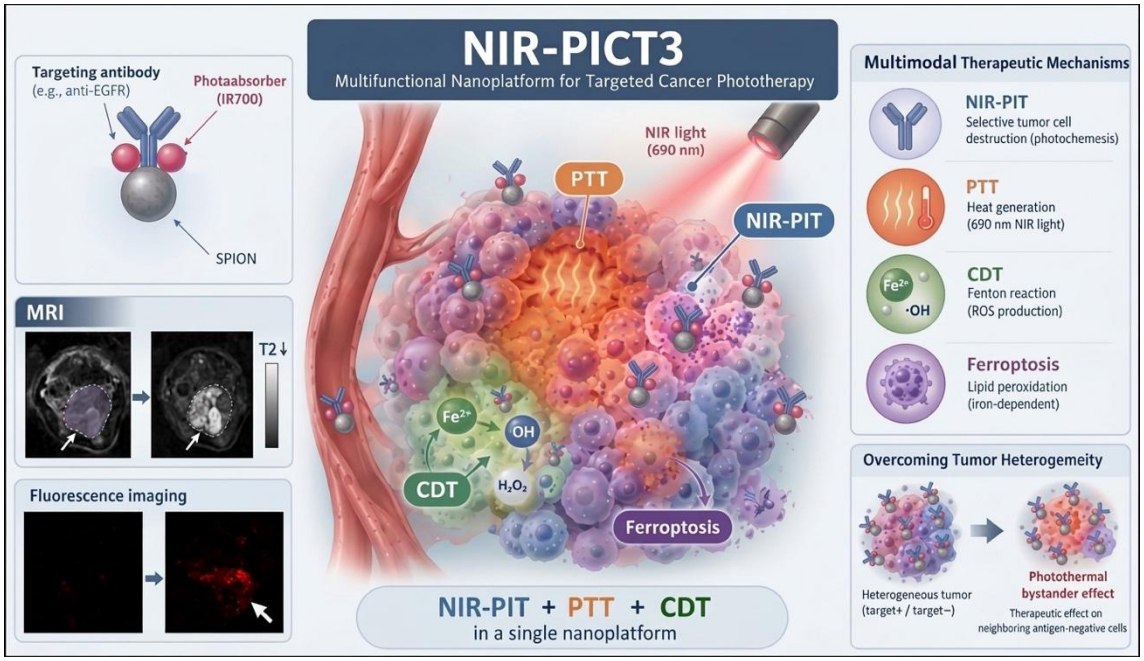
News Press Research Release

Development of MRI-Trackable Next-Generation Cancer Phototherapy “NIR-PICT^3” — Discovery of a Photothermal Bystander Effect to Overcome Tumor Heterogeneity



Key Points

- Near-infrared photoimmunotherapy (NIR-PIT) is a highly selective cancer treatment that has received conditional approval in Japan. However, its clinical application still faces challenges, including difficulty in evaluating drug delivery to tumors and limited therapeutic effects on cancer cells that do not express the target antigen. In this study, we overcame these limitations by integrating advanced nanoparticles into the NIR-PIT platform.
- We successfully developed NIR-PICT^3, a novel platform for molecularly targeted cancer phototherapy that enables treatment monitoring by magnetic resonance imaging (MRI).
- By integrating ultrasmall superparamagnetic iron oxide nanoparticles with an antibody–photoabsorber conjugate, we successfully combined conventional NIR-PIT with the synergistic effects of photothermal therapy (PTT) and chemodynamic therapy (CDT).

- We newly identified a photothermal enhancement effect in NIR-PICT^3, in which heat generation became progressively more efficient with each cycle of near-infrared light irradiation.
- Tumors exhibit heterogeneity in target antigen expression. We newly demonstrated that NIR-PICT^3 produces a photothermal bystander effect, enabling therapeutic effects even against neighboring tumor cells that do not express the target antigen.
- Iron oxide nanoparticles have already been clinically approved as MRI contrast agents for the imaging of liver cancer and liver metastases, which may facilitate the clinical translation of this therapeutic platform.
- Because the targeting antibody can be replaced according to the cancer-associated antigen of interest, this platform could potentially be applied to a wide range of cancer types while simultaneously enabling therapy and MRI-based treatment monitoring.

Summary 1

A research team led by Kazuhide Sato, Designated Lecturer at the Nagoya University Graduate School of Medicine, Institute for Advanced Research, and Medical-Engineering Collaboration Unit and a principal investigator in the first cohort of the JST FOREST Program; Akira Ito, Professor in the Department of Chemical Systems Engineering, Graduate School of Engineering, Nagoya University; Mitsuo Sato, Professor in the Department of Omics and Medical Science, Graduate School of Medicine, Nagoya University; and Junko Shimada, Senior Researcher at JSR Corporation, has successfully developed a novel nanotechnology-based molecularly targeted phototherapeutic platform in which ultrasmall iron oxide nanoparticles are incorporated into antibody therapeutics.

