2013 Marks the Beginning of a New Era for Blood, the Official Journal of ASH

Celebrating 10 Years

Succeeding Dr. Cynthia Dunhar as Blood editor-in-chief is Bob Löwenberg, MD, PhD, professor of hematology at Erasmus University Medical School, Rotterdam, The Netherlands. Dr. Löwenberg is the journal’s first non-North American editor-in-chief. Another change for 2013 is the addition to the editorial board of the journal’s first-ever deputy editor, Nancy Berliner, MD, chief of hematology at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School in Boston. Dr. Löwenberg and Dr. Berliner assumed their positions on January 1 and marked the beginning of their tenure with a new article type – Blood Spotlight. Blood Spotlights are brief articles (less than 2,000 words) that focus on emerging scientific and clinical developments or on a recent burst of advances within a circumscribed area. The first Spotlight article (“Sense and nonsense of high-dose cytarabine for acute myeloid leukemia” authored by Dr. Löwenberg) appeared in the January 3, 2013, issue. Going forward, Blood Spotlight articles will be solicited and published based on the editors’ view of their relevance and impact. A number of other new Blood features will be introduced to readers over the next few months including a series of review articles that highlight particularly significant advances in biomedical and clinical/translational research. The four review series to be published in 2013 will focus on the following topics: epigenetics in hematology, cancer-related thrombotic disease, genome sequencing and its impact on hematology, and blood cells in vascular inflammation. Additionally, readers are now introduced to “Blood Hubs.” The idea behind this feature is to make available for the convenience of journal readers micro-websites that can be used to aggregate content and services around a particular topic or theme. Blood Hubs will be complementary to the Blood journal website and will provide a centralized place for readers to find content, including journal article lists, images and slideshows, and relevant multimedia. Visit the first Blood Hub on Pediatric Hematology at http://pediatrics.bloodjournal.org. The next Blood Hub will focus on thrombocytopenia.

Read more about these new article types and products, and learn about the new editor and deputy editor in the continuation of the Blood editor interview on page 6. Dr. Jose Buill, 2012 ASH News Daily contributor, sat down with Dr. Löwenberg and Dr. Berliner to discuss their vision for the future of the world’s premier hematology journal and what inspires their work.

Platelets Reveal a New Weapon in the Fight Against Malaria


Platelets are increasingly recognized for their role in innate immunity. Their capacity to detect erythrocytes infected with malarial parasites and kill the invading organism is a remarkable example of this function. Studies evaluating the physiologic significance of platelet-mediated killing in controlling malaria have demonstrated that both thrombocytopenia and inhibition of platelet activity increase mortality in mouse models of the disease. These observations raise the question of how platelets recognize infected red cells and destroy the invading parasites.

Studies from the laboratory of Dr. Simon Foo et al. The Menzies Research Institute in Hobart, Tasmania, now demonstrate that platelet factor 4 (PF4, CXCL4) mediates malaria parasite killing in interactions with Duffy antigen on erythrocytes. In a follow-up study of their work showing that platelets kill P. falciparum, Dr. Foo’s group found that activated platelets use CD36 to bind to erythrocytes. Platelets then release PF4, which is highly concentrated in platelet granules. Immunofluorescence of red cells infected with P. falciparum demonstrates colocalization of PF4 with dead intraerythrocytic parasites following exposure to platelets. Subsequent studies found that PF4 binds to the chemokine receptor Duffy antigen. The investigators showed that purified PF4 killed P. falciparum within erythrocytes expressing Duffy antigen, but not in red cells that lacked this surface antigen. These results support a model in which platelets bind to infected red cells and release PF4, which then kills the intracellular parasite (Figure). Working independently at the University of Pennsylvania, Dr. Nancy Berliner and her colleagues screened a panel of human defense peptides to discover circulating proteins that possess activity against P. falciparum. The screen identified PF4 as the most potent inhibitor of parasite survival. PF4 is made up of an N-terminal domain, a central domain, and an amphipathic C-terminal domain. The authors localized the antimalarial activity of PF4 to a 12-amino-acid amphipathic helical domain at the C-terminus of the peptide. Based on this analysis, they screened a library of small molecules capable of adopting amphipathic secondary structures to identify compounds capable of killing P. falciparum. Two compounds, PMX1207 and PMX207, demonstrated potency at nanomolar concentrations against both chloroquine-sensitive and chloroquine-resistant strains of the organism. The two compounds were subsequently tested in mouse models of malaria. Both PMX1207 and PMX207 decreased parasitemia as measured by the number of erythrocytes containing lysed parasitic digestive vacuoles. In a murine malaria model, PMX207 totally reversed P. berghei-induced death.

Nearly half the world’s population is at risk for malaria, and 216 million cases were reported in 2010. The parasite is so prevalent and so lethal that it has created a selective pressure that has altered the genetic composition of the human population in the at-risk areas. Among the genes that have been selected against is the Duffy antigen, which serves as a receptor for the parasite. The work by McMorran et al., however, reveals the flip side of this story. The Duffy antigen on erythrocytes serves as the binding site for platelet-derived PF4 that mediates killing of the parasite. Whether Duffy-negative individuals have an alternative mechanism for controlling parasite growth is not known. However, this new understanding of the role of PF4 in killing parasites within erythrocytes has informed the development of drugs based on PF4 structure, directing the design of a new class of antimalarials capable of killing chloroquine-resistant P. falciparum. If converted to orally available drugs, this novel approach to treat malaria could have a significant impact on an enormous global health problem.


Platelets then release PF4, which is highly concentrated in platelet granules. Image: K. Sutliff/Science. Used with permission by AAAS.
Mentorship is a Core Value of ASH

“The mind is not a vessel to be filled, but a fire to be kindled.”

This quote is attributed to Plutarch (born 46 A.D.) as a variant translation of his statements in On Listening to Lectures. Plutarch was a Greek historian, biographer, and essayist and an excellent observer of societal values. To me, this metaphor captures the pragmatics of mentorship: the why we mentor and how we mentor.

Mentors were critical to my career success. My mentors shared their excitement about hematology with me but, more importantly, encouraged and believed in me, even when the path ahead was muddled or difficult to navigate. At our annual meeting this past December, both Drs. Tim Ley, 2012 E. Donnell Thomas lecturer, and Jim George, 2012 Wallace H. Coulter Lifetime Achievement recipient, credited mentors for their successes. As most members feel similarly about their mentors, supporting mentorship is and should be a core mission of ASH.

In 2003, Drs. Jim George and Bev Mitchell helped establish and co-directed ASH’s first Clinical Research Training Institute (CRTI) for fellows and junior faculty interested in patient-directed research or outcome studies. Then and in each subsequent year, 20 trainees and 20 faculty mentors participate in an intense week-long program that combines lectures with small group sessions that refine the participant’s clinical research protocol. Each participant is assigned a faculty mentor and mentorship continues throughout the year and often longer. A recent evaluation of the program revealed that nearly 90 percent of CRTI graduates were active clinical investigators and some early trainees had tenured faculty positions. The vast majority felt that the CRTI experience was an important contributor to their career success and that mentorship and the active networking that developed among participants were the reasons for this. As former trainees now return as enthusiastic mentors, the program’s ongoing success is secure.

Building on the success of this mentorship effort, ASH, in conjunction with the European Hematology Association, established a program for Translational Research Training in Hematology (TRTH) in 2010. And this year, in association with the Highlights of ASH® in Latin America (HOA-LA) meeting in Santiago, Chile, ASH will host a one-day workshop on clinical investigation needs. Each program has a different focus to fit different needs and each has metrics for expected accomplishments that will be prospectively evaluated. TRTH is a year-long program that is formatted like CRTI but focuses on translational research as well as academic career development. The HOA-LA workshop will target hematology faculty members, not trainees, with the intent of improving the infrastructure for clinical hematology research in Latin America by strengthening the skills of established faculty. However, key to both programs is establishing one-to-one connections between instructor and participant and the concept that mentorship will empower (kindle) the next generation of investigators.

Similarly, ASH’s Minority Medical Student Award Program (MMSAP), an eight-to 12-week research experience for first- or second-year medical students, prioritizes mentorship by pairing each participant with an ASH member who serves as a career-development advisor during medical school and residency. In addition, ASH supports underrepresented minority junior faculty hemato-oncologists through the partnership with the Harold Amos Medical Faculty Development Program of the Robert Wood Johnson Foundation, and thus partners with this extraordinarily successful mentorship effort.

ASH also highlights mentorship each year when awarding the ASH Mentor Award to one basic scientist and one clinician. These awards were established in response to a proposal by the hematology fellows of ASH’s Trainee Council in 2004 and annually remind us that it is the quality of mentoring relationships that counts – being trustworthy and honest, but not judgmental; having time to talk; and providing insight into work-life balance.

As colleagues we also mentor each other. ASH facilitates this with programs such as Consult-a-Colleague. Last year more than 50 volunteers who are at the top of their field provided insights to 421 clinical queries from colleagues. Less formal mentorship also abounds. Most importantly, the annual meeting provides an ideal opportunity to make and renew our one-to-one connections, and the fire, once kindled, is thus sustained.

Janis L. Abkowitz, MD

Volunteer and Make a Difference in Patients’ Lives in Uganda

In partnership with Health Volunteers Overseas (HVO), ASH members provide consultative training in the clinics, classrooms, and laboratories of health-care institutions in the developing world. In Kampa, Uganda, the need for hematology support is especially dire. The full spectrum of hematologic disorders is observed at Mulago Hospital in Kampa, Uganda. Daily rounds are conducted on the wards, and an outpatient clinic, with a census of approximately 50 patients, is held weekly. The expertise of ASH members is crucial for appropriate diagnosis and management of this large cohort of hematology patients. Education and training of local personnel are core components of the program that ensure sustainability. Volunteers at Mulago Hospital spend time with medical students from the affiliated Makerere University and provide clinical and classroom teaching while school is in session. Formal lectures held at the hospital are attended by medical staff, residents, and medical students.

