Preclinical study finds antitumor effects of bispecific antibody

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Chugai Pharmaceutical announced today that the preclinical study findings on its original bispecific antibody ERY974, a molecule that binds Glypican-3 and CD3 simultaneously, and that is currently under development as a Phase I clinical study for solid tumors, were published in the online edition of *Science Translational Medicine* on October 4, 2017.

"ERY974 is a bispecific antibody created under the joint research between Chugai and Chugai Pharmabody Research with the application of Chugai's proprietary innovative antibody engineering technologies. We are extremely pleased that our research findings on ERY974 have been published in *Science Translational Medicine*," said Dr. Hisafumi Okabe, senior vice president for research and translational clinical research. "It is said that cancer immunotherapy has made a paradigm shift in cancer treatment and that the role of the immune system in cancer treatment is likely to continue to grow in the future. As a cancer immunotherapy, we have high hopes that ERY974 will demonstrate anti-tumor effects in future clinical studies and become a drug that can contribute to the treatment of patients."

Glypican-3 (GPC3) is a membrane protein that is expressed with high frequency on the cellular membranes of various tumor cells including hepatocellular carcinoma, lung cancer, and gastric cancer. GPC3 is reported to be expressed in various tissues in the fetal stage and play an important role, but is rarely expressed in normal adult tissues. As GPC3 expression is observed through the malignant transformation of cells,

GPC3 is thought to be a protein specific to cancer (tumor-associated antigen).

ERY974 is a bispecific antibody that binds to both GPC3 on the cancer cell membrane and to CD3, a membrane protein expressed on T cells, a type of lymphocyte. ERY974 is a T cell Redirecting AntiBody (TRAB) created with Chugai's proprietary antibody engineering technology, and while simultaneously binding to GPC3 and CD3 and directing T cells to cancer cells, it also activates T cells, specifically attacking and killing neighboring cancer cells. Based on this mechanism whereby it activates T cells and attacks cancer cells, TRAB is classified as a type of cancer immunotherapy.

The following points were shown in this research:

- According to the immunohistochemistry, GPC3 is expressed in various cancers (a hepatocellular carcinoma, a squamous lung cancer, a small cell lung cancer, an esophageal cancer, a gastric cancer and a head and neck cancer), and as previously reported, it is rarely expressed in normal tissues (30 different tissues) (in vitro)
- GPC3-dependent T cell activation and killing of cancer cells by ERY974 was observed in vitro
- In three different experimental tumor models using mouse, ERY974 demonstrated anti-tumor effects
- Anti-tumor effects were observed even in cancers where other cancer immunotherapies are ineffective (Mouse)
- Tolerability of ERY974 was observed in toxicity testing in animal

Based on the results of this preclinical study, Chugai began phase I clinical trial of ERY974 in patients with GPC3 positive solid tumors in the United States in August 2016 (NCT02748837).

More information: Takahiro Ishiguro et al. An anti–glypican 3/CD3 bispecific T cell–redirecting antibody for treatment of solid tumors, *Science Translational Medicine* (2017). DOI: 10.1126/scitranslmed.aal4291 Daniel Baumhoer et al.

Glypican 3 Expression in Human Nonneoplastic, Preneoplastic, and Neoplastic Tissues, *American Journal of Clinical Pathology* (2008). DOI: 10.1309/HCQWPWD50XHD2DW6

Provided by Chugai Pharmaceutical

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