The Birrer laboratory has had a long-term interest in characterizing the molecular origins of gynecologic cancers. This interest includes the identification and characterization of mutations in oncogenes and tumor suppressor genes within cancers of the ovary, endometrium and cervix. In addition, we have extensively characterized the differential gene expression in these tumors. The role of these genes in the development of these cancers has been tested using in vitro and in vivo model systems. Our laboratory is focused on using the genomic events characterized in these cancers to produce translational science endeavors, which will result in clinically important discoveries. These genomic abnormalities form the basis for early detection assays, prevention strategies, and novel therapeutic approaches. Our laboratory focuses on bench-to-bedside-and-back-again approaches to produce clinically relevant strategies to improve the outcome of women with these types of cancers.

Our laboratory focuses on characterizing the function and clinicopathologic impact of key genes and pathways in ovarian cancer. The laboratory was awarded an NCI Director’s Challenge grant for the genomic analysis of ovarian cancer and, in collaboration with Memorial Sloan Kettering Cancer Center, University of Pennsylvania, Fox Chase Cancer Center, and the Australia Ovarian Cancer Study, has conducted a large-scale study of expression profiling. These efforts have characterized differential gene expression on the whole-genome level between ovarian tumors of different histology and tumor grade. The study identified pathways that underlie the clinical pathologic characteristics of these tumors and identified clear cell and mucinous tumors of the ovaries as unique tumors unrelated to other histologic subgroups. This discovery has established for the first time unique trials for patients with these cancers. We have also shown that low malignant potential tumors of the ovary (Grade 0) are a unique form of serous tumors and require specific therapeutic approaches. As a result, the laboratory has been instrumental in testing the MEK inhibitor AZD6244 for Grade 0 tumors. More recently, the laboratory was awarded an RC4 grant (in collaboration with Giovanni Parmigiani, PhD, of the Dana-Farber Cancer Institute) to validate previously identified gene expression signatures which classify patients into good versus poor prognosis, utilizing 1600 clinical trial specimens from the recently completed GOG clinical trial 218. The results will be rapidly integrated into prospective clinical trials of patients with advanced-stage ovarian cancer.

To further facilitate biomarker analysis and target identification for effective management of ovarian cancer, our laboratory has contributed to the development of a curatedOvarianData database that provides standardized gene expression and clinical data for 2,970 ovarian cancer patients from 23 studies spanning 11 gene expression measurement platforms (http://bcb.dfci.harvard.edu/ovariancancer). This work facilitates biomarker discovery through a robust meta-analysis framework that limits the impact cohort-specific biases while combining the statistical powers of numerous studies.
Co-amplification and overexpression of FGF18 and its receptor FGFR4 (on chromosome 5q31.3-qTER) have been validated as predictive of poor clinical outcome in this patient with advanced stage, high-grade serous ovarian cancer. Using cell culture and xenograft models, we show that FGF18/FGFR4 signaling activated NF-kB signaling and promoted tumor progression by modulating the ovarian tumor aggressiveness and microenvironment.

Through collaboration with Steven Skates, PhD, the laboratory received an Early Detection Research Network U01 grant to identify novel early detection approaches to this disease. We will compare the gene expression profiles of ovarian cancer with its normal counterparts found on the surface of the ovary and fallopian tube. Through a collaborative effort with Steven Carr, PhD of the Broad Institute, we will identify the early genomic abnormalities in ovarian cancer and validate these findings using specimens from Massachusetts General Hospital, Brigham and Women’s Hospital and DFCI to translate our work into serum-based early detection assays.

Presently, we are analyzing the function of newly identified activated pathways in ovarian cancers and utilizing in vivo models for the discovery of novel therapeutic approaches. An NIH R-01 grant was awarded to investigate the role of FGF18/FGFR4 signaling, previously shown to be associated with poor clinical outcome, in the pathogenesis of serous ovarian cancer. Large-scale prospective validation and pharmaceutical targeting studies are underway.

Research directions for the future include: 1) Characterizing the function of genes associated with clinicopathologic characteristics of ovarian cancer; 2) characterizing new tumor cellular subsets of ovarian cancer for their clinical features and their role in tumor formation; 3) identifying novel early detection, prevention and therapeutic targets; and 4) using the genomic abnormalities found in ovarian cancer as targets for novel imaging techniques. Our laboratory efforts remain highly translational and collaborative in nature, and we are committed to bringing laboratory-based and scientifically rational concepts into the clinic to improve the lives of women with these cancers.

Selected Publications:


