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REVIEW

Multimodal Key Anti-Oncolytic Therapeutics Are Effective In Cancer Treatment?

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Abstract: Oncolytic virus (OVs) therapy has emerged as a promising modality in cancer immunotherapy, attracting growing attention for its multifaceted mechanisms of tumor elimination. However, its efficacy as a monotherapy remains constrained by physiological barriers, limited delivery routes, and suboptimal immune activation. Phototherapy, an innovative and rapidly advancing cancer treatment technology, can mitigate these limitations when used in conjunction with OVs, enhancing viral delivery, amplifying tumor destruction, and boosting antitumor immune responses. This review provides the first comprehensive analysis of synergistic integration of OVs with both photodynamic therapy (PDT) and photothermal therapy (PTT). It also explores their applications in optical imaging-guided diagnosis and optogenetically controlled delivery. Furthermore, it discusses emerging strategies involving biomimetic virus or viroid-based vectors in conjunction with phototherapy, and delves into the immunomodulatory mechanisms of this combinatorial approach. While promising in preclinical models, these combined strategies are still largely in early-stage research. Challenges such as limited light penetration, delivery efficiency, and safety concerns remain to be addressed for clinical translation. Consequently, the integration of OV therapy and phototherapy represents a compelling strategy in cancer treatment, offering significant promise for advancing precision oncology and next-generation immunotherapies.

Keywords: phototherapy, oncolytic virus, immunotherapy, optogenetics

Introduction

Due to its multifactorial nature, cancer exhibits significant heterogeneity across individuals and tumor types, this heterogeneity originates not only from the tumor cells themselves, but also encompasses alterations in immune cells, vascular components, stromal cells and secretory factors in the tumor microenvironment, collectively compounding the complexity and challenge of treatment.[1,2] While surgery, radiotherapy and chemotherapy remain mainstay treatments for cancer, substantial therapeutic advancements are still required to effectively combat the disease.[3,4] Therefore, it is urgent to explore more effective, selective and lower-toxicity therapeutic approaches that overcome the limitations of conventional treatments and address patients' pressing demand for improved therapies.

Traditional surgical resection is effective for early-stage cancers, but remains inadequate for treating distant metastatic tumors. In contrast, chemoradiotherapy often induces severe side effects that can negatively impact patient prognosis, and tumors frequently develop drug resistance during the course of treatment.[5] Currently, the development of tumor immunotherapy, exemplified by tumor gene therapy and virus therapy, offers promising new approaches for cancer treatment. Notably, immune checkpoint inhibitors,[6] adoptive cell transfer therapy,[7] monoclonal antibodies[8] and cancer vaccines[9,10] have demonstrated some efficacy. However, their overall therapeutic remain suboptimal due to limitations such as single targets, significant individual variability, and the emergence of drug resistance in certain patients. These challenges have prompted further exploration into oncolytic virus therapy. Oncolytic virus therapy employs naturally

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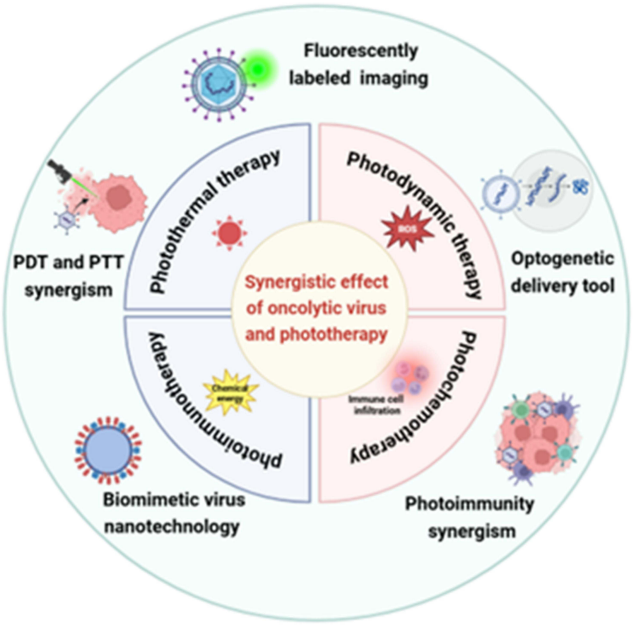
occurring or genetically modified tumor-selective viruses to specifically infect and kill tumor cells.[11,12] Upon reaching the tumor site, the virus replicates within tumor cells, leading to their lysis. This process not only directly eliminates cancer cells but also promotes the release of tumor-associated antigens, which in turn recruit immune cell infiltration and activate systemic anti-tumor immune responses. Thus, oncolytic virotherapy exerts a dual therapeutic effect by combining local oncolysis with immune-mediated systemic tumor control, offering a promising strategy for comprehensive cancer treatment.[13,14] For activating of tumor immunity, OVs demonstrate advantages over immune checkpoint inhibitors and small molecule drugs, offering broader targeting range. Beyond selectively ablating tumor cells, OVs degrade the extracellular matrix barrier effectively "opening the door" for therapeutic agents and disrupt tumor neo vasculature to inhibit metastasis. They simultaneously reverse the immunosuppressive tumor microenvironment and convert immunogenic "cold" tumors into "hot" tumors.[15] However, tumor heterogeneity and ecosystem complexity limit OV monotherapy. It often fails to achieve sustained therapeutic outcomes, inadequately activates systemic antitumor immunity, and triggers rapid immune recognition which leads to premature viral clearance, restricted viral spread, and insufficient intratumoral distribution.[16,17]

Phototherapy has found broad application in oncolytic virus therapy due to its precision, immune-stimulating capabilities, minimal drug resistance, and high degree of controllability. Photocatalytic therapy, being a relatively non-invasive treatment modality, enables the targeted accumulation of non-toxic, high-dose photosensitizers on cancer cells under specific wavelengths of light, thereby achieving precise cytotoxicity. Critically, this approach permits repeated treatments, contributing to sustained tumor suppression and significantly improved therapeutic outcomes.[18,19] Moreover, phototherapy induces tumor cells apoptosis, enhances cellular immunogenicity, and promotes the release of damage-associated molecular patterns (DAMPs). These DAMPs interact with pattern recognition receptors (PRRs) on the surface of dendritic cells, ultimately leading to the activation of both innate and adaptive immune responses.[20,21] By activating photosensitizers to generate singlet oxygen or elevate local temperature, phototherapy directly kills tumor cells and modulates the tumor microenvironment. This enhances OV dissemination and intratumoral penetration, creating synergistic e local effect and systemic immune activation that amplifies treatment specificity and efficacy.[22] To fully leverage OV potential within the tumor ecosystem, combining phototherapy with OV therapy overcomes monotherapy limitations, significantly improving overall outcomes through this immune-mediated synergy. Although these approaches demonstrate significant therapeutic potential, challenges persist in deep tissue imaging, breakthroughs in therapeutic depth, and side effect management. Further research is needed to optimize photosensitizer selection, refine viral vector tropism, and design precise combination regimens.

In this paper, we explore the potential of fluorescence labeling imaging,[23–27] optogenetics,[28–35] photodynamic therapy[36–42] and photothermal therapy,[43–49] along with the application of viroid vectors,[50–55] and the integration of viral nanotechnology with phototherapy in cancer treatment,[56–61] especially in improving therapeutic accuracy, enhancing targeting, and improving immune response (Scheme 1).

How Advanced Is Phototherapy In Cancer Treatment?

Phototherapy (PT) is a minimally invasive treatment strategy using light energy.[20] Relying on its advantages of strong targeting, low invasiveness and good controllability, it has shown important application prospects in the treatment of tumor,[62,63] ophthalmology[64] and superficial skin diseases.[65] The principle of phototherapy is based on the interaction between light and biological tissues, where light can trigger biochemical processes with therapeutic effects. With advancements in laser technology, photosensitizers and nanotechnology, phototherapy has evolved into various modalities, particularly in cancer treatment, where its therapeutic potential is increasingly being explored.[19] Phototherapy utilizes light sources—including near and far infrared lasers,[66] LED,[67] chemical bioluminescence[68] or self-luminescence, that interact with light-sensitive molecules in the body, and the photosensitizer absorbs specific wavelengths to induce photochemical, photothermal or photodynamic reactions to further achieve therapeutic effects (Figure 1).[69] According to different mechanisms of light action, phototherapy mainly includes photodynamic therapy (PDT), photothermal therapy (PTT), photochemotherapy (PUVA) and photoimmunotherapy (PIT).



Scheme 1 Strategies for enhancing cancer diagnosis and treatment based on oncolytic viral therapy combined with phototherapy.

