

Near Infrared Photoimmunotherapy for Lung Cancer: Recent Development and Perspective

Ryu Okada^{1,3,*}, Mizuki Yamada^{1,3,4,*}, Mitsuo Sato^{1,4}, Kazuhide Sato^{1,3,5}

¹Graduate School of Medicine, Nagoya University, Nagoya, Japan; ²Research Unit for Life Sciences with Light Modulation, B3 Unit, Institute for Advanced Research, Nagoya University, Nagoya, Japan; ³Advanced Analytical and Diagnostic Imaging Center (AADIC) / Medical Engineering Unit (MEU), B3 Unit Frontier, Institute for Advanced Research, Nagoya University, Nagoya, Japan; ⁴Division of Host Defense Sciences, Department of Integrated Health Sciences, Graduate School of Medicine, Nagoya University, Nagoya, Japan; ⁵FOREST-Souhatsu, Japan Science and Technology Agency, Tokyo, Japan

*These authors contributed equally to this work

Correspondence: Kazuhide Sato, Graduate School of Medicine, Nagoya University, Nagoya, Aichi, 466-8550, Japan, Tel +81-052-744-2167, Fax +81-052-744-2176, Email sato.kazuhide.k5@mail.nagoya-u.ac.jp

Background: Lung cancer is the leading cause of cancer mortality worldwide, and despite advances in surgery, chemotherapy, radiotherapy, and immunotherapy, challenges persist due to off-target toxicity and limited specificity. Photodynamic therapy (PDT), a minimally invasive treatment using photosensitizers and light to induce ROS-mediated cell death, has been explored for early-stage lung cancer; however, its clinical utility remains limited by poor tissue penetration, nonspecific photosensitizer uptake, and oxygen dependence.

Discussion: Near-infrared photoimmunotherapy (NIR-PIT) is a highly specific cancer treatment that overcomes many limitations of conventional PDT. It employs antibody–photoabsorber conjugates, such as monoclonal antibodies linked to IRDye700DX, which bind selectively to cancer cell surface antigens and are activated by 690-nm NIR light. This illumination induces a unique, non-ROS-dependent cell death, “photochemosis”, marked by immediate physical disruption of cancer cell membranes. Beyond direct cytotoxicity, NIR-PIT elicits robust immunogenic cell death, promotes systemic antitumor immunity, and permits repeated treatment cycles without compromising safety. The air-rich lung environment and deep penetration of NIR light make lung cancer an ideal NIR-PIT candidate. Advances in light-delivery devices—including endoscopic catheters, flexible LED systems, and endovascular therapy—based technologies—have greatly improved the feasibility of targeting deep pulmonary lesions for clinical implementation. Moreover, the modular design of NIR-PIT allows adaptation to diverse tumor targets, including EGFR and components of the tumor micro-environment, broadening its applicability.

Conclusion: In this review, we provide a comprehensive overview of the mechanisms, advantages, and recent technological innovations of NIR-PIT, with a focus on its potential as a transformative therapeutic approach for lung cancer.

Keywords: near-infrared photoimmunotherapy, IR700, photo-chemical reaction, lung cancer, immunotherapy

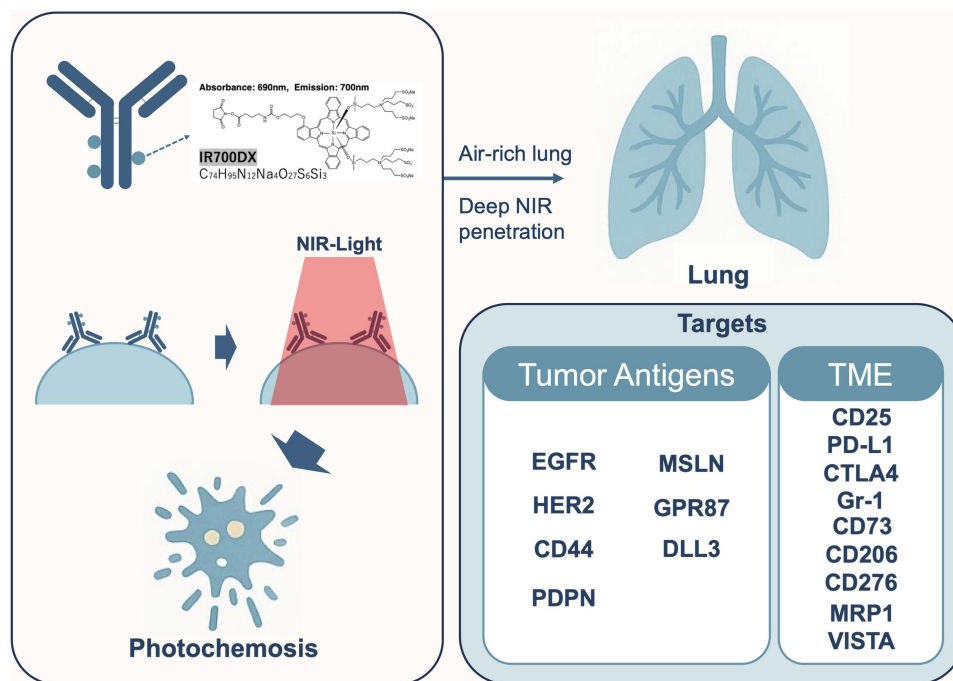
Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.^{1,2} Conventional treatments for lung cancer include surgery, anti-cancer drugs, radiation, and cancer immunotherapy; however, they are associated with challenges such as non-specificity, cytotoxicity against normal cells, and systemic side effects.

Phototherapy has been used as an alternative treatment for lung cancer. Conventional phototherapy, also known as photodynamic therapy (PDT), has been used to treat patients with minimally invasive lung cancer, especially those with early-stage central lung cancers.³ Although the relative prevalence of PDT as a treatment for lung cancer is low, many clinical studies have shown it to be an effective cancer treatment strategy that improves the quality of life and survival of patients with inoperable cancer.⁴

In this review, we summarize recent developments in near-infrared photoimmunotherapy (NIR-PIT) and discuss its potential application to lung cancer treatment. First, we outline the principles and limitations of conventional PDT, with

Graphical Abstract



particular attention to issues such as limited tumor selectivity, oxygen dependence, and insufficient light delivery to deep pulmonary lesions. We then describe the basic mechanism of NIR-PIT, including the design of antibody–photoabsorber conjugates, target-specific binding to cancer cell surface antigens, and NIR light–induced cancer cell death. In particular, we focus on the unique cell death mechanism of NIR-PIT, which differs from conventional ROS-dependent PDT and is characterized by rapid physical disruption of the plasma membrane.

We also review candidate molecular targets for NIR-PIT in lung cancer, including tumor-associated antigens such as EGFR, HER2, CEA, and other emerging targets, as well as components of the tumor microenvironment. Furthermore, we discuss the immunological consequences of NIR-PIT, including immunogenic cell death, activation of antitumor immunity, and the potential for combination with immune checkpoint inhibitors and other systemic therapies. Finally, we highlight recent advances in light-delivery technologies, including endoscopic, interstitial, flexible LED-based, and endovascular approaches, which may expand the clinical feasibility of NIR-PIT for both superficial and deep-seated lung tumors. Through this review, we aim to provide an integrated perspective on how NIR-PIT may overcome the limitations of existing phototherapies and contribute to the development of a more selective and effective therapeutic strategy for lung cancer.