Current training needs at Mulago Hospital include the following:

• Diagnosis and treatment of chronic myeloid leukemia
• Diagnosis and treatment of chronic lymphocytic leukemia
• Management of sickle cell patients
• Training in differential diagnosis
• Preparation and interpretation of peripheral blood films and bone marrow aspirates

Volunteers have the option of living in the HVO apartment or in the Mulago Guesthouse. The accommodations are basic but comfortable and well-kept and include Internet access. Cleaning and laundry services are available for a minimal fee.

To find out how you can make a difference as a hematology volunteer in Uganda, please contact Danielle Stonehirsch at d.stonehirsch@hvoua.org.

Volunteer at New ASH-HVO Site in Tanzania

Tanzania was recently added to the current list of ASH-HVO sites, which includes Uganda, Peru, and Cambodia. Go online (www.hematology.org/volunteerinTanzania) to read about why Tanzania was selected as the next site and to learn more about how to volunteer. The volunteer initiative at Muhimbili National Hospital represents a special opportunity for ASH members to share their time and expertise to advance patient care in an exceptionally high need area of the world. If you are interested in learning more about Muhimbili National Hospital in Dar es Salaam, Tanzania, or volunteering your time and expertise, please contact Chase Willett, ASH International Programs Specialist, at cwwillet@hematology.org.

Honor Your Mentor by Nominating Him or Her for a Mentor Award

Mentorship, as ASH President Dr. Jan Abkowitz writes about in her column, is one of the most important determinants of a successful career in hematology. In recognition of the value the Society places on mentorship, the ASH Mentor Award was created to reward outstanding mentors in the hematology community. Superb mentors from any of the different branches of hematology are eligible for this award, including adult or pediatric hemato-oncologists; academic or community practitioners; basic, clinical, or translational researchers; hematopathologists; transfusion medicine specialists; and individuals working in industry or government. Each year an award of $5,000 and a plaque will be presented to two outstanding mentors. Nomination packages are due April 4. Get more information at www.hematology.org/Awards/Mentor/2505.aspx.
ASH Opposes NCAA Policy Requiring Screening for Sickle Cell Trait

Last March, we reported on the National Collegiate Athletic Association (NCAA) requiring screening for sickle cell trait in Division I institutions. This issue continues to generate controversy, and on January 19, the NCAA approved a policy requiring Division III institutions to mandate screening for sickle cell trait on all incoming student athletes. This policy is an expansion of the screening policy already in place in Divisions I and II. Just as ASH opposed the policy for Division I and II, the Society believes the NCAA policy is medically groundless and is focused more on protecting the NCAA from legal liability than on protecting the health of student-athletes.

Prior to the vote, ASH worked with leaders of several Division III institutions in an effort to urge the NCAA to reassess the policy and consider the recommendations outlined in ASH’s Policy Statement on Screening for Sickle Cell Trait and Athlete Participation, including specifically mandating athletic programs to adopt universal preventive interventions in their training programs designed to protect all athletes from exertion-related illness and death. ASH’s advocacy contributed to a very close vote after a 45-minute debate.

ASH will continue to engage in a dialogue with the NCAA about how both organizations can work together to protect athletes, namely by supporting further research on the relationship between sickle cell trait and exertion-related illness and by educating NCAA trainers, coaches, and athletic departments on how to protect all student-athletes comprehensively from exertion-related injuries.

ASH Bridge Grant: Applications for Second Round Due April 5

In response to the impact of NIH funding cuts on hematology, ASH will assist unfunded R01 grant applicants through one-year, $100,000 awards designed to help sustain the recipient’s research. In 2013 and for the next two years, the ASH Bridge Grant program will provide at least 30 one-year awards annually. ASH members who applied for an NIH R01 grant or equivalent but were denied funding due to budget cutbacks are eligible to apply. Applications for the second round of awards are due April 5. Learn more about the ASH Bridge Grant program at www.hematology.org/Awards/Bridge-Grants/8669.aspx.

20 Early-Career Hematologists Set to Gain Invaluable Translational Research Tools

ASH and the European Hematology Association (EHA) have selected 20 early-career hematologists in the Translational Research Training in Hematology (TRTH) program. Now in its fourth year, TRTH provides junior researchers from around the world with an unique, yearlong training and mentoring experience with the goal of fostering the next generation of global leaders in translational research. The TRTH program begins with a week-long course held March 16-23, at a learning center near Milan, Italy, followed by a meeting at the EHA Annual Congress in June, and finally a meeting at the ASH annual meeting in December, where trainees present the status of their research. To learn more about the TRTH program, visit www.hematology.org/Awards/TRTH/2632.aspx.
Ask the Hematologists

P. BRENT FERRELL, MD,1 AND MARK J. KOURY, MD2

1. Clinical Fellow, Division of Hematology/Oncology, Vanderbilt University
2. Professor of Medicine, Division of Hematology/Oncology, Vanderbilt University and Veterans Affairs Tennessee Valley Healthcare System

Patient History

A 64-year-old man had a history of two years of weight loss and mild normocytic anemia, but over the preceding two months, worsening polyarthritides, fatigue, and anemia (Hgb 8.6 g/dL, Hct 25%, MCV 91 fL) were noted. The reticulocyte count was 14 percent with a normal WBC and normal platelet count. He had normal serum cobalamin, methylmalonate, LDH, RBC lolate, and negative hepatitis serologies. Laboratory tests were consistent with normal renal, thyroid, and liver function. Abnormal laboratory tests included an elevated reticulocyte sedimentation rate of 87 mm/h, serum C-reactive protein (CRP) of 145 mg/L, haptoglobin of 447 mg/dL, and serum albumin of 2.5 g/dL. Iron studies showed a serum iron of 25 µg/dL, TIBC of 209 µg/dL, transferrin saturation of 11 percent, and serum ferritin of 299 ng/mL. He was transfused with two units of packed erythrocytes, begun on low-dose prednisone, and referred for evaluation of anemia.

The Question

What is your approach to the diagnosis and management of the anemia of chronic inflammation (ACI)?

Our Response

Overview

The traditional disease categories associated with ACI are malignancy, infection, and connective tissue disorders. When excess cytokine production is a pathologic manifestation, ACI may be associated with such processes as severe heart failure and poorly controlled diabetes that fall outside of the customary listing of chronic inflammatory diseases. ACI is often subtle and inidious in onset, presenting as a mild, persistent anemia that may worsen over time. Causes of the underlying inflammation such as rheumatoid arthritis may be obvious, or the basis of the anemia may not be immediately apparent as in cases of occult malignancy or chronic infection.

Pathophysiology

Multiple mechanisms are responsible for the development of ACI.1-3 Although erythrocytes in ACI have slightly shortened survivals, the following three mechanisms, mediated by inflammatory cytokines, exert major effects in sequential periods of erythropoiesis (Figure): 1) inhibited survival and differentiation of erythroblast progenitor cells; 2) suppressed erythropoietin (EPO) production; and 3) hepcidin-mediated sequestration of reticuloendothelial iron. Chronic inflammatory states increase production of cytokines such as IL-1, TNF-α, and interferon-γ that directly inhibit the survival and differentiation of erythroblast progenitor cells.1 Inflammatory cytokines suppress EPO production, decreasing plasma EPO concentration and increasing apoptosis of erythroid cells in the EPO-dependent stages of differentiation.1 Finally, the inflammatory cytokines IL-6 and members of the bone morphogenetic protein (BMP) family diminish serum iron concentration by inducing transcription of hepcidin, the master regulator of iron homeostasis.1 Hepcidin restricts its effects primarily through interaction with the cellular iron exporter, ferroportin, expressed on the basolateral surface of enterocytes and on reticuloendothelial cells. Binding to hepcidin induces endocytosis and degradation of ferroportin thereby restricting gastrointestinal iron absorption and impairing macrophage export and recycling of iron from phagocytosed senescent erythrocytes. The trapping of iron in reticuloendothelial cells accounts for the characteristic iron-laden macrophages observed in ACI bone marrow aspirates stained with Prussian blue. Because iron absorption and iron recycling are impaired, plasma iron concentration is low, and transferrin saturation is often subnormal (as in our case), resulting in a functional iron deficiency state with consequent suboptimal delivery of iron to maturing erythroblasts. Interpretation of transferrin saturation must also take into account the fact that transferrin is a negative acute phase reactant, and as such, the serum concentration is often subnormal or at the lower end of the normal range in patients with ACI (as illustrated in our case).

Diagnostic Considerations

In most instances, ACI is normocytic, normochromic, but approximately one-third of cases fall into the microcytic, hypochromic morphological classification. In the latter cases, functional iron deficiency as a consequence of excess hepcidin production dominates the pathophysiology, and review of the peripheral blood film reveals features similar to other processes, such as iron deficiency or thalassemia, that affect production of heme or globin. ACI is typically a mild-to-moderate hypoproliferative process manifested as grade I or grade II anemia. If more severe, (grade III or worse, hemoglobin < 8.0 g/dL), the anemia is likely multifactorial with other processes, such as concurrent gastrointestinal bleeding contributing to the etiology. Blood loss and inflammation may coexist, especially in patients with renal failure on hemodialysis, in patients with gastrointestinal malignancy or inflammation, or in patients with arthritis treated with corticosteroids or non-steroidal anti-inflammatory drugs. In those cases, determining the relative contributions of absolute iron deficiency and functional iron deficiency can be challenging without performing a bone marrow analysis.

