When it comes down to it, quality science, member engagement, and innovative programs are three attributes that distinguish ASH. These features were once again on display at ASH’s inaugural scientific meeting on Lymphoma Biology held August 10-13, 2014, in Colorado Springs, Colorado. This three-day working event brought together more than 400 experts from 22 countries to discuss the latest lymphoma science and to address the current challenges that the field faces in 2014 and beyond.

This meeting was organized to respond to the lymphoma community’s need for a forum specifically focused on basic lymphoma biology and translational research in the United States. It was felt that a smaller working meeting would galvanize the lymphoma biology community and ultimately accelerate development of new therapeutic strategies. A proposal for this meeting, developed by its three co-chairs, Dr. David Weinstock, Dr. Lou Staudt, and Dr. Ari Melnick, was brought forward to the ASH Committee on Scientific Affairs and was subsequently endorsed by the ASH Executive Committee. ASH invited the co-chairs and to the steering committee — Dr. Riccardo Dalla-Favera, Dr. Randy Gascoyne, Dr. John Leonard, Dr. Ronald Levy, Dr. Izidore Lossos, Dr. Grzegorz Nowakowski, Dr. Oliver Press, Dr. Kerry Savage, and Dr. Margaret Shipp — for an outstanding job. They were all very hands-on and committed to this new kind of focused meeting, spending many hours developing the program, reviewing abstracts, and helping with the marketing and fundraising.

The steering committee organized an impressive program that included lectures by many of the acknowledged experts (Cont. on page 2)
Inaugural Lymphoma Biology Meeting

(Cont. from page 1)

in the field of lymphoma biology, including a particularly insightful keynote address by Dr. Klaus Rajewsky from the Max Delbrück Center for Molecular Medicine in Berlin. More than 150 abstracts containing cutting-edge, previously unpublished results were presented in either oral or poster sessions. One of the most exciting outcomes of this inaugural program was that 75 trainees attended the meeting. As evidence of the Society’s commitment to ensuring participation by junior investigators, ASH supported 11 Abstract Awards of $500 each to trainees with the highest-scoring abstracts.

In addition to formal presentations, the meeting included small interactive sessions that were designed to be conducive to building relationships and collaborations. These sessions provided an opportunity for participants to catch up with colleagues, make new connections, and discuss science in a relaxed, informal setting. Additionally, the meeting featured breakout sessions during which participants identified areas of investigation to be included in a collaborative roadmap for lymphoma science. The roadmap generated at the meeting will be submitted for publication in a peer-reviewed journal, and subsequently, the published version will be distributed to investigators, funding agencies, and advocates who support lymphoma research.

The demographic profile of the attendees was broad and included basic and translational scientists from academia and industry, clinicians, established investigators, and trainees. Feedback from conference participants has been overwhelmingly positive, and plans are underway for the next ASH Meeting on Lymphoma Biology scheduled for the summer of 2016. For more information, please visit www.hematology.org/MLB.

The ASH Meeting on Lymphoma Biology is another example of the Society’s innovative approach to providing leadership and resources in support of the vibrant community of clinicians and investigators interested in malignant hematology. By the time this article is published, we will have concluded our State-of-the-Art Symposium focused on the newest developments in malignant hematology, and I am pleased to report that, of the record-breaking 6,500 abstracts submitted for presentation at this year’s annual meeting, more than 3,500 deal with malignant hematology. I am proud that the ASH annual meeting remains the premier venue for the presentation of the most outstanding clinical, basic, and translational research related to malignant hematology, and that ASH remains committed to ensuring that members and nonmembers who identify with this broad field that includes acute and chronic leukemias, lymphoproliferative disorders, plasma cell dyscrasias, myeloproliferative neoplasms, and related transplantation biology know that their scholarly contributions are recognized and respected by the Society.

This column will be my last as President of ASH. I hope that you’ve had as fulfilling a year in your endeavors as I have had representing all of you in serving ASH. It’s been a pleasure and an honor! I’ll be “passing the gavel” to Dr. David Williams in San Francisco, and I know he is looking forward to leading the Society in fulfilling its mission in 2015.

Charles J. Burtnieks, MD

Linda J. Burns, MD

HIF and Hemoglobin in the Himalayas

(Cont. from page 1)

more effectively than wild-type PHD2 under low oxygen tension. In vitro, the development of erythroid colonies (burst-forming unit-erythroid [BFU-E]) and sensitivity to EPO were subsequently compared between Tibetan and control peripheral blood samples under hypoxic conditions of 1 percent and 5 percent O2 (Figure). Whereas increased proliferation, size, and hemoglobinization of BFU-E (as well as heightened sensitivity to EPO) were demonstrated with normal erythroid progenitors, these BFU-E readouts from Tibetans with double variant PHD2 were significantly decreased at 5 percent O2, and growth was abrogated at 1 percent O2. Surprisingly, however, erythroid progenitors from Tibetans homozygous for the double PHD2 variant were hypersensitive to EPO under normoxic conditions—a finding that is unexplained but that mirrors the erythropoiesis phenotypes associated with the aforementioned mutations of EGLN1, EPAS1, and VHL.

Previously described mutations in EGLN1, a negative regulator of HIFs, are loss-of-function variants that result in erythropoiesis. In contrast, the work described here points to c.12CDG,386CG>C as a gain-of-function variant in PHD2 that results in increased degradation of HIF and consequent protection from polycythemia under hypoxic conditions. One of the expected outcomes of gain-of-function at low oxygen tension of variant PHD2 would be decreased EPO production, but the role of EPO in the adaptation to high altitude by Tibetan highlanders was not clarified by the studies of Dr. Felipe Lorenzo and colleagues. Additional genetic variants related to oxygen homeostasis and alterations in other physiologic pathways are likely to contribute to Tibetans’ and other populations’ adaptive response to habitation at high altitude. The evolutionary forces that have selected for emergence of these genetic changes may protect against complications related to increased blood viscosity and pulmonary hypertensive associated with polycythemia, but this hypothesis has not been formally investigated.

The genetic and functional data gleaned from this study should lend more insight into the ubiquitous role of hypoxia in health and disease.

ASH Foundation 3K – 5K Run/Walk

On Sunday, December 7, come kick off your day in a fun and healthy way – run or walk in the ASH Foundation 3K – 5K Run/Walk! Participants can choose between the two distances and will have the option to run or walk. All race proceeds will fund programs supported by the ASH Foundation.

The route will take runners and walkers along San Francisco’s scenic Embarcadero. ASH will operate a continuous-loop shuttle service between the Moscone Center and the Embarcadero before and after the Run/Walk.

Registration is now open at www.hematology.org/runwalk.
The Hematologist Welcomes Its Fifth Editor-in-Chief

CHARLES PARKER, MD, EDITOR-IN-CHIEF OF THE HEMATOLOGIST

It's a real pleasure for me to introduce Dr. Jason Gotlib as the next Editor-in-Chief of The Hematologist. Many of our regular readers will recognize Jason's name as he has served stably as a Contributing Editor since 2010. Jason is currently Associate Professor of Medicine in the Division of Hematology at Stanford University School of Medicine. He has a long-standing interest in myeloproliferative neoplasms in general and in mast cell disease in particular.

After graduating from Franklin and Marshall College in Lancaster, Pennsylvania, Jason attended Stanford University Medical School, and like many who have found their way to Palo Alto, he never left. In addition to his outstanding record as a clinical investigator, Jason's commitment to medical education and training is exemplary. He is Director of the Hematology Fellowship program at Stanford, and since 2005 he has been honored with the Stanford Hematology Division Faculty Teaching Award four times. Jason has served ASH in a number of capacities, including his work with the Committee on Training. Jason is an avid nature photographer, and you can see examples of his work featured in our new sister publication, ASH Clinical News.

Dr. Gotlib will serve a one-year term as editor-in-chief.

The Hematologist: 2014 Annual Meeting Brings a Wave of New Events to San Francisco

The 56th Annual Meeting and Exposition is quickly approaching, and there are several sessions that have recently been added to the program, including Featured Topic sessions, a Special Education session, and a new Friday Scientific Workshop.

As the number of older patients with hematologic disorders increases, there is great need for an enhanced focus on the implications of aging on the development, progression, and optimal treatment of these disorders. To address this scientific need, ASH is now offering a new interactive “Friday Scientific Workshop on Hematology and Aging: Highlighting Novel Science and Developing a Research Agenda,” organized by the Hematology and Aging Special Interest Group, scheduled to take place Friday, December 5, 1:00 to 6:00 p.m., at the 56th ASH Annual Meeting and Exposition. All are welcome to attend this new and exciting workshop, particularly laboratory-based investigators and clinician researchers with an interest in aging and hematology.

Also new this year, ASH's acclaimed ASH/FDA webinar series on newly approved drugs will be extended as the “Special Education Session: Newly Approved Drugs.” This session will feature a selection of hematologic drugs that are newly approved in 2014. Presenters will have significant clinical experience with the new agents. The focus of the session will be for those in the treatment of patients with the new drugs: appropriate population, dosing, side effects, adverse events, drug/drug interactions, and off-label use. The session will be held Monday, December 8, from 4:30 to 6:00 p.m., and speakers will include Dr. Margaret V. Ragni from University of Pittsburgh and Hemophilia Center of Western Pennsylvania; Dr. Dinauer from Cleveland Clinic (Brutinel); and Dr. Steven Coutre, Stanford University School of Medicine (Iself)ablis).

Be sure to keep these sessions in mind when booking your travel and look for more details and updated program information online at www.hematology.org/Annual/Meeting.

ASH Elects New Leadership

VICE PRESIDENT:

Kenneth C. Anderson, MD
Director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Dana-Farber Cancer Institute in Boston; Kraft Family Professor of Medicine and Vice Chair of the Joint Program in Transfusion Medicine at Harvard Medical School

Dr. Anderson will serve a one-year term as vice president, followed by successive terms as president-elect and president.

TREASURER:

Susan B. Shurin, MD
Senior Advisor to the Center for Global Health of the National Cancer Institute at the National Institutes of Health in Bethesda

Dr. Shurin will serve a four-year term as treasurer.

COUNCILLORS:

Mary C. Dinuier, MD, PhD
Fred M. Sighe Distinguished Chair in Pediatric Research and Professor of Pediatrics and of Pathology and Immunology at Washington University School of Medicine in St. Louis; Scientific Director at the Children’s Discovery Institute of Washington University and St. Louis Children’s Hospital

Dr. Dinuier will serve a four-year term as councillor.

Terry B. Gernsheimer, MD
Medical Director of the Platelet Immunology Laboratory at Puget Sound Blood Center, Medical Director of Transfusion at the Seattle Cancer Care Alliance, and Assistant Medical Director of Clinical Transfusion Service at the University of Washington Medical Center; Professor of Medicine in the Division of Hematology and Adjunct Professor of Laboratory Medicine at the University of Washington

Dr. Gernsheimer will serve a four-year term as councillor.

ASH Members Elected to Institute of Medicine of the National Academy of Sciences

The Institute of Medicine (IOM) has announced the election of 70 new members, including two ASH members, one of whom is ASH Councilor, Margaret A. Shipp, MD. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

The two ASH members elected to the IOM are:

Margaret A. Shipp, MD
Chief, Division of Hematologic Neoplasia, Dana-Farber Cancer Institute, Boston

Todd R. Golub, MD
Investigator, Howard Hughes Medical Institute; Chief Scientific Officer, Broad Institute of Harvard and MIT; and Charles A. Dana Investigator, Dana-Farber Cancer Institute, Cambridge

Their communication skills to make these articles understandable and relevant for all of our readers. It’s their contributions that make The Hematologist unique. I would also like to thank those who so generously contributed their expertise and time to development of the “Ask the Hematologist” articles, Mini Reviews, and profiles. These articles have lasting value, and archived versions are now much easier to access through The Hematologist section of the ASH website.

"Only kings, presidents, editors, and people with tapeworms have the right to use the editorial ‘we’."

— Mark Twain

Our focus has been on content, and our editorial mantra has been communication, education, and scholarship. We have aimed to effectively communicate to our diverse readership both information from the Society and information about issues that affect our dynamic field. Education has been at the forefront of our editorial vision. We appreciate the pressure on our readers’ time, and accordingly, every article has been developed with the goal of ensuring that the writing was clear, that the content was easily understandable, and that each contribution had the maximum amount of self-contained educational value. Scholarship and educational value are two sides of the same coin. Most of the responsibilities for maintaining the academic integrity of the publication fell on the shoulders of the Contributing Editors and on the shoulders of those who contributed “Ask the Hematologist” articles and Mini Reviews. The emphasis on scholarship reflects our respect both for the readership of The Hematologist and for the authors of the articles that were reviewed.

I find that one of my greatest ongoing challenges is trying (and often failing) to avoid cynicism. The business and politics of medicine now demand the art and science of medicine, and learning has become regimented and marked by prosaic end-points with names such as MOC and PIM. For me, the best antidote against creeping cynicism is the joy of discovery. Most often now, I am a discovery voyeur, deriving pleasure from reading about a remarkable solution to a long-standing problem, listening to senior colleagues lecture with restrained pride about their research, or hearing trainees excitedly present the results of their first forays in the lab. When you find yourself bemoaning the time and frustrating effort expended on fulfilling the latest billing documentation requirement by your electronic medical record, open The Hematologist; it’s largely a record of accomplishment.
The Use of Genotyping in Transfusion Medicine

MARYLyn J. TeLeN, MD
Wellcome professor of Medicine, Division of Hematology, Associate Medical Director, Duke Hospital Transfusion Service

Potential Benefits of Genotype-Matched RBC Transfusion

SCD
Dr. Daniel Ambruso and colleagues have found in two prospective studies that the incidence of developing antibodies per unit transfused was diminished 10-fold when all patients received such units from ABO and RHD-matched donors.[8] Dr. Osvaldo Castro and colleagues calculated that if all transfusions had been selected by limited phenotype matching (Co+, RhD, and ABO), and alloantibody development would have been prevented for more than half (53.3%) of the 137 alloimmunized SCD patients studied.[9] Recently, Dr. Sale Mine Bakanyan and colleagues showed that previous transfusion led to errors in traditional phenotyping in 51 percent of such patients.[10] Moreover, the RbD and RHCe genes are highly polymorphic, so that D-positive and -negative individuals can be alloimmunized and have a similar frequency of alloantibodies, and thus, the majority of crossmatch failed in negative blood samples are due to alloantibodies.

Clinical Need

One to 2 percent of all patients who receive transfusions develop antibodies to RBC antigens. In patients receiving chronic transfusion (e.g., for sickle cell disease [SCD]), the frequency of alloimmunization is higher, affecting about 20 to 30 percent of recipients,[11] though most patients who develop alloantibodies do so before the 15th transfusion.[2] For patients with hematologic malignancies, the incidence of RBC alloimmunization is estimated at 9 percent to 15 percent,[12] and while the immunosuppressive effects of the chemotherapy patients receive. Thus, alloimmunization to RBC antigens in hematologic patients is relatively common.

Once alloimmunization occurs, the likelihood of additional antibody responses is also relatively high. In surgical patients, pregnant, and non-hematologic malignancy patients, once RBC antibodies have been induced, 20 to 25 percent of patients form additional antibodies after subsequent transfusions.[13] A study in a retrospective study from the Netherlands that covered a 24-year period, 95 of 115 immunized patients (21.7%) had additional antibodies after subsequent transfusions[14] and 25 of 115 immunized patients (21.7%) formed an alloantibody to a previously unrecognized antigen.[15] To confirm the identity of the alloantibody type, all donors and recipients are tested for the presence of isoagglutinins directed against A and B antigens, as plasma from all immunologically normal individuals without an A or B antigen would contain such antibodies. For example, if a recipient’s RBCs type as A, the plasma from that recipient will have anti-B antibodies. Anti-D is neither expected nor naturally occurring in D-negative individuals. In addition, a sensitive screen for alloantibodies to other blood group antigens is done to avoid the mostly delayed hemolytic transfusion reactions that can be caused by such alloantibodies and thus become multiply alloimmunized.

Alloantibodies are formed against blood group alloantigens as a result of transfusions, infections, or other insults. Thus, while ABO and Rh antibodies are easily recognized, thousands of other alloantigens may also exist and cause alloimmunization.

Molecular Basis of Blood Group Antigens and Genotyping Methodology

The molecular basis of erythrocyte blood group antigens began to be defined in the 1980s and 1990s. Before then, relatively few antigens were even characterized biochemically. Most blood group antigens were elucidated at the molecular level during the 1990s and the first decade of the 21st century. Today, 26 erythrocyte blood group antigen systems have been characterized at the molecular level. Most minor blood group antigens reside on proteins whose polymorphisms are due to exchange of one amino acid, arising from differences in the amino acid sequence for which they are encoding gene. The notable exception to this is the MN polymorphism, which involves exchange of two nonadjacent amino acids. For carbohydrate antigens, such as ABO and Lewis, the genetic mechanism of polymorphism resides in the alteration of genes encoding glycosyltransferases involved in synthesis of the antigenic oligosaccharides. However, various variant phenotypes are caused by codon changes in a specific gene. Complex genetic changes, including intra- and intergenic exchanges, inversions, insertions, and deletions, can occur. The RHD and RHCe genes are highly polymorphic, so that D-positive and -negative individuals can be alloimmunized and have a similar frequency of alloantibodies, and thus, the majority of crossmatch failed in negative blood samples are due to alloantibodies.

Several common antigens, to identify those rare donors who are RBC antigen-negative phenotypes resides only in a few reference laboratories that have the scarce (often expensive) test reagents available. Again, genotyping relieves neither on rare antigens nor on reagents of human origin. Thus blood donors can be more readily genotyped than phenotyped for rare alloantigens.

Autoimmune hemolytic anemia

Transfusing patients with autoimmune hemolytic anemia is challenging because the autoantibodies coat the cells, obscuring the differences between negative and positive reactions obtained by using Coombs’ serum (anti-IgG)-induced agglutination. Serological phenotyping in such situations requires that the autoantibody first be chemically stripped off the patient’s own cells before they can be phenotyped. Thus, genotyping of the patient and donors has the potential to allow the transfusion of antigen-matched blood to patients with autoimmune hemolytic anemia,

Alloantibodies to common antigens are only rarely made and are generally reactive at a low titer. Thus, genotyping of the patient and donors has the potential to allow the transfusion of antigen-matched blood to patients with autoimmune hemolytic anemia, saving both time and money. Moreover, methods such as absorption, which are used to remove reactivity due to autoantibodies, run the risk of obscuring the presence of alloantibodies, especially if they are of low titer. Thus, transfusion of genotypically matched blood would also be a safer practice than the use of traditional serological methods in patients with an IgG autoantibody.

Recently transfused patients

In the setting of suspected immune destruction of transfused cells, the transfusion service needs to determine the native phenotype of the recipient in order to correlate that information with any detected RBC alloantibodies. However, after transfusion of several units of blood, much of the circulating RBCs are of donor origin. Given the short half-life of such transfused cells and the fact that an increasing proportion of transfused RBCs are now leukoreduced, genotyping in the setting of recent transfusion is not feasible. Moreover, methods such as absorption, which are used to remove reactivity due to autoantibodies, run the risk of obscuring the presence of alloantibodies, especially if they are of low titer. Thus, transfusion of genotypically matched blood would also be a safer practice than the use of traditional serological methods in patients with an IgG autoantibody.

Rare phenotypes

Alloantibodies to common antigens are only rarely made and are generally reactive at a low titer. Thus, genotyping of the patient and donors has the potential to allow the transfusion of antigen-matched blood to patients with autoimmune hemolytic anemia, saving both time and money. Moreover, methods such as absorption, which are used to remove reactivity due to autoantibodies, run the risk of obscuring the presence of alloantibodies, especially if they are of low titer. Thus, transfusion of genotypically matched blood would also be a safer practice than the use of traditional serological methods in patients with an IgG autoantibody.
**Prenatal diagnosis and risk of HDN**

Routine serologic methods for the prediction of risk for HDN consist of performing a serologic screen for unexpected alloantibodies in the mother’s serum and then titrating any antibodies found. However, it is well recognized that titer and severity of HDN do not necessarily correlate, especially for some common culprits such as anti-K. A second method for determining risk is to phenotype the father’s cells serologically to determine if the father is likely to confer the gene for a particular antigen to the fetus. Fetal genotyping, such testing is especially valuable when the father is not available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive availability, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest. Definitive available, his phenotype is indeterminate serologically, or he is heterozygous for an antigen of interest.

Once the patient’s red blood cells (RBCs) are phenotyped for ABO and RhD antigens, providing appropriate ABO- and RhD-matched RBCs for transfusion is straightforward if no alloantibodies or autoantibodies are detected. However, if the patient’s serum or plasma reacts with reagent RBCs, the specificity of each antibody present must be identified. The patient’s own RBCs are phenotyped to confirm the validity of antibody identification. In the presence of autoantibody or an antibody that reacts with a very high frequency antigen, the process of antibody identification and phenotyping of the patient’s RBCs becomes technically difficult, often requires the availability of rare reagent cells and sera, and is highly time-consuming.

**Are We Ever Going to be Able to Avoid Transfusion of Units Likely to Engender Alloimmunization?**

Although delayed hemolytic transfusion reactions rarely cause more than transient clinical problems, there are particular populations in which this is not true. Patients at particular risk are those with frequent transfusion requirements, limited capacity to produce RBCs, or chronic hemolysis. High-throughput genotyping methods can be applied to both patients and blood donors, resulting for the first time in the possibility of providing genotype-matched, rather than just ABO/RhD-matched or crossmatch-compatible, RBCs. This approach has the great advantage of potentially avoiding almost all alloimmunization, along with the consequent medical complications of such alloimmunization.

It is also likely that even genotype-matching of RBCs will neither be foolproof nor become the sole methodology used in blood centers and transfusion services. DNA-based methods thus far are designed to detect known gene variations that affect protein sequence or, in rare cases, protein expression (such as the GATA site mutation in the FY allele). Rare alleles that interfere with gene expression (such as ones affecting mRNA splicing, for example) are likely to lead to results predicting positivity for an antigen that is actually unexpressed, and occasional variants may exist but evade detection for technical reasons. Some complex genetic changes, such as hybrid alleles common in the RH and MNS systems, may lead to false-negative and false-positive results. And the number of known alleles for some blood group systems (especially RH and ABO) are too large to be practicably addressed by currently available technology. Finally, some systems remain to be characterized on the molecular level. Nevertheless, it is likely that technologies such as next-generation sequencing will ultimately supplant current methods and lead to the capacity to genotype more completely even the complex RH and ABO systems, as well as to identify the molecular basis of yet uncharacterized antigens.

In Helsinki in 1924, Dr. Erik von Willebrand noticed a 7-year-old girl with excessive bleeding in Finland who had a history suggestive of an inherited bleeding abnormality. Subsequent investigation revealed that 23 of 66 family members were affected by a disease process with an apparent autosomal dominant mode of inheritance that was characterized clinically by abnormally mucocutaneous bleeding.

The eponymous disease first characterized by von Willebrand 90 years ago is thought to be the world’s most common inherited bleeding disorder, associated with the >1700 vWF sequence variants that have been shown to affect binding and internalization of vWF in vitro, is particularly difficult to standardize and has a coefficient of variation as high as 50%. Despite this high coefficient of variation, and acknowledging that ristocetin-induced platelet agglutination is not a normal physiologic process, vWF:RCo has remained the gold standard for diagnostic laboratory testing for vWF activity. Recently, modifications of the platelet aggregation using chemiluminescence and turbidimetric detection methods have been introduced in an effort to improve vWF:RCo’s utility,3,4 and a ristocetin-independent ELISA assay that uses a gain-of-function GPIbα mutant to mediated vWF binding activity has been developed.6 Another measure of activity is based on the capability of vWF to form multimers of collagen type IV. The plasma concentration of vWF is a continuous variable and because mild bleeding abnormalities of vWF with an autosomal recessive inheritance pattern due to homozygous or compound heterozygous mutations of vWF is relatively straightforward, such is not the case for hereditary vWD. In addition, a mild to moderate quantitative deficiency of vWF, approximately 70 to 80% of vWF cases are classified as type 1.

**Diagnosis of Type 1 VWD**

According to the National Heart, Lung, and Blood Institute (NHLBI) Guidelines1 and a recent publication by the British Committee for Standards in Haematology,2 a definitive diagnosis for type 1 VWD requires the following:

- A personal history of abnormal mucocutaneous bleeding.
- Quantitative deficiencies in plasma vWF.
- Functional consequences of mutations affecting the particular binding site.8 Thus, testing for vWF activity is considered the best tool for making a diagnosis of type 1 vWd. molecular testing is not a definitive approach for the diagnosis of type 1 vWd. Molecular testing is being used in research to study vWF abnormalities with an autosomal dominant mode of inheritance, and type 3 vWd (complete or near-complete absence of vWF) has remained the same throughout the past decade, but the level of vWF required to meet the diagnostic criteria for type 1 VWD has been lowered.

While diagnosis of type 2 vWd (a group of qualitative abnormalities of vWF with an autosomal dominant mode of inheritance), and type 3 VWD (complete absence of vWF with an autosomal recessive inheritance pattern due to homozygous or compound heterozygous mutations of vWF) is relatively straightforward, such is not the case for hereditary vWD. In addition, a mild to moderate quantitative deficiency of vWF, approximately 70 to 80% of vWF cases are classified as type 1.

**Conclusions**

Although progress has been made in understanding the functional consequences of mutations affecting vWF, studies in the European Union, United Kingdom, Canada, and the United States have reported that sequence variations in the vWF gene are not as rare as once thought when using polymerase chain reaction testing has proven to be clinically problematic, however, because individuals with low vWF may be at risk for bleeding and may warrant desmopressin (DDAVP) or other replacement therapy, yet insurance providers may balk at covering treatment for patients who do not carry a type-specific diagnosis of vWD.

In practice, experienced clinicians decide on whether or not to recommend prophylactic DDAVP or replacement therapy in patients with a bleeding history using vWF levels in a manner analogous to the way that practitioners use risk factors in caring for patients with coronary disease or diabetes when making a decision about the use of heparin prophylaxis.2 Thus, an argument can be made that drawing a “line in the sand” for diagnosis of type B vWD by requiring vWF levels of 30 IU/dL is a flawed strategy that compromises patient care. In support of this position, emerging evidence suggests that the functionally relevant vWF concentration (the concentration below which pathologic bleeding is observed) lies somewhere between 30 and 50 IU/dL.14 Most clinicians experienced in the management of patients with disorders of hemostasis recommend treating patients with type 1 vWd (low vWF) only if their patients with type 1 vWd are at higher risk for bleeding, or if their patients with type 1 vWd have a history of abnormal bleeding or have an affected family member. In some settings, such as before surgery, or in the case of patients with a bleeding history, educating insurance providers about the need for such treatment is important. Management of patients with low vWF is to forego prophylaxis prior to minor surgery but to have treatment available in the event that excessive bleeding is observed. This approach can also guide future management recommendations. For example, a patient rescued from excessive bleeding following a minor surgical treatment would be a candidate for prophylactic treatment should a subsequent procedure be required.

Progress in the diagnosis of type 1 vWD during the last few years has focused on 1) improvements in laboratory testing, 2) alternative tests of platelet-vWF-binding activity that do not rely on the use of ristocetin as the agonist for vWF binding to collagen, 4) incorporating genetic testing into laboratory diagnosis, and 5) development and validation of new therapeutic strategies for vWD. The rvWF product was found to differ from plasma-derived vWF concentrates in that it contained high molecular-weight polymers, a property that might enhance its specific activity.

For those who do not respond to the aforementioned treatment, those with certain type 2 vWd variants, those with type 3 vWd, or those undergoing major surgical procedures, plasma-derived vWF concentrates are used as factor replacement therapy. All commercially available vWF concentrates are subject to viral inactivation manufacturing steps but differ in the methods of protein fractionation and purification. More recently, a recombinant vWF concentrate (rVWF) has been found to be safe in a prospective clinical trial, but this product is awaiting approval by the FDA.20 The rVWF product was found to differ from plasma-derived vWF concentrates in that it contained high molecular-weight polymers, a property that might enhance its specific activity.

**Management of VWD**

Management of type 1 vWd has remained largely the same for the last 20 years. DDAVP is widely used to treat mucocutaneous bleeding and bleeding associated with minimally invasive surgical procedures.21 However, in some patients with type 1 vWd with increased clearance of vWF, referred to as type 1C vWd,21 and in type 2 vWd variants (qualitative abnormalities), DDAVP may not be effective. Moreover, for reasons that are not understood, some type 1 patients simply do not respond to DDAVP. Patients in whom DDAVP therapy is being considered should be subjected to a therapeutic challenge with measurements of vWF:Ag, vWF:RCo, and FVIII:C at baseline, and at one, two, and four hours after DDAVP administration. Other therapeutic options include the antifibrinolytics (aminocaproic or tranexamic acid) and oral contraceptives for menorrhagia in women with vWD.

References


FY 2015 Funding for NIH Still in Question; Congress to Tackle Funding Issues During “Lame Duck” Session

Because of a shortened congressional schedule due to the mid-term elections, Congress was unable to complete work on any of the fiscal year (FY) 2015 spending bills that fund federal government programs, including the National Institutes of Health (NIH). The federal fiscal year began on October 1 with the appropriations process not finalized. To avoid a government shutdown, Congress passed a continuing resolution that appropriates funding of federal government programs at FY 2014 levels through December 11, 2014. For NIH, this means a budget of $28.9 billion per year.

Following the November elections, Congress will convene a “lame duck” session to complete work on the FY 2015 appropriations bills. While Democrats in the House and Senate are expected to continue efforts to restore NIH funding to its pre-sequester level of approximately $30.6 billion, many political observers suggest that if the Senate flips (with Republicans in the majority beginning in January), most Republicans will want to postpone finalizing spending legislation for 2015 until the 114th Congress convenes in January, when they have control of both chambers.

Meanwhile, as part of the Society’s continued advocacy in support of NIH, ASH was a sponsor and supporter of the September 18 Rally for Medical Research Hill Day in Washington, DC. The Hill Day included nearly 200 organizations and represented another opportunity for the NIH advocacy community to join together to push for sustainable investments in medical research that will ultimately benefit patients. Hundreds of scientists, medical research advocates, health-care providers, and patients (including ASH members and staff) were in attendance, calling on our nation’s policymakers to make funding for the NIH a priority and raising awareness about the importance of continued investment in scientific research.

ASH will continue its advocacy efforts, supporting increases for NIH on Capitol Hill throughout the remainder of the FY 2015 budget debate. The Society encourages all members to visit the ASH Advocacy Center at www.hematology.org/advocacy to join ASH’s campaign urging Congress to support increased funding for NIH.

ASH Co-Hosts Congressional Briefing on Sickle Cell Disease

On September 16, in support of the new evidence-based expert panel report on the management of sickle cell disease (SCD) published by the National Heart, Lung, and Blood Institute (NHLBI), and in recognition of Sickle Cell Awareness Month, ASH co-hosted a briefing on Capitol Hill to highlight the need for state-of-the-art clinical care for patients with SCD. The briefing highlighted the recommendations from the NHLBI report, identified challenges facing patients, discussed how the recommendations will impact patient care, reviewed NHLBI’s SCD portfolio, identified gaps in current medical research, and proposed areas for future study that were identified in ASH’s recently released list of research priorities for SCD and sickle cell trait. The briefing featured remarks from the co-chairs of the co-hosts: Sickle Cell Disease Caucus, Rep. Danny Davis from Chicago and Rep. Charles Rangel from New York, and included presentations from the following speakers:

- Gary Gibbons, MD, Director of the National Heart, Lung, and Blood Institute, who provided an overview of the NHLBI expert panel report and NHLBI’s SCD research portfolio.
- Carlton Haywood Jr., PhD, MA, from the Johns Hopkins School of Medicine and Berman Institute of Bioethics – a sickle cell patient advocate who spoke about the challenges for SCD patients and potential benefits of the new recommendations.

### MARK YOUR CALENDAR: POLICY AND PRACTICE EVENTS AT THE ASH ANNUAL MEETING

**Join ASH leaders and colleagues at the ASH Grassroots Network Lunch on Saturday, December 6, from 11:15 a.m. to 12:15 p.m. in the Intercontinental San Francisco, Grand Ballroom A/B.** In addition to learning how you can participate in ASH’s advocacy efforts, communicate with Congress and the White House, and become an effective advocate for hematology, you will hear about the impact of federal deficit reduction on health care and biomedical research and how the results of the November congressional elections may affect hematology. The program will also feature an overview of ASH advocacy highlights from 2014 and a preview of the 2015 ASH advocacy agenda.

The ASH Practice Partnership (APP) is ASH’s network for practice-based hematologists to enable them to elevate their issues of importance within the Society. The APP Lunch is a special session during the ASH annual meeting dedicated to the practice community. The program will be held on Sunday, December 7, from 11:15 a.m. to 12:30 p.m. in the Metropolitan Ballroom of the Westin San Francisco Market Street. The 2014 session will focus on the challenges associated with mergers between traditional community-based private practices and larger health-care systems. The format will feature a dialogue between a hematologist who has successfully navigated a merger with a larger health-care system and a nationally recognized health-care attorney who has worked on mergers involving hematology practices. The final part of the session will provide a networking opportunity for practice-based hematologists to meet with colleagues and ASH leaders.

Twelve-five hematologists (pictured) from throughout the United States came to Washington, DC, in early October to attend ASH’s Advocacy Leadership Institute (ALI). Participants learned about the major issues facing the field of hematology today, including congressional budget cuts to the National Institutes of Health (NIH). ASH members called on their representatives to reverse the damaging impact that cuts to the NIH have had on research and their patients and advocated for legislation to provide insurance coverage parity for all cancer drugs. For more information on ALI please visit www.hematology.org/ALI or contact ASH Legislative Advocacy Manager, Tracy Roades, at troades@hematology.org.

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Flipping in the Plasma Membrane


The phospholipid composition of the plasma membranes of most eukaryotic cells is composed primarily of phosphatidylcholine (PC), sphingomyelin; and two aminophospholipids, phosphatidylserine (PS) and phosphatidylethanolamine (PE). PC and sphingomyelin are asymmetrically distributed to the outer leaflet of the membrane, whereas PS and PE are located primarily in the inner leaflet. Disruption of the lipid asymmetry and movement of PS to the outer leaflet results in phagocytosis by macrophages of cells undergoing apoptosis. Additionally, PS exposure on the platelet surface promotes assembly of coagulation complexes, which is necessary for normal hemostasis.

Phospholipid membrane asymmetry is regulated by three types of enzymatic activity.1 Flippases are ATP-dependent translocases that transport aminophospholipids from the outer leaflet to the inner leaflet (Figure). Conversely, scramblases transport lipids from the inner leaflet to the outer leaflet. Scramblases are ATP-independent translocases that move aminophospholipids in both directions (Figure). Although TMEM16F and Xkr8 have been identified as scramblases involved in apoptosis and platelet function, respectively,2-3 the enzyme(s) responsible for flippase activity are not well characterized. Leading candidates for flippase activity are members of the type 4 subfamily of P-type adenosine triphosphatases (P4-ATPases), including ATP11C.4

Dr. Katsumori Segawa and colleagues in the laboratory of Shigekazu Nagata at Kyoto University used a gene-trapping strategy5 to identify and characterize flippase function in mammalian cells. A retroviral vector was used to introduce inactivating insertions in the haploid KBM7 human cell line. The advantage of haploid cells over diploid cells is that inactivation of one allele rather than two alleles is required to induce complete loss of function. An additional advantage of the gene-trapping method used by Dr. Segawa and colleagues is that the integrated DNA sequences provided a tag that allowed the investigators to readily identify the disrupted gene. Loss of flippase function in KBM7 cells was assayed by measuring cellular uptake of the fluorescent dye, 7-Nitro-2,1,3-benzoxadiazol-4-y1–tagged PS (NBD-PS), a process that requires flippase activity. Mutagenized cells with low flippase activity were identified by flow cytometry and isolated by fluorescence-activated cell sorting. The advantage of haploid cells over diploid cells is that live, non-apoptotic cells can be engulfed if PS is exposed. The possible clinical relevance of this finding is underscored by the observation that phagocytosis of living, healthy neurons may play a role in the pathophysiology of neurodegenerative disorders, and, conversely, evasion of phagocytosis by cancer cells may contribute to malignancy.6 The results of this study also provide a possible explanation for the observation that B-cell maturation in ATP11C-defective mice is abnormal. If ATP11C were the only P4-ATPase expressed in early B-cell development, ATP11C-deficient cells would expose PS and be cleared by macrophages.

The CDC50A gene in W3 cells also was mutated using the CRISPR/Cas system. Cell lines containing CDC50A truncations displayed loss of flippase function, exposed PS on the cell surface, and could not support the expression of ATP11C on the plasma membrane. These functional defects were rescued by transformation with the wild-type CDC50A gene. Living (non-apoptotic) CDC50A-deficient cells, but not CDC50A-rescued cells, were engulfed by macrophages in vitro. Engulfment of living CDC50A-deficient KBM7 cells by macrophages was also observed, and engulfment was blocked by D89E MFG-E8, a protein that binds PS.

The results of this study demonstrate that ATP11C is a PS flippase and that CDC50A is a functional subunit of ATP11C. The finding that macrophages engulf CDC50A-deficient cells indicates that live, non-apoptotic cells can be engulfed if PS is exposed. The possible clinical relevance of this finding is underscored by the observation that phagocytosis of living, healthy neurons may play a role in the pathophysiology of neurodegenerative disorders, and, conversely, evasion of phagocytosis by cancer cells may contribute to malignancy.6 The results of this study also provide a possible explanation for the observation that B-cell maturation in ATP11C-defective mice is abnormal. If ATP11C were the only P4-ATPase expressed in early B-cell development, ATP11C-deficient cells would expose PS and be cleared by macrophages.


Dr. Lollar indicated no relevant conflicts of interest.
When most hematologists happen to think about Factor XIII (FXIII), for example when taking a maintenance of certification (MOC) exam encouraged by The American Board of Internal Medicine, they might remember being called by an obstetric or pediatric colleague to assess a newborn with bleeding from the umbilical stump or by a neurologist or neurosurgeon to evaluate a patient with a spontaneous intracranial hemorrhage, the two most common clinical manifestations of congenital FXIII deficiency. Formerly known as fibrin-stabilizing factor, FXIII is a transglutaminase that circulates in the plasma as a proenzyme. When activated by thrombin, FXIII catalyzes the formation of intermolecular crosslinks between epsilon-N-(γ-glutamyl)-lysine residues in the γ- and α-chains of fibrin to stabilize and prevent dissolution of the clot, thereby promoting wound healing.

Red blood cells (RBCs) have long been thought to be bystanders in the process of clot formation, passively trapped in thrombi and doing little more than accounting for most of the bright color in the photographs of occlusive thrombi in the pulmonary arteries of patients whose cases were under discussion at our morbidity and mortality conferences. Recently, however, renewed attention has focused on the role of RBCs in thrombosis and hemostasis. RBCs can influence the clot’s fibrin network, its viscoelastic properties, and its rate of fibrinolytic degradation. Furthermore, RBCs can interact with fibrinogen, while red cell–derived microparticles can activate coagulation and complement pathways. A recent rate of fibrinolytic degradation. Furthermore, RBCs can interact with fibrinogen, while red cell–derived microparticles can activate coagulation and complement pathways. A recent report showed that RBCs in the clot assume a polyhedral shape that functions to seal the clot and aid in clot retraction.1 Now, Dr. Maria Aleman and colleagues in the laboratory of Dr. Alisa Wolberg at the University of North Carolina, Chapel Hill, demonstrate that FXIII is critical for RBC retention within clots, thereby directly affecting thrombus size and providing a potential new target for preventing or limiting the extent of venous thrombosis.

This study critically redefines the physiology of venous thrombus formation and suggests a novel therapeutic target to reduce venous thrombosis. Rather than simply being snared in the fibrin net, RBCs are actively retained through a fibrin-FXIII–dependent process. On the one hand, this process would favor a seal to support wound healing. On the other hand, venous thrombus size is dependent on RBC content, and thus, hypothetically, clot size could be reduced by limiting RBC incorporation by interfering with FXIII function (Figure 2).

The number 13 is usually associated with bad luck, and fear of the number 13 is a specifically recognized neurosis, triskaidekaphobia. The studies of Dr. Aleman and colleagues, however, suggest that, in hematology, 13 is potentially a lucky number because development of specific inhibitors of FXIII is a strategy that could be exploited to lessen the morbidity and mortality of thromboembolic disease by reducing thrombus formation and size.

When Dr. Maria Aleman and Dr. Alisa Wolberg determined that the source of this unusual red cell behavior was FXIII, they hypothesized that FXIII–dependent process. On the one hand, this process would favor a seal to support wound healing. On the other hand, venous thrombus size is dependent on RBC content, and thus, hypothetically, clot size could be reduced by limiting RBC incorporation by interfering with FXIII function (Figure 2).

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### Lucky 13: How Factor XIII Helps Recruit Red Blood Cells into Clots

When Stem-Cell Transplantation Becomes Preventive Medicine: Early Diagnosis and Treatment of Primary Immunodeficiencies


Inherited deficiencies of the adaptive immune system are rare diseases, but the consequences of such diseases are grave because affected infants and children are rendered susceptible to life-threatening infections. Among the inherited immunodeficiency syndromes, severe combined immunodeficiency (SCID) presents particularly complex diagnostic and therapeutic challenges because the syndrome is so diverse at both the genetic and cellular levels. Transplantation of allogeneic hematopoietic stem cells has long been known to be curative in children for whom a suitable matched allograft is available. Outcomes for recipients of unrelated grafts and older children appeared to be less successful than those observed for patients who have a matched sibling donor; however, the rarity of the condition, in conjunction with the variability of transplantation approaches used in clinical trials, compromised the quality of evidence on which such impressions were based.

Now, by retrospectively analyzing transplantation outcomes in 240 children treated at 29 North American centers, Dr. Sung-Joon Paik and colleagues on behalf of the Primary Immune Deficiency Consortium, provide compelling data that can be used to guide more rationally the management of patients with SCID. Predictably, patients in the study were genetically diverse, with heterogeneous infections of donor source, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis. Nonetheless, the authors found that the presence of prior infections and older age at the time of transplantation were key factors that predicted for shorter survival. The authors suggested that recipients younger than 3.5 months at the time of transplantation had less time and fewer opportunities to develop invasive infections and resulting organ compromise, they fared best, with a 94 percent overall survival at 5 years, regardless of donor type. This interpretation was supported by the observation that children who were older than 3 months at the time of transplantation had a significantly lower overall survival rate (80% 95% percentile, 5-year survival). Other noteworthy findings included the relationship between immune reconstitution and graft source (more favorable for matched sibling donors) and the impact of pretransplant conditioning (more favorable for reduced-intensity or myeloablative). The genetic subtype of SCID affected the quality of CD3+ T-cell recovery but not of survival. Together, the findings of this study suggest that transplants from donors other than matched siblings are associated with excellent survival among infants with SCID identified before the onset of infection, and that all available graft sources are expected to lead to excellent survival among asymptomatic infants.

The impact of early diagnosis and prompt treatment on survival is particularly exciting when considered alongside a recent report on the results of newborn screening for primary immunodeficiency diseases. Dr. Antonia Kwan and colleagues reported on the results of a SCID screening program that included 3 million infants from 10 states and the Navajo Nation. Those investigators found that molecular testing for T-cell receptor excision circles provides a cost-effective screening tool that can be efficiently combined with flow-cytometry when necessary for validation of selected cases. Using this approach, the study found that the incidence of SCID (one in 58,000 births) is higher than generally thought. Remarkably, no cases of SCID were missed in the target population, nor did this strategy result in false-positive assignment of disease. These results clearly illustrate that there are currently available cost-effective diagnostic techniques that can reliably identify SCID patients based on analysis of postnatal blood spots. This study also validates the U.S. Department of Health and Human Services’s 2010 recommendation to expand SCID testing in newborn screening panels beyond the 23 states currently participating in the program.

The value of disease screening is ultimately tied to the effectiveness of available therapeutic interventions, and, when considered together, these two timely studies make a compelling case for nationwide SCID screening. Dr. Kwan and colleagues acknowledge that the molecular techniques used for screening must be standardized, and they emphasize the importance of improving existing administrative infrastructure to allow for more efficient and timely referral of patients.

Collaborative group studies such as these can provide unique insights into the natural history of rare diseases. Together, the studies of Dr. Kwan and colleagues and Dr. Pai and colleagues show that genetic screening can identify patients with inherited immunodeficiencies, enabling the opportunity for expedited referral at a time when stem-cell transplantation serves as an effective, and almost uniformly successful, treatment option. While the high cost of the transplantation procedure cannot be ignored, the upfront cost of transplantation compares favorably with the cumulative cost of noncurative approaches that merely address the downstream complications of primary immunodeficiencies. Disease prevention remains the most clinically beneficial and cost-effective strategy for long-term health improvement in the population. Avoiding much of the medical, emotional, and financial burden currently facing patients and their families should be more than sufficient motivation to implement nationwide screening and preemptive treatment programs for SCID and other well-characterized inherited diseases.

Epigenetic Therapy Holds Promise for G6PD-Deficient Patients and Malaria Elimination Strategies


Epigenetic control of gene expression is a complex process involving interactions between genomic DNA, a functionally diverse group of nuclear proteins, and small regulatory RNA molecules. These factors modify DNA and chromatin without changing the sequence of genes. The epigenetic processes of post-translational acetylation and deacetylation of histone proteins are important regulators of gene transcription. In general, histone acetyltransferases (HATs) activate gene transcription, whereas histone deacetylases (HDACs) are associated with transcription silencing. Epigenetic therapy holds much promise for the treatment of a variety of hematologic diseases, and HDAC inhibitors (HDACis) are currently in clinical use for the management of hemoglobinopathies, as well as for hematologic malignancies and some enzympathies. The therapeutic mechanism of HDACis is diverse, in that induced cytotoxicity is determined by the stage of the cell cycle, its exposure to HDACis, and the epigenetic status of the genome. HDACs cause a general increase in histone acetylation, but this effect is heterogeneous, both in terms of the genes that are affected and of the level of activity induced. Two recent studies examined the role of HDACis in the restoration of some genes is upregulated by this process, and expression of others is downregulated. Similar anomalies are observed with other epigenetic modifiers such as hypomethylating agents.

Disorders of red cell enzymes involved in glycolysis and the pentose phosphate pathway are caused by defects in the genes encoding these enzymes and are characterized by chronic hemolytic anemia. The underlying mutations are typically missense events that cause a decrease in enzyme activity (as opposed to nonsense mutations that cause complete loss of function). These observations prompted Dr. Kalliopi Makarona and colleagues in the laboratory of Dr. Anastasios Karadimitris of Hammersmith Hospital in London to investigate whether HDACis could be used to upregulate expression of genes involved in the glycolytic and pentose phosphate pathways and thereby ameliorate clinical symptoms. Initial analysis in B cells and proerythroblasts that had been treated with the HDACi sodium butyrate revealed that both of the 16 enzymes involved in the glycolytic and pentose phosphate pathways, only glucose-6-phosphate dehydrogenase (G6PD) mRNA was increased. Further investigation revealed the mechanism underlying increased G6PD transcription. HDAC inhibition resulted in hyperacetylation of the G6PD gene promoter, which led to the recruitment of selected HAT and HDAC proteins and a change in the dynamic equilibrium between members of these two protein families. This change increased accessibility of the promoter, enabling the transcription factor Sp1 to bind and recruit RNA polymerase II, thereby initiating transcription of the G6PD gene. The next step was to investigate the effect of HDACi on erythroid precursor cells from patients with G6PD deficiency. Samples derived from five patients, each with a different missense mutation, were studied. In all five cases, there was an increase in G6PD mRNA from the defective allele located on the X chromosome and a concomitant increase in the amount of functional enzyme that was sufficient to restore activity to normal levels.

These exciting findings provide proof of principle that G6PD deficiency can be overcome in nucleated erythroid precursors in vitro by epigenetic therapy, but they also highlight the gaps in our knowledge about the basis of the specificity of HDACis (i.e., Why was G6PD the only one of the 16 genes involved in the glycolytic and pentose phosphate pathways whose expression was enhanced by the HDACi?). Nonetheless, the results of these preclinical experiments are encouraging and suggest that further studies aimed at investigating in vivo efficacy are warranted. An effective epigenetic therapeutic strategy would have important consequences not only for treating G6PD-deficient individuals with clinical significance, but also for the management of malaria. G6PD deficiency is common in areas where malaria was or still is endemic, as it ameliorates disease severity and thus provides an evolutionary advantage. Development of resistance to antimalarials can be triggered in G6PD-deficient patients by primaquine, an antimarial drug that targets hypoxanotes of Plasmodium vivax and gametocytes of Plasmodium falciparum. Evasion of these parasite stages are of crucial importance in malaria elimination efforts. Therefore, a treatment option that would allow patients with G6PD deficiency to be safely treated with primaquine would be particularly relevant clinically.
Targeting Bromodomain Proteins in DLBCL

Recent studies have demonstrated that inhibition of the bromodomain and extraterminal (BET) family of proteins leads to suppression of c-MYC expression. BET proteins fall into the category of epigenetic readers because they contain tandem protein modules (bromodomains) that ‘read’ (i.e., bind to) acetylated lysines in histone tails. BRD4, a member of the BET family, facilitates transcription of activated chemotherapy via a cascade of protein complexes, including the mediator complex and the super elongation complex. Through this mechanism, BRD4 contributes to malignant transformation by increasing expression of oncoproteins such as c-MYC. In the current article, Dr. Sally Trabucco and colleagues from the University of Massachusetts School of Medicine studied JQ1, a novel agent that holds exciting promise for improving outcomes in poor-prognosis populations are urgently needed.

The studies of Dr. Trabucco and colleagues suggest that targeting BRD proteins with JQ1 in both ABC and GCB subtypes of DLBCL was independent of the molecular subtype of DLBCL. In the current article, Dr. Sally Trabucco and colleagues from the University of Massachusetts School of Medicine studied JQ1, a novel agent that holds exciting promise for improving outcomes in poor-prognosis populations are urgently needed.

Heme-Regulated Differentiation of Monocytes to Macrophages Reveals Interconnections of Hemolysis, Metabolism, and Macrophage Differentiation

Using transgenic mice engineered to co-express Spi-C and green fluorescent protein, Dr. Malay Haldar in the lab of Dr. Kenneth Murphy at Washington University in St. Louis identified the location and characteristics of cells expressing Spi-C. Such cells were found in splenic red pulp, the bone marrow, and the liver. Spi-C expression was found to have a moderate effect in the bone marrow, liver, and spleen. The spleen and liver of transgenic mice lost their Spi-C-expressing macrophages as a consequence of heme toxicity when exogenous heme administration was combined with either genetic deficiency or chemical inhibition of heme oxygenase, or with phenylhydrazine-induced hemolysis. As the Spi-C-expressing macrophages were killed by heme toxicity, a population of cells with the myeloid marker CD11b and low expression of Spi-C appeared in both of these organs.

The mechanism for the heme-mediated induction of Spi expression was shown to be heme-mediated enhancement of proteasome-dependent degradation of Bach1, a transcriptional repressor of Spi-C.

Some hemeolytic disorders may be sufficiently severe such that they cause excessive accumulation of cytotoxic heme that is lethal for the splenic, marrow, and hepatic macrophages responsible for the normal, steady-state metabolism of heme and iron due to erythrocyte turnover. Under these pathological conditions, the excess heme mediates differentiation of monocytes into macrophages restoring the capacity of the spleen, marrow, and liver to metabolize the excess heme and recycle the iron needed for the increased erythropoiesis that accompanies this hemolysis. This induction of macrophages that result in heme degradation and iron recycling is critical in those studying monocyte-macrophage differentiation, transcription factors, and heme and iron metabolism.

In the clinical setting, a heme-mediated increase in splenic macrophage numbers helps explain the splenomegaly that arises during active hemolysis in malaria and autoimmune hemolytic anemia. In terms of therapy, spleenectomy reduces the numbers of erythrophagocytic macrophages in severe cases of immune-mediated hemolytic anemia and hereditary spherocytosis, but suppression of heme-mediated differentiation of monocytes in such situations could potentially reduce the hemeolytic rate and, thereby, obviate splenectomy.


11
The functional capacity of hematopoietic stem cells (HSCs) declines with age, due in large part to the consequences of cumulative DNA damage, with age-related deficiency in DNA repair leading to acquisition of mutations that lead to bone marrow failure and myeloid malignancies. With the aging of the baby boomer generation, the incidence of myeloid disorders is expected to rise. Therefore, understanding the basis of both age-related bone marrow dysfunction and the origins of myeloid neoplasms is essential for development of strategies for addressing these disorders. The recent studies of Dr. Johanna Flach and colleagues in the laboratory of Dr. Emmanuelle Passegué at the University of California, San Francisco, provide novel insights into the mechanisms that underlie age-related decline of HSC function and identify molecular targets for rejuvenation strategies. In experiments that compared outcomes in purified HSCs from young and old mice, those investigators presented data suggesting that replication stress contributes to the chromosomal damage and functional decline characteristic of old HSCs (Figure).

The term "replication stress" encompasses a variety of mechanisms that impair DNA copying at replication forks, including delay in cell cycle kinetics, defective prereplication cycle activity, altered replication dynamics, and chromosomal breaks/gaps (Figures). The capacity to circumvent replication stress is central to the maintenance of genomic stability. Replication stress is accompanied by phosphorylation of histone H2AX (γH2AX) – an epigenetic mark that serves as the nidus for recruitment of DNA repair proteins (Figure). Dr. Flach and colleagues found evidence of increased replication stress in old HSCs compared with young HSCs during cell cycling that was accompanied by accumulation of γH2AX foci (Figure, small green stars). Subsequent studies identified decreased expression of minichromosome maintenance (MCM) helicase components MCM 4 and MCM 6 as the mechanism underlying the greater replication stress observed in old cycling HSCs. The deficiency of MCM components altered replication fork dynamics and impaired progression through the cell cycle, resulting in chromosome gaps and breaks. Nonetheless, old HSCs remain competent in activating canonical DNA damage repair and thereby survive replication unless confronted by a strong replication challenge such as treatment with a replication stressor drug or transplantation (Figure).

To test the relative sensitivity of young and old HSCs, the investigators treated samples with aphidicolin, a DNA polymerase inhibitor that induces replication stress by stalling the copying process at the replication fork. After treatment with aphidicolin, old HSCs had significantly greater γH2AX accumulation and rates of apoptosis compared with treated young HSCs, demonstrating the relative insensitivity of young HSCs to replication stress compared with their old counterparts. However, compared with untreated young HSCs, transplantation of aphidicolin-treated young HSCs resulted in impaired reconstitution capacity, reduced engraftment, and early-onset bone marrow failure and death in transplant recipients – outcomes that were similar to those observed with treated or untreated old HSCs. Thus, forced induction of replication stress in young HSCs recapitulated the aging defect.

Once old HSCs re-established quiescence after cycling, aggregated, residual γH2AX is observed in reformed nucleoli of the postmitotic cells (Figure, large green stars). Because replication stress is intrinsically linked to cell proliferation, the authors sought an alternative mechanism that could account for the large γH2AX foci in quiescent old HSCs. The authors discovered that the persistence of γH2AX in old, quiescent HSCs was due to misregulation of PP4c, a γH2AX phosphatase (Figure). In this case, PP4c remained in the cytoplasm rather than translocating to the nucleus where it would be available to dephosphorylate γH2AX. In this setting, persistent nuclear γH2AX functions noncanonically as a histone modifier, epigenetically silencing transcription of ribosomal DNA genes, resulting in decreased ribosomal biogenesis in quiescent old HSCs (Figure). Whether this decreased ribosomal DNA synthesis induced by γH2AX accumulation creates a ribosomopathy that contributes to age-related bone marrow failure remains to be determined (Figure).

The studies of Dr. Flach and colleagues suggest that replication stress contributes to the functional decline of old HSCs. Their rigorous studies identified decreased expression of components of the MCM helicase complex as the basis of the replication defect in cycling old HSCs and suggested that ribosomal biogenesis is impaired in quiescent old HSCs due to aberrant epigenetic silencing of ribosomal DNA transcription by γH2AX. This important work identifies decreased expression of MCM genes, and perhaps decreased ribosomal biogenesis owing to mislocalization of PP4c, as molecular targets for pharmacological intervention aimed at rejuvenating old HSC function. Aging of the hematopoietic system has many untoward consequences, such as reduced immune function, anemia, and increased risk of myeloid disorders. Therefore, deciphering the key mechanisms involved in HSC aging and determining how these physiologic changes lead to age-related bone marrow dysfunction will identify additional new approaches to therapy. As certain chemotherapeutic agents and incising radiation induce replication stress in HSC, these results have broader implications for older patients undergoing cancer treatment. Rejuvenation of old HSC function could lead to diminished risk of myeloid disorders and bone marrow failure, or shorten the duration of chemotherapy-induced myelosuppression, and recent parasitobiosis studies have shown that symbiotic factors can rejuvenate marrow-cell function.1,2 Maybe the fountain-of-youth is not a myth after all.
Public Funding of Biomedical Research: A Hematologist’s Education

SUSAN B. SHURIN, MD
Senior Advisor, Center for Global Health, National Cancer Institute; Former Deputy Director, National Heart, Lung and Blood Institute

My family tells me I have wanted to be a doctor since I was two years old. I had wonderful family role models – my grandfather and my great-aunt were pediatricians, and an uncle was an oncologist. In college, however, I was encouraged to get a PhD degree instead, reflecting both the favorable state of basic science research funding in the 1960s and the bias against women in medicine. I saw the transformation of academina as an undergraduate, being in one of the first Radcliffe classes to get Harvard degrees. As a result of this encouragement, we struck curfews for women and the school functioned in loco parentis and leaving when all the rules were honored only in the breach. Two years in graduate school, I left my first love to medicine; inspirational teachers including Dr. Bill Zinkham at Hopkins set me on a path to academina; Dr. Jane Desforges and Dr. David Nathan were the chemotrajectants to hematology; and Dr. Tom Stossel cemented my interest in nonmalignant hematologyn.

Moving to Cleveland, my lab at Case was the only regional facility that could do the necessary research on the diseases of hospital patients, and interacting with my outstanding team was an endless pleasure. Working in the changing world of academic medicine, however, became increasingly unpleasant. The extent to which managed care prevented rather than facilitated the good practice of medicine, the limited vision of hospital administrators to run almost continuously on a contingency basis, and the lack of institutional commitment to academic pursuits all made day-to-day work less fun. Serving on NIH study sections felt like an exercise in futility – no matter how we scored the applications, only a fraction of those deserving would be funded. I thought it was bad in the 1980s and 1990s; it is infinitely worse today.

So after a quarter of a century on the faculty of a line medical school, hospital, and cancer center, I decided there must be more to life than having tenure. It was also clear that the ability of dedicated faculty to fulfill their teaching, research, and service mission was being undermined by institutional pathologies. So I took a deep breath and went over to the dark side of administration. I spent three years as a university vice president, dealing with governance and fiscal issues. It was there that I received experience on a larger scale so that I could appreciate how complex institutions work; grasp the importance of clarity of purpose and accurate, meaningful data; and understand the crucial role that honest, committed leaders with integrity play in the success (and failure) of large enterprises.

I arrived at NIH not knowing that it was my destination, only that there were important things going on. I knew that the $3 billion spent on blood, heart, Lung and Blood Institute (NIHBB) could accomplish much, if not enough; that while my immediate impact might be small, the sphere of influence would be much larger than I had experienced previously; and that it was a privilege to work with Dr. Betsy Nabel. All those things proved to be true. We embarked on modernizing and updating multiple aspects of how the Institute was organized and doing business. We put in place actionable reviews of what we were doing and adjusted resource investments to ensure relevant outcomes. We also worked to increase the breadth and depth of our network of advisors so that we were skiing to where the puck was going. As an example, this strategy led us to take advantage of opportunities that our large, well-phenotyped cohort of colleagues offered during the rapid expansion of research in genomic science. All of these initiatives were difficult, took a long time to accomplish, and had winners and losers. Some remain as ongoing projects now under the stewardship of Dr. Gary Giannoni.

NIH is a wonderful place to work. The majority of the nearly 1,000 NIH staff are committed to science and committed to the science they support or conduct. The accomplished intramural scientists and the amazing work done by the extramural scientists that the Institute supports are sources of immense pride and enthusiasm.

The chronic failure of Congress to consistently pass a budget means that NIH institutes do not know how much will be available in any given year, forcing administrators to run almost continuously on a contingency treadmill, with the associated uncertainty leading to anxiety at best and mistrust at worst among grantees and grant applicants.

a severe form of leukocyte adhesion deficiency. As my administrative responsibilities increased, I moved out of the lab and on to clinical research on sickle cell disease, hemophilia, and pediatric oncology. Teaching, taking care of patients, and interacting with my outstanding team was an endless pleasure.

In academia, most of my ability to accomplish things were different at NIH compared with academic programs. As older investigators continue to work, we see the end of mandatory retirement in higher education in the United States limits one’s sphere of influence. At NIH, I had the advantage of opportunities that have enhanced the study and treatment of blood and blood-related diseases. In addition to her stellar scientific achievements as a researcher and her service as an advocate for patients, Dr. Shurin has made key contributions to ASH as a member of the ASH Scientific Committee on Pediatric Hematology; as a past member of the ASH Committee on Public Information and Government Affairs; as a liaison to the ASH Government Affairs Committee; and as a faculty member for the ASH Clinical Research Training Institute (CRTL). ASH wishes Dr. Shurin Godspeed on her new journey that will allow more time with her family but also include travel as part of her participation in development of global health strategies. We look forward to her continued engagement with the Society as the newly elected ASH Treasurer in 2015.

The Hematologist: ASH NEWS AND REPORTS

Hubert Humphrey: “Once a fiery liberal spirit, now when he speaks, he must clear it.” I wasn’t there as myself, but as a representative of NIH and NRB. But having the imprimatur of NIH and NHLBI also meant that decisions that were well thought-out and justified could be implemented. Compared with academic medicine, at NIH both status and quality of life for many staff depend more on you in the hierarchy of the institution. Priorities and institutional identity were clearer and more focused at NIH. Everyone there had a sense that their successes and failures of each reflected on all. This ethos was less common within the loosely coupled system of an academic medical center in which different components valued different things.

Several things are similar in the two settings. All of us tend to put more weight on input (how we expend energy and resources) than output (what we have actually accomplished). This myopic view of purpose obscures real achievement. In both settings, human beings tend to resist change and respond to the same incentives (money, power, status, praise) and disincentives (criticism, unreasonable or ill-conceived demands, and lack of respect). The most important decisions you will make in a leadership roles have to do with how you hire and manage your staff. Honesty, integrity, trust, and treating people with respect and decency are essential for long-term success. Even when this philosophy seems counterproductive for achieving short-term goals, applying it is likely to make it much more enjoyable and rewarding in the end, the goodwill that accrues will make the collaborative effort more productive and rewarding for all involved. In both settings, I dealt with many people who were suffering, sometimes because of and sometimes in spite of things I had done. There is no substitute for empathy.

What did I learn that members of ASH should know? The NIH manages the public investment in biomedical research. Democracy doesn’t mean that you always get what you want individually, but rather that your voice should be, and is, heard. Speak up, make your thoughts known to both the NIH and political leaders, and you will certainly have an impact. Submit the best applications you can. Talk to the NIH staff; they are honestly there to serve, and they get both personal satisfaction and reward from their leaders when they build strong relationships with investigators. Winston Churchill made two very wise observations to keep us going in difficult times:

“Democracy is the worst form of government, except for all those other forms that have been tried from time to time.”

“You can always count on Americans to do the right thing – after they’ve tried everything else.”

Editor’s Note

The Society would like to thank Dr. Susan Shurin for her leadership and service to hematology, and to congratulate her on her recent well-deserved retirement. Dr. Shurin’s contributions to hematology-related initiatives at the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the U.S. Department of Health & Human Services were the driving force behind a number of pivotal innovations that have enhanced the study and treatment of blood and blood-related diseases. In addition to her stellar scientific achievements as a researcher and her service as an advocate for patients, Dr. Shurin has made key contributions to ASH as a member of the ASH Scientific Committee on Pediatric Hematology; as a past member of the ASH Committee on Public Information and Government Affairs; as a liaison to the ASH Government Affairs Committee; and as a faculty member for the ASH Clinical Research Training Institute (CRTL). ASH wishes Dr. Shurin Godspeed on her new journey that will allow more time with her family but also include travel as part of her participation in development of global health strategies. We look forward to her continued engagement with the Society as the newly elected ASH Treasurer in 2015.
Sickle cell disease (SCD) is the most common inherited blood condition in the United States. The molecular basis of SCD has been known for more than 50 years, and while the genetics are straightforward, the pathophysiology is surprisingly complex, and management poses many challenges for patients and providers. SCD is uncommon (but not rare), and consequently, individual physicians may have limited experience both in developing a comprehensive, longitudinal care plan and in managing complications of the disease. As a result, expert practitioners, clinical practice guidelines (CPGs) have been developed by several groups including the National Heart, Lung, and Blood Institute (NHLBI). First published in 1984, NHLBI’s “The Management of Sickle Cell Disease” (the Red Book) underwent three subsequent revisions with the fourth edition being published in 2002. Now, after more than five years in development, the Red Book has been supplant by NHLBI’s Expert Panel Report titled “Evidence-Based Management of Sickle Cell Disease” (www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines), and key aspects of the report have been summarized recently in the Journal of the American Medical Association. The guidelines are intended to assist health professionals with management of both common issues and adverse events associated with SCD, including health maintenance, acute pain, chronic complications, blood transfusions, and indications for using and monitoring of hydroxyurea (Table). The target audience for these new NHLBI guidelines are primary and secondary care providers who manage patients (children and adults) with SCD.

Clinical practice guidelines (CPGs) have been promulgated for numerous conditions with variable quality and therefore variable utility. In general, guidelines are prepared by expert panels that use the scientific literature to collect, organize, interpret and assess evidence as part of a formal systematic review process. Results of the review are evaluated along with other evidence that incorporates expert opinion and patient preferences to produce CPGs and recommendations with a goal of optimizing patient care. CPGs can also assist health-care providers in weighing treatment options when there is limited evidence, absence of a consensus, or both. And deficiencies in published literature identified during the review and CPG development can be used to highlight priorities for research.

In March 2011, the Institute of Medicine (IOM) published the report “Clinical Practice Guidelines We Can Trust,” which summarized the work of an expert committee tasked with examining best methods for developing high-quality CPGs. In this document, the IOM proposed a set of standards for the development of robust and reliable guidelines that included establishment of representative multidisciplinary committees to complete a rigorous, systematic review of existing evidence. The report emphasized that CPG development process should be transparent and should minimize bias, distortion, and conflicts of interest. Further, the quality of evidence should be weighed, and this information should be incorporated into a measure of the strength of the recommendations. The process should consider patient preferences and provide both clear explanations and alternative care options as appropriate. Finally, trustworthy CPGs require revision and reconsideration as new evidence arises.

The CPG development process has limitations and many of them are reflected in the NHLBI SCD Expert Panel Report. The NHLBI Expert Panel was convened prior to publication of the IOM report. Nonetheless their process and methodology encompassed many of the IOM standards, but regrettably excluded others. The Expert Panel included professionals in hematology, primary care, psychiatry, and emergency medicine who were very knowledgeable about SCD, but there was no patient or public involvement in the development of the NHLBI-sponsored guidelines. Representatives from community-based patient advocacy organizations were, however, among the stakeholders providing external review of the final report. Results of a systematic literature review identified randomized control clinical trials, other nonrandomized interventional studies, and observational studies that were supplemented with additional information from case series or case reports only when considering outcomes that might involve harm. One inherent challenge in developing CPGs for SCD is that there are limited numbers of large-scale, randomized controlled clinical trials, and the relatively small numbers of subjects in many nonrandomized studies weakens the strength of evidence. In areas where a comprehensive review was not feasible due to limited or absence of high-quality evidence, the Expert Panel provided consensus recommendations or made recommendations based on existing guidelines developed by specialty societies. Some areas of emerging importance in SCD were not addressed at all.

There are several areas of the Expert Panel Report where strong recommendations are based on moderate- to high-quality evidence, and many deal with issues where there is broad acceptance of scientific evidence, but perhaps less than universal practice, including the following:

- Penicillin prophylaxis in young children with SCD
- Annual Transcranial Doppler (TCD) screening with transfusions for primary stroke prevention in children with abnormal TCD velocities
- Use of parenteral opioids for children and adults with severe SCD-related pain
- Hydroxyurea therapy for recurrent severe pain or acute chest syndrome
- Watchful waiting for asymptomatic children and adults with gallstones

Guidelines from the American Pain Society in collaboration with the American Association of Pain Medicine on management of acute and chronic pain in SCD were largely the basis for “adapted consensus” and “panel expertise” recommendations. Similar recommendations by the Expert Panel on Routine Vaccinations follow existing guidelines from the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. The Panel also made strong to moderate recommendations in several areas where evidence is fairly weak. These include screening for pulmonary hypertension, use of exchange transfusions for acute chest syndrome, and use of hydroxyurea to prevent stroke recurrence. Such disparity between strength of evidence and strength of recommendation has prompted at least one alternative set of guidelines (focused on pulmonary hypertension) to be developed (in this case by the American Thoracic Society).

Conflicting guideline recommendations erode the confidence of relatively inexperienced providers who are charged with managing patients with complex problems. The Expert Panel Report is extensive but not comprehensive. Guidance on assessments and interventions for neurocognitive deficits, which impacts both children and adults with SCD, was not included in the NHLBI-sponsored document. Based on low to very low evidence, the Expert Panel strongly recommended against neuromonitoring with MRI or CT. This recommendation is unfortunate as it may limit insurance coverage for clinically driven neuroimaging and may discourage scientific exploration into an area where knowledge is evolving. The recent publication from the Silent Infarct Transfusion Trial suggests that benefit may accrue from chronic transfusions in SCD-related cerebral infarcts, which may only be detected in asymptomatic children by using MRI. The Report recommendations for consultation with an expert hematologist when patients have serious complications such as stroke or brain failure, acute intrahepatic cholestasis, or splenic sequestration, or require perioperative transfusion management, seems to be prudent (if not evidence-based). Hematopoietic stem-cell
transplantation, a curative therapy for SCD, is not addressed in the Expert Panel Report.

NBLLB sponsored the development of the guidelines but at present has no provisions for revising or updating them—a notable departure from the CPG standards set by the IOM. Regular monitoring of the scientific literature may reveal new data that contradict existing evidence or that suggest another alternative therapy not included in current CPGs. The investment needed to create the Expert Panel Report was substantial, but the report’s impact on optimizing patient care will likely diminish without regular surveillance and maintenance. The establishment of the Expert Panel Report as an authoritative CPG for SCD could generate opportunities for coordinating care and clinical research. It could also inform further studies in the emerging area of implementation science, which seeks to investigate and address major impediments (social, behavioral, political, and economic) to the adoption of evidence-based interventions. This report and similar CPGs can facilitate integration of research findings into clinical practice and health-care policy for SCD; however, doing so will require continued evaluation of their validity.

How has ASH contributed to the SCD guidelines? Several participants in the Expert Panel as well as external reviewers of final drafts are active ASH members. During the public comment period, ASH solicited additional input from members of the ASH SCD Taskforce, compiling an extensive list of suggestions for revision. ASH has formally endorsed the CPGs and is examining ways to disseminate them (www.ashematology.org/Newsroom/PressReleases/2014/3157.aspx). Transformation of key elements into more targeted and concise guidelines (in the form of an ASH pocket guide) will increase the accessibility, and likely the implementation, of the Expert Panel Report’s recommendations that are important to patient care and decision making. The methodology used for the systematic review and the inclusion of more information from the scientific literature has resulted in a document that is very different from the treasured Red Book. Still, where the scientific evidence was insufficient to support a conclusion, recommendations were based on expert consensus that was generally grounded in what might be considered common practice standards.

As such, the Expert Panel Report identifies knowledge gaps that can and should be used to drive a research agenda. The recently released ASH Research Priorities for Sickle Cell Disease and Sickle Cell Trait (www.hematology.org/Research/Recommendations/Sickle-Cell) further highlights areas where discovery and innovation, accompanied by research funding and training, are needed. Acknowledging that there are parts of the CPG that could be improved upon, and implying support for a living document, the NBLLB-sponsored SCD guidelines are a valuable resource whose wide-scale adoption and implementation by hematologists will empower more informed health-care choices and thereby improve outcomes and quality of life for patients.

**RATIONALIS**: SCD is the name for a group of related genetic disorders of blood caused by a predominance of sickle hemoglobin (Hb S) in red blood cells (RBCs). In SCD, RBCs become dehydrated, inflexible, and abnormally adhesive. These characteristics promote sludging, vaso-occlusion, or vaso-occlusion, due to intercellular adhesive interactions among RBCs, leukocytes, platelets, and the endothelium. The consequences of vaso-occlusion are ischemia, infarction, and ischemia-reperfusion injury of multiple organs and tissues. The hallmark vaso-occlusive clinical syndrome of SCD is the acute painful episode (previously called “crisis”).

Many studies within the past 15 years, mainly in murine models of SCD, have demonstrated a key role for P-selectin and its ligands in the intercellular adhesive interactions and pathophysiology of SCD. Specifically, P-selectin is involved in the prevention of vaso-occlusive complications of SCD, specifically acute painful episodes. SelG1 is being tested as monthly infusions at two dose levels (5 mg/kg and 2.5 mg/kg). Potential adverse effects of P-selectin inhibition that will be monitored include bleeding, the inhibition of P-selectin on activated platelets, and the possibility of infection because P-selectin is a mediator of neutrophil adhesion to the vascular endothelium.

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As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter ([www.twitter.com/ASH_hematology](http://www.twitter.com/ASH_hematology)), and find ASH videos on YouTube ([www.youtube.com/user/ASHWebmaster](http://www.youtube.com/user/ASHWebmaster)). Our newest offering is ASH on Facebook.

The complete 2014 annual meeting program will be available as a mobile app for iPhone and Android smartphones and tablet devices. Download this exclusive app to access the full text of all annual meeting abstracts, articles from Hematology 2014 (ASH Education Program), maps of the Moscone Center, other general meeting information, and more. The app also allows users to create personalized meeting itineraries and communicate in real time with other annual meeting attendees via a messaging function.

To download, search for “ASH 2014” in your device’s app store. Attendees are strongly encouraged to download the app prior to their arrival at the meeting in order to enjoy the full benefits of the app and avoid delays during the download process. For more information, including FAQs visit [www.hematology.org/ash2014app](http://www.hematology.org/ash2014app).

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**December**

6-9  56th ASH Annual Meeting and Exposition
San Francisco, CA  [www.hematology.org/meetings](http://www.hematology.org/meetings)

**January 2015**

2  Deadline to request a mentor for the 2015 Minority Medical Student Achievement Award
Washington, DC  [www.hematology.org/awards](http://www.hematology.org/awards)

8  Eligibility Review Deadline for ASH Clinical Research Training Institute
Washington, DC  [www.hematology.org/awards](http://www.hematology.org/awards)

19  Letters of intent deadline for 2015 Visitor Training Program
Washington, DC  [www.hematology.org/awards](http://www.hematology.org/awards)

16-17  Highlights of ASH
New York, NY  [www.hematology.org/meetings](http://www.hematology.org/meetings)

Highlights of ASH
Austin, TX  [www.hematology.org/meetings](http://www.hematology.org/meetings)

23-24  Highlights of ASH
Washington, DC  [www.hematology.org/meetings](http://www.hematology.org/meetings)

Highlights of ASH
San Diego, CA  [www.hematology.org/meetings](http://www.hematology.org/meetings)

30-31  Highlights of ASH
Orlando, FL  [www.hematology.org/meetings](http://www.hematology.org/meetings)

Highlights of ASH
Seattle, WA  [www.hematology.org/meetings](http://www.hematology.org/meetings)

**February 2015**

28  Highlights of ASH in Asia
Bangkok, Thailand  [www.hematology.org/meetings](http://www.hematology.org/meetings)

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Help *The Hematologist* Select “The Year’s Best in Hematology” for 2014

You are invited to cast your ballot for 2014’s breakthroughs in hematology, which will be featured in the next issue of *The Hematologist*.

These standout themes can represent a singular published discovery (basic, clinical, or translational research), realization of a concept that has finally reached breakthrough status, approval of game-changing drug(s) for a disease, or a groundbreaking technological innovation that has transformed basic research or clinical diagnostics/management in the field of hematology.

The survey link will be available from November 17 through December 5, and results will be published in the January/February 2015 issue of *The Hematologist*, as incoming Editor-in-Chief Dr. Jason Gotlib and members of the Editorial Board take part in an in-depth discussion of their choices for the 2014 breakthrough, in addition to several notable honorable mentions.

Get involved and take advantage of a unique opportunity to spotlight the topics most important to you. Cast your vote by visiting [www.surveymonkey.com/s/bestinhematology](http://www.surveymonkey.com/s/bestinhematology).