ARE YOU READY?

In April 2003, a silent killer quietly invaded Toronto just days before the annual meeting of the American Association for Cancer Research (AACR). Thousands were quarantined after six people died of severe acute respiratory syndrome (SARS) and the number of suspected cases spiked. The world watched as colleagues in Canada struggled to find a way to deal with this medical emergency and public health crisis that forced ACCR to cancel their meeting. While we do not know when the next crisis may hit, we do know that future natural or man-made emergencies are a certainty. Given this likelihood, are you prepared to care for your patients, your staff, and yourself when the next crisis hits? How does care change in the face of a crisis when you may be at risk? These are just some of the important issues hematologists must consider and lessons we must learn from past experiences around the world.

Emergency preparedness is the topic of this year’s ASH-EHA Policy Forum. In partnership with the European Hematology Association (EHA), ASH will explore important strategic questions that force us to reflect on the role we need to prepare to play as hematologists during public health crises. This year’s session will take place immediately before the year’s ASH-EHA Policy Forum. In partnership with the European Hematology Association (EHA), ASH will explore important strategic questions that force us to reflect on the role we need to prepare to play as hematologists during public health crises. This year’s session will take place immediately before the year’s session. 

Sowing Seeds of Discontent


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hronic myeloid disorders are a heterogeneous group of nonlymphoid hematopoietic neoplasms that can be divided into those which display the myeloproliferative syndromes (MPDs) or do not display the myeloproliferative disorders (MPDs). MPDs typically exhibit terminal myeloid cell expansion in the blood and bone marrow (BM). The classic types include polycythemia vera, essential thrombocytosis, chronic myelogenous leukemia, and chronic idiopathic myelofibrosis. In these disorders, the neoplastic clone is considered intrinsic to the hematopoietic cell and originates in a multipotent progenitor cell, whereas the marrow microenvironment has long been thought a bystander and not a cause. In a recent article in Cell, Walkley and colleagues make mice deficient for RARγ, which promote hematopoietic cell proliferation or inhibit apoptosis. Taken together, these data suggest that the RARγ−/− microenvironment increases the proliferation and production of the relatively mature hematopoietic cells but does not affect the numbers of the immature progenitor and HSCs.

It was previously shown that the retinoic acid receptor (RAR) subtypes RARα and RARγ are widely expressed in immature and maturing hematopoietic cell types. To further determine the role of RARγ in the production of hematopoietic cells, Walkley and colleagues made mice deficient for RARγ and report that these mice developed significantly increased granulocytes and granulocyte/macrophage progenitors (GMPs) in the blood, BM, and spleen by eight weeks of age. The myeloproliferative phenotype was continued throughout the lifespan of the mice and became more pronounced with age. By 12 months of age the RARγ−/− mice developed splenomegaly, extramedullary hematopoiesis, and anemia with steady progressive granulocytosis and thrombocytosis. Unexpectedly, this phenotype was due entirely to a deficiency of RARγ in the microenvironment and was not intrinsic to the hematopoietic cell; transplant studies revealed that BM from wild-type mice transplanted into RARγ−/− mice rapidly developed the myeloproliferative phenotype. In contrast, wild type recipients of RARγ−/− or RARγ−/+ BM had similar blood, marrow, and spleen cellularity during the six months of monitoring. Histologic sections of the marrow showed significantly reduced trabecular bone in the RARγ−/− mice, yet this reduction in the osteoblastic marrow niche did not impair hematopoietic stem cell (HSC) self-renewal. Taken together, these data suggest that the RARγ−/− microenvironment increases the proliferation and production of the relatively mature hematopoietic cells but does not affect the numbers of the immature progenitor and HSCs.

Walkley and colleagues demonstrate that loss of one of the major receptors for vitamin A, RARγ, results in a marrow microenvironment that induces a myeloproliferative phenotype. Although the mice failed to develop leukemic transformation, this study raises the possibility of a tumorigenic niche and provides data supporting the idea that niche dysfunction may have a role in the development of hematopoietic malignancies. It is easy to speculate how this can occur: a tumorigenic niche can supply inappropriate levels of growth factors that promote hematopoietic cell proliferation or inhibit apoptosis. The loss of trabecular bone following RARγ deficiency may lead to HSC expansion and/or mobilization of these or other progenitor cells to the spleen and extramedullary sites that provide a more permissive environment to myeloid proliferation and differentiation due to the loss of inhibitory signals normally provided by the osteoblastic niche. This study does not negate the importance of acquired genetic change in the malignant transformation to leukemia. Rather, it adds a complementary concept and suggests that understanding the contributions of how the marrow microenvironment sows seeds of discontent in the MPDs and other hematologic malignancies is important in understanding the pathogenesis of these diseases.
Plenary Scientific Session, on Sunday, December 9, from 12:30 to 1:30 p.m. in Hall A1. The session will be co-chaired by ASH President Dr. Andrew Schafer and EHA President Dr. Willem Fibbe. We are delighted that renowned experts Drs. Don Low and Albert Osterhaus have agreed to stimulate our thinking about this topic and allow us to learn from their personal experiences.

Dr. Low saw the SARS epidemic unfold from his vantage point as Microbiologist-in-Chief at the Toronto Medical Laboratories and Mount Sinai Hospital, a diagnostic laboratory serving 100 hospitals in the Greater Toronto area. He will share his unique perspective about the challenges his colleagues and staff faced and offer insights that hematologists will want to consider in his presentation titled “SARS Outbreak in Toronto: Lessons Learned.”

Dr. Osterhaus, widely recognized as “The Virus Hunter” for his expertise and sometimes unconventional methods in studying infectious diseases, was trained as a veterinarian. He turned to virology after he recognized the significance and impact of viruses that cross the species barrier. He founded the Netherlands’ National Institute for Public Health and Environment and heads a 100-person lab at Erasmus MC in Rotterdam. At the height of the SARS epidemic, he headed the first laboratory to provide evidence demonstrating that the disease was caused by a coronavirus that usually resides in civet cats and other carnivorous animals.

There will be time for questions from the audience after the speakers have shared their remarks. Please mark your calendar for this special policy forum.

LETTERS TO THE EDITOR — SOLICITATION

The Hematologist welcomes letters of up to 200 words. These letters may be in response to editorials or on any subject of interest to our readers. Please include a postal address, e-mail address, and phone number. Publication will be based on editorial decisions regarding interest to readers and space availability. We may edit letters for reasons of space or clarity. The Hematologist reserves the right to publish your letter, unless it is labeled “not for publication.”

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Karen Learner, Managing Editor
The Hematologist: ASH News and Reports
1900 M Street, NW, Suite 200
Washington, DC 20036
klearner@hematology.org

ASH-ASCO CLINICAL PRACTICE GUIDELINE UPDATE ON THE USE OF EPOETIN AND DARBEPOETIN NOW AVAILABLE

J. DOUGLAS RIZZO, MD, MSH

Dr. Rizzo is Associate Professor of Medicine at the Medical College of Wisconsin.

The ASH-ASCO 2007 Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin has recently been completed. In addition to updating recommendations made in 2002, new recommendations address the use of darbepoetin, thromboembolic risks of erythropoiesis-stimulating agents (ESAs), and comment on the risks of disease progression and survival.

Comprehensive systematic reviews support the equivalence of darbepoetin and epoetin with respect to safety and effectiveness. For patients with chemotherapy-associated anemia, the guideline recommends use of an ESA as a treatment option as hemoglobin approaches or falls below 10 g/dL, to increase hemoglobin or decrease transfusions. ESAs continue to be recommended for patients with low-risk myelodysplasia. Conclusive evidence is lacking that, absent clinical circumstances necessitating earlier treatment, initiating ESA treatment at hemoglobin levels greater than 10 g/dL spares more patients from transfusion or substantially improves their quality of life. ESA therapy is associated with a statistically significant relative risk of thromboembolism that is 1.67 times that of patients not receiving an ESA. This finding suggests that clinicians should carefully weigh the risks of thromboembolism when prescribing an ESA in patients with anemia. The guideline panel recommends that clinicians follow recommendations in the U.S. Food and Drug Administration (FDA) package insert for starting dose and dose modification of ESAs. Alternative dose initiation or escalation schedules are not adequately supported by evidence. Assuming an appropriate dose increase has been attempted in nonresponders, continuing ESAs beyond six to eight weeks in the absence of response does not appear to be beneficial. The guideline recommends monitoring iron stores and supplementing iron intake, though it also acknowledges that this remains an area where further clinical investigation is needed to guide recommendations for iron formulation and dosing. ESAs should not be used in patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolism and decreased survival in these patients.

The guidelines are based on evidence derived mainly from systematic reviews and meta-analysis of published clinical trials. Systematic reviews and evidence-based guidelines also provide valuable insight into important deficiencies in current knowledge that may affect practice. ESAs are no exception. Future research should include better assessment and reporting of adverse events graded by severity, such as thromboembolism, progression, and survival; better efforts to understand the impact of ESAs on tumor progression; more studies to understand appropriate dosing and formulation of iron supplementation; more trials to characterize benefits and harms in patients with MDS; additional evidence regarding quality of life; and studies comparing economic outcomes between alternative strategies to raise hemoglobin.

While it is anticipated that the 2007 guideline will provide important guidance to clinicians and inform regulatory agencies and payors, it should be acknowledged that closing the evidence gap described above is essential to establishing appropriate use of ESAs to maximize the benefits of therapy while reducing potential harm to patients.

To read the updated guideline, visit http://bloodjournal.hematologylibrary.org/papbyrecent.dtl on the ASH Web site, and scroll down to the October 22 listing. For more information on the update, don’t miss the Practice Forum on Saturday, December 8, at 6:00 p.m. during the annual meeting. There will also be a discussion on the latest regulatory issues surrounding ESA coverage.
ASH LEADERSHIP ELECTION RESULTS

Dr. Hal Broxmeyer, Scientific Director of the Walther Oncology Center and Chair of the Department of Microbiology and Immunology at the Indiana University School of Medicine, was elected vice president of ASH and will serve as vice president in 2008, becoming president-elect in 2009 and then president in 2010. Dr. Stephanie Lee, an Associate Member of the Fred Hutchinson Cancer Research Center and Associate Professor at the University of Washington, and Dr. Thomas Bensinger, Chief of the Hematology/Oncology Department at Washington Adventist Hospital, were elected ASH councillors. Each will serve a four-year term. Dr. Bensinger holds the councillor position designated for a hematologist in clinical practice.

What is the role of a councillor? We asked Nancy Andrews, MD, PhD, an ASH councillor from 2004-2007.

Councillors serve as voting members of the Executive Committee and attend four Executive Committee meetings per year. In their fourth year of service, councillors serve with the treasurer on the Subcommittee on Program Support. In 2007, councillors approved various items by motion including a late-breaking abstract policy, the new Research Training Award for Fellows, an enhanced public relations campaign ($2 million over three years), a joint workshop with AACR, and the institution of a relationship with Health Volunteers Overseas (HVO).

Serving as a Councillor has given me a chance to see ASH from the inside and to have a role in determining how ASH can best serve its members. Councillors participate in planning the annual meeting program and in making all major decisions during their terms. It requires a real commitment of time and energy, but Marty Luggett and the ASH staff are superb—working with them makes this job a real pleasure.
A Report on Financial Support

Charlotte Niemeyer, MD, Chair of ASH’s International Members Committee (IMC) and Professor of Pediatrics at the University Children’s Hospital in Freiburg, Germany
Guillermo J. Ruiz-Arreguiles, MD, FACOP, FRCPA, Regional Coordinator of the IC-APL for Mexico, Clinica Ruíz de Puebla, Centro de Hematología y Medicina Interna de Puebla in Puebla, Mexico
Lem Martinez, MD, Regional Coordinator of IC-APL in Montevideo, Uruguay

The IC-APL became successful because of the enormous effort and enthusiasm of national coordinators, local data managers, and laboratory scientists. However, not surprisingly, some funding from local and national sources of the participating countries had to be relocated to support the initiative. In Mexico, the Fundación Mexicana para la Salud (Mexican Foundation for Health), a non-government organization, supported the salary for data managers, while Roche Mexico ensured that molecular studies could be conducted in all the patients. Similarly, in Brazil a private organization made certain that there was no shortage of medications for IC-APL patients. In addition to local sponsorship, the IC-APL is grateful for a grant of €100,000 by the Umberto Veronesi Foundation in Milano, Italy. With this generous donation, the IC-APL was able to establish a network of well-trained data managers in all participating hospitals. This infrastructure will allow the participating countries to later undertake network-based clinical studies on patients with APL or other hematologic diseases. Last, but not least, it was the initiative by ASH which brought together international experts and physicians from Brazil, Mexico, and Uruguay to engage in this pioneer work. ASH continues to support IC-APL with two annual meetings, regular phone conferences, and staff resources. With this combined local, national, and international support, capacities for clinical studies can be established in countries with limited resources as demonstrated by the IC-APL.

A Report from the National Reference Laboratories on Molecular Diagnostics on the Implications of the IC-APL

Eduardo M. Rego, MD, Associate Professor, Division of Hematology, Department of Internal Medicine, Medical School of Ribeirão Preto, University of São Paulo, Brazil
Francesco Lo-Coco, MD, Professor of Hematology of the University Tor Vergata in Rome and Chairman of the Subcommittee on APL of the Italian Cooperative Group GIMEMA
Javier García-Esple, PhD, Consultant, Department of Molecular Biology, Laboratorios Clinicos de Puebla, Mexico

As an integrating and fundamental part of the project, laboratory investigators were involved since the beginning in the IC-APL group to standardize diagnostic and genetic studies for patients enrolled in the protocol. To this end, an ad-hoc subcommittee was created under the supervision of an investigator from each country and a few other external experts. The team has edited a manual containing guidelines for logistical issues (sample collection, shipment, storage, etc.) and for standardized RT-PCR, antibody-based and FISH methods for diagnostics, and specific recommendations for coagulation studies. The PG.M3 (anti-PML) antibody for rapid, specific, and low-cost identification of APL cells in diagnostic smears was distributed before the start of the protocol to central reference laboratories in the three participating countries. The group meets regularly using the virtual meeting facilities provided by the Cure4Kids Web site (www.cure4kids.org) at St. Jude Hospital to discuss diagnostic tests for individual patients, including PCR and immunofluorescence images, which are uploaded and visualized for discussion during the meeting. Such activity has resulted in the availability of diagnostic confirmation and in patient-sample banking to be used for future research studies.

A Report on the IC-APL Protocol Data Management Project

Reul Ribeiro, MD, Director of the International Outreach Program and Leukemia/Lymphoma Division at St. Jude Children’s Research Hospital
Rafael Jácomo, MD, Staff Physician at the University Hospital, Medical School of Ribeirão Preto, University of São Paulo

A critical component of the IC-APL project is to store and frequently analyze data generated by collaborating institutions. Systematic and constant monitoring is required to assure uniformity of protocol guidelines and detect possible inconsistencies among participants. Because the project is being simultaneously developed at multiple sites in different countries, a Web-based solution has been necessary. Cure4Kids, developed by the St. Jude International Outreach Program, supports free, secure online meetings for training, case-by-case review of patients, and discussion of protocol issues. The Pediatric Oncology Networked Database (POND) (www.pond4kids.org) is a secure, multilingual online database customized to meet IC-APL protocol requirements. POND allows each institution to store its own data and generate site-specific reports. Selected and authorized data from the institutions can be automatically shared with the protocol coordinator in an anonymized way (using a unique study identification number) to facilitate coordination of the protocol and monitoring of eligibility and data quality. Minimal requirements include a computer with an Internet browser (any platform), speakers, a microphone, and a medium- or high-speed Internet connection. Data managers were trained through online classes and provided with a detailed manual for both POND and the IC-APL protocol. The data managers, participating physicians, and study coordinator meet online every two weeks to review the cases. Over a 10-month period, 40 patients with APL have been considered for enrollment on the IC-APL protocol. Three patients were ineligible because of a low-performance score or absence of the t(15;17) by RT-PCR. Three additional patients were excluded because of protocol violations. POND and online communication tools in Cure4Kids are reliable and easy to use. The initial findings underscore the need for close monitoring of treatment protocol guidelines.
THE FUTURE OF HEMATOLOGY IN THE PRIVATE-PRACTICE SETTING

ELAINE G. CHOTTOMER, MD
Ann Arbor Hematology Oncology Associates, P.C., Section Head, Division of Hematology/Oncology at Saint Joseph Mercy Hospital in Ann Arbor, MI.

Over the past decade, ASH has increasingly focused on the shortage of hematologists in the United States. While this has been readily apparent in academic institutions, the effect has been much more insidious in the private-practice setting where many of the areas of expertise traditionally attributed to the hematologist have gradually been taken over by other disciplines—pathology, cardiology, and pulmonary and general internal medicine, among others. At the same time, some fellows elect medical oncology training alone, and fewer fellows who have completed training requirements for dual-board certification ultimately choose to certify in hematology over medical oncology.

We may now have come to the crossroads. In Michigan, we are seeing lawsuits involving benign hematologic disorders in which the defendants include not only the treating physicians but also the groups and hospitals that allowed members without hematology Board certification to practice hematology. In addition, the Joint Commission has decided to focus upon delineation of privileges. Our Chief of Medicine recently informed me that I must separate the privileges for hematology and oncology within our division. Our group has been fortunate that in all of us have had dual training and certification or were "grandfathered" in. However, the newest member will not be Board eligible in hematology, and this requirement would mean an inconvenient back-up system for handling patients in the hospital and complex hematology consultations. As I opened my mouth to protest, I realized that I couldn’t. Not only is it the right thing to do, but it validates the role of the hematologist in a tertiary-care teaching hospital such as ours.

Hematology has long been considered to be primarily an academic discipline devoted to complex clinical problems and research. Until the last few years, ASH has been, for the most part, an academic organization with a strong commitment to educate community hematologists, but has had limited involvement in the realities of private practice. The role of the private-practice hematologist has never been well defined, and there is no role model within academic training programs. As a consequence, it is very difficult to encourage medical students and house officers interested in private practice to consider hematology fellowships. Those who are interested in hematology but not oncology have been indoctrinated to believe that there are no opportunities to practice "pure" hematology in the community setting, and those who are interested in oncology don’t perceive a need to fulfill the requirements for dual certification, particularly in view of the requirements for ongoing recertification.

Hematology/oncology practices have also been at fault. In an era when there is a growing shortage of oncologists in the United States, it has become difficult to recruit qualified physicians. All aspects of the practice of oncology—clinical, financial, administrative, and regulatory—have grown increasingly complex. Reimbursement for chemotherapy services far exceeds reimbursement for the more time-oriented services associated with benign hematologic diseases. In practices where income is apportioned according to billing, there is little incentive for the overworked oncologist to see anemias and coagulation disorders, and these problems are willingly ceded to other specialties whenever possible. However, it is the hematologist/oncologist who ultimately must deal with the most complex problems—those that fall outside the algorithms or encounter the serious complications.

ASH leadership has been actively addressing these issues over the last few years, in part by the basic work of defining what a hematologist is and what value the hematologist provides. Those of us who practice hematology in the community setting need to participate in these discussions in order to provide our insight and perspective. We need to look at dual fellowship programs to determine whether they adequately prepare physicians to practice hematology. We need to educate fellows regarding the changing requirements for hematology practice in the community. We need to look at ASH’s educational programs to determine if there are ways in which we can improve the practice of hematology in the community. We need assistance in developing a curriculum that will stimulate an interest in the field among our house officers, who are most likely to remain in private practice. We need to work with our hospital systems to determine the best way to deliver hematology services including multidisciplinary approaches. We need to think about models other than the hematologist/oncologist that might work better in the community setting—the hematologist/internist or the hematologist/pathologist.

It is likely that many more of my colleagues in the community will encounter the challenge that has been posed to our practice. I hope that it will provide the stimulus for us to join ASH in addressing the concerns about the future of our subspecialty.
The National Heart, Lung, and Blood Institute (NHLBI) is looking for a visionary and inspired Director to lead the Division of Blood Diseases and Resources into the next decade. Several retirements have created an unusual opportunity for the new Director to build his or her own leadership team, including a Deputy Director and a Director of the Hemostasis and Thrombosis Branch. NHLBI has recently completed a Strategic Plan (www.nhlbi.nih.gov), the implementation of which, as it applies to blood disorders and resources, will be the responsibility of the Director and team. This is a unique opportunity to have an impact on the field of hematology and the broader research agenda. For information, please contact Susan B. Shurin, MD, Deputy Director, NHLBI, at shurin@nhlbi.nih.gov.

**NHLBI SEeks NEW DIRECTOR**

FY 2008 Funding for NIH Still in Question

With fiscal year (FY) 2008 having begun on October 1 and funding levels for the year still not approved and finalized, Congress passed a continuing resolution (CR) to continue funding the federal government and various federal programs at FY 2007 levels while completing work on FY 2008 funding bills. When this issue of The Hematologist went to print, Congressional leaders had established mid-November as their target date for adjournment for the year and to finalize FY 2008 funding levels.

The House and Senate Appropriations Committees’ proposed FY 2008 NIH funding essentially represents a cut for NIH, because the small increases it provides do not keep pace with the projected 3.7 percent increase in biomedical inflation. The House version of the FY 2008 Labor-HHS spending bill provides a net increase of $549 million (1.9 percent) over FY 2007 for NIH. Meanwhile, the net increase proposed by the Senate for the NIH budget in its draft bill is $799 million (2.8 percent) over FY 2007.

Though the full House ultimately passed its version of the funding bill, timing for consideration by the full Senate remained in question as this issue of The Hematologist went to print, though congressional leaders sought to complete all outstanding work on FY 2008 funding bills by mid-November. It is likely that the Labor-HHS funding bill will be combined with additional funding bills into an “omnibus” bill.

ASH encourages all members to visit the ASH Advocacy Center at www.hematology.org/takeaction to help influence the budget process and find the most up-to-date information about NIH funding and ASH’s advocacy efforts.

Congress Approves FDA Authorization Bill

Both the House and Senate approved a comprehensive legislative package to reauthorize drug industry user fees, provide greater incentives for pediatric drug testing, and require reporting of clinical trial results. The final legislation (H.R. 3580) reflects a compromise between House and Senate bills to reauthorize various programs at the U.S. Food and Drug Administration (FDA). The measure reauthorizes through FY 2012 the Prescription Drug User Fee Amendments (PDUFA) and the Medical Device User Fee Amendments (MDUFA), and includes a number of provisions intended to improve drug safety. Also included in the bill is a provision expanding the ClinicalTrials.gov data bank at the Library of Medicine to include registry information for clinical trials of all drugs, biologics, and devices, as well as results for clinical trials of approved products.
I recently received the following question from an ASH member through the Society’s new Consult-a-Colleague program. He asked:

How would you counsel a patient who is an asymptomatic heterozygote with the Factor V Leiden mutation who is planning her first pregnancy and wants to take enoxaparin thromboprophylaxis? No other thrombophilic factor is identified, but her mother, who is also heterozygous for Factor V Leiden, had her first episode of DVT in the mother—were there other risk factors that she had that are not present in the daughter? These might include older age at the time of the first pregnancy, obesity, or prolonged immobilization due to preeclampsia, C-section, or post-partum. If the doctor was able to identify such a risk factor, he might use this in bolstering her of the potential risks (e.g., bleeding, low risk of heparin-induced thrombocytopenia) and discomfort of low-molecular-weight heparin injections (as well as the cost of the medication) for many months along with the benefit (albeit small).

In working through the issues with the patient, it could be useful to try to get as much information as possible regarding the occurrence of the first episode of DVT in the mother—were there other risk factors that she had that are not present in the daughter? These might include older age at the time of the first pregnancy, obesity, or prolonged immobilization due to preeclampsia, C-section, or post-partum. If the doctor was able to identify such a risk factor, he might use this in bolstering her of the potential risks (e.g., bleeding, low risk of heparin-induced thrombocytopenia) and discomfort of low-molecular-weight heparin injections (as well as the cost of the medication) for many months along with the benefit (albeit small).

The participating trainees are selected by a review process that is based on the candidates’ potential for a successful career in hematology, their home mentoring environment, and the submission of a concept for a clinical protocol. The 20 applicants travel to Dana Point in early August for a week-long intensive course designed to prepare them for their academic careers. Participating faculty, usually in a ratio of 1:1 with the trainees, are encouraged to stay the entire week and interact with the trainees through morning didactic sessions and you faculty-trainee interactions continue over meals, in evening sessions devoted to issues of mentoring and career development, through the presentations of prominent hematologists on relevant aspects of their own careers, and on the veranda over an after-dinner drink. The result has been a truly amazing and enduring bonding of the participants with each other, as well as the faculty. This bond is renewed at the ASH Meeting and the following spring, when participants discuss their progress or problems they have encountered in the ensuing months.

What has been the result of this undertaking over the last five years? We believe that the Clinical Research Training Institute has established an extraordinary group of talented young investigators who will ensure the future of clinical research in hematology. The tremendous enthusiasm that is felt by both the faculty and the trainees is reflected in the very positive assessments obtained at the end of each session.

ASH’s large investment in this initiative, both financial and through outstanding staffing, will continue to further its mission of sustaining hematology through the development of its young members. A better investment cannot be made.
Dr. Anderson has done research work on proteasome inhibitors for multiple, different pharmaceutical companies.
Another Piece in the Antiphospholipid Antibody Syndrome Puzzle


Most patients with the pro-thrombotic condition known as antiphospholipid antibody (APLA) syndrome have circulating autoantibodies reactive with the phospholipid binding plasma protein B2-glycoprotein I (B2-GPI). Although B2-GPI circulates at very high concentrations, it has been studied for many years, its biologic function remains obscure. In this manuscript, a team from the Netherlands has uncovered a potential role for B2-GPl in regulating primary hemostasis. Using two well-established ex vivo assays for platelet glycoprotein Ib complex-dependent binding to von Willebrand Factor (vWF) (ristocetin-induced platelet aggregation and shear stress induced adhesion of resting platelets to immobilized vWF), they found that adding increasing concentrations of B2-GPI inhibited binding to a moderate, but statistically significant, degree. They then used in vitro binding assays to demonstrate that purified B2-GPI binds directly to vWF with affinity well within the range of typical plasma levels. Importantly, B2-GPI did not bind to "native" vWF, but only to the form rendered competent to bind GPIb when vWF is subjected to shear stress or incubated with ristocetin. Recombinant vWF proteins lacking the GPIb-binding A1 domain did not bind B2-GPI, while a mutant A1 domain found in patients with type IIb von Willebrand Disease (vWD) that is constitutively competent to bind GPIb bound B2-GPI even in the absence of shear or ristocetin. To relate their findings to the APLA syndrome, the authors showed that antibody to GPIb binds to plasma vWF circulating in patients with type IIb vWD and that this antibody is autoantibody (as determined by competitive binding to immobilized vWF). The investigators focused on diffuse large-cell lymphoma cell lines where BCL-2 was over-expressed and therefore more likely to respond whereas those with other types of lymphoma lines that contained t(14;18) or did not. The different blocks were confirmed by analysis of BCL-2 proteins that were predicted by the B3H3 peptide. Interestingly, their profiling predicted sensitivity to BCL-2 antagonism by the B3H3 peptide ABT-737. High abundance of BCL-2: BIM complex predicted sensitivity to ABT-737, and further characterization revealed that BCL-2 levels correlated with sensitivity. The investigators took this analysis beyond ABT-737 and treated the lymphoma cell lines with agents that have previously been shown to induce apoptosis through the mitochondrial pathway and confirmed that this model was predictive of relative chemotherapeutic sensitivity beyond inhibitors of B3H3 domains.

Predicting sensitivity and understanding resistance to chemotherapeutic agents in diseases that are biologically similar but molecularly heterogeneous is of critical importance. The investigators focused on diffuse large-cell lymphoma and were able to classify cell lines based upon their sensitivity to B3H3 peptides into groups that had differences in apoptotic block. Although this work was done in cell lines, the authors' findings not only confirmed their ability to profile at the molecular level but also put forth an explanation of why high BCL-2 levels may not uniformly provide protection against chemotherapeutic agents. BCL-2, from their model, would be proposed to be occupied in contrast to cell lines where BCL-2 was over-expressed and therefore largely unoccupied. Because BCL-2 is largely occupied, the cancer cell is felt to be primed for high sensitivity to chemotherapeutic agents. The data using conventional chemotherapeutic agents that use intrinsic apoptotic pathways support the idea that cells primed for cell death are more likely to respond whereas those with other types of blocks are not as likely to respond. The work presented within this manuscript suggests that profiling can be achieved and that sensitivity to ABT-737 can be predicted by B3H3 profiling. More detailed analysis may allow us to learn whether classification will enable us to distinguish sensitivity to different chemotherapeutic agents.

RDY L. SILVERSTEIN, MD
Dr. Silverstein indicated no relevant conflicts of interest.

Priming the Program for Cell Death in Cancer Cells


Cancer cells exhibit molecular changes that potentially could result in apoptosis; however, cancer cells often select for a block in apoptotic signaling that results in survival. BCL-2 family members function and control apoptotic signals in the mitochondria, and the authors probe the mechanism by which BCL-2 family members can be affected to overcome the proapoptotic signals. The work outlined in this manuscript takes a sweeping analysis of the BH3-containing family members and their expression in different lymphoma cell lines and correlates the mechanism of apoptotic block with sensitivity to chemotherapeutic agents. The investigators draw from an array of knowledge about proteins in the BCL-2 family and their specific function in programmed cell death and apply this knowledge to classifying apoptotic block in lymphoma cell lines. Diffuse large B-cell lymphomas that represent the same class of disease but have heterogeneous mechanisms for overcoming apoptotic signals were used as a model in their studies. BH3 peptides were used to distinguish or profile three types of apoptotic block: a) inhibition of upstream activation of BH3-only proteins, b) loss of BAX and BAK so that the effector of apoptosis is lost, and c) expression of antiapoptotic proteins that prevent activation of BAX and BAK ("primed cancer cells"). Different classes of BH3 peptides were used to probe the models and predict the block in lymphoma cell lines that contained t(14;18) or did not. The different blocks were confirmed by analysis of BCL-2 proteins that were predicted by the B3H3 peptide. Interestingly, their profiling predicted sensitivity to BCL-2 antagonism by the B3H3 antagonist ABT-737. High abundance of BCL-2: BIM complex predicted sensitivity to ABT-737, and further characterization revealed that BCL-2 levels correlated with sensitivity. The investigators took this analysis beyond ABT-737 and treated the lymphoma cell lines with agents that have previously been shown to induce apoptosis through the mitochondrial pathway and confirmed that this model was predictive of relative chemotherapeutic sensitivity beyond inhibitors of B3H3 domains.

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LILI PETRUZZELLI, MD
Dr. Petruzzelli indicated no relevant conflicts of interest.
Mutations Forming Subgroups in AML: Just Like Cells, They Are Constantly Dividing and Interacting

As we move beyond a morphologic classification system of acute myeloid leukemia (AML) and into the era of genetic classifications for subgroups of AML, two of the major subgroups that have thus far emerged are those AML patients with disruptions of the core binding factor (CBF) complex and those patients with disruptions of the FLT3 gene.

The FMS-like tyrosine kinase 3 (FLT3) gene is a membrane-bound receptor tyrosine kinase. Many hematopoietic cells produce FLT3 ligand, which promotes dimerization and activation of the receptor tyrosine kinase, FLT3. Similar to many cytokine-signaling pathways, upon activation FLT3 exerts positive effects on a multitude of downstream pathways including Ras and phosphatidylinositol 3-kinase (PI 3-K). There are two major classes of disruptions of the FLT3 gene in AML. Internal tandem duplications (ITDs) in the juxtamembrane domain involve head-to-tail duplication of 3-400 base pairs in exons 14 or 15 (Figure 1). FLT3 ITDs occur in 15 to 35 percent of patients with AML. The other major class is missense point mutations in exon 20 in the intracellular domain at D835. These missense point mutations occur in 5 to 10 percent of patients with AML.2,3

The CBF complex is a transcription factor complex critical for regulation of hemopoiesis and normal myeloid development. Disruptions of the CBF complex, (t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22), constitute AML subgroups with favorable prognosis. The problem exists that in both the FLT3 and CBF groups of patients with AML considerable clinical heterogeneity exists that implies there must be additional biologic or genetic heterogeneity. Three manuscripts, all in the August 15, 2007, issue of Blood, shed new light on these subgroups and also highlight some possible interactions between genetic lesions.

Mead and colleagues screened 1,107 young adult patients with AML for FLT3 ITDs and for FLT3 point mutations (utilizing dHPLC analysis). They found a 23 percent incidence for FLT3 ITDs alone, 8 percent incidence for FLT3 point mutations alone, and, interestingly, 2 percent of patients that had both kinds of FLT3 aberrancies. There was a highly significant difference between patients with FLT3 ITD and patients with an FLT3 point mutation, both in terms of cumulative incidence of relapse and overall survival, with FLT3 ITD patients having a poorer prognosis in all analyses.

Bullinger and colleagues utilized gene-expression profiling to examine 93 AML patients with disruptions in the CBF complex, 55 with inv(16), and 38 with t(8;21). By unsupervised hierarchical clustering, they identified two subgroups of CBF AML patients based on distinct patterns of gene expression. The “unfavorable” subgroup was associated with elevated white blood cell counts and FLT3 ITDs. The gene-expression signatures associated with this “unfavorable” group included proliferative-type genes such as JUN, FOS, and others in the MAPK pathway as well as high-level expression of genes involved in the response to DNA damage and in DNA repair. Conversely, the “favorable” subgroup of the CBF AML patient samples was characterized by prominent gene-expression features of anti-apoptotic pathways.

Overall, these three papers teach us several things. First, that the FLT3 tyrosine kinase can be involved in leukemogenesis by a number of different genetic mechanisms. Secondly, it teaches us that even if it’s the same gene being activated, the different mechanisms for activation can have significantly different phenotypic behaviors. And finally, that the two major subgroups of genetic disruptions in AML (CBF complex and FLT3) can demonstrate interaction in initiating and maintaining the leukemic clone.


Figure 1

MAPK pathway as well as high-level expression of genes involved in the response to DNA damage and in DNA repair. Conversely, the “favorable” subgroup of the CBF AML patient samples was characterized by prominent gene-expression features of anti-apoptotic pathways. Finally, Dicker and colleagues investigated AML1/RUNX1 gene mutations as a part of disruption of the CBF complex. In different patient cohorts they noted a recurring theme of RUNX1 mutations being associated with trisomy 13 independent of the FAB subgroup. Since the FLT3 gene is localized on chromosome 13, they hypothesized that RUNX1 mutations might cooperate with trisomy 13 by increasing FLT3 transcript levels. These results pointed to a potential third type of involvement in AML by FLT3 gene abnormalities, namely, in the absence of ITDs or point mutations, FLT3 gene overexpression could be a third route for FLT3 activation, which could potentially cooperate in leukemic transformation together with RUNX1 (CBF) mutations.
SNP-Chip-Based Genome-Wide Analysis of Genetic Alterations in Hematologic Disorders: The Way Forward?


With the completion of the Human Genome Project and its sister HapMap Project that mapped single nucleotide polymorphisms (SNPs), the last few years have seen a revolution in how information about DNA sequences and genotypic variation are utilized in research. SNP chips, however, offer improved levels of genomic resolution, facilitating detection of both cryptic defects as well as their copy numbers during mitotic recombination but is not detectable by cytogenetic analysis.

Surprisingly, both groups identify a high frequency of segmental losses and additional abnormalities using conventional metaphase chromosome analysis. High-resolution, genome-wide SNP chips, following the example of other high-tech devices, are being increasingly used in association studies of inherited predispositions for both rare and common human diseases. However, three recent studies also highlight their use for the identification of somatic point mutations and cryptic chromosomal lesions in blood disorders when applied to large cohorts of patient samples.

In an important study, Mullighan and colleagues describe an unprecedented-genome-wide SNP analysis of 242 pediatric patients with acute lymphoblastic leukemia (ALL) using high-resolution SNP chips. This newer generation of chips features detections of more than 350,000 loci and permits analysis of copy-number changes at an average resolution of <5kb across the entire human genome. The study identified 54 recurrent somatic regions of deletion, of which 24 contained only a single gene. Further analysis of selected genes from these regions revealed that 40 percent of patients had deletions or mutations in genes that control B lymphocyte development and differentiation, with the PAX5 gene being the most frequent target of somatic mutation (in 31.7 percent of patients). The study also found deletions in additional genes important in B-cell differentiation including EBF1 and IKAROS (IKZF1), suggesting a contribution of these genes to the pathophysiology of B-progenitor ALL.

Though examining a different clonal hematologic malignancy, myelodysplastic syndrome (MDS), two other papers published this year explored the usefulness of SNP chips in studies of acquired genetic imbalances. In MDS, a considerable percentage of patients do not exhibit cytogenetic abnormalities using conventional metaphase chromosome analysis. High-resolution SNP chips, however, offer improved levels of genomic resolution, facilitating detection of both cryptic defects as well as their copy number. In independent studies, Mohamedali et al. and Gondek et al. carried out genome-wide SNP analysis in 119 and 66 cases of MDS, respectively. Surprisingly, both groups identify a high frequency of segmental loss-of-heterozygosity due to UPD, which is not detectable by traditional cytogenetic analysis. UPD results from duplication of one of the parental alleles during mitotic recombination but is not detectable by cytogenetic analysis. UPD was previously found to be common in polycythemia vera and other myeloproliferative disorders, but had not been appreciated in other hematologic malignancies. These three studies confirm the greater power of SNP chips over the cumbersome metaphase-dependent cytogenetics, bypassing the need for laborious low-resolution and costly metaphase examination. It remains to be established whether SNP chips could avoid the need for bone marrow tissue since easily accessible clonal circulating granulocytes may provide the same information as analysis of hematopoietic progenitors.

Taken together, these three pioneering manuscripts show the amazing ability of SNP chips to detect somatic mutations associated with acquired clonal hematologic disorders and demonstrate UPD as one of the most common genetic mechanisms found. These elegant studies highlight the increasing speed, specificity, and power of genome-wide approaches in the systematic search for pathogenic lesions. As the cost of SNP chips has recently dropped to within reach of most laboratories ($250 per sample), and as genome-wide chips are being produced with even higher densities (the current-generation chip contains 1 million SNPs), the way we investigate, diagnose, and stratify therapy for both germ line and somatic mutations will likely be transformed. With these rapidly evolving technologies, the possibility of having the entire 3-billion-base-pair human genome sequence hybridized to a single chip could actually come a lot sooner than we thought.

1. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:616-78.


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YAN-TAT LIU, PhD, and JOSEF T. PRchal, MD

*Dr. Liu and Prochal indicated no relevant conflicts of interest.*

ASH NEWS AND REPORTS

The Hematologist: ASH NEWS AND REPORTS

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Venous Thrombosis Takes Center Stage at ASH 2007

ROY L. SILVERSTEIN, MD
Dr. Silverstein is Chairman of the Department of Cell Biology at the Lerner Research Institute, Cleveland Clinic, Cleveland, OH.

Venous thromboembolism is a common and serious disorder with enormous public health impact. It is becoming increasingly clear that hematologists are well positioned to provide the national and local leadership needed in this field. Along with the usual robust collection of scientific poster and oral presentations related to the mechanisms, diagnosis, treatment, prevention, and epidemiology of venous thromboembolic disorders (VTE), the ASH annual meeting in Atlanta will offer an extraordinary array of special sessions and events that will be notable to anyone interested in the topic.

At 2:00 p.m. on Saturday, December 8, the ASH Standing Committees on Government Affairs and Practice will jointly host a Special Educational Symposium titled “Thrombosis in the Elderly: A Public Health and Scientific Problem of Unrecognized Dimensions.” VTE incidence increases at an exponential rate beginning at about age 50 with annual incidence approaching one in 100 among octogenarians. This session will feature state-of-the-art presentations by four renowned experts. Drs. Mary Cushman, Charles Esmen, Kenneth Bauer, and William Ershler will outline the significance and magnitude of VTE in the elderly; review current knowledge of its epidemiology and pathophysiology; address specific problems faced by clinicians when diagnosing, treating, offering prophylaxis, or designing clinical research for elderly patients; and discuss multidisciplinary approaches used by geriatricians to address the special needs of older patients.

Immediately following the Special Educational Symposium will be a truly unique event hosted by ASH President Andrew Schafer, MD, that will focus on the broader public health and scientific issues relevant to VTE. Melanie Bloom, national patient spokesperson for the Coalition to Prevent DVT and wife of the late NBC correspondent David Bloom, will share her thoughts on the impact of VTE on patients and their families, as well as discuss her efforts to develop a national coalition to prevent DVT. Tanja Popovic, MD, PhD, Chief Science Officer for the Centers for Disease Control and Prevention (CDC), will bring her unique expertise to shed light on the impact of VTE on public health, and Jeffrey Weitz, MD, and David Ginsburg, MD, will provide an update on the latest developments in clinical and basic research in venous thrombosis. This special session will take place at 4:00 p.m.

These exciting sessions serve as prelude to the second annual Special Symposium on the Basic Science of Hemostasis and Thrombosis which will again follow the regular ASH meeting from 1:30 to 5:30 p.m. on Tuesday, December 11. The organizers have put together a spectacular program featuring six invited speakers (Joel Moake, MD; Benjamin T. Kile, PhD; Shahin Rafii, MD; Armin J. Reininger, MD, PhD; Roy L. Silverstein, MD; and Nigel Mackman, MD) spanning all areas of research in hemostasis, thrombosis, platelet biology, and vascular biology, as well as a number of oral presentations selected from the abstracts submitted for the annual meeting. During the session, the most important basic science contributions in 2007 in each of the three major areas of the field (thrombosis, blood coagulation and fibrinolysis, and platelet biology) will be highlighted.

Learning to Live After DVT

MELANIE BLOOM
M s. Bloom is the National Patient Spokesperson for the Coalition to Prevent DVT.

Editor’s Note: This is a compelling example of a disease that all of us take for granted, and we assume or think everyone in the lay public also knows about it. However, as pointed out in this article, 74 percent of Americans have no knowledge about what DVT is. This should reinforce to us the job we need to do as hematologists to educate the lay public. ASH is pleased that Ms. Bloom will be in attendance at this year’s annual meeting and she is very anxious to be a part of the special session on venous thromboembolism.

Four years ago, I received a phone call that changed my life forever. My husband David Bloom, a reporter for NBC News who had been embedded with the 3rd Infantry Division in Iraq, lost his life. But, the killer was not an insurgent’s bullet or an IED explosion; rather the bomb was buried deep inside David’s own body. His death was due to a blood clot.

Prior to David’s death, I had never heard of deep-vein thrombosis (DVT) or pulmonary embolism, and I wasn’t alone. In 2003, I was just one of the 74 percent of Americans who had no knowledge of this condition. For me and millions of patients nationwide, DVT is much more than a nameless and faceless condition. David’s DVT changed my life, but it has also given me a new purpose. Serving as the national spokesperson for the Coalition has allowed me to channel my grief into something positive and transform tragedy into a message of hope. I have learned that helping others is the greatest healer of all.

I continue to be inspired by the many patients who have shared their stories with the Coalition, some with happy endings and some with heartbreaking endings like my own. As I know firsthand, it is both encouraging and comforting to realize that no one is facing this alone. To me, the most inspiring part of being the national patient spokesperson for the Coalition to Prevent DVT is knowing that by getting the message out we can have an impact on others’ lives. After all, how often do we get the chance to do work that can have such a profound effect?

The Coalition to Prevent DVT is a national organization made up of more than 50 representatives from medical societies, patient advocacy groups, and other public health organizations. The organization is dedicated to reducing the immediate and long-term dangers of deep-vein thrombosis and its potentially fatal complication, pulmonary embolism. Ms. Bloom is one of four panelists for the 2007 annual meeting special session on venous thromboembolism. This special session is scheduled for Saturday, December 8, at 4:00 p.m.
Hematology Leaders Honored at 2007 Annual Meeting

E. Donnall Thomas Lecture & Prize

ROBERT THOMAS, MD
Dr. Thomas is Professor and Chief of Hematology-Oncology at the University of New Mexico Health Science Center.

Hal E. Broxmeyer, PhD, hand carried the cord blood to France in 1988 for the first cord blood stem cell transplant in the world. The recipient, a young boy with severe Fanconi anemia, needed these cells obtained at birth from his baby sister to replace his own damaged marrow. The recipient is now a thriving young man. Since then, about 10,000 such transplants have been performed worldwide to treat many malignant and non-malignant disorders.

For showing that cord blood was a source of transplantable hematopoietic stem cells, and for the first processing and cord blood banking industry, Dr. Broxmeyer is the recipient of the E. Donnall Thomas Lecture & Prize this year. For this contribution, he has also won the Karl Landsteiner Award from the American Association of Blood Banks and the Gold Medal of the City of Paris.

Dr. Broxmeyer has also led studies on negative regulators of hematopoiesis and chemokine-controlled trafficking of hematopoietic stem cells. This latter effort produced novel clinical methods of mobilizing peripheral blood stem cells for transplantation. In all, Dr. Broxmeyer has published more than 620 papers. He currently is the Scientific Director of the Walther Oncology Center, and Chair of the Department of Microbiology and Immunology at the Indiana University School of Medicine. He has been a Councillor for ASH, Chair of the NIH Hem-2 Study Section, and President of the ISEH. He also organized the first International Conference on Cord Blood Transplantation. Dr. Broxmeyer’s lecture, “The Road to and Future of Cord Blood Transplantation,” will take place on Monday, December 10, at 9:30 a.m. during the ASH annual meeting.

Dr. William P. Vainchenker, MD, PhD, who is recognized for his seminal contributions to the understanding of the molecular genetics of lymphomas and leukemias, Dr. Croce has had a distinguished career and is currently Professor and Chairman of the Department of Molecular Virology, Immunology, and Medical Genetics and Director of the Human Cancer Genetics Program at The Ohio State University School of Medicine in Columbus. He was among the first to recognize the importance of chromosomal translocations in B-cell neoplasia, opening new avenues of research into genetic mechanisms of disease pathogenesis. Among his many contributions have been the discovery, molecular cloning, and characterization of a number of oncogenes, tumor suppressor genes, and microRNAs, including bcl-1, bcl-2, Tcl-1, and MLL1. Dr. Croce is a member of the National Academy of Sciences and has been recognized by numerous prestigious honors and awards, including the Mott Prize from the General Motors Cancer Research Foundation, and the Pezcoller International Award for Cancer Research and the Clowes Award from AACR. The Henry M. Stratton Medal will be presented to Dr. Croce on Tuesday, December 11, at 9:30 a.m. during the Presidential Symposium.

Sharon B. Murphy, MD
Dr. Murphy is Director of the Greenway Children’s Cancer Research Institute at The University of Texas Health Science Center at San Antonio. Dr. Murphy is also Chair of the ASH Awards Committee.

The 2007 recipient of the Henry M. Stratton Medal is Carlo Croce, MD, who is recognized for his seminal contributions to the understanding of the molecular genetics of lymphomas and leukemias. Dr. Croce has had a distinguished career and is currently Professor and Chairman of the Department of Molecular Virology, Immunology, and Medical Genetics and Director of the Human Cancer Genetics Program at The Ohio State University School of Medicine in Columbus. He was among the first to recognize the importance of chromosomal translocations in B-cell neoplasia, opening new avenues of research into genetic mechanisms of disease pathogenesis. Among his many contributions have been the discovery, molecular cloning, and characterization of a number of oncogenes, tumor suppressor genes, and microRNAs, including bcl-1, bcl-2, Tcl-1, and MLL1. Dr. Croce is a member of the National Academy of Sciences and has been recognized by numerous prestigious honors and awards, including the Mott Prize from the General Motors Cancer Research Foundation, and the Pezcoller International Award for Cancer Research and the Clowes Award from AACR. The Henry M. Stratton Medal will be presented to Dr. Croce on Tuesday, December 11, at 9:30 a.m. during the Presidential Symposium.

Kenneth Keushansky, MD, FACP
Dr. Keushansky is Helen M. Ranney Professor and Chair of the Department of Medicine at the University of California, San Diego. Dr. Keushansky is also President-Elect of ASH.

The 2007 recipient of the William Dameshek Prize is William P. Vainchenker, MD, PhD, who has made an outstanding contribution in hematology during the preceding years. Dr. Vainchenker has had a distinguished career and is currently INSERM Directeur de Recherche Exceptionnel and Director of the INSERM Unit 790, focusing on hematopoiesis and normal and leukemia stem cells at the Institut Gustave Roussy in Villejuif, France. Dr. Vainchenker was among the first investigators to grow megakaryocyte colonies in vitro. He participated in the characterization of the c-Mpl proto-oncogene, contributed to the understanding of the physiology of thrombopoietin and its receptor, and identified the humoral mediators of myelofibrosis. Three years ago, Dr. Vainchenker was the first to identify the JAK2V617F mutation in virtually all patients with polycythemia vera and about half of patients with idiopathic myelofibrosis and essential thrombocythemia. Dr. Vainchenker has received numerous awards from a number of French and international scientific organizations. The William Dameshek Prize will be presented to Dr. Vainchenker on Tuesday, December 11, at 9:30 a.m. during the Presidential Symposium.

Nominate Your Colleagues

Every year, ASH recognizes the achievements of members like Drs. Broxmeyer, Croce, and Vainchenker with prestigious honorary awards. These awards include the William Dameshek Prize, the Henry M. Stratton Medal, and the E. Donnall Thomas Lecture & Prize.

William Dameshek Prize
This award is named for the late Dr. William Dameshek, a past president of the Society. Dr. Dameshek made major contributions to the Society and was the first editor of ASH’s journal, Blood. The Dameshek Prize is to be awarded to an individual who has made an outstanding contribution in hematology during the preceding years.

Henry M. Stratton Medal
The prize is named after the late Henry Maurice Stratton, who made significant contributions to the Society and founded the medical publishing house of Grune and Stratton with Mr. L.H. Grunebaum. The Henry M. Stratton Medal is intended to honor an individual whose contributions to hematology are well recognized and have taken place over a period of several years.

The E. Donnall Thomas Lecture and Prize
This lectureship was created in 1982 and named after the Nobel Prize laureate and past society president E. Donnall Thomas, MD. The E. Donnall Thomas Lecture and Prize is intended to recognize pioneering research achievements in hematology. Award recipients are selected by the Awards Committee with final approval by the ASH Executive Committee. To nominate a candidate for any of these awards, please complete the nomination form located on the ASH Web site at www.hematology.org/education/awards/honorific.cfm. Once completed, the form can be sent to Courtney Krier, Awards Program Coordinator, via e-mail (ckrier@hematology.org), or fax to 202-292-0270. Nominations must be submitted by February 1, 2008, and include all requested information.
Mentors are especially important to the development of anyone pursuing an academic career. Mentors are needed for individuals at all levels of experience, from the trainee to the accomplished full professor. In recognition of the important role that mentors and their mentorship play in individuals’ career development, ASH established the ASH Mentor Award. This prestigious award, now in its second year, was created to recognize the importance of mentoring and the individuals who exemplify the role of “mentor.”

For the purposes of this award, “mentoring” is defined as the process of guiding, supporting, and promoting the training and career development of others. The key roles of a mentor include, but are not limited to, stimulating intellectual growth and career development, being a role model, and providing professional guidance and advocacy. Each year, both a basic scientist and a clinical investigator will be recognized through a competitive and rigorous selection process that includes interviews with several of the individuals that were mentored by the nominee (mentees). The selection of the honorees is based on the training experiences and success of the nominee’s mentees, not on the individual’s career achievements. This year’s ASH Mentor Awards will be presented to Drs. Edward Benz and Harold Roberts.

Edward J. Benz, Jr., MD, is currently on the faculty of Harvard Medical School where he is President of the Dana-Farber Cancer Institute, CEO of Dana-Farber/Partners Cancer Care, and Director of the Dana-Farber/Harvard Cancer Center. He has become a passionate spokesperson advocating the importance of mentoring. Dr. Benz’s mentees describe him as “a consummate scientist, physician, and teacher who leads by example as a research advisor, career counselor, and multi-faceted role model” who “has had a lifelong commitment to medical education—teaching, advising, and nurturing the careers of students, fellows, and junior faculty.” He “has had a transforming role in the lives of his mentees.” Many of Dr. Benz’s mentees still seek his input and guidance regarding significant matters in their careers and personal lives.

Harold R. Roberts, MD, is currently a faculty member at the University of North Carolina (UNC) at Chapel Hill where he has held several leadership roles, including Chief of the Division of Hematology/Oncology, Director of the Center for Thrombosis and Hemostasis, and Director of the Clinical Coagulation Laboratory. He was the founding Director of the UNC Hemophilia Center, which now bears his name. Dr. Roberts taught his mentees “how to think, how to teach, how to communicate with patients, and how to present [their] research.” He is identified as being “the singularly most influential person” in the lives of his mentees and one who nurtures undergraduates, medical students, and faculty at all levels. His mentees state that “he has mentored our lives.”

The ASH Mentor Award will be presented to Drs. Benz and Roberts on Sunday, December 9, at 1:30 p.m. during the 2007 ASH Annual Meeting, allowing proper recognition to be given to these two outstanding examples of what a mentor should be and to celebrate the mentoring that is provided by so many.

Nominations for the 2008 ASH Mentor Award are due on May 5, 2008. The application is posted on the ASH Web site. International members are eligible to receive the ASH Mentor Award.
Maxwell Myer Wintrobe: Influential Teacher in the Field of Hematology

JAMES P. KUSHNER, MD

Dr. Kushner is the Maxwell M. Wintrobe Distinguished Professor of Medicine at the University of Utah School of Medicine.

Maxwell M. Wintrobe became a hematologist before the discipline of hematology existed. In 1925, he received his medical degree from the University of Manitoba in Winnipeg, Canada, where he graduated first in the class. Following his internship and a medical-biochemistry fellowship at the University of Manitoba, he accepted a faculty position at the Medical School at Tulane University in New Orleans. At the time, Chief of Medicine John Musser, Jr., MD, was an editor of the Textbook of Medicine. He asked Dr. Wintrobe to write the section on “Diseases of the Blood.” This request set the stage for Dr. Wintrobe to enter an extremely productive research career in hematology. While at Tulane, he developed the now-famous Wintrobe Hematocrit Tube. He realized that there were no published, reliable, normal blood values to use in clinical practice. He was the first to document statistically normal values in adults and children. An important part of this effort was the derivation of the red blood cell indices that remain in wide use. From these indices, Dr. Wintrobe classified anemia morphologically as microcytic, normocytic, or macrocytic, a classification that has been in continued use ever since. Dr. Wintrobe earned a PhD at Tulane (His thesis title was The Erythrocyte in Man.) and became intensely interested in the nutritional requirements necessary for effective erythropoiesis. His PhD work formed the basis of later studies establishing the role of pyridoxine as a cofactor for amino acid synthesis and for studies defining the important roles of iron and copper in the development of the red cell.

Dr. Wintrobe was recruited to the faculty at Johns Hopkins University School of Medicine in 1930 and remained there for 13 years. While there, he continued to be a productive investigator. He correctly recognized the Mendelian mode of transmission of Cooley’s anemia and described the phenotype of thalassemia minor. He was the first to characterize the nature of cryoglobulins and did pioneering studies establishing clinical phenotypes and laboratory abnormalities in a wide variety of hematologic disorders. While at Johns Hopkins, he published the first edition of Clinical Hematology. This was a single-authored, exhaustively and meticulously referenced 792-page textbook. For the first six editions of Clinical Hematology, Dr. Wintrobe remained the sole author and it was not until the 7th Edition that five of his former fellows were appointed as co-editors.

In 1943, Dr. Wintrobe left Johns Hopkins to become the University of Utah’s first Chair of Medicine at the newly formed four-year medical school. He recruited a small but outstanding faculty including his long-term partner in research, Dr. George Cartwright. Dr. Wintrobe did important studies on the effects of nitrogen mustard, folate antagonists, and adrenocortico steroids on the hematopoietic system. He was one of the first to recognize the potential of chloramphenicol to produce aplastic anemia. He and Dr. Cartwright were the first to characterize the anemia of chronic inflammation and demonstrate the associated abnormalities of iron metabolism. He was awarded the first extramural grant funded by the NIH for the study of muscular dystrophy and inherited disorders of the blood. He established one of the country’s earliest hematology training programs, a program from which more than 80 percent of the fellows trained went on to develop careers in medical schools and research institutes around the world. He demanded much of his trainees, but never more than he demanded of himself. He was firm but fair and praised only those whose performance was exceptional. His unwavering commitment to excellence made him intolerant of mediocrity. He never wasted a moment at work, but he knew how to relax. He was an avid skier and established a tradition of skiing at Alta with the fellows and faculty on Wednesday afternoons. All who skied on Wednesdays were expected to work a full day on Saturdays. He appreciated the fine arts, especially music. He enjoyed playing the violin and often participated in evenings of chamber music with fellows and faculty. Musical skills were considered a positive attribute in fellowship candidates and probably tipped the balance for many.

Dr. Wintrobe served as President of the American Society of Hematology in 1972. He also served as President of the Association of American Physicians and the Association of Professors of Medicine. In 1973, he was elected to the National Academy of Sciences and the University of Utah named him Distinguished Professor of Internal Medicine, the highest academic rank achievable in the School of Medicine. He died of heart failure in 1986 at the age of 85, ending six decades of outstanding clinical research and teaching. Dr. Wintrobe had no mentors and no formal scientific training in hematology; his work was responsible for establishing hematology as a subspecialty. His textbook, Clinical Hematology, remains one of the most authoritative in the field. He had a favorable and profound influence on countless medical students, residents, and hematology fellows, as they have in turn had on their students. This was, perhaps, his most profound and enduring contribution to the field.

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Above, top: Dr. Wintrobe practices with his violin.
Below: Dr. Wintrobe skiing at Alta.
The ASH Web site (www.hematology.org) offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH.

Read about the latest hematology drug approvals from the FDA.

- On September 19, the FDA APPROVED ALEMTUZUMAB for the Treatment of B-CLL (www.hematology.org/policy/resources/fda/09202007.cfm).
- On September 6, the FDA APPROVED DEIXRAZOXANE HYDROCHLORIDE for injection (www.hematology.org/policy/resources/fda/09072007.cfm).

Preparing for the annual meeting in December? Get the most up-to-date information about ASH’S 49TH ANNUAL MEETING AND EXPOSITION (www.hematology.org/meetings/2007).

Search through job listings or post your own position on the ASH JOB BANK (www.hematology/education/jobs). Subscribe to the RSS feed to be notified of new postings.

Read THE HEMATOLOGIST ONLINE (www.hematology.org/publications/hematologist) and catch up on the latest news in the field of hematology right on your desktop.