Serum ferritin concentration is less than 20 ng/mL in uncomplicated iron deficiency anemia. Although as an acute-phase protein, the ferritin concentration can be driven into the normal range by the underlying inflammatory process, a ferritin concentration greater than 150 ng/mL is rare in ACI patients who have concomitant absolute iron deficiency. As noted above, low serum iron is characteristic of ACI, and low serum transferrin concentration and low transferrin saturation are also observed routinely in ACI.

Transferrin receptor (TfR) expression is regulated post-transcriptionally by intracellular iron concentration through the iron regulatory element (IRE)/IRE binding protein (IRBP) system. When intracellular iron concentration is low, the IRE/IRBP system stabilizes TfR mRNA, thereby increasing translation and protein expression. The effect of intracellular iron concentration on TfR production led to development of a clinical test of iron status. In this case, the concentration of TfR in plasma (soluble TfR or sTfR) serves as a surrogate marker of iron status (i.e., the concentration of sTfR is elevated in absolute iron deficiency). Subsequent studies suggested that the sensitivity of the assay in distinguishing absolute iron deficient states from inflammatory processes that affect iron metabolism can be improved by calculating the sTfR index by dividing the sTfR concentration by the log of the serum ferritin concentration. Another proposed method for identifying iron deficiency is to measure reticulocyte hemoglobin concentration (Chr) by flow cytometry. As the most recently produced 1 percent of erythrocytes in the blood, the reticulocytes are the subpopulation most affected by iron deficiency at the time the blood sample is obtained, and decreased Chr is a sensitive indicator of iron-restricted erythropoiesis.3 Combining Chr with sTfR index has been used to improve the identification of absolute iron deficiency in patients with inflammation.1 While these studies may have value in some particularly problematic cases, their clinical utility is relatively modest. This interpretation is based on the fact that functional iron deficiency plays an important role in the pathophysiology of ACI, and patients with functional iron deficiency, without absolute iron deficiency, may benefit from supplemental iron. Therefore, the practical value of distinguishing functional iron deficiency from absolute iron deficiency is arguable because iron supplementation can be therapeutic in either case.

Treatment

Although many patients have mild anemia that does not require treatment, establishing a diagnosis of ACI is important as doing so implies an ongoing inflammatory process, the etiology of which should be investigated. Furthermore, effective treatment of the underlying disease results in improvement or resolution of the anemia. In some instances, however, the underlying disease may be resistant to therapy (e.g., poorly responsive malignancy or refractory connective tissue disease). In such cases, red cell transfusion support and therapy that targets the pathophysiologic mechanisms that underlie ACI (Figure) are the mainstays of management. ACI may respond to recombinant human EPO (rhEPO), but the response may be blunted by concomitant functional iron deficiency. Iron supplementation, with a goal transferrin saturation of > 20 percent, may increase the effectiveness of rhEPO, and some patients respond to iron supplementation in the absence of rhEPO support. Infused

Mechanisms of inflammatory cytokine inhibition of erythropoiesis in ACI. Three mechanisms (shown in red) that are mediated by inflammatory cytokines are key elements in the pathophysiology of ACI and represent potential therapeutic targets. The main period of erythropoiesis in which each of the respective mechanisms has its major effect is indicated by arrows. The stages of erythropoiesis begin with the hematopoietic stem cell (HSC) and extend through the mature erythroblast (RBC). The periods of erythropoietin (EPO) dependency and hemoglobin synthesis are shown below those specific stages of differentiation.

[Figure showing stages of erythropoiesis and mechanisms of cytokine inhibition]
The patient described in the introduction was diagnosed with seronegative rheumatoid arthritis, and two months after beginning therapy with prednisone and methotrexate, his arthritis symptoms had improved and his Hgb was 12.5 g/dL. Theurl I, Schroll A, Sonnweber T, et al. Pharmacologic activation of iron recycling by anti-TNF-α agents has been shown to increase hemoglobin concentration in patients with ACI independent of an effect on EPO concentration. Anti-TNF-α agents may also defers, for two months, sequestration cuts that included an additional two percent reduction in Medicare payments that were slated to start January 1 and keeps rates frozen at current levels for one year. The legislation went to press, it was expected that the fiscal year (FY) 2014 budget request from the Obama administration would be delayed. By law, the budget request is due before Congress by the first Monday in February. However, because of ongoing uncertainty over the fiscal cliff and sequestration, it was expected that the fiscal year (FY) 2014 budget request from the Obama administration would be delayed. By law, the budget request is due before Congress by the first Monday in February. However, because of ongoing uncertainty over the fiscal cliff and sequestration, it was expected that the fiscal year’s request would be postponed until mid-March. The late delivery of the President’s request to Capitol Hill will likely mean a delay in the entire budget process for FY 2014 and lingering budget uncertainty for NIH.

Advocacy by Hematologists Crucial to Safeguarding Biomedical Research Funding

Last year, ASH launched an aggressive multifaceted strategy to protect research funding and take a balanced approach to reducing the deficit without further cutting NIH and other core federal programs. This approach involved enhanced advocacy efforts, including a “Fly-In Day,” advocacy leadership training, and online advocacy campaigns, letters-to-the-editor; the creation of the ASH Bridge Grant program; and expanded communication efforts to educate ASH members, the media, and the public about the value of research funding.

What’s the takeaway? Advocacy by hematologists and members of the research community is critical to obtaining Congressional support for biomedical research funding.

One-Year ‘Doc Fix’ Included in Fiscal Cliff Package

The fiscal cliff legislation passed by the Congress on January 1 includes a one-year payment patch for physicians who treat Medicare patients. The deal blocks the scheduled 27 percent payment cuts to Medicare physicians that were slated to start January 1 and keeps rates frozen at current levels for one year. The legislation also defers, for two months, sequestration cuts that included an additional two percent reduction in Medicare payments. ASH encourages all clinicians to join the Society in continuing to pressure Congress to repeal permanently the Sustainable Growth Rate (SGR) formula by visiting the ASH Advocacy Center (www.hematology.org/takeaction) and sending an email to your elected officials.
A Conversation With the New Editors of Blood

Dr. Löwenberg: Dissemination and education should go together. What Blood brings to the table should make a difference to our readers. Our content and how it’s presented should help them grow in their understanding of the biology and pathology of hematologic disorders. We aspire to serve Blood readers by offering a resource with information that is right, novel, and impactful.

Dr. Berliner: And I might add, that we want to offer context. When there are differences of opinion regarding a research finding or clinical approach, we’ll try to present the three sides and let readers draw their own conclusions.

Q: Dr. Löwenberg, you’ve mentioned the notion of Blood’s “impact” several times in your comments. How do you feel about the “impact factor” and its effect on scientific publishing?

Dr. Löwenberg: I would yield to the expert!

Dr. Berliner: The “impact factor” was originally intended to keep track of how often a journal was requested from a library. Librarians wanted to know how many copies of a journal they needed so that readers would not complain! It seemed to be a good idea at the time. Today it refers to the number of citations a given article receives in other publications. In a sense, it asks: “Do people pay attention to the articles that appear in this journal?” The results never used to be published. It has now acquired a level of importance that requires us to take it seriously. It should be recognized, however, that it is not a good measure of quality, and also that it is subject to manipulation.

Q: What proportion of articles will report original research versus review articles under your tenure?

Dr. Löwenberg: There is no rigid, predefined proportion for this. An issue of Blood may contain from one to three review articles, a special article such as “How I Treat,” plus several original research articles covering any area in hematology.

Q: What proportion of articles will report original research versus review articles under your tenure?

Dr. Löwenberg: While ASH as the publisher and owner is American, Blood as a matter of fact is an international journal. Our readers and authors represent all corners of the globe. The international perspective of the Journal will require a considerable level of active involvement of associate editors and editorial board members from different parts of the world, which we consider essential. I am in fact the first non-American editor-in-chief in an American tradition of more than 60 years. I am convinced that there is considerable and growing interest in Europe, Asia, and South America in Blood. There is great growth potential there!

Q: People do get sick in the same way around the world, but access to care — to effective medications, to trained physicians and support services — varies widely. How can Blood address the needs of hematologists in developing countries? Is this a priority for you?

Dr. Löwenberg: For Blood this is also a matter of education. The American Society of Hematology through its International Members Committee is actually playing a major role in this area by making Blood available in less privileged areas and by its outreach educational activities. Blood is interested in studies on major health-care issues in other parts of the world, and we will continue to publish interesting reports about hematologic health-care issues in developing countries.

Q: You’re served on the editorial boards of several journals in the United States and Europe. Do you view the “role” of the medical journal simply as a means to disseminate new information — a neutral platform, so to speak — or as a means to actively educate? Is there a difference?

Dr. Löwenberg: The need for an internationalized editorial board is a trend that has been actively initiated by my predecessors at Blood. The treatment approach in a patient with a particular subtype of leukemia is fundamentally identical for patients in America, Asia, or Europe. And scientific knowledge obviously has generic value independent of geography. Blood as the premier journal in hematology by virtue of its role, has acquired a high-profile position as the leading journal of our field. We have just begun to review and revisit various aspects of the role of the editorial board, and in this respect we will also pay attention to the challenge of Blood’s progressively evolving international presence.

Q: Will you reach out to more international physicians to serve as editorial board members?

