Phenomena™

THE NEWSLETTER OF PHENOPATH LABORATORIES

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PhenoPath is pleased to announce PhenoNet™

a state-of-the-art, web-based reporting system allowing clients timely, secure, and convenient access to PhenoPath reports.

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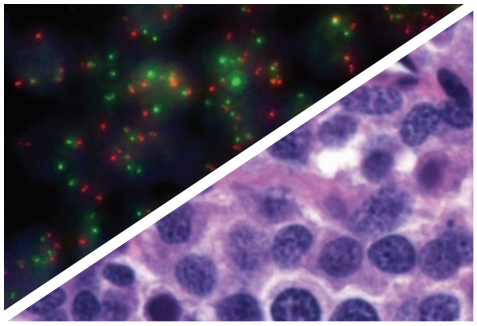
For more information, or to sign up for PhenoNet™, please contact us at 206-374-9000.



NOW AVAILABLE!

NOW AVAILABLE!

TRANSLOCATION IN MYELOMA:

Plasma cell myeloma is a bone marrow-based plasma cell malignancy characterized by elevated circulating monoclonal paraprotein and multifocal skeletal destruction due to osteolytic bone lesions caused by the neoplastic plasma cells. Patients often have associated bone pain, hypercalcemia, and anemia. This disease primarily affects elderly patients, with a median age at diagnosis of 68 to 70 years, and is more common in patients of African American descent. Plasma cell myeloma spans a spectrum of disease, from localized and/or indolent forms to more disseminated and/or agressive disseminated forms. Diagnosis of this disease is based upon a combination of pathologic, radiographic, and clinical features. All forms are currently incurable with conventional chemotherapy.

Recent research studies suggest that plasma cell myeloma is a heterogeneous disease composed of several distinct subgroups with different prognoses. Chromosomal alterations have been reported to be one of the most important prognostic parameters in patients with plasma cell myeloma. Although conventional karyotyping often can be performed on plasma cells isolated from patients, the slow growth of plasma cells in culture occasionally hampers karyotypic evaluation. Because of the risk of false-negative results with routine karyotyping, interphase FISH is the most sensitive and specific methodology for detecting recurrent chromosomal alterations in plasma cell myeloma. These chromosomal alterations most commonly are translocations involving the immunoglobulin heavy chain gene locus on 14q32. Many of these IgH-related translocations result in the juxtaposition of oncogenes, whose expression is controlled by the powerful IgH chain gene enhancer at this locus.

Specific recurrent chromosomal alterations in myeloma currently identifiable at PhenoPath include the t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). The latter two translocations involve IgH/FGFR3 and IgH/c-MAF, respectively, and have been associated with a poor prognosis and short overall survival, while the t(11;14) involves IgH/Cyclin D1, and is associated with an intermediate prognosis. Separation of plasma cell myeloma into different subgroups based upon recurrent chromosomal alterations provides important prognostic information and may be helpful in tailoring therapy.

REFERENCES:

1. *Dewald GW, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. Blood. 2005 Nov 15;106(10):3553-8.*
2. *Fonseca R, et al. The recurrent IgH translocations are highly associated with nonhyperdiploid variant multiple myeloma. Blood. 2003 Oct 1;102(7):2562-7.*
3. *Fonseca R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res. 2004 Feb 15;64(4):1546-58.*
4. *Fonseca R, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood. 2003 Jun 1;101(11):4569-75.*

Combining Flow Cytometry, IHC, and FISH to Make Urgent Diagnoses in Hematopathology

With a wide range of diagnostic modalities at our disposal, the hematopathology service at PhenoPath Laboratories is well suited to make urgent diagnoses requiring immediate therapeutic intervention. These diagnostic modalities include flow cytometry (several-hour turnaround time in emergent situations), FISH (24-hour turnaround time in emergent situations), and IHC (24-hour turnaround time in emergent situations). The following two recent cases illustrate how PhenoPath's integrated hematopathology service generates definitive diagnoses within 24 hours in clinically urgent situations.

Case #1

A 44-year-old female presented with a highly atypical peripheral lymphocytosis in conjunction with constitutional ("B") symptoms. *Figure 1A* demonstrates the morphology of the atypical lymphocytes (denoted by arrows). Flow cytometric evaluation of the peripheral blood *(Figure 1B)* demonstrated a lambda-restricted B cell population (colored red in the flow histograms) coexpressing CD19, CD20, CD38, and CD10, without CD5, and with no obvious cytoplasmic bcl-2 expression in comparison with the internal control T cell population. Because the morphologic and immunophenotypic findings were strongly suggestive of Burkitt lymphoma, cytologic preparations of the material were made the day the specimen was received, and hybridized overnight with breakapart FISH probes to the c-MYC gene on chromosome 8. Evaluation of the FISH signals the following day revealed the clear presence of a chromosomal translocation involving the c-MYC gene *(Figure 1C)*, consistent with the diagnosis of Burkitt lymphoma. This diagnosis was rendered approximately 24 hours after the specimen was received, and enabled the rapid initiation of appropriate chemotherapy.

