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ASH & NHLBI Launch Recruitment and Retention Initiative

Are there enough hematologists to advance the science and care for patient needs?

LINDA BURNS, MD

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A meeting to address this question was held in late January and appropriately focused on ensuring the future of our field. In a joint effort by ASH and the National Heart, Lung, and Blood Institute (NHLBI), members of the two organizations met to launch a new initiative aimed at recruiting and retaining hematologists, particularly in non-malignant areas of expertise. I had the opportunity to attend this meeting, which was led by Dr. J. Evan Sadler, ASH president-elect, and Dr. Keith Hoots, director of the NHLBI Division of Blood Diseases and Resources. The primary goal was to identify ways our organizations can work independently and together to strengthen hematology as a profession. The group discussed emerging opportunities in hematology, projected workforce needs, barriers to trainees pursuing and sustaining a career in hematology, and current programs and resources.

Four major topics emerged:

1) We need to increase the pool of trainees entering the field by reaching out to "undecided" trainees and sharing the enthusiasm and vision we have for the field of hematology.

2) For those interested in pursuing hematology as a career, we must identify opportunities for broadening the practice of hematology, both in academic and non-academic settings.

3) In order to sustain life-long careers in hematology, we need to diversify sources of funding to include institutions, reimbursement from public and private insurers, and programs that attract NIH funding.

4) We must enhance the profile ("value-added") of a hematologist's involvement in patient care to patients, referring physicians, and payors.

To encourage early-career trainees to enter hematology, two short-term strategies will be explored. The first is a Visiting Professor Program for medical schools. Nationally and internationally recognized hematologists would be recruited and made available to visit schools and meet with students in order to convey enthusiasm for a career in hematology, serve as positive role models and mentors, and help students overcome the barriers that may be preventing

(Cont. on Page 2)

DIFFUSION

Fountain of Youth

Mayack SR, Shadrach JL, Kim FS, et al. Systemic signals regulate ageing and rejuvenation of blood stem cell niches. Nature. 2010;463:495-500.

Mark Twain famously said, "Age is an issue of mind over matter. If you don't mind, it doesn't matter." True, but then it really does matter. All multicellular organisms age, generally as cellular repair processes slow down. How many of us now notice how much longer it takes to heal from a cut, a torn tendon, a back strain, or a bruised muscle compared to when we were teenagers? Osteoporosis is another example in which bone loss can lead to devastating consequences. And yet other examples are forgetfulness and dementia, as we lose neurons that are not replaced. Aging and the associated pathology are a major and growing challenge, as a significant portion of the population in many of the developed countries is becoming older. Our life span continues to improve, and thus we encounter more frequently what are thought to be the limits of repair possible for a particular organ. The hematopoietic system, which functions remarkably well throughout our lives, does age as well. Hematopoietic stem cells (HSCs) decline in numbers with a shortening of telomeres. Aging is associated with a decline in immune function, marrow dysplasia, and malignancies.

One can think of aging or loss of cells, for example HSCs, in an autonomous and non-autonomous fashion. Autonomous signals would include normal responses to oxidative stress, DNA damage and apoptosis, and expression of senescence genes. However, there is also evidence for non-autonomous signals, especially the important interactions of the HSC with its niche. These niches help regulate HSC function and have an impact on HSC fate and age-related dysfunction. This manuscript by Mayack et al. from Amy Wagers lab at Harvard demonstrates clearly that there are systemic signals that can rejuvenate aged HSCs. Using parabiotic pairs (sharing a common circulation and CD45.1 vs. 45.2, so they can track the animals), they attached a young mouse (2 months old) to an aged partner (>21 months old) and compared these pairs to young-young and old-old animals. As expected, the creation of parabiotic pairs had no impact on HSCs or their function in the young-young or old-old pairs. However, in the young-old pairs, there was a significant recovery of primitive reconstituting HSCs in the older animals, approaching those found in the young ones. The osteoblastic niche, acting through a soluble systemic factor, appeared to be responsible for this remarkable rejuvenation. They demonstrated that the HSC deregulation could be reversed by the systemic circulation of a young mouse or by neutralization (with a monoclonal antibody) of the conserved longevity regulator, insulin-like growth factor-1 (IGF-1) in the marrow microenvironment in the old animals. Therefore, the aged osteoblastic niche relays an aging phenotype to HSCs, and the effects on the niche are modulated by as-yet-undefined factors in the circulation.

While much remains to be worked out, including the systemic factor(s) responsible for this observation, this study opens the possibility that regenerative signals for HSCs and other stem cells could be transmitted through the circulation. However, the effects of any one of these signals may have competing antagonistic effects. For example, IGF-1 in these studies made aging worse in HSCs, while in other studies IGF-1 was shown to maintain the regenerative capacity in muscle cells.

And you thought all of those human growth hormone ads against aging on the back of the airline magazines were a sham!

NELSON J. CHAO, MD, MBA

Dr. Chao indicated no relevant conflicts of interest.

FEATURES

4-5 MINI REVIEW: THE EVOLVING ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE TREATMENT OF MULTIPLE MYELOMA – Drs. Jacob Laubach, Paul Richardson, Nikhil Munshi, and Kenneth Anderson explore the effectiveness of autologous stem cell transplantation (ASCT) in the treatment of multiple myeloma.

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ASH & NHLBI Initiative

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them from entering hematology. The second strategy is to address the increasing problem of debt burden borne by medical school graduates that causes many to enter more procedurally oriented, higher paying fields. Jointly, ASH and NHLBI will consider development of a loan repayment program, particularly for trainees choosing an academic research career in non-malignant hematology.

One of the major barriers to recruitment and retention identified by the group is the lack of a viable business model for non-malignant hematology practice. The group suggested that hematologists need to develop a practice model, similar to those that have been implemented by hospitalists, diabetologists, and infectious disease specialists (e.g., antibiotic utilization teams) to provide specialized inpatient and consultative care delivery in the hospital (especially in ICU-type settings) and outpatient clinics that includes reimbursement for "gate-keeper" services inherent to quality hematologic care. The model would be based on the concept that hematologists can more effectively manage care, reduce associated care costs, and increase quality of care for patients with abnormal blood counts and/or hemostasis/thrombosis problems. The ASH Committee on Practice and its Subcommittee on Quality have already initiated a research project to determine the value added by a hematologist. As pilot programs would need to be created and tested, ASH will need to identify health systems, payors, and large practice groups with which to collaborate.

Many graduates of training programs enter practices in which they care for patients with diverse hematologic and oncologic diseases. As time passes, hematology skills may diminish and ultimately be lost. In discussing how best to assist hematologists in maintaining their skills and knowledge base, the group suggested that ASH develop refresher courses in hematology. The group recommended that ASH develop an educational program for hematologists on how to diagnose and manage classical hematologic problems, including a plan for how to reach other non-hematology health practitioners who need education on the management of common hematology-related illnesses and when to request a hematologist consult.

Improving the recruitment and retention of hematologists will require the collaborative efforts of ASH and NHLBI and both short- and long-term strategies. A multifaceted approach that engages all ASH members and involves many committees of the Society will be needed. ASH is eager to partner with NHLBI in the development and implementation of the short-term strategies as outlined above and to begin seeking innovative solutions to ensure the future of the hematology profession.

LETTERS TO THE EDITOR SOLICITATION

The Hematologist **welcomes letters of up to 200 words. These letters may be in response to editorials or on any subject of interest to our readers. Please include a postal address, e-mail address, and phone number. Publication will be based on editorial decisions regarding interest to readers and space availability. We may edit letters for reasons of space or clarity.** ***The Hematologist*** **reserves the right to publish your letter, unless it is labeled "not for publication."**

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President's Column

Scholarships and Awards Ensure the Future of Hematology

To some of our members, ASH is simply known as the organization that sponsors the annual meeting in December and publishes *Blood* each week. But this past March, while attending the inaugural Translational Research Training in Hematology (TRTH) program in Marbella, Spain, it became apparent to me that, through programs such as TRTH and other ASH scholarships and awards, our Society is a catalyst for ensuring a future generation of global leaders in the field of hematology.

During the week of March 20-27, ASH, in collaboration with the European Hematology Association (EHA), brought together a class of 20 promising trainees from across Europe and North America and immersed them in the first part of a year-long program designed to help them successfully launch a career in translational research. The program was spearheaded by a world-renowned faculty committed to teaching, mentoring, and informally networking with the trainees and ensuring their long-term success in their chosen research disciplines. This program, sponsored in part by a generous grant from the Wallace H. Coulter Foundation, is just one of the many impressive scholarship and award programs that make up the portfolio of benefits/services that our Society offers to its members.

While TRTH may be the newest of our award programs, ASH has a long tradition steeped in awarding scholarships and grants. For instance, at the ASH annual meeting in December 2009, we celebrated the 25th anniversary of the ASH Scholar Awards Program. This flagship program has a rigorous review process and has funded more than 200 of our most promising members in the areas of scientific and clinical investigation. I had the privilege of serving on the ASH Scholar Awards Study Section around the same time I chaired the NIH Hematology II Study Section and can attest first-hand to the professional manner in which reviewers of the Scholar Awards make their selections.

