

Tumor Diagnostic Laboratories

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Members of the Pathology Department are active participants in collaborative research activities both within and outside of the institution. The diagnostic services of the Department of Pathology consist of surgical pathology, immunohistochemistry, flow cytometry, cytopathology, hematopathology, molecular pathology, clinical pathology, and autopsy pathology. An important part of the pathology program is the training of residents and fellows. We currently have three anatomic pathology fellowships. In addition, residents from Drexel University and Thomas Jefferson University Schools of Medicine are trained in our department throughout the year.

Research Projects

Early molecular events in multiple intestinal neoplasia. Cooper, in collaboration with Clapper[§]

Recent generation of mouse strains with genetic deficiencies in the “colon cancer genes” has provided a novel opportunity to evaluate the functional relationship between the molecular and biochemical events associated with the formation of precancerous and cancerous colon lesions. The chemically induced mouse mutation called Multiple Intestinal Neoplasia (Min) produces a phenotype reminiscent of human familial adenomatous polyposis. Min mice develop a large number of polyps in the small and large intestine due to disruption of the adenomatous polyposis coli (*APC*) gene; the putative “gatekeeper” of human colorectal carcinogenesis. We have generated a new strain of *Apc* Min mice (*Apc*^{Min-FCCC}), which has significantly greater numbers of colorectal adenomas and incidence of small intestinal cancers than reported in the literature and that are found in Jackson Lab male and female breeding pairs (*Apc*^{Min-JAX} × C57 BL/6J) bred in our facility under identical conditions. We plan to examine the molecular and/or genetic basis for the unique phenotype of the *Apc*^{Min-FCCC} strain. We are presently performing brother sister matings (inbred) to see if we can enhance our phenotype.

Screening for chemopreventive agents in a mouse model of ulcerative colitis. Cooper, in collaboration with Clapper[§]

We are screening the agents, 5-aminosalicylic acid (5ASA) and Celecoxib (Cox-2 inhibitor), for efficacy as chemopreventive agents for the

prevention of colitis associated neoplasia in the multiple intestinal neoplasia/dextran sulfate sodium (Min/DSS) colitis model and the azoxymethane/dextran sulfate sodium (AOM/DSS) model in the Swiss Webster Mouse. Celecoxib caused a 50% reduction in the multiplicity of dysplastic lesions in the AOM/DSS/Celecoxib group (7.9) vs. the AOM/DSS group (16.0). The incidence of dysplasias was 100% and 72% in the AOM/DSS group compared to the AOM/DSS/Celecoxib group. Celecoxib significantly decreased the multiplicity of the DALM group compared to controls but had no effect on multiplicity of flat lesions. We found that in the Min/DSS model Celecoxib had no significant chemopreventive effect. Presently we are examining the molecular mechanism of action of Celecoxib in these models. In contrast to the Celecoxib study, 75 mg/kg of 5ASA significantly reduced the total multiplicity of dysplastic lesions. This was specific for flat lesions. We are now investigating the molecular basis for these findings.

Molecular events in dysplasia and cancer in the dextran sulfate sodium (DSS) p53^{-/-} mouse colitis model. Cooper, Coudry,[§] Clapper,[§] in collaboration with W.C. Chang[§]

In human UC (ulcerative colitis) associated neoplasia, the loss of p53 is an early event. We have studied the effects of DSS colitis in a group of mice (p53^{+/+}, p53^{+/-}, and p53^{-/-}). The incidence of colitis associated carcinoma and dysplasia was significantly greater in the p53^{-/-} mice and p53^{+/-} mice had significantly greater numbers of colitis associated neoplasia lesions than p53^{+/+} and p53^{+/-}.

Imaging molecular changes during colon tumorigenesis. Cooper, in collaboration with Clapper[§]

Alterations in the Apc/B-catenin/Tcf pathway are among the earliest changes that persist throughout colorectal tumorigenesis. Imaging dysregulation of this pathway will allow us to identify and follow colorectal lesions before they become malignant and refractory to chemoprevention. We will develop sensitive optical methods for monitoring the interaction of B-catenin with a Tcf binding element within the colonic mucosa of FCCC Apc^{min} mice. A multidisciplinary research team with expertise in areas of molecular biology, MRI, chemoprevention and pathology has been assembled to achieve this goal.