Dr. Löwenberg: In the 70s and 80s of the last century, the major therapeutic clinical trials were conducted in the United States by the leading cooperative groups and major institutions. In the recent decade there has been a shift toward the major trials being conducted in Europe. The latter trend reflects a highly unfortunate development since clinical trials with adequate enrollment remain a cornerstone for evaluating new diagnostic procedures and novel treatment approaches. This shift is most likely caused by differences in the health-care system that keeps private physicians from referring their patients to institutions that have the required infrastructure and advanced know-how for clinical trials.

Dr. Löwenberg: I grew up in a country where the health-care system is socialized in the sense that it ensures equal access to health care for the citizens and ensures a certain basic quality standard throughout the society of the country. I see that as an advantage. There is however also an economic advantage. In such a regulated system, we spend a smaller health-care budget than the United States does.

Q: What practical advantages or challenges arise from the time zone differences?

Dr. Berliner: We are looking for articles that are novel, original, and impactful. Those are the three ingredients, the three legs of the stool. Proportions of each of these ingredients might vary, but this is what we would like to see.

Q: There is still competition not only for “eyeballs” but also for quality articles. How can Blood attract high-impact articles and authors?

Dr. Berliner: The best way to attract good articles is to have a good journal. Blood has a very strong reputation as a premier journal with excellent peer review that presents outstanding clinical and basic research. But you are right, competition is increasing. We will recruit outstanding content and emphasize the advantages of publishing in Blood. We have a rapid review process that can offer fast turn-around. In addition, articles accepted to Blood are made available online on a daily basis.

Q: Dr. Löwenberg, will the editorial board of Blood under your tenure reflect this increasing “internationalization” or “globalization” of hematology?

Dr. Löwenberg: While ASH as the publisher and owner is American, Blood as a matter of fact is an international journal. Our readers and authors represent all corners of the globe. The international perspective of the Journal will require a considerable level of active involvement of associate editors and editorial board members from different parts of the world, which we consider essential. I am in fact the first non-American editor-in-chief in an American tradition of more than 60 years. I am convinced that there is considerable and growing interest in Europe, Asia, and South America in Blood. There is great growth potential there!

Q: People do get sick in the same way around the world, but access to care — to effective medications, to trained physicians and support services — varies widely. How can Blood address the needs of hematologists in developing countries? Is this a priority for you?

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Q: Your experience in medical practice and research spans two continents. Can you contrast the pros and cons of the European and American systems? Are clinical trials easier to carry out in one place or the other?

Dr. Löwenberg: I grew up in a country where the health-care system is socialized in the sense that it ensures equal access to health care for the citizens and ensures a certain basic quality standard throughout the society of the country. I see that as an advantage. There is however also an economic advantage. In such a regulated system, we spend a smaller health-care budget than the United States does.
emails fly back and forth at all hours, and I often forget that we are on separate continents.

**Q:** What will your role be in editing *Blood*? How will you and Dr. Löwenberg share the hard work of editorship? How will your responsibilities differ?

**Dr. Berliner:** On a day-to-day basis, we are both responsible for the triage of new submissions and selecting which associate editor ought to review a given manuscript. We both answer pre-submission inquiries. The rest is a work in progress. I have to say that I’m delighted to partner with Bob in this adventure. We’ve been good friends and colleagues for many years.

**Dr. Löwenberg:** I am grateful to Nancy for accepting this position. We have been friends for years, and we make a great team!

**Q:** You’re a teacher working in both laboratory and clinical settings …

**Dr. Berliner:** I enjoy patient care and research, and the decision to go into academic medicine reflected my desire not to give either of them up. My career has morphed many times over the years, but I have always loved being able to mix research, patient care, and teaching, although the mix has changed over time. Most of all, my passion is mentoring fellows and junior faculty.

**Dr. Löwenberg:** Right after graduating from medical school, I became a PhD student in one of the leading research institutes in Europe in Rijswijk-Rotterdam. These were the pioneering days of experimental hematology. I became excited about the prospects and challenges of the newest developments. This was in the early days of stem cell research – the discovery of spleen colony-forming assay, *in vitro* colony-forming assays, the media with colony-stimulating activity that contained CSFs – and the very first successes of clinical stem cell transplantation. There was excitement all over the place. My supervisor, Dirk van Bekkum, was involved in one of the first successful human allogeneic bone marrow transplantations in an infant with severe combined immunodeficiency disease. He worked in radioisotopic research and stem cell research. I decided then that I wanted to work at the interface of preclinical research and clinical advances. This is how it happened, and why and how I ended up in hematology.

**Q:** If not a physician, then what professional work would you have chosen?

**Dr. Löwenberg:** Probably in any field where I would meet the challenge of innovation and also in a setting where I would be able to work with people. Thus, I could have found myself in another challenging academic area, but perhaps it could also have been as an entrepreneur in business.

**Q:** Dr. Berliner, can you recall a decisive moment in your life – a person or event – that moved you toward medicine?

**Dr. Berliner:** Well, I was a comparative literature major in college. But my dad was my hero, and he was a physician-scientist, so I tried to keep options open in case I decided for science rather than the humanities. But I don’t remember a particular moment in time when I decided to take the plunge and apply to medical school.

**Q:** Was he a hematologist?

**Dr. Berliner:** Actually, he was a renal physiologist, who was one of the scientists to describe the counter current multiplier system by which urine is concentrated. After serving as the deputy director for science at the National Institutes of Health, he became dean at the Yale School of Medicine.

**Q:** And you attended Harvard for medicine residency. You were the first woman chief resident there.

**Dr. Berliner:** But I went to Yale for college and medical school. I was on the Yale faculty for more than 20 years, and my husband still teaches in the School of Architecture there. Yale is family.

**Q:** Any other comments you might like to make?

**Dr. Löwenberg:** *Blood* is a monument, and it is a reference point in the professional life of any hematologist. We are well aware of this inheritance. I am particularly grateful to Cindy Dunbar, my predecessor for the past five years. She and her team have done an outstanding job! While science and medicine are changing profoundly, we are committed to take *Blood* forward in the interest of our field and serve the hematology community worldwide in the best possible way. We want to improve wherever we can. Therefore, I encourage everyone to get in touch with us. Readers or authors, clinicians or basic scientists, wherever you may live and work anywhere in the world, we want you to share your creative ideas and suggestions about the content and the future direction of our journal! Don’t hesitate to speak out!
The Cat’s Out of the Bag: How Mitochondrial Heme is Exported


In support of Virchow’s perspective, a number of notable advances in hematology have their origins in observations made in animals. For example, cats infected with feline leukemia virus C (FeLV-C) develop red cell aplasia, and investigation of the pathobiology of this process led to identification of the receptor for FLV (FLVCR1) as a cytoplasmic heme exporter.2,4 Free heme is toxic, and FLVCR protects erythroid progenitors from injury by exporting, from the cytoplasm, heme that is produced in excess of that required for pairing with globin, cytochromes, and other proteins that use heme as a prosthetic group (Figure). But the heme biosynthetic pathway ends in the mitochondria (Figure), so how does newly synthesized heme move from the mitochondria to the cytoplasm? The answer to that question can again be traced to the study of cats, as Deborah Chiabrando and colleagues, in the laboratory of Emanuela Tolosano at the University of Torino, have identified an isoform of FLVCR1 that mediates efflux of mitochondrial heme into the cytoplasm.

Examination of the DNA structure of FLVCR1 suggested to the authors the possibility of alternatively spliced transcripts, and their hypothesis was confirmed when they ultimately identified an isoform (that they named FLVCR1b) that consists of amino acids 277-555 of FLVCR1 (renamed FLVCR1a in their paper to distinguish it from the newly discovered FLVCR1b). In mice, Flvcr1b is ubiquitously expressed, with the highest transcript levels in the brain, heart, muscle, spleen, and bone marrow. When overexpressed in vitro, Flvcr1b shows a strikingly different subcellular localization compared with Flvcr1a. Flvcr1b has a mitochondrial targeting sequence and is found enriched in mitochondria, whereas Flvcr1a is a plasma membrane protein (Figure). Overexpression of Flvcr1b leads to intracellular heme accumulation, while silencing of expression results both in heme accumulation exclusively in the mitochondria and in termination of erythroid differentiation. Thus, normal erythropoiesis depends upon FLVCR1b-mediated regulation of mitochondrial heme efflux without which hemoglobin and other hemoproteins cannot form (Figure). Remarkably, mice lacking Flvcr1a but expressing Flvcr1b have normal erythropoiesis. The Flvcr1a/Flvcr1b−/− mice are characterized phenotypically by edema, hemorrhage, and skeletal abnormalities. These observations suggest that the block in erythroid differentiation observed in the original Flvcr1−/− knockout model that eliminated both isoforms4 was due to aberrant regulation of mitochondria heme regulation due to absence of Flvcr1b function rather than to cytoplasmic accumulation of heme due to loss of Flvcr1a activity. On the other hand, the edema and hemorrhage that characterizes the Flvcr1a/Flvcr1b−/− model may be a consequence of endothelial cell injury due to cytosolic accumulation of heme. This same process may account for the observed skeletal deformities as endothelial cell injury could lead to tissue hypoxia, thereby impairing cartilage development.

The exquisite control of heme metabolism and the potential toxicities associated with excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia). But are there excess heme accumulation are highlighted by this paper (Figure). The hypochromic, microcytic anemias that are familiar to all hematologists are due to abnormal production of heme (e.g., iron deficiency) or globin (e.g., thalassemia)
Targeting Chromosome Loss in Down Syndrome Cells


Down syndrome (DS) is the most common viable trisomy in humans, with several thousand affected infants born in the United States every year. Patients with DS have a wide spectrum of clinical problems dominated by cardiac and developmental abnormalities. Up to 10 percent of DS infants experience a transient myeloproliferative disorder that can progress to a rare form of acute megakaryocytic leukemia, whereas pre-school-age children with DS have an abnormally high risk of developing acute precursor B-cell leukemia. DS patients with leukemia present unique management challenges owing to a combination of organ vulnerability and increased susceptibility to drug toxicity. Progress in understanding the hematopoietic defects and the molecular basis of leukemogenesis of DS has been hampered by a lack of a faithful murine disease model and the problems inherent in comparing results obtained using cells from different patients.

