Meeting Report

Association for Molecular Pathology 2000 Annual Meeting

Genetics Session

Attendees of the 2000 Meeting of the Association for Molecular Pathology (AMP), held November 9–12 in Denver, came away with a wealth of fascinating new information, in the rapidly expanding world of genetic diseases. The meeting opened with plenary lecture by the 2000 “AMP Award for Excellence” recipient, Dr. Henry Ehrlich of Roche Molecular Systems, including a global review of the past, present, and future of common genetic alterations for the diagnosis and management of common, complex human diseases, with an emphasis on diabetes and cardiovascular disease. As discussed by Dr. Ehrlich, the complex multigene etiologies of these most common human killers will ultimately require diagnostic approaches incorporating simultaneous analyses of dozens, or perhaps hundreds, of distinct genetic loci.

The meeting's second day was highlighted by two excellent Genetics plenary session talks. The first, by Dr. Rudy Leibel (Columbia University), detailed the molecules and signaling pathways controlling the phenotype of body weight. Given that 70% of the variability in human body weight appears to be genetically controlled, Dr. Leibel provided glimpses of several of the proteins (and mutations) regulating this complex genetic network, including the adipocyte product leptin and its receptor. The second Genetics plenary speaker, Emile Skamene (McGill University), provided a fascinating update of his lab's long-standing search for genes controlling susceptibility to infectious pathogens, particularly *Mycobacterium tuberculosis*. One such protein described in Dr. Skamene's lab, NRAMP, is a macrophage-specific transmembrane intracellular transport protein for divalent cations (including iron), the expression of which is presumably required to provide the intracellular MTb with essential ionic nutrients. Of great interest is the more recent discovery that the natural resistance-associated macrophage protein (NRAMP) homologue DMT1 is the predominant intestinal brush border transporter for ferrous iron. DMT1 is significantly overexpressed in patients with the most common Caucasian single-gene disorder, hereditary hemochromatosis, perhaps to compensate for the absence of the transferrin receptor binding protein HFE, mutations of which are directly responsible for the ma-

jority of cases of hemochromatosis. This is an excellent example of the interrelatedness of two apparently divergent scientific fields, and how the search for a susceptibility gene for a bacterium inadvertently led to a better understanding of the pathogenesis of a common Mendelian genetic disorder.

In addition to these basic science presentations, the Denver meeting also included several practically oriented genetics workshops. These included a hands-on session showing the utilization of web-based, sequence-manipulative genetics tools available from the National Center for Biotechnology Information (Peter Cooper, NCBI) and an overview by Bonnie Pagon (University of Washington) of the web-based GeneTests genetic test database detailing clinical and research-based tests available from hundreds of labs around the world. Preliminary discussions are underway to explore the feasibility of merging the AMP test directory into the GeneTests directory, so this extensive database may soon become quite familiar to AMP members. The final Genetics workshop of the Denver meeting included a discussion of American College of Medical Genetics/College of American Pathologists (ACMG/CAP) proficiency testing results (by Tim Stenzel, Karen Snow, and Brad Popovich) and detailed the significant progress of genetics testing labs toward more standardized and quality-controlled diagnostic testing. Finally, Wayne Grody (University of California Los Angeles) updated the audience on the soon-to-be released consensus recommendations of the ACMG and the American College of Obstetrics and Gynecology to offer universal prenatal population-based cystic fibrosis screening to certain ethnic groups (Caucasians and Ashkenazi Jews).

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Hematopathology Session

The Hematopathology Section of the 2000 AMP Annual Meeting enjoyed excellent plenary session talks, as well as two informative and interactive workshops. Plenary

session speakers were Dr. James Downing of St. Jude Children's Research Hospital, who gave an elegant update on core binding factor leukemias, and Dr. Lawrence Weiss of City of Hope National Medical Center, who spoke about the role of Epstein-Barr virus in malignancies.

The first Hematopathology workshop was organized by Dr. Adam Bagg, Program Chair-Elect of the Hematopathology Section, and was focused on the clinical significance of minimal residual disease detection and quantitative polymerase chain reaction in leukemias and lymphomas. Speakers included Janina Lontine of Brigham and Women's Hospital, Sheila Shurtleff of St. Jude Children's Research Hospital, and Kojo Elenitoba-Johnson of ARUP Laboratories. After the talks and an animated discussion, it became clear that many labs in the AMP Hematopathology Section are struggling with the same questions about using these assays for clinical purposes.

Clearly, there is a great deal of concern about how to determine the actual clinical relevance of a single quantitative PCR result, and there is no clear consensus on how to report quantitative PCR results in leukemias and lymphomas. This will obviously be a topic of continued interest to the AMP Hematopathology Section.

The second Hematopathology workshop, presented by Rita Braziel of Oregon Health Sciences University and Dan Arber of City of Hope National Medical Center, was a continuation of previous AMP workshops focused on interlaboratory sample exchanges. The 2000 surveys included a very extensive study of the JH/Bcl-2 - t(14;18) translocation in follicular lymphomas, and a smaller, more preliminary study of reverse transcription-polymerase chain reaction analyses for the Bcr-Abl - t(9;22) translocation in chronic myelogenous leukemia. More than 40 labs participated in these surveys and submitted their results. Summary data tables and results were presented at the workshop; work is underway to digitize and put the submitted results on the Hematopathology Section Web site for all to review.

The objective of these Hematopathology Section sample exchanges was not only to provide validation of hematopathology molecular assays for participating labs, but also to identify optimal testing procedures and develop some standardization of clinical hematopathology molecular testing. It is clear that the AMP surveys have indeed had an impact on clinical testing in many participating AMP laboratories. An examination of the submitted results from labs participating in exchanges over the past 3 years shows that many labs have altered their procedures in response to survey results, and have shown an improvement in results in subsequent assays. Attendees at the sample exchange workshop showed strong support for continuation of sample exchanges between AMP labs. Ideas for additional exchanges in 2001 and volunteers from other labs to help with the exchanges are needed and are being solicited. Information about 2001 sample exchanges will be announced on AMP's e-mail listserv, CHAMP.

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Infectious Diseases Session

The Infection Disease plenary session, presented jointly with the Genetics Session, was entitled, "Genetics of Mycobacterial Infection", and was given by Emile Skamene, M.D., FRCP(C), FACP, FRSC, of McGill University. This session was described previously.

The first workshop, entitled "Review and Discussion of the National Committee for Clinical Laboratory Standards Proposed Guidelines for Quantitative Molecular Methods for Infectious Diseases," was moderated by Angela Caliendo M.D., Ph.D., of Emory University School of Medicine, and Roberta Madej, M.S., M.B.A., of Roche Molecular Systems. The panel consisted of John Ticehurst, M.D., from the Food and Drug Administration, Stephen Day, Ph.D., from Visible Genetics, Frederick Nolte, Ph.D., from Emory University, and Andrea Ferreira-Gonzalez, Ph.D., from the Medical College of Virginia.

This workshop provided a forum for discussion of the proposed guidelines for quantitative molecular methods for infectious diseases. The panel members and the moderators were all part of the National Committee for Clinical Laboratory Standards (NCCLS) subcommittee that was responsible for drafting the guidelines. The workshop gave interested AMP members an opportunity to provide the subcommittee direct feedback on the guidelines. Discussion topics included the use of independent controls, alternative approaches to proficiency testing, results reporting, and the role of the FDA in establishing clinical utility for new viral load tests.

Suggestions from the audience will be incorporated into the document before its distribution for public comment. The workshop also served to acquaint the membership with the activities of the NCCLS in area of molecular diagnostics. The audience was encouraged to volunteer for appropriate NCCLS subcommittees.

The second workshop, presented by Frederick Nolte of Emory University, was entitled, "Hepatitis C Virus [HCV] Genotyping." Dr. Nolte provided a review of the clinical utility of genotyping HCV and how to use the information in patient management decisions. HCV genotype is one of five factors that can be used to determine the length of therapy with interferon and ribavirin. The other factors are viral load, age, gender, and liver biopsy results. The various genotyping methods were reviewed, including automated sequencing, line probe assay, and cleavase length fragment polymorphisms. The relative strengths and limitations of each approach were highlighted. Points to consider when selecting a method for the laboratory include cost, complexity, flexibility, throughput, sensitivity, and the ability to recognize mixed infections. Several commercially available methods are feasible for use in clinical laboratories.

The third workshop, "Human Immunodeficiency Virus Genotyping and Phenotyping," was presented by Timothy Alcorn, Ph.D., of LabCorp. Dr. Alcorn provided an

overview of HIV resistance testing. Most HIV genotyping is performed by automated sequencing, but microarray and line probe assays are also available. Two companies, Virco and Virologics, offer phenotype assays using recombinant nucleic acid methods. The virtual phenotyping approach was also discussed. The limitations of these tests include inability to detect minor variants (<10%), lack of correlation between genotype and phenotype, and inability to predict the interaction between mutations. The important clinical issues discussed included sample collection and transport, the need for drug selective pressure, and the difficulties involved with interpreting the results.

HCV and HIV genotyping are now a standard of care. This workshop provided important practical information for laboratory professionals performing these assays.

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Solid Tumors and Special Topics Session

The Solid Tumors subsection of AMP presented several timely topics. In the plenary session, a superb overview of the Her-2/Neu field was presented by Dr. Dennis Slamon of UCLA. Dr. Slamon has devoted the majority of his career to the study of the molecule. He reviewed the initial findings regarding amplification of Her-2/Neu in breast cancer and discussed the basis for early conflicting results in the literature. He followed up with a look at current methods for detection of amplification, including immunohistochemistry and fluorescence *in situ* hybridization, and discussed the use of herceptin in treatment of breast cancer. In the second plenary lecture, Dr. Tobin Orntoft of Aarhus University Hospital in Denmark very elegantly presented his work on the molecular classification of bladder cancer using microarrays. Dr. Orntoft had on the previous day presented a workshop on the development and use of microarrays for the study and classification of human tumors. In time, this approach will provide us with valuable information on human samples, fulfilling both research and clinical needs.

The second solid tumor workshop focused on the molecular detection of occult tumor cells, both in the circulation and in lymph nodes. Dr. Ronald Ghossein of Memorial Sloan-Kettering Cancer Center discussed his group's extensive work on detection of occult cells in the bloodstream of prostate cancer patients using reverse transcription-polymerase chain reaction (RT-PCR) to detect the PSA gene transcript. Although tumor cells can be detected, the clinical utility of RT-PCR for assessment of

prostate cancer remains undefined. RT-PCR can also be used for assessment of patients with melanoma. RT-PCR results targeting the tyrosinase gene transcripts appear to show a good correlation to patient outcome; thus, application of RT-PCR in this setting appears more promising. Dr. Richard Cote of the University of Southern California then spoke eloquently of his work utilizing both RT-PCR and immunohistochemistry for detection of occult micrometastasis in the bone marrow and lymph nodes of patients with breast, lung, and colorectal cancers. Both approaches increase the sensitivity rate in detection of occult tumor cells, though false positivity is problematic with some molecular assays. Dr. Cote presented convincing evidence supporting further investigation in this area and suggesting the eventual incorporation of these approaches into patient diagnosis and management.

The closing sessions of the meeting focused on two important regulatory issues impacting on molecular diagnostics. First, the deliberations of the Secretary's Advisory Committee on Genetic Testing (SACGT) and the Clinical Laboratory Improvement Act Committee (CLIA) were presented by Drs. Ed McCabe and Patricia Charache, respectively. Dr. McCabe, who chairs the SACGT, covered the issues and concerns regarding genetic testing that led to the establishment of SACGT, and discussed the various approaches the group was considering to regulate and oversee genetic testing and the labs performing this service. The current model attempts to divide genetic tests into those requiring low and high levels of scrutiny, and establish appropriate oversight for each category. Dr. Charache, a member of CLIA and SACGT, presented the CLIA viewpoint in terms of defining a "genetic test," and requiring oversight of pre-analytic, analytic, and post-analytic phases of testing, as well as the requirement of informed consent. Dr. Bradley Popovich of Oregon Health Sciences University followed with a discussion of the various complexities and issues that the proposed regulation and oversight would present to labs performing genetic testing.

In the second session, a discussion of issues related to the patenting of genes took place. Dr. Stanton, a scientist with the U.S. Patent and Trademark Office, presented an overview of the current policies regarding gene patents, followed by a presentation of the benefits of patents by Lila Feisee, representing the Biotechnology Industry Organization. Lastly, Dr. David Korn of the American Association of Medical Colleges cautioned us about the difficulties resulting from patenting and exclusive licensing of gene. A lively discussion followed the presentation.

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