Nobel Prize in Medicine Goes to Two Physician Scientists With Close Ties to ASH

ASH member Ralph M. Steinman, MD, of Rockefeller University in New York was awarded the Nobel Prize in Medicine or Physiology for his pioneering discovery of dendritic cells and their role as critical antigen presenting cells of the immune system. Unfortunately, Dr. Steinman never knew of this great honor; he died after a four-year battle with pancreatic cancer the day before the announcement. Dr. Steinman was born in Montreal, Canada, on January 14, 1943, and, having graduated from McGill University, went on to receive his medical degree, magna cum laude, from Harvard Medical School. While a postdoctoral fellow at Rockefeller, he began research on primary white cells in the immune system and later concentrated on the role of dendritic cells, a term that he coined, in immune responses.

Dr. Steinman shared the award with two other physician scientists, Bruce Beutler, from University of Texas Southwestern Medical Center and Scripps Research Center, and Jules Hoffman, from University of Strasbourg. Dr. Beutler, a former ASH member, hematologist and past ASH president, then identified a related family of innate immune receptors in mammalian white blood cells now known as Toll-like receptors (TLRs). These receptors, when stimulated by endogenous or exogenous “danger signals” such as bacterial endotoxin, activate the immune system and can cause septic shock. These landmark discoveries laid the foundation for innovative approaches to treat or prevent sepsis and to stimulate the immune system to attack tumors.

Hydroxyurea’s Leukemogenicity in Myeloproliferative Neoplasms: A “Not Guilty” Verdict


Among patients who suffer from myeloproliferative neoplasms (MPNs), and for some doctors who treat them, an uncomfortable concern has lingered about hydroxyurea’s role in the risk of transformation into myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In addition to the inherent capacity of MPNs to transform into leukemia, prior studies have established the increased leukemogenic risk of alkylator therapies or radioactive phosphorus (32P). Data from several trials over the last 40 years suggest little of a conspiratorial role of hydroxyurea monotherapy but increased potential for leukemic evolution when the drug is combined with other cytotoxicants. Because longer follow-up times have revealed a higher incidence of leukemia in MPN patients treated with myelosuppressive agents, apprehension over the use of hydroxyurea is particularly relevant to younger persons who may be exposed to the drug for decades.

To better define risk factors for transformation of MPNs, investigators from the Swedish Chronic Myeloproliferative Neoplasm Study Group and the National Cancer Institute harnessed data from an MPN cohort of 11,039 patients derived from Sweden’s centralized National Cancer Registry. A nested case-control study compared 162 MPN patients with transformation (153 to AML, 9 to MDS) with 242 matched MPN control patients without disease evolution. The overall incidence of AML transformation into MPNs was 35-fold compared with the general population, with the greatest risk in primary myelofibrosis (PMF), followed by polycythemia vera (PV) then essential thrombocythemia (ET). Of interest, 25 percent of MPN patients who developed AML or MDS were never exposed to hydroxyurea, alkylating agents, or 32P, and this is consistent with the intrinsic genetic instability of these disorders. There was no significant increased risk of AML/MDS development with prior exposure to hydroxyurea, irrespective of the cumulative dose level (e.g., 1-499 vs. 500-999 g vs. > 1,000 g). Patients who received relatively higher doses of 32P (> 1,000 MBq) and alkylators (> 1 g) exhibited a significantly increased odds ratio for leukemia development (e.g., 4.6- and 3.4-fold, respectively) compared with the 1.3-fold insignificant increase with the highest dose range of hydroxyurea. Treatment with two or more cytoreductive agents similarly increased the odds of leukemic transformation (2.9-fold) and was greater than any single treatment alone. Approximately 75 percent of patients treated with alkylating agents or 32P developed AML/MDS five years or later after their MPN diagnosis compared with ~40 percent of patients who received no treatment or hydroxyurea alone. Overall, only 2.8 percent of the 11,039 MPN patients converted to AML/MDS.

Despite the potential shortcomings related to a population-based analysis, this study’s large sample size and durable follow-up provide more compelling evidence for disease and non-treatment-related factors in MPN transformation. However, the report also confirms the unambiguous risk associated with relatively high doses of alkylating agents and 32P, and the potentiating leukemogenic effect of multiple cytoreductive drugs. In conjunction with these data, given its experience in sickle cell disease and its lack of increased mutagenicity ex vivo with cells from MPN patients, hydroxyurea should be considered a nominal risk in this patient population.

Is Anybody in Washington Listening?

ROY L. SILVERSTEIN, MD
The Linda and John Mallices Professor and Chairman, Department of Medicine, Medical College of Wisconsin

“We do not have a government of the majority. We have a government of the majority who participate.”
—Thomas Jefferson

As a member of ASH, you have probably received requests from the Society to take some kind of legislative action: Call or email your Congressman. Many of you may find these requests annoying and wish they were captured in your junk mail folder. Or, you may feel — even if sympathetic to the policy issue — that you don’t have the time to respond. You may also wonder if anybody on Capitol Hill actually reads the emails ASH asks you to write and if they make any difference.

The fact is nearly all constituent communications are counted and responded to by Members of Congress and their staff. While it is true that individualized communications with some expression of personal sentiment or opinion are most likely to be influential, nearly all legislators do use constituent communications as a gauge of public opinion and integrate it into their decision-making. Consequently, the form letters ASH provides, at a minimum, are aggregated into the “for” or “against” category when received on Capitol Hill and help the legislator understand constituent feelings. Often, ASH email campaigns have been used by Members of Congress in their speeches or when they are questioning witnesses during Congressional committee hearings. The Legislative Alerts you receive from ASH also have the added benefit of timing. The ASH Government Affairs Department monitors legislative action in Washington and only notifies the ASH membership when contact with a Congressional office is likely to have the most impact, i.e., when Congress is focusing on that specific issue.

There are a few organized groups that have a powerful voice because of their reputation for organizing grassroots efforts in legislative battles. These include the National Rifle Association, AARP, and teachers unions. Media critics often confuse this grassroots power with funding capabilities, suggesting it is “special interest money” that influences lawmakers. The reality is it comes down to sheer numbers. The more people who share a common belief and are willing to put their voices behind that belief, the more influence they have in Washington. As we have seen in recent Congressional debates over the debt ceiling and belief, the more influence they have in Washington. As we have seen in recent Congressional debates over the debt ceiling and

(Cont. on page 7)

Research Funding 2012 – The New Normal is Getting Old

Throughout my career, funding for biomedical research has been tight at times, but science in the United States has remained vibrant, and these short dry spells have not prevented remarkable advances in basic knowledge and clinical care. Why should the current contraction in federal research support be different?

Maybe it won’t. In the face of declining funds, NCI, NHLBI, and NIDDK have used a variety of tactics to protect the number of investigator-initiated research grants. The NIH budget doubled between 1999 and 2003. Since then, total NIH appropriations increased from $27.1 billion in 2003 to $30.9 billion in 2011, which in constant dollars represents a decrease of 7 percent. A further decrease of at least 1 percent is expected for the next fiscal year, the first time in 45 years that the NIH budget will decrease in current dollars. To make available funds go further, all noncompeting awards have been cut 1 percent and annual inflationary adjustments limited to 2 percent. NCI has been more aggressive, decreasing noncompeting awards by 3 percent from the previous year, cutting new awards by 17 percent, and decreasing support for cancer centers by 5 percent. Nevertheless, between 2003 and 2010 total research grant funding at these three Institutes — all key for hematologic research — decreased 8 percent in constant dollars from $6.4 billion to $5.9 billion, and the number of funded research grants decreased 6 percent from 15,444 to 14,736.

These numbers are disappointing, but a deeper look uncovers trends that could be even more disruptive. For example, the success rate for new R01 applications — the fraction actually funded — is a leading indicator, because new awards comprise only about 10 percent of all R01 grants and several years would be needed to see much change in the total number of funded grants. From 2003 to 2009, the success rate for new R01 applications declined 22 percent (NIDDK), 27 percent (NCI), and 30 percent (NHLBI). Across all three Institutes, the total number of new R01 awards has decreased 18 percent since 2003, a much steeper decline than the 6 percent decrease in the number of all funded research grants. If this trend continues, the total number of R01 grants will eventually fall to the same extent.

The lengthening odds of receiving a new research award hits young scientists particularly hard, and NIH has tried valiantly to keep them in the pipeline. Thanks to adjustments in scoring, newly trained scientists and established investigators have essentially equal success rates for R01 funding.

Unfortunately, young scientists do not enjoy some practical advantages of maturity. For the last decade, renewal applications have had about twice the success rate of new R01 applications. This fact is not surprising; good research results make for strong renewal applications. However, scientists can’t submit renewal applications before they win their first awards. In addition, to be eligible for preferential scoring as an “Early-Stage Investigator,” applicants must be within 10 years of completing their terminal research degrees or medical residencies. During the past few years, the average first-time R01 awardee has become older and now is about 42 years of age, by which time many investigators are bumping against the time limit to qualify as “Early Stage.” These pressures significantly reduce the chance of making the transition to independent research support.

Judged by the acquisition of independent research support, it takes more than 40 years to train successful biomedical scientists, but failure to hit that critical funding benchmark can divert them permanently from basic research. Unless the NIH budget can be stabilized, those of us trying to sustain the career development of young scientists will have to be extraordinarily creative to prevent the loss of this precious human capital, which could disappear almost overnight and require many years to replenish.

What would be the consequences of failure? Several recent analyses have concluded that NIH-funded research has been spectacularly rewarding in terms of return on investment, job creation, and the development of innovative treatments for disease. Basic research is the engine of discovery. Without it, translational and clinical research run out of raw material and become exercises in futility. Faced with tough budgetary choices, we should not inadvertently cede our leadership in medical discovery, which is the foundation for advances in medical care as well as our biotechnology and pharmaceutical industries. Viewed in this light, cutting support for NIH-funded research would cost far more than the dollars saved. Whether this message survives the current debate on deficit reduction will have lasting implications for the economy and public health in the United States.