The recent study by Li and colleagues from the University of Washington in Seattle now provides evidence for the feasibility of deriving strictly diploid, induced pluripotent stem cells (iPSCs) from the trisomic fibroblasts of DS patients. The paper is at once a technical tour de force and an illustration of the effectiveness of combining targeted genome engineering approaches with induced pluripotency. The investigators initially generated iPSCs that were confirmed to be trisomic for chromosome (chr) 21. Next, they used an adeno-associated viral vector to insert a dual selectable marker into a gene located on chr 21 via homologous recombination. By using a strategy that selects against the vector-bearing chr 21, clones that had lost a complete copy of chr 21, and were hence disomic for chr 21, were generated. Subsequent experiments showed that the derived chr 21 disomic iPSCs had a higher proliferative rate than their trisomy chr 21 counterparts, but in vitro hematopoietic differentiation was not consistently different.

As noted above, patients with DS have a several hundred-fold increased risk of developing megakaryocytic myeloid leukemia in infancy and acute lymphocytic leukemia in early childhood. In another recent paper, this one by MacLean and colleagues from Dana-Farber Cancer Institute in Boston, the authors used isogenic disomic pluripotent stem cells to investigate differences in hematopoiesis between stem cells with diploid chr 21 and stem cells with trisomy chr 21.1 The Dana-Farber group did not engineer their diploid chr 21 cell lines as did the University of Washington group, but instead isolated spontaneous disomic revertants from human embryonic stem cell and iPSC clones. Differences in immunophenotype and a significant increase in progenitor colony formation by chr 21 trisomic cells compared with chr 21 disomic cells was observed, consistent with developmental dysregulation of hematopoiesis in DS individuals.

The study by Li offers a unique perspective on advances in genome engineering, and publication of their strategy for high-efficiency generation of disomic iPSCs provides investigators with a valuable tool to use in exploring the pathology that underlies the potential DS hematopoietic complication of CS. Looking to the future, the ability to engineer disomic isogenic iPSCs offers the possibility of generating autologous hematopoietic grafts for stem cell transplantation. While much additional work will be needed to accomplish this futuristic goal, the studies of Li and colleagues present a strategy by which the power of stem cell biology can be used to explore the pathobiology that underlies the generation of disomic iPSCs provides investigators with a valuable tool to use in exploring the pathobiology that underlies the development of hematopoietic malignancies in DS individuals.


Irons in the Fire: Developing New Therapies for Iron Overload


Iron is highly toxic because it generates tissue-damaging reactive oxygen species by the Fenton reaction. Thus, although necessary for life, careful regulation of all aspects of iron metabolism is critical. A key regulator of iron homeostasis is hepcidin, a peptide hormone produced by the liver. Hepcidin negatively regulates cellular iron export from macrophages, duodenal enterocytes, and hepatocytes by promoting degradation of ferroportin, a transmembrane iron exporter. Human diseases that involve primary or secondary dysregulation of hepcidin include hereditary hemochromatosis (HH) and j-thalassemia intermedia, respectively. HH is an autosomal recessive disorder caused by mutation (C282Y homozygosity) in HFE, a key regulator of hepcidin expression. The iron overload of HH is the result of failed upregulation of hepcidin despite ongoing dietary iron loading, while hepcidin synthesis is suppressed due to ineffective erythropoiesis in j-thalassemia intermedia. The mechanism whereby ineffective erythropoiesis suppresses hepcidin expression is largely speculative although trans-acting factors produced in the bone marrow (e.g., GDF-15 and TWSG1) are candidate signaling molecules. The result of dysregulated suppression of hepcidin is iron overload. Hypothetically, patients with such seemingly disparate diseases as HH and j-thalassemia intermedia could be treated by pharmacologic manipulation of hepatic expression. Indeed, genetic studies using animal models of HH showed that constitutive expression of hepcidin or deletion of Tmprss6, a negative regulator of hepcidin expression, could reverse iron overload. In models of j-thalassemia intermedia, targeted deletion of Tmprss6 decreased iron loading and also reduced ineffective erythropoiesis.

Based upon these and other observations, Schmidt et al. sought to demonstrate that systemic administration of lipid nanoparticle (LNP)-formulated siRNAs designed to silence Tmprss6 (LNP-Tmprss6; LNP-Tmprss6) could increase hepatic expression and diminish iron uptake in murine models of HH and j-thalassemia intermedia, while also reducing ineffective erythropoiesis in j-thalassemia intermedia. The first set of experiments showed that they could, in fact, silence Tmprss6 using LNP-Tmprss6, thereby upregulating hepcidin mRNA expression in a dose-dependent fashion. A single infusion of LNP-Tmprss6 decreased Tmprss6 for 14 days, increased hepatic levels for seven days, and decreased transferrin saturation for nearly a month. Next, these investigators administered LNP-Tmprss6 to Hfe-/- mice to determine whether the HH phenotype could be ameliorated. They found sustained decreases in serum iron, transferrin saturation, and non-heme hepatic iron. There was also an increase in splenic iron, attributed to hepcidin-induced sequestration of iron in splenic macrophages, and all of the mice developed a hypocellular, microcytic, iron-deficient anemia by six weeks after onset of therapy. Notably, patients with Tmprss6 deficiency due to inherited mutations of the gene have a similar phenotype as the treated mice (i.e., high serum hepcidin and iron refractory, iron deficiency anemia). The final set of experiments tested the effects of LNP-Tmprss6 in a murine model of j-thalassemia intermedia (Hbbtm1j1). These mice have iron overload, similar to humans with j-thalassemia intermedia, due to suppression of hepcidin by ineffective erythropoiesis. As anticipated, LNP-Tmprss6 silenced Tmprss6, increased hepcidin, and decreased serum iron and transferrin saturation. Most interestingly, however, LNP-Tmprss6 decreased ineffective erythropoiesis, as evidenced by higher hgbmoglobin concentration; prolonged red blood cell (RBC) lifespan; lowered the reticulocyte count; decreased erythropoietin concentration; and reduced splenic volume. Splenic iron was lower, unlike the Hfe-/- mice, likely because of the reduction in splenic volume. RBC membrane-bound -globin, a pathophysiologic consequence of j-thalassemia, was also markedly decreased, and peripheral blood morphology nearly normalized except for a modest increase in central pallor. Together, these results suggest that iron plays an important but as yet incompletely understood role in the pathobiology of thalassemia.

These experiments show the potential of novel therapeutics that manipulate hepatic expression for a number of disorders characterized by iron overload, both primary (e.g., HH) and secondary (e.g., j-thalassemia intermedia). Here, Schmidt et al. explored RNAi therapeutics, but others have investigated biomimetic “mini-hepcidins” and exogenous transferrin in similar animal models. Ultimately, such therapies will need to meet a very high standard to supplant phlebotomy, which is both inexpensive and effective, for the resolution of iron overload in typical HH patients. Most intriguing is the therapeutic potential of reducing hepatic expression in j-thalassemia intermedia, where amelioration of both iron loading and ineffective erythropoiesis is observed.

A New Ripple for $\textit{Mpl}$: Eltrombopag for Aplastic Anemia


**Thrombopoietin (TPO)** is the growth factor that stimulates platelet production through interaction with its receptor, $\textit{Mpl}$, on megakaryocytes. Surprisingly, patients with immune thrombocytopenia (ITP) exhibit a relative deficiency of TPO and respond to exogenous stimulation by TPO receptor agonists. Two TPO mimetics, romiplostim and eltrombopag, have been FDA-approved for the treatment of ITP in patients with an insufficient response to corticosteroids, intravenous immune globulin, or splenectomy; both bind to $\textit{Mpl}$ at a site distinct from the TPO binding site, and neither shares homology with TPO. Eltrombopag is an oral drug that activates the Jak-Stat and MAPK pathways (Figure). A phase III trial of eltrombopag versus placebo demonstrated its capacity to improve platelet counts, reduce bleeding occurrences, and improve quality of life in patients with chronic ITP. Eltrombopag was also recently granted FDA approval in November 2012 for patients with hepatitis C, as it effectively supports platelet counts during treatment with interferon.

In contrast to patients with ITP, patients with aplastic anemia exhibit markedly elevated TPO levels, but they still have thrombocytopenia. There are few options for patients with aplastic anemia who have relapsed after immunosuppressive therapy ($\textit{IST}$) with anti-thymocyte globulin, cyclosporine, and steroids. The salvage therapies include a second course of IST or an allogeneic stem cell transplant. The former has a poor response rate, and the latter, a high mortality rate, especially for those who do not have a matched family donor.

As has been extensively studied, thrombopoietin receptors are expressed by primitive hematopoietic stem cells, and TPO is a critical cytokine for ex vivo stem cell expansion and lentiviral gene therapy. In addition, eltrombopag successfully expands cord blood stem cells in vitro. Together, these observations suggested that TPO agonists could be therapeutically active in diseases such as aplastic anemia in which the hematopoietic stem cell pool is depleted.

