Medicine (diagnosis and treatment of cancer), Drug development

Theranostics targeting glypican-1 in pancreatic cancer

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Abstract

In recent years, theranostics, which enables a seamless approach from cancer diagnosis to treatment by changing the radiolabel on compounds that bind to specific targets, has gained significant attention. For diagnosis, imaging using PET (Positron Emission Tomography) is often employed, while radionuclides emitting alpha or beta radiation are used for treatment. In this study, we successfully developed a new PET imaging probe targeting glypican-1, which is expressed in pancreatic cancer, along with an alpha-therapeutic agent, a [^{89}Zr/^{211}At]-labeled anti-glypican-1 antibody. In preclinical studies using cancer-bearing models, we demonstrated theranostics technology, achieving an integrated approach from PET imaging diagnosis to alpha radiation therapy.

Background & Results

At Osaka University, we are developing cancer therapeutics using the alpha-emitting radionuclide astatine-211 (^{211}At), which can be produced using the accelerator (cyclotron) at the Nuclear Physics Research Center. Due to the short range and high energy release of alpha particles, specific targeting for cancer allows for treatment of metastatic lesions throughout the body without affecting surrounding normal tissues. Currently, Investigator-initiated clinical trials using astatine and astatine-labeled drugs are being conducted at the university hospital (for refractory thyroid cancer and prostate cancer; Principal Investigator: Dr. Tadashi Watabe). In collaboration with Iwate Medical University, we have developed a novel radiolabeled antibody targeting glypican-1, which is expressed in pancreatic cancer, and validated its utility in pancreatic cancer model mice. Glypican-1 is a type of heparan sulfate proteoglycan expressed on the cell surface of cancers and is found in pancreatic cancer cells and stroma. Additionally, glypican-1 is also known to be expressed in many other cancers, including breast, esophageal, cervical, and cholangiocarcinomas. Initially, by labeling anti-glypican-1 antibodies with the positron-emitting radionuclide zirconium (^{89}Zr) and administering it intravenously, we successfully visualized pancreatic cancer clearly in vivo using PET. Subsequently, administration of an alpha-emitting radionuclide astatine (^{211}At)-labeled antibody (with internalization capability) efficiently induced double-strand DNA breaks, leading to tumor growth suppression. This demonstrated the theranostics technology integrating PET imaging diagnosis with alpha therapy using glypican-1-targeted antibodies.

Significance of the research and Future perspective

Pancreatic cancer is known to be a challenging malignancy to detect early using conventional imaging modalities and is also difficult to treat, often progressing rapidly, with a five-year relative survival rate of only 11.8%. By utilizing the newly developed PET imaging antibody and the astatine-labeled antibody, it is expected that early detection of pancreatic cancer through imaging will become possible, and for advanced-stage cancers, whole-body treatment using alpha radiation can offer a breakthrough therapy for refractory pancreatic cancer. Additionally, as glypican-1 is known to be expressed in various types of cancers, it is anticipated that this approach may have cross-cancer applications.

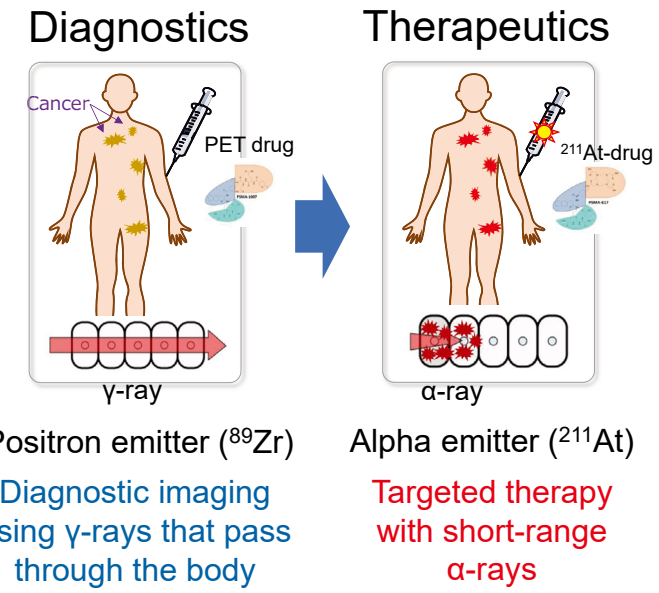

Fig. 1. Concept of Theranostics: new medical technology that integrates Diagnostics and Therapeutics

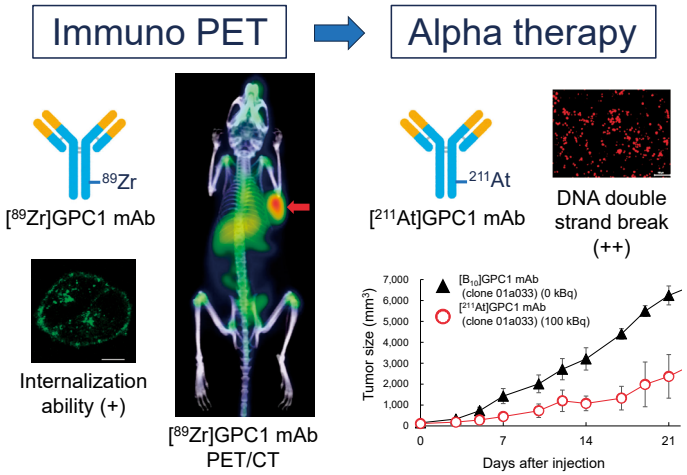

Fig. 2. Theranostics targeting glypican-1 (GPC1): (Left) PET imaging of Zr-89 labeled GPC1 antibody using pancreatic cancer model mouse (red arrow indicates tumor), (Right) Alpha radiation therapy using At-211-labeled anti-GPC1 antibody in a pancreatic cancer model.

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