitate the maturation of dendritic cells (DCs) and promote the secretion of pro-inflammatory cytokines such as interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-12 (IL-12), interferon-gamma (INF-γ), and tumor necrosis factor-alpha (TNF-α). The immunostimulatory properties of PT significantly augment anti-tumor immunity in comparison to immunotherapy administered in isolation. While immunotherapy can effectively initiate an immune response at the tumor site, it often falls short in completely eliminating primary tumors [79–85]. The integration of phototherapy with immunotherapy, known as photoimmunotherapy (PIT), has been observed to create a synergistic effect. Phototherapy directly induces apoptosis in tumor cells while simultaneously eliciting a systemic immune response. When paired with immunotherapy, this approach fosters the development of immunological memory. Photoimmunotherapy combines the benefits of phototherapy with the capacity to activate an immune response, rendering it particularly effective for the treatment of metastatic cancer. Consequently, PIT not only targets primary tumors but also enhances immune memory, thereby offering the potential to inhibit tumor recurrence and metastasis [86–88]. Apoptosis, typically not included among the inflammatory cell death causes, represents an efficient biological process to be used by optogenetics. For instance, the emergence of optogenetics-controlled cell death effectors (optoCDEs) has been documented, representing a novel category of optogenetic instruments that facilitate the light-mediated activation of three distinct forms of programmed cell death (PCD): apoptosis, pyroptosis, and necroptosis [89]. This innovation utilizes the photosensitive protein Cryptochrome-2 derived from Arabidopsis thaliana. OptoCDEs allow for the swift and highly targeted induction of PCD in human, mouse, and zebrafish cells, making them applicable for a diverse array of purposes, including the induction of sub-lethal cell death or the precise removal of individual cells or specific cell populations, both in vitro and in vivo [90]. Another example is represented by the LiPOP tools (light-induced non-apoptotic tools), facilitating the reconstruction of essential molecular processes associated with two distinct non-apoptotic cell death pathways by utilizing light-based technology. Additionally, the integration of LiPOPs with up-conversion nanoparticles or bioluminescence has been shown to enable wireless optogenetic or chemo-optogenetic elimination of cancer cells across various mouse tumor models. LiPOPs are capable of inducing necroptotic and pyroptotic cell death in both cultured prokaryotic and eukaryotic cells, as well as in live animal subjects, thereby providing a framework for investigating the significance of non-apoptotic cell death pathways in the context of microbial infections and antitumor immune responses [91]. Interestingly, it was developed a light-sensitive variant of MLKL that quickly oligomerizes and is directed to the plasma membrane in cells when exposed to light, leading to swift cell death. Our findings illustrate that this tool can be manipulated both spatially and temporally, enabling its application in a chemical genetic screen to discover compounds and pathways that confer protection against MLKL-mediated cell death. Furthermore, it facilitates the investigation of signaling responses in non-dying bystander cells. In supplementary experiments, we modified MLKL to inhibit its cytotoxic effects while preserving its ability to be recruited to the membrane upon light activation, resulting in a novel single-component optogenetic tool that permits the modulation of protein activity at the plasma membrane [92].

Under a nanotechnological point of view, Zhang et al. [54] have successfully designed and established a novel dual-modal phototherapeutic nanoplatform that facilitates both photothermal therapy (PTT) and photodynamic therapy (PDT) using a single near-infrared (NIR) laser (660 nm). This innovative approach employs a core-shell structure comprising CuS nanoparticles (NPs) encased in a carbon shell, integrated with chlorin e6 (Ce6). The incorporation of the carbon shell enhances the tumor accumulation of the small CuS NPs and markedly improves their photothermal efficacy when exposed to 660 nm laser irradiation. Additionally, the presence of Ce6 within the carbon shell imparts a photodynamic effect under the same laser conditions. Consequently, the developed Ce6/CuS@Carbon nanoplatform successfully achieves dual-modal phototherapy, leading to significant tumor growth inhibition while minimizing adverse effects and ensuring superior biosafety.

6. Conclusion

Light-based technologies offer exciting new possibilities in the field of immunotherapy. From the precise control of immune cell activation using optogenetics to the enhanced targeting of cancer cells through photoimmunotherapy, light technology is revolutionizing the way we approach immune modulation. While these technologies are still in the developmental phase for many applications, the early results are promising, particularly in cancer treatment and immune modulation. Further research and clinical trials are needed to fully realize the potential of light technology in immune cell therapy.

7. Future perspectives

Over the next decade, the integration of photodynamic therapy (PDT) and immunotherapy is expected to revolutionize cancer treatment. With increasing advancements in nanotechnology, the development of targeted nanocarriers capable of precisely delivering photosensitizers (PS) to tumors will significantly enhance the therapeutic efficacy of PDT. These innovations will address current challenges, such as tumor hypoxia and the aggregation-caused quenching (ACQ) phenomenon, by ensuring optimal oxygen levels and controlled PS release at the tumor site. This progress will not only improve PDT's ability to induce immune responses but also reduce phototoxicity in healthy tissues, thereby making the treatment safer and more effective. The synergy between PDT and immunotherapy will likely become a cornerstone of cancer care. PDT's ability to trigger immunogenic cell death (ICD) and stimulate the immune system will complement existing immunotherapies like checkpoint inhibitors and adoptive cell therapy, creating a potent combination for fighting advanced-stage cancers. In the next ten years, we can expect the FDA to approve a range of novel PDT-based immunotherapies, particularly for cancers that are currently resistant to traditional treatments.Additionally, as the understanding of cancer immunology deepens, the use of PDT in combination with emerging technologies like optogenetics and photoimmunotherapy will further enhance its potential, improving both tumor targeting and immune system activation, offering hope for more durable responses and reduced cancer recurrence.

Author contributions

Davide Frumento: conceptualization, methodology, investigation, validation, writing-original draft, writing review and editing. Ștefan Țălu: resources, software, funding acquisition, project administration, writing review and editing. All authors have read and approved the published version of the manuscript.

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ORCID

Davide Frumento http://orcid.org/0000-0002-1548-5392
Ștefan Țălu http://orcid.org/0000-0003-1311-7657

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