NU Tech
Technology Partnership of Nagoya University, Inc.

(A68)

Novel Drug for the Treatment of Juvenile Myelomonocytic Leukemia

Background:

Juvenile Myelomonocytic Leukemia (JMML) is a rare type of blood cancer that occurs in infants and during early childhood. And JMML is caused by excessive myelomonocytic cell proliferation. More than 80% of patients harbor either somatic or germline mutations in RAS pathway genes, and previous studies have identified several biomarkers associated with poor prognosis. However, the molecular pathogenesis of 10% to 20% of patients and the relationships among these biomarkers have not been well defined.

Technology Overviews:

Nagoya University researchers have successfully identified a drug for the treatment of JMML using integrated molecular profiling. RNA- sequencing identified ALK/ROS1 tyrosine kinase fusions in 18 % patients who lacked canonical RAS pathway mutations. Crizotinib, an ALK/ROS1 inhibitor, markedly suppressed ALK/ROS1 fusion–positive JMML cell proliferation in vitro. Further, administered to a chemotherapy- resistant patient, crizotinib achieved complete molecular remission. Also, Genome-wide methylation analysis identified the hypermethylation profile associated with poor clinical outcome. This technology revealed the relationships among biomarkers for
JMML and identified a crizotinib as a candidate drug of JMML, which suppressed proliferation of JMML cells with canonical RAS pathway mutations.

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Figures:

Figure 1. Clinical and genetic profiles of 150 patients. Each column indicates 1 patient. The methylation analysis included 106 (71%) of the 150 patients. HbF, fetal hemoglobin; LOH, loss of heterozygosity; Plt, platelet count.

