

## ASH Volunteers Recount Rewarding Experiences Overseas

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As ASH expands its global presence, the Society's members find greater opportunities to contribute to the hematology community. Through a partnership with Health Volunteers Overseas (HVO), a nonprofit organization dedicated to improving global health through education, ASH members can share their hematology expertise by teaching clinicians and laboratory scientists in Uganda, Peru, and Cambodia. ASH member HVO volunteers provide education through day-to-day training, making a sustainable difference at the hospitals where they serve.



EPASTRILANDOV

Dr. Troy Lund, ASH member and HVO volunteer, treats patients at the Mulago Hospital after the July 11 bombings in the capital of Kampala, Uganda.

(Cont. on Page 4)

### DIFFUSION

## Optimizing the Dose for Prophylactic Platelet Transfusions: Will PLADO Shape the Future of Transfusion Practice?

Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med.* 2010;362:600-613.

The fear of catastrophic hemorrhage during severe hypoproliferative thrombocytopenia compels physicians to act preemptively with prophylactic platelet transfusions. Without additional risk factors, spontaneous bleeding increases significantly at platelet counts  $< 5 \times 10^9/L$ . The current accepted prophylactic platelet transfusion trigger of  $\leq 10 \times 10^9/L$  derives from multiple randomized, prospective platelet transfusion trials and reflects the use of standardized platelet concentrate doses ( $3 \times 10^{11}$  to  $6 \times 10^{11}$  platelets for adults).<sup>1</sup> To meet the increasing demand for donor platelets in an era of dwindling supply, there is great interest in defining a minimum, safe prophylactic platelet dose that is also cost-effective. One recent study to determine whether low-dose products might provide equivalent safety as standard-dose products (the SToP trial) was prematurely closed after enrolling only 130 patients when  $> 5$  percent absolute difference in WHO grade 4 bleeds occurred in the lower-dose arm.<sup>2</sup>

The platelet dose (PLADO) trial reported by Slichter et al. for the Transfusion Medicine/Hemostasis Clinical Trials Network prospectively evaluated 1,351 pediatric and adult patients (body weights 10-135 kg) with chemotherapy-induced hypoproliferative thrombocytopenia. Patients were randomized to receive low-, medium-, or high-dose products ( $1.1 \times 10^{11}$ ,  $2.2 \times 10^{11}$ , or  $4.4 \times 10^{11}$  platelets/ $M^2$  BSA, respectively) when their morning platelet count was  $\leq 10 \times 10^9/L$ . Among the 1,272 evaluable patients, the primary endpoint of WHO grade 2 or higher bleeding was not significantly different between the three groups (71 percent, 69 percent, and 70 percent, respectively), nor were there differences for the highest grade of bleeding. However, the total number of platelets transfused ( $9.25 \times 10^{11}$ ,  $11.25 \times 10^{11}$ , and  $19.63 \times 10^{11}$ , respectively) and the median number of transfusion events (five in the low-dose group and three in the other two) were significantly different. The median post-transfusion platelet counts were  $22 \times 10^9/L$ ,  $34 \times 10^9/L$ , and  $50 \times 10^9/L$ , respectively, while the median number of days until the

next transfusion were 1.1, 1.9, and 2.9, respectively. Physician-initiated change to higher-dose product occurred more commonly in low-dose patients.

What are the key findings of the PLADO trial, and should these results change transfusion practice? This large and carefully performed study refutes the safety concerns raised by the SToP trial and suggests that relatively few transfused platelets can maintain vascular hemostatic integrity and prevent clinically relevant bleeding. From a clinical and resource perspective, lower overall platelet requirements should translate into less donor exposures (when pooled products are used) and increased platelet inventories. However, cost-benefit analyses are eagerly awaited, since gains in product availability may be offset by greater administration and nursing costs, as suggested by an economic study of a smaller platelet dosing trial. Moreover, providing customized, body surface area-based platelet products will present technical challenges. Thus, implementation of a low-dose transfusion policy must be guided by further economic and logistical review of the PLADO data. Concurrent with these efforts, an ongoing, randomized controlled trial of prophylactic versus no-prophylactic platelet transfusions (the TOPPS trial) should yield valuable insights into whether therapeutic, rather than prophylactic, transfusions can be a safe and efficient practice for some patients.<sup>1</sup>

1. Blajchman MA, Slichter SJ, Heddle NM, et al. New strategies for the optimal use of platelet transfusions. *Hematology.* (ASH Education Program Book). 2008:198-204.
2. Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood.* 2009;113:1564-1573.
3. Ackerman SJ, Klumpp TR, Guzman GI, et al. Economic consequences of alterations in platelet transfusion dose: analysis of a prospective, randomized, double-blind trial. *Transfusion.* 2000;40:1457-1462.

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Drs. Shenoj and Linenberger indicated no relevant conflicts of interest.

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## Enhancing Clinical Trials Accrual Requires Changes in the Governmental Conference Room and Exam Room

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Clinical research in hematology has never been more important, yet clinical investigators are facing unprecedented challenges. Constantly changing (and at times inconsistent) regulations, chaotic reimbursement policies, increasing demands on physician time, and scientific advances demonstrating the complex differences among individual patients all complicate hematology clinical research.

The opportunities and obstacles are not unique to hematology and include problems with how we organize, support, and conduct clinical research. These are starting to receive considerable attention. The Institute of Medicine (IOM) recently released a report that calls for an overhaul of the National Cancer Institute's (NCI) Cooperative Group Program. The report<sup>1</sup> identifies four overarching goals:

- Improving the speed and efficiency of the design, launch, and conduct of clinical trials
- Making optimal use of scientific innovations
- Improving selection, prioritization, support, and completion of clinical trials
- Fostering expanded participation of both physicians and patients in clinical research

These are all vital issues, and addressing these goals is important for all aspects of clinical hematology research, not just those studies that are part of the NCI cooperative groups. An excellent summary of this report was recently published in the *New England Journal of Medicine* by Robert Young.<sup>2</sup>

The issue of clinical trials for both malignant and non-malignant hematologic diseases and conditions is a priority for the Society. ASH has consistently advocated for Medicare and private insurer coverage of routine patient costs associated with clinical trial participation. Most recently, ASH supported a provision included in health reform that requires coverage of routine patient costs associated with clinical trial participation and prohibits insurers from dropping coverage because an individual chooses to participate in a clinical trial. ASH has also advocated for legislative language that encourages the Department of Health and Human Services to determine if changes could be made to better harmonize the federal policies and regulations on clinical trial operations that currently exists at various federal agencies, which has the potential to expedite the initiation of new trials and access to promising treatments for patients.

At the same time, let's not forget that at the heart of clinical research is the interaction between the physician and patient. We need to take a long, careful look at what we can do to improve the efficiency of the aspect of the clinical research process that takes place in the exam rooms of hematologists and other clinical investigators across the country.

An idea came to mind recently, when I came across a 30-year-old informed consent document. It was clear, concise, and short — in marked contrast to informed consent documents we use today. Our current consents have multiple pages of text to protect the institution and the sponsor, not the subject. Indeed, physicians involved in clinical research know how difficult it is to convince potential subjects to read and understand long and complex informed consent documents. Clearer, shorter, simpler informed consent documents would be easier for clinical investigators to present to potential subjects, easier for those potential subjects to understand, and better at protecting the rights of the subjects. They would result in enhanced accrual to clinical trials.

The IOM is to be commended for their thoughtful and forward-looking approach to how our nation's clinical research leaders select, prioritize, and support clinical trials. However, changing how we organize clinical research in the governmental conference rooms is not enough. We also need to consider how we can improve the vital part of clinical research that takes place in the exam room. It is time to consider ways we can revise the informed consent process to make documents simpler and more efficient. This will be a difficult and complex discussion, but with careful thought we can improve the efficiency of the informed consent process, enhance accrual, and at the same time do a better job protecting the rights of patients.

1. A national cancer clinical trials system for the 21st century: reinvigorating the NCI cooperative group program. Report. Institute of Medicine. April 15, 2010.
2. Young RC. Cancer clinical trials — a chronic but curable crisis. *N Engl J Med*. 2010;363:306-309.



### Joint Society Symposia

One of the privileges of being ASH president is the opportunity to represent our Society at other organizations' meetings where we have the opportunity to bring a "taste of ASH" to researchers and clinicians in related disciplines. Whenever I attend these meetings, I am struck by the scientific and clinical diversity of our membership, the breadth of impact that hematologists have in related fields, and the respect that ASH and its members engender all around the world. Our global reach has grown significantly during this past year; we have a number of joint and ongoing efforts with the European Hematology Association (EHA), and we have extended our renowned Highlights of ASH<sup>®</sup> programs internationally.

As I reported in the last issue of *The Hematologist*, our Society held its second Highlights of ASH in Latin America in Rio de Janeiro in May. We are now planning a third Highlights of ASH in Latin America, which will be held in Punta del Este, Uruguay, on April 29-30, 2011. Drs. Raul Gabus and Sebastian Galeano of the Sociedad de Hematología del Uruguay are working with ASH Co-Chairs Drs. Bradford Schwartz and Joseph Mikhael to organize what I know will be an excellent scientific program.

I've also had the pleasure of meeting with Dr. Changgeng Ruan, president of the Chinese Society of Hematology (CSH), and Dr. Kaiyan Liu, secretary of CSH, who will serve as co-chairs of the first Highlights of ASH that will be held in Beijing, China, April 1-3, 2011. We are planning scientific presentations featuring not only the highlights from the ASH meeting, but also topics of special interest to Chinese hematologists.

On June 4, I had the opportunity to co-chair the American Society of Clinical Oncology (ASCO)/ASH Joint Session at ASCO's annual meeting in Chicago with ASCO President Dr. Douglas Blayney. This was put together from presentations at the last ASH annual meeting in New Orleans that we felt ASCO members would find of interest. Dr. Mark Levis, from Johns Hopkins University, presented results from a randomized trial of salvage chemotherapy followed by lestaurtinib for FLT3 mutant AML patients in first relapse. Dr. Noopur Raje, from Massachusetts General Hospital Cancer Center, spoke about a phase III study to determine efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. Dr. Mathias J. Rummel, of Hospital of Justus-Liebig University, touched on the final results of a randomized phase III study of the Study Group Indolent Lymphomas, Germany (StiL), and Dr. Peter Borchmann, of University Hospital of Cologne, presented the final analysis of the randomized German Hodgkin Study Group (GHSG) High-Dose Therapy (HDT) trial examining optimal treatment of early-stage disease. I anticipate an exciting ASH/ASCO Symposium at our upcoming annual meeting in Orlando, and I look forward to working with new ASCO President, Dr. George Sledge, a colleague at Indiana University.

On June 12, at the EHA meeting in Barcelona, EHA and ASH coordinated a joint symposium: "Challenges and Opportunities in Hematology and Oncology in Developing Countries." This was co-chaired with long-time friend Dr. Robin Foà, EHA president. The talk was given by Dr. Ian Magrath, president of the International Network for Cancer Treatment and Research (INCTR) in Brussels. I received positive feedback regarding his presentation from a number of EHA members who felt, as we do, that more needs to be done to help those in developing countries attain access to better health care.

This September, ASH will participate in the 72nd Japanese Society of Hematology (JSH) Annual Meeting. With Dr. Keiya Ozawa, I will co-chair a joint symposium on Comprehensive Genomic Analyses of Lymphoid Malignancies: Future Clinical Applications. This will be the first JSH/ASH joint symposium; Drs. Louis Staudt of the National Cancer Institute and Margaret Shipp from the Dana-Farber Cancer Institute will join me in representing ASH in this exciting program.

I look forward to continuing the partnerships we are building through symposia and other joint initiatives, as we continue to extend our reach as an organization and collaborate with hematologists both here and abroad.

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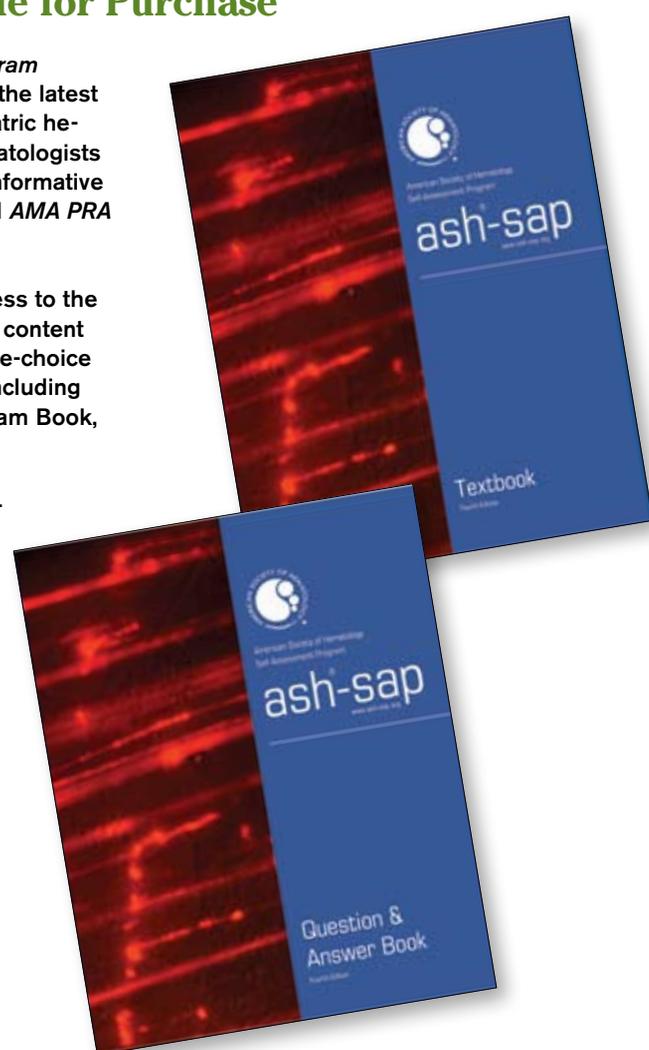
## ASH-SAP 4th Edition Now Available for Purchase

The *American Society of Hematology Self-Assessment Program (ASH-SAP)* is an educational resource that brings together the latest advances in the ever-evolving disciplines of adult and pediatric hematology. This comprehensive publication, created for hematologists and others working in hematology-related fields, features informative content, thorough board and recertification preparation, and *AMA PRA Category 1 Credits™*.

