

"Control of Prostate Cancer Progression by Ezh2-mediated Cytosolic Protein Lysine Methylation"

Principal Investigator:

- Alexander Tarakhovsky, MD, PhD, The Rockefeller University

Co-Principal Investigator:

- Dinshaw Patel, PhD, Memorial Sloan-Kettering Cancer Center

Funding Category: A

Abstract: Alteration of enzymes that mediate histone lysine methylation can have direct implications in deregulation of the gene expression program associated with tumor growth and progression. One such enzyme is lysine methyltransferase Ezh2, which is overexpressed in metastatic human prostate tumors. Our recent findings suggest that in addition to its role in gene transcription, Ezh2 possesses a signalling function in the cytosol where it participates in the formation of a multi-protein methyltransferase complex associated with Vav1, a known signal transducer involved in actin polymerization. Using mice with conditional *ezh2* gene inactivation, we discovered an essential and direct role of cytosolic Ezh2 in actin polymerization in various cell types. This proposal aims to identify the role of cytosolic Ezh2 in prostate cancer progression *in vivo*. We will address the contribution of cytosolic Ezh2 and its interaction with Vav1 in prostate cancer development and progression. We have identified a putative Ezh2 substrate in the cytosol of the prostate cancer cells. Further characterization of this substrate and the composition of the Ezh2 cytosolic protein complex will facilitate our understanding of the role of Ezh2 mediated protein methylation in signalling. Finally, we will establish the structural basis for Ezh2 interaction with Vav1 as well as its essential co-factor Su(z)12. Understanding of the Ezh2-Vav1 and Ezh2- Su(z)12 interaction will allow the rational design of selective Ezh2 inhibitors that could be used for prostate cancer treatment. Our proposal has the potential to generate new methods of cancer monitoring and treatment. It is conceivable to use cytosolic Ezh2 or its substrate(s) as a refined marker for cancer prognosis. It is also possible that selective inhibitors of Ezh2 function in cytosol will have the potential to suppress tumor growth and reduce tumor cell ability to metastasize.