A Function for the Inflammatory Cytokine Oncostatin M during Different Stages of Breast Cancer Metastasis, CHERYL JORCYK (Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725-1515; cjorcyk@boisestate.edu).

Oncostatin M (OSM) is an interleukin-6 (IL-6)-family cytokine that has been implicated in a number of biological processes including inflammation, hematopoiesis, immune responses, and development. It is produced by multiple cell types, including activated T cells, macrophages, neutrophils, and tumor cells such as breast. OSM was initially shown to inhibit the proliferation of breast cancer cells in vitro, and was therefore evaluated as a potential cancer therapy. Evidence in the literature and data from our laboratory; however, suggests that OSM promotes tumor invasion and metastasis. In breast cancer cells, OSM induces secretion of proteases important for breakdown of the extracellular matrix during invasion and metastasis, promotes expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1alpha (HIF1alpha), and induces expression of pro-metastatic inflammatory factors such as cyclooxygenase-2 (COX2). The results from our novel in vitro and in vivo studies will be presented and may provide evidence that OSM is an important therapeutic target for the prevention of breast cancer metastasis.

Synthetic Aziridinomitosenes: Probing the Role of the C6/C7 Electrophilic Sites in Human Carcinoma Cytotoxicity, DON L WARNER (Department of Chemistry and Biochemistry, Boise State University, 1910 University Drive, Boise, ID 83725-1520; dwarner@boisestate.edu).

Many significant anticancer agents exhibit their biological properties through the covalent modification of DNA, and the interstrand cross-link is often the most relevant adduct. We have shown that several synthetic aziridinomitosenes (AZMs), derivatives of the antitumor antibiotic mitomycin C (MC), covalently modify DNA to form interstrand cross-links (ICLs) and DNA/protein cross-links (DPCLs). Unlike MC and related analogs, the new AZMs do not require reductive activation prior to DNA binding, suggesting that adduct formation must be occurring via a novel mechanism. Synthetic AZM analogs with alkyl substitutions at C6 and C7 have led to increased potency. The C6-methyl analog currently exhibits the lowest IC_{50} values of 3 nM and 12 nM in HeLa and HL-60 cell lines, respectively, which is a 300-fold enhancement over MC. Caspase-3 studies indicate AZMs induce protease activity greater than MC and HeLa nuclear morphology experiments indicate that MC produces nuclear swelling, while AZMs cause nuclear condensation. Together, these experiments suggest a different cytotoxic mechanism for the AZMs. Additional studies aim to isolate nuclear and mitochondrial DNA for detection of interstrand cross-links, and investigating reactive oxygen species levels post AZM treatment. This talk will present these and related studies that aim to ascertain cytotoxic mechanistic details.

Epithelial to Mesenchymal Transition in Gynecological Carcinomas, RAFAEL MALAGOLI ROCHA (Department of Pathology, Hospital AC Camargo, Rua Professor Antônio Prudente 211, Liberdade São Paulo, SP, 01509-900, Brazil; rafael.malagoli@gmail.com).

Epithelial-to-mesenchymal transition (EMT) is a process whereby epithelial cells lose cell polarity and cell–cell contact, displaying remarkable morphological alterations. These changes represent a critical early event in tumor invasion and metastasis. However, the role of EMT in vulvar squamous cell carcinoma (VSCC) has not been elucidated yet. Previous studies of our group show the HPV infection is detected in 39.1% of the cases, being HPV16 the most frequent type (35.3%). There is no difference in E-cadherin, Slug, Snail and Twist2 expression between the tumor center and the invasive front of
each tumor. However, lower β-catenin and higher Vimentin expression is observed at the invasive front when compared to the tumor center. Higher expression of E-cadherin in central tumor is significantly related to absence of vascular and perineural invasion, lower invasion depth, and ≤ 2 lymph node involvement. Loss of β-catenin and high Slug, Snail and Twist2 expression at the invasive front is significantly associated with absence of HPV infection. Moreover, β-catenin lower expression associated with gain in Slug expression predicts a subgroup with worst outcome (p=0.001). Lower expression of β-catenin in both tumor center and invasive front correlate with lower overall survival. Also, β-catenin expression is independently associated with poorer outcome. We suggest the comparative analysis of β-catenin between invasive front and tumor center as a key issue for establishing prognosis of vulva cancer and that HPV-related tumors do not progress through EMT phenomenon, showing usually better prognosis and more satisfactory outcome.