Another ASH program, the Clinical Research Training Institute (CRTI), engages leaders in our field to train young investigators about the principles of clinical research through didactic sessions, small working groups focused on protocol refinement, and insightful career retrospectives. This program has been in existence for seven years, and we can proudly report that a number of our CRTI "graduates" have been awarded ASH Scholar Awards, published in *Blood*, and gone on to assume volunteer leadership roles in our Society. I encourage you to read "Profiles in Hematology" in this issue of *The Hematologist* to learn more about two individuals who were both participants in CRTI and recipients of ASH Scholar Awards (see page 15).

Our Society is also dedicated to helping and promoting the careers of young students and investigators from underrepresented minorities through programs such as the Minority Medical Student Award Program (MMSAP) and The Robert Wood Johnson Foundation's Harold Amos Medical Faculty Development Program (AMFDP). ASH is also looking into the feasibility of a similar program geared toward graduate students pursuing PhD degrees in hematology-related disciplines. Through the use of scholarship funds, research support, and mentorship, these promising programs are helping attract strong leaders into academic hematologic research.

Clearly, ASH is about much more than our annual meeting and *Blood*; our mission includes a myriad of scholarship and research initiatives in the field of hematology. You can learn more about ASH's scholar and awards programs by visiting *www.hematology.org/Awards*.

It was noted in a recent editorial[1] that if societies want to promote their fields of investigation and the careers of their members, they needed to embrace new perspectives and approaches. I am proud to say that this has been and continues to be a primary focus for ASH.

Hal E. Broxmeyer, PhD

1. Wiley, S. To Join or Not to Join. The Scientist. 2010;24:33.

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Mark Your Calendar: Important Dates for 2010 ASH Annual Meeting

June 14: ASH annual meeting abstract submission process opens

July 20: Early-bird registration open to ASH members

August 4: Advance registration open to members and non-members

August 12: Abstract submission deadline

Save the Date: 2010 ASH State-of-the-Art Symposium

The 2010 ASH State-of-the-Art Symposium will take place September 24-25, 2010, in Chicago, IL. This clinically focused event will provide the same high-quality educational content for which the ASH annual meeting is known and give you a first look at the latest research developments in the field. Join your colleagues and discuss new treatment approaches and solutions for your day-to-day cases.

Sign Up for Find a Hematologist

Find a Hematologist is an online tool provided by ASH for members and the general public to help match patients with hematologists in their area. If you are an ASH member in practice and accepting patients or willing to consult on cases, join today by e-mailing *ash@hematology.org.*

Want to Get Involved in ASH? Call for Nominations to Serve on an ASH Committee

We need your help identifying "new blood!" The Society seeks a balanced committee membership that mixes bright, enthusiastic people with seasoned committee members. Since ASH is a volunteer-run association, we encourage and welcome any ASH member's self-nomination for committee service. Nominations received for committee membership are compiled and reviewed by the Nominating Committee in the summer. For more information, including nomination forms, go to *www.hematology.org/About-ASH/2654.aspx.* The deadline for submitting nominations for 2011 is May 31, 2010.

Editor Search Announcement

The American Society of Hematology is in the initial stage of the selection process for the next Editor-in-Chief of *The Hematologist* (term: 2012-2014).

Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills.

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

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The application deadline is September 1, 2010.

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Do you want to stay current with the latest advances in the rapidly evolving field of hematology, or are you in need of a valuable reference and teaching tool? Find an educational resource that meets your needs at the ASH Store. Visit *www.hematology.org/ASHStore* to browse all ASH products online. Some new products that are currently available include:

- 2010 Highlights of ASH Program Book and DVD
- 2009 Complete Annual Meeting DVD
- Abstract Book: 2009
- *Hematology 2009*: The Education Program Book

E-Letters: A New Feature in *Blood*

In April, ASH launched a new feature called e-Letters to serve as a forum for feedback and discussion about articles recently published in *Blood*. The editors hope e-Letters will facilitate rapid, lively, and constructive interactions between readers and authors. Submissions of e-Letters are open to all researchers and health-care professionals with expertise and interest in hematology and related fields. E-Letters should be submitted electronically by clicking on a link from the article being discussed. Comments must be concise (less than 300 words) and will undergo an internal review prior to posting to cull out contributions that are incomprehensible, inflammatory, or otherwise inappropriate. E-Letters will be posted online within days and will remain linked to published articles in perpetuity via the journal Web site; however, e-Letters will not be indexed in Medline. Authors of published articles will be encouraged to respond to e-Letters that have been posted in reference to their articles with comments of their own.

The current Letters to the Editor section of the journal will still exist both online and in print, but it will be reserved for stand-alone letters that do not pertain to articles published in *Blood* or letters containing primary data of particular importance, even if the letter pertains to a prior published *Blood* article. Submitted e-Letters and regular Letters to the Editor will be screened by the editors, and those more appropriate for the alternate pathway will be re-routed. For more information on e-Letters, please visit *Blood*'s Author Guide at *http://bloodjournal.hematologylibrary.org/authors/authorguide.dtl#other*.

MINI REVIEW

The Evolving Role of Autologous Stem Cell Transplantation in the Treatment of Multiple Myeloma

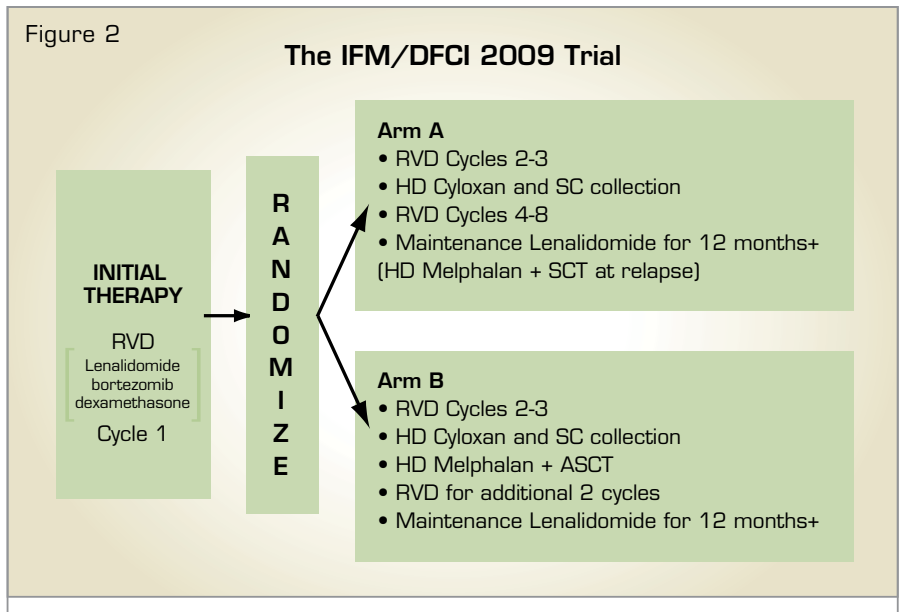
JACOB LAUBACH, MD, PAUL RICHARDSON, MD, NIKHIL MUNSHI, MD, AND KENNETH ANDERSON, MD

The authors are all in the Department of Medicine at Harvard Medical School and Dana-Farber Cancer Institute. Dr. Laubach is Instructor in Medicine, and Dr. Richardson is Associate Professor and Clinical Director, Jerome Lipper Center for Multiple Myeloma. Dr. Munshi is Associate Professor and Associate Director, Jerome Lipper Center for Multiple Myeloma, and Dr. Anderson is Kraft Family Professor of Medicine and Director, Jerome Lipper Multiple Myeloma Center.

High-dose therapy with autologous stem cell transplantation (ASCT) has played a central role in multiple myeloma (MM) therapy since the approach was first introduced by McElwain and colleagues in 1983.[1] ASCT was initially most often utilized in the management of relapsed and refractory disease, wherein it provided a means to overcome drug resistance through dose intensification. Although brief, significant responses were observed in this setting. ASCT was subsequently evaluated in newly diagnosed MM patients following induction therapy. In a pivotal trial comparing standard-dose chemotherapy to standard-dose therapy followed by ASCT, the incorporation of ASCT improved overall response, complete response, event-free survival, and overall survival.[2] Subsequent clinical trials comparing conventional therapy to ASCT yielded conflicting results, as some demonstrated improvement in event-free and overall survival associated with ASCT patients, while others did not. Comparison of single versus tandem ASCT showed benefit of a second transplant limited to those who did not achieve at least a very good partial response after the first and to patients with otherwise favorable disease characteristics, such as normal cytogenetics and low β2-microglobulin.[3] With respect to timing, early ASCT following induction therapy is associated with improvement in event-free survival relative to delayed transplant at time of relapse, but not with improvement in overall survival.[4]

ASCT has traditionally been undertaken with caution in the context of high-risk disease as defined by cytogenetic abnormalities such as translocation (t)(4;14), due to shortened time-to-progression and overall survival post-transplant in this population. Outcomes with ASCT are best among individuals who achieve maximal reduction in tumor burden, and multiple studies have shown that complete response following ASCT is associated with prolonged event-free survival and overall survival. It would thus appear that the benefit of ASCT in MM derives from its ability to induce deeper responses through dose intensification and thereby suppress the tumor clone for an extended period.

