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Stella Pharma Corporation
Mitsubishi Chemical Group Corporation
Graduate School of Arts and Sciences, the University of Tokyo

**Stella Pharma, Mitsubishi Chemical Group, and the University of Tokyo
Conclude Joint Research Agreement
—Accelerating practical application of polyvinyl alcohol (PVA)
for boron neutron capture therapy (BNCT)—**

Stella Pharma Corporation (Head office: Chuo-ku, Osaka City; President and COO: Koki Uehara; hereinafter, “Stella Pharma”), Mitsubishi Chemical Corporation of the Mitsubishi Chemical Group (Head office: Chiyoda-ku, Tokyo; hereinafter “the MCG Group”), and the University of Tokyo (Headquarters: Bunkyo-ku, Tokyo; President: Teruo Fujii; hereinafter, “UTokyo”) have concluded an agreement on joint research into the composition of and formulation method for a boron neutron capture therapy (BNCT) drug consisting of polyvinyl alcohol*¹ and p-boronophenylalanine*² with a view to practical applications.

[Research background of the joint research]

BNCT is a cancer therapy in which boron (¹⁰B) is irradiated with thermal neutrons to cause a nuclear reaction, producing highly cytotoxic alpha particles and lithium recoil nuclei that treat cancer.

The key to this therapy lies in the degree to which ¹⁰B can be selectively aggregated in cancer cells. Currently, the boron compound chiefly used in clinical practice is a substance called p-boronophenylalanine (BPA) (generic name: borofalan [¹⁰B]). As BPA has the property of being taken up by cancer cells via LAT1, an amino acid transporter that is abundantly expressed on the cells, it can be selectively accumulated in cancer tissue.

However, BPA cannot always be retained in the cells for long periods of time following selective aggregation. It is believed that a prolonged retention of BPA in cancer cells will further improve the therapeutic efficacy of BNCT. In an earlier research project, Dr. Takahiro Nomoto, Associate Professor at the Graduate School of Arts and Sciences, UTokyo (then Assistant Professor at Tokyo Institute of Technology), and others discovered that when polyvinyl alcohol (PVA) was bound with BPA, the substance remained in cancer cells for significantly longer periods of time after having been selectively and actively taken up by them.*³

Dr. Nomoto’s earlier research project was selected for the Acceleration Transformative Research for Medical Innovation (ACT-M) initiative, a project undertaken by the Japan Agency for Medical Research and Development (AMED), for the period between August 2020 and March 2023. Dr. Nomoto served as the leader of the project to optimize the formulation composition for practical

application, working in partnership with Stella Pharma, which had developed a BPA formulation, obtained regulatory approval, and become the world's only seller of an approved BNCT drug. Through the research, it was discovered that, by adding PVA to the currently marketed BNCT drug, a new BNCT product in the form of a PVA-sorbitol-BPA formulation could be developed for possible practical application. The new drug is anticipated to enhance ¹⁰B accumulation and retention in tumors, thereby improving the efficacy of BNCT and expanding its scope of application.

However, PVA-sorbitol-BPA still has issues to be addressed, including in terms of storage stability as a pharmaceutical product. With a view to solving these issues, the MCG Group joined the research team. The MCG Group is a PVA manufacturer and the first in Japan to acquire the EXCiPACT certification for Good Manufacturing Practice (GMP)^{*4}, with a proven track record of PVA sales to domestic and overseas pharmaceutical companies and diverse applications of PVA in solid and non-solid formulations. It has joined the project to make a new start on research with the aim of optimizing the composition of and formulation method of PVA-sorbitol-BPA for practical application.

[Purpose of the joint research]

The joint research will aim to optimize the composition of and formulation method for the BNCT drug composed of PVA, sorbitol, and BPA for the purpose of conducting non-clinical studies.

The three parties involved each have their respective roles: Dr. Nomoto's group at UTokyo will verify the efficacy of the PVA-sorbitol-BPA formulation; Stella Pharma will provide the BPA and determine the specifications of the PVA-sorbitol-BPA formulation by drawing on its development experience; and the MCG Group will use its expertise in PVA to develop a new PVA-based formulation and evaluate its physical properties.

The three parties will study the optimal composition of PVA-sorbitol-BPA, set its specifications, and accelerate the solution of the issues faced by evaluating its safety and therapeutic efficacy with the aim of achieving practical application of the formulation at the earliest possible timing.

[Future development]

This industry-academia collaborative research is conducted to achieve practical application based on the close partnership between the parties concerned. Through the joint research, the standardization of a PVA-sorbitol-BPA formulation is expected to be accomplished, and efforts will be made to obtain non-clinical proof of concept (POC) in order to proceed to clinical development by using public research and development support programs at an appropriate time.

*1 Polyvinyl alcohol (PVA): Colorless, odorless, water-soluble polymer with excellent biocompatibility. The MCG Group manufactures and markets high-quality PVA with impurities removed (product name: GOHSENOL™ EG Series), which is used as a pharmaceutical excipient in Japan and overseas.

*2 P-boronophenylalanine (BPA): A compound with a structure similar to that of essential amino acid phenylalanine, but containing boron atoms. It is known to be selectively and efficiently taken up by cancer cells. When irradiated with thermal neutrons, the boron atoms in the compound cause a nuclear reaction that kills cancer cells.

*3 Dr. Nomoto's group reported on "the utilization of slime chemistry" in 2020, drawing attention for his discovery that PVA, the main ingredient of liquid glue, can be applied to develop formulations for BNCT. The research forms the basis of this joint research.

*4 EXCiPACT GMP is an international certification program for the manufacture and distribution of pharmaceutical excipients. It serves as a proof of compliance with the stringent demands of pharmaceutical manufacturers on an international level.

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