**Title:** Wisconsin Prostate Cancer SPORE

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**Link:** https://cancer.wisc.edu/research/innovation/wisconsin-prostate-cancer-spore/

**Funding:** University of Wisconsin Carbone Cancer Center, under the direction of Dr.’s David Jarrard and Douglas McNeel, has been designated as recipient of a Specialized Program of Research Excellence, or SPORE, grant by the National Cancer Institute (NCI) for research initiatives to advance new prostate cancer treatments as of June 2023.

**Scientific Abstract:**

Overview:

The ultimate goal of the UW Prostate Cancer SPORE is to conduct interdisciplinary, translational research that exploits unique institutional strengths combined with national connections to improve outcomes for prostate cancer (PC) patients. Over 34,000 men in the US die from PC that has progressed beyond primary localized therapy. The impact of this disease worldwide is even greater with 4% of all cancer deaths being attributed to the disease. The program at UW builds on several historically strong, interactive research groups established at UW and seeks to expand and leverage new investigators and collaborators. This UW Prostate Cancer SPORE will align our unique strengths in basic and translational research with the clinical care of men with advanced PC to improve PC outcomes. These areas include imaging, immunology, bioengineering and clinical care. Success of these novel projects will significantly address several barriers to successful treatment including resistance to therapy, inter- and intratumoral heterogeneity, and predicting patient-specific responses to therapy. Specific Objectives and Goals of the UW Prostate Cancer SPORE include:

1. Increase multidisciplinary translational research in PC with an emphasis on developing a new generation of PC researchers.

2. Develop and expand common resources (e.g., 3D prostate tumor molds; image quantitation) to be shared with other institutions to promote advances in PC research and treatment outcome.

3. Translate promising new approaches developed at UW (e.g., patient-derived tumor microenvironment biochips; identification by automated image evaluation and selective ablation of nonresponding lesions; anti-cancer vaccine combinations) through preclinical testing in PC tumor models and into human clinical trials.

4. Improve overall survival and quality of life for patients with PC.

Project 1: Tumor Microenvironment Initiators of the Metastatic Cascade in High-Risk Prostate Cancer

There is an increasing incidence of men with newly diagnosed prostate cancer (PC) presenting with locally advanced or metastatic disease, a population that comprises >60% of the men who die from the disease. The failure of early detection has led to the initiation of multiple clinical trials testing neoadjuvant therapies in an attempt to cure these patients. Analysis of pre-treatment samples from neoadjuvant trials has identified genomic alterations that associate with treatment resistance. More recent studies indicate the tumor microenvironment (TME) can initiate the metastatic cascade. However, it remains unclear how and when genomic alterations co-opt different cell types in a complex 3-dimensional TME to initiate the metastatic cascade. We have recently found that activated fibroblasts and macrophage sub-populations induce lymphovascular sprouting and permeability. Based on these data sets, we hypothesize that somatic alterations in tumor DNA co-opt stromal and immune cells in the TME to promote invasion and intravasation of lympho-vascular channels. To test this hypothesis, we have three cohorts of patients with high-risk prostate cancer (treated with surgery alone, neoadjuvant abiraterone, or neoadjuvant chemohormonal therapy) that undergo PSMA PET/MRI scans prior to surgery. These scans are used to develop 3D molds of the prostate to perform whole mount sectioning and dissection of multi-focal PC for multi-plex molecular analysis. Samples from these specimens are used to create patient-specific “TMEs on a Chip” using a humanized Micro-Physiologic System (MPS) of the prostate with surrounding lympho-vasculature. This novel model system allows culture of patient tumor cells and stromal cells to identify the factors that induce lymphatic permeability and culminate in tumor invasion and intravasation.

Success in these studies will identify the biologic interactions in the TME that can initiate the metastatic cascade as potential biomarkers and therapeutic targets for men with high-risk, locally advanced PC. In Aim 1 we will perform whole exome and transcriptome sequencing, across 3D whole mount sections identified by PSMA PET/MRI, in untreated patients to evaluate heterogeneity and determine the impact of neoadjuvant ARSIs and docetaxel across 3D multifocal PC. In Aim 2, we extend spatial mapping with PSMA PET/MRI and IHC data to perform transcriptional Digital Spatial Profiling (DSP) on whole-mount sections collected in Aim 1. This integration will test whether distinct cancer-associated fibroblasts and immune cell infiltrates associate with genomic alterations in a spatial configuration of cells invading regional lymphovascular channels. In Aim 3, we will use LumeNEXT MPS technology to create humanized lymphatic vessels cultured in patient-specific humanized prostate TMEs, with genomically engineered PC cells, that reflect the molecular and cellular signatures identified in Aims 1 and 2. When completed, the outcome of this work will advance the field by helping us to understand how prostate cancer metastasizes for both biomarker and drug development.

