Expansion and selection

Amniotic fluid-derived cells (from amniocentesis specimens destined to be discarded)

Multipotential c-Kit+ AFS cells

The investigators further demonstrated that these AFS cells could give rise to a number of different cell types, including a propensity for adipogenic, osteogenic, myogenic, endothelial, neurogenic, and hepatic cell generation. Evidence that the AFS cells truly gave rise to functional cell types of many lineages included differentiation to: (1) nestin-positive neural stem cells maturing into dopaminergic and glutamate-responsive neurons; (2) putative hepatocytes, secreting urea and expressing albumin, α-fetoprotein, hepatocyte nuclear factor, and growth factor; and (3) functional osteoblasts that produce bone-like material when embedded in collagen scaffolds and grafted in immunodeficient mice.

So, in many ways, cloned AFS cells were proven to be broadly multipotent and maybe even approaching the pluripotentiality of embryonic stem cells. But, importantly, none of the four AFS cell lines treated formed teratocarcinomas when implanted in vivo. Teratocarcinomas can be seen deriving from embryonic stem cells but are not seen from normal somatic stem cells. This potentially makes them safer than ES cells, at least from the viewpoint of the FDA, but does it also suggest a limitation and that maybe they do not have as much plasticity as embryonic stem cells? This question can only be answered by further study.

But will these important results and findings regarding AFS cells be misunderstood and misused in the contentious political debate over stem cells? A similar scenario has already arisen over the reprogramming of adult stem cells. Harvard University researchers Kevin Eggan, Chad Cowan, and Douglas A. Melton were quoted in the January 22, 2007, issue of The Washington Post as saying, “We are surprised to see our work on reprogramming adult stem cells used to support arguments that research involving human embryonic stem cells is unnecessary. On the contrary, we assert that human embryonic stem cells hold great promise to find new treatments and cures for diseases…”

### Definitions

**Unipotent**

**Multipotent**

**Pluripotent**

**Committed Progenitor Cell**

**Adult Stem Cell**

**Amniotic Fluid Stem Cell**

**Embryonic Stem Cell**

#### Cartoon

- **Fat**
- **Bone**
- **Muscle**
- **Endothelial**
- **Nerve**
- **Liver**

**Expansion and selection**

**Anntriotic fluid-derived cells**

**Multipotential c-Kit+ AFS cells**

**Related**

- **Estroff SA, Eggan K, Melton DA. A new model for human embryonic stem cells. Science 2007;316:1680-1685.**
- **Eggan K, Melton DA. The case for human embryonic stem cells. Science 2007;316:1686-1687.**

**Peter Emanuel, MD**

Dr. Emanuel indicated no relevant conflicts of interest.
Letters

CORPORATE SUPPORT AND SCIENTIFIC INTEGRITY

To the Editor:

The medical industrial complex’s compromising of academic medicine’s scientific integrity is one of the most serious issues and problems for current day medical care. Any interested observer can pick out numerous clinical protocols whose design and aims were compromised by the need to come up with a result that would help sell a drug or device. To see the effect on societies such as ASH, one could look at the symposium sensationally titled, “Anemia in the Elderly: A Public Health Care Issue.”

Could this emphasis on the issue of mild anemia in the elderly have anything to do with the fact that all the speakers were consultants for companies selling erythropoietin?

There needs to be some way to treat the rampant problem of financial conflict of interest in medical research. Self-regulation can never compete with self-serving. Thus, as bad as it is, outside regulation or changes in the way research is financed or administratively organized (e.g., the industry’s funding of a truly independent foundation to support clinical research vs. direct industry trial support) is necessary to assure that medical care and medical research are not being perverted by the reality of the profit motive coming before medical need and necessity.

Irwin Nash, MD
Department of Pathology
Hospital of St. Raphael
New Haven, CT

RE: CORPORATE SUPPORT AND SCIENTIFIC INTEGRITY

To the Editor:

The issue raised by Dr. Nash is serious. But in his passion to identify and correct the abuses, which are real, he uses what I’ll call a Rovian approach. That is the use of incomplete material to damn with a broad brush.

I was a speaker at the anemia education session, and I did record a consultation for Amgen on my disclosures. Actually, I did a single consultation for a company called Tularik that was testing an agent (for a non-hematologic condition) which produced an interesting form of anemia in animal models. Amgen bought Tularik, so I listed both. So much for my role as a consultant for erythropoietic materials and companies.

However, I was ASH president in 2004, and during our regularly scheduled meetings with the NIH we learned from members of the National Institute on Aging (NIA) about the forthcoming NHANES 3 study that showed an unanticipated and severe impact of anemia in the elderly. Struck by the seriousness of the clinical condition and the lack of hard data, we officers worked with ASH members and staff to run an ASH/NIA-sponsored agenda-setting meeting on anemia of the aged. Financial support for this conference from the relevant companies was neither requested nor accepted; furthermore, the companies were explicitly excluded from attending the conference.

That conference was successful in identifying an agenda, based on which the NIA established an RFA. More than 20 proposals were submitted, and several were identified for funding, pending the passing of a Congressional budget. Certainly, we all hope that the outcome will be good for basic and clinical research, which in turn will lead to better care for our patients. That is, of course, what ASH is all about. Consistent with that goal, the ASH Committee on Practice sponsored the education session on anemia of the elderly. Carefully collected feedback indicated that ASH members felt that the education session made an impact on their knowledge and practice.

Stanley L. Schrier, MD
2004 ASH President
Stanford University School of Medicine

RE: CORPORATE SUPPORT AND SCIENTIFIC INTEGRITY

To the Editor:

I read with disappointment the letter to The Hematologist by our colleague Dr. Nash concerning the topic of corporate support and scientific integrity. In it, he appropriately calls attention to the issue of the potential for compromise of clinical research in pursuit of corporate profit. Unfortunately, he chooses to use the 2005 ASH Committee on Practice educational symposium on anemia of the elderly as the poster child for such abuse. Specifically Dr. Nash writes (and I quote exactly): “To see the effect [of corporate influence] on societies such as ASH, one could look at the symposium sensationally entitled ‘Anemia in the Elderly: A Public Health Care Crisis’ in Hematology.”

Could this emphasis on the issue of mild anemia have anything to do with the fact that all of the speakers were consultants for companies selling erythropoietin?