Dr. Cynthia Dunbar’s group at the National Institutes of Health conducted a non-randomized, phase II study of eltrombopag in patients with severe aplastic anemia and severe persistent thrombocytopenia who had failed to respond to immunosuppressive therapy. They successively enrolled 25 adult patients and initiated eltrombopag at a dose of 50 mg daily, the typical starting dose for ITP. The dose escalated every two weeks by 25 mg if the platelet count remained below 20,000/mm$^3$, until a maximum daily dose of 150 mg was reached. All but one patient reached this maximum dose. Response was assessed at 12 weeks as follows: 1) platelet response defined as an increase in platelet count by 200,000 or freedom from platelet transfusions for eight weeks if previously dependent; 2) red cell response defined as an increase in hemoglobin by 1.5 g/dl or reduction by four units of red cells transfused in eight weeks as compared with the eight weeks prior to enrollment; and 3) neutrophil response defined as a rise in count to a 500/mm$^3$ or if < 500 then at least doubling the count. Forty-four percent of the patients responded with improved production in at least one cell lineage. All 25 patients were dependent on platelet transfusions prior to treatment, and nine were able to discontinue them. The average increase of the platelet count was 44,000/µl. Nine patients had a neutrophil response, and six had an erythroid response. Higher reticulocyte count was one characteristic that predicted a favorable response. Of the four patients who had a response of at least eight months, three attained normal bone marrow cellularity. None of the patients’ bone marrows exhibited the reticulin fibrosis seen in some ITP patients treated with eltrombopag. The severe adverse events included abdominal pain due to gastroenteritis; skin rash on cephalosporin, febrile neutropenia, and gingival bleeding. Seven of 11 patients with a response remained on treatment for 16 months. One patient who stopped treatment after nine weeks because of development of a cataract exhibited a continued response for 16 months.

Mice deficient in mpl (the murine thrombopoietin receptor) exhibit bone marrow aplasia, and humans with congenital amegakaryocytic thrombocytopenia develop multi-lineage marrow failure. Moreover, patients with familial aplastic anemia have recently been found to have a defect in mpl.

The other thrombopoietin mimetic, romiplostim, has also been investigated in a randomized, double-blind, placebo-controlled trial for low or int-1 risk myelodysplastic syndrome with thrombocytopenia. There was sustained improvement in platelet counts among the romiplostim-treated patients, but the study was stopped prematurely due to possible increased incidence of progression to acute myeloid leukemia. The most recent analysis of the data, presented at the 2012 ASHA Annual Meeting, however, did not show a statistically significant difference in progression to AML between romiplostim and placebo. Nonetheless, the hypothetical risk of transformation induction remains, as another recent study demonstrated elevated mpl expression in some leukemia cells with t(8;21) that produces the Runx1-ETO fusion gene, and thrombopoietin-mediated signaling via PI3K/Akt led to development and maintenance of AML in a mouse model expressing Runx1-Eto. In fact, two non-responding patients in the eltrombopag trial exhibited clonal evolution with development of monosomy 7, and one of them progressed to AML. Thus, a key objective in utilizing thrombopoietin mimetic therapy for aplastic anemia will be to stimulate normal hematopoiesis without potentiating leukemogenesis.
A New B Cell With a New B-Cell Function


The colony-stimulating factors, granulocyte/macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), and granulocyte colony-stimulating factor (G-CSF), were originally defined as hematopoietic cell growth factors. Subsequently, CSFs have been found to have complex, pleiotropic effects in inflammation and in other states. In most murine models of inflammation and autoimmune disease (e.g., experimental autoimmune encephalomyelitis, rheumatoid arthritis), CSF deletion results in the suppression of the disease state. These findings, which are consistent with a proinflammatory function of CSFs, have led to clinical trials of anti-GM-CSF and anti-M-CSF antibodies in rheumatoid arthritis.

Prior to the present study by Rauch et al. from the laboratory of Filip Swirski, GM-CSF was thought to be produced by non-hematopoietic cells, macrophages, or T cells. However, the authors examined murine GM-CSF expression by flow cytometry and made the surprising observation that in response to lipopolysaccharide (LPS), GM-CSF was found mainly in a splenic B-cell subpopulation. Consistent with this interpretation, immunofluorescence of spleen sections from LPS recipients co-localized GM-CSF expression to red pulp cells that co-expressed the B-cell markers, IgM, B220, and PAX5. In addition to GM-CSF, the cells under expression to red pulp cells that co-expressed the B-cell markers, IgM, B220, and PAX5. In addition to GM-CSF, the cells under investigation secreted IgM and IL-3, but not pro–IL-1β, IL-6, or tumor necrosis factor-α. This set of phenotypic markers defined these cells as a unique mature B-cell population. The authors named the cells “innate response activator B cells” (IRA B cells) because of the known role of GM-CSF in activating innate leukocytes.

To assess the functional significance of IRA B cells, the authors employed a murine cecal ligation and puncture (CLP) sepsis model. They produced mixed chimeras by reconstituting lethally irradiated mice with bone marrow from a B-cell-deficient mouse called µMT and from a GM-CSF–deficient (Csf2–/–) mouse. The B cells of these mice (called GM/µMT chimeras) cannot produce GM-CSF. The mortality of GM/µMT mice was significantly greater than that of normal mice in the CLP model. Additionally, the peritoneal cavities of GM/µMT chimeras had more neutrophils, and the mice developed an IL-1β, IL-6, and TNFα cytokine storm. This cytokine profile is associated with a defect in bacterial clearance. Neutrophils from the GM/µMT chimeras also phagocytosed bacteria poorly and had higher levels of bacteria.

The evidence provided by this landmark study justifies the current clinical practice of maintaining the hematocrit < 45 percent, a target that is associated with a significant reduction in the rates of cardiovascular death and major thrombosis. Similar to prior studies, this trial spotlights the potential role of leukocytes in promoting thrombosis given the significantly higher white blood cell count in the high-hematocrit group. The higher white blood cell count likely has functional consequences – leukocyte activation has been associated with activation of endothelial cells and the pro-coagulant response at sites of vascular injury. Randomized studies are now needed to parse out whether a particular leukocyte threshold impacts a significant difference in rates of thrombosis/death and is additive to the target hematocrit.
Predicting the Clinical Outcomes in Patients With Hodgkin Lymphoma


Until recently, the systems for predicting outcome in patients with Hodgkin lymphoma have been based upon clinical factors, including the sedimentation rate, blood count, and serum albumin concentration. These parameters reflect indirect indicators of the biologic heterogeneity of the disease, but only at one remove. Such baseline prognostic indices, however, have proven inferior to predictors based on functional imaging with FDG-PET performed as a measurement of response during chemotherapy. Despite this shift toward using in-treatment imaging as the prognostic benchmark, the recent description of the clinical implications of macrophage infiltration has revived interest in pathobiology both as an indicator of outcome and as a potential target for therapy. But enumeration of macrophages is difficult to reproduce using immunohistochemistry, especially on tissue microarrays that may sample only a small region of each biopsy. Now, a collaboration between the Department of Pathology and Experimental Therapeutics of the British Columbia Cancer Agency and four North American cooperative groups has tested a method of multigene expression analysis to derive a prognostic score from routine diagnostic microscopy material. This approach holds the prospect of a new means of predicting outcome based upon molecular phenotypes.

In this study, requiring as little as 200 ng of RNA extracted in most cases from a single 10 mm section of formalin-fixed, paraffin-embedded diagnostic biopsy material, the authors used a new technique called NanoString technology to examine the pattern of expression of 259 genes. Cases for a training set were drawn from the recently reported intergroup E2496 trial that showed a substantial reduction in mortality among patients with advanced Hodgkin lymphoma treated with either ABVD or the Stanford V regimen. From a total of 794 available biopsies, 290 were studied, and based on overall survival of the patients from whom the samples were derived, a 52 gene prognostic set was developed. Next, this prognostic set was tested on a validation cohort consisting of 78 patients treated with ABVD. This validation cohort was enriched for treatment failure but was otherwise similar to patients treated with ABVD in a population-based registry. From the original 52 gene set, analysis of expression of 23 genes was found to generate a robust prognostic index. Of those 23 genes, 20 were overexpressed and three were underexpressed in the group at highest risk of death. The genes overexpressed reflected the presence of increased macrophage numbers, such as CD68, IL15RA, and STAT1; genes indicative of a Th1 response such as IFN-γ; the targets of IFN-γ such as CXCL10 and TNFSF10; genes of macrophage origin, such as those expressed by cytotoxic T cells or NK cells. The high-risk group was found to have an excess of patients with a high international prognostic index score, and positive Epstein-Barr virus-encoded RNA (EBER) expression, and a histology other than nodular sclerosis, although the molecular signature remained independently predictive in multivariate analysis.

Gene-expression profiling, which is already making a significant impact on our understanding of the molecular basis of non-Hodgkin lymphoma, has until now given relatively little information about the heterogeneity of Hodgkin lymphoma. It is clear to clinicians that such heterogeneity exists, and, given the complex infiltrate seen on histology, it is not surprising that the microenvironment in general, and the presence of macrophages and NK cells in particular, would play a central role in the natural history of the disease. This study represents an important contribution to our understanding of the key interactions that drive Hodgkin lymphoma and suggests that therapies that specifically target the inflammatory component of the disease may be capable of improving outcome for those destined to fare poorly with conventional chemotherapy. The NanoString technology used in this study holds the promise of a broad application for gene-expression profiling because RNA sufficient for analysis can be obtained routinely from a single formalin-fixed, paraffin-embedded tissue sample, whereas the need to acquire relatively larger amounts of RNA from formalin-fixed, paraffin-embedded tissue has limited the applicability of standard microarray analysis as a clinical tool. If the results of this study can be replicated by other groups, it may be possible to apply this type of analysis to survival and outcome in routine clinical practice, thus allowing the prospect of real-time molecular phenotyping closer to the bedside.
Ibrutinib for del(17p13.1) CLL Patients: A Potential Bonanza

STUDY TITLE: A Multicenter Phase II Study of PCI-32765 (Ibrutinib) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) With 17p Deletion

STUDY DESIGN: This is a single arm trial of ibrutinib in previously treated, relapsed, or refractory CLL patients with del(17p13.1). The primary endpoint is IWCLL 2008 overall response (partial + complete) response, and secondary endpoints are safety, progression-free survival (PFS), and overall survival.

