



Epigenetic Modulation for Restoration of Drug Sensitivity in Cancer Chemotherapy (Dr. Debabrata Banerjee, CINJ 06-06) *Oncology*

Background

Colorectal cancer is a second leading cause of cancer-related deaths in the United States. 5-Fluorouracil (5-FU) remains a main regiment used in the clinic for the last decade to treat patients diagnosed with this deadly disease. The response rate to 5-FU is typically less than 30% and the intrinsic or acquired resistance to the drug is the main obstacle to therapeutic success. Two delivery methods of 5-FU are relevant from the clinical point of view: bolus infusion of high doses of the drug given weekly or continuous infusion of low doses. Depending on the schedule of drug administration it may have different mechanisms of action. 5-FU is converted intracellularly to active metabolites, FdUMP, FdUTP and FUTP. These active metabolites can either act as a thymidylate synthase (TS) inhibitor and interfere with DNA synthesis, or may be incorporated into RNA. Significant evidence has accumulated to support the concept that bolus treatment results in metabolism to F-UTP and exerts its cytotoxic effect predominantly through incorporation into the RNA. Researchers at UMDNJ have recently shown that resistance to bolus 5-FU is due to lower incorporation of F-UTP into RNA as a result of lower levels Uridine Monophosphate Kinase (UMP5K).

Description of the Invention

UMP5K (also known as UMP/CMP kinase) is an enzyme that catalyzes the transfer of a phosphate group to UMP, CMP and dCMP using ATP as a cofactor. This enzyme is crucial for the de-novo and salvage synthesis of pyrimidine nucleotides and no other enzymes with the same substrate specificity as UMP5K kinase has been identified so far. The important role of UMP5K in bolus 5-FU resistance was determined by analyzing patient samples of colon cancer metastatic to the liver which lower level of this enzyme, especially in the group of patients, who were previously treated with 5-FU and was further confirmed by modulation of this enzyme level in our in vitro colorectal cancer model. **UMDNJ researchers have found a way to increase the level of this enzyme making the resistant cells sensitive to treatment with 5FU.**

Patent Status

United State provisional patent application filed

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A novel class of mTOR inhibitors (Zheng, RWJ 06-34) *Oncology*