National Taiwan University and Academia Sinica Joint Program Office

◆ SEPTEMBER 2023 ◆ Issue 01

https://jpoas.ntu.edu.tw/

NEWSLETTER

Special Report in the First Issue

The NTU/AS Innovative Joint Program has been implemented for several years, and lots of PIs achieved excellent outcomes.

The first issue lists 3 representative articles about Cancer Research and Treatment published in top journals in recent years.

Contact us
ntujpoas@ntu.edu.tw

國立臺灣大學 National Taiwan University
中央研究院 ACADEMIA SINICA

Development of Metastatic Tumor-Targeting NIR Persistent Luminescence Nanomaterials to Chemotherapy for Lung Cancer

Wen-Tse Huang[1] , Ming-Hsien Chan[2] , Michael Hsiao[2,*] and Ru-Shi Liu[1,*]

Lung cancer remains the leading cause of cancer-related deaths worldwide, surpassing the combined fatalities caused by breast, colon, and prostate tumors. Effective treatment options for non-small cell lung cancer (NSCLC) are limited, posing a significant challenge in improving patient outcomes. Targeted therapy and precise tracking of drugs within the body are crucial for successful lung cancer diagnosis and treatment. This article presents a study using near-infrared persistent luminescence nanoparticles (NIR PLNs) as a promising nanoplatform for enhanced diagnostic and therapeutic interventions in lung adenocarcinoma (LUAD) metastasis. NIR PLNs possess unique properties, such as long-lasting luminescence and non-toxicity (Figure 1), making them suitable for efficient accumulation in lung cancer cells. These nanoparticles are conjugated with a specific aptamer sequence called the MAGE-A3 aptamer (MAp), enabling targeted drug delivery (Afatinib, AFT) to tumor cells. This innovative approach offers a potential strategy for precise diagnosis and effective therapeutic treatment of lung cancer metastasis. The nanocarrier's efficacy is evaluated *in vitro* lung cancer cell and *in vivo* mouse models. The study demonstrates the accumulation of AFT-PLN@MAp in tumor areas, leading to significant tumor reduction and weight reduction compared to control groups.

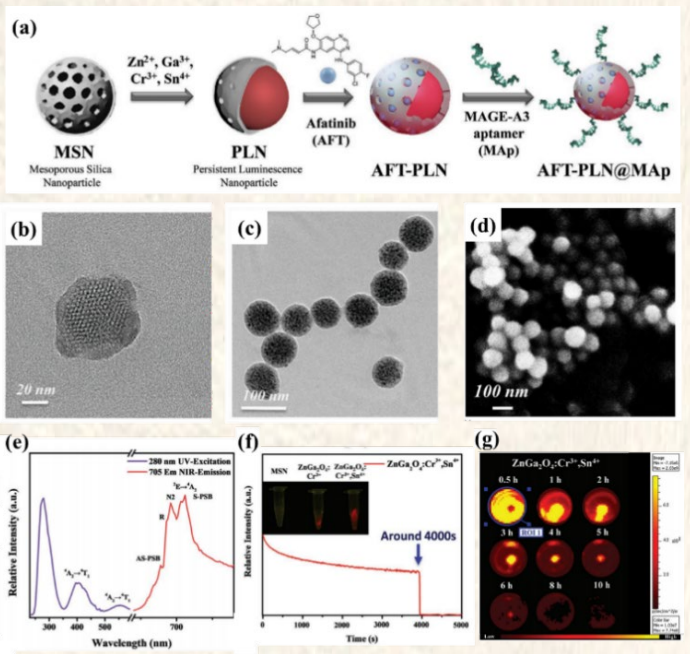


Figure 1. Basic characteristics of NIR PLNs and the derivative PLNs.

