Phenomena™

THE NEWSLETTER OF PHENOPATH LABORATORIES

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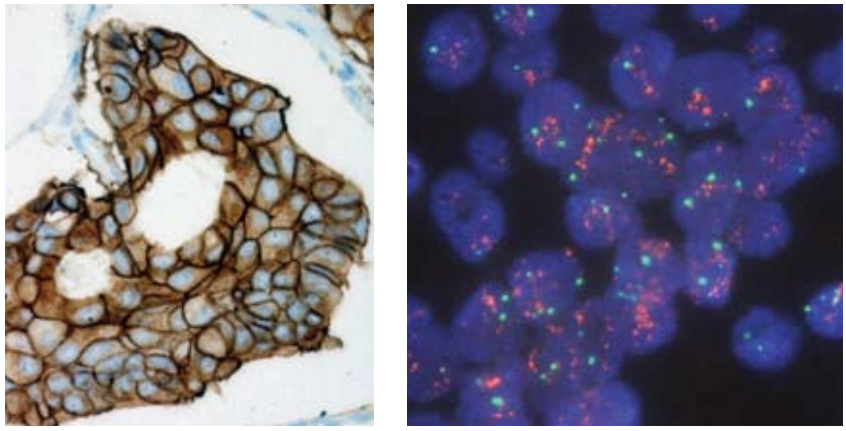
PhenoPath at the USCAP Meeting in Denver

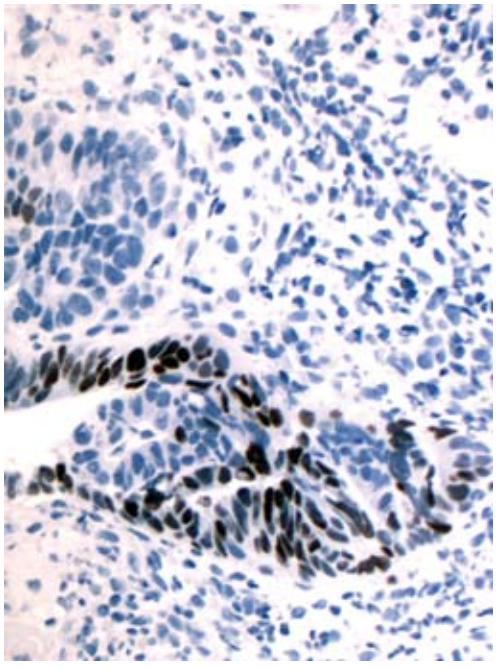
Tuesday morning, Platform Presentation – Breast Pathology Section B:

Choice of Primary Anti-HER2 Antibody Affects Concordance of Immunohistochemistry (IHC) with Fluorescence In Situ Hybridization (FISH) for Determination of Breast Cancer HER2 Status **March 4, 2008**

Dr. Allen M. Gown will present data on the use of SP3, a new rabbit monoclonal antibody to HER2, comparing the results and correlations with FISH data concerning HER2 gene status in a set of 416 breast cancer cases. Interestingly, compared with the standard Dako rabbit polyclonal antibody utilized in the HercepTest™ kit, the overall concordance between HER2 status as determined by immunohistochemistry (IHC) and FISH was virtually the same. However, significant numbers of nonamplified cases that yielded equivocal (2+) results with A0485 yielded negative (1+) results with SP3, and significant numbers of amplified cases yielded equivocal (2+) results with A0485 and positive (3+) results with SP3. This suggests that the rabbit monoclonal HER2 antibody, SP3, might prove to be a more efficient IHC tool for the analysis of HER2 overexpression.



Breast cancer positive for HER2 overexpression (3+) and amplified by FISH



Focal immunoreactivity with TTF-1 (SPT24) in a colorectal adenocarcinoma.

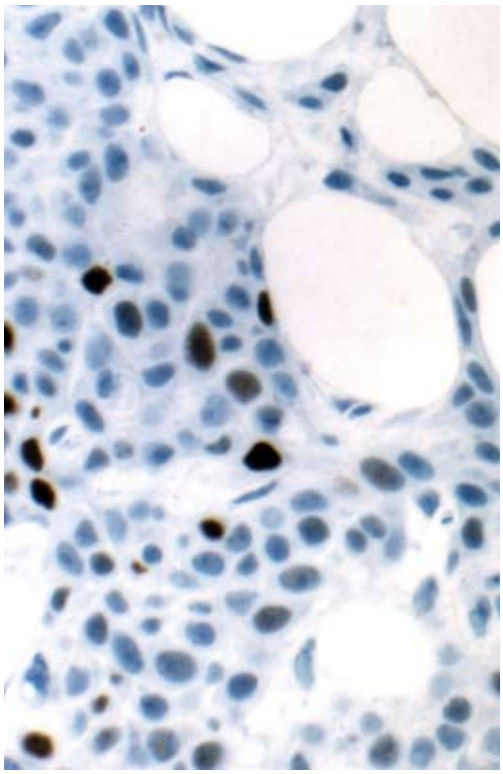
Tuesday afternoon, Poster Session IV:

Lineage Infidelity of Nuclear Transcription Factor [Estrogen Receptor (ER), Thyroid Transcription Factor-1 (TTF1), and CDX2] Expression in Identification of Carcinomas **March 4, 2008**

In the immunohistochemical workup of a carcinoma presenting as a metastasis from an unknown site, one relies heavily on the nuclear transcription factors (NTF) to identify the most likely primary site. Three NTFs are commonly sought in practice to identify breast/gynecologic (ER), lung/thyroid (TTF-1) and gastrointestinal (CDX2) adenocarcinomas. In this study, we immunostained primary breast, lung and colorectal adenocarcinomas with all three markers (including two different commonly employed clones of TTF-1 antibody) to better understand the specificity of these markers for their intended targets. In our sample, we found ER rarely in lung adenocarcinomas and never in colorectal adenocarcinomas, CDX2 rarely in lung adenocarcinomas and never in breast adenocarcinomas, and TTF-1 (Novocastra clone) uncommonly in colorectal adenocarcinomas and never in breast carcinomas. A second TTF-1 clone (Dako) immunostained fewer colorectal adenocarcinomas, but also missed more lung adenocarcinomas. These findings support the continued practice of NTF immunostaining in the setting of metastatic carcinomas from unknown primary sites, but caution that there can be some crosstalk between the markers, especially in the setting of colorectal adenocarcinomas immunostaining positively with antibodies to TTF-1.

Wednesday afternoon, Poster Session VI:

Basal-Like Invasive Breast Carcinoma: How Specific Are Immunohistochemical Markers? **March 4, 2008**



The basal-like variant of invasive breast carcinoma, originally defined by gene expression profiling, carries a poor prognosis. By immunohistochemistry, these carcinomas are found to lack estrogen receptor (ER), progesterone receptor (PR), and HER2 (hence the name "triple-negative" tumors), but they frequently immunostain positively for cytokeratin 5/6, p63, c-kit, epidermal growth factor receptor (EGFR), and p53. Previous studies have shown that the sensitivity of these positive markers ranges from 50-76%; this study is a systematic evaluation of the specificity of these markers, intended to further define their diagnostic utility. Immunostaining 200 non-basal breast carcinomas (defined as non-"triple-negative" tumors), we found specificities ranging from 80-96% for these markers. Cytokeratin 5/6 seems to be the single best marker of the basal-like variant, with a specificity of 96% and a reported sensitivity of 76%.

p63 immunoreactivity is seen in approximately 50% of basal-like breast carcinomas, but less than 10% of non-basal-like breast carcinomas (low-level immunoreactivity in an ER-positive breast carcinoma is shown here).

"Best Practices" Guides to Diagnostic Immunohistochemistry

Best Practices in Diagnostic Immunohistochemistry

Hepatocellular Carcinoma Versus Metastatic Neoplasms

Sanjay Kakar, MD; Allen M. Gown, MD; Zachary D. Goodman, MD; Linda D. Ferrell, MD

Context.—Immunohistochemistry plays a crucial role in the diagnosis of hepatocellular carcinoma and in its distinction from other primary and metastatic neoplasms. Because limited tissue is available with fine-needle and core biopsies, appropriate selection of antibodies is imperative.

Objective.—To review the antibodies used for the diagnosis of hepatocellular carcinoma and to outline an immunohistochemical approach in commonly encountered clinical situations.

Data Sources.—Our experience and review of research articles published in the English literature between 1987 and 2006.

Conclusions.—Hep Par 1 and polyclonal carcinoembryonic antigen are the most reliable markers for hepatocellular differentiation, but they have low sensitivity for poorly differentiated cases. Immunohistochemistry for glypican-3 shows promise for the diagnosis of poorly differentiated hepatocellular carcinoma and for its distinction from benign processes such as hepatic adenoma. Further studies with a large number of cases are required before it can be widely used. The combination of Hep Par 1 and MOC-31 will allow for the diagnosis of hepatocellular carcinoma in most cases and will guide the selection of immunohistochemical markers for further workup.

(*Arch Pathol Lab Med.* 2007;131:1648–1654)

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

COMMONLY USED MARKERS

Most Useful Antibodies

Arch Pathol Lab Med 131:1648-54, 2007

Recognizing the need for up-to-date reviews of the most appropriate immunohistochemistry (IHC) markers to be used in critical diagnostic settings, a series of very useful papers has begun to be published in the *Archives of Pathology and Laboratory Medicine*, an official publication of the College of American Pathology.

