



2018 ACS-IRG Pilot Project

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PROJECT TITLE: EXPLORATION OF LMPTP AS A NEW TARGET FOR PROSTATE CANCER THERAPY

ABSTRACT:

OUR OBJECTIVE IS TO OBTAIN PILOT EVIDENCE THAT THE LOW MOLECULAR WEIGHT PROTEIN TYROSINE PHOSPHATASE (LMPTP) IS A NOVEL TARGET FOR PROSTATE CANCER THERAPY. PROSTATE CANCER IS A LEADING CAUSE OF CANCER DEATH IN AMERICAN MEN, THUS NEW THERAPIES TO INHIBIT METASTATIC PROSTATE TUMOR GROWTH ARE A MAJOR UNMET MEDICAL NEED IN CANCER. SEVERAL LINES OF EVIDENCE SUGGEST A ROLE FOR LMPTP AS A PATHOGENIC FACTOR IN PROSTATE CANCER. LMPTP IS REPORTEDLY UPREGULATED IN HUMAN PROSTATE TUMORS, AND HIGH LMPTP EXPRESSION IN PROSTATE TUMORS SIGNIFICANTLY CORRELATES WITH A SHORTER PATIENT SURVIVAL TIME. WE SOUGHT TO EXPLORE A POTENTIAL ROLE FOR LMPTP IN PROSTATE CANCER, AND FOUND THAT LMPTP IS A KEY DRIVER OF PROSTATE TUMOR CELL GROWTH *IN VITRO* AND *IN VIVO*. OUR DATA ALSO SUGGESTS THAT LMPTP REGULATES THE PHOSPHORYLATION OF EPHA2, A RECEPTOR TYROSINE KINASE THAT IS OVEREXPRESSED IN A NUMBER OF HUMAN CANCERS AND PROMOTES TUMORIGENICITY AND METASTASIS. OUR LONG-TERM GOAL IS TO DEFINE THE ROLE OF LMPTP IN PROSTATE CANCER AND ASSESS ITS POTENTIAL AS A TARGET FOR PROSTATE CANCER THERAPY. IN THIS PROPOSAL, OUR OBJECTIVE IS TO GAIN A DEEPER UNDERSTANDING OF THE ROLE OF LMPTP IN PROSTATE CANCER BY CONFIRMING WHETHER LMPTP MRNA AND PROTEIN EXPRESSION IS UPREGULATED IN HUMAN PROSTATE TUMORS AND ASSESSING THE ROLE OF LMPTP IN PROSTATE TUMOR CELL FUNCTIONS SUCH AS GROWTH, MIGRATION, INVASION, AND EPHA2-MEDIATED SIGNALING. TO PERFORM THIS WORK, WE HAVE GENERATED UNIQUE RESEARCH REAGENTS, SUCH AS A HIGHLY SELECTIVE, ORALLY BIOAVAILABLE SMALL-MOLECULE LMPTP INHIBITOR AND PROSTATE CANCER CELL LINES LACKING EXPRESSION OF LMPTP. THIS PILOT AWARD WILL CONSTITUTE AN ESSENTIAL INITIAL STEP TOWARDS ELUCIDATING THE MECHANISM OF ACTION OF LMPTP IN PROSTATE CANCER AND WILL PAVE THE WAY FOR FUTURE STUDIES TO MORE DEEPLY INVESTIGATE THE MOLECULAR MECHANISM OF ACTION OF LMPTP IN PROSTATE CANCER AND ITS POTENTIAL AS A TARGET FOR THERAPY.