In 2006, Dale Lloyd Jr., a 19-year-old freshman at Rice University, was killed in a car accident while collapsing during football practice. It is an event that I remember well. My son was a sophomore at Rice at that time, and he was a member of the MOB (Marching Owl Band) that played in tribute.

At post-mortem examination, it was discovered that Dale had sickle cell trait (SCT). A wrongful death lawsuit was brought against Rice University and the sports conference to which the University belonged, and as part of the settlement and the aftermath of that tragic event, the National Collegiate Athletic Association (NCAA) began, in 2010, the practice of screening all Division I athletes for SCT. In 2012, the policy was extended to include Division II athletes, and in 2013 Division III athletes were also included. Now, to participate in NCAA sanctioned athletics, a student must have a sickle cell test and report the results to his or her coach and trainer, or he or she can decline the test and sign a legal document that releases his or her respective university from liability.

ASH felt that this litigation-motivated response was medically and ethically inappropriate. We hosted a workshop in June 2011 that included Society members with clinical and research expertise in hemoglobin biology, SCT, and sickle cell disease. With the support of groups such as the Sickle Cell Disease Association of America, American Society of Pediatric Hematology-Oncology, the CDC, and the American Public Health Association, we issued a policy statement and then reached out to the NCAA to engage in a dialogue about their SCT screening policy.

What are the facts? SCT is common. One in 12 African-Americans (~8%) has SCT. Based on this estimate, perhaps 200,000 American athletes may have SCT. These athletes represent a unique study population to evaluate the natural history of SCT and the impact of SCT on physical performance and athletic achievement.

What are the implications? Figure 1 shows the percentage of athletes in the 2001-2012 National Football League (NFL) who had SCT. It is interesting to note that the percentage of athletes with SCT increased from 2001 to 2012, and that athletes with SCT were significantly more likely to have a history of a lower blood hemoglobin level (Hgb) at the time of the preparticipation examination compared to athletes without SCT. These findings suggest that athletes with SCT are more likely to be identified at preparticipation examination and that the increased prevalence of SCT in the NFL may be due to the implementation of the current policy of screening all athletes for SCT.

However, the implications of SCT on athletic performance and health outcomes are not well understood. Further research is needed to determine the impact of SCT on athletic performance and health outcomes, and to develop safe and effective management strategies for athletes with SCT.

Figure 1. Prevalence of Sickle Cell Trait in National Football League (NFL) Players from 2001 to 2012. A) The percentage of NFL players with SCT increased from 2001 to 2012. B) Athletes with SCT were significantly more likely to have a lower hemoglobin level at the time of the preparticipation examination compared to athletes without SCT.

All in the Family: Fine Tuning Targeted Attack on BCL-2


Malignant transformation and clonal expansion require the survival of both proliferative and survival advantages relative to normal cells. The BCL-2 family is composed of both pro-apoptotic and anti-apoptotic proteins, and aberrant expression of anti-apoptotic family members underlies the survival advantage in several types of B-cell lymphoproliferative disorders. Programmed cell death is a consequence of mitochondrial disruption induced by the pro-apoptotic proteins BCL-2-associated-X-protein (BAX) and BCL-2 homologous antagonist killer (BAK). Apoptosis is inhibited by the binding of BCL-2 (and related proteins including B-cell lymphoma extra large [BCL-XL]) to the BAX domain of BAX and BAK. The importance of anti-apoptosis in the pathobiology of lymphoma is underscored by the consequence of the t(11;14) translocation that is present in the majority of follicular lymphomas and also occurs in up to 30 percent of diffuse large cell lymphomas. In this case, the translocation brings BCL-2 under the control of the immunoglobulin-heavy-chain gene enhancer, resulting in constitutive expression of BCL-2. Aberrant expression of BCL-2 is also observed in mantle cell lymphoma and in acute and chronic leukemias and is one of the two genes (along with myc) that is overexpressed in the markedly aggressive "double-hit" lymphomas. Because of the important role that it plays in the pathobiology of B-cell lymphoproliferative disorders, BCL-2 is a tantalizing therapeutic target. ABT-26 (navitoclax) was developed as an inhibitor of BCL-2, but its clinical utility has been compromised by dose-limiting thrombocytopenia. The problem is that, in addition to inhibiting BCL-2, ABT-263 binds with high affinity to BCL-XL, the anti-apoptotic protein that is critical for platelet survival.

Souers and colleagues utilized structure-based drug design with guidance provided by x-ray crystallography to develop a more selective BCL-2 inhibitor, ABT-199, through successive modifications of ABT-263. ABT-199 has potent activity against BCL-2 while sparing BCL-XL, and thus does not have a detrimental effect on platelet survival. Using lymphocytic leukemia and non-Hodgkin lymphoma cell lines, in vitro experiments demonstrated that ABT-199 was pro-apoptotic as evidenced by activation of caspases 3 and 7, induction of annexin V expression, and accumulation of cells in the sub G0/G1 phase of the cell cycle. ABT-199 was shown to inhibit growth of BCL-2-dependent tumors in mouse xenograft models, with complete responses being observed when ABT-199 was used together with rituximab and prolonged response noted with the combination of ABT-199, bendamustine, and rituximab.

Because ABT-199 induced apoptosis with an average EC50 of 3 nM in 15/15 primary CLL samples, the first human clinical trial of ABT-199 was aimed at refractory CLL. Three patients participated in the study. Within 24 hours of drug administration, there was a reduction in palpable lymphadenopathy in all patients and a 3-95 percent reduction in peripheral blood lymphocytes in the two subjects with pretreatment lymphocytosis. Minor, transient decreases in platelet counts were observed, and evidence of tumor lysis was documented in all three patients.
4 million people in the United States carry the trait (with about 300 million worldwide being affected). Although exercise-associated death in individuals with SCT is extremely rare, there are epidemiologic, but not cause-effect, data that suggest a link. A landmark study showed a 37-fold greater relative risk of sudden death during basic training in army recruits with SCT. Confronted with this data, the U.S. Army responded, not by screening recruits for SCT, but by implementing changes in hydration and rest rules designed to protect all inductees from the adverse effects of overexertion and hyperthermia.

A recent study surveyed newspaper reports and incident records that covered 2 million NCAA student-athlete-years and identified 273 cases of sudden death. Only five (2%) of these were associated with SCT. All five SCT-related deaths occurred in football players, none occurred during games, and most occurred during preseason conditioning practices and thus involved less well-conditioned student athletes, akin to the less well-conditioned soldiers with SCT who died during basic military training. ASH’s statement encourages research into the effects of SCT on exercise tolerance and urges the NCAA to implement universal precautions to reduce exercise-induced injury, such as those implemented by the Army. Research topics include studying whether rhabdomyolysis is the inciting event in the catastrophic cascade that can lead to multiorgan failure and death, whether rhabdomyolysis is due to muscle hypoxia and sickness, and whether a second genetic risk factor with overlapping prevalence is also required.

What are ASH’s specific concerns? First, the NCAA policy attributes risk inappropriately. Student athletes testing negative for SCT may have a false sense of security and ignore or not recognize more prevalent risks such as asthma and long QT interval. Student athletes testing positive for SCT may falsely assume that their risk is alarmingly high because only SCT testing is mandated. That SCT testing is a prerequisite to play all college sports, including low-intensity sports such as bowling and golf, reinforces this inaccurate message of risk severity and may falsely frighten the broader public. Anecdotally, ASH members described African-Americans with SCT, diabetes, and obesity who abandoned their exercise programs because they feared that they might die from overexertion.

Second, although the NCAA mandates SCT testing, neither counseling nor intervention is required. The NCAA screening program thus does not conform to ethical standards, such as those endorsed by the World Health Organization.

Comprehensive and accurate counseling is especially important when screening for a genetic trait because having the trait is immutable. ASH believes that testing for SCT, discussion of its implications, and decisions about sharing this information, like any other health issue, should involve the athlete and his or her family and physician, not trainer or coach.

What happened next? Recognizing the challenges from the culture of college sport, its focus on toughness, and the huge financial imperative to win, ASH calmly presented an evidenced-based view at a roundtable cosponsored by the NCAA and American College of Sports Medicine in February 2012. Although the NCAA recently extended SCT testing to include Division III athletes, the debate was vigorous and the vote relatively close. Gratifyingly, the NCAA strengthened rules limiting the duration and intensity of preseason football practices, a step toward universal precautions. My direct interactions with the new (first) NCAA Chief Medical Officer have been positive and transparent.

The CDC, with ASH co-sponsorship, is developing and will broadly distribute educational materials that should improve the public’s understanding of SCT and sickle cell disease. Because of ASH’s advocacy and especially that of Alexis Thompson, MD, the Army and NIH may support new studies of the health consequences of SCT in soldiers. Military records are not new (first) NCCA Chief Medical Officer have been positive and transparent.

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The Hematologist: ASH NEWS AND REPORTS
2013 ASH Annual Meeting and Exposition
December 7-10, 2013
Ernest N. Morial Convention Center
New Orleans, LA

The American Society of Hematology invites you to New Orleans for its 55th annual meeting. As the premier hematology event of the year, this meeting is an invaluable educational experience and provides:

- Opportunities to grow professionally by learning about the latest developments in research and practice by attending the Education and Scientific Programs
- Networking events that will allow you to connect with more than 20,000 colleagues from around the globe
- A chance to see thousands of selected scientific abstracts presented orally and in poster sessions

Key Dates

June 6 Abstract submission site opens
July 24 Members-only registration and housing opens
August 8 Abstract submission deadline
August 14 Registration open to all
November 6 (at 11:59 p.m. EST) Advance registration ends
November 7 Late/on-site registration begins

For more information, go to www.hematology.org/Meetings/Annual-Meeting.

ASH State-of-the-Art Symposium Program Chairs Announced

This year’s ASH State-of-the-Art Symposium (SAS) program co-chairs are Dr. Roy L. Silverstein, from Medical College of Wisconsin, Blood Center of Wisconsin, and Dr. David P. Steensma, from Harvard Medical School, Dana-Farber Cancer Institute.

SAS will once again take place in two U.S. cities – Chicago, IL, September 27-28, and Los Angeles, CA, October 11-12. In addition, the ASH Consultative Hematology Course (CHC) is scheduled for September 26 in Chicago. This is the day before the SAS meeting begins. This refresher course targets board-certified hematologists and oncologists who see patients with non-malignant hematologic disorders infrequently and would like to update their core knowledge of hematology. It will be led by faculty familiar with consultative practice issues and cover commonly encountered clinical problems that arise in everyday practice.

What is SAS?

SAS provides up-to-date, evidence-based continuing medical education that spans the practice of hematology. The smaller, clinically focused program format provides attendees with ample opportunities to discuss challenging cases with experts in the field. Additionally, in order to enhance the exchange of information, panel discussions and “Lunch with the Experts” are offered as part of the meeting content.

ASH strongly encourages attendance by fellows currently enrolled in training programs. The program will include dedicated time for trainees to network with speakers and a forum to discuss specific cases and address questions.

ASH State-of-the-Art Symposium Program Chairs Announced

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

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

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

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Deadline to receive applications is September 3.
emphasized that there are existing treatment strategies for gastrointestinal bleeding.1,2 Further, it must be noted that both dabigatran and rivaroxaban appear to increase the risk of intracranial hemorrhage compared to warfarin. In the United States alone, more than 2 million patients have stopped their warfarin anticoagulation to a novel oral anticoagulant (NOAC). When patients query me about whether they should switch to a NOAC, I often find myself echo
ing the Chinese Premier and stating that it is still too soon to say with confidence. For well over a decade, pharmaceutical companies have attempted to replace vitamin K antagonists such as warfarin. In the United States alone, more than 2 million people are treated with anticoagulation, making this avenue of pursuit quite lucrative. All of us who manage patients on warfarin easily understand the desire to replace warfarin with a drug with less complicated dosing. But, are we there yet? The initial contender was an oral thrombin inhibitor, ximelagatran. However, liver failure in several recipients of this medication caused the drug to be removed from clinical evaluation. Now, there are three NOACs that have been approved by the FDA. These are the oral thrombin inhibitor dabigatran and two factor Xa inhibitors, rivaroxaban and apixaban. But, what do we know about these novel agents, and, more importantly, what don’t we know?

What Do We Know?
A lot, but not all of what we know about the NOACs is good. Dabigatran, rivaroxaban, and apixaban each have the obvious advantage over warfarin of fixed doses that do not require laboratory monitoring. They also exhibit similar or, even improved, efficacy when compared with warfarin. But, if there is improved efficacy for any of these drugs when compared to warfarin, such advantages are modest.

To date, the safety of these agents when used in clinical trials also appears to be acceptable. However, one would have anticipated that fixed dosing and relatively fewer drug interactions would have resulted in a vastly superior safety profile and far fewer hemorrhagic complications. Consistent with this assumption, the risk of the dreaded intracranial hemorrhage is significantly reduced in patients taking an NOAC when compared with warfarin. Improvement in other types of hemorrhages, however, has not been a consistent finding. In fact, in the calendar year 2011, dabigatran replaced warfarin as the drug most frequently reported to the FDA as being associated with adverse events, and when compared with warfarin, both dabigatran and rivaroxaban appear to increase the risk of gastrointestinal bleeding.12 Further, it must be emphasized that there are existing treatment strategies for reversing anticoagulation induced by warfarin but not for anticoagulation induced by any of the available NOACs.

Similar to warfarin, non-hemorrhagic adverse effects appear to be rare in patients taking NOACs. However, as post-marketing data have accumulated, dabigatran, when compared with warfarin, has been found to be associated with a small, but definite, increased risk of myocardial infarction.13,14 Finally, we know that patient compliance is not great. For all of the NOACs, failure to adhere to the dosing schedule is in the range of 20 to 25 percent, even in the setting of clinical trials.1,5

What Don’t We Know?
Almost all of the available evidence for NOACs is derived from patients enrolled in clinical trials, many of whom were treated for only a few months. Because clinical outcomes for patients treated in “real-world” settings may differ from those for patients enrolled in clinical trials, I find it difficult to inform my patients about the true risks and benefits of these new agents.

A big question is how these drugs will perform in patients who receive less intensive, non-continuous education. In a typical clinical practice, the average time spent educating a patient about the rationale, efficacy, and safety of a new medication is less than a minute.1 This short amount of time spent educating real-world patients is in striking contrast to the amount of time spent educating patients enrolled in clinical trials who are informed and re-informed about the properties of the new agents. What impact brief patient education will have on adherence to treatment with an NOAC and what the risk of bleeding will be in a less-than-ideally informed patient are completely unknown.

Although patients and health-care providers grumble about monitoring the INR in patients treated with warfarin, this action actually offers a tremendous educational opportunity. As a consequence of encounters mandated by the monitoring requirement, patients on warfarin are continuously re-educated about the warning signs of excessive bleeding. This process also helps to monitor patients who are actually taking their medication and affords an opportunity to intervene when they are not. In contrast, given that monitoring is not required, the NOACs have the danger of being categorized as prescribe-and-forget drugs. Since no drug works when it is not taken, and since patients frequently do not openly report their non-compliance, the absence of a monitoring requirement might, ironically, turn out to have a major negative impact on the safety and efficiency of these drugs in the everyday clinical setting. The compliance issue is especially concerning given that all three of the NOACs have a half-life much shorter than warfarin, and two of them (dabigatran and apixaban) require twice-daily dosing to maintain a therapeutic level.

When compared with warfarin, the long-term outcome of NOACs in patients who are elderly and who have suboptimal renal function is also incompletely understood. On average, the patients in clinical studies of NOACs have been younger than those found in typical clinical practices. Patients in clinical studies are also not on drugs that might impact their renal function or otherwise affect the pharmacodynamics of the NOACs. Common drugs such as NSAIDs can affect the glomerular filtration rates of patients. Drug-induced changes in kidney function can lead to changes in the drug levels, which in turn may lead to changes in anticoagulation status that will go unrealized because monitoring is not part of the standard management of patients taking NOACs.

Caveat Emptor
When I speak with my patients, I can confidently state the adverse effects of warfarin in patients that have been treated for not only months, but also for decades. In recent years, we have seen several drugs that have significant toxicity that only became detected after more widespread use by the public. Some examples include rosiglitazone and rofecoxib. The link between dabigatran and myocardial infarctions was also discovered in post-marketing studies that followed FDA approval. Elucidation of the true efficacy and safety of NOACs requires still more time. Perhaps the Chinese Premier Zhou Enlai was right after all.


Dr. Abrams indicated no relevant conflicts of interest.
Inhibition of B-Cell Receptor Signaling as a Therapeutic Strategy for Treatment of CLL

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Over the past several years, excitement has been building surrounding the clinical and therapeutic importance of B-cell receptor (BCR) signaling in chronic lymphocytic leukemia (CLL) and other B-cell lymphoproliferative disorders. Small molecule inhibitors of kinases that participate in BCR signaling pathways, specifically inhibitors of Bruton tyrosine kinase (BTK) and the delta isoform of phosphoinositide 3-kinase (PI3Kδ), have received the most attention. The results of recent clinical studies using these agents have demonstrated efficacy and low toxicity in CLL patients with relapsed/refractory disease and in those with high-risk molecular abnormalities. Given the impressive results thus far, will these agents transform the care of CLL patients much as imatinib and other tyrosine kinase inhibitors have done for patients with chronic myeloid leukemia (CML)?

BCR signaling is biologically important for normal B-cell activation and proliferation, as well as for initiation and progression of B-cell lymphoid malignancies. The BCR consists of two parts: the ligand-binding moiety and the signal-transduction moiety (Figure). The ligand-binding moiety (the portion of the receptor that recognizes antigen) is, in essence, a membrane-bound antibody that is integrated into the lipid bilayer of the plasma membrane through a hydrophobic transmembrane domain within the immunoglobulin heavy chain. The signal-transduction moiety is a disulfide-linked heterodimer (CD79). The cytoplasmatic tail of each of the two chains (CD79a and CD79b, respectively) contains an immunoreceptor tyrosine-based activation motif (ITAM). Binding of antigen to the membrane-associated immunoglobulin triggers phosphorylation of ITAM tyrosine residues by the kinases Lyn and Syk that initiates a second messenger cascade through activation of Syk, Lyn, and Btk, with subsequent propagation through the PI3K/Akt, MAPK, and NF-κB pathways, resulting in B-cell activation and proliferation (Figure).

In B-cell lymphoid cancers, BCR-activated downstream signaling pathways are involved in both disease initiation and disease progression. The central role that Helicobacter pylori plays in gastric MALT lymphomagenesis is an example of the importance of signaling through the B-cell receptor in disease initiation. In this case, lymphoma pathogenesis appears to be a consequence of chronic antigenic stimulation of gastric B cells by H. pylori in a process facilitated by reactive T-cells. Antigenic stimulation via the BCR causes oligomerization of BCL10 and MALTI, which ultimately activates the NF-κB pathway and stimulates gastric B-cell proliferation (Figure). In time, clonal expansion arises as a consequence of genetic alterations (particularly translocations that amplify the expression of BCL10 or MALTI), leading to an antigen-independent, malignant state. Thus, antigen-independent BCR signaling drives the oncogenic process.4

In CLL, immunoglobulin heavy chain usage is restricted, implying that exposure to particular antigens (either foreign or self) initiates leukemogenesis. However, as in the example of gastric MALT lymphoma, actual leukemic transformation is believed to be an antigen-independent process in which downstream pathways that propagate BCR signaling are constitutively active or amplified, and the involved kinases are overexpressed when compared with normal B cells.1 This aberrant signaling cascade underlies the malignant/survival advantage, particularly when combined with additional genetic alterations that affect expression of p53, ATM, miR-15a, miR-16-1, Notch1, and SFB1.1

Our increasingly nuanced understanding of CLL biology, particularly as it pertains to BCR signaling, suggests that there is therapeutic potential in inhibiting the BCR itself or inhibiting the downstream kinase signaling cascade. Because these kinases are overactive or overexpressed in CLL compared with normal lymphocytes, such inhibitor therapy should have a favorable therapeutic index.

Currently, the most active therapeutic regimens used for treatment of CLL are combinations of conventional chemotherapy together with the monoclonal anti-CD20 antibody rituximab. In both initial and relapsed treatment settings, these regimens are highly effective, with excellent overall response rates.6,7 However, efficacy is compromised in the subset of patients with loss of normal p53 activity due to deletion of chromosome 17p or somatic mutation of p53.1 Thus, in addition, these regimens are associated with significant morbidity as a result of myelo- and immune-suppression. Such toxicity often necessitates dose reduction or truncation of treatment and discourages use in elderly patients. Thus, new treatments that may hold benefit for patients with high-risk disease and that have a favorable therapeutic index are needed.

Ibrutinib (PCI-32765) is an oral BTK inhibitor (Figure). Results of a phase IIb/study suggest that the drug is active in patients with relapsed/refractory disease.8 Notably, a temporary increase in lymphocytosis, beginning after about one week of treatment and typically resolving after several treatment cycles, is observed in patients treated with ibrutinib (and other inhibitors of BCR signaling). The increase in lymphocytosis is thought to be due to redistribution of CLL lymphocytes from the lymph nodes into the peripheral circulation.6,8 The temporary rise in circulating CLL lymphocytes introduces a problem in assessment of response to treatment, because criteria for complete and partial responses require resolution or reduction in both lymphadenopathy and lymphocytosis.10 To resolve this issue, investigators testing BCR signaling inhibitors report results based on the strict definitions of response, but also report the fraction of patients who have a nodal response of a 50 percent with co-existing lymphocytosis.

Updated results of the phase IIb clinical trial of ibrutinib monotherapy were presented at the 2012 ASH Annual Meeting (abstract 189). Treatment-naïve patients ≥65 years old, patients with relapsed/refractory disease, and patients with high-risk disease were included in the study that enrolled 116 patients who were treated with either 420 or 840 mg of ibrutinib daily until disease progression. Seven patients discontinued therapy due to adverse events. The majority of adverse events were grade 2. With a median follow-up period of 16 months, the overall response rate ranged between 50 and 71 percent for the three different cohorts, with between 10 and 29 percent achieving a partial remission with lymphocytosis.

Idealisib (GS-1101 or CAL-101) is an oral inhibitor of PI3Kδ, another mediator of BCR signaling (Figure). In a phase I study of single-agent idealisib, originally presented at the 2010 ASH Annual Meeting (abstract 55), 37 relapsed or refractory CLL patients were treated either daily or twice daily with escalating doses of idealisib for up to 12 months. This agent was well tolerated. Partial responses were seen in 11 patients, and an additional 18 patients had a 50 percent reduction in lymph node size accompanied by an increase of lymphocytosis of > 50 percent. Thus, 29/37 (78%) of these heavily pretreated patients responded to treatment with idealisib.

Researchers have also begun to test both ibrutinib and idealisib in combination with conventional chemotherapy and/or anti-CD20 immunotherapy in patients with CLL. This combination strategy would be expected to improve the overall response rate compared with either compound alone and to reduce the extent and duration of lymphocytosis caused by ibrutinib or idealisib. A phase II study of ibrutinib and rituximab in patients with either high-risk cytogenetics or somatic mutations or with relapsed-refractory disease after initial therapy found that 17 of 20 patients achieved a partial remission at three months and that the remaining three patients achieved a complete remission with lymphocytosis.8 A phase II study of the combination of idealisib with rituximab and/or bendamustine demonstrated complete responses in 7 in 29 percent of patients treated with the combination of idealisib, bendamustine, and rituximab, while no complete responses were observed in the other two treatment groups. However, between 78 and 82 percent of patients in the different treatment groups achieved a partial response.8

Other inhibitors of BCR signaling are undergoing evaluation in pre-clinical and clinical studies. At the 2012 ASH Annual Meeting, the results of in vivo or in vitro studies of at least five different PI3K/Akt inhibitors were presented (abstracts 3928, 3663, 3914, 2907, and 1805) and results of a phase I study of the BTK inhibitor AVL-292 in the treatment of CLL was presented at the 2012 American Society of Clinical Oncology Annual Meeting (abstract 8032). In addition, ibrutinib and idealisib appear to have clinical activity in other B-cell malignancies, such as mantle cell lymphoma, subtypes of diffuse large B-cell lymphoma, and indolent lymphoma. The results of clinical studies involving ibrutinib and idealisib, along with the development of other kinase inhibitors of BCR signaling pathways, support the concept that a detailed understanding of the pathobiology of CLL can lead to development of safer, effective targeted therapy. Because these agents are well tolerated, patients may be able to continue therapy for extended periods, but extended treatment translate into deeper, more durable clinical responses or even into cytogenetic or molecular remissions as observed in patients with CML treated with tyrosine kinase inhibitors.

(Cont. on page 7)

The Hematologist: ASH NEWS AND REPORTS
Sequestration Cuts Implemented; NIH Cut by More Than $1 Billion

Because Congress was unable to reach an agreement on how to reduce the deficit, automatic, across-the-board spending cuts known as “sequestration” went into effect on March 1. Despite the addition of more than $70 million to its fiscal year (FY) 2013 budget by congressional supporters, the National Institutes of Health (NIH) budget will still be cut by more than $1 billion over the remainder of FY 2013. Each Institute and Center at NIH will determine their approach to meeting the new budget level, including, but not limited to, not issuing continuation awards, negotiating a reduction in the scope of awards to meet the constraints imposed by sequestration, or delaying or cancelling new grants or cooperative agreements.

What’s the takeaway?
While the impact of these cuts may not be felt all at once or immediately, the harm caused to biomedical research will be devastating. All ASH members are urged to visit www.hematology.org/ASH to join the Society’s advocacy campaign and contact their elected officials to tell them how these cuts will harm research.

ASH Committees on Government Affairs and Scientific Affairs on Capitol Hill to Discuss Research Funding

In March, while Congress was voting on the final FY 2013 funding measure, the ASH Committees on Government Affairs and Scientific Affairs conducted a Hill Day to discuss with congressional offices the importance of biomedical research and the need to protect NIH from further funding cuts. These meetings with Congress are an important component of ASH’s advocacy efforts, providing an opportunity for Members of Congress and their staff to gain insight into issues of concern to hematologists. However, the Society needs the help of all members to bring issues important to the future of hematology to the attention of the U.S. Congress and other governmental agencies.

What’s the takeaway?
ASH strongly encourages members to let the Government Relations & Practice Department know when you are in Washington, DC, and available to meet with your congressional delegation. You can also have your voice heard in the halls of Congress and play an important role in the Society’s advocacy efforts by visiting the ASH Advocacy Center and participating in the ASH Grassroots Network. Visit www.hematology.org/takeaction.

ASH Urges Congress to Find a Permanent Medicare Physician Payment Solution as Medicare Announces Mandatory Sequestration Payment Reductions

ASH submitted comments to the House Ways & Means and Energy & Commerce Committees in response to the Committees’ proposal to repeal the sustainable growth rate (SGR) formula and reform Medicare’s physician fee-for-service payment system. ASH supports repealing the SGR and replacing the current payment formula with predictable payment rates for at least five years while stakeholders develop a new payment system based on quality. The Society’s comments noted the difficulty both in developing metrics that meaningfully and accurately correlate with the quality of health-care delivery and with physicians participating in current federal quality-related programs and urged lawmakers to consider these issues as they look at reforming physician reimbursement guidelines.

Meanwhile, the Centers for Medicare and Medicaid Services (CMS) has announced that Medicare fee-for-service claims, with dates of service or dates of discharge on or after April 1, 2013, will incur a 2 percent reduction in Medicare payment as a result of sequestration.

What's the takeaway?
ASH continues to advocate for appropriate and stable Medicare physician reimbursement. Clinicians are strongly encouraged to visit www.hematology.org/takeaction to join the Society’s online advocacy campaign urging Congress to repeal the current payment formula based on the ill-conceived SGR template.

ASH Submits Comments to FDA Regarding Strategic Plan for Drug Shortages

ASH recently submitted comments to the U.S. Food and Drug Administration (FDA) in response to the agency’s request for comments on its strategic plan to alleviate drug shortages. ASH urged the FDA to include biologics in the early notification requirements; work more closely with other federal agencies to mitigate shortage problems; continue its current tactics to mitigate product shortages, but at a faster pace; and increase communication to specialty groups about impending shortages. The Society’s comments also address the negative impact drug and biologic shortages have on clinical research.

What’s the takeaway?
Visit the drug shortage information page on the ASH website (www.hematology.org/drugshortages) to read the Society’s full comments and for details about current shortages of hematologic therapies.

CDC Announces New Director for Division of Blood Disorders

ASH member Dr. Lisa Richardson joined the National Center on Birth Defects and Developmental Disabilities (NCBDDD) Division of Blood Disorders as the Division Director in mid-April.

Prior to joining NCBDDD, Dr. Richardson served as the associate director of science in the Division of Cancer Prevention and Control in the National Center for Chronic Disease Prevention and Health Promotion where she oversaw the research and scientific content of the Division’s programs and products, including the National Breast and Cervical Cancer and Early Detection Program and the National Program of Cancer Registries.

