Educational and Networking Opportunities for Trainees Abound at the ASH Annual Meeting

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The Society appreciates that trainees will determine the future of hematology and is therefore committed to fostering the early careers of Associate members by enhancing the training experience through programs that target both the MD and PhD trainees. Every year the Committee on Training Programs presents educational and social events at the annual meeting designed especially for physicians and researchers who are in training and for those involved both in administration and in training and educational curricula development. These events, supported by members of the Trainee Council, include Trainee Day, Career-Development Lunch sessions, Trainee Simultaneous Didactic sessions, and the Trainee Welcome Reception. The Committee is also responsible for outreach to trainees at various stages of their education and conducts workshops at the annual meeting for training program directors and hematology course directors.

A major component of our program during the annual meeting is Trainee Day, a concept initially proposed by the Trainee Council to address the process of career development. The program for Trainee Day consists of an ongoing four-year curriculum, and this year’s theme is “Asking a Research Question.” Trainee Day is held the Friday before the annual meeting and includes lunch, poster presentations, and didactic presentations. The program will consist of “Defining the Hypothesis/Research Questions” by a basic science researcher and a clinical investigator. These presentations, Trainee Day attendees break into small groups to discuss “Developing a Collaborative Research Program.”

D I F F U S I O N

The Challenge of Hitting PAR

Platelet-activator receptor 1 (PAR1) is a critical platelet receptor linking the coagulation cascade to activation of platelets during thrombosis. It is an attractive target for an antithrombotic because of its established importance in arterial clotting. Over the past decade, several programs to develop PAR1 antagonists have been launched. However, these programs have encountered multiple complications peculiar to this unusual receptor. PAR1 is activated by a tethered ligand generated by cleavage of the N-terminus by thrombin (Figure). To prevent this tethered ligand from interacting with its binding site, an active site inhibitor must have special pharmacologic properties such as tight binding and a slow off-rate. Animal testing of PAR1 inhibitors is complicated by the fact that most species use PAR4 rather than PAR1 to activate platelets. For this reason, the usual rodent repertoire used in preclinical studies for drug development cannot be relied on for development of drugs that inhibit PAR1.

Clinical trials of PAR1 antagonists must consider the bleeding risk associated with anti-platelet drugs. Despite these challenges, vorapaxar (formerly SCH 530348) has emerged as the preeminent PAR1 inhibitor. In the highly anticipated phase III clinical trial, TRACER, Tricoci et al. have now evaluated vorapaxar in a study large enough to critically assess the efficacy and safety of this new antithrombotic strategy.

TRACER is a double-blind, randomized trial that enrolled 12,944 patients with acute coronary syndromes. Vorapaxar was compared with placebo in patients receiving standard antiplatelet regimens, including aspirin, clopidogrel, or both. The primary endpoint was composite death from cardiovascular causes, myocardial infarction, stroke, rehospitalization secondary to recurrent ischemia, or urgent coronary revascularization. After a median of 502 days of follow-up, 18.5 percent of patients receiving vorapaxar and 19.8 percent of patients receiving placebo had reached the primary endpoint (hazard ratio of 0.92, p<0.007). Death from cardiovascular causes was decreased with vorapaxar use (hazard ratio of 0.89, p<0.02). However, since superiority with respect to the primary endpoint was not achieved, superiority with respect to this secondary endpoint could not be declared. The safety results were more sobering. Rates of moderate to severe bleeding were significantly increased (hazard ratio of 1.35, p<0.001) and rates of intracranial hemorrhage were markedly increased (hazard ratio of 3.39, p<0.001). Overall, these results indicate a non-significant trend toward improved efficacy at the cost of a significant increase in bleeding. The increased bleeding risk in patients receiving vorapaxar led to the early termination of the study in patients with a history of stroke.

Recurrent myocardial infarction or stroke despite current antithrombotic therapy is common and associated with a high mortality rate. There is a clear and pressing need to improve prevention in this setting. Phase II studies using vorapaxar in TRA-PCI raised the possibility that inhibition of PAR1 could be added to inhibition of thromboxane A2-mediated pathways (by aspirin) and P2Y12-mediated signaling (by clopidogrel) without increasing bleeding risk. That this result was not borne out in the TRACER trial has forced a re-evaluation of what role PAR1 antagonism might play in antithrombotic therapy. Recently, Merck announced that in a second large phase III trial, TRA-SP, vorapaxar significantly reduced the primary endpoint of cardiovascular death, heart attack, stroke, or urgent revascularization, but caused increased bleeding, including intracranial hemorrhage.

The results of these phase III trials raise several questions regarding the path forward for PAR1 antagonists. Is there a way to identify susceptible patients so as to avoid intracranial hemorrhage? Should PAR1 antagonism be tested as replacement for, rather than supplementation of, clopidogrel, aspirin, or both? Could the risk-versus-benefit ratio of PAR1 antagonism be improved by modifying the duration of vorapaxar therapy? Might PAR1 inhibitors with different pharmacologic properties demonstrate an improved risk-versus-benefit ratio compared with vorapaxar? Although we have learned much about PAR1, the recent phase III clinical experience with vorapaxar indicates that we have more to learn about this fascinating receptor before we can apply this knowledge in the clinic.

Every once in a great while, a scientific discovery is truly galvanizing. In the field of regenerative medicine, such an event occurred in 2006 with the discovery of a method to generate induced pluripotent stem cells (iPSC). This imaginative technological achievement, replicated by hundreds of laboratories worldwide, provided a mechanism for generating novel cell lines carrying different disease mutations, thereby opening the way for experiments that were previously thought to be impossible. The combination of iPSC technology, advances in next-generation sequencing, and the ability to modulate or engineer the genome with high efficiency put biomedical science on the cusp of a fundamental change in approach to research and translational design. The National Institutes of Health (NIH) recognized this unique position and developed a strategy to address the impending paradigm shift in human biology research. Following a thorough canvassing of the field, NIH created the Common Fund initiative from which arose, in 2010, the Center for Regenerative Medicine (NIH CRM).1

The Center’s mandate is to accelerate, responsibly, stem cell technology toward therapeutic applications. To achieve this goal, the Center needed to identify and resolve roadblocks to progress and optimally utilize existing resources. The following two major problems were targeted: 1) lack of agreed-upon standards and 2) absence of a coordinated funding strategy.

Standardization is most needed in the areas of patient consent, cell line development, and access to uniform controls.2,3 A broadly applicable consent form was developed based on input from experts in the field and from institutional review boards. Under the auspices of CRM, well-characterized cell lines, controls, and reagent standards were obtained from both academic collaborators and commercial vendors and made available for dissemination to the scientific community. In tandem, protocols for generating, characterizing, and differentiating cell lines were compiled for use by investigators, and in an ongoing process, the Center is working with the FDA Stem Cell Task Force to develop and certify clinical-grade cell lines and controls intended for use in clinical trials.

Coordination of funding has been particularly challenging because stem cell research has been the focus of major support initiatives at the state level, each program with its own mandate and administrative process. While the state funding initiatives are generally beneficial for the field, minimizing programmatic redundancies will reduce cost and increase efficiency. Given California’s prominent and successful voter-funded program, the Center has taken the first step toward addressing state-level coordination by forging collaboration between NIH and the California Institute for Regenerative Medicine (CIRM). With CRM, we are focusing primarily on Parkinson’s disease and retinal pigment epithelium biology. A planned outgrowth of this collaborative effort is the development of standardized methods and research tools that then become available to other investigators. In this way, the program serves as a technology conduit for the broader regenerative community. The Center continues to explore similar alliances with other state agencies with the goal of encouraging and supporting promising therapeutic initiatives.

Inter-governmental partnership is also part of CRM’s developmental strategy as the Center is uniquely positioned to facilitate interactions that are not feasible at the institutional or even the state level. For example, CRM, in cooperation with the NIH Fogarty International Center, is exploring collaborative opportunities with other international centers of stem cell biology, including those in India and Korea. Similarly, the Center has had success in establishing agreements at the institutional level with stem cell research groups, both in the United States and abroad. Notably, a memorandum of understanding has been put in place with both iCeMs at Kyoto University in Japan and with Gachon University in South Korea.

While encouraging scientific collaboration, CRM’s policy is to maintain strict separation of each institution’s contribution to funding of all projects including clinical trials.

There is potential for exponential growth in the field of regenerative medicine, and despite the initial emphasis on large programmatic development, individual investigators, and small collaborative groups are encouraged to initiate interactions with NIH CRM, although, currently, the Center does not support an extramural grant program.


Dr. Rao indicated no relevant conflicts of interest.
Save the Dates: 2012 ASH State-of-the-Art Symposium

Due to continuously increasing demand for this meeting, the 2012 ASH State-of-the-Art Symposium (SAS) will be offered in two locations on two different dates. This year’s topic, “Recent Advances in Hematologic Malignancies Including a Special Focus on Thrombosis,” will give attendees the opportunity to discuss their patient cases and practice challenges with experts in the field. In order to enhance the exchange of information, panel discussions and "breakfast with the experts" are offered.

September 28-29, 2012
Chicago, IL
Sheraton Chicago

October 12-13, 2012
Los Angeles, CA
Renaissance Hollywood Hotel

ASH Clinical Practice Webinar Series

ASH continues to host a series of webinars on issues practicing hematologists frequently confront. These sessions will feature presentations by experts in the field, provide time for questions and answers, and cover the most current information on how to best diagnose and care for patients.

Registration is free and available to ASH members and non-members. All webinars will be held at 8:00 p.m. Eastern Time.

