The mission of our translational research laboratory is to develop biomarkers that inform clinical decisions in the treatment and management of patients with genitourinary malignancies. In prostate cancer, there is an unmet clinical need for prognostic and predictive biomarkers to guide therapy in settings that range from localized to metastatic disease. For example, multiple therapeutic options are available for metastatic castration-resistant prostate cancer (mCRPC) including next-generation androgen receptor (AR) targeted therapies, bone-targeting radionuclides, PARP inhibitors, and cytotoxic chemotherapy, but we lack non-invasive biomarkers that can reliably predict and monitor treatment responses, and thus guide the selection and sequencing of these therapies. In localized prostate cancer, standard clinicopathologic parameters are insufficient to accurately distinguish indolent from aggressive disease, and molecular signatures could potentially be used to classify tumors that can be safely monitored and tumors that require immediate treatment.

For the latter, there is an urgent need for biomarkers to guide the rational selection of appropriate treatment options, which may include radical prostatectomy, brachytherapy, photon or proton external beam radiation therapy, androgen deprivation therapy, or different combinations of the above.

A major focus of our laboratory is the investigation of circulating biomarkers in prostate cancer patients. Circulating tumors cells (CTCs) are rare cancer cells shed from primary and metastatic tumors into the peripheral blood, and represent a “liquid biopsy” that may be performed repeatedly and non-invasively to monitor treatment efficacy and study tumor evolution during therapy. In collaboration with a multidisciplinary team of bioengineers, molecular biologists, and clinician scientists at MGH, we have studied the application of novel microfluidic technologies to isolate and analyze CTCs from the peripheral blood of prostate cancer patients. We have used CTC analyses to monitor therapy in patients with localized and metastatic prostate cancer, interrogate androgen receptor (AR) signaling status in patients undergoing treatment with AR-targeted therapies, and studied the significance of CTC clusters in...
the development of metastases. Through comprehensive single cell RNA-sequencing of prostate CTCs, we demonstrated that activation of noncanonical Wnt signaling contributes to anti-androgen resistance in metastatic prostate cancer, and that expression of β-globin in CTCs contributes to a cytoprotective effect from oxidative stress during blood-borne metastasis. Ongoing projects include the development of CTC molecular signatures to predict outcomes after AR-targeted therapy and PARP inhibitors in mCRPC, and to monitor patients with localized prostate cancer who are undergoing local therapy or active surveillance.

A second focus of the laboratory is the development and evaluation of novel tissue based biomarkers to guide prostate cancer care. We utilize technologies including microfluidic real-time PCR, next-generation sequencing, and branched chain RNA in situ hybridization (RNA-ISH) to evaluate molecular signatures in limited quantities of formalin-fixed paraffin-embedded (FFPE) tumor biopsy tissues. These molecular findings are correlated with clinical outcomes to identify and validate potential novel tissue biomarkers predictive of treatment response. We recently developed an RNA-ISH assay to detect the constitutively active androgen receptor mRNA splice variant AR-V7 in archival FFPE tissues, and demonstrated that this assay has prognostic value in patients with treatment-naïve prostate cancer who are initiating first-line therapy. We are currently evaluating these and other candidate tissue and circulating biomarkers as predictors of treatment response in the context of several clinical cohorts, including a multi-institutional randomized phase 3 trial of proton vs. photon radiation therapy for low and intermediate risk prostate cancer. Through these approaches, we aim to develop and prospectively evaluate circulating and tissue-based biomarkers in the context of both radiation therapy and systemic therapy, and develop and actualize the concept "real-time precision medicine", integrating genomic analyses of liquid and tissue biopsies to guide the personalized care of patients with prostate cancer.