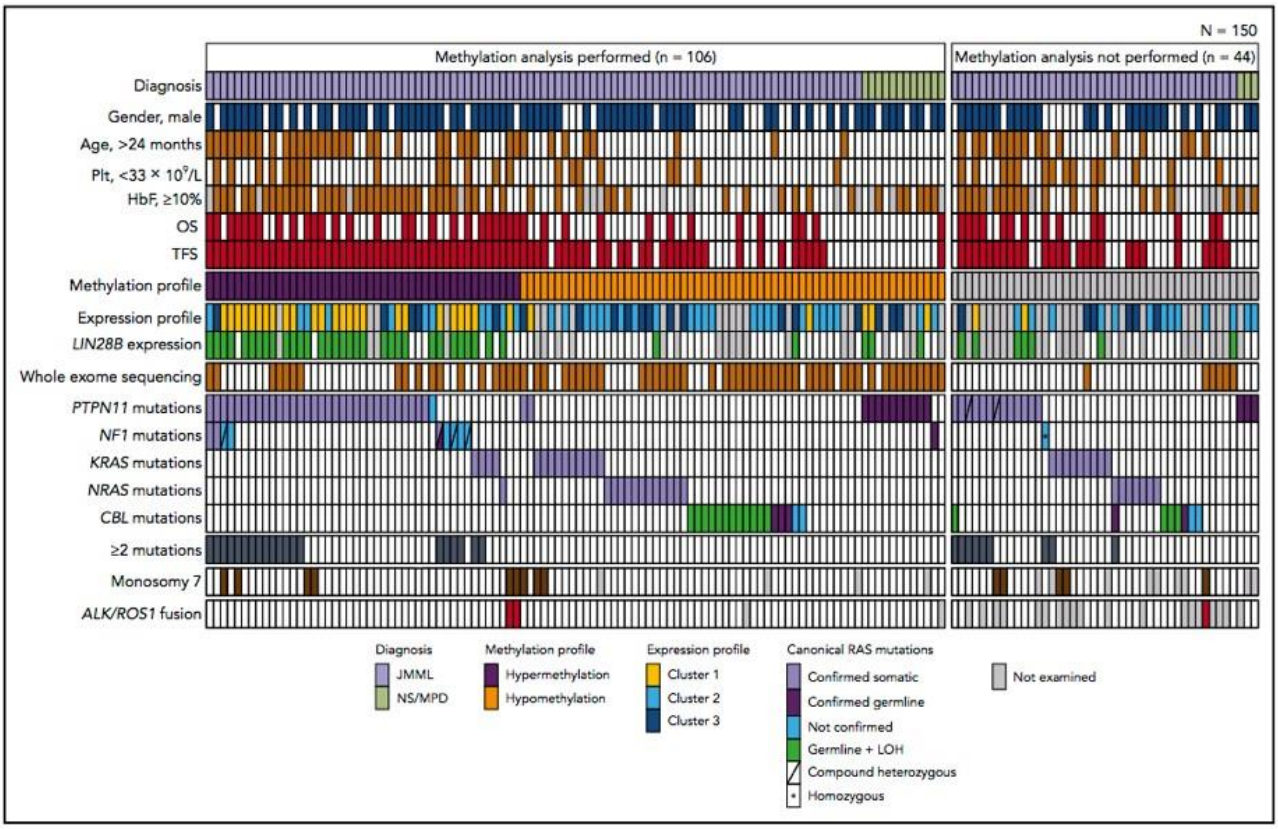

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Figure 2. Effect of crizotinib on colony formation by JMML cells with ALK/ROS1 fusion. (A-C) Effect of crizotinib (ALK/ROS1/MET inhibitor) on colony formation by RANBP2- ALK1 CD341 cells. A total of 1 3 103 CD341 cells from a patient with RANBP2-ALK was cultured for 2 weeks with or without cytokine-supplemented culture media in the presence or absence of the indicated amount of crizotinib. (A) Microscopic appearance of colony-forming unit, granulocyte-macrophage (CFU-GM) colonies. (B-C) Numbers of colonies (B) with and (C) without cytokines. (D-F) Effect of crizotinib on colony formation by DCTN1-ALK1 CD341 cells. (D) Microscopic appearance of CFU-GM colonies. (E-F) Numbers of colonies (E) with and (F) without cytokines. BFU-E, burst-forming unit erythroid. †P , .01.