Figure 2



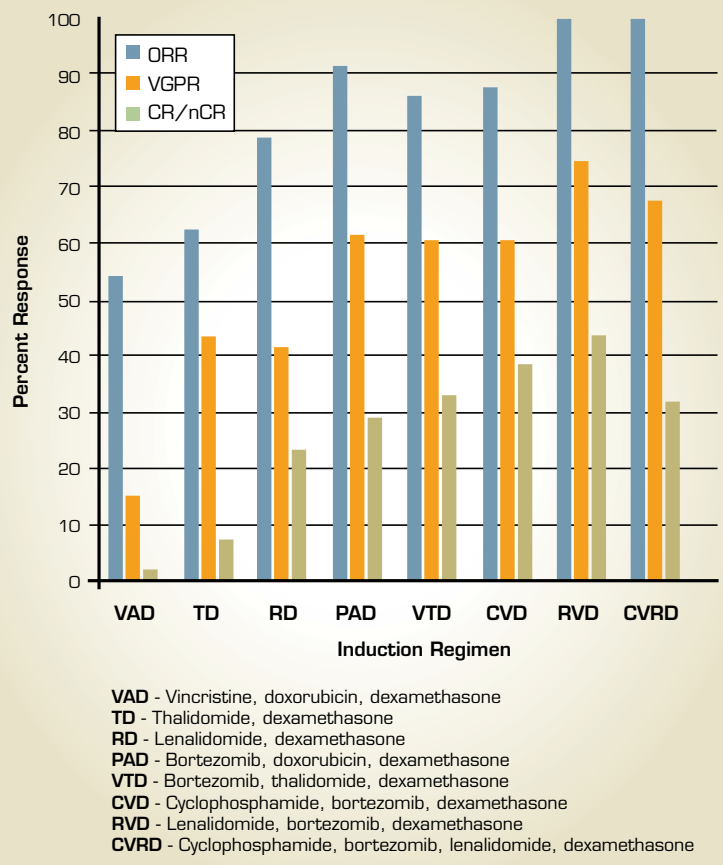
Schema for international, randomized, phase III clinical trial of RVD induction/consolidation and lenalidomide maintenance with early versus delayed ASCT in newly diagnosed multiple myeloma

Figure courtesy of Dr. Paul Richardson

The Impact of Thalidomide, Bortezomib, and Lenalidomide on Myeloma Therapy

Although ASCT remains a critical treatment option for appropriately selected MM patients, the introduction of thalidomide, bortezomib, and lenalidomide in the past decade has dramatically altered the overall therapeutic management of MM. Clinical trials comparing the historical standard of care for upfront therapy in transplant-ineligible patients — melphalan and prednisone (MP) — to MP in combination with either thalidomide[5] or bortezomib[6] showed superior overall and complete response rates, as well as improved duration of response and overall survival. Likewise, preliminary analysis of a phase III study comparing MP, MP plus lenalidomide, and MP plus lenalidomide followed by lenalidomide maintenance demonstrated substantial improvement in rates of overall and complete response as well as a significant improvement in progression-free survival in the regimen that included lenalidomide maintenance.[7]

Figure 1



Comparison of response rates (overall, very good partial, and complete/near complete response) associated with combination regimens in newly diagnosed multiple myeloma. This research was originally published in *Blood* and adapted. Stewart AK, Richardson PG, San-Miguel JF. Blood. 2009;114:5436-43.

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Thalidomide, bortezomib, and lenalidomide also figure prominently in the treatment of newly diagnosed, transplant-eligible MM patients. Whereas the combination of vincristine, adriamycin, and dexamethasone formerly represented standard induction therapy for such patients, the regimen has been supplanted on the basis of data from randomized trials by thalidomide plus dexamethasone and by bortezomib plus dexamethasone. Specifically, the majority of patients receiving these regimens achieve at least a very good partial response after induction and a single ASCT, so that fewer patients are candidates to benefit from a second transplant. Lenalidomide plus low-dose dexamethasone is also well tolerated and active as induction therapy in transplant-eligible patients.[8] Bortezomib, lenalidomide, and/or their combination are particularly attractive for patients with high-risk disease based on staging criteria and cytogenetic abnormalities such as t(4;14) and del(13), as several studies indicate that they may overcome the poor prognosis associated with these genetic findings in relapsed disease.

The application of thalidomide, bortezomib, and lenalidomide in MM therapy has been refined in recent years through a series of important clinical investigations. Combinations of these agents, such as bortezomib, thalidomide, and dexamethasone[9] and lenalidomide, bortezomib, dexamethasone,[10] are being evaluated in newly diagnosed MM and have proven to be very effective, yielding complete response rates approximating those previously achieved with high-dose therapy and ASCT. In addition, schedule modifications have been introduced with the aim of minimizing toxicity while preserving the activity of chemotherapeutic regimens. Finally, building on previous studies of thalidomide maintenance therapy following ASCT, ongoing clinical trials are evaluating lenalidomide and bortezomib consolidation and maintenance following ASCT, and preliminary results suggest that increased extent of response and prolonged progression-free survival can be achieved with these agents, both as monotherapy and in combination. Figure 1 shows response rates associated with various combination regimens.

Reevaluating Stem Cell Transplantation in the New Era of Myeloma Therapy

In light of the fact that new approaches to MM induction now produce a level of response previously seen only with the incorporation of ASCT, it is critical for ASCT to be reevaluated in the context of new induction and maintenance strategies. Questions of significant interest and importance in the field include: Can highly active induction regimens followed by maintenance therapy replace upfront ASCT for patients who have been traditionally managed utilizing transplant? Conversely, will such active induction regimens followed by ASCT, and thereafter by maintenance, extend suppression of the myeloma clone beyond what has been previously achieved, with resulting prolongation of progression-free and overall survival? In addition, what is the optimal sequence of new induction regimens and ASCT; should ASCT be performed immediately following induction therapy or delayed until time of relapse?

A randomized, international clinical trial developed by the Dana-Farber Cancer Institute and a consortium of U.S. transplant centers working in partnership with the Inter-Groupe Francophone du Myelome (IFM) has been designed to definitively address these issues (Figure 2). After receiving one

cycle of induction with lenalidomide, bortezomib, and dexamethasone, previously untreated MM patients will be randomized to receive either: a) further induction with lenalidomide, bortezomib, and dexamethasone followed by stem cell collection and ASCT, or b) further induction and stem cell collection but no ASCT until time of relapse. Patients in both treatment groups will receive consolidation with lenalidomide, bortezomib, and dexamethasone and then lenalidomide maintenance for at least 12 months. It is anticipated that results of this clinical trial will, together with other ongoing studies, guide optimal timing and sequence of ASCT in the rapidly evolving field of MM therapy, as well as provide insight on key surrogates and prognostic features, such as cytogenetics and gene expression profiling. MM remains a formidable adversary and must be countered with all available, active treatment modalities in the most informed, coordinated manner possible to further improve patient outcome, with the integration of novel therapies and ASCT offering a paradigm for just such an approach.

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Drs. Richardson, Munshi, and Anderson are advisory board members for Celgene and Millennium. Dr. Munshi also consults for Celgene and Millennium.

NHLBI Responds to Questions About the Restructuring of the Sickle Cell Disease Research Program

RICHARD LOTTENBERG, MD

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Chair, ASH Government Affairs Committee's Sickle Cell Disease Subcommittee

Two years have passed since the National Heart, Lung, and Blood Institute (NHLBI) announced the restructuring of its sickle cell disease (SCD) research program, and despite steps to strengthen the program and research in hemoglobinopathies, the SCD community is still unclear about the Institute's plans for creating a sustainable program that encourages innovative and ongoing research. ASH has received questions from members about NHLBI's long-term plans for large-scale clinical trials, basic and translational research, SCD scholar and trainee programs, and support for health services research. In response to these concerns, ASH met with NHLBI leadership to clarify the Institute's plans for moving forward. ASH will continue to work with NHLBI as the Institute restructures its hemoglobinopathy portfolio to ensure that the program encourages and supports important research. The Society will continue to keep members apprised. The following is an update provided by Dr. Keith Hoots, director of NHLBI's Division of Blood Diseases and Resources (DBDR), summarizing the Institute's current and future hemoglobinapothy research program.

NHLBI New R34 Hemoglobinopathy Initiative and Restructured Sickle Cell Disease Research Program

The DBDR continues to adjust its programs to ensure their alignment with the research goals outlined in the Institute's Strategic Plan (*www.nhlbi.nih.gov/about/strategicplan/*). The Institute is focused on the scientific opportunities, informed by the public health needs. Two key principles in program development are working in partnership with multiple constituencies and ensuring that the mechanisms of grant or contract support (investigator-initiated research, organized programs, or a combination of these) are appropriate to achieve the goals. Decisions about renewal of all programs at NHLBI are dependent upon an analysis of their productivity and ongoing research needs, as well as emerging scientific opportunities.

The DBDR recently created a new R34 planning grant for large clinical studies in hemoglobinopathies. The focus of this initiative is to validate new and scientifically provocative hypotheses for development into phase III clinical trials. During the one- to three-year period the grant investigators will be funded (up to $250,000/year, maximum $450,000 over 3 years) to do any or all of the following: design, establish feasibility, determine sufficient statistical power, recruit trial sites, establish an IRB plan, and/or even perform phase I or II pharmacokinetics on a candidate IND drug for treating hemoglobinopathies. Up to six such planning grants will be funded (likely in early 2011) to represent the vanguard of a planned broad portfolio of funded phase III clinical trials in hemoglobinopathies.

In addition, DBDR has a number of completing, ongoing, or soon-to-be-enrolling clinical trials: SWiTCH (a randomized study comparing hydroxyurea and phlebotomy to hypertransfusion in patients with SCD and previous stroke), TWiTCH (a phase III non-inferiority study that compares hypertransfusion to hydroxyurea in children with abnormal transcranial Doppler studies to prevent stroke), Baby HUG (a pediatric phase III clinical trial of hydroxyurea versus placebo), Walk PHaSST (a recently completed double-blind randomized clinical trial of sildenafil vs. placebo to enhance exercise capacity in patients with SCD and pulmonary artery hypertension), and IMPROVE (a comparison of a high-demand/low-dose strategy of opiate therapy vs. low-demand/high-dose opiate administration in SCD patients with pain secondary to vaso-occlusive crisis). NHLBI also funds bone marrow transplantation trials for patients with SCD and thalessemia through the Blood or Marrow Transplantation Clinical Trials Network.

Several active research initiatives have been developed to supplement the capacity of hematologists to assess clinical outcomes: The Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) is an effort to develop, validate, and disseminate a psychometrically sound and clinically useful instrument to assess health-related quality of life among adults with SCD. It is fully integrated into an NIH-wide Patient-Reported Outcomes Measurement Information System (PROMIS).

NHLBI's Basic and Translational Research Program (BTRP) supports research in hemoglobinopathies. This is designed to supplement the bedrock of all DBDR research support, which is investigator-initiated research projects (R01s and program project grants) that represent approximately 75 percent of all DBDR extramural funding. The BTRP initiative supports 10 large grants that focus on such diverse objectives as endothelial function in patients with SCD, gene therapy for SCD, red cell membrane function in SCD, and innovative physiological measurements in SCD patients. Each of these funded sites also has a hemoglobinopathy-focused training component that supports career development of Sickle Cell Scholars.

Fundamentally, a national hemoglobinopathy research program requires a focused collaboration with federal partners, such as the Health Resources Service Administration (HRSA), which supports care, and the Centers for Disease Control and Prevention (CDC), which directs the public health role for hemoglobinopathies. Accordingly, the three federal partners are working together with state health departments through the newly constituted Registry and Surveillance Program in Hemoglobinopathies (RuSH) to expand public health tracking of patients with hemoglobinopathies. Further, the three have partnered to insure that expanded hemoglobinopathies-focused goals and objectives have been included in Healthy People 2020 targets for the U.S. Department of Health and Human Services.

HEADLINES FROM Washington

Medicare Physician Payment Unresolved

As this issue went to press, Congress had still not resolved the issue of Medicare physician payment. Fixing the formula used to calculate Medicare physician payment had originally been thought of as a key component of health reform. The high cost of the fix ($250 million over 10 years), however, brought the total cost of the health reform bill above a trillion dollars, so it was excluded from the health overhaul package.

The Senate was expected to consider a new short-term extension bill H.R. 4851 that would extend the 2009 Medicare physician payment rates and prevent scheduled cuts until April 30, 2010. The Senate had approved a longer-term extension H.R. 4213 earlier, but the House of Representatives opted to pass the 30-day extension included in H.R. 4851. Updated information about this issue is available on the ASH Web site at *www.hematology.org*.

Online Resource: ASH Federal Grants Web Page

Drawing together the multitude of hematology-related research grant opportunities that are available through the National Institutes of Health (NIH) and other federal agencies, the Society has created a section on the ASH Web site to simplify members' search for requests for blood and blood disease research topics. ASH regularly updates this page and will expand its scope in the future when other grants are published that may be of interest to hematologists. To view this page, go to *www.hematology.org/Research/2884.aspx*.

Stem Cell Bill Introduced in House of Representatives

Reps. Diana DeGette (D-CO) and Mike Castle (R-DE) introduced legislation on March 10 "to ensure a lasting ethical framework" for human stem cell research at the National Institutes of Health (NIH).

The Stem Cell Research Advancement Act (H.R. 4808) builds on President Obama's March 2009 Executive Order overturning former President Bush's restrictions on federal funding for embryonic stem cell research. The bill authorizes the Department of Health and Human Services (HHS) to conduct and support research on human stem cells, including embryonic stem cells, under the following conditions:

- The stem cells were derived from human embryos that have been donated from *in vitro* fertilization clinics, were created for the purposes of reproductive treatment, and were in excess of the clinical need of the individuals seeking such treatment.
- It was determined through consultation with the individuals seeking reproductive treatment that the embryos to be donated would never be implanted in a woman and would otherwise be discarded.
- The individuals seeking reproductive treatment donated the embryos with written informed consent and without receiving any financial or other inducements to make the donation.

In addition, the bill requires NIH to maintain guidelines on human stem cell research conducted or supported by HHS and to review the guidelines at least every three years and update them as warranted. The bill also explicitly bans federal funding for human cloning.

Historic Health Reform Legislation Signed Into Law

President Barack Obama signed a landmark health-care bill into law March 23, enacting a sweeping overhaul of the nation's $2.5 trillion health system after a year-long effort.

More than a dozen Republican state attorneys general filed lawsuits challenging it as unconstitutional minutes after the President signed it into law.

The legislation would cost $940 billion over the next decade and extend health insurance coverage to an estimated 32 million Americans who are currently uninsured. The package is aimed at stemming the soaring growth in the cost of health care and reducing the federal deficit by more than $1.3 trillion over the next 20 years.

Some of the benefits that kick in this year include a provision barring insurance companies from excluding children with preexisting conditions and another that allows children to remain on their parents' health insurance policy under certain circumstances until age 26.

A few of the less popular provisions will be phased in over several years, including the requirement that all Americans buy health insurance.

Please visit the ASH Web site at *www.hematology.org* for an analysis of how the health reform law will impact hematologists.

Timeline of Provisions in Health Reform Bill

90 days after enactment	Provides immediate access to high-risk pools for people who have no insurance because of preexisting conditions.
Six months after enactment	Bars insurers from denying people coverage when they get sick. Bars insurers from denying coverage to children who have preexisting conditions. Bars insurers from imposing lifetime caps on coverage. Requires insurers to allow young people to stay on their parents' policies until age 26.
Within a year	Provides a $250 rebate to Medicare prescription drug plan beneficiaries whose initial benefits run out.
2011	Requires individual and small-group market insurance plans to spend 80 percent of premium dollars on medical services. Large group plans would have to spend at least 85 percent.
2013	Increases the Medicare payroll tax and expands it to dividend, interest, and other unearned income for singles earning more than $200,000 and joint filers making more than $250,000.
2014	Provides subsidies for families earning up to 400 percent of the poverty level — or, under current guidelines, about $88,000 a year — to purchase health insurance. Requires most employers to provide coverage or face penalties. Requires most people to obtain coverage or face penalties. Requires health insurance plans to provide coverage for routine costs associated with participation in clinical trials.
2018	Imposes a 40 percent excise tax on high-end insurance policies.
By 2019	Expands health insurance coverage to 32 million people.

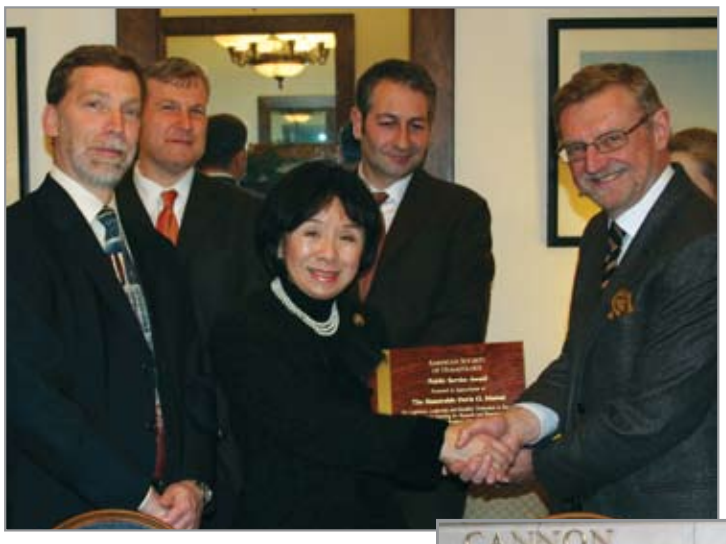
ASH Heads to Capitol Hill in Support of Hematology Research

GEORGE WEINER, MD

Chair, ASH Committee on Government Affairs

In early March, with Washington still abuzz with the uncertainty surrounding health reform, ASH Committee on Government Affairs members met with Representatives, Senators, and senior staff from more than 25 congressional offices to share ASH's legislative priorities as part of the Committee's annual Capitol Hill Day.

Committee members shared ASH's "Principles for Health-Care Reform" and the Society's support for increasing coverage to the uninsured and under-insured, improving Medicare physician payment, maintaining access to specialists, and increasing access to preventive services. They also expressed concern about the instability in Medicare physician payment and urged congressional support for legislation that will provide a positive update in fees as well as a permanent replacement for the flawed formula currently used to calculate Medicare physician fees.



The Committee also focused on advocating for increased funding for biomedical research, which was a challenging task given the tight federal budget situation. ASH Committee members described the many advances made possible through federally funded hematology research. They urged Congress to maintain the commitment it made to NIH with the short-term funding provided recently through the American Recovery and Reinvestment Act and urged Congress to provide predictable and sustained long-term growth in NIH funding in the fiscal year 2011 budget and beyond. To further support NIH-funded research, the Committee shared ASH recommendations for language that accompanies the annual funding bill that would encourage research in the field of regenerative medicine and propose simplifying clinical trials oversight.

One of the highlights of this year's Capitol Hill Day was meeting with Rep. Doris Matsui (D-CA) to present her with the 2009 ASH Award for Public Service. Rep. Matsui has been a champion of issues related to bone marrow failures and hematologic malignancies since taking office in 2005 following the death of her husband, Rep. Robert Matsui, from complications related to myelodysplastic syndrome (MDS).

Rep. Matsui thanked the Committee for the award and for all of the Society's advocacy efforts. She was particularly appreciative of ASH's efforts to gain congressional support for the Bone Marrow Failure Disease Research and Treatment Act (H.R. 1230), legislation Rep. Matsui introduced to increase the federal government's commitment to researching and treating acquired bone marrow failure diseases.

Members of the ASH Government Affairs Committee participate in Hill Day, congressional visits, and ASH grassroots activities because they know such efforts make a difference. Our legislative representatives want to hear from us. Every ASH member can play an important role in the Society's advocacy efforts. You can also have your voice heard in the halls of Congress by participating in the ASH Grassroots Network and visiting the ASH Advocacy Center. For more information about ASH advocacy efforts and the ASH Grassroots Network, visit *www.hematology.org/takeaction*, or contact the ASH Policy & Practice Department at 202-776-0544.

Use of ESAs to Treat Patients With Myelodysplastic Syndromes

PETER GREENBERG, MD

Director, Stanford Myelodysplastic Syndrome Center and Emeritus Professor, Stanford University School of Medicine
Chairman of the NCCN Panel on MDS

On February 16, the U.S. Food and Drug Administration (FDA) announced that drugs categorized as erythropoiesis-stimulating agents (ESAs) must be prescribed under a risk management program, known as a Risk Evaluation and Mitigation Strategy (REMS), to ensure their safe use. The FDA cited safety concerns from data in clinical studies with ESAs in patients with solid tumors (breast, non-small-cell lung, head and neck, lymphoid, and cervical cancers) in which shortened overall survival and/or increased risk of tumor progression or recurrence, as well as increased thrombotic events in those patients with renal disease, occurred *(www.fda.gov/Drugs/DrugSafety/)*. As part of the REMS, a *Medication Guide* explaining the risks and benefits of ESAs will be provided to all patients receiving ESAs. In addition, Amgen, the manufacturer of these products, is required to develop the ESA Assisting Providers and Cancer Patients With Risk Information for the Safe Use of ESAs (APPRISE) Oncology program for health-care professionals who prescribe ESAs to patients with cancer. Only those hospitals and health-care professionals who have enrolled and completed training in the program will be able to prescribe and dispense ESAs to patients with cancer. The program was implemented on March 24, and doctors will have a year grace period to sign up.

Since the FDA announced the REMS program, questions and concerns have been raised about how the program will apply to patients with myelodysplastic syndromes (MDS). ESA use in MDS is off-label. The FDA has indicated that patients with MDS who are prescribed ESAs are not included in the APPRISE program, because this program does not address off-label uses of ESAs. However, as part of the REMS program, a *Medication Guide* is required to be distributed to all patients whenever an ESA is dispensed, for either an approved or an unapproved indication.

This review is written to aid the understanding of the risks and benefits of ESAs in MDS. Numerous studies have indicated the relative efficacy of ESAs in large numbers of adults with MDS.[1,2] Of importance for enhancing the efficacy of these agents (i.e., decreasing RBC transfusion requirements) is patient selection to include those symptomatically anemic patients with baseline hemoglobin levels ≤10 gm/dl who have relatively low serum erythropoietin (Epo) levels (<200 or 500 mU/ml). Improved responses are noted in International Prognostic Scoring System (IPSS) lower risk patients (low/intermediate-1) compared to the more advanced higher risk (intermediate-2/high) category patients. Recommended Epo doses are 40 to 60,000 units once or twice weekly for approximately two months in order to determine potential responsiveness. For non-responding patients, particularly those with ring sideroblasts, the addition of lenograstim (granulocyte-colony stimulating factor, G-CSF) is often synergistic.[3]

Investigations assessing the long-term efficacy and safety of RBC transfusion support plus Epo with or without G-CSF in an ECOG phase III study of lower-risk MDS patients compared to either randomized controls receiving transfusion support only[4] or others using historical controls[5,6] have shown effective erythroid responses to the cytokines in approximately 40 percent of patients with no negative impact on survival or AML evolution. In addition, Jadersten et al. reported improved survival in lower-risk MDS patients with low transfusion who were treated with these agents.[5] A study by Park et al. indicated improved survival and decreased AML progression of the lower-risk patients treated with Epo/G-CSF compared to

(Cont. on Page 13)

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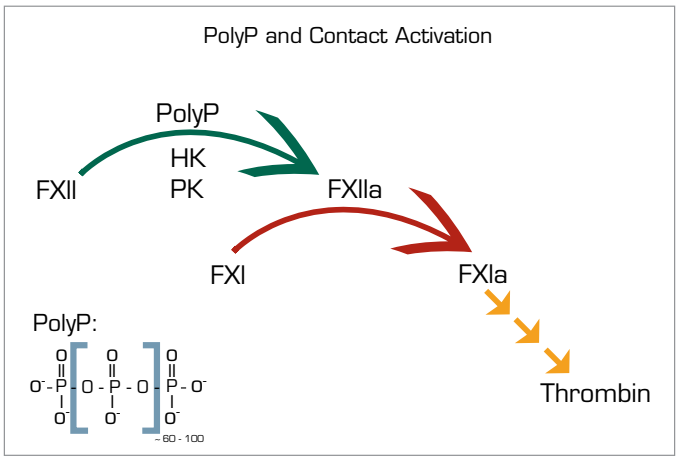
Polyphosphate: Putting the Contact Into Contact Activation

Müller F, Mutch NJ, Schenk WA, et al. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. Cell. 2009;139:1143-56.

For the hematologist lecturing on hemostasis, it has never been a pleasant task to march students through the intrinsic pathway and then tell them that the initiating reactions in the pathway apparently are not necessary *in vivo.* The intrinsic pathway starts when blood comes into contact with a variety of negatively charged surfaces, including non-physiological materials such as glass, kaolin, and ellagic acid. Binding to these surfaces induces a conformational change in factor XII (FXII) that allows it to proteolytically activate prekallikrein (PK). PK proteolytically activates FXII, producing a positive feedback loop that amplifies the system and leads to activation of FXI and cleavage of high-molecular-weight kininogen (HK) by kallikrein. Cleavage of HK in turn produces the inflammatory mediator bradykinin.

These contact activation reactions represent the "activated" part of the activated partial thromboplastin time. However, severe deficiencies of FXII, PK, or HK do not produce a bleeding diathesis, leading to the teaching that the contact system is somewhat of an orphan in search of a function. In fact, the first patient who was diagnosed with FXII deficiency, John Hageman, died of pulmonary embolism. However, recent work in several laboratories has indicated that the contact system may contribute to the formation of pathologic intravascular thrombi.[1]

Now Müller et al. in the laboratory of Thomas Renné, in collaboration with the laboratory of James Morrissey, provide evidence that platelet or *E. coli*-derived polyphosphate (PolyP) provides a surface for activation of FXII and the contact system and promotes a prothrombotic/proinflammatory diathesis in mice. PolyP is linear polymer of ~60 to 100 orthophosphate units that is found widely in prokaryotes and eukaryotes. Recently, PolyP was identified in platelet dense granules[2] and found to have procoagulant properties and antifibrinolytic properties.[3]



Müller et al. found that platelet-derived PolyP-dependent FXII activation resulted in proteolysis of HK and release of bradykinin, leading to increased vascular permeability. FXII-deficient and bradykinin receptor-deficient mice were resistant to PolyP-induced vascular permeability. Intravenous infusion of platelet-derived PolyP produced lethal pulmonary embolism in normal mice, which was significantly reduced in FXII-deficient and/or FXI-deficient mice. A specific inhibitor of FXII also protected against PolyP-induced pulmonary embolism. A thrombin receptor agonist, TRAP6, also produced lethal pulmonary embolism in normal mice, which was significantly decreased in FXII-deficient mice. Degradation of PolyP with phosphatases inhibited contact activation *in vivo* and *in vitro* and decreased platelet PolyP-induced thrombosis in mice. Additionally, *E. coli*-derived PolyP initiated the activation of FXII, KK, and FXI and the production of bradykinin. Finally, addition of PolyP restored the plasma clotting defect of Hermansky–Pudlak syndrome platelets, which lack PolyP.

