Background and Objectives:
Both diabetes and cancer are prevalent diseases with increasing incidence worldwide and especially in countries that are undergoing rapid industrialization (i.e. Gulf countries). Epidemiological studies provide strong evidence that subjects with diabetes are at a significantly higher risk of developing many forms of cancer and in particular solid tumors including colorectal cancer. While diabetes and cancer share many risk factors, the biological links between the two diseases are poorly characterized. In this study we will determine the role of AMPK and mTOR and their crosstalk with NADPH oxidases in normal and cancerous colon epithelial cells and their response to high glucose (HG), high insulin (HI) and their combination. We will also explore the mechanism by which diabetes accelerates tumor development and tumor burden.

Methods:
Cancer migration, cancer proliferation, cancer invasion, Noxs, fibronectin, AMPK, mTOR proteins expression and ROS production were studied by immunohistochemistry.

Results:
We have evidence that HG or HI induces reactive oxygen species (ROS) production in both normal human epithelial colon cells (NCM356) and human epithelial colon adenocarcinoma cells (CaCo₂). To a greater interest, colon cancer itself is a major source of ROS production. Treating CaCo₂ cancerous cells with either HG or HI inactivates adenine monophosphate kinase (AMPK), up-regulates NADPH oxidases Nox1 and Nox4-induced ROS production, associated with increased fibronectin expression and activates the mTOR pathway. In addition, HG or HI enhance cancer cell migration, proliferation, and invasion. Pharmacologic activation of AMPK by 5-aminoimidazole-4-carboxamide-1-riboside AICAR or inhibition of mTOR by rapamycin restores AMPK phosphorylation/activity, downregulates Nox1, Nox4, and fibronectin expression, increases mTOR phosphorylation/activity, and regulates cell migration, proliferation, and invasion.

Conclusion:
Our results may uncover a novel and critical role for AMPK and mTOR in cancer cell proliferation and extracellular matrix accumulation in the diabetic milieu; this pathway is through an oxidative stress-dependant mechanism. Our work will set the stage for additional studies to explore new therapeutic approaches for the treatment of cancer in diabetic patients and maybe to a larger extent treatment of cancer.