This study was supported by the Japan Science and Technology Agency (JST) FOREST Program (Fusion Oriented REsearch for disruptive Science and Technology; first cohort, JPMJFR2017, Principal Investigator: Kazuhide Sato), a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant No. 25K03451, Principal Investigator:

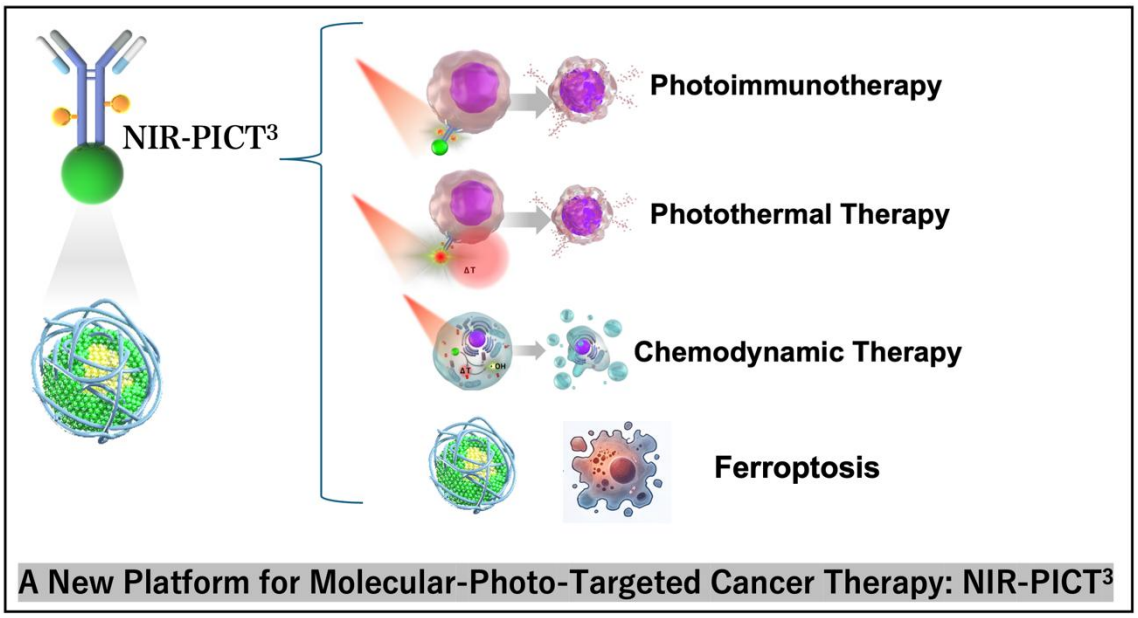
Kazuhide Sato), a collaborative research program with JSR Corporation, and other sources.

In recent years, antibody–drug conjugates (ADCs), in which therapeutic agents are conjugated to antibodies, have been increasingly applied as molecularly targeted therapies for a wide range of cancers. Among these approaches, near-infrared photoimmunotherapy (NIR-PIT) has attracted considerable attention as a novel form of molecularly targeted cancer phototherapy. NIR-PIT induces “photochemosis,” a recently identified mechanism of cell death triggered by near-infrared light. NIR-PIT was first approved worldwide in Japan in 2020 and is expected to further develop as a light-activated ADC-like therapeutic platform in which treatment effects can be spatially and temporally controlled by light irradiation. However, as with other antibody-targeted therapies, including ADCs, heterogeneity of target antigen expression within tumors, known as tumor heterogeneity, remains a major factor limiting therapeutic efficacy.

In this study, the researchers developed a next-generation phototherapeutic platform by incorporating ultrasmall iron oxide nanoparticles into antibody therapeutics. This design enabled visualization of target tumors by magnetic resonance imaging (MRI) and simultaneously produced multiple therapeutic effects, including conventional NIR-PIT, photothermal therapy (PTT) induced by 690-nm near-infrared light, chemodynamic therapy (CDT), and the induction of ferroptosis. The researchers named this integrated therapeutic strategy NIR-PICT^3 (Near-Infrared Photoimmuno-Chemodynamic Thermal Targeting Therapy).

Furthermore, the team discovered that repeated light irradiation progressively enhanced the photothermal effect of NIR-PICT^3. They also identified a photothermal bystander effect, through which the treatment exerted therapeutic effects on neighboring tumor cells that did not express the target antigen, and elucidated the mechanism underlying these effects.

