Hematology-2013
OMICS Group Conferences
Accelerating Scientific Discovery
International Conference on
Hematology & Blood Disorders
September 23-25, 2013 Raleigh, USA

Antagonism of SET as a new approach to the treatment of hematological malignancies

Dale J. Christensen
Oncotide Pharmaceuticals and Duke University, USA

Abstract

In cancer, the activity of Protein Phosphatase 2A (PP2A) must be reduced for transformation and tumorigenesis to occur. PP2A is a critical negative regulator of signal transduction pathways and activation of PP2A produces the same net effect as kinase inhibitors. Decreased PP2A activity in cancer cells is associated with resistance to apoptosis through aberrant Akt signaling and stabilization of the c-Myc oncoprotein.

As an novel approach to pharmacological activation of PP2A, we have been investigating the antagonism of PP2A inhibitory proteins. The activity of PP2A is suppressed in leukemia cells through overexpression of physiological inhibitory proteins including SET and CIP2A or through introduction of viral inhibitors like SV40 small T. We have determined the levels of SET in normal cells and leukemia cells and found that SET is overexpressed in most hematological malignancies at both the protein and mRNA levels. Knockdown of SET protein levels by shRNA reduced the ability of SET overexpressing cancer cells to form tumors in immuno-compromised mice.

Antagonism of SET using cell penetrating peptide antagonists results in activation of PP2A and dephosphorylation of p38, JNK, and ERK MAPKs as well as Akt, IKK, and c-Myc. Furthermore, SET antagonist peptides show potent cytotoxicity in SET overexpressing leukemia patient cells with a large safety window and inhibit tumor growth in several xenograft models. These data validate SET antagonism as a target for development of new therapeutics for treatment of multiple leukemias, including patients with resistance to tyrosine kinase inhibitors.

Biography

Dr. Christensen is the President and Chief Scientific Officer at Oncotide Pharmaceuticals and an Adjunct Associate Professor of Medicine (Hematology) at Duke University. He has 15+ years of research experience at the interface of chemistry and biology, with senior positions at Cognosci, Affinergy Inc., Aryzun Pharmaceuticals, and KaroBio USA, formerly Novalon Pharmaceuticals. Dr. Christensen received his B.S. in Chemistry from Utah State University, and a Ph.D. in Organic Chemistry from the University of Utah before an NIH Postdoctoral Fellowship at Texas A&M University. He published many papers and is an inventor on numerous patents and patent applications in drug discovery.