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National Cancer Center Japan
Shonai Regional Industry Promotion Center
Sumitomo Dainippon Pharma Co., Ltd.

National Cancer Center Japan, Shonai Regional Industry Promotion Center and Sumitomo Dainippon Pharma Announce Start of Phase 1/2 Study on New Drug Candidate Compound in Acute Myeloid Leukemia

National Cancer Center Japan (Headquarters: Chuo-ku, Tokyo; President: Hitoshi Nakagama; hereafter, "National Cancer Center"), Shonai Regional Industry Promotion Center (Headquarters: Tsuruoka City, Yamagata Prefecture; President: Osamu Minakawa) and Sumitomo Dainippon Pharma Co., Ltd. (Head Office: Osaka; Representative Director, President and CEO: Hiroshi Nomura; hereafter, "Sumitomo Dainippon Pharma") have conducted a collaborative research on the search of biomarker candidates and applicable disease subtypes for DSP-5336 (Development code; hereafter, "the compound"), a novel MENIN-MLL interaction inhibitor. We announce today that the first patient has been administered with the compound in the Phase 1/2 clinical study that Sumitomo Dainippon Pharma is conducting in US, Canada, and Japan for acute myeloid leukemia.

Chemotherapy continues to be the major treatment for acute leukemia to date. But there are some cases with an unfavorable prognosis where a cure is difficult to be achieved. In particular, the 5-year survival rate for the acute leukemia patients with chromosomal translocations of the *MLL* gene is extremely poor (less than 20%), and thus there is a great need for the development of innovative molecularly targeted therapies.

Chromosomal translocations of *MLL* generate MLL fusion genes, whose products induce abnormally high expression of some leukemia-associated genes, causing malignant leukemia. The research team of National Cancer Center Tsuruoka Metabolomics Laboratory at Shonai Regional Industry Promotion Center led by Akihiko Yokoyama was the first in the world to discover that the onset of acute leukemia involved association of MLL fusion protein with a co-factor protein called MENIN. This provided a basis on which compounds that disrupt MLL-MENIN protein interaction would have inhibitory effects on leukemia cell growth. Based on this notion, the compound, a selective, potent inhibitor of MENIN-MLL interaction, was developed in the collaborative research project (DSK project) between Yokoyama's research team then in Kyoto University (Headquarters: Kyoto; President: Nagahiro Minato) and Sumitomo Dainippon Pharma. In addition, the team of Issay Kitabayashi at National Cancer Center, and the Yokoyama's team then in National Cancer Center Tsuruoka Metabolomics laboratory performed nonclinical studies (hereafter, "the studies*") for the compound, demonstrating an excellent antitumor activity of the compound against various types of leukemia using human clinical specimens accumulated by the National Cancer Center as well as various mouse leukemia models.

Sumitomo Dainippon Pharma will continue to develop the compound as an anti-cancer drug, aiming to apply for the patients with the acute myeloid leukemia with *MLL* gene rearrangements or with NPM1 mutations.

Leveraging the knowledge of cancer research accumulated in the National Cancer Center and the knowledge of drug discovery research accumulated in Sumitomo Dainippon Pharma, they aimed to deliver innovative therapies to acute myeloid leukemia patients with an unfavorable prognosis.

* The studies are supported by Japan Agency for Medical Research and Development (AMED) for the basic scheme of its Acceleration Transformative Research for Medical Innovation Program (ACT-M) (collaboration among industry, academia and government).
The National Cancer Center is also supported by an AMED Project for Cancer Research and Therapeutic Evolution (P-CREATE) for related blood cancer research.

Additional information

About acute myeloid leukemia

Acute myeloid leukemia, a type of blood cancer, is caused by overgrowth of myeloid-type blood cells (leukemia cells) with impaired differentiation capability in the bone marrow where the most blood cells are produced. It is a fatal disease that causes severe symptoms in a short period of time if appropriate treatment is not given, because abnormal proliferation of leukemia cells inhibits normal hematopoietic function. Around 7,000 people are diagnosed with this disease in Japan annually. In recent years, more sophisticated disease type classification based on chromosomal karyotype/gene mutation analysis of leukemia cells has helped determine treatment strategies suitable for each patient. Although potent anticancer agents (chemotherapy) are used as the primary treatment option for acute myeloid leukemia, the patients with treatment-resistant type disease and the elderly patients who cannot endure such a strong treatment, do not have sufficient treatment options.

About *MLL*-rearranged leukemia and *NPM1*-mutated leukemia

MLL-rearranged leukemia is induced when the *MLL* gene located on chromosome 11 is damaged and translocated to other gene locus, generating chimeric MLL fusion genes. More than 80 MLL fusion genes have been reported to date and the prognosis of the *MLL*-rearranged leukemia is known to be extremely poor. The 5-year survival rate for *MLL*-rearranged leukemia is around 20% due to the resistance to standard therapy using chemotherapy agents. Therefore, development of innovative new drugs has been awaited.
As for *NPM1*-mutated leukemia, mutations occur in the nucleophosmin 1 (*NPM1*) gene, which encodes a nuclear phosphorylated protein, and the leukemia develops due to its abnormal function. While a NPM1 mutation itself is not a poor prognostic factor for acute myeloid leukemia, other gene mutations (FLT3 mutation, IDH1/2 mutation, TP53 mutation, etc.) coexist in many cases and the combinations of these mutations cause leukemia with a moderate or poor prognosis. While molecularly targeted drugs focused on these coexisting

mutations may be effective in some cases, no drug targeting the NPM1 mutation has not been approved.

Development chronology

This drug has been developed through more than twenty years of basic research. Yokoyama and Kitabayashi started the research on the cancer biology of *MLL*-rearranged leukemia since 1998 in National Cancer Center. Yokoyama continued on this research as a postdoctoral scholar in United States and discovered that both normal and abnormal oncogenic forms of MLL proteins physically associate with MENIN (Yokoyama et al., 2004) (Figure 1A). He showed that oncogenic MLL fusion proteins needed to form a complex with MENIN to transform normal hematopoietic cells into leukemia cells (Yokoyama et al., 2005). He further demonstrated that MLL proteins became capable of binding to LEDGF as a complex with MENIN in order to recognize the genomic regions that regulated the expression of leukemia-associated genes (Yokoyama et al. 2008). These discoveries revealed that the abnormal expression of leukemia-associated genes in leukemia cells was achieved by an MLL/MENIN complex directly binding to specific genomic regions. These notions established molecular basis on which a compound that inhibits MLL-MENIN interaction would incapacitate MLL fusion proteins (Figure 1B). Since then, academia and industry embarked on the development of MENIN-MLL interaction inhibitors, resulting in competition among multiple pharmaceutical companies. This drug was developed in the DSK project where Yokoyama's research group (then in Kyoto University) and Sumitomo Dainippon Pharma collaborated in an effort to develop novel MENIN-MLL inhibitors. Later, Yokoyama joined National Cancer Center, where he evaluated the drug efficacies using mouse disease models at Tsuruoka metabolomics laboratory, Kitabayashi also evaluated it with human clinical materials collected in National Cancer Center Research Institute. These preclinical studies were supported by the AMED ACT-M research grant. There, they confirmed that some non-*MLL*-rearranged leukemias such as NPM1 mutations are also susceptible to this drug in addition to *MLL*-rearranged leukemia. Sumitomo Dainippon Pharma has started a Phase I/2 clinical studies in US, Canada, and Japan and the first administration to a patient has been performed recently. This is one of the cases where understanding of the disease mechanism by basic medical research led to the development of a drug, underscoring the importance of basic medical research.