As chairman of this session, and on behalf of the speakers and the Committee of Practice, the “facts” surrounding this session are as follows and not as Dr. Nash suggests:

1) This topic was chosen in support of a joint ASH/NIA consensus panel on anemia in the elderly that resulted in a joint research agenda/funding plan. Corporate participation was specifically avoided and there was no consultation with private companies concerning choice of topic.

2) Once the topic became known, we offered a) unrestricted educational funds, b) data availability, and c) logistical support from commercial concerns. All were turned down.

3) I am not a consultant for a company that sells erythropoietin, nor have I ever been one.

4) Although the title was deliberately worded to be provocative, this was done to call attention to a significant, but poorly recognized health care issue that affects millions of Americans, increases mortality, and contributes in a major way to cardiovascular, renal, neuropsychiatric, and orthopedic morbidity. Given the gentrification of American society represented by the elderly represents a major health concern.

In short, corporate interests had no role whatsoever in the construct of this symposium. To imply differently does a disservice to the participants, the Committee on Practice, and the ASH membership.

Vincent J. Piccirillo, MD, MMM
Chairman, ASH Subcommittee on Quality
Chairman, ASH Anemia in the Elderly Symposium
Virginia Mason Clinic
Highlights of ASH™ DVDs

Did you miss the Highlights of ASH meeting in February? If you would like to see the presentations from the meeting and review the workbook, you can now purchase the Highlights of ASH DVD online at www.hematology.org. The DVD includes all nine sessions and four panel discussions, as well as the program and workbook (which contains the session slides with space available for note taking).

Editor Search Announcement

The American Society of Hematology is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist (term: 2009-2011). Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic ASH Mentor Award. Clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills.

Members of ASH are invited to submit the names of potential candidates, accompanied by a brief, informal endorsement and a brief description of the candidate's editorial experience, to:

The Hematologist: ASH News and Reports
C/o Molly Polen, Managing Editor
The American Society of Hematology
1900 M Street, NW, Suite 200
Washington, DC 20036
mpolen@hematology.org

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NO MINATE A MENTOR FOR THE 2007 ASH™ MENTOR AWARD BY MAY 4

Mentorship, although known as one of the most important determinants of a successful career, often goes unrecognized. Dr. Margaret Ragni illuminated the importance of mentors and the need to honor them in her 2006 ASH Mentor Award. This award is based on the mentor's personal career achievements. In 2006, the first ASH Mentor Awards were given to Samuel E. Lux IV, MD, for clinical investigation and to Deane F. Mosher, MD, for basic science.

May 4 is the deadline to nominate a mentor for this prestigious award. For more information about the award, eligibility, and selection process, or to download a nominations form, visit www.hematology.org/education/awards/mentor-ship.cfm.
NEWS HEADLINES FROM WASHINGTON

Fiscal Year 2007 Budget Process Continues as Fiscal Year 2008 Process Begins

Members of Congress returned to Washington in January to mark the beginning of the 110th Congress and to complete the FY 2007 budget process that remained unfinished upon the 109th Congress’ adjournment

As this issue of The Hematologist went to press, congressional leaders had announced plans to pass a year-long continuing resolution (CR) to fund federal programs at FY 2006 levels through the remainder of the 2007 fiscal year. Though efforts by ASH and others continued to urge Congress to add additional funding to the FY 2007 budget in discretionary funding for health, education, and labor programs, ultimate FY 2007 funding levels are still expected to produce shortfalls for biomedical research

ASH will continue its NIH advocacy efforts on Capitol Hill in the FY 2008 budget debate. The projected shortfall for FY 2007 will make the FY 2008 budget process crucial to ensuring that groundbreaking hematologic research is continued at NIH. For more information about NIH funding and ASH’s advocacy, please see the Take Action box on this page or visit the ASH Web site at www.hematology.org/takeaction.

Stem Cell Legislation Debate Continues

As one of its first acts in January, the U.S. House of Representatives approved the Stem Cell Research Enhancement Act (H.R. 3) by a substantial margin (253-174). This legislation is identical to legislation passed by the House and Senate last year. As this issue of The Hematologist went to press, the Senate was also expected to pass the bill, and, like last year, President Bush is expected to veto it. The final outcome of this year’s battle over the science and ethics of embryonic stem cell research, however, is not as predictable as it may seem. Because the new majority in Congress supports stem cell research, they will be able to work Congress’ complex rules in their favor.

Announcement from Centers for Disease Control and Prevention

The National Center on Birth Defects and Developmental Disabilities has announced that the Division of Hereditary Blood Disorders now has an official new name: the Division of Blood Disorders (DBD). The new name better represents its work in this arena. DBD collaborates extensively with health-care providers, academic centers, community-based organizations, and national and international preventive health agencies to implement specialized prevention programs for persons with blood disorders and their families. DBD has programs in the areas of hemophilia, thrombophilia, thalassemia, and other related disorders. For more information about DBD’s work in the area of blood disorders, visit its Web site at www.cdc.gov/nccdphp/dbcdd.

NIDDK Sponsors Workshop on MicroRNA in Cellular Development and Hematopoiesis

A two-day workshop on MicroRNA in Cellular Development and Hematopoiesis, sponsored by the Hematology and Endocrine Biology Programs of NIDDK at the National Institutes of Health, will be held at The Historic Inns of Annapolis in Annapolis, MD, on April 23 and 24. This workshop will review current information on the biogenesis and function of miRNAs and on how microRNA-mediated post-translational regulation influences organ and tissue development and function, with a particular focus on hematopoiesis. The program will include plenary talks by a panel of invited speakers, selected talks from submitted abstracts, and a poster session. The setting and format of the workshop should favor interactions and discussion among workshop participants. Travel grants will be made available to registrants whose abstracts are selected for oral presentation at the workshop. Information about registration and abstract submission is available at www.niddk.nih.gov/fund/other/micror-nna2007.
THE PATIENT

A 72-year-old man is referred for iron deficiency anemia not responding to iron therapy. His past history is notable for longstanding rheumatoid arthritis. Physical examination is consistent with rheumatoid arthritis. Repeated stool tests are heme negative. Laboratory studies show a hemocrit of 29 percent with normocytic indices, normal white blood cell and platelet counts, a low serum iron concentration, and an elevated serum ferritin concentration.

SHOULD THE TERM “ANEMIA OF CHRONIC DISEASE” STILL BE USED?