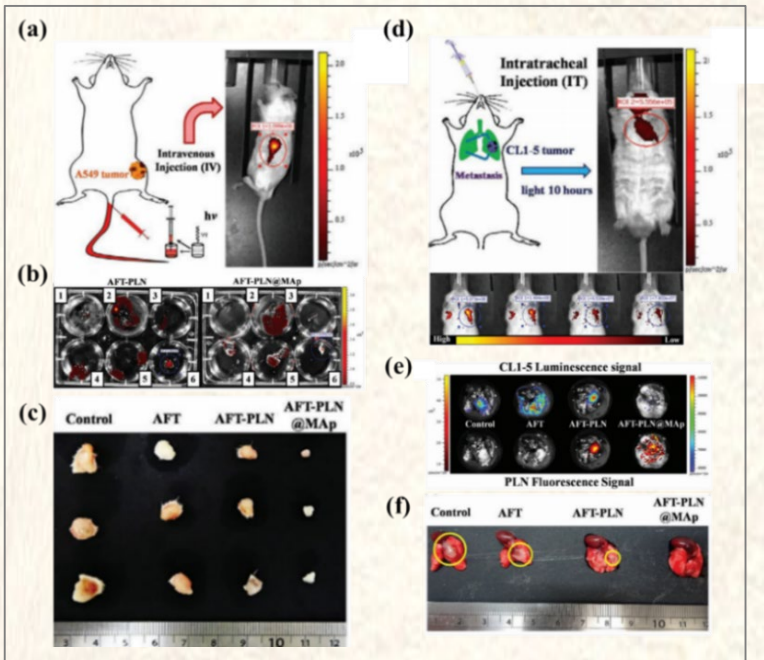


Figure 2. *In vivo* IV injection to cure A549 lung tumors and *in vivo* IT drug delivery to cure an orthotopic CL1-5 lung tumor.

Furthermore, the active transport of AFT-PLN@MAp in metastatic tumor tissues is validated, showcasing its potential to suppress tumor growth and reduce metastatic risk (Figure 2). The long-lasting luminescence capability of NIR PLNs provides an opportunity for real-time tracking of tumor changes and metabolism over an extended period. This technology holds promise for improving lung cancer prognosis. The potential applications extend beyond lung cancer, with prospects for utilization in other materials and cancers. Market opportunities exist for equipment manufacturers specializing in biomedical imaging, and partnerships with technology companies can facilitate patent authorization and effective market expansion. The development of multifunctional nanoparticles, such as NIR PLNs, offers a promising approach for enhancing the diagnosis and treatment of lung cancer metastasis. The results from *in vitro* and *in vivo* studies demonstrate the potential of the nanocarrier AFT–PLN@Map in suppressing tumor growth and inhibiting metastasis. Moreover, the commercialization prospects highlight the market potential for this technology in the field of biomedical imaging and clinical diagnostics.

[1] Department of Chemistry, National Taiwan University
[2] Genomics Research Center, Academia Sinica

All of the above have been published : *Adv. Sci.* **2020**, *7*, 1903741 (doi: 10.1002/advs.201903741)

Click or Scan the QR code to read the original journal article in Advanced Science

Info

◆ Principal Investigators

Ru-Shi Liu, Professor
Department of Chemistry, NTU
✉ rsliu@ntu.edu.tw

Michael Hong-Sheng Hsiao, Research Fellow
Genomics Research Center, AS
✉ mhsiao@gate.sinica.edu.tw

◆ Joint Program Title

Development of Metastatic Tumor-Targeting NIR Persistent Luminescence Nanomaterials to Chemotherapy for Lung Cancer

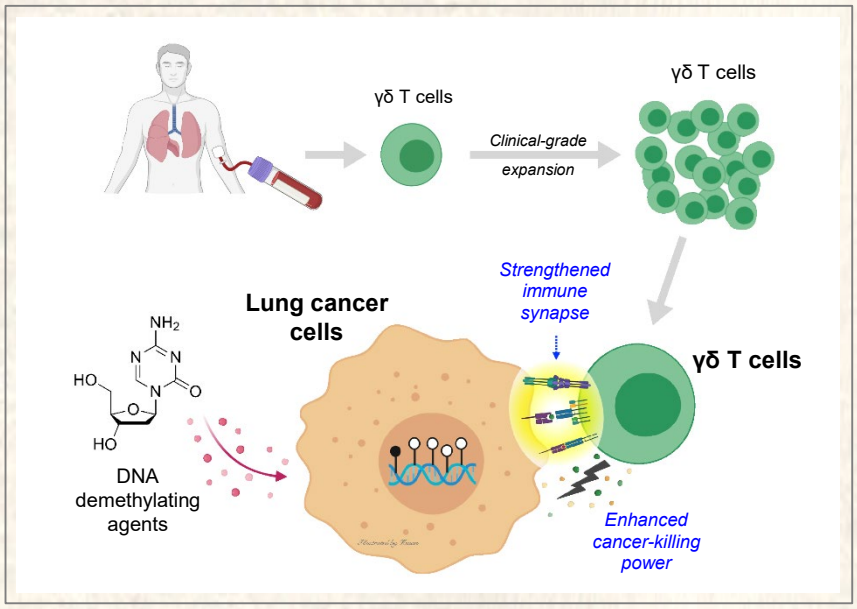
◆ Program Duration

2019.01.01-2020.12.31

Building a stronger bond between cancer and fighter immune cells to combat cancer

Cell-based immunotherapy, a type of therapy that takes immune cells from a patient, grows and expands these cells in the laboratory, and infuses the cells back into the patient, has shown some promise in the clinical setting. Nevertheless, inconsistent cancer-killing capacity remains one of the major obstacles to its widespread clinical uses. A research team led by Dr. Hsing-Chen Tsai from the Graduate Institute of Toxicology at NTU has developed a new therapeutic strategy to enhance the efficacy of cell-based immunotherapy by combining DNA demethylating agents and γδ T cells for the treatment of lung cancer. The study was published in Nature Communications in April 2021.