Early Detection and follow up of urinary tract cancer by hypermethylation. Al-Saleem, in collaboration with Cairns[§]

The major goal of this project is to use detection of bladder and renal cancer cell DNA in urine by a highly sensitive, cancer specific methylation PCR, for early diagnosis and molecular staging. In order to construct molecular genetic progression models for bladder and renal cancer, we ascertain the frequency and timing of hypermethylation in candidate precursor lesions. Tumors of all grades and stages (including tobacco exposure related and non-related) are included in the investigation of new markers in a hypermethylation panel. Chip technology will be applied to this panel.

DNA ploidy, Ki-67, Bcl-2, Bax and MDM2 in prostatic carcinoma. Al-Saleem, in collaboration with Pollack[§]

This is a large analysis of proliferation and apoptosis markers in prostate cancer patients treated in a multi-center national trial. Slides from the cases are currently being stained and quantified for various markers by immunohistochemistry. This will be the largest cell proliferation, marker/Ploidy study in radiotherapy patients ever performed. The findings may have significant impact on future stratification of patients for clinical trials and on clinical practice.

Impact of flow cytometry on diagnosis and follow up of lymphoma. Al-Saleem in collaboration with Smith,[§] Borghaei,[§] Litwin[§]

We are evaluating detection of circulating lymphoma cells and its contribution to diagnosis and

outcome. We are also assessing, the impact of flow cytometry in gastric, skin and other biopsies.

Genomic basis of reproductive history in breast cancer. Al-Saleem, in collaboration with J. Russo[§]

This study is part of a larger project to elucidate the genomic signature induced in the breast by early pregnancy. Using normal breast tissue from women who underwent cosmetic surgery, we are comparing cDNA array genes that are differentially expressed in parous and nulliparous women.

Breast cancer biomarkers in nipple aspirates of individuals treated with estrogen receptor blockers. Ehya, in collaboration with Sauter^a

In earlier studies, we showed that the presence of abnormal cells in nipple aspirate fluid (NAF) correlates with breast cancer risk in healthy women. Now we are collecting NAF samples from women participating in the "Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer" to evaluate various biomarkers, including cytomorphology and DNA ploidy. These estrogen blockers significantly reduce the risk of *in situ* and invasive breast cancer in high-risk individuals. To determine whether tamoxifen and Raloxifene affect the biomarkers in the nipple aspirate fluid and whether the changes are consistent with the reduction in cancer incidence in women receiving these agents, we will compare the biomarkers in the NAF before and after six months of therapy with the above agents.

Ductoscopic cytology to detect breast cancer. Ehya, in collaboration with Sauter,^a Klein-Szanto[§]

Fiberoptic ductoscopy (FD) allows direct visualization of the breast ductal lumen, providing a targeted approach to the diagnosis of intraductal disease. We are investigating the feasibility of performing various tests on cells using ductoscopic lavage. We are also trying to find biomarkers of early breast cancer and precancerous conditions by utilizing non-invasive methods. In our experience, lavage cytology is highly specific for detecting breast cancer, but has a low sensitivity. We have shown that intraductal papillomas are the source of atypical cells in some specimens, which could lead to a false positive diagnosis of breast cancer. Recently we analyzed the cytomorphologic

findings of ductoscopic lavage from 100 patients who underwent surgical biopsy or mastectomy in order to find out whether there were differences in ductoscopic findings of women with (60 patients) and without (40 patients) spontaneous nipple discharge (SND). We found that significant visual ductoscopic differences exist between patients with and without SND. Image analysis for DNA ploidy was a helpful ancillary test, as every case with a malignant cytology and aneuploidy had carcinoma. A model incorporating cytology and SND was 92% sensitive and 60% specific for predicting which women had breast cancer.

