Division (I): ASH Opposes NCAA Requirement for Screening for Sickle Cell Trait

ALEXIS THOMPSON, MD, MPH
A. Watson and Sarah Armour Endowed Chair for Blood Diseases and Cancer; Hematology Section Head, Division of Hematology/Oncology Transplantation; Children’s Memorial Hospital, Professor of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

Sickle cell disease, an autosomal recessive disorder caused by the inheritance of two abnormal β-globin genes, is routinely diagnosed and managed by hematologists, but sickle cell trait has been the focus of recent heightened attention. Millions of Americans and hundreds of millions of people worldwide are carriers of the sickle cell mutation affecting one of their two β-globin genes. Individuals with sickle cell trait generally live normal, healthy lives; however, under extreme conditions, such as severe dehydration and high-intensity physical activity, complications including rhabdomyolysis, spenic infarction, and papillary necrosis can occur. The National Collegiate Athletic Association (NCAA) estimates that approximately 400,000 student athletes compete each year in sports under its sanction. During a five-year period from 2004 to 2008 in which athletes logged nearly 2 million participant-years, 273 deaths were reported by the NCAA with five of those deaths occurring in athletes with sickle cell trait. In April 2010, the NCAA adopted a policy requiring Division I institutions to perform testing for sickle cell trait on all incoming student athletes. This requirement followed a lawsuit that was filed after the death of a college football player who had sickle cell trait. The lawsuit was filed after the death of a college football player who had sickle cell trait.

Diffusion

New Clues About the Origin of Hematopoietic Stem Cells

The date, scientists have yet to succeed in differentiating pluripotent human stem cells (either embryonic stem cells or induced pluripotent stem cells) into functional hematopoietic stem cells (HSCs). Optimal in vitro differentiation of pluripotent cells into HSCs will likely require that we recapitulate the key stages of embryonic development in which these cells develop. Recent findings from the laboratory of Dr. Nancy Speck at the University of Pennsylvania have brought us one step closer in our understanding of the critical stages of hematopoietic development during embryogenesis.

Embryonic hematopoietic development is complex, with distinct hematopoietic populations appearing at different times and in different anatomical sites. One of the early waves of blood cell production is initiated in the yolk sac from erythroid-myeloid progenitor (EMP) cells, which give rise to erythrocytes, platelets, and myeloid cells but not lymphocytes. While EMP cells and their progeny are critical for the viability of the developing fetus, they provide only transient blood cell production. The final definitive stage of blood cell production occurs later in development, and, in contrast to EMP cells, is derived from HSCs, which supply all blood cell types – erythroid, megakaryocytic, myeloid, and lymphoid – for the entire lifespan of the organism. A key feature that sets HSCs apart from EMP cells is that only HSCs are capable of long-term engraftment in a myeloblated (usually by irradiation) host animal. Prior to this study by Chen et al., it was predicted that both EMP cells and HSCs develop from special endothelial cells, termed hemogenic endothelial cells, but it was not clear which endothelial subpopulations give rise to EMP cells and whether these were the same endothelial cells that also give rise to HSCs later in development.

The critical new finding in this paper is that EMP cells and HSCs are derived from two distinct hemogenic endothelial cell precursors. Formation of both EMP cells and HSCs requires a transcription complex containing a heterodimer of Runx1 (also known as AML1) and Core Binding Factor-beta (CBFβ). In order to test their hypothesis, the investigators used mice lacking the CBFβ gene, which make neither EMP nor HSC, and die early in gestation. In this study, the investigators restored CBFβ expression using either the TEK or the Ly6a promoters, which are activated in endothelial cells at different developmental stages. In TEK:CBFβ mice, the TEK promoter drives CBFβ expression in endothelial cells of the early yolk sac as well as endothelial cells of the aorto-gonad-mesonephros (AGM) region. In contrast, CBFβ expression is restored in Ly6a:CBFβ mice only at a later time in the AGM region. In TEK:CBFβ mice, normal EMP cells developed, but the HSCs did not survive to provide long-term hematopoiesis, which caused perinatal death. In contrast, in the Ly6a:CBFβ mice, the early transient EMP population was completely absent but fully functional HSCs developed. These data strongly suggest that these two major waves of hematopoietic cell development are derived from two different hemogenic endothelial populations, which are separate biological entities differing in the expression of key genes.

The clinical implications of these findings are critical to regenerative medicine. To date, the blood cells generated in vitro from pluripotent stem cells have failed to provide long-term hematopoietic engraftment. Based on the data presented by Chen et al., it is likely that the hematopoietic cells derived in vitro are not HSCs, and thus, the near-term goal must be to generate the correct hemogenic endothelium directly leading to HSCs. However, because there is not a human homologue for Ly6a, the search for appropriate markers identifying this hemogenic endothelium in human development must continue.
Highlights of ASH®

2012 Highlights of ASH in Asia Co-Chairs Drs. Wee-Joo Chng and Daniel G. Tenen met with representatives from the Chinese Society of Hematology, Hematology Society of Australia and New Zealand, Hematology Society of Taiwan, Indian Society of Hematology and Blood Transfusion, Indonesian Society of Hematology and Transfusion Medicine, Japanese Society of Hematology, Korean Society of Hematology, National Cancer Center Singapore, National University Cancer Institute of Singapore (NCIS), Singapore Society of Hematology, and Thai Society of Hematology during the 2011 ASH Annual Meeting.

Program co-chairs and representatives from the 2012 Highlights of ASH in Latin America partner societies in Brazil, Colombia, Paraguay, Uruguay, Venezuela, Chile, and Argentina met with ASH leadership during the past annual meeting in San Diego. (Front row, left to right: ABHH Co-Chair Dr. Roberto Passetto Falcao, ASH Co-Chair Dr. Mikael Sekeres, ASH President Dr. Armand Keating, and ABHH Co-Chair Dr. Carlos Sergio Chiattone; ASH President-Elect Dr. Janis Akbikowicz is pictured in the back row, fourth from right.) ASH Co-Chair Dr. Charles Quinn is not pictured.

Apply for the ASH Scholar Awards

It’s time to start thinking about the application process for the ASH Scholar Awards. Part of ASH’s Career-Development Awards, the Scholar Awards provide talented researchers with the financial support critical during the transitional period between completion of training and achievement of status as an independent investigator. For more information, go to www.hematology.org/Awards/Scholar/2407.aspx.

Timeline

Letter of Intent: May 1 (5:00 p.m., PST)
Application made available for those who successfully submit a letter of intent by the deadline: June 4
Application deadline: August 1 (5:00 p.m., PST)
Winners notified mid-November
Activation of award: July 1, 2013

LETTERS TO THE EDITOR SOLICITATION

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

Letters should be sent to:
Karen Learner, Managing Editor
The Hematologist: ASH News and Reports
2021 L Street, NW, Suite 900
Washington, DC 20036
klearner@hematology.org


Increasing Our Global Presence With Highlights of ASH

Over the past five years, the outreach programs of our Society have expanded and now extend globally. An example of our commitment to the international community is the staging of Highlights of ASH in both Latin America and Asia. These educational initiatives were developed in response to requests from our international members, with the support of a diverse group of national and regional hematology societies, who saw the importance of informing colleagues of the latest developments in the field. The meeting format is a modified version of that used for Highlights of ASH, first introduced in the United States in 2006. The idea behind Highlights of ASH was to provide busy clinicians with a timely summary of the scientific, translational, and clinical presentations that headlined the annual meeting. Case presentations and panel discussions were included to enliven these intimate meetings that typically attract 125 to 250 attendees. The success of the Highlights program in the United States (now called Highlights of ASH North America [HOA NA]) is evidenced by expansion of the number of venues from two initially to six currently, with presentations this year in New York, Atlanta, Orlando, Las Vegas, Austin, and San Francisco.

The favorable response to HOA NA suggested that the concept might travel well, thereby providing the opportunity for a unique educational experience for the international community. ASH had a strong relationship with Brazilian hematologists that had developed through their service on the ASH International Members Committee and their participation in the International Consortium on Acute Promyelocytic Leukemia. Hematologists from Brazil suggested the Associação Brasileira de Hematologia e Hemoterapia (ABHH) as the meeting co-sponsor. With ABHH as a partner, the first Highlights of ASH in Latin America took place in São Paulo, Brazil in 2009. It was a resounding success with more than 500 in attendance. This initial foray into South America was followed by another successful meeting, this one in Rio de Janeiro in 2010. The decision was then made to hold the HOA LA meetings annually, alternating the location between Brazil and another Latin American country. The meeting in 2011, with 670 in attendance, was held in Punte del Este, Uruguay, with the enthusiastic co-sponsorship of Sociedad de Hematologia y Hemoterapia del Uruguay. A specially designed session on how to prepare abstracts for the annual meeting and manuscripts for submission to Blood specifically targeted trainees and junior faculty members.

Planning meetings for HOA LA are attended by the leadership of Latin American hematology societies, and it has been gratifying to see increasing interactions among various regional and national societies with the HOA LA site serving as a common venue for presenting data and discussing issues of common interest. As a result of these interactions, an organized program to collect information about the status of patient care in Latin American countries was implemented. Some of the data generated by these studies was presented at HOA LA in Uruguay, and a paper summarizing the findings was recently published in Revista Brasileira de Hematologia e Hemoterapia, ABHH’s journal.1 Prior to ASH’s involvement in Latin America, a forum around which the societies could meet collectively had not been developed. Following two years of discussions, ASH held its first HOA Asia meeting in Beijing, China, in 2011, co-sponsored by the Chinese Society of Hematology and the Chinese Medical Association. This meeting attracted almost 900 attendees. In May, the first regional HOA Asia will be held in Singapore with the Cancer Science Institute of the National University of Singapore as co-sponsor, marking the first such involvement with an academic center. We are delighted that the following 10 hematology societies have signed on as partners, making this a truly pan-Asian meeting: Chinese Society of Hematology, Hematology Society of Australia and New Zealand, Hematology Society of Taiwan, Indian Society of Hematology and Blood Transfusion, Indonesian Society of Hematology and Transfusion Medicine, Japanese Society of Hematology, Korean Society of Hematology, National Cancer Center Singapore, National University Cancer Institute of Singapore (NCSI), Singapore Society of Hematology, and the Thai Society of Hematology.