The second in this series appeared in the November 2007 issue, and addresses the distinction of primary hepatocellular carcinoma from metastatic carcinoma to the liver. The authors of this paper are Sanjay Kakar and Linda D. Ferrell of the University of California-San Francisco, Zachary D. Goodman of the Armed Forces Institute of Pathology in Washington, DC, and Allen M. Gown of PhenoPath Laboratories.

In the paper, the experience of the authors is summarized, along with almost twenty years of the published literature, from 1987 through 2006. The importance of new highly sensitive hepatocellular-restricted markers such as the HepPar1 antigen is reviewed and discussed, along with markers such as the MOC-31-defined glycoprotein (a marker found in 80-100% of carcinomas metastatic to the liver). Also noted are other markers which possess high specificity but suffer from low sensitivity (e.g., identification of CD10-positive or CEA-positive bile canaliculi and CD34-positive sinusoids). Some more "traditional markers" such as alpha-fetoprotein show both low sensitivity and specificity, and cannot be recommended in this setting. The utility of new markers that can distinguish hepatocellular carcinoma from nonmalignant hepatic nodules (e.g., glypican 3) is also discussed.

The first "best practices" article on IHC analysis of pleomorphic cutaneous spindle cell tumors appeared earlier last year (Folpe AL and Cooper K, Arch Pathol Lab Med 131:1517-24, 2007).

PhenoPeople Profile

Virgil Minden

Virgil Minden, Director of Sales and Marketing, joined PhenoPath in July of 2006, bringing with him many years of experience. Virgil left his position as President and Consultant to Marketing Business Associates to head the PhenoPath marketing effort. He has served as CEO of several clinical labs, most recently Central Plains Laboratories; he was also a Senior Consultant at Park City Solutions. Virgil received his degree in Management and Communication/Marketing from Concordia University, Portland, Oregon.

As Director of Sales and Marketing Virgil travels extensively, meeting with representatives of hospitals and laboratories to promote PhenoPath's services. While traveling Virgil is accessible by phone and, by receiving calls forwarded to him through PhenoPath, is able to inform current and potential referring laboratories about our latest test offerings and how they might be of use to their practices. Virgil's extensive knowledge of the laboratory field has been instrumental in bringing a number of pathology laboratories into the PhenoPath circle.

Virgil and his wife Carol Ann have four children and fourteen grandchildren whom they enjoy visiting in their "spare time." His other interests include boating, skiing, antiquing, photography and ham-radio operating. At one time he and Carol Ann raised prize-winning Arabian racehorses. Horseback riding is still a recreation they enjoy.

We hope you'll have the opportunity to speak with Virgil soon; you'll quickly discover why he is such a welcome addition to the PhenoPath family.

VISIT US AT THE FOLLOWING MEETINGS:

For up-to-date information, visit our website: www.phenopath.com

Scientific Symposium International CME Course:
GI, Liver and Pancreatic Pathology: Histologic, Immunohistochemical and Molecular Diagnosis
February 17-21, 2008, The Princeville Resort, Princeville, Kauai, HI
Allen M. Gown, MD is a featured speaker and will present four talks entitled "The Laws of IHC," "IHC in the Analysis of Tumors of the Gastrointestinal Tract," "Prognostic and Predictive Markers of Colorectal Adenocarcinoma," and "Current Issues in HER2 Testing in Breast Cancer." www.scientificsymposiums.com

USCAP 2008 Annual Meeting:
97th Annual Meeting United States and Canadian Academy of Pathology
March 1-7, 2008, Hyatt Regency Hotel & Denver Convention Ctr, Denver, CO
PhenoPath pathologists are presenting at the USCAP meeting as follows:
March 2, 2008: Allen M. Gown, MD presents "Predictive and Prognostic Immunohistochemical Markers in Breast Carcinoma" at the Arthur Purdy Stout Society of Surgical Pathologists Companion Meeting, Common and Current Problems in Surgical Pathology: Perspectives from the Experts.
March 3, 2008: Allen M. Gown, MD presents "Integration of the Molecular Classification of Breast Cancer in the Routine Diagnostic Workup of Cases" at the Special Course: Basic Principles & Practice of Molecular Pathology in Cancer.
March 4, 2008:
Allen M. Gown, MD presents a platform presentation entitled "Choice of Primary Anti-HER2 Antibody Affects Concordance of Immunohistochemistry (IHC) with Fluorescence In Situ Hybridization (FISH) for Determination of Breast Cancer HER2 Status."
Geoffrey S. Baird, MD, PhD, 2007-2008 PhenoPath Fellow, presents a poster session entitled "Lineage Infidelity of Nuclear Transcription Factor [Estrogen Receptor (ER), Thyroid Transcription Factor-1 (TTF1), and CDX2] Expression in Identification of Carcinomas."
March 5, 2008: Geoffrey S. Baird, MD, PhD presents a poster session entitled "Basal-Like Invasive Breast Carcinoma: How Specific Are Immunohistochemical Markers?"
March 6, 2008: Todd S. Barry, MD, PhD presents the Short Course entitled "Update and Troubleshooting IHC for Pathologists."
PhenoPath will be represented at an exhibit booth. www.uscap.org