Included with the purchase price of the print edition is access to the *ASH-SAP* website ([www.ash-sap.org](http://www.ash-sap.org)). In addition to the full content of the book, the electronic version offers interactive multiple-choice questions and hyperlinks to other educational resources, including *Hematology*, the Society's annual meeting Education Program Book, and the ASH Image Bank.

Two versions of the fourth edition of the *ASH-SAP* are available for purchase: one offering *AMA PRA Category 1 Credits™* and the other offering both *AMA PRA Category 1 Credits™* and American Board of Internal Medicine (ABIM) Maintenance of Certification Credits. Both versions are the same price and can be purchased as a print and online package or as an online-only version.

	Print and Online Access	Online Access Only
Members	\$335	\$260
Non-Members	\$435	\$360
Associates/Trainees	\$240	\$165



## ASH Acknowledges National Sickle Cell Awareness Month and the 100th Anniversary of the Description of the Sickle Cell Trait

Congress has designated September as National Sickle Cell Awareness Month to help focus attention on the need for more research and improvements in the treatment of sickle cell disease.

Also marking an important date related to sickle cell disease, the National Institutes of Health (NIH) is hosting the "James B. Herrick Symposium – Sickle Cell Disease Care and Research: Past, Present, and Future" in commemoration of the 100th anniversary of Dr. James Herrick's initial description of sickle cell anemia. It will be held November 16-17, 2010, on the NIH campus in Bethesda, MD. This symposium will convene leading sickle cell experts to celebrate research advances and explore promising new scientific opportunities. A number of ASH members will be speakers. Look for a summary of the event in the January/February 2011 edition of *The Hematologist*.

ASH continues to work with Congress, the NIH, the Centers for Disease Control and Prevention (CDC), and other federal agencies to increase sickle cell research, treatment options, and access to care for patients with sickle cell disease. ASH has developed a sickle cell working group to help identify ways the Society can support federal programs and enhance the Society's advocacy efforts to improve research and treatment.

Information about NHLBI's recent workshop on "Framing the Research Agenda for Sickle Cell Trait" can be found on page 4 of this issue. To register for the Herrick Symposium, visit the symposium website at [www.nhlbi.nih.gov/meetings/James-Herrick-SickleCell](http://www.nhlbi.nih.gov/meetings/James-Herrick-SickleCell).

## Register for ASH Webinar Series on Thrombosis

ASH will present a series of three webinars on thrombosis issues practicing hematologists frequently confront. The sessions, moderated by Dr. Mark Crowther, of Aberdeen Royal Infirmary, United Kingdom, 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. All webinars will be one hour in length and occur at 8:00 p.m. (EST).

**September 14** – Heparin-Induced Thrombocytopenia (HIT)

Speakers include: Andreas Greinacher, MD; Ted Warkentin, MD; and Adam Cuker, MD

**October 20** – Coagulation Management in Cancer  
 Speakers include: Kenneth Mann, PhD; Ken Bauer, MD; and David Garcia, MD

**November 17** – Non-Hemophilia-Associated Conditions Associated With Bleeding

Speakers include: Catherine Hayward, MD, PhD; and Sarah O'Brien, MD

For more information or to register for these complimentary webinars, please visit [www.hematology.org/webinars](http://www.hematology.org/webinars).

## Election Ballots Due September 30

Active members in good standing (i.e., dues paid) should have received election materials for this year's ASH leadership election for Vice President, Treasurer, and Councillors. The results of the election will be announced in the November/December issue of *The Hematologist*.

(Cont. from page 1)

A typical day for Dr. Troy Lund while in Kampala, Uganda, is teaching pediatric residents and caring for children at the Mulago Hospital, which is part of the HVO program. Dr. Lund, an ASH member and a pediatric hematologist/oncologist at the University of Minnesota Medical Center, Fairview, has been traveling to Uganda for years, long before ASH and HVO had a program; he's been seven times. However, the day of the bombings was certainly unique. Two explosions struck two establishments in Uganda's capital on Sunday, July 11, in an apparent terrorist attack targeting crowds that gathered to watch the final World Cup soccer match. Dr. Lund himself was nearby watching the game. At half-time, he went to check on the children in the hospital and received a text message about the attack. He waited in the pediatric acute care unit thinking there would be children coming in, but there was not much activity. A resident then grabbed him, and they trucked down the hill to the main hospital's intake ward.

"It was like a scene from a movie – wall-to-wall people, at least 100 people down there with head injuries and various traumatic wounds from the explosions," Dr. Lund recounted. He spent the rest of the night treating head injuries, stopping bleeding, and closing wounds. He focused on stabilizing patients until 7:00 the next morning.

Dr. Lund explained, "This was a unique experience, and I had to revert back to my original training in med school." They lost seven individuals that night. More than 60 people died as a result of the blasts.

After the bombings occurred in Kampala, Dr. Lund still had another week left before heading back to the states. He said that no one left early from the group he had taken over there; everyone continued on with their work. His stays typically range from two weeks to two months.

Dr. Lund said he enjoys his work in pediatric hematology and working with the faculty at Mulago Hospital, and he looks forward to returning. His next visit is tentatively planned for this September.

While Dr. Lund spends time in Uganda, Dr. Lynn Bemiller recently spent time volunteering in Peru. "This was an outstanding experience for me, both professionally and culturally," said Dr. Bemiller. While in Peru, Dr. Bemiller traveled to hospitals in two cities. In Lima, Rebagliati Hospital serves as the main referral hospital in the country. Dr. Bemiller lectured staff and trainees on the diagnosis and management of thrombophilia and thrombosis. She also gave a talk on blood component therapy at a symposium presented by the hospital's hemophilia department.

"I spent time reviewing the hospital's capabilities and procedures for coagulation and coagulopathy testing. Based on its current practices, I worked with the director of the hematology laboratory to design a standard format for thrombophilia testing. This could be expanded into a standardized order set for testing and inpatient anticoagulation," Dr. Bemiller explained.

In Arequipa, a UNESCO World Heritage Site, Hospital Escobedo serves as the teaching site for two medical schools in the region. Dr. Bemiller participated in bedside teaching by discussing inpatient cases with residents and staff. She presented daily lectures on thrombosis, thrombophilia, transfusion medicine, and hematologic complications of pregnancy and also participated in a case-management conference on thrombocytopenia.

The volunteer experience extends to more subtle interactions than just clinical care, as Dr. Bemiller described: "For me, the most gratifying part of the experience was the recognition that medicine is a universal language, jokes and all, and that all of us in medicine have much more in common than we may think. Compassion is, likewise, independent of culture and language. We had two seriously ill patients that I will not forget. One was a young girl dying incredibly bravely of relapsed leukemia, the other, an older Native American man who spoke a language neither my hosts nor I could speak. We conveyed understanding by touch and eye contact, which was enough."

Doctors and laboratory scientists interested in volunteering through HVO must be members of ASH and become members of HVO. There is no restriction on nationality to apply; HVO accepts hematology volunteers from around the world for both adult and pediatric hematology. Some program sites offer opportunities for fellows. The first step in applying is to submit the Volunteer Profile Form, which is available on the HVO website at [www.hvousing.org](http://www.hvousing.org). An HVO volunteer coordinator will contact the applicant to discuss expectations and identify an appropriate country site. The applicant will then work closely with the site's program director, an ASH member who has been to the site and works closely with the staff to meet the site's educational needs. To learn more about volunteering, visit the ASH website at [www.hematology.org/hvo](http://www.hematology.org/hvo), or visit the HVO booth in the exhibit hall at the upcoming annual meeting in Orlando this December.

## NEWS AND REPORTS

## Framing the Research Agenda for Sickle Cell Trait

### NHLBI Workshop Focuses on Current Scientific Understanding of the Health Implications for Individuals With SCT

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On June 4 and 5, the National Heart, Lung, and Blood Institute (NHLBI) hosted a workshop at the NIH campus in Bethesda, MD, titled "Framing the Research Agenda for Sickle Cell Trait." The purpose of the meeting was to review the current scientific understanding of the health implications for individuals with sickle cell trait. In particular, the stated purpose was to focus on "sudden death in young adults, organ system complications, and ethical, legal, social, and public health impacts." The impetus for this workshop was the National Collegiate Athletic Association's (NCAA) 2009 decision to recommend screening of all college athletes for sickle cell trait (SCT). This recommendation, constituting part of a legal settlement, was precipitated by the death of Dale Lloyd Jr., a football player with SCT who died in practice at Rice University in 2006. In addition to NHLBI staff and members of the academic hematology community, a number of other stakeholders were represented by delegates and speakers, including CDC's Division of Hereditary Blood Disorders, HRSA's Maternal and Child Health Bureau, the Uniformed Services University of the Health Sciences, and several leading organizations, such as the Sickle Cell Disease Association of America.

The agenda on the first day focused on the exercise-related complications that have been described in subjects with SCT and exertional heat illness. These complications have included exertional rhabdomyolysis

with or without sudden or sub-acute death. Dr. John Kark from Thomas Jefferson University presented an update of the military experience that he originally described in a landmark paper in the *New England Journal of Medicine* in 1987. By studying records and autopsy reports of all sudden deaths among approximately 2 million Armed Forces recruits from 1977 to 1981, he demonstrated that, compared to African-American military recruits without SCT, subjects with the sickle trait had approximately a 30-fold risk of exercise-related death. About half of the described cases suffered exertional heat illness (rhabdomyolysis, heat stroke, and/or acute renal failure), while the remainder suffered idiopathic sudden death from cardio-pulmonary arrest. During the ensuing decade, drill instructors were trained to adjust workouts according to daily ambient temperature, to increase rest cycles and hydration, and to measure affected subjects' core temperature in the case of suspicious early symptoms. These simple measures, applied across the board for all recruits ("universal precautions"), resulted in an enormous reduction in the rate of death related to sickle trait.

Dr. E. Randy Eichner reviewed the clinical details of the 18 cases of NCAA Division I football players who died since 1974. SCT, present in just 3 to 4 percent of Division I players, has been linked to 63 percent of reported non-traumatic deaths in the past decade. A discussion of the ethical and practical concerns surrounding the NCAA's approach to the problem highlighted the history

of community screening for SCT, which has been fraught by a number of examples of poorly conceived programs resulting in stigmatization and/or discrimination. The overall consensus seemed to be that, while it seems a reasonable priority to support studies that will result in a better understanding of the pathophysiologic mechanisms and associated (exogenous and endogenous) risk factors underlying exertion-related complications, the military experience suggests that prevention of complications in college athletes should be possible by applying universal precautions without the need to single out affected individuals for special treatment.

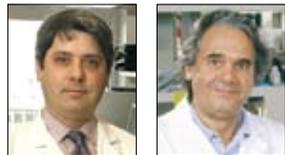
The second day of the workshop focused on some of the organ-specific complications of SCT. For several decades, numerous case series have reported a variety of adverse medical outcomes in individuals with SCT, and this segment was an effort to sift through those areas in which there exist not only higher quality clinical studies, but also some biologic rationale for the association. After hearing the evidence, the delegates were challenged to prioritize the areas in which further study appears warranted. By consensus, renal complications and thrombosis were thought to be the highest priority areas. Given that SCT affects approximately 3 million individuals in the United States, this may be an issue of genuine public health concern. It is very clear, however, that better data are needed before proceeding to mass screening, with all of its potential for undesirable stigmatization.

# MicroRNAs in Hematologic Malignancy

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MicroRNAs (miRNAs) are small non-coding RNAs of about 18 to 24 nucleotides in length that regulate gene expression and thus influence such processes as development, differentiation, proliferation, and apoptosis.<sup>1</sup> MiRNAs exert their biological effects by binding in a sequence-specific manner

for the most part to the 3' untranslated region (3' UTR) of the target mRNA, causing protein translation inhibition and/or mRNA degradation. It has been estimated that miRNAs regulate about 30 percent of human genes.<sup>1</sup> Findings over the past eight years strongly support a role for deregulated miRNA activity in the initiation and progression of cancer, including hematologic malignancies (HM).<sup>1</sup> We will briefly summarize the state of the field and discuss future directions.