γδ T cells are a special kind of immune cells that fight cancer. Unlike regular fighter T cells (cytotoxic CD8+ T cells) that need activation and only recognize cancer antigens presented on a group of surface proteins called major histocompatibility complex (MHC), γδ T cells respond rapidly and do not require MHC-assisted antigen presentation for cancer recognition. DNA demethylating agents are a safe medication widely used to treat leukemia. Dr. Hsing-Chen Tsai's team discovered a new use for these drugs. They showed that treating lung cancer cells with DNA demethylating agents can help γδ T cells kill cancer cells much more effectively. The NTU team, in collaboration with Dr. Jung-Chi Liao's team at Academia Sinica, found that DNA demethylating agents cause cytoskeleton reorganization in lung cancer cells and increase the expression of ICAM-1, a protein that facilitates the formation of an immune synapse (the structure at the interface between γδ T and cancer cells). As a result, γδ T cells can target and destroy



DNA demethylating agents can increase the expression of adhesion molecules on lung cancer cells, thereby strengthening the immune synapse to enhance the killing of lung cancer by γδ T cells.

lung cancer cells more efficiently by releasing cancer-killing substances via a strengthened immune synapse. The research team also showed that this combination therapy significantly prolonged the survival time of lung cancer-bearing mice. Moreover, through large-scale genomic analysis, the team identified a gene signature composed of 33 cytoskeleton-related genes that can stratify lung cancer patients and predict whether they will potentially respond to γδT cell-based therapy.

Dr. Tsai anticipates that the combination therapy can be applied to other cancer types as well, such as colon cancer, ovarian cancer, etc. Furthermore, since γδT cells can recognize cancer cells without the requirement for the presence of specific MHC molecules, it is possible to utilize γδT cells from mismatched (allogeneic) donors to treat cancer. The team hopes to conduct clinical trials in the near future to benefit more lung cancer patients in need.

Research article:

Weng RR, Lu HH, Lin CT, Fan CC, Lin RS, Huang TC, Lin SY, Huang YJ, Juan YH, Wu YC, Hung ZC, Liu C, Lin XH, Hsieh WC, Chiu TY, Liao JC, Chiu YL, Chen SY, Yu CJ, Tsai HC*. Epigenetic modulation of immune synaptic-cytoskeletal networks potentiates γδT cell-mediated cytotoxicity in lung cancer. Nat Commun. 2021 Apr 12;12(1):2163. *Corresponding author

https://www.nature.com/articles/s41467-021-22433-4

Click or Scan the QR code to read the original journal article in Nature Communications

Info

◆ Principal Investigators

Hsing-Chen Tsai, Associate Professor
Graduate Institute of Toxicology, NTU
✉ htsai@ntu.edu.tw

Jung-Chi Liao, Research Fellow
Institute of Atomic and Molecular Sciences, AS
✉ liaojc@gate.sinica.edu.tw

◆ Joint Program Title

Superresolution imaging and optoproteomics of immunological synapses to decipher their role in T cell-based antitumor immunity

◆ Program Duration

2019.01.01-2020.12.31

ALTERNATIVE LENGTHENING OF TELOMERES

The maintenance of telomere length is closely related to the processes of cancers and aging. How do telomeres extend their length? It has been well-known that an enzyme called telomerase can lengthen telomeres. However, some cancers do not rely on telomerase activity to lengthen their telomeres. They utilized "Alternative lengthening of Telomeres (ALT)", a mechanism that includes a break-induced replication to extend telomeres and is highly conserved in many eukaryotes. Patients with ALT cancers have a higher risk of death compared with those having non-ALT cancers.

How do cells initiate the breaks at telomeres? Dr. **Hsueh-Ping (Catherine) Chu's** team in the Molecular and Cellular Biology department at NTU collaborates with **Liuh-Yow Chen's** team at Academia Sinica discovered that TERRA R-loops and XPF are the drivers. TERRA is a long non-coding RNA, which contains telomeric repeat sequences and forms DNA:RNA hybrids at telomeres. The DNA:RNA hybrid and a displaced single-stranded DNA form an R-loop structure. TERRA R-loops are specifically enriched at telomeres in cancer cells utilizing the ALT mechanism. The research team uncovered that TERRA R-loops trigger telomere clustering and activate DNA damage response by recruiting XPF. Such DNA damage response at telomeres is required for inducing homologous recombination and telomere synthesis in ALT cancer cells.