American Pathology Foundation:
March 13-14, 2008, Hilton Scottsdale Resort & Villas, Scottsdale, AZ
Allen M. Gown, MD is participating in a panel discussion entitled "Pathology Practices Evolving" and will present a talk entitled "Finding a Niche in a Crowded Market" on March 13, 2008. www.apfconnect.org

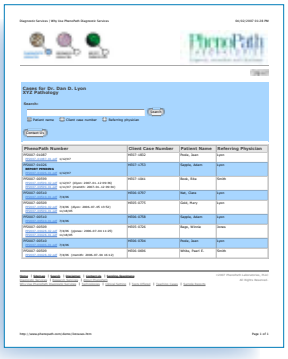
Principles and Applications of Immunocytochemistry:
A Technique-Oriented Short Course presented at Experimental Biology 2008
April 5, 2008, Marriott San Diego Hotel and Marina, San Diego, CA
Allen M. Gown, MD will present two talks on "Antibodies" and "Antigen Retrieval."
immunocytochem.wordpress.com

48th Annual Spring Symposium - Houston Society of Clinical Pathologists:
Pathology of the Breast, Current Issues & Future Directives
April 11-12, 2008, Hilton Houston Post Oak, Houston, TX
Allen M. Gown, MD is a featured speaker and will present two talks entitled "Myoepithelial Markers and Markers of Basal-like Breast Carcinomas" and "ER/PR and HER2 Testing." www.utcme.net

What are Your lab's HER2 concordance numbers?

Ours are 94.7 and 99.2
(stay tuned for the next issue of Phenomena for details)

Have you heard about **PhenoNet**, PhenoPath's new electronic reporting system?



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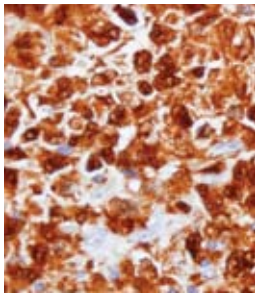
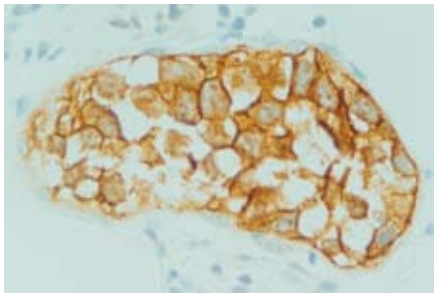
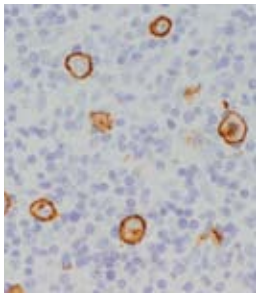
551 North 34th Street, Suite 100
Seattle, Washington, 98103
P (206) 374-9000
F (206) 374-9009

Dr. Lawrence Weiss Was Featured At Our Winter Quarterly Conference







Dr. Lawrence Weiss, of City of Hope National Medical Center in Duarte, CA, presented "What's New in WHO in Lymphoma" at the Quarterly Pathology/Immunohistochemistry Conference on ***Thursday, February 7, 2008***.

Dr. Weiss is currently the Chairman of the Division of Pathology at the City of Hope National Medical Center and President of City of Hope Medical Group. He received his B.S. summa cum laude and his M.D. summa cum laude from the University of Maryland. He subsequently completed his residency in Anatomic Pathology at the Brigham & Women's Hospital in Boston, MA, and a Surgical Pathology Fellowship at Stanford University Medical Center.

Dr. Weiss's research interests encompass surgical pathology, hematopathology, and immunohistochemistry. He has authored over 400 papers and book chapters, as well as seven books, including a recently published text on lymph nodes. His laboratory discovered the first molecular evidence linking the Epstein-Barr virus with Hodgkin's disease. Among his numerous awards, Dr. Weiss is the recipient of the Benjamin Castleman Award, Arthur Purdy Stout Award, and the Young Investigator Award from the United States-Canadian Academy of Pathology, and has been listed in the book *The Best Doctors in America* since 1994. A distinguished speaker, Dr. Weiss has delivered over 150 national and international talks in pathology. Dr. Weiss is on the editorial board of eleven scientific journals.