conferenceseries.com

David J Bearss, J Hematol Thrombo Dis 2017, 5:5(Suppl)
DOI: 10.4172/2329-8790-C1-004

9th International Conference on

LEUKEMIA AND HEMATOLOGIC ONCOLOGY

October 05-06, 2017 London, UK

David J Bearss

Tolero Pharmaceuticals Inc., USA

Targeting MCL1 dependent cancers by CDK9 inhibition

One of the hallmarks of cancer cells is the ability to avoid apoptotic cell death. Acquiring cell survival mechanisms is critical for the development and growth of tumors and the Bcl2 family of proteins have emerged as important mediators of these cell survival mechanisms. BCL2 family members regulate mitochondrial function in apoptosis and play a central role in pathogenesis, prognosis and responsiveness to chemotherapy of many cancers. The pro-survival BCL2 family protein, myeloid cell leukemia 1 (MCL1), is overexpressed and active in many cancers and is thought to drive cell survival in these cancers. These observations suggest that MCL1 may be a potential drug target for the treatment of cancer. Direct therapeutic targeting MCL1 has been challenging but recent advances in our understanding of how MCL1 is expressed and regulated have opened up new approaches to target this important survival protein. Development of cyclin dependent kinase (CDK) inhibitors have been the focus of research for nearly 20 years due to their regulation of critical functions within the cell and dysregulation in cancer cells. Recently the CDK family member, CDK9, has surfaced as a druggable target for the development of cancer therapeutics. CDK9 plays an important role in transcription regulation of short-lived anti-apoptotic proteins, like MCL1, that are critical for the survival of cancer cells. The MCL1 gene is critically regulated by CDK9 activity under super-enhancer-mediated transcriptional control. We have developed a CDK9 inhibitor, Alvocidib, which we have shown can potently target MCL1 in MCL1 dependent cancers. Alvocidib has proven to be highly effective in both frontline and relapsed/refractory AML patients when sequentially administered before cytarabine and mitoxantrone in a regimen known as ACM. This clinical activity of alvocidib in AML strongly correlates with inhibition of CDK9 and subsequent disruption of super enhancer-mediated transcription. Treatment with alvocidib results in a rapid and powerful down-regulation of MCL1 expression, along with other genes known to be regulated by super-enhancers (cMYC, HOXA9, etc.). In AML cell lines, we observe a consistent decrease in MCL1 following alvocidib treatment, sensitizing AML cells to subsequent sequential treatment with other drugs, by potentiating apoptosis. Additional data indicates that Alvocidib targets MCL1 in a variety of both solid and hematological cancer suggesting that this mechanism may be active in many tumor types. Taken together, these data suggest that MCL1 targeting by Alvocidib mediates the clinical activity of the drug and may be useful in identifying individuals whose cancers are dependent on MCL1.

Biography

David J Bearss pursued PhD and has a consistent and successful track record of drug discovery and development that spans the last 17 years in both academic and industrial settings. He is an expert in small-molecule drug development and in the use of genetic model systems in drug discovery and has deep experience in translational research focused on drug development and the use of genetic markers to predict drug sensitivity. He served as Chief Scientific Officer at SuperGen overseeing early drug discovery and development and subsequently as Co-director of the Center for Investigational Therapeutics at the Huntsman Cancer Institute. He is an Associate Professor in the Department of Oncological Sciences at the University of Utah and Associate Professor of Physiology & Developmental Biology at Brigham Young University. He has published more than 70 manuscripts and book chapters, has over 30 patents issued or pending and has won several awards for his scientific achievements.

dbearss@toleropharma.com