UPCOMING WEBINARS

MAY 31
Oral Anticoagulants for the Management of Venous Thromboembolism: The Old and the New
Moderator: Adam Cuker, MD, MS, University of Pennsylvania
1. Introduction to the New Oral Anticoagulants and Evidence of Their Efficacy and Safety
   David Garcia, MD, University of New Mexico Cancer Center
2. Optimizing Therapy with Vitamin K Antagonists
   Neil Zakai, MD, MSc, University of Vermont
3. Management of the Bleeding Patient on Oral Anticoagulation
   Sam Schulman, MD, PhD, MCMaster University

JUNE 20
Evaluation and Management of Immune Thrombocytopenia
Moderator: Wendy Lim, MD, MSc, MCMaster University
1. Update in Adult ITP
   Mark Crowther, MBChB, Worcestershire Royal Hospital, Worcestershire, UK
2. Update in Pediatric ITP
   Cindy Neunert, MD, Georgia Health Sciences University
3. Novel Agents in ITP Management: The Evidence
   Lawrence Solberg Jr., MD, PhD, Mayo Clinic, Jacksonville, FL

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

The patient is a 29-year-old male who presented with a two-year history of progressive pancytopenia (WBC 2200/μL, ANC 830/μL, Hb 9.9 g/dL with 2.9% reticulocytes; platelet count 26,000/μL). He was of short stature with discrete facial dysmorphism and mildly impaired cognitively. The family history was negative for bone marrow failure (BMF), but there was an extensive history of early cancer on the maternal side. Bone marrow examination revealed marked hypocellularity without dysplasia or excess blasts. The patient became transfusion-dependent, so an unrelated bone marrow transplant (BMT) had been recommended as definitive treatment.

The Question

How do you evaluate a young adult with BMF? What features suggest an underlying inherited bone marrow failure syndrome (IBMFs) as the etiology? How do you evaluate for these disorders, and why is it important?

Our Response

IBMFs is a collection of genetic disorders including Fanconi anemia (FA), dyskeratosis congenita (DC), Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), severe congenital neutropenia, and congenital megakaryocytic thrombocytopenia that are associated with insufficient blood cell production, congenital anomalies, and, in some cases, an increased risk of malignancies including myelodysplastic syndrome (MDS), leukemia, and certain solid tumors. IBMFs is not always inherited. Disease may also occur sporadically due to a de novo mutation, which may account for more than 50 percent of all cases for some of the IBMFs (e.g., certain genetic forms of DBA or DC). Sporadic appearance of disease may also be due to low penetrance of the causative mutation or genetic anticipation in which clinical phenotype becomes more severe in successive generation as the affected parent passes the genetic defect to their offspring. These disorders are thought to be strictly the domain of pediatric hematologists, with improved insights into the biologic pathways (e.g., the FA DNA repair pathway, the maintenance of telomeres in DC, or ribosome biogenesis in DBA). Some clinically available screening tests investigate the integrity of the affected pathway and, if abnormal, direct a focused and more economical approach to genetic testing. Given the important therapeutic implications associated with diagnosis and the availability of sensitive diagnostic tests, screening for FA and DC is recommended in every patient presenting with BMF or early MDS leukemia. Due to abnormal DNA repair, chromosomes of dividing cells of patients with FA are hypersensitive to breakage induced by cross-linking agents such as depurinylating (DEB) or mitomycin C (MMC), and this characteristic is the basis of the diagnostic test for the disease.1 The DEB/MMC sensitivity test uses patient lymphocytes in the analysis and is available in several major medical centers with a specific interest in FA. Telomere lengths of nucleated peripheral blood cells are excessively short in DC.7

Clinical telomere length measurements by PCR, flow cytometry, or Southern blotting are available through several commercial laboratories. Results are usually provided as “percentile” in comparison to normal controls. The interpretation of the clinical significance of the measured telomere lengths can be difficult and often needs to be done in the context of disease manifestations. In general, telomere lengths within the normal distribution exclude the cause of BMF. In children and young adults with BMF caused by DC, the telomere lengths of total peripheral blood lymphocytes are usually 2 to 3 standard deviations below the telomere lengths distribution of age-matched healthy controls. Short telomere lengths in granulocytes are less specific for DC and can be short in a number of other IBMFs. As telomeres get shorter with age, telomere length becomes less diagnostic for DC in older individuals. If one of these screening tests is abnormal, subsequent genetic testing should be pursued, as only the identification of a disease-causing mutation can confirm the diagnosis of an IBMF. More specific tests for other IBMFs have to be chosen on an individual basis depending on clinical presentation, family history, and laboratory findings. For example, DBA may be considered in patients who present with macrocytic anemia, low reticulocyte count, and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of purpura; intestinal bleeding with microcytosis; and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte deaminase activity may further support a diagnosis of DBA.

When?

For all patients presenting with BMF, the possibility of an underlying IBMFs should be considered. Such consideration is particularly relevant for patients in whom BMF is being considered as treatment. IBMFs should also be considered in children and young adults presenting with MDS or MDS leukemia, as these clonal disorders are late complications of IBMFs and may be the first symptom of disease in about 20 percent of cases, typically in the young adult population.1 IBMFs, with disease onset in adults, often lack the classic physical stigmata, such as abnormal thumbs (FA) or dystrophic fingernails (DC), and other extra-hematopoietic manifestations, such as small stature or discrete facial anomalies, may be subtle. Therefore, it is difficult to propose an age limit for the exclusion of an IBMFs, as these disorders may be diagnosed even in old age. However, the therapeutic consequences are probably most significant when diagnosed in pediatric and young adult patients. The diagram below suggests the diagnostic genetic workup for the young adult presenting with BMF.
The Evolving Hematopoietic Stem Cell Niche

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There has been a keen interest over the past few years in understanding the cellular and molecular constituents of the stem cell niche. The notion that specific microenvironments could support hematopoietic stem cell (HSC) self-renewal and differentiation dates back several decades, but the exact nature of the niche has remained enigmatic. The conceptual framework of a stem cell niche, supported by experimental work in germline stem cells from C. elegans, has suggested that stem cells interact with a specific nurturing niche cell. Whether this idea holds true for the mammalian HSC niche remains a matter of intensive investigation and debate. Recent studies point, in fact, to an integrated multicellular complex that orchestrates HSC behavior and likely influences other microenvironments dedicated to committed, lineage-restricted progenitors.

That adult hematopoiesis takes place largely in the confines of bone cavities that suggest osteolymphnevma might play an important role in HSC homeostasis. Several studies noted that progenitor activity was found under steady state, or after transplantation, near bone surfaces (Figure). The field took a giant leap forward following advances in mouse genetics and imaging capabilities. Studies using those techniques revealed both that alterations in osteoblast function could lead to significant changes in HSC numbers and that HSCs localized near osteoblasts in the endosteum (Figure). However, that there are many more osteoblasts than HSCs in the bone marrow begged the question, which osteoblast acts as the niche cell?

Sometimes scientific advances come serendipitously from unexpected directions. Searching for novel HSC markers, SLAM antigens (CD50 and CD48) were found to discriminate between HSCs and lineage-committed cells, and based on these phenotypic characteristics, most HSCs were found (using imaging analyses) to localize near blood sinusoids (Figure) rather than near osteoblasts. Other studies have found that β-adrenergic signals from the sympathetic nervous system (SNS) promote HSC mobilization from the bone marrow (Figure). These adrenergic signals were also found to be regulators of circadian HSC egress under homeostatic conditions, suggesting a role of SNS nerves in physiological regulation of the niche. Consistent with the perivascular location of HSCs, SNS nerves associate closely with pericyte-like cells identified through transgenic expression of the green fluorescent protein (GFP) under control of the Nestin gene promoter elements. These Nestin-GFP+ cells are physically associated with HSCs and express high levels of genes involved in HSC maintenance such as stem cell factor (SCF), Cxcl12, angiopoietin, and vascular cell adhesion molecule-1 (Vcam-1) (Figure). After administration of granulocyte colony-stimulating factor or β3 adrenergic agonists, these four “retention” factors are downregulated selectively in Nestin-GFP+ cells, but not in other bone marrow stromal cells, indicating that these specialized cells have a functional role in the regulation of HSC behavior.

The niche itself is also regulated by hematopoietic cells. For example, regulatory T cells protect allogeneic HSCs in their niche, allowing their persistence for long periods in the bone marrow even when the recipient marrow was not treated with a preparative regimen. In addition, depletion of mononuclear phagocytes using clodronate liposomes increased the number of circulating HSCs. This effect was mediated by bone marrow CD169+ macrophages that secrete factor(s) that promote the synthesis of the four aforementioned HSC retention genes by Nestin-GFP+ cells (Figure).

A prevalent idea in the field suggests that two niche compartments, the osteoblastic and vascular niches, may house distinct types of stem cells. For example, it has been suggested that the osteoblastic (also called “endosteal”) niche may promote HSC quiescence and that HSCs may then migrate to the vascular niche to proliferate and differentiate. While this idea may be intellectually appealing, supporting evidence remains controversial. Cell-cycle quiescence is a hallmark of stem cells, as it is thought to protect them from exogenous stress. Searching for sites enabling the activation of transforming growth factor-β (TGF-β), a powerful factor capable of inducing HSC quiescence, glial fibrillary acidic protein (GFAP)- Schwann cells that ensheathe SNS nerve fibers were reported to promote TGF-β activation. These GFAP+ cells, and the nerves that they protect, are found around blood vessels in the bone marrow, suggesting that HSC quiescence is promoted in the “vascular niche.” Although both the vascular and niche are broadly distributed in the bone marrow, differences in HSC proliferative and homing capacity have been reported between cells harvested from the endosteal or central niche. 

Modified from original figure design by Daniel Lucas, PhD, and Sandra Pinho, PhD, both from Albert Einstein College of Medicine.

Drs. Osborne and Bessler indicated no relevant conflicts of interest.

Figure

Schematic representation illustrating the major cellular constituents of the bone marrow HSC niche. A variety of cells, including osteoblasts, Cxcl12-abundant reticular (CAR) cells, Nestin+ mesenchymal stem cells (MSC), Laptin receptor (Lpar)-expressing perivascular cells, and endothelial cells, have been reported as possible components of this niche. Schwann cells, wrapping sympathetic nerve fibers, promote HSC quiescence. In total, the structural makeup of these various cells provides a specialized microenvironment regulating HSC self-renewal and differentiation, either through soluble factors such as Cxcl12, Kit ligand (also known as SCF), angiopoietin-1, and Vcam-1, or through contact-dependent signaling.
ASH Committee on Government Affairs Goes to Capitol Hill to Discuss Research Funding and Drug Shortages

Following its March 21 meeting in Washington, DC, the ASH Committee on Government Affairs visited more than 40 congressional offices to explain to Members of Congress and their staff the impact of potential cuts in funding to the National Institutes of Health (NIH) for research aimed at developing effective treatment strategies for patients with serious hematologic diseases. Committee members also discussed the topic of drug shortages with congressional offices. Last year, ASH helped bring the drug shortage crisis to Congress’s attention and called for congressional hearings to understand what was causing the problem. This year, the ASH Committee urged support for legislative initiatives (H.R. 2245, the Preserving Access to Life-Saving Medications Act, H.R. 3839, the Drug Shortage Prevention Act, and S. 296, the Preserving Access to Life-Saving Medications Act).

These meetings with Congress are an important component of ASH’s advocacy efforts, providing an opportunity for Members of Congress and their staff to gain insight into issues of concern to hematologists. However, the Society needs the help of all members to bring issues important to the future of hematology to the attention of the U.S. Congress and other governmental agencies. Society members are encouraged to let the ASH Government Relations & Practice Department know when you are in Washington, DC, and available to meet with your congressional delegation. You can also have your voice heard in the halls of Congress and play an important role in the Society’s advocacy efforts by visiting the ASH Advocacy Center and participating in the ASH Grassroots Network. For more information, visit www.hematology.org/takeaction.

Health Reform Law Marks Second Anniversary: What the Health Law Has Done

As this issue of The Hematologist was going to press, the U.S. Supreme Court was ready to hear three days of arguments on the constitutionality of the Patient Protection and Affordable Care Act (PPACA), signed into law two years ago. The Court’s ruling is expected in June or July. Meanwhile, the Obama Administration continues to implement provisions of the law.

While many of the most significant provisions of the 2010 health law don’t take effect until 2014, below is a list of the changes that have been implemented:

**EXPANDING COVERAGE**

- Pre-Existing Condition Insurance Program provides health coverage from 2010 to 2014 for adults who have been uninsured for at least six months and who have a pre-existing medical condition.
- Insuring young adults provision requires private insurers to extend coverage of children until age 26, effective September 23, 2010, regardless of their tax status or whether they are students, unless he or she has another offer of employer-based coverage.
- Children with pre-existing conditions younger than 19 cannot be denied coverage. The provision applies to all job-related health plans as well as to individual health insurance policies issued on or after March 23, 2010.
- Owners of small businesses may qualify for tax credits up to 35 percent of their contribution to employees’ health insurance. The credits were made available beginning in tax year 2010.
- Early Retiree Reinsurance Program encourages employers and unions to continue coverage of early retirees and their families by providing temporary reimbursement for some of their insurance costs.
- Sales tax on indoor tanning services, effective July 1, 2010, to help fund coverage expansions.
- Many preventive benefits must be provided without cost-sharing to people with private health insurance if they are enrolled in plans issued after March 23, 2010.

**SENIORS BENEFITS**

- Rebates for prescription drugs, in the form of a one-time, tax-deductible payment of $250, were sent to Medicare Part D beneficiaries for drugs purchased in 2010 when they reached the coverage gap, or “doughnut hole.”
- Prescription drug discounts are to be provided to Medicare Part D beneficiaries beginning in 2011 on covered brand-name and generic drugs when they reach the coverage gap, or “doughnut hole.”
- Many preventive benefits must be provided without cost-sharing to Medicare beneficiaries, effective January 1, 2011.

**CONSUMER PROTECTIONS**

- Proposed premium rate increases of 10 percent or higher for individual or small group plans must be justified to state or federal reviewers beginning in September 2011 for plans issued after March 23, 2010. Regulators in 37 states can reject a requested increase. If a state has no review authority, federal regulators can step in. However, federal officials can ask, but not require, an insurer to reduce a proposed hike.
- Insurers must spend at least 80 percent of beneficiaries’ premiums on medical care or health quality improvements. “Mini-med” plans that offer limited benefits have a one-year exemption. Self-insured employers, who pay claims directly instead of through an insurance company, are not covered.
- Grants for consumer assistance to help states strengthen consumer assistance programs.
- Insurers can no longer impose lifetime dollar limits on essential health services for plans issued or renewed after September 23, 2010.

ASH Advocacy in Action

ASH is active in representing the interests of its members to Congress and federal agencies. Below is a list of the latest advocacy efforts of the Society and an update on the progress of these initiatives. Complete details on all of these issues can be found on the ASH website.

**Combating Drug Shortages** – ASH has endorsed several bills (S. 296; H.R. 2245, The Preserving Access to Life-Saving Medications Act, and H.R. 3839, the Drug Shortage Prevention Act) that would give the Food and Drug Administration (FDA) the authority and resources it needs to effectively prevent or mitigate future drug shortages. It is expected that drug shortage legislation would be bundled or incorporated into a larger bill known as the Prescription Drug User Fee Act (PDUFA) rather than being passed as individual bills. Initial drafts of the PDUFA legislation are being circulated currently with the expectation that the bill will come to the floor for debate in the summer.

**Supporting FY 2013 Funding for NIH** – ASH has called for at least $32 billion for NIH in FY 2013. Advocacy activities so far have included an online campaign by the ASH Grassroots Network; Capitol Hill Day of the ASH Government Affairs Committee; the development of personalized fact sheets indicating how much NIH funding has meant to a legislator’s state, district, and local institution; and obtaining congressional support for efforts in the House of Representatives and the Senate to notify the Appropriations Committees about the need to protect NIH funding.

**Opposing the Grant Review and New Transparency (GRANT) Act** – ASH opposed legislation that would require the publication of all grant proposals and publication of the names of all peer reviewers. The legislation has been derailed in the House of Representatives and taken off the calendar for consideration at this time.

**Delaying ICD-10 Compliance Date** – ASH shared with the Department of Health & Human Services its concerns about the administrative burdens created by the significant change to ICD-10 and advocated reexamination of the pace at which HHS implements this change to the health-care system. HHS has announced the initiation of a process to postpone the date by which certain health-care entities are required to comply with ICD-10.

**Reducing the Scope of the Proposed Rule on Transparency Reports and Reporting of Physician Ownership or Investment Interests** – ASH submitted comments to the Centers for Medicare and Medicaid Services (CMS) urging modifications to a proposed rule concerning the implementation of the Physician Payments Sunshine Act (“Sunshine Act”). The Sunshine Act was incorporated into the Patient Protection and Affordable Care Act of 2010 and mandates disclosure of physicians’ financial relationships with drug and device manufacturers. Though ASH supports the proposed rule’s goal of discouraging inappropriate influence on clinical decision-making by increasing transparency, the Society’s recommendations focus on reducing the scope of the rule and reducing regulatory burdens on physicians. Specific recommendations included the following: stating that attending an industry-supported educational session is not reportable as long as the program meets CME-certification requirements, stating that reprints of peer-reviewed articles intended for physician education meet the educational materials reporting exemption; and delaying reporting until a final rule has been issued.

**Supporting National Priorities for Patient Outcomes Research** – Health reform included the creation of the Patient-Centered Outcomes Research Institute (PCORI), an independent organization focused on comparative effectiveness research. The goal of PCORI is to commission research that is guided by patients, caregivers, and the broader health-care community and that is designed so as to produce high-quality, evidence-based information. ASH submitted comments on PCORI’s proposed National Priorities for Research and its initial research agenda. ASH’s comments offered considerations for how to include research on hematologic diseases and related conditions.
Hematopoietic Stem Cell Niche

Minireview

It is important to note that although this study of perivascular cells (leptin receptor-positive, lepR+ cells) regions.12 Whether identical perivascular structures comprise all HSC niches remains unclear at present. However, there is evidence that perivascular niches are subject to different signals when situated near osteoblasts compared to when they are situated away from osteoblasts.

The complexity of the niche was further illustrated by a recent study in which the cell origin of stem cell factor (SCF) production, the ligand of c-kit receptor, was investigated. It has been known for many years that SCF is produced in non-transplantable bone marrow stromal cells. When expressed under the Scf locus, GFP expression was found to be localized primarily around sinusoids (Figure).12 Additional studies using transgenic models suggested that SCF was produced by both endothelial cells and a subset of pericytes expressing the receptor for SCF (LepR cells) (Figure). It is important to note that although this study proposed that LepR cells are distinct from nestin-positive cells, nestin-positive cells were reported to express high levels of leptin receptor transcripts, suggesting some overlap between the two putative niche components.

The emerging contributions of multiple stromal cell types to the HSC niche raise the bar for translational medicine aimed at expanding HSC for transplantation. Although we know of a few secreted or contact factors that regulate HSC maintenance, most signals that HSCs integrate to make fate decisions remain unknown. If these signals were provided by different cells, one can imagine the difficulty of creating a multicellular niche that will meet the rigorous regulatory criteria for clinical cell therapy. Additionally, the propensity of HSCs to remain quiescent represents a significant challenge to bringing ex vivo expanded stem cells to the patient. The solution for clearing these hurdles will undoubtedly be found through greater understanding of the cellular and molecular basis of the niche. Hearteningly, the niche is evolving in our minds much faster than it does in nature. We should be catching up soon.


