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# Focal Adhesion Kinase Inhibitors Reverse the Stromal Adhesion Phenotype of Ikaros-Mutant B-ALL, Induce Apoptosis, and Synergize with ABL1 Tyrosine Kinase Inhibitors: A New Paradigm for Pathogenesis and Therapy of High-Risk B-ALL

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## Abstract

B-cell acute lymphoblastic leukemia (B-ALL) is a malignancy of precursor B-lymphocytes affecting both children and adults. Deletions and dominant-negative mutations in *IKZF1*, the gene encoding the Ikaros transcription factor, are found in ~85% of Ph<sup>+</sup> B-ALL and in some cases of Ph<sup>-</sup> B-ALL, and are associated with poor prognosis. Genomic studies of high-risk Ph<sup>+</sup> or "Ph-like" B-ALLs have revealed frequent mutation and activation of TK genes and signaling pathways. While ABL1 tyrosine kinase inhibitors (TKIs) such as dasatinib and imatinib have been added to chemotherapy regimens for Ph<sup>+</sup> B-ALL, over half of these patients will still relapse, which correlates with residual disease burden in the bone marrow (BM) following induction therapy. Hence, new therapeutic strategies are needed for patients with Ikaros-mutant, high-risk Ph<sup>+</sup> and Ph<sup>-</sup> B-ALL.

Using mice with a conditional *Ikzf1* mutation (*Ike5<sup>fl</sup>*) where the recombined allele is similar to the dominant-negative Ik6 mutant found in human B-ALL, we demonstrated recently that Ikaros DNA-binding function is required in the B-lymphoid lineage for transition from the large to small pre-B cell stage of differentiation, and that arrest at this stage of development can give rise to B-ALL (Joshi et al., Nat. Immunol. 2014;15:294). The survival and proliferation of Ikaros mutant pre-B cells is dependent on increased Integrin-mediated stromal adhesion and activation of focal adhesion kinase (FAK). FAK is a non-

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receptor TK, downstream of integrins and growth factor receptors, which plays important roles in cancer stem cell biology, the tumor microenvironment and tumorigenesis. VS-4718 and VS-6063 (defactinib) are potent, orally bioavailable FAK inhibitors that inhibit tumor growth and metastasis in preclinical models, and are currently under evaluation in clinical trials in patients with various solid tumors. VS-6063 has demonstrated tolerability and preliminary signs of clinical activity as a single agent and in combination with paclitaxel in phase I trials (ASCO, 2014). Here, we show that BCR-ABL1 cooperates with *Ikzf1* mutation to accelerate B-leukemogenesis in mice. BCR-ABL1<sup>+</sup> Ikaros-mutant B-ALLs exhibit stroma-mediated resistance to ABL1 TKIs, while the FAK inhibitors VS-4718 and VS-6063 are effective in blocking stromal adhesion and inducing apoptosis in both mouse and human Ikaros-mutant B-ALL samples.

To test whether dysregulation of TK signaling cooperates with *Ikzf1* mutation in the pathogenesis of high-risk B-ALL, we isolated BM B-lymphoid progenitor cells from wild-type (WT), *IkE5<sup>fl/+</sup> CD2-Cre*, and *IkE5<sup>fl/fl</sup> CD2-Cre* donors, transduced them with BCR-ABL1 retrovirus and transplanted the cells into recipient mice. We observed a dramatic acceleration of precursor B-lymphoid leukemia induced by BCR-ABL1 in *IkE5<sup>Δ/+</sup>* and particularly in *IkE5<sup>Δ/Δ</sup>* donor cells that correlated with a striking (~30-fold) increase in the frequency of engrafting leukemia-initiating or leukemic stem cells (LSCs). Relative to *Ikzf1* WT BCR-ABL1<sup>+</sup> leukemic cells, *Ikzf1*-mutant BCR-ABL1<sup>+</sup> blasts showed significant resistance to imatinib and dasatinib that was dependent on the presence of OP9 stroma.

The effect of FAK inhibition, using the FAK inhibitors VS-4718, VS-6062, and VS-6063 (Verastem), was first tested on murine B-ALL cells (genotypes *Ikzf1* mutant, *Ikzf1* mutant BCR-ABL1<sup>+</sup>, and *Ikzf1* WT BCR-ABL1<sup>+</sup>) grown on OP9 stroma. FAK inhibitor treatment abolished stromal adhesion of *Ikzf1*-mutant B-ALL and induced apoptosis in non-adherent cells, but had little effect on *Ikzf1* WT B-ALL cells. VS-4718 and VS-6063 were each synergistic with dasatinib in reducing the viability of *Ikzf1*-mutant BCR-ABL1<sup>+</sup> B-ALL cells cultured on OP9 stroma. For primary human B-ALL samples grown on OP9 stroma, *IKZF1*-mutant cells were also more sensitive to FAK inhibitor treatment than WT *IKZF1* WT B-ALL, with or without BCR-ABL1 expression.

Collectively, these observations suggest a new model to explain the pathogenesis of high-risk B-ALL and its resistance to therapy. B-ALLs with *IKZF1* mutations may be resistant to TKIs and to chemotherapy by virtue of their stromal adhesion phenotype, resulting in failure to eliminate BM LSCs. Inhibition of FAK signaling in Ph<sup>+</sup> or Ph<sup>-</sup> *IKZF1*-mutant B-ALL may reverse the stromal-mediated resistance to ABL1 TKIs and/or chemotherapy. Therefore, FAK inhibitors warrant further investigation for the treatment of high-risk *IKZF1*-mutant B-ALL patients.

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