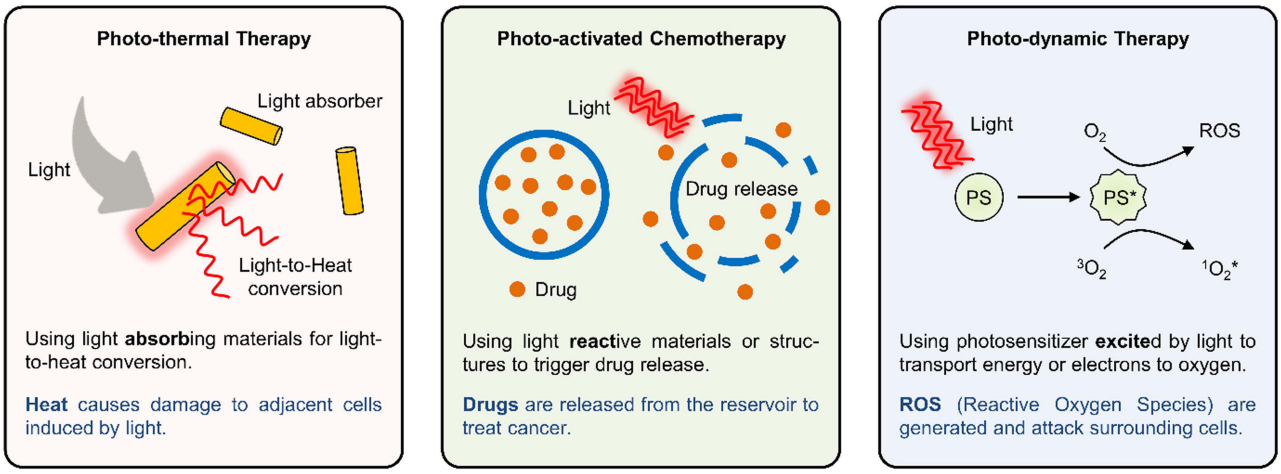


Figure 1 Comparison of different mechanisms of action of phototherapy. Phototherapy is divided into photothermal therapy, photochemotherapy and photodynamic therapy. Reproduced from Seung Lee J, Kim J, Ye YS, et al. Materials and device design for advanced phototherapy systems. Adv Drug Deliv Rev. 2022;186:114339.[69] Copyright 2022, Elsevier.

Photodynamic Therapy

Photodynamic therapy (PDT) effectively eliminates tumor cells by generating reactive oxygen species (ROS) upon light irradiation. This process requires three essential components: a light sources, molecular oxygen present in tissues, and photosensitizers (PS).[70] When exposed to light of a specific wavelength, t the photosensitizer is excited into a singlet state. Due to its short lifetime, it rapidly either returns to the ground state or converts to a longer-lived triplet state via intersystem crossing. Trilinear photosensitizers effectively transfer energy to molecular oxygen (O_2), producing singlet oxygen ($^1O_2$). This reactive oxygen species damages cellular organelles, induces apoptosis, and disrupts biomolecules in tumor cells and nearby vasculature, thereby inhibiting tumor growth. An illustrative example is CyOH–NSe, a highly efficient triplet-state photosensitizer. Under near-infrared (NIR) light, CyOH–NSe not only generates ROS but also triggers the release of carbon monoxide (CO) from a responsive donor. This dual mechanism synergistically disrupts mitochondrial function and suppresses inflammatory responses in tumor cells, leading to enhanced therapeutic effects

through the combined photodynamic and gas therapy .[71] The ROS generated in PDT include hydroxyl radical (•OH), superoxide anion (O_2^-•) and hydrogen peroxide (H_2O_2). These species collectively initiate a pro-apoptotic cascade that promotes tumor cell death.

PDT, recognized for its precise targeting, non-invasiveness, favorable safety profile, and repeatability, has demonstrated remarkable clinical efficacy in the treatment of superficial tumors, dermatological disorders, ophthalmic diseases, and microbial infections. Building on its unique therapeutic advantages, a variety of advanced optical delivery technologies have been developed in recent years, including fiber-optic transmission,[39] implantable LED,[38,40] two-photon excitation technology,[36] up-conversion nanoparticles,[42] and photoacoustic image-guided light therapy methods.[37] The advent of these innovations has not only significantly enhanced penetration depth and treatment precision of phototherapy,[41] but also paved the way for its application in personalized and precision medicine. (Figure 2). However, the efficacy of PDT remains constrained by the limited by the penetration of light through biological tissues. Light scattering and absorption significantly reduce the light intensity reaching deep-seated lesions, restricting clinical application to superficial or endoscope-accessible areas, and posing challenges in treating metastatic and deeply embedded tumors.[72] Moreover, conventional PSs often lack specificity, are rapidly cleared following systemic administration, and exhibit poor accumulation at tumor sites. Post-treatment, patients may also develop heightened photosensitivity, increasing the risk of skin damage and allergic reactions. Despite these challenges, PDT continues to hold great promise in oncology and other medical fields. Its therapeutic potential may be further enhanced through combination strategies with other treatment modalities, the integration of nanotechnology, and the optimization of photosensitizers and light delivery systems.

Photothermal Therapy

PTT employs photothermal agents to absorb photons energy, converting light into heat. This process generates localized high temperature in tissues, enabling the ablation or killing of tumor cells. Near-infrared light (NIR) known for its strong tissue penetration capability, is commonly used in PTT. When the agents are irradiated with light at a specific wavelength, their photothermal molecules enter an excited state and collide intensely with surrounding molecules, thus releasing heat. This process converts light energy into kinetic energy, which is subsequently released as heat, leading to

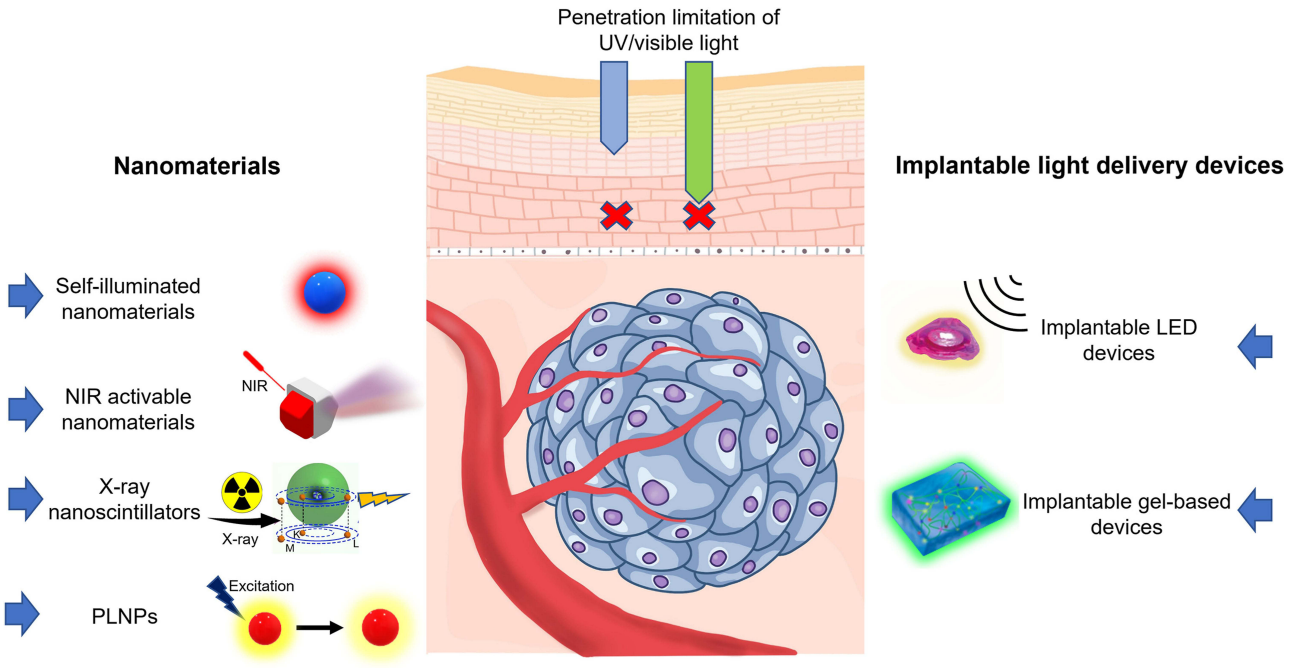


Figure 2 Light delivery strategies to overcome deep PDT. Reproduced from Sun B, Bte Rahmat JN, Zhang Y. Advanced techniques for performing photodynamic therapy in deep-seated tissues. Biomaterials. 2022;291:121875.[41] Copyright 2022, Elsevier.

a localized temperature increase.[47] When tumor tissue heats up, the metabolism and growth of tumor cells are disrupted. Prolonged exposure to high temperatures can damage cell membranes and DNA. This damage often leads to cell death through necrosis or apoptosis. When tumor cells are exposed to hyperthermia, some of the heat-resistant proteins denature and aggregate with natural aggregation-sensitive proteins.[43] Protein denaturation and aggregation induced by hyperthermia can interfere with multiple downstream signaling pathways, such as enzyme inactivation, structural changes in chromatin, and inhibition of DNA synthesis and repair, leading to cancer cell death. PTT is classified into traditional PTT (≥45 °C) and mild photothermal therapy (MPTT) (42–45 °C), both of which have been widely applied in cancer treatment. Although MPTT minimizes damage to normal tissues, its limited thermal intensity often results in suboptimal tumor ablation, as cancer cells can activate protective mechanisms such as heat shock proteins and autophagy to resist treatment.[73] Nevertheless, MPTT exerts significant modulatory effects on the tumor microenvironment. By disrupting the dense and hypoxic architecture of solid tumors, MPTT enhances intratumoral permeability and oxygenation, facilitating the infiltration of immune cells and reducing the expression of immunosuppressive cytokines.[74] These changes help alleviate the immunosuppressive microenvironment, thereby improving the therapeutic response. As such, MPTT holds great promise as a synergistic approach to enhance the efficacy of immunotherapy, chemotherapy, and other treatment modalities. Due to the high heterogeneity of tumors and the complexity of the tumor microenvironment, the effective distribution of therapeutic agents plays a critical role in determining treatment outcomes.[44] Solid tumors are surrounded by disorganized and abnormal vasculature. In addition, physical barriers within the tumor, such as the dense extracellular matrix and non-malignant stromal cells, further restrict the penetration and efficacy of therapeutic agents.[46] PTT exerts its antitumor effects primarily through localized thermal damage. This heat-induced injury not only directly kills tumor cells, but also disrupts tumor vasculature and surrounding stromal components. By breaking down physical barrier within the tumor, PTT facilitates effective delivery of therapeutic agents, and enhances both drug targeting and permeability.[45] Moreover, the thermal stimulation triggers an inflammatory response in the tumor microenvironment, leading to the recruitment of endogenous immune cells via activated local inflammatory signals. The infiltration of these immune cells contributes to further clearance, reshaping of the tumor microenvironment and the establishment of long-term immune memory against the tumor.