Dr. Frenette indicated no relevant conflicts of interest.
A Mechanism-Based Approach to the Treatment of Sickle Cell Disease


Fetal hemoglobin (HbF, α2γ2) is the main oxygen transport protein in the fetus during the last months of embryonic development and during the first few months of life after birth. The β-chain of adult hemoglobin (HbA, α2β2) and the γ-chain of HbF are encoded by a cluster of genes called the β-globin locus. In a complex, highly regulated process called hemoglobin switching, HbF is nearly completely replaced by HbA at six months of age.

Sickle cell disease (SCD) is caused by substitution of valine for glutamic acid at amino acid 6 in the β-globin chain of HbA, which produces HbS (α2β2γ2). Deoxygenation of HbS results in its polymerization, which starts a chain of events that includes red cell sickling, hemolysis, microvascular occlusion, and painful crises. HbF inhibits sickling by interfering with the polymerization of hemoglobin S. Thus, the switch from HbF to HbA is critical to the pathogenesis of SCD and the β-thalassemias. Hydroxyurea and other pharmacologic agents have been identified that promote the production of HbF, and hydroxyurea has been shown in randomized clinical trials to decrease the frequency of painful crises in human SCD.1

Recent human genetic studies have identified the gene encoding BCL11A as a locus that is important for control of HbF synthesis.2 Subsequent studies in mice and in human erythroid cell culture have demonstrated that BCL11A is a transcriptional factor that represses HbF synthesis. Knockout of the BCL11A gene in mice is postnatally lethal. To circumvent this difficulty, Xu et al. in the laboratory of Stuart Orkin at Harvard Medical School examined the contribution of BCL11A to HbF synthesis in non-SCD adult transgenic mice carrying the human β-globin gene cluster on a yeast artificial chromosome transgene and in an SCD mouse model.

HbF constituted greater than 80 percent of the hemoglobin population in fetal liver in mice manipulated to have erythroid-specific inactivation of BCL11A, and these animals developed normally and displayed normal erythropoiesis in fetal liver and adult bone marrow. After birth, the level of γ-globin declined to a level of ~11 percent in adults, indicating the presence of other, yet unidentified regulators of HbF synthesis. The expression of erythroid transcriptional regulators, including GATA1, FOG1, NF-E2, KLF1, SOX6, and MYB, in adult bone marrow of BCL11A-null erythroid cells was normal. These results demonstrated that BCL11A is highly selective and appears to control only the expression of globin genes.

To determine whether the γ-globin gene that is silenced during postnatal development can be reactivated, the BCL11A gene was deleted in the human β-globin transgenic adult mice. This was accomplished using a “floxed” BCL11A gene, which allowed it to be excised after activation of Cre recombinase, which in turn was under control of an interferon-inducible promoter. Inactivation of BCL11A resulted in a sustained increase of γ-globin synthesis to 14 percent of total β-like human globins. Additionally, BCL11A enhanced effects of the known HbF inducers, 5-aza-2’-deoxycytidine and suberoylanilide hydroxamic acid.

Next, Xu et al. determined whether inactivation of the BCL11A gene could be used to ameliorate disease symptoms in the Berkeley mouse model of SCD. These mice produce human HbS and low levels of HbF and develop many of the pathologic features of human SCD. BLC11A-floxed SCD mice, called SCD/Bcl11a-/- mice, displayed a marked increase in expression of HbF. Red blood cells containing HbF, called HbF cells, were also markedly elevated in SCD/Bcl11a-/- compared with control non-SCD and SCD mice. The level of HbF expression achieved by reducing BCL11A expression exceeded levels estimated to be necessary to eliminate the pathologic features of SCD. Abnormalities in red cell counts, red cell hemoglobin content, red cell survival, reticulocyte counts, and white blood cell counts were corrected in the SCD/Bcl11a-/- mice. Sickled red cells were absent in SCD/Bcl11a-/- mice (Figure), and splenomegaly was markedly decreased. Additionally, urine osmolality, which is abnormal in human and murine SCD, was normal in SCD/Bcl11a-/- mice.

The study identifies BCL11A as a pharmacologic target for treatment of patients with SCD. The authors propose that this approach also may apply to the β-thalassemias. BCL11A is a transcription factor, which makes it a difficult target. However, the potential treatment for SCD by interfering with the function of a single component involved in globin gene regulation will likely spur extensive efforts to overcome this barrier.


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Figure

From Xu et al. Science 334:8058 (18 Nov 2011). Reprinted with permission from AAAS.
The Added Value of 18-F FDG PET/CT in Defining Prognosis and Response in Myeloma


In this study, Zamagni and colleagues from Bologna evaluated 192 patients with newly diagnosed myeloma using positron emission tomography integrated with computerized tomography (PET/CT) at the time of diagnosis, as well as after bortezomib-dexamethasone induction therapy followed by tandem high-dose melphalan and autologous stem cell transplantation. At the time of diagnosis, the finding of three or more focal lesions, standardized uptake value (SUV) > 4.2 for any lesion, and extramedullary disease (EMD) (defined as FDG-avid soft tissue not continuous with bone) portended shorter progression-free survival (PFS), whereas both SUV > 4.2 and EMD were associated with shorter overall survival (OS). Moreover, SUV > 4.2 persisting after bortezomib-dexamethasone induction therapy predicted shorter PFS. Most importantly, patients with negative PET/CT at three months post-transplant had significantly longer PFS and OS compared to patients whose scans remained positive. Finally, both identification of EMD and a lesion associated with SUV > 4.2 at baseline were found in multivariate analysis to be independent, adverse prognostic factors for PFS.

This is a landmark study. Multiple staging systems based upon clinical factors, laboratory features, and cytogenetics have been used over time to assess burden of disease and predict response to therapy in myeloma. Staging systems have evolved from the Dune-Salmon system of the past to the International Staging System of the present. Cytogenetic analyses have defined standard and high-risk patient subgroups. Theses analyses have been used to stratify patients in innovative clinical studies that have identified treatment strategies that overcome some of drug resistance. Magnetic resonance imaging, though still used in some centers, has fallen out of favor because of its limited capacity to assess burden of disease and predict response to therapy in myeloma. PET/CT scanning, on the other hand, has proven to be a valuable tool for staging and monitoring disease in myeloma, and its use is becoming more widespread.

Primed for Destruction: Why are Some Cells More Chemosensitive Than Others?


The characteristics that trigger differences in chemosensitivity between different tumor types and different individual malignancies remain largely unexplained. It is not clear why some neoplasms are sensitive to a range of agents with very different mechanisms of action, while others remain broadly resistant. Apoptosis induced by loss of mitochondrial integrity is an important pathway of chemotherapy-induced cell death, and one effect of mitochondrial outer membrane permeabilization (MOMP) in response to cytotoxic therapy is the release of cytochrome c, which, in turn, activates the caspase cascade in the cytosol, leading to programmed cell death (Figure). Control of MOMP is effected by members of the Bcl-2 protein family, and some years ago, overexpression of Bcl-2 was reported to render cells much less sensitive to cytotoxic drugs in vitro while clinically, chemotherapy failure was observed to correlate with Bcl-2 expression.1 Subsequent studies investigated the roles of other Bcl-2 family proteins, some of which are anti-apoptotic (Bcl-2, Mcl-1) and some pro-apoptotic (BAK, BADI). A crucial feature of this family is their capacity to oligomerize, with the balance of pro- and anti-apoptotic partners determining the effect on MOMP. A key region of interaction, the BH3 domain, can be bound by a variety of smaller BH3-only proteins (BIM, NOXA, BMF, PUMA) that exert a powerful pro-apoptotic effect.

This study from the Department of Medical Oncology at the Dana-Farber Cancer Institute sheds light on one possible determinant of chemosensitivity. Using a small library of different peptides from pro-apoptotic BH3-only proteins to induce MOMP, the investigators devised an assay to determine the intrinsic “fragility” of the mitochondria in different cell types. The MOMP effect of these peptides was assessed using a fluorescent dye, JC-1, which measures the inner mitochondrial membrane potential and can be detected using flow cytometry. What they found was that in a variety of hematologic malignancies (e.g., AML, ALL, myeloma) the degree of mitochondrial depolarization on exposure to the BH3-peptide library in tumor material ex vivo was a predictor of clinical responses to chemotherapy, whether reflected by the decline in paraprotein level for myeloma, the probability of remission induction in AML, or the durability of remission in ALL. There was also a correlation between BH3 peptide-induced mitochondrial fragility and both CA-125 response and progression-free survival in ovarian cancer. Which BH3 peptide was the best predictor varied between tumor types. For myeloma, it was BMF; for AML, it was BIM; and for ALL or ovarian cancer, it was PUMA. Having observed these correlations, the investigators suggested that mitochondrial priming to apoptosis has therapeutic potential, by showing that the BH3 mimetic drug ABT-737 increased chemosensitivity in the CML K562 cell line. Finally, they examined the sensitivity of mitochondria from a variety of normal tissues to priming and found that those that are considered chemo-resistant, such as the kidney, ovary, myometrium, and foreskin showed much lower sensitivity to BH3 peptides than malignant cells.

The search for a reliable in vivo chemosensitivity test has been going on for many years, and, to date, none have proven convincing or readily applicable in the clinic. Although the number of cases studied here is relatively small, the preliminary data are encouraging and merit further exploration in prospective clinical trials. The idea that targeting the mitochondria with BH3 mimetics in chemoresistant tumors may improve results is especially appealing, and this assay may provide a method to identify those cases in which it might be most successful.

