

AML targeted therapy: Impact of small molecules alone or in combination on AML stem/progenitor cells

Cedric Dos Santos University of Pennsylvania, USA

A cute Myeloid Leukemia (AML) is a clonal hematopoietic disorder characterized by an accumulation of immature leukemic cells and by a differentiation block. Despite recent progress, current treatment of AML remains unsatisfactory, with a 5-year relapse-free survival rate lower than 50% in younger adults and 12% in elderly adults, underscoring the need for improved targeted therapy. Current opinions on the molecular basis of AML suggest that leukemic events are driven by at least two types of cooperative mutations ("the two hits model"). Class II mutations, affecting hematopoietic transcription factors and impairing normal differentiation, are classically associated with class I mutations, affecting receptor tyrosine kinases and/or key components of signaling pathways, conferring a growth and proliferative survival advantages.For example, Fms-like tyrosine kinase 3 (FLT3), c-Kit or Ras mutations contribute to aberrantly activate several signalling pathways such as MAPK, mTORC1/S6K/4E-BP1, NF-κB, PI3K/Akt, STAT or SFKs (Src Family Kinases). Pharmacological targeting of these pathways using drugs as a monotherapy has not been very successful in AML. In the first part of the talk, we will show that the combination of the dual SFKs and c-Kit inhibitor dasatinib with conventional chemotherapy enhances eradication of AML stem cells both *in vitro* and *in vivo* using primary AML specimen engrafted in NSG mice. In the second part, we will provide evidences that the combination of the JAK2 inhibitor ruxolitnib with the hypomethylating agent decitabine can selectively enhance elimination of elderly AML stem/progenitor cells *in vitro*, suggesting a new exciting therapeutic avenue.

Biography

Cedric Dos Santos received his Bachelors and Masters degrees from University Paul Sabatier, Toulouse III, France, and completed his PhD from the same University in December 2008. He has a long times past in studying deregulated signaling pathways and he have published several high impact publications in 2008 in Blood, like "A critical role of Lyn in Acute Myeloid Leukemia" and in 2009 in Leukemia. He joined Dr. Ravi Bhatia laboratory, City of Hope, Duarte, CA, as a Post-doctoral fellow in February 2009. In one of his work, he discovered a new original and efficient therapeutic avenue for the treatment of AML, and this study is published in the journal Blood last month. He accepted a faculty position at the University of Pennsylvania in the group of Martin Carroll and Gwenn Danet-Desnoyers where he continues his research on AML targeted therapy and drug discovery.

ced_dos@hotmail.com