Photochemotherapy

Photochemotherapy (PUVA) is a photopharmaceutical technology that utilizes light-activated drugs or drug cages. It employs specific light source (such as ultraviolet, visible or near-infrared light) to activate photosensitizers or light-responsive components within drug cage.[75] These activated molecules absorb light energy and convert it into chemical energy, enabling therapeutic actions that are not entirely dependent on the oxygen concentration within the tumor microenvironment. This makes PUVA particularly suitable for treating tumors in hypoxic conditions.[76] Upon Light activation, these molecules can generate localized heat, trigger-controlled drug release, or break chemical bonds to release therapeutic agents precisely at the target site, thereby minimizing collateral damage to healthy tissues. However, achieving effective and safe treatment requires precise control over light intensity, exposure duration, and the design of the drug cage. A variety of nanocarriers have been explored for PUVA-based applications, including liposome, polymer vesicles, up-conversion nanoparticles (UCNP) and nanocage, offering diverse platforms for light-responsive drug delivery.[77]

Photoactivated chemotherapy, combining photoactivated nanocarriers with chemotherapy drugs, offers the advantage of synergetic therapy, enabling more effective elimination of cancer cells. By encapsulating therapeutic agents within nanocarriers composed of light-responsive materials,[78] drugs can be precisely released upon light activation, thereby enhancing the specificity of the treatment and minimizing systemic toxicity and off-target effects on healthy tissues. Light sensitive carrier design can enable selective drug release at tumor sites, effectively increasing the local drug concentration and improving therapeutic outcomes. However, this strategy also presents several challenges, particularly regarding the penetration depth of the activating light and the precision of drug delivery in deep-seated tumors. Although photoactivated nanocarriers enable enhanced drug release in superficial tumor regions, their efficacy diminishes in deep lesions, particularly those distal to tumor vasculature or central zones, due to inadequate drug penetration. Consequently, optimizing drug delivery and release in deep-seated tumor areas remains a critical challenge for advancing this technology.

Photoimmunotherapy

Phototherapy has emerged as a highly effective therapeutic modality for primary tumor ablation, owing to its precise targeting capability, minimal invasiveness, and potent tumor-destructive efficacy within the irradiated tissue. PIT represents a groundbreaking advancement in cancer therapeutics, integrating the synergistic benefits of phototherapy and immunotherapy. This dual-modality approach not only achieves direct tumor cell eradication but also elicits robust anti-tumor immune responses, primarily through the induction of immunogenic cell death (ICD), which subsequently initiates systemic immune activation.[79] PIT represents a groundbreaking advancement in cancer therapeutics, integrating the synergistic benefits of phototherapy and immunotherapy.[80] This dual-modality approach not only facilitates direct tumor cell eradication but also elicits robust anti-tumor immune responses, primarily through the induction of ICD, which subsequently initiates systemic immune activation.[81]

During PIT, the induction of ICD not only initiates stress response-mediated tumor cell apoptosis but also robustly activates the host's anti-tumor immune response. This dual mechanism—combining direct cytotoxicity with immune system engagement—significantly enhances therapeutic efficacy .[82,83] Initially, tumor cells release tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) in response to external stimuli. For example, calreticulin (CALR) is translocated to the tumor cell surface, serving as an "eat me" signal that promotes phagocytosis and antigen presentation by dendritic cells (DCs). High mobility histone 1 (HMGB1) is transferred from the nucleus to the cytoplasm and subsequently released into the extracellular space, where it facilitates the activation of antigen specific T cells and initiates a potent anti-tumor immune response. Additionally, heat shock protein 70 (HSP70) and adenosine triphosphate (ATP) are released as "find me" signals to recruit effector immune cells, such as T cells and natural killer (NK) cells, further enhancing immune-mediated tumor clearance .[84] Synergistic therapies incorporating immune adjuvants such as immune stimulators and immune checkpoint inhibitors[85] has demonstrated superior therapeutic efficacy compared to conventional treatment approaches (Figure 3).[79] The enhanced outcomes observed with the combination of phototherapy and immunotherapy can be attributed to three key mechanisms. First, phototherapy induces ICD in tumor cells, facilitating the release of tumor-specific antigens and thereby generating an in situ autologous vaccine. Second, the phototherapy upregulates pro-inflammatory cytokines, thereby activating the immune system and amplifying antitumor

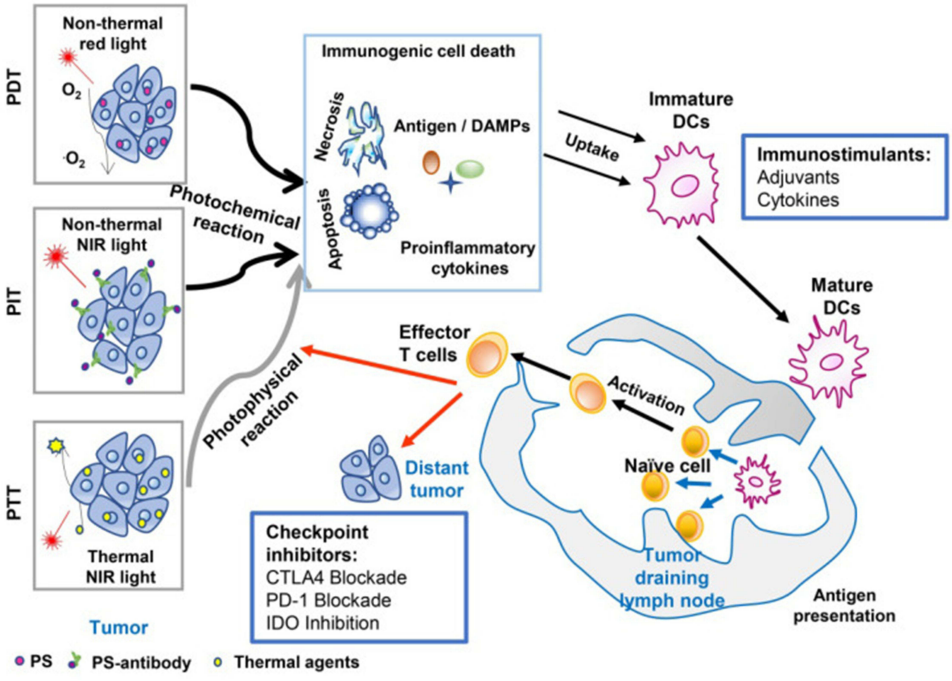


Figure 3 Overview of combined phototherapy and immunotherapy for cancer. When combined, phototherapy and immunotherapy can work synergistically to achieve enhanced control of tumor growth at both the primary tumor site and distant metastatic sites. Reproduced from Wang M, Rao J, Wang M, et al. Cancer photoimmunotherapy: from bench to bedside. Theranostics. 2021;11(5):2218–2231.[79] Copyright The Authors. Creative Commons Attribution Licences.

immune responses. Third, the integration of phototherapy and immunotherapy achieves comprehensive tumor control by enabling primary tumor ablation, elimination of residual tumor cells, and suppression of metastatic lesions.[86,87]

How Oncolytic Virus Play A Role in Ant-Cancer Treatment?

Oncolytic virus (OVs) represents a novel class of anti-cancer agents that harness the natural or engineered ability of certain viruses to selectively target and destroy cancer cells. Unlike conventional therapies, OVs not only lyse tumor cells directly but also stimulate robust anti-tumor immune responses, thereby initiating a dual mechanism of action. These viruses can be either naturally occurring or genetically modified to enhance tumor specificity and therapeutic efficacy, while minimizing toxicity to normal tissues. OVs mainly includes herpes virus,[88] adenovirus,[89] measles virus,[90] vaccinia virus[91,92] and Newcastle disease virus.[93,94] Most viruses have been attenuated or genetically modified to increase their targeting and aggressiveness against tumors while reducing their toxicity to non-malignant cells.[95] OVs exert their antitumor effects through both direct and indirect mechanisms. They can directly infect, replicate within, and lyse cancer cells, leading to tumor cell destruction. Indirectly, OVs stimulate the immune system by promoting the release of tumor-associated antigens and pro-inflammatory signals, thereby enhancing antigen presentation and activating cytotoxic immune responses. This dual action contributes to the amplification and reinforcement of the cancer-immunity cycle, making OVT a powerful modality for both local tumor control and systemic anti-tumor immunity. Exposure to pathogen-associated molecular patterns (PAMPs), including viral capsids, DNA, and proteins, induces endoplasmic reticulum (ER) stress, which subsequently triggers various forms of immunogenic cell death. Concurrently, viral infection promotes tumor antigens release, recruiting antigen-presenting cells (APCs), such as dendritic cells and macrophages. Chemokines produced during viral infection, along with interferon, enhance the expression of MHC-I molecules, further promoting the recruitment of tumor-specific T cells. When combined with other immunotherapies, oncolytic viruses demonstrate significant therapeutic effects (Figure 4).[17] Specific T cells proliferate in the lymph nodes and then enter the bloodstream, where they search for both local and metastatic cancer cells, identifying them through the T cell receptor (TCR) on the tumor surface. After TCR-MHC engagement, OV-primed tumor-specific cytotoxic T lymphocytes (CTLs) execute potent tumor cell elimination through dual

