Research Proposal

To: Dr. XXX
From: XXX
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# Aim 1: Wnt signalling blocking agent can inhibit cancer proliferation.

**Background:** It has been proved that multiple signalling pathways take an important part in self renewal of the normal stem cells. Deregulation of such pathway could result in the proliferation of cancer stem cells capable of both self renewal and generating mature cancer cells. Wnt signalling is one of those biochemical pathways that are thought to be involved in the stem cell renewal and embryonic development. However, aberrant activation of this signalling pathway often occurs early in carcinogenesis. Therefore, specific inhibitors for Wnt signalling in cancer cells may be an attractive therapeutic target for cancer.

**Overview of proposed work:** My primary focus will be on the finding novel inhibitor of Wnt signalling and I plan to investigate following properties. First, I will compare of the β-catenin expression level (cytosolic and nuclear, respectively) in normal cells and cancer cells. Next, to determine the effect of inhibitor on Wnt signalling activation, I will examine Axin2 and Cyclin D1 level as well as Frizzled-1 and LRP6 gene expression. I will also plan to check the cancer cell anti-proliferative activity of the inhibitor.
Aim 2: Role of Mitogen-activated protein kinase phosphatase-1 (MKP-1) enhancer or repressor in cancer.

**Background:** Mitogen-activated protein kinases (MAPKs) play crucial roles in cell proliferation, differentiation, and apoptosis. MKP-1 inactivates MAPKs, and therefore, inhibits a number of cellular responses mediated by ERK, JNK, and p38 MAPK. Since MAPK pathway has been implicated in tumorigenesis, down-regulation of MAPK signalling via MKP-1 enzyme activity may improve clinical outcomes of cancer. However, the precise pathological role of MKP-1 in different cancers is a highly controversial topic. Several previous reports suggest that the up-regulation of MKP-1 in different cancers does not always correlate to a better prognosis. This is supported by the facts that MKP-1 attenuates ERK and p38 MAPK activity which are thought to induce apoptosis.

**Overview of proposed work:** I plan to verify the effect of MKP-1 enhancer or repressor on the metastasis and apoptosis of specific invasive cancer cells such as melanoma and breast cancer cells. The candidates for MKP-1 modulator can be NSAIDs and the materials which were already known to have anti-metastatic potential. First, I will confirm the MAPKs levels depending on the MKP-1 activity using transfected cancer cells and check the effect of MKP-1 modulator on MAPKs expression. I will further confirm whether MKP-1 modulator acts post-transcriptionally or post-translationally. Second, I will determine the metastatic potential of the MKP-1 modulator, whether MKP-1 enhancer and repressor exhibit down-regulation and up-regulation of metastasis, respectively. MKP-1 modulator’s effect on the cancer metastasis will be assessed by several factors, including matrix metalloproteinase (MMP) activity, cancer cell migration and invasion. Finally, I will investigate the effect of the MKP-1 modulator on cancer cell apoptosis.
# Aim 3: Notch signalling targeted cancer therapeutics.

**Background:** The Notch signal transduction pathway has been implicated in various processes, including cell-fate determination, cell differentiation, cell proliferation, and cell death. Especially, this pathway is critical in embryonic stem cell maintenance and development. Since tumorigenesis and organ development share similar mechanisms, dysregulation of the Notch pathway is believed to be associated with lots of cancers. However, the Notch pathway also could be tumor suppressive depending on the limited number of tumor types, including skin cancer, human hepatocellular carcinoma, medullary thyroid, cervical cancer, and small cell lung cancer, suggesting that further mechanistic studies are warranted to evaluate the specific role of Notch-related proteins in different cancers.

**Overview of proposed work:** Because Notch pathway acts as oncogenic, at least in part, in melanoma and breast cancer cells, I will focus to find the blocking agent of Notch signal for the treatment of such malignant cells. The $\gamma$-secretase inhibitor (GSI) that has been used in treating Alzheimer’s disease is capable of inhibiting the Notch receptor and may be an excellent candidate. I plan to examine the $\gamma$-secretase inhibitory action of the material and assess the NICD level change by the material. Next, I will also check the cytotoxicity of the material.