Current Research in Pathology

CANCER BIOLOGY

Jeffrey Sklar, M.D., Ph.D.

Research in the Sklar lab concerns the molecular biology of human disease, particularly in the areas of the molecular genetics of cancer, lymphocyte biology, endometrial function, and the development of molecular methods for disease diagnosis. The research is of both a basic and translational nature.

Most recently, two previously unknown genes—*JAZF1* and *JJAZ1* (now also referred to as SUZ12)—were discovered by us to be fused head to tail in most cases of endometrial stromal tumors. These two genes are currently the focus of intense investigation within the laboratory. *JJAZ1* is a Polycomb group gene, the product of which is an essential member of the protein complex (Polycomb repressive complex 2, or PRC2) that in most or perhaps all cells catalyzes specific methylations of histone 3, leading to chromatin compaction and transcriptional silencing of DNA. The function of *JAZF1* is less well understood; however, separate single nucleotide polymorphisms (SNPs) within two introns of this gene have recently been shown to be associated with a strongly increased risk of type 2 diabetes and a decreased risk of prostate cancer. Both associations are now being investigated in the laboratory.

Katerina Politi, Ph.D.

The research in the Politi laboratory focuses on lung cancer, the most common cancer worldwide. In particular, we study a subset of lung tumors that have mutations in the epidermal growth factor receptor (EGFR). EGFR mutations are found in approximately 10% of non–small cell lung cancer cases in the U.S.—most commonly in never-smokers—and are associated with sensitivity to a class of drugs called EGFR tyrosine kinase inhibitors. Our research aims to understand which signaling pathways underlie EGFR mutant lung tumor development, identify novel therapeutic strategies to treat the disease, and uncover mechanisms of drug resistance.

David Rimm, M.D., Ph.D.

The Rimm laboratory spans a range of topics in 3 main areas, which include 1) basic issues, including regulation of growth factor mediated cell signaling and metastasis; 2) translation issues, including tissue biomarkers, circulating cancer cells, tissue microarrays and digital pathology; and 3) clinical issues, including advanced objective diagnostics using novel information gathering technologies. Recent studies include:

1) Translational studies using tissue microarray technology and digital pathology algorithms (AQUA) to apply rigorous molecular technology to diagnostic problems in pathology toward the goal of development of new predictive and prognostic tissue biomarkers. This effort includes quantitative in situ analysis of protein, mRNA, and microRNA.

2) Quantitative measurement of proteins from Cooperative Group trials toward more accurate prediction of response to therapies in breast cancer.

3) Use of multiple markers to build expression models for prediction of recurrence in lung cancer and melanoma.

4) Use of machine learning tools to define malignancy and other properties of cells based on spectral and spatial analysis.

Demetrios Braddock, M.D., Ph.D.

The Braddock lab is interested in biologically validating and structurally defining oncologic molecular targets that are readily approachable by small molecule inhibitors. We are currently focused on the pyrophosphatase/phosphodiesterase (NPP) family of enzymes, which hydrolyze either pyrophosphate or phosphodiesterase bonds to yield extracellular signaling small molecules. Several of these proteins have been linked to signaling cascades that drive multiple steps in the development and progression of human malignancy, ranging from tumor initiation all the way to the development of bone metastasis. We have recently determined the structure of one member, NPP4, and determined a novel role for the enzyme in hemostasis. We are currently working on anti-thrombotic agents targeting this novel pro-thrombotic agent.

David Stern, Ph.D.

The Stern laboratory investigates processes by which cancer is caused: genetic and epigenetic changes that alter hormone-regulated signal transduction pathways, leading to growth dysregulation, and that alter protective responses to DNA damage, leading to genomic instability.

Twenty-five percent of breast cancers are driven by the receptor tyrosine kinase ErbB2/HER2. In order to understand why this receptor is so important in human cancer and to improve its therapeutic targeting, we investigate its normal and pathological functions in mammary tissue. ErbB2 works in close partnership with other members of the EGF receptor (ErbB family) of tyrosine kinases, so we also study differential signaling by the three related receptors (EGF receptor [HER], ErbB3 [Her3], ErbB4 [Her4]).

We are also investigating signal transduction in DNA checkpoint control pathways. This involves analysis of checkpoint signaling in both budding yeast and humans, with the focus on the double-strand DNA break response pathway encompassing tumor suppressor gene Atm and Chk2/Rad53, and mediator proteins NFBD1/MDC1, 53B1, BRCA1, and MCPH1.

In response to a growing need to develop integrated methods for best matching of patients to the appropriate target drugs, we are investigating use of DNA-based and functional approaches for predicting response to targeted therapies in breast cancer and melanoma.

Robert Homer, M.D., Ph.D.

Dr. Homer's research is focused on understanding how scar forms in the lung. It has been known for years that a molecule called transforming growth factor beta-1 (TGFbeta-1) is important in lung fibrosis. However, this molecule has so many functions that blocking it directly has many side effects, including the development of cancer. Dr. Homer is looking at co-factors that are needed for it to function properly and expects that blocking them will have fewer side effects.