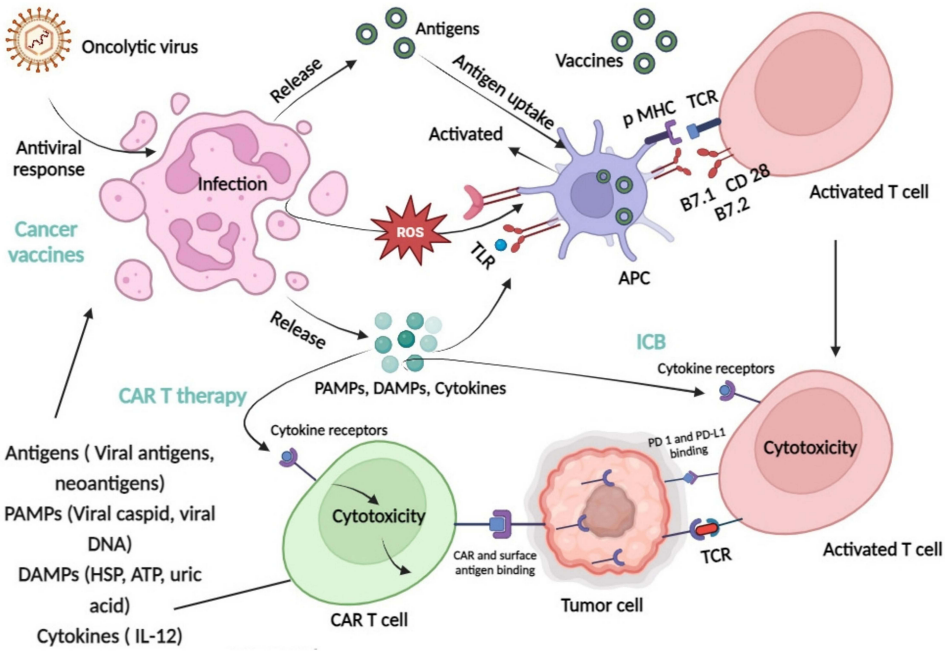


Figure 4 Oncolytic viruses in combination with immunotherapies. Reproduced from Chattopadhyay S, Hazra R, Mallick A, et al. A review exploring the fusion of oncolytic viruses and cancer immunotherapy: an innovative strategy in the realm of cancer treatment. Biochim Biophys Acta Rev Cancer. 2024;1879(4):189110.[17] Copyright 2024, Elsevier.

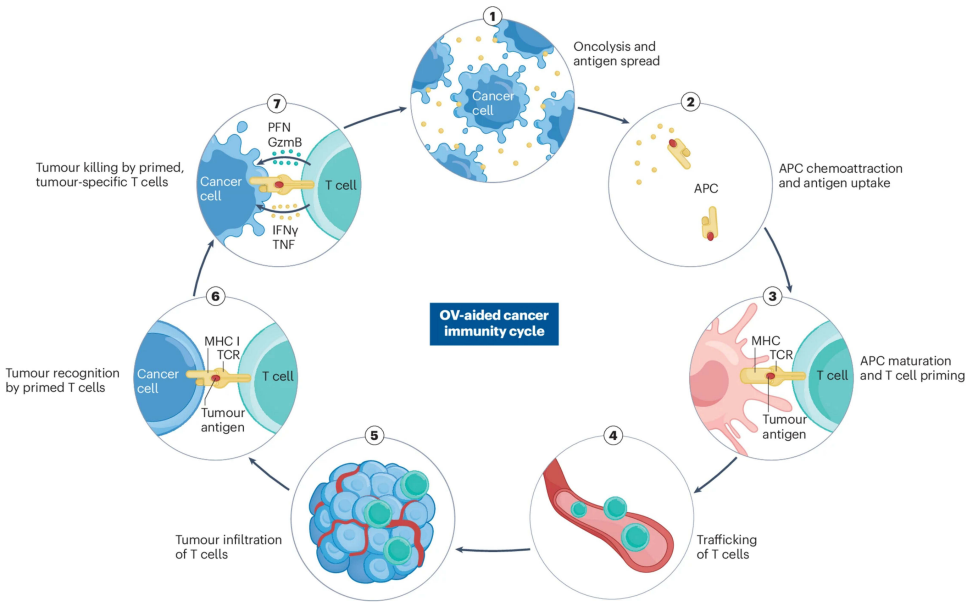


Figure 5 OV-aided cancer-immunity cycle. Reproduced from Gujar S, G PJ, Kumar V, et al. Tutorial: design, production and testing of oncolytic viruses for cancer immunotherapy. Nat Protoc. 2024;19(9):2540–2570.[96] Copyright 2024, Springer Nature.

mechanisms: direct cytotoxicity and immune system activation, thereby amplifying the cancer-immunity cycle (Figure 5).[96] Notably, during oncolytic virotherapy, interferon-mediated immunoregulatory effects may paradoxically induce the upregulation of immune checkpoint molecules on tumor cells, facilitating immune evasion. This mechanistic insight establishes a compelling rationale for combining oncolytic viruses with immune checkpoint blockade therapy to overcome tumor-mediated immunosuppression.[97]

Engineered oncolytic viruses can be tailored to improve tumor selectivity through deletion or modification of viral genes, enhancing replication in malignant cells, or incorporating functional transgenes into the viral genome.[98] These transgenes may encode immune-stimulatory molecules or therapeutic payloads that promote tumor cell death while eliciting robust and sustained antitumor immune responses.[16] Among various platforms, DNA viruses are widely favored due to their large genomic capacity and ability to support long-lasting transgene expression and immune activation. Additionally, engineered viruses carrying suicide genes can be precisely delivered to cancerous regions in response to tumor-specific promoters, thereby minimizing collateral damage to healthy cells. Through rational design promoter elements and gene switches, an optimal balance can be achieved among viral replication, transgene expression, and therapeutic dosage, ultimately ensuring efficient and targeted delivery of therapeutic payloads.[99]

However, the efficacy of virus as monotherapy remains limited due to restrictive biological barriers. Overcoming these key hurdles to OV functionality is a critical prerequisite for successful clinical translation. First, the tumor microenvironment imposes an intrinsic physical and physiological barrier that hinders the efficient penetration and distribution of OVs. Second, the host's innate and adaptive antiviral immune response rapidly recognize and eliminate OVs, limiting their replication and intratumoral spread. Furthermore, circulating neutralizing antibodies and hepatic clearance by the liver's immune surveillance systems significantly reduce the efficacy of systemic OV delivery, posing a major challenge to achieving sufficient viral accumulation at the tumor site.[100] To address these challenges, this study proposes several strategies. For instance, leveraging intrathecal delivery[101] can circumvent the tumor vascular basement membrane barrier. However, persistent physical constraints within the tumor microenvironment and vascular limitations remain significant hurdles. By modifying the viral surface through covalent and non-covalent assembly, electrostatic interactions,[102] surface glycosylation,[103] or the formation of a protein corona,[104] virus can be effectively shielded from immune recognition. In addition, "Trojan horse" strategies employing tumor cells or immune cells as carriers have been developed to exploit their natural tumor-homing abilities. These cell-based delivery systems can stealthily transport oncolytic viruses into the tumor microenvironment, thereby bypassing host immune surveillance and overcoming physical barriers to enhance intratumoral delivery and therapeutic efficacy.[105]

Synergistic Phototherapy and Virotherapy for Cancer: A Promising Approach?

As clinically emerging cancer therapies, both phototherapy and oncolytic virus therapy (OVT) exhibit unique therapeutic advantages yet face inherent limitations in practical implementation. OV monotherapy often encounters obstacles to the tumor microenvironment, including immunosuppression, hypoxia and restricted viral dissemination, all of which contribute to sub-optimal replication and therapeutic efficacy. Similarly, although phototherapy can furnish accurate and local tumor ablation, its limited tissue penetration makes it less effective for deep-seated tumors. Moreover, when applied as a standalone treatment, phototherapy fails to fully address the immunological and structural complexity of the tumor microenvironment. However, combining these two modalities can achieve synergistic effects and overcome their respective limitations. Phototherapy induces oxidative or thermal stress, increases tumor cell membrane permeability, and thereby facilitates the infection and replication of oncolytic viruses. In addition, it can trigger ICD and promote the release tumor-associated antigens to further enhance the efficacy of OVs by modulating the tumor microenvironment. Conversely, OVs selectively lyse tumor cells and reshape the immune landscape, thereby amplifying and prolonging the therapeutic benefits of phototherapy (Table 1). Therefore, the integration of phototherapy and oncolytic virotherapy not only combines physical and biological intervention, play a synergistic role, but also leverages both local and systemic anti-tumor responses, ultimately improving treatment precision and overall efficacy.

