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DBT - AIST International Laboratory for Advanced Biomedicine

DAILAB

Classroom for Advanced & Frontier Education

CAFE

DAILAB CAFÉ

Series 51

DAILAB-CAFE

Series - 51

Date & Time: November 4, 2020 (3:30- 4:15 PM JST)
Speaker: Tomohiro EGUCHI
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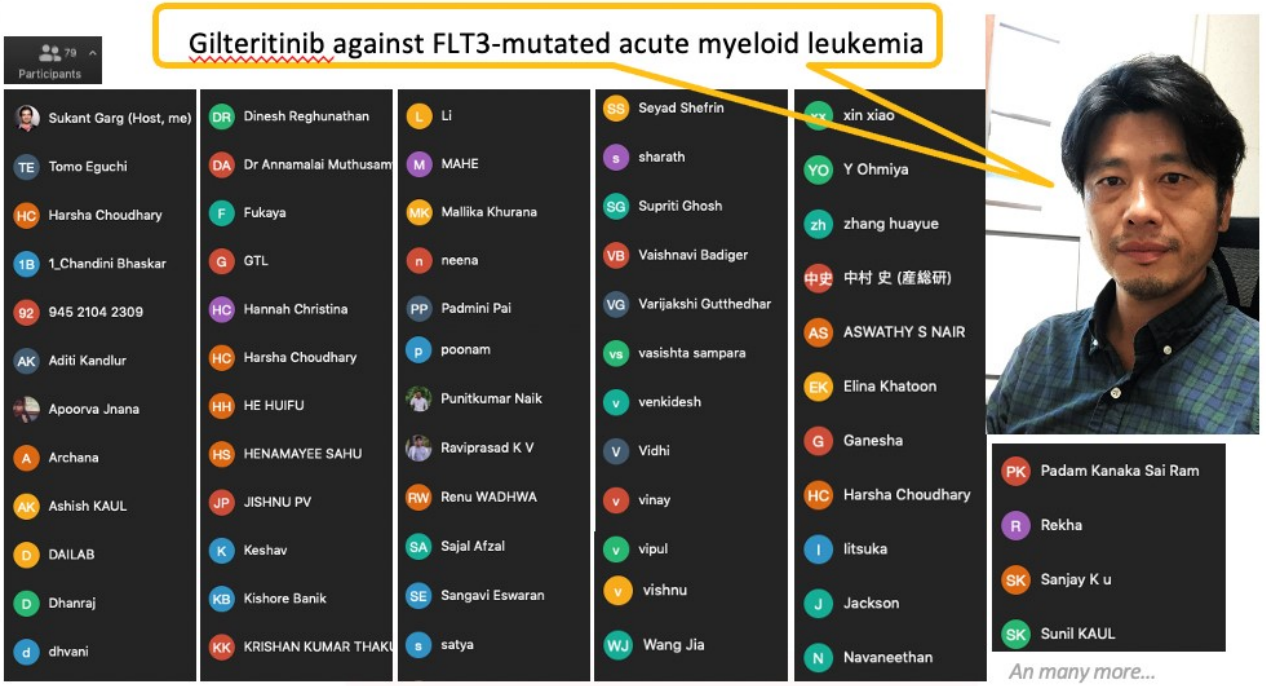
Title: Effect of Fms-like tyrosine kinase 3 (FLT3) ligand (FL) on antitumor activity of gilteritinib, a FLT3 inhibitor, in mice xenografted with FL-overexpressing cells

Therapeutic effects of FLT3 inhibitors have been reported in acute myeloid leukemia (AML) with constitutively activating FLT3 mutations, including internal tandem duplication (ITD) and point mutation, which are found in approximately one-third of AML patients. One of the critical issues of treatment with FLT3 inhibitors in FLT3-mutated AML is drug resistance. FLT3 ligand (FL) represents a mechanism of resistance to FLT3 inhibitors, including quizartinib, midostaurin, and sorafenib, in AML cells harboring both wild-type and mutant FLT3 (FLT3 wt/FLT3 mut). Here, we investigated the effect of FL on the efficacy of gilteritinib, a FLT3 inhibitor, in AML-derived cells in vitro and in mice. In contrast to other FLT3 inhibitors, FL stimulation had little effect on growth inhibition or apoptosis induction by gilteritinib. The antitumor activity of gilteritinib was also comparable between xenograft mouse models injected with FL-expressing and mock MOLM-13 cells. In the FLT3 signaling analyses, gilteritinib inhibited FLT3wt and FLT3-ITD to a similar degree in HEK293 and Ba/F3 cells, and similarly suppressed FLT3 downstream signaling molecules (including ERK1/2 and STAT5) in both the presence and absence of FL in MOLM-13 cells. Co-crystal structure analysis showed that gilteritinib bound to the ATP-binding pocket of FLT3. These results suggest that gilteritinib has therapeutic potential in FLT3-mutated AML patients with FL overexpression.



*Live online, via 'Zoom', From **AIST, Japan***

DAILAB (DBT-AIST International Laboratory for Advanced Biomedicine) CAFÉ (Classroom for Advanced and Frontier Education) is held once in six weeks and provides a relaxed CAFÉ-like environment for study and learning. This is a Classroom setting rather than a lecture on data presentation. Frontier topics are selected for CAFÉ talks that are presented by eminent scientists on an educational level and are skyped to all the overseas institutions (DAILAB CAFE and its Satellites). Participating Institutions include AIST (Tsukuba, Japan), IIT Delhi (India), Hanyang University (South Korea), Peking Medical University (China), Brawijaya University (Indonesia), Manipal University (India), IIT-Guwahati (India) and Guru Nanak Dev University (India). **Tomohiro Eguchi from Astellas Pharma and the University of Tsukuba (Japan) has been working on not one but a variety of research domains as a pharmaceutical inventor and researcher. He has authored various high impact publications. One of these were presented today in the DAILAB CAFÉ Series 51 by Eguchi San. The title of his presentation was "Effect of Fms-like tyrosine kinase 3 (FLT3) ligand (FL) on antitumor activity of gilteritinib, a FLT3 inhibitor, in mice xenografted with FL-overexpressing cells".** Therapeutic effects of FLT3 inhibitors have been reported in acute myeloid leukemia (AML) with constitutively activating FLT3 mutations, including internal tandem duplication (ITD) and point mutation, which are found in approximately one-third of AML patients. One of the critical issues of treatment with FLT3 inhibitors in FLT3-mutated AML is drug resistance. FLT3 ligand (FL) represents a mechanism of resistance to FLT3 inhibitors, including quizartinib, midostaurin, and sorafenib, in AML cells harboring both wild-type and mutant FLT3 (FLT3 wt/FLT3 mut). Here, Eguchi San and his colleagues investigated the effect of FL on the efficacy of gilteritinib, a FLT3 inhibitor, in AML-derived cells *in vitro* and in mice. They observed that in contrast to other FLT3 inhibitors, FL stimulation had little effect on growth inhibition or apoptosis induction by gilteritinib. The antitumor activity of gilteritinib was also comparable between xenograft mouse models injected with FL-expressing and mock MOLM-13 cells. In the FLT3 signaling analyses, gilteritinib inhibited FLT3wt and FLT3-ITD to a similar degree in HEK293 and Ba/F3 cells, and similarly suppressed FLT3 downstream signaling molecules (including ERK1/2 and STAT5) in both the presence and absence of FL in MOLM-13 cells. Co-crystal structure analysis showed that gilteritinib was bound to the ATP-binding pocket of FLT3. Their results suggest that gilteritinib has therapeutic potential in FLT3-mutated AML patients with FL overexpression.

Thanks for participation