Current Status and Limitations of Phototherapy for Lung Cancer (Conventional Photodynamic Therapy)

PDT is a noninvasive form of modern non-ionizing radiation therapy. This treatment is based on the local or systemic administration of a photosensitizing compound (PS), which preferentially accumulates in cancerous cells and tissues through active or passive mechanisms,⁵ in combination with activation by light of a single wavelength. Upon absorbing light of an appropriate wavelength, PS molecules initiate activation processes that generate reactive oxygen species (ROS), leading to the selective destruction of cancer cells.^{5,6} Free radicals are generated when a ground-state PS absorbs a photon and transitions into an excited singlet state. This singlet state subsequently undergoes intersystem crossing to form a triplet state that can interact with the surrounding molecules. The PS may abstract an electron from nearby

reducing molecules to produce ROS or interact directly with molecular oxygen to generate singlet oxygen.⁷ In this two-step process, the otherwise harmless PS is activated exclusively by light exposure, causing localized tissue destruction and significantly minimizing side effects. Organelles and cellular membranes can be directly damaged by PDT, depending on the type, concentration, and intracellular localization of the PS, as well as light fluence and spatial distribution of the radicals (Figure 1).⁸

While PDT has advantages over other therapies, such as being minimally invasive and having less impact on surrounding normal tissues owing to its target specificity and cancer tissue visualization, it has limitations when immediate results are required because of the need for a certain amount of time after drug administration, and the nonspecific uptake of PS into normal cells may cause undesirable side effects. It may also mediate the production of ROS, which may damage not only target cancer cells but also normal cells.^{6,9}

Therefore, phototherapy based on mechanisms other than ROS production is highly desirable.

NIR-PIT as a Novel Cancer Therapy

Conventional PDT uses a hydrophobic photosensitizer to pass through the lipid cell membrane, limiting its ability to selectively target and biodistribute drugs at the target site.^{10–12} Conventional PDT drugs conjugated to a target moiety have limited biodistribution because the target moiety is usually hydrophilic. Therefore, the PDT antibody conjugates may be less biocompatible. To overcome this problem, a hydrophilic photosensitizer is required. Moreover, absorption wavelengths ranging from 650 to 900 nm (ie, the biological window) would be ideal for penetrating biological tissues.¹³

In 2011, Hisataka Kobayashi et al developed NIR-PIT as a new phototherapy to overcome the challenges associated with conventional PDT.¹⁴ NIR-PIT, a novel cancer therapy, is a localized cancer therapy with dual selectivity for antibodies and light. The therapeutic agent consists of an antibody-photoabsorber conjugate (APC) that binds to the cell surface markers of cancer. In other words, this therapy can selectively kill cancer cells because of the cancer specificity of the monoclonal antibody and the photoabsorber IRDye700DX (IR700) bound to the antibody, which is activated with local NIR-light irradiation (Figure 2).¹⁵

Antibodies play a role in the target specificity of this therapy because they can bind specifically and stably to cell membrane surface molecules. More than 100 antibody drugs are currently approved in Japan, the US, and Europe.

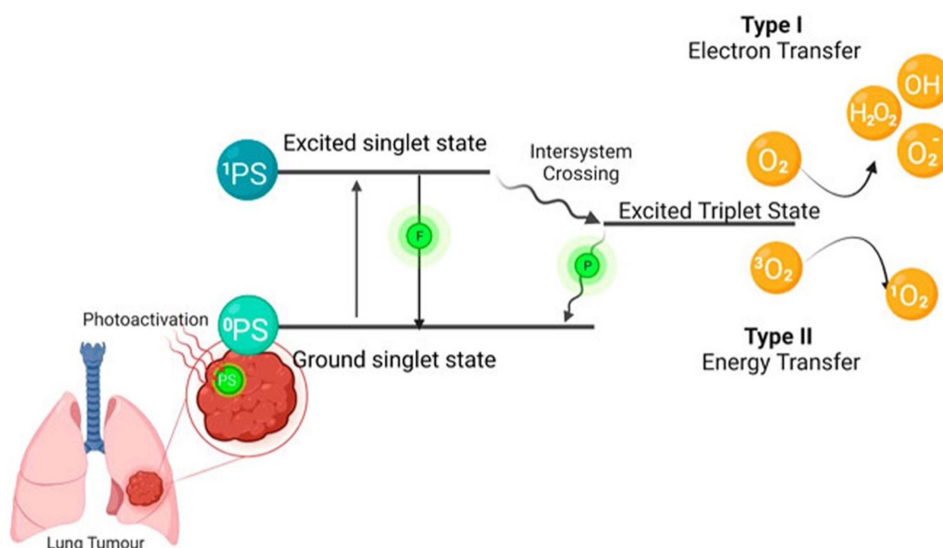


Figure 1 The mechanism of photodynamic therapy (PDT) The photosensitizer (PS) is absorbed when the PS is in its ground state. It goes into its first excited singlet state because of photoactivation. This state can be broken down by emitting fluorescence, or it can cross over to the more stable excited triplet state. Type I is when the PS in its excited triplet state reacts with biomolecules (such as lipids, proteins, and nucleic acids), and the radical mechanism is used to transfer hydrogen atoms. It generates free radicals and radical ions (the type of radical varies depending on the target molecule, such as lipids, proteins, or nucleic acids), which react with oxygen to produce reactive oxygen species. Type II reactions are based on a phenomenon known as triplet–triplet annihilation. In these reactions, the PS in its excited triplet state reacts with oxygen in its triplet ground state. This results in the formation of highly reactive and cytotoxic singlet oxygen. Reproduced from Crous and Abrahamse, 2022,⁸ *Frontiers in Pharmacology*, 13:932098, under the terms of the Creative Commons Attribution License (CC BY). No changes were made.

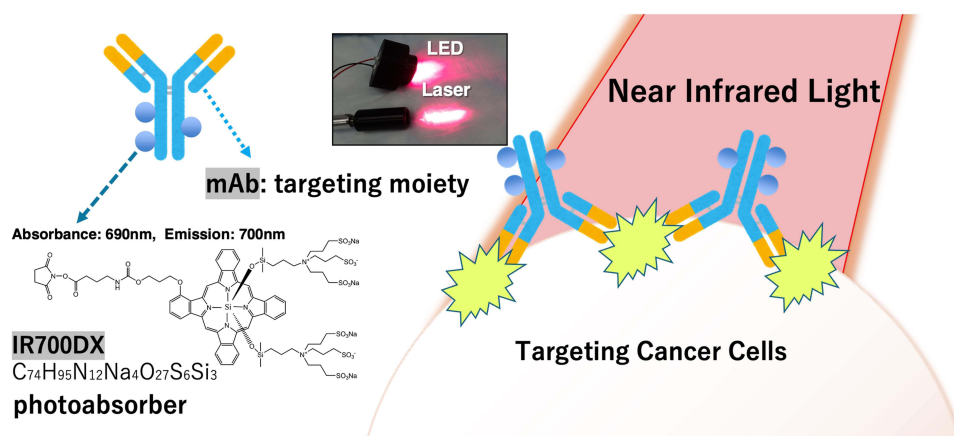


Figure 2 Scheme of NIR-PIT NIR-PIT is composed of antibody and photoabsorber, IR700DX. Monoclonal antibodies (mAbs) can target specific antigen on targeting cancer cells. IR700DX absorbs light with a peak wavelength of 690 nm and emits fluorescence at 700 nm. mAb-IR700 is a type of antibody-drug conjugate (ADC) and can be considered a photo-activated antibody-drug conjugate. It enables dual targeting with light and antibodies, making it a highly selective cancer therapy. NIR-PIT is a molecularly photo-targeted cancer therapy, which represents a next-generation anti-cancer treatment modality.

Recently, the development of various modified antibody drugs and antibody drugs for new therapeutic targets has been progressing in order to improve efficacy and safety.