Coordinating Nuclear Disposal and Mammalian Erythropoiesis


Among vertebrates, mammals and birds have small erythrocytes with high surface-to-volume ratios that optimize oxygen delivery for the high oxygen requirements of warm-blooded animals. With relatively smaller genome sizes, birds can meet the high surface-to-volume ratio requirement by producing small erythrocytes with tightly condensed nuclei, while mammals with their larger genomes produce small erythrocytes by extruding the nucleus at the orthochromatic erythropoietic stage of maturation. Newborn mammals extrude erythrocytes circulate for months, but the extruded nucleus are rapidly phagocytosed with subsequent DNA degradation and recycling of nuclear constituents. Nuclear disposal is mediated by central macrophages located in erythroid islands. The erythroid island is the functional unit of definitive mammalian erythropoiesis and consists of a central macrophage surrounded by adherent erythroblasts at various stages of differentiation (Figure). Rigorous studies by Porc et al. demonstrate that erythroid Krüppel-like factor (EKLF/KLF1), a zinc-finger transcription factor that binds CACC sequences in regulatory regions of genes expressed in differentiating erythroblasts, controls expression of DNase II in central macrophages of erythroid islands. Because definitive mammalian erythropoiesis requires DNase II for erythroid nuclear disposal in central macrophages, EKLF/KLF1 plays a key role in coordinating the function of both macrophages and erythroid cells in erythroid islands.

Extensively characterized in relation to β-globin transcription, EKLF/KLF1 also regulates genes involved in the erythroid cell cycle and in erythrocyte membrane and cytoskeletal development. Human erythroid diseases with EKLF/KLF1 mutations include hereditary persistence of fetal hemoglobin, Lutheran antigen extrusion occur (shown with the extruded nucleus nearby the irregularly shaped, hemoglobin-filled reticulocytes (A). decreases, hemoglobin accumulates (shown as increasingly orange-red cytoplasm), and nuclear condensation and erythroblast (round nucleated cells) differentiation, including those related to cell division. Consequently, cell size of β-globin expression of DNase II in central macrophages of erythroblastic islands. Because definitive mammalian erythropoiesis requires DNase II for erythroid nuclear disposal in central macrophages, EKLF/KLF1 is a key factor in coordinating the function of both macrophages and erythroid cells in erythroid islands.

That EKLF/KLF1 deficiency in non-erythroid cells might contribute to the embryonic-lethal anemia of EKLF/KLF1 null embryos could be improved experimentally using a transgene expression result of failure of definitive erythropoiesis in the fetal liver. Although the diseases with EKLF/KLF1 mutations include hereditary persistence of fetal hemoglobin, Lutheran antigen extrusion occur (shown with the extruded nucleus nearby the irregularly shaped, hemoglobin-filled reticulocytes (A). decreases, hemoglobin accumulates (shown as increasingly orange-red cytoplasm), and nuclear condensation and erythroblast (round nucleated cells) differentiation, including those related to cell division. Consequently, cell size of β-globin expression of DNase II in central macrophages of erythroblastic islands. Because definitive mammalian erythropoiesis requires DNase II for erythroid nuclear disposal in central macrophages, EKLF/KLF1 is a key factor in coordinating the function of both macrophages and erythroid cells in erythroid islands.

EKLF/KLF1 null fetal livers. In wild-type central macrophages, EKLF1 induces DNase II activity were decreased while interferon-β expression of DNase II in central macrophages of erythroblastic islands. Because definitive mammalian erythropoiesis requires DNase II for erythroid nuclear disposal in central macrophages, EKLF/KLF1 is a key factor in coordinating the function of both macrophages and erythroid cells in erythroid islands.

Death in AML is principally related to relapse due to the emergence of clones that have escaped the body’s mechanisms to suppress cancer, developed resistance to treatment, or both, emerging as better characters for the molecular chronology of relapse in AML transformation, Li and Dong and colleagues from Washington University, St. Louis utilized whole-genome sequencing to profile genetic mutations in paired samples taken at the time of diagnosis and at the time of relapse. Two basic patterns of clonal evolution emerged from investigation of paired specimens from eight AML patients; in the first, relapse was related to the acquisition of new mutations in the dominant clone identified in the primary leukemia sample; in the second, a minor sub-clone of the founding clone was selected at diagnosis. A minor sub-clone with a distinct cluster of mutations expanded at relapse due to the acquisition of additional mutations in ETB, MTO1, and the fusion gene WNK1-WAC. The pattern of relapse described in the first was identified in three patients, and the remaining five patients conformed to the second pattern. Despite chemotherapy, the founding clone was observed in all eight patients at both diagnosis and relapse. In addition, analysis of relapse versus diagnosis-specific mutations revealed a statistically significant increase in transversions. Compared with traditional mutations in which one purine or pyrimidine nucleotide is substituted for another, transitional mutations involve substitution of a purine nucleotide for a pyrimidine nucleotide in DNA, and this latter type of mutation is associated with DNA damage mediated by cytotoxic therapy.

These data that illuminate the patterns of clonal evolution and the dynamic persistence of leukemia cells in the face of conventional chemotherapy provide a new level of clarity on the biological diversity and aggressivity of AML and are a humbling reminder of the vexing inadequacies of current treatment. The complex genetics of relapsed AML is in stark contrast to chronic-phase CML, where BCR-ABL is the primary driver of disease and is highly susceptible to imatinib and second-generation tyrosine kinase inhibitors. In AML, the adoption of treatments that target a complex genetic landscape—the so-called “Achilles heel” of complex ecosystems, wherein cancer sub-clones that are best fitted to survive and reproduce. Selective pressures may promote the expansion or extinction of specific cancer cell populations, resulting in a clonal architecture that mimics Darwin’s branching evolutionary tree of species.
S

ever aplastic anemia (SAA) is a potentially fatal, acquired disease characterized by pancytopenia and a hypoplastic bone marrow. In most cases, the disease is idiopathic, but compelling indirect evidence suggests that the attack on bone marrow cells is immune-mediated. Durable remission can be achieved using immunosuppressive therapy, but alloporter is the only truly curative treatment. Optimal outcome depends upon the age of the patient and the availability of an HLA-matched sibling donor, meaning that the majority of patients with SAA undergo allogeneic stem cell transplantation. Still, with more than three decades of aggressive immunosuppression and thousands of patients treated, long-term outcome for this group is the envy of the transplant field. Taking advantage of successive improvements in HLA matching, transfusion practices, and infection prophylaxis, survival rates after matched sibling transplantation approach 90 percent and are higher yet in very young patients. Without the need to eradicate an underlying malignancy, the conditioning strategies are sub-myeloablative and avoid the toxicity associated with high-dose, total-body irradiation. Treatment is carefully tailored to minimize rejection, resulting in low rates of graft-versus-host disease (GVHD) when bone marrow is used as the stem cell source.1

Prior studies suggested an improved outcome for very young SAA patients (those <20 years old) when bone marrow (as opposed to peripheral blood) was used as the stem cell source. Now, a large retrospective, multinational study demonstrates, with a wide margin of statistical significance, that such findings hold true across all age groups.

By way of background, the Center for International Blood and Marrow Transplant Research (CIBMTR) has shown that among patients 20 or older undergoing allogeneic transplantation between 2005 and 2009, 80 percent received peripheral blood stem cell (PBSC) grafts. Of course, the enthusiastic and rapid embrace of PBSC grafting during the preceding decade largely reflects allogeneic transplants unproven by randomized, prospective clinical trials. The purported advantages of using PBSCs (e.g., rapid engraftment, reduced incidence of rejection), however, appear to have been extrapolated to SAA as unpublished data from both CIBMTR and the European Group for Blood and Marrow Transplantation (EBMT) registries indicate that up to 60 percent of patients transplanted for SAA in 2009 received PBSCs.

On behalf of the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSA-EVMT), Bacigalupo and colleagues recently summarized outcomes in more than 1,800 patients across 305 centers who underwent matched sibling transplantation for SAA between 1999 and 2009. The analysis revealed highly significant negative predictors of outcome, including patient age >20 years, prolonged interval between diagnosis and transplantation, and conditioning strategies not including cyclophosphamide or anti-thymocyte globulin. But most striking was the negative impact observed when mobilized peripheral blood was used as the stem cell source (Figure). The authors were careful to investigate potential bias attributable to center effects, demographics, and conditioning treatment. To exclude confounders, they assigned factor scores and developed cohorts with substantial survival differences. Remarkably, across three cohorts and in multivariate analysis, PBSC as the stem cell source resulted in significantly inferior survival with a concurrent two-fold increase in GVHD. These results follow up on an earlier study of more than 600 patients that showed the increased risk of GVHD for recipients of PBSC grafts and comes on the heels of another study that showed a survival advantage for BM stem cell recipients after matched unrelated transplantation.2

What then are the lingering reasons for advocating the use of peripheral blood stem cell grafts in SAA? Some are intuitive, but unproven. While the abundance of progenitors in mobilized PBSC collections can hasten hematologic recovery, early engraftment did not translate into appreciable differences in transplant-associated mortality (Figure). Rejection was not different between the two stem cell sources, and the use of stem-cell-mobilized peripheral blood grafts did not decrease donor morbidity, a widely held perception (Figure). Infection rates actually increased after PBSC transplantation (Figure), leaving, broadly speaking, logistical preference and procedural ease as deciding factors. What clinical indications are left for using mobilized peripheral blood grafts in SAA? One example may be transplantation of patients following rejection of their first graft. Another reason could be specific donor health risks that preclude the use of general anesthesia that is required for bone marrow harvest procedure. As always, clinical equipoise is key. However, evidence from multiple sources and across several large studies now uniformly favors the use of bone marrow as the stem cell source for patients with SAA undergoing allogeneic bone marrow transplantation.


