# News Press Research Release

**Title**

Near Infrared Photoimmunotherapy Targeting DLL3 For Small Cell Lung Cancer

**Key Points**

- Development of new treatments for small cell lung cancer (SCLC) has not progressed for decades, and new therapeutic way is highly wanted. Especially, the development of molecularly targeted drugs and treatments for SCLC are required.
- Successful development of near-infrared photoimmunotherapy (NIR-PIT) targeting DLL3, which is a molecule specifically expressed in SCLC and large cell neuroendocrine lung cancer.
- NIR-PIT targeting DLL3 for SCLC would be a new different therapeutic modality.
- Since NIR-PIT is under an international phase III clinical trial, DLL3-targeted NIR-PIT is thought to be easy translatable into the clinic.

**Summary 1**

Graduate student **Yoshitaka Isobe (1st author)** at the department of Respiratory Medicine, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu), Assistant Professor **Kazuhide Sato (corresponding author)**, at Institute for Advanced Research, Nagoya University (Director: Yoshiyuki Suto), Associate Professor Hiroshi Yukawa and Professor Yoshinobu Baba at Department of Biomolecular Engineering, Professor Toyofumi F. Chen-Yoshikawa at the department of Thoracic Surgery, Yoshinori Hasegawa in Nagoya Medical Center, and their collaborators succeeded in developing near-infrared photoimmunotherapy targeting DLL3 for small cell lung cancer.

Small cell lung cancer (SCLC) is a highly aggressive tumor with limited treatment options. A cell surface protein, DLL3, has recently been discovered as a new therapeutic target for SCLC. Rova-T, an antibody-drug conjugate, was developed for the treatment of SCLC with targeting DLL3, and clinical trials have been conducted. However, the trial was discontinued due to problems with effects and side effects. Therefore, new treatments targeting DLL3 are highly needed.

Near infrared photoimmunotherapy (NIR-PIT) is a novel cancer treatment reported in 2011 by Dr. Hisataka Kobayashi at the National Cancer Institute, National Institutes for Health (NCI/NIH), USA. The treatment employs an antibody photosensitizer conjugate followed with NIR light exposure. An antibody photosensitizer conjugate consists of a cancer cell-specific monoclonal antibody and a photosensitizer, IR700. It binds target molecules on the cell membrane and induces immediate cell death after exposure to

NIR light at 690 nm.

In this study, we synthesized IR700 conjugates with anti-human DLL3 antibody which has been already assessed in clinical trials, and demonstrated the effect of DLL3 targeting near infrared photoimmunotherapy for SCLC in cell and animal experiments.

This work was published in EBioMedicine on Jan 23, 2020.

**Summary 2**

**Research Background**

Small cell lung cancer (SCLC) is a high-grade tumor that accounts for 15% of lung cancer. SCLC is often found in an advanced state where surgery is difficult, and is often treated with conventional systemic chemotherapies.

In recent years, molecular targeted therapies such as tyrosine kinase inhibitors, immune checkpoint inhibitors, and angiogenesis inhibitors for non-small cell lung cancer have been developed. However, pharmacotherapy for small cell lung cancer has not changed for much over the past 20 years and treatment options are limited, so new treatments are needed.

Recently, DLL3 was found not to be expressed in adult body tissues but specifically expressed in the cell membrane of SCLC, and has attracted attention as a new therapeutic target. Rova-T, an antibody-drug conjugate, was developed as a drug antibody conjugates targeting DLL3, and clinical trials have been conducted. However, development was discontinued due to problems with effects and side effects. Therefore, a new approach to DLL3 is required.

Near infrared photoimmunotherapy (NIR-PIT) is a novel mechanism of cancer treatment reported in 2011 by Dr. Hisataka Kobayashi of the National Cancer Center (NCI / NIH). The treatment employs an antibody photosensitizer conjugate followed by NIR light exposure. An antibody photosensitizer conjugate consists of a cancer cell-specific monoclonal antibody and a photosensitizer, IR700. It binds target molecules on the cell membrane and induces immediate cell necrosis after exposure to NIR light at 690 nm.

In this study, we demonstrate DLL3-targeted NIR-PIT to develop a novel molecularly targeted treatment for SCLC.

**Research Results**

Immunostaining of tumor tissue was performed using samples of Japanese patients who underwent surgery at Nagoya University Hospital, who had agreed to use surgical specimens for research purposes. In SCLC, DLL3-expression was observed in 80% of the cases. The expression of DLL3 in Caucasian and Japanese SCLC cell lines was evaluated. DLL3-expression was also found in cell lines of both races. Thus,

these data suggested that DLL3 is widely expressed between the different races.

