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Targeting metastasis and drug resistance for treating pancreatic cancer

Pancreatic Ductal AdenoCarcinoma (PDAC) is a deadly disease with no effective treatment. PDAC cells are highly proliferative and metastatic. We have developed a new drug called Metavert that targets, at the same time, the Glycogen Synthase Kinase 3 beta (GSK-3 β) and histone deacetylase (HDAC- class 1/2), important mediators of cancer progression. We have designed and synthesized a novel drug that shows a significant anti-cancer effect *in vitro* in PDAC cells and patient-derived Circulating Tumor Cells (CTCs) and *in vivo* in the most aggressive mouse model of experimental PDAC using the Kras^{LSL-G12D/+}, Trp53^{LSL-R172H/+} and Pdx^{cre} (KPC) mice. Metavert significantly (at nano-molar concentrations) decreased cancer cell survival and increased apoptosis in several PDAC cells lines and CTCs. The same doses of Metavert did not affect survival of normal hepatocytes and pancreatic ductal cells. Metavert decreased expression of markers of Epithelial to Mesenchymal Transition (EMT) and cancer stemness, the two driving forces of metastasis and drug resistance. Metavert prevented invasion of the cancer cell lines. Furthermore, Metavert sensitized PDAC cells and CTCs to chemotherapy drugs Gemcitabine and Paclitaxel. Treatment with Metavert significantly increased KPC mice survival by ~50% and sensitized the tumors to Gemcitabine. Distal metastasis was decreased from 29% in control KPC mice to 0% in Metavert treated KPC mice. Fibrosis, M2 macrophages and pro-cytokine levels in the blood were decreased by Metavert treatment without affecting the function of healthy organs. Avenzoar Pharmaceuticals has licensed Metavert and it has obtained the orphan drug status for it. The pre-clinical PK, PD, toxicity studies are ongoing and the drug is expected to be approved for clinical testing within one year.

Biography

Mouad Edderkaoui has research goal to understand the mechanism of pancreatic cancer initiation and progression and to develop a treatment strategy for the disease. He focuses on the role of cells present in the tumor microenvironment and how histone deacetylases (HDACs) regulate the interaction between these cells. He works as associate professor at the Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA.. He was awarded with Career Development Award, National Institute of Health in 2011, Hirshberg Foundation Award in 2012 and he is also an Associate Editor of *Frontiers in Science*.

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