The findings were published in the Springer Nature journal *Journal of Nanobiotechnology* on October 21, 2026, at 7:00 p.m. JST.



Summary 2

1. Research Background

In recent years, antibody-based therapeutics in which antibodies are conjugated with drugs, photoabsorbers, radionuclides, or other functional agents have been increasingly used in cancer treatment. Among these, antibody–drug conjugates (ADCs)[*1] have attracted considerable attention as a new class of anticancer therapeutics. By using antibodies that specifically recognize tumor-associated antigens, these therapies can preferentially target cancer tissues while reducing damage to normal tissues and thereby limiting adverse effects. In particular, ADCs in which antibodies are linked to cytotoxic drugs through chemical linkers have become an important area of oncology, and several domestically developed ADCs have already entered clinical use.

Near-infrared photoimmunotherapy (NIR-PIT) is a novel cancer treatment developed in 2011 by Dr. Hisataka Kobayashi and colleagues at the National Cancer Institute/National Institutes of Health (NCI/NIH), USA. In NIR-PIT, an antibody that specifically recognizes a protein expressed on cancer cells is conjugated with the photoabsorber IR700[*2]. When the antibody–IR700 conjugate is bound to the target protein on the cell surface and irradiated with near-infrared light at approximately 690 nm, the cancer cells are

rapidly destroyed.

Regarding the mechanism of this cell death, Designated Lecturer Kazuhide Sato, the corresponding author of this press release, and colleagues demonstrated in 2018 that NIR-PIT induces a previously unrecognized form of cell death initiated by a photochemical reaction (Sato K, et al. ACS Cent Sci. 2018 Nov 28;4(11):1559–1569. DOI: 10.1021/acscentsci.8b00565). In 2025, they further identified and demonstrated the detailed molecular mechanism, showing that NIR-PIT disrupts the cortical actin meshwork underlying the plasma membrane (Sato K, et al. ACS Nano. 2025 Mar 4;19(8):8338–8356. DOI: 10.1021/acsnano.5c00104). Based on these findings, this newly identified form of cell death was named “Photochemosis.”

Because this unique mechanism enables cancer cells to be selectively destroyed in a manner distinct from conventional therapies, NIR-PIT has been proposed as a potential “fifth modality” of cancer treatment, following surgery, radiotherapy, chemotherapy, and cancer immunotherapy. In September 2020, Japan became the first country in the world to approve NIR-PIT for previously treated recurrent head and neck cancers with high EGFR expression under the SAKIGAKE designation and conditional early approval system of the Pharmaceuticals and Medical Devices Agency (PMDA), and the treatment is covered by the national health insurance system. Because NIR-PIT uses an antibody conjugated with a photoabsorber, it can also be broadly regarded as a form of ADC-based therapy, or a “photo-ADC.”

However, antibody-based therapies targeting cell-surface antigens in solid tumors face an important clinical limitation: their high target specificity can restrict therapeutic efficacy when target antigen expression is heterogeneous within the tumor. Such heterogeneous antigen expression is one manifestation of tumor heterogeneity[*3]. Although various therapeutic strategies and drug-development approaches have been investigated to overcome this problem, tumor heterogeneity remains a major contributor to limited treatment

efficacy and cancer recurrence.

2. Research Findings

In this study, we developed a next-generation phototherapeutic platform by incorporating ultrasmall iron oxide nanoparticles into antibody therapeutics. This platform enabled visualization of target tumors by magnetic resonance imaging (MRI) and simultaneously integrated the therapeutic effects of NIR-PIT with multiple additional mechanisms, including photothermal therapy (PTT)[*4] induced by near-infrared light, chemodynamic therapy (CDT)[*5], and the induction of ferroptosis[*6]. We named this integrated platform NIR-PICT[3] (Near Infrared Photoimmuno-Chemodynamic Thermal Targeting Therapy).

In addition, we discovered that repeated light irradiation enhanced the targeted photothermal effect of NIR-PICT[3], a phenomenon termed the cycle-enhanced photothermal effect. We also identified a photothermal bystander effect, in which therapeutic effects extended to non-targeted tumor cells, and elucidated the mechanism underlying these phenomena. Light irradiation increased the permeability and accumulation of the nanoparticle-based NIR-PICT[3] agent within tumors, thereby further enhancing heat generation.

The principal findings of this study are summarized below.

Effects of ultrasmall iron oxide nanoparticles

The iron oxide nanoparticles provided multiple functions, including negative MRI contrast, a chemodynamic effect mediated by the Fenton reaction, a photothermal effect induced by 690-nm near-infrared light, and the induction of ferroptosis.