The term “anemia of chronic disease” (ACD) refers to an underproduction anemia characterized by a low serum iron concentration despite adequate reticuloendothelial iron stores (generally shown by a normal or increased serum ferritin concentration). This term is frequently criticized because it does not indicate the mechanism producing anemia, and because anemias associated with some disorders that are chronic (i.e., hypothyroidism) do not result from ACD. The advantage of the term is its long usage — most hematologists and internists understand what ACD means. The most frequently suggested alternative, “anemia of inflammation,” has the advantage of indicating the pathophysiologic mechanism underlying the syndrome, but its meaning in clinical terms is less established. One group has defined it as anemia with an elevated serum ferritin concentration in the appropriate clinical setting. It is clear that both ACD and “anemia of inflammation” refer to the same clinical and pathophysiologic entity.

WHAT ARE THE PATHOPHYSIOLOGIC PROCESSES LEADING TO ACD?

In ACD, a modest decrease in RBC survival creates a demand for increased red cell production which cannot be met (because of impaired mobilization and utilization of reticuloendothelial iron) and an impaired erythropoietic response. The impaired erythropoietic response has two components — a blunted erythropoietin increment in response to anemia and a relative resistance of erythroid progenitors to erythropoietin. All of these processes are induced by the cytokines that mediate the inflammatory response — cytokine activation is the feature linking the syndromes associated with ACD.

Shortened RBC survival in ACD may result from selective hemolysis of young RBC induced by erythropoietin deficiency (neocytolysis). The iron abnormalities of ACD are due to the cytokine-induced peptide hepcidin. Hepcidin binding causes degradation of the iron export protein ferroportin; iron is then retained in reticuloendothelial cells where it is unavailable for erythropoiesis.

WHAT ARE THE DIAGNOSTIC DIFFICULTIES IN ACD?

Hypoferrremia may cause ACD to be confused with iron deficiency anemia. This is more likely in that minority of ACD patients with mild microcytosis. Demonstration of reticuloendothelial iron stores rules out iron deficiency. Ferritin is an acute-phase reactant and can be elevated to variable degrees by concurrent inflammation. However, even with significant inflammation, a serum ferritin concentration greater than 100 µg/L is unlikely in iron-deficient individuals, and a serum ferritin concentration greater than 200 µg/L essentially rules out iron deficiency. Other tests, such as the serum soluble transferrin receptor concentration or the reticulocyte hemoglobin concentration, may help resolve difficult cases.

Although the serum erythropoietin concentration in ACD patients tends to be lower than would be predicted from the degree of anemia, its measurement is rarely helpful in diagnosing ACD in individual patients.

HOW IS ACD TREATED?

Depending on the patient’s specific clinical circumstances and the degree of anemia, therapy of ACD may not be necessary. The standard approach is to treat the associated clinical syndrome — as disease activity decreases, the hematocrit generally improves. If more active correction of anemia is required, an extensive literature indicates the effectiveness of recombinant erythropoietin in ACD. The use of routine iron supplementation with erythropoietin therapy of ACD is debated, but a number of reports suggest it enhances the response to erythropoietin. Iron therapy by itself does not correct ACD; if a patient with ACD develops superimposed iron deficiency, iron replacement can correct that component of the anemia.

FURTHER READING


Access to ASH™-SAP Second Edition Online to End May 1

In order to comply with ACCME guidelines, online access to the ASH-SAP second edition will expire on May 1, 2007, although users will still be able to claim CME credit with the paper test sheet through December 31, 2007. Similarly, points earned toward American Board of Internal Medicine Maintenance of Certification using the second edition of the ASH-SAP must be claimed by May 1.

Contact the ASH Education & Training Department at 202-776-0544 or cme@hematology.org with any questions or concerns about the ASH-SAP, online access, or claiming credits.
Receptors, Not Clots: Coagulation and Fibrinolytic Enzymes Modulate Stroke Outcome by Targeting Endothelial Cells, Not Cerebral Thrombi


Using an in vitro brain endothelial cell model of ischemia in which cells were subject to an environment of oxygen and glucose deprivation, these investigators showed that tissue plasminogen activator (tPA) induces increased expression and activity of MMP9, a matrix metalloproteinase that targets critical components of the blood-brain barrier. They also studied two rodent models of stroke, one induced by transient occlusion of the middle cerebral artery in mice and one by inducing cerebral thromboembolism in rats, and showed that tPA delivered systemically led to increased MMP9 expression and activity in the infarct zone along with significantly increased cerebral hemorrhage. In both the in vitro and in vivo models, MMP9 expression, infarct volume, and cerebral hemorrhage were dramatically and significantly inhibited by giving the animals or cells activated protein C (APC) along with or a few hours after the tPA. With inhibitory antibodies, short hairpin inhibitory microRNAs, and cells from genetically engineered mice they showed that the damaging effects of tPA required expression of the endothelial cell receptor PAR1 and that the protective effects of APC required expression of the endothelial cell receptors EPCR and PAR1.

Very little effective therapy is available to mitigate brain damage and tissue loss once a patient begins to experience symptoms of a stroke. Recombinant human tPA is of benefit, but only if given within a very narrow time window. Furthermore, enthusiasm for its use is tempered by increased risks of cerebral hemorrhage with catastrophic sequelae. These authors have used cell culture and rodent models to define a brain microvascular endothelial signaling pathway activated by tPA that is responsible for some of its untoward effects. They then showed that these effects could be prevented by concomitant delivery of APC. The major “problem” with tPA is apparently not related to clot dissolution or clot instability, but rather to its ability to bind and activate an endothelial cell receptor known as LRP1. This receptor then triggers a cascade of events involving activation of the pro-inflammatory transcription factor NFκb, increased expression and activity of matrix metalloproteinase-9 (MMP9), and then MMP9-dependently disrupted the blood-brain barrier with subsequent hemorrhage. APC prevents hemorrhage in this setting by blocking NFκb activation and MMP9 up-regulation. This effect is apparently not due to its ability to slow thrombin generation by proteolytic cleavage of Factor V and VIII, but rather to activation of an alternative signaling pathway mediated by its two endothelial cell surface receptors, PAR1 and EPCR. This is consistent with recent studies from other groups describing the mechanistic basis of sepsis protection by APC and helps define a “new” paradigm by which coagulation and fibrinolytic enzymes mediate systemic and localized effects in the vasculature by acting as paracrine ligands for endothelial receptors, not by “busting” clots or blocking thrombin generation. From these studies emerge several exciting potential avenues for drug development, including simply adding APC (drotrecogin alfa [Xigris®]) to tPA infusion during acute stroke. More appealing would be designing drugs that specifically target LRP1 and/or the PAR1/EPCR system without influencing the coagulation and fibrinolytic pathways.

