49.$CD34^+/CD38^-$ acute myelogenous leukemia cells aberrantly express Aurora kinase A

Jing Yang[1)], Takayuki Ikezoe[1)], Mutsuo Furihata[2)], Chie Nishioka[1)],
Akihito Yokoyama[1)]
[1)]Department of Hematology and Respiratory Medicine,
[2)] Department of Pathology, Kochi Medical School, Kochi University,

Aurora kinase A (AURKA) plays a pivotal role in the mitotic processes during cell division. We previously showed that AURKA was aberrantly expressed in hematological malignant cells including those from acute myelogenous leukemia (AML), compared to bone marrow mononuclear cells (BMMCs) isolated from healthy volunteers. We have recently shown that $CD34^+/CD38^-$ AML cells, enriched for leukemia stem cells (LSCs), were relatively resistant to cytarabin-mediated growth inhibition compared to their $CD34^+/CD38^+$ counterparts. This study attempted to identify therapeutic targets in $CD34^+/CD38^-$ AML cells and found that freshly isolated $CD34^+/CD38^-$ AML cells from patients (n=12) expressed a greater amount of AURKA than their $CD34^+/CD38^+$ counterparts, as well as $CD34^+$ normal hematopoietic stem/progenitor cells (HSCs) isolated from healthy volunteers (n=6) as measured by real time RT-PCR. Blockade of AURKA by a specific inhibitor MLN8237 significantly inhibited proliferation and induced apoptosis of $CD34^+/CD38^-$ AML cells in association with downregulation of anti-apoptotic proteins such as Bcl-2, Bcl-xL and Mcl-1 and increase in Bax/Bcl-2 ratio. Importantly, inhibition of AURKA in $CD34^+/CD38^-$ AML cells by MLN8237 significantly impaired engraftment of these cells in severly immunocompromised mice and prolonged their survival. Moreover, MLN8237 potently inhibited proliferation of engrafted human AML cells in association with reduction in a population of $CD34^+/CD38^-$ AML cells in murine BMs and spleens. Taken together, AURKA may be a promising molecular target to eliminate chemotherapy-resistant $CD34^+/CD38^-$ AML cells.