Our laboratory focuses on characterizing the function and clinicopathologic impact of key genes and pathways in gynecologic cancers. The majority of our work is focused on ovarian cancer. In 2000, the laboratory was awarded an NCI Director’s Challenge grant for the genomic analysis of ovarian cancer. The laboratory—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 systematically characterized differential gene expression on the whole-genome level between ovarian tumors of different histology and tumor grade. The study led to the identification of activated biochemical pathways, which underlie the clinical pathologic characteristics of these tumors. Subsequently, our findings made possible the identification of clear cell and mucinous tumors of the ovaries as unique tumors essentially unrelated to the majority of ovarian cancers. This discovery has led to a change in clinical trial structure in the gynecologic cancer group, establishing for the first time unique trials for patients with these cancers.

We are presently testing activated pathways within these tumors, utilizing in vivo models for the discovery of novel therapeutic approaches. Our laboratory has validated the co-amplification and overexpression of FGF18 and its receptor FGFR4 as predictive of poor clinical outcome in patients with advanced stage, high-grade serous ovarian cancer. An NIH R-01 grant has been awarded to investigate the role of FGF18/FGFR4 signaling in the pathogenesis of serous ovarian cancer. Large-scale prospective validation and pharmaceutical targeting studies are currently underway.

Recently, the laboratory completed two large profiling studies on advanced-stage papillary serous tumors of the ovary. These studies generated differential gene expression signatures which classify patients into good versus poor prognosis and identify new and novel targets for therapy and prevention. The laboratory has been awarded an RC4 grant (in collaboration with Giovanni Parmigiani, PhD, of the Dana-Farber Cancer Institute) to extend these studies into a validation study, utilizing 1600 clinical trial specimens from the recently completed GOG clinical trial 218. The results
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.

Selected Publications:


