# WHAT ARE HDAC-INHIBITORS AND CAN THEY BE APPLIED TO WM THERAPY?

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At its most fundamental level, all cancers are diseases of DNA. Either there are genes that are turned 'on' when they should be turned off (oncogenes or proto-oncogenes), or there are genes turned 'off' when they should be turned 'on' (tumor suppressor genes). This differential expression of 'good' and 'bad' genes often, in very simplistic terms, governs the development of the malignant state.

In all cells, be they malignant or normal, DNA is known to exist in an 'open' or 'closed' state, being wrapped around an octomer (an aggregation of 8 proteins assembled in a cluster or core) of proteins called histones. The closed, or condensed state of DNA, is characterized by the tight coiling of DNA around this protein complex in a way that helps organize the DNA, like string around a ball. In this closed, or *condensed state*, the DNA is considered transcriptionally silent, hence the information from the DNA cannot be translated into signals for the cell to act upon (grow - don't grow, die - don't die). In the open state, the coiling of the DNA around the protein is *decondensed*, as it is pushed off the protein core, assuming an open configuration. This open configuration allows the information in the DNA to be translated, thus signaling specific behaviors of the cell. The balance between 'closed' and 'open' DNA is managed by a complex of enzymes known as ***histone acety-transferases***, or HATs, and ***histone deacteylases***, or HDACs.

HATs are responsible for adding small chemical groups (termed acetyl-moieties) to the core of protein around which the DNA is wrapped, facilitating a more open, or decondensed structure to the DNA. In this state, the massive amount of information in the DNA can be translated into specific signals. HDACs are responsible for removing those same small chemical groups, facilitating a more condensed or silent form of the DNA, in which the information cannot be translated. The *ying* and *yang* of HAT and HDAC activity is what governs the expression of almost all genes in a cell.

In its simplest terms, if scientists could find a way to 'turn-on' the good genes, and 'turn-off' the bad genes, we would have the best and potentially least toxic therapy for cancer. While scientists are trying to move in this direction, a new class of drugs, the ***HDAC-inhibitors*** theoretically offer such a prospect. HDAC-inhibitors disallow the removal of those small chemical groups from the protein core, allowing DNA to remain in the open or decondensed state, allowing translation of the information stored in the DNA. In a variety of labs, this has been shown to 'turn off' select 'bad-gene' and 'turn-on' select 'good genes' in a manner that results in tumor cell death. To date, one drug in this class, vorinostat, has been approved by the U.S. FDA for the treatment of cutaneous T-cell lymphoma. At present, there are many new HDAC-inhibitors in development, and new data have suggested that these drugs potently complement the activity of many drugs, including ones active in myeloma and WM.

During this presentation, we will describe the present state of knowledge regarding how these agents work, and present exciting new data that will demonstrate the remarkable potential of these agents to change the nature of many different types of blood cancers, including Waldenstroms macroglobulinemia.