Cell Therapy-2013

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference and Exhibition on
Cell & Gene Therapy

October 23-25, 2013 Holiday Inn Orlando International Airport, USA

New histone deacetylase inhibitors upregulate PTEN expression

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Abstract

The epigenetic control of gene expression is operated through post-translational modifications such as lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation. One of the betterunderstood histone modifications is histone acetylation. Two enzymes are involved in this process: HAT (histone acetyl transferase) and HDAC (histone deacetylase). Acetylation plays an important role in transcription because it remodels chromatin structure enhancing access to DNA-binding factors. By contrast, histone deacetylation mainly results in transcriptional repression. HDAC inhibitors have been shown to be potent inducers of growth arrest, differentiation, and apoptotic cell death both *in vitro* and *in vivo* transformed cells. Histone deacetylase inhibitors (HDACi) comprise structurally diverse compounds that are a group of targeted anticancer agents. To date several HDACi are in clinical trials and two of them have been approved by FDA for treating patients with cutaneous T-cell lymphoma. All of HDACi act binding to the zinc ion located in the catalytic pocket of the enzyme and thereby inhibit enzymatic activity. Following our recent interest in the research of more potent HDAC inhibitors, we have projected and synthesized a series of compounds containing new zinc binding groups. In particular, CAN and CAF compounds have been tested over different head and neck squamous cell carcinoma showing growing inhibition at nanomolar concentration of drugs. Our molecules produced acetylation of histone H3 along with the regulation of PTEN/mTOR pathway known to contribute to abnormal activation and cancer growth.

Biography

Chiara Zagni received her degree Pharmaceutical Chemistry and Technology at the University of Catania (Italy) and her Ph.D at the age of 27 years from Catania University in Pharmaceutical Science. She spent two years as post doc at University of Michigan (Ann Arbor, USA) working on cell biology and stem cells research. Dr. Zagni research is focused on design and synthesis of novel therapeutic agents for the treatment of cancer.