CHUGAI PHARMACEUTICAL CO., LTD.
Corporate Communications Dept.
1-1, Nihonbashi-Muromachi 2-chome,
Chuo-ku Tokyo, 103-8324 Japan
TEL：+81-(0) 3-3273-0881
FAX：+81-(0) 3-3281-6607
E-mail:pr@chugai-pharm.co.jp
URL:http://www.chugai-pharm.co.jp

CHUGAI
Roche Group

Translation

Chugai Succeeds in Establishing Stable Cell Lines of Cancer Stem Cell for the First Time

- A step forward in elucidating the mechanisms of recurrence/metastasis and drug resistance of cancer and in the development of a new therapeutic agent -

October 19, 2012 - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama (hereafter, “Chugai”)] has succeeded for the first time in the world in establishing stable cell lines with the nature of colon cancer stem cells that are thought to be involved in the recurrence/metastasis of cancer. Chugai discovered that the cancer stem cells change to non-proliferative drug-resistant cells after administration of an anticancer drug and restore their proliferative properties when the administration of the anticancer drug is discontinued. Chugai also found that an antibody that binds to a protein expressed on these cancer stem cells can inhibit metastases when administered into mice that had been injected with the cancer stem cells.
These results were published on the electronic version of “STEM CELLS,” a scientific journal in the US, on October 18, 2012 (http://onlinelibrary.wiley.com/doi/10.1002/stem.1257/abstract).
This research was performed through the collaboration of PharmaLogicals Research Pte. Ltd. (Singapore), Forerunner Pharma Research Co., Ltd. (Tokyo), and the Research Division of Chugai and was conducted in cooperation with academia in Japan and overseas.
Chugai believes that these important findings will lead to the development of a new type of anticancer drug that targets cancer stem cells.

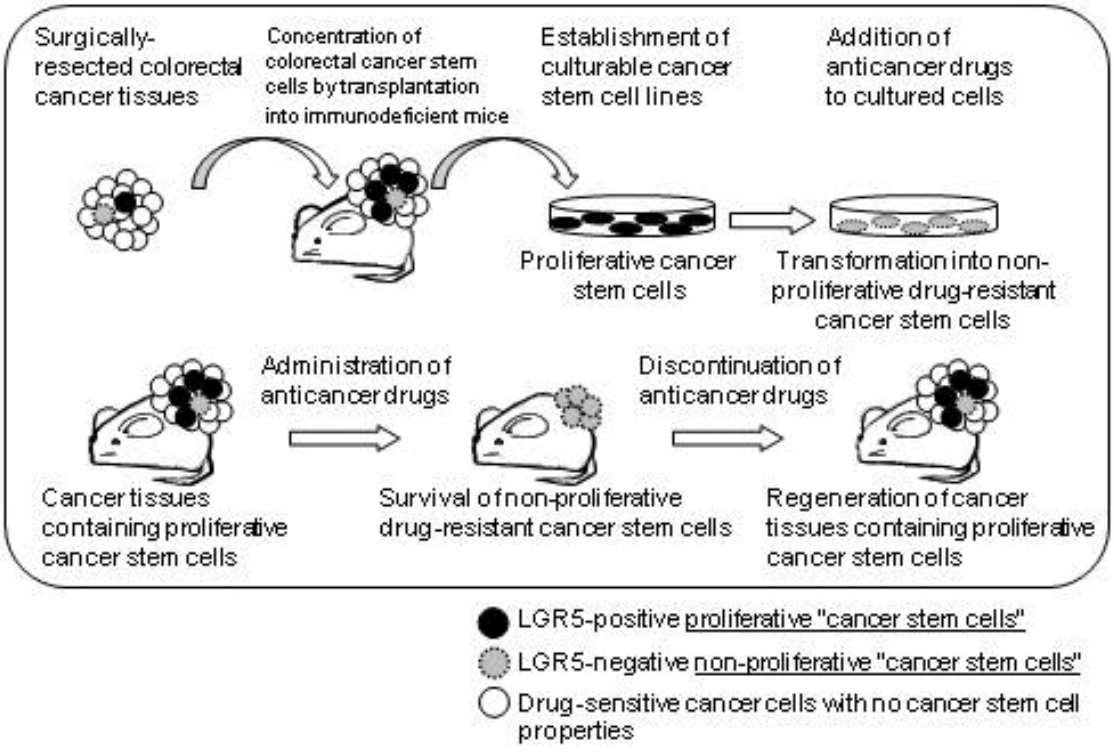
Recurrence and metastases of cancer occur despite regression and resection of cancer by chemotherapy and surgery, and the presence of cancer stem cells has been hypothesized as one of the causes. It has been believed that only small numbers of cancer stem cells exist in cancer tissues, but they can cleverly elude cancer therapies, such as the administration of anticancer drugs, by changing their state. They resume proliferation and cause metastasis when there is a change in the host environment, such as in the physiological condition of the patient. Therefore, the development of a therapeutic drug that specifically attacks cancer stem cells is necessary for the effective treatment of cancer.