Small Molecule Inhibition of the Inflammatory Cytokine Oncostatin M? JIM MOSELHY1✉, CHERYL JORCYK2, DONG XU3 (1Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725-1515; jimmoselhy@boisestate.edu; 2Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725-1515; cjorcyk@boisestate.edu; 3Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, Idaho State University, 1311 E Central Dr, Meridian ID 83642; dxu@pharmacy.isu.edu).

Inhibition of cytokine and receptor interaction using small molecules represents an attractive alternative approach to classical antibody mediated inhibition of signal transduction. The development of small molecule inhibitors against IL-2/IL-2Ra axis suggests other cytokine-cytokine receptor interactions may also represent viable targeted therapies for various cytokine signaling-associated pathologies. Results of de novo computational screening of small molecule inhibitors of model cytokine-cytokine receptor interactions will be presented. The identification of lead compounds from chemical libraries is described on the basis of potential ligand binding sites optimized for shape matching structures against 3-dimensional templates of target surfaces coupled with site geometry search for clefts and pockets. The preliminary evaluation and validation of biological activity of select small molecule inhibitors identified by in silico screen against cytokine-mediated signaling is presented. ACS RSG-09-276-01-CSM, Susan G Komen KG100513, NIH/NCRR P20RR016454 and P20GM103408, NIH/NCI R15CA137510, and NASA NNX10AN29A.

A Co-Evolutionary Strategy to Discovery Novel Anticancer Drugs Breast Cancer Metastasis: A Role for the Inflammatory Cytokine Oncostatin M? JENNIFER S FORBEY (Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725-1515; jenniferforbey@boisestate.edu).

The majority of current cancer-related deaths are attributed to the evolutionary response of cancer to develop resistance to anticancer drugs. Finding methods to overcome drug resistance in cancer cells represents one of the most urgent needs in the field of cancer treatment. Although natural products from plants have long been praised for their anticancer properties, random screening approaches which are both costly and inefficient have led to reduced investment in natural products by pharmaceutical companies and a deficit in effective lead chemicals in the anticancer drug pipeline. This represents a critical gap in the battle against cancer - between available anticancer drugs and the discovery of effective natural products that are cytotoxic and overcome resistance. A novel approach to bridging this gap is one that takes into consideration the evolution of plant chemical defenses, herbivore offenses that aid in resistance to chemical defenses, and plant counter-defense that overcome resistance in herbivores. The co-evolutionary “arms race” between herbivores and plants is a natural experiment occurring over millennia, selecting for natural products that overcome drug resistance. I showcase several plant-herbivore systems that are ecologically and evolutionarily predisposed to have diverse and biologically active chemicals that are cytotoxic against cancer and can overcome drug resistance.

Prostate Tumor Progression and Metastasis: The Cytokine Connection, STEVE R PEKOVIČ1 and CHERYL L JORCYK3 (1Department of Biology, Northwest Nazarene, 623 S. University Blvd, Nampa, ID 83686; spekovich@nnu.edu; 3Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725-1515; cjorcyk@boisestate.edu)

Prostate cancer (PCa) is one of the most common types of cancer in American men, second only to skin cancer. For 2012, the American Cancer Society estimates that approximately 241,740 men will have been diagnosed with, and 28,170 men will die of, PCa in the United States. Most PCa is lethal as a result of local invasion and the metastasis of cancer cells from the primary tumor to peripheral tissues and vital organs. Patients with metastatic disease display metastasis to bone, lung, liver, pleura, and adrenals. The role of cytokines, particularly inflammatory cytokines, in PCa invasion and metastasis will be discussed. Particular attention will be focused on the inflammatory cytokine interleukin-6 (IL-6), which is well documented in PCa metastasis, especially to bone. Oncostatin M (OSM) is an IL-6 family cytokine that plays an important role in inflammation and other cellular processes such as development, hematopoiesis, liver function, neurogenesis, and bone homeostasis. OSM expression has been shown to be directly associated with metastatic potential in human prostate carcinomas, with increasing OSM and OSM receptor expression being found in higher Gleason grade tumors. Targeting inflammatory cytokines in the IL-6 family may be an important therapeutic strategy for patients with metastatic prostate cancer. NIH/NCRR P20RR016454 and P20GM103408.