## Expression-profiling studies in disease classification/diagnosis

Following our initial demonstration of deletion/down-regulation of *miR-15a/miR-16-1* in B cells of patients with chronic lymphocytic leukemia (CLL), additional studies established that malignant hematopoietic cells exhibited distinctive miRNA expression signatures compared to their normal counterparts. The advent of high-throughput miRNA profiling established that such miRNA expression signatures allowed discrimination with high accuracy among different cytogenetic and molecular subtypes of leukemias/lymphomas and multiple myelomas.<sup>2</sup> Although there were similarities in miRNA signatures among the disease-specific miRNA profiling studies published in the literature, substantial differences were also noted. This could be explained by the use of different platforms to interrogate miRNA expression, heterogeneity in the sample population, or control cells used (CD34<sup>+</sup> selected vs. total bone marrow).<sup>2</sup> Novel platforms are now increasingly available, including next generation sequencing, which may improve sensitivity and accuracy of miRNA detection and, in addition, may enable discovery of novel miRNAs and mutations/polymorphisms. The presence of circulating miRNAs within microvesicles in the peripheral blood is intriguing; however, the functional significance remains to be fully understood.

## Functional studies

Gain- and loss-of-function experiments, including animal models in combination with target prediction analyses have provided insights into the role of miRNAs in leukemogenesis. In AML, *miR-29b* is emerging as an important tumor suppressor.<sup>3-4</sup> We have reported that *miR-29b* modulates DNA methylation by targeting DNA methyltransferases (*DNMT-1*, *3A*, and *3B*). Restoring *miR-29b* expression in AML cell and primary samples resulted in global DNA hypomethylation and gene re-expression of methylated and silenced tumor suppressor genes.<sup>3</sup> Furthermore, *miR-29b* overexpression suppresses cell proliferation and induces cell death by directly targeting the cell-cycle regulator *CDK6* and the anti-apoptotic *MCL-1*. The antitumor effects were validated in murine xenograft models.<sup>4</sup>

Recently, we established the central role of *miR-29b* in a transcriptional network that regulates *KIT* transcription in AML cells.<sup>5</sup> Loss of *miR-29b* unblocks expression of the transcription factor Sp1 that in combination with NF- $\kappa$ B binds to the *KIT* promoter and activates its transcription. We further showed that *KIT* overexpression is prognostic in AML and is involved in leukemogenesis promoting cell proliferation.<sup>5</sup> In CML, our group identified that upon disease progression to blast crisis there is loss of *miR-328*, which directly interferes with the activity of hnRNP-E2, a poly(rC)-binding protein that suppresses neutrophil maturation in blast-crisis CML through translational inhibition of *C/EBP $\alpha$*  expression.<sup>6</sup> In contrast to the classical miRNA effector pathways, the C-rich mature *miR-328* interacts in a non-sequence-specific manner with hnRNP-E2 and prevents its binding to the *CEBPA* intercistronic region (decoy activity), thus allowing *C/EBP $\alpha$*  expression, which directly enhances *miR-328* transcription.<sup>6</sup>

Lastly, *miR-15a/miR-16-1*, which is lost in CLL patients by genomic deletion and mutations, directly targets *BCL-2*, a known anti-apoptotic gene that is up-regulated in a subset of CLL patients. A negative correlation was found between *miR-15a/miR-16-1* and *Bcl-2* protein expression in CLL patients, and ectopic overexpression resulted in apoptosis in leukemic cells. It was recently reported that *miR-15a/miR-16-1* knockout mice developed a CLL-like disease and lymphomas, further supporting a tumor suppressor role in CLL. These are some examples of functional implications of miRNAs in HM, thereby supporting a critical pathogenic role of miRNAs. The challenge for the future is to integrate miRNAs into the context of oncogenic pathways in HM and develop more animal models with gain or loss of function of miRNAs.

## MiRNAs as biomarkers

In AML, two studies reported miRNA signatures associated with outcome. In high-risk, cytogenetically normal, young patients (< 60 years old), defined by the presence of FLT3-ITD mutations or wild-type nucleophosmin or the combination of both genotypes, high levels of *miR-181* family members were associated with better event-free survival.<sup>7</sup> In a different subset of AML patients (older with intermediate and poor-risk cytogenetics), high levels of *miR-199a* and *miR-191* were associated with lower overall and disease-free survival.<sup>8</sup> It has been reported that lower levels of *miR-29b* are associated with worse

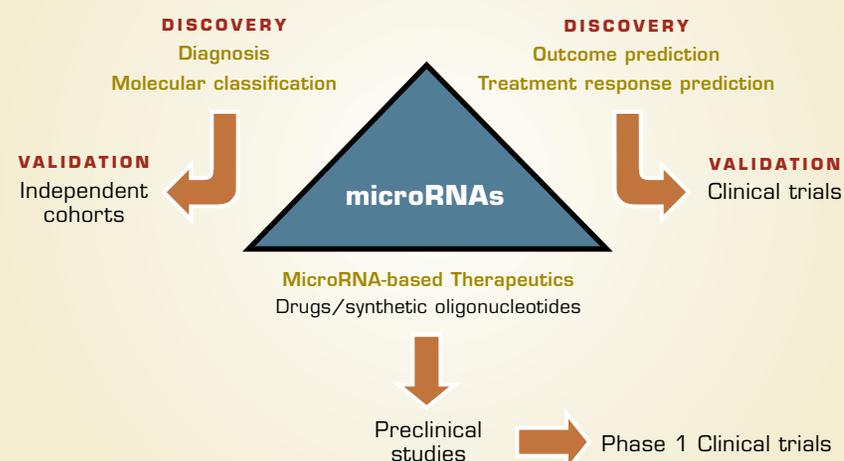
outcome in mantle cell lymphoma. In CLL, an miRNA signature, including high levels of *miR-155* and *miR-146*, was associated with disease progression.<sup>9</sup> Concerning miRNAs as predictor for treatment response, our group recently reported that higher pre-treatment levels of *miR-29b* were associated with achievement of clinical response to single-agent decitabine (20 mg/m<sup>2</sup> for 10 days) in elderly AML patients.<sup>10</sup> Future directions include standardization of assays to measure miRNAs in a reliable and reproducible way to test further their biomarker potential in clinical trials.

## Targeting miRNAs in hematologic malignancy

One of the most appealing properties of miRNAs as therapeutic agents is their ability to target multiples genes, frequently within the context of a network, making them very efficient in regulating distinct biological cell processes relevant to normal and malignant cell homeostasis. One can envision that there is potential to use strategies to modulate miRNA expression in specific diseases. In CLL, restoring *miR-15a/miR-16-1* may block *BCL-2* expression and induce apoptosis, while in AML over-expressing *miR-29b* may block apoptosis pathways (*MCL-1*), proliferation (*CDK6*), methylation (*DNMT1*, *3a*, and *3b*), and kinome alterations (*c-KIT*). These strategies may include the use of mimic or antisense oligonucleotides, drugs or small molecule compounds that affect miRNA transcription. Current challenges include delivery of synthetic oligonucleotides, stability, and safety.<sup>11</sup>

Figure

### From the bench to the clinic: potential clinical application of microRNAs in hematologic malignancy



In this schema, we outline the potential clinical applications of microRNAs in hematologic malignancies. Translation of molecular and prognostic biomarker discoveries to the clinic will require extensive validation in independent cohorts of patients using validated and reliable platforms for miRNA detection. These results should then be tested prospectively in clinical trials. Targeting microRNA's expression in hematologic malignancy requires identification of the candidate microRNAs, evaluation of the different strategies to achieve expression modulation (drugs, antisense, or oligonucleotide mimics), and validation in preclinical animal models. Successful candidates then can be moved forward to phase I clinical trials for toxicity evaluation and pharmacokinetics/pharmacodynamics studies.

In summary, miRNA deregulation is involved in the initiation and progression of HM, and there is potential to use miRNAs to improve disease molecular classification and to establish novel biomarkers to predict outcome and treatment response and develop novel miRNA-based therapeutic strategies (Figure).

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Drs. Garzon and Croce indicated no conflicts of interest.

# HEADLINES FROM Washington



## HHS Announces Final Rules to Expand Use of Electronic Health Records

The U.S. Department of Health and Human Services (HHS) recently announced final rules aimed at increasing safety and reducing health-care costs through expanded use of electronic health records (EHRs). Under a provision included in the American Recovery and Reinvestment Act of 2009 (ARRA), eligible health-care professionals and hospitals can qualify for Medicare and Medicaid incentive payments when they adopt certified EHR technology and use it to achieve specified objectives. A final rule issued on July 13 by the Centers for Medicare and Medicaid Services (CMS) defines the minimum requirements (or “meaningful use” objectives) that providers must meet through their use of certified EHR technology in order to qualify for incentive payments.

CMS anticipates that enrollment in the EHR incentives program will begin in January 2011, with the first payments to eligible professionals and hospitals expected around May 2011. For more information, please read Dr. Larry Solberg’s article on page 14 in the July/August issue of *The Hematologist*.

## CMS Releases Proposed 2010 Regulations Affecting Physician Payment

Earlier this summer, the Centers for Medicare and Medicaid Services (CMS) released proposed rules for the Medicare Physician Fee Schedule (MPFS) and the Hospital Outpatient Prospective Payment System (OPPS). The proposed MPFS would provide a 6.1 percent cut for physician payment in 2011 based on the sustainable growth rate (SGR). This reduction would be in addition to the 23 percent reduction that will occur on December 1, 2010, if not prevented by new legislation. The proposed rule would cut physician payments further by some rescaling of the fee schedule. ASH strongly opposes these proposed cuts and will continue to advocate to Congress and CMS the need to provide appropriate physician reimbursement and find a long-term solution to the flawed payment formula.

The OPPS proposed rule will update policies and payment rates for the more than 4,000 hospitals that provide hospital outpatient services to Medicare beneficiaries and for the approximately 5,000 Medicare-participating Ambulatory Surgery Centers. In addition, OPPS will implement provisions of the Patient Protection and Affordable Care Act (PPACA). CMS is proposing a 2.15 percent increase for hospitals that successfully reported CMS designated quality measures in 2010. Detailed analyses of these proposed rules may be found at [www.hematology.org/Practice](http://www.hematology.org/Practice).

## FY 2011 NIH Funding Process Moves Forward

The Senate Appropriations Committee approved its draft fiscal year (FY) 2011 Labor, Health and Human Services (HHS), Education and Related Agencies Appropriations bill on July 29. The Committee-approved bill, which must still be voted on by the full Senate, recommends just over \$32 billion for NIH — approximately \$1 billion (3.2 percent) over the final FY 2010 funding levels that were enacted in December of last year. This falls short of the \$35 billion in funding ASH and the biomedical research community have advocated for NIH in FY 2011.

Meanwhile, the House Labor-HHS Appropriations Subcommittee approved its version of the FY 2011 Labor-HHS bill on July 15. As with the Senate bill, the House Subcommittee bill recommends that NIH be funded at just over \$32 billion. However, neither the House Appropriations Committee nor the full U.S. House of Representatives were able to consider the bill prior to adjourning for the month-long August district work period.

With both the Senate and House adjourned until the week of September 13, it remains unlikely that the appropriations process will be completed by the start of the new fiscal year on October 1. As a result, Congress would have to implement what is known as a continuing resolution that would simply fund the government at current levels to avoid a government shut-down.

ASH will continue its advocacy efforts supporting increases for NIH on Capitol Hill throughout the remainder of the FY 2011 budget debate. The Society encourages all members to visit the ASH Advocacy Center at [www.hematology.org/takeaction](http://www.hematology.org/takeaction) to take action to support increased funding for NIH. With a very tight year expected for the entire federal budget and many domestic programs facing cuts or minimal increases, significant grassroots support for NIH funding is critical to gain any further traction for increasing NIH funding in the budget process.

## FDA Announces Reorganization of the Office of Oncology Drug Products

As part of recent organizational changes within the Food and Drug Administration (FDA), the Office of Oncology Drug Products (OODP) is planning a reorganization that is expected to take effect in 2011. The OODP, which currently comprises three divisions, will change its name to the Office of Hematology and Oncology Products (OHOP) and create a new structure with four divisions:

- The Division of Hematology Products (DHP)
- The Division of Hematology Oncology Toxicology (DHOT)
- The Division of Oncology Products 1 (DOP 1)
- The Division of Oncology Products 2 (DOP 2)

The Oncology Program, which coordinates oncology activities across FDA Centers and with the National Cancer Institute (NCI) and other cancer-related organizations, will remain in the main Office of Hematology and Oncology Products.

As a result of the reorganization, review of biologic and drug products will be integrated within each review division; review staff within the two divisions of oncology products will specialize in specific oncologic diseases (e.g., breast cancer, gastrointestinal cancer, melanoma); and there will be a distinct division, DHOT, dedicated to reviewing the non-clinical pharmacology and toxicology of oncology products.