Rovalpituzumab-IR700 (Rova-IR700) was synthesized with rovalpituzumab, an anti-human DLL3 antibody previously administered to the human body and the photosensitizer IR700. We performed NIR-PIT on cell lines using Rova-IR700. Microscopic observation showed that the cells immediately swelled, ruptured, and died after irradiation with near-infrared light. When target cells and non-target cells were irradiated with near-infrared light at the same time, cell death occurred only in the target cells, and there was no particular effect on non-target cells. The mouse tumor-bearing model showed significant suppression of tumor growth and prolonged survival. (Fig. 1)

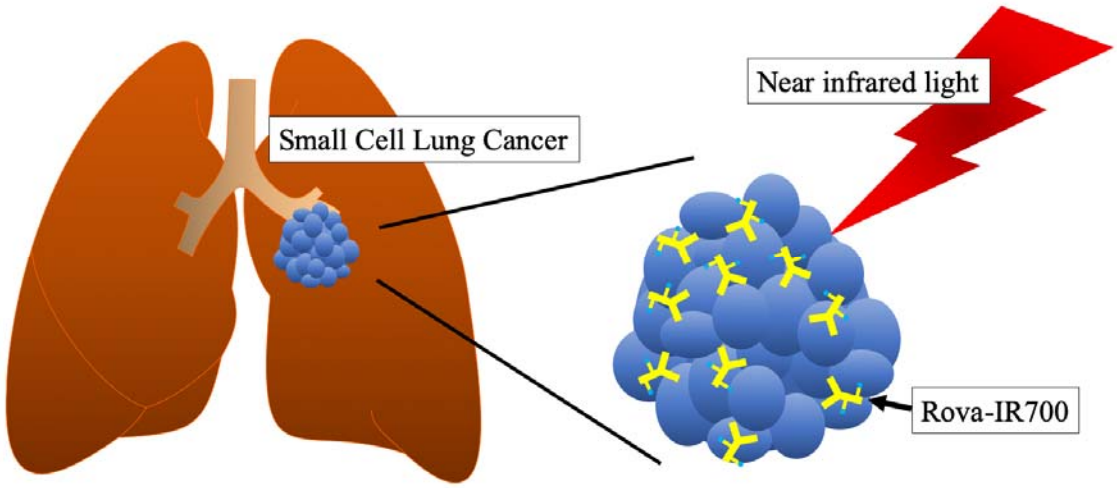


Figure 1. Overview of near-infrared photoimmunotherapy for small cell lung cancer targeting DLL3.

**Research Summary and Future Perspective**

The effect of NIR-PIT for SCLC targeting DLL3 was confirmed *in vitro* and *in vivo* experiments. It was also confirmed that DLL3 was widely expressed in Caucasian and Japanese SCLC. This study provides the proof of the concept that DLL3-targeted NIR-PIT for SCLC patients will be a promising new treatment. Since NIR-PIT is undergoing an international phase III clinical trial, DLL3-targeted NIR-PIT is thought to be easy translatable into the clinic. Further applications, such as the development of near-infrared light irradiation devices for lung cancer and the combination therapies with conventional treatments, has to be conducted in future studies.

Publication

Yoshitaka Isobe[a], Kazuhide Sato*[a,b,c], Yuko Nishinaga[a], Kazuomi Takahashi[a], Shunichi Taki[a], Hirotoshi Yasui[a], Misae Shimizu[a,c], Rena Endo[a,c], Chiaki Koike[a,c], Noriko Kuramoto[c], Hiroshi Yukawa[c,d,e], Shota Nakamura[f], Takayuki Fukui[f], Koji Kawaguchi[f], Toyofumi F. Chen-Yoshikawa[f], Yoshinobu Baba[d,e], Yoshinori Hasegawa[g]

[a] Respiratory Medicine, Nagoya University Graduate School of Medicine

[b] Nagoya University Institute for Advanced Research, S-YLC

[c] Nagoya University Institute for Advanced Research, B3-Unit, Advanced Analytical and Diagnostic Imaging Center (AADIC) / Medical Engineering Unit (MEU)

[d] Nagoya University Institute of Nano-Life-Systems, Institutes of Innovation for Future Society

[e] Department of Biomolecular Engineering, Nagoya University Graduate School of Engineering

[f] Department of Thoracic Surgery, Nagoya University Graduate School of Medicine

[g] National Hospital Organization, Nagoya Medical Center

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