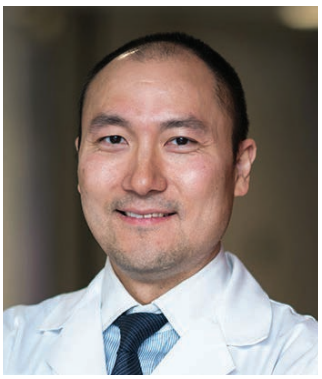
David T. Miyamoto, MD, PhD



The Miyamoto laboratory focuses on the discovery and development of novel biomarkers to guide the personalized treatment of patients with prostate and bladder cancer. We analyze molecular profiles of tumor biopsies as well as circulating tumors cells (CTCs) in the blood that can be sampled non-invasively and repeatedly. By studying these patient-derived specimens, we have identified new molecular predictors of response to therapy and potential mechanisms of treatment resistance. Our overall aim is to develop tools for "real-time precision medicine" to probe the molecular signatures of cancers as they evolve over time, and to guide the rational selection of appropriate therapies for each individual patient with cancer.

Miyamoto Laboratory

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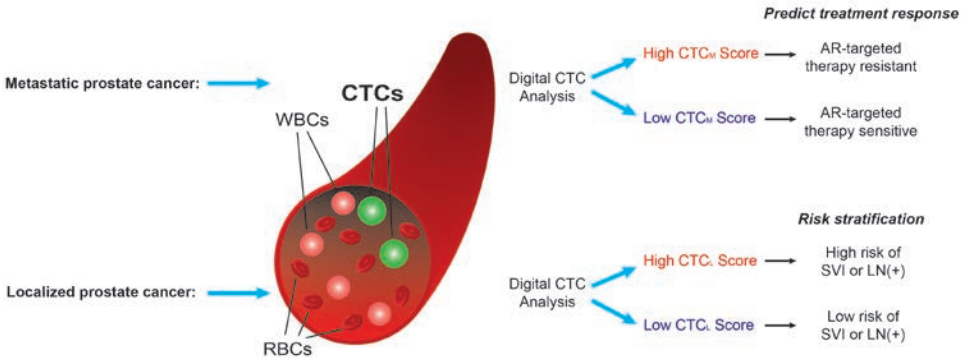
The mission of our translational research laboratory is to discover and develop molecular biomarkers that inform clinical decisions in the management of patients with genitourinary malignancies. We aim to develop circulating and tissue-based biomarkers in a variety of clinical contexts to actualize the concept "real-time precision medicine," integrating genomic analyses of liquid and tissue biopsies to guide the personalized care of patients with genitourinary malignancies.

Prostate cancer is the most common cancer in men and the second leading cause of cancer-related death in men. There is a critical unmet need for predictive biomarkers to guide the rational selection of appropriate treatment options for each patient with prostate cancer in settings ranging from localized to metastatic disease. A major focus of our laboratory is the investigation of circulating tumors cells (CTCs), which are rare cancer cells shed by primary and metastatic tumors into the peripheral blood circulation. CTCs represent a type of "liquid biopsy" that may be performed repeatedly and non-invasively to monitor treatment efficacy and study tumor evolution during therapy. As part of a collaborative, multidisciplinary team at MGH, we have developed novel molecular assays using microfluidic technologies to isolate and analyze CTCs from cancer patients. Our recent studies include the use of CTC expression profiling to interrogate signaling pathways and derive CTC RNA signatures that predict resistance to androgen receptor (AR)-targeted therapy in metastatic cancer and early dissemination in localized cancer. Ongoing projects include the development of CTC molecular signatures to predict clinical outcomes after radiation therapy as well as novel prostate cancer therapies currently in Phase 1/2 clinical trials. Another focus is the development of novel tissue-based biomarkers. We utilize technologies including next-generation sequencing and RNA in situ hybridization (RNA-ISH) to evaluate prognostic and predictive molecular signatures in limited quantities of archival prostate tumor tissues from clinical trials or carefully selected clinical cohorts. Our ongoing efforts are directed at correlating molecular findings with clinical outcomes to identify novel biomarkers predictive of treatment response that can be useful in the clinic.

Bladder cancer is the fifth most common cancer in the US, causing 18,000 deaths per year. Muscle-invasive bladder cancer has a high propensity for metastasis and requires aggressive treatment with either radical



Potential clinical applications of digital CTC analysis in metastatic and localized prostate cancer. AR, androgen receptor; CTC, circulating tumor cell; LN, lymph node; RBC, red blood cell; SVI, seminal vesicle invasion; WBC, white blood cell (Miyamoto et al. Cancer Discovery 2018).

cystectomy or bladder-sparing trimodality therapy (transurethral tumor resection followed by chemoradiation). However, the decision regarding which treatment to pursue is often made based on arbitrary factors including patient or physician preference. There is an urgent unmet need for molecular biomarkers to guide patients towards the most appropriate therapy based on the biology of their tumor. We recently performed gene expression profiling of bladder tumors from patients treated with trimodality therapy and identified immune and stromal molecular signatures predictive of outcomes after chemoradiation. Ongoing projects include the development of CTC RNA signatures to predict outcomes and monitor for minimal residual disease after bladder cancer therapy. We are currently evaluating these and other candidate biomarkers as predictors of treatment response in prospective clinical trials and carefully defined retrospective clinical cohorts.

Selected Publications:

Guo H, Vuille JA, Wittner BS, Lachtara EM, Hou Y, Lin M, Zhao T, Raman AT, Russell HC, Reeves BA, Pleskow HM, Wu CL, Gnirke A, Meissner A, Efstathiou JA, Lee RJ, Toner M, Aryee MJ, Lawrence MS, **Miyamoto DT***, Maheswaran S*, Haber DA*. DNA hypomethylation silences anti-tumor immune genes in early prostate cancer and CTCs. *Cell*. 2023; 186:2765-2782.

Kamran SC, Zhou Y, Otani K, Drumm M, Otani Y, Wu S, Wu CL, Feldman AS, Wszolek M, Lee RJ, Saylor PJ, Lennerz J, Van Allen E, Willers H, Hong TS, Liu Y, Davicioni E, Gibb EA, Shipley WU, Mouw KW, Efstathiou JA, **Miyamoto DT**. Genomic tumor correlates of clinical outcomes following organ-sparing chemoradiation therapy for bladder cancer. *Clinical Cancer Research*. 2023; in press.

Efstathiou JA, Mouw K, Gibb E, Liu Y, Wu CL, Drumm M, da Costa JB, du Plessis M, Wang NQ, Davicioni E, Feng FY, Seiler R, Black PC, Shipley WU, **Miyamoto DT**. Impact of immune and stromal infiltration on outcomes following bladder-sparing trimodality therapy for muscle-invasive bladder cancer. *European Urology*. 2019; 76:59-68.

Miyamoto DT, Lee RJ, Kalinich M,... Toner M, Maheswaran S, Haber DA. An RNA-based digital circulating tumor cell signature is predictive of drug response and early dissemination in prostate cancer. *Cancer Discovery*. 2018; 8:288-303.

Saylor PJ, Lee RJ, Arora KS, Deshpande V, Hu R, Olivier K, Meneely E, Rivera MN, Ting DT, Wu CL, **Miyamoto DT**. Branched chain RNA in situ hybridization for androgen receptor splice variant AR-V7 as a prognostic biomarker for metastatic castration-sensitive prostate cancer. *Clinical Cancer Research*. 2017; 23:363-369.

Miyamoto DT, Zheng Y, Wittner BS,... Toner M, Maheswaran S, Haber DA. RNA-Seq of single prostate CTCs implicates noncanonical Wnt signaling in antiandrogen resistance. *Science*. 2015; 349:1351-1356.

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