Platform versatility through antibody substitution

We demonstrated that the antibody component of NIR-PICT[3] can be replaced with antibodies against different tumor-associated

antigens, indicating that this platform can potentially be adapted to a broad range of cancer types expressing different specific target antigens.

Favorable pharmacokinetics and tumor accumulation

The use of ultrasmall iron oxide nanoparticles enabled favorable in vivo pharmacokinetics and efficient accumulation of the therapeutic agent within target tumors.

Potent antitumor activity and enhanced photothermal effects through repeated light irradiation

NIR-PICT^{3} demonstrated potent antitumor activity. Furthermore, repeated near-infrared light irradiation progressively enhanced heat generation and increased tumor temperature. Mechanistic analysis revealed that this newly identified cycle-enhanced thermal effect was associated with the SUPR (super-enhanced permeability and retention) effect, whereby NIR-PIT increased the permeability and retention of nanoparticles within the treated tumor.

Therapeutic effects on non-targeted tumor cells: the photothermal bystander effect

Using a mixed-tumor mouse model, we demonstrated that NIR-PICT^{3} exerted therapeutic effects not only on tumor cells expressing the target antigen but also on neighboring tumor cells lacking the target antigen. We termed this phenomenon the photothermal bystander effect.

3. Future Perspectives

In this study, we established a simple strategy for combining antibody therapeutics or ADCs with iron oxide nanoparticles. Following accumulation in tumors, the iron oxide nanoparticles simultaneously provided several functions, including negative MRI contrast, a Fenton reaction-mediated chemodynamic effect, a

photothermal effect induced by 690-nm near-infrared light, and ferroptosis induction. By further integrating these effects with NIR-PIT, a photo-ADC-based treatment, we constructed a multimodal and integrated cancer therapeutic platform capable of simultaneously inducing selective cancer cell damage through near-infrared light irradiation.

By activating multiple mechanisms of tumor cell injury at the same time, this therapeutic strategy offers a new approach to overcoming one of the major clinical limitations of antibody therapeutics and ADCs: heterogeneous expression of target antigens within tumors. Through its effects on surrounding cells, including cancer cells with low or absent target-antigen expression, this platform may help suppress therapeutic resistance and cancer recurrence.

In addition, although the iron oxide nanoparticles used in this study differ in size from clinically approved formulations, iron oxide nanoparticles of the same general material class have already been approved and routinely used as MRI contrast agents for liver imaging. NIR-PIT has also received conditional approval in Japan. These precedents may facilitate the clinical translation of the present therapeutic strategy.

Furthermore, because the targeting antibody can be replaced according to the tumor-associated antigen of interest, the platform can potentially be applied to a wide range of cancer types expressing different target antigens. Thus, NIR-PICT^3 may serve as a highly versatile therapeutic platform for cancer treatment.

This approach may represent an important advance in antibody-based treatment of solid tumors, in which heterogeneous expression of tumor-specific antigens remains a major cause of recurrence. It may also provide a new strategy for further improving the therapeutic efficacy of NIR-PIT, which has only recently entered clinical practice, and may ultimately contribute to future clinical cancer treatment.

*1 Antibody–drug conjugate (ADC):
An antibody-based therapeutic in which an antibody that specifically binds to a protein expressed on the surface of cancer cells is conjugated with an additional therapeutic agent.

*2 IR700:
A water-soluble photoabsorber with a silicon phthalocyanine structure. It absorbs light at wavelengths around 690 nm and emits fluorescence at approximately 700 nm.

*3 Tumor heterogeneity:
Solid tumors consist of cancer cells with diverse biological characteristics. Gene expression, drug resistance, and the expression levels of tumor-associated target antigens can vary substantially among tumor cells. This so-called tumor heterogeneity is an important cause of therapeutic resistance and cancer recurrence, and overcoming it remains a major challenge in cancer treatment.

*4 Photothermal therapy (PTT):
A therapeutic approach in which a photothermal agent is administered and allowed to accumulate in a tumor. External light, such as near-infrared laser light, is then applied to the tumor, causing the photothermal agent to generate heat and thereby kill cancer cells.

*5 Chemodynamic therapy (CDT):
An emerging cancer treatment strategy that uses iron or other metal ions to induce chemical reactions, such as Fenton or Fenton-like reactions, converting relatively non-toxic hydrogen peroxide within tumors into highly reactive and cytotoxic radicals that damage and kill cancer cells.

*6 Ferroptosis:
An iron-dependent form of regulated cell death caused by abnormal accumulation of intracellular iron ions and lipid peroxides.

Publication

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Synergistic Nanotheranostic Platform for Fluorescence/Magnetic Resonance Bimodal Imaging-Guided Near Infrared Photoimmuno-Chemodynamic Thermal Targeting Therapy

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