ROS-1 is an orphan receptor tyrosine kinase that is phylogenetically related to the ALK tyrosine kinase gene. ROS-1 rearrangements occur in approximately 2% of lung adenocarcinomas, and several gene fusion partners have been identified including CD74, LRIG3, SDC4, TPM3, and FIG. Tumors that harbor a ROS-1 gene rearrangement have been found to be responsive to treatment with the ALK inhibitor drug crizotinib (Xalkori®). Recent studies have demonstrated that FISH can be used to identify ROS-1 rearrangements in lung adenocarcinoma (positive ROS-1 FISH shown). A positive result with this test would therefore indicate that the patient may respond to treatment with crizotinib. PhenoPath recommends testing for ROS-1 in all non-small cell lung carcinomas (NSCLC), especially when EGFR PCR and ALK FISH are negative. Please contact PhenoPath at 888-927-4366 for further information or ordering details.

GATA-3: a novel marker of breast and urothelial carcinomas

Breast cancer frequently appears high in the differential diagnosis of carcinomas presenting as metastases. While markers such as estrogen receptor (ER) can be helpful, only a subset of metastatic breast cancers manifest ER positivity, and ER expression can be seen in a significant fraction of metastatic carcinomas of other sites such as endometrium, thyroid, and lung. Breast-restricted markers such as GCDFP-15 and mammaglobin A have been utilized for many years in this context, but their sensitivities are in the 70-80% range, and expression of these has also been described in ovarian and other cancers, leaving room for improvement.

GATA-3 is a new marker for the identification of carcinomas of the breast and urothelium. A member of a family of transcription factors (GATA1 through GATA6), it derives its name from an ability to bind to the DNA sequence GATA. GATA-3 regulates luminal epithelial differentiation in the breast, but is not a breast-restricted target: for example, GATA-3 is an important regulator of T cell development. Published studies have demonstrated that GATA-3 expression, as determined by immunohistochemistry, is found in urothelial carcinomas as well as breast cancers; in fact, GATA-3 may be one of the most sensitive markers of high-grade urothelial carcinomas. And within breast carcinomas GATA-3 shows significantly higher sensitivity than the reported sensitivity of GCDFP-15 or mammaglobin A, although it may be in the context of “triple negative” breast cancers in which GATA-3 shows greatest superiority over previous breast-restricted markers. GATA-3 expression is highest in lobular carcinomas of the breast, where its sensitivity approaches 100%. The specificity of GATA-3, however, has not yet been fully determined, as there are conflicting reports of GATA-3 expression in squamous cell carcinomas and carcinomas of other sites, such as stomach. Furthermore, caution should be exercised as GATA-3 may prove to be a marker in which the apparent specificity and sensitivity may be antibody dependent, as has been shown with other transcription factors CDX2 and TTF-1.


p40: the new p63? Antibody p40 clone BC28 recognizes the ΔNp63 isomer of p63

Although generally referred to as a single molecule, p63 actually consists of at least two isoforms, referred to as TAp63 and ΔNp63. Furthermore, p63 has been described as a ‘two-in-one’ family of opposing molecules: TAp63 is a p53-like tumor suppressor gene, while ΔNp63 functions as an oncogene. Antibodies to p63 have been used for many years to identify myoepithelium in the breast, the outer cell layer in prostatic glands, and squamous (and transitional cell) differentiation. More recent studies have suggested that the predominant p63 isoform in basal and myoepithelial cells is the ΔNp63 isoform. This latter isoform is also the predominant p63 transcript in squamous cell carcinomas of lung and other sites. The TAp63 isoform has a much wider tissue distribution. The 4A4 anti-p63 clone that has been in use for many years is actually a “pan-p63” antibody, identifying both the ΔNp63 and the TAp63 isoforms; a far more squamous-specific marker would theoretically be a monoclonal antibody identifying epitopes unique to the ΔNp63 isoform; indeed, such reagents have now become available and have recently been demonstrated to be significantly more specific for squamous cell carcinoma than the older “pan p63” monoclonal antibodies.

PhenoPath is pleased to announce the p16 (CDKN2A) FISH assay to detect homozygous p16 gene deletions in formalin-fixed paraffin-embedded (FFPE) tissue specimens. A common diagnostic challenge in lung and pleural biopsy pathology is the assessment of atypical mesothelial proliferations where the main differential is reactive mesothelial cells versus mesothelioma. One molecular marker that has been investigated to aid in this differential is the cell cycle regulatory protein p16INK4a. In recent studies, homozygous deletion of p16INK4a by FISH has been reported in 22-74% of mesotheliomas. This characteristic of mesothelioma can therefore be employed in the often-difficult differential diagnoses of spindle cell mesothelial proliferations where immunohistochemical markers cannot distinguish between benign and malignant mesothelial proliferations. Importantly, while a positive result is highly specific for mesothelioma in the appropriate clinical setting, it should be noted that a negative result does not rule out the possibility of a mesothelioma. This FISH assay has been validated on formalin-fixed paraffin-embedded (FFPE) tissue sections. Please contact PhenoPath Client Services for details.


