

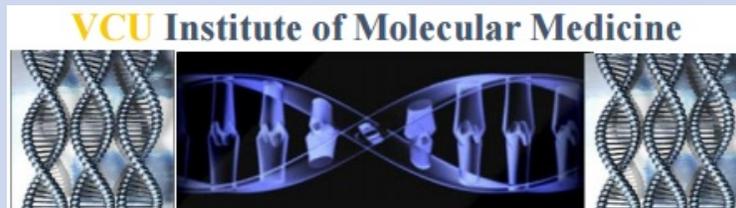

VCU

VIRGINIA COMMONWEALTH UNIVERSITY

Institute of Molecular Medicine

VCU Institute of Molecular Medicine (VIMM) NEWS & VIEWS

The VIMM, established in 2008 by Paul B. Fisher, M.Ph., Ph.D., the Founding Director, is comprised of outstanding scientists/clinicians from VCU School of Medicine focusing on important medical-related research in cancer, neurodegeneration and infectious diseases. The purpose of this NEWS & VIEWS is to highlight the exciting research being performed by the VIMM members.



Targeting Epigenetic Complexes to Achieve a Novel Cancer Immunotherapy

- Immunotherapies have emerged as effective cancer treatments, however several cancer types have not benefited because of reduced immunogenicity.
- This report describes the novel epigenetic regulator NURF (The Nucleosome Remodeling Factor) as a suppressor of breast and melanoma cancer immunogenicity.
- Targeting and inhibiting NURF in mouse models of breast and melanoma cancer results in enhanced antitumor immunity and reduced tumor growth.
- Strategic manipulation of epigenetic regulators of gene expression may provide a novel approach for cancer immunotherapy.

NURF Depletion Enhances T Cell Mediated Antitumor Immunity

In this study, a novel epigenetic regulator of tumor immunogenicity was discovered using mouse breast and melanoma tumor models. Tumors suppress immunogenicity in order to avoid the antitumor immune response. This is largely achieved by altering gene expression through both genetic and epigenetic mechanisms. Unlike genetic mechanisms, epigenetic mechanisms are reversible, and therefore can be targeted for therapeutic benefit. Previously, Dr. Landry's laboratory used bioinformatic analyses to discover a correlation between the abundance of the NURF complex and gene signatures reflective of an antitumor immune response, in a variety of human tumor types. This led to the hypothesis that the tumor cell intrinsic activity of NURF suppresses antitumor immunity. To test this, NURF was depleted in syngeneic mouse breast and melanoma tumor models. Tumors depleted of NURF were more susceptible to a T cell mediated antitumor immune response. Molecular analyses determined that NURF depletion enhances the expression of several genes important for tumor antigen processing and presentation. The increased tumor cell antigenicity that occurs due to NURF depletion improves the antitumor cytotoxic activities of T cells (Figure 1). Because NURF is not essential for cell viability, T cell activity, or in the adult mammal in general, this establishes NURF as a viable target in a novel method for immunotherapy.

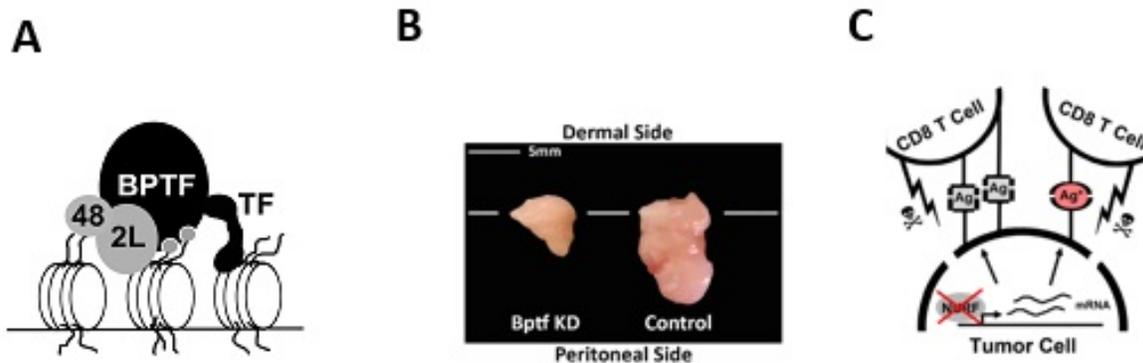


Figure 1.) A Model for NURF Function as a Suppressor of Tumor Antigenicity. (A) Cartoon showing NURF as a complex of BPTF (Bromodomain PHD Finger Transcription Factor), the ATPase SNF2L (2L) and the WD repeat protein pRbAp46/48 (48). NURF is recruited to chromatin through interactions with transcription factors (TF), and posttranslational modifications (grey balls) found on nucleosomal histones (shown as transparent disks). **(B)** Significant reductions in primary tumor size were observed after NURF was depleted (through Bptf shRNA knockdown) from mouse breast and melanoma tumor models. **(C)** Molecular analysis shows that NURF suppresses the expression of genes important for tumor antigen (Ag) processing and presentation. When NURF is depleted these processing genes are upregulated improving tumor cell antigenicity, and correspondingly T cell anticancer cell activity.

Publications:

Mayes K, Alkhatib S, Peterson K, Alhazmi A, Song C, Chan V, Blevins T, Roberts M, Dumur C, Wang XY and **Landry J**. BPTF Depletion Enhances T Cell Mediated Antitumor Immunity. *Cancer Res.* 2016 Nov 1;76(21):6183-6192. PMID:[PMC5093041](https://pubmed.ncbi.nlm.nih.gov/27111111/)

This project represents a collaborative effort between Joseph Landry, PhD and Xiang-Yang (Shawn) Wang, PhD, faculty members of the VCU Institute of Molecular Medicine (VIMM) and Department of Human and Molecular Genetics (HMG), and Catherine Dumur, PhD, a faculty former member in the VCU Molecular Diagnostics Core and Department of Pathology. It was performed in the laboratories of the Massey Cancer Center (MCC) and supported by funds from the V Foundation for Cancer Research, the MCC, and the Department of HMG. This work was largely completed by HMG graduate student Kimberly Mayes with support from HMG graduate students Suehyb Alkhatib, Kristen Peterson, Aiman Alhazmi and Mark Roberts, and VCU undergraduate students Carolyn Song and Vivian Chan.

About the Investigators Joseph Landry, PhD, is Assistant Professor of Human and Molecular Genetics (HMG), and a Member of the Massey Cancer Center (MCC) and the VCU Institute of Molecular Medicine (VIMM), Virginia Commonwealth University, School of Medicine, Richmond, VA. Xiang-Yang Wang, PhD, is Professor of HMG, Associate Scientific Director of Immunology of the VIMM and Mary Anderson Harrison Distinguished Professor in Cancer Research in the VCU MCC. Catherine Dumur is a former Director of the Molecular Diagnostics Core and Associate Professor in the Department of Pathology, Virginia Commonwealth University, School of Medicine.