Diagnosis of non-Hodgkin lymphoma and other lymphoproliferative disorders by fine needle aspiration cytology. Young, Al-Saleem, Ehya, in collaboration with Smith[§]

The cytopathology and flow cytometry laboratories in collaboration with medical oncology have a strong partnership investigating the use of fine needle aspiration biopsy (FNA) to diagnose non-Hodgkin lymphoma (NHL) and other lymphoproliferative disorders. The use of this procedure avoids the morbidity and delay from unnecessary invasive surgery in the diagnosis of patients with lymphoma. This diagnostic area requires expertise in both specialties of Cytopathology and Hematopathology. Collaboration between our on site flow cytometry laboratory and trained cytopathologists allows application of FNA to the diagnosis of NHL and other lymphoproliferative disorders. While this method is slowly gaining acceptance as a definitive test for primary diagnosis of non-Hodgkin lymphoma, there is a great deal of resistance among many pathologists and oncologists. We are currently reviewing our experience with this method in the past ten years and comparing our results with patients' outcomes to determine the accuracy of the test.

Comparison of performance of conventional and ThinPrep[®] gynecologic preparations in the College of American Pathologists Gynecologic Cytology Program. Young, in collaboration with Renshaw,^b Colgan^c

Results of clinical trials suggest that liquid based cytology (LBC) preparations are more accurate and are associated with less screening error than interpretation of conventional smears. In this study, the performance of participants in

interpreting ThinPrep[®] (TP) preparations was compared with the performance on conventional Pap smears in the College of American Pathologists Gynecologic Cytology Program (PAP). The results of the PAP from the year 2002 were reviewed, and the discordancies to series and exact match error rates for the two cytologic methods were compared. For this study, a total of 89,815 interpretations from conventional smears and 20,886 interpretations from TP samples were analyzed. Overall, interpretations of TP preparations had both significantly fewer false positive (1.6%) and false negative rates (1.3%) than those of conventional smears for validated or validated-equivalent slides as assessed by concordance to the correct diagnostic series. In this assessment of concordance to series, interpretations of educational TP and conventional preparations were similar, except for HSIL, in which the performance was significantly worse for educational TP preparations (false negative rate of 8.1% versus 4.1% for conventional smears). When interpretations were matched to the exact diagnosis, validated-equivalent TP preparations were generally more accurate for diagnoses than conventional smears. Notably, for the reference diagnosis of squamous cell carcinoma, the exact match error rate on validated equivalent TP slides was significantly greater than that of conventional slides (44.5% versus 23.1%). Interpretations of educational TP preparations also had a significantly higher error rate in matching to the exact reference diagnosis for squamous cell carcinoma (33.7% versus 22.8%). Overall, TP preparations in this program are associated with significantly lower error rates than conventional smears for both validated and educational cases.

Tumor cell viability following radiofrequency ablation of resectable primary lung cancer: Initial results from an ablate and resect study. Young, in collaboration with Scott,[§] Goldberg,[§] Langer,[§] Movsas,^d Rogatko^e

Alternative local therapies for patients with primary lung cancer are needed. Radiofrequency ablation (RFA) of lung cancer has been used but there are minimal data on the histologic response of lung cancers to RFA ablation. We performed a prospective study of RFA ablation of lung cancers in patients undergoing curative resection. The primary endpoint was the number of patients in whom we observed cell death

in 80% or more of the tumor cells treated with RFA. RFA-related toxicity was also recorded (e.g., bleeding from the lung following probe placement or burns to the skin from the dispersive electrodes). Study participants underwent intraoperative RFA ablation of the tumor followed immediately by lobectomy or pneumonectomy and lymph node sampling. Cell death was determined by supravital staining. In four of the first five evaluated patients, cell death was 100% in areas of tumor contained in the ablation zone. In the remaining patient the estimate of tumor cell death in the ablated zone was 95%. No episodes of either bleeding from probe placement in the lung or skin burns from the dispersive electrodes were observed. We concluded from this preliminary study that RFA was safe and tumor cell necrosis was complete or nearly complete in all treated areas.

Analysis of cutaneous lymphomas using flow cytometry. Al-Saleem, Wu, in collaboration with Lessin,[§] Smith,[§] Millenson,[§] Nicolaou[§]

The diagnosis and subclassification of cutaneous lymphomas has undergone significant changes in recent years with broadened utilization of immunohistochemical and molecular analyses. Flow cytometry has the added advantage of simultaneously analyzing multiple surface and/or cytoplasmic markers. It is especially useful in detecting a clonal proliferation by studying the surface immunoglobulins, which are often difficult to assess by immunohistochemical staining of tissues. We have shown that a routine skin punch biopsy can yield sufficient material for diagnostic flow cytometry. Flow cytometry is superior to immunohistochemical staining in detecting B-cell monoclonality. Additional immunophenotypic markers detected by flow cytometry facilitate lymphoma subclassification.