Allogeneic Stem Cell Transplant Donors: Sibling or Stranger?


Allogeneic stem cell transplantation (SCT) provides a curative option for many patients with relapsed hematologic malignancies and for others with high risk of recurrence after initial therapy. Traditionally HLA-matched sibling donors were preferred as the source of stem cells, but the availability of such a donor in only about one-third of patients has led to the use of matched unrelated donors. This French multicenter study assessed the outcomes for patients with standard-risk hematologic malignancies undergoing allogeneic SCT from related versus unrelated donors, utilizing a uniform prophylaxis regimen of total body irradiation plus high-dose cyclophosphamide and uniform graft-versus-host disease (GVHD) prophylaxis with cyclosporin-A and short-course methotrexate for all patients. The study population included patients with acute leukemia in first or second complete remission, CML, and myelodysplastic syndrome. Bone marrow rather than peripheral blood was used as the source of stem cells for all patients. One hundred and eighty-one patients had a HLA-matched sibling donor, while 55 had an HLA-matched unrelated donor identical at 10/10 allelic loci. Patient characteristics in the two groups were largely comparable, and all but seven patients engrafted. With a median post-transplantation follow-up of 34.6 months, there was no significant difference in time to engraftment, acute GVHD, event-free survival, or overall survival (Figure). A retrospective review of patients in this trial showed increased occurrence of chronic GVHD in unrelated versus sibling transplants. Mortality was increased in CMV seropositive recipients, in those who developed >/= grade II acute GVHD, and in those with stem cell donors > 37 years of age.

This study supports the conclusion that curative outcomes for 10/10 HLA-matched unrelated donors are comparable to matched sibling donors for patients transplanted for standard-risk hematologic malignancies. Additional studies will be needed to determine the impact of alternative conditioning regimens, peripheral blood rather than marrow stem cells, related- versus unrelated-donor nonmyeloablative allogeneic SCT, alternative GVHD-preventive regimens, and the impact of these on and for higher-risk hematologic malignancies.

ROY SILVERSTEIN, MD
Dr. Silverstein indicated no relevant conflicts of interest.

Michael Williams, MD
Dr. Williams indicated no relevant conflicts of interest.

The Hematologist: ASH News and Reports
Thrombo-Mimetics

Shown are three classes of pharmaceuticals that share little homology to thrombopoietin (TPO), yet still activate the TPO-receptor (TPO-R).

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**Are TPO-Mimetics Better Than the Real Thing?**


**Promise and Obstacles to Gene Expression Profiling in Multicenter Trials**


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**This** is a phase 1/II trial that tests the hypothesis that inducing increased platelet production would be beneficial in ITP. AMG 531 is a recombinant form of the thrombopoietin (TPO) receptor; but bears no structural similarity to TPO. Therefore, it is a TPO-mimetic and, in theory, should increase platelet production in man. In the first phase, 24 patients were exposed to two injections of escalating doses of AMG 531. Doses greater than 3 micrograms/kg induced an increase to some extent in platelet counts in all subjects. All doses up to 10 micrograms/kg were well tolerated. In phase II, 16 long-term ITP patients were enrolled in a double-blind, placebo-controlled trial of AMG 531. Patients were treated with weekly subcutaneous injections of 1 or 3 micrograms/kg of the study drug. AMG 531 increased the platelet count to greater than 50,000/µl in twelve patients (a 75 percent response rate). Notably, two patients who received 3 micrograms/kg of AMG 531 had platelet counts that increased above 500,000/µl. Interestingly, there appeared to be no relationship between baseline platelet counts and response. This implies that TPO-mimetics are able to overdrive platelet production even in patients with appropriate (i.e., normal) TPO levels. Reassuringly, the overall toxicity was low.

Although the majority of ITP patients have a compensatory increase in megakaryopoiesis, plasma from some ITP patients can inhibit platelet production. These data suggest that, in addition to increased platelet destruction, impaired megakaryopoiesis is another reason for the thrombocytopenia in this disease. The fact that TPO levels in the plasma of ITP patients are not as high as TPO levels in patients with other types of thrombocytopenia suggests that there might be room to overdrive platelet production in ITP patients by administration of exogenous TPO. Several years ago, a small trial demonstrated that platelet counts could indeed be significantly increased in some ITP patients exposed to a truncated form of recombinant thrombopoietin (PEG-MGDF). Unfortunately, PEG-MGDF-induced auto-antibodies against endogenous thrombopoietin, which ultimately necessitated the discontinuation of further product development.

Several investigators proposed the hypothesis that molecules that bear no structural resemblance to TPO, but still bind and activate the TPO receptor (so called TPO mimetics), might be useful for the treatment of ITP without the risk of inducing anti-TPO antibodies. Since that time, a few groups have been able to identify peptides that bind the TPO receptor with high affinity. AMG 531 is the most developed pharmacological TPO mimetic in the TPO mimetic category. It is composed of several copies of a TPO receptor-binding peptide spliced into a recombinant antibody. This peptide mimetic competes with thrombopoietin for binding to the TPO receptor and activates the receptor in an identical fashion to endogenous thrombopoietin. As shown in this paper, AMG 531 produces a dose-dependent increase in platelet counts in ITP patients.

A similar approach has been used to identify other small molecules that bear little structural similarity to TPO, yet are still capable of binding and activating the TPO receptor. Screening small-molecule libraries for compounds that have TPO-like activity identified these so-called TPO nonpeptide mimetics. The most developmentally advanced of this category is Ebtrombopag. Like subcutaneously administered AMG 531, oral Ebtrombopag also produces a dose-dependent increase in the platelet counts of both healthy volunteers and patients with ITP. Although less far along in clinical development, orally administered AKR-501 also functions by a similar mechanism. A final class of drugs that stimulate the TPO receptor are agonist antibodies, although these are not far along in clinical development.