This study indicates that PolyP is a potentially important mediator of platelet-driven proinflammatory and procoagulant disorders. PolyP, thus, is a logical target for the development of a new class of antithrombotic agents.

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PETE LOLLAR, MD

Dr. Lollar indicated no relevant conflicts of interest.

Mapping the Gains and Losses of Malignancy: Some Old Friends Appear

Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010;463:899-905.

Localized alterations in copy number are found widely across the genomes of malignancies, almost all of them acquired during the lifetime of the host. These somatic copy-number alterations (SCNA) indicate regions of gain or loss, which may play a role in pathogenesis; although, given their high frequency and broad distribution, it may be hard to distinguish those that are causal from secondary phenomena. This paper, from a large collaborative group led by Matthew Meyerson and others in Boston, used an Affymetrix technology to catalogue patterns of SCNA in 3,131 specimens across a range of tumor types. These came from primary tumor material in most cases, with a minority derived from cell lines or short-term cultures.

A mean of 24 gains and 18 losses were found in each sample, although higher frequencies were seen in some solid tumors. The alterations could be separated into focal changes (median of 1.8 Mbases long) or those representing gain or loss of the whole arm of a chromosome. In a typical malignancy, some 25 percent of the genome was affected by arm-length SCNAs and 10 percent by focal changes, with around 2 percent overlap. The amplitude of change was generally a single copy, although some showed much higher amplifications. By determining which focal areas of SCNA appeared at a frequency higher than predicted by their size, the investigators identified 158 regions of apparently significant change: 76 amplifications and 82 deletions. The amplifications contained a median of 6.5 genes (ranging from 0-143), with 25 containing previously identified oncogenes. The deletions contained a median of seven genes with a smaller proportion (11%) containing known tumor suppressors, perhaps because deletions as secondary events are more likely to occur in gene-poor regions. Grouping involved genes by family revealed that several known pathogenic targets, including kinases, cell-cycle regulators, and MYC family members, were frequently affected. Apoptosis-modulating genes stood out as particularly often involved; both MCL1 and BCL2L1 (BCL-XL) were amplified in a relatively large proportion of samples. NF-κB pathway genes were also frequently found. To test the functional significance of MCL1 and BCL2L1 amplifications they used shRNA to knock down their expression in cell lines and demonstrated growth retardation and induction of apoptosis, which were more pronounced in lines with the relevant amplification, supporting the hypothesis that these are pathogenetic events.

Genome-based array technologies can now generate massive amounts of data on copy-number changes in malignant cells, and the substantial overlap among different tumor types is quite revealing, suggesting common pathways of transformation even in quite disparate tissues. Genes such as MCL1 and BCL2L1, long known to be abnormal in lymphomas, are more widely implicated in a variety of cancers. The fact that this mapping has brought up genes known to play a role in malignant transformation is evidence for its accuracy, and the functional studies on the two anti-apoptotic genes confirm the apparent role of amplification in maintaining growth potential in the cells where this occurs, even at relatively low copy number. The real interest in this approach is in the potential to identify new pathogenic events in malignancy. More than three-quarters of the 158 peak regions of SCNA did not contain known targets, suggesting that much more information may be forthcoming, even if one discounts the deletions that are simply evidence of "noise" and the loss of regions that can be readily tolerated. This approach will be particularly powerful when combined with deep sequence analysis of somatic mutations in tumors, as is now being undertaken in the International Cancer Genome Consortium. The convergence of these techniques will soon yield an immensely detailed map of the events driving malignant transformation.

PETER JOHNSON, MD

Dr. Johnson indicated no relevant conflicts of interest.

Be Good and You Will Be Lonesome*

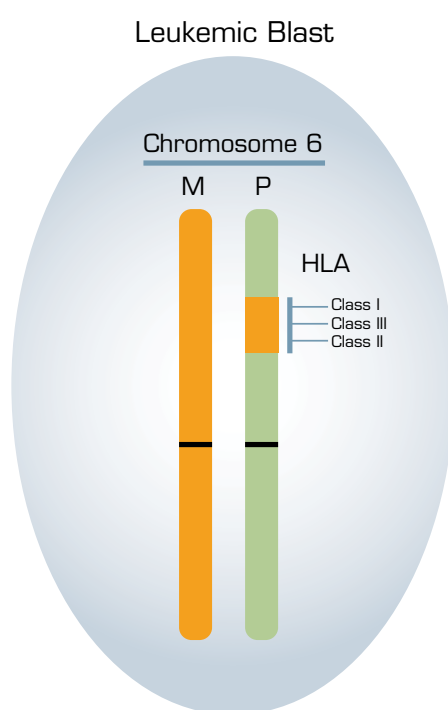
Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem cell transplantation. N Engl J Med. 2009;361:478-88.

Haploidentical transplantation could just as easily be called haplounidentical transplantation, because recipient and donor are matched at HLA loci on one chromosome 6 (haploidentical) but not on the other (haplounidentical) (Figure). For treatment of patients with hematologic malignancy, transplanted cells serve two purposes. First, transplanted hematopoietic stem cells rescue the recipient from the myeloablative injury induced by lethal doses of chemotherapy and/or radiotherapy that comprise the preparative regimen. Second, transplanted lymphocytes are the source of the graft-versus-tumor effect that is essential for eradication of residual chemotherapy/radiation-resistant malignant cells. Therefore, the haplounidentical part of the equation is equally important therapeutically as the haploidentical part, as it is the mismatched HLA proteins that target the leukemic blasts for destruction by donor T cells. Haploidentical transplantation has the advantage over matched-sibling donor transplantation of higher probability of donor availability, as both parents and half of all siblings will be "matches." On the downside, however, is the greater risk of high-grade graft-versus-host disease (GVHD) because all host tissue will be haplounidentical in relation to the donor lymphocytes. Despite the seemingly insurmountable task of transplanting across HLA barriers, haploidentical transplantation has become an important part of the hematologist's armamentarium for treatment of high-risk and relapsed acute leukemia and relapsed lymphoma, and insightful translational research has led to clever new, more effective strategies for ameliorating GVHD while allowing for robust immune reconstitution.

Regrettably, however, not all is good on the haploidentical transplantation front, as recently, investigators from Milan led by Katharina Fleischhauer and Fabio Ciceri reported an unexpected victory of sorts for the bad guys. Those investigators longitudinally evaluated donor-host hematopoietic chimerism in 43 patients who had undergone a haploidentical transplant. They were looking for the reappearance of recipient hematopoiesis that often heralds disease relapse, and they used both microsatellite markers and HLA typing for their analysis of chimerism. Seventeen patients (14 of whom received transplants when they had persistent disease) had a leukemic relapse, and in all cases, the leukemic blasts were found to be of recipient origin based on microsatellite analysis. But, surprisingly, no HLA proteins unique to the recipient were detected on the bone marrow cells of five of the relapsed patients. In other words, the haplounidentical antigens were no longer detectable on the leukemic blasts of those five patients despite the fact that microsatellite markers had shown that the cells were of host origin. The Milan group investigated the molecular basis of this phenomenon using single nucleotide polymorphism-array analysis and found that the leukemic blasts had acquired their homozygous HLA phenotype through the process of uniparental disomy (Figure). This remarkable outcome is a vivid example of Darwinian evolution in the microcosm of the bone marrow. In this case, donor T cells exerted a powerful selection pressure on the host bone marrow cells, destroying the cells based on recognition of the haplounidentical HLA proteins. Only the leukemic blasts that had eliminated the mismatched HLA loci through uniparental disomy escaped immune surveillance (Figure). Armed with their understanding of the molecular basis of relapse in these patients, the investigators subjected two of the patients to a subsequent transplant using cells from a different donor who was mismatched for the HLA haplotype retained by the leukemic cells. Remarkably, one of the two patients was alive and in complete remission more than 16 months after the second transplant. Together, these observations demonstrate a novel mechanism for development of treatment resistance in patients undergoing haploidentical transplant. That the process occurred in 5 out of 17 (29%) of the relapsed patients indicates that this mechanism is a relatively common cause of treatment failure. Importantly, understanding the basis of the resistance allows for a tailored approach to treatment of relapse and hope for long-term survival for affected patients – a victory for the good guys.

*Quote by Mark Twain. 2010 marks the centennial of Twain's death (November 30, 1835 - April 21, 1910).

Figure



Acquired uniparental disomy in a leukemic blast in a patient in relapse following haploidentical transplant.

In the example illustrated, the original mismatched HLA alleles were located on the paternal (P) chromosome 6. During mitosis, a recombinant event occurred in one of the leukemic blasts in which a portion of the long arm of chromosome 6 containing the HLA loci was exchanged between a maternal and a paternal chromosome 6. Subsequently, a leukemic blast derived from this process contained the original maternal (M) chromosome 6 (orange) paired with the recombinant paternal chromosome 6 (green). That particular leukemic blast acquired a survival advantage in the setting of haplounidentical transplantation because it no longer expressed the mismatched paternal HLA proteins, thereby escaping immune surveillance by donor T cells that were haploidentical at the maternal HLA loci. Such recombinant events are not detected by standard karyotyping because there is no observable net loss or gain of genetic material. However, this process can be identified by using single nucleotide polymorphism-array analysis and is called copy number neutral loss of heterozygosity.