“Designer Nines” Provide Fashionable Alternative to Bypass Therapy


Because patients with hemophilia A are congenitally deficient in factor VIII (FVIII), they lack immune tolerance toward the protein, and, consequently, replacement FVIII is seen as a foreign substance by their immune system. Approximately 25 percent of patients with severe hemophilia develop an alloimmune response against FVIII that results in production of inhibitory antibody titers sufficient to block or blunt the effectiveness of replacement therapy.1 While “bypass” agents, such as factor Vlla and FEIBA,2 are available, response to these agents is unpredictable, short-lived, and expensive.2 Thus, there is interest in developing a more effective treatment for inhibitor patients.

Recently, novel factor IX (FIX) variants that support intrinsic pathway coagulation in the absence of FVIII have been engineered, and these recombinant proteins have therapeutic potential for patients with hemophilia who have a clinically significant anti-factor VIII inhibitor titer.

Milanov and colleagues from Goethe University, in Frankfurt, Germany, generated FIX variant molecules by introducing amino acid substitutions in the human FIX cDNA by site-directed mutagenesis. Subsequently, the variant FIX proteins were expressed in vitro in cell culture and in vivo in FVIII knockout mice (an animal model of hemophilia A) and assessed for their capacity to restore coagulation function. The most promising FIX variant amino acid substitutions was and called IVT was based on the one letter amino acid code that indicated each of the substituted residues. The amino acid substitutions induce a conformational change in the catalytic site that enhances the interaction between FIX and its natural substrate factor X. As a result, the prothrombin activating tenase complex can be generated in the absence of FVIII.

In standard in vitro clotting assays, FIX IVT was found to have 16 percent FVIII activity and 100 percent FIX activity, demonstrating that the mutant protein retained full FIX activity while providing significant FVIII bypass activity. In the in vivo model, FIX IVT reduced blood loss both following laser-induced vessel injury as measured by intravital microscopy and after tail clip. Importantly, using an in vivo animal model of hemophilia A with acquired anti-FVIII antibodies, expression of FIX IVT was shown to reduce blood loss after tail clip with no evidence of an immune response to the recombinant protein.

The rigorous studies of Milanov and colleagues add a new member to the rapidly growing portfolio of potential therapeutics for patients with hemophilia that includes fusion proteins with longer functional half-life, biocompatible peptides with enhanced stability, and liposomal nanoparticle platforms that improve tolerance. However, despite early evidence of safety and efficacy, concerns about the immunogenicity of these novel agents persist. The hypothetical advantage of FIX IVT is that its therapeutic activity is derived from a protein (FIX) for which immune tolerance exists in patients with hemophilia A. Determining therapeutic value in inhibitor patients will require non-inferior trials of humans that test the safety (including risk of thrombosis) and efficacy of this Designer Nine. Implementing these studies will be challenging given competition with clinical trials that are testing novel and efficacious of other “designer” constructs in patients with hemophilia A. Nonetheless, if FIX IVT proves safe and effective, it will add to the currently limited armamentarium available to treat these challenging patients. One could even imagine a way to overcome some of these challenges of gene therapy for hemophilia A by bypassing the need for FVIII by using a FIX IVT construct.

Looking Under the Hood of Early T-Cell Precursor Acute Lymphoblastic Leukemia


About 15 percent of ALL cases are of T-cell lineage, defined by cytoplasmic expression of CD3, a component of the T-cell receptor. CD3-positive leukemic blasts frequently co-express other T-lineage-associated markers, such as CD1a, CD2, CD4, CD5, CD7, or CD8. There are three immunologic subtypes of T-lineage ALL corresponding to different stages of T-cell ontogeny: thymic (also referred to as cortical) T-ALL, which expresses CD1a, with or without surface CD3 expression, and also expresses CD2 and CD4 or CD8, mature (medullary) T-ALL, which expresses surface CD3 but not CD4a; and ETP ALL, which expresses neither surface CD3 nor CD1a.

ETP ALL is also characterized by weak or absent expression of CD5, lack of expression of CD4 and CD8, frequent aberrant expression of myeloid lineage markers including CD33, and a unique gene expression profile similar to that of murine early T-cell precursors.1 The probable cell of origin of ETP ALL is also called the “double negative 1” (DN1) thymocyte, which is capable of both T-cell and myeloid differentiation, but cannot follow a B-cell differentiation program.2 ETP ALL represents about 15 percent of T-ALL and is associated with a poor prognosis and a higher risk of treatment failure in both children and adults compared with thymic (cortical) T-ALL. Several leukemia groups are testing a strategy to treat these high-risk patients for stem cell transplantation.3 Until now, molecular genetic insights into this uncommon subset have been limited.

A multi-institutional consortium, led by investigators at St. Jude Children’s Research Hospital in Memphis and the Genome Institute at Washington University in St. Louis, performed whole-genome sequencing of 12 ETP ALL samples, then assessed the frequency of identified somatic mutations in 94 additional T-ALL cases, including 52 ETP ALL cases and 42 other types of pediatric T-ALL. The investigators observed that the average non-silent coding mutation rate was nine per case, similar to previous reports of acute myeloid leukemia (AML) – 8 mutations/case), but a mutation rate three- to four-fold less than for common adult tumors such as prostate, breast, or lung carcinoma (23-302 mutations/case).

Specific recurrent changes in ETP ALL included activating mutations in genes regulating cytokine receptors and RAS signaling (e.g., NRAS, KRAS, FLT3, IL7R, JAK3, SH2B3, and BRAF), which were much more frequent in ETP ALL (67% of cases) than other T-ALL (19%). In the case of IL7R, clonogenic assays of murine cells expressing murine IL7R demonstrated a high clonal growth factor-independent repopulating potential compared with control cells, confirming that such mutations give cells a clonal advantage.

Furthermore, inactivating lesions predicted to impair hematopoietic development and differentiation (e.g., GATA3, ETW, RUNX1, IKZF1, and EP300) were common in ETP ALL (58% of cases), as were mutations in genes encoding histone-modifying enzymes (e.g., EZH2, EED, SUZ12, SETD2, and EP300; 48%), particularly members of the polycomb repressive complex PRC2.

Notably, this mutational spectrum is more similar to myeloid neoplasms than it is to other ALL subtypes. Coupled with the unique immunophenotypic profile of ETP ALL, the findings raise the possibility that the addition of myeloid-directed therapies – such as high-dose cytarabine or in cases that express CD33, gemtuzumab ozogamicin – might improve the poor outcomes currently associated with ETP ALL.

Among the newly identified recurrent mutations in ETP ALL that need to be explored further are DNMT3, encoding DNA methyltransferase 3, a TGFbeta family member with diverse cellular functions; GATA2, encoding “epithelial cell transforming sequence 2 oncogene like,” a putative guanine nucleotide exchange factor of uncertain function; and RELN, encoding reelin, a secreted extracellular matrix protein critical for normal neuronal migration (genetic mutations in RELN cause the tragic brain formation defect lissencephaly). For several genes, both deleterious germline and somatic mutations were detected in the same gene, similar to other pediatric cancers.

ETP ALL is important to recognize as a unique subtype of ALL as it may require different treatment from other ALL types. While the discovery of a unique ETP ALL-associated mutation profile with a high frequency of mutations activating cytokine and RAS signaling, impeding differentiation, and altering histone modifications with AML implications remain to be seen whether incorporation of cytotoxic agents currently recognized as useful in AML can alter outcomes in ETP ALL, or whether substantive improvements will need to await the advent of more narrowly targeted treatments.


Microparticles, Thrombosis, and Atherosclerosis: The Tissue Factor


The latest Russell Ross championed the concept that atherosclerosis is an inflammatory disease whose accumulation of lipids in the vessel wall, as 50 percent of patients with cardiovascular disease have normal cholesterol levels. According to this response-to-injury hypothesis, modified lipids, endothelial dysfunction, monocytes, lymphocytes, platelets, cytokines, and coagulopathic factors all conspire to mediate the atherogenic process. In 1999, Dr. Ross suggested that selective modification of the harmful effects of inflammation would be an effective strategy for ameliorating cardiovascular disease.1 The success of statin therapy validates the prescient insights of Dr. Ross, as these drugs not only lower cholesterol but also have both anti-inflammatory and anti-thrombotic properties (Figure). In a sentinel study, Owens et al. in the laboratory of Dr. Nigel Mackman at the University of North Carolina provide additional compelling evidence in support of Dr. Ross’ hypothesis by showing that inhibiting monocyte tissue factor (TF)–dependent activation in mice and monkeys with simvastatin alters the course of cardiovascular disease.

The investigators hypothesized that hypercholesterolemia leads to elevated levels of oxidized LDL (oxLDL) in plasma and that this bioactive product induces the expression of procoagulant TF in monocytes. In support of this hypothesis, patients with familial hypercholesterolemia were shown to have elevated levels of plasma microparticle (MP) with TF activity. In vitro, oxLDL induced TF expression in human mononuclear cells, and this effect was attenuated by the administration of simvastatin. In addition, Owens and colleagues demonstrated that, in LDL receptor-deficient mice, a high fat diet induced a time-dependent increase in both plasma MP TF activity and activation of coagulation and that these effects were blocked by statin therapy. That monocyte-derived TF is responsible for the activation of coagulation was further supported by experiments demonstrating that hypercholesterolemic mice transplanted with bone marrow genetically deficient in TF were not hypercoagulable. The mechanism for oxLDL-induced TF is likely due to oxLDL binding to the heterotrimeric complex CD36/TLR4/TLR6 in monocytes. (Figure). Thus, as anticipated, deficiency of either TLR4 or TLR6 reduced levels of MP TF activity in hypercholesterolemic mice. Further, simvastatin treatment of African green monkeys fed a high-fat diet reduced oxLDL, monocyte TF expression, MP TF activity, activation of coagulation, and inflammation without affecting total cholesterol levels.