Specific Aims:

Aim 1 – To evaluate molecular features across multi-focal lesions associated with recurrence and

metastatic disease in high-risk prostate cancer.

Aim 2 – To identify the underlying molecular mechanisms in the prostate TME that initiate invasion and metastatic disease.

Aim 3 – To examine functional alterations induced by cellular components and interactions in the

prostate TME that initiate the metastatic cascade.

Project 2: Androgen deprivation as an immune modulating therapy in combination with targeted immunotherapy of prostate cancer

Prostate cancer is a significant worldwide health problem for which new treatments are needed. The goal of our laboratory for the past twenty years has been to develop immunotherapy treatments for prostate cancer. We have evaluated multiple cancer-associated proteins as anti-tumor vaccine targets and have focused recent efforts on the ligand-binding domain of the androgen receptor (AR LBD) as a target. We demonstrated that a DNA vaccine encoding the AR LBD (pTVG-AR) can elicit epitope-specific cytolytic CD8+ T cells in HLA-A2 transgenic mice, and immunization of prostate tumor-bearing mice elicited anti-tumor responses and significantly prolonged their overall survival. Based on these results, we recently completed a multi-center phase I clinical trial using the pTVG-AR vaccine for patients with metastatic prostate cancer and demonstrated that vaccination is safe and immunologically active. Consistent with our preclinical studies, the development of T-cell immune response to the AR LBD was associated with a prolonged time to castration resistance. In preclinical studies, we have found that androgen deprivation (AD) leads to overexpression of the AR protein in prostate cancer cells, and this in turn makes them more recognized by CD8+ T cells activated by AR- targeted vaccination. We have subsequently demonstrated that AD can thus be used strategically with immunization. In other preclinical studies, we have further found that CD8+ T cells activated by vaccination express multiple immune checkpoint receptors (ICR), and that blockade of certain ICR with vaccination leads to greater anti-tumor effects. Together, these findings have led to the hypothesis to be tested in this proposal that combined AD, with AR-targeted vaccination and T-cell checkpoint blockade, will lead to increased tumor-specific CD8+ T cell infiltration, tumor eradication, and persistent immune memory. We will use relevant murine models of prostate cancer to conduct a mechanistic evaluation of the effects of AD with vaccination and ICR blockade on the development of T cell memory and antigen spread. This approach will also be evaluated in an investigator- initiated clinical trial in patients with high-risk prostate cancer prior to prostatectomy, with a design amenable to modification of study arms depending on the outcomes from the preclinical studies. This proposal, consequently, capitalizes on development of a novel anti-tumor vaccine that has now completed phase I clinical trial evaluation, and explores methods to increase its therapeutic effect in preclinical models and in a biomarker-driven clinical trial. This proposal will identify optimal strategies and clinical scenarios for further clinical development of this treatment approach.

Specific Aims:

Aim 1 – To determine whether different methods of AD affect the immune recognition of prostate tumors and lead to increased anti-tumor immune response in combination with AR-targeted vaccination.

Aim 2 – To determine whether AR-targeted vaccination, in combination with AD and ICR blockade, leads to increased AR-specific CD8+ T-cell infiltration and persistent anti-tumor immune memory.

Aim 3 – To determine whether AR-targeted vaccination, in combination with AD and PD-1 blockade, leads to increased tumor-infiltrating CD8+ T cells with memory and effector function, and persistent CD8+ T-cell memory, in patients with newly diagnosed high-risk prostate cancer.