Although the data on TPO mimetics are currently tantalizing, the long-term effects of these compounds remain to be established. A concern is the development of reticulin bone marrow fibrosis in one patient who took AMG 531 for an extended period of time. Thus far, this specific toxicity has been reversible after discontinuation of the medication. Also notable is that TPO can increase the sensitivity of platelets to standard platelet agonists in vitro. Therefore, whether these agents will lead to thrombotic complications over time remains to be seen. But for now, the news is good. Trials of TPO-mimetics appear to be heralding a new era of non-immunosuppressive therapy for ITP.

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Does It or Doesn’t It? Can Imatinib Eradicate the Stem Cell Clone?


A central question that arose from the successful use of the BCR-ABL targeted agent imatinib in CML is whether the leukemic stem cell can be eradicated. Rapid relapse that is observed upon cessation of the drug suggested that the leukemic stem cell was at most only mildly affected by drug therapy. In this paper, the investigators present a model based upon the effects of imatinib on BCR-ABL transcripts in patients treated with the drug. This model hypothesizes that imatinib has an effect on the proliferating BCR-ABL positive cells by inducing degradation and then has a declining percentage of transcript positive cells by reducing stem cell numbers. The model predicts that many of the stem cells are in a dormant state, possibly because of their interaction with the microenvironment, and are then not susceptible to the drug. Their prediction is that relapse is associated with rapid release and growth of the leukemic stem cell from this population. Their model allows for a prediction that moving cells into a more frequent cycling state may make them more responsive to imatinib and that by reducing the stem cell pool, the rapid relapse that is observed on removing the drug may be abrogated. Resistance forms part of their model as well — it fits with introduction of resistant clones early as well as late emergence of imatinib-resistant clones. The investigators propose that the leukemic stem cell can eventually be eradiated by continuous long-term treatment with imatinib unless mutations that result in drug resistance occur. The investigators propose that stem cells may be eradicated by moving stem cells into a proliferative compartment. Resistance remains the main foe, and it may appear early so that some stem cells cannot be eradicated.

Directing future targets in a disease such as CML remains important because of continual need for the drug and relapse in its absence. The model generated from the two patient populations examined in this manuscript present a contrast to the hypothesis on the behavior of the BCR-ABL positive CML in the manuscript by Michor et al. Both manuscripts put forth models for behavior of hematopoietic stem cells based upon in vivo data and observations that focus on the biphasic decline in BCR transcripts on the initiation of imatinib therapy. Where the two manuscripts differ is on the question of whether the hematopoietic stem cell can be a target for imatinib. In the manuscript by Michor, the rapid relapse rate is attributed to the stem cell not being sensitive to chemotherapy. In the model presented in this paper, the investigators propose that it is not chemotherapy insensitivity but rather location of the stem cell in an environment or stage that is quiescent so that it is only slowly responsive to therapy. This distinction is important because moving toward therapy that targets the stem cell is different in these two models. The model here would favor inducing proliferation or movement from one niche to another to more rapidly affect the stem cell, whereas the manuscript by Michor and colleagues suggests that a different approach may be required to target the stem cell. The proof may be in the introduction of an additional therapy, and it remains to be seen whether this should be early, or later after initiation of imatinib.


LILLI PETRUZZELLI, MD, PHD
Dr. Petruzzelli indicated no relevant conflicts of interest.

The Hematologist: ASH News and Reports

Prion Transmission by Blood Transfusion: The Report of a Third Infected Recipient, and the Second to Die With Variant Creutzfeldt-Jakob Disease, Intensifies the Focus on Preventative and Therapeutic Strategies


Prion proteins (PrPc) vs Misfolded prion proteins (PrPSc)

The first studies linking a variant form of Creutzfeldt-Jakob disease (vCJD) to transmission of bovine spongiform encephalopathy (BSE) were published a decade ago. At that time, measures were taken to prevent exposure to contaminated cattle-derived food products, and programs were implemented to both minimize the theoretical risk of prion transmission by transfusion and to monitor recipients of blood products from donors who were subsequently diagnosed with vCJD. This paper describes a third case of autopsy-confirmed prion infection, and the second case of clinical vCJD, identified within a cohort of 66 at-risk transfusion recipients followed by the U.K. Transfusion Medicine Epidemiological Review (TMER) study. The patient was a 31-year-old man with ulcerative colitis who developed neurological symptoms six years after receiving non-leukodepleted red cells from an individual who was diagnosed with vCJD at 20 months after donation. The patient suffered progressive cognitive impairment, leg dysesthesias, ataxia, and dysarthria. An MRI scan eventually revealed changes in the posterior medial thalamus typical of the pulvinar sign associated with vCJD. The patient died in hospice after a 32-month course, having failed a therapeutic trial of PRNP, the gene encoding the prion precursor protein (PrPc), ruled out mutations associated with inherited prion disease. He was homozygous for methionine [M/M] at codon 129 and a polymorphism found in all vCJD cases and implicated in disease predisposition and pathogenesis. Post-mortem analyses confirmed the presence of misfolded prion protein (PrPSc) in tissue homogenates of tonsil and brain. Abnormal PrP was identified in immunohistochemical sections of the tonsil and within areas of glia and plaques in brain cortical sections.

This case, along with the post-mortem detection of infection in two other recipients from the TMER cohort (one of whom died with neurodegenerative symptoms consistent with vCJD), strongly reinforces the concern that pathogenic prion proteins may be transmitted through blood transfusions. The donors in these cases developed their clinical symptoms of vCJD at 18, 26, and 40 months following donation. The two recipients with vCJD were homozygous for M/M at codon 129 (the asymptomatic, infected recipient was heterozygous for methionine and valine), and they developed symptoms at six and 6.5 years after transfusion. Notably, of the 32 individuals in the original TMER cohort who survived beyond five years after transfusion, two developed clinical vCJD. Thus, pre-clinical infection appears to be sufficient for blood transmission; the “incubation period” for transfusion-associated prion disease is likely shorter than that for foodborne vCJD (which is estimated to be decades); infectivity rates may be high, at least under certain donor and/or recipient conditions; and recipient genotype at codon 129 may be an important disease-modulating factor. Given the lack of a blood assay for infection, uncertainty about prion tropism and host susceptibility, and incomplete knowledge of disease pathogenesis, a number of preventative measures have been in effect, and additional interventions are in various stages of development. These include (see Figure): (A) elimination of potentially contaminated cattle feed; (B) removal of older and diseased animals from the food chain; (C) generation of cloned cattle that lack the normal PrP protein, which is required to propagate misfolded PrPSc prions; (D) treatment of infected individuals with agents that reduce PrPSc production, such as lenti viral vector-mediated transfer of small interfering RNAs; (E) screening and deferral policies to prevent horizontal transmission from potentially infected blood donors; and (F) removal of infectious prions from blood-derived products by leukodepletion, filtration, resin adsorption, and/or physical purification. Although prion diseases are a growing concern worldwide, the urgency for progress is greatest for the U.K. and France, which account for 85 percent and 10 percent, respectively, of all the vCJD cases reported to date. The blood donor populations in those countries are estimated to include the highest numbers of individuals with asymptomatic, undetected prion infections.