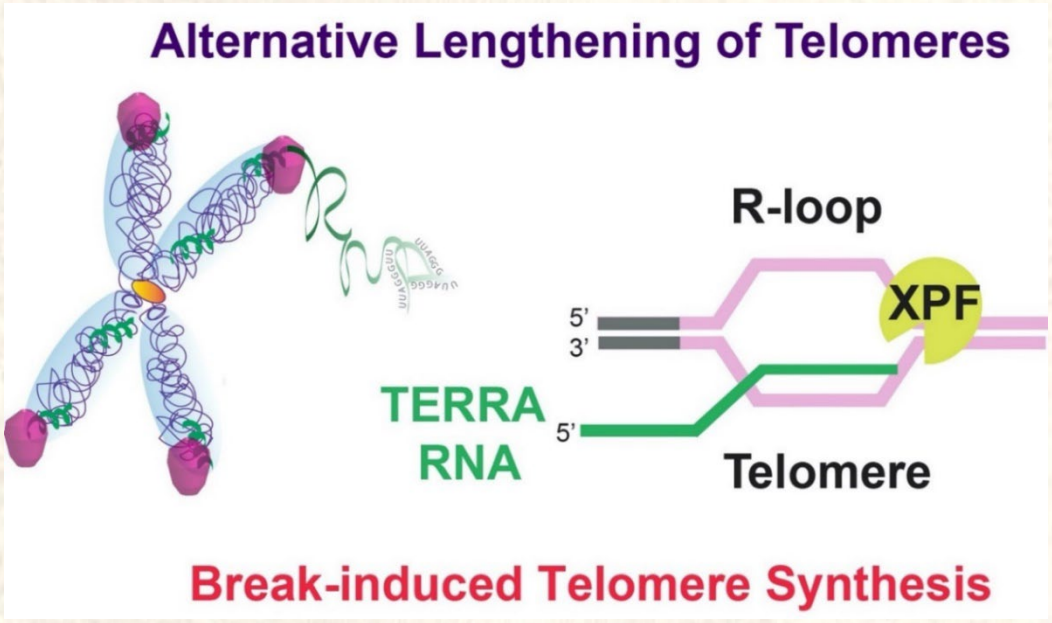


Figure Legend

TERRA is a non-coding RNA, which is transcribed from the ends of chromosomes and forms an R-loop with telomeric DNA. TERRA R-loops recruit XPF, an enzyme that cuts DNA to induce DNA synthesis to extent telomeres and drive Alternative Lengthening of Telomeres.

They developed an RCas9 system to specifically deplete TERRA RNA without editing telomeric DNA in ALT cells and found that TERRA depletion shortens telomere length in ALT cancer cells. They systematically identified TERRA interacting proteins in ALT cells and revealed that TERRA interacts with a large subset of proteins involved in the DNA repair pathway. Interestingly, TERRA interacts with several nucleotide excision repair factors including XPF, an enzyme that cuts DNA. They showed that TERRA R-loops recruit XPF to telomeres, leading to DNA double-strand breaks to activate break-induced telomere synthesis at ALT telomeres.

Targeting XPF by small interference RNAs inhibits cell growth in ALT cancer cells and reduces telomere lengthening. These findings provide new insights into ALT cancer therapy.

This research was published in : **Oct 2022. *Nature communications***
https://www.nature.com/articles/s41467-022-33428-0

Chia-Yu Guh[1, #], Hong-Jhih Shen[1, #], Liv WeiChien Chen[1,#], Pei-Chen Chiu[1, #], I-Hsin Liao[1], Chen-Chia Lo[1], Yunfei Chen[1], Yu-Hung Hsieh[1], Ting-Chia Chang[1], Chien-Ping Yen[1], Yi-Yun Chen[2], Tom Wei-Wu Chen[3], Liuh-Yow Chen[4], Ching-Shyi Wu[5], Jean-Marc Egly[6,7] and **Hsueh-Ping Catherine Chu** [1,*]. XPF activates break-induced telomere synthesis. ***Nature Communications (SCI)***, 2022 Oct 2;13(1):5781. ***Corresponding author.**

Click or Scan the QR code to read the original journal article in Nature Communications

Info

◆ Principal Investigators

Hsueh-Ping Catherine Chu, Associate Professor
Institute of Molecular and Cellular Biology, NTU
✉ cchu2017@ntu.edu.tw

Liuh-Yow Chen, Associate Research Fellow
Institute of Molecular Biology, AS
✉ lyowchen@gate.sinica.edu.tw

◆ Joint Program Title

TERRA-CST interaction in regulating telomere integrity

◆ Program Duration

2019.01.01-2020.12.31