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PHAGE DISPLAY LIBRARY SCREENING IDENTIFIES NOVEL BINDING PEPTIDES THAT PREFERE NTIALLY TARGET CASTRATION-RESISTANT PSA-/lo PROSTATE CANCER STEM CELLS

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Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer (PCa). Despite an initial response, the majority of patients relapse resulting in castration-resistant prostate cancer (CRPC). Both untreated advanced PCa and CRPC are enriched in phenotypically undifferentiated PCa cell populations that expresses little or no prostate specific antigen (i.e., PSA-/lo). We have demonstrated that the PSA-/lo PCa cell population harbors self-renewing prostate cancer stem cells (PCSCs) that are intrinsically resistant to ADT and can long-term propagate tumors, mediate recurrence, and serve as a cell-of-origin for CRPC (Cell Stem Cell, 2012; Oncotarget, 2015; Clin Cancer Res, 2016; Oncotarget 2016). Consequently, it is important to find therapeutics that can preferentially target these cells. By employing phage display technology, we screened a combinatorial library for peptides that preferentially bind to PSA-/lo LNCaP PCa cells. An initial competitive assay identified the JRM1 peptide that showed slight preferential binding to the PSA-/lo LNCaP cells. With this knowledge, we carried out another screen using an indirect subtraction assay to identify the peptide JRM2, which demonstrated preferential and statistically significant binding to the PSA-/lo LNCaP cells. Fluorophore-conjugated JRM2 could be internalized into cells. When conjugated to a pro-apoptotic peptide, JRM2 specifically inhibited cell proliferation in PSA-/lo PCa cells. Preliminary *in vivo* studies showed tumor-inhibitory effects of the JRM2-killer peptide conjugates. Our findings demonstrate the feasibility of utilizing novel ligand-directed therapeutics to target undifferentiated (AR-)PSA-/lo CRPC cells.

BIOGRAPHY

Kiera Rycaj, PhD, is currently Assistant Professor at the Roswell Park Comprehensive Cancer Center (RPCCC) in Buffalo, NY, USA. She obtained her PhD from the University of Texas M.D Anderson Cancer Center (MDACC) in 2012 Her PhD thesis work focused on the expression and biological functions of HERV-K (Human Endogenous Retrovirus – K) in breast and ovarian cancer (OC) cells. Her work has demonstrated that the HERV-K env protein not only is expressed on the surface of breast cancer and OC cells but also can function as TAA (tumor-associated antigen) to elicit T-cell and antibody responses. She developed HERV-K specific vaccines and demonstrated their utility in killing autologous patient cancer cells. She conducted her postdoc training in Dr. Tang's laboratory during 2012-2015 and her work focused on elucidating prostate cancer (PCa) cell heterogeneity and therapeutically targeting the phenotypically undifferentiated AR-/lo(PSA-/lo) prostate cancer stem cells (PCSCs). Her recent published study on high-throughput screening shows that treatment-reprogrammed castration-resistant PCSCs are AR-PSA- and completely refractory to antiandrogens but remain partially sensitive to inhibitors of BCL-2 and certain kinase. She became a junior faculty in 2015, and her lab has been focusing on elucidating how primary tumor microenvironment regulates functional properties of metastatic PCSCs and on developing novel immunotherapeutic strategies to target undifferentiated, therapy-resistant and metastasis-prone PCa cells.

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