As The Hematologist was going to press, a fourth case of transfusion-associated prion infection, and a third case of probable vCJD, was reported among a surviving member of the TMER recipient cohort [see www.hpa.org.uk/infec tions/topics/cjd/vCJDBloodDonors.htm#mfn].


MICHAEL LINENBERGER, MD
Dr. Linenberger indicated no relevant conflicts of interest.
The alternative pathway of complement (APC) is in a state of continuous, low-grade activation, and host erythrocytes are normally protected against complement-mediated injury by two glycosyl phosphatidylinositol (GPI)-anchored membrane proteins [Figure]. Decay accelerating factor (DAF, CD55) inhibits the formation and stability of the APC C3 and C5 amplification convertases and membrane inhibitor of reactive lysis (MIRL, CD59) blocks the assembly of the cytolytic membrane attack complex (MAC) [Figure]. Coombs-negative, complement-mediated intravascular hemolysis, the clinical hallmark of paroxysmal nocturnal hemoglobinuria (PNH), is a consequence of deficiency of CD55 and CD59. A logical strategy for controlling the hemolysis of PNH is to compensate for deficiency of CD55 and CD59 by blocking the APC pharmacologically.

In this paper by Hillmen and colleagues, this approach was employed in a phase III, randomized, placebo-controlled trial in which a humanized monoclonal antibody (eculizumab) that binds the fifth component of complement (C5) was used to inhibit formation of the MAC [Figure]. Treatment with eculizumab (43 patients vs. 44 in the control group) resulted in a dramatic, sustained decrease in the concentration of plasma LDH (a sensitive surrogate marker for intravascular hemolysis). A marked reduction in red cell transfusion requirement was also observed in the eculizumab-treated group. Patients in the treatment group, however, remained anemic, and an earlier phase II study showed essentially no change in reticulocyte count in patients treated with eculizumab. The persistent anemia may be the result of extravascular hemolysis of C3-coated erythrocytes, as the anti-C5 antibody eculizumab does not inhibit formation of the amplification C3 convertase [Figure]. Quality-of-life measurements suggested that inhibition of complement-mediated intravascular hemolysis ameliorates the fatigue associated with PNH, but the effects of eculizumab therapy on such PNH-associated symptoms as dysphagia/odynophagia and abdominal pain were not specifically addressed in the study. Neither was the study designed to determine the effects of eculizumab on thromboembolic complications of PNH; however, only one thrombotic event [affecting a patient in the placebo group] was reported. Four serious adverse events [none infectious and none considered treatment-related] were reported among patients in the eculizumab group.

Although not yet FDA-approved, eculizumab appears to be an effective, safe treatment for controlling the complement-mediated intravascular hemolysis of PNH. Patients most likely to benefit are those with classical PNH. These patients have large PNH clones, and their symptoms are primarily a consequence of uncontrolled hemolysis. With infusional therapy treatments developed for other orphan diseases, the cost will certainly be high, and treatment must continue indefinitely as eculizumab has no apparent long-term effect on the underlying PIGA-mutant clonal hematopoiesis or on the marrow failure component of the disease. Whether eculizumab therapy will have an impact on thrombosis, the major cause of mortality in PNH, is uncertain.

Complement-mediated lysis of PNH erythrocytes.

Upper panel: Normal erythrocytes (left) are protected against complement-mediated lysis primarily by CD55 and CD59 (triangles). Deficiency of these GPI-anchored complement regulatory proteins results in complement activation on PNH erythrocytes (right). Consequently, the MAC forms a pore in the red cell membrane resulting in colloid osmotic lysis and release of hemoglobin into the intravascular space.

Treatment with eculizumab allows us a glimpse of PNH without its trademark intravascular hemolysis. What we see so far is a relatively benign clonal myeloid disorder, distinct from myeloproliferative and myelodysplastic processes. Continued investigation is needed to understand the basis of the clonal selection and clonal expansion of PNH so that strategies can be developed to treat the disease, not just the symptoms.


CHARLES PARKER, MD, AND JOSEF PRCHAL, MD

Drs. Parker and Prchal indicated no relevant conflicts of interest.

A Backhand to Complement

The ASH™ Scholar Awards are designed to support hematologists who have chosen a career in research by providing partial salary or other support during that critical period required for completion of training and achievement of status as an independent investigator. Each year ASH grants roughly 15 of these awards. The following individuals submitted outstanding applications and the Society congratulates these winners on their success.

