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Synergistic pharmacology: Targeting two epigenetic enzyme targets in a protein complex

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Cancer patient treatment with single agent or single target modulation leads to poor clinical outcome. This is due to tumor cell heterogeneity, pathway redundancy in cancer cells and presence of cancer stem cells that are difficult to eradicate. In a clinical setting, drug cocktail is the preferred choice of treatment to address this but has its limitation. Therefore targeting epigenetic pathways has the ability to modulate number of disease specific genes and offers the opportunity to address multifactorial diseases. In this regard, a single small molecule inhibitor modulating two or more disease relevant protein pathways overcome regulatory and developmental hurdles of cocktail drug development in a clinical trial. Hence, a targeted therapy with poly pharmacology will be beneficial and better tolerated for cancer patients. Many epigenetic targets are over expressed in human cancer tissue as compared to normal tissue. Epigenetic alterations of the genome are through the modification of the DNA/ histone proteins that lead to modulation of oncogenes and tumor suppressor genes that regulate cancer specific processes. A histone modification influences the recruitment of other epigenetic/ transcription factor proteins that in turn influence the gene expression. Understanding the targets of such multi protein complex regulates gene expression can help in building targeted pharmacological approaches leading to the design of compounds with better efficacy. In my presentation, I will cover our approach in testing this hypothesis with few epigenetic targets and tool compounds using mechanistic studies and preclinical models.

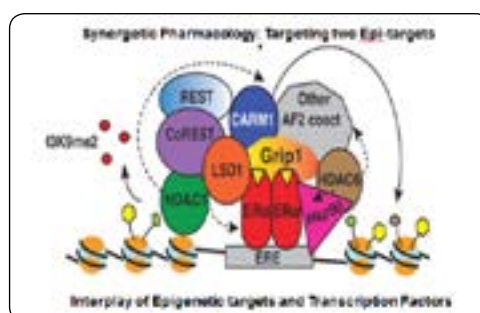


Figure 1: Interplay of Epigenetic targets and Transcription Factors

Recent Publications

1. Jay H Kalin (2018) Targeting the CoREST complex with dual histone deacetylase and demethylase inhibitors. *Nature Communication* 9(1):53.
2. Perri F, et al. (2017) Epigenetic control of gene expression: Potential implications for cancer treatment. *Critical Reviews in Oncology/Hematology* 111:166–172.
3. Po-Hsien Haung, et al. (2011) Histone deacetylase inhibitors stimulate histone h3 lysine 4 methylation in part via transcriptional repression of histone h3 lysine 4 demethylases. *Molecular Pharmacology* 79(1):197–206.

Biography

Sriram Rajagopal—PhD—has 25 years of research experience in Oncology/Diabetes/ Antibacterial Drug Discovery. He received his PhD in 1989 from Anna University, Chennai, India and carried out Post-doctoral research work at University of Washington, School of Medicine, Neuroscience Department, Seattle, USA. He moved to M. D. Anderson Cancer Center, Houston, Texas as Junior Faculty and worked on different types of cancer using primary cancer and cell line to understand how to sensitize cancer cells to current anticancer drugs. After 15 years of academic work in USA, he moved to India and started his drug discovery work with Indian pharma industry. Through his understanding of the complete R&D value chain he has built and managed effective research teams for in-house, collaborative integrated drug discovery and functional services. He has to his credit in identifying 15 preclinical candidates out of which six have moved to different stages of clinical development.