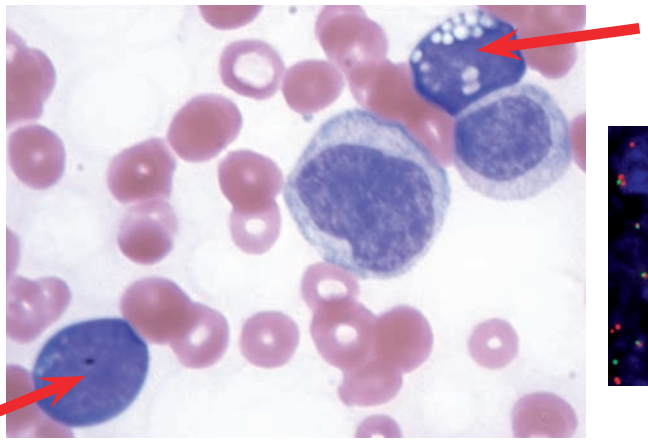


Fig 1A

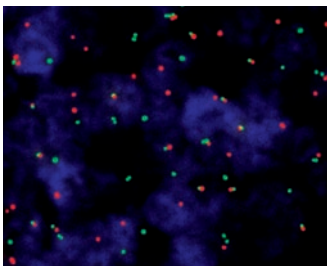


Fig 1C

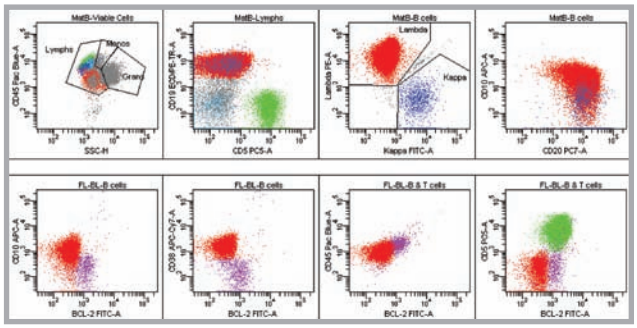


Fig 1B

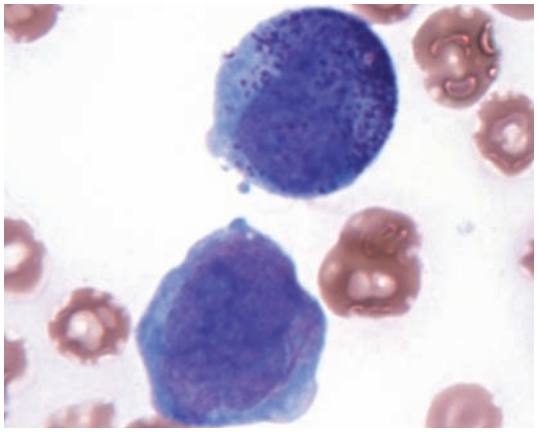


Fig 2A

Case #2

A 49-year-old female with pancytopenia had a bone marrow evaluation. Wright-Giemsa-stained bone marrow aspirate smears demonstrated marrow replacement by a population of immature myeloid cells with variably prominent granularity, and readily identifiable Auer rods. Scattered "faggot cells" with multiple Auer rods were identified *(Figure 2A)*. A myeloperoxidase stain showed uniform intense positivity on the leukemic cells *(Figure 2B)*. By flow cytometry, the neoplastic cells showed an immunophenotype characteristic of abnormal promyelocytes, with very low to negative CD34, low CD117, low-intermediate CD33 and CD13, low aberrant CD2, and no significant HLA-DR *(Figure 2C)*. Importantly, FISH studies performed within 24 hours of the receipt of the specimen demonstrated the clear presence of the t(15;17), confirming the diagnosis of acute promyelocytic leukemia *(Figure 2D)*.

These two cases illustrate the ability of the PhenoPath hematopathology service to render rapid, definitive diagnoses in emergent clinical settings, such as those arising in cases of Burkitt lymphoma and acute promyelocytic leukemia.

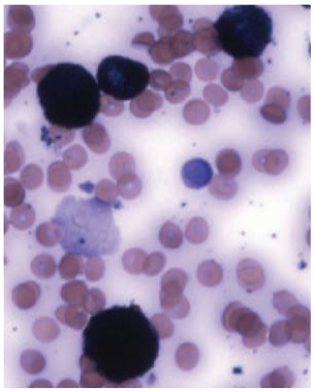


Fig 2B

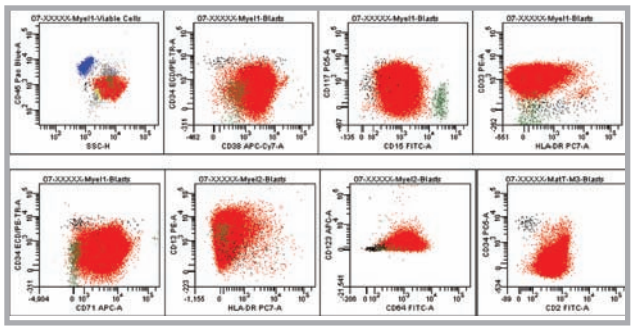


Fig 2C

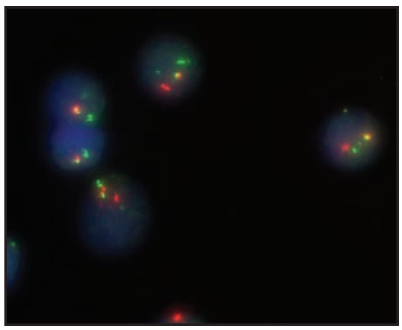
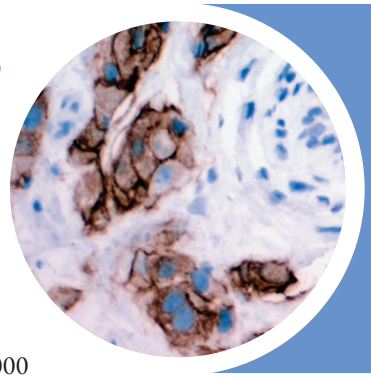
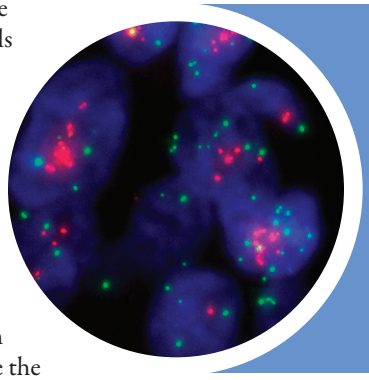


Fig 2D

PhenoPath Laboratories is pleased to announce our HER2 Validation Studies





The newly published ASCO-CAP HER2 testing guidelines mandate that laboratories performing HER2 immunohistochemistry (IHC) validate the accuracy of their IHC by documenting concordance with HER2 gene status in 25-100 breast cancer cases. These guidelines require a 95% concordance of HER2 IHC and fluorescence in situ hybridization (FISH) for positive and negative cases (i.e., 3+ by IHC for gene amplification by FISH and 0 or 1+ by IHC for absence of gene amplification by FISH).

PhenoPath Laboratories will help you meet these new requirements by performing HER2 FISH studies on cases tested by IHC in your laboratory. Unique among reference laboratories, PhenoPath has published its IHC FISH concordance data incorporating results on more than 6,000 cases, most recently in presentations at the San Antonio Breast Cancer Symposium (2006) and the United States and Canadian Academy of Pathology (2007). The extremely high concordance levels attained at PhenoPath reflect our many years of experience in HER2 testing. In contrast to many other laboratories, at PhenoPath, all FISH studies are interpreted by pathologists, not technologists. Furthermore, we use MetaSystems™ morphometric image analysis to quantify the FISH results, which enhances both the accuracy and precision of the data generated.

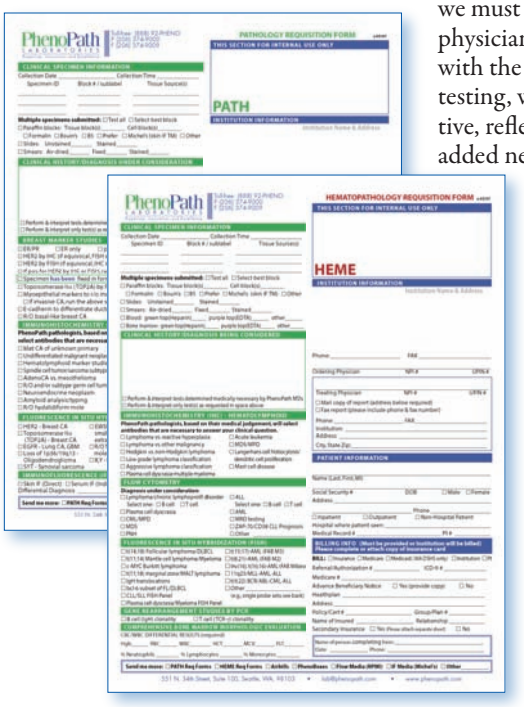
As part of our HER2 validation studies, FISH results on the 25-100 cases will be reported in a spreadsheet; as a value-added feature, results of parallel IHC testing (always performed at PhenoPath as part of the ongoing QA/QC program on cases sent for FISH) will also be reported, if requested.

Please contact PhenoPath Laboratories for additional information concerning HER2 validation studies. PhenoPath pathologists and staff appreciate the opportunity to work with you to improve the overall quality of HER2 testing in breast cancer, fulfilling the mission of the ASCO-CAP Guidelines.

NEW REQUISITION FORMS

To accommodate the increasingly complex menu of test offerings at PhenoPath, we are pleased to introduce new test request forms. As a result of your suggestions to improve readability, we have created two separate requisition forms: one for hematopathology studies, and the second for all other testing.

We have increased space and readability throughout the requisition forms, and have made some changes to the information requested for billing. To comply with new federal regulations, we must now collect the ordering and treating physician NPI numbers. In addition, in compliance with the new ASCO-CAP guidelines for HER2 testing, when HER2 by IHC results are 2+ positive, reflex HER2 FISH will be run. We have also added new tests to our FISH and IHC menus.



Multiple copies of each new requisition form have been mailed to our active clients. These forms can be downloaded from our website, filled out electronically, printed and sent with your specimens.

Periodically you will receive new releases. The version is now indicated on the top right hand side of the requisition form, indicated by the month and year of release (e.g., "v.03/07"). Please discard any old versions of PhenoPath's requisition form. Please call us should you need additional requisition forms or if you have any questions.

PhenoPeople Profile

Christopher Tse, MBBS

Dr. Tse is a Senior Pathologist with exceptional expertise in the analysis of FISH studies. Dr. Tse works closely with Dr. Todd Barry in PhenoPath's Molecular Pathology Laboratory, participating in the development and validation of new clinical FISH assays.

Dr. Tse received his Bachelor of Medicine and Bachelor of Surgery degrees from the University of Hong Kong, and subsequently received extensive postgraduate training in pathology at Queen Elizabeth Hospital (Hong Kong), Princess Margaret Hospital (Hong Kong), Royal Marsden Hospital (London), Royal Free Hospital (London), St. Mark's Hospital (London), and the Western Infirmary (Glasgow, UK). He received subspecialty training in neuropathology at the Institute of Neurological Sciences (Glasgow, UK), and completed the IHC Fellowship at PhenoPath Laboratories in 2004-2005.

Prior to joining PhenoPath, Dr. Tse was the Chief of the Pathology Service at the Queen Elizabeth Hospital in Hong Kong for 10 years. Dr. Tse has published extensively in various areas of diagnostic pathology, including hepatitis and hepatocellular carcinoma, as well as other solid tumors.

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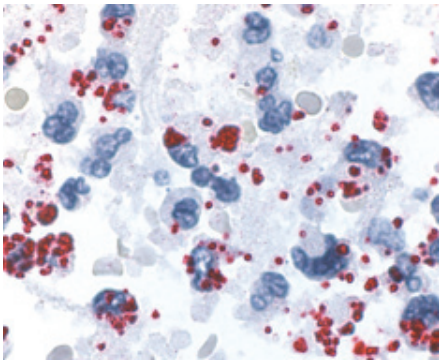
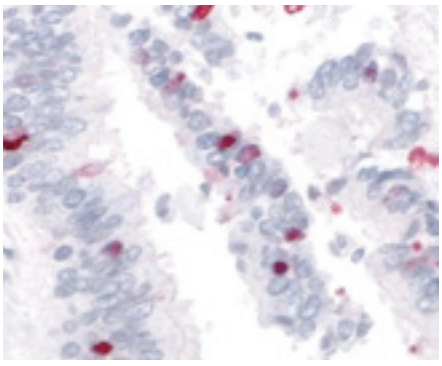
Featuring Dr. Jeannette Guarner

At Our Spring Quarterly Conference

Dr. Jeannette Guarner of Emory University and the Centers for Disease Control and Prevention in Atlanta, GA, will present "Use of IHC in Detection of Emerging and Reemerging Infectious Diseases" at the Quarterly Pathology/Immunohistochemistry Conference on ***Thursday, May 10, 2007***. The format of the conference is a social hour commencing at 6:30 p.m. followed by Dr. Guarner's lecture at 7:30 p.m. A light catered dinner will be served during the social hour.





Dr. Guarner is currently Associate Professor, Department of Pathology & Laboratory Medicine at Emory University School of Medicine, and Director of the Clinical Laboratories at Children's Healthcare of Atlanta. She was formerly a Staff Pathologist at the Infectious Disease Pathology Activity, Division of Viral and Rickettsial Diseases at the National Center for Infectious Diseases, Centers for Disease Control and Prevention. Her research interests include the acute and chronic pathologic effects of infectious agents, in particular Helicobacter pylori and preneoplastic gastric lesions, and the use of immunohistochemical assays to identify infectious agents in tissues.

The Spring Quarterly Conference will be co-sponsored by Dako.