### 2007 SCHOLAR AWARD WINNERS

<table>
<thead>
<tr>
<th>Basic Research Fellow</th>
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<tr>
<td>Larry D. Bozulic, PhD</td>
<td>Jaiila Chagauri, PhD</td>
<td>Francesca Ficara, PhD</td>
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<td>University of Louisville</td>
<td>University of Montreal</td>
<td>Stanford University</td>
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<tr>
<td>Neoadjuvant Conditioning to Establish Induction of Islet Transplants</td>
<td>Regulation of HSC Self-Renewal by Bmi1 and Associated Proteins</td>
<td>Role of the PBEF1 Proto-Oncogene in the Regulation of Adult Hematopoiesis</td>
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<th>Basic Research Fellow</th>
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<tr>
<td>Maria E. Figueroa, MD</td>
<td>Paul J. Galardy, MD</td>
<td>Hanno Hock, MD, PhD</td>
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<td>Albert Einstein College of Medicine of Yeshiva University</td>
<td>Mayo Clinic Minneapolis, MN</td>
<td>Massachusetts General Hospital</td>
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<td>An Integrative Genetic and Epigenetic Characterization of Normal Karyotype Acute Myeloid Leukemia (AML)</td>
<td>De-ubiquitination and the IL-2 Response: An In Vivo Approach</td>
<td>Zinc Finger Transcriptional Repressor Gfi-1 in Stem Cells of Normal Hematopoiesis and Leukemia</td>
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<th>Clinical/Translational Research Junior Faculty</th>
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<td>Hanna Mikkola, MD, PhD</td>
<td>David Miklos, MD, PhD</td>
<td>Sattva Neelapu, MD</td>
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<td>University of California, Los Angeles</td>
<td>Stanford University</td>
<td>University of Texas, M.D. Anderson Cancer Center</td>
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<td>Mouse Models For Defining Hematopoietic Stem Cell Development in the Placenta</td>
<td>Allogeneic B-Cell Responses and Chronic GVHD After Hematopoietic Cell Transplantation</td>
<td>Identification of Novel Tumor-Associated Antigens in Follicular Lymphoma</td>
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<td>Emmanuelle A. Passegue, PhD</td>
<td>Tobias Ragoczy, PhD</td>
<td>John B. Walker, PhD</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Fred Hutchinson Cancer Research Center</td>
<td>University of Alberta</td>
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<td>Role of JunD in Leukemic Stem Cell Transformation: Implications for Myeloid Leukemia and Targeted Therapy</td>
<td>Peripheral Localization and Regulation of the Marine B-Globin Locus Therapy</td>
<td>Identifying the Component in Plasma that Inhibits the Intrinsic Antifibrinolytic Activity of Carboxypeptidase N</td>
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<td>Dan Vogl, MD</td>
<td>John B. Walker, PhD</td>
<td>Junping Wei, MD, PhD</td>
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<tr>
<td>University of Pennsylvania School of Medicine</td>
<td>University of Alberta</td>
<td>Cincinnati Children’s Hospital Medical Center</td>
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<td>Individualization of High-Dose Melphalan for Myeloma: Effect of Obesity and Renal Function on Melphalan Pharmacokinetics Therapy</td>
<td>Identifying the Component in Plasma that Inhibits the Intrinsic Antifibrinolytic Activity of Carboxypeptidase N</td>
<td>A Novel Model of MLL-AF9 Leukemia Using Primary Human HSPC in NOG/scid Mice</td>
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<td>Ethan J. Weiss, MD</td>
<td>Robert Zeiser, MD</td>
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<td>University of California, San Francisco</td>
<td>Stanford University</td>
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<tr>
<td>Sex Differences in Hemostasis and Thrombosis in Mice: The Role of the Growth Hormone Signaling Pathway</td>
<td>Visualizing Regulatory T-Cell Function and Trafficking Patterns after Murine Allogeneic Bone Marrow Transplantation Via In Vivo Bioluminescence Imaging</td>
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### 2008 SCHOLAR AWARD DEADLINE

The application process for the 2008 Scholar Awards has begun. The letter-of-intent deadline is May 3, and the application deadline is August 30. Applications are only available to those who successfully submit a letter of intent and are confirmed to be eligible. If interested in applying, visit the ASH Web site at www.hematology.org/education/awards/scholar.cfm for complete details, including eligibility requirements.
Drs. Marta Crespo and Giovanni Roti Are Inaugural Recipients of the EHA-ASH™ International Fellowship Award

EVA HELSTROM-LINDBERG, MD, PHD

Dr. Hellstrom-Lindberg is the President of EHA.

Today the field of hematology is more international than ever before, and both ASH and the European Society of Hematology (EHA) recognize the importance of building stronger ties between the North American and European scientific communities. It is in this spirit of collaboration that ASH and EHA recently created the EHA-ASH International Fellowship Award Program. This program provides hematologists in training or early in their careers the opportunity to conduct research in another country. The intent of the program is to give both clinical and laboratory-based researchers an opportunity to establish new collaborations and experience research in a different environment.

At this time, we are delighted to announce the EHA-ASH International Fellowship Award inaugural recipients: Marta Crespo, PhD, and Giovanni Roti, MD.

A Barcelona native, Dr. Marta Crespo earned her bachelor’s degree in biology and her doctorate in biopathology medicine at the University of Barcelona. She has spent the past five years working in the hematology department of the Hospital Clinic of Barcelona in Barcelona, Spain. She recently obtained her PhD after publishing two papers under the guidance of her mentor, Dr. Francesca Bosch. Dr. Bosch describes her with passion saying, “From the first day, the enthusiasm and desire to learn were some of the most remarkable characteristics of this young investigator.” In July, Dr. Crespo will take her experience to the Institute for Cancer Genetics at Columbia University. There, under the direction of 2006 William Damphouse Prize recipient, Dr. Riccardo Dalla-Favera, Dr. Crespo will develop her research project Zap-70 and c-Cbl Protein Interactions in Chronic Lymphocytic Leukemia.

Dr. Giovanni Roti is a resident in the department of hematology at Perugia University in Perugia, Italy. Dr. Roti’s research project is entitled Modulating Notch1 with Signature-Based Small Molecule Library Screening, and he will be working at the Dana-Farber Cancer Institute in Boston, MA, under host mentor Dr. Kimberly Stemzner, a current ASH Scholar. In her introduction Dr. Roti writes, “As a European scientist, I have always admired the American academic model and aspired to train in this environment…This opportunity will broaden my exposure to new genomic models of scientific discovery and deepen my knowledge about a field of research not accessible in my current laboratory in Italy.”

ASH and EHA are pleased to support the research of these promising young investigators through this unique new award. We extend our sincere congratulations to Drs. Crespo and Roti. For more information about this program, visit the ASH Web site at www.hematology.org/education/awards/ifa.cfm.

What Has the ASH Trainee Council Done For You Lately?

CHRISTINE CSETTI, MD, AND RACHEL ROSOVSKY, MD

Drs. Csetti and Rosovsky are members of the ASH Trainee Council.

As two members of the ASH Trainee Council (TC) in our second year of service, we have much to say about how our experience has influenced our careers and how it can influence the careers of other trainees. You may ask, “What is the ASH TC and what could I accomplish as part of the council?” The ASH TC was established in 2001 with a mission of increasing the involvement of hematology trainees in the administration of the Society through the solicitation of their input on issues related to training and education. For our trainee members it has been full of benefits. The interactions with other representative trainees from across the continent’s training programs have been a collective feast, consisting not only of the excitement of brainstorming on the issues that face us, but also of fruitful advocacy.

