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TOTAL SYNTHESIS AND NONCLINICAL STUDY RESULTS OF A NOVEL ANTICANCER DRUG CANDIDATE E7130 DERIVED FROM TOTAL SYNTHESIS OF HALICHONDRIN FOUND IN JOINT RESEARCH BETWEEN EISAI AND HARVARD UNIVERSITY SCIENTISTS, PUBLISHED IN SCIENTIFIC REPORTS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that a joint research group including scientists from Eisai and Professor Yoshito Kishi's group of Harvard University has achieved a total synthesis and obtained results of nonclinical studies of the novel compound, E7130, derived from total synthesis of halichondrin. These results have been published in *Scientific Reports*, a scientific journal of *Nature*.[1] Currently a Phase I study to investigate E7130 in solid tumor is underway in Japan.

Halichondrins, which was isolated from the marine sponge *Halichondria okadai* in 1986, was known for their outstanding antitumor activity in mice, however the supply from natural sources were limited. Furthermore, the very complicated chemical structure has prevented drug discovery and development based on intact halichondrins. The joint research group strictly controlled 31 asymmetric carbons and achieved a total synthesis of E7130, on a >10 g scale with >99.8% purity under GMP (good manufacturing practice) conditions.
The joint research team also demonstrated that E7130 is not only a novel microtubule dynamics inhibitor but can also increase intratumoral CD31-positive endothelial cells (vascular remodeling activity) and reduce alpha-SMA (smooth muscle actin)-positive cancer-associated fibroblasts (anti-CAF effect), which are important constituents of the tumor microenvironment and may be involved in the malignant transformation of cancers in nonclinical in vivo studies.
According to these unique effects, E7130 augments the effect of antitumor treatments in nonclinical studies. Overall, our work demonstrates that a total synthesis can address the issue of limited material supply in drug discovery and development even for complex natural products.

"In 1992, it was unthinkable to synthesize a gram-quantity of a halichondrin," said Yoshito Kishi, Morris Loeb Professor of Chemistry, Emeritus, in the Department of Chemistry and Chemical Biology at Harvard University, said "but three years ago we proposed it to Eisai. Organic synthesis has advanced to that level, even with molecular complexity that was untouchable several years ago. We are very delighted to see our basic chemistry discoveries have now made it possible to synthesize this compound at large scale."

Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. We will maximize the potential of halichondrins by adding E7130 project to two investigational projects of Eisai's eribulin platform; MORAb-202 (antibody-drug conjugate with eribulin as the payload) and liposomal formulation of eribulin, as it seeks to contribute further to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families, and healthcare providers.

* Harvard has exclusively licensed the intellectual property associated with this research project to Eisai for the commercial development of therapeutics.

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[Notes to editors]

About E7130

E7130 is a next-generation agent improving tumor microenvironment, which has been developed by a joint research with Eisai and Harvard University. E7130 is derived from total synthesis of halichondrin, a natural product isolated from the marine sponge *Halichondria okadai*. E7130 is believed to improve tumor microenvironment by unique action for potential effect on immune activation by releasing hypoxia and suppressing interaction between cancer cells and stroma. A Phase I study to investigate E7130 in solid tumor is currently underway in Japan.

[1.] Kawano S et al., “A landmark in drug discovery based on complex natural product synthesis” *Scientific Reports* 2019.