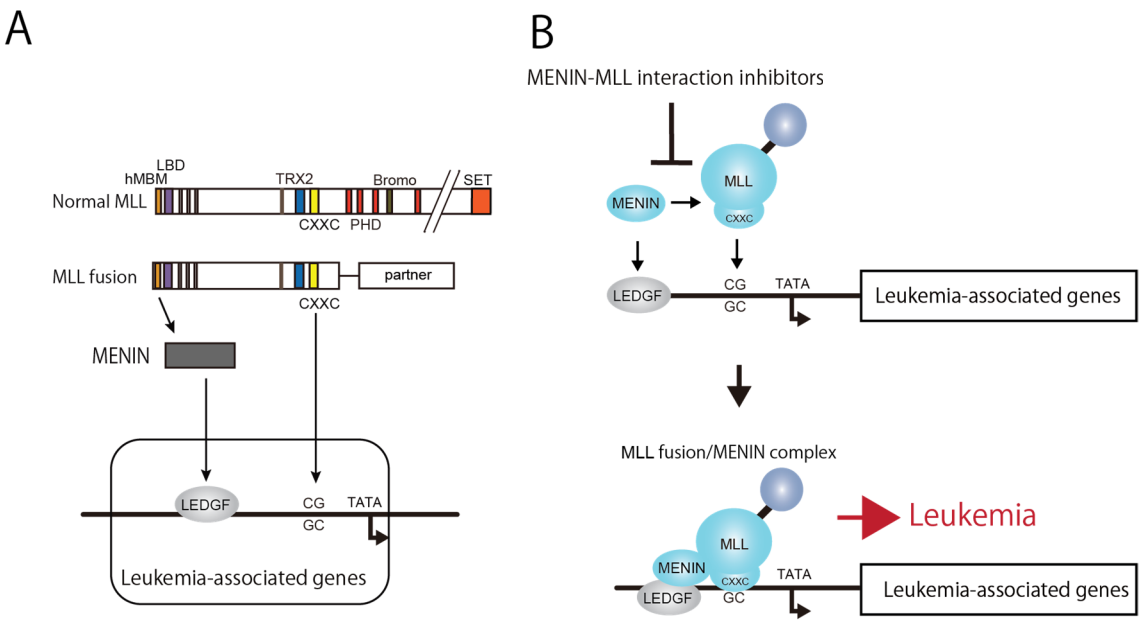

Figure 1 Inhibitory mechanism of MENIN-MLL interaction inhibitors.

A. The structures of normal MLL and oncogenic MLL fusion proteins. MLL proteins associate with LEDGF through MENIN, while the CXXC domain of MLL binds to CG DNA sequence in the genome.

   MLL fusion proteins stably bind to the genomic regions through two molecular interactions. One is through the CXXC domain which recognizes CG DNA sequence that is clustered in the regulatory regions of genes. The other is through the MENIN binding structure that tightly binds to MENIN (Yokoyama et al. 2004 Yokoyama et al. 2005). The MLL fusion/MENIN complex then associates with a protein called LEDGF, which binds to the genomic regions that regulate gene expression. (Yokoyama and Cleary, 2008). It is necessary for the MLL fusion/MENIN complex to have these two molecular interactions to bind stably to the genomic regions of leukemia-associated genes. (Okuda et al. 2014).

B. By inhibiting MENIN-MLL interaction using MENIN-MLL interaction inhibitors such as DSP-5336, we can keep MLL fusion proteins from the leukemia-associated genes, and render leukemia cells into non-cancerous benign cells.

About DSK Project

This project was an industry-academia collaborative project between Sumitomo Dainippon Pharma and Kyoto University and had been conducted from March 2011 to March 2021 mainly at Medical Innovation Center of Kyoto University, the Japan's first open innovation base. A research team from Sumitomo Dainippon Pharma worked together with research teams of Kyoto University toward the creation of innovative anticancer agents, diagnostic tools, and therapeutic methods. Since April 2021, research activities have continued as a collaborative research laboratory.

About National Cancer Center

The National Cancer Center is one of the largest cancer research institutes in Japan. We support a wide range of activities from extremely original basic research to research on the development of actual therapeutic and diagnostic agents in cooperation with the National Cancer Center Hospital (Tokyo) and National Cancer Center Hospital East (Chiba).

So far, we have achieved many results in cancer genome analysis by developing various sequencers and unique bioinformatics, which has led to drug development based on the discovery and clinical studies in collaboration with the hospitals. We are also focusing on the development of elemental technologies for cancer genomic medicine. We are working on the development of Japan's first oncogene panel test and its insurance coverage, and a gene panel test method for hematopoietic malignancies and pediatric cancers. Furthermore, in expanding bioresources, more than 400 types of patient-derived xenograft mice and more than 20,000 types of fresh frozen tumor tissue biobanks have already been established, and these can be effectively utilized in Japan. We are developing joint research with outside academia and companies.

For more details, please visit the National Cancer Center's website.
(https://www.ncc.go.jp/jp/about/index.html)

About Shonai Regional Industry Promotion Center

Shonai Regional Industry Promotion Center was established in 1987 as a public foundation with the objectives of creating vibrant regional economies and communities and contributing to improve the lives of local people by fostering and supporting the development of local industry. This is the organization responsible for implementing the projects of the National Cancer Center Tsuruoka Metabolomics Laboratory.

For more details, please visit Shonai Regional Industry Promotion Center's website. (https://www.shonai-sansin.or.jp)

About Sumitomo Dainippon Pharma

Sumitomo Dainippon Pharma defines its corporate mission as to "broadly contribute to society through value creation based on innovative research and development activities for the betterment of healthcare and fuller lives of people worldwide". By channeling our total efforts into research and development for new drugs, we aim to provide innovative and effective pharmaceutical solutions to people not only in Japan but also worldwide in order to realize our corporate mission.

For more details, please visit Sumitomo Dainippon Pharma's website. (https://www.ds-pharma.co.jp/)

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Reference

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