Dr. Richardson received her medical degree and Bachelor of Science from the University of North Carolina at Chapel Hill and her Master in Public Health (epidemiology) from the University of Michigan, School of Public Health. She completed her internal medicine residency and hematology/medical oncology fellowship at the University of Florida, School of Medicine. She continues to provide clinical services to patients at the Atlanta Veteran’s Administration Medical Center. Dr. Richardson is board-certified in hematology and medical oncology, a Robert Wood Johnson Clinical Scholar, and a member of the Alpha Omega Alpha Medical Honor Society.
kinase inhibitors? Given the range of genetic complexity in Cll, such a clinical response could be expected in some patients, but likely not in all. Nonetheless, the BCR signaling inhibitors show promise in the treatment of lymphoproliferative neoplasms, particularly Cll, justifying additional basic and clinical studies to understand the full potential of this therapeutic modality.


10. Dr. Friedman received research funding from Rhizen Pharmaceuticals and TG Therapeutics, both of which have been developing a PI3Kδ inhibitor.

Dr. Weinberg indicated no relevant conflicts of interest.

ASH Supports Rally for Medical Research

In early April, ASH took part in the “Rally for Medical Research,” in Washington. ASH was the sole Platinum Sponsor, which was the highest level of support. The Rally, which was held in conjunction with the American Association for Cancer Research’s annual meeting and backed by more than 200 partner organizations across the country, served as a unified call to action to researchers, clinicians, patients, and other advocates to raise awareness of the need for sustained investment in the National Institutes of Health (NIH) to improve health, spur more progress, inspire more hope, and save more lives.

ASH’s support of the rally is one of many components of a multifaceted approach the Society launched last year to address devastating NIH budget cuts, which included the establishment of the Bridge Grant program, the creation of the ASH Foundation, enhanced advocacy, and increased communication to the media about the importance of federally funded biomedical research and to the ASH membership to encourage everyone to join the effort and make their voices heard. For more information and to watch a short video of the Rally, go to www.hematology.org/

Left: Thousands of individuals came out to lend support and make their voices heard. Above: ASH was a Platinum Sponsor of the event.
G-protein-coupled receptors (GPCR) represent the largest and most diverse receptor family and are the most common targets of currently marketed therapeutics. Common drugs targeting GPCRs include ranitidine (an H2 receptor antagonist), albuterol (a β2-adrenergic receptor antagonist), atenolol (a β1-adrenergic receptor antagonist), ondansetron (a 5HT3 receptor antagonist), and caffeine (an adenosine receptor antagonist). Because of their importance in biology and medicine, high-resolution analysis of the structures of GPCRs is needed, but such information has been slow to materialize because of technical problems affecting expression and crystallization of the proteins. After initial success in solving the structure of bovine rhodopsin in 2000,1 there was a seven-year hiatus before the structure of the human β2-adrenergic receptor was solved.2 Over the past five years, however, advances in technology combined with the concerted efforts of leading structural laboratories have led to the solution of the structure of over a dozen GPCRs with the solution of many more on the way. The latest success story is that of protease-activated receptor 1 (PAR1).

PAR1 is a widely expressed receptor that responds with high sensitivity to protease activity in the extracellular environment. The activation mechanism is unusual in that it involves an intramolecular process in which thrombin (or other thrombin-like proteases) cleaves an N-terminal proteolytic site, generating a tethered peptide that interacts with the extracellular face of the receptor (thus both receptor and ligand are part of the same structure). Binding of the tethered ligand causes a conformational change in PAR1 that results in the activation of the heterotrimeric G protein-coupled complex on the cytoplasmic surface of the plasma membrane. PAR1 is the most abundant GPCR on platelets and connects, through thrombin activation, the coagulation cascade to platelet-mediated thrombus formation. As a result of its importance in thrombosis, PAR1 has been the target of several drug development programs focused on generation of novel antiplatelet agents. The most advanced compound in clinical development is vorapaxar, which is a highly specific PAR1 inhibitor. In phase III trials, vorapaxar was found to be protective against recurrent myocardial infarction, but at the cost of increased bleeding, including intracranial hemorrhage.3 One key to solving the structure of GPCRs is identifying small molecules capable of stabilizing the tertiary structure of the receptors. Vorapaxar served this purpose for PAR1, allowing the crystal structure of the PAR1-vorapaxar complex to be solved at a resolution of 2.2 Å (Figure). The crystal structure of PAR1 complexed with vorapaxar provides the first high-resolution depiction of this unusual receptor and demonstrates how a small molecule (vorapaxar) can block receptor activation by binding to a relatively superficial site on the protein (Figure). The PAR1 structure elucidated by Zhang and colleagues will inform additional structure-function studies aimed at understanding how engagement of the tethered ligand of PAR1 transmits a signal through the receptor. That and other information generated from the crystal structure will enable more rational design of improved PAR1 inhibitors.


**Figure**

**Not PAR for a GPCR**

The Effects of Leukemogenic Isocitrate Dehydrogenase 1 Mutations on Proliferation and Differentiation are Reversible


The 2009 discovery of somatic mutations affecting isocitrate dehydrogenase 1 and 2 (IDH1/2) in about 20 percent of karyotypically normal acute myeloid leukemia (AML) cases raised puzzling questions about how mutations in a pair of isoenzymes so fundamental to normal cellular metabolism could induce cancer. Normal IDH enzymes convert isocitrate to α-ketoglutarate (2-oxoglutarate, 2-OG), which is an essential nitrogen transporter and co-factor for oxidation reactions. As subsequent investigations revealed, the specific mutations in IDH1 and IDH2 observed in leukemia (and in malignant glioma) generate neomorphic enzyme activity. In contrast to production of α-ketoglutarate of the (R)-enantiomer of 2-hydroxyglutarate (2-HG), which inhibits enzymes such as TET2 (itself commonly mutated in AML) and augments the activity of the family of prolyl hydroxylases that down-regulate hypoxia-inducible factor (HIF).1,2 While these observations were suggestive that (R)-2-HG is an oncometabolite, it has been unclear whether (R)-2-HG is actually leukemogenic, since IDH1 mutants have several other effects on the cellular metabolome besides (R)-2-HG generation.

Julie Losman, in Bill Kaelin’s lab in Boston, and her colleagues have now shown that (R)-2-HG is indeed sufficient to promote leukemogenesis, and they have also provided new mechanistic insights into how that transformation might occur. The investigators transfected the peculiar TF-1 erythroleukemia cell line, which remains cytokine-dependent and retains differentiation potential, with tagged versions of IDH1 R132 and with control wild-type and catalytically inactive versions of IDH1. Losman and her colleagues observed that the IDH1 R132 mutation conferred cytokine independence and resulted in differentiation block. Hematopoietic growth factor independence and differentiation-failure are hallmarks of leukemia.

Similar behavior with IDH1 R132 transfection was also observed in an immortalized murine hematopoietic progenitor cell line (SCF ER-HoxB8), confirming that these changes are not unique to TF-1 cells. Furthermore, incubation of non-infected TF-1 cells with (R)-2-HG showed that this oncometabolite (we can now safely call it that) itself induced cytokine independence and loss of differentiation similar to that promoted by the mutant IDH1 that generates (R)-2-HG. TET2 knockdown resulted in similar effects. A lentiviral shRNA knockdown screen of all known 2-OG-dependent dioxygenases pointed to TET2 as a candidate for conferring cytokine independence when inhibited.

Importantly, the effects of (R)-2-HG on cell behavior were reversible in this model system, despite early fears that the dangerous epigenetic patterns resulting from altered function of TET2 and other enzymes under the influence of (R)-2-HG might be permanent. Incubating the transformed TF-1 cells and the murine cell line with a specific IDH1 R132 inhibitor (AGX-891) led to cell differentiation and loss of growth-factor independence. Presumably, the same would be true of mutation-specific inhibitors of IDH2 R140 and R172 mutants. Collectively, this work suggests that inhibition of IDH mutants by small molecules may be a potent therapeutic strategy in patients with AML who have these mutations. IDH1 and IDH2 inhibitors are in an advanced phase of preclinical development and will hopefully soon be ready for early-phase clinical trials.


Stitching Trainers Together to Subtype Diffuse Large B-Cell Lymphoma


The identification of two biologically distinct subtypes – activated B cell (ABC) and germinal center (GC) – of diffuse large B-cell lymphoma (DLBL) by their gene expression profiles transformed our understanding of disease pathogenesis and led to high expectations for the development of novel targeted therapies, especially for the unfavorable ABC type. Progress in the field has been hampered, however, by inconsistencies inherent in using immunohistochemistry (IHC) staining to distinguish the subtypes. Although several IHC algorithms have been proposed to separate the good-prognosis GC type from the aggressive ABC type, inter-observer variability in interpretation of pathologic specimens has plagued this approach. For this reason, gene expression arrays remain the optimal approach to subtyping, and the technical complexities of these systems are steadily becoming more manageable. Methods to extract sufficient mRNA from formalin-fixed, paraffin-embedded (FFPE) tissue have been improved to the extent that routine diagnostic studies can now be used without having to rely on fresh tissue. The other obstacle to clinical implementation of microarray analysis has been the lack of bioinformatic tools sufficiently robust to allow for real-time classification of individual cases as they occur in routine practice. Previous instruments depended on retrospective analysis of bulk data and were therefore useful for research studies but not for analysis of individual samples. The groups from the Haematological Malignancy Diagnostic Service at St. James’s University Hospital, Leeds, UK, and the Bioinformatics Group at the University of Leeds appear to have now resolved this problem as well.

Starting from the cell-of-origin classifier developed at the National Cancer Institute, Care et al. evaluated more than 30 different machine learning tools used to determine the DLBL cell of origin that have been reported in the literature. Machine learning tools derive from artificial intelligence research and center on algorithms that learn to identify recurring patterns from available data and link them to specific decisions or assigned classes. Once trained, the algorithms can apply the learned rules to new data. The paper by Care and colleagues showed that a combination of four of these machine learning tools, voting in a balanced fashion, could effectively classify DLBL data sets from a range of different tissue sources and array platform types. Importantly, this combination of tools was better at separating the good (GC) and poor (ABC) risk groups in most data sets, including those derived from either FFPE or fresh material. They did this without assigning more cases to the “unclassified” type III category, although a small molecular gray zone always persists. In validating this classifier, the authors performed an extensive meta-analysis of gene expression across 10 data sets (more than 2,000 samples) of DLBL. Interestingly, the optimized classifier requires only 20 of the genes that were included in the original NCI classifier, and the authors were also able to show that increasing the number of analyzed genes up to 180 did not improve the ability to classify subtypes with significant differences in survival.

