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Commentary

Expanding the application of cancer near-infrared photoimmunotherapy

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Near-infrared photoimmunotherapy (NIR-PIT) is a newly developed cancer treatment which induces selective immunogenic cell death in targeted cells [1-3]. NIR-PIT utilizes an antibody–photoabsorber conjugate (APC) which is activated after tumour binding by NIR light (typically administered as laser light). A large body of research has developed around NIR-PIT, showing that it can kill many types of cancer cell by targeting unique transmembrane proteins overexpressed on the cell surface. Currently on the clinical side, a global phase III clinical trial of NIR-PIT for inoperable head and neck cancer patients is currently underway using an anti-epidermal growth factor receptor (EGFR)-antibody IR700 conjugate (https://clinicaltrials.gov/ct2/show/NCT03769506). In Japan, the first APC (ASP-1929, Akalux^{TM}, Rakuten Medical Inc., San Mateo, CA) targeting EGFR and utilizing a near infrared laser system (BioBlade^{TM}, Rakten Medical Inc.) was approved for clinical use in September 2020. Although NIR-PIT has been primarily developed using antibodies against cancer membrane antigens, it can also selectively kill a specific kind of normal host cells, especially those that promote cancer cell growth by inhibiting the immune system locally via targeting specific cell surface markers including CD25 and CTLA4 [4, 5].

NIR-PIT utilizes an antibody conjugated with the NIR photon-absorbing silicon phthalocyanine dye, IRDye700DX (IR700) [1, 3]. When injected intravenously, APCs bind to a specific cell membrane antigen. Once bound, NIR light (~690 nm) exposure kills only APC-bound target cells, sparing non- or minimally-expressing cells nearby [3]. Immediately after NIR light exposure to APC, axial ligands of IR700 dissociate from the molecule, converting the APC from very hydrophilic to very hydrophobic. This change in the chemical characteristics of IR700 promotes conformational changes and aggregation of APCs that damage the cell membrane, causing weakening and eventually rupture of the cell [6]. NIR-PIT can clearly be distinguished from conventional photodynamic therapy (PDT) or photothermal therapy (PTT), which rely on cytotoxic singlet oxygen or hyperthermia, respectively, and cause non-selective damage to light-exposed cells. In addition to direct cancer cell killing, NIR-PIT rapidly induces immunogenic cell death (ICD) [7] which initiates activation of the adaptive immune response employing dead-cell-associated antigens including calreticulin (CRT), adenosine triphosphate (ATP), high-mobility group box 1 (HMGB1), heat shock protein (Hsp) 70, and Hsp90. These danger signals activate local immature dendritic cells (DCs) to stimulate the presentation of tumour antigens, which are released from NIR-PIT-treated cancer cells. DCs present these antigens to T cells, resulting in priming and educating naive T cells to become cancer-specific CD8+ *T* cells [8]. Therefore, NIR-PIT has the potential to reset anti-tumour host immunity due to ICD. These factors have contributed to the initial success of NIR-PIT.

Therefore, NIR-PIT was initially developed to target cells expressing EGFR, human epidermal growth factor receptor-2 (HER2), and prostate-specific membrane antigen (PSMA) [3]. Since those early days, NIR-PIT has expanded to target a variety of transmembrane proteins using monoclonal antibodies designed to bind to these antigens. Numerous NIR-PIT cancer and immune targets have been explored over the past decade resulting in numerous research reports [1]. However, applicable target molecules expressed on some types of cancers, including lung cancers, are still under investigation. Therefore, a new target molecule for lung cancers, GPR87, expressed on various lung cancers as reported recently in *EBioMedicine*, might be promising for further clinical application of NIR-PIT against lung cancer because this single antibody against GPR87 could cover a large proportion of lung cancer patients [9].

Tumour-targeted NIR-PIT evokes a profound immune response. This can be augmented with various checkpoint inhibitors [8]. The first such agent, Ipilimumab, was a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and was approved in March 2011 to treat patients with late-stage melanoma. This class of immune checkpoint inhibitor (ICI) has continued to expand over the last decade with many ICIs approved. While these agents have been highly effective in some patients, immunotherapy-related side effects, termed immune-related adverse events (irAEs), have been widely reported in various organs. irAEs occur because ICIs activate immunity throughout the body, not just in the tumour. These side effects can cause syndromes that mimic autoimmune disease in normal organs. Ideally, a comprehensive cancer therapy would selectively kill tumour cells and activate local tumour immunity. None of the existing major therapies (surgery, radiation, and chemotherapy), do this. Tumour and immune cell-targeted NIR-PIT can kill tumour cells selectively and deplete local immune suppressor

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cells in the tumour bed [10]. This leads to dramatically more-active immune responses against tumours without inducing autoimmune irAEs in non-target tissues that could represent the ultimate form of NIR-PIT for cancer.

Contributors HK soley wrote this commissioned Commentary.

Declaration of Competing Interest

The author declares no conflicts of interest.

References

[1] Kobayashi H, Choyke PL. Near-Infrared Photoimmunotherapy of Cancer. Acc Chem Res 2019;52:2332–9.
[2] Kobayashi H, Griffiths GL, Choyke PL. Near-Infrared Photoimmunotherapy: photoactivatable Antibody-Drug Conjugates (ADCs). Bioconjug Chem 2020;31:28–36.
[3] Mitsunaga M, Ogawa M, Kosaka N, Rosenblum LT, Choyke PL, Kobayashi H. Cancer cell-selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules. Nat. Med. 2011;17:1685–91.
[4] Okada R, Kato T, Furusawa A, Inagaki F, Wakiyama H, Choyke PL, et al. Local depletion of immune checkpoint ligand CTLA4 expressing cells in tumor beds enhances antitumor host immunity. Advanced Therapeutics 2021;4:2000269.
[5] Sato K, Sato N, Xu B, Nakamura Y, Nagaya T, Choyke PL, et al. Spatially selective depletion of tumor-associated regulatory T cells with near-infrared photoimmunotherapy. Sci Transl Med 2016;8:352ra110.
[6] Sato K, Ando K, Okuyama S, Moriguchi S, Ogura T, Totoki S, et al. Photoinduced ligand release from a silicon phthalocyanine dye conjugated with monoclonal antibodies: a mechanism of cancer cell cytotoxicity after near-infrared photoimmunotherapy. ACS Cent Sci 2018;4:1559–69.
[7] Ogawa M, Tomita Y, Nakamura Y, Lee MJ, Lee S, Tomita S, et al. Immunogenic cancer cell death selectively induced by near infrared photoimmunotherapy initiates host tumor immunity. Oncotarget 2017; 8:10425–36.
[8] Nagaya T, Friedman J, Maruoka Y, Ogata F, Okuyama S, Clavijo PE, et al. Host immunity following near-infrared photoimmunotherapy is enhanced with PD-1 checkpoint blockade to eradicate established antigenic tumors. Cancer Immunol Res 2019;7:401–13.
[9] Yasui H, Nishinaga Y, Taki S, Takahashi K, Isobe Y, Shimizu M, et al. Near-infrared photoimmunotherapy targeting GPR87: development of a humanized anti-GPR87 mAb and therapeutic efficacy on a lung cancer mouse model.. EBioMedicine 2021 (In press).
[10] Maruoka Y, Furusawa A, Okada R, Inagaki F, Fujimura D, Wakiyama H, et al. Combined CD44- and CD25-targeted near-infrared photoimmunotherapy selectively kills cancer and regulatory T cells in syngeneic mouse cancer models. Cancer Immunol Res 2020;8:345–55.