Joshua Brody, MD, Associate Professor, Department of Medicine, Division of Hematology & Medical Oncology, and Director of the Lymphoma Immunotherapy Program at the Tisch Cancer Institute

Project Title: "Preventing antigen escape relapse post-immunotherapy by potentiating fas-mediated bystander signaling"

Project Summary: Cancer immunotherapy has revolutionized how we care for patients with common cancers including lung cancer, lymphoma, and some types of breast and colon cancers. These therapies allow the patient's immune system to target specific 'antigens' present on cancerous cells, but not healthy cells, making these approaches better tolerated than most types of chemo- or radio-therapy.

However, a common problem of immunotherapies is that among billions of tumor cells, some fraction may be lacking these targeted antigens. In other words, these tumor cells can proliferate, known as 'antigen escape' and ultimately cause patients to relapse. Though it may be difficult to treat antigen escape, we have studied a novel approach to prevent antigen escape.

Though the most important anti-cancer immune cells – called T cells – primarily only target antigen-expressing cancer cells, they also have a limited ability to target the neighboring cancer cells, even if they lack the antigen – also known as 'bystander killing.' We recently discovered a primary mechanism as to how T cells accomplish bystander killing, which prompted a search for how this type of cancer killing might be enhanced.

The current project will be testing several therapies – some FDA-approved, some currently being assessed in clinical trials – that appear to enhance bystander killing to see if they can actually prevent antigen escape in pre-clinical models, and thereby increase T cell efficacy. If so, it could be a straightforward path to push these candidate therapies into clinical trials in combination with a variety of cancer immunotherapies.

Headshot:

Nihal Mohamed, PhD, Associate Professor of Psychology, and Director of Patient Education & Behavioral Research in the Department of Urology

Project Title: "Mobile Ostomates Resources intervention for patients and caregivers (MORE)"

Project Summary: Approximately 700,000 individuals in the United States have an ostomy – a surgically created opening in the body for the discharge of body wastes (e.g., urine and feces). Patients treated with ostomy surgeries and their family caregivers typically undergo unmet informational and supportive care needs. They also commonly experience decreased quality of life due to the psychological impact of having a stoma on patient emotional well-being and ostomy care requirements (e.g., lifelong use of ostomy appliances).

To address patients' and family caregivers' unmet needs, and supported by an NIH award, we have developed a web-based, interactive program to facilitate post-surgical stoma care education and psychological adjustment for patients with new ostomies and dubbed it "MORE" (short for *Mobile Ostomates REsources intervention*).

In this new study, we will examine the acceptability and feasibility of MORE with 45 new ostomy patients and their family caregivers. We hope to see improvements in patient and caregiver knowledge about ostomy surgeries and skills needed for ostomy care. We also hope to see improvements in patient quality of life and psychological adjustment. For the family caregivers, we expect the study to increase their ability to support patients with information and ostomy care, and to reduce their caregiving burden.

Headshot:

David Mulholland, PhD, Associate Professor of Oncological Sciences

Project Title: "Therapeutic modulation of intermediate tumor subpopulations to delay treatment induced neuroendocrine prostate cancer"

Project Summary: Targeting of the Androgen receptor (AR) provides significant benefits for individuals with localized and metastatic prostate cancer. However, there has been an increasing clinical observation of the prevalence of prostate cancers which have adapted to use clinical AR inhibitors including Xtandi, Apalutamide, and Bavdegalutamide. In some instances, patients who have been heavily treated with these drugs will go on to form neuroendocrine prostate cancer, which is characterized by aggressive metastasis and poor survival outcome.

Our research has identified a mechanism and rate limiting progress required by prostate cancer cells that escape sensitivity to AR targeting drugs to form neuroendocrine prostate cancer. Specifically, we have used patient tumor samples to develop novel preclinical models to show that prostate cancer cells must transition through a critical 'intermediate' lineage state. While in the intermediate lineage state, cells remain responsive to AR inhibitors, but can subsequently lose AR expression, thus becoming metastatic and may take on neuroendocrine features.

Until now, the process by which prostate cancer cells transition from epithelial → intermediate → neuroendocrine is poorly understood. We have discovered that by treating patient tumor models with drugs targeting a molecule called EZH2, prostate cancer cells remain more sensitive to AR inhibitors, undergo more cell death, and are less likely to progress to neuroendocrine disease. If our preclinical studies continue to be successful, our results could provide new clinical regimens consisting of the combined targeting AR and EZH2. This may allow for the extended and more effective use of Xtandi, Apalutamide, and Bavdegalutamide in localized and AR-positive metastatic prostate cancer while avoiding adaptive neuroendocrine lineage changes.

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