PROJECT TITLE

Biomarker Validation and Phenotypic Insights into Metformin's Effect on Prostate Cancer Progression

PRINCIPAL INVESTIGATOR

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SCIENTIFIC SUMMARY

Prostate Cancer (PCa) exhibits a diverse progression spectrum, with a large percent of cases following a slow trajectory. Existing biomarkers, like PSA and PSMA offer clinical support, but possess limitations in prognostic and predictive capacities. However, the distinct metabolic features of PCa suggest the existence of biomarkers associated with metabolism that may better predict disease progression or treatment response. The overarching design of this research incorporates these two features of low-risk PCa, the long time-to-progression and unique metabolic properties. The first phase will measure changes in expression of candidate biomarkers (mTOR/AMPK, GDF15, COX-2/PGE2) in specimens at baseline and last time-point without progression then weighted for time between sampling, to calculate the degree and magnitude of change. The second phase of this strategy will address the unique metabolic properties not captured using traditional genomic techniques. Rather, metabolomic and proteomic profiles will be overlayed to elucidate critical biomarkers that can better reflect PCa progression and response. This will be done leveraging the MAST trial, which was designed to collect well-annotated PCa specimens at defined timepoints while simultaneously examining the effects of metformin on PCa progression and adherence to active surveillance (AS). Also, the team includes partners from Olink®, which specializes in precision proteomic techniques, and Dr. Montenegro Burke, a leading expert in metabolomics research. Together, this proposal addresses objectives pertaining to biomarker development for low-risk PCa including:

1. To clarify the utility of mTOR/AMPK, GDF15, and COX-2 induced PGE2 as biomarkers of progression and metabolic response in patients with low-risk PCa treated with/without metformin using proteomic and metabolomic strategies on longitudinal biospecimens
2. To develop a model of the dynamic expression and metabolic implications of the pathway components of mTOR/AMPK, GDF15, and PGE2 associated with the pathophysiology of low-risk PCa progression or response to metformin
3. To assess the relationship and added predictive/prognostic value of biomarker scores to clinical features used in decision making that are associated with PCa progression and outcome

These will be addressed by leveraging the MAST cohort stemming from double-blind, placebo-controlled trial that randomized (1:1) participants to receive metformin or placebo for 3 years while on AS. A total of 408 male subjects with a clinical diagnosis of low-risk, localized PCa. AS biopsies and biofluids were collected at baseline, 6, 18, and 36 months for future research. First, time-dependent changes in candidate biomarkers, namely mTOR/AMPK, GDF15, and PGE2, will be measured in 44 cases using the Olink® Explore 3072 platform. Olink offers the versatility to perform either extensive discovery or customized targeted screening. Integrating this with well-established Liquid Chromatography-Mass Spectrometry (LC-MS) workflows will provide an opportunity to explore related-targets and develop a robust multi-feature biomarker signature. These results will then be secondarily validated using targeted approaches and assessed for relationships with additional clinical features as assessed for performance and added clinical value. The results from this study will be used to understand longitudinal biomarkers for potential use in the clinic to increase adherence to AS and reduce unnecessary deferral to definitive therapy.