## NIH Announces Availability of Educational Loan Repayment Programs

The National Institutes of Health (NIH) recently announced the continued availability of educational loan repayment through its extramural Loan Repayment Programs (LRPs). The NIH LRPs provide promising researchers and scientists the opportunity to pursue research careers by repaying up to \$35,000 of their qualified student loan debt each year. The application period for new and renewal extramural applicants is September 1 through December 1, 2010.

Applicants accepted into the programs will engage in NIH mission-relevant research for at least two years, during which time a minimum of 50 percent of their work hours (not less than 20 hours based on a 40-hour work week) must be applied toward their NIH research activities. The NIH extramural LRPs are intended to increase the recruitment and retention of research investigators in the following areas of research: clinical, pediatric, health disparities, and contraception/infertility. Each of the LRPs has specific eligibility requirements and funding set-asides. Details of the NIH LRPs may be found on the LRP website at [www.lrp.nih.gov](http://www.lrp.nih.gov).

# Update on Health Reform – Initial Implementation and Impact

MILA BECKER, ESQ.

Director, Government Relations and Practice, ASH



*On March 23, President Obama signed into law the Patient Protection and Affordable Care Act, and, one week later, he followed with modifications in a budget reconciliation bill. Soon after The Hematologist included a summary of the new law and a timeline of when the major provisions would go into effect. Below is an update on the health reform implementation and its initial impact.*

Health reform is now the law of the land. A major focus of the legislation was to expand insurance coverage, and it is estimated that the new law will result in 32 million uninsured Americans and legal immigrants obtaining coverage by 2019. One of the first provisions to go into effect is a program designed to provide access to high-risk insurance pools for people who have been uninsured for at least six months and have been unable to obtain private health coverage because of a pre-existing health condition. Application details and coverage dates vary by state, but the Department of Health & Human Services expects that 200,000 individuals will gain coverage this year through the “pre-existing condition insurance plan.” Other coverage-related initiatives that will be implemented this year include closing the coverage gap in the Medicare prescription drug benefit by providing a \$250 rebate to beneficiaries who reach the benefit cap, expanding preventive coverage in Medicaid, and covering annual physicals and wellness visits for some Medicare beneficiaries.

Also being implemented this fall are several private insurance market reforms that were designed to address some of the behaviors of the insurance industry that upset consumers. This includes barring insurers from denying people coverage when they get sick or denying children who have pre-existing conditions, barring insurers from imposing lifetime caps on coverage, and requiring insurers to allow young adults to stay on their parents’ policies until age 26.

The nearly \$1 trillion cost of expanding coverage will be financed in part by higher Medicare payroll taxes on upper income families, excise taxes on so-called “Cadillac” health insurance policies, and fees paid by pharmaceutical

companies, hospitals, and insurers. Payments to Medicare Advantage, the private Medicare plans, will also be restructured to eliminate current overpayments. All of these efforts, however, will not take effect for several years.

A second goal of the new law is to reduce health-care costs. One of the new cost containment tools will be the Independent Payment Advisory Board, which will make Medicare payment and waste-reduction recommendations to Congress (hospitals are exempt through 2019). Another is the Center for Medicare and Medicaid Innovation, which will allow patient-centered care models to be tested and introduced system-wide with more speed and flexibility than traditional demonstration projects. These new institutions could have significant impact on hematologists by introducing new payment and delivery systems and experimenting with new ways to reward care management and coordination. ASH has been monitoring the development of these organizations, has submitted comments on initial regulatory proposals and priorities, and has recommended hematology experts to advise the new Center. Additional cost containment provisions included in the new law are the creation of a pathway for approval of biogenerics (drugs derived from live cells, including recombinant proteins and monoclonal antibodies), steps to strengthen the primary-care workforce, and a new Patient-Centered Outcomes Research Institute to oversee federally sponsored comparative effectiveness research to determine what drugs, devices, or procedures work best. Although the Institute’s creation is still in early regulatory phases, ASH has nominated hematologists to work with the new Institute and has already weighed in on a number of early proposals, as the Society believes this entity could have a major impact on hematologists.

The third goal of health reform is to improve quality of care. Many of the law’s provisions are modest steps or pilots, focused on government-run programs like Medicare and Medicaid, and it is not clear how quickly or effectively they will ripple through the whole health-care system. The law, however, requires a national quality improvement strategy, which includes wellness and population health, as well as a new effort to document and address health-care disparities. Among the initiatives aimed at creating a high-performing health system that ASH is monitoring are: encouraging the creation of Accountable Care Organizations (groups of providers who can jointly be held accountable for the quality and cost of care for a defined population) that would use a more integrated and evidence-based approach to care by meeting quality benchmarks; providing financial incentives for hospitals to reduce unnecessary re-admissions and bring down rates of hospital-acquired infections and related conditions; establishing payment bundling programs that would pay a team of providers for one episode of care across several health-care settings in a way that would regard quality, coordination of care among providers, and outcomes; and providing funding to assist and incentivize “meaningful use” of health information technology.

As President Obama noted at the law’s signing, passage of health reform was a “remarkable and improbable” achievement. Yet, in the country’s current polarized and partisan environment, it remains fraught with political and policy uncertainties that could shadow implementation in the years to come. The law and its implementation is a work in progress. The 2010 legislation will need tweaks, adjustments, and, possibly over time, major amendments. States will also continue to experiment on their own. Some insurers and health plans may resist change. ASH will continue to be actively involved and represent members’ interests and concerns as implementation moves forward.

## ASH Hosts Patient Advocates Reception

On May 24, ASH hosted the annual Patient Advocates Reception in Bethesda, MD. This reception was held in conjunction with the National Heart, Lung, and Blood Institute’s (NHLBI) Public Interest Organization Conference. As chair of the Committee on Communications, I represented ASH, along with several members of the ASH staff. Patient advocate groups in attendance represented a wide swath of hematologic diseases including:

- American Autoimmune Related Diseases Association
- Aplastic Anemia & MDS International Foundation
- Barth Syndrome Foundation
- Daniella Maria Arturi Foundation
- Churg Strauss Syndrome Association
- Hermansky-Pudlak Syndrome Network
- National Blood Clot Alliance
- National Hemophilia Foundation
- Platelet Disorder Support Association
- Pulmonary Hypertension Association
- Vasculitis Foundation

These attendees were informed about the mission and background of ASH, the numerous ASH resources and services available to their constituents, and the ways their organizations can interact with ASH. Following this introduction, Dr. Keith Hoots, director of the Division of Blood Diseases and Resources at NHLBI, highlighted NHLBI’s relationships with various patient groups. A number of other representatives from NHLBI were present including the Acting Director of NHLBI, Dr. Susan Shurin.

This reception was initiated four years ago, following a roundtable meeting of patient advocate groups, during which the advocates expressed a desire to have a venue for networking and exchanging ideas. The Committee on Communications has recently re-affirmed that this is an excellent venue where ASH can reach out to these patient groups while also providing an informal environment for them to interact with one another.

—Peter Emanuel, MD



# DIFFUSION

## A Step Toward Safer Immunomodulatory Drugs

Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science*. 2010;327:1345-1350.

In this study, Ito and colleagues from the Tokyo Institute of Technology delineate the mechanism whereby thalidomide causes phocomelia or amelia when administered to pregnant women. They showed that a carboxylic thalidomide derivative conjugated to inert beads precipitated two proteins from extracts of HeLa cells – cereblon (CRBN) and damaged DNA binding protein-1 (DDB1). To show specificity of the interactions, they demonstrated that CRBN binding was inhibited by free thalidomide and that recombinant CRBN could bind to the thalidomide beads. They then demonstrated that CRBN serves as a substrate receptor of E3 ubiquitin ligase cullin-4 (Cul4A) complexes containing DDB1, suggesting that DDB1 binds to thalidomide through its interaction with CRBN. This complex has E3 ubiquitin ligase activity, evidenced by auto-ubiquitination in a Cul4A- and DDB1-dependent fashion. Importantly, this activity was inhibited by thalidomide in wild-type cells, but not in cells with mutated CRBN binding sites that prevent thalidomide binding. These findings were confirmed *in vivo* in both zebrafish and chicks, since binding of thalidomide to CRBN homologous genes during embryogenesis also blocked ligase activity and conferred teratogenic phenotypes, again not observed when thalidomide binding sites were mutated. Downstream targets implicated in mediating these processes include fibroblast growth factors (fgf) 8 and 10, which are known to be responsible for limb outgrowth and which were reduced by thalidomide treatment. Conversely, overexpression of CRBN restored expression of fgf8 and 10 and abrogated the teratogenic effects. Most importantly, these investigators mapped the thalidomide binding site to a highly conserved C-terminal 104 amino acid region in CRBN.

Thalidomide was first used empirically to treat multiple myeloma (MM) based on its anti-angiogenic effects and has remarkable activity even in patients with advanced refractory disease. It is FDA-approved for initial treatment of MM and has also prolonged progression-free survival when used as a maintenance therapy. In addition to anti-angiogenic activity, preclinical studies have shown that thalidomide has modest direct MM cell cytotoxicity, abrogates binding of MM cells to bone marrow, inhibits constitutive and MM cell binding-induced transcription and secretion of cytokines, and augments host cytolytic T and NK cells with anti-MM activity. Which of these activities is most important in terms of mediating clinical benefit remains unknown. Nonetheless, next generation immunomodulatory drugs lenalidamide and pomalidamide more potently mediate these effects and have remarkable clinical activity even in thalidomide-refractory MM. However, each of these agents also causes teratogenicity in preclinical models, and therefore elaborate systems have been set up to assure that pregnant women do not receive these immunomodulatory drugs.

This study is a major advance with important implications for clinical use of this class of immunomodulatory drugs. First, understanding thalidomide targets will allow for further characterization of its effects during embryogenesis. Second, it will facilitate delineation of the mechanisms of anti-tumor activity of thalidomide and, specifically, whether binding to CRBN is required for the aforementioned anti-MM cellular effects. If anti-tumor activity is preserved even in CRBN mutants that do not bind thalidomide, then the opportunity for synthesis of novel derivatives lacking CRBN binding for preclinical testing and eventual clinical application represents a major potential therapeutic advance. Already second-generation immunomodulatory drugs lenalidamide and pomalidamide have retained potent anti-MM clinical activity but lack the somnolence, neuropathy, and constipation attendant to thalidomide use, suggesting that altering structure to maintain potency but favorably impact adverse effects is possible. The current study, therefore, may lay the groundwork for synthesis of potent immunomodulatory drugs that lack CRBN binding and could have major implications for expansion of the spectrum of diagnoses and patients eligible for treatment with these agents.

KENNETH ANDERSON, MD

Dr. Anderson has served on the advisory board for Celgene.

## Targeting CD20: Still Much to Learn

Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct- and immune effector cell-mediated B-cell cytotoxicity. *Blood*. 2010;115:4393-4402.

Since the approval of the first anti-CD20 monoclonal antibody, rituximab, in December 1997, significant advances have been made in moving this therapeutic modality forward to wide use in virtually all CD20-positive B-cell malignancies, as well as for many autoimmune diseases. While the clinical operation to advance rituximab has been quick, understanding how CD20 monoclonal antibodies mediate their direct effect and how we can improve them has been a slower process. Early work suggested that CD20 was neither internalized nor shed significantly, thereby justifying pursuit of this target for immune-based therapy.

CD20 antibodies mediate their biologic effects against tumor cells through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and direct apoptosis. Type I CD20 antibodies (rituximab, ofatumumab) redistribute into lipid rafts, fix complement, mediate ADCC, and promote modest apoptosis only with cross linking. In contrast, type II CD20 antibodies (e.g., GA-101) remain outside of the rafts, lack significant complement fixation, mediate ADCC, and promote direct cell death through homotypic adhesion. Although type I CD20 antibodies are utilized in clinical practice, type II antibodies are still being tested in clinical trials with promising results. The finding that type II CD20 antibodies work well against CLL is quite exciting, as the type I antibodies have shown less (although still significant) efficacy.

A very promising series of studies by several different groups remind us that there is still much to understand about CD20 antibody-based treatment. In this latest paper, Mössner and colleagues from a biotechnology company in Switzerland demonstrated that type II CD20 antibodies are much more efficient than type I at depleting normal B cells in a human CD20 transgenic model that is dependent upon macrophages and Fcγ receptors. This difference in B-cell depletion relates to the degree of CD20 internalization following antibody binding. Specifically, type II antibodies undergo far less internalization and degradation than type I. Surprisingly, but in agreement with clinical data collected thus far, the authors demonstrated that internalization and degradation of type I CD20 antibodies is most pronounced in CLL, whereas it occurs less in other types of B-cell lymphoma. These data provide a rational explanation for why type II CD20 antibodies might be more effective in CLL and, again, are supportive of what has been observed to date in early phase I clinical trials of the first type II CD20 antibody, GA-101.

The importance of this paper to B-cell immunotherapy is clear, and there are many lessons we can take from it. Despite the success of rituximab, and recently of atumumab, in several different B-cell malignancies and autoimmune diseases, our understanding of the mechanism by which this class of drug works is still very much evolving. The uniqueness of each neoplastic disease (CLL and NHL) and often contrasting mechanisms in pathologic, but not transformed, B cells must always be considered. For example, type II CD20 antibodies may be effective both for B-cell-dependent autoimmune diseases, where rituximab has had modest effect, and for CLL. In contrast, the benefit of type II CD20 antibodies in other types of lymphoma where antibody internalization and degradation are not as apparent may yield less significant improvements. Along with tailoring antibodies to specific diseases, we might also take better advantage of the antibody-cell interactions themselves. Type I antibodies are internalized with no measurable shaving, and this may make such antibodies ideal for the delivery of conjugated cytotoxic agents. Other possibilities undoubtedly exist and are waiting to be explored. As new therapeutic agents continue to be identified, early basic and translational investigation, such as that of Mössner et al. will form the foundation for tailoring and optimizing treatments, not only to each disease, but to each patient.

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JONATHAN P. BUTCHAR, PhD, AND JOHN C. BYRD, MD

Drs. Butchar and Byrd indicated no relevant conflicts of interest.

## Clearing Your Head by Translocation of Emboli

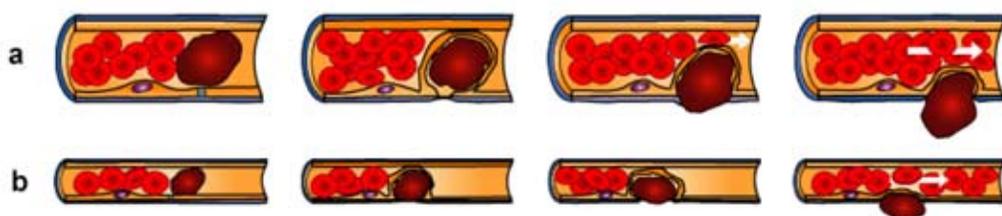
Lam CK, Yoo T, Hiner B, et al. Embolus extravasation is an alternative mechanism for cerebral microvascular recanalization. *Nature*. 2010;465:478-482.

**M**aintenance of blood flow through the cerebral microvasculature is essential to normal cerebral function. Fibrinolysis and hemodynamic forces clear fibrin-rich clots from the cerebral microcirculation rapidly and efficiently. However, fragments from atherosclerotic plaque and complex clots not susceptible to fibrinolysis can also occlude the cerebral microvasculature. Such emboli are not effectively cleared by the fibrinolytic system. What is the fate of these fragments? Lam et al. from Northwestern University in Chicago have now identified a heretofore unrecognized mechanism for maintaining patency of the microvasculature. They demonstrated that the endothelium is capable of clearing the microvasculature of occlusive emboli by translocation, thereby restoring blood flow.

The investigators used transcranial two-photon microscopy of the cerebral microvasculature to evaluate the fate of fluorescent fibrin clots, cholesterol emboli, and microspheres infused through the internal carotid arteries of mice. Mice expressing Tie2-green fluorescent protein were used in these studies to visualize the endothelium following infusion of fluorescent emboli. The investigators found that emboli that were not lysed within the first few hours following infusion were extravasated from the vessel over a two- to seven-day period. Electron microscopy of tissue samples from these mice confirmed that the emboli had been extruded into the surrounding tissue. An open luminal space completely surrounded by an endothelial layer was observed next to the extravasated emboli, consistent with the observation that blood flow is restored after translocation. Time-lapse imaging demonstrated how the endothelium generated the proto-lumen. Endothelial membrane projections formed around the emboli. The new endothelium grew all the way around the emboli to create the proto-lumen (Figure). The original endothelium concurrently underwent retraction, enabling the extravasation of emboli into the perivascular parenchyma. Inhibitors of matrix metalloproteinases interrupted this process, suggesting that proteases participate in the remodeling of the endothelium and are required for embolic extravasation. The authors also compared emboli extravasation in younger mice to that of older mice. They found that the rate of emboli extravasation is substantially slower in older mice. In addition, the older mice suffered increased synaptic injury and death following infusion of emboli.

Figure

Extravasation of emboli from cerebral arterioles and capillaries



Flow is reestablished rapidly during the extravasation process allowing vessel survival. (a) In arterioles  $> 20 \mu\text{m}$  in diameter, blood flow is reestablished, at least partially, even before complete embolus extravasation given that multiple rows of cells can circulate simultaneously. (b) In capillaries, blood flow is generally reestablished following complete embolus translocation.

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Loss of patency within the cerebral microvasculature can result in tissue ischemia and cognitive impairment. The observations that microvessels are capable of clearing emboli and that this ability declines with age may improve our understanding of age-related cognitive decline and stroke recovery. That similar age-related processes occur in humans will need to be demonstrated. In addition, the effect of impaired embolic translocation on neuronal damage will need to be more clearly defined. Nonetheless, these studies elegantly demonstrate an unexpected function of the cerebral microvasculature. As the innovative imaging techniques used to make these observations come into wider use, we will likely find out whether this function is observed in other microvascular beds or whether it is a unique feature of cerebral endothelium.

ROBERT FLAUMENHAFT, MD, PhD

Dr. Flaumenhaft indicated no relevant conflicts of interest.

## Complex Approaches are Complex

Bendle GM, Linnemann C, Hooijkaas AI, et al. Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. *Nat Med*. 2010;16:565-570.

**A** major component for the success of allogeneic hematopoietic cell transplantation (HCT) is the graft-versus-leukemia (GVL) effect. It is a form of adoptive immunotherapy, albeit crude, in that the donor cells are polymorphic and heterogeneous, sometimes leading to GVL but often to graft-versus-host disease (GVHD) with or without GVL. The ability to induce GVL without GVHD remains the Holy Grail in HCT. There has been great interest in specific adoptive immunotherapy. The thinking is that perhaps one could remove all the non-specific T cells that could cause GVHD and give only those that are targeting a particular antigen, be it a tumor antigen or an infectious agent such as cytomegalovirus (CMV). Tumor- (or viral-) specific T cells can be created through transfer of the genes of unique T-cell receptor (TCR) into cytotoxic T cells (CTLs). These T cells will then express high levels of the transfected TCRs, creating CTLs that will recognize the targeted antigen although it will also express its original endogenous TCR. Clinical trials that are testing these approaches are currently ongoing.

The paper from the lab of Schumacher in Amsterdam raises a significant caution to these approaches. The concern is that the exogenous TCR (composed of the  $\alpha$  and  $\beta$  chains) could rearrange with the endogenous  $\alpha\beta$  chains, as each chain is expressed individually and then combined, creating a novel TCR that would be auto-reactive. Sufficient auto-reactive T cells would then lead to GVHD, especially in the setting of HCT, where there is a major component of homeostatic T-cell proliferation after lymphodepletion. The authors demonstrated this concern by transfecting  $\alpha\beta$  TCR chains directed against the model antigen ovalbumin (OVA). They then gave these cells to mice that had been lymphodepleted by irradiation followed by interleukin-2 *in vivo*. Within two weeks, the authors noted that the animals developed cachexia, lymphopenia, colitis, and marrow failure, similar to findings of GVHD (called TCR gene transfer induced GVHD [TI-GVHD]). This induced GVHD occurred in animals that expressed OVA in their tissues and in animals that did not. They then demonstrated that this phenomenon was directly related to the infused OVA specific T cells, which had gained specificity for unidentified host antigens through recombination with the endogenous TCR; a single  $\alpha$  or  $\beta$  chain was sufficient for this new specificity. The control T cells transduced with green fluorescent protein (GFP) did not develop GVHD.

Perhaps it should not have been surprising that TI-GVHD occurred in these experiments since the introduction of a polyclonal population of T cells, even with transfected TCRs, would likely represent many TCRs that could result from cross-pairing. The use of oligoclonal or monoclonal transgenic T cells does not result in TI-GVHD. It is not clear how relevant these observations are in humans as many of these studies are just beginning. However, these data suggest that it is important to develop strategies that would prevent such cross-pairing of transduced and native  $\alpha$  and  $\beta$  chains. Such approaches include the addition of cystine-modified transduced TCRs that allow for a new disulfide bond, thus reducing the cross-pairing or use of unique chimeric antigen receptors (CARs) that utilize the variable regions of immunoglobulin that are not likely to recognize host minor antigens. Other approaches could be to simultaneously introduce suicide genes, so that if these transduced T cells cause TI-GVHD, they could be destroyed. These are indeed complex systems.

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Dr. Chao indicated no relevant conflicts of interest.

## Chemotherapy and Drug Tolerance: Is There a Path to Least Resistance?

Sharma SV, Lee DY, Li B, et al. A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. *Cell*. 2010;141:69-80.

The primary imperative of a cell is to survive. This is fine when the cell is healthy. For a cell transformed into a cancer, this underlying biological drive blocks our ability to bring cures to patients. The cancer cell has many strategies to undermine our treatments, including drug efflux, hiding in protective microenvironment niches, and employing genetic instability to create clones that can emerge during chemotherapy through natural selection. A recent manuscript by Sharma et al. documents another fascinating and frustrating adaptation for drug resistance.

In a very simplistic fashion, one can imagine three varieties of cancer. The first is a homogeneous population of sensitive cells, representing those rare patients for whom chemotherapy works immediately and dramatically. The second type, made up of a homogeneous population of refractory cells, results in early therapeutic failure. The vast majority of cancers are those with a heterogeneous population of both sensitive and resistant cells. Here, therapy is a continual experiment of Darwinian selection, with resistant clones emerging through the selective pressure of the chemotherapy. Sometimes in the setting of relapse, newly emergent clones can be detected by the presence of genetic markers not present in the original sample. Yet, sometimes these cells appear the same as in the original disease. Even more baffling, sometimes retreatment with the original agents will yield a response. How can one explain sensitivity (however brief) in the same cells that were previously resistant?

In this fascinating study, Sharma et al. from Massachusetts General Hospital reported on the phenomenon of reversible, drug-tolerant cells emerging during exposure to chemotherapy agents. The experiments were performed in cell lines, predominately the EGFR mutant non-small cell lung cancer derived cell line, PC9. This cell line is very sensitive to EGFR tyrosine kinase inhibition (TKI). Upon exposure to TKI, a small residual population (< 1 percent) of the original cells persisted with radically (> 100-fold) reduced sensitivity to the TKI. These "drug-tolerant persisters" (DTPs) could also be found after the PC9 cells were exposed to cisplatin. DTPs were generally quiescent, though ~20 percent resumed normal proliferation in the continued presence of drug, thereby becoming "drug-tolerant expanded persisters" (DTEPs).

Several lines of experiments demonstrated that tolerance was not due to drug efflux or clonal selection of a new mutation. Other key observations in this study were that: 1) PC9 cells plated at low density, even without exposure to drug, occasionally yielded DTP cells, consistent with low-level spontaneous emergence of the resistant phenotype; 2) DTPs and DTEPs, when subsequently grown without drug, would eventually revert back to the sensitive phenotype; 3) mechanistically, the tolerance exhibited by DTPs required the chromatin-remodeling gene histone demethylase KDM5A; treatment of DTPs and DTEPs with histone deacetylase (HDAC) inhibitors caused a reversion back to the drug-sensitive state; 4) formation of DTPs appeared to require IGF-R1 signaling, thus, co-treatment of PC9 cells with a TKI (which would generally permit the emergence of DTPs), and with an IGF-R inhibitor and an HDAC inhibitor virtually eliminated the emergence of the drug-tolerant state.

Why is this study important? First, it illuminates a new mechanism of drug tolerance – a transient, fully reversible strategy of the cell to protect itself from a hostile environment (think of a tortoise ducking into its shell, only to emerge when the coast is clear). Second, it suggests that drug intervention to force the cells back down a pathway of drug sensitivity may be possible. Lastly, it may explain why in some cases resistant cells become sensitive again – a potential biological explanation of the phenomenon of the benefit of a drug holiday.

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Dr. Radich indicated no relevant conflicts of interest.

## Tired Blood: How Stored RBCs Can Promote Inflammation Mediated by Iron

Hod EA, Zhang N, Sokol SA, et al. Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. *Blood*. 2010;115:4284-4292.

Red blood cell (RBC) transfusions are lifesaving procedures for severe blood loss, but needless transfusions performed on anemic euvoletic patients may be detrimental. Clinical trials restricting transfusions improved clinical outcomes in acutely ill individuals.<sup>1</sup> Prolonged storage of RBCs (> 14-21 days before transfusion) increases mortality, infections, inflammation, and multi-organ failure.<sup>2,3</sup> The proposed mechanisms linking RBC storage duration to adverse clinical consequences include impaired ability to deliver oxygen and stimulation of pro-inflammatory pathways.<sup>4</sup> The former may be attributed to storage-mediated changes in RBC metabolites (such as 2,3-DPG), ATP depletion, or hemolysis, while the latter may be due to activation of cytokines, coagulation, or cells (including white blood cells [WBCs], platelets, and endothelial cells). Pathophysiologically, prolonged RBC storage may promote RBC microparticle formation, altered membrane phospholipids, impaired clearance, free hemoglobin release with subsequent scavenging of nitric oxide (NO), release of free iron, and oxidative stress. Hod et al. from Steven Spitalnik's laboratory at Columbia College of Physicians and Surgeons in New York demonstrated that "tired" stored red cells are rapidly cleared by the monocyte/macrophage system and deliver an excess iron load that can activate cytokine production and enhance proliferation of certain bacterial pathogens.

In these experiments, murine leuko-reduced RBCs, fresh or stored for 14 days, were transfused into normal recipients. Sixteen percent of the stored RBCs were rapidly (< 2 hours) cleared by the spleen. The fate of hemoglobin iron was compared in mice infused with fresh RBCs, stored RBCs, washed stored RBCs, supernatants from stored RBCs, or RBC ghosts derived from stored RBCs. Only stored and washed stored RBCs increased plasma nontransferrin-bound iron (NTBI) two hours after infusion. Twenty-four hours later NTBI levels returned to baseline. Macrophages in the liver and spleen were responsible for clearing the stored RBCs. Only stored RBCs, but not ghosts or hemoglobin containing RBC lysates, induced elevated plasma cytokine levels. Transfusions using stored RBCs induced an acute-phase inflammatory response and exacerbated inflammation induced by endotoxin. Plasma from these animals promoted the growth of *E.Coli in vitro*. Remarkably, iron-chelators desferoxamine (DFO) or iron-laden feroxamine (FO) partially ameliorated the inflammatory response.

Obviously, the study invokes more questions than answers. It is fascinating that something essential in the stored RBCs caused enhanced clearance of these cells by monocyte/macrophages with rapid breakdown of heme iron with release into the plasma. What caused these cells to be so rapidly eliminated? Was there oxidative damage to the RBC membrane? Was deformability affected by DPG and ATP depletion? Did phospholipid vesiculation, excessive membrane phosphatidylserine expression, loss of complement/cytokine clearance, enhanced "senescence" antigen expression, Band-3 modifications, or altered interaction with microvascular endothelium play a role? Why was iron so rapidly released? Was heme oxygenase-1 not fully upregulated? Was apo-ferritin not available to store the iron? Were haptoglobin, hemopexin, and transferrin overwhelmed? If NO is pivotal in the adverse outcomes of stored blood, why didn't hemoglobin lysate induce the cytokine response? Why did both DFO and FO modulate the cytokine response?

Blood is precious, and as hematologists we must not allow colleagues to inappropriately transfuse patients. But, how can we expand the blood supply by allowing safe prolonged storage? Would adding anti-oxidants or iron chelators help? Years ago an advertisement for an iron tonic promised to be an antidote for "tired blood." Today, we need prospective human studies to further clarify whether stored "tired" RBCs could be rejuvenated and not deliver toxic iron.

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Dr. Vercellotti indicated no relevant conflicts of interest.

## Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: Passing the Baton

Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010; 362:2251-2259.

Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010; 362:2260-2270.

The IRIS study<sup>1</sup> and its companion long-term analyses<sup>2,3</sup> established the natural history of imatinib-treated newly diagnosed chronic-phase (CP) CML. The trial cemented the importance of achieving an early complete cytogenetic response (CCR) and major molecular remission (MMR) – therapeutic milestones that translate into excellent long-term responses. No patients who achieved an MMR by 18 months progressed to the accelerated or blast phase. With eight years of follow-up, 85 percent of patients remain alive, the estimated event-free survival is 81 percent, and freedom from progression to advanced CML is 92 percent.<sup>3</sup> Annual rates of progression to advanced CML remain less than 0.5 percent after five years.

Despite ushering in a revolution in the treatment of CML, these data indicate that imatinib leaves some people behind on the battlefield. Naturally, the rally cry has been “stronger, quicker, better.” Although higher starting doses of imatinib in newly diagnosed patients generated more rapid and higher-quality cytogenetic and molecular remissions, standard dosing exhibited a “catch-up” phase and comparable long-term results.<sup>4</sup> With their ability to overcome most *BCR-ABL* kinase domain mutations, the more potent second-generation ABL kinase inhibitors dasatinib and nilotinib could salvage responses in a substantial proportion of patients with imatinib-resistant or intolerant CML and outperform dose-escalated imatinib in CP patients. Thus, the stage was set for a frontline showdown.

Results from the upfront trials of standard-dose imatinib versus nilotinib (ENESTnd) and dasatinib (DASISION) are reported in the *New England Journal of Medicine*. In the ENESTnd trial, two doses of nilotinib (300 mg and 400 mg bid) were evaluated; in the DASISION study, a dasatinib dose of 100 mg daily was employed. Dasatinib and both nilotinib doses exhibited more rapid and significantly higher rates of CCR and MMR by 12 months (Table). Dasatinib’s benefits over imatinib were maintained across all Hasford risk categories; similarly, both nilotinib doses were superior to imatinib among patients with a high Sokal risk score. Progression to accelerated or blast-crisis CML occurred in a fewer number of patients treated with nilotinib or dasatinib. The safety profiles of the drugs were generally similar, with low rates of discontinuation and several non-overlapping, manageable toxicities.

**Table. Comparable efficacy of nilotinib and dasatinib versus imatinib in newly diagnosed CP CML**

	ENESTnd			DASISION	
	Imatinib 400 mg daily	Nilotinib 300 mg bid	Nilotinib 400 mg bid	Imatinib 400 mg daily	Dasatinib 100 mg daily
% CCR: 12 months	65%	80%	78%	66%	77%
% MMR: 12 months	22%	44%	43%	28%	46%
% MMR: 3,6,9 months	1%, 12%, 18%	9%, 33%, 43%	5%, 30%, 38%	0.4%, 8%, 18%	8%, 27%, 39%
Progression to AP/BC	11 (4%)*	2 (<1%)*	1 (<1%)*	9/260 (3.5%)**	5/259 (1.9%)**

\*Both doses of nilotinib were significantly better than imatinib with respect to the time to progression to the accelerated phase or blast crisis (P = 0.01 for the 300-mg group; P = 0.004 for the 400-mg group)

\*\*At 12 months, the estimated rates of progression-free survival were similar for patients receiving dasatinib and imatinib.

These data support the efficacy and safety of nilotinib and dasatinib in patients with newly diagnosed CP CML. The 12-month outcomes for both drugs indicate superiority of imatinib; however, longer follow-up will determine whether these efficacy margins are maintained and substantial differences in progression-free and overall survival materialize. At the time this article went to press, nilotinib (300 mg twice daily) had been approved by the FDA for frontline treatment. Dasatinib was under FDA review and bosutinib remained under trial investigation. Both physician and patient choice regarding which tyrosine kinase inhibitor to use will depend on several factors, such as dosing schedule (daily for dasatinib and twice daily for nilotinib) and distinct side effect profiles. For patients with in-depth responses to imatinib, there is no reason to change. In newly diagnosed patients, it may be time to pass the baton. Even so, reports of imatinib’s demise are greatly exaggerated.

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Dr. Gotlib serves on the Steering Committee of a Novartis-sponsored trial of midostaurin (PKC412) for systemic mastocytosis and is a member of the National Comprehensive Cancer Network’s Guidelines Committee for CML.

## Warfarin: Not Just Rat Poison

Dutton RJ, Wayman A, Wei JR, et al. Inhibition of bacterial disulfide bond formation by the anticoagulant warfarin. *Proc Natl Acad Sci USA*. 2010;107:297-301.

Vitamin K-dependent proteins undergo post-translational modification in which the  $\gamma$ -carbon on selected glutamic acid (Glu) residues is carboxylated, producing  $\gamma$ -carboxyglutamic acid (Gla). The vitamin K-dependent proteins include the coagulation proteins prothrombin, factor VII, factor IX, factor X, protein C, protein S, and protein Z, as well as proteins involved in bone formation and other processes. The  $\gamma$ -carboxylation reaction is catalyzed by vitamin K  $\gamma$ -glutamyl carboxylase. Vitamin K hydroquinone is a co-substrate for the carboxylase and undergoes oxidation to vitamin K epoxide during the carboxylation reaction. To cycle back and participate in another reaction, vitamin K epoxide is reduced to vitamin K hydroquinone by the vitamin K epoxide reductase (VKOR).<sup>1,2</sup> The anticoagulant activity of warfarin is due to its ability to inhibit VKOR.

Homologs of VKOR recently have been identified in bacteria and participate in a pathway leading to disulfide bond formation, which is necessary for the stability of many secreted bacterial proteins. Although bacterial oxidation of cysteine that leads to disulfide bond formation is a different reaction than  $\gamma$ -glutamyl carboxylation, both bacterial and human VKOR participate in the transfer of electrons to a quinone. Additionally, human VKOR and bacterial homologs both contain an active site CXXC sequence, which cycles between reduced and disulfide-bonded states.

Now, Dutton et al., in the laboratory of Dana Boyd at Harvard, show that warfarin inhibits the VKOR homolog from *Mycobacterium tuberculosis*, the causative agent of human tuberculosis. Additionally, using a random mutagenesis strategy they identified three warfarin-resistant *M. tuberculosis* VKOR mutations at sites homologous to those of human warfarin-resistant VKOR mutants. Deletion of VKOR in another mycobacterial species, *M. smegmatis*, produced a growth defect that was rescued by expression of *M. tuberculosis* VKOR. Additionally, the growth of *M. tuberculosis* was inhibited by warfarin.

Does this mean that warfarin should be added to the armamentarium of drugs used to treat tuberculosis? No. *M. tuberculosis* VKOR shares only 18 percent amino acid identity with its human homolog. Millimolar concentrations of warfarin are required to inhibit mycobacterial VKOR, in contrast to the micromolar concentrations required to inhibit human VKOR. Additionally, mutants of *M. tuberculosis* VKOR that were warfarin-resistant when expressed in *E. coli* were not warfarin-resistant when expressed in *M. smegmatis*, indicating that the effect of warfarin on mycobacteria may involve additional targets other than VKOR.

Although further work is necessary to understand the actions of warfarin and the structure and function of VKOR in mycobacteria and possibly other pathogenic bacteria, this study suggests that bacterial VKOR may represent a therapeutic target. Additionally, because human VKOR is a membrane-bound enzyme and difficult to study, bacterial VKOR may represent a useful model for structure-function studies of human VKOR, as witnessed by the recent description of an X-ray structure of *Synechococcus* VKOR.<sup>3</sup>

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Dr. Lollar indicated no relevant conflicts of interest.

## Altered Niche Causes Myelodysplasia

Raaijmakers MH, Mukherjee S, Guo S, et al. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. *Nature*. 2010;464:852-857.

**H**ematopoiesis is tightly regulated within the bone marrow space: stem cell quiescence, self-renewal, and differentiation are affected by both cell-intrinsic factors and by neighboring cells constituting the stem cell niche. Leukemias and congenital hematologic diseases are thought to result almost entirely from genetic mutations and/or epigenetic alterations in the hematopoietic stem/progenitor cell (HSPC) compartment. However, recent data suggest that the bone marrow (BM) microenvironment may play a significant role in promoting clonal disorders such as myelodysplasia and leukemia. In this paper by Raaijmakers et al. from David Scadden's laboratory at Harvard, genetic mutations induced solely in osteoblast progenitors, key regulators of HSPC in the stem cell niche, induced myelodysplasia with occasional transformation to myeloid leukemia.

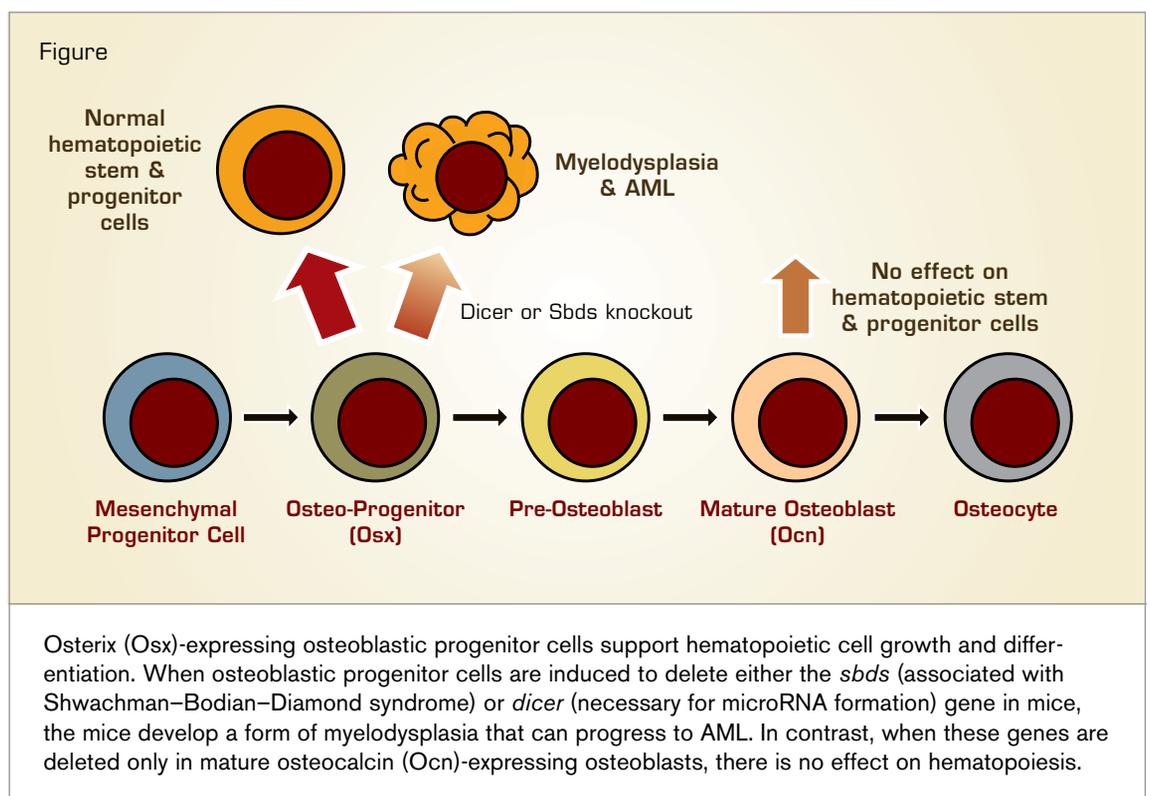
The investigators developed transgenic mice that delete the gene *dicer* only in osteoblast progenitor cells, which express osterix (*Osx*). Although *dicer*, which encodes a critical enzyme in the formation of microRNAs, was not deleted from the hematopoietic cells, these mice developed a form of myelodysplastic disease (MDS) with ineffective hematopoiesis and dysmorphic hematopoietic cells. In spite of normal cellularity and HSC numbers in the BM, the mice developed leukopenia with variable levels of anemia and thrombocytopenia. Hematopoietic progenitor cells showed increased apoptosis, and, morphologically, megakaryocytes were small and hypolobated, platelets enlarged, and granulocytes hypersegmented. Two percent of the mice developed a leukemia resembling AML M4 preceded by facial myeloid sarcomas. Of note, these leukemias expressed normal levels of *dicer* but were found to have abnormal genetics, proving that AML occurred in response to the microenvironment and not because of cell intrinsic deletion of *dicer* within the myeloid cells.

Both by *in vitro* co-culture of hematopoietic cells with *dicer*-deficient osteoprogenitor cells and by *in vivo* deletion of *dicer* specifically in more differentiated (osteocalcin positive) osteoblasts, the investigators proved that the induction of MDS is stage-specific to osteoblast progenitor cells.

To identify the mechanism by which *dicer* deletion in osteoblast progenitors may cause MDS, the investigators performed gene expression analysis. Differentially expressed genes and pathways included cytokines and stress response pathways, including significant down-regulation of the Shwachman–Bodian–Diamond (*sbds*) gene, which is linked to the human Shwachman–Diamond syndrome. Although the mechanism by which *dicer* deletion is linked to *sbds* expression is not clear, the investigators showed that knockdown of just the *Sbds* gene in osteoblast progenitors reproduces much of the MDS phenotype.

This paper complements, in a very elegant way, prior data showing not only that the BM microenvironment and stem cell niche support physiologic hematopoiesis, but that alterations of the microenvironment, such as decreased expression of the retinoblastoma gene in cells of the BM microenvironment,<sup>1</sup> can induce disease. It is particularly interesting that genetic alterations are induced within hematopoietic cells. Although this study does not prove that osteocytic lineage cells in the BM are directly involved in malignant processes in people, there are several lines of evidence that may point to abnormal BM niches in leukemia. For example, in patients with leukemia, there is decreased normal hematopoietic cell function even before the marrow has been entirely populated with leukemic cells, and, in CML, the marrow stromal cells also have the *bcr-abl* fusion protein. These data pose interesting questions for how we treat hematologic malignancies, and in particular for the field of HSC transplantation and whether increased attention to the BM microenvironment could improve treatment outcomes.

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## Oral Anticoagulation

**STUDY TITLE:** **Apixaban Versus Enoxaparin for Thromboprophylaxis After Knee Replacement (ADVANCE-2): A Randomized Double-Blind Trial**

**COORDINATOR:** The study was coordinated by the ADVANCE-2 steering committee, chaired by M.R. Lassen, MD, from the University of Copenhagen.

**SPONSORS:** Bristol-Myers Squibb and Pfizer

**CLINICALTRIALS.GOV IDENTIFIER:** NCT00452530

**PARTICIPATING CENTERS:** This is an international study that includes medical centers in North America, Europe, Latin America, South Africa, and Asia.

**ACCRUAL:** The investigators enrolled 3,221 patients. The total number of patients eligible for primary efficacy analysis was 1,973.

**STUDY DESIGN:** A multicenter, randomized, double-blind study was performed to compare the efficacy and safety of oral apixaban to that of subcutaneous enoxaparin in patients undergoing knee replacement. Patients received twice-daily dosing of 2.5 mg oral of apixaban beginning 12 to 24 hours after knee surgery or 40 mg subcutaneous of enoxaparin starting 12 hours before surgery. Both drugs were continued for 10 to 14 days. All participants had venography following treatment. The primary endpoint was a composite that included asymptomatic and symptomatic deep-vein thrombosis, non-fatal pulmonary embolism, and death from any cause during treatment.

**RATIONALE:** The last orally active anticoagulant to receive FDA approval was warfarin in 1954. Warfarin has a very slow onset of action, and its narrow therapeutic window necessitates frequent monitoring. Low-molecular-weight heparins, such as enoxaparin, are effective anticoagulants but require subcutaneous administration. These shortcomings have fostered the development of orally active direct thrombin inhibitors and factor Xa (fXa) inhibitors, such as apixaban. Venous thromboembolism is a common complication following total knee replacement and is an established clinical setting for the evaluation of antithrombotics. The objectives of this study were to determine whether apixaban was non-inferior to enoxaparin in preventing thrombosis following knee replacement and to compare the bleeding risk of the two regimens.

**COMMENT:** Several direct thrombin inhibitors and fXa inhibitors are in advanced clinical development. Ximelagatran was approved in Europe but subsequently withdrawn owing to concerns about hepatotoxicity. Rivaroxaban and dabigatran have been approved in Europe and Canada, and rivaroxaban is awaiting a decision from the U.S. FDA. The ADVANCE-2 trial represents the second phase III trial for apixaban. The primary efficacy analysis of 1,973 patients demonstrates that 2.5 mg BID apixaban is superior to 40 mg of enoxaparin QD in preventing thrombosis following knee replacement without causing increased bleeding or transaminitis. Event rates (15 percent for apixaban and 24 percent for enoxaparin) in this study were considerably higher than the 9 percent event rates observed in ADVANCE-1 for both 2.5 mg BID apixaban and 30 mg enoxaparin BID. However, the event rates in ADVANCE-2 were more consistent with anticipated results. The ADVANCE studies provide further evidence that orally active fXa inhibitors are promising agents for thrombosis prophylaxis. Which inhibitors find their way into clinical practice and the degree to which they replace warfarin and low-molecular-weight heparins remain intriguing questions.

– Robert Flaumenhaft, MD, PhD

## Chronic Lymphocytic Leukemia

**STUDY TITLE:** **Phase II Study of Reduced-Intensity Allogeneic Stem Cell Transplant for High-Risk Chronic Lymphocytic Leukemia (CLL)**

**SPONSOR:** Cancer and Leukemia Group B (CALGB)

**STUDY IDENTIFIERS:** CALGB 100701; NCT01027000

**PARTICIPATING CENTERS:** Member institutions of CALGB and the Blood and Bone Marrow Transplant Clinical Trials Network

**STUDY DESIGN:** CALGB 100701 is a multicenter phase II study of reduced intensity HLA matched-related and matched-unrelated allogeneic stem cell transplantation in two distinct cohorts of patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). While CALGB is the lead coordinating group (Study Chair, Dr. Edwin Alyea), the CLL Research Consortium is directing the immunologic correlative science (Correlative Science Co-Chair, Dr. John Gribben), and the Blood and Bone Marrow Transplant Clinical Trial Network has also agreed to participate. The first cohort (Cohort 1) consists of patients with high-risk disease who have received a single therapy. Risk stratification is based on genetic characterization and response to treatment, and high-risk patients include those with del(17p13.1) in complete or partial remission, del(11q22.3) in partial remission, or any other patient who does not attain a partial or better response to any chemoimmunotherapy-based treatment. These patients can be treated with another cytoreductive treatment to prepare them for transplant, but they can receive no more than two treatments prior to transplant. Cohort 2 consists of patients with a brief first remission (< 24 months) following therapy and those who have relapsed following two or more prior therapies. Each cohort will be treated with one of two standard immune suppressive and cytoreductive regimens (rituximab, busulfan, and fludarabine or rituximab, fludarabine, and cyclophosphamide) commonly used for reduced-intensity allogeneic stem cell transplantation with defined graft-versus-host disease (GVHD) prophylaxis along with rituximab maintenance to further reduce development and severity of GVHD. The primary endpoint of this study is to determine if two-year progression-free survival (PFS) of Cohort 1 is improved over that observed in historical controls receiving only chemoimmunotherapy. A variety of secondary endpoints will also be addressed that are of interest to the field of CLL and transplant, including determination of whether two-year PFS of  $\geq 50$  percent can be achieved and two-year PFS of  $\leq 30$  percent can be excluded in patients with CLL and SLL in the advanced disease cohort (Cohort 2).

**RATIONALE:** Available chemoimmunotherapy options for high-risk CLL are unsatisfactory, with many patients dying in the first two years post-treatment. Application of transplantation after first relapse is suboptimal because candidates often have significant residual disease as a consequence of incomplete cytoreduction due to drug-resistant tumor. This trial addresses a sentinel question: Can allogeneic immune therapy ameliorate the adverse outcome observed in patients with high-risk genetic abnormalities and in those with primary refractory disease? Participation in this clinical trial will necessitate referral to a CLL transplant team by treating physicians at a time either prior to or early in first treatment of high-risk CLL patients.

**COMMENT:** This trial brings together three separate groups (through the hard work of Dr. Charles Linker) supported by the NCI and NHLBI, with expertise in CLL and transplantation (CALGB), CLL transplant immunology (CLL Research Consortium), and transplantation (Blood and Bone Marrow Transplant Clinical Trial Network). It is strongly endorsed by each of the groups and represents

an outstanding option for eligible patients who have either a related or an unrelated HLA matched donor.

– John C. Byrd, MD

## Myelodysplastic Syndrome

**STUDY TITLE:** **A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Deferasirox in Patients With Myelodysplastic Syndromes (Low/Int-1 Risk) and Transfusional Iron Overload (TELESTO)**

**SPONSOR:** Novartis, Inc.

**CLINICALTRIALS.GOV IDENTIFIER:** NCT00940602

**PARTICIPATING CENTERS:** This is an international trial with a goal accrual of 630 patients (2:1 deferasirox : placebo randomization) at approximately 125 centers in North America, Latin America, Europe, South Africa, and Asia.

**STUDY DESIGN:** Disease-specific eligibility criteria include chelation-naïve MDS patients classified as low risk or intermediate-1 risk based on International Prognostic Scoring System (IPSS) criteria. Study patients will have a history of 20 to 50 red blood cell transfusions and a serum ferritin concentration of > 1,000 to < 2,500 mcg/L. Patients are permitted to receive treatment with hypomethylating agents, lenalidomide, and erythropoietin. The primary objective is to evaluate event-free survival, a composite endpoint that includes death and non-fatal events related to cardiac dysfunction (i.e., worsening of left ventricular ejection fraction, hospitalization for congestive heart failure) and liver impairment (i.e., clinicopathologic evidence of progressive liver dysfunction, cirrhosis, or both). The study will also explore secondary endpoints including overall survival, endocrine function (e.g., thyroid function and glycemic control), changes in the serum ferritin concentration, and disease outcomes such as evolution to higher-risk MDS and acute myeloid leukemia.

**RATIONALE:** Prospective studies have established that iron chelation can significantly reduce morbidity and mortality from transfusional iron overload in patients with thalassemia. To date, phase II trials have shown that deferasirox can reduce serum ferritin concentration and liver iron content in transfusion-dependent, lower-risk MDS patients. However, no prospective studies have yet been performed in MDS to establish the benefits of iron chelation on organ function, MDS natural history, and overall survival despite retrospective studies suggesting improvements in these endpoints. This pivotal study aims to close that data gap.

**COMMENT:** Therapeutic nihilism regarding iron chelation in MDS is still pervasive despite infusional deferoxamine being supplanted by oral agents. This attitude commonly prevails among physicians treating older patients with higher-risk disease where life expectancy is limited and a chelation program would not be expected to have a meaningful impact on overall survival. However, in chronically transfused lower-risk patients, reversal of organ dysfunction, improvement of impaired hematopoiesis, and prolongation of overall survival (endpoints achieved in prior observational or retrospective studies) are eminently reasonable clinical objectives. This phase III study may also clarify the optimal serum ferritin concentration or the appropriate cumulative number of red blood cell transfusions at which to initiate iron chelation.