RATIONALE: The gene locus of the master tumor suppressor, p53, is chromosome 17p13.1, and patients with a CLL clone deficient in p53 because of deletion (del) involving that locus have a particularly poor prognosis. Although patients with del(17p13.1) often respond to cytotoxic chemotherapy in combination with rituxan, responses are usually not durable, and, typically, response duration is short. High-risk CLL is managed with a combination of targeted therapies. B-cell receptor (BCR) signaling in the pathobiology of CLL and subsequent development of BCR signaling pathway inhibitors, such as ibrutinib, has created a sense of optimism in the field that effective targeted therapy is not only feasible but imminent. Large, completed phase I/II studies with ibrutinib in relapsed CLL have shown responses in approximately 71% of patients with another 18% benefiting from disease control but with persistent lymphocytosis.

The toxicity of ibrutinib appears modest with the major adverse effects being low-grade diarrhea, dyspepsia, infection, and rash. Notably, patients have been dosed beyond two years without observed late cumulative events. While many therapies do not work well in relapsed del(17p13.1) CLL, response to ibrutinib is similar (68%) to that observed in non-del(17p13.1) CLL, and remissions are durable with an estimated PFS at 26 months of 55 percent. Although comparative, randomized data are not yet available, this response rate and PFS duration are better than any other single-agent therapy previously tested in relapsed del(17p13.1) CLL. Physicians caring for patients with relapsed del(17p13.1) CLL should encourage patients to enroll in this study. Given that effective treatment of relapsed del(17p13.1) CLL represents an unmet medical need, the hope is that this trial will rapidly accrue patients and meet its designated endpoints, and by doing so, gain accelerated approval by the FDA for marketing of ibrutinib for this indication.

– John C. Byrd, MD, and Sam Penza, MD

Dr. Byrd and Dr. Penza indicated no relevant conflicts of interest.
Embedded in the Red Cell

H. Franklin Bunn, MD
Professor of Medicine, Harvard Medical School; Physician, Brigham and Women’s Hospital

I have been a science nerd for as long as I can remember. My rite of passage began with my first chemistry set and home laboratory, followed by a series of summer jobs in industrial labs.

During my undergraduate years at Harvard College, I became increasingly intrigued with medical science and obtained an MD in 1961 from the University of Pennsylvania School of Medicine. I then completed a three-year medical residency at New York Hospital, Cornell Medical Center. One of my first admissions was a very gallant and courageous young teenager with Cooley’s anemia (thalassemia). “Alfred” had all of the indications of severe iron overload, including progressive congestive heart failure and endocrine hypofunction that delayed transition into puberty. After he was discharged from the hospital, I saw Alfred in our clinic about once a month over a two-year period, and we became quite close. I will always remember a clinic visit at which he seemed particularly upbeat. He took me aside and said “Dr. Bunn, there is something I want to tell you. On Saturday night I am going out on my first date!” He died about six months later. Alfred and his illness impelled me to go into hematology.

From 1964 through 1967 I was a hematology fellow at the Thorndike laboratory at Boston City Hospital (now known as the Boston Medical Center) under the inspiring mentorship of James Jandl, arguably the leading experimental hematologist of that era. Jim’s research focused on the red blood cell and disorders thereof. The intellectual atmosphere at the Thorndike laboratory was transforming, particularly so at a weekly conference in which cases were thoroughly dissected and reassembled by Jim, along with William Castle and Jane DesForges, abetted by younger colleagues, Harry Jacob, Dick Aster, and others who have left a solid imprint on hematology.

After two years in the army at a blood research lab in Fort Knox, KY, I left I needed an apprenticeship in a strong biochemistry lab before initiating an independent research program. Ruth and Reinhold Benesch had recently reported that the oxygen affinity of hemoglobin in human red cells was tightly regulated by 2,3-diphosphoglycerate (2,3-BPG), an abundant intermediate in the glycolytic pathway. They were aware of experiments I had done at Fort Knox on the impact of failing levels of 2,3-BPG in stored blood, and they gave me the opportunity to join their lab at Columbia University.

Six weeks after my arrival I faced the first and only bona fide crisis in my career. I telephoned Helen Ranney at Albert Einstein College of Medicine and told her that Reinhold had just fired me from his lab, for reasons that I at was a loss to explain. Helen, who at that time was a heavy smoker, replied, “Wait a minute. Let me go get a cigarette. I can see this conversation is going to take a while.” She then arranged for me to join Robin Ebiel’s lab at Einstein. While there, I measured the effect of the addition of 2,3-BPG on the oxygen affinity of several human hemoglobins and, after reviewing papers by Max Perutz, made an educated guess regarding sites on deoxyhemoglobin that bind to 2,3-BPG. I communicated these results to Perutz and several months later received an indescribably gratifying handwritten letter telling me that confirmed the proposed binding site. Thus began close friendships with Helen and Max, who, with Jim Jandl, were my most influential and generous scientific mentors.

In the 1970s, my lab worked on non-enzymatic glycation of hemoglobin and other proteins. A minor component Hb Alc was known to be elevated in red cells of diabetics. Following earlier work of Bob Bookchin and Paul Gallop at Einstein, we showed that glucose formed a stable adduct with the N-terminal amino of β-globin by a ketoamine linkage. In order to study the biosynthesis of Hb Alc in vivo, I cloned the β-globin gene and transfected the cell line bound to Fe of high specific activity and then monitored the incorporation of radioactivity into the major and minor hemoglobin components. This rather impetuous foray into human experimentation showed that Hb Alc is formed continuously during the red cell’s life span and that the ketoamine linkage is virtually irreversible. Thus, measurement of Hb Alc could be, and indeed has proven, useful in monitoring therapeutic control of hyperglycemia in diabetic patients independent of fluctuations of blood glucose levels.

In 1980, I used my first and only sabbatical leave to go to the National Institutes of Health and work first with Bill Eaton and then with Art Nienhuis. Bill and I addressed a seemingly simple but clinically relevant question: Why is sickle cell trait (AS) benign, whereas sickle cell (SC) patients have significant morbidity? Contrary to an early report, Bill and I showed that polymerization of mixtures of Hbs S and C was identical to mixtures of Hbs S and A. However, we found that two other factors contributed equally to enhanced sickling in SC patients. First, the level of Hb S in these patients is about 10 percent higher than that in AS individuals because op dimers assemble at about the same rate as op dimers but more slowly than op dimers. In addition, and of equal importance, polymer formation is favored in SC red cells because Hb C induces water loss and thus higher intracellular hemoglobin concentration.

My six months in Art’s lab provided me with sorely needed hands-on tutelage in molecular genetic technology and enabled my lab to switch its focus from hemoglobin to erythropoietin. This transition was greatly facilitated by the creative input of a research fellow Mark Goldberg, who, during college and medical school, had worked with me on sickle hemoglobin. After an exhaustive search, Mark found two human hematopoietic cell lines that produce erythropoietin in response to hypoxia. These cells enabled us and others to identify key elements in the Epo gene that are important in hypoxic induction. Jean-Paul Boissel and I prepared a large number of site-directed mutants of erythropoietin that helped to confirm its three-dimensional structure and also to determine the sites that bind to the erythropoietin receptor.

I have also had the opportunity to oversee some timely and fulfilling clinical research projects including one of the early trials of hydroxyurea therapy for SC patients and the use of subcutaneous deferoxamine for treatment of iron overload in transfusion-dependent patients with myelodysplasia.

During my tenure at Brigham and Women’s Hospital, I have tried to fulfill a meaningful role in patient care, a task made a lot easier and more fun by having the opportunity to work closely with remarkable colleagues. My predecessor as chief of hematology was William Moloney, a master clinician with uncanny wisdom reinforced by boundless energy and wit. My successors, Bob Handin and Nancy Berliner are also superb clinicians who have not only taught me a lot about hematology, but have also been supportive and tolerant of my idiosyncrasies, geriatric and otherwise. I never found it easy to remain viable in competitive areas of research while hanging on to and hopefully enhancing my clinical skills. However, this ongoing challenge has been greatly ameliorated by exposure to two generations of extraordinarily bright and effective fellows, house staff, and students at the Brigham and Harvard Medical School.

I am also indebted to the American Society of Hematology. I was fortunate to have helped in the leadership of this wonderful organization, including a role in enabling ASH to own and publish Blood and a 10-year stint as an associate editor. For a while, I was “impressario” of the musical events that were previously such a haven of civility and repose at our annual meetings. On one blissful occasion, prior to an ASH concert in San Francisco, I had the opportunity to play the piano in a movement of a Schubert trio with Yo Yo Ma and violinist Lynn Chang! The Society fosters a remarkable climate of collegiality and cooperation that has been an enormous boon to hematology in an era when our specialty has faced a variety of challenges that threaten its livelihood.
Thoughts From a Former Protégé

MARK A. GOLDBERG, MD
Senior Vice President of Medical & Regulatory Affairs, Synagene Biopharma Corp.
Clinical Associate Professor of Medicine, Harvard Medical School

Webster’s Dictionary defines a mentor as “a trusted counselor or guide.” I would go a step further. To me a true mentor is someone whom you can rely upon to give you sound, experienced direction that, above all else, is in your own best interest, even if that conflicts with the mentor’s best interest. By this definition, true mentors are a very rare breed. In Frank Bunn, I have been fortunate enough to have been mentored by one of the best of this rare breed for more than 39 years.