Fluorescence-Labeled Virus Assisted Optical Imaging-Cancer Diagnosis and Treatment

As a critical therapeutic modality for malignant tumors, surgical resection integrated with advanced medical imaging technology demonstrates significant advantages in the diagnosis, preoperative localization and treatment. However, conventional imaging modalities like magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound imaging struggle to provide real-time intraoperative monitoring.[107] Additionally, these methods remain inadequate for accurately distinguishing malignant tissues from adjacent non-malignant regions within tumor. Therefore, there is an urgent need to develop more direct and convenient approaches for "tumor visualization"[27] and tumor surgery navigation. In recent years, fluorescence-based imaging has emerged a powerful tool for cancer diagnosis and treatment. By tracking tumor cells distribution through multiplexed fluorescent labeling, this technology provides critical support for early cancer detection and targeted therapy. For invasive tumors with metastatic dissemination, conventional surgical approaches relying on visual inspection and standard resection often fail to achieve complete removal. Consequently, it is essential to accurately and comprehensively identify metastatic lesions, and delineate tumor margins to enable precise surgical resection.[24]

The GFP-labeled recombinant adenovirus system has been demonstrated to facilitate real-time intraoperative navigation with high efficiency.[26] The virus system uses the hTERT promoter, which is highly active in tumor cells. This promoter drives the expression of essential r viral replication genes. As a result, fluorescent proteins are selectively expressed in tumor tissues, and ultimately enables precise visualization and removal of tumor margins (Figure 6). Sentinel lymph nodes (SLNS) are often

Table 1 Summary of Combination Strategies Involving Phototherapy and OVs

Combination Strategy	Major Advantages	Main Limitations	References
Fluorescence-labeled virus +Optical imaging	Enables real-time virus tracking; improves tumor diagnosis	Limited tissue penetration; potential impact on viral function	[23,25,26]
OV+PDT/PTT	Synergistic tumor killing; induces immunogenic cell death	Light penetration and tumor hypoxia limit efficacy	[48,49]
OV as optogenetic tool carrier	Precise control of gene expression and immune activation	Complex design; early-stage clinical translation	[28–31,34,106]
Quasi-virus/VLPs +Phototherapy	Reduced antiviral immunity; co-delivery potential	Complex formulation; safety data limited	[51,54]
Phototherapy+OV: Immune synergy	Enhances antigen release, DC activation, T cell priming	Effect depends on tumor context; risk of immune overactivation	[57,60]

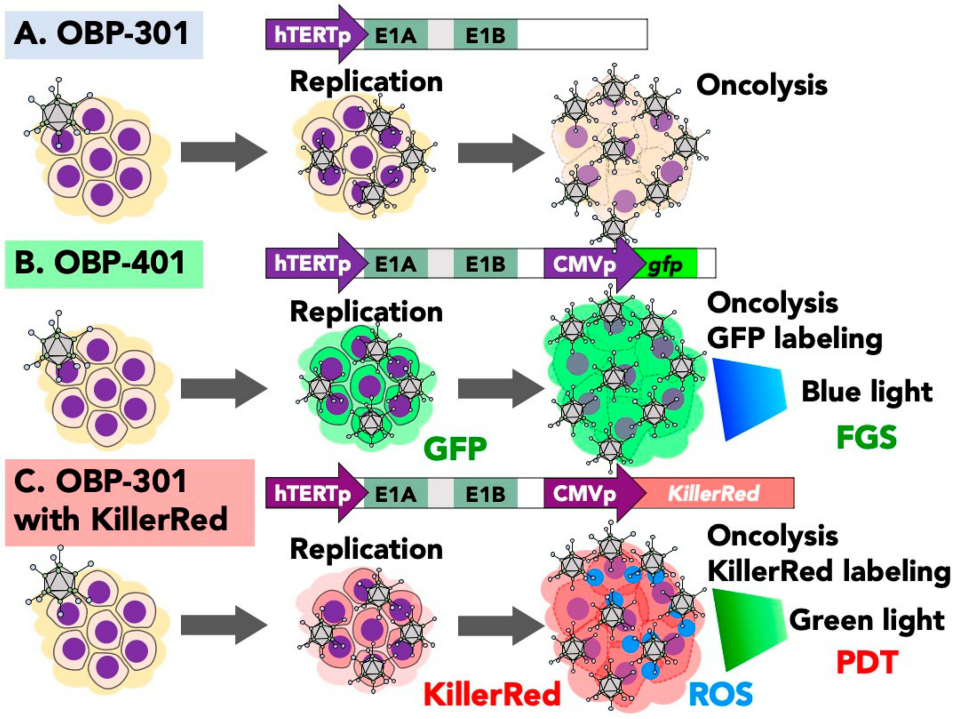


Figure 6 (**A**) OBP-301 replicates in cancer cells with high-end granase expression and induces cancer-specific cell death after replication. (**B**) OBP-401 preferentially tags cancer cells with GFP, killing them according to the multiplicity of infection. (**C**) OBP-301 containing KillerRed has the dual function of adenovirus-mediated killing of cancer cells and PDT. Reproduced from Yano S, Tazawa H, Kishimoto H, et al. Real-Time Fluorescence Image-Guided Oncolytic Virotherapy for Precise Cancer Treatment. Int J Mol Sci. 2021;22(2):879.[26]

the first site of metastasis in cancers such as breast cancer, head and neck cancer. Their detection plays a key role in cancer staging and prognosis. In this system, adenovirus express fluorescent proteins like GFP or Killer Red in SLNs. These fluorescent signals allow real-time monitoring of early metastasis. Even small metastases in SLNs can be directly visualized. This improves the accuracy of surgical navigation and resection.[23] Oncolytic virus exerts a triple function by directing lysing tumor cells, activating antitumor immunity. To achieve precise targeting of tumor tissues and sentinel lymph nodes, genetic engineering and covalent modification techniques have been employed to optimize the structure of adenovirus or conjugate targeting peptides, thereby enhancing delivery accuracy and therapeutic efficacy. Through efficient targeting, sensitive imaging techniques and real-time monitoring capabilities, fluorescently labeled oncolytic viruses can provide strong support for early diagnosis, accurate staging and personalized treatment of cancer. In addition, gene-induced melanin production following viral colonization enables photoacoustic imaging and MRI in deep tissues. Oncolytic virus strains engineered to overproduce melanin not only facilitate tumor visualization but also enhance subsequent oncolysis and tumor regression, offering a promising new avenue for cancer diagnosis and therapy.[25]

Photodynamic and Photothermal Synergistic Therapy with Oncolytic Virus

PDT and PTT have achieved remarkable efficacy in the treating superficial localized tumors, including skin cancer,[108,109] bladder cancer,[110] esophageal cancer,[111,112] and head and neck cancer.[33] However their clinical application for deeper-seated malignancies such as colorectal cancer, faces many challenges. One major limitation of PDT and PTT is the restricted tissue penetration of light. Since most photosensitizers are activated by visible or ultraviolet light, the limited penetration depth significantly compromises their therapeutic efficacy against deep-seated tumors. In addition, most current photosensitizers are organic molecules with conjugated π-bonds structures, which often exhibit poor water solubility and a tendency to aggregate. These properties result in suboptimal accumulation at the tumor site and reduced therapeutic effectiveness.[113] Moreover, tumor microenvironmental factors such as heterogeneity, hypoxia, and treatment resistance further hinder the overall efficacy of PDT and PTT. To address these limitations, various strategies have been

proposed to enhance the therapeutic efficacy of PDT, including increasing light intensity at the tumor site, developing novel excitation sources, and improving photosensitizer delivery efficiency.[114] However, these approaches alone remain insufficient to fully overcome the inherent challenges, particularly in the treatment of deep-seated tumors.

Under this background, OVs as novel tumor treatment strategies demonstrate potential for synergistic effects. Viral vectors can effectively deliver of genes, proteins and anticancer drugs to tumor sites.[115] When combined with PT, OV can not only enhance the accumulation of photosensitizers in the tumor area, but also further amplify local immune responses through their specific tropism for infecting and lysing tumor cells, thereby improving therapeutic outcomes. Furthermore, OV-mediated viral replication and tumor cell lysis overcome inherent limitations of phototherapy in treating deep-seated tumors, offering a promising approach to enhance the depth and efficacy of phototherapeutic interventions. Huang et al developed a novel therapeutic strategy leveraging the heat-resistant properties of vaccinia virus. By encapsulating a vaccinia virus loaded with the photosensitizer indocyanine green (ICG) within a platelet membrane, they constructed the PLTM-ICG-OVV (PIOVV) system. This platform exhibited strong photothermal conversion efficiency and excellent tumor-targeting capability, effectively inducing in vivo thermal ablation of tumors and subsequently activating antitumor immune responses. (Figure 7).[48] The application of exogenous excitation light is constrained by poor tissue penetration, particularly in deep-tumor therapy where its penetration depth often proves inadequate. In contrast, internally generated self-excited light (based on autofluorescence or chemical bioluminescence) operates independently of external sources.[116] This excitation process, triggered by intrinsic physical or chemical reactions, circumvents limitations imposed by external light penetration. Upon infecting tumor cells, OV@C catalyzes its luciferase substrate to produce bioluminescence. This endogenous light bypasses tissues barrier and scattering effects, uniformly "illuminating" the entire tumor tissue to activate the photosensitizer Ce6. This mechanism not only enables tumor lysis but also provides an efficient, tissue-penetrating light source for PDT, simultaneously achieving effective photosensitizer aggregation. Consequently,

