（第 12 号様式）

学 位 論 文 の 要 約
（研 究 成 果 の ま と め）

氏　　名 武　洲英

学位論文名　*HMGA2* は *MLL-AF4* 融合遺伝子を有する乳児急性リンパ性白血病での分子標的になりうる

学位論文の要約

Acute lymphoblastic leukemia (ALL) in infants is an intractable cancer in childhood. Although recent intensive chemotherapy progress has considerably improved ALL treatment outcome, disease cure is often accompanied by undesirable long-term side effects, and efficient, less toxic molecular targeting therapies have been anticipated. In infant ALL cells with *MLL* fusion, the microRNA *let-7b* is significantly downregulated by DNA hypermethylation of its promoter region. We show here that the expression of *HMGA2*, one of the oncogenes repressed by *let-7b*, is reversely upregulated in infant ALL leukemic cells, particularly in *MLL-AF4* positive ALL. In addition to the suppression of *let-7b*, MLL fusion proteins positively regulate the expression of *HMGA2*. HMGA2 is one of the negative regulators of the cyclin-dependent kinase inhibitor p16INK4A. The HMGA2 inhibitor netropsin, when combined with demethylating agent 5-azacytidine, upregulated and sustained the expression of $p16^{INK4A}$which resulted in growth suppression of *MLL-AF4*-expressing cell lines. This effect was more apparent compared to treatment with 5-azacytidine alone. These results indicate that the *let-7b*-HMGA2-$p16^{INK4A}$ axis plays an important role in cell proliferation of leukemic cells and could be a possible target for molecular targeting therapy of infant ALL with *MLL-AF4*.

In conclusion, although the complete mechanism underlying the induction of leukemogenesis in *MLL*-rearranged infant ALL remains obscure, our results suggest that downregulation of the miRNA *let-7b* and upregulation of oncogenic HMGA2 by an MLL fusion protein play key roles in this process. HMGA2 inhibitors such as netropsin could be new therapeutic agents for *MLL-AF4*-positive infant ALL, particularly in combination with demethylating agents such as 5-azacytidine.

The contents of this thesis is already accepted and published in the following original papers。

The main thesis : Zhouying Wu, Minenori Eguchi-Ishimae, Chihiro Yagi, Hidehiko Iwabuki, Wenming Gao, Hisamichi Tauchi, Takeshi Inukai, Kanji Sugita, Eiichi Ishii,and Mariko Eguchi: HMGA2 as a potential molecular target in *MLL-AF4*-

positive infant acute lymphoblastic leukemia. British journal of haematology (Accepted)

Reference paper : Masanori Nishi, Minenori Eguchi-Ishimae, Zhouying Wu, Wen ming Gao, Hidehiko Iwabuki, Sanae Kawakami, Hisamichi Tauchi, Takeshi Inu kai, Kanji Sugita, Yuhei Hamasaki, Eiichi Ishii, and Mariko Eguchi: Suppression of the *let-7b* microRNA pathway by DNA hypermethylation in infant acute lymphoblastic leukemia with *MLL* gene rearrangements. Leukemia. 27, 2, 389-97. DOI: 10.1038/leu.2012.242