



2018 ACS-IRG Pilot Grant

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PROJECT TITLE: CLINICAL STRATEGIZING OF PARP INHIBITORS IN PROSTATE CANCER

ABSTRACT:

THE MANAGEMENT OF CASTRATION RESISTANT PROSTATE CANCER (CRPC) IS AN UNMET CLINICAL NEED GIVEN DISEASE LETHALITY AND LACK OF EFFECTIVE TREATMENTS. EMERGING DATA DEMONSTRATE THAT DEFECTS IN HOMOLOGOUS RECOMBINATION (HR) GENES ARE ENRICHED IN ADVANCED CRPC. THIS DISCOVERY IS HIGHLY RELEVANT GIVEN SUSCEPTIBILITY OF HR-DEFICIENT (HRD) TUMORS TO POLY ADENOSINE DIPHOSPHATE RIBOSE POLYMERASE (PARP) INHIBITION. CURRENTLY, HOWEVER, COMMERCIALY AVAILABLE TESTS TO DETERMINE HRD RELY PRIMARILY ON ASSESSING MUTATION STATUS OF COMMON DNA REPAIR GENES, THUS OVERLOOKING PATIENTS THAT MAY HARBOR HRD AS A RESULT OF ALTERNATIVE MOLECULAR ALTERATIONS. WE ESTABLISHED A COMPUTATIONAL METHOD TO ASSESS HRD BY UTILIZING PATTERNS OF SOMATIC MUTATIONS, KNOWN AS MUTATIONAL SIGNATURES. **WE HYPOTHESIZE THAT PATIENTS WITH METASTATIC CRPC (MCRPC) WITH AN HRD SIGNATURE INDEPENDENT OF HR GENE MUTATION STATUS WILL DERIVE BENEFIT FROM PARP INHIBITION.** TO TEST THIS HYPOTHESIS, WE WILL COLLECT PRE-TREATMENT METASTASIS BIOPSIES FROM MEN WITH CRPC FOR WHOLE GENOME SEQUENCING FOR HRD SIGNATURE DETERMINATION. PATIENTS WILL RECEIVE TREATMENT WITH PARP INHIBITION IN THE CONTEXT OF TWO OLAPARIB BASED CLINICAL TRIALS AND CLINICAL OUTCOMES WILL BE CORRELATED WITH HRD SIGNATURE STATUS. ADDITIONALLY, WE WILL INVESTIGATE MECHANISMS OF RESISTANCE TO PARP INHIBITION VIA COLLECTION OF PROGRESSION BIOPSIES IN A SUBSET OF PATIENTS. LASTLY, WE WILL INTERROGATE GERMLINE DNA FOR HRD AND CORRELATE SIGNATURE STATUS WITH CLINICAL AND DISEASE CHARACTERISTICS. OUR GOAL IS TO DEVELOP A COMPREHENSIVE DIAGNOSTIC TEST TO IDENTIFY MEN WITH HRD AS THIS COULD INFORM TREATMENT. **THIS WORK HAS THE POTENTIAL TO EXPAND THE TREATMENT ARMAMENTARIUM IN MEN WITH MCRPC. BY HARNESSING VAST ADVANCES IN TECHNOLOGY, GENETICS, AND BIOMEDICAL RESEARCH, THIS WORK HAS THE POTENTIAL TO BETTER INFORM PATIENT SELECTION FOR A GIVEN TREATMENT AND TRANSFORM CLINICAL DECISION MAKING.** IF SUCCESSFUL, THIS DIAGNOSTIC TEST HAS A POTENTIAL APPLICATION IN ALL HR DEFICIENT TUMORS INCLUDING BREAST, OVARIAN, PANCREATIC, GASTRIC, AND OTHER CANCERS.