Construction of high-density tissue microarray for melanoma analysis. Wu, Huang, in collaboration with Lessin,[§] Klein-Szanto[§]

High-density tissue microarrays provide a rapid means to efficiently analyze protein expression in large numbers of specimens. The microarrays contain a large number of benign nevi, malignant melanomas at various stages of tumor progression and metastatic melanomas. This will facilitate the identification of new biomarkers of tumor progression, and potential targets for

developmental therapeutics. The microarrays may also provide more efficient tissue utilization in cases where the materials are limited and help preserve important tissue resources.

Antitumor responses in precursor stage of cutaneous T-cell lymphoma. Wu, in collaboration with Lessin[§]

Parapsoriasis is a term for a distinct precursor stage (TONOMO) of cutaneous T-cell lymphoma (mycosis fungoides) and is defined by the presence of skin lesions clinically and/or histologically suggestive of, but not diagnostic of cutaneous T-cell lymphoma (CTCL). Bexarotene (Targretin®) is a novel synthetic retinoid analogue that binds preferentially to the members of the RXR subclass of receptors and has been approved for use in the treatment of CTCL. As part of a phase II trial evaluating the efficacy of topical bexarotene (Targretin®) gel in patients with parapsoriasis, we are evaluating the antitumor host response by performing immunohistochemical analysis on pre- and post-treatment skin biopsies.

BRAF mutational analysis in mucosal melanomas. Wu, in collaboration with Edwards,^f Lessin,[§] Weber^f

Mutations in the *BRAF* gene were recently identified in a significant percentage of cutaneous malignant melanomas. The large majority (>95%) of these mutations occur at a hotspot in exon 15 involving the kinase domain (V599E; T1796A), leading to constitutive activation of BRAF and increased phospho-ERK. To evaluate a possible role of UV exposure in the genesis of BRAF mutations, we analyzed exon 15 of BRAF in a panel of UV-protected mucosal melanomas and compared the mutation rate with the cumulative published BRAF mutation rate in primary cutaneous melanomas (33%). No mutations were identified in the mucosal melanomas raising the possibility that UV exposure does play a role in generating *BRAF* mutations in cutaneous melanocytic lesions.

Cortactin in melanocytic tumor progression. Wu, in collaboration with Spittle,[§] Chernoff,[§] Lessin[§]

Cortactin is a member of a family of highly conserved actin-binding proteins enriched in the cell cortex. The dynamic rearrangement of cortical actin cytoskeleton is important in cell motility,

cell-cell adhesion, cell-matrix interaction and transmembrane signaling. Cortactin is known to function in cortical actin remodeling, organization of transmembrane protein complexes and receptor endocytosis. We sought to characterize the role of cortactin in melanocytic tumor progression and evaluate cortactin as a potential biomarker in melanoma. We analyzed the level and pattern of cortactin expression in benign and malignant human melanocytic tumors by immunohistochemistry (IHC), and studied tyrosine phosphorylation of the protein in melanoma cell lines. Our preliminary data indicate that cortactin is differentially expressed across melanocytic tumor progression. In melanoma cell lines, the protein is phosphorylated on tyrosine. We hypothesize that the alteration in level and pattern of cortactin expression in malignant melanomas may contribute to an abnormality in the cell's cytoskeleton structure, which may result in a change in the cell's directionality, polarity and interaction with its microenvironment. This phenotypic change may be a part of the melanocytic transformation process. Future studies will include IHC studies on a larger number of tumors, and functional significance of cortactin expression in melanoma cell lines.

Diagnostic Laboratories

Surgical Pathology. Flieder, Patchefsky, Cooper, Al-Saleem, Wu, Ehya, Young, Huang, Rader, Ferrizzi

The role of the surgical pathology laboratory is to provide accurate diagnostic services to clinicians so that patient care is best served. A correct and meaningful diagnosis of an individual's neoplasm is essential for proper clinical management. The members of the department actively participate in the Breast Evaluation Center and daily multidisciplinary clinics, and are also actively involved in helping procure tissue for the tumor bank.