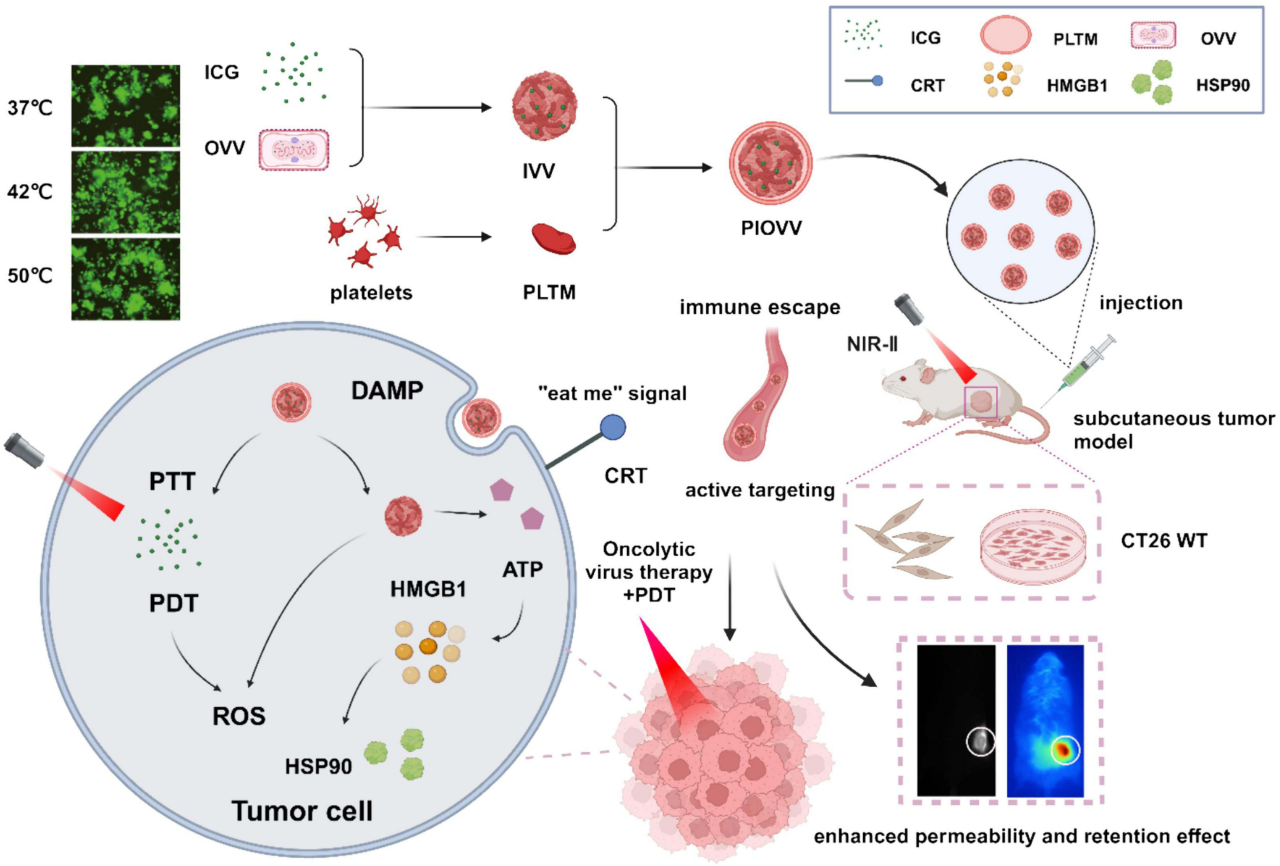


Figure 7 PIOVV nanoparticle complex for the treatment of colorectal cancer and its mechanism. Reproduced from Huang J, Ji L, Si J, et al. Platelet membrane-coated oncolytic vaccinia virus with indocyanine green for the second near-infrared imaging guided multi-modal therapy of colorectal cancer. J Colloid Interface Sci. 2024;671:216–231.[48] Copyright 2024,Elsevier.

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this approach significantly suppresses tumor growth and reverses the tumor immunosuppressive microenvironment.[49] Beyond enhancing the OV's therapeutic efficacy, this combination strategy also promotes rapid tumor cell death via localized PTT/PDT effects and activates the host immune system to reinforce tumor immune surveillance.

OVs as Delivery Vehicles for Optogenetic Therapy

OVs employ multiple strategies to regulate gene expression and control viral replication, thereby enhancing therapeutic efficacy while minimizing off-target effects on normal tissues. These strategies include the use of tumor-specific promoters,[28,117] CRISPR/Cas system,[118,119] microRNA-mediated regulation,[120] conditional promoters[121,122] and modulation by external immune signals.[123] Conditional promoters such as drug-induced and light-induced promoters are activated by external stimuli. By integrating photogenetic technology and photosensitive proteins,[124] the tumor selectivity of oncolytic viruses can be precisely controlled, allowing for targeted delivery and tumor-specific regulation of viral replication and gene expression (Figure 8).[106] For example, the CRISPR-Cas9 system can be activated by blue or infrared light to control the expression of multiple target genes can solve the problem of infinite replication of viral vectors, and improve the safety of cancer gene therapy while achieving obvious therapeutic effects.[29] In addition, precise control of viral replication and oncolytic activity is achieved by inserting reversible heterodimeric magnetin into the polymerase domain of monostatic viruses, such as measles and rabies viruses, and using blue light to activate the viral polymerase.[30] Although blue light has limited tissue penetration,[31] near-infrared light can reach deeper tissues. When combined with optogenetics and optical imaging, NIR light allows researchers to study biological processes in deep tissues using transgenic mice. It also expands photoacoustic tomography (PAT) to achieve high-resolution imaging at greater depths. (Figure 9).[34]

Optogenetic studies using adeno-associated viruses (AAV) have shown promising progress in several areas such as skeletal muscle contraction,[125] ganglion neurons,[35] gene transcription regulation,[32] and retinal degenerative diseases.[126] By introducing light-sensitive proteins or regulators into specific cells, combined with the efficient gene delivery of AAV and the precise spatiotemporal control of optogenetics, researchers are able to regulate cell activity, gene expression, and nerve signaling, which provides new ideas and possible solutions for neuroscience, gene therapy, and the study and treatment of retinal diseases.

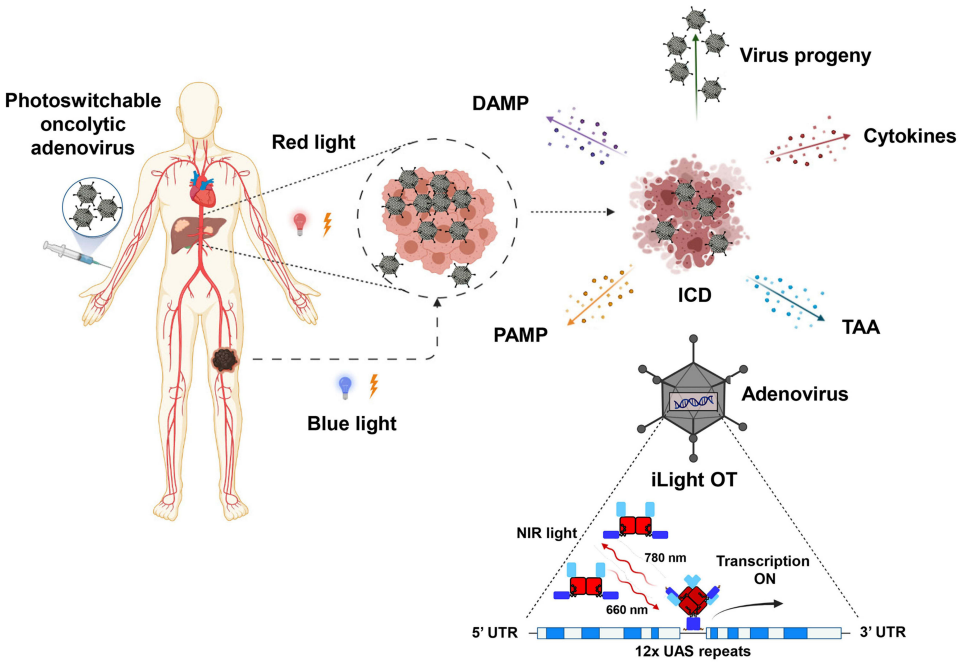

Figure 8 Schematic representation of modes of action of an optogenetic oncolytic adenovirus. Reproduced from Malogolovkin A, Egorov AD, Karabelsky A, et al. Optogenetic technologies in translational cancer research. Biotechnol Adv. 2022;60:108005..[106] Copyright 2022, Elsevier.