While many studies on the presence of cancer stem cells have been reported so far, it has been extremely difficult to isolate and elucidate the detailed nature of cancer stem cells because cancer stem cells are rare in cancer tissues. Even under such circumstance, Chugai has succeeded in isolating cancer stem cells from tumor tissues by using a protein called LGR5 as a marker. After cancer tissues from colon cancer patients were transplanted and passaged in immunodeficient mice, cancer stem cells were isolated and cancer stem cell lines capable of being stably cultured in a highly pure form were established. LGR5 is used to

define the cancer stem cells from the tumors. The cell lines obtained in this way are proliferative cancer stem cells that specifically express the LGR5 protein. However, when these cancer stem cells were cultured in the presence of an anticancer drug, they changed to non-proliferative drug-resistant cells. Furthermore, when the anticancer drug was removed from the culture media, they restored their original proliferative cancer stem cell properties. The transition between a proliferative state and a non-proliferative drug resistant state of the cancer stem cells was also reproduced in a mouse experimental model. These results support the hypothesis that a mechanism exists by which cancer stem cells resist cancer therapies by alternating their nature in order to survive, and when the host environment becomes favorable for cancer stem cells, they restore their original nature and resume proliferation, causing recurrence or metastases of cancer. Furthermore, a protein expressed on these cancer stem cells was discovered, and an antibody that specifically binds to this protein was produced. When the antibody was administered to mice that had been injected with cancer stem cells, metastasis of cancer to other organs was inhibited.

Based on these findings, Chugai will pursue drug discovery and the development of therapeutic drugs with a new concept that targets cancer stem cells.

[Study outline]



[Reference]

About PharmaLogicals Research Pte. Ltd. (Singapore)

The company was established jointly in Singapore by Chugai, Mitsui & Co., Ltd. and Central Institute for Experimental Animals in May 2002 as a base for drug discovery research in Asia. Since December 2011, it has operated as a 100%-owned subsidiary of Chugai.

The company focuses on the advancement of novel drug discovery that efficiently produces therapeutic antibodies through analysis of the pathobiology of diseases using human tissues and model animals, and also through the understanding of the pathophysiology and genome information of diseases using methods such as genomic analysis.

About Forerunner Pharma Research Co., Ltd. (Tokyo)

The company was established jointly within the University of Tokyo Komaba Open Laboratory by Chugai, Mitsui & Co., Ltd. and Central Institute for Experimental Animals in April 2005. In September 2010, a new business office was opened within the Yokohama Bio Industry Center and joint research with RIKEN was initiated.

The company made a new start as a 100%-owned subsidiary of Chugai in October 2011 and focuses on drug discovery that efficiently produces antibody drugs based on pathophysiology and genome information, and discovery research for new drug targets through research on epigenomes and transcription factors.

About LGR5

LGR5 is a protein expressed on the cell membrane that was discovered to be a marker of normal stem cells in the small intestine of mice, and was later found to exist in colorectal cancer stem cells.