Immunohistochemistry. Cooper, Adams-McDonnell, Davis, Koch

Immunohistochemistry is an integral part of tumor diagnosis. It is also helpful in discriminating between benign and malignant lymphoid lesions, and in better characterizing lymphoid malignancies for more relevant therapy. The immunohistochemistry laboratory uses labeled antibodies to detect various epitopes

employed in the diagnosis of neoplastic disorders. These tests are also adopted for prognostication (e.g., estrogen and progesterone receptors, and proliferation markers) and for identification of tumor sites (e.g., prostate specific antigen, and thyroglobulin, TTF-1). During this past year, we adopted the following new tests for clinical use: EGFR (used for targeting antibodies therapeutically), FISH technique for c-erbB2.

Hematopathology and Flow Cytometry Laboratory. Al-Saleem, Kunwar, Phill

Morphological and immunophenotypic studies are performed on peripheral blood, bone marrows, lymph nodes, or extranodal sites or body fluids for diagnosis and clinical research. The laboratory has extensive experience in the examination of fine needle aspirates. In cooperation with the cytopathology department we provide a team approach for the diagnosis, classification, and follow-up of lymphomas. The recent adoption of four-color flow cytometry enables us to examine markers on a limited number of cells vital for the recognition of minimal residual disease in fine needle aspirates.

For a long time flow cytometry was utilized to search for only surface markers. Cells are incubated with fluorescent antibodies, then run through the flow cytometer, exposed to laser beams, and the emitted light is analyzed by computer. Now we augment cell permeability and examine for intracellular antigens, e.g., TdT, myeloperoxidase, and immunoglobulins. A combination of the surface and intracellular antigen information furnishes valuable data for tumor recognition and characterization (e.g., CD38 and Zap70 are useful prognostic markers in CLL prognosis).

Hematopathology, cytopathology, immunohistochemistry, molecular pathology, and surgical pathology work together as one team in the diagnosis and research of hematologic malignancies. This approach facilitates the diagnostic accuracy and the understanding of the biology and clinical behavior of hematological malignancies.

Cytopathology Laboratory. Ehya, Young, Huang, Patchefsky, Clarici, Sellecchia, Shaw, German, Caniz

The Cytopathology Laboratory offers a full range of diagnostic cytology tests, including

cervical smears, body fluids, endoscopically collected specimens and fine needle aspirations (FNA). Liquid-based Pap test technology is used, combined with HPV testing when necessary, to identify uterine cancer and pre-cancerous conditions. In all radiologic and endoscopic-ultrasound guided FNAs, as well as superficial aspirations performed by the clinicians, cytotechnologists are present to ensure adequacy of the material and optimal preparation of the samples. Within minutes, the cytopathologists examine the samples microscopically, render a preliminary diagnosis and determine whether additional ancillary diagnostic tests will be necessary for classification of the tumor. The laboratory closely interacts with surgical pathology, immunopathology, flow cytometry and molecular pathology laboratories. Our laboratory is one of the pioneer laboratories in the country that provides definitive diagnosis and classification of malignant lymphoma on FNA specimens in conjunction with flow cytometry.

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Outpatient Laboratory. Young, Al-Saleem, Wu, Carroll-Tapley, Acevedo, Barner, Barow, Clendaniel, Duffy, Hollerbach, Hoy, McKeon, Schuima, Warren

The outpatient/clinical pathology laboratory performs complete blood counts, differential counts, chemistry profiles, coagulation studies, and tumor markers. The laboratory provides phlebotomy services, usually on the same day as the patient's clinic visit, making it more convenient to have blood work performed. In addition to providing services for our patients, the laboratory actively supports ongoing research protocols, as well as phlebotomy for genetic studies.

Autopsy Pathology. Young, Patchefsky, Cooper, Ehya, Al-Saleem, Wu, Flieder, Huang, Ferrizzi

The anatomic pathology laboratory offers autopsy services for the institution. The autopsy increases our knowledge about the causes and course of an illness, and the effects of different types of treatment. The postmortem examination is an important aspect of hospital quality improvement, and findings are used for correlative clinicopathological teaching purposes.

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