The tool, described as the DLBL automatic classifier (DAC), is available as an open source, free-standing application. It can be found at www.bioinformatics.leeds.ac.uk/~bgv/imo/DAC/ and can be downloaded and used to classify both whole data sets and individual cases. For the latter, all that is required is a background data set of at least 30 cases for the array platform type being used before starting to type individual cases.

Taking molecular phenotyping from a research tool into clinical application has been slower than expected, mainly for technical reasons. DAC may represent an important step in bringing microarray analysis to the clinic by providing a widely applicable platform for allocating cases to ABC or GC subtypes, prospectively. Because the gene set involved is relatively small, it is also potentially applicable to gene expression assessments derived from RT-PCR or nanostring platforms. Although the DAC diverges in some details of the algorithm from the original cell-of-origin classifier, the extensive analyses reported in this paper indicate that the classification choices it makes are fully consistent with the cell-of-origin subtypes in such data sets. The major classes are greater using this tool than any other. We now look forward to seeing the results of its use in prospective clinical trials.

Selective Therapeutic Targeting of iNKT Cell-Mediated Inflammation in Sickle Cell Anemia


Sickle cell anemia is a genetic disorder of red blood cells caused by a point mutation in the \( \beta \)-globin gene (HBB; \( \beta^s \)). Sickle hemoglobin (HbS; \( \beta^s \delta^A \)) polymerizes upon deoxygenation leading to the two main pathophysiologic features of sickle cell anemia: hemolysis and vaso-occlusion. We now understand vaso-occlusion to be a complex, multicellular process involving erythrocytes, leukocytes, platelets, endothelial cells, and soluble coagulation and inflammatory factors. Ischemia-reperfusion injury (IRI), which is thought to underlie the pathogenesis of the vaso-occlusive complications, is also associated with a profound pro-inflammatory environment. This inflammation causes activation, adhesion, and migration of leukocytes that can sustain and propagate vaso-occlusion. Thus, inflammation can be considered a cause of vaso-occlusion as well as a consequence. Inflammation has long been considered a therapeutic target in this disease, and several investigators have tested corticosteroids for the treatment of painful vaso-occlusive events and acute chest syndrome. Although corticosteroid therapy can shorten vaso-occlusive events, it can also precipitate “rebound” painful events, which decreases the net benefit.

In search of a better treatment, Field and colleagues have begun to explore a finely targeted approach to anti-inflammatory therapy in sickle cell anemia. Based on the knowledge that invariant natural killer T (iNKT) cells appear to be key to propagating the inflammatory cascade associated with IRI and that iNKT cells are both increased in number and activated in sickle cell anemia, they conducted a phase I trial of regadenoson to decrease iNKT activation during painful events. iNKT cells are a rare subset of lymphocytes that link innate and adaptive immune responses, and they express high amounts of adenosine A2a receptors (A2AR) upon activation. Regadenoson is a selective A2AR agonist used to induce myocardial hyperemia for imaging, but its anti-inflammatory actions occur at drug concentrations 10 to 100 times lower than its cardiovascular actions. As such, a low-dose infusion of regadenoson has the potential to decrease inflammation yet avoid cardiovascular side effects.

Field and colleagues studied iNKT cell activation and administered regadenoson as a low-dose, 24-hour infusion (1.44 mcg/kg/hour, determined during a dose-finding phase) to 12 adults with sickle cell anemia — six at steady-state and six during a painful vaso-occlusive event. iNKT activation was assessed by analyzing the degree of expression of NKG2D, A2AR, and IFN-\( \gamma \) by flow cytometry. They found that iNKT activation was highest during painful events compared with steady-state and normal controls. During painful events, regadenoson infusion reduced iNKT activation to levels similar to steady-state and normal controls, chiefly as measured by reduced expression of NKG2D. The infusion of regadenoson was well tolerated at all dose levels. The only potentially dose-limiting toxicity was transient bradycardia (heart rate = 49 bpm) while asleep at the 0.6 mcg/kg/hr dose level, but this event was adjudicated not to be medication-related. Heart rate and blood pressure were a concern because bolus doses of regadenoson used for myocardial imaging cause vasodilation; however, both were relatively stable throughout the regadenoson infusion, showing only normal physiologic variation, and the infusion did not interfere with the provision of usual medical care for the patients with pain.

These early-phase experiments demonstrate that selective therapeutic targeting of iNKT-related inflammation appears to be better tolerated than “brute force” immunotherapy with high-dose corticosteroids that can actually cause more vaso-occlusive pain. Specifically, a 24-hour infusion of low-dose regadenoson appears to be safe when given to adults during painful vaso-occlusive events, and iNKT cell activation can be reduced to steady-state levels. Of course, the next step is the evaluation of efficacy, and these investigators have already planned a phase II randomized clinical trial of regadenoson for the treatment of painful events and acute chest syndrome in patients with sickle cell anemia.


Balancing the Stem Cell Budget


To combat age-related decline, or in response to injury, organ function is maintained by a pool of tissue-specific stem cells. The capacity of stem cells to undergo mitotic cell division that produces both one daughter cell that fully retains all attributes of “stemness,” and a second daughter cell committed to differentiation (termed asymmetric cell division) is part of the working definition of a hematopoietic stem cell (HSC). Simplistically viewed as a binary decision, cell division can be adjusted between symmetric and asymmetric mode, i.e. commitment of both progeny to differentiation or to balanced HSC maintenance, respectively. Short-term, immediate response to infection or injury may require rapid production of mature progeny via all-out symmetric commitment, whereas long-term integrity of the HSC compartment requires the sustained maintenance of a population of stem cells. Thus, balancing divisional symmetry/asymmetry in the postnatal HSC-pool is akin to a toggle switch. Persistent symmetric division risks HSC pool-exhaustion. Conversely, the inability to respond swiftly to states of injury via invariant asymmetric division may compromise short-term needs. How HSCs control self-renewal decisions has been one of the more enigmatic aspects of their regulation.

Coinciding with a general interest in understanding stem cell metabolism, the recent paper by Ito and colleagues now provides evidence to suggest that lipid catabolism is central to the regulation of self-renewal. The authors show that the activity of peroxisome-proliferator activated receptor \( \gamma \) (PPAR-\( \gamma \)), a nuclear receptor involved in the transcriptional regulation of fatty acid oxidation (FAO), is important in regulating HSC maintenance. In a series of experiments involving genetic and pharmacologic manipulation, the authors show that PPAR-\( \gamma \) activity and mitochondrial FAO are critical in preventing the successive erosion of the murine HSC pool. Combining adoptive cell transfer with the use of a pharmacologic inhibitor of FAO, the authors confirmed the reduction in HSC potency via this pathway and showed that the phenotype was transferable, implying a lack of microenvironmental impact. Building on prior work by the group, Ito et al. provide further evidence to support PPAR-\( \gamma \) activation through signaling by the well-known tumor suppressor \( \beta\text{-catenin} \). This observation, in essence, establishes a linear metabolic connection between fatty acid oxidation and HSC attrition. However, in what may be the most surprising and influential finding in this study, the authors took advantage of the canonical surface immunophenotypes that distinguish HSCs from differentiating progeny and performed serial fluorescent microscopy to track division events at the single-cell level. Their in vitro studies persuasively show that interference with the PML – PPAR-\( \delta \)– FAO pathway compromises asymmetric division events and leads to stem cell pool depletion via excessive symmetric commitment. In other words, fatty acid oxidation is required for asymmetric divisions to occur at a rate that maintains post-natal HSC pool size.

The authors point out that in vivo validation for their study is lacking, and they highlight the more general need for in vivo imaging approaches to complement existing functional and molecular assays. Additional questions arise: What is the role of hypoxia and glycolysis in ascertaining adequate asymmetry in the HSC self-renewal division? Does metabolic regulation apply to the net HSC expansion that occurs during fetal hematopoietic development? The notion of manipulating FAO and division symmetry in stem cell populations may also have more immediate applications. In addition to the FAO inhibitor etomoxir used here, rapamycin, a clinically approved mTOR inhibitor, rescues genetic loss of pmf function and activates FAO while promoting PPAR signaling.

The studies of Ito and colleagues provide the first evidence suggesting that lipid oxidation is a key regulator for HSC maintenance and establish divisional symmetry as the key mechanism. The data not only lend strong support to the study of metabolism in stem cell regulation, but also describe pharmacologic approaches to intervention. While the authors were unable to demonstrate cases of symmetric self-renewal, i.e. net stem cell expansion, it would seem worthwhile to learn if such an outcome can be forced via the same regulatory pathway. Such a scenario may be of interest in the setting of stem cell transplantation and perhaps relevant to efforts to expand cord blood samples. Hematopoietic stem cell biology has served as a paradigmatic model for regenerative activities in other organ systems. The notion of a tightly organized pyramid with the stem cell at the top has been challenged, but the “standard model” of hematopoietic stem cell biology continues to provide useful conceptual guidance and occasional groundbreaking mechanistic insights. In this case, biology appears to hold lessons for asset management and wise budgeting.
The Hematologist: dr. ragni indicated no relevant conflicts of interest.

Microvascular thrombotic lesions are commonly found in the heart of patients with progresses unchecked, leading to diffuse small vessel thrombi in multiple organs, vWF multimers, thereby diminishing vWF-platelet interaction and local thrombosis. appears to contribute to the pathophysiology of acute coronary syndrome (ACS). The mediators of ischemia/reperfusion (i.e., prothrombotic vWF) damage endothelial cells. During vessel injury, collagen-bound vWF binds to platelets, decelerating their flow and thereby promoting receptor interaction, cellular activation, and thrombus formation. At the same time, prothrombotic vWF is cleaved by ADAMTS13 to prevent excess thrombosis. These observations suggest the hypothesis that a disturbance in the balance between ADAMTS13 and vWF (i.e., normally low ADAMTS13 activity or abnormally high vWF activity) could contribute to the pathogenesis of coronary artery disease and that ADAMTS13 has therapeutic potential in the treatment of myocardial ischemia.