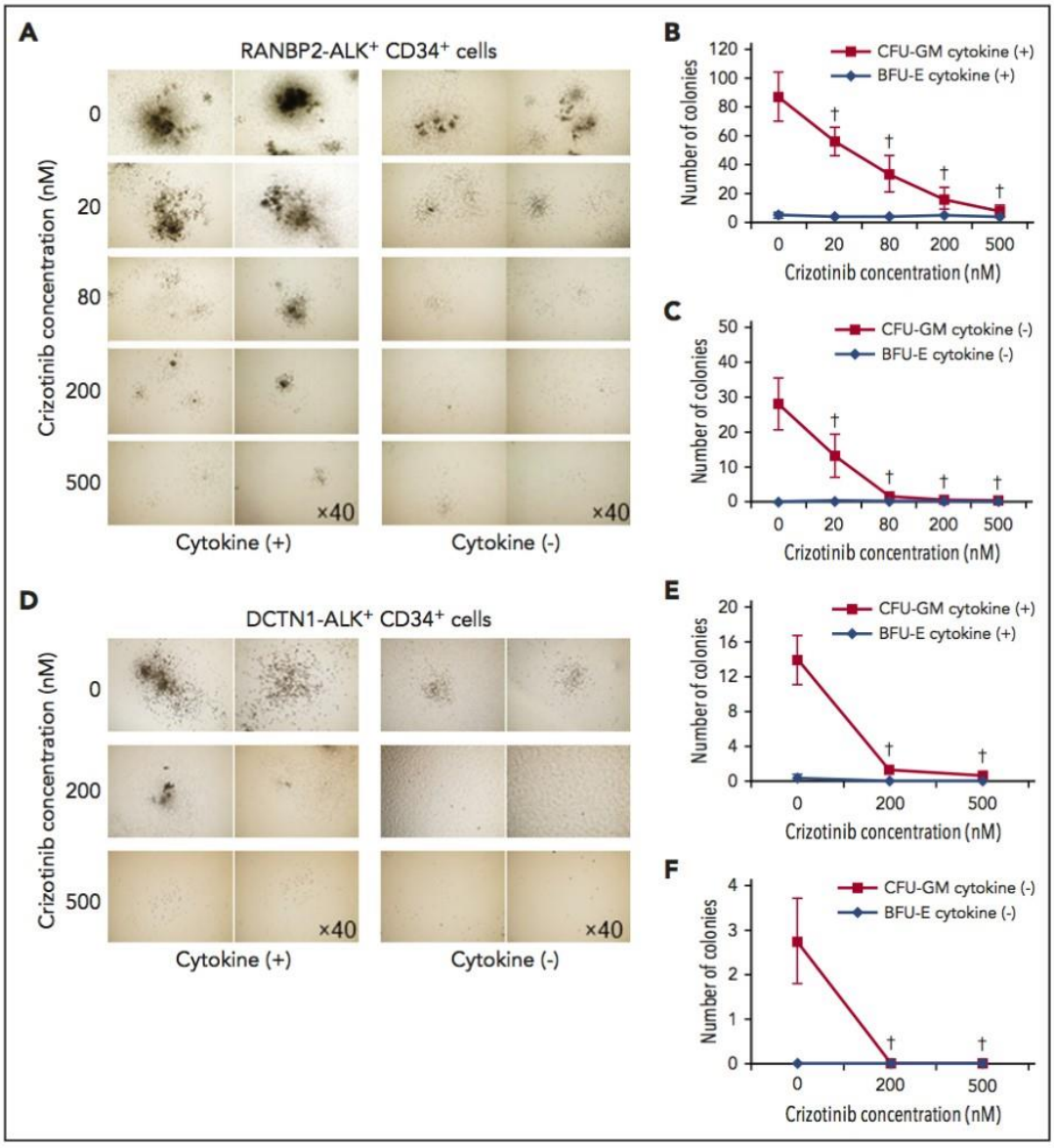

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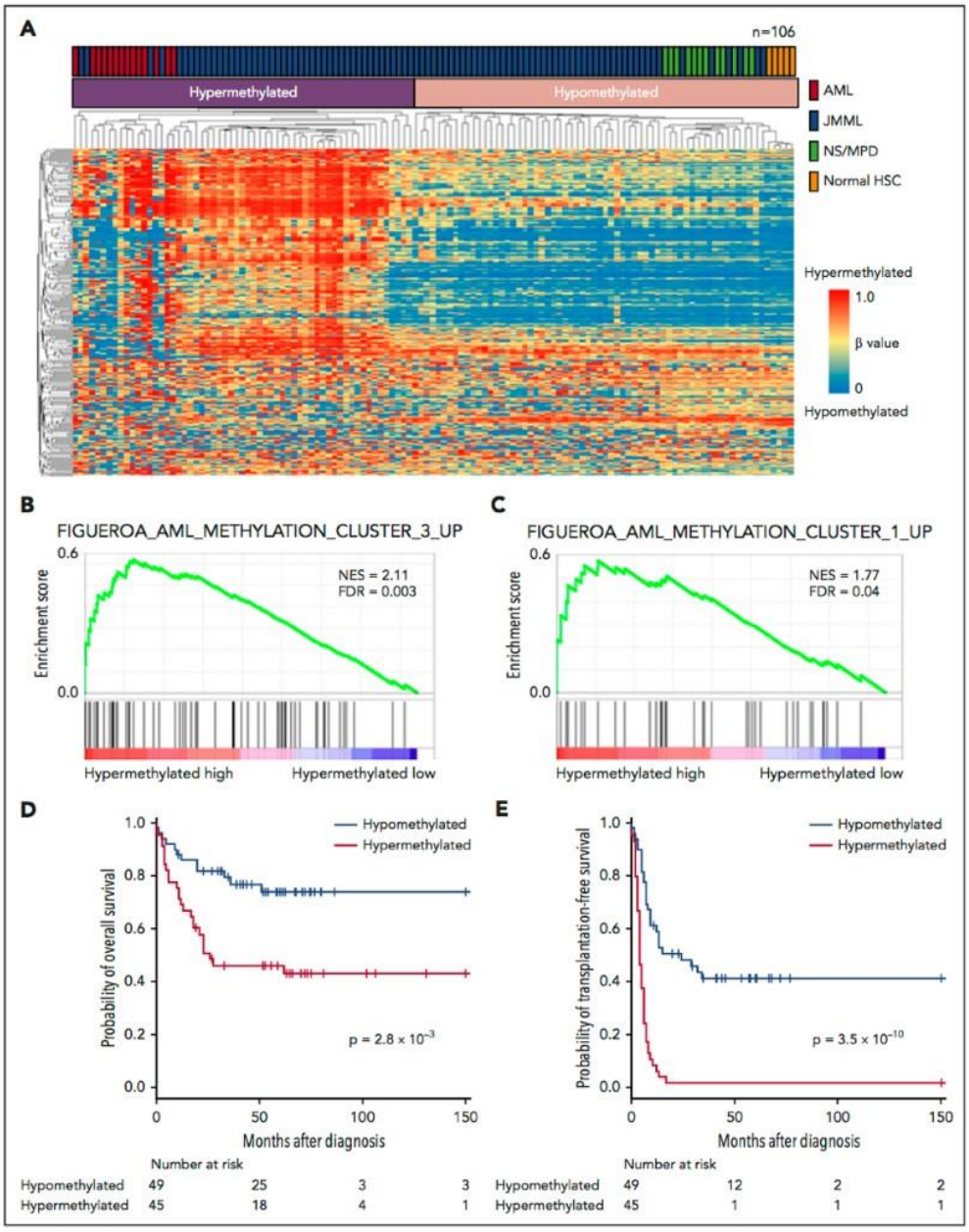
Figure 3. Genome-wide methylation analysis. (A) Unsupervised hierarchical clustering based on methylation profiles of patients with JMML (n 5 94) or NS/MPD (n 5 12) and repository data from normal CD341 (n 5 5) and AML CD341CD382 samples (n 5 14). (B-C) Gene set enrichment analysis. (D) OS and (E) TFS of patients with JMML according to the methylation profiling-based classification. Patients with NS/MPD were excluded from survival analyses. FDR, false discovery rate; HSC, hematopoietic stem cell; NES, normalized enrichment score.



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Further Details: Norihiro Murakami *et al*., Integrated molecular profiling of juvenile myelomonocytic leukemia. Blood 2018 131:1576-1586; doi: https://doi.org/10.1182/blood-2017-07-798157

Seeking: Licensing

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