

Co-clinical Trials Using Organoids for Patients with Advanced Prostate Cancer

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Abstract: In the past few years, we have witnessed a rapid growth in the number of clinically approved agents that prolong survival and in the number of novel promising targets in the treatment of advanced prostate cancer. However, each of these agents only benefits a subset of patients and predictive biomarkers that help patient selection are urgently needed. In the majority of other cancer types, validated biomarkers have been discovered using *in vitro* models. However, prostate cancer is hampered by the lack of *in vitro* models that recapitulate the diversity of the disease. To address these limitations, we have optimized 3D culture conditions that generate "organoids" of metastatic prostate cancer from biopsy samples. We propose to generate organoid lines from patients enrolling into two specific clinical trials for advanced prostate cancer at our respective institutions motivated by preclinical work from our laboratories: 1) ARN-509 plus everolimus in abiraterone acetate resistant prostate cancer and 2) Arora kinase inhibitor MLN8237 in advanced neuroendocrine prostate cancer. The trials are part of the multi-institutional Stand Up to Cancer (SU2C) project where all patients undergo pre-treatment biopsy that is genetically characterized by whole-exome sequencing. These organoid lines will therefore be highly clinically and genetically annotated. We proposed to generate mutational and copy number data of each organoid line and determine the level of correlation with the metastasis sample. For the treatment drugs, we propose to determine whether *in vitro* sensitivity for organoids can predict for patient response. Further, using bioinformatics analysis of genomic and drug sensitivity data, we will generate potential biomarkers for response for further validation and potential clinical study.