

FARYDAK MECHANISM OF ACTION (MOA) VIDEO SCRIPT

Ch1: The Therapeutic Landscape of Myeloma

In multiple myeloma, plasma cells undergo genetic and epigenetic alterations that contribute to transformation into cancer. Transformed plasma cells, or myeloma cells, accumulate within the bone marrow leading to local and systemic complications. Multiple myeloma can be treated with a variety of agents; despite this, nearly all patients will relapse after treatment and many will die of the disease.

Current treatments for multiple myeloma include proteasome inhibitors, immunomodulatory agents, cytotoxic chemotherapy, and corticosteroids. In contrast to these myeloma therapies, FARYDAK, or panobinostat, is a pan-deacetylase inhibitor that is believed to affect gene expression through epigenetic mechanisms by increasing acetylation of histone proteins in the nucleus. In addition, FARYDAK may increase acetylation of nonhistone proteins in the cytoplasm. By impacting protein acetylation in both the nucleus and cytoplasm of myeloma cells, FARYDAK may contribute to reestablishing control over myeloma cell growth and apoptosis.

Ch2: Epigenetic Dysregulation and the Role of FARYDAK

In normal cells, epigenetic factors control tightly-regulated gene expression programs without changing the underlying DNA sequence. In cancer, including multiple myeloma, epigenetic factors are often dysregulated, altering the expression of genes that regulate normal cell processes such as growth, differentiation, and apoptosis. Perturbation of gene expression can promote the expansion of transformed cells and resistance to therapy.

In the nucleus of myeloma cells, FARYDAK is believed to play a role in addressing this epigenetic

dysregulation through the inhibition of deacetylases, or DACs. DACs control gene expression by removing acetyl groups from amino acid side chains of histones in chromatin, the complex of DNA wrapped around histone proteins. By inhibiting DACs, FARYDAK can contribute to increases in histone acetylation, causing the DNA in chromatin to become more loosely wrapped around histones. When chromatin is in this conformation, gene expression is increased. By increasing gene expression, FARYDAK treatment is believed to reactivate tumor suppressor genes and genes involved in apoptosis of myeloma cells. Because other myeloma therapies are not epigenetic modulators, one of the causative factors in multiple myeloma is not addressed.

Ch3: FARYDAK Impacts Pathways Outside of the Nucleus

As a pan-DAC inhibitor, FARYDAK also inhibits DACs that modify nonhistone targets outside of the nucleus. Through inhibition of these enzymes, FARYDAK can contribute to altering the activity or stability of proteins such as tubulin and HSP90 in myeloma cells.

Ch4: Overcoming Resistance

Synergism of FARYDAK and bortezomib in the treatment of myeloma is an example of how DAC-inhibition of nonhistone targets may overcome the myeloma resistance to bortezomib. Proteasome inhibitors, such as bortezomib, disrupt the primary protein degradation pathway (the proteasome), which is critical for myeloma cell survival. However, this can potentially be overcome by upregulation of an alternative pathway, known as the aggresome pathway. The aggresome pathway also removes the excess M protein that accumulates in multiple myeloma and is an escape mechanism important in bortezomib-resistant myeloma. FARYDAK, also a DAC6 inhibitor, alters the acetylation of alpha tubulin, interfering with the aggresome pathway. FARYDAK inhibition of the aggresome pathway in vitro prevents M protein destruction by a different mechanism and may contribute to overcoming resistance to bortezomib.

Ch5: Summary

As the first pan-DAC inhibitor approved in multiple myeloma, FARYDAK may help regulate multiple cellular pathways: First, FARYDAK is believed to work at the DNA level to prevent histone deacetylation, resulting in increased gene expression, including tumor suppressor genes and genes involved in apoptosis. In addition, FARYDAK may affect the modification of other key proteins in the cytoplasm, including tubulin and HSP90, that leads to decreased myeloma cell survival. Through these mechanisms, FARYDAK may help to control multiple myeloma cell growth and apoptosis in vitro.