CHARLES PARKER, MD

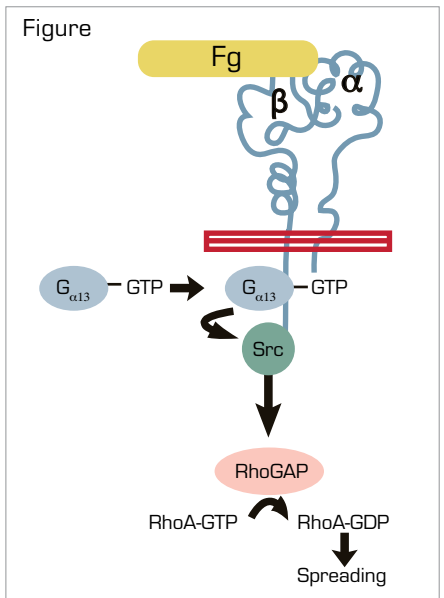
Dr. Parker indicated no relevant conflicts of interest.

The Odd Coupl(ing)

Gong H, Shen B, Flevaris P, et al. G protein subunit Gα13 binds to integrin αIIbβ3 and mediates integrin "outside-in" signaling. Science. 2010;327:340-43.

αIIbβ3 is the dominant platelet integrin with approximately 50 to 80,000 copies per platelet. Activation of platelets induces a conformational change in αIIbβ3, which promotes the binding of fibrinogen to the integrin. This process is termed "inside-out" signaling. The binding of fibrinogen to αIIbβ3 then induces "outside-in" signaling, which mediates cytoskeletal changes involved in platelet spreading. Studies to determine how the binding of fibrinogen to activated αIIbβ3 induces "outside-in" signaling have demonstrated an association of Src family kinases, adaptor proteins, and other kinases with the β3 cytoplasmic tail.[1] Signaling mediated by Src and other associated proteins promotes platelet spreading by mechanisms that are not completely understood. Src also inhibits RhoA, enabling spreading by preventing RhoA-mediated cytoskeleton retraction.[2] However, the molecular details of how RhoA activity is controlled by signaling proteins associated with the β3 cytoplasmic tail has remained a puzzle. Gong et al., working in the laboratory of Xiaoping Du at University of Illinois Chicago, have now elucidated an unexpected piece of this puzzle by showing that the heterotrimeric G protein, $G_{\alpha13}$, interacts directly with the β3 cytoplasmic tail.

The authors observed that silencing of $G_{\alpha13}$ in platelets inhibited spreading on immobilized fibrinogen. In addition, depletion of $G_{\alpha13}$ abolished autophosphorylation of Src, suggesting that $G_{\alpha13}$ acts upstream of the kinase. Proof that $G_{\alpha13}$ was interacting with the β3 cytoplasmic tail was derived from immunoprecipitation studies demonstrating an association of $G_{\alpha13}$ and β3. Direct binding of $G_{\alpha13}$ to the β3 cytoplasmic tail was shown using recombinant proteins. Of note, the association of $G_{\alpha13}$ with β3 was substantially enhanced by either platelet activation or incubation with GTP-γ-S or AlF_4- to drive the formation of GTP-loaded $G_{\alpha13}$. The authors identified switch region I as the domain of $G_{\alpha13}$ responsible for binding β3. With this knowledge, they designed a cell-penetrating synthetic peptide to interfere with the $G_{\alpha13}$-β3 interaction. This peptide inhibited integrin-dependent Src phosphorylation, accelerated RhoA activation, prevented platelet spreading, and promoted clot retraction. These studies form the basis of a new model of dynamic regulation of RhoA during platelet spreading and demonstrate that a heterotrimeric G protein can interact directly with an integrin cytoplasmic tail.



Interaction of $G_{\alpha13}$ with β3. GTP-loaded $G_{\alpha13}$ binds to β3 integrin.

This interaction appears to regulate Src, resulting in the deactivation of RhoA and facilitating platelet spreading.

Figure adapted from Flevaris P et al. J Cell Biol. 2007;179:553-65.

Although it is appreciated that signaling through G-protein coupled receptors can indirectly influence integrin function by acting through downstream effectors, the conventional wisdom has been that these receptor types use distinct secondary signaling machinery. The observation that $G_{\alpha13}$ binds directly to β3 challenges this dogma. The implications of these findings are far-reaching. Several mouse models demonstrate that "outside-in" signaling contributes to hemostasis and thrombus formation following vascular injury.[3,4] Targeting the $G_{\alpha13}$-β3 interaction may be a viable strategy for antithrombotic therapy. More compelling, however, is the possibility that G protein-integrin interactions are not limited to platelets. Integrins and heterotrimeric G proteins are ubiquitous proteins, and it is possible that $G_{\alpha13}$ interacts with other integrins in other cells. Indeed, the authors demonstrate an interaction between $G_{\alpha13}$ and β1. The extent to which $G_{\alpha13}$ – and perhaps other G proteins – bind to non-G-protein coupled receptors and contribute to downstream signaling of these other receptor types remains to be determined. This work, however, lays the foundation for future efforts to understand the degree to which G protein coupling to noncanonical receptors affects signal transduction.

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Dr. Flaumenhaft indicated no relevant conflicts of interest.

Platelet-Stimulating Agents in Myelodysplastic Syndromes: Ready for Prime Time?

Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol. 2010;28:437-44.

In the field of supportive care for myelodysplastic syndromes (MDS), an anthropomorphic view would leave platelets feeling neglected. Erythropoiesis-stimulating agents and granulocyte colony-stimulating factors were already available for clinical use before the discovery of thrombopoietin and its receptor c-MPL in the mid 1990s. Development of first-generation thrombopoietins (e.g., recombinant human megakaryocyte growth and development factor, rHuMGDF) ultimately faltered because of the occasional appearance of neutralizing antibodies to endogenous thrombopoietin and thrombocytopenia in trials of healthy volunteers undergoing platelet donation. Other agents, such as interleukin-11, demonstrated modest benefit in MDS but never gained traction. Non-immunogenic thrombopoiesis-stimulating agents have now emerged, including the TPO nonpeptide mimetic eltrombopag, TPO antibody mimetics, and the peptibody romiplostim. Romiplostim and eltrombopag have demonstrated efficacy in short- and/or long-term studies of immune thrombocytopenic purpura[1] and are now FDA-approved for this condition.

Because of the presence of TPO receptors on early hematopoietic progenitors, and pre-clinical data demonstrating that TPO can stimulate myeloid blasts,[2] trepidation has surrounded the use of TPO receptor agonists in MDS. The initial foray of romiplostim in thrombocytopenic MDS patients is now reported by Kantarjian and colleagues. The study was conducted in subjects with lower-risk disease having platelet counts <30,000/mm³, and treatments were done in dose cohorts of 300, 700, 1,000, and 1,500 mcg subcutaneously weekly. Increases in the median platelet count at the respective doses were to 60, 73, 38, and 58 x 103/mm³ at week 4. According to International Working Group (IWG), 2000 criteria, 45 percent of patients had complete or major platelet responses during the treatment phase, with a higher proportion of responses in patients with a platelet count >20,000/mm³ versus <20,000/mm³ (57% vs. 25%, respectively). There was no difference in platelet response rates among the dose cohorts. In the extension phase of 41 patients, 46 percent of patients experienced durable platelet responses and the median duration of treatment was 37 weeks. Bleeding events and platelet transfusions were less common among patients who achieved a durable platelet response compared to those who did not (4.3 vs. 39.3 per 100 patient-weeks). Regarding clinically relevant safety issues, four patients experienced transient increases in marrow blast counts, and two progressed to acute myeloid leukemia; these results were felt to be within the expected frequency of this MDS population. Of the 24 patients for whom pre- and post-treatment marrow reticulin studies were available, the reticulin grade was increased in seven, unchanged in 10, and decreased in seven. Neutralizing antibodies to either romiplostim or endogenous TPO were not identified, and no drug-attributable deaths occurred.

While romiplostim appears to be a feasible option for low/intermediate-1-risk MDS patients, several points merit consideration. Although 700 mcg weekly was selected for future studies, there was no dose-response relationship; therefore, evaluation of clinical efficacy at lower dose ranges is justified. In addition, as this trial was not designed to elucidate romiplostim's impact on the rate of AML transformation, a randomized, placebo-controlled study with longer follow-up is needed. Because of the very low frequency of severe thrombocytopenia in *de novo*, untreated low/intermediate-1-risk patients,[4] this study group may have limited applicability to the general MDS population. The greatest need for platelet-stimulating agents will be in patients with clinically significant bleeding and/or those requiring chronic platelet transfusions – features of higher-risk patients. Trials assessing romiplostin and similar agents in combination with lenalidomide and hypomethylating drugs are currently underway. Reducing therapy-related thrombocytopenia may allow preservation of dose intensity and frequency with the potential for optimizing the frequency and quality of remissions.