Project 3: Extending Clinical Benefit by Selective Treatment of Resistant Lesions in mCRPC

Development of treatment resistance is the main reason for disease progression in patients with mCRPC. What is under-appreciated is that many patients who are experiencing progression have the majority of individual lesions that continue to respond to therapy. Identification of resistant lesions would allow for administration of localized ablative therapies, especially if the systemic therapy is still effective for the majority of metastases. We hypothesize that selective treatment of resistant lesions (e.g. with stereotactic body radiation therapy) will extend duration of clinical benefit in men with mCRPC. We will identify resistant lesions by employing our unique advanced quantitative molecular image analytics – Quantitative Total Extensible Imaging (QTxI) which allows lesion-level assessment of treatment dynamics. This project will first conduct a clinical trial in which patients who are being treated for advanced prostate cancer have serial PET scans to monitor the development of new lesions using this analytic software. Machine learning tools will then be used to determine which types of lesions, if treated, would have produced the greatest treatment response. In the third part of this proposal, this will then be tested in a separate clinical trial in which patients with advanced prostate cancer already on therapy will undergo serial imaging to identify lesions that could be treated with targeted radiation therapy, and thus prolong the efficacy of the underlying therapy. This project is highly innovative as it explores lesion-level treatment resistance in mCRPC, uniquely characterized by our technology, as a treatment target. Assessment of resistance at the time of clinical progression is critical, as it triggers high anxiety in the patient and provider, and thus it is an urgent area of unmet clinical need. We will conduct the first trial of its kind to identify and treat resistant lesions in the setting of widespread metastatic disease with the goal of improving clinical benefit.

Specific Aims:

Aim 1 – To characterize resistance at early progression in men with mCRPC treated with second-generation androgensignaling inhibitors by employing QTxI of PET/CT starting at nadir PSA response, PSA progression, and again in 12 weeks

Aim 2 – To conduct virtual selective radio-ablation study using different PET metrics for target lesion selection of resistant lesions and to model impact of radio-ablation on total tumor burden and anticipated improvement in clinical benefit

Aim 3 – To test clinical feasibility of radio-ablation using SBRT to selective resistant lesions in a prospective therapeutic clinical trial.

**Written Lay Abstract:**

**Overview:**

The UW Prostate Cancer Specialized Program of Research Excellence (SPORE) was funded by the National Cancer Institute. The Prostate Cancer SPORE has a team of researchers at UW Carbone Cancer Center that work together to improve outcomes for prostate cancer patients. The program also funds training and research to create the next generation of prostate cancer researchers and cutting-edge studies. Researchers in this program study prostate cancer all the way from the cellular level up to the clinical level. There are three main research projects of the Prostate Cancer SPORE.

**Project 1: Understanding resistance to prostate cancer treatments**

More people are dying of advanced and metastatic (spreading) prostate cancer. Recent research tells us many people who have prostate cancer may have cancers that are resistant to treatment. In this project, the researchers want to know what is happening in the tumor microenvironment (the area around the cancer) that may be causing resistance to treatment and causing cancer to spread to other parts of the body. The researchers will study prostate cancer cells from patients to see how the tumor microenvironment affects cancer cells and to find better treatments for early prostate cancers.

**Project 2: Creating new prostate cancer treatments**

One type of treatment for prostate cancer is anti-tumor vaccines, which target specific proteins in the cancer cells. One protein that can be targeted is the androgen receptor, which is the main target for many hormonal treatments of prostate cancer. Recent research tells us that vaccines targeting this androgen receptor protein may work best when also used with other immunotherapy and hormonal treatments. In this project, the researchers will test the vaccine and these other treatments together in the laboratory and in a human clinical trial.

**Project 3: Improving outcomes for patients with treatment resistant prostate cancer**

One type of prostate cancer is called metastatic castration-resistant prostate cancer (mCRPC). In this advanced prostate cancer, the cancer has spread to other parts of the body and no longer responds to hormone treatments that lower testosterone. However, in people with mCRPC, some cancer spots in the body can still respond to hormone treatments. In this project, the researchers will use computer analysis methods they created to look at PET scans and find all spots of prostate cancer that have spread in the body. The computer analysis will determine which cancer spots are responding to treatment and which are not. The researchers can then use radiation therapy to target these spots that are not responding to treatment. This will be tested in clinical trials to see if this approach can improve prostate cancer treatments.

**The Next Generation: Funding Training and Research**

Career Enhancement Program (CEP): To move our research findings into care for patients with prostate cancer, we need scientists with special knowledge. The CEP provides formal training for scientists who want to focus their careers on prostate cancer research and treatment.

Developmental Research Program (DRP): This program supports new and unique cancer studies that will improve the survival and quality of life of people with prostate cancer. Our goal is for studies funded by this program to turn into larger projects of the Wisconsin Prostate SPORE or become projects that can be funded by other institutes.

**Visual Lay Abstract:**

A blue and white poster with images of people in medical equipment

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Description automatically generated with medium confidenceA poster for a prostate cancer treatment

Description automatically generatedA poster with a person talking to another person

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