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Restoration of Ikaros tumor suppressor function as a novel therapeutic approach for high-risk pediatric acute lymphoblastic leukemia

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B-cell acute lymphoblastic leukemia (B-ALL) is the most common childhood malignancy. High-risk B-ALL remains a therapeutic challenge. Relapse occurs in 20% of B-ALL cases and the overall survival ofrelapsed B-ALL is only 50%. This survival rate has remained unchanged over the last 40 years. Thus, there is an urgent need to understand the pathogenesis of high-risk B-ALL and to develop targeted treatment for this disease. Clinical studies using next-generation sequencing showed that the chance for relapse in B-ALL is increased 12-fold when there is deletion/mutation of one copy of the IKZF1 gene that encodes the Ikaros tumor suppressor protein. Here, we present recent advances in understanding the tumor suppressor function of Ikaros, and the development of targeted therapy that aims to restore Ikaros activity as tumor suppressor. Ikaros is a zinc finger DNA binding protein, that binds to the upstream regulatory elements of its target genes and regulates their transcription. DNA-binding analysis, along with functional studies, showed that Ikarossuppresses leukemia by repressing transcription of genes that are essential for cell cycle progression and for the PI3K signaling pathway. Our results also demonstrated that Ikaros function in B-ALL is impaired by Casein Kinase II (CK2), a pro-oncogenic kinase that directly phosphorylates Ikaros, resulting in the loss of Ikaros activity as a transcriptional regulator. In B-ALL, the ability of Ikaros to control cell cycle progression and the PI3K pathway is impaired by CK2, which is overexpressed in leukemia. Inhibition of CK2 with a novel, specific inhibitor, CX-4945, restoresIkaros function as a regulator of cell cycle progression and PI3K and results in a strong anti-leukemia effect. The therapeutic efficacy of CK2 inhibition and its ability to restore Ikaros tumor suppressor function have been demonstrated in vivo, in preclinical models of high-risk B-ALL. These include primary xenografts derived from patients with high-risk B-ALL, including B-ALL with deletion of one Ikaros allele. In conclusion, this is the first demonstration that Ikaros tumor suppressor function can be reactivated, even in cases of high-risk B-ALL with deletion of a single Ikaros allele. These results present a novel treatment mechanism for high-risk B-ALL – restoration of Ikaros tumor suppressor activity – and provide a mechanistic rationale for the use of CK2 inhibitor for treatment of B-ALL.

Biography:

Dr. Dovat completed his clinical training in Pediatrics at Pennsylvania State University, and in Pediatric Hematology/Oncology at UCLA-Children's Hospital. He received his research training at Cornell University Graduate School of Medical Sciences and at Howard Hughes Medical Institute at UCLA. As an independent investigator at the University of Wisconsin, Dr. Dovat focused his work on the regulation of the tumor suppression in childhood leukemia. Dr. Dovat is the recipient of The Young Investigator Award by The American Society of Pediatric Hematology/Oncology and has been included in the Best Doctors in America list. Since September 2010, Dr. Dovat has served as the Four Diamond Endowed Chair and Director of Translational Research and Developmental Therapeutics in Pediatric Hematology/Oncology at Pennsylvania State University College of Medicine, Hershey, PA. Dr. Dovat's research interests include epigenomic regulation and transcriptional control of cellular immortalization and senescence in leukemia and experimental therapy of malignant diseases.