THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

ANDREA MARIE PATTERSON

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Monday, November 16, 2015, 12:00 p.m.
Room 109, Biomedical Research Center, OUHSC

HLA CLASS I EPITOPES FOR IMMUNOTHERAPEUTIC TARGETING OF OVARIAN CANCER

COMMITTEE IN CHARGE: William Hildebrand, Ph.D., Chair, Madeleine Cunningham, Ph.D., Darrin Akins, Ph.D., Doris Benbrook, Ph.D., Noah Butler, Ph.D.

ABSTRACT: Class I human leukocyte antigens (HLA) serve as tiny molecular informants utilized by all human nucleated cells to signal health or disease to the immune system. A cancerous protein repertoire can be revealed at the cell surface by peptides bound to class I HLA,

and these complexes are targeted by cytotoxic T lymphocytes (CTL). In ovarian cancer, the most deadly gynecologic cancer, CTL tumor infiltration corresponds with significantly improved survival, indicating effective class I HLA presentation of cancer-specific peptides. **The hypothesis of this study was that a large number of previously unidentified peptides distinguish ovarian cancer cells and can be exploited for novel immune therapies.** To test this hypothesis, we first performed a large-scale characterization of the ovarian cancer ligandome from four diverse cell lines using techniques of molecular biology, human cell culture, and advanced proteomics. The natural processing of many recognized tumor associated antigens was revealed, including BIRC6, HER2, MIF, P53, EPCAM, MSLN, MUC16, and many others. Comparative analyses were performed at the cell line and tissue levels to identify novel ligands that might distinguish cancer from normal. The tissue comparison took advantage of the extensive, defined peptide spectra in our novel ligand library and illustrated the potential for large-scale ligand identification from individual tumors. Finally it was shown by flow cytometry, immunohistochemistry, and cytotoxicity assays that a proteomically-defined class I HLA/peptide complex (HLA-A*02:01/MIF_{19-27}) can be specifically targeted in ovarian cancer by a monoclonal antibody (RL21A), providing a novel therapeutic strategy for further development in ovarian cancer and illustrating an alternative form of HLA/peptide-centered immunotherapy in ovarian cancer. Overall, extensive characterization of the ovarian cancer HLA ligandome has revealed many novel TAA ligands, as well as peptides appearing unique to ovarian cancer cells and tissues. These findings, along with the demonstration of direct HLA/peptide complex targeting in ovarian cancer, have supported the hypothesis that numerous ovarian cancer ligands are presented by class I HLA with the potential for use as immunotherapeutic targets.