Epithelial Ovarian Carcinoma (EOC) is the sixth most common malignancy in women and the leading cause of death of gynecological cancer in the world. EOC has a predisposition to metastasis to the peritoneal cavity. A late stage peritoneal dissemination results in ascites and high mortality rates with an overall survival of 20 to 30 percent at 5 years after surgery.

While many studies in the literature address the issue of distant metastasis, the biology of peritoneal tumor spread in advanced ovarian cancer is not clear. Development of peritoneal carcinomatosis involves well-defined critical steps, including cell shedding and transport, interaction and adhesion to the mesothelial layer, and colonization of and proliferation into the sub-mesothelial microenvironment. It is now appreciated that there must be an initiation of a pre-metastatic niche within the target organ, one that facilitates the survival of tumor cells in a non-receptive organ. We think that a dual approach looking at oncogenomics and heterocellular interaction will allow us to better understand ovarian cancer metastasis biology and help design new therapeutic strategies. Oncogenomic approaches restricted to a given methodology may hinder mechanisms driving progression. We used a comprehensive approach utilizing integrated systems biology platforms to assess the genetic and genomic modifications within a tumor compared to the metastatic lesions. Using this approach we were able to demonstrate the implication of many pathways, in particular the Jak/Stat pathways in the occurrence of metastatic lesions. Moreover we were able to identify NOTCH3 as an amplified locus in primary and metastatic lesions and were able to demonstrate using a cell biology approach the role of the Notch pathway in chemo-resistance.

We will present evidence demonstrating our ability to integrate our oncogenomic approaches with our cell biology findings. Using a comprehensive multi-disciplinary approach allowed us to identify some pathways implicated in the development of metastatic lesion in ovarian carcinomas. This will enable us to create new therapeutic strategies aiming at disrupting the interaction between the cancer cells and a permissive environment.

Arsenic/Interferon Combination: A Novel Therapeutic Approach to Target CML Stem Cells

Imatinib is currently the standard drug used in the treatment of CML patients. However, imatinib is not curative since most patients who discontinue therapy will relapse. Interferon alpha (IFN) induces hematologic and cytogenetic remissions and interestingly, prior exposure to IFN allowed Imatinib discontinuation in some CML patients. Arsenic trioxide inhibits the proliferation of BCR-ABL-expressing cells.

We have investigated the effects of the combination arsenic/IFN on the proliferation of CML cell lines. We found that IFN alone had minimal effect. Arsenic alone significantly decreased their proliferation in a time and dose-dependent manner. Interestingly, the addition of IFN to arsenic was synergistic in AR230 and additive in K562. This synergistic effect between IFN and arsenic was accompanied by dose-dependent apoptosis as evidenced by annexin V staining, TUNEL positivity and caspase activation. Colony-forming assay was performed on bone marrow and CD34+ cells collected from CML patients. Interestingly, arsenic and IFN produced a synergistic decrease in myeloid colony formation, especially when compared to Imatinib.

Preliminary results of an in vivo study using the retroviral transduction CML mouse model showed prolonged survival of secondary recipients that received cells from primary leukemic mice treated with arsenic/IFN, as compared to those that received cells from untreated controls. These results suggest that arsenic and IFN synergize to inhibit proliferation, induce apoptosis and target dormant CML stem cells that are spared by Imatinib.