"The Role of PHLPP Phosphatases in *PTEN*-Mutant Prostate Cancer Progression"

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Abstract: The *PTEN* tumor suppressor is among the most frequently lost or mutated genes of human prostate cancer (CaP). PTEN is a phosphatase that suppresses AKT kinase activity, which promotes cell survival and proliferation. Recently, another phosphatase that directly antagonizes AKT, namely PHLPP, has been identified and we are studying its role in CaP alone and in combination with *PTEN* alteration. Genetic analysis of its status in a cohort of over 250 CaP specimens obtained at MSKCC reveals consistent co- deletion with PTEN, specifically in metastatic cancer. Since identification of patients with potential of progression to advanced disease is a key goal in CaP therapy, we will test the causal role of PHLPP in this process. To test if PHLPP is a tumor suppressor of CaP, we have studied *Phlpp*-knockout mice and found high grade PIN and focally invasive CaP. We therefore propose to (Aim 1) expand our preliminary human genetic analysis of PHLPP in prostate through analysis of PHLPP protein levels on tumor tissue microarrays and through PHLPP-mutation status by gene sequencing. In addition (Aim 2), we will determine spontaneously occurring genetic alterations in our mouse models of Phlpp- and Pten/Phlpp-mutant prostate tumors in order to identify common alterations between the human and mouse PTEN/PHLPP mutant cases. Thus, we will determine a set of genes that are linked to progression of *PTEN*-mutant CaP and given our expertise with *in vivo* and *in vitro* RNAi will be in a position to establish their causal contribution to the process.