Role of Bone Marrow Stromal Antigen 2 (BST-2) in Viral Pathogenesis and Breast Cancer Progression

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Bone marrow stromal antigen 2 (BST-2) is an innate immunity gene and a restriction factor induced upon infection by different enveloped viruses. BST-2 is expressed at the cell surface where it tethers viruses preventing their release and dissemination. Retroviruses including HIV and mouse mammary tumor virus (MMTV), the causative agent of breast cancer in mice are susceptible to the antiviral function of BST-2. During acute MMTV infection, the virus suppresses BST-2 expression in immune cells, permitting virus replication and spread to the mammary gland. Interestingly, viral load and BST-2 expression are elevated in mammary tumors induced by MMTV, an indication that the antiviral role of BST-2 may not be operative once mammary epithelial cells are transformed and/or tumors have developed. These data provided the initial evidence for the hypothesis that BST-2 functions as both an antiviral and protumor factor.

The objective of this thesis was to determine whether BST-2 plays a functional role in the initiation and progression of breast cancer. Using in silico analyses of various human breast cancer datasets, we showed that BST-2 is overexpressed in human breast tumors compared to normal breast tissue and that levels of BST-2 are correlated to disease grade/aggressiveness. We also showed that overexpression of BST-2 in breast tumors is a result of hypomethylation of CpGs in and at close proximity to the BST-2 promoter. These in silico analyses were the basis to test the response to reduction in BST-2 activity in a mouse model of breast cancer. We found that knock down of BST-2 in breast cancer cells reduced tumor size, increased time to primary tumor development, and reduced metastatic burden. In vitro, BST-2 enhanced breast cancer cell adhesion, migration, invasion and anchorage independent growth. These BST-2-mediated functions are dependent on the ability of BST-2 to form homodimers. Thus, breast cancer cells that express BST-2 dimers are more adherent, resistant to anoikis, survive in suspension, and grow in mice. While cells expressing monomers of BST-2 are deficient in all named processes.

Future studies will aim at determining the molecular mechanism of BST-2-induced anoikis and developing BST-2-based therapeutics aimed at disrupting BST-2 dimerization. The Okeoma laboratory has developed a small peptide, B49 that disrupts BST-2 dimerization. B49 shows potential as it slows tumor growth in vivo. Improving B49 stability and therapeutic index will constitute the main project in Wadie’s postdoctoral career.

Wadie Mahauad Fernandez
Biographical Sketch

Wadie was born in Loja, Ecuador. During his Junior and Senior years of high school in Ecuador he leaned towards the sciences growing fascinated by his biology, physiology and anatomy classes. In 2007, Wadie came to the US for the first time as an exchange student to study English. He was lucky to be sent to Watertown, SD where he, besides improving his English, got to experience a real winter that made Iowa winters later in his life feel like summer. In 2008, Wadie entered Augustana University in Sioux Falls, SD to pursue his Bachelor of Arts with an emphasis in Biology/PreMed. During his Junior year at Augustana, Wadie performed undergraduate research through the Sanford Program for Undergraduate Research (SPUR) where he studied the symbiotic relationship of oral bacteria under the guidance of Dr. Paul Egland (former UI Ph.D. graduate). Realizing that research fulfills his thirst for discovery and understanding of how things work down to the molecular level, Wadie decided to pursue his Ph.D. In 2012, Wadie was admitted to the Molecular and Cellular Biology program at The University of Iowa. A year later, Wadie began his thesis work exploring the role of antiviral factors in viral pathogenesis and breast cancer under the guidance of Dr. Chioma Okeoma. Wadie has presented his work at local and national meetings immersing himself in the fields of virology and oncology. Wadie will continue his work on BST-2 and breast cancer with Dr. Okeoma to develop BST-2-based therapeutics; a rare opportunity to bring his discovery a step closer to the clinic.

When not at the lab, Wadie enjoys playing the guitar, going out with friends and watching and playing sports. Especially soccer, he loves soccer.