I first met Frank in the fall of 1973. I was a college sophomore with a little lab experience that I gained during high school, and Frank was a young assistant professor of medicine at Peter Bent Brigham Hospital and Harvard Medical School. After interviewing with Frank, he offered me a position in his laboratory and I joined him immediately. I learned about the basic biology of hematology and how it leads to many of the clinical manifestations of the disease. We studied the regulation of erythropoietin gene expression by hypoxia and made a number of interesting observations.

After I had started my own lab as an independent investigator, Frank remained very supportive. I still spoke often with him. Once when I was preparing a manuscript for publication, I discussed with Frank having him as a co-author. Frank felt it was important for me to publish independently of him and suggested that he not be a co-author.

Throughout my formative years as a hematologist, Frank always made sure to introduce me to leaders in the field. Shortly after I received my first R01 award, Frank told me that Ernie Beutler wanted to have lunch with me at ASH to discuss recruiting me to Scripps. During lunch, Ernie shared with me that when he told Frank about his desire to recruit me, Frank appeared as if he was giving away his firstborn. Nonetheless, Frank made the introduction because he wanted me to have every opportunity.

For close to four decades I have had the privilege of seeing firsthand the hard work and innovative thinking that allowed Frank to make very significant contributions to our basic understanding of hemoglobin structure and function, as well as the regulation of erythropoiesis, and to translate those findings to clinical applications that have helped patients with diabetes mellitus and sickle cell anemia. I have also seen Frank’s commitment to teaching, as he has assumed a leadership role in teaching hematology to generations of Harvard medical students.

My career has evolved in ways that I had never imagined. While still maintaining my academic appointment at Harvard and the Brigham, I have spent most of the past 15 years working in the biotechnology industry. I still frequently seek out Frank for his advice and opinions. We get together regularly for lunch. I always look forward to these dates. We still talk about science and medicine but much more about our lives and our families. I have been extremely fortunate to have such a caring, thoughtful mentor. I hope that I can pay forward what I have learned from Frank about the meaning and value of true mentorship. I hope I can be like Frank.

I worked in Frank’s lab throughout college and during medical school and then did my postdoctoral research with him. Under Frank’s mentorship, I learned a tremendous amount about science, hematology, and life. During that time he taught me how to rigorously approach scientific problems and how to design and conduct well-controlled experiments. I learned about the importance of working as a team and how it leads to many of the clinical manifestations of the disease. We studied the regulation of erythropoietin gene expression by hypoxia and made a number of interesting observations.

Karl received his medical education at the University of Freiburg, Germany. An early interest in abnormalities of red cell enzymes led him to work with Dr. Ernest Beutler at City of Hope National Medical Center in Duarte, CA, from 1971 to 1972. That mentor-mentee relationship blossomed particularly, and Karl and Ernie became lifelong friends. Upon returning to Freiburg, Karl’s clinical responsibilities included managing patients with acute leukemia. The high mortality rate that inevitably accompanied disease relapse caused Karl to rethink the direction of his career path, and the change in trajectory became fixed after a fortuitous one-day visit to Fred Hutchinson Cancer Research Center in Seattle, WA, in 1974. There, Karl met Dr. Domnall Sloan and became convinced of the concept of marrow ablative chemotherapy followed by bone marrow rescue as a mechanism for curing patients with acute leukemia. In 1975, Karl was recruited to City of Hope by Dr. Beutler to develop a bone marrow transplantation program. At that time, bone marrow transplantation was being performed at only a few institutions, and as a pioneer in the field, Karl interacted frequently with colleagues at the Fred Hutchinson Cancer Research Center and, in the process, developed a number of enduring friendships. When the program at the City of Hope began, times were a bit shaky, and Karl once showed me a letter that he received from hospital administration stating that, because he was doing such a good job, they had decided to continue the transplant program for another six months. The administrators’ judgment proved prescient, and Karl went on to lead the City of Hope program to international prominence. He was particularly proud of the young physician-scientists he mentored there, most notably Steve Forman, who took over the program after Karl was recruited to Stanford and who continues to lead that exemplary group.

Karl was recruited to Stanford in 1987 by Dr. Stanley Schrier and Dr. Ronald Levy. They tell the story that when they went to City of Hope to interview him for the position, Karl immediately took control of the meeting and described his vision of a bone marrow transplant program at Stanford. Karl recruited Nelson Chao and me to his team, and we shared every third night call. Those were heady times, filled with new ideas and difficult challenges. Karl was a charismatic, visionary leader who saw the importance of including all members of the patient care team (nurses, social workers, dieticians, physical therapists) in management planning. This team-based treatment model was new at Stanford at the time, but the concept is now widely emulated. Nelson went on to become the head of transplant at Duke University, and that program has thrived under his leadership. Therefore, Karl contributed to development of the three of the major bone marrow transplant programs in the United States and, in the process, mentored a number of fellows who have made important, independent contributions to hematology.

In 2003, late in his academic career and after stepping down as Division Chief, Karl took on the formidable challenge of developing a National Cancer Institute (NCI)-designated Cancer Center at Stanford. Working with Dr. Beverly Mitchell and with the cooperation of colleagues from throughout the Medical Center and the University, an outstanding group of clinicians and investigators was assembled, and NCI designation was awarded in three years.

Karl was known for his dedication, discipline, compassion, and sense of humor. He was a particular fan of Stanford sports and knew at all times the updated scores of the competition for the Directors’ Cup that is awarded annually to the top intercollegiate athletic program in the nation. Karl was a forceful and effective mentor and took great pride in his mentees’ accomplishments. He was a driving force behind both development of the American Society of Blood and Marrow Transplantation (ASBM) and creation of Biology of Blood and Marrow Transplantation, the official journal of that society, serving as its first co-editor. Karl became the first honorary member of ASBM. He was devoted to the American Society of Hematology, serving as the first chair of the Development Committee and serving on the Executive Committee. He was also a member of the Scientific Committee on Transplantation Biology. Karl received many awards and honors both in the United States and Germany, but his legacy is the impact he had on the thousands of patients that he treated and the hundreds of students and trainees that he mentored.

– Robert Negrin, MD
Professor of Medicine, Chief, Division of Blood and Marrow Transplantation, Stanford University

Karl Blume, MD (1938-2013)

Karl G. Blume, a pillar of the bone marrow transplant community and the American Society of Hematology, died January 9, 2013. Although he had endured a long illness, his death was unexpected.

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– Robert Negrin, MD
Professor of Medicine, Chief, Division of Blood and Marrow Transplantation, Stanford University

Karl G. Blume, MD (1938-2013)
As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster), and visit ASH on Facebook at www.facebook.com/AmericanSocietyofHematology.

On-demand webcasts of all the Education Program sessions and the special lectures are now available for purchase on the ASH website (www.hematology.org/webcasts). Users can purchase access to all webcasts or they can purchase individual sessions of interest. Full access is $195 for members and $375 for non-members. Please see the ASH website for individual session prices. Users can access audio recordings of the presentations while viewing associated color slides.

Sessions available include:
- All Education Program Sessions, including "The Trade Secrets of a Successful Academic" and "Junior-Faculty Development Education Program: Mentorship – How to Be Successful in Your First ‘Real’ Job"
- Education Spotlight Sessions
- Presidential Symposium
- Ham-Wasserman Lecture
- E. Donnall Thomas Lecture
- Ernest Beutler Lecture
- ASH/EHA Joint Symposium
- Trainee Simultaneous Didactic Sessions
- Special Symposium from the Quality of Care Subcommittee – Quality Improvement: A Toolkit for Hematology Practice
- Practice Forum

March

1 Application deadline for Active and International Membership
   Washington, DC
   www.hematology.org/Membership

1 Application deadline for Clinical Research Training Institute*
   Washington, DC
   www.hematology.org/awards

8 Application deadline for the Minority Medical Student Award Program (MMSAP)
   Washington, DC
   www.hematology.org/awards

14 Deadline for ASH-AMFDP online application
   Washington, DC
   www.hematology.org/awards

23-24 Highlights of ASH in Asia
   Shanghai, China
   www.hematology.org/meetings

April

4 ASH Mentor Award nomination packages due
   Washington, DC
   www.hematology.org/awards

6-10 American Association for Cancer Research Annual Meeting
   Washington, DC
   www.aacr.org

12 Deadline to claim CME credits and print a CME certificate for the
   54th ASH Annual Meeting
   Washington, DC
   www.hematology.org

24 Clinical Research Training Institute in Latin America
   Santiago, Chile
   www.hematology.org

24-27 American Society of Pediatric Hematology/Oncology
   Annual Meeting
   Miami, FL
   www.aspho.org

25-26 Highlights of ASH in Latin America
   Santiago, Chile
   www.hematology.org/meetings

May

1 Scholar Awards letter of intent due
   Washington, DC
   www.hematology.org/awards

2 Application deadline for Visitor Training Program
   Washington, DC
   www.hematology.org/awards

15-18 American Society of Gene & Cell Therapy Annual Meeting
   Salt Lake City, UT
   www.asgct.org

*In order to submit an application for the Clinical Research Training Institute, you must have submitted a letter of intent by January 8, 2013.

For additional meeting dates and award deadlines, go to www.hematology.org/Calendar.