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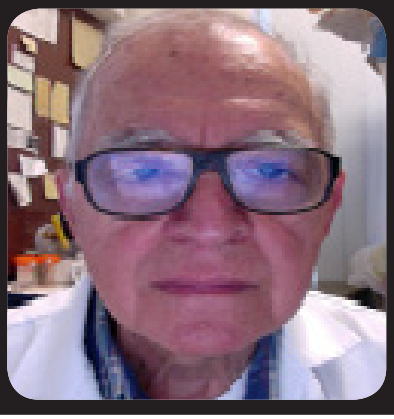

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TARGETING LEUKEMIC STEM CELLS USING AN INHIBITOR OF DNA METHYLATION (5-AZA-2'-DEOXYCYTIDINE) IN COMBINATION WITH AN INHIBITOR OF EZH2 (3-DEAZANEPLANOCIN A)

Preclinical studies have shown that the potent inhibitor of DNA methylation, 5-aza-2'-deoxcytidine (5AZA-CdR) shows remarkable antineoplastic activity against acute myeloid leukemia (AML). 5AZA-CdR is approved for the treatment of the hematologic malignancies, AML and MDS. However, the optimal dose-schedule remains to be determined. Colonies assays reveal that 5AZA-CdR can eradicate >99.9% of myeloid leukemic cells. We have to determine how <0.01% of the leukemic cells survive the treatment with 5AZA-CdR. One possible mechanism is due to the deficiency in deoxycytidine kinase (DK), the enzyme that activates the prodrug, 5AZA-CdR. A second mechanism that can limit the curative potential of 5AZA-CdR against leukemia is the presence of epigenetic gene-silencing marker, H3K27me3, on key tumor suppressor genes (TSGs). The methylation of H3K27 is catalyzed by EZH2 histone methyltransferase. I propose that leukemic stem cells (LSC) that have a double "lock" mechanism (DNA methylation and H3K27me3) on key TSGs so as to escape the chemotherapeutic action of 5AZA-CdR and block its curative potential. This hypothesis is supported by the preclinical data that shows that 5AZA-CdR in combination with an inhibitor of EZH2, such as 3-deazaneplanocin A (DZNep) display a remarkable synergy against leukemic cells that is much greater than either agent alone. In addition, the combination of these agents exhibits a pronounced activation of gene expression of thousands of genes, indicating that the "double lock" mechanism of gene silencing is a predominant epigenetic alteration in LSCs. One of the hallmarks of LSCs is the block in normal differentiation, which requires the "turning off" the expression of thousands of developmental genes. LSCs most likely use this mechanism to program the malignancy phenotype. Curative therapy of AML requires the complete eradication of all the LSCs. These observations suggest that the combination of 5AZA-CdR and DZNep target LSCs and have the curative potential of AML

Biography

Richard L Momparler has received his PhD in Pharmacology from the University of Vermont. He completed Post-doctoral studies at Yale University and International Laboratory of Genetics and Biophysics, Naples, Italy. He was an Associate Professor in Pharmacology at the University of Southern California and Children's Hospital of Los Angeles. He is currently Full Professor in Pharmacology at Université de Montréal and Centre de recherche, Service d'hématologie/ oncologie, CHU-Saint-Justine, Montréal, Québec, Canada. He has more than 100 publications on the pharmacology of nucleoside analogues and epigenetic therapy of cancer.

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