The Wallace Coulter Foundation encouraged ASH to broaden the Society’s reach to Latin America and Asia and has generously supported trainee travel and attendance at every international HOA program. In all, more than 100 trainees have benefitted from the Foundation’s vision and philanthropy.

ASH’s involvement in Latin America and Asia has led to greater cooperation and interaction among hematologists both regionally and internationally, resulting in improved patient care, new opportunities for research collaboration, and a broader exchange of ideas. Somewhat analogous to Janus with his two faces that allowed him to look both forward and backward, the success of these programs encourages the Society to continue to look outward while simultaneously maintaining its inward focus.

Armand Keating, MD
ASH member Terry Hamblin, MD, who died on January 8, 2012, was one of the senior figures in hematology, particularly in the fields of chronic lymphocytic leukemia (CLL) and myelodysplasia. He was author of more than 300 papers, review articles, editorials, and chapters, and co-editor of Leukemia Research for 25 years.

Professor Hamblin was born in Worcester, England, in 1943. He qualified in medicine from Bristol University and, after training in the south of England, was appointed consultant hematologist in Bournemouth in 1974. Prof. Hamblin was one of the pioneers of the idea of hematology as a clinical discipline in the United Kingdom and among the first to use new techniques including plasmapheresis and peripheral blood progenitor cell transplantation. Long and productive collaborations with Professors George and Freda Stevenson at the University of Southampton resulted in seminal papers on the use of anti-idiotypic antibodies and DNA vaccines for the treatment of B-cell tumors, and in 1987, he was appointed professor of immunohematology at Southampton. In 1989, he was the lead author on one of the most influential papers published on CLL, showing that the mutational status of immunoglobulin heavy chain variable region genes defined a distinct biology and predicted the clinical outcome. In recognition of his contributions, he was a joint recipient of the Binet-Rai Medal in 2003 for his research in CLL. In 2000, he founded the UK CLL Forum and served as its chairman until 2006. He was also a founding member of the UK myelodysplasia forum and gained much satisfaction from the significant contribution that both bodies have made to the education of clinicians, scientists, and patients.

Prof. Hamblin was a devoted family man (married to Diane for 43 years with four children) and a devout Baptist. The breadth and depth of his knowledge on many topics including literature, music, theology, and sports (he was once mascot for the Aldershot Town Football Club), combined with an engaging personality and sparkling sense of humor, ensured that he was always excellent company.

– Peter Johnson, MD

Don’t Forget to Claim Your Annual Meeting CME Credits

Be sure to claim your CME credits for the ASH annual meeting. The online process for claiming CME credits and printing a CME certificate for the 53rd ASH Annual Meeting must be completed by April 13.

ASH Clinical Practice Webinar Series

During 2012, ASH will host a series of webinars on issues practicing hematologists frequently confront. These sessions will feature presentations by experts in the field, provide time for questions and answers, and cover the most current information on how to best diagnose and care for patients. Registration is free and available to ASH members and non-members. All webinars will be held at 8:00 p.m. Eastern Time.

UPCOMING WEBINARS

MARCH 26

Thrombosis and Cancer
Moderator: Vincent Picozzi, MD, Virginia Mason Medical Center
1. Epidemiology and Risk Assessment
   Alok A. Khorana, MD, James P. Wilmot Cancer Center
2. Treatment
   Agnes Y. Lee, MD, MSc, Diamond Health Care Centre
3. Thrombosis and Central Venous Catheters
   Elie Akl, MD, University of Buffalo

LATE APRIL

Plasma Cell Malignancies
Moderator: Dan Vogl, MD, University of Pennsylvania

MAY 31

Oral Anticoagulants for the Management of Venous Thromboembolism: The Old and the New
Moderator: Adam Cuker, MD, MS, University of Pennsylvania
1. Introduction to the new oral anticoagulants and evidence of their efficacy and safety
   David Garcia, MD, University of New Mexico Cancer Center
2. Optimizing therapy with vitamin K antagonists
   Neil Zakai, MD, MSc, University of Vermont
3. Management of the bleeding patient on oral anticoagulation
   Sam Schulman, MD, PhD, McMaster University

Visit www.hematology.org/webinars for more information on dates, speakers, registration, and audio versions of previous webinars.
Ask the Hematologist

JASON R. GOTLIB, MD, MS
Associate Professor of Medicine (Hematology) and Director, Hematology Fellowship Program, Stanford University School of Medicine and Stanford Cancer Institute

The Question

How does the recent FDA approval of the JAK inhibitor ruxolitinib influence your management of patients with myelofibrosis?

My Response

Myelofibrosis (primary and post-PV/ET MF) is a Philadelphia chromosome-negative myeloproliferative neoplasm with a natural history characterized by progressive anemia, spleen enlargement due to extramedullary hematopoesis, and potential for evolution to acute myeloid leukemia (AML). Impairment of quality of life is due to both massive splenomegaly (e.g., early satiety and abdominal discomfort) and inflammatory cytokines, which mediate debilitating symptoms such as night sweats, levers, muscle/bone pain, and cachexia. Activating JAK2 V617F mutation is present in 50 to 60 percent of patients, and this JAK2 mutation (W515K/L) resulting in ligand-independent activation of the thrombopoietin receptor, is identified in an additional 5 to 10 percent of individuals. It has become abundantly clear, however, that MPNs such as MF are more genetically complex. Molecular alterations in additional genes and dysregulation of the epigenetic machinery also contribute to disease pathogenesis.

Prognostic staging systems based on clinical and laboratory factors obtained either at the time of diagnosis (IPSS) or during the disease course (dynamic IPSS, or DIPSS) have been developed in order to estimate both overall survival and risk of progression to AML. The IPSS uses five adverse prognostic factors: age >65, hemoglobin <10 g/dL, white blood cell count >25,000/mm3, constitutional symptoms, and peripheral blood blasts >1 percent. The DIPSS-Plus refines prognosis assessment by incorporating three additional adverse risk factors: platelet count >100,000/mm3, the need for red blood cell transfusions, and poor-risk cytogenetics. Using the IPSS as an example, patients can be stratified into one of four risk groups.

Given this patient’s younger age and relatively poor prognosis, evaluation for a potentially curative myeloablative hematopoietic stem cell transplant would be encouraged.

For patients who require treatment and are not candidates for transplantation, available therapies for MF-related cytopenias, splenomegaly, and symptoms are considered palliative. These options have included chemotherapy such as hydroxyurea; erythropoiesis-stimulating agents (e.g., epoetin alfa or darbepoetin alfa); immunomodulatory drugs such as thalidomide or lenalidomide; with or without corticosteroids; splenectomy; splenic irradiation; and clinical trials. In November 2011, only four years after commencing clinical trial evaluation, ruxolitinib became the first JAK inhibitor approved by the FDA for MF patients (intermediate- and high-risk).

The registration trials for ruxolitinib consisted of two large phase III trials: COMFORT-I was a randomized (1:1), double-blind, multicenter study comparing ruxolitinib 15 mg or 20 mg twice daily (dose stratified according to baseline platelet count) versus placebo, and COMFORT-II was a randomized (2:1), open-label, multicenter trial comparing ruxolitinib 15 mg or 20 mg bid versus best available therapy (BAT; investigator-selected including no treatment). Both trials met the primary endpoint of the percentage of ruxolitinib versus control patients achieving >35 percent reduction in spleen volume at week 24 (COMFORT-I: 41.9% vs. 0.7% and week 48 (COMFORT-I: 28.5% vs. 0.6%). After 24 weeks in the COMFORT-I trial, the proportion of patients with ≥50 percent improvement in total symptom score (using the myelofibrosis symptom assessment form) was 45.9 percent versus 5.3 percent (ruxolitinib vs. placebo, p<0.0001). Anemia and thrombocytopenia were common ruxolitinib-related adverse events but rarely led to drug discontinuation, and the drug was otherwise well tolerated. In an updated analysis of COMFORT-I, there was a significant overall survival benefit with ruxolitinib; at a median follow-up of 51 weeks, there were 13 (8.4%) deaths in the ruxolitinib group and 24 (15.7%) deaths in the placebo arm.

The implications of these short-term data are unclear since JAK inhibitors exert modest or no impact on fundamental disease-related features such as JAK2 mutant allele burden or marrow fibrosis.

Ruxolitinib’s potency as a “spleen shrinker” and “symptom mitigator” is shared by other JAK inhibitors currently in clinical trials (e.g., SAR302503 [formerly TG101308], CYT387, SB518, etc.). Patients with or without the JAK2 V617F mutation respond similarly. Therefore, first-line treatment with a JAK inhibitor would be an ideal choice for Patient 2 described in the table and could be considered a bridging option for Patient 3 until a transplant is performed.

In an ad hoc analysis of the COMFORT-I and COMFORT-II trials, worsening of spleen size as well as symptoms and quality-of-life scores were similar between the placebo and BAT control groups. Although it may be premature to abandon conventional treatments such as hydroxyurea, the comparative superiority of ruxolitinib in these trials justifies its frontline use for intermediate- and high-risk MF patients in whom the primary goal is improvement of splenomegaly and constitutional symptoms. For MF patients with anemia or BCR-ABL translocation-dependence as the predominant clinic issue, no standard of care currently exists. In this regard, differences among JAK inhibitors may prove informative in tailoring particular agents to specific patient presentations. For example, the JAK 1/2 inhibitor CYT387 has demonstrated improvements in hemoglobin/transfusion-dependence in an ongoing phase II trial. Lenalidomide (or pomalidomide, on a trial basis) may also elicit benefits in anemia in ~20 to 30 percent of MF patients.

The recent FDA approval of the JAK inhibitor ruxolitinib for the treatment of MF could markedly influence treatment options. The drug is indicated in patients who are not likely to be candidates for allogeneic hematopoietic stem cell transplant.

The implications of these data are profound and wide-reaching, and given the current lack of conventional therapies for this disorder, the approval of ruxolitinib represents a welcome step forward in the management of MF.