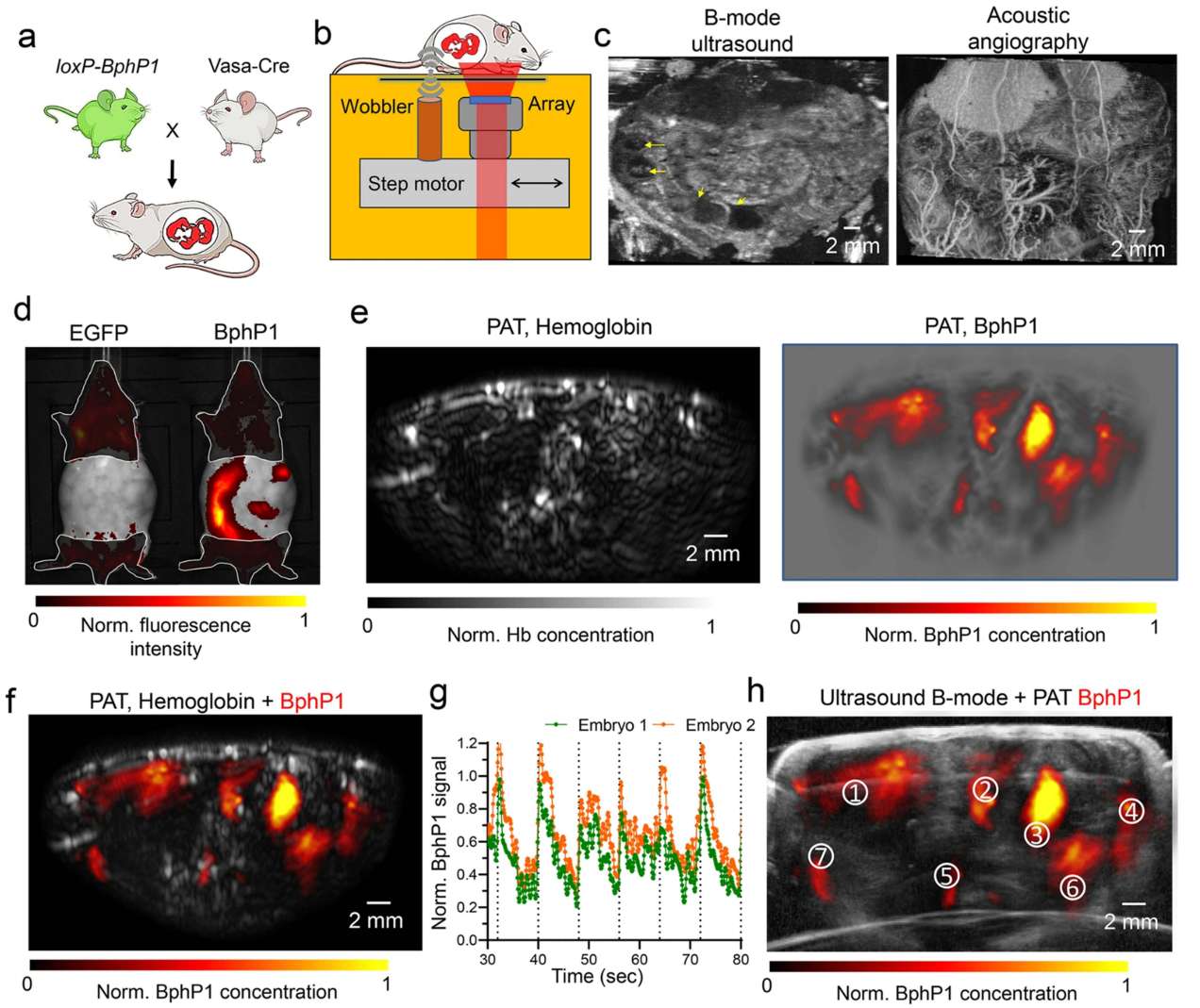

Figure 9 Non-invasive PA imaging of BphP1-expressing embryo in vivo. (**a**) Male LoxP-BphP1 mice were crossed with female Vasa-Cre mice, and the embryos all expressed BphP1. (**b**) Schematic diagram of PA and ultrasound imaging system: The linear ultrasound array and the focusing rocker share atranslation stage. (**c**) Ultrasound and angiography images of pregnant mice show multiple embryos at different depths. (**d**) IVIS images of pregnant mice showed the expressionof BphP1, but no EGFP signal. (**e**) PAT images of maternal organ hemoglobin and BphP1 signals of seven embryos. (**f**) Superimposed image of hemoglobin (gray) and BphPl (color) signals. (**g**) Verification of the photoswitching effect of BphP1 on two embryos. (**h**) Superimposed image of ultrasound (gray) and BphP1 embryo (color) signals. Reproduced from Kasatkina LA, Ma C, Matlashov ME, et al. Optogenetic manipulation and photoacoustic imaging using a near-infrared transgenic mouse model. Nat Commun. 2022;13(1):2813.[34] Copyright 2022, Nature Communication. Creative Commons Attribution 4.0.

Synergistic Effect of Biomimetic Virus or Viroid-Based Vectors and Phototherapy

On account of the complex tumor microenvironment, including abnormal vascular structure, physical barriers such as tumor matrix, hypoxic environment, immune escape and other factors, as well as the low permeability of drugs and heterogeneity, the delivery of nanomedical drugs in vivo faces challenges. To address this issue, researchers have designed temperature, PH[52] or enzyme-responsive[53] nanomaterials, or modified nanomaterial surfaces by coupling targeted peptides[50] to improve the delivery effect of nanomaterials. These strategies help optimize the chemical and physical properties of nanomaterials, thereby enhancing their targeting capability and adaptability within the tumor microenvironment. Consequently, they significantly promote drug accumulation and tissue permeability at tumor sites. Notably, natural viruses possess unique advantages for tumor targeting, as they can selectively infiltrate tumor tissues through specific receptor-mediated pathways or membrane fusion mechanisms. By mimicking the unique nanoscale spiky characteristics of viruses (such as adenovirus fibrin), we break through the traditional study of viral surface proteins

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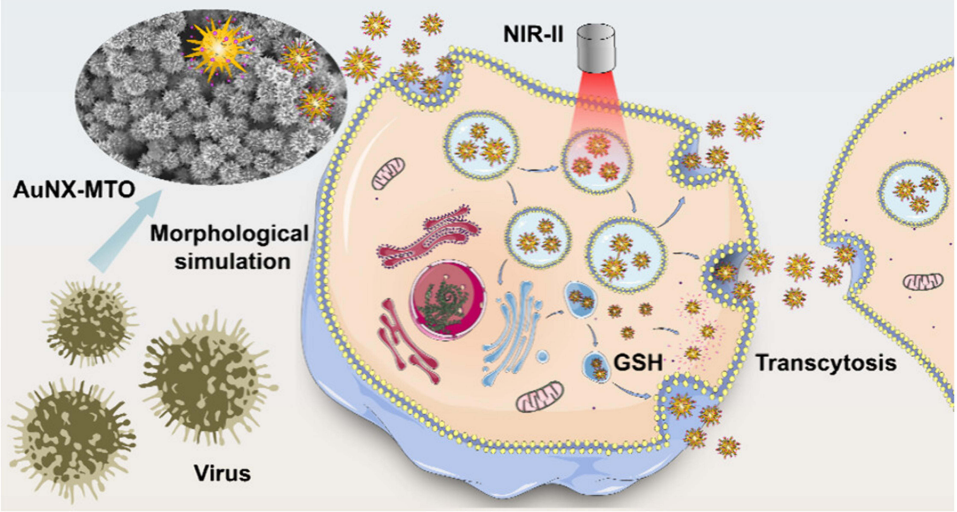

Figure 10 Interaction between virus-like AuNV-MTO particles and cancer cells. Reproduced from Wang Z, Su Q, Deng W, et al. Morphology-mediated tumor deep penetration for enhanced near infrared II photothermal and chemotherapy of colorectal cancer. ACS Nano. 2024;18(41):28038–28051.[54] Copyright 2024, American Chemistry Society.

and design virus-like spiky gold nanoparticles responsive to glutathione (GSH). These nanoparticles can enter cells through giant pinocytosis to achieve deep infiltration of tumor sites. Effective chemo photothermal therapy was achieved under the excitation of the near infrared second window (NIR-II) (Figure 10).[54] Viral glycoprotein is a key structural protein in the process of virus infection, which promotes virus adsorption and penetration by binding to receptors in host cells.[55] Vesicular stomatitis virus glycoprotein (VSV-G), as a membrane fusion protein, not only binds to receptors on the surface of host cells, but also delivers drug molecules coupled on the surface of cell membranes to the interior of cells by membrane fusion through surface modification and simulation of glycoprotein properties, thus increasing the therapeutic effect.[51] The combination of biomimetic virus or viroid-based vectors and phototherapy can achieve accurate drug delivery and tumor targeting accumulation through the unique receptor targeting of virus, membrane fusion ability and simulation of natural characteristics. The local photothermal and photodynamic effects of phototherapy further enhance the permeability and facilitate controlled drug release, and promote the local cumulative effect of tumor therapy. Simultaneously, this synergistic interaction activates the immune response, improves treatment effectiveness, and minimizes adverse effects on normal tissues, offering an efficient and safe cancer treatment strategy.

Immunosynergistic Mechanism of Phototherapy and OV

Phototherapy has been increasingly integrated with various immunotherapeutic approaches, including immune checkpoint inhibitors (ICB),[58] tumor vaccines,[59] and chimeric antigen receptor T-cell (CAR-T) therapies, to synergistically boost systemic anti-tumor immune responses. This has led to the emergence of photoimmunotherapy, a novel and promising paradigm in cancer treatment.[56,61] When combined with oncolytic virotherapy, phototherapy further amplifies antitumor immunity, establishing a powerful platform for combination therapy. Phototherapy not only augments the direct oncolytic effect of virus, but also enhances both local and systemic anti-tumor immune response through its immunostimulatory properties. For instance, in immunosuppressive cholangiocarcinoma, a novel tripartite oncolytic adenovirus platform integrating PDT, immunotherapy, and virotherapy has demonstrated synergistic efficacy. This system induces ICD, promotes the release of tumor-associated antigens, targets hypoxic factors, and modulates the PD-1/PD-L1 immune checkpoint pathway, collectively reversing the immunosuppressive tumor microenvironment and eliciting a robust anti-tumor immune response (Figure 11).[57] Following tail vein administration, p-Adv-CAT-KR demonstrated potent antitumor activity upon phototherapeutic activation. The PEG-PEI coating was confirmed to facilitate efficient lysosomal escape and tumor targeting, with no observable systemic toxicity during systemic administration (Figure 12).[57] Similarly, in colorectal cancer, an engineered oncolytic vaccinia virus expressing luminescent protein enables