MP delivery of TF to sites of plaque rupture appears to be of paramount importance in the pathophysiology of deadly coronary thrombosis, so as predicted by Dr. Ross, selectively decreasing inflammation is heart-healthy. The studies of Owens and colleagues demonstrate the interplay between oxidation of LDL, activation of the innate immune system, and formation of monocyte–derived TF MPs (Figure), suggesting that interrupting TF and/or MP formation or inhibiting the CD36/TLR4/TLR6 receptor would be reasonable strategies for ameliorating cardiovascular disease. While developing new drugs that regulate these processes poses important pharmacologic challenges (e.g., bleeding in the case of TF inhibitors or complications of decreased host defense in the case of blocking the innate immune system), identifying safe, cost-effective approaches to treating or preventing a disease that affects the health of hundreds of millions worldwide is an urgent need and an understanding of the molecular basis of the disease process is an essential step toward achieving this lofty goal.


Figure

Pathway linking hypercholesterolemia to activation of coagulation

A western diet increases LDL levels some of which is converted to oxidized LDL (oxLDL). OxLDL activates a TLR4/TLR6/CD36 complex on the surface of monocytes (Mo) and induces tissue factor (TF) expression. Activated monocytes release TF-positive microparticles (MP) that then activate the monocyte TF on the coagulation cascade.

Figure courtesy of Nigel Mackman, BiSc, PhD, at the University of North Carolina.

GREGORY M. VERCELLOTTI, MD
Dr. Vercellotti indicated no relevant conflicts of interest.
Epigenetic Therapy for Elderly Patients With AML

**STUDY TITLE:** Decitabine With or Without Bortezomib in Treating Older Patients With Acute Myeloid Leukemia

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01420926

**STUDY SPONSOR:** Alliance for Clinical Trials in Oncology (This is a U.S. Cooperative Group focused on performance of clinical trials that replaced the former Cancer and Leukemia Group B. This group receives funding from the National Cancer Institute.)

**PARTICIPATING CENTERS:** More than 20 centers around the United States currently

**ACCURAL GOAL:** 172 patients will be enrolled (86 per treatment arm); this trial is currently actively recruiting new patients.

**STUDY DESIGN:** This trial seeks to enroll patients 60 years and older with acute myeloid leukemia (AML) who are FLT3 negative, CBF negative, and PML-RARA negative as assessed by a central reference laboratory. Patients with treatment-related AML are eligible as well. Patients may have had select prior therapy for myelodysplastic syndrome but not for AML. This is a phase II study with a primary endpoint of survival for patients treated with a combination of decitabine and bortezomib compared with those treated with decitabine alone. Patients are randomized to receive either decitabine alone given as a 10-day infusion or this same schedule of decitabine with subcutaneous bortezomib given on days 1, 4, 8, and 11. Cycles are repeated every 28 days. Once response is obtained, consolidation therapy consists of the same schedule of decitabine with decitabine in combination with bortezomib is used to modify gene expression through effects on epigenetic silencing. While these regimens have some of the same risks as standard cytotoxic therapy (e.g., cytopenias and infections), they lack many of the other toxicities associated with aggressive chemotherapy. Consequently, administration of this therapy is more feasible in elderly patients and in those with co-morbid conditions. With any new treatment approach, it is important to verify that a single institution study is reproducible when the regimen is tested in a large, multicenter trial.

This trial will meet this goal and inform us as to whether either of these treatment regimens warrants future clinical investigation. In addition, the laboratory correlates and the geriatric assessment studies, performed in a uniform manner, may identify subsets of patients who particularly benefit from one of these approaches to treatment. Taking an entirely different approach to treatment of elderly patients with AML, as is done in this trial, is justified based upon the limited success of other treatment approaches that are currently available to this patient population.

-John C. Byrd, MD

**RATIONAL:** AML is the most common type of acute leukemia diagnosed in the elderly and represents a major treatment challenge. Elderly patients with AML often have significant co-morbidities and an increased frequency of high-risk cytogenetic and molecular features that together explain their poor response to traditional cytotoxic therapy. A major driving force in the pathogenesis of both myelodysplastic syndromes and AML in the elderly is epigenetic silencing of cell-cycle regulatory elements and tumor suppressor genes as a consequence of promoter methylation or chromatin modification. Aberrant activity of transcription factors such as NFI-Ab also contribute to the underlying pathobiology of these diseases. Likewise, non-coding RNAs are known to have an important role in disease pathogenesis and response to treatment. These observations have prompted clinical investigations using therapeutics such as hypomethylating agents (decitabine and 5-azacytidine) that reverse gene silencing, histone deacetylase inhibitors that restrict chromatin modification, and direct or indirect inhibitors of NF-κB. Several studies with hypomethylating agents in AML have shown modest clinical activity, but unfortunately, treatment schedules were not optimized to achieve the goal of reversing epigenetic gene silencing. Subsequent studies optimized the hypomethylating activity of decitabine (Blum W et al. J Clin Oncol. 2007), and a single institution phase II study based on that work demonstrated that a 10-day schedule of decitabine given as induction to elderly AML patients was not only acceptable tolerated but also produced complete response rates and progression-free survival durations similar to those observed in patients treated with standard chemotherapy (Blum W et al. Proc Natl Acad Sci USA. 2010). A follow-up to this trial incorporated bortezomib with decitabine based on the hypothesis that the combination would enhance the reversal of epigenetic silencing and thereby improve response rates. The current study compares decitabine alone to the combination of decitabine plus bortezomib in a randomized phase II study aimed at identifying the best regimen that will then be used in a subsequent phase III study.

**COMMENT:** Despite progress made in the management of many other hematologic malignancies, the high morbidity and mortality associated with standard induction regimens and the high frequency of treatment failure with this approach highlight the need for novel therapeutic approaches to the treatment of elderly patients with AML. This trial targets AML using a different therapeutic strategy in which decitabine or decitabine in combination with bortezomib is used to modify gene expression through effects on epigenetic silencing. While these regimens have some of the same risks as standard cytotoxic therapy (e.g., cytopenias and infections), they lack many of the other toxicities associated with aggressive chemotherapy. Consequently, administration of this therapy is more feasible in elderly patients and in those with co-morbid conditions. With any new treatment approach, it is important to verify that a single institution study is reproducible when the regimen is tested in a large, multicenter trial.

This trial will meet this goal and inform us as to whether either of these treatment regimens warrants future clinical investigation. In addition, the laboratory correlates and the geriatric assessment studies, performed in a uniform manner, may identify subsets of patients who particularly benefit from one of these approaches to treatment. Taking an entirely different approach to treatment of elderly patients with AML, as is done in this trial, is justified based upon the limited success of other treatment approaches that are currently available to this patient population.

-John C. Byrd, MD

### Old, But Not Too Old

**STUDY TITLE:** Study to Determine Efficacy and Safety of Lenalidomide Plus Low-Dose Dexamethasone Versus Melphalan, Prednisone, Thalidomide in Patients With Previously Untreated Multiple Myeloma (FIRST)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT00689936

**COORDINATOR:** Thierry Facon, Hopital Huriez, CHRU, Lille, France

**SPONSORS AND COLLABORATORS:** Intergroupe Francophone du Myélome (IFM) and Celgene Corporation

**PARTICIPATING CENTERS:** This study is being conducted in 281 medical centers worldwide

**ACCURAL GOAL:** This study has reached its enrollment goal and is no longer recruiting participants. A total of 1,623 patients have been enrolled.

**STUDY DESIGN:** Multicenter, open-label, randomized, phase III study to determine the efficacy and safety of lenalidomide plus low-dose dexamethasone (RD) when given either until disease progression or for a total of 18 four-week cycles versus the combination of melphalan, prednisone, and thalidomide (MPT) given for a total of 12 six-week cycles in patients with previously untreated multiple myeloma who are either 65 years of age or older or who are not candidates for stem cell transplantation. The primary endpoint is progression-free survival (PFS), with the hypothesis that RD until progression will prolong PFS as compared with MPT.

**RATIONAL:** In recent years, significant progress has been observed in the treatment of myeloma in elderly patients with the incorporation of either bortezomib (Velcade®; V) or immunomodulatory drug (either thalidomide [T] or lenalidomide [Revlimid®; R]) onto the historical platform of melphalan and prednisone (MP). Two of these regimens, MP+V and MP+T, have been approved in Europe and, compared with MP, have shown significant improvement both in response rates and, more importantly, in survival. However, these two regimens have demonstrated a peculiar neurotoxicity profile that renders their efficacy/toxicity ratio suboptimal. Studies from the U.S. ECOG group have demonstrated a significant improvement in the toxicity profile, without loss of efficacy, when lenalidomide is combined with low-dose dexamethasone (RD) as compared with lenalidomide in combination with high-dose dexamethasone. This two-drug regimen is of interest for treatment of the elderly, as, conceivably, patients could be maintained on treatment for a longer period of time before progressing. However, no direct comparison with the MP-based regimens has been undertaken previously. The IFM2007-01/FIRST study is not only the largest phase III trial conducted in myeloma but is also the first study to compare, head-to-head, two different treatment strategies (i.e., the MP+T, three-drug regimen, versus the RD, two-drug regimen).