Table: MF Patient Profiles

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>ECOG Performance Status</th>
<th>Hb (g/dL)</th>
<th>Platelet Count (x10^9)</th>
<th>PB Blasts (%)</th>
<th>Constitutional Symptoms</th>
<th>Splenomegaly</th>
<th>Cytogenetics</th>
<th>IPSS Score/Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>63/F</td>
<td>0</td>
<td>11.1</td>
<td>155,000</td>
<td>0</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
<td>0/low</td>
</tr>
<tr>
<td>Patient 2</td>
<td>61/M</td>
<td>1</td>
<td>10.5</td>
<td>218,000</td>
<td>2</td>
<td>Yes</td>
<td>4 cm</td>
<td>Monosomy 5</td>
<td>2/Intermediate</td>
</tr>
<tr>
<td>Patient 3</td>
<td>48/M</td>
<td>1</td>
<td>8.2</td>
<td>85,000</td>
<td>5</td>
<td>Yes</td>
<td>15 cm</td>
<td>Normal</td>
<td>4/High</td>
</tr>
</tbody>
</table>

In summary, BET inhibition appears to be a promising therapeutic strategy for a range of hematologic malignancies.
ASH Unveils New Agenda for Hematology Research

ASH is urging federal agencies to coordinate hematology funding in order to introduce the greatest impact on specific high-need areas. The newly released ASH Agenda for Hematology Research: 2012-2014 is a third update of a strategic plan the Society releases every three years. The latest update describes the many contributions of hematologists both to their own field and to other fields of medicine and articulates the necessity of placing hematology among the top priorities for funding within the health-care community, both today and in the future.

The ASH Agenda for Hematology Research: 2012-2014 was developed by the ASH Committee on Scientific Affairs with extensive input from all members of the Society’s 17 scientific committees and the Executive Committee. The Agenda consists of two parts. The first section uses stories of success in treating hematologic diseases to illustrate, in human terms, the return on investment of past research support. The second part outlines the foremost challenges confronting the field and identifies the highest priority scientific themes. This section focuses on areas of investigation considered to be the most promising and exciting in the field, including stem cell biology and regenerative medicine, myelodysplastic syndrome and acute myeloid leukemia in the elderly, hematopoietic stem cell transplantation and management of graft-versus-host disease, sickle cell disease, deep-vein thrombosis and venous thromboembolism, and childhood leukemia.

The ASH Agenda for Hematology Research: 2012-2014 is a valuable tool for use in promoting hematology research to the scientific community, funding agencies, political and legislative bodies, philanthropic organizations, patients and their advocacy groups, and the American public. The Agenda is available for download on the ASH website; go to www.hematology.org/researchagenda.

Congress Faces Tight Budgetary Squeeze for FY 2013; Advocacy by Hematologists Needed to Protect Funding for NIH

Congressional leaders are in the midst of planning for the annual spending bills, including federal funding for the National Institutes of Health (NIH). The process formally began with the Administration’s budget proposal, which, as this issue of The Hematologist went to press, was expected to be released on February 13.

The fiscal year (FY) spending measures, covering the 12-month period starting October 1, 2012, are restricted by last year’s budget control agreement, which capped spending at $1.047 trillion. Barring a change in the formula, major new spending initiatives are unlikely. Funding increases for most federal programs, including NIH, are also unlikely. Further complicating the appropriations process is the fact that FY 2013 spending bills are subject to $97 billion in across-the-board spending cuts, through a process known as sequestration, mandated by the failure to reach agreement on a deficit-reduction proposal last year by the Joint Select Committee on Deficit Reduction (commonly referred to as the “Super Committee”).

While programs such as NIH will face sequestration cuts, Medicaid is exempted from sequestration, and Medicare cuts are limited to a 2 percent reduction in provider payments (which would be in addition to any potential physician payment cut for 2013). According to an analysis by the House of Representatives Appropriations Committee Ranking Member Norman Dicks (D-WA), the sequestration plan will likely include at least a 7.8 percent cut for agencies, including NIH. Such a cut at NIH would mean the agency would be able to fund about 2,500 to 2,700 fewer research grants per year.

Grassroots support is critical in order to have a voice in the congressional budget process sufficiently strong to ensure that NIH does not experience significant cuts in funding. Please look for ASH Legislative Alerts and visit the ASH website for updates on the FY 2013 budget process and for information about how you can contact your senators and representative to protect NIH funding in FY 2013.

NIH Formally Establishes National Center for Advancing Translational Sciences

In a move to re-engineer the process of translating scientific discoveries into new drugs, diagnostics, and devices, the National Institutes of Health (NIH) announced the formal establishment of the National Center for Advancing Translational Sciences (NCATS).

The formation of NCATS has been in progress since a December 2010 recommendation of the NIH Scientific Management Review Board to create a new center dedicated to advancing translational science by overcoming hurdles that slow the development of treatments and cures. The formal creation of the Center was made possible by Congress’ approval of the fiscal year 2012 spending bill, which included the establishment of NCATS with a budget of $375 million.

To meet the goals of NCATS, NIH is reorganizing a wide range of preclinical and clinical translational science entities within NIH. The following programs will comprise NCATS:

- Bridging Intervventional Development Gaps, which makes available critical resources needed for the development of new therapeutic agents
- Clinical and Translational Science Awards (CTSA), which fund a national consortium of medical research institutions working together to improve the way clinical and translational research is conducted nationwide
- Cures Acceleration Network, which enables NCATS to fund research in new and innovative ways
- FDA-NIH Regulatory Science, which is an interagency partnership that aims to accelerate the development and use of better tools, standards, and approaches for developing and evaluating diagnostic and therapeutic products
- Office of Rare Diseases Research, which coordinates and supports rare diseases research
- Components of the Molecular Libraries, which is an initiative that provides researchers with access to the large-scale screening capacity necessary to identify compounds that can be used as chemical probes to validate new therapeutic targets
- Therapeutics for Rare and Neglected Diseases, which aims to encourage and speed the development of new drugs for rare and neglected diseases

Various other programs and grants once housed at the now-defunct National Center for Research Resources have been moved both to NCATS and to various other institutes and centers.

While the effort to recruit an NCATS director continues, organizational changes and realignment of resources will move forward under the leadership of Acting Director Thomas R. Insel, MD, and Acting Deputy Director Kathy Hudson, PhD.

For additional information on NCATS, visit http://ncats.nih.gov. For more information regarding the new location of former NCCR grants, contact ncrctransition@mail.nih.gov or go to http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-026.html.
Epigenetic Readers

(Cont. from page 5)


Sickle Cell Testing

(Cont. from page 1)

player during preseason training. Post-mortem investigation into the cause of death revealed that the player had sickle cell trait. The NCAA policy includes an opt-out provision for students who can provide results from a prior test and for those who are willing to sign a waiver exempting both their university and the NCAA from liability. Because ASH is devoted to the study and treatment of blood disorders, including sickle cell trait, the Society initiated a process to address the scientific, medical, and ethical issues raised by the NCAA’s policy.

In June 2011, ASH hosted a workshop aimed at determining whether evidence-based available evidence, individuals with sickle cell trait are at increased risk for exertion- or heat-related illness or sudden death. The workshop also sought to determine if there was evidence-based support for requiring adult screening for sickle cell trait as a prerequisite for participation in athletics. Physicians and researchers with expertise in sickle cell biology and treatment joined with representatives from the U.S. military and other federal agencies for an in-depth discussion of scientific data on the association between sickle cell trait and adverse health outcomes, including but not limited to exertion-related illnesses. In addition to an assessment of data published in scientific journals, panel members reviewed information on efforts by the military to mitigate heat-related risk, quality of life research on the impact of the NCAA mandate on athletes, and records of deliberations by other organizations on this topic.

As part of the discussion, the workshop participants reviewed and affirmed the Society’s support of screening of newborns for sickle cell disease. Newborn screening for sickle cell disease is currently performed in the United States in all 50 states as a public health imperative, because there is strong empirical evidence that early detection and intervention reduces morbidity and mortality in young children. While the Society supports newborn screening for sickle cell disease, there are no comparable well-controlled, prospective clinical studies that demonstrate a direct benefit for large-scale screening for adults. Voluntary screening beyond the newborn period paired with confidential counseling by knowledgeable providers can assist individuals in evaluating their own personal health status.

Published reports from the U.S. military in the 1980s identified an association of sickle cell trait and increased deaths during training. Subsequent work by the Army has focused on modification of their procedures related to the conduct of training, including heat acclimatization, monitoring rest/work cycles, and developing extensive protocols on the identification and treatment of suspected exertional heat-related illness (EHI). The Army discontinued screening for sickle cell trait in 1996, and their intervention measures have been fully implemented, which have resulted in a marked decline in deaths due to EHI in all recruits, including soldiers with sickle cell trait. Similar reductions in deaths have not been reported in other branches that have not adopted universal interventions.

ASH believes the current NCAA policy is not based on sufficiently strong scientific evidence and has the potential to cause inadvertent harm to the student athlete. The panel concluded that the NCAA policy for sickle cell trait screening of Division I athletes does not comply with best practices of testing and counseling of individuals for inherited conditions. The sickle solubility test lacks sufficient specificity and may give misleading results, as it cannot distinguish carrier status from diseases, which is particularly important in variant sickling syndromes such as HSSC disease. Safeguards for protecting genetic information are not apparent, putting the athlete at risk for stigmatization and discrimination. These issues extend beyond the playing field and persist long after the athlete’s four-year NCAA eligibility has expired.

Other organizations have raised similar concerns. In May 2011, the Medical and Research Advisory Committee (MARAC) of the Sickle Cell Disease Association of America (SCDDA) released recommendations in response to the NCAA ruling. MARAC concluded that given the lack of scientific evidence to substantiate a significant correlation between sickle cell trait in athletes and training-related deaths, SCDDA does not support screening of athletes for sickle cell trait as a means of reducing heat-related illness or death. SCDDA supports the implementation of universal, safe training guidelines for all athletes and recommends rigorous education to improve the capacity of athletic coaches and trainers to recognize signs and symptoms of heat-related illness and to provide medical care to athletes who become ill or injured under their supervision.

The U.S. Department of Health and Human Services (HHS) Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children developed a report in 2010 on screening of U.S. college athletes for sickle cell trait. The committee recommended that genetic testing should not be a prerequisite for participation in sports, unless deemed medically necessary, and that evaluation should include counseling, with safeguards in place to assure the privacy of genetic information. The committee also recommended that all athletes be given education on safe practices for the prevention of exercise- and heat-related illnesses. These recommendations were formally endorsed by HHS Secretary Kathleen Sebelius in June 2011.

Early this year, ASH contacted the NCAA to share its concerns and, on January 26, released its own policy statement on sickle cell trait and athletic participation that takes a different approach than the NCAA policy (see sidebar). A number of other organizations have announced their support of ASH’s position, including SCDDA, the American Society of Pediatric Hematology/Oncology, the American Public Health Association, the Association of Public Health Laboratories, and the American Society of Clinical Pathology.

The NCAA has expressed its willingness to discuss its policy with ASH and other stakeholders and explore these issues in an effort to better protect the health of athletes with sickle cell trait. As this article went to press, ASH was working to assemble a meeting with experts from the appropriate disciplines to review further the scientific data on the complex associations between sickle cell trait and health outcomes. Check the ASH website for the latest updates on this important public health initiative.

ASH’s Policy Statement on Screening for Sickle Cell Trait and Athletic Participation

• ASH does not support testing or disclosure of sickle cell trait status as a prerequisite for participation in athletic activities.

• ASH recommends the implementation of universal interventions to reduce exertion-related injuries and deaths, since this approach can be effective for all athletes irrespective of their sickle cell status.

• ASH believes that the NCAA Division I policy, as currently written and implemented, has the potential to harm the student athlete and the larger community of individuals with sickle cell trait.

• ASH strongly supports increased biomedical and population-based research on sickle cell trait as it relates to exertion-related illness, as well as other conditions.

For more information about the policy statement, go to www.hematology.org/advocacy/policy-statements/7704.aspx.
GT for GT: Gene Therapy for Canine Glanzmann Thrombasthenia


Glanzmann thrombasthenia (GT) is an autosomal recessive bleeding disorder with an incidence of ~1:1,000,000 that was first reported by Edward Glanzmann in 1918. It results from mutations in genes encoding the heterodimeric αIIbβ3 complex on platelets. More than 170 genetic abnormalities have been described that produce the clinical phenotype. Because expression of αIIb and β3 are co-dependent, a defect in expression of one component of the heterodimeric complex leads to subnormal expression of the other component. Fibrinogen binds αIIbβ3 and bridges platelets, leading to platelet aggregation. GT is associated with a platelet aggregation defect and mucocutaneous bleeding, which can be life-threatening. Patients with GT are treated with platelet transfusions and non-specific measures, including anti-fibrinolytics and recombinant factor VIIIa. Patients frequently become refractory to platelet transfusions due to the development of anti-platelet antibodies. Allogeneic bone marrow transplantation can be curative but insufficient donor availability and procedure-associated morbidity and mortality complicate treatment.

Great Pyrenees dogs can have a severe bleeding diathesis due to GT caused by a splicing defect in the αIIb gene.1 Fang et al. in the laboratory of David Wilcox in the Department of Pediatrics at the Medical College of Wisconsin and the Blood Research Institute at the Blood Center of Wisconsin now report treatment of three dogs with GT by autologous transplantation of αIIb gene-corrected hematopoietic stem cells (HSCs). In these studies, HSCs were mobilized from bone marrow into peripheral blood by treating the dogs with the cytokines, granulocyte-colony stimulating factor (G-CSF), and stem cell factor (SCF). CD34+ cells, which are enriched in HSCs, were isolated from G-CSF/SCF-mobilized peripheral blood. The human αIIb gene was introduced into HSCs ex vivo using a lentiviral vector derived from the HIV-1 virus. Lentiviral vectors are attractive in gene therapy because they efficiently transduce both dividing and non-dividing cells; produce long-term, stable transgene expression; and are less immunogenic than other vectors. Currently, lentiviral vectors are being evaluated in 40 human gene therapy clinical trials for a variety of hematologic and non-hematologic disorders, including β-thalassemia and adenoleukodystrophy.2

As a safety feature, Fang et al. used a self-inactivating (SIN) lentivirus that was produced by removal of the U3 enhancer/promoter from the 3' viral long-terminal repeat (Figure). The 5' long-terminal repeat of HIV-1 consisting of U3, R, and U5 elements was left intact. The αIIb gene promoter containing binding sites for the GATA and Ets transcription factors was used to target transcription specifically to megakaryocytes. Additionally, a cDNA encoding expression of a drug-resistant protein, P140K methylguanine methyltransferase (MGMT) under control of the murine stem cell virus promoter (MSCV), was added to allow for in vivo enrichment of lentivirus-transduced HSCs. The woodchuck hepatitis post-transcriptional regulatory element (WPRE) was included to enhance the efficiency of transgene expression. Nonmyeloablative pretransplant conditioning using either low-dose total body irradiation or busulfan was used to create a niche in the bone marrow for the transplanted cells to engraft.

Flow cytometry revealed that an average of 5,000 αIIbβ3 molecules was expressed on platelets from transplanted dogs. In contrast, normal canine platelets contain ~80,000 αIIbβ3 molecules. After transplantation, the dogs received O6-benzylguanine and carmustine to allow enrichment of genetically modified cells containing P140K MGMT. This treatment led to an increase in the number of platelets that expressed αIIbβ3 to ~10 percent of the total platelet population. Despite the relatively low density of αIIbβ3, platelet aggregation, clot retraction, platelet fibrinogen binding, and buccal mucosa, bleeding times were corrected in all three dogs. One of the dogs developed high-affinity anti-αIIb antibodies that blocked platelet aggregation. The antibody titer decreased but remained measurable after treatment with intravenous immunoglobulin (IVIG). The dogs remained well for two, four, and five years after the gene therapy procedure with no evidence of hematologic or other abnormalities associated with vector insertional mutagenesis.

The results of the study by Fang et al. demonstrate the feasibility of gene therapy for GT in a large animal. Relatively low-density expression of platelet αIIbβ3 compared with that of normal dogs sufficed to correct the hemostatic abnormalities associated with GT. The development of anti-αIIb antibodies in one of the dogs was a significant complication and suggests that immunosuppression may be a necessary adjunct to gene therapy of GT in humans.


Figure

Anatomy of the Glanzmann thrombasthenia lentiviral gene therapy vector

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PETE LOLLAR, MD
Dr. Lollar indicated no relevant conflicts of interest.

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Putting Hematopoietic Stem Cells to Sleep


Hematopoietic stem cells (HSCs) during times of increased demand. A wide range of stimuli (e.g., blood stem cells to maintain routine organ function and activate larger numbers of hematopoietic progenitors) induce a condition of dormancy known as "hibernation." This allows HSCs to maintain their quiescent state between self-renewal, differentiation, and apoptosis. While this process is essential for hematopoietic system homeostasis, the mechanisms underlying this phenomenon are not fully understood.

Recent studies have revealed that nonmyelinating Schwann cells (NMSCs) play a critical role in maintaining HSC quiescence. NMSCs are located in the bone marrow niche, which is the site where HSCs are normally quiescent. NMSCs indirectly influence HSC fate by modulating the expression of various factors, including transforming growth factor beta (TGF-β), which is a key regulator of HSC dormancy.

In a recent study, Yamazaki and colleagues identified transforming growth factor beta (TGF-β) as a key regulator of dormancy in HSCs. The authors demonstrated that NMSCs express TGF-β, which is involved in the maintenance of HSC quiescence through interactions with HSCs. They also showed that depletion of NMSCs results in an increase in HSC activation and proliferation, suggesting a role for NMSCs in regulating HSC dormancy.

The authors propose that NMSCs contribute to HSC dormancy through the secretion of TGF-β, which is known to suppress cell proliferation and promote quiescence. This suggests that NMSCs are involved in the regulation of HSC activation and proliferation, and may play a role in the maintenance of HSC quiescence.

In conclusion, the study by Yamazaki and colleagues provides new insights into the mechanisms underlying HSC dormancy and the role of NMSCs in maintaining HSC quiescence. Further studies are needed to fully understand the role of NMSCs in the regulation of HSC activation and proliferation.

References:

Delineating Molecular Mechanisms of Proteasome and Histone Deacetylase Inhibitor-Induced Myeloma Cytotoxicity


In this study, Mannava and colleagues identified Kruophil-like family member 9 (KLF9) as an important transcriptional regulator of apoptosis in multiple myeloma (MM) cells. Based on the observation of increased KLF9 transcript levels in tumor cells from patients with relapsed MM who responded to bortezomib, they characterized the role of KLF9 in mediating cytotoxicity. Indeed, KLF9, as well as proapoptotic Noxa, were induced in MM cells by bortezomib in association with an observed increase in acetylation of histone H3 due to inhibition of histone deacetylase. They showed that histone deacetylase inhibitor LBH589 (parnonostat) not only increased acetylated H3 and Noxa, but also increased KLF9 at both the gene and protein levels, and conversely, that knockdown of KLF9 inhibited both bortezomib- and LBH589-induced Noxa induction and related MM cell death. In their studies, bortezomib-induced KLF9 was shown to bind directly to the Noxa promoter, and Noxa knockdown, at least in part, abrogated cytotoxicity in MM cells induced either by bortezomib or by KLF9 overexpression. Together, these studies implicate KLF9 as a transcriptional regulator of drug-induced apoptosis in MM cells.

The proteasome inhibitor bortezomib is approved to treat both relapsed/refractory and newly diagnosed MM and confers an overall survival benefit at the five-year follow-up when used as initial therapy. In preclinical studies, bortezomib effects a remarkable variety of biologic events in MM cells including the following: direct targeting of proteasome chymotryptic and caspase-like activities; decreased MM cell growth and survival (inhibition of NF-κB, MAPK, and Jak/STAT with activation of PK3-Akt signaling); ER stress induction (caspase 12 cleavage, increased phospho-PERK, GADD153, ATF4, GRP78, and XBP1 splicing); triggering of apoptosis (increased JNK, caspases and PARP cleavage, ROS, cytochrome c and Smac release, mitochondrial Ca influx, Bid cleavage, Fas and FasL, BH3 only proteins Bim, Bik, and Noxa, along with decreased mitochondrial membrane potential and IAP proteins); induction of heat shock proteins (increased Hsp 27, 70, and 90) and inhibition of DNA repair (decreased DNA-PK); and cell-cycle inhibition (increased p21, p27, p53 with cyclines D1, E1, A, and B). Moreover, bortezomib targets the tumor cell-bone marrow microenvironment interaction (decreased expression of adhesion molecules ICAM, VCAM, and vitil) as well as IGF-1, IL-6, BAFF, and RANKL) and inhibits angiogenesis (decreased migration and VEGF, MMP9, and cavelin-1) and modulates bone turnover (decreased osteoclastogenesis, MP1+, and BAFF with increased osteoblast formation). Which of these and other preclinical activities confer the observed clinical benefits remains unclear. Importantly, profiling studies of clinical samples from treated patients can give clues as to targets and mechanisms of response (i.e., NF-κB activation in tumor cells is associated with response). Here, profiling of patient samples showed that KLF9 expression identified responders, and elegant bedside-back-to-bench studies delineated the mechanism linking drug-related upregulation of KLF9 gene and protein expression to Noxa, and ultimately to MM cell apoptosis.

Prior preclinical studies in MM have provided the basis for combining bortezomib with the Akt inhibitor perifosine, as well as with histone deacetylase inhibitors panaccominostat and vorinostat, ultimately leading to phase III clinical trials of these combinations. Mannava and colleagues add further mechanistic evidence underlying this synergistic activity. Bortezomib downregulates class I histone deacetylase activity, and HDAC inhibitor panaccominostat further enhances histone H3 and H4 acetylation induced by bortezomib. Importantly, KLF9 upregulation by bortezomib is further enhanced by panaccominostat, thereby defining the molecular mechanism of enhanced apoptosis through transcriptional enhancement of Noxa expression. These studies therefore identify KLF9 as a target for novel single-agent and combination therapies in MM.

References:
Portal vein thrombosis (PVT) complicates up to 30 percent of myeloproliferative neoplasms (MPNs), a group of disorders that includes polycythemia vera, essential thrombocytopenia, and primary idiopathic myelofibrosis.1 PVT may be the presenting sign of an MPN, yet our understanding of the natural history of PVT/MPN is limited by the paucity of published longitudinal studies. Now, in a retrospective analysis covering 28 years, Hoekstra and colleagues from the Netherlands have reported on the long-term follow-up of MPNs complicated by PVT.2

Of 44 patients with MPN and PVT (median age at diagnosis 48 years old) identified by computerized hospital records covering the period between 1980 and 2008, 70 percent presented with PVT prior to diagnosis of MPN (for this subgroup, the median time between presentation with PVT and diagnosis of MPN was seven months). Spleenomegaly was present in 75 percent of the cohort with abdominal pain reported in 70 percent and ascites documented in 34 percent. PVT was confirmed by radiographic or laparoscopic studies with thrombosis confined to the portal vein in approximately half. Of the 29 patients in whom testing was feasible, JAK2 V617F was detected in 90 percent, a value that is 2.6-fold higher than the 34 percent prevalence of this mutation in an all-inclusive study of patients with PVT.1

Twenty patients were found to have additional risk factors for thrombosis, including oral contraceptives or pregnancy in 37 percent, an underlying prothrombotic condition in 24 percent, and local prothrombotic factors in 16 percent, including abdominal surgery and intra-abdominal infection. At a median of 2.3 years from PVT diagnosis, 17 patients (38%) experienced nonfatal gastrointestinal bleeding, of which two were anticoagulated. Of the 15 with bleeding in the absence of anticoagulation, eight (47%) had variceal bleeding at PVT presentation. In contrast, at a median 7.5 years from PVT diagnosis, 12 (27%) developed thrombosis recurrence, fatal in one-fourth (3/44, 18% overall), one of whom was receiving anticoagulation.

Anticoagulation with oral vitamin K antagonists (VKA), low-molecular-weight heparin, or unfractionated heparin was initiated after a diagnosis of PVT in 52 percent and was continued long-term in 34 percent (VKA in all cases). Antiplatelet drugs were given in 36 percent of the cohort (27% after diagnosis and 9% before diagnosis of PVT). The four patients who were treated before diagnosis of PVT were prescribed the antiplatelet agent at the time of diagnosis of the MPN.

Whether long-term anticoagulation improves survival in patients with MPN-associated PVT is unknown, and because MPN/PVT is uncommon, organizing a sufficiently powered randomized clinical trial to address this issue would be challenging. In patients with MPN/PVT, long-term anticoagulation appears to be a double-edged sword, as 39 percent of the group studied by Hoekstra and colleagues developed gastrointestinal bleeding (similar findings were reported from a larger PVT trial) while 27 percent developed recurrent thrombosis, with a mortality rate of 25 percent in this group with recurrent thrombosis. These data underscore the difficulty of balancing risks of thrombosis recurrence with anticoagulation-associated bleeding risks in patients with MPN/PVT. Moreover, the results of a multicenter, observational study of 102 non-cirrhotic PVT patients (20% of whom also had a diagnosis of MPN) showed that anticoagulation failed to restore PVT patency in two-thirds. In this group with persistent thrombosis, ascites or splenic vein obstruction was more commonly observed (hazard ratio 3.5).3

We would be treading on thin ice to base recommendations for prophylactic anticoagulation on the data provided by Hoekstra et al. that showed that MPN/PVT can be complicated by either gastrointestinal hemorrhage (tissue-fatal in this report) or recurrent thrombosis (fatal is some cases) or by the findings of Plessier et al.1 (that identified patients with ascites or splenic vein obstruction as being at high risk for persistent thrombosis). Further, whether limiting anticoagulant choices to anti-Xa inhibitors (that have lower bleeding risks than VKA) will improve outcomes remains to be seen. We also don’t know how new approaches to treatment of MPNs will affect outcome. Although the study of Hoekstra provides valuable information on the natural history of MPN/PVT, how to best manage these complex patients remains an unanswered question.

3. Why are these results important? The inhibitors of BCR signaling are active in CLL, yet their effects on lymphocyte trafficking challenge our traditional way of assessing disease response in which finding an increase in lymphocytosis is seen as an indication of disease progression. PCI-32765-induced lymphocytosis appears to be a consequence of aberrant trafficking in which movement into compartments outside of the peripheral blood system is inhibited. Therefore, PCI-32765-induced lymphocytosis likely results from cellular redistribution, independent rather than clonal expansion. The studies of Ponader et al. have expanded our understanding of the effects of inhibition of BCR signaling kinases on the properties of CLL cells in vitro. Importantly, their adoptive transplant system appears to be a suitable model for investigating the effects of BCR signaling inhibitors in vivo. By incorporating use of genetically modified TCL1 cells, this model provides a tool for future studies aimed at teasing out the precise mechanism by which inhibitors of BCR signaling kinases modulate lymphocyte trafficking. The inhibitors of BCR signaling kinases are an exciting new class of drugs for treatment of CLL, and the studies of Ponader and colleagues and others build upon our knowledge of how these agents work.

A normal adult produces 100 to 200 billion platelets each day. These platelets are remarkably homogenous in size and shape, and platelet counts are typically maintained within a relatively narrow physiological range. Despite advances over the past decade in our understanding of megakaryopoiesis, the genetic underpinnings that control platelet counts and volume remain poorly understood. Initial approaches aimed at understanding these molecular processes focused on identifying mutations in patients with congenital thrombocytopenias, some of whom also have abnormalities in platelet size (either abnormally large or abnormally small). Studies involving these well-characterized hereditary disorders have identified genes important in megakaryocyte and platelet biology, but the rarity of these diseases leaves unanswered questions about the existence of other genes that regulate platelet count and size in the general population. Genome-wide association studies (GWAS) allow for an unbiased approach to identifying genetic variants in large populations. GWAS are challenging, however, because success depends both on collecting samples from a large group of carefully phenotyped individuals and having the resources available to analyze the complex genetic data that are generated. Such an unbiased and comprehensive approach to studying platelet formation has not been attempted previously.

Now, however, Gieger et al. report the results of a GWAS designed to identify genes that control platelet number and size. The study enrolled 68,857 individuals and used a array technique that analyzed approximately 2.5 million single nucleotide polymorphisms (SNPs) per sample. The investigators tested the association between platelet count (PLT) and mean platelet volume (MPV) for each SNP to identify genomic loci that met their stringent criteria for a significant association. They identified 68 loci that reliably associated with platelet count and/or platelet volume. Nearly a quarter of the loci associated with both traits, likely reflecting the correlation that results in tight control of total platelet mass (PLT x MPV). In this case, the involved genes would be expected to act in opposite direction on platelet count and platelet volume in order to maintain a constant platelet mass. The investigators focused on 54 core genes. They evaluated megakaryocyte and erythroid lineages in cord-blood-derived hematopoietic stem cells and showed an increase in transcription of core genes in megakaryocytes but not in erythroblasts. Based on this observation, the authors suggest that lineage specification during hematopoiesis is driven by the emerging expression of increasing numbers of transcripts of specialized genes. Using model systems, the authors also directly evaluated the role in hematopoiesis of selected core genes. Gene silencing morpholinos in zebrafish and evaluation of mutant fruit flies validated the specificity of the selected core genes identified as essential for formation of blood cells. Many of these genes had not been implicated previously in hematopoiesis.

In a tour de force that included 124 investigators from 13 countries studying more than 66,000 patients, Gieger et al. provided an elegant demonstration of how GWAS data can be translated into important functional insights at the molecular level. A significant strength of this paper is that the hypothesis upon which the GWAS was based was challenged in model organisms using genetic silencing techniques. This strategy verified the functional significance in hematopoiesis of genes identified by GWAS. However, the 68 loci identified in the current study explained only 4.8 percent of the phenotypic variance in platelet number and 9.9 percent of the variance in platelet volume. This result is consistent with the previously documented limitation of GWAS in explaining the phenotypic variance of complex traits. Nonetheless, this strategy was successful in identifying genes previously not recognized to function in megakaryopoiesis. In addition, the protein-protein interaction network (Figure) and databases generated by this study will be useful resources for investigators in the fields of megakaryocyte biology and hematopoiesis.

Protein-protein interaction network of platelet loci as revealed by high-powered genome-wide association studies. Genes are represented by round symbols. Transcript levels in megakaryocytes are shown on a continuous scale from low (dark green) to high (white).


ROBERT FLAUMENHAFT, MD, PhD
Dr. Flaumenhaft indicated no relevant conflicts of interest.

Don't Lose Your Cereblon


Some readers will recall vividly the tragic events of the late 1950s and early 1960s when more than 10,000 children worldwide were born with deformities due to the teratogenic effects of thalidomide that had been prescribed for pregnancy-associated nausea and vomiting. Recently, Ito and colleagues identified cereblon (CRBN) as a primary target of thalidomide teratogenicity.1 Those investigators showed that binding of thalidomide to CRBN interrupts the function of the E3 ubiquitin ligase complex, resulting in down-regulation of expression of fibroblast growth factor genes. A number of mechanisms (e.g., antiangiogenic, proapoptotic, antiproliferative, immunomodulatory) have been suggested as the basis of the tumoricidal activity of thalidomide, but the findings of Ito et al. led Zhu and colleagues in the laboratory of Keith Stewart at Mayo Clinic, Arizona, to investigate the role of CRBN in the anti-myeloma effects of thalidomide and two other related immunomodulatory drugs (IMiDs), lenalidomide and pomalidomide.

Those investigators demonstrated that both absence and down-regulation of expression of CRBN in human myeloma cells resulted in IMiD resistance in human myeloma cells. Cells with stable CRBN depletion were resistant to IMiDs but not to unrelated myeloma drugs bortezomib, dexamethasone, and melphalan. Moreover, using a myeloma cell line, deletion of the gene that encodes CRBN was found to mark cells that had been selected in culture for resistance to IMiDs, and gene-expression profiling showed a 40-fold reduction in CRBN expression in the resistant cells. In patients characterized as resistant to lenalidomide, CRBN levels in paired samples (before and after initiation of IMiD therapy) were lower at the time that drug-resistance was noted. Gene knock-down experiments showed that inhibition of CRBN expression caused a reduction in expression of interferon regulatory factor 4 (IRF4), one of the known targets of lenalidomide.

The studies of Zhu and colleagues suggest that CRBN plays a central role in the anti-myeloma activity of IMiDs, perhaps because CRBN and IMiDs work in concert to down-regulate expression of IRF4. However, mechanisms of resistance that do not involve quantitative expression of CRBN are likely to exist. This hypothesis is supported by the observation that while most patients become resistant to IMiDs, few unselected cases show genomic abnormalities affecting CRBN. In these cases, resistance may be a consequence of aberrant expression of molecules downstream of CRBN or of modulation of completely different pathways targeted by IMiDs. Still, CRBN expression appears to be an essential requirement for activity of these compounds as loss of expression renders myeloma cells resistant to this class of drugs. The current study supports the aphorism that to better understand the mechanism of action of a drug, one must unravel its mechanisms of resistance. The current findings suggest that quantifying expression of CRBN may be a useful biomarker for assessing sensitivity/resistance to IMiDs in patients with myeloma. Understanding the CRBN-dependent basis of the anti-myeloma effects of IMiDs may lead to development of novel agents with anti-tumor activity distinct from the teratogenic effects associated with currently available IMiDs.

Salmonella and Hemolysis: How Heme Stymies the Immune Response


Hematologists often battle life-threatening infections in patients with hemolytic anemia. For example, in children with sickle cell disease, encapsulated bacteria such as pneumococcus are a constant threat to the host, due in part to hyporesponsiveness. An unusual predilection for salmonella osteomyelitis has been cited in numerous texts on sickle cell disease, purportedly due to gastrointestinal or gallbladder leak of these bacteria into the blood with subsequent seeding of skeletal infarcts. In sub-Saharan Africa, invasive nontyphoid Salmonella (NTS) infection is a common and often fatal complication of Plasmodium falciparum infection. Malaria infection lyses RBCs, releasing hemoglobin, which in turn bathes the vasculature with cytotoxic, pro-oxidative heme. Heme oxygenase-1 (HO-1) detoxifies heme by metabolizing it to biliverdin and bilirubin, releasing carbon monoxide and iron, with the latter constituent being safely sequestered (HO-1) detoxifies heme by metabolizing it to biliverdin and bilirubin, releasing carbon monoxide and iron, with the latter constituent being safely sequestered in ferritin. Heme induction of HO-1 affords protection against non-cerebral forms of severe malaria, in part through generation of carbon monoxide.1 3 5 However, HO-1 induction may be a two-edged sword with respect to tolerance of malaria, as Cunnington et al. from the London School of Hygiene and Tropical Medicine now show that induction of HO-1 during malarial hemolysis impairs resistance to NTS by limiting production of bactericidal reactive oxygen species.

The investigators demonstrate that co-infection of mice with Plasmodium yoelii 17XL (Py17XL) and Salmonella typhimurium causes acute, fatal bacteremia with a high bacterial load. Similarly, if hemolysis is induced by phenylhydrazine (PHZ) or mimicked by heme administration, none of the mice survived 16 hours after Salmonella infection, with all such treated mice having high bacterial loads compared with controls (saline-treated mice). S. typhimurium localizes in granulocytes following hemolysis or heme infusion, but the bacteria are not killed. Infection with Py17XL induces the granulocyte oxidative burst, and hemolysis induces dysfunctional granulocyte mobilization. Treatment with heme or PHZ followed by infection with Py17XL caused marked depletion of Gr-1hi (a marker of mature granulocytes) cells from bone marrow. For PHZ and heme treatment, loss of Gr-1hi cells from bone marrow was accompanied by an increase in granulocytes in peripheral blood, confirming the effect of free heme in mobilization of neutrophils from the bone marrow into the periphery. Although the proportion of circulating granulocytes did not increase during Py17XL infection, granulocyte mobilization may have been obscured by an overall increase in leukocyte count or by granulocyte redistribution. HO-1 is induced in immature bone marrow myeloid cells; however, PHZ or heme treatment accompanied by Py17XL infection led to induction of HO-1 in peripheral blood monocytes, and HO inhibition using tin-protoporphyrin restored resistance to S. typhimurium.

Together, these data indicate that intravascular heme (released during hemolysis) mobilizes granulocytes from bone marrow and simultaneously impairs their capacity to generate an oxidative burst. Thus, in the setting of concurrent intravascular, granulocytes entering the circulation in response to infection are able to phagocytose S. typhimurium but, owing to their reduced oxidative burst capacity, fail to kill them, providing instead a safe house for bacterial replication and dissemination.

This elegant study provides another example of why systems that regulate heme clearance and toxicity are numerous and redundant. In patients with malarial infection, HO-1 provides tolerance and cytoprotection but may also exacerbate bacterial infections. The potential role of heme-derived iron in promoting bacterial infections and blockade of toll-like receptor-4 also merits further investigation.

**References**


**GREGORY M. VERCELLOTTI, MD**

Dr. Vercellotti indicated no relevant conflicts of interest.
Ironing Out a New Wrinkle in the Anemia of Renal Failure

**STUDY TITLE:** A Three-Period, 58-Week Safety and Efficacy Trial of KRX-0502 (Ferric Citrate) in Patients With End-Stage Renal Disease (ESRD) on Dialysis

**CLINICALTRIALS.GOV IDENTIFIER:** NCT0191255

**COORDINATOR:** The Collaborative Study Group

**SPONSOR:** Keryx Biopharmaceuticals, Inc.

**PARTICIPATING CENTERS:** 54 medical centers in the United States, two in Israel, and two in Puerto Rico

**ACCRUAL GOAL:** 441 subjects randomized; enrollment closed

**STUDY DESIGN:** This phase III trial has a two-week washout period of oral phosphate binders in ESRD subjects on hemodialysis or peritoneal dialysis. After washout, subjects are randomized 2:1 to open-label ferric citrate or calcium acetate and/or sevelamer carbonate as their oral phosphate binder for a 52-week safety assessment period. Subjects completing the safety assessment period on ferric citrate are re-randomized 1:1 to receive open-label ferric citrate or calcium acetate and/or sevelamer carbonate for a four-week efficacy assessment period. The primary goal is to determine safety and efficacy of oral ferric citrate as a phosphate binder. A secondary goal is to determine changes in iron status of subjects receiving ferric citrate.

**RATIONALE:** Currently available phosphate binders have safety and cost issues. ESRD patients have excessive iron losses due to blood loss with hemodialysis and frequent laboratory tests. In comparisons of oral and intravenous iron therapies (MacDougall IC et al. Kidney Int. 1996; Fudin R et al. Nephron. 1998), oral supplementation with ferrous salts failed to meet erythropoietic demands of intravenous iron. Intravenous iron is routinely given to hemodialysis patients who develop iron deficiency or respond insufficiently to erythropoietin.

**COMMENT:** Hemodialysis patients lose 4 to 8 mg iron daily. Fasting, iron-deficient hemodialysis patients were considered capable of absorbing this amount of iron per day from ferrous salt supplements, but gastrointestinal side effects, lack of compliance, and reduced absorption as iron stores are repleted prevented these maximal absorption rates (Skikne BS et al. J Lab Clin Med. 2000).

Daily iron intake is much higher in this ferric citrate trial than in supplementation trials with ferrous preparations. However, negligible iron absorption had been expected because ferric ions must be reduced to ferrous ions for absorption. Furthermore, ferric citrate is given with food to maximize phosphate binding, thereby decreasing iron available for absorption. The wrinkle that arose in phase II trials of ferric citrate in hemodialysis patients was that an increase in serum iron, transferrin saturation, and ferritin was observed. The increased iron absorption was not accompanied by serious gastrointestinal side effects and, in one study, erythropoietin and intravenous iron administration decreased.

This ongoing phase III trial should provide answers about how iron absorption is regulated with long-term ferric citrate use, whether long-term ferric citrate is associated with as few gastrointestinal side effects as were found in the shorter phase II trials, and how much intravenous iron and erythropoietic stimulating agent usages might be reduced in hemodialysis patients taking ferric citrate. If iron absorption is well regulated and not associated with adverse gastrointestinal events in ESRD patients, ferric citrate may be potentially useful in those very common patients without ESRD who have iron deficiency but cannot tolerate oral ferrous supplements.

– Mark Koury, MD

Dr. Koury is a medical monitor and safety committee member for this clinical trial and a consultant for Keryx Biopharmaceuticals, Inc.

**Doubling Up on MDS/CMLM:** Left Hook + Right Hook + T.K.O., Or Just ‘More Weight’?

**STUDY TITLE:** A Randomized Phase II Study of Azacitidine in Combination With Lenalidomide versus Azacitidine Alone for Higher-Risk Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMLM)

**SPONSOR:** National Cancer Institute (NCI); a southwest Oncology Group (SWOG)-led Intergroup Study with participation from The Alliance (including the former Cancer and Acute Leukemia Group B and North Central Cancer Treatment Group), the Eastern Cooperative Oncology Group (ECOG), and NCI-Canada

**CLINICALTRIALS.GOV IDENTIFIER:** NCT0152976

**PARTICIPATING CENTERS:** More than 50 trial sites across the United States and Canada are participating in the study.

**ACCRUAL GOAL:** 240 patients (80 patients randomized per treatment arm). This trial is not yet open for participant recruitment.

**STUDY DESIGN:** Eligible patients are 18 years of age, have a Zubrod performance status of 0-2, have been diagnosed with higher-risk MDS or CMLM, and have not previously received azacitidine, decitabine, lenalidomide, or vorinostat. For this study, higher-risk MDS is defined as 5 to 19 percent marrow blasts or an International Prognostic Scoring System risk stratification of either intermediate-2 or high risk. Patients are randomized in a 1:1:1 manner to receive either azacitidine 75 mg/m2 daily for seven days subcutaneously or intravenously every 28 days (azacitidine monotherapy); parenteral azacitidine plus oral lenalidomide, 10 mg daily for 21 out of every 28 days; or parenteral azacitidine plus concomitant oral vorinostat 600 mg per day. The primary objective is to compare overall response rate (ORR) between the three study arms using the 2006 International Working Group (IWG 2006) standardized response criteria for MDS (Cheson BD et al. Blood. 2006). The study is powered to have an 81 percent probability of detecting a 20 percent difference in ORR with alpha 0.05 in the comparison of either combination arm versus azacitidine monotherapy. Secondary study objectives include the following: comparison of rates of disease progression and overall survival between the treatment arms, correlation of outcomes with pre-treatment cytogenetic results, and evaluation of the comparative safety and tolerability of each regimen.

**RATIONALE:** Based on a prospective, randomized study that showed a statistically significant enhancement of median survival from 15 months in the conventional therapy control arm to 24 months in the experimental treatment arm (Fenaux P et al. Lancet Oncology. 2009), azacitidine has become the standard of care for patients with higher-risk MDS. However, complete responses (CRs) with azacitidine monotherapy are uncommon (observed in less than 25 percent of treated patients) and relatively short-lived (median response duration of less than two years). In an effort to augment response rates and response duration, combination approaches that build on the backbone of azacitidine’s success are being investigated. A phase I/II trial conducted by Mikael Sekeres (the principal investigator of this trial) and his colleagues in the Bone Marrow Failure Consortium that combined azacitidine with lenalidomide showed an overall response rate of 72 percent, including a 42 percent CR rate, in 36 evaluable patients (Sekeres M et al. Blood. 2011 ASH Annual Meeting abstract #607; Sekeres M et al. J Clin Oncol. 2010). The biologic basis for the improved efficacy of this combination is unclear. Based on effects on gene expression, in vitro synergism between hypomethylating agents (HMAs), such as azacitidine, and deacetylase inhibitors (DACIs), such as vorinostat, has been observed, leading to a number of trials using HMA/DACI combinations. Two early-phase studies have evaluated azacitidine in combination with vorinostat. One such study (Silverman LR et al. Blood. 2008 ASH Annual Meeting abstract #3656) demonstrated an impressive 86 percent response rate in patients with higher-risk MDS, while another study, which enrolled 30 patients with MDS or acute myeloid leukemia who were ineligible for other clinical trials due to comorbid conditions, found a 30 percent ORR (Garcia-Manero G et al. Blood. 2011 ASH Annual Meeting abstract #608).

**COMMENT:** MDS drug development is moving forward again after a relatively torpid period following FDA approval between 2004 and 2006 of the three currently available MDS disease-modifying therapies. Hopefully, this study, with “two chances to win” over azacitidine monotherapy, will fare better than E1905, which was a randomized, 150-patient, phase II cooperative group trial that compared azacitidine monotherapy with the combination of azacitidine and the DACI entinostat/MS-275 (Prebet T et al. Blood. 2010 ASH Annual Meeting abstract #601). Combination therapy did not improve response rate in the E1905 study. While it is perhaps unfortunate that the current trial is not powered to detect a survival difference as the primary endpoint, such a design would have required a prohibitively large number of patients.

– David P. Steensma, MD

Dr. Steensma participated in a one-time scientific advisory board for Celgene in 2011.
Breaking into the Translational Research Arena
How to develop a sense for “the other side”

STEPHAN LINDSEY, PhD,1 AND CRAIG ECKFELDT, MD, PhD

1NIH National Research Services Award Postdoctoral Scholar, Department of Chemical Engineering, University of Delaware
2Fellow, Department of Internal Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota Medical School

Most biomedical researchers understand the importance of developing translational research plans, but how to accomplish this goal requires thoughtful planning. A “translational” approach to biomedical research requires the ability to integrate relevant research questions with a clinical problem. Initiating planning early in one’s career (i.e., during postdoctoral or medical training) is an essential component for developing a successful career strategy. While clinical and graduate training provide a solid foundation for MDs and PhDs respectively, challenges remain for trainees (and beyond) who wish to develop a sense for “the other side.” One approach to overcome these challenges is to pursue combined research and clinical training in a dual-track program, such as those offered in the well-established NIH-sponsored Medical Scientist Training Programs for MD/PhD degrees or to enroll in one of the newer translational PhD training programs, such as the Howard Hughes Medical Institute-sponsored “Med into Grad” program. Perhaps one of the most important aspects of integrating basic research and clinical medicine is to join together basic researchers of the most important aspects of integrating basic research and clinical investigators to develop collaborative and clinical medicine is to join together basic researchers of the most important aspects of integrating basic research and clinical investigators to develop collaborative

The NIH Clinical and Translational Science Award (CTSA) program has made effective and efficient translational research a top priority at the national level and is one example of how NIH funding decisions are steering academic research in a translational direction. As a result of these investments, most trainees need not look beyond their own institutions to explore the interface between basic research and clinical medicine. Departmental and Divisional grand rounds, institutional seminar series, and journal clubs are all important venues at which laboratory researchers, clinical researchers, and clinicians can meet regularly to establish local collaborations to fuel translational research. Trainees should take advantage of these and other interdisciplinary seminars as opportunities for exploring translational research questions and potential collaborations.

While training programs are developing formal programs to bring together investigators to facilitate a “bench-to-bedside” research strategy, trainees should take a proactive role in creating their own translational career niche. Doing so requires developing connections across the lab/clinic divide. One of the most effective strategies to accomplish this aim is to network early and often, taking advantage of common research interests as a starting point. As a trainee’s research progresses, he or she should seek opportunities to present his or her work whenever possible. Presentations at national and regional meetings, such as the ASH annual meeting, provide an opportunity not only to showcase one’s research but also to test new hypotheses. In these settings, hypotheses can be presented and discussed with potential collaborators through both formal presentations and “curbside” discussions.

Similarly, trainees should aim to interact with visiting scientists at their home institutions, remembering to act not just as a student, but as a colleague who wants to explore a deeper understanding of the science presented. By actively participating in the discussion during research seminars, trainees can demonstrate to colleagues and mentors that they are engaged in the scientific process. Demonstrating such interest may lead to additional opportunities to engage expert speakers on a more formal level. While it can be intimidating as a trainee to take this type of initiative, it is important to recognize that senior researchers generally take great pleasure in engaging with early-career colleagues. The goal of these interactions is not to provide expert advice to senior investigators but to build a supporting framework from which a successful career can grow. Not every endeavor will bear collaborative fruit, but venturing across the lab/clinic divide through networking is an important step toward reaching the goal of a productive translational research career.

### OBITUARY

Samuel I. Rapaport, MD (1921-2011)

DONALD I. FEINSTEIN, MD, MACP
L. VAJAYA RAO, PhD
BJARNE BUSTERUD, PhD

Samuel I. Rapaport, MD, 19th president of the American Society of Hematology, died on December 20, 2011, just after his 90th birthday. In 1958, Dr. Rapaport became the first head of the Division of Hematology at the University of Southern California. He remained in that position until 1974 when he moved to the University of California at San Diego, retiring in 1996. Whether in his role as an investigator, clinician, mentor, or leader, Dr. Rapaport’s goal was excellence.

Dr. Rapaport was born in Los Angeles to Hyman and Bertha Rapaport. In 2006, he authored a book, Hyman Rapaport, His Life and Times, about his father and family. His father was a distinguished local physician, and his mother was a lawyer active in Democratic politics. His father was known in Los Angeles as the “Angel of Temple Street” because of his unselfish dedication to the needs of his patients throughout the Great Depression era. He learned from his parents to champion both civil and women’s rights and to treat his fellow man with kindness and respect.

Dr. Rapaport’s illustrious research career spanned four-and-a-half decades. He made seminal contributions to our basic understanding of blood coagulation, and he developed the activated partial thromboplastin time test that is used worldwide to monitor response to intravenous, unfractonated heparin and to screen for blood coagulation abnormalities. He published more than 200 peer-reviewed journal articles, 25 book chapters, and four books, including the classic, single-authored Introduction to Hematology.

Dr. Rapaport was the subject of a profile that was published in this newsletter in 2008. The article recounted how he became interested in coagulation and highlighted his most important scientific accomplishments. His career is also chronicled on the American Society of Hematology’s website that has archived the oral history of some of the Society’s most prominent members.

In addition to being president of ASH, Dr. Rapaport held leadership positions in other academic and scientific societies. He was a member of the Governing Board of the American Board of Internal Medicine, chairman of the Council on Arteriosclerosis, Thrombosis, and Vascular Biology, and a member of the Advisory Council of the National Heart, Lung, and Blood Institute (NHLBI).

His contributions to medicine, hematology, and hemostasis have been recognized with many honors including ASH’s Henry M. Stratton Medal, membership in the American Society of Clinical Investigation and the Association of American Physicians, a merit award from NHLBI, and the Wright-Schulte Lecture and Robert P. Grant Medal from the International Society of Thrombosis and Haemostasis. Selection for a named Visiting Professorship reflects the esteem of colleagues, and Dr. Rapaport was so honored more than 20 times.

Sam Rapaport was a thoughtful listener who will be remembered by his academic progeny not only for his penetrating insights but also for his friendship and humanity. He brought out the best in all who had the good fortune to be a part of his life.

For those who wish to make a contribution in his honor, the family suggests a donation to the American Society of Hematology.
Go East Young Man!

Wendell Rosse, MD
Florence McLalister Professor of Medicine Emeritus at Duke University

My story starts out in several small towns in rural Nebraska, far from where I have ended up both intellectually and geographically. My family moved to Omaha so that my two brothers and I could get a better education than was offered in the boondocks, and we took advantage of the opportunity. I was accepted into the University of Chicago and started out studying classical languages, but through work in a staphylococcus research laboratory (washing dishes), I became acquainted and entranced with science and its methods.

I went to medical school at the University of Nebraska, where I learned how to be an evening laboratory technician. I was fascinated by blood films and the precision of hematologic examination. The University offered a year of research between the second and third year. I took it, did a research project, and was hooked. I went back to the University of Chicago for the last two years of medical school, where my second research project (the first involved shock in dogs and was not followed up) was defining the circulating life of neutrophils by injecting myself with a unit of blood from a patient I had diagnosed with the Pelger-Huet anomaly; then, IRBs were unknown. The area that I was assigned to was in the laboratory of Ernie Beutler, who stopped by nearly every day to inquire whether I was finished.

After two superb learning years on the house staff at Duke, I went to the National Institutes of Health to work with the brilliant and still active Tom Waldmann on erythropoietin. After three years of interesting research, we decided one day that the field was going to make progress only when erythropoietin was purified, and we recognized we weren’t going to do that. (Eugene Goldwasser had been trying for 10 years with limited success at that time.) I remembered a patient that I had as an intern who had paroxysmal nocturnal hemoglobinuria (PNH), a mysterious disease that I conjectured had something to do with complement. I resolved to learn something about complement and did so in the wonderfully active laboratory of Tibor Borsos and Herb Rapp in London under the tutelage of John Dacie, a wise and helpful mentor. From that year came the papers, at first rejected by the Journal of Clinical Investigation as not pertinent to human disease, which defined the populations of red cells in PNH and the role of the late acting components in accounting for the peculiar sensitivity of these cells to the hemolytic action of complement. I spent the rest of my career trying to understand those facts.

After returning to NIH, I subsequently went back to Duke where I established a research laboratory and a clinic. For the rest of my career, I saw patients for half a day a week and tried to understand their problems with the rest of the time. I had a series of excellent fellows, including the editor of this publication, as we pursued various aspects of immunologically related hematologic disease. We didn’t stray far, always returning to PNH.

When I arrived at Duke, I saw that the patients with sickle cell disease represented a greatly underserved population, so I established a clinic designed to seek ways of getting better care to them. Over the years the clinic grew into a large center. I was helped by the enlightened attitude I found in the state government of North Carolina and by the devoted co-workers and members of the community, as well as by the support of Clarice Reid and her colleagues at NIH.

As much as I love medicine and science, I’ve never forgotten that there is more to the world. I still read Latin and Greek (particularly when the English translation is on the facing page to help out), and I still read all kinds of history to try to understand how we got here. I’ve got DuPuytren’s contracture so my cello playing, which was never good, is now unsuitable; gone are the days of the hematology piano trio with Frank Bunn on piano and Larry Lessen on violin.

All of my work was done in the context of my wonderful family and of my colleagues, both at Duke and in the community-at-large; I’ve always felt that the American Society of Hematology was a home away from home and have seldom missed a meeting since 1965. I was asked when I retired what I would have done differently. I replied that, with some minor adjustments, nothing. I still think that is the case.

All of my work was done in the context of my wonderful family and of my colleagues, both at Duke and in the community-at-large; I’ve always felt that the American Society of Hematology was a home away from home and have seldom missed a meeting since 1965.

Thoughts From a Former Protégé

Russell E. Ware, MD, PhD
Professor of Pediatrics and Vice-Chairman of Global Health, Director, Texas Children’s Center for Global Health; Director, Texas Children’s Hematology Center, Baylor College of Medicine and Texas Children’s Hospital

Thirty years ago, I had the good fortune of joining the Rosse laboratory to begin a medical student project investigating the role of anti-platelet antibodies in immune-mediated thrombocytopenia. I quickly learned that not only was Dr. Rosse a distinguished hematologist (past president of ASH and associate editor of Blood), but he was also a brilliant scientist. He taught me various hematologic and immunologic techniques including platelet isolation, radioimmunoassay, and immunohufluorescence. He spent hours with me reviewing data, organizing results, making slides, and writing the abstracts and manuscripts. I still recall his calming influence at my first ASH oral presentation.

More importantly, however, I learned to design and implement patient-oriented research, long before such “translational research” was popular. Dr. Rosse had a keen eye for identifying interesting hematologic problems that lent themselves to laboratory investigation. Almost all of his studies involved human samples (usually blood) from patients with sickle cell disease, immune thrombocytopenia, or his beloved paroxysmal nocturnal hemoglobinuria.

However, the most influential experiences arose from my time spent in the clinic with Dr. Rosse. Throughout his long and distinguished academic career, he maintained a busy clinical practice. I saw his compassion for patients who suffered and noted how patients and families trusted his judgment. I learned that medicine was an art as much as it was a science, and saw the beauty of “all things hematologic” firsthand.

If imitation is the most sincere form of flattery, then my own career reflects my affection for Dr. Rosse. I pursued pediatric hematology (our only disagreement – he loved children but objected to “those mothers”) and for more than 20 years have enjoyed a combination of clinical care and laboratory investigation for children with blood disorders. I owe him many debts of gratitude and still cherish his mentorship.
The ASH website offers a convenient way for members to find information about upcoming Society events and provides easy access to many valuable products and services.

ASH recently released a new mobile app that will house all of the Society's Clinical Quick Reference Guides. The initial release of the app includes the 2009 Clinical Practice Guideline on the Evaluation and Management of Heparin-Induced Thrombocytopenia (HIT). Throughout 2012, ASH will introduce additional mobile versions of the Society's entire Clinical Quick Reference Guide collection, including immune thrombocytopenia (ITP), von Willebrand disease, epoetin and darbepoetin, and its newest Quick Reference Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults. The app is currently available for iOS, Android, and Blackberry devices. To install the app, simply search for “ASH Guides” in your device’s app store. For more information about the guides and app, go to www.hematology.org/Practice/Guidelines/2934.aspx.

### Mark Your Calendar

#### March

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<tr>
<td>8</td>
<td>Deadline to submit application for Minority Medical Student Award Program (MMSAP)</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<td>21-24</td>
<td>8th Annual Conference of the Hematology/Oncology Pharmacy Association</td>
<td>Orlando, FL</td>
<td><a href="http://www.hopax.org">www.hopax.org</a></td>
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<td>25-28</td>
<td>New Directions in Leukaemia Research Conference</td>
<td>Queensland, Australia</td>
<td><a href="http://www.ndlconference.com">www.ndlconference.com</a></td>
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<td>31-April 4</td>
<td>Annual Meeting of the American Association for Cancer Research</td>
<td>Chicago, IL</td>
<td><a href="http://www.aacr.org">www.aacr.org</a></td>
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#### April

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<tr>
<td>13</td>
<td>Deadline to obtain CME credit for the 53rd ASH Annual Meeting</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<tr>
<td>16-18</td>
<td>Annual Scientific Meeting of the British Society for Haematology</td>
<td>Glasgow, UK</td>
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<td>18-19</td>
<td>French Hematology Meeting</td>
<td>Buenos Aires, Argentina</td>
<td><a href="http://www.acamedbai.org">www.acamedbai.org</a></td>
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<td>19-21</td>
<td>American College of Physicians Internal Medicine 2012</td>
<td>New Orleans, LA</td>
<td><a href="http://www.acponline.org">www.acponline.org</a></td>
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<td>25-28</td>
<td>2012 World Congress of Hematology</td>
<td>Cancun, Mexico</td>
<td><a href="http://www.hematology2012.com">www.hematology2012.com</a></td>
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<td>27-28</td>
<td>9th International Chicago Lymphoma Symposium</td>
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<td><a href="http://www.chicagolymphoma.com">www.chicagolymphoma.com</a></td>
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#### May

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<tr>
<td>3-5</td>
<td>Thrombosis and Hemostasis Summit of North America</td>
<td>Chicago, IL</td>
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<td>9-12</td>
<td>American Society of Pediatric Hematology/Oncology 25th Annual Meeting</td>
<td>New Orleans, LA</td>
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<td>18-19</td>
<td>Highlights of ASH® in Latin America</td>
<td>Foz do Iguaçu, Brazil</td>
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<td>21-24</td>
<td>XXVth International Symposium on Technological Innovations in Laboratory Hematology</td>
<td>Nice, France</td>
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