Access to the vast “human resources” of ASH has introduced us to new mentors, advisors, and collaborators. We are welcomed by the ASH leadership to play a direct role in shaping academic and educational initiatives, for example, by providing peer review for the ASH™-SAP publication, the abstracts given category for the annual meeting, or the online hematology teaching cases. In promoting various trainee awards and opportunities to our own peers, we have also been inspired to strive for higher standards of excellence ourselves.

The issues that face trainees bind us together, and the inner workings of the leadership to which we have been exposed have shown those of us on the council what it takes to effect changes and advancements. This service has enhanced our experience and eligibility for the privilege of ongoing leadership opportunities and given us the opportunity to enjoy connections with influential leaders throughout ASH, especially those on the ASH Committee on Training Programs.

Connecting strongly with peers is the root of the TC mission. Career-inspiring clinical elective opportunities have been discovered through the friendly ground-level exchanges between trainees in the Fellows Lounge at the ASH annual meeting, and developing, leading, and facilitating ASH annual meeting sessions that are specifically geared toward trainees are key ways that we, as members of TC, help promote education and advocacy for trainees. These events have included the Trainee Welcome Reception, career development lunches, and didactic sessions with trainee-focused topics such as How to Find Your Perfect Job, How to Write a Publishable Paper, and How to Find a Mentor. By collecting feedback via an e-mail survey after the annual meeting, we have been able to devise new ways to improve the numerous educational and networking opportunities for trainees offered at each annual meeting.

The TC has undertaken several other important initiatives this year. Through the Trainee section of the ASH Web site, the ASH TC has developed an article titled “Making Sense of NIH Funding Opportunities,” a primer on various NIH-funded grant opportunities; a PowerPoint presentation on “Preparation for Life After Fellowship,” which includes suggestions to guide fellows in preparation for life after training; and a “Career Development Timeline for Trainees,” a generalized framework for the career development of trainees at various stages. In an effort to concretely encourage trainees in whom an interest in research has formed, the TC has responded with the development of a Grants Clearinghouse, which lists and updates funding opportunities for trainees, with the understanding that procuring such endorsements is crucial to start-up success and career-long support in academic medicine.

The future activities of the TC will extend beyond those already in place, incorporating new initiatives such as an increased dialogue with trainees through quarterly updates and the development of the ASH Trainee Day at the annual meeting, the goal of which is to provide a condensed training experience in matters of greatest interest to trainees, such as a grants workshop.

All in all, we feel that we make big and positive differences in this forum — as much in our lives as in others. On the TC, we can’t help but be eager about the future of ASH, however hematology might manifest itself in our own careers. We urge trainees to self-nominate and apply (www.hematology.org/education/training/trainee_council.cfm) to this vibrant and innovative arm of ASH and make a special call to trainees who hail from graduate study or research programs to join us in making the young and emerging voice of hematology heard.
The ASH™ Web site offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH. At www.hematology.org you can:

- Read THE HEMATOLOGIST ONLINE (www.hematology.org/publications/hematologist) and catch up on the latest news in the field of hematology right on your desktop.

- Download an application for the CLINICAL RESEARCH TRAINING INSTITUTE (www.hematology.org/education/training/2007_CRITI_ApplicationWord.doc), a unique learning experience that prepares hematologists for careers in patient-oriented clinical research. Applications are due by March 30.

- Assess your treatment of IDIOPATHIC THROMBOCYTOPENIC PURPURA with ASH’s latest Practice Improvement Module (www.hematology.org/education/recertification/pims.cfm).

- Learn about the partnership between ASH AND THE HAROLD AMOS MEDICAL FACULTY DEVELOPMENT PROGRAM (AMFDP) OF THE ROBERT WOOD JOHNSON FOUNDATION (www.hematology.org/education/awards/ash-amfdp.cfm), designed to increase the number of underrepresented minority scholars from the field of hematology with academic and research appointments. Applications for the ASH-AMFDP Award are due by March 23.

- Apply for the TRAINEE RESEARCH AWARD (www.hematology.org/education/awards/trainee.cfm), which includes $4,000 in research support for a research project of three months in duration and $1,000 for travel to the Society’s annual meeting. The application deadline is March 15.

- Visit the ASH ADVOCACY CENTER (www.hematology.org/takeaction) to contact Congress about such important hematologic issues as NIH funding, stem cell research, and genetic nondiscrimination legislation.

ASH LAUNCHES NEW PUBLICATIONS SEARCH CAPABILITY

The ASH™ Hematology Library (www.hematologylibrary.org) is a new search feature that allows one to easily search across ASH’s many publications online, and will include the ASH™-SAP third edition when it launches in May 2007. More details will be forthcoming.

MARK YOUR CALENDAR

**MARCH**

15
Deadline for applications for the ASH™ Minority Medical Student Award Program
Washington, DC www.hematology.org

19 - 23
Advanced Haematopathology
London, United Kingdom www1.imperial.ac.uk

20 - 24
31st Annual Congress of the International Society of Hematology
Punta del Este, Uruguay www.2007ish.org

23
Deadline for ASH™-AMFD P Award applications
Washington, DC www.hematology.org

24 - 27
58th Annual Scientific Session of the American College of Cardiology
New Orleans, LA www.acc07.acc.org

24 - 30
96th Annual Meeting of the United States and Canadian Academy of Pathology
San Diego, CA www.uscap.org

25 - 28
33rd Annual Meeting of the European Group for Blood and Marrow Transplantation
Lyon, France www.ebmt.org

**APRIL**

1 - 6
2007 Meeting of the International BioIron Society
Kyoto, Japan www.bioiron.org

14 - 18
98th Annual Meeting of the American Association for Cancer Research
Los Angeles, CA www.aacr.org

17 - 20
41st Annual Scientific Meeting of the European Society for Clinical Investigation
Uppsala, Sweden www.esci.eu.com

18 - 20
12th International Congress on Antiphospholipid Antibodies
Florence, Italy www.antiphospholipid.net

19 - 21
Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference 2007
Chicago, IL www.americanheart.org

30 - MAY 2
47th Annual Scientific Meeting of the British Society of Hematology
Bournemouth, United Kingdom www.b-s-h.org.uk