ASH Adds New Features to Enhance Collaboration and Interaction at the 2013 Annual Meeting

Although it’s mid-summer, it’s not too early to begin planning for the ASH 55th Annual Meeting and Exhibition (in New Orleans, LA, December 7-10). For those who have been to the meeting previously, you will notice exciting changes this year’s agenda. If this is your first meeting, there are programs that have never been offered previously, so your timing is excellent. For instance, the Trainee Day curriculum has been completely redesigned; the Education Program will have a translational component in each session aimed at meeting the needs of practicing physicians and trainees; and the Scientific Posters will offer Special Symposia focusing on cutting-edge sub-disciplines of hematology, with the goal of bringing together scientists with overlapping interests who might not otherwise interact. On the logistic front, ASH has in place new strategies to reduce some of the nuisances associated with attending a large meeting in a big convention center, including remote viewing lounges that will allow participants to “attend” popular sessions at designated sites within the convention center and overflow rooms that will provide access to lectures even if the session meeting room is full. Look for enhancements in the popular mobile meeting app and for improvements in information distribution through social network sites.

In Celebration of Wallace H. Coulter
A Special Symposium on Innovation and the Future of Hematology will mark the 100th anniversary of the birth of Wallace H. Coulter. The Symposium is scheduled for Sunday afternoon, December 8. As many know, Mr. Coulter developed the method for counting and sizing microscopic particles suspended in fluid. His invention of the Coulter Counter revolutionized the practice of laboratory hematology, and the principles that he elucidated guided development of another indispensable tool of modern hematology – flow cytometry.

This Special Symposium will feature two accomplished translational scientists, Stuart H. Orkin, MD, Harvard Medical School and Dana-Farber Cancer Institute, and Bruce A. Beutler, MD, University of Texas Southwestern Medical Center in Dallas and UT Southwestern. Dr. Orkin and Dr. Beutler will discuss how novel concepts and technologies are poised to revolutionize hematology in the future.

We asked the current chair of the Committee on Training Programs and the 2013 co-chairs of the Education and

(Cont. on page 2)
ASH's strengths are our diversity and that we are a single voice for a broad field. However, while ASH continues to provide resources and services for hematologists in all areas, the enormous growth in the size of the annual meeting has made it increasingly more difficult to maintain a sense of community among our various smaller, sometimes distinct and sometimes overlapping, constituencies. ASH's leadership is committed to ensuring that these communities persist and thrive.

This past fall we conducted an email survey of membership. Thirty-four percent of you responded, representing a broad spectrum of interests. At the ASH Executive Committee spring retreat, we looked closely at what you said. You value ASH and especially the annual meeting. Since the best hematology science and best clinical research are presented, ASH is the natural and supportive home for translation in hematology. But there were repetitive concerns such as the meeting is too big, that it is too difficult to navigate, and that your specific subgroup interest (e.g., hemostasis/thrombosis, hematopathology, transfusion medicine, hematologic malignancies, red cells, pediatric hematology) was not specifically prioritized. This led us to consider how we might ensure that ASH (as a meeting and a society) better serve the communities and sub (sub) communities that we are.

Here are some plans for December 2013: We have committed to having a better geographic coordination of topics at the annual meeting so that like sessions are nearby, allowing for more seamless transitions between abstract presentations. Tables and chairs will be grouped outside sessions on similar topics to encourage informal conversations among attendees with similar interests. In addition, the format of the Scientific and Education sessions will be consistent (with questions following each talk) so that timing between sessions is concordant.

Although more tables and chairs throughout the meeting venue will benefit networking among all communities, different groups have different needs. For example, the myeloid biology research community hosts a Friday workshop where scientific ideas are presented in a five-minute rapid-fire format and then discussed. We plan to invite other science subgroups to apply for similar support. Please visit www.hematology.org/FSW for the application forms.

Most importantly, however, we want to hear from you. While the member survey shows an overall high rate of satisfaction with ASH, we know that more can be done. We want to better understand how you identify with communities within the organization, the value you derive from these relationships, and how ASH can foster these smaller groups to flourish within the larger organization. We will be soliciting feedback from the membership on this issue in mid-July. Please respond with concrete suggestions — not about how you as an individual might be better served, but about how ASH might help your subset group(s) both at the annual meeting and throughout the year.

We will use what we learn to develop a proactive strategy to strengthen this valuable aspect of ASH membership. Creativity is encouraged! We look forward to piloting the best ideas, much as we did with the myeloid workshop, and when successful, the new activity will serve as a model for other communities.

Janis L. Ackowitz, MD

Maintaining a Sense of Community Within ASH

ASH Adds New Features to 2013 Annual Meeting

Scientific Programs to give their perspectives on this year’s annual meeting program. Below are their insights.

Training Events

Trainee Day will have an entirely new curriculum. The major emphasis of this year’s program is on support of trainees interested in a career in academic hematology. Didactic sessions will focus on clinical trial design and tools for statistical analysis, while breakout sessions will provide attendees with detailed information on mechanisms of funding, guidance on management of a research team, and insights into career development, including how to locate job opportunities in hematology, how to interview for a position, and how to negotiate a contract. These sessions are intended for both MD and PhD trainees, and the program is diversely populated with speakers from basic science as well as translational and clinical research.

The program for trainees also includes a separate session designed for junior faculty development, titled “Which Grant is Right for Me?” which will inform participants, in detail, about the range of available career-development grants and will provide experienced guidance on how to prepare an application for a mentored award. When resubmitting an application that was not funded initially, the importance of responding appropriately to reviewers’ critiques cannot be over-emphasized. Accordingly, a session devoted specifically to that topic will feature speakers with decades of experience as both applicants and reviewers.

The Careers Development Lunch Program on Saturday, December 7, is the best way to get personal mentoring and career counseling. Tables will be designated for attendees interested in clinical, translational, and basic research as well as in hematopathology, transfusion medicine, and positions in industry. For trainees interested in careers in government, both the FDA and the NIH will be represented at the Career-Development Lunch. These events are intended for both MD and PhD trainees, with other parts of the program aimed primarily at career development for PhD scientists, including a session titled “Bridging the Translational Divide: The Role of the PhD.” Several Trainee Didactic Sessions are offered on Sunday. These sessions will include talks on Time Management and Balance, Practical Biostatistics, and Giving a Scientific Presentation.

— Gary Schiller, MD, David Geffen School of Medicine at UCLA

Education Program

A goal of the Education Program is to ensure that attendees are updated on the most important developments in hematology so that they can deliver state-of-the-art care to their patients and communicate to colleagues and students the progress being made in the field. With this goal in mind, a number of lectures will focus on the newest therapies, and a special effort has been made to include a translational component in each of the sessions. In addition, we have added several new Education Program sessions including one on genomics for the practicing hematologist and one on drug development in hematology. Other new sessions are designed to span multiple disciplines. For example, the program includes a session focused on the relationship of infectious agents to the pathogenesis of hematologic malignancies.

The Education Program also includes a variety of new Spotlight Sessions. Each 90-minute session will be presented in a small-vessel format for approximately 150 ticketed attendees. Speakers will discuss the topic with ample time reserved for audience questions and participation. The topics range from debates about the place of the newest anti-coagulants in our therapeutic armamentarium, to the implementation of transplantation programs in the developing...
John H. Kersey, MD (1938-2013)

J

ohn H. Kersey, a pioneer in bone marrow transplantation and studies of childhood leukemia, died suddenly in March at the age of 74. John obtained his MD from the University of Minnesota where he was a lifetime faculty member. He had several legendary mentors, including Robert Good, Carlos Martinez, Bill Krivit, and Mark Nesbit. John dedicated his professional career to the integration of laboratory research with bedside care, always remembering that patients should be the beneficiaries of research.

John had an infectious enthusiasm for the translation of preclinical science to the bedside. He was an inspiration for two generations of hematologists/oncologists and transplant physician-scientists, at Minnesota and elsewhere, who embraced his mission and now continue his legacy. His published work encompassed studies of bone marrow engraftment and graft-versus-host disease, as well as the immunophenotypic and molecular characterization of pediatric hematologic malignancies. He pioneered the first successful allotransplants for lymphoma, developed the important clinical model of prospectively analyzing transplant efficacy by comparing outcomes in patients undergoing high-dose chemotherapy followed by stem cell rescue with those who were transplant-eligible but lacked a donor, and authored a landmark report comparing the results of autologous-transplanted marrow grafts with sibling donor allografts for acute lymphocytic leukemia.

In addition to serving as councilor on the Executive Committee of ASH and as associate editor for Blood (1988-1992), John was elected president of the International Society for Experimental Hematology and the American Society for Blood and Marrow Transplantation. He also served on the National Cancer Institute (NCI) Board of Scientific Counselors and was chair of the Scientific Advisory Committee of the Children’s Oncology Group. Recognizing the need for organized multidisciplinary cancer research and care, he was! the founding director of the University of Minnesota Masonic Cancer Center, which became an NCI-designated Comprehensive Cancer Center in 1998. He was the recipient of NIH funding continuously from 1977 to the present during which time he received an Outstanding Investigator Award from the NCI.

With his engaging persona, John led colleagues and trainees on a quest for discovery that spanned five decades. Through it all, his investigation was guided by thoughts of patients whose diseases were incompletely understood and whose care was imperfect.

–Tucker W. LeBien, PhD; Bruce R. Blazar, MD; Daniel J. Weisdorf, MD; and Gregory M. Vercellotti, MD
University of Minnesota

The Hematologist Editor Search Announcement

The American Society of Hematology is in the initial stage of the search process for the next Editor-in-Chief of The Hematologist (term: 2015-2017).

Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills.

Members of ASH are invited to submit the names of potential candidates, accompanied by a brief, informal endorsement and a short description of the candidate’s editorial experience. Self-nominations are also welcome. Please send materials to:

The Hematologist: ASH News and Reports
c/o Karen Learner, Managing Editor
American Society of Hematology
2021 L Street, NW, Suite 900
Washington, DC 20036
klearner@hematology.org

Deadline to receive applications is September 3.

CORRECTIONS AND UPDATES: May/June 2013

The authors’ titles in the Mini Review, “Inhibition of B-Cell Receptor Signaling as a Therapeutic Strategy for Treatment of CLL” were inadvertently switched. Dr. Daphne Friedman is Instructor, Hematologic Malignancies and Cellular Therapy, at Duke University Medical Center. Dr. Bruce Weinberg is Professor of Medicine and Immunology at VA and Duke University Medical Centers.

On page 13, Dr. Margaret Ragni’s Clinical Trials Corner article title should have read: “Factor VII and IX: Making a Long-Lasting Impression.” Factor VII should not have been listed.

Since publishing the content about the new Physician-Scientist Career Development Award on page 3, there have been updates made to the eligibility criteria. Instead of being open to medical students between either their first and second or second and third years of medical school, it is now open to students between their first and second, second and third, or third and fourth years of medical school. Get more information about this award at www.hematology.org/Awards/Physician-Scientist-Career-Development-Award/9239.aspx.

ASH Members Named Fellows of the American Academy of Arts and Sciences

Joseph Loscalzo, MD, PhD
Hershey Professor of the Theory and Practice of Medicine (Physiology), Chair, Department of Medicine, Harvard Medical School; Physician-in-Chief, Brigham & Women’s Hospital

Charles J. Sherr, MD, PhD
Investigator, Howard Hughes Medical Institute; Herrick Foundation Chair, Member and Chair, Department of Tumor Cell Biology, St. Jude Children’s Research Hospital

Bruce Alan Butler, MD
Director, Center for the Genetics of Host Defense, Regental Professor, Raymond and Ellen Willie Distinguished Chair in Cancer Research, University of Texas Southwestern Medical Center

ASH Member Named to the National Academy of Sciences

Louis M. Staudt, MD, PhD
Deputy Chief, Metabolism Branch, Center for Cancer Research, National Cancer Institute

world, to a session focusing on psychosocial, economic, and therapeutic challenges that are faced by both clinicians and patients who must deal with the life-altering consequences of advanced hematologic malignancies.

The quality of the Education Program depends on excellence of the lecturers. We are particularly enthusiastic about this year’s group of speakers that includes rising young stars whose enthusiasm will complement the experience of our well-established leaders.

– Wendy Stock, MD. The University of Chicago and John Tisdale, MD, National Heart, Lung, and Blood Institute, National Institutes of Health

Scientific Program

A cross-section of Scientific Program sessions has been chosen for additional audience interaction with the session speakers in a format called “Continuing Conversations: Strategies to Address the Next Questions.” The program will be organized as a round-table discussion with the session speakers led by the session chair. The topics of 2013 Continuing Conversations are: Non-Coding RNAs in Normal and Malignant Hematopoiesis, Targeting Apoptosis in Lymphoid Malignancies, Histone Modifications in Normal and Malignant Hematopoiesis, and Platelets and Cancer. Tickets are limited and only available on site on a first-come, first-served basis. There is no additional fee; however, only one ticket per person is allowed.

To further increase the breadth of the science presented at the meeting, we have organized additional Special Scientific Symposia featuring international experts in cross-cutting scientific disciplines. These cross-disciplinary symposia are intended to cover topics of interest to more than one of ASH’s scientific constituencies. The topic for this year’s Special Scientific Symposium in non-malignant hematology is “Redox in Hematology.” This topic was chosen because redox/oxidation chemistry touches many areas of hematopoiesis, but it is not often discussed in a way that provides unifying themes that allow for broader understanding among investigators whose interest may be more narrowly focused. The Special Scientific Session in malignant hematosis is titled “Approaches for Inhibiting ‘Undruggable’ Targets in Cancer” and features presentations on approaches to therapeutically targeting RAS oncogenes and the p53 tumor suppressor in cancer.

With much enthusiasm, we announce the creation of a new Ad-Hoc Scientific Committee on Epigenetics and Genomics, chaired by Ross Levine, MD, of Memorial Sloan-Kettering Cancer Center. The inaugural program titled “Histone Modifications in Normal and Malignant Hematopathology” will focus on the role of epigenetic modifications in normal and malignant hematopoiesis, including a review of recently discovered DNA and histone modifications that affect gene expression, self-renewal, and transformation. For the first time, the Scientific Program will feature Epigenetic Spotlight Sessions. Similar to the Education Spotlights, these sessions are intended to focus on areas of special interest and, in some cases, address controversies in hematology. They are ticketed events, the intent being to limit attendance and thereby provide a more intimate environment for discussion. Two malignant and two non-malignant sessions are planned for this year’s meeting.

– Kevin Shannon, MD, University of California – San Francisco, and José López, MD, Puget Sound Blood Center, Seattle, WA

The four-day annual meeting program will provide attendees with the opportunity to learn about the latest progress in the field and to connect with colleagues and friends within the hematology community. Member registrations and a housing reservation requests can be made at the same time. The abstract submission deadline is August 14. More information will be posted in the coming months. Plan to check www.hematology.org/annualmeeting_info for updates.

This article has been edited for space. Read the full article at www.hematology.org/annualmeeting2013.
Ask the Hematologists

HUY P. PHAM, MD, AND STEVEN L. SPITALNIK, MD,1
1. Transfusion Medicine Fellow, Department of Pathology and Cell Biology, Columbia University and the New York-Presbyterian Hospital
2. Professor and Vice-Chairman for Laboratory Medicine, Department of Pathology and Cell Biology, Columbia University Medical Center and the New York-Presbyterian Hospital

The Question
What is your approach to the diagnosis and management of transfusion-related acute lung injury (TRALI)?

Our Response

Epidemiology
The blood supply in the United States is safe. Although non-life-threatening adverse events such as allergic and febrile transfusion reactions are encountered regularly by clinicians, transfusion-related fatalities are rare. From 2007 through 2011, 212 fatalities following blood collection and transfusion were reported to the FDA.1 Non-infectious complications pose the greatest mortality risk to the transfused patient with TRALI accounting for 43 percent of deaths and hemolytic transfusion reactions due to ABO (10%) and non-ABO (33%) incompatibility accounting for 23 percent.2 In comparison, 11 percent of transfusion-related deaths were due to microbial infections. Although usually associated with infusion of blood products containing high volumes of plasma (e.g., fresh-frozen plasma and platelets), TRALI has also been linked to red blood cell transfusions. Estimates of the incidence of TRALI as an acute event vary from 0.01 to 0.3% of transfusions.3

Pathophysiology
Although the exact mechanism of TRALI is uncertain, a "two-hit" process has been proposed.4 According to this hypothesis, the first “hit” is induced by an underlying condition, such as trauma or sepsis, which primes granulocytes and/or activates endothelial cells, thereby causing neutrophils to become sequestered in the pulmonary vasculature. The second “hit” results from passive infusion of donor antibodies in the blood product that recognize either human leukocyte antigens (HLA) on recipient endothelial cells or human neutrophil antigens (HNA) on recipient neutrophils. Alternatively (or in addition), infusion of biologic response modifiers (e.g., CD40 ligand) in the plasma portion of the donor product could induce the second hit. Together, these processes induce capillary endothelial damage, resulting in vascular permeability and pulmonary edema.5

Clinical Presentation and Diagnosis
The diagnosis of TRALI is made on clinical grounds, and no single laboratory or radiologic test definitively identifies or excludes this entity. We currently use the criteria and case definitions proposed by a Canadian Consensus Conference (Table).3 Thus, TRALI is an acute event presenting during a transfusion or within six hours of its completion. Characteristic signs and symptoms include fever, chills, dyspnea, hypoxemia, hypotension (or potential transient hypertension), and the new onset of bilateral non-cardiogenic pulmonary edema (e.g., chest x-ray showing bilateral alveolar and interstitial infiltrates in the absence of cardiomegaly). TRALI is often associated with transient leukopenia or neutropenia. A diagnosis of “Possible TRALI” is made based on the same criteria as TRALI except that an alternative risk factor for acute lung injury is present concurrently (Table).

The differential diagnosis of TRALI includes the following: transfusion-associated circulatory overload (TACO), anaphylaxis, and sepsis.6 Distinguishing TACO from TRALI may be challenging because some of the signs and symptoms of the two entities overlap; in addition, the two processes can occur concurrently in a given patient. The key difference between these two conditions is the pathophysiologic origin of the pulmonary edema (i.e., cardiogenic in the case of TACO and non-cardiogenic in the case of TRALI). Thus, clinical improvement after treatment with a diuretic and/or an inotropic agent is characteristic of TACO, but not TRALI. Other findings suggestive of TACO include persistent hypertension, a post-transfusion brain natriuretic peptide (BNP) level of at least 100 pg/mL, and a post-transfusion/pre-transfusion BNP ratio of >1.5.7 Although anaphylaxis can present with hypotension, cyanosis, and hypoxia due to bronchospasm and laryngeal edema, the absence of fever and pulmonary edema distinguish this process from TRALI. Although transfusion-induced sepsis, particularly after a platelet transfusion, typically presents with pyrexia and hypotension, respiratory distress is an infrequent complication. Other entities, such as myocardial infarction, pulmonary embolism, and other causes of acute lung injury share clinical features with TRALI and should be considered in the differential diagnosis.

Pathophysiology
Although the exact mechanism of TRALI is uncertain, a “two-hit” process has been proposed. According to this hypothesis, the first “hit” is induced by an underlying condition, such as trauma or sepsis, which primes granulocytes and/or activates endothelial cells, thereby causing neutrophils to become sequestered in the pulmonary vasculature. The second “hit” results from passive infusion of donor antibodies in the blood product that recognize either human leukocyte antigens (HLA) on recipient endothelial cells or human neutrophil antigens (HNA) on recipient neutrophils. Alternatively (or in addition), infusion of biologic response modifiers (e.g., CD40 ligand) in the plasma portion of the donor product could induce the second hit. Together, these processes induce capillary endothelial damage, resulting in vascular permeability and pulmonary edema.

Based on this proposed mechanism, one might hypothesize that the incidence of TRALI would be higher for plasma-rich transfusion products and that the incidence would be lower when plasma derived from female donors (who have a higher prevalence of anti-HLA antibodies) is restricted; available data support these two hypotheses. In addition, recent studies indicate that circulating platelets are involved in TRALI pathophysiology, suggesting that anti-platelet therapy may be beneficial clinically.

Management
The first step in managing any suspected transfusion reaction is to stop the transfusion. Once the patient is stabilized, the episode should be reported to the transfusion medicine service so that a transfusion reaction evaluation can begin. Because hemolytic transfusion reactions are associated with significant morbidity and mortality, the transfusion medicine service will first perform a “clerical check” to ensure that the correct unit was transfused into the correct patient. Next, the ABO type of the patient and the transfused unit will be confirmed, the post-transfusion blood sample will be inspected for viable evidence of hemolysis, and an indirect and direct anti-globulin test will be performed on the post-transfusion sample to determine if circulating and/or red blood cell-bound antibodies are present. Additional laboratory tests to investigate for hemolysis, including a complete blood count, urinalysis, and plasma concentration of bilirubin, lactate dehydrogenase, and haptoglobin, are often needed. To diagnose TRALI, physical exam, chest x-ray, and arterial blood gas studies are recommended. In distinguishing TRALI from TACO, an echocardiogram may be useful in determining whether the observed pulmonary edema is of cardiogenic origin. Other causes of adverse events that share clinical features with TRALI (e.g., sepsis, myocardial infarction, and pulmonary embolus) should be promptly investigated.

Current management of TRALI consists of respiratory and circulatory support based on clinical severity. Oxygen supplementation is required in almost all patients; in severe cases, mechanical ventilation may be necessary. Hypotensive episodes can be treated with pressors. Corticosteroid treatment has not improved outcome.8 In theory, the non-cardiogenic pulmonary edema of TRALI should not respond to diuresis. Most patients improve within two to three days, but those who do not improve over this period typically have a protracted clinical course or a fatal outcome.

Patients who have experienced an episode of TRALI are not at greater risk for a second episode, assuming that the initial event was a consequence of infusion of donor antibodies that were present in the transfusion product and that subsequent blood products do not come from the initial donor. However, notification of the transfusion medicine service about a possible TRALI episode has important implications for the donor and the safety of the blood supply. If TRALI is suggested by both clinical presentation and laboratory results (e.g., finding anti-HLA and/or anti-HNA antibodies in the transfused blood product that match the corresponding antigens in the patient), the donor must be evaluated for consideration of their continued eligibility to donate. Indeed, many centers choose to exclude such donors permanently. The product from a particular donor caused an episode of TRALI may be difficult to prove unequivocally, however, because patients often receive products from multiple donors.

Prevention
Approaches to reducing the risk of TRALI have included avoiding the use of plasma from female donors, using plasma derived only from males or from never-pregnant females, and testing female donors for anti-HLA antibodies.9 Although these measures reduce the incidence, they do not completely eliminate risk because TRALI can be induced by other blood products (e.g., red blood cells, platelet concentrates, cryoprecipitate). In addition to avoiding the

Table 1: Canadian Consensus Conference on the Definition of TRALI

TRALI:
1) Acute lung injury
   a. Acute onset
   b. Hypoxemia
   i. Research setting: PaO2/FI02 < 300 and/or SpO2 < 90% on room air
   ii. Non-research setting: PaO2/FI02 < 300 and/or SpO2 < 90% on room air
   c. Bilateral infiltrates on frontal chest x-ray
   d. No evidence of left atrial hypertrophy (i.e., no circulatory overload)
2) No pre-existing acute lung injury before transfusion
3) During or within 6 hours of transfusion
4) No temporal relationship to an alternative risk factor for acute lung injury

Possible TRALI:
1) Acute lung injury
2) No pre-existing acute lung injury prior to transfusion
3) During or within 6 hours of transfusion
4) A clear temporal relationship to an alternative risk factor for acute lung injury

use of high-risk blood products, conservative transfusion strategies and interventions that address the “first hit” could also help reduce TRALI incidence. Nonetheless, TRALI continues to be the most common cause of transfusion-related mortality, making rapid recognition and institution of appropriate supportive care imperative.1,7

1. Fatalities reported to FDA following blood collection and transfusion: annual summary for fiscal year 2011. www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatilities/discretionary spending level at $966 billion and shifted allocations such that non-defense discretionary accounts will absorb all of the spending cuts mandated by the second year of sequestration. In contrast, Senate Appropriations Committee Chair Barbara Mikulski (D-MD) has indicated that she is committed to writing spending bills that total $1.058 trillion, the amount both agreed to in the Budget Control Act and requested by President Barack Obama in his FY 2014 budget proposal. As a result of this nearly $90 billion difference, the House and Senate bills are certain to be widely divergent, making finalizing a funding bill challenging, if not impossible, unless a compromise agreement is brokered later in the fall. Both the House and Senate Appropriations Committees intend to consider the majority of the spending bills by August 2, the date on which Congress adjourns for a month-long recess.

What’s the takeaway?
As Congress continues to formulate the FY 2014 budget, the Society encourages all ASH members to visit the ASH Advocacy Center (www.hematology.org/takeaction) and take action in support of funding for NIH in FY 2014. Senators and representatives need to hear from their constituents about the negative impact that cuts in funding have had (and will continue to have) on hematology research. To find the latest information about the FY 2014 budget and its potential impact on NIH, please visit www.hematology.org.

Congress Working on Legislation to Reform Physician Payment; ASH Advocates for a Minimum of Five Years of Congressionally Mandated Stable Payment

Republicans in the House of Representatives recently released a detailed version of their proposal for repealing the Sustainable Growth Rate (SGR) formula and plan to move forward with a vote this summer. ASH submitted comments in response to the proposal indicating the Society’s support for repealing the SGR and replacing the current payment formula with predictable payment rates for at least five years while stakeholders develop a new system that combines a base payment rate with a variable rate tied to performance parameters.

The Senate Finance Committee has also sought input from ASH and other health-care providers and groups on how to reform Medicare physician payment, and there appears to be room for optimism. Unlike previous years when only short-term patches were passed, policy analysts expect that legislation to reform Medicare payment is likely to be completed this year. Two factors have influenced this position shift: the cost estimate for repealing the SGR has been reduced significantly, and Members of Congress have finally come to understand that the current system, which has scheduled significant payment cuts each year, is not sustainable.

What’s the takeaway?
Members of the ASH Committee on Practice met with congressional offices in April to advocate for appropriate and stable Medicare physician reimbursement. ASH clinicians are strongly encouraged to join the Society’s online advocacy campaign (www.hematology.org/takeaction) urging Congress to repeal the current payment formula and provide appropriate Medicare reimbursement to physicians.

Oral Cancer Drug Parity Legislation Introduced in Congress; ASH Advocates for Patients to Have Equal Access to Treatment

Representative Brian Higgins (D-NY) and Peter King (R-NY) have introduced bipartisan legislation, the Cancer Drug Coverage Parity Act (H.R. 1801), in the U.S. House of Representatives that would ensure that patients enrolled in certain federally regulated health plans have access and insurance coverage for all anti-cancer regimens. The bill would require any health plan that provides coverage for cancer chemotherapy treatment to establish a reimbursement rate for orally administered and self-injectable medications that is no less favorable than that used for payment of port-administered or injected drugs.

Rep. Higgins introduced similar legislation in the 112th Congress, but the bill was not considered in committee or by the full House. Senator Al Franken (D-MN) has expressed an interest in introducing a bipartisan companion bill to the Cancer Coverage Parity Act in the Senate. A number of states have already passed payment parity bills or are currently reviewing related legislation.

What’s the takeaway?
While legislation will not solve the problem of the high cost of drugs, it does seek to lift the economic burden from patients. ASH supports this legislation and encourages members to join ASH’s advocacy campaign (www.hematology.org/takeaction) urging Congress to support oral cancer drug payment parity.
Inside TRTH

DAVID SYKES, MD, PHD, AND FABIENNE MCCLANAHAN, MD

1. Assistant in Medicine at Massachusetts General Hospital and Instructor of Medicine at Harvard Medical School
2. PhD Student, Centre for Haemato-Oncology, Barts Cancer Institute, University of London

This year marks the fourth anniversary of the Translational Research Training in Hematology (TRTH) program, a joint venture between the American Society of Hematology (ASH) and European Hematology Association (EHA). The yearlong teaching and mentoring program was developed to support and encourage careers in translational hematology.

The 2013 spring course brought together an international cadre of 20 trainees and 16 faculty members who met at the Villa Gallarati Scotti, a picturesque Italian villa-turned-conference-center outside of Milan. Once the gates of the estate closed behind the airport shuttles, we were cloistered for six days during which we were immersed in formal didactic sessions and intense small-group discussions, interspersed with lively, informal mentoring events.

Introductions were made over a welcome luncheon where the initial advice from the faculty focused on how to operate the intimidating espresso machine and how to avoid the temptation of the plentiful and delicious Italian desserts. We had come prepared with brief presentations and thus spent our first afternoon outlining our research projects and answering enthusiastic questions from other trainees. Fueled by caffeine and cookies to stave off jet lag, we universally exceeded the 15 minutes assigned to each presentation, and this initial session lasted well into the evening. Dinner was a boisterous affair as faculty and trainees followed up on questions and got to know each other.

Members of the trainee group originally hailed from North America, Europe, Israel, and the Philippines. (All 20 are currently residing in either the United States, United Kingdom, Germany, or Sweden.) Among the 10 women and 10 men that composed the group were 11 MDs, 5 MD/PhDs, and 4 PhDs, all working on clinically oriented, laboratory-based projects. The faculty was a star-studded cast of hematology (see photo top page 7) that included past and present editors of Blood and Hematologica, as well as past presidents of ASH and EHA. It was something of a surreal experience viewing Leonardo da Vinci’s The Last Supper reminded us that evening, David Bodine spoke passionately about the importance of mentorship (more about mentorship below).

While last year’s group was apparently able to enjoy breakfasts outside in the Villa’s beautiful quadrangle, our Monday morning was cold and snowy. Sessions on bone marrow failure syndromes, flow cytometry, and bioinformatics transitioned to another afternoon of small-group work. As the workload intensified, some members of the group light-heartedly suggested changing the design of the TRTH program to a “Survivor”-style format in which only one trainee would be voted out of the Villa each day. But we were quickly reminded of our good fortune by Michaela Gruber who provided a reassuring and inspiring talk over dinner. Michaela was a trainee in the inaugural TRTH program four years ago, and she walked us through her “TRTHisation” process. She credits participation in the TRTH program as being instrumental in focusing her PhD thesis and helping her publish a manuscript in Blood, obtain fellowship support from EHA, and transition to a postdoctoral position at the Dana-Farber Cancer Institute.

Tuesday broke cool and clear as Bob Löwenberg, Editor-in-Chief of Blood, led the morning discussion on how to publish a scientific manuscript. After another small-group session, we boarded a bus to Milan to visit the monastery of Santa Maria delle Grazie, where having the privilege of viewing Leonardo da Vinci’s The Last Supper reminded us once again that we were in a special place. The afternoon was spent walking into the Duomo and up the 250 stairs to the top of the Cathedral, exploring the beauties of downtown Milan, and enjoying Italian gelato. Over dinner that night, we amusingly recalled how often we had stored laboratory samples in the home freezer overnight but also reflected on how important it is to spend time each day with friends and family.

Wednesday’s didactic sessions were followed by a mock study section during which faculty introduced trainees to the process whereby grants are reviewed at the National Institutes of Health. “Don’t annoy the reviewers,” was among the critical pointers that were emphasized by the faculty who among them had decades of experience with the intricacies of the review process. As the small groups became more and more familiar with each other’s projects, general suggestions transitioned to more detailed discussions of experimental design and personal presentation style. Over dinner, 2013 TRTH Co-Chairs John Gribben and Hal Brommeyer shared inspirational and insightful stories about their professional journeys. John and Hal have helped shape the organization and focus of the TRTH program since its inception and will be handing over the reins of leadership to new directors next year.

By Thursday, after spending five days and the better part of some nights together, a sense of comfort and camaraderie took over. Inside jokes and healthy competition between the small groups developed. Over dinner, the trainees and faculty revealed interesting facts in a game of “Two Truths and One Lie” between the main course and dessert. As part of that game, we tried to guess who among us completed half a dozen marathons in less than three hours and who once flew into the Bratislava airport thinking it was near Vienna! Strictly limited to eight minutes, Friday’s final presentations were practiced and polished, with a clear emphasis on what had been modified. It was remarkable to see how the projects had developed during the week with input from peers and faculty. As the presentations came to an end, there was a small sense of relief that was quickly overwhelmed by a much larger disappointment that the week was over. It was time to get back to the lab and put into practice all of the week’s advice!

With the spring course and EHA annual conference behind us, we look forward to our next meeting in December at the ASH annual meeting in New Orleans both to hear updates of our projects and also to reunite with our new friends.

Mentorship was a standout focus of the TRTH spring course. Meals and coffee breaks provided the perfect venue for faculty and trainees to discuss personal and scientific questions, and precious free time was happily exchanged for first-hand advice. From aspects of career development to setting up xenotransplantation experiments, the faculty was dedicated to their roles as teachers and mentors, and these “hallway conversations” were among the highlights of the week. The course benefited from the different backgrounds and training stages of the participants, which brought together experienced postdocs with more junior trainees to share protocols and interpret experimental data.
Many Streams, Same Ocean: the Different Pathways to Translational Hematology in North America and Europe

One of the goals of TRTH is to bring together translational hematologists from around the globe. While TRTH is designed to establish lasting friendships and scientific collaborations, it is interesting to note some of the differences in training and career development between the American and European systems.

In North America, the most common path to becoming a hematologist starts with a four-year undergraduate degree, followed by four years of medical school, three years of internship and residency training, and three years of fellowship in a combined hematology and oncology program. One common deviation from this plan includes the Medical Scientist Training Program (MSTP), where one applies to a three- to five-year PhD program between the second and third years of medical school. And while the three-year fellowship is officially set up as 12 to 18 months of clinical training followed by 24 months of research, the research experience is generally extended into a postdoctoral fellowship program that provides the time and resources to complete research projects begun during fellowship with a goal of becoming a principal investigator with an independent laboratory. These postdoctoral fellowships often last from four to six years during which one publishes papers and applies for mentored grants (usually NIH K08, K23, or K99/R00) designed to support the transition from senior post-doc to junior faculty member.

In Europe, there are key differences in career development, made even more complicated by differences in program design among individual countries. Most students enter into medical school (a six-year program) directly out of high school. Graduation from medical school is followed by specialization in internal medicine and then hematology, the specific course and duration of which varies from country to country. In Germany, for example, one applies to pursue training in hematology immediately after medical school. During the hematology specialty training, rotations in different departments ensure good general medical knowledge, though it is possible to find oneself able to confidently manage the work-up of a patient with newly diagnosed acute leukemia before being able to properly interpret an electrocardiogram. From the European perspective, the concept of “protected research time” is less well-developed, and physician-scientists will often have 50 percent or more of their time committed to clinical duties, including ward and shift work. While this time allocation keeps MDs in the clinic, it also makes it more difficult to advance a research project when so much of one’s effort is spent seeing patients. Consequently, experiments must be done after a full day of clinic or on weekends. In addition, many countries do not credit the research time toward hematology specialty requirements, further prolonging the training period.

In the United States, the National Institutes of Health provides grants both to individuals and to teams of individuals to pursue whatever research was outlined in the successful investigator-initiated application. In Europe, money is often awarded directly to a department or to a group, and the chair or group leader allocates the funds. Truly independent and investigator-initiated applications are rare in Europe, and the criteria often exclude MDs because of their dual clinical and scientific commitments.

Though there is a clear need for translational research – research that ultimately has a direct impact on patients – the pathway to becoming an independent physician scientist is rife with uncertainty. Individually, TRTH trainees had somewhere between 15 and 20 years of post-secondary education, and despite this personal investment in education and the societal investment in us, we universally expressed concern over both research funding cuts and the ultimate availability of independent research positions. Nevertheless, trainees and mentors alike are carried by our enthusiasm and inspired by the possibility of making an impact on patient care. Many of us hope that TRTH has better positioned us for success and that we will be back one day as TRTH faculty members.
A New Mechanism for Resistance to Nucleoside Analogues in ALL


More than half of adults and about 20 percent of children who are diagnosed with acute lymphocytic leukemia (ALL) and achieve remission with combination cytotoxic chemotherapy will eventually relapse. Among the many factors contributing to relapse risk in ALL are individual variations in drug metabolism, non-adherence to and intolerance of therapy, and inherent drug resistance of neoplastic subclones. Two groups have now uncovered evidence of a new mechanism of drug resistance: somatic gain-of-function mutations in the NT5C2 gene encoding cytosolic 5’ nucleotidase II, an enzyme responsible for dephosphorylation of 6-hydroxypurine nucleotide monophosphates. Such mutations are present in approximately 19 percent of relapsed pediatric T-cell ALL (T-ALL) cases and in a smaller proportion of relapsed pediatric B-cell ALL (B-ALL) cases.

High levels of NT5C2 expression had previously been associated with both worse outcomes and cytarabine (AraC) resistance in acute myeloid leukemia. The newly discovered activating mutations accelerate both metabolism and export active metabolites of nucleoside analogue drugs such as 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG), commonly used agents in various ALL treatment regimens recently found to be of particular therapeutic importance in T-ALL.

Adolfo Ferrando at Columbia University led the first study in which the investigators performed whole-exome sequencing of five pediatric T-ALL cases at the time of diagnosis, remission, and relapse in a study designed to identify new mechanisms of therapy resistance and disease relapse. Among 60 somatic mutations affecting coding regions, 24 were confined to relapsed T-ALL samples. Affected genes included entities known to be involved in disease pathogenesis such as TP53 and NRAS as well as the new finding of mutations affecting NT5C2. Targeted exon sequencing of NT5C2 in 98 additional cases of relapsed T-ALL and 35 cases of relapsed B-ALL identified NT5C2 mutations in 19 percent of relapsed T-ALL cases and one of 35 (3%) of relapsed B-ALL cases. NT5C2 mutations could not be identified in any specimens obtained at the time of initial diagnosis, suggesting that the mutations were acquired during therapy or were present at very low levels before selection by purine nucleoside exposure between the time of diagnosis and relapse.

In the second study, William Carroll and colleagues at New York University performed full transcriptome sequencing of 10 matched diagnosis and relapse pediatric B-ALL samples and identified 20 novel non-synonymous mutations unique to the relapse samples, with two out of 10 patients harboring mutations in the NT5C2 gene. Full exon sequencing of NT5C2 in 61 additional relapse samples identified five more cases with recurrent mutations in this gene, giving an overall occurrence of 10 percent in relapsed pediatric B-ALL specimens. Unlike the group at Columbia, Carroll and colleagues were able to show the presence of rare NT5C2-mutated clones in two out of seven diagnostic samples using ultra-deep sequencing, arguing that the resistant clone was present at low levels from the outset of the disease.

Structure-function analysis supports the hypothesis that these are gain-of-function mutations that result in increased NT5C2 enzymatic activity. In addition, treatment of ALL cell lines expressing wild-type and mutant NT5C2 with nucleoside analogs 6-MP and 6-TG demonstrated increased resistance of cells expressing mutant NT5C2 to nucleoside analogs, but not to doxorubicin, gemcitabine, prednisolone, or guanosine arabinoside (AraG) or its FDA-approved methoxy analogue nelarabine, both of which are metabolized distinctly from 6-MP and 6-TG.

Together, these studies provide information about a new mechanism underlying relapse in a subset of patients with ALL, paralleling recognized drug resistance mechanisms in other neoplasms (Figure). Incorporation of 5’ nucleotidase inhibitors targeting NT5C2 to initial therapy regimens or to salvage regimens at the time of relapse, or greater use of anti-tumor agents that are not affected by changes in this metabolic pathway, may prevent drug resistance and disease relapse in this vulnerable subset of ALL patients.


Mechanisms of drug resistance in hematologic malignancies can include selection of resistant clones present at very low levels at the time of diagnosis. For instance, in chronic myeloid leukemia (CML), treatment with a tyrosine kinase inhibitor (TKI) such as imatinib can reduce the dominant neoplastic clone (green circles) and permit recovery of normal hematopoiesis (blue circles), but in some cases TKIs also apply selective pressure allowing outgrowth of pre-existing neoplastic subclones harboring BCL2-like kinase mutations such as T315I (red circles), which eventually leads to resistance and treatment failure. Targeting of the resistance clone with a third-generation TKI such as ponatinib can lead to long-term remission; it remains to be seen whether earlier treatment with ponatinib will prevent emergence of resistant clones. Similarly, in ALL, the presence of an activating NT5C2 mutation can lead to relapse during 6-MP maintenance therapy and will require use of adjuvant or non-cross-resistant therapies to overcome.
Students of hematology are taught that hemostasis involves a two-step process. After vascular injury, primary hemostasis consists of platelet adhesion to subendothelial elements followed by platelet aggregation to form a platelet plug. Secondary hemostasis consists of consolidation of the platelet plug by a fibrin clot. Recently, increasing attention has been paid to inflammatory hemostasis that occurs in the absence of a vascular injury, i.e., without a laceration or rent in the vascular wall. Platelets play conflicting roles in inflammatory hemostasis. They increase inflammation by promoting tissue infiltration by white blood cells. However, they also reduce hemorrhage by nurturing vascular integrity during inflammation. 1

One possible way to study platelet function would be to transfuse platelets that have been modified in some way into thrombocytopenic mice. For example, the function of a particular signaling pathway could be evaluated by comparing pathway-deficient platelets and normal (wild-type) platelets in their capacity to prevent bleeding in thrombocytopenic mice. But how does one go about producing a thrombocytopenic recipient mouse? Antibodies to platelet glycoproteins, e.g. anti-GPIbα, have been shown to produce severe thrombocytopenia and a bleeding diathesis. However, these antibodies would persist in mice. But how does one go about producing a thrombocytopenic recipient mouse?

The authors employed two inflammatory hemostasis models in the thrombocytopenic transgenic hIL-4Rα/GPIbα α/ mice. In an Arthus reaction model, in which inflammation is immune-complex mediated, mice received intravenous bovine serum albumin (BSA) and intradermal injection of anti-BSA antibodies. The resulting BSA/anti-BSA immune complexes produce a complement-dependent inflammatory response and quantifiable dermal hemorrhage. In a pulmonary inflammation model, mice received lipopolysaccharide (LPS) intranasally. Bleeding in this model was quantitated by measuring hemoglobin in lavage fluid.

In both models, transfusion of wild-type platelets prevented bleeding, setting the stage for analysis of platelets with defective signaling pathways. The role of G-protein-coupled receptor (GPCR) signaling was studied using four types of platelets: 1) platelets deficient in the thrombin receptor PAR4; 2) platelets treated with clioquinol to inhibit the ADP receptor, P2Y12; 3) platelets treated with aspirin to inhibit thromboxane A2 synthesis; and 4) PAR4-deficient platelets treated with both clioquinol and aspirin. All four platelet preparations were defective in producing primary hemostasis following laser-induced vascular injury. However, surprisingly, they were functionally equivalent to wild-type platelets in preventing bleeding in both the Arthus reaction and LPS inflammation models. These results indicate that GPCR signaling is required for normal hemostasis following vascular injury but not following vascular inflammation.

The authors next determined whether signaling via platelet immunoreceptor tyrosine activation motif (ITAM) receptors is required to protect against inflammatory hemorrhage in the thrombocytopenic transgenic hIL-4Rα/GPIbα α/ mice. Mouse platelets express two ITAM receptors: GPVI, which binds collagen and laminin in the extracellular matrix, and C-type lectin–2 (CLEC2), a receptor for podoplanin on the surface of extravascular cells. Four preparations were tested: a) platelets treated with an anti-GPVI mononclonal antibody, JAQ1; b) platelets isolated from Clec2Δ/Δ mice; c) Clec2Δ/Δ-treated Clec2Δ/Δ platelets; and d) Slp76Δ/Δ-deficient platelets, which have a defect downstream of ITAM receptors. In both the Arthus reaction and LPS models, transfusion of JAQ1-treated platelets or Clec2Δ/Δ platelets only partially corrected the bleeding diathesis. Furthermore, complete inhibition of ITAM signaling pathways using JAQ1-treated Clec2Δ/Δ platelets or Slp76Δ/Δ platelets completely failed to correct the bleeding diathesis. These results indicate that maintenance of vascular integrity during inflammation depends on platelet ITAM signaling.

The paper by Boulaftali et al. describes a novel model system for studying how platelets protect against bleeding in response both to vascular injury and to inflammation. GPCR-dependent signaling is required for the former, but not the latter. In contrast, ITAM-dependent signaling is required for the latter. The authors speculate that bleeding at sites of inflammation may be an adverse effect of drugs currently under development that target platelet ITAM signaling pathways.

Blood performs a remarkable function in response to vascular injury. It rapidly detects the injury and forms around it a new structure, the thrombus, capable of preventing blood loss. The thrombus achieves hemostasis in this pressurized system despite significant shear stress and, except in cases of pathologic thrombus formation, without interrupting blood flow. We have learned much about thrombus formation by dissecting, at a molecular level, the pathways leading to platelet activation and fibrin generation. Considerably less is known about the structural organization and physical characteristics of the thrombus, but available data suggest that a thrombus is not a hodgepodge of randomly distributed platelets and fibrin, but rather a defined structure with a distinct architecture. Yet, how this structure is assembled, in a kinetically and spatially regulated manner, is largely enigmatic.

Stalker and colleagues at the University of Pennsylvania have now used in vitro microscopy to follow the construction of the thrombus over time, to detail certain physical parameters, and to define the platelet signaling pathways that direct its organization. First, the authors confirmed previous studies demonstrating that platelet activation (as detected by platelet P-selectin expression) during thrombus formation is localized to a central core, surrounded by a shell of unactivated platelets. They then evaluated the packing density of the thrombus by studying the penetration of fluorescently labeled albumin and dextrans. These studies demonstrated that large molecules penetrated the core poorly but that they flowed relatively easily through the loosely packed outer shell. Formation of the tightly packed core required the generation of thrombin and was blocked by the thrombin inhibitor hirudin. Platelet-platelet interactions were also essential but rather a defined structure with a distinct architecture. Yet, how this structure is assembled, in a kinetically and spatially regulated manner, is largely enigmatic.

Understanding the architecture of a thrombus could have clinical implications in the treatment of thrombotic disease. It is possible, for example, that targeting pathways responsible for formation of the thrombus shell will impair occlusive thrombosis without substantially impairing hemostasis. The efficacy and safety of shell-targeted therapies that inhibit thromboxane-mediated signaling (e.g., aspirin) or ADP-mediated signaling (e.g., clopidogrel or ticagrelor) may support this notion. On the other hand, ADP-mediated signaling is known to function in hemostasis, and a relationship between thrombus architecture and clinical outcomes remains to be explored. Understanding the architecture of clots in different pathologic scenarios and in different vascular beds may show differences in thrombus structure that reveal regions of the clot are best to target and which are best to preserve. Ultimately, in providing a new set of parameters by which to evaluate the effects of anticoagulants on clot formation, the studies by Stalker et al. could facilitate our efforts to coerce blood to build safer clots.


Clot Construction


Hematopoietic Stem Cells Recycle Cellular Components to Adapt to Metabolic Stress


Over our lifespan, somatic cells that comprise our various organs have to contend with diverse stress-inducing processes, the consequences of which are amplified by aging. Metabolic stress is especially relevant in the setting of endothelial compromise. The inner core of the thrombus by activation of cellular molecules such as ADP and thromboxane A_2 (TXA_2).

ASHLEY KAMME-LANNING, BS, AND PETER KURRE, MD

Mr. Kamm-Lanning and Dr. Kurre indicated no relevant conflicts of interest.

ASMC News and Reports

The Hematologist

Good Things Happen With Time

Enthusiasm for the use of new approaches to treatment can be influenced by clinical trial design. For example, a novel agent may be shown to be active as first-line therapy but may have more importance in treatment of relapsed disease in patients who have failed standard therapy and are left with no effective second-line options. Another potential source of bias is length of follow-up when a survival benefit is demonstrated based on data analysis performed at an early time point calculated to yield a statistically significant benefit based on the number of patients enrolled in a particular study. Such relatively early analysis may also obscure adverse effects that become apparent only after a longer follow-up period. This latter issue is particularly important for patients with myeloma in whom the risk of developing a second primary malignancy may increase over time. Because of these concerns, physicians treating patients with multiple myeloma are certain to welcome the results of the rigorous studies of San Miguel and colleagues.

The combination of bortezomib (Velcade®), melphalan, and prednisone (VMP) became the standard of care for treatment of transplant-ineligible patients with multiple myeloma (MM), at least in Europe, following publication of the initial results of VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone), an international, phase III study that compared outcomes in patients randomized to receive VMP with those randomized to receive MP.1 That study served as the pivotal trial that led to approval in 2008 by both the U.S. FDA and the European Medicines Agency of bortezomib as initial therapy for myeloma in patients ineligible for transplant, including the elderly, and, consequently, VMP is one of the most frequently specified regimens worldwide. The data from the initial analysis, with its relatively short median follow-up of 16.3 months, showed that VMP was superior to MP across all efficacy endpoints, including response rates, time to progression, and overall survival (OS).

In the current study, the authors report the analysis of data from the VISTA trial after a median follow-up period of five years. This analysis was undertaken both to determine whether the significant OS benefit observed in the initial study was maintained after five years, taking into account the effects of salvage therapy, and to explore for the first time the incidence of second primary malignancies in the two treatment arms. OS benefit with VMP was confirmed across all pre-specified patient subgroups that included patients 75 years and older, those with stage III disease, and those with renal insufficiency (creatinine clearance of <60 ml/min). A 31 percent reduction in risk of death was observed for patients in the VMP arm, and the OS for the two groups was 56.4 months and 43.1 months for the VMP cohort and the MP cohort, respectively. Sixty-three percent of VMP patients and 73 percent of MP-treated patients received salvage therapy. Median time to next therapy was significantly longer for the VMP arm (30.7 months) compared with the MP arm (20.5 months), whereas survival from the start of subsequent therapy was similar for the two groups (28.1 months for the VMP group compared with 26.8 months for the MP group). Importantly, exposure-adjusted incidence rates for malignancies were similar for the two groups and consistent with background rates.

Demonstrating an OS benefit for VMP that included the longer follow-up period and that allowed for salvage therapy, including crossing over to bortezomib for the MP cohort, supports the conclusions drawn from the earlier analysis of the VISTA study that demonstrated superior efficacy for VMP. Notably, the OS for patients in the MP arm of VISTA was longer than the median OS observed for MP-treated patients reported in previous phase III trials and met the protocol-specified OS benefit observed in the VISTA, not due to a substandard outcome for the MP-treated group. The current studies confirm the efficacy and safety of VMP, and based on the studies of San Miguel and colleagues, this regimen can be considered a standard of care for first-line treatment of transplant-ineligible patients with MM, and, consequently, for another regimen to become standard of care for this group of patients, superiority to VMP must be demonstrated.


Getting into the Flow: Red Cells Go on a Roll

The main function of erythrocytes, the transporting of gasses (oxygen, carbon dioxide, and nitric oxide) involved in tissue respiration, occurs in small vessels. Shear forces on erythrocytes vary as blood flows from small arterioles through capillaries into venous sinuses. Under conditions of low and moderate shear force experienced in small vessels, the rheologic properties of human erythrocytes are largely determined by specific changes in their shape and motion. Two basic motions of erythrocytes (Figure) have previously been described as tumbling or flipping when exposed to low shear rates, and tank-treading when the shear rate and/or the viscosity of the suspending medium are increased. The membrane of a tank-treading erythrocyte has fluidity and elasticity that allows its rotation around the hemoglobin-filled cytoplasm, while the biconcave shape is maintained at moderate shear rates, and a more ellipsoid shape is assumed with higher shear rates.1 When the shear force is removed, the formerly tank-treading erythrocyte membrane reorient itself to assume the same position relative to the rim and biconcave dips that it had prior to the initiation of tank-treading (i.e., erythrocytes have shape memory).1

In their videomicroscopy study, Dupire et al. demonstrated that at low and moderate shear rates, erythrocytes maintain their biconcave shapes with only slight long-axis distortion. With low shear rates, an erythrocyte tumbles or flips. As the shear rate is increased, the tumbling erythrocyte can undergo a transition in its orientation so that it rolls like a wheel. This tumbling-to-rolling transition requires a limited amount of membrane elasticity, but after achieving the rolling orientation, the energy expended in cell shape maintenance is minimized compared with that expended in preserving cell shape during tumbling or that expended in the membrane rotation of tank-treading. At progressively higher shear rates, the rolling erythrocytes undergo a 90-degree orientation change to a Frisbee-like spinning motion that precedes a transition to tank-treading with fluctuations of the angle of orientation in the shear plane, a process termed swinging.2

Dupire and colleagues demonstrated specific transition states as an erythrocyte goes from rolling/spinning to tank-treading and also when it makes the opposite transition from tank-treading directly to tumbling. In the former transition, focal areas of the membrane appear to remain solid as the rest of the membrane has acquired the fluid movement of tank-treading. In the transition from tank-treading to tumbling caused by decreasing shear rate, the erythrocyte have short periods in which tank-treading is interrupted by one or two flips of the erythrocyte before there is complete loss of membrane fluidity and a return to a tumbling motion.

The fascinating studies of Dupire et al. demonstrate that transitions in cell shape and motion in response to changes in shear rate may help erythrocytes adapt to the vicissitudes of transit through the various components of the microvasculature, but future experiments will be needed to verify the roles of these rheologic changes in vivo. Characterization of the rheologic properties of normal erythrocytes enhances our understanding of the pathophysiology of diseases that involve abnormalities of the erythrocyte membrane, serum viscosities, and microvessels, including sickle cell anemia, malaria, polycythemia, macroglobulinemia, vasculitis, and diabetes.


XAVIER LELEU, MD, PhD
Dr. Leleu indicated no relevant conflicts of interest.
ASH Releases ASH-SAP, Fifth Edition, and Introduces the ASH Academy

ASH is dedicated to keeping members informed and up to date on the latest and most important clinical information. With this aim in mind, in early June, the American Society of Hematology Self-Assessment Program (ASH-SAP), Fifth Edition (www.hematology.org/ashsap5) was released, and the ASH Academy (www.hematology.org/ashacademy), an eLearning website for hematologists, was launched. These new offerings come at a particularly opportune time as the American Board of Internal Medicine (ABIM) announced that changes in recertification will become effective in January 2014 (read the sidebar below). In fact, the decision to develop this new website was driven in part by these anticipated changes to ABIM’s process of Maintenance of Certification (MOC), which will affect not only hematologists certified by ABIM but pediatric hematologists and hematopathologists as well. The concept of the ASH Academy is to house most of ASH’s “credit earning” activities on one website, allowing for improved user service and accessibility. The new, fifth edition of ASH-SAP is currently available through the Academy, and beginning this summer, new products such as practice-improvement modules (PIMs) will be added to the Academy inventory.

As a reminder, ASH-SAP, which is updated every three years, is a comprehensive educational resource containing information about the latest developments in hematology. From the ASH Academy site, users can access the online textbook, download the eBook version, earn continuing medical education (CME) credit by passing the ASH-SAP exam, and, for an additional fee, access an ABIM-approved MOC module. Users can claim up to 50 CME credits by taking an online examination that tests their knowledge of the material contained in ASH-SAP, Fifth Edition, and completion of the MOC module allows participants to earn 20 ABIM MOC points. Once users have submitted their responses for credit, answers can be cleared so that the exams questions can be used for study purposes. This reuse feature is an ASH Academy innovation. The ASH-SAP, Fifth Edition, is also available in textbook form and contains a question-and-answer book that includes a self-assessment test with accompanying answers and annotations. Up to 50 American Medical Association (AMA) Physician’s Recognition Award (PRA) Category 1 Credits™ can be earned by completing the test material.

The newly released fifth edition of ASH-SAP has a number of enhancements, including the following:

- Three new chapters: “Consultative Hematology II: Women’s Health Issues” (Chapter 3); “Clinical Bone Marrow and Stem Cell Transplantation” (Chapter 14); “Hodgkin Lymphoma” (Chapter 20)
- A comprehensive review of both malignant and non-malignant hematology
- eBook access for the textbook
- An exam that can yield up to 50 CME credits based on response to 232 new questions hosted on the ASH Academy platform
- Peer comparisons on first responses to questions as well as critiques of right and wrong answers with supporting references
- Participants can sign on using their existing ASH password
- An MOC module that can yield up to 20 ABIM credits based on response to 60 new questions hosted on the ASH Academy website
- Real-time reporting to ABIM of MOC module test results for fast crediting of MOC points

What are the changes that ABIM is making?

The changes that will take effect in 2014 include a more continuous ABIM MOC program. ABIM has created a mini site to alert physicians about impending changes in certification, recertification, and MOC requirements in advance of their implementation. ABIM will be rolling out a new, personalized Physician Portal on ABIM.org that will inform individuals about what to do and when. It will provide information on specific deadlines, make recommendations on products relevant to a particular specialty, and outline a step-by-step sequence for completing certification requirements.

ABIM will honor time remaining on all certifications. Clinicians will continue to be certified for the length of their current certification(s), assuming that they hold a current and valid license. For those who hold certifications that are valid indefinitely, that certification will continue to be honored.

For all ABIM-certified physicians, ABIM and the American Board of Medical Specialties (ABMS) will begin reporting whether practitioners are “Meeting MOC Requirements” (i.e., completing an MOC activity every two years and earning 100 points every five years). An individual will be deemed as meeting MOC requirements at the launch of the program, assuming he/she is enrolled in the MOC program and has both a license in good standing and a currently valid certification. In order to be reported as meeting MOC requirements, clinicians are required both to complete an MOC activity at least every two years and to earn 100 ABIM MOC points every five years with the points earned every two years being counted toward the five-year requirement.

The exam requirement has not changed. Every 10 years practitioners will need to pass the exam(s) specific for each subspecialty for which certification is sought. MOC points are awarded for first exam attempt in each certification area.

The points earned apply to all certifications that are being maintained. MOC points can be earned by completing ABIM-approved MOC products, such as the ASH-SAP MOC Module, or by using MOC products developed directly by ABIM.

Why is ABIM changing its program?

MOC tenors continue to evolve. ABIM and ABMS, of which ABIM is a member, believe that a more continuous MOC program helps physicians keep abreast of both new developments in medical science and improvements in delivery of patient care. The Institute of Medicine has argued that in a profession with a “continually expanding knowledge base” a mechanism is needed to ensure that practitioners remain up-to-date with current best practices. This growing knowledge base requires that training and ongoing licensure and certification reflect the need for lifelong learning and evaluation of competency.

Double Cord Versus Haploidentical: Which Alternative Donor Source is Better?

**STUDY TITLE:** A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) Versus HLA-Haploidentical Related Bone Marrow (Haplo-BM) for Patients With Hematologic Malignancies (BMTC CTN #1101)

**CLINICAL TRIALS.GOV IDENTIFIER:** NCT01597778

**SPONSOR:** Medical College of Wisconsin

**COLLABORATORS:** National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), and Blood and Marrow Transplant Clinical Trials Network (BMTC CTN)

**PARTICIPATING CENTERS:** 15 core study participants (consortium or individual institutions) of the BMTC CTN and 15 affiliate study participants

**ACCRUAL GOAL:** 410 patients

**STUDY DESIGN:** This is a multicenter, phase III, randomized trial. The primary objective is to compare progression-free survival (PFS) at two years post-randomization. Patients in both study groups undergo the same RIC preparative regimen. Post-conditioning, patients in one randomized group receive unrelated double cord blood units as the stem cell source while the other receives HLA-haploidentical bone marrow. Secondary objectives include comparison of neutrophil and platelet recovery time, rates of primary and secondary graft failure, donor cell engraftment, incidence of acute and chronic graft-versus-host disease (GVHD), overall survival, treatment-related mortality, relapse rates, incidence of disease progression, number of hospital admissions and length of stay, quality of life, and cost effectiveness. Patients ages 18 to 70 are eligible if they have both of the following: one or more related haploidentical donors and at least two identified umbilical cord blood units of sufficient size matched at a minimum of 4/6 HLA loci. Patients in both study groups undergo the same RIC preparative regimen. Post-conditioning, patients in one randomized group receive unrelated double cord blood units as the stem cell source while the other receives HLA-haploidentical bone marrow. Secondary objectives include comparison of neutrophil and platelet recovery time, rates of primary and secondary graft failure, donor cell engraftment, incidence of acute and chronic graft-versus-host disease (GVHD), overall survival, treatment-related mortality, relapse rates, incidence of disease progression, number of hospital admissions and length of stay, quality of life, and cost effectiveness. Patients ages 18 to 70 are eligible if they have both of the following: one or more related haploidentical donors and at least two identified umbilical cord blood units of sufficient size matched at a minimum of 4/6 HLA loci. Patients with stable, transfusion-dependent multiple-organ dysfunction score (MODS) may be eligible for this study.

**RATIONALE:** One-third of patients eligible for allogeneic stem cell transplant lack a suitable HLA-matched related or unrelated donor. Previous studies showed that the outcomes of transplant in adults using single cord blood units as the donor source was inferior to that using haploidentical bone marrow. To address further the efficacy and safety of alternative donor transplants, two parallel phase II trials were conducted that used similar reduced-intensity preparative regimens followed by transplant using either haploidentical bone marrow (NCT00849147; BMTC CTN 0603) or double umbilical cord blood units (NCT00864227; BMTC CTN 0604) as the stem cell source. Both trials had the same objectives, eligibility criteria, and clinical endpoints, and each enrolled 50 patients. The outcomes were comparable with those using HLA-matched, unrelated donors, and because the data showed similar survival, neutrophil recovery time, and rates of GVHD for the two alternative donor approaches, the stage was set for the current randomized trial.

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**COMMENT:** Allogeneic stem cell transplantation is the only curative therapy for several hematologic malignancies, but the inability to identify a suitable HLA-matched donor in a timely manner can preclude the use of this potentially lifesaving procedure. Sequential clinical trials have led to the refinement of successful approaches using alternative donor sources, either combined cord blood units or haploidentical-related family members. This pivotal trial is powered to detect a 15 percent increase in PFS at two years. Given the resources required to support each of these transplant approaches and the potential to cure life-threatening disorders, it is essential to learn whether one is superior to the other using criteria including longer survival, less toxicity, better quality of life, and lower cost.

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Are Old, Stored Red Cells Dangerous to Your Health? The RECESS Trial

**STUDY TITLE:** Red Cell Storage Duration Study (RECESS)

**CLINICAL TRIALS.GOV IDENTIFIER:** NCT00993414

**SPONSOR:** New England Research Institutes

**COLLABORATOR:** National Heart, Lung, and Blood Institute (NHLBI)

**PARTICIPATING CENTERS:** 26 study locations in the United States

**ACCRUAL GOAL:** 1,696 subjects (enrollment is ongoing)

**STUDY DESIGN:** This phase III trial will compare the effects of transfusing red blood cell units stored ≤ 14 days with those stored ≥ 21 days in patients who are undergoing complex cardiac surgery and who are likely to need red blood cell transfusion. The hypothesis being challenged is that patients transfused with red cell units stored for a shorter time have a significantly more favorable clinical outcome compared with patients transfused with units stored for a longer time. The study’s primary outcome measure is change in the composite multiple-organ dysfunction score (MODS) from the pre-operative baseline. The worst post-operative values of each component of MODS will be used to calculate the change in MODS through post-operative day 7, hospital discharge, or death, whichever occurs first. Secondary outcome measures include all-cause mortality through day 28 post-surgery; major in-hospital, post-operative complications (e.g., death, stroke, myocardial infarction, renal failure, culture-proven sepsis/septic shock) through post-operative day 7, hospital discharge, or death, whichever occurs first; major cardiac and pulmonary events; ventilation duration; and a panel of relevant laboratory/clinical measurements.

**RATIONALE:** Current U.S. FDA guidelines allow for storage of red cells for up to 42 days. In practice, the average red blood cell storage time is 28 days, with most blood banks adhering to the policy of using the oldest blood first. Concern over the safety of blood transfusion has existed for decades, and recent clinical studies have suggested that storage of blood affects clinical outcomes. For example, in a retrospective study involving patients who had undergone cardiac surgery, 30-day mortality was significantly greater for patients transfused with red blood cells stored for more than 14 days compared with that of patients transfused with blood stored for less than 14 days (Koch CG et al. N Engl J Med. 2008;358:1229-39). But other studies have come to different conclusions as evidenced by a recent randomized control trial of young (7 days or less in storage) versus standard-issue red cell transfusions in premature neonates that showed no difference in outcome (Ferguson DA et al. JAMA. 2012;308:1443-51).

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**COMMENT:** The RECESS trial will provide valuable information on whether blood stored for more than 21 days is suboptimal for cardiac surgery patients, and some of the secondary endpoints of the study may generate new insights into the biologic effects of storage on the properties of red blood cells. However, caution must be exercised when extrapolating the results of the RECESS study to other indications for transfusion. For example, patients with stable, transfusion-dependent MODS may respond differently than patients undergoing cardiac surgery, just as the outcome for neonates, cited above, appears to be different from that of cardiac surgery patients. Still, we must be prepared to deal with definitive studies that demonstrate that stored blood is detrimental, even if the outcome affects only a subgroup of patients. For this reason, continued basic investigation designed to understand the nature of the red cell storage lesion is of paramount importance, as are studies aimed at developing methods both for rejuvenating stored blood and for generating sale, effective blood substitutes.

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**COMMENT:** The ReCess trial will provide valuable information on whether blood stored for more than 21 days is suboptimal for cardiac surgery patients, and some of the secondary endpoints of the study may generate new insights into the biologic effects of storage on the properties of red blood cells. However, caution must be exercised when extrapolating the results of the ReCess study to other indications for transfusion. For example, patients with stable, transfusion-dependent MODS may respond differently than patients undergoing cardiac surgery, just as the outcome for neonates, cited above, appears to be different from that of cardiac surgery patients. Still, we must be prepared to deal with definitive studies that demonstrate that stored blood is detrimental, even if the outcome affects only a subgroup of patients. For this reason, continued basic investigation designed to understand the nature of the red cell storage lesion is of paramount importance, as are studies aimed at developing methods both for rejuvenating stored blood and for generating sale, effective blood substitutes.

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Dr. Vercellotti indicated no relevant conflicts of interest.
Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The citations are annotated to provide readers both with a concise description of the thrust of the article and an explanation of why the paper is particularly important. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

APRIL 18, 2013


The NTPTase CD39 (a dense granule constituent), degrades the primary platelet activating/recruiting molecule ADP, and as such, represents a promising target for antithrombotic therapy. In this Plenary paper, Hohmann and colleagues examine the effects of targeting of CD39 to a developing clot. Their strategy involved creating a chimeric protein consisting of CD39 fused to a single-chain antibody specific for glycoprotein Ib/IIa. The investigators report that binding of this construct (called targCD39) to activated platelets impeded the perpetuation phase of thrombus formation, thereby retarding growth of the clot without interfering with formation of the initial sealing layer of platelets. Thus, the targCD39 construct is a novel antithrombotic agent as it retards clot growth while allowing for adequate hemostasis.

APRIL 11, 2013


Two manuscripts report the unexpected finding that a significant proportion of patients undergoing cardiopulmonary bypass develop antibodies against pro tease. In the first study, Bakchoul et al. report that nearly 10 percent of patients had anti-pro tease antibodies at baseline, increasing to nearly 27 percent within 10 days of bypass. Lee et al. report similar findings: 29 percent of post-bypass patients developed antibodies within 30 days. Antibodies were more common in patients with diabetes, and pro tease-heparin complexes cross-reacted with pro tease-containing insulin preparations. In most patients, these antibodies were clinically silent and declined in titer over several months; however, in a small number of patients, the antibodies bound and activated platelets in the presence of pro tease. This process may be a rare cause of unexplained thrombocytopenia and thrombosis, sharing clinical and pathophysiological features with heparin-induced thrombocytopenia.

Mr. 28, 2013

This Plenary paper reports on the mechanism of invasive fungal infections in individuals with Caspase recruitment domain-containing protein 9 (CARD9) deficiency. Candida fungal infections can be either mucosal or systemic, and the pathways that protect against the two types of infection are distinct. Mucosal candida is controlled by IL-17 producing lymphocytes (Th17 lymphocytes) that are components of the adaptive immune system, while prevention of systemic candida is mediated by neutrophils that are constituents of innate immunity. Drewnia and colleagues report that a patient with CARD9 deficiency suffering from Candida dublinensis meningocoeptophilis had both a selective neutrophil killing defect and a subnormal number of Th17 lymphocytes. These studies, which indicate a role for CARD9 in both Th17 development and neutrophil function, suggest that this pleotropic protein sits at the intersection of the two pathways of immunity.

MARCH 21, 2013

While the neural transcription factor SOX11 is a commonly upregulated gene in mantle cell lymphoma but not in other mature B-cell lymphomas, its role in the pathogenesis of the disease has remained largely obscure. In this paper, Veglia and colleagues report the results of studies designed to delineate the oncogenic and mechanistic effects of SOX11. The investigators analyzed the genes and transcriptional programs controlled by SOX11, integrating genomic and biologic approaches and demonstrating effects on plasma cell differentiation. The findings represent a conceptual advance in our understanding of the pathobiology of this aggressive form of malignant lymphoma.

MARCH 15, 2013

In this study, researchers report on a recurrent mutation in the MYD88 gene detected in more than 90 percent of patients with Waldenström macroglobulinemia. Additionally, allele-specific polymerase chain reaction detected the same mutation in more than half of patients with IgM MGUS (monoclonal gammopathy of undetermined significance), but not in patients with other forms of multiple myeloma, chronic lymphocytic leukemia, or splenic lymphoma. These findings suggest that MYD88 mutation may be an early cancer-causing event in a specific subset of lymphoproliferative diseases characterized by clonal expansion of IgM-producing lymphoplasmatocytic cells.

Coming soon: The next two Blood Hubs – centralized places for readers to find content – will focus on multiple myeloma and sickle cell disease. Go to http://bloodjournal.hematologylibrary.org for more information.

Frank H. Gardner, MD
(1919-2013)

Frank H. Gardner, MD, secretary of the American Society of Hematology from 1968 to 1970, died at his home in Galveston, Texas, on April 6, 2013, at the age of 93. A brilliant clinician and teacher, Frank was an inspiration to scores of medical student, residents, fellows, and young aspiring hematologists. He was also a committed clinical investigator. Along with Scott Murphy, one of his fellows at the Peter Bent Brigham Hospital in Boston (now Brigham and Women’s Hospital) and then at the Presbyterian-University of Pennsylvania Medical Center in Philadelphia (now Penn Presbyterian Medical Center), Gardner was the first to show that platelets stored for four to five days at room temperature retain viability and function while storage at 4 degrees centigrade led to immediate removal of transudated platelets from the circulation.

Dr. Gardner, the son of a physician, was born and raised in San Bernardino, California, and went to college and medical school at Northwestern University in Chicago. His internship and residencies were in Chicago and San Francisco. He then joined the Harvard Medical School affiliated Thorndike Memorial Laboratory at the then Boston City Hospital under the watchful eyes of William Bosworth Castle and Thomas Hale Ham. Soon the neighboring Peter Bent Brigham needed a hematologist. Frank was appointed to that position and remained on the faculty from 1949 until 1966 except for two years of military service (1953-1955). During that time, he undertook rewarding research on sprue while stationed in Puerto Rico at the U.S. Army’s Tropical Research Medical Laboratory. At Brigham, his strong program produced more members of the American Society for Clinical Investigation than any other division in the Department of Medicine. Further, based on a mutual interest in the management of congenital and acquired bone marrow failure, Gardner established an innovative collaboration with Louis K. Diamond at the neighboring Children’s Hospital.

In 1966, he moved to Philadelphia where he was professor of medicine at the University of Pennsylvania School of Medicine. He found his happiest academic home at the University of Texas Medical Branch in Galveston, which he joined in 1975, remaining for 35 years until his retirement. His clinical, mentoring, and teaching skills were highly valued in Galveston. In 2011, he was honored by the University of Texas Medical Branch with the John B. McCovern Lifetime Achievement Award in Oncixer Medicine.

Those of us who had the good fortune to train with Frank were never out of his sight. We constantly received journal reprints or other thoughtful reminders from him as he watched our progress with a gimlet eye. He was proud of our achievements, but insisted that medical research, like clinical work and teaching, must focus on the patient. Through his own efforts and those of his trainees, his legacy was surely improved patient care.

— David G. Nathan, MD, President Emeritus Dana-Farber Cancer Institute, Physician-in-Chief Emeritus Boston Children’s Hospital and Robert A. Stranahan Distinguished Professor of Pediatrics and Professor of Medicine, Harvard Medical School, and Blanche P. Altor, MD, MPH, Senior Clinician, Division of Cancer Epidemiology & Genetics, Clinical Genetics Branch, National Cancer Institute
A Career in Hematology With Unexpected Turns

BEVERLY M. MITCHELL, MD
George E. Becker Professor of Medicine, Director, Stanford Cancer Institute
Past President of ASH

From the time I was eight, there was no question that I would become a physician. Encouraged by a surgeon father who led an academic department at Tufts while remaining completely devoted to his patients, I entered Harvard Medical School, one of 10 women in my class. It was there that I encountered William Castle, a true pioneer in hematology and discoverer of intrinsic factor. Not only did Dr. Castle tell the incredible story of his clinical investigations that dovetailed with those of Whipple, Minot, and Murphy and led to the cure of pernicious anemia, he also nobly submitted himself to the torture of second-year students drawing his blood.

Later, as a resident at the University of Washington, I encountered many other facets of hematology. The discovery and characterization of colony-stimulating factors had catalyzed the creation an entire new field of research, and at the University of Washington, John Adamson introduced me to the world of experimental hematopoiesis. It is no coincidence that a number of today’s prominent academic hematologists, including three other ASH presidents, Ken Kaushansky, Evan Sadler, and Jan Ablowitz, also benefited from John’s expert training and mentorship.

As wonderful as the University of Washington was, I was anxious to explore new environments in conjunction with my husband, a geneticist who had just completed a postdoctoral fellowship. Following two years of research in Zurich, we settled in Ann Arbor, Michigan, where I met William Kelley, then the chair of medicine. Bill is a rheumatologist who worked on purine metabolism. Fortuitously, the link between two inherited disorders of purine metabolism (deficiencies of adenosine deaminase and purine nucleoside phosphorylase activity) and two immunodeficiency diseases (severe combined immunodeficiency disease and primary depletion of T lymphocytes) had just been discovered. It was a short conceptual leap from understanding the pathobiology of these disorders to envisioning novel therapeutic strategies for lymphoproliferative disorders. Thus, the transition to Bill’s laboratory diverted my research from hematopoiesis to the study of enzyme inhibitors such as 2’-deoxycoformycin (pentostatin) and purine analogs such as guanine arabinoside (ara-G) and their clinical application in the treatment of lymphoid malignancies.

Motherhood also worked its way into my life while in Ann Arbor. Combining motherhood with a career as a physician-scientist presented many challenges and many rewards. With probable contributions from both nature and nurture, our two children have ended up in academic careers in the natural sciences.

After a number of years in Michigan, we moved to the University of North Carolina at Chapel Hill, where I had the opportunity to merge a great hematology program, which had been developed under Harold Roberts, with a less well-developed oncology program. This leadership opportunity had been developed under Harold Roberts, with a less well-developed oncology program. This leadership opportunity had been catalyzed by the creation of the Clinical Research Training Institute; interacting with a host of energetic, enthusiastic, dedicated hematologists and ASH staff; and attending the annual meeting without fail have enriched my career and my life. The recent pace of discovery in hematologic malignancies has been breathtaking, and my hope is that future generations of hematologists will be able to look back on the cure of chronic leukemias and myeloma as I looked back on the cure of pernicious anemia as a triumph of curiosity, imagination, and tenacity. There can be no better career than one in hematology.

“Of all the experiences I have had during my career, the opportunity to be involved with ASH has clearly been a highlight.”

Thoughts From a Former Protégé

DANIEL A. POLLYEA, MD, MS
Assistant Professor of Medicine, Division of Hematology and Oncology, Clinical Director of Leukemia Services, University of Colorado School of Medicine

In retrospect, I have no idea how I came to be sitting on a couch in the office of the director of the Stanford Cancer Center. Liking to the director herself about a proposal I was considering sending as the focus of my application for a position in ASH’s Clinical Research Training Institute. Perhaps someone had mentioned offhandedly that I might want to run my idea by Bev Mitchell, as she had expertise in a field in which I had voiced some burgeoning interest. I certainly had no business, as a first-year fellow, being there at all, occupying a highly coveted time slot on her extraordinarily busy schedule with meanderings, half-baked ideas. But as we talked, first about my proposal, then about leukemia, then about research and career development, I got the sense that Dr. Mitchell regarded this meeting, with a somewhat rudderless first-year fellow, as important as anything she had to do that day. And as I left her office and walked back outside into the sunny afternoon, it occurred to me that I had just gotten myself a mentor.

And what a mentor she is. Despite my inexperience, Bev took me into her laboratory, helping me develop a project that may not have been particularly consistent with the focus of her lab, but one that uniquely suited my needs. She taught me how to think critically and scientifically about my own work and that of others. Through it all, Bev maintained the ability to filter out all of her many other administrative, research, and clinical responsibilities, laser focusing on the concerns of her mentees. Generous with her advice and expertise, she always had time, no matter what grant was due or what meeting required her attendance.

Many of the important lessons I learned from Bev were not based on pearls of wisdom expressed from her mouth to my ear but rather came from observations made by watching her interactions with others. These lessons took shape as a series of clearly discernable patterns: 1) Bev never asks anyone to do anything that she did not do herself; 2) she treats everyone with the utmost respect and consideration; and 3) her motivation outshines any other factor, without relying on confidence-shattering admonitions or reprimands. As a junior faculty member now, I find these leadership-by-example lessons of critical importance and recognize that these are crucial elements of being an effective mentor and leader.

Over the years, I have been the beneficiary of the committed attention and guidance that all of Bev’s mentees enjoy. Her impact on my career, as well as the careers of many before me and many more in the future, is a wonderful legacy for a remarkable mentor.
Consult a Colleague is an online service for ASH members that helps facilitate the exchange of information between hematologists and their peers. ASH members can seek consultation on clinical cases related to the following categories:

- Anemias
- Hematopoietic Cell Transplantation
- Hemostasis/Thrombosis
- Leukemias
- Lymphomas
- Lymphoproliferative Disorders
- Multiple Myeloma and Waldenström Macroglobulinemia
- Myeloproliferative Disorders
- Myelodysplastic Syndromes

To use Consult a Colleague, please visit www.hematology.org/consult. Assigned colleagues will respond to inquiries within two business days either by email or phone. Information about participating consultants is available, including their disclosures.

Consult a Colleague
Get advice on difficult cases from specialists in the field

As technology and the Web have evolved, so too have ASH's online offerings. Now you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster), and visit ASH on Facebook at www.facebook.com/AmericanSocietyofHematology.

What's on the Web

Learn More About the ASH Advocacy Leadership Institute

The third annual ASH Advocacy Leadership Institute will take place in Washington, DC, October 22-23, 2013. This two-day workshop provides an unique opportunity for ASH members to gain a better understanding of the Society and its activities and to learn about legislation and health policy affecting hematology research and practice.

The selection of participants is based on a nomination process, and participation will be by invitation only. Up to 20 participants will be invited to attend the two-day workshop. Nominations are now being accepted through July 31. The exemplary candidate is an ASH member who is a U.S. citizen and is interested in health policy and advocacy and wants to become more involved in ASH activities. Self-nominations are welcome. For more information or to submit a nomination online, please visit www.hematology.org/ALI. You may also send nominations to ASH Legislative Advocacy Manager Tracy Rochele (trochele@hematology.org), and include the following information: nominator's name/phone number; nominee's name/institution; and reason for nomination (short paragraph describing the nominee's interest in this opportunity).