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Dr. Gotlib indicated no relevant conflicts of interest.

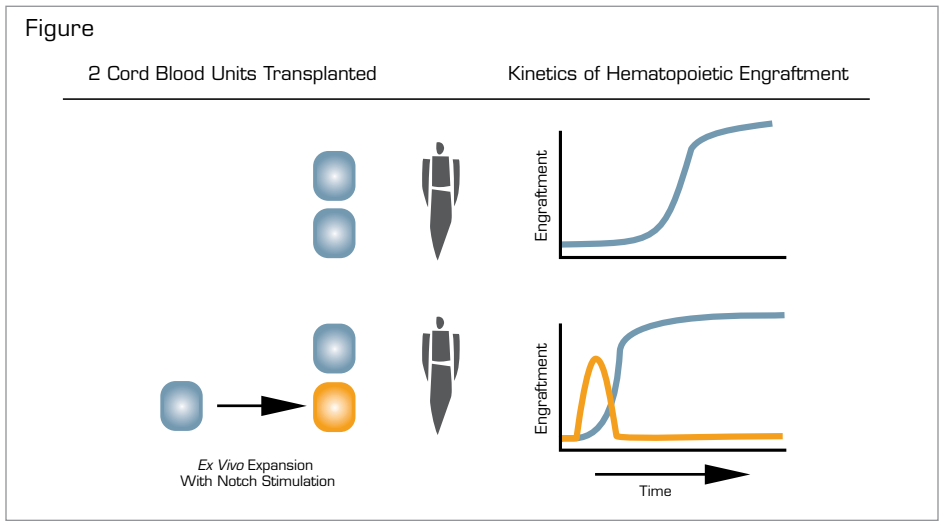
Add Another "Notch" to the Successes for Cord Blood Transplantation

Delaney C, Heimfeld S, Brashem-Stein C, et al. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med. 2010;16:232-36.

Cord blood transplantation has been limited for adults in part because engraftment is significantly delayed compared to bone marrow or peripheral blood stem cells (PBSCs). Times to reach an absolute neutrophil count (ANC) of 500/μL and to become independent of platelet transfusions with a platelet count of at least 20,000/μL generally are within 10 to 14 days when PBSCs are transplanted, but times increase to 27 days for ANC and 60 days for platelets in adults receiving transplantation with a single cord blood unit (with the minimum nucleated cell dose of 1x107/kg recipient weight).[1] When two cord blood units are administered, the times to engraftment are 23 and 62 days, on average.[2]

This paper reports the results of a clinical trial from Irwin Bernstein's group at the Fred Hutchinson Cancer Research Center in which patients received two cord blood units, one unmanipulated and the other expanded *in vitro* prior to transplantation. For the *ex vivo* expansion of hematopoietic progenitor cells, they used an approach previously developed in the Bernstein laboratory[3] in which thawed cord blood cells were stimulated for 16 days with delta-like 1, a ligand for notch receptors. Previous studies showed that stimulation of the notch signaling pathway promotes expansion of hematopoietic stem/progenitor cells. *Ex vivo* stimulation led to a 160-fold increase in the number of CD34+ cells derived from the thawed cord blood unit, and these human CD34+ cells were able to engraft the hematopoietic system of immunodeficient mice for months.

Figure



The paper describes the preclinical validations as well as preliminary results from 10 patients (ranging from 3-43 years old and 16-79 kg in weight) in an ongoing phase I clinical trial. All patients had high-risk leukemias that were in morphologic remission at the time of transplant. Cord blood units were at least a four of six HLA match with the recipient and three of six match with one another. The average infused CD34-cell dose from the expanded cord blood unit was 6 x 10^6 CD34+ cells/kg, while that from the unmanipulated unit was 0.24 x 10^6/kg. Safety was the primary objective of the trial, and there were no apparent adverse events reported. One of the 10 patients experienced primary graft rejection. The nine other patients on the trial showed a median time to ANC engraftment of 16 (range 7-34) days. There are no data yet available on the time to platelet engraftment. As depicted in the figure, the investigators found that nearly all of the early ANC engraftment was derived from the expanded unit, while in all but one patient the longer-term engraftment (beyond 20 days) was predominantly from the unmanipulated cord blood unit. Even though engraftment from the expanded unit was transient, engraftment overall and from the non-expanded unit was accelerated compared to patients who received two unexpanded units. Those patients with later engraftment (20-30 days) showed no engraftment from the expanded unit.

Ex vivo expansion of hematopoietic stem cells, which by definition are cells that are capable of long-term multi-lineage hematopoietic reconstitution in a myeloablated host, remains a Holy Grail of hematology research. However, in this study, Delaney and colleagues have successfully expanded hematopoietic progenitor cells to provide short-term multi-lineage reconstitution of myeloablated individuals. This provided a clinically important function in patients undergoing cord blood transplantation by producing much needed leukocytes prior to engraftment of long-term hematopoietic stem cells.

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Drs. Krause and Laughlin indicated no relevant conflicts of interest.

Iron Biovailability and Effective Erythropoiesis in β-Thalassemia: A Delicate Balancing Act

Li H, Rybicki AC, Suzuka SM, et al. Transferrin therapy ameliorates disease in β-thalassemic mice. Nat Med. 2010;16:177-82

The pathophysiology of β-thalassemia involves both ineffective erythropoiesis and hemolysis. Reduced or absent β-globin synthesis leads to excess free α-globin chains, increased apoptosis of erythroid precursors, and markedly shortened erythrocyte survival due to membrane precipitates of denatured α-globin. Clinical features, which vary depending on the degree of α:β globin imbalance, include microcytic anemia, extramedullary hematopoiesis, hepatosplenomegaly, and iron overload related to dysregulated iron absorption and recycling and chronic transfusions. In addition to the deleterious effects of parenchymal cell iron deposition, alterations in iron trafficking and distribution may contribute to ineffective erythropoiesis through inadequate delivery of transferrin-bound iron to the massively expanded erythron and generation of non-transferrin-bound labile plasma iron (LPI), which can mediate free radical tissue damage.

Previous work by Yelena Ginzburg and colleagues at the New York Blood Center using the $Hbb^{th1/th1}$ mouse model of β-thalassemia intermedia demonstrated that iron dextran treatment significantly improved reticulocyte production, red cell numbers, and hemoglobin levels by stimulating extramedullary, but not intramedullary, erythropoiesis.[1] Suspecting there was a relative lack of transferrin-bound iron delivery to the marrow, Li et al. in the Ginzburg laboratory investigated the effects of human transferrin therapy in $Hbb^{th1/th1}$ mice. Wild-type (WT) and β-thalassemic mice were given daily intraperitoneal human apotransferrin or holotransferrin for 60 days. β-thalassemic mice receiving transferrin demonstrated significant amelioration of anemia, normalization of erythrocyte lifespan, marked lowering of serum erythropoietin levels, increased proportion of mature erythroid precursors with fewer apoptotic cells, and decreased circulating reticulocytes compared to untreated animals. In addition, serum LPI levels normalized, intraerythrocytic α-globin precipitation decreased, extramedullary hematopoiesis was suppressed, and spleen size regressed to near normal. Notably, red cell numbers increased by roughly 50 percent, but mean cell volume (MCV) and mean cell hemoglobin (MCH) decreased further below the low baseline values. Hepcidin levels, which are inappropriately low in β-thalassemic patients and $Hbb^{th1/th1}$ mice, increased significantly with a corresponding reduction in hepatic Kupffer cell ferroportin expression. No differences were noted between mice receiving apotransferrin versus holotransferrin. WT mice exhibited no transferrin-related toxicities; however, like treated $Hbb^{th1/th1}$ mice, red cell numbers increased, and MCV and MCH decreased significantly.

The mechanisms responsible for the impressive beneficial effects of transferrin injections in this mouse model were not fully defined. The decreases in MCV and MCH in both WT and thalassemic mice suggest that excess apotransferrin actually resulted in less iron per transferrin molecule delivered to individual erythroid precursors. This would presumably down-modulate heme and globin production[2] and reduce α-globin excess, α-chain precipitates, and cell death. The increase in hepcidin, which could limit toxicity due to macrophage iron release, might be modulated by regulatory factors associated with apoptotic erythroid precursors[3,4]; however, this too remains speculative. Short-term apotransferrin administration was safe in one human trial.[5] Therefore, pilot studies in patients with intermediate/severe β-thalassemia are feasible. Recapitulating these results would be a major advancement if transfusions can be avoided and complications from extramedullary hematopoiesis and secondary iron overload can be mitigated. By extension, this principle of "iron redirection" to the erythron may prove useful in other diseases exhibiting ineffective erythropoiesis and iron overload.

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

Attacking the Root of the Problem in CML

Naka K, Hoshii T, Muraguchi T, et al. Nature. 2010;463:676-80.

The introduction of the Bcr/abl kinase inhibitor imatinib mesylate (Gleevec) revolutionized treatment of CML and represents the prototype of molecularly targeted therapy. However, while imatinib continues to produce impressive clinical results, aside from a subset of patