

New therapeutic target in myeloma discovered

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Despite new therapies, Multiple Myeloma (MM) remains incurable causing most patients to ultimately develop drug resistance and succumb to the disease. The pursuit of drugs that inhibit cell cycle regulators especially cyclin-dependent kinases (CDKs), has been an intense focus of research in cancer. A new study by researchers at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai has shown that targeting both CDK4 and ARK5, proteins responsible for maintaining energy balance within the cell, was extremely effective in causing cell death in myeloma. Their research, published in the March issue of the journal *Cancer Research*, identifies new targets for myeloma drug development.

Multiple myeloma (MM) is a fatal blood cancer accounting for over 10,000 deaths in the United States each year. Better understanding of the molecular basis of myeloma has led to a growing list of treatments for this challenging disease. Despite recent advances in new therapies, this disease remains incurable with a median survival of 7 to 8 years.

"Even in the era of great drug development, there is an urgent need an urgent need to develop drugs that are less toxic and achieve longer remissions for all patients," said Samir Parekh, MD, Associate Professor of Medicine, Hematology and Medical Oncology, and Oncological Sciences at Icahn School of Medicine at Mount Sinai and co-author of the study.

The team along with Onconova Therapeutics, Inc. USA developed a

compound, ON123300 that included multi-targeted inhibitors ARK5 and CDK4. The researchers treated both primary myeloma cells and cells line with ARK5/CDK4 inhibitor ON123300 which resulted in tumor [cell death](#), and halted cancer cell growth in vitro and in vivo mouse models.

"ARK5 is critical for myeloma survival and this study suggests a novel function for ARK5 in bridging the mTOR and MYC pathways," said Deepak Perumal, PhD, lead author of the study and post-doctoral scientist, Hematology and Medical Oncology at Icahn School of Medicine at Mount Sinai. "Given that MYC is critically over expressed in myeloma, we sought to determine whether selective inhibition of ARK5 and CDK4 could be an effective way to target MYC-driven proliferation in myeloma."

Researchers evaluated the effect of ARK5/CDK4 inhibitor ON123300 against myeloma cell lines and primary samples from patients with recurring myeloma. Myeloma cells were sensitive to ON123300 while normal peripheral blood cells were spared from the effects of the compound confirming a potent and specific anti-cancer effect of ON123300.

"Our study results show that ON123300 induces cell death and negatively regulates key oncogenic pathways in [multiple myeloma](#) cells," said Dr. Parekh. "This is the first report showing potent cytotoxicity of CDK4/ARK5 inhibition in MM and provides the foundation for further clinical trials using CDK4/ARK5 inhibitors to improve outcomes for MM patients."

Provided by The Mount Sinai Hospital

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