National Cancer Center (NCC) Japan, NCC Seed Acceleration Program（NCC SAP）

Manufacturing of Active Pharmaceutical Ingredients for Innovative Metabolic Inhibitors Targeting Refractory Cancers

S2-225105

Keiichi I. Nakayama, M.D., Ph.D.
Chief Scientific Officer, AntiCancer Technologies, Inc.

Vision

- We aim to develop an innovative, low-toxicity anticancer agent that demonstrates superior efficacy against refractory cancers, including small cell lung carcinoma (SCLC).
- For refractory or recurrent cancers where, standard treatments are existing therapies such as platinum-based drugs like cisplatin are often used. However, there are still many challenges, including severe toxicity and the emergence of resistance.
- In mouse model evaluations, the seed compound (ACT-001), which we are developing, has shown minimal toxicity and superior tumor penetration and cytotoxic effects compared to the current standard treatment drug cisplatin. Furthermore, it demonstrated strong efficacy even against cisplatin-resistant cancers, as evidenced by preclinical data.
- Through the development of ACT-001 as an anti-cancer agent, the expansion of treatment options for malignant tumors, including refractory and recurrent cancers, is expected.

Marketability

- Based on our basic research findings, we have initiated development as a therapeutic drug for small cell lung carcinoma, a malignant tumor with a poor prognosis that newly diagnosed in over 330,000 people annually worldwide, aiming to potentially replace platinum-based anti-cancer agents such as cisplatin, which are standard treatments (with a projected global market size exceeding 300 billion yen in 2030).
- Based on the basic data, the compound is expected to be effective not only for small cell lung carcinoma but also for a variety of other cancers except for those of the gastrointestinal tract. The number of potential new patients for the target cancers is more than 2 million worldwide every year, and the overall market size of drug therapy not limited to platinum-based drugs is expected to be 57 trillion yen by 2030.
- ACT-001 has shown superior efficacy and is likely to have lower toxicity compared to existing and competing drugs. The development of combination therapies with other treatments is also anticipated.

Innovation

- We were the first in the world to demonstrate that phosphoribosyl pyrophosphate amido transferase (PPAT), the rate-limiting enzyme in the *de novo* purine nucleotide biosynthesis pathway, is an essential factor in the malignant progression of small cell lung carcinoma(Nat. Commun., 11:1320, 2020).
- In the evaluation using SCLC cell line-derived xenograft mouse models, no significant toxicity was observed, and greater antitumor efficacy was demonstrated compared to cisplatin.
- The development of this seed compound is expected to enable a new cancer treatment that comprehensively targets all phases of the cell cyde. Through combination or replacement therapies, it may help resolve or reduce the disadvantages of current standard treatments, such as high toxicity and limited tumor selectivity.

Partnering

【 Expected partners 】
Pharmaceuticals・CMO/CDMO/CRO/SMO・Venture capitals

【 Expectation 】
Formulation of intellectual strategies, manufacturing of investigational drugs, execution of clinical trials, and financial support.

Research Outline

Key Words: #Small molecule, #Metabolic pathway

[Background]

1. A comprehensive absolute quantification method for expression of metabolic enzymes (~1,000 types) was developed (iMPAQT system), and by the system, PPAT was identified as the most significant difference between cancer cells and normal cells.
2. In parallel, a meta-analysis was conducted to analyze the correlation between the expression levels of metabolic enzymes and prognosis in cancer patients (~12,000 individuals), identified PPAT as the enzyme with the strongest correlation.
3. Furthermore, knockdown experiments of various metabolic enzymes revealed PPAT as the gene that most significantly affects the proliferative capacity of cancer cells.
   Taken together, these three independent lines of evidence strongly support PPAT as a promising candidate for cancer treatment.

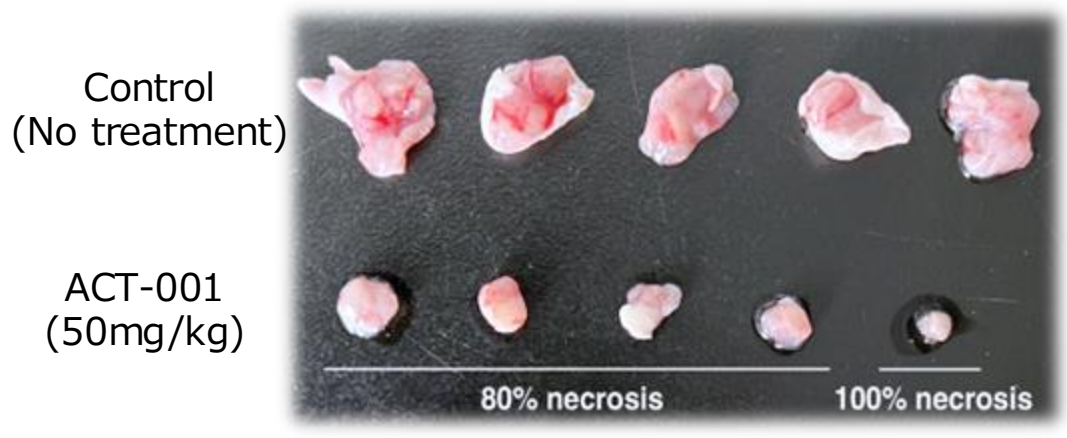
Matsumoto, et al. (2017) Nat. Methods 14: 251-8.
Kodama, et al. (2020) Nat. Commun. 11: 1320.

[Drug Development]

We developed a lead compound (ACT-001) with the following characteristics:

1. **Physicochemical properties**: A covalent drug that binds to PPAT.
2. **Toxicity**: Almost no toxicity even at high doses in mouse.
3. **Pharmacokinetics**: Orally administrable, has a long plasma half-life, and demonstrates excellent distribution to tumors.
4. **Efficacy**: Shows stronger tumor-suppressive effects than the standard treatment drug (cisplatin) and exhibits potent efficacy against cisplatin-resistant small cell lung cancer (right).

Treatment effect on the mouse xenograft tumor model
(Cisplatin-resistant small lung cell cancer from a human patient)



[Objective of This Research Project]

The goal of the project is to manufacture the active pharmaceutical ingredient of the PPAT inhibitor. Specifically, the following five steps will be carried out: Development of the manufacturing process, Batch production for GLP-tox, GMP production for Phase1 clinical trial, Development of the formulation, and GMP formulation for Phase1 trial.