—Evans Sadler, MD, PhD

The Only Official Highlights of ASH® in North America
Three Dates, Six Locations, One Great Program

January 20-21, 2012
Austin, TX
Orlando, FL

January 27-28, 2012
Atlanta, GA
Las Vegas, NV

February 3-4, 2012
New York, NY
San Francisco, CA

Attend one of these six meetings to hear experts translate the most influential research from the 53rd ASH Annual Meeting and Exposition into cutting-edge patient care. The limited attendance, panel discussions, and “Breakfast with the Experts” will provide numerous opportunities for attendees to discuss real patient cases with leaders in the field.

Taking part in this educational activity will allow you to:

• Examine advances in clinical and translational hematologic research
• Evaluate the role of new diagnostic techniques and therapeutic approaches as applied to the care and management of people with blood diseases
• Implement new patient management and care strategies or revise existing ones

Don’t miss your chance to network with colleagues and gain knowledge that can impact your practice strategies. Register for a meeting in the location that is most convenient for you.

The program has been approved for a maximum of 11 AMA PRA Category 1 Credits™.

For more information, visit [www.hematology.org/highlights](http://www.hematology.org/highlights).

ASH Clinical Practice Webinar Program

Throughout the fall, ASH is hosting a series of webinars on clinical issues that practicing hematologists frequently confront. The sessions feature presentations by experts in the field who provided current information on how to best diagnose and care for patients with various hematologic conditions. The next webinar focuses on pain in sickle cell disease. The speakers are Jennifer Haythornthwaite, PhD, Wally Smith, MD, and Carlton Haywood, PhD. It is scheduled for November 14 at 8:00 p.m. ET.

The webinar program is organized by the ASH Subcommittee on Quality of Care. Registration for all webinars is complimentary. For more information including speakers, dates, registration, and audio versions of previous webinars, go to [www.hematology.org/webinars](http://www.hematology.org/webinars).

Upcoming 2012 Webinars

**FEBRUARY**
Pregnancy and Hormone-Related Vascular Hematologic Complications
Moderator: Mary Cushman, MD, MSc, University of Vermont

**MARCH**
Thrombosis and Cancer
Moderator: Vincent Picozzi, MD, Virginia Mason Medical Center

**APRIL/MAY**
Plasma Cell Malignancies
Moderator: Dan Vogl, MD, University of Pennsylvania
Ask the Hematologist

KEITH MCCRAE, MD
Director, Benign Hematology, Taussig Cancer Institute, Professor of Molecular Medicine, Cleveland Clinic Lerner College of Medicine

(Editor’s Note: This question was submitted through the Consults-Colleague Program. Dr. McCrae was asked to respond.)

The Question

How often do you see immune thrombocytopenia (ITP) with pulmonary embolism (PE)?

The management of thrombosis in thrombocytopenic patients with ITP is challenging and not addressed by current guidelines. Likewise, there are no evidence-based data on whether to draw from for recommendations. Many experts suggest that the risk of anticoagulation is acceptable at platelet counts above 40,000 to 50,000/µl, although the severity of the thrombotic event and clinical characteristics of the patient should be considered. In the case presented here, the clot burden is extensive and the platelet count close to where anticoagulation is reasonable. Risk factors for bleeding in ITP include a prior history of bleeding and age ≥60 years, the latter of which is applicable to this patient. I would recommend aggressive treatment of this patient’s ITP, initially using corticosteroids, since agents such as IVIg may potentially predispose to further thrombosis, and I would consider institution of anticoagulation with intravenous heparin or another short-lived anticoagulant once the platelet count increases to ≥45,000/µl. The use of an IVC filter is a matter of preference; it may be more strongly justified if there is evidence of progressive thrombosis, or if the thrombocytopenia does not respond quickly. However, given the association of ITP with thrombosis, I would avoid intravascular devices if possible, and if an IVC filter is used, I would recommend a removable model.

The decision to perform a bone marrow aspirate and biopsy should not be influenced by a thrombotic event. If the peripheral blood smear shows isolated thrombocytopenia and the history and physical examination do not suggest other disorders, bone marrow aspirate would not be required.

Dr. McCrae indicated no relevant conflicts of interest.

My Response

ITP is a fascinating disorder with a complex pathogenesis that has only recently begun to be understood in detail. While a number of immune abnormalities underlie the development of ITP, the disease is largely mediated by antibodies reactive with glycoproteins expressed on platelets and megakaryocytes. These antibodies cause accelerated platelet destruction in the spleen as well as deficient platelet production secondary to impaired maturation of megakaryocytes.

The most common clinical presentation of ITP is bleeding, the severity of which correlates with the degree of thrombocytopenia. However, many patients with ITP have few bleeding complications even with very low platelet counts, an observation that may be related to the presence of young, highly functional platelets, increased levels of plasma microparticles, or other factors. Surprisingly, recent studies have also demonstrated that patients with ITP have an increased risk of thrombosis. The data concerning ITP and thrombosis are derived from several sources. A retrospective study from Aledort et al. suggested an increased risk of thrombosis in patients with ITP, with 18 thromboembolic events occurring in 186 adults (the majority after the diagnosis of chronic ITP). In another retrospective study reported in an abstract by Bennett et al., 18 thromboembolic events occurring in 186 adults (the majority after the diagnosis of chronic ITP). In another retrospective study reported in an abstract by Bennett et al., 18 thromboembolic events occurring in 186 adults (the majority after the diagnosis of chronic ITP). In another retrospective study reported in an abstract by Bennett et al., 18 thromboembolic events occurring in 186 adults (the majority after the diagnosis of chronic ITP).

While acute portal vein thrombosis has been reported in up to 15 percent of ITP patients undergoing splenectomy, and an increased risk of subsequent thrombosis has been associated with splenectomy for thalassemia, the review from Sarpawati et al. demonstrates a similar incidence of thrombosis in splenectomized and non-splenectomized ITP patients.

The mechanisms underlying the paradoxical development of thrombosis in patients with ITP have not been defined, though several have been postulated. The incidence of antiphospholipid antibodies (APLA) appears to be increased in patients with ITP, and several studies suggest that ITP patients with APLA develop thrombosis more frequently. In a prospective study, Diz-Kučiukkaya assessed 82 newly diagnosed patients with ITP, finding 31 (37.8%) positive for APLA. After five years, the cumulative thrombosis-free survival of APLA-positive and APLA-negative patients was 39 percent and 97.7 percent, respectively (p<0.004). Though current guidelines do not recommend routine screening of ITP patients for APLA, this should be considered in those who develop thrombosis. Additional factors contributing to the development of thrombosis in patients with ITP may include elevated levels of platelet-derived microparticles and complement activation on antibody-coated platelets.
Targeting DNA Repair to Enhance Cancer Therapy

ROBERT HROMAS, MD
Professor and Chair, Department of Medicine, University of Florida Health Science Center, Shands Hospitals

Cancer is a disease of DNA repair. Since every cancer must have at least one mutation in BRCA1/2, it makes sense that the characteristic uncontrolled proliferation that defines neoplasia, at least one instance of abnormal DNA repair must have occurred in every cancer. Indeed, the genomes of cancers sequenced thus far have demonstrated multiple DNA mutations implying that abnormal DNA repair can be both the cause and the effect of neoplastic transformation.

For some cancers, the defect in DNA repair is obvious. For example, inherited mutations of the Ataxia Telangiectasia-Mutated (ATM) gene, the NBS1 gene, or Fanconi Anemia genes can lead to acute myeloid leukemia.1 Perhaps the best known example of a defect in DNA repair leading to cancer is BRCA1/2 mutations in breast, ovarian, and peritoneal malignancies.2 What is just now beginning to be understood is that all cancers, not just the familial malignancies, will have some aspect of DNA repair that is less functional than normal. However, discovering the specific defects in DNA repair for each tumor type, or even between individuals with the same tumor type, will take lengthy investigation.

The paradox that all cancer cells face is that to replicate they need DNA repair. Each replication fork moving along the DNA strand will use several DNA repair pathways just to maintain DNA synthesis. The replication fork can hit strand breaks, cross-links, or damaged nucleotides, all of which occur commonly in all types of cells, and it stalls at these blockades. To restart the replication fork, the cell must repair these blocking lesions. How can this occur if all cancers have some underlying abnormality in DNA repair?

Typically, cancer cells resolve this paradox by overusing an alternative DNA repair pathway that can achieve the same end. In other words, in order to replicate, cancer cells become addicted to a defined DNA repair pathway other than the one that was defective in the origin of their transformation.3 This means that cancer cells have a fundamental weakness that their normal counterparts do not have. Targeting the alternative pathway to which a given cancer is addicted can stop replication forks from progressing, without affecting the replication of normal cells. This novel and potentially revolutionary therapeutic insight is called "synthetic lethality."4

The best example of this is in the hereditary breast and ovarian cancer syndromes mentioned earlier. These BRCA1/2-deficient tumors are defective in the repair of DNA double-strand breaks (DSBs). When a replication fork in one of these tumors hits a DNA single-strand break (SSB), it converts that into a DSB, but the replication apparatus cannot progress past that DSB. Since BRCA1/2 are both required for DSB repair, the tumor cells with those mutated repair components will rely heavily on, even be addicted to, repair of SSBs to prevent these DSBs from occurring. These cancer cells must repair the SSB before a replication fork hits it and converts it into a DSB. The DNA repair protein PARP1 is required for repair of SSBs, and there are small molecular inhibitors of PARP1 that will prevent repair of SSBs, but this is only a problem for the cells that are deficient in BRCA1/2 (Figure) — in this case, the tumor cells. Normal cells have the ability to repair the DSBs generated at the replication fork, because they have at least one normal allele of BRCA1/2. This has been proven clinically, where the PARP1 inhibitor olaparib improves the progression-free survival of familial breast cancer.1 Of course, not all breast or ovarian tumors have mutant BRCA1/2, but many more tumors behave as if they have such defects. For example, many ER-negative, PR-negative, and Her-2-negative (triple negative) breast cancers behave as if they were defective in BRCA1 or 2. In these patients, inhibiting PARP1 produced superior outcomes than not inhibiting PARP1.5 These patients may not have mutations in BRCA1 or 2, but they likely had deficiencies in other steps in this DSB repair pathway that generated the same characteristics. In other words, just because a given cancer is sporadic as opposed to familial does not mean it does not have a defect in DNA repair.