Two independent investigative teams recently challenged the hypothesis in a murine myocardial infarction model induced by coronary artery ligation. Following one hour of occlusion and 23 hours of reperfusion, De Meyer and colleagues observed larger myocardial infarct size in ADAMTS13-/- mice as compared with wild-type mice. The infarct injury in the ADAMTS13 null mice was also accompanied by greater inflammation, by greater granulocyte monocyte infiltration and activation, and by greater myocardial apoptosis. To evaluate whether ADAMTS13 could reduce myocardial damage, recombinant human ADAMTS13 (rhADAMTS13) was infused into wild-type mice subjected to coronary artery ligation. Infarct size was reduced significantly as compared with infarct size in the control/wild-type animals (those who did not receive rhADAMTS13 infusion) and accompanied by three-fold lower plasma cardiac troponin-I concentrations and nine-fold lower neutrophil infiltration into ischemic myocardium. No adverse events were observed in the mice treated with rhADAMTS13.

Gandhi et al., using a similar coronary artery ligation model, independently confirmed the larger myocardial infarct size in ADAMTS13-/- mice as compared with wild-type mice and showed that infarct size and troponin levels in ADAMTS13-/- mice were similar to wild-type mice. In correlative experiments, they found that infarct size was smaller and troponin levels were lower in vWF-/- mice than in wild-type mice. When ADAMTS13-/-/vWF-/- double knockout mice were analyzed in the coronary artery ligation experiment, infarct size and troponin levels were found to be similar to those of vWF-/- single knockout mice, supporting the concept that the greater myocardial injury observed in the setting of ADAMTS13 deficiency is vWF-dependent.

These studies provide evidence that ADAMTS13 deficiency exacerbates myocardial damage in an animal model of ischemia/reperfusion injury and that vWF deficiency or ADAMTS13 infusion ameliorates the process. Thus, it is reasonable to postulate that treatment with ADAMTS13 would lessen myocardial damage in patients with ACS. But whether the findings in mice are applicable to humans is speculative, and testing in humans will require carefully controlled trials as combinations of anticoagulation, platelet inhibition, and thrombolytics are standard therapy in patients with myocardial injury. Extrapolation of the findings in mice to humans is also tempered by differences in the pathology and cardiovascular physiology. For example, atherosclerotic plaque formation contributes to ACS in humans but is not part of the pathophysiology of the animal model used in the current studies; and arterial and venous flow rates differ between mice and men, and this difference may impact shear stress and local conditions that predispose to microvascular thrombosis. Additionally, the relative contributions to myocardial ischemia of ULvWF compared with cleaved, low-molecular-weight vWF multimers is unknown. Despite the unanswered questions, these provocative findings have important clinical implications that merit further investigation.


Naturally occurring inorganic platelet polyphosphates and polyphosphate nucleic acid scavengers including RNA and DNA have recently attracted considerable attention as procoagulants and prothrombotic agents. Polyporphosphates promote the activation of the contact activation system, which initiates the intrinsic pathway of blood coagulation. Platelet polyphosphate, a dense granule linear polymer containing 60 to 100 orthophosphate groups, binds factor XII and high-molecular-weight kininogen (HMWK), resulting in reciprocal activation of factor XII and prekallikrein. A plethora of other activities associated with polyphosphates has been reported, including activation of factor XII-activating protease, acceleration of factor XI activation by both thrombin and factor Xa, profibrinolytic activity, and acceleration of the production of the inflammatory mediator bradykinin.

The identification and characterization of polyphosphate activity has raised new interest in the ongoing puzzle of contact activation. In the clinical laboratory, the intrinsic pathway is probed using the activated partial thromboplastin time (APTT), which uses artificial, non-physiologic substances such as glass, kaolin, or ellagic acid to activate the contact system. Human deficiencies of factor XII, prekallikrein, or HMWK produce prolonged APTTs, yet they are not associated with a bleeding diathesis. If in vitro properties of the contact system represent some sort of clinically relevant activity, then potent contact activators found in platelets or released from cells play physiologic or pathophysiologic roles?

Jain et al. in the laboratory of Bruce Sullenger at Duke University evaluated the anticoagulant and antithrombotic activity of several polyphosphate-binding polymers, including (1-cyclohexyl-containing-containing cation (CDP), hexadimethrine bromide (HDMBr), polyamidoamine dendrimer, 1,4-diaminobutane core, generation 1 (PAMAM G-1), PAMAM G-3, and PAMAM-G5. Polyphosphates with an average chain length of 60 and 130 residues were used as procoagulant activators. All of the polyphosphate-binding polymers neutralized the procoagulant activities of Polyp 60 and Polyp 130. PMAM G-3 was chosen for further study because of its relative potency and reportedly favorable toxicity profile. PAMAM G-3 neutralized the procoagulant properties of Polyp 60 in human whole blood measured by thromboelastography. Binding studies using isothermal titration calorimetry revealed that PMAM G-3 binds Polyp 60, Polyp 130, CyGy, poly IC, and plasmid DNA with high affinity, displaying dissociation constants ranging from 0.2 to 10 nM. In a murine carotid artery injury model, PMAM G-3 neutralized the shortening of the carotid artery occlusion time induced by Fe3O4. PMAM G-3 also decreased mortality of mice in a collagen/epinephrine-induced pulmonary thromboembolism model. In contrast, PMAM G-3 did not increase blood loss in a murine tail transection model under conditions in which standard heparin significantly increased bleeding.

Based on these observations, Jain et al. concluded that PMAM G-3 is an antithrombotic agent that does not produce a bleeding diathesis. Hemostasis often is viewed as a yin-and-yang balance between hemorrhoa and thrombosis. Based rational strategies to identify the perfect antithrombotic agent have not been entirely successful. For example, tissue plasminogen activator initially was proposed as a potential non-normothrombic thrombolytic agent because of its fibrin specificity. However, clinical evaluation, bleeding became its dose-limiting feature. Only time will tell if the contact activation system represents the ideal antithrombotic target.


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The Hematologist: ASH NEWS AND REPORTS
Knowing When to Stop: Cell Cycle, MCV, and RBC Count

erythrocyte mean corpuscular volume (MCV) provides important information about anemia, anemia with decreased MCVs, such as iron deficiency or thalassemia, is a consequence of inadequate heme or globin synthesis. Anemias with elevated reticulocytes, like those resulting from blood loss or hemolysis, have increased MCVs because reticulocytes are larger than mature erythrocytes in macrocytic anemias with an inappropriate low reticulocyte number. In contrast, increased MCVs are the result of impaired DNA synthesis, as found in megaloblastic anemia, myelodysplasia, Diamond-Blackfan anemia, and Fanconi anemia. Among vertebrates, a reciprocal relationship exists between MCV and RBC counts such that with lower MCVs, there are a higher concentration of circulating erythrocytes and those with larger MCVs have a lower concentration of circulating erythrocytes. Using human genome-wide associated studies, Sankaran et al. identified an erythroid-specific enhancer 15 kb upstream of the promoter of CCND3, the gene encoding cyclin D3. The D-type cyclins bind and activate cyclin-dependent kinases CDK4 and CDK6, which promote cell-cycle progression from the gap1 (G1) to the subsequent DNA-synthesis (S) phase. Cyclin D3 has a role in the development of T and B lymphocytes, and rearrangements of CCND3 have been associated with T- and B-lymphoid malignancies. Sankaran et al. report that cyclin D3 regulates cell division in terminally differentiating erythroid cells, thereby controlling final exit from cell cycle and ultimate erythrocyte size (Figure).

In avian and mammalian erythropoiesis, in vitro, progenitors at the colony-forming-unit-erythroid/ proerythroblast stages, which proliferate without differentiating, can be induced to terminally differentiate by altering culture conditions. During terminal differentiation, erythroblasts undergo dramatic changes that transform them into much smaller cells containing high concentrations of hemoglobin. Cell size reductions during terminal erythroblast differentiation result from shortening the G1 phase of cell cycle while the length of S and gap2/mitosis (G2/M) phases remain unaffected. After these accelerated cell divisions, terminally differentiating erythroblasts abruptly stop dividing and mature into reticulocytes. In mammals, this erythroblast maturation includes enucleation. Sankaran et al. demonstrate that mature erythroblasts with Ccnd3 knockout or knockdown or with inhibition of CDK4 and CDK6 have fewer divisions during terminal differentiation. Erythrocytes produced in these in vitro studies and in vivo in Ccnd3 knockout mice had increased MCVs. Compared with wild-type littermates, Ccnd3 knockout mice had a 40 percent increase in MCVs and a 38 percent decrease in RBC counts, with only very mild anemia secondary to slightly decreased mean corpuscular hemoglobin concentrations. Indeed, the deficit in cell divisions during terminal erythrocyte differentiation is required to be independent of other events in terminal differentiation, including the capacity to respond to erythropoietin. In vivo knockdown of CCND3 showed similar decreased numbers of cell divisions and increased cell size in terminally differentiating primary human erythroid cells. The human polymorphism that led to identification of the erythroid-specific enhancer in CCND3 has enhanced enhancer function, and it is associated with increased MCVs and decreased RBC counts.

Sankaran et al. have demonstrated a central role for cyclin D3 in terminal erythroid differentiation where rapidly dividing erythroblasts progressively decrease their cell size and then abruptly cease cell division. Absent or reduced cyclin D3 activity decreases cell divisions and yields fewer but larger erythrocytes. Whether decreased cell divisions are responsible for large MCVs in inherited or acquired macrocytic anemias remains to be determined. However, understanding cyclin D3’s role in the reduction of cell size and the final exit from cell cycle in terminal erythroid differentiation will likely provide information about its role in normal and malignant lymphopoiesis in particular and terminal differentiation in general.


The Benefits of a “Sexist” RNA

Quality between the sexes is not just a social and economic imperative. On a biologic level, X-chromosome inactivation (XCI) ensures balanced gene expression between males and females. A major effect of XCI is the long, non-coding RNA, Xist. A 17-kb X-inactive specific transcript that is a component of the X-chromosome inactivation center on the inactive X chromosome. Transcriptional silencing of one X chromosome commences during embryonic development and mechanistically is mediated by Xist RNA coating of the X chromosome and cis-regulation of X-linked genes through binding of polycomb-repressive complexes. Although expression of Xist continues in the post-embryonic state, some in vitro models indicate that Xist may not be required to maintain XCI since its deletion does not always lead to reactivation of the inactive X chromosome. After XCI is established, the biologic effect of deleting Xist is unclear. A corollary issue is whether reactivation of X-linked genes occurs, and if so, what are the consequences? It is known that individuals with supernumery chromosomes (e.g., 47,XXY karyotype) exhibit an increased risk of developing various types of cancer. In addition, certain tumors are characterized by X chromosome aneuploidies, including loss of the inactive X, duplication of the active X, or acquisition of additional X chromosomes. However, the causal relationship between these abnormalities and tumor initiation or progression remains uncertain.

Using murine models where Xist is conditionally deleted in hematopoietic stem cells after establishment of XCI, Eda Yildirim, Jeanie Lee, and colleagues at Harvard Medical School demonstrate a direct link between Xist and development of cancer. Those investigators created two types of mutants by deleting Xist from either the inactive X in 100 percent of cells or from the inactive X in 50 percent of cells and from the active X in 50 percent of cells. Although pups were born normally, mutants started to die at 1.5 months, and only 10 percent were alive after two years of monitoring. Notably, lethality was restricted to females (and was similar in frequency between the two types of mutants), whereas males and controls demonstrated no pathology. Mutant animals frequently exhibited the clinical and laboratory features of a chronic myelomonocytic leukemia or erythroleukemia. Histopathology analysis of necropsied mice confirmed features of an overlap myeloproliferative/myelodysplastic syndrome. With progression, some animals died of a wasting illness characterized by a predominantly myeloid hyperproliferation accompanied by massive splenomegaly. In these cases, histopathology revealed progressive reticulocytosis, leukoerythroblastosis, leukocytosis, myelofibrosis, and extramedullary hematopoiesis involving the spleen and liver, consistent with myelofibrosis. Histocytic sarcoma, sometimes widely metastatic, and multi-organ lymphoproliferative vasculitis were also present in a significant proportion of the mutant animals.

Transplantation experiments confirmed that the MDS/MPN phenotype is derived from a hematopoietic cell rather than from a stromal cell origin. In addition, HSCs with deleted Xist exhibited qualitative and quantitative defects, including impaired mobilization and bone marrow reconstitution in lethally irradiated hosts. Gene expression profiling of Xist-mutants showed a significant upregulation of expression of X-linked genes, confirming that Xist is in fact required not only for initiation of XCI but also for maintenance of XCI. Changes in expression were not confined to X chromosome genes but also affected the autosomal genome, resulting in perturbation of molecular pathways involved in DNA replication, chromosome segregation, cell-cycle regulation, and hematopoiesis.

In addition to its role in equalizing the dosage of X-linked genes, these experiments implicate the long, non-coding RNA Xist as a sequela of the development of cancer. Although murine models demonstrate that the sequelae of Xist loss are restricted to females, these data refocus the spotlight on X chromosome aneuploidies and their pathogenic role in different cancer types. Regardless of gender, unraveling how Xist RNA coating drives a cascade of genome-wide changes and ultimately tumorigenesis is the next chapter in this fascinating story.
Factor VII, VIII, and IX: Making a Long-Lasting Impression

**STUDY TITLES:** Multiple studies of long-acting recombinant replacement factors for treatment of hemophilia A and B

**STUDY DESIGN:** The table lists 13 currently enrolling trials of long-acting recombinant factor VIII (rF VIII) or IX for treatment of patients with hemophilia A or B, respectively. These are multinational phase II/III or II trials designed to test whether long-acting factors are safe and effective in the treatment of hemophilia. The trials test the agents in the setting of active bleeding and for prophylaxis (for use in preventing spontaneous bleeding or in preventing excess bleeding in patients undergoing surgical procedures). In some studies, pharmacokinematics are assessed. Eligibility criteria are males with previous factor exposure with severe hemophilia A or B, defined as a plasma F.VIII or F.IX concentration of < 0.01 U/ml in some studies, or up to < 0.02 U/ml in other studies. The products include rF VIII or rF IX that are pegylated, glycopegylated, fused with albumin, or fused with the Fc fragment of IgG. Phase I studies of the products listed in the table (left) have to date demonstrated safety, prolonged half-life, and delayed clearance as compared with standard rF VIII and rF IX. The dosing regimens, modeled from pharmacokinetic data, vary from approximately twice weekly for the long-lasting rF VIII products to approximately once weekly for the long-lasting rF IX products. The primary endpoint for the non-surgical prophylactic studies is incidence of anti-VIII antibody or anti-IX antibody formation, and secondary endpoints include hemostasis for bleeding episodes and annualized bleed rates. For the surgical studies, the primary endpoint is hemostasis.

**RATIONAL:** It is well established that prophylaxis prevents spontaneous bleeding in individuals with severe hemophilia. Using current available replacement therapy to maintain the goal for effective prophylaxis (+1% plasma factor levels), rF VIII is dosed approximately three times weekly and rF IX is dosed approximately twice weekly. Although prophylaxis clearly reduces the incidence of major morbidity and disability, patient compliance is poor due to venous access problems frequently encountered in children and to inconvenience in the case of adults (Walsh CE et al. Haemophilia. 2009;15:1014-1021). The availability of replacement factors with a longer half-life than that of currently available products might reduce the frequency of infusion such that ports may no longer be required in young children, and a reduction in dosing frequency may encourage participation by those who have been reluctant previously to attempt prophylaxis. The more favorable pharmacokinetics of the longer-acting replacement factors may further reduce the morbidity that is a consequence of recurrent hemorrhathoses and thereby improve the quality of life of patients with hemophilia. A long-range goal is to tailor therapy based on individual pharmacokinetic modeling.

**COMMENT:** Although the development of longer-acting replacement therapy has generated a great deal of excitement in the field, the cost-benefit ratio is a concern as the pricing of the new agents is unknown. To address this issue, the current cost of replacement therapy for an adult with severe hemophilia A ranges from $149,000 to $360,000 annually. Thus, depending on pricing, the availability of the longer-acting recombinant proteins could conceivably lower the cost of replacement therapy because less frequent dosing would be required, provided constraints, however, limit treatment options for patients with hemophilia in much of the world as approximately 75 percent of replacement therapy is used by 15 percent of the total affected population (Shiner M. Haemophilia. 2012;18(Suppl 5):1-5). Without a major reduction in cost, this skewing of use of replacement therapy is likely to persist despite the advent of the longer-acting recombinant proteins. Although much work is left to be done in the field, patients with hemophilia A and hemophilia B and their treating physicians have reasons for optimism given the development of long-acting replacement proteins and the recent progress in gene therapy for hemophilia B. A trove of information should accrue from the broad range of studies being conducted on the long-acting replacement factors, and the effort and resources invested in the organization and implementation of these multinational clinical trials merits recognition.

-- Margaret V. Ragni, MD, MPH

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**Clinical Trials Corner**

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Beginning with this issue, a new column called "Editors' Choice" will appear in The Hematologist on a regular basis. This concept was developed in conjunction with the new editorial team of Blood. Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) will combine efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The citations will be annotated to provide readers both with a concise description of the thrust of the article and an explanation of why the paper is particularly important. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field. We hope you will enjoy the column, and we look forward to receiving your comments about this new initiative.

MARCH 7, 2013


These two manuscripts report the first in vivo identification of a newly discovered neutrophil-dendritic cell hybrid. This work extends previously published studies on the functional plasticity of neutrophils and reports on the adaptive immune capabilities of this major granulocyte subset. Both manuscripts describe the function of this novel population of hybrid neutrophil-dendritic cells that appear to have an important role in inflammation.

FEBRUARY 28, 2013

Controlled modulation of the hematopoietic differentiation process of pluripotent stem cells holds great promise for therapeutic application for a range of blood disorders. This manuscript reports results of experiments using chemical activators, inhibitors, and suppressed or over-expressed regulators to manipulate a critical pluripotent stem cell differentiation pathway known as the hedgehog. Experimental data show that augmentation of the hedgehog intracellular pathway alters the output from human pluripotent stem cells to produce hematopoietic cells that have acquired some aspects of adult hematopoiesis. These findings represent a major advance in the fields of developmental biology and regenerative medicine.

FEBRUARY 21, 2013

Induced pluripotent stem (iPS) cells offer the promise of individualized cellular therapy; however, to date, the derivation of hematopoietic stem cells (HSCs) from iPS cells has proved inefficient. In this manuscript, Amabile and colleagues report successful derivation of HSCs from human iPS cells. The authors report that immunodeficient mice injected with iPS cells form teratomas from which transplantable myeloid and lymphoid cells can be derived. These observations represent substantial progress toward the ultimate goal of using iPS cells as a means of individualizing treatment of blood disorders.

FEBRUARY 14, 2013

This manuscript provides proof of principle that several key features of X-linked lymphoproliferative disease (XLP1) can be corrected by gene therapy. The observation, that immune functions that are defective in this disorder can be normalized, represents a major step toward the development of clinically applicable gene therapy for infants with this severe inborn immune disorder.

FEBRUARY 21, 2013


Two papers published together in the January 24 issue of Blood elucidate the heterogeneity of familial hemophagocytic lymphohistiocytosis (HLH), a rare, often fatal immunologic disorder caused by impaired cell-mediated cytotoxicity that has been linked to mutations in a number of HLH genes. This project aimed at characterizing a critical marker of blood-forming stem cells, and a study of how proteins, when modified, induce arterial thrombosis. For a list of the award recipients, go to www.hematology.org/bridgegrantrecipients.

ASH Selects 17 Members to Receive New Bridge Grant

Last fall, the Executive Committee of the Society responded to grave concern over the impact that across-the-board cuts to the National Institutes of Health (NIH) budget would have on critical research by establishing the ASH Bridge Grant Program. The Bridge Grant is a key priority of the organization and demonstrates the Society's commitment to protecting the careers of those who are dedicated to hematology research.

This year and for the next two years, the Bridge Grant Program will provide at least $30 one-year awards annually, in the amount of $100,000 each, to ASH members who applied for an NIH RO1 grant or equivalent, but whose proposals went unfunded because of budget cuts. The long-term goal of the award is to help sustain research in the field and to contribute to retention of outstanding investigators focused on hematology research.

The first round of award winners was announced in mid-April. The 17 investigators who will be receiving the $1.7 million in grant money are from 26 U.S. institutions and represent a wide spectrum of seniority – four are professors, seven are associate professors, and six are assistant professors. Nine of the 17 funded projects focus on non-malignant diseases. Research supported by ASH's inaugural round of bridge grants spans the breadth of hematology. Funded projects range from characterizing a gene signaling pathway that will provide a better understanding of the basis of chemotherapy resistance in children with acute myeloid leukemia to exploring how red blood cells respond to oxidative stress. Other projects that received ASH bridge grant funding include a study designed to gain insight into gene regulation in lymphoma, a project aimed at characterizing a critical marker of blood-forming stem cells, and a study of how proteins, when modified, induce arterial thrombosis. For a list of the award recipients, go to www.hematology.org/bridgegrantrecipients.

Beyond the Society's financial commitment through 2016, additional awards will be supported by corporate and individual donors. Generous support from Amgen, Atlanta Convention & Visitors Bureau, Genentech, GlaxoSmithKline, The Takeda Oncology Company, and Novartis enabled the Society to award additional Bridge Grants in the first round.

Applications for the second round of funding were due in mid-April, and the recipients will be announced in July.

Details About the Award

* From 2013 through 2015, ASH will award at least 90 (30 per year) $100,000 bridge grants, for a total investment of $9 million.
* ASH membership is required at the time of application to the Bridge Grant Program and must be maintained throughout the award period.
* There will be two award cycles per year.

The Society is currently seeking support from individual and corporate donors in order to expand the program. Go to www.hematology.org/Foundation if you'd like to make a donation to this program.
Hematology in the Shadow of Kilimanjaro

Editor’s Note: Last summer, ASH leadership and staff traveled to Muhimbili National Hospital in Dar es Salaam, Tanzania, to consider adding a program at this institution to the current list of ASH/HVO sites, which includes Uganda, Peru, and Cambodia.

The national referral hospital in Dar es Salaam is faced with a tall order: provide care for hematology patients throughout Tanzania. In a country that is similar in size to Egypt and that has one of the highest incidences of sickle cell disease in the world, this charge is formidable. At Muhimbili National Hospital (MNH), eight dedicated clinicians—six hematologists and two internists—lead the effort to address the hematologic needs of the entire country. Can ASH do anything to help?

It was late July when the ASH contingent visited. Despite the 90°F heat, it was winter in Tanzania (the country lies between 1° and 12° south latitude). The MNH campus, a collection of blue and white buildings, sprawls across dozens of acres just outside of downtown Dar es Salaam, a city of 3 to 4 million located on the Indian Ocean (and 468 kilometers southeast of Mt. Kilimanjaro National Park). Drovers of Tanzanians could be seen making their way toward one of the many wards of the facility, most of them with food in hand. It was visiting hours at Muhimbili, and local patients depend on relatives for their daily meals. Trooping constantly through this crowd was the team of ASH representatives, led by members Dr. Theresa Coetzter, vice chair of the International Members Committee, and Dr. Enrico Novelli, a member of ASH and an expert in sickle cell disease. The group was there to conduct a site evaluation, assessing the hospital as a potential host of ASH member volunteers sponsored by the Society in conjunction with Health Volunteers Overseas (HVO). This partnership recruits ASH members to conduct clinical and laboratory training and classroom education at sites in the developing world. As is the custom with this program, the impetus to assess the site in Tanzania was a request from the potential host country’s hematologists.

Over the course of a week, the ASH/HVO assessment team got to know the hematologists and other clinicians at Muhimbili, heard of their needs, listened to their concerns, and reviewed the long-term goals they have for hematologic care in Tanzania. The group visited inpatient facilities and outpatient clinics, the pediatric unit of the hospital that features a separate sickle cell disease ward, the laboratories that perform diagnostics for hematologic, the on-site blood bank, and the Muhimbili University of Health and Allied Sciences (MUHAS/MNH), the university that educates specialists in hematology. Uniformly, personnel affiliated with each of these units, including high-level administrators, articulated a shared dedication to advancement of hematologic care at Muhimbili.

The conclusion of the site assessment can be easily summarized: Yes, the need for assistance is great; yes, ASH hematologists can have an immediate impact on patient care. The appeal of Muhimbili is that the challenges it faces are significant but, given the dedication of on-site personnel, not insurmountable. ASH members have the opportunity to elevate patient care at MNH and build a foundation for both program sustainability and growth.

The laboratories at MNH have their own set of needs. The performance and interpretation of basic diagnostic studies, such as bone marrow analysis, need to be improved, but the rapid impact that the ASH/HVO program can have on the host site is exemplified by an observation made by a member of the site-visit team. While reviewing the PCR capabilities of the hospital, Dr. Coetzter showed that by using available technology, a prohibitively expensive diagnostic test that had been outsourced to South Africa could be performed rapidly and inexpensively on site. Other technical and diagnostic laboratory issues that can be resolved through the interaction of volunteer hematologists with the physicians and technicians at MNH appear numerous.

The ASH/HVO team visited the National Blood Transfusion Service (NBTS) in Dar es Salaam, the state-run institution charged with the safe collection, allocation, and distribution of blood and blood components to Tanzania’s health-care providers. AABB, formerly the American Association of Blood Banks, has established a training and support program at NBTS to help meet this national mandate. However, the AABB initiative is limited to support of NBTS centers, such as that in Dar es Salaam. The site assessment team brought together, for the first time, personnel from the on-site blood bank at MNH with the NBTS staff and established the foundation for a program whereby AABB and the ASH/HVO program will work with the other stakeholders to ensure that the transfusion service at MNH has the capacity and technical expertise necessary to support advanced patient care.

ASH understands the need for building hematologic capacity in the developing world. In Tanzania, where the burden of hematologic disorders is especially high, ASH’s members stand ready to support our dedicated local colleagues.

More About Health Volunteers Overseas

To improve the quality of medical care in developing countries, ASH, in 2007, partnered with Health Volunteers Overseas (HVO), a nonprofit organization dedicated to improving global health through education. HVO-member volunteers travel to countries in need of education and training for health-care providers who care for patients with blood disorders. This program covers the management of a wide range of blood diseases, from the many forms of anemia (including those associated with malaria, pregnancy, iron deficiency, thalassemia, and sickle cell disease), to disorders that lead to abnormal bleeding and thrombosis, to malignant disorders such as leukemia and lymphoma.

HVO training programs focus on diseases and health conditions that are endemic to a particular region, and the procedures and skills taught are relevant and realistic. Accordingly, an overarching goal of ASH-HVO is sustainability, with stewardship of the programs being passed into the hands of local personnel so that patients in the home country continue to benefit after the volunteers have departed. In addition to teaching, ASH-HVO participants shape curricula, influence national health policy, and promote realistic health interventions in real time.

Volunteers are provided with a clean, safe place to live. Travel costs to and from the site are the responsibility of the volunteer. (These expenses are tax-deductible.) All volunteers also receive detailed orientation materials from both HVO and the program director in advance of their departure. Get more information at www.hematology.org/Global/3808.aspx.
**WHAT'S ON THE WEB**

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

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**MARK YOUR CALENDAR**

### May

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<td>1</td>
<td>Scholar Awards letter of intent due</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<tr>
<td>2</td>
<td>Application deadline for ASH Visitor Training Program</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<td>31-June 4</td>
<td>Annual Meeting of the American Society of Clinical Oncology</td>
<td>Chicago, IL</td>
<td><a href="http://www.asco.org">www.asco.org</a></td>
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<td>3</td>
<td>Scholar Award application available*</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<td>6</td>
<td>ASH annual meeting abstract submission site opens</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<td>13-16</td>
<td>18th Congress of European Hematology Association</td>
<td>Stockholm, Sweden</td>
<td><a href="http://www.ehaweb.org">www.ehaweb.org</a></td>
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<td>29</td>
<td>Translational Research Training in Hematology letter of intent due</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<td>29-July 4</td>
<td>Congress of the International Society on Thrombosis and Haemostasis</td>
<td>Amsterdam, The Netherlands</td>
<td><a href="http://www.isth2013.org">www.isth2013.org</a></td>
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<td>2</td>
<td>Nomination deadline for the 2014 ASH Honorific Awards</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<td>15</td>
<td>ASH Visitor Training Program finalists notified</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org/awards">www.hematology.org/awards</a></td>
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<tr>
<td>24</td>
<td>Members-only registration and housing opens for 2013 ASH Annual Meeting and Exposition</td>
<td>New Orleans, LA</td>
<td><a href="http://www.hematology.org/meetings">www.hematology.org/meetings</a></td>
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*In order to submit an application for the Scholar Award, you must have submitted a letter of intent by May 1, 2013.

For additional meeting dates and award deadlines, go to [www.hematology.org/Calendar](http://www.hematology.org/Calendar).