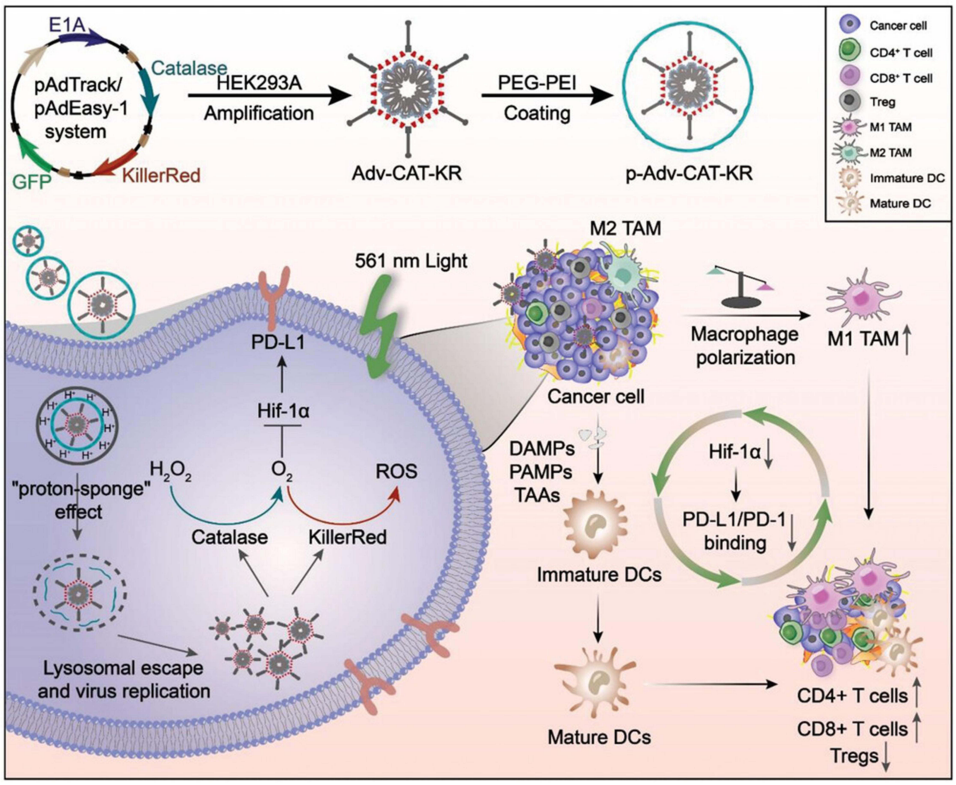

Figure 11 Schematic diagram of the three-in-one oncolytic system p-Adv-CAT-KR for cancer photodynamic immunotherapy. Reproduced from Wang J, Zhu Y, Chen Y, et al. Three-in-one oncolytic adenovirus system initiates a synergetic photodynamic immunotherapy in immune-suppressive cholangiocarcinoma. Small. 2023;19(34):e2207668.[57]

endogenous photodynamic therapy, eliminating reliance on external light sources. This approach not only ensures safe and effective photosensitizer delivery but also transforms immunologically "cold" tumors into "hot" ones by leveraging the immunostimulatory potential of the virus, thereby enhancing the anti-tumor immune response.[49] Moreover, nanoengineered oncolytic viruses have shown unique advantages in liver cancer therapy. Nanoparticle modification enhances viral targeting and photosensitivity, improves tumor-specific distribution, and optimizes photodynamic efficacy. By modulating the tumor microenvironment, this strategy magnifies the synergistic immune activation effects of virotherapy and PDT, significantly improving the therapeutic outcomes.[60] In summary, combining phototherapy with oncolytic virotherapy strengthens anti-tumor immunity, improves tumor microenvironment modulation, and enhances viral targeting and therapeutic efficacy. This integrated approach not only overcomes the limitations of conventional treatments but also markedly improves immune surveillance and tumor clearance.

The Future Prospective

Both phototherapy and virotherapy possess notable advantages but also exhibit inherent limitations when applied as monotherapies. Phototherapy, particularly PDT and PTT, is constrained by tumor-associated features such as hypoxia, dense stroma, and limited light penetration. Although oncolytic virotherapy demonstrates high tumor selectivity and immunostimulatory potential, its efficacy is often hampered by inefficient viral delivery, tumor immune evasion, and host antiviral responses. Combining phototherapy with virotherapy offers a promising strategy to overcome these limitations through synergistic mechanisms. Phototherapy can damage tumor vasculature, enhancing viral penetration and distribution, while virotherapy complements this by directly lysing tumor cells and initiating robust antitumor immune responses.

However, several challenges persist. Treatment synchronization is critical, as phototherapy requires precise control of light intensity and exposure duration, whereas virotherapy relies on time-dependent viral replication and immune

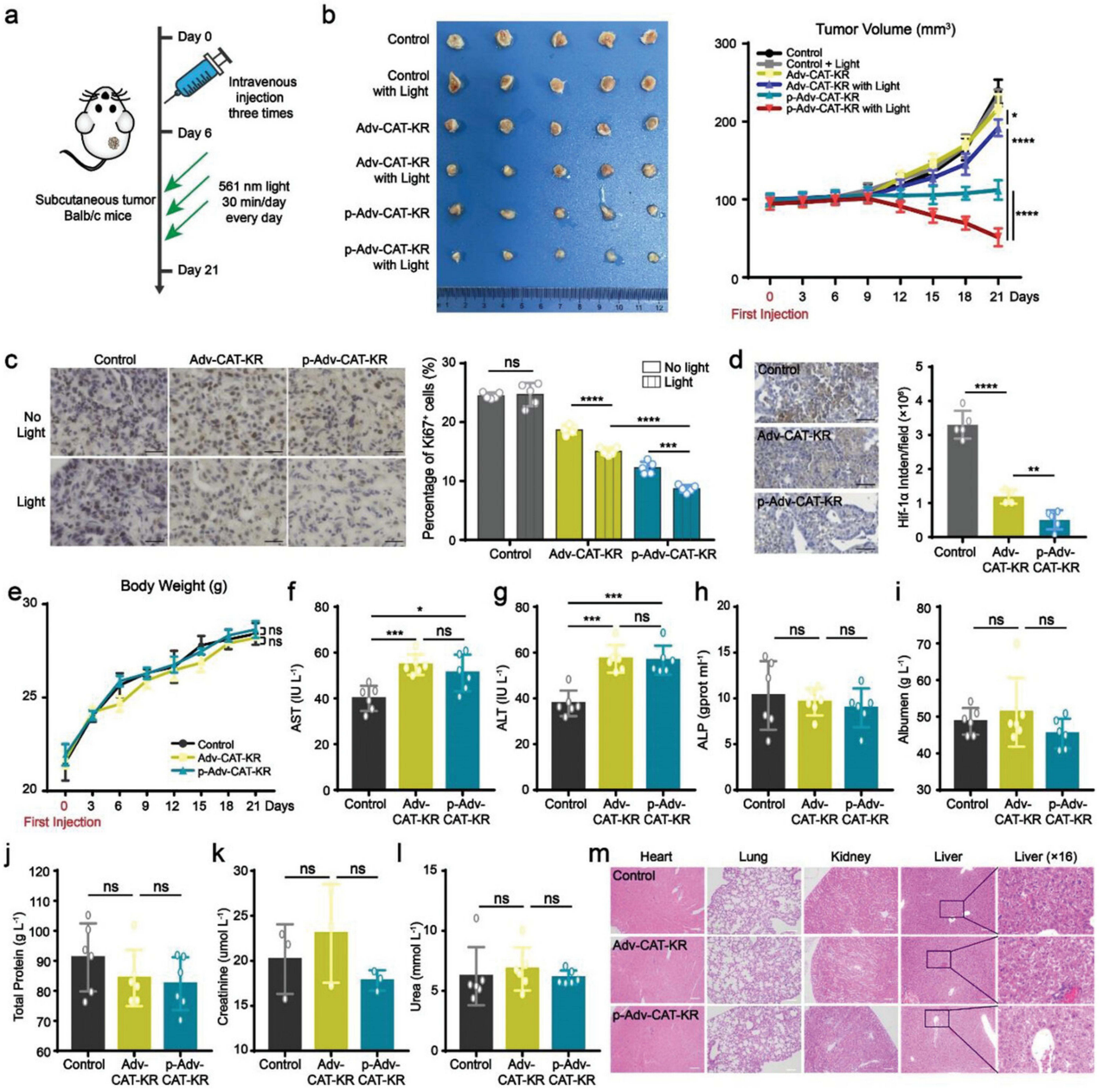

Figure 12 Evaluation of the in vivo therapeutic efficacy of the p-Adv-CAT-KR triple-functional oxygen self-supplying oncolytic adenovirus system. (**a**) Schematic diagram of the tumor regression experiment. (**b**) Tumor images and volume change curves of each group. (**c**) Tumor Hif-1α IHC and quantification. (**d**) Tumor Ki67 IHC and quantification. (**e**) Changes in body weight of mice in each group. (**f-j**) Liver biochemical indicators (ALT, AST, ALP, protein, TP). (**k-l**) Creatinine and urea levels. (**m**) H&E staining of the heart, lungs, kidneys and liver. Reproduced from Wang J, Zhu Y, Chen Y, et al. Three-in-one oncolytic adenovirus system initiates a synergetic photodynamic immunotherapy in immune-suppressive cholangiocarcinoma. Small. 2023;19(34):e2207668.[57] © 2023 Wiley-VCH GmbH.

activation Additionally, phototherapy may induce thermal injury and allergic reactions, while oncolytic virus can trigger local inflammation and systemic antiviral immunity. These combined effects may increase the risk of adverse effects, such as photo anaphylaxis and difficulties in viral dose management. Furthermore, tumor resistance remains a significant concern. Tumor cells may resist phototherapy via reduced uptake of photosensitizers, enhanced antioxidant defenses, and efficient DNA repair mechanisms. Similarly, resistance to OVs can arise from altered surface receptor expression, increased viral clearance, or activation of antiviral signaling pathways, reducing therapeutic efficacy and increasing unpredictability in treatment outcomes.

Despite these obstacles, the combined application of virotherapy and phototherapy has shown encouraging progress in preclinical research. Their integration enables precise tumor imaging and enhanced therapeutic response Optical imaging technologies facilitate real-time monitoring of the tumor microenvironment, offering valuable insights into treatment efficacy evaluation. The incorporation of optogenetic tools enables spatial and temporal control over viral replication and gene expression, offering potential in fields like gene therapy, neuroscience, and ophthalmology. Moreover, strategies involving biomimetic virus vectors combined with targeted phototherapy and light-controlled gene regulation are opening new avenues for cancer therapy. Coupled with nanotechnology and immunotherapy, these approaches enhance the precision and immunogenicity of tumor eradication. As personalized medicine and smart delivery systems continue to evolve, future efforts should focus on optimizing combination regimens tailored to individual tumor profiles, ultimately leading to safer and more effective treatments for cancer patients.

Data Availability Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed. All data referenced in this review are available in the cited publications.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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