【Grant-in-Aid for Specially Promoted Research】

Novel cancer treatment by using the synergy of alpha-emitting radiopharmaceuticals and synthetic vaccines

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Project Information	Project Number : 25H00006　Project Period (FY) : 2025-2029 Keywords : targeted radionuclide therapy, adjuvant, cancer vaccine, anti-tumor immunity

Purpose and Background of the Research

●Outline of the Research

Targeted alpha therapy (TAT) involves the uptake of short-lived radionuclides that emit α rays by specifically targeting tumor cells, allowing α-radiation within cells and effectively inhibiting cancer growth. This therapy induces an anti-tumor immune response, which is considered a key factor in its potent anti-tumor effects, although the mechanism remains unclear. This research aims to develop astatine-based TAT drugs and elucidate the mechanisms of immune activation. Additionally, the research will focus on developing anti-cancer vaccines that induce effective anti-tumor immunity while achieving precise immune modulation. Furthermore, the study will develop combination therapies that induce effective anti-tumor responses by combining astatine-based TAT drugs and anti-tumor vaccines.

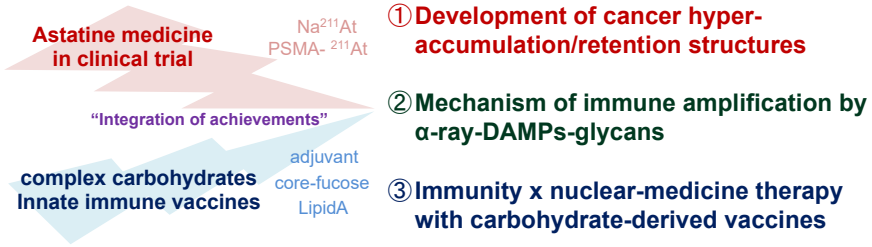

Figure 1. Development of a Cancer Treatment Approach by Integrating Targeted Alpha Therapy and Immunotherapy

●Potential of Targeted alpha therapy (TAT)

TAT is an advanced form of radiation therapy that delivers alpha-emitting radiopharmaceuticals to target metastatic cancer lesions throughout the body. By utilizing radiolabeled molecular-targeted drugs that bind specifically to cancer-associated molecules, this therapy enables precise uptake by cancer cells, allowing for internal radiation exposure that effectively eliminates tumors. One of the key advantages of α particles is their short range and high energy, which enables them to deliver strong cytotoxic effects to cancer cells while minimizing damage to surrounding healthy tissues. These properties make TAT a promising approach for treating refractory cancers.

A notable example of TAT is prostate-specific membrane antigen (PSMA)-targeted therapy using Actinium-225 (^{225}Ac, half-life: 10 days), which has shown cases of complete remission. However, because ^{225}Ac must be introduced via chelation, it can significantly affect the physicochemical properties of small-molecule and middle-molecule targeted drugs, posing a challenge for drug design and optimization.

●Our Approach to Astatine-211 (^{211}At) in TAT

We are actively developing a novel TAT using Astatine-211 (^{211}At, half-life: 7.2 hours), an α-emitting radionuclide that can be produced from bismuth using a cyclotron. ^{211}At, as a halogen element, can be incorporated into a wide range of molecules and possesses moderate hydrophobicity, making it highly compatible with both small-molecule and middle-molecule targeted drugs. This property enables ^{211}At-based radiopharmaceuticals to target a diverse range of cancers while overcoming molecular design limitations. This breakthrough could significantly expand the therapeutic applications of α-emitting radiopharmaceuticals, enhancing precision and efficacy in cancer treatment.

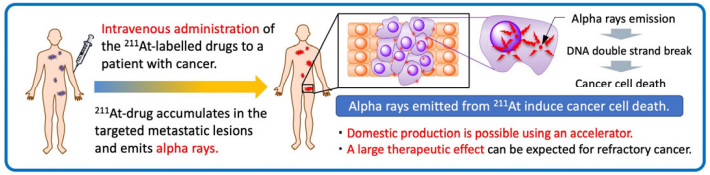

Figure 2. Treatment concept by targeted α-therapeutics

Expected Research Achievements

●Development of ^{211}At-Labeled Radiopharmaceuticals

This study aims to establish ^{211}At-based Targeted Alpha Therapy (TAT) by addressing key challenges:

- Enhancing targeted delivery to maximize selective uptake by cancer cells while minimizing sequestration by stromal cells
- Improving intracellular retention of ^{211}At-labeled drugs to maximize cytotoxic effects

By overcoming these challenges, we seek to advance innovative ^{211}At-based cancer therapies.

●Elucidating the Mechanism of Immune Activation Induced by α-Radiation

DNA double-strand breaks alone cannot fully explain the remarkable efficacy of TAT. Our preliminary studies indicate that ^{211}At-irradiated cancer cells effectively induce anti-tumor immunity. This study aims to elucidate the molecular basis of immune activation triggered by ^{211}At therapy and clarify its therapeutic mechanism.

●Development of Cancer Vaccines Utilizing Glycans and Glycolipids

Glycans play a key role in innate and adaptive immunity, enabling self/non-self recognition. We have studied bacteria-derived immunostimulatory glycans and the immune functions of host-derived N-glycans, particularly core fucose. Our research has shown that FUT8 inhibitors suppress T-cell inflammatory responses. This study aims to develop innovative glycan-based therapies, including:

- Immune adjuvants
- Cancer vaccines using adjuvant-antigen complexes
- Utilization of FUT8 inhibitors for anti-tumor immune regulation

By integrating these approaches with TAT, we aim to develop new therapeutic strategies for refractory cancers like pancreatic cancer.

●Clinical Translation at Osaka University

Investigator-initiated clinical trials are underway at Osaka University, led by our group, for the refractory thyroid cancer treatment [^{211}At]NaAt and the refractory prostate cancer treatment PSMA-5.

Through this project, we aim to develop new ^{211}At-based therapeutic candidates and establish a treatment strategy that effectively enhances anti-tumor immunity while preventing excessive immune responses. By combining cancer vaccines with TAT, this approach has the potential to suppress cancer recurrence and improve treatment outcomes.

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