**COMMENT:** Currently, there is no consensus on the optimal upfront treatment of myeloma affecting elderly patients or those who are not candidates for high-dose chemotherapy with autologous stem cell rescue. Three-drug regimens that include MP in combination with either Velcade or an immunomodulatory drug (thalidomide or lenalidomide) are highly efficacious, but treatment is often complicated by debilitating neurotoxicity. Lenalidomide in combination with low-dose decadron (RD) is an active regimen with a favorable toxicity profile; however, whether RD is equally (or more or less) efficacious than MP+T is unknown. The current study is designed to compare the two regimens with a goal of illuminating the optimal approach to managing previously untreated myeloma in elderly patients and those who are not transplant candidates. The fact that the study has already reached its accrual goal means that results will be reported in the near future. Evidenced-based guidance will be welcomed by clinicians who are often challenged by the dilemma of how best to manage this frequently encountered patient category.

-Xavier Leleu, MD

Dr. Leleu has received lecture fees and a research grant from Celgene and Janssen.
Addressing Workforce and Infrastructure Challenges to the Growth of Hematopoietic Cell Transplantation: The System Capacity Initiative

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Approximately 20,000 patients receive either autologous or allogeneic hematopoietic cell transplantation (HCT) in the United States each year. The National Marrow Donor Program (NMDP) estimates that the demand for unrelated donor HCT will double over the next decade, but our health-care system lacks the capacity to accommodate this projected growth. To understand and address workforce shortages and infrastructure limitations, the NMDP, in collaboration with the American Society for Blood and Marrow Transplantation (ASBMT) and other professional organizations, has organized a multi-year program called “Hematopoietic Cell Transplantation in 2020: A System Capacity Initiative” (www.marrow.org/SCI).

The program commenced in September 2009 and has utilized a deliberative process model to engage professional organizations, experts, and stakeholders in a national collaborative effort (Figure 1). A steering committee oversees seven working groups (WG). Each WG meets monthly via conference call and then all WGs convene annually for a symposium. WG recommendations are prioritized through roundtable discussions and member polling (Figure 2). The program is in its third year and has developed a number of approaches designed to increase efficiency, using current capacity to identify future capacity requirements and to ensure adequate reimbursement of HCT. SCI is funded by the NMDP with many experts and organizations volunteering their time and talent to the program. The National Heart, Lung, and Blood Institute partly funded the Year-II symposium (1R13HL110705-01).

Year 1 focused on needs assessment. WGs calculated future capacity, and recommendations were reviewed and prioritized in a one-and-a-half-day symposium in September 2010. Year 2 emphasized data analysis and development of actionable pilot projects. Recommendations were further prioritized in a subsequent symposium in September 2011. Year 3 of the program is in progress and is focusing on establishment of metrics for program evaluation, implementation of pilot demonstration projects, and dissemination of findings (Fig. 2).

Beyond Year 3, the momentum created by the initiative will encourage target organizations to continue support of priority programs. For example, the Physician Workforce WG is chaired by Linda Burns, MD, ASH vice president, and includes representation from ASH, ASBMT, and transplant physicians. To identify HCT physician recruitment and retention barriers, the WG collected data from focus groups (targeting fellowship program directors and fellows) and webinars (targeting fellows) and conducted a survey of ASBMT members. Based on these assessments, an elective course for fourth-year medical students and first- and second-year residents is under development that would provide early exposure to HCT as a career path. Another byproduct of the assessments has been the incorporation of a new program for fellowship directors into the schedule of ASBMT’s annual meeting. Other initiatives are under development to aid in understanding workforce capacity and to improve recruitment and retention rates for physicians.

With the growing health-care needs of the U.S. population, workforce and infrastructure challenges are relevant for many medical specialties. Hematopoietic Cell Transplantation in 2020: A System Capacity Initiative can serve as a template for the transplant community and for other specialties that are experiencing or anticipating workforce and infrastructure shortages.

That led me to become a hematologist? This question is, perhaps, asked at one time or another of virtually all of our colleagues. I do not believe this question is meant to be idle chit-chat. My experience has been that in most cases, the question provides an important insight into the thinking and motivations of that person. My answer to this question is not simple. I first have to answer why I chose to become a doctor and follow with why hematology became my calling.

As a young boy growing up in Jodhpur, a small town in India, I intensively watched my uncle, a practicing general physician and an overall charismatic guy. Very early on, he had a profound influence on me. Because of his influence, I had made up my mind that I would also become a doctor, but instead of doing general practice, I decided that I would become a pediatrician and treat sick children in the poverty-stricken, rural areas of India. That was the decision I made in 1942 when I was just 10 years old.

I became a physician, but instead of practicing pediatrics in rural India, I ended up practicing hematology in Long Island, New York. I had never considered hematology, and the change in my plans was not one which I made deliberately, nor do I recall experiencing mental anguish or inner struggles. A combination of certain circumstances and the guiding hands of two important mentors who entered my life in the course of my training, led me to become a hematologist. I have some explaining to do.

I received my medical degree in 1955 from the SMS Medical College in Jaipur, India, and in 1957 I came to New York for residency training in pediatrics. I spent a year in the South Bronx at the Lincoln Hospital and then moved to North Shore University Hospital in Manhasset, NY, to serve as chief resident in Pediatrics. Everything seemed to be going according to my plan; I was scheduled to take the Pediatric Boards and then return to rural India. But that was before I met a charming three-year-old girl whom I will call Lauri. I was on-call on a weekday like any other in September 1958, and I had to perform the admission history and physical on Lauri whom I recall as a vibrant, vivacious young girl who had developed petechiae and had a fever. The attending hematologist came soon after the physical was completed and together we did a bone marrow examination on a screaming, frightened child. The pain and shock on the face of the innocent Lauri still remain etched into my mind. The attending, Dr. Arthur Sawitsky, took me by the hand and showed me how to stain the slides. As we looked at those slides, alongside some normal blood and marrow slides for comparison, for the first time I was face-to-face with an abundance of very angry-looking leukemic lymphoblasts. It took a good part of that night’s work for me to realize that I had actually participated in making a diagnosis of acute lymphocytic leukemia (ALL) on this three-year-old Lauri. I asked Dr. Sawitsky how we would treat Lauri and what her prognosis would be. He told me what drugs we would use, and then he told me that Lauri would die in six months to a year. I thought that Dr. Sawitsky was a heartless, evil person, but of course, he was no such thing. This was 1958, and the stark numbers were unfortunately and tragically solid: 90 percent of children with ALL died between six and 18 months after diagnosis.

I became bonded to Lauri. I took care of her during that first admission and two more times in the next seven months until she died with me at her bedside. I was devastated. Dr. Sawitsky had observed all along how deeply affected I was by Lauri’s death, thus he decided for me that I should become a hematologist; I became a fellow in hematology under him at the Long Island Jewish Hospital after finishing the pediatric residency.

Thus, the seeds of becoming a hematologist were sown entirely by chance: the making of a new diagnosis of ALL on a very young child, being deeply affected and challenged by the hopeless statistics of that cruel disease, and a fortuitous combination of a caring senior clinician-teacher who recognized that a younger physician was ripe to enter training as a hematologist. I, the “younger physician,” was ready and, more than a half-a-century later, have never looked back or asked what-if’s or where did my ambition to treat sick children in the villages of India go?

Looking back, 1958 was a turning point in the battle that eventually ended up with a cure for a disease that was once universally fatal. For a detailed chronicle of this story of the battle to defeat childhood acute lymphocytic leukemia, I refer you to Siddhartha Mukherjee’s fascinating book, The Emperor of All Maladies: A Biography of Cancer.

There is more to my story — entry of yet another mentor named Eugene P. Cronkite, MD (a past ASH president) who introduced me to leukemia research and the study of lymphocytes which led to my life that is tied to chronic lymphocytic leukemia. But we will tackle that relationship at another time.
The ASH website offers a convenient way for members to find information about upcoming Society events and provides easy access to many valuable products and services.

ASH Launches Blood Journal App

ASH recently released the Blood journal app for iPhone and iPad. By downloading the free application, users can access First Edition articles, conduct full-text searches, and view listings of articles by author and date with the in-app browser. The app also allows users to share articles via email and Twitter and download multiple issues on their devices and access them regardless of Internet connectivity. Following its introduction for Apple products, ASH will launch a version of the Blood journal app for Android devices in the future.

To download the Blood journal app, search for "blood journal" in the Apple App Store.

Visit www.hematology.org/bloodjournalapp for more information.

Mark Your Calendar

May

3-5  Thrombosis & Hemostasis Summit of North America
     Chicago, IL  www.fhsna.org

9-12  American Society of Pediatric Hematology Oncology Annual Meeting
     New Orleans, LA  www.aspho.org

15-19  15th Annual American Society of Gene & Cell Therapy Meeting
       Philadelphia, PA  www.asgct.org

18-19  Highlights of ASH in Latin America
       Foz do Iguacu, Brazil  www.hematology.org

21-24  XXVth International Symposium on Technological Innovations in Laboratory Hematology
       Nice, France  www.islh.org

24-27  Canadian Society for Transfusion Medicine Conference
       Halifax, Nova Scotia  www.transfusion.ca

31  ASH Webinar on Oral Anticoagulants
     Washington, DC  www.hematology.org

31  Deadline to submit nominations for ASH leadership and committee positions for term year 2013
     Washington, DC  www.hematology.org

June

1-5  Annual Meeting of the American Society of Clinical Oncology
     Chicago, IL  www.asco.org

5-8  18th Annual International Society for Cellular Therapy Meeting
     Seattle, WA  www.celltherapysociety.org

13-16  10th Annual International Society for Stem Cell Research Meeting
       Yokohama, Japan  www.iscr.org

14-16  Society for Vascular Medicine 23rd Annual Scientific Sessions
       Minneapolis, MN  www.vascularmed.org

14-17  17th Congress of European Hematology Association
       Amsterdam, The Netherlands  www.ehaweb.org

July

1-5  25th World Congress of the International Union of Angiology
     Prague, Czech Republic  www.iua2012.org

2  Nomination deadline for the ASH Honorific Awards
     Washington, DC  www.hematology.org