Tumor cells that are defective in DNA repair are clever, though. They can escape therapy based on synthetic lethality via the inherent instability of their own DNA. The best example of this is that some BRCA2-mutated breast cancers treated with PARP1 inhibitors generate a mutation leading to re-expression of a functional BRCA2 gene.6 These breast cancer cells with mutated BRCA2 actually deleted the mutated part of the gene under the selective pressure of PARP1 inhibitor therapy. This resulted in a smaller but functional BRCA2 protein, which could now repair the extra DSBs that occurred during replication in the presence of PARP1 inhibition.

Lest one think that targeting DNA repair for cancer therapy is solely the province of solid tumor oncology, there are several examples that indicate its applicability to hematologic neoplasia as well. Bortezomib synergizes with the alkylating agents in the treatment of myeloma by inhibiting DNA repair,7 and there is a subset of CLL with poor prognosis that has mutations in the ATM gene,8 which is also important in DSB repair. These CLL cells have been found to be amenable to therapy with PARP1 inhibitors. Finally, AML cells can be sensitive to PARP1 inhibition because of their intrinsic genomic instability.9

In the future, it may be that every individual's cancer genome will be sequenced. This would better define which defective DNA repair pathways to target using the synthetic lethality approach. Once such defective pathways are defined for all tumor types, drug development can target the alternative, required pathway. In addition, this information can be used as a biomarker to predict response to these agents. Thus, targeting DNA repair to enhance cancer therapy is one of the most innovative advances in cancer drug development in the last decade and may become widely applied in many areas of oncology.


ASH Calls for Increased FDA Authority and Resources to Address Drug Shortages

Calling the increase in national drug shortages “a tsunami of medical risk,” ASH Committee on Practice Chair Lawrence A. Solberg Jr., MD, PhD, offered several recommendations on strategies to combat drug shortages during a meeting of the U.S. Food & Drug Administration (FDA) Center for Drug Evaluation and Research.

As a member of the meeting panel, Dr. Solberg provided the Society’s perspective on strategies to both prevent and mitigate drug shortages, including increasing FDA authority under The Preserving Access to Life-Saving Medications Act (S. 296/H.R. 2245), improving FDA communication with stakeholders, examining the impact of current FDA requirements on shortages, developing a national drug registry, and expanding “orphan drug” status to incentivize continuous production of generics. ASH also submitted comments (image of letter below) to a hearing of the Subcommittee on Health and the Environment of the House Energy & Commerce Committee that expand on these recommendations and express the Society’s position that the current situation is unacceptable, and action must be taken now to alleviate critical shortages. ASH was the first organization to call on Congress to address the problem of drug shortages and the need to provide increased authority and resources to FDA.

Read more about ASH’s advocacy efforts related to drug shortages, the latest update on the status of hematologic drug shortages, and resources for physicians at www.hematology.org/drugshortages. ASH’s recommendations to the FDA and Congress are available online at www.hematology.org/Advocacy/Testimony.

The Super Committee will meet several times this year and must report a bill with its recommendations by November 23, 2011. The recommendations have to be voted on by the full House and Senate. If the Super Committee or Congress fails to act by December 23, 2011, the bill calls for automatic across-the-board cuts, split 50-50 between defense and non-defense spending, including Medicare.

Because health-related programs were largely spared from cuts in the Budget Control Act, funding for many health-related programs remains at risk. For example, researchers worry about protecting funding for the National Institutes of Health and other federal agencies; and medical schools are concerned about proposals to create savings by severely cutting graduate medical education.

The Super Committee is also considering physician payment reform as part of its recommendations. ASH has contacted the Super Committee and urged it to thwart the scheduled 29.5 percent reduction in 2012 Medicare physician payments and permanently repeal the flawed Medicare payment formula.

To obtain the latest information about the Super Committee’s work and its impact on hematology, please go to www.hematology.org.

Absent Congressional Action, 30 Percent Medicare Physician Payment Cut Scheduled to Begin January 1

Physicians are scheduled to receive a 29.5 percent cut from Medicare beginning January 1, 2012, unless Congress takes legislative action to prevent it. ASH strongly opposes the proposed draconian cuts to physicians and has long advocated for repeal of the sustainable growth rate formula and the need for an adequate and stable physician payment system. In recent comments to the Centers for Medicare & Medicaid Services, ASH shared its concerns and urged the agency to actively support legislative efforts to change the payment system. As noted above, ASH also has urged the new “Super Committee” on deficit reduction to include physician payment reform in its deficit reduction plan.

A major barrier to reforming physician payment is the cost of repealing the current payment formula. The Congressional Budget Office (CBO) has priced the cost of a payment overhaul at about $300 billion over 10 years. Complicating the situation further, the Medicare Payment Advisory Committee (MedPAC), an advisory committee to the Congress, is considering a proposal that would pay for the reform by allowing specialists’ payments to be cut while maintaining the rates for primary-care physicians. All other services covered by the physician fee schedule would be cut by 5.9 percent per year for three years and then frozen. (Subspecialists, including hematologists, are not considered primary-care providers, even when performing that function.) ASH has strongly opposed this approach.

ASH continues to advocate that physicians cannot tolerate a nearly 30 percent pay cut. Please visit the ASH Advocacy Center (www.hematology.org/takeaction) to take action.

Congress Passes Bill to Extend Funding for NIH and Other Federal Programs Through November 18

After a contentious battle that narrowly averted a government shutdown, Congress passed a short-term continuing resolution (CR) to keep the government operating through the start of the new fiscal year that began October 1. The CR extends funding for federal programs through November 18 at a rate of $1.043 trillion, the amount mandated in the Budget Control Act of 2011, which is nearly $7 billion below the current year. As a result, most federal programs, including the National Institutes of Health (NIH), received a cut in funding for the start of fiscal year (FY) 2012.

The CR allows Congress additional time to complete work on the annual spending bills. However, with the two parties once again locked in a showdown over spending, additional cuts in funding for NIH remain a possibility. All Members of Congress need to hear from their constituents about the need to adequately fund NIH. To contact your Representative and Senators quickly and easily, please use the email template offered online at www.hematology.org/takeaction. The Society encourages you to personalize the letter, providing examples of why NIH funding is important to you and your research.
Is Anybody in Washington Listening?

(Cont. from page 2)

Department is a constant presence in Washington, and it continually works on building relationships with Congress and federal agencies to represent the interests of the Society. In order to truly influence policy, however, members of this Society must develop long-term personal relationships with policy-makers. There are several strategies to accomplish this including: personalizing your correspondence with the legislator to share stories about your patients, visiting your congressional delegation to your institution or practice, speaking with your Member of Congress at a town hall forum, and making yourself recognized as a helpful expert and resource by the lawmaker’s office. For those who are interested, the Society offers many resources to help do all of these and wants to work with you.

There are many important policy fights ahead. Legislative battles including federal spending for research, physician payment, and drug patents will need to be fought before the end of this year. The outcomes will significantly impact our research, practices, and patients. The Society will implement several advocacy campaigns, and I strongly encourage you to join with your ASH colleagues to voice your concerns and interests. Your views matter and your message will make a difference.

For more information about how to become involved in ASH Grassroots Advocacy, please contact the ASH Government Affairs Department at grassroots@hematology.org or 202-776-0544.

**Influence Factors on Legislators**

This chart depicts the answer to the following question posed in two Congressional Management Foundation surveys of more than 350 congressional staffers:

“If your Member/Senator has not already arrived at a firm decision on an issue, how much influence might the following advocacy strategies directed to the Washington office have on his/her decision?”
Sorting Out Platelet α-Granules


For the past 50 years, platelet biologists have looked at platelets under the electron microscope and have observed three types of granules: dense granules, lysosomes, and α-granules. The α-granules outnumber the other two granule types by an order of magnitude and contain hundreds of different protein cargos. Some of these cargos have opposing activities, such as prothrombotic and anti-thrombotic or angiogenic and anti-angiogenic. How can cargos with opposing activities efficiently elicit physiological responses? One possibility is that α-granule contents are released indiscriminately and the physiological activity of platelet releasate is dictated solely by stoichiometry and kinetics of their activities on target receptors. However, recent evidence suggests that the release of specific contents from platelets is controlled at the level of the α-granule exocytosis. These studies indicate that specific platelet cargos are stored in different subsets of α-granules that are released only in response to particular agonists. Alternatively, cargos may be randomly distributed among granules but segregated within the granule and released preferentially in response to different agonists (Figure).

A recent series of articles published in Blood address this controversy. Kamykowski et al. from Little Rock, AR, used confocal microscopy with three-dimensional reconstruction and quantitative analysis to assess the co-distribution of 15 different α-granule cargos. The frequency of co-distribution of the different granule pairs followed a Gaussian distribution, consistent with the interpretation that cargos are randomly distributed among α-granules. The authors attributed segregation of α-granule contents previously observed by investigators to compartmentalization of cargo within single α-granules (Figure A, Resting). Two other reports, however, demonstrated that angiogenic factors localize to different α-granules and are released upon stimulation by different agonists (Figure B). Battinelli et al. from Joseph Italiano’s lab in Boston demonstrated that the angiogenic factor vascular endothelial growth factor (VEGF), but not the anti-angiogenic factor endostatin, is released from granules following exposure of platelets to ADP. In response to thromboxane A₂, endostatin is released, but VEGF is not. Chatterjee et al. from Stockholm also showed that ADP is a potent secretagogue for VEGF and other angiogenic factors but not for anti-angiogenic factors such as endostatin. Further studies by this group were consistent with previous results demonstrating that PAR1 agonists release angiogenic factors, while PAR4 releases anti-angiogenic factors. Differential secretion of granule contents in response to different agonists is difficult to reconcile with the hypothesis that cargo proteins are randomly distributed among α-granules. A model including partial selective release of specific granule cargos from individual platelets has been proposed (Figure A).

Over the past decade, we have come to expect a lot more of platelets. In addition to their established role in hemostasis and thrombosis, they have been credited with roles in inflammation, atherosclerosis, angiogenesis, wound healing, antimicrobial host defense, and malignancy. Central to many of these activities is the function of α-granules. The mechanisms that enable platelets to control the release of α-granule contents that, in some cases, have opposing activities are unknown. In many nucleated cells, different subtypes of granules contain different granule cargos that are released in response to different agonists. The studies by Battinelli et al. and Chatterjee et al. indicate that the same is true in platelets. However, the study by Kamykowski et al. suggests a random distribution of cargo among platelet granules. How will this controversy be resolved? Future studies of α-granule formation may demonstrate that the delivery of cargos into nascent α-granules at the trans Golgi network occurs in a random fashion, or instead that this delivery is patterned to provide for the formation of α-granule subtypes containing different cargos. A better understanding of the distribution of the machinery that controls secretion, such as SNAREs and Rab proteins, could reveal the mechanism of differential α-granule release. Alternatively, understanding the dynamics of the fusion pore may reveal how platelets manage the release of cargos with opposing functions.


Allogeneic Transplantation in Myeloma: Is It Worth a Price to Pay?


Even in the era of targeted novel agents, autologous stem cell transplantation (autoSCT) remains the standard frontline approach for patients with multiple myeloma who are eligible for high-dose therapy. With the incorporation of novel agents during the induction, consolidation, and maintenance phases, as in the Total Therapy 3 protocol, the five-year estimates of overall survival (OS) and event-free survival (EFS) reach 70 percent. Does this imply that allogeneic transplantation (alloSCT) might also be an option for myeloma? Use of alloSCT with myeloablative conditioning in myeloma has been limited by severe toxicity and a high incidence of treatment-related mortality (TRM) in the range of 30 to 50 percent. On the other hand, reduced-intensity conditioning (RIC) alloSCT is associated with less toxicity, and the contribution of GVHD to TRM by RIC alloSCT has reduced TRM to 15 percent or less. However, the role of RIC alloSCT in relation to autoSCT in the frontline approach to myeloma remains undefined.

Björkstrand and colleagues from the Karolinska Institute in Sweden compared single (auto) or double autoSCT (auto-auto) to autoSCT followed by RIC matched sibling donor alloSCT (auto-allo) in previously untreated patients with multiple myeloma. All patients received induction with conventional chemotherapy, and none were treated with novel agents. Patients with an HLA-identical sibling donor were assigned to the auto-allo arm (n=108), while the others were randomized to either auto (n=145) or auto-auto (n=104). Median follow-up was 61 months, and long-term outcomes (at 60 months) of progression-free survival (35% vs. 18%, P=0.01), overall survival (85% vs. 58%, P=0.006), and relapse rate (49% vs. 76%, P=0.003) were superior after auto-allo compared with auto only. However, the cumulative non-relapse mortality rates at 24 and 60 months were 12 percent and 16 percent for the auto-allo group and 3 percent and 4 percent for the auto group (P<0.001). Furthermore, the patients in the auto-allo arm did worse during the first and second year, with favorable outcomes not emerging until after two to three years. The incidence of grade 2 to 4 acute graft-versus-host disease (aGVHD) was 20 percent, and the incidence of limited and extensive chronic GVHD was 31 percent and 23 percent. The authors did not comment on the ability to start a salvage treatment for patients with multiple myeloma who are eligible for high-dose therapy. With the incorporation of novel agents during the induction, consolidation, and maintenance phases, as in the Total Therapy 3 protocol, the five-year estimates of overall survival (OS) and event-free survival (EFS) reach 70 percent. Does this imply that allogeneic transplantation (alloSCT) might also be an option for myeloma? Use of alloSCT with myeloablative conditioning in myeloma has been limited by severe toxicity and a high incidence of treatment-related mortality (TRM) in the range of 30 to 50 percent. On the other hand, reduced-intensity conditioning (RIC) alloSCT is associated with less toxicity, and the contribution of GVHD to TRM by RIC alloSCT has reduced TRM to 15 percent or less. However, the role of RIC alloSCT in relation to autoSCT in the frontline approach to myeloma remains undefined.

AlloSCT is a treatment with curative potential for myeloma, in part due to the GVH effect, but also due to induction of sustained remissions after donor lymphocyte infusions. Favorable outcome may also be due in part to absence of contaminating myeloma cells in the donor graft. Still, the role of alloSCT in myeloma remains under debate because of the high mortality and morbidity, while convincing evidence for a survival benefit is lacking. Furthermore, many questions remain unanswered, especially who should receive alloSCT and when to transplant. However, one must keep in mind that the expected median survival of patients with myeloma is unlikely to exceed seven to 10 years using current approaches, even with the introduction of maintenance therapy and the addition of novel agents at each step of the intensive autoSCT procedure. Therefore, some patients who might benefit from alloSCT, and, considering that myeloma is an incurable malignancy, we cannot deny alloSCT to patients – especially young patients – with myeloma as an additional option for treatment.

The Bleak Outlook for Patients With MDS After Hypomethylating Agents Fail


For many years there were no approved therapies for patients with myelodysplastic syndromes (MDS). Prior to 2004, only general supportive care, off-label use of medications such as hematopoietic growth factors or thalidomide, clinical trial enrollment, or, rarely, allogeneic hematopoietic stem cell transplantation were available. Then, between 2004 and 2006, three drugs were approved by the Food and Drug Administration for MDS: azacitidine (AZA), lenalidomide, and decitabine. Since then, MDS drug development has entered another era of stagnation from which it has yet to emerge, with no new disease-modifying therapies approved in more than five years.

During this comparatively quiet period, a multicenter trial formally demonstrated that AZA treatment confers a survival advantage compared to supportive care for patients with higher-risk MDS or oligoblastic acute myeloid leukemia (AML) with <30% blasts.3 But this survival advantage is relatively modest (median ~9 months), and AZA is not curative. Although some patients experience an excellent and durable treatment response with AZA, the drug eventually fails, as do all of the other agents now available to treat patients with MDS; the median duration of AZA benefit is less than two years.3

Thomas Prébet and his colleagues in Le Groupe Francophone des Myelodysplasies (GFM) recently underscored the pressing need for new approaches in MDS by analyzing 435 patients with higher-risk MDS or oligoblastic AML in whom AZA had failed. The GFM investigators reviewed outcomes from four patient cohorts: 138 patients enrolled in the AZA001 randomized international study of AZA monotherapy,1 27 participants in Johns Hopkins University-led pilot AZA combination studies, and 270 patients registered in a French AZA compassionate use program. Types of treatment failure included inability to tolerate AZA therapy (9% of patients), lack of any clinical response (“primary failure”; 55% of patients), or relapse after an initial response (“secondary failure”; 36% of patients).

The median overall survival after AZA failure for these 435 patients was just 5.6 months, and only 15 percent of the patients were still alive two years later. These results are almost identical to an M.D. Anderson Cancer Center review of 87 patients with MDS for whom decitabine failed; that cohort had a median post-failure survival of only 4.3 months.4 In a multivariate analysis, characteristics of the AZA-failing patients who did most poorly in the GFM study included older age, male sex, high-risk cytogenetics, a bone marrow blast count ≥10 percent, and primary rather than treatment failure.

None of the GFM patients who were subsequently treated with decitabine achieved a response, suggesting that switching from one failing hypomethylating agent to another is an ineffective general strategy. For 270 patients from whom information was available on subsequent treatments after AZA failure, the subset of 37 patients (8.5% of the overall cohort) who were young and healthy enough to undergo allogeneic stem cell transplantation had the best outcomes (median survival 19.5 months), followed by those who participated in investigational trials (13-month survival) and those who were treated with low-dose or high-dose chemotherapy (7.3 or 8.9 months median survival, respectively). But the largest subgroup, the 45 percent of patients who received only supportive care, lived just 4.1 months on average. These post-AZA survival differences likely represent selection bias in how clinicians triaged patients for subsequent treatment approaches, yet they also highlight the poor outcomes for most patients in whom AZA treatment becomes ineffective.

Several ongoing clinical trials are enrolling patients for whom the hypomethylating agents have failed, including studies of various deacetylase inhibitors and other novel targeted agents, as well as a multicenter randomized trial comparing rigosertib (a PI3 kinase inhibitor) with low-dose cytarabine or supportive care. However, markedly better treatment options will likely emerge only after increasing our understanding of molecular pathobiology of MDS allows us to move beyond the current empiric approaches.


A Step Forward in Understanding Leukemogenesis in NPM1c+ AML


Acute myeloid leukemia (AML) represents a heterogeneous group of malignancies with great variability in clinical course and response to therapy. Mutations involving the nucleophosmin (NPM1) gene are found in one-third of all AML cases and roughly 60 percent of cytogenetically normal AML. NPM1, an oligomeric, nucleolar chaperone protein, normally shuttles molecular partners between the nucleolar, nucleoplasmic, and cytoplasmic compartments and also participates in nucleolar assembly, ribosome biogenesis, chromatin organization, centrosome duplication, nuclear mRNA maturation, and DNA repair. NPM1 mutations (referred to as NPM1c+) cause aberrant localization of NPM1c to the cytoplasm. AMLs with NPM1c+ characteristically exhibit low CD34 expression, FLT3-ITD mutations, a characteristic gene expression profile (e.g., HOX overexpression) and microRNA signature, multi-lineage involvement, and a relatively favorable prognosis (in the absence of FLT3-ITD). Clinical observations that NPM1c+ stably persists during AML relapses while associated genetic mutations may be lost or acquired suggest that mutant NPM1 is an important “founder” genetic lesion and may therefore be a valuable target for anti-leukemic therapy.

To better understand the molecular and cellular roles of NPM1c+ in AML pathobiology, Vassiliou and colleagues in the laboratory of Allan Bradley at Cambridge Institute for Medical Research studied a conditional knock-in mouse model that expressed the common, type A (humanized) form of NPM1c mutation. They observed that hematopoietic cells from the Npm1cA transgenic mice recapitulated the human phenotype with cytoplasmic NPM1c localization, differential expression of Hox and other genes, and expansion and increased self-renewal of myeloid progenitors. Some of these mice also developed late-onset AML, suggesting that additional genetic lesions facilitated leukemic outgrowth. A transposon mutagenesis approach was then employed to induce secondary, cooperative events. Roughly 80 percent of mice that co-expressed Npm1cA and the Sleeping Beauty transposon developed rapid-onset AML, and all leukemias had persistent Hox overexpression, implying continued dependence on NPM1c-induced mechanisms. Common insertion site analyses identified GM-CSF mutagenesis and activation in many cases along with exclusive integrations in Flt3 or Rasgrf1 and involvement by a number of genes not previously linked with NPM1c+ AMLs, including Nup98, Nfl, Bach2, and Dleu2.

These data establish NPM1c+ as an initiator of myeloid cell transformation—a key mediator, at least in part, by Hox gene overexpression and increased self-renewal. Secondary leukemogenic mutations may involve alterations of proliferation signals (e.g., Flt3, as observed in human NPM1c+ cytogenetically normal AML), transcription factors (Bach2), other signaling molecules (Rasgrf1, Nfl), and/or tumor suppressors (Dleu2) (Figure). Understanding the foundational role of NPM1c+in AML reinforces the notion that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD (Figure). Understanding the foundational role of NPM1c+ in AML involves the recognition that disabling NPM1c might interrupt the collaborative, downstream Nf1-ITD.

Leaky Vessels, Valves, and Veins: How Lymphangiogenesis Genes are the Valve Regulators in Veins


Deep-vein thrombosis, varicose veins, and post-thrombotic syndrome are all associated with abnormalities of the bicuspid venular valves. From the time of Virchow, clinicians have recognized that stagnation of blood flow at the valve leaflet/vessel wall junction initiates microthrombus formation. Recent studies have demonstrated that aging, a significant risk factor for venous thrombosis, is associated with thickening of the venous valve leaflets, which in turn is inversely related to valve function. Further, valvular sinus endothelium maintains a thrombo-resistant phenotype wherein expression of the anticoagulant proteins thrombomodulin and endothelial protein C receptor is up-regulated and the procoagulant protein von Willebrand factor is down-regulated, compared with vein lumen endothelium. Thus, understanding how venous valves operate and mature may aid in developing new therapies for venous hypertension and possibly protect valves, preventing chronic venous insufficiency. Utilizing insights derived from the morphogenesis of cardiac valvular and lymphatic endothelium, Bazigou and colleagues in the laboratory of Taija Makinen at the London Research Institute in the U.K., defined genes responsible for valve development in veins, finding a common molecular mechanism involving integrin-β9 and ephrin-B2 signaling in both veins and lymphatics.

First, the investigators showed that mouse and human venous valves express common morphologic features. Scanning electron micrograph analysis showed that the edges of valve leaflets were lined by transversely aligned fusiform cells, while the cells on the leaflet and downstream on the outflow side of the valve had a rounded morphology. In contrast, endothelial cells located upstream on the inflow side of the valve aligned in the direction of blood flow. Similar cell arrangement was observed around lymphatic valves. In developing mice, venous valves express markers of arterial and lymphatic endothelia, including ephrin-B2, integrin-β9 and its ligand, an alternatively spliced form of fibronectin known as Fn-βIIIa. The molecular identity of venous valve endothelial cells was further characterized by examining the expression of prospero-related homebox 1 (PROX1) and VEGFR3, two major regulators of lymphangiogenesis that are highly expressed in lymphatic valves. Immunofluorescence staining revealed strong and specific expression of PROX1 in the endothelial cells of developing and mature murine venous valves. PROX1 was also expressed in human venous valves. Valve selective deletion of integrin-β9 and ephrin-B2 disrupted venous valve morphogenesis, demonstrating the continuous requirement of integrin-β9 and ephrin-B2 signaling for the maintenance of venous valves. Ephrin-B2, but not integrin-β9, was additionally required for the maintenance of lymphatic valves.

These studies describe the molecular regulators of venous valves and the remarkable involvement of common morphogenetic processes and signaling pathways in controlling valve formation in veins and lymphatic vessels. Potentially, agents that modulate integrin-β9 or ephrin-B2 may prevent venous hypertension and even the post-thrombotic syndrome. Could the thickening of the valve leaflets be due to excess connective tissue matrix proteins expressed in response to stimuli such as thrombin or cytokines? Nature’s parsimony is always fascinating. Might lymphatic dysfunction go hand-in-hand with venous valve dysfunction? Might the bad edema cases be a double-whammy for activating a few key mediators locally? Or might this explain the occasional patient who gets lymphedema even after superficial phlebitis?


FABIANA D'ISTROFFON, MD, AND MICHAEL LINENBERGER, MD

Drs. D'ostroff and Linenberger indicated no relevant conflicts of interest.

GREGORY M. VERCELLIOTTI, MD

Dr. Vercellotti indicated no relevant conflicts of interest.
**Streptococcus:** Exploiting the Symmetry of Fibrinogen to Make a Pathogenic Tinkertoy


Streptococcus pyogenes infection is associated with disease ranging from mild pharyngitis to severe, potentially fatal events, including streptococcal toxic-shock syndrome. Additionally, rheumatic fever and post-streptococcal acute glomerulonephritis continue to be common in developing nations. Streptococcal M protein, which was discovered by Rebecca Lancefield in 1928, is a 48-kDa fibrillar, surface-associated major virulence factor in streptococcal infections. Soluble M protein is produced by proteolytic cleavage at the cell surface by neutrophil proteases. There are more than 100 types of M proteins, of which the M1 type is the most common. M1 protein binds fibrinogen, which results in vascular leakage and tissue injury, which are hallmarks of toxic-shock syndrome. The M1-fibrinogen complex binds J2 integrins on neutrophils, resulting in the secretion of heparin-binding protein (also known as azurocidin), which is an important mediator of the vascular pathology associated with streptococcal infection. The M1-fibrinogen interaction also results in integrin-dependent platelet activation, leading to additional pro-inflammatory events.

To address the question of how the M1-fibrinogen complex produces neutrophil activation, Macheboeuf et al. determined a 3.3 Å crystal structure of a 174-kDa fragment of M1 in complex with the 86-kDa fibrinogen fragment D. In the structure, M1 forms a dimer to which four fragment D molecules are bound (as shown schematically in the left of the Figure). Fibrinogen has two D domains and a central E domain, producing a symmetrical D-E-D molecule. After proteolytic cleavage of fibrinogen by thrombin and intermolecular association of the D and E domains, the D-E-D symmetry is the basis for the polymerization of fibrin to form the three-dimensional clot network. Macheboeuf et al. propose that streptococcus takes advantage of the symmetry of fibrinogen by using M1 protein to form its own Tinkertoy-like version of a three-dimensional fibrinogen network (as shown in the right of the Figure). Transmission electron microscopy of M1-fibrinogen complexes was consistent with this network structure. In their model, binding and clustering of J2-integrin molecules by the M1-fibrinogen network leads to neutrophil activation. To test this model, they compared heparin-binding protein release by neutrophils stimulated with M1 deletion constructs that retained the ability to bind fibrinogen but did not produce networks. Wild-type M1 protein, but not the deletion constructs, stimulated release of heparin-binding protein from neutrophils. Consistent with this, fibrinogen fragment D, which does not support network formation due to lack of D-E-D symmetry, inhibited M1-mediated neutrophil activation.

Macheboeuf et al. have demonstrated that neutrophil activation associated with M1 protein, a major streptococcal virulence factor, is due to the organization of fibrinogen by M1 protein into a network. The M1-fibrinogen network produces a high density of integrin-binding sites, which it proposes leads to integrin clustering and neutrophil activation. Based on these results, they propose that the M1-fibrinogen interaction is a potential therapeutic target for the treatment of streptococcal toxic-shock syndrome.

**Zinc Fingers Cut and Paste F9 Gene to Cure the Hemophilia B Mouse**


Despite nearly 50 human subjects enrolled in seven hemophilia gene therapy trials over 10 years, gene therapy is still not a feasible alternative for patients with hemophilia. In situ correction has now been successfully accomplished in an animal — specifically, in the hemophilia B mouse. Katherine High and her colleagues from Children’s Hospital of Philadelphia, for the first time, have successfully inserted a normal F9 gene into the genome of a hemophilia B mouse using zinc finger nucleases (ZFNs) to accomplish genome editing and correction of the mutated gene in situ. ZFNs are fusion proteins that recognize specific DNA sequences in a gene to induce site-specific double-strand DNA breaks to allow insertion of a normal gene at that locus.

To accomplish the in vivo genome editing in the hemophilia B mouse model, the investigators designed a ZFN targeting intron 1 of the human F9 gene. This approach was based on the fact that nearly all of the mutations causing hemophilia B are distributed across the coding sequences of exons 2-8. Thus, by targeting intron 1, the investigators hypothesized that they would be able to correct nearly all, if not all, of the disease-causing mutations in the human F9 gene.

In their in vitro studies, High’s group demonstrated that ZFN efficiently induced double-strand breaks at a locus in intron 1, and that when co-delivered with a gene-targeting vector this ZFN could insert the normal F9 gene at the specific locus targeted in exon 1. Because ZFN targets only the human F9 gene, the investigators engineered a mouse to carry a mutated human F9 gene. To correct the mutated human F9 gene, the ZFN was co-administered by intraperitoneal injection with an AAV-8 donor vector and a cDNA cassette containing exons 2-8 of the wild-type human F9 gene.

Human factor IX activity levels detected in mouse plasma two days later by ELISA assay averaged 3 to 7 percent of normal. The degree of correction of factor IX levels was noted to be dependent on the dose of AAV-donor: higher the vector dose, the higher the level. Several days after ZFN injection in the mouse, hematectomy was performed to demonstrate stable persistence of factor IX levels after the “gene editing.” There was an accompanying correction of the hemophilia B phenotype, demonstrated by a shortening of the APTT, from mid-60s to the normal range, mid-30s.

So, is this approach ready for use in humans? Unlike vector-based gene therapies currently under clinical investigation, ZFN-directed gene editing would produce a permanent correction after a single treatment (presumably intravenous in humans rather than the intraperitoneal route used in mice); and if proven safe and effective in dogs and in phase III trials in humans, it might be a potential approach. Is ZFN-directed genome editing of a mutated F9 gene sufficient to result in normal hemostasis? In the mouse model, this approach achieved a factor IX level high enough to prevent spontaneous bleeding. If it resulted in similar levels in man, this would also prevent spontaneous bleeding, which accounts for the major morbidity of the disease. Will this approach be safe? Dog studies, followed by careful phase I clinical trials in humans, would be required to answer this question. For humans, the critical steps will be to analyze any potential integration sites in the human genome in addition to intron 1 of the F9 gene. Will there be an immune response to AAV? The answer to this question will require prospective assessment with careful monitoring of liver function tests to detect the transient transaminitis that may accompany exposure to some AAV vectors. It is of note that small studies indicate that short-term immunosuppression with mycophenolate and rapamycin may alleviate or prevent this problem. Will it be possible to escalate AAV vector dosing to achieve higher factor IX levels? This will require careful escalation of vector dose in future clinical trials.

3. The Hemophilia Center of Western Pennsylvania, Royal Prince Alfred Hospital, Sydney, Australia, University of Campinas, Brazil. Gene transfer for subjects with hemophilia factor IX deficiency. ClinicalTrials.gov Identifier: NCT00515710.

**Figure**

Streptococcal M1 protein – fibrinogen complex. Left, schematic of the x-ray structure of a 174Da M1 fragment complexed to fibrinogen fragment D. Right, model of the M1-fibrinogen complex based on the D-E-D fibrinogen symmetry.

**Dr. Pete Lollar**

Dr. Lollar indicated no relevant conflicts of interest.

**Margarret V. Ragni, MD, MPH**

Dr. Ragni indicated no relevant conflicts of interest.
The Case of the Vanishing CD20: A Culprit is Named


There is mounting evidence that engagement of CD20 on the surface of B cells by monoclonal antibodies may result in the disappearance of the antigen, an effect that has been reported as more marked with the type I reagents such as rituximab and ofatumumab than with the type II obinutuzumab (GA101) and tositumomab.1 This may be important, not only because disappearance of the antigen can impair binding of anti-CD20 to the target cell, but also because it appears to reduce the half-life of the antibody by internalization of the CD20:anti-CD20 complexes and their intracellular degradation.

Martin Glennie and Mark Cragg from the University of Southampton, UK, have previously shown that this process is heterogeneous across disease types, occurring much more frequently in chronic lymphocytic leukemia and mantle cell lymphoma than in the germinal center types.1 The same group has now expanded these observations, and, having hypothesized that the effect might be mediated by Fc receptor binding on the target cells themselves, they went on to look at the dominant type of Fc receptor found on B cells – the inhibitory FcγRIIb (CD32b). Comparisons of the level of expression of CD32b with the degree of CD20 internalization on a variety of normal or malignant human B cells following rituximab treatment showed a clear correlation. This finding was reinforced by the prevention of internalization by a blocking anti-CD32b antibody and by comparing a CD32b-negative cell line to the same cells transfected with the FcγRIIb. This showed that those with the highest levels of expression underwent the most CD20 internalization. This process was accompanied by phosphorylation of the Fc receptor, an effect dependent mainly upon the presence of the Fc receptor on the same cells as the CD20, following which the complexes could be tracked to the B-cell lysosomes, where they were degraded.

The potential effects of this internalization were tested in an in vitro model of antibody treatment, where there was a markedly reduced level of macrophage phagocytosis following type I antibody, while the type II antibodies were largely unaffected. Once again, Fab fragments to CD32b were capable of reversing the fall in phagocytosis after rituximab treatment. Finally, the authors examined the relationship between the expression of CD32b and the outcomes of rituximab-based therapy in a small retrospective series of patients with mantle cell lymphoma. They found that the progression-free survival was significantly shorter among patients with high FcγRIIb expression on the lymphoma cells, as determined by immunohistochemistry.

It is becoming clear that engagement of various Fc receptors is a critical part of the mechanism of action for anti-CD20 antibodies, although previous attention focused on the stimulatory FcγRIIIa on host myeloid effector cells, following the observation that different idiotypes of mouse monoclonal antibodies may result in the disappearance of the antigen, an effect that has been reported as more marked with the type I reagents such as rituximab and ofatumumab than with the type II obinutuzumab (GA101) and tositumomab.2 This may be important, not only because disappearance of the antigen can impair binding of anti-CD20 to the target cell, but also because it appears to reduce the half-life of the antibody by internalization of the CD20:anti-CD20 complexes and their intracellular degradation.


CD20
Rituximab
Lysosomes
B cell

Internalization

PETER JOHNSON, MD
Dr. Johnson is an author on this study.

NHLBI Special Symposium on MDS
HAL E. BROXMeyer, PhD
Distinguished Professor, Mary Margaret Walther Professor Emeritus Professor of Microbiology/Immunology, Program Leader, NC1-Designated IU Simon Cancer Center Program on Hematopoiesis, Heme Malignancies, and Immunology

Myelodysplastic syndromes (MDS) remain a priority for ASH, and the Society has advocated for coordinated research in this field over the last several years. In 2008, ASH sponsored an agenda-setting workshop on MDS to further explore research needs in this area. Based on the workshop’s report, the Society developed research recommendations and priorities for the scientific community and National Institutes of Health (NIH). Most recently, ASH helped to promote a state-of-the-science symposium on MDS that was held this past September. This symposium was organized by Drs. Nancy DiFrancesco and Manjit Hanspal of NHLBI and included staff from NHLBI, NIDDK, NCI, and the VA. In addition, a closed session working group on MDS organized by NHLBI met after the symposium. The symposium and workshop were co-chaired by Dr. Pierre Fenaux and me. The purpose of the symposium was to inform and provide updates on scientific and clinical efforts in MDS, and the objectives of the working group were to identify key questions that remain to be answered and ways that NIH can facilitate collaborations between investigators and encourage and accelerate future research efforts. Among the topics covered were prognostic markers, pathobiology, genomics, epigenomics, and novel therapeutics. Most of the world’s experts in MDS attended and participated, and a report of the meeting will be submitted for publication. A workshop summary will be posted soon. Go to www.nhlbi.nih.gov/resources/docs.
Multiple Myeloma: To T or Not to T, What Will the Answer Be?

**STUDY TITLE:** Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib, and Dexamethasone (RVD) to High-Dose Treatment With Peripheral Autologous Stem Cell Transplant in the Initial Management of Myeloma in Patients Up to 65 Years of Age

**COLLABORATORS:** Dana-Farber Cancer Institute, University Hospital, Toulouse, France (for the Intergroupe Francophone du Myelome), Celgene Corporation, and Janssen-Cilag, Ltd.

**CLINICALTRIALS.GOV IDENTIFIER:** NCT0191060

**STUDY DESIGN:** One thousand patients, 65 years of age or less, with newly diagnosed multiple myeloma who are stem cell transplant candidates with adequate cardiac, pulmonary, renal, and hepatic function will receive one cycle of RVD and then be randomized to arms A or B, with stratification based on International Staging System criteria (stage I, II, or III) and cytogenetics (standard vs. high-risk vs. FISH failures). Subsequently, all patients will receive two additional courses of RVD and have collection of peripheral blood stem cells mobilized using cyclophosphamide and filgrastim. Patients in arm A receive an additional five cycles of RVD; those in arm B undergo treatment with high-dose melphalan and autologous stem cell transplant (AsCT) followed by two cycles of RVD. All patients then receive maintenance lenalidomide for at least one year, with AsCT used for patients in Arm A at relapse.

**RATIONALE:** This clinical trial will compare the progression-free survival between Arms A and B, and therefore determine the added value of early use of AsCT in the context of RVD therapy. Response rates, time to progression, overall survival, toxicity, and definition of prognostic groups by gene expression profiling with determination of the best treatment in each group are secondary endpoints. Additionally, both quality of life and resource utilization data will be collected for use in economic evaluation models.

**COMMENT:** AsCT has been a standard of care in myeloma due to achievement of both high extent and frequency of response and to the prolonged progression-free survival compared with conventional chemotheraphy. However, the availability of novel therapies, including bortezomib and lenalidomide, that have improved outcome has impacted the transplant paradigm. Both lenalidomide and bortezomib in combination with dexamethasone achieve high-quality responses pre-AsCT that portend improved outcome post-AsCT. Further, the combination of lenalidomide, bortezomib, and dexamethasone achieves responses universally, with 74 percent very good partial response or better and 52 percent complete and near complete responses, including molecular complete responses, when used as initial therapy without AsCT. Thus, the stage is set to examine the role of AsCT in the context of this remarkable response to combined novel therapies, a comparison that is arguably one of the most pressing issues in clinical myeloma research today. Already, the incorporation of novel therapies into induction therapy has increased response extent and frequency both before and after single AsCT, as well as prolonged, progression-free, and overall survival thereafter, making the examination of RVD therapy with and without transplant especially timely.

Importantly, this study will not only compare clinical outcomes between arms A and B, but also utilize gene expression profiling to define prognostic groups for each therapeutic arm, and carefully assess side effect profile, quality of life, and cost. Correlative studies will also evaluate the impact of various genomic variables including copy number alteration using single nucleotide polymorphism array technology, alternate splicing, microRNA profiling, and whole-genome sequencing at the time of diagnosis and relapse in order to characterize disease heterogeneity, mechanisms of sensitivity versus resistance, and molecular response rates, and to define new therapeutic targets, thus making the study a major advance toward personalized medicine in myeloma. Finally, it should add to the encouraging, emerging data suggesting that lenalidomide maintenance prolongs both progression-free and overall survival.

--Kenneth C. Anderson, MD

Dr. Anderson indicated no relevant conflicts of interest.

Non-Hodgkin Lymphoma: Is 1 plus 1 > 2?

**STUDY TITLE:** Phase II Trial of Bortezomib and Vorinostat in Mantle Cell and Diffuse Large B-Cell Lymphomas

**COORDINATORS:** Southeast Phase II Consortium (SEP2C) of the H. Lee Moffitt Cancer Center (Tampa) in conjunction with the VCU Massey Cancer Center (Richmond)

**SPONSOR:** H. Lee Moffitt Cancer Center

**CLINICALTRIALS.GOV IDENTIFIER:** NCT00703664

**PARTICIPATING CENTERS:** 8 participating centers supported by NCI N01 programs representing, in addition to the SEP2C, the New York and University of Chicago Phase II Consortia

**STUDY DESIGN:** This is a phase II non-randomized study utilizing a two-stage mini-max design. The two cohorts are as follows: A) bortezomib-naive patients with mantle cell lymphoma (MCL) and B) patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Both cohorts achieve first-stage response endpoints and will proceed to second-stage accrual. Patients receive vorinostat 400 mg PO on days 1-5 and 8-12 and bortezomib 1.3 mg/m² IV on days 1, 4, 8, 11 every 21 days. The primary endpoint is the objective response rate. Secondary endpoints are safety and tolerability, progression-free survival and response duration, and relationship between pre-treatment lymphoma cell nuclear RelA (NF-κB) and response. Projected trial duration is three years.

**ACCURAL GOAL:** 79 subjects (39 in Cohort A, 40 in Cohort B)

**RATIONALE:** The proteasome inhibitor bortezomib is highly active in untreated or relapsed/refractory multiple myeloma and has moderate activity in relapsed MCL. The drug is FDA-approved for both of these diseases (in the case of MCL, approval is for patients who have received at least one prior therapy). Bortezomib has minimal single-agent activity in DLBCL, but it may be of value in combination with conventional cytotoxic chemotherapy in a subset of patients [those with the activated B-cell (ABC) subtype]. Histone deacetylase inhibitors (HDACis) are approved for the treatment of cutaneous T-cell lymphoma, and, in preclinical studies designed to test activity against a diverse group of malignant hematopoietic cell types (including multiple myeloma and non-Hodgkin lymphoma), these agents have shown synergism when combined with proteasome inhibitors. In support of these observations, initial results of clinical studies testing a combination of proteasome and HDACis in patients with multiple myeloma have been encouraging. The goal of the current trial is to determine whether HDACis can enhance efficacy in diseases in which bortezomib has limited (MCL) or negligible (DLBCL) single-agent activity.

**COMMENT:** This phase II study will help to determine whether abundant pre-clinical evidence of proteasome/HDAC inhibitor synergism translates into improved clinical outcomes for patients with MCL, DLBCL, or both. Early results from the MCL arm are encouraging (8/17 responses). Achievement of the second-stage goals will lay the foundation for establishing the efficacy of this strategy more definitively in a phase III trial. Additionally, correlative studies may identify subsets of patients more likely to benefit from this combination.

--Steven Grant, MD

Dr. Grant is the study chair for this trial.

Representatives from Mexican laboratories participating in the U.S.-Mexico Cytogenetics pilot (Refer to the cover story in the July/August 2011 issue for more information about this program) participated in a two-day training workshop at St. Jude Children’s Hospital in Memphis, TN, this past August. The participants became conversant with the Pediatric Oncology Networked Database (POND), a Web-based data collection tool that facilitates the exchange of information among oncologists in diverse geographic regions. The POND, administered by St. Jude, is the interface where scientific reviewers will receive data from all four Mexican laboratories to assess progress and provide recommendations in cytogenetic diagnosis under the guidelines of the Cytogenetics pilot. ASH would like to extend its appreciation to the staff and affiliates of St. Jude for making this training a remarkable success.

A special thank you to Paula Naidu, MPH; Scott Howard, MD; Susana C. Raimondi, PhD; Raul C. Ribeiro, MD; and Yuri Quintana, PhD.

(Pictured left to right): Susana Raimondi, PhD; Carlos Alonso Muñoz, BS CLSP/CG; Yvette Neme; Verónica González Martínez; Alfredo Corona Rivera, PhD; Emérida Corona-Bobadilla, MS(MS); Teri Brown; Guadalupe Cárdenas Gómez, PhD; and Paula Naidu, MPH.
The HVO Volunteer Experience: What It Meant to Me
LYNN SLOANE BEMILLER, MD, MPH
South County Hematology and Oncology, in Chula Vista, CA

At the annual meeting in December 2008, on an evening when I had little to do, I wandered into an ASH-Health Volunteers Overseas (HVO) session, which described volunteer programs that ASH and HVO were recruiting members to participate in. I was motivated primarily by a desire to listen to something different, something to take my mind off the daily grind, but by the end of the session, I felt so compelled by the presentations and by the possibilities they represented, that I volunteered on the spot for two weeks with a new project in Peru. I traveled in October of 2009.

HVO’s mission is education; with this in mind I must admit that I had some trepidation about my usefulness as a clinician in practice. I had not been actively involved in clinical teaching for 10 years, while most of the other volunteers I encountered had university appointments, research projects, and active academic practices. I was delighted to find, however, that the variety of clinical practice in Peru provides excellent opportunities for a variety of volunteers.

I spent the first week at Rebagliati Hospital in Lima, a national referral center and teaching hospital, offering services including autologous and allogeneic stem cell transplantation. As a tertiary center with a hematology residency and 15 sub-specialized hematologists on staff, this site provides excellent teaching opportunities for those in academic hematology.

As a community clinician, I found the work at the regional hospital in Arequipa, where I spent my second week, to be more rewarding. Hematologists on staff (and at a third volunteer site in Cusco) manage a broad range of hematologic diseases in both adults and children and train students from two local medical schools.

My role was not as much didactic as it was collegial. Hematologists in Peru train one year in general medicine and three years in hematology. I found their knowledge of hematology to be excellent, and thanks to the Internet they have access to much of the same information that we do. The main differences in patient care arose from their inexperience in general internal medicine (and a heavy reliance on consultants) and from the limitations of the system.

We spent many hours, as one might with colleagues at home, discussing approaches to difficult clinical situations. On some occasions, I was able to offer insight; on other occasions, I was the one learning. For example, what do you do in a resource-poor setting with a thrombocytopenic patient who may be having a CNS bleed? What if there is no MRI, a CT scan cannot be done until tomorrow, and the only way to get platelets is if one of the medical students will volunteer to get apheresed? What do you do with a patient with relapsed myeloma when your only treatment options are steroids, cyclophosphamide, and bortezomib? What is the best second therapy for ITP if your general surgeons do not perform splenectomies? What do you do when your hospital buys rituximab from the lowest-price source, and you suspect it’s no good, because none of your patients have ever had a response to it? And, just like at home, what do you do with a patient who can’t speak your language and you can’t speak his? There are no academic answers to these questions, just the best judgment of smart and caring clinicians.

I returned to the United States with a new respect for clinicians who work in difficult situations and a new appreciation for all of the marvelous things our medical system can do. My colleagues in Peru gained some new insights, but more so, I think they gained in the knowledge that all of us have dilemmas and challenges, and no one has all of the right answers or tools.

Perhaps something in this article has resonated with one of you among the ASH membership. If there are any clinical hematologists with a sense of adventure or a desire to “give back,” there are colleagues around the world who would benefit greatly from sharing experiences with you. Volunteer … you’ll be glad you did.

Drs. Andrews and Brenner Demonstrate Exemplary Guidance of Young Hematologists

The ASH Mentor Award was established to recognize mentors and the critical role they play in the field of hematology. This year ASH honors Nancy C. Andrews, MD, PhD, of Duke University School of Medicine with the award in basic science and Malcolm K. Brenner, MD, PhD, of Baylor College of Medicine, with the award in clinical investigation for the part they have played in the intellectual growth and career development of their trainees, in addition to their professional guidance and role modeling.

Dr. Andrews is vice chancellor for academic affairs and dean of the Duke University School of Medicine. Prior to becoming the first woman to serve as dean in Duke’s medical school history, she was a professor at Harvard Medical School. Of the 13 fellows who completed postdoctoral training under Dr. Andrews while she was at Harvard, nine have gone on to independent faculty positions. “She has this amazing capacity to develop her trainees. She gradually releases the strings as a mentor and lets you explore, and somehow she senses when you are ready to go on to the next step. It’s so seamless, the way you transition,” one of her former students commented.

Dr. Brenner is director of the Center for Cell and Gene Therapy at Baylor College of Medicine. One former student and colleague said, “One of Malcolm’s major achievements in [the Center for Cell and Gene Therapy] was to establish an environment that encourages every member, from senior faculty to graduate student, to become a mentor to others.” Some of his former trainees send their own trainees to be mentored by him, thus continuing the tradition of excellence of which they were a part. Dr. Brenner currently has more than 200 people under his supervision and also works with other mentors on improving their own mentorship skills.

Drs. Andrews and Brenner will be formally presented with their awards at the Announcement of Awards session on Sunday, December 11, from 1:30 to 2:00 p.m. in Hall AB.
Similar Dreams, Different Journeys

As the 10-year anniversary of the Clinical Research Training Institute approaches, ASH highlights two early participants. Dr. Ghbrial participated in 2003 (the inaugural year), and Dr. Blum participated in 2004.

IRENE GHOBRIAL, MD
Assistant Professor of Medicine, Dana-Farber Cancer Institute, Harvard Medical School

If someone had told me 15 years ago that I would be a faculty member at Dana-Farber Cancer Institute as a principal investigator with a laboratory and clinical trials, I would have laughed at them. After all, I was a medical student at Cairo University School of Medicine. I knew that if I worked hard, I could go to the United States to get into a residency program so that I could receive top-notch training and a cutting-edge education. I never thought that my journey would take me to Harvard Medical School, and I did not know that the American Society of Hematology (ASH) would help me achieve this unimaginable dream.

During my hematology/oncology training at Mayo Clinic, I learned about clinical trials and clinical research as well as translational research. I was fascinated by the research that was going on around me, and I wanted to be part of it. I credit my great mentors who believed in me and who cared enough to improve my career path. I remember going to my first ASH annual meeting in Philadelphia. There was a snowstorm and some of the Plenary Scientific Session speakers could not make it. I was fascinated and overwhelmed by the scientific discoveries, the opportunities for research, and the great achievements of the scientists and clinicians around me. What I loved most about the ASH meeting was that science and clinical application were presented hand-in-hand. The meeting attendees felt like a great community who were enjoying creating new scientific discoveries. I knew from that first meeting that I would be an ASH advocate for the rest of my life. I was in love with a society that represented everything I believed in, so when I saw the email requesting applications for the first ASH Clinical Research Training Institute (CRTI), I pounced on the opportunity.

It will sound like a cliché to say that my experience in CRTI shaped my life. I remember talking with Jim George about my interest in academic medicine and trying to land a job during my third year in fellowship. I also remember talking to Beverly Mitchell about science and discovery. I was inspired by Brian Druker discussing his stories of failure before succeeding in his work on imatinib. From that point on, the faculty of CRTI, including past presidents of ASH, became my mentors who wrote letters of recommendation for me, and who helped me in my decisions regarding jobs, interviews, and NIH grant submissions. They were my new academic family. I was encouraged to write grants while I was at CRTI, and soon after returning from the initial one-week training, I started applying for the ASH, Multiple Myeloma Research Foundation (MMRF), Leukemia and Lymphoma Society (LLS), and American Society of Oncology (ASCO) grants.

I am now a faculty member at Dana-Farber Cancer Institute. I have received multiple R01 grants from NIH and FDA along with grants and awards from professional societies and nonprofit organizations. I have a lab full of young postdoctoral fellows, technicians, and students and a clinical practice with five active clinical trials, and a great clinical team of research nurses and clinical research coordinators. I am still working hard, hoping to make a significant contribution in the discovery and treatment of multiple myeloma and Waldenström macroglobulinemia. I have my daily challenges in life, but I occasionally have to pinch myself when I think that just a few years ago I was a student in a developing country with no research training and now I am a faculty member of the Harvard Medical School. I believe that my mentors and the ASH community have made this dream come true for me and for many others. I know that whenever the ASH leadership asks me to do anything for the Society, I can never say no, as I will never be able to pay back what ASH has made possible for me.

Dr. Ghbrial participated in 2003 (the inaugural year).

WILLIAM BLUM, MD
Associate Professor of Medicine, The Ohio State University and James Cancer Hospital

I have always liked looking at blood. Even from my preteen years in grade school, I have been fascinated by blood and the peripheral blood smear. Except for a few wayward years when I thought about being an astronaut, my career plans were focused on medicine and ultimately the care of patients with leukemia. I have been fortunate to have had mentorship and serendipity cooperate in leading me toward the career that I envisioned during my youth. As an undergraduate at Notre Dame in 1989, I needed a job. As luck would have it, Dr. Morris Pollard, a world-renowned virologist and cancer researcher, needed a lab assistant. My years with Dr. Pollard exposed me to research in animal models of cancer and the scientific method. Perhaps most importantly, I learned the impact that a mentor can have on a career and a life. One spring day, I came in to work and Pollard asked me what my summer plans were. I was planning to return home and get a job at the lake just like past summers, but he had a different plan for me. Through his intercession, I was accepted into the Baylor (Houston) summer research program and had the pleasure of working in the Tumor Biology department at M.D. Anderson Cancer Center in the lab of Dr. Douglas Boyd. It was a completely different laboratory experience than what I had seen up to that point. At the time, I thought my project focused on mechanisms of cancer cell migration/metastasis; I realize now that the “project” was me.

Beyond the tremendous experience of talking with Dr. Boyd every day about science or the personal experiences of living with other like-minded students in the heart of Houston, my time there deepened my interest in hematology. The Boyd lab happened to be right around the corner from a small auditorium where taped to the door was a schedule for the hematology fellows to give and/or hear lectures on hematology topics of interest. My schedule was reasonably flexible, so whenever the topic was leukemia, I slipped in the back door. I was hooked on hematology.

Both Drs. Boyd and Pollard helped open the door for me to another research experience — the summer student research program for the following year at The Jackson Laboratory in Bar Harbor, Maine. Living with other students on the coast of Mt. Desert Island in a mansion bequeathed to the lab within walking distance of Acadia National Park is not a bad way for a college junior to spend a summer. I was fortunate to land in Dr. Dave Harrison’s lab. Dr. Harrison and his wonderful assistant, Mike Astle, studied hematopoietic stem cells. I worked (unsuccessfully) for the summer trying to identify a unique, hematopoietic stem cell-specific surface marker. If ever there was a “successful failure” for me, this was it. An intense environment, but one of cooperation and collegiality, permeated both the Harrison lab staff and the students in the mansion. Students from all walks of life and nationalities lived together united in a desire to learn how things work. We and the senior scientists met regularly in small group sessions about our various research projects (or hiking trips); these were the highlights of the summer experience. I don’t remember too many of the topics. But I do remember the meetings; they became for me a model of how to foster cooperation among sometimes disparate groups of people to achieve a collective goal, and one that I have carried forward with me in both research environments and the care of patients.

Ultimately, I reached the point when I needed to decide where I would primarily spend my time, the clinic or the lab. For me, I did not feel that “both” was the right answer. To make my decision, I took the advice of Dr. Andy Albritton at the Medical College of Georgia who asked me, “What do you like to read?” I realized that my interests lay in taking care of patients, not in the old or traditional ways but rather in translating laboratory discoveries into the clinic. Later, I became involved in the American Society of Hematology Clinical Research Training Institute (CRTI) at the encouragement of Dr. Jim George, then president of the Society. With the aid of my still mentor and now friend Dr. Guido Marcucci, I developed a clinical trial with a hypomethylating agent for older patients with acute myeloid leukemia; this project has become a cornerstone for my ongoing research, with clinical or laboratory surprises and discoveries seemingly at every turn. I have since tried to fashion a career in bringing new drugs to patients, working closely with laboratory colleagues at The Ohio State University and James Cancer Hospital in a very productive loop that is an excellent example of bedside-to-bench-to-bedside clinical research in practice.

Finally, no “summary of my academic journey” would be complete without the acknowledgment that my primary achievements live back home in our house in Worthington, Ohio. I have missed many activities through the call of work and science, but I have also sacrificed work time to coach soccer, throw the ball, or from time to time go with my lovely wife (the better looking and smarter other Dr. Blum) out to dinner.

Dr. Blum participated in 2004.
November

24
World Conference on Regenerative Medicine
Leipzig, Germany
www.wcrm-leipzig.com

9
Deadline for advance registration for ASH annual meeting
San Diego, CA
www.hematology.org

10-12
Annual Meeting of the National Hemophilia Foundation
Chicago, IL
www.hemophilia.org

14
ASH Webinar: Pain in Sickle Cell Disease
Washington, DC
www.hematology.org

29
ASH annual meeting registration cancellation deadline
San Diego, CA
www.hematology.org

December

10-13
53rd ASH Annual Meeting and Exposition
San Diego, CA
www.hematology.org

January 2012

12-14
Clinical Hematology and Oncology 2012
Scottsdale, AZ
www.mayo.edu/cme

20-21
Highlights of ASH
Austin, TX
www.hematology.org

Highlights of ASH
Orlando, FL
www.hematology.org

27-28
Highlights of ASH
Atlanta, GA
www.hematology.org

Highlights of ASH
Las Vegas, NV
www.hematology.org

February

3-4
Highlights of ASH
New York, NY
www.hematology.org

Highlights of ASH
San Francisco, CA
www.hematology.org