PhenoPath upgrades its BCR-ABL PCR reports

Chronic myelogenous leukemia (BCR-ABL1+) is a myeloproliferative neoplasm characterized by a neutrophilic leukocytosis and the presence of the chromosomal translocation t(9;22)(q34;q11.2), which results in the BCR-ABL1 fusion gene. This fusion encodes an abnormal oncoprotein with constitutively activated tyrosine kinase activity.

The 2013 National Comprehensive Cancer Network (NCCN) practice guidelines for the diagnosis and management of chronic myelogenous leukemia (CML) recommend a baseline quantitative RT-PCR measurement of BCR-ABL1 transcripts as part of the initial diagnostic work-up of patients suspected of having CML, and post-therapeutic monitoring of BCR-ABL fusion transcripts as an integral part of subsequent treatment and management. To facilitate clearer reporting of BCR-ABL real-time PCR results, PhenoPath has updated its reporting format to include a graphical representation of current and historical data. These reports will allow patients and oncologists to view how a patient is responding to tyrosine kinase inhibitor therapy over time, and more clearly indicate whether a patient has reached a major molecular response (MMR), an important milestone in CML therapy.

PhenoCases

PhenoPath is pleased to present clinical case studies (PhenoCases) that provide educational insights into the latest developments in tumor analysis. We will post challenging and informative case studies on our website (phenopath.com/#/educational-media) on a monthly basis. Many cases will highlight the optimal and selective use of ancillary techniques such as immunohistochemistry, fluorescence in situ hybridization, PCR, and flow cytometry to supplement and complement the H&E sections in arriving at the correct diagnosis.

The first PhenoCase involves a 32-year-old male who presented with a retroperitoneal mass displacing the pancreas and duodenum anteriorly, with no other significant history and no apparent adenopathy. The submitting pathologist considered desmoplastic small round cell tumor (DSRCT) as the most likely diagnosis, based on the histology as well as the co-expression of desmin and cytokeratins demonstrated in their laboratory. A prior biopsy of the lesion one month earlier had been interpreted as tumor showing myogenin positivity by IHC in their laboratory, raising the question of the diagnosis of rhabdomyosarcoma. Please refer to our website for the diagnostic findings, discussion, conclusion and references.
FEATURED At Our Fall Quarterly Conference
Wayne W. Grody, MD, PhD

PhenoPath Laboratories, November 21, 2013, 6:30 PM (light dinner), 7:30 PM (talk)

Wayne W. Grody, MD, PhD, will present “Adventures in Clinical Genomics: Diagnostic Yield, Incidental Findings, Genetic Privacy and Gene Patents” at the PhenoPath Fall Conference at 7:30 PM on Thursday, November 21, 2013. Dr. Grody will also be giving a daytime lecture at noon the same day entitled, “Reflections on the Evolution and Future of Molecular Pathology and Cytogenetics.”

Dr. Grody is a Professor in the Departments of Pathology & Laboratory Medicine, Pediatrics, and Human Genetics at the UCLA School of Medicine. He is the director of the Molecular Diagnostic Laboratories and the Clinical Genomics Center within the UCLA Medical Center, one of the first such facilities in the country to offer DNA-based tests for diagnosis of a wide variety of genetic, infectious, and neoplastic diseases, as well as bone marrow engraftment, patient specimen identification and paternity testing by DNA fingerprinting, and clinical genomic DNA sequencing for undiagnosed disorders. Dr. Grody has been one of the primary developers of quality assurance and ethical guidelines for DNA-based genetic testing for a number of governmental and professional agencies including the FDA, AMA and CAP. He served as a member of the NIH-DOE Task Force on Genetic Testing, and was the working group chair for development of national guidelines for cystic fibrosis and factor V-Leiden mutation screening.

As a sidelight, Dr. Grody has been active in the film and television industries for many years, first as film critic for MD Magazine, a national leisure journal for physicians, then as technical advisor and sometime writer for a number of feature films, TV movies, and television series including Life Goes On, Chicago Hope, CSI, Medium, Law and Order, Heroes, and both Nutty Professor movies.