– Jason Gotlib, MD, MS

Dr. Gotlib serves on the Steering Committee of a Novartis-sponsored trial of midostaurin (PKC412) for systemic mastocytosis.

## 2010 MMSAP PARTICIPANTS

The Minority Medical Student Award Program (MMSAP) encourages minority medical students to pursue an interest in hematology research. For an eight- to 12-week period, MMSAP participants will work closely with their mentors on a hematology-related research project. The subjects investigated by this year's students include thrombotic thrombocytopenic purpura (TTP), sickle cell anemia, MDS, and acute myeloid leukemia. The awardees will have the opportunity to present the results of their research at ASH's annual meeting in December.

This year's program has the largest number of participants yet, including four returning students. Each award recipient will receive the support of a research mentor and a career-development mentor, travel stipends to attend medical meetings, and subscriptions to *The Hematologist* and *Blood*.

### RETURNING PARTICIPANTS



**Imo Akpan**

University of Illinois at Chicago

**Research Project:**

Determination of the manner in which changes within the  $\gamma$ -globin gene are linked to differences in histone H3 (lys9) methylation following decitabine administration in the baboon model

**Research Mentor:**

Joseph DeSimone, PhD  
University of Illinois at Chicago



**May Cho**

Meharry Medical College

**Research Project:**

Structural requirements of LDB1 function

**Research Mentor:**

Stephen Brandt, MD  
Vanderbilt University Medical Center



**Tiffany D. Jackson**

Mercer University School of Medicine

**Research Project:**

Production of erythrocytes from human embryonic stem cells

**Research Mentor:**

Kenneth Zuckerman, MD  
H. Lee Moffitt Cancer Center/University of South Florida



**Courtney Nicole Johnson**

University of Southern California, Keck School of Medicine

**Research Project:**

Disease knowledge in chronic myelogenous leukemia patients as a predictor of compliance to treatment

**Research Mentor:**

Sikander Ailawadhi, MD  
Norris Comprehensive Cancer Center/University of Southern California, Keck School of Medicine

### FIRST-TIME PARTICIPANTS



**Tiana Carrillo**

University of Illinois at Chicago

**Research Project:**

Iron-mediated ROS production as a mechanism for RARS and the basis for therapeutics

**Research Mentor:**

Seth J. Corey, MD  
Northwestern University



**Stacey Pereira**

Rush Medical College

**Research Project:**

Kinetics of engraftment: single-donor dominance versus dual-donor chimerism in double cord blood transplant outcomes

**Research Mentor:**

Colleen Delaney, MD  
University of Washington



**Drees Griffin Jr.**

University of Alabama School of Medicine

**Research Project:**

Creation of the UAB thrombotic thrombocytopenic purpura-hemolytic uremic syndrome registry

**Research Mentor:**

Marisa Marques, MD  
University of Alabama at Birmingham



**Pablo N. Quintana**

University of Illinois at Chicago

**Research Project:**

Targeting miRNAs that regulate the glucocorticoid receptor as a potential therapeutic for multiple myeloma

**Research Mentor:**

Steven T. Rosen, MD  
Northwestern University



**Michelle Long**

Wake Forest University School of Medicine

**Research Project:**

Pediatric immune thrombocytopenic purpura: drug treatments and responses

**Research Mentor:**

Ellis J. Neufeld, MD, PhD  
Children's Hospital, Boston



**Vanessa Sarfoh**

University of Buffalo School of Medicine and Biomedical Sciences

**Research Project:**

Magnetic resonance imaging of liver and cardiac iron

**Research Mentor:**

Janet Kwiatkowski, MD  
Children's Hospital of Philadelphia



**Myntee Ngangana**

The Ohio State University College of Medicine

**Research Project:**

Association between epigenetic changes and acute myeloid leukemia

**Research Mentor:**

Michael Caligiuri, MD  
The Ohio State University



**Ngozidilenna Wilkins**

University of Arkansas for Medical Sciences

**Research Project:**

Characterization of platelet  $\alpha$ -granule dynamics

**Research Mentor:**

Brian Storrie, PhD  
University of Arkansas for Medical Sciences



**Jennifer Nichols**

University of Illinois at Chicago

**Research Project:**

The effects of environmental cues and differentiation state on hematopoietic stem cell colony growth, morphology, and fetal hemoglobin production

**Research Mentor:**

Joseph DeSimone, PhD  
University of Illinois at Chicago



**Kandyce Pearson**

University of Iowa

**Research Project:**

Characterization of K13-NEMO interaction

**Research Mentor:**

Preet Chaudhary, MD, PhD  
Norris Comprehensive Cancer Center/  
University of Southern California, Keck School of Medicine

# The Accident That Changed My Life

## *How an Engineer Got into Hematology Research*

MOHANDAS NARLA, DSc

Vice President for Research, New York Blood Center  
Councillor, ASH Executive Committee

**M**y entrée into hematology was a total accident. I arrived in the United States in 1968 with a degree in chemical engineering to begin graduate studies in the School of Engineering at Washington University, St. Louis. Having suddenly lost a mentor (though happily, not through carelessness) with whom I had started on my doctoral dissertation on properties of gases at high temperatures, I had to quickly find a new topic for my dissertation. By good fortune, I met Bob Hochmuth, who had just started a research program on mechanics of blood flow through capillaries. As his first doctoral student, I measured elastic and adhesive properties of human red blood cells, equipped only with a comprehensive ignorance of all things biological. When Marcel Bessis, a renowned French hematologist, visited St. Louis in 1973, I casually mentioned that I would be interested in working with him in Paris. A few months later he offered me a position at his Institute of Cellular Pathology; I accepted with alacrity, not realizing I would be the only non-biologist in the Institute — nor did I speak a word of French. The three years I spent in Paris transformed my career; they revealed to me the complexity of biology in general and red cells and erythropoiesis in particular. I was smitten with the idea of applying my engineering background to the study of red cells, and I have stayed faithful to this pursuit ever since. Gil Tchernia, a pediatric hematologist in Paris, had an enormous impact on my career, because throughout the years he regularly identified for me clinical problems that were worth pursuing from a scientific perspective, and much of what I have done and I am doing still has origins in the discussions I have had with him.

My first contribution to hematology research was inventing, with Marcel Bessis, the ektacytometer to study differences in the deformability of red cells in a variety of disorders. Realizing that my engineering background had not prepared me for a deeper understanding of the

pathophysiological implications of the phenomenon I was studying, I began, in 1976, to look for collaborators with expertise in such fields as hematology, biochemistry, biophysics, cell biology, molecular biology, and genetics to expand the depth and scope of my research activities. This

journey, spanning the last four decades, first at University of California, San Francisco, then at Lawrence Berkeley National Laboratory, and now at New York Blood Center, has been extraordinarily rewarding in that it has allowed me to work closely with a succession of wonderful colleagues with diverse expertise from around the world. Our research efforts have focused on red cell membrane disorders; hemoglobinopathies, including sickle cell disease and thalassemias; malaria; and, more recently, normal and disordered erythropoiesis. An appealing aspect of the red cell field is its collegiality, and it has been a pleasure to be associated with so many talented scientists, whose friendship and support has meant so much to me.

As my research career progressed, I was pressed to take on administrative responsibilities, first as director of the Human Genome Project at Berkeley National Laboratory for three years in the mid 1990s and most recently as vice president for research at New York Blood Center since 2001. While these administrative positions take time away from research, they provide me with an opportunity to recruit and mentor young scientists, which is a truly pleasurable experience. It gives me great joy to see my former students, postdoctoral fellows, and young investigators pursue exciting and rewarding careers in research.

I have been a member of the American Society of Hematology since the 1980s and have attended every annual meeting since 1976. As a basic scientist, I feel completely at home in our Society and have been privileged to serve on numerous committees and as an associate editor of *Blood* since 2003.

My fascination with red cells continues unabated. There is still a lot to learn, and there are more people to meet and opportunities to watch the discipline of hematology flourish and grow. My family constantly reminds me of the charmed life I lead with wonderful colleagues and great friends around the world. I tell them that my accidental embrace of a career in hematology research is totally responsible for this joyous life, and I cleave to the fine sentiment expressed by the poet, Hilaire Belloc: “There’s nothing worth the wear of winning/Save laughter and the love of friends.”



*I was smitten with the idea of applying my engineering background to the study of red cells, and I have stayed faithful to this pursuit ever since.*

The **ASH website** offers a **convenient way for ASH members to find information** relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH.

Featured in the Web spotlight this month is the **Patient Information area** of the ASH website, [www.hematology.org/patients](http://www.hematology.org/patients). ASH's patient information site provides **credible information about blood disorders**, including information about risk factors, preventive measures, and treatment options. The mission of the Society is to further the understanding, diagnosis, treatment, and prevention of disorders affecting the blood, bone marrow, and the immunologic, hemostatic and vascular systems, by promoting research, clinical care, education, training, and advocacy in hematology; **patients are at the core** of this mission. As part of ASH's effort to keep patients informed, numerous resources are provided through the Society's website.

Please help ASH promote this valuable resource by directing your patients to [www.hematology.org/patients](http://www.hematology.org/patients).



### The site includes:

- Hematologist-approved information on various blood disorders and issues:
  - Anemia
  - Bleeding and clotting
  - Cancer
  - Blood-related women's health issues
- A "Find a Hematologist" tool that allows patients to search ASH's online directory for a doctor near them
- Short films that explain what hematology is and why it is important
- Animated video clips that illustrate basic blood functions and disorders
- Tips for how patients can communicate effectively with their doctors
- A guide to clinical trials
- A list of major medical advances in hematology



Read *The Hematologist* online at [www.hematology.org/hematologist](http://www.hematology.org/hematologist), and catch up on the latest news in the field of hematology right at your desktop.

## Mark Your Calendar

# September

- 13 – 15** **2010 caBIG® Annual Meeting**  
Washington, DC <https://cabig.nci.nih.gov/2010AnnualMeeting>
- 14** **ASH Webinar Series on Thrombosis: Heparin-Induced Thrombocytopenia (HIT)**  
Washington, DC [www.hematology.org](http://www.hematology.org)
- 15 – 18** **Annual Meeting of International Society for Hematology and Stem Cells**  
Melbourne, Australia [www.iseh.org](http://www.iseh.org)
- 22 – 23** **Beaumont's 19th Annual Symposium on Molecular Pathology**  
Troy, MI [www.beaumont.edu/dnasymposium](http://www.beaumont.edu/dnasymposium)
- 24 – 25** **2010 ASH State-of-the-Art Symposium**  
Chicago, IL [www.hematology.org](http://www.hematology.org)
- 24 – 26** **Society for the Advancement of Blood Management 2010 Annual Meeting**  
San Juan, Puerto Rico [www.sabm.org](http://www.sabm.org)
- 24 – 26** **Annual Meeting of the Japanese Society of Hematology**  
Yokohama, Japan [www.jshem.or.jp/en](http://www.jshem.or.jp/en)

# October

- 1 – 4** **Annual Meeting of the International Society for Biological Therapy of Cancer**  
Washington, DC [www.isbtc.org](http://www.isbtc.org)
- 10 – 13** **XXXIII World Congress of the International Society of Hematology**  
Jerusalem, Israel [www.kenes.com/ish2010](http://www.kenes.com/ish2010)
- 20** **ASH Webinar Series on Thrombosis: Coagulation Management in Cancer**  
Washington, DC [www.hematology.org](http://www.hematology.org)
- 21** **ASH Late-Breaking Abstract Submission Site Opens**  
Washington, DC [www.hematology.org](http://www.hematology.org)
- 21 – 24** **XI European Symposium on Platelet and Granulocyte Immunobiology**  
Beaune, France [www.sfts.asso.fr](http://www.sfts.asso.fr)
- 21 – 24** **Congress of the International Society of Pediatric Oncology (SIOP)**  
Boston, MA [www.siopboston2010.com](http://www.siopboston2010.com)
- 22 – 24** **Annual European Hemophilia Consortium Conference**  
Lisbon, Portugal [www.ehc2010.eu](http://www.ehc2010.eu)

# November

- 2 – 6** **Annual Meeting of the American Society of Human Genetics**  
Washington, DC [www.ashg.org/2010meeting](http://www.ashg.org/2010meeting)
- 11 – 13** **Annual Meeting of the National Hemophilia Foundation**  
New Orleans, LA [www.hemophilia.org](http://www.hemophilia.org)
- 16 – 17** **James B. Herrick Symposium – Sickle Cell Disease Care and Research: Past, Present, and Future**  
Bethesda, MD [www.nhlbi.nih.gov/meetings/James-Herrick-SickleCell](http://www.nhlbi.nih.gov/meetings/James-Herrick-SickleCell)
- 17** **ASH Webinar Series on Thrombosis: Non-Hemophilia-Associated Conditions Associated With Bleeding**  
Washington, DC [www.hematology.org](http://www.hematology.org)

# December

- 4 – 8** **ASH Annual Meeting**  
Orlando, FL [www.hematology.org](http://www.hematology.org)