Regarding light, which contributes to the selectivity of the treatment, NIR light at 690 nm was chosen because, unlike ultraviolet light, it efficiently induces photochemical reactions that damage the target cells through physical and chemical mechanisms without causing DNA damage. Furthermore, NIR light avoids the absorption spectrum of hemoglobin, which is abundant in the body, and allows sufficient light to penetrate relatively deep tissues. The silicon-phthalocyanine derivative IR700 was employed as a photosensitizer that absorbs NIR light, generates energy, and selectively damages cells bound by antibodies. In contrast, conventional a PS typically absorbs only visible light and exhibits limited tissue penetration.^{14,16,17}

PS is a crucial component that confers target specificity in phototherapy, and IR700, used in NIR-PIT, is a next-generation dye with numerous properties that are well suited for cancer therapy.¹⁶ IR700, as well as other phthalocyanine PS, has a large molar extinction coefficient, moderate quantum yield, and relatively good photochemical stability under natural light.¹⁴

A key advantage of IR700 is its hydrophilic properties resulting from specific chemical modifications. Unlike conventional hydrophobic PSs, IR700's hydrophilicity prevents aggregation or precipitation in buffered physiological solutions, even at high dye-to-protein ratios, making it more suitable for therapeutic drug formulations and applications. Additionally, while traditional hydrophobic PS-antibody conjugates tend to aggregate and accumulate in the liver for metabolism, hydrophilic IR700 remains evenly dispersed in the bloodstream and does not impair the tumor-targeting ability of the antibody or alter tissue distribution following intravenous administration. Furthermore, the mechanism of cell death in NIR-PIT is involved protein aggregation of the conjugates and cancer cell surface antigens, along with physical damage to the cell membrane caused by the photochemical reactions—referred to as “photochemosis”—that are triggered by NIR light exposure.^{18,19} This photochemosis-induced disruption of the plasma membrane, unlike the ROS-dependent apoptosis or delayed cell death observed in conventional PDT, is accompanied by a rapid collapse of osmotic balance and induce necrotic cell death within only a few minutes.²⁰ Therefore, there is no need for a therapeutic agent that is internalized or dependent on ROS. Thus, it is expected to overcome the challenges of conventional hydrophobic PS that hinder target selectivity and anti-tumor efficacy. The fact that IR700 is a hydrophilic photopigment without phototoxicity or biotoxicity also allows IR700 to dissociate from APCs by photoirradiation and be safely and rapidly excreted via urine.²¹

Third, IR700 can emit NIR fluorescence, facilitating fluorescent imaging of target tissues. This feature could facilitate more specific tumor irradiation and real-time monitoring of treatment progress by attenuating the IR700 fluorescence signals.²²

Thus, NIR-PIT facilitates highly precise cancer treatment with minimal damage to normal tissues by combining target-specific APCs with light irradiation limited to tumors.

A further important point is that, unlike conventional cancer therapies, photochemosis by NIR-PIT activates diverse tumor-specific immune responses without compromising host immunity against cancer. When cancer-specific antigens and danger signals at the time of membrane damage are rapidly released extracellularly by NIR-PIT, local dendritic cells are activated. The activated dendritic cells then activate and educate cancer-specific naïve T cells, which in turn cause the proliferation of newly primed CD8⁺ T cells and cell-mediated cancer cell death. This process is known as immunogenic cell death (ICD), and NIR-PIT could be an ideal method for inducing anti-tumor immunity.^{12,23} Furthermore, the number of NIR-PIT repeat treatments is not limited; therefore, multiple NIR-PIT sessions can help overcome these challenges.

An international Phase III clinical trial for locoregional recurrent head and neck squamous cell carcinoma (HNSCC) (LUZERA-301, NCT03769506) was initiated in 2018 and is ongoing. The trial was approved by the US Food and Drug Administration (FDA) and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) under Fast Track and SAKIGAKE, respectively.²⁴

Although clinical studies in head and neck cancer have provided important proof of concept for the feasibility of NIR-PIT in humans, these findings should be distinguished from the current status of NIR-PIT in lung cancer. At present, direct clinical evidence for NIR-PIT in lung cancer remains limited, and its potential application to lung cancer is supported mainly by preclinical studies and ongoing advances in light-delivery technologies. Further investigation is required to establish its efficacy and safety in lung cancer.

Mechanism of NIR-PIT

Oxidative stress, the primary mechanism of PDT, is thought to be cellular damage caused by oxidative stress agents such as free radicals and singlet oxygen (type I and type II).^{25,26} The energy difference between the photoexcitation and photoemission of PSs acts on mitochondria and other structures, mainly inside cells, leading to cell apoptosis.²⁷ This oxidative stress affects not only the target cells but also non-targeted adjacent cells.

By contrast, the mechanism of cell death induced by NIR-PIT is unique, termed “photochemosis” (Figure 3).¹⁸ When an antibody-photoabsorber (IR700) conjugate bound to a cancer cell surface antigen undergoes a photochemical reaction upon local near-infrared light irradiation, protein aggregation of the conjugates and the cancer cell surface antigen occurs,

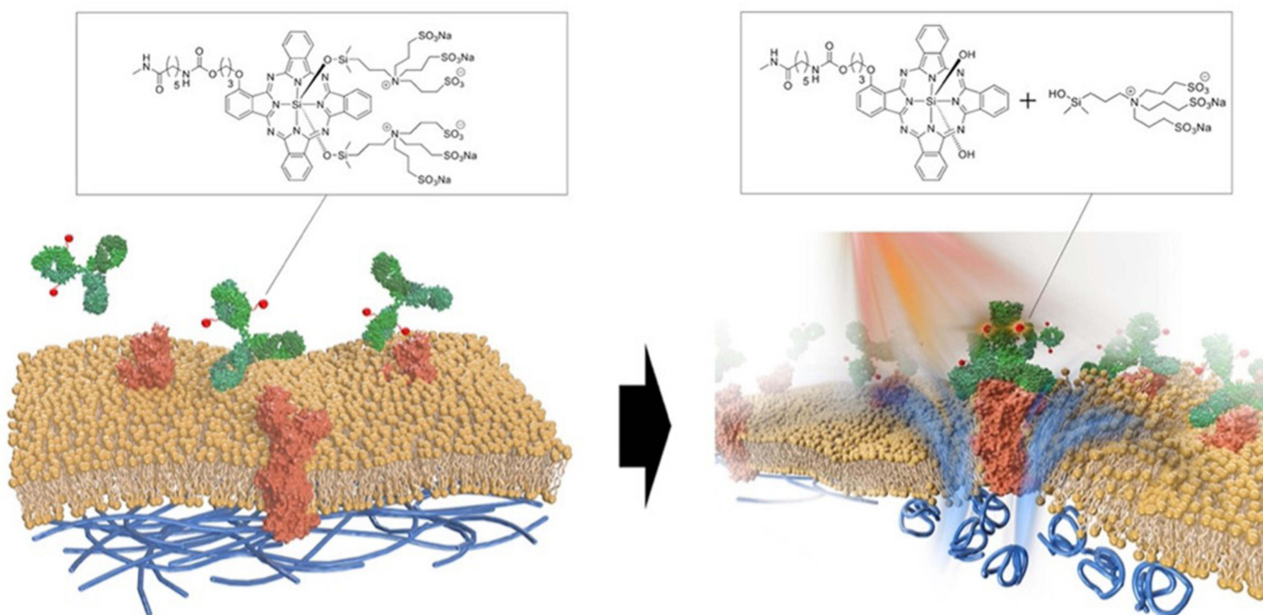


Figure 3 Scheme indicates the proposed mechanism of NIR-PIT. An antibody-IR700-antigen complex is formed on the cell membrane. With NIR light irradiation, the ligands of IR700 were released from the antibody-IR700-antigen complex. The physical changes in aggregation and solubility of the antibody-IR700-antigen complex may produce physical stress on the membrane locally impairing cellular membrane function for maintaining membrane pressure, and then the water outside of the cell was flown into the cell to burst the cell. Reproduced from the graphical abstract of Sato et al, *ACS Nano*, 2025,¹⁸ under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0). No changes were made.

which causes physical cell membrane damage. An influx of water into the cell causes an osmotic difference, which ruptures the cell and induces cell death, a mechanism that is very different from that of existing cancer therapies.¹⁹ This therapy shows rapid therapeutic effects with few side effects owing to its high target specificity.¹²

In NIR-PIT, the chemical properties of IR700 (hydrophilic) are rapidly changed to hydrophobic by the release of the silanol side chain under NIR light. The hydrophobic IR700 aggregates in an aqueous solution, resulting in the loss of IR700 fluorescence from the solution, which is a series of photochemical reactions. This hypothesis was proven using analytical chemistry and nano-in-liquid imaging.¹⁹

Furthermore, after PIT, damage-associated molecular patterns (DAMPs) are rapidly released to activate an anti-tumor immune response,²³ known as ICD, which makes NIR-PIT a promising approach for the treatment of distant metastases and heterogeneous tumors.

This mechanism can be proposed as a new light-induced cell-death mechanism that does not depend on oxygen and is completely different from the oxidative stress proposed in conventional phototherapy, establishing a theory that NIR-PIT has advantages as a new anti-cancer modality that is different from previous cell-death concepts.¹⁹

NIR-PIT as a Treatment for Lung Cancer (Tissue Characteristics of the Lung and Physical Properties of NIR)

The NIR light used in NIR-PIT is easily transmitted through air-filled tissues. Therefore, lungs with their high air content are suitable organs for NIR-PIT. In addition, NIR light in the 650–900 nm wavelength range is not readily absorbed by water or hemoglobin and exhibits maximum tissue penetration.²⁸ Therefore, the 690 nm wavelength used in NIR-PIT is considered suitable for human therapy and can be used for treatment without harming the body.

In addition, the lung can be said to be a relatively easy organ to access internally due to their high air content, but there have been challenges in delivering sufficient light to deep cancer cells. However, recent developments in NIR light delivery devices, such as needle catheters that can be inserted into deep tumors,²⁹ endoscopy, optical fiber-based techniques,^{30,31} and endovascular therapy-based catheter systems (endovascular therapy-based light illumination technology, ET-BLIT),³² are expected to be effective for deep cancer approaches.

Promising Therapeutic Targets for NIR-PIT in Lung Cancer

NIR-PIT can be used to alter the treatment pathway by creating mAb-IR700 using antibodies that target different ligands. Here, we summarize the promising therapeutic targets with a focus on NIR-PIT for lung cancer (Table 1).

Table 1 Potential Molecular Targets for NIR-PIT in Lung Cancer

Target	NSCLC	SCLC	References
EGFR	34-84%	Rare	[33–35]
HER2/ ERBB2	2-22%	Rareappen	[36,37]
CD44	50-70%	Rare	[38–40]
PDPN	< 73%	Usually negative	[41,42]
MSLN	25-55%	< 6%	[43]
GPR87	46-51%	37%	[30,44,45]
DLL3	< 49%	85%	[46,47]

Notes: All percentages reflect immunohistochemistry (IHC) positivity. Reported rates depend strongly on the antibody clone/platform, epitope retrieval, and scoring method (eg, any positive, intensity grade, % cutoff, H-score). Moreover, positivity also varies with cohort characteristics—histologic subtype (LUAD/LUSC/SCLC), ethnicity/region, disease stage, specimen type (resection vs biopsy), fixation/time-to-fixation, and prior therapy. The ranges shown are representative rather than universal. Consequently, values may vary across studies.

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor belonging to the erythroblastosis oncogene B (ErbB) family.^{48,49} EGFR overexpression has been observed in a variety of solid tumors, including lung cancers, especially squamous cell carcinoma,^{50,51} and is associated with poor prognosis in several tumor types.⁵²

Several preclinical studies have confirmed the therapeutic efficacy of EGFR-targeted NIR-PIT in several types of cancers, including lung cancer.^{53–56} Cetuximab-IR700, a chimeric IgG1 monoclonal antibody against EGFR, was first conditionally registered and conditionally approved for clinical use in recurrent head and neck cancer (HNC) clinical use in Japan in 2020.⁵⁷

HER2

HER2 is a membrane tyrosine kinase receptor and a member of the ErbB family along with EGFR.⁵⁸ Overexpression of Her2 is found in a variety of cancer cells, including breast,^{59,60} gastric,⁶¹ and esophageal cancers.⁶²

Her2-targeted NIR-PIT, including trastuzumab-IR700, has demonstrated therapeutic efficacy in several cancers, including lung metastases^{63,64} and non-small cell lung cancer (NSCLC) models.⁶⁵ Recent studies have shown that Her2-targeted NIR-PIT is more effective in CDDP chemoresistant small-cell lung cancer because chemotherapeutic agents, especially cisplatin-resistant (SBC-3/CDDP) cell lines, upregulate HER2 expression.⁶⁶

Moreover, a previous study demonstrated the induction of a cytotoxic photo-bystander effect resulting from the photo-triggered release of the drug from IR700-conjugated trastuzumab emtansine (T-DM1), T-DM1-IR700.⁶⁷

CD44

CD44 is a non-kinase transmembrane glycoprotein and a cancer stem cell marker that promotes tumor initiation and progression.^{68,69} CD44 overexpression is a poor prognostic factor in various types of cancer, including lung cancer.⁷⁰

Anti-CD44 monoclonal antibodies (mAbs) can play crucial roles in the regulation of cancer cell growth and progression. For instance, in acute myeloid leukemia (AML), a malignant clonal disorder characterized by the abnormal proliferation of immature myeloid cells, monoclonal antibodies such as H90 and A3D8 have been shown to induce cell differentiation by targeting and inhibiting the CD44 antigen. In addition to promoting differentiation of AML cell lines, these mAbs can inhibit cell proliferation and induce apoptosis.⁷¹ Moreover, CD44-targeting antibodies have been used to block lymphocyte migration, lymphohematopoiesis, and tumor metastasis.⁷² In a different study focused on lung diseases, treatment with anti-CD44 antibodies disrupted fibroblast adhesion to the substratum, thereby increasing the apoptosis of fibroblast cells.⁷³

A study using CD44-positive oral squamous cell carcinoma and breast cancer models confirmed the benefits of NIR-PIT.^{74,75} In addition, the combination of type 1 cytokines (short-term IL-15 administration) was shown to further enhance CD44-targeted NIR-PIT coupled with immune activation compared with monotherapy for lung tumors.⁷⁶

Podoplanin

Podoplanin (PDPN) is a mucin-type transmembrane glycoprotein expressed on the cell surface that plays an essential role in tumor progression and normal development of the lungs, kidneys, and lymphatic vasculature.⁷⁷

PDPN expression has been documented in a wide range of malignancies,^{78,79} including squamous cell carcinomas of the head and neck, lungs, uterus, oral cavity, and esophagus, as well as in malignant gliomas,^{80,81} mesotheliomas,⁸² bladder cancer,⁸³ osteosarcoma,⁸⁴ ovarian cancer,⁸⁵ and testicular tumors.⁸⁶

PDPN is expressed not only in tumor cells but also within the tumor stroma, including cancer-associated fibroblasts (CAFs). Increased PDPN expression in CAFs derived from lung,^{87–89} breast,⁹⁰ and pancreatic⁹¹ tumors is associated with greater tumor aggressiveness and poorer patient prognosis.⁷⁷

Several studies using malignant pleural mesothelioma (MPM) and pleural disseminated lung cancer models have demonstrated that NZ-1 antibody-based PDPN-targeted NIR-PIT has demonstrated therapeutic efficacy.⁹²

Mesothelin

Mesothelin (MSLN) is a glycoprotein that attaches to the plasma membrane via a glycosphosphatidylinositol (GPI) anchor. The *Mesothelin* gene encodes a 69-kDa precursor protein, which is cleaved into two parts: a 31-kDa secreted fragment known as megakaryocyte potentiating factor and a 40-kDa membrane-bound form referred to as MSLN.^{93,94} MSLN is largely absent in normal tissues and its expression is limited to the mesothelial cells of the peritoneum, pleura, and pericardium.⁹⁵ In contrast, it is highly expressed in a wide range of cancers, including nearly all cases of mesothelioma, and in a significant proportion of solid tumors, such as lung cancer (60–70%), pancreatic cancer (80–85%), cholangiocarcinoma (60–65%), ovarian cancer (60–65%), gastric cancer (50–55%), colon cancer (40–45%), breast cancer (25–30%), and endometrial cancer (20–25%).⁹⁶ Owing to its high prevalence in tumors, MSLN has emerged as a promising target for immunotherapy, and its soluble fragment is under investigation as a potential biomarker for cancer diagnosis.^{96,97}

Recently, a humanized non-region I antibody (hYP218) with a high binding affinity for the C-terminal region (residues 487–581) of mesothelin was developed. Promising results have been reported regarding the mesothelin-specific cytotoxic activity.⁹⁸

The hYP218-IR700 conjugate demonstrated strong efficacy in treating mesothelin-expressing tumors using NIR-PIT. In vitro, NIR-PIT with hYP218-IR700 induced rapid cell death, whereas in vivo, it significantly reduced tumor growth and improved survival outcomes. These findings suggest that hYP218-IR700 could serve as an effective platform for NIR-PIT targeting mesothelin-expressing tumors.⁹⁹

GPR87

GPR87 belongs to the G protein-coupled receptor (GPCRs).¹⁰⁰ GPR87 is generally expressed at very low levels in most normal human tissues, except in the prostate, placenta, and head and neck regions.^{78,79,101,102} However, markedly elevated levels of GPR87 have been observed in various malignancies, including squamous cell carcinomas of the lung, urinary bladder, cervix, testis, skin, and head and neck, as well as in lung adenocarcinomas and transitional cell carcinomas of the urinary bladder. Moreover, GPR87 expression is associated with clinical stage, disease recurrence, resistance to immunotherapy and chemotherapy, and reduced overall and progression-free survival in patients with lung cancer.^{102–106}

Studies in mouse models of transplanted lung adenocarcinoma, small cell lung cancer (SCLC), and MPM cell lines have confirmed the therapeutic efficacy of GPR87-targeted NIR-PIT.¹⁰⁷

Delta-Like Canonical NOTCH Ligand 3

Delta-like canonical Notch ligand 3 (DLL3), a single-pass transmembrane protein and member of the Notch ligand family, plays a role in cell signaling.^{108–110} Although it is predominantly expressed in neural and neuroendocrine tissues during embryonic development, its expression is minimal or absent in normal adult tissues. However, it is found on the surface of tumor cells.^{109,110} DLL3 expression is markedly elevated in glioblastoma, lower-grade glioma, skin cutaneous melanoma, tenosynovial giant cell tumors, and uterine carcinosarcoma compared to that in normal tissues. Additionally, high DLL3 expression has been linked to more aggressive diseases, indicating its potential role in promoting malignant phenotypes.^{46,111} DLL3 has also been detected in circulating tumor cells and blood of patients with cancer.^{112–115} Based on these findings, DLL3 is under investigation as a biomarker for cancer diagnosis and prognosis, as well as a therapeutic target.^{114,116} Its minimal expression in normal tissues relative to tumors makes it a promising candidate for targeted therapies designed to reduce off-target effects.

DLL3, a ligand for the Notch receptor, is a promising therapeutic target for SCLC and other neuroendocrine tumors. Rovalpitumab tesirin, the first antibody targeting DLL3, was discontinued in August 2019 after the TAHOE (NCT03061812) and MERU (NCT03033511) clinical trials yielded negative results.¹⁰⁹ However, a study using an SCLC xenograft model showed that rovalpituzumab demonstrated therapeutic efficacy against DLL3-targeted NIR-PIT.^{117,118}

Current Clinical Status of NIR-PIT in Lung Cancer

At present, NIR-PIT has not yet been established as a standard clinical treatment for lung cancer, and large-scale clinical trials specifically targeting lung cancer have not been completed. The most advanced clinical experience with NIR-PIT has been obtained in recurrent or unresectable head and neck cancer using cetuximab sarotalocan sodium, an EGFR-targeted antibody–photoabsorber conjugate. Therefore, the clinical evidence from head and neck cancer provides important proof of concept for the safety and feasibility of NIR-PIT in humans, but it should be clearly distinguished from the current developmental status of NIR-PIT in lung cancer. Although direct clinical evidence in lung cancer remains limited, accumulating animal model studies and advances in light-delivery devices provide a strong rationale for future clinical investigation. Further studies are required to identify optimal target antigens, select appropriate patient populations, establish safe and effective light-delivery methods, and evaluate combination strategies with chemotherapy, molecular targeted therapy, radiotherapy, or immune checkpoint inhibitors.

Therapeutic Targets of Non-Tumor Cells in the Tumor Microenvironment

In the TME, T and NK cells that recognize cancer cells are abundant; however, the presence of neighboring immunosuppressive cells serves as a mechanism to circumvent cytotoxic functions.¹¹⁹ Immune checkpoint molecules inhibit anti-tumor immune responses. Therefore, modulation of immunosuppressor cells or immune checkpoint molecules in the TME is an important step in enhancing the anti-tumor immune response and inhibiting tumor growth.¹²⁰ Here, we summarize the promising therapeutic targets for non-tumor cells in the TME (Table 2).

CD25

CD25 is an IL-2 receptor expressed on the surface of Tregs and is associated with the immunosuppression of effector T and NK cells at the tumor site. A high percentage of Tregs among tumor-infiltrating lymphocytes is associated with poor prognosis. In HNSCC, the extent of TME Treg infiltration is correlated with prognosis.^{143,144}

CD25-targeted NIR-PIT selectively eradicated Tregs in the TME without eliminating local effector T cells or Tregs present in other organs, and induced tumor regression, resulting in the rapid activation of CD8+ T cells and NK cells. Furthermore, this effect was observed in non-irradiated, distant, and untreated tumors, confirming the abscopal effect.¹⁴⁵

Table 2 Potential Molecular Targets for NIR-PIT in the Lung Cancer Tumor Microenvironment

Target	NSCLC	SCLC	References
CD25	94%	Rare	[121–123]
PD-L1	34–70%	< 83%	[124–126]
CTLA4	50–78%	72–90%	[126–129]
Gr-1	-	-	[130,131]
CD73	10%	Rare	[132,133]
CD206	-	-	[134,135]
CD276	60–80%	60–70%	[136,137]
MRP1	50–87%	52%	[138–140]
VISTA	21%	Rare	[141,142]

Notes: All percentages indicate immunohistochemistry (IHC) positivity. Reported expression frequencies are highly influenced by methodological variables—including antibody clone/platform, epitope retrieval, and scoring criteria (eg, any positive, intensity grade, % cutoff, H-score). Positivity rates also differ among study cohorts depending on histologic subtype (LUAD/LUSC/SCLC), ethnicity/region, disease stage, specimen type (resection vs biopsy), fixation conditions, and prior treatment history. The shown ranges represent typical rather than universal values; actual frequencies may vary across reports. Only dash (“–”) entries indicate not reported, not applicable, or very low/rare in the referenced cohorts.

In addition, repeated depletion of Tregs, anti-CD25-F(ab')₂NIR-PIT, which is characterized by rapid clearance while avoiding Fc-mediated ADCC and complement-dependent cytotoxicity (CDC),¹⁴⁶ and CD25-targeted NIR-PIT in combination with CD44- or hEGFR-targeted NIR-PIT¹⁴⁷ showed better therapeutic efficacy.

Programmed Death Ligand 1

Programmed death ligand 1 (PD-L1) is a transmembrane protein and an immune checkpoint protein that binds to PD-1 expressed on tumor-infiltrating lymphocytes and induces immune tolerance in tumor cells by reducing immune response cytokines.^{148,149} Overexpression in many cancer cells, including lung cancer cells, is associated with poor prognosis.^{150–153}

Two anti-PD-L1 antibodies, atezolizumab and durvalumab, have been approved by the European Medicines Agency (EMA) and the US FDA for the treatment of advanced NSCLC.¹⁵⁴

PD-L1-targeted NIR-PIT promotes rupture of PD-L1-positive cells. Furthermore, by inhibiting tumor immunosuppressive pathways, it activates CD8⁺ T cells and NK cells in the TME, resulting in enhanced anti-tumor immunity.^{155,156} Enhanced anti-tumor effects have been observed in various major types of models, including mouse models of lung cancer, whereas in vitro studies on cytotoxic effects are limited.^{157,158}

Cytotoxic T-Lymphocyte-Associated Protein 4

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is an immune checkpoint molecule primarily expressed on activated T lymphocytes and regulatory T cells (Tregs), where it inhibits T cell activation.^{159–162} Ipilimumab, an anti-CTLA4 antibody, was among the first immune checkpoint inhibitors developed for clinical use; it binds to CTLA4 on T cells, blocking its inhibitory function, and thereby enhancing T cell activation and anti-tumor responses.^{163,164}

Local depletion of CTLA4-expressing Tregs by NIR-PIT is a promising anti-tumor therapy that promotes CD8⁺ T cell activation and infiltration in the TME. Furthermore, the combination with cancer cell-targeted NIR-PIT showed better therapeutic efficacy.^{165,166}

Gr-1

Gr-1, together with CD11b, is a widely characterized target of murine myeloid-derived suppressor cells (MDSCs), with two major cell subsets: granulocytic MDSCs (PMN-MDSCs, CD11b+Ly6ClowLy6G⁺) and monocytic MDSCs (M-MDSCs, CD11b+Ly6ChighLy6G⁻).^{167,168} MDSCs, such as Tregs and tumor-associated macrophages (TAMs), are immunosuppressive cells that act as a suppressive time component to attenuate the immune response^{169,170} and are of increasing interest because of their role in the prognosis, development, and therapy of lung cancer.^{171–173}

Gr-1-targeted NIR-PIT has been used to eliminate splenic MDSCs, suggesting the potential of eliminating MDSCs from tumors to reduce immunosuppression.

CD73

CD73, also known as extracellular 5'-nucleotidase, is a ribonucleotidase encoded by the NT5E gene. Predominantly anchored to the cell membrane via GPI, CD73 catalyzes the conversion of extracellular adenosine monophosphate (AMP) into adenosine and inorganic phosphate.^{174,175} A soluble form of CD73 also exists that retains functional properties partially similar to those of its membrane-bound counterpart.^{176–178}

Overexpression of CD73 in cancer cells leads to increased adenosine levels, whereas tumor-driven proliferation creates a hypoxic environment that causes normal cell lysis and ATP release, which is subsequently converted to adenosine via the CD39/CD73 axis, promoting immune evasion and facilitating cancer metastasis, persistence, and proliferation.¹⁷⁹

In lung adenocarcinoma and NSCLC, CD73 expression is associated with increased PD-L1 levels and increased infiltration of tumor-associated immune cells, thereby promoting an immunosuppressive TME.^{180–186}

CD73 has emerged as a promising therapeutic target for various cancers, including breast and lung cancers.^{187–189} In breast cancer, CD73 promotes local invasion via the epidermal growth factor (EGF)/EGF receptor signaling pathway.^{190–192}

Moreover, studies on glioblastoma have shown that, although treatment can elevate CD73 expression, its depletion significantly improves survival,^{193–196} offering valuable insights into future anti-CD73 therapeutic strategies.

CD73-targeted NIR-PIT simultaneously eliminates tumor cells and key immunosuppressor cells.^{16,197}

CD206

CD206 is a highly specific marker of M2 macrophages that lack intracellular signaling domains¹⁹⁸ and is primarily regarded as an endocytic receptor involved in the internalization of extracellular substances for clearance or antigen presentation.¹⁹⁹ Recent studies have suggested that CD206 also plays an active role in the immune response by directly modulating the activity of other immune cells,²⁰⁰ although the relationship between CD206 expression and tumor metastasis remains controversial owing to conflicting findings.^{201,202}

M2 macrophage polarization promotes metastasis in various malignancies, including colorectal, pancreatic, and gastric cancers.^{203–205} In NSCLC, M2 TAMs facilitate the proliferation and migration of cancer cells.^{206,207} An increased number of M2 TAMs is associated with metastasis and poor prognosis in patients with SCLC.²⁰⁸ Moreover, macrophages in the lungs of the SCLC mouse transplant models predominantly exhibited the M2 phenotype, indicating their potential immunosuppressive role in facilitating SCLC invasion.²⁰⁸

TAM-targeted NIR-PIT using anti-CD206 antibodies demonstrated therapeutic efficacy and inhibited lung metastasis in a mouse model of breast cancer.²⁰⁹

CD276

CD276 is a type I transmembrane protein expressed in many tissues and cell types and has been implicated in the regulation of T cell-mediated immune responses by functioning as both a T cell co-stimulator and co-inhibitor.²¹⁰ It is overexpressed in a wide range of human solid tumors, has been implicated in cancer progression and metastasis, and has been investigated as a potential target for cancer immunotherapy.^{211,212}

NIR-PIT with IR700- α CD276/Fab significantly inhibited subcutaneous 4T1 tumor growth and lung metastasis. In addition, it caused in vivo anti-tumor immunity. Combined with an anti-PD-1/PD-L1 blockade, it significantly inhibited tumor growth and prevented lung metastasis by recruiting CD8⁺ T cells for tumor infiltration.²¹³ It could be argued that local and systemic anti-tumor responses, both by CD276 targeted therapy for local immunomodulation and combination therapy with PD-L1/PD-1 axis inhibition, may be promising strategies for eliminating primary tumors and disseminated metastases in NIR-PIT.

Multidrug Resistance-Associated Protein 1

Multidrug resistance-associated protein 1 (MRP1) encodes plasma membrane proteins that perform distinct and essential physiological transport functions and actively export various xenobiotics and their metabolites (including both hydrophobic and hydrophilic antineoplastic agents) against their concentration gradients (drug threshold). MRP1 can transport a wide range of substrates.^{214,215} MRP1 is overexpressed in leukemia, esophageal cancer, and NSCLC.²¹⁶

MRP1 contributes to the resistance to several chemotherapeutic agents, including anthracyclines (eg, doxorubicin), vinca alkaloids, podophyllotoxins, mitoxantrone, methotrexate, and alkylating agents.²¹⁷ It also recognizes and effluxes newer targeted anti-cancer agents that alter tumor growth, proliferation, and metastatic signaling pathways. One such targeted agent is vandetanib, a small-molecule TKI that blocks the ATP-binding domains of ABC drug transporters. However, the exact mechanism remains unclear.²¹⁸ Other targeted therapies targeting MRP1 include geldanamycin, the farnesyl protein transferase inhibitor lonafarnib, and nutlin-3.^{218–221} Additionally, MRP1 has been implicated in various physiological and pathophysiological processes, such as inflammatory responses, oxidative defense mechanisms, and the pathogenesis and prognosis of cancer.^{222,223} Leukotriene C4 (LTC4), a pro-inflammatory product of arachidonic acid involved in asthmatic and allergic reactions as well as smooth muscle constriction, is a key physiological substrate of MRP1.^{224,225}

Recent studies by Li et al have demonstrated that Mab-IR700, an anti-MRP1 antibody, exerts a strong modulatory effect on H69AR cells. NIR-PIT with an anti-MRP1 antibody (Mab)-IR700 conjugate (Mab-IR700) exhibited therapeutic efficacy, suggesting its potential of MRP1 as a new target for the treatment of drug-resistant SCLC.²²⁶

V-Domain Immunoglobulin Suppresses T Cell Activation

The V-domain immunoglobulin suppressor of T cell activation (VISTA),²²⁷ also referred to as Dies1,²²⁸ GI24,²²⁹ PD-1H,²³⁰ or DD1alpha,²³¹ is a newly identified member of the B7 family that has gained attention as a promising target for combination cancer immunotherapy.²³² Initially, VISTA was described by two research groups in the context of embryonic development and tumor invasion.^{228,229} Subsequent studies have primarily focused on the role of VISTA in the regulation of immune responses.^{230,233–235} VISTA, a protein encoded by the B7/CD28 immunomodulatory gene family, is expressed on antigen-presenting cells and exerts an inhibitory effect on T cell activity. In mouse models, the blockade of VISTA exacerbated the progression of T cell-mediated autoimmune diseases, whereas the agonistic antibody MH5A, targeting VISTA (PD-1H), was shown to suppress graft-versus-host disease (GvHD).^{227,230}

In addition to its role as an immune receptor on T cells, VISTA can function as a ligand on antigen-presenting cells or tumor cells, triggering immune regulatory activities. Several studies on human cancers have shown that VISTA is expressed in melanoma, NSCLC, ovarian cancer, endometrial cancer, malignant pleural epithelial mesothelioma, and various other tumors or tumor cell lines.^{236–239}

In a study on NSCLC, the VISTA protein was found in most samples, with expression observed in 21% of tumor cells and 98% of stromal cells.¹⁴¹ The proteins displayed membrane and cytoplasmic staining. Similarly, other studies have demonstrated that VISTA is highly expressed in the lymphocytes of lung squamous cell carcinoma and adenocarcinoma.^{240–242} VISTA expression positively correlated with the PD-1 axis, CD8+ T cells, and CD68+ macrophages. In lung adenocarcinoma, an increase in VISTA expression within stromal cells was significantly associated with the absence of EGFR mutations, whereas higher VISTA expression in tumor areas correlated with improved 5-year survival rates.¹⁴¹ Conversely, other studies have reported that high VISTA expression in tumor-associated immune cells is associated with poor survival outcomes and increased mortality.^{241,242}

Animal model studies have demonstrated that dual inhibition of VISTA and PD-L1 significantly suppresses the growth of B16BL6 melanoma tumors, whereas treatment with a single monoclonal antibody is largely ineffective.²⁴³

VISTA-targeted NIR-PIT using two mouse tumor models, MC38-luc (colon cancer) and LL2-luc (lung adenoma), showed that the TME effectively treated tumors by locally reducing the number of VISTA-expressing immunosuppressor cells.²⁴⁴

NIR Light Delivery Device for Pulmonary NIR-PIT

For effective NIR-PIT, irradiation of the target tissue with NIR light is critical; the depth of penetration of NIR light into the tissue is approximately 2–3 cm from the surface and attenuates significantly with increasing distance. Accurate irradiation with NIR light is necessary to produce effects on therapeutic targets without adversely affecting normal tissues, even in deep areas, such as the lungs. Here, we summarize the information on light irradiation to enable localized NIR-PIT for lung cancer and highlight the development of a variety of new devices.

The first is a needle catheter that allows the introduction of a tissue irradiation diffuser into the tissue for intra-tissue therapy. Fiber-optic diffusers placed in needle catheters can be inserted into deep tumors; this technique has been used in clinical practice.²⁹

Another option is to administer NIR light endoscopically. In respiratory diseases, optical fibers are utilized through bronchoscopes to deliver NIR light to critical areas. Modern bronchoscopic techniques deliver NIR light to any intrapulmonary lesion. This bronchoscopic technique can be navigated using a 3D navigation system based on previous CT images to precisely guide the fiber to the tumor in the lung, thereby minimizing damage to the normal lung field.³⁰

More recently, a new catheter with LEDs was developed to remedy the problems of conventional devices, which risk twisting during deep insertion. The new catheter with LEDs mounted on a flexible printed circuit board is flexible, does not twist, and allows for deep insertion and irradiation using an endoscope or guidewire. It also has a temperature sensor to prevent thermal injury. Tests on mice with cholangiocarcinoma xenografts demonstrate the effectiveness of this new device.³¹

However, attention should be paid to the risk of thermal injury caused by light irradiation. According to the report by Okuyama et al, thermal damage with skin burns was observed in NIR-PIT when the power density of light exceeded 600 mW/cm². In contrast, it was demonstrated that cooling the irradiation surface with air, or lowering the power density while extending the irradiation time to maintain the total energy, could prevent thermal injury while preserving

therapeutic efficacy.²⁴⁵ This finding provides important implications for the safe design of various devices, including LED-mounted catheters and wireless LEDs.

Other developments include ET-BLIT, which delivers light deep into the body. The ET-BLIT catheter system consists of a catheter tip with a transparent distal end attached to a thermocouple head that can fit multiple vessels and a distal portion with a light-emitting function, which consists of two distinctive components: (i) a tip-partially transparent catheter with a transparent distal end connected to a thermocouple head, with an outer diameter of approximately 1–5 mm to accommodate multiple vessels, and (ii) a light diffuser equipped with a luminescent function at its distal portion. Once the catheter is navigated to the target lesion using the guidewire, the light diffuser is introduced into the lumen of the tip-partially transparent catheter. To confirm light emission, the catheter allows manual adjustment by rotating the light diffuser toward the lesion. The basic procedure of this system is comparable to that of existing endovascular therapies and is a promising way to bring light anywhere in the body for clinical use. In addition, tests in animal models have proven the effectiveness of this system, with NIR light penetrating the walls of blood vessels and reaching the liver and kidneys without causing temperature increase, vascular damage, or changes in blood composition in the big artery.³² This technology can produce better therapeutic effects than single-treatment repetitive therapy,^{246,247} which would be less invasive.

An implantable, wireless-driven LED has also been developed to limit the invasive nature of repetitive treatments in deep tissues while maintaining efficacy. The power supplied to the embedded LED is replenished by electromagnetic induction from an external transmitter coil coupled to the LED to an embedded receiver coil. *In vitro* and implanted tumor-bearing mouse tests revealed that this device may be a possible solution for treating tumors in deep areas of the human body, *in vitro*, and in implanted tumor-bearing mice.³²

Thus, additional light irradiation devices are being developed to enable localized NIR-PIT. The use of a variety of advanced devices combined with other treatment modalities will make it possible to select the appropriate local NIR-PIT for a patient's disease.

Challenges and Limitations of Pulmonary NIR-PIT

Although NIR-PIT has several theoretical and experimental advantages for lung cancer treatment, there are still important challenges that must be overcome before its broad clinical application to pulmonary lesions.^{12,248} The most critical issue is light delivery. Unlike superficial tumors or lesions directly accessible from the body surface, many lung cancers are located deep within the thoracic cavity and are surrounded by complex anatomical structures, including bronchi, pulmonary vessels, pleura, ribs, and mediastinal organs. Therefore, sufficient and homogeneous irradiation of the entire tumor volume can be technically difficult, particularly for peripheral lesions or tumors located far from the central airway. To address this limitation, several light-delivery strategies, including endoscopic, interstitial, and endovascular approaches, have been investigated as potential methods to expand the applicability of NIR-PIT to deep-seated tumors.^{30,32}

Another important limitation is the treatment of multiple pulmonary lesions. Lung cancer frequently presents with multifocal disease, intrapulmonary metastases, pleural dissemination, or microscopic residual lesions. Because NIR-PIT requires both selective accumulation of antibody–photoabsorber conjugates and local light irradiation, untreated lesions outside the illuminated field may remain viable. Thus, pulmonary NIR-PIT may initially be more suitable for selected local lesions, such as centrally located tumors, endobronchial tumors, pleural dissemination, or tumors accessible by endoscopic, interstitial, or endovascular light-delivery approaches. Previous preclinical studies have demonstrated the feasibility of NIR-PIT in lung metastasis or thoracic cancer models, but these findings also underscore the importance of defining which lesion types are technically accessible to light irradiation.^{56,63} For multifocal lung disease, strategies such as repeated irradiation, multiple light-delivery routes, image-guided illumination, or combination with systemic therapies may be required.

Respiratory motion is another specific challenge in lung cancer treatment. During irradiation, the target lesion can move due to breathing, cardiac motion, or patient positioning. This displacement may reduce the accuracy of light delivery and cause insufficient irradiation of the tumor margin. In addition, excessive irradiation of surrounding normal tissues should be avoided, especially in fragile pulmonary structures. In radiotherapy for lung cancer, respiratory motion management, four-dimensional imaging, respiratory gating, and image-guided techniques have been developed to improve dose accuracy and reduce exposure

to normal tissues.^{249,250} Similar concepts may be important for pulmonary NIR-PIT. Therefore, respiratory motion management, real-time imaging guidance, respiratory gating, and flexible or catheter-based light-delivery devices may be necessary to improve the precision and reproducibility of pulmonary NIR-PIT.

Tumor heterogeneity also represents a major biological limitation. The efficacy of NIR-PIT depends on the expression of target antigens on the tumor cell surface. However, lung cancers are highly heterogeneous, and antigen expression may differ among histological subtypes, metastatic sites, individual lesions, and even within the same tumor. Large-scale multiregion sequencing studies, including TRACERx, have demonstrated substantial intratumor heterogeneity and branched evolutionary patterns in non-small cell lung cancer, which can contribute to treatment resistance and disease progression.^{251,252} Incomplete antigen expression can result in residual antigen-negative tumor cells after treatment. Therefore, careful selection of target antigens, assessment of antigen expression before treatment, and the development of multi-target or sequential NIR-PIT strategies may be important for improving therapeutic efficacy.

The immune response induced by NIR-PIT should also be considered in the pulmonary tumor microenvironment. NIR-PIT can induce immunogenic cell death and may enhance antitumor immunity; however, the lung tumor microenvironment often contains immunosuppressive cells and stromal barriers that may limit durable immune responses.^{23,253} In this context, antibody-mediated immune mechanisms may be relevant. Gu et al recently highlighted the importance of antibody-dependent cellular phagocytosis in cancer immunotherapy, emphasizing the role of macrophages and Fc receptor-mediated immune responses.²⁵⁴ These findings suggest that, in addition to direct phototoxicity, the immunological properties of antibody-based therapeutics may influence the therapeutic outcome of NIR-PIT. Future studies should clarify how NIR-PIT interacts with macrophages, dendritic cells, and other immune components in lung cancer.

Another emerging strategy to improve the selectivity and flexibility of NIR-PIT is pre-targeting. Conventional NIR-PIT requires direct conjugation of IR700 to a target-specific antibody, which may limit the flexibility of target selection and pharmacokinetic optimization. Mohiuddin et al reported a synthetic zipper-mediated pre-targeting system for NIR-PIT, in which an IR700-conjugated Zip1-SNAP protein was combined with scFv-ZIP2 fusion proteins targeting tumor-associated molecules.²⁵⁵ Such pre-targeting approaches may help separate tumor targeting from photoabsorber delivery, potentially improving tumor selectivity, reducing off-target exposure, and expanding the range of applicable target molecules. Although further validation in lung cancer models is required, this concept may be useful for addressing antigen heterogeneity and optimizing the therapeutic window of pulmonary NIR-PIT.

Overall, pulmonary NIR-PIT should not be regarded as a universally applicable treatment for all lung cancer lesions at the present stage. Its clinical translation will require optimization of target selection, antibody–photoabsorber conjugates, light-delivery devices, imaging guidance, respiratory motion management, and combination strategies. Addressing these technical and biological challenges will be essential for establishing NIR-PIT as a practical therapeutic option for selected patients with lung cancer.

Conclusion

In this review, we summarized the recent development of NIR-PIT and its potential application to lung cancer. Compared with conventional PDT, NIR-PIT offers several advantages, including target-specific cytotoxicity mediated by antibody–photoabsorber conjugates, rapid light-induced membrane damage, and the potential to induce antitumor immune responses.^{12,248} Preclinical studies using lung cancer and thoracic malignancy models have suggested that several molecular targets, including EGFR, HER2, PDPN, MSLN, GPR87, DLL3, and MUC1, may be applicable to NIR-PIT-based strategies.^{24,56,64,107,256,257}

However, the clinical translation of NIR-PIT for lung cancer remains at an early stage. Unlike head and neck cancer, in which clinical experience has already provided proof of concept for NIR-PIT in humans, direct clinical evidence in lung cancer is still limited.^{258,259} Several challenges specific to pulmonary application must be addressed, including light delivery to deep or multiple lung lesions, respiratory motion during irradiation, anatomical complexity of the thoracic cavity, heterogeneous antigen expression, and the need for image-guided treatment strategies.^{32,249,251} In addition, the interaction between NIR-PIT and the lung tumor microenvironment, including antibody-mediated immune mechanisms such as antibody-dependent cellular phagocytosis, should be further investigated.²⁵⁴

Future advances in target selection, antibody engineering, pre-targeting systems, light-delivery devices, and respiratory motion management may expand the therapeutic potential of NIR-PIT for selected lung cancer patients.^{30,32,251,255} In particular, novel approaches such as synthetic zipper-mediated pre-targeting systems may provide additional flexibility for optimizing tumor selectivity and photoabsorber delivery.²⁵⁵ Therefore, while pulmonary NIR-PIT is a promising therapeutic candidate, further preclinical and clinical studies are required to establish its efficacy, safety, and optimal clinical indications in lung cancer.

Abbreviations

NIR-PIT, Near-infrared photoimmunotherapy; ROS, Reactive oxygen species; PDT, Photodynamic therapy; LED, Light emitting diode; EGFR, Epidermal growth factor receptor; NIR, Near-infrared; APC, Antibody-photoabsorber conjugate; IR700, IRDye700DX; PS, Photosensitizer; DNA, Deoxyribonucleic acid; ICD, Immunogenic cell death; ADC, Antibody-drug conjugate; HNSCC, Head and neck squamous cell carcinoma; FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; DAMPs, Damage-associated molecular patterns; ET-BLIT, Endovascular therapy-based light illumination technology; mAb, Monoclonal antibody; ErbB, Erythroblastosis oncogene B; HNC, Head and neck cancer; HER2, Human epidermal growth factor receptor 2; TKI, Tyrosine kinase inhibitor; ADCC, Antibody-dependent cell-mediated cytotoxicity; NSCLC, Non-small cell lung cancer; CDDP, Cis-diamminedichloro-platinum(II); T-DM1, Trastuzumab emtansine; AML, Acute myeloid leukemia; PD-1, Programmed death 1; CTLA4, Cytotoxic T-lymphocyte-associated protein 4; CRC, Colorectal cancer; RIT, Radioimmunotherapy; NK, Natural killer; PDPN, Podoplanin; CAF, Cancer-associated fibroblast; MPM, Malignant pleural mesothelioma; MSLN, Mesothelin; GPI, Glycophosphatidylinositol; GPCR, G protein-coupled receptor; SCLC, Small cell lung cancer; DLL3, Delta-like canonical Notch ligand 3; TME, Tumor microenvironment; CDC, Complement-dependent cytotoxicity; PD-L1, Programmed death ligand 1; EMA, European Medicines Agency; MDSC, Murine myeloid-derived suppressor cell; TAM, Tumor-associated macrophage; AMP, Adenosine monophosphate; MRP1, Multidrug resistance-associated protein 1; LTC4, Leukotriene C4; VISTA, V-domain immunoglobulin suppressor of T cell activation; GvHD, Graft-versus-host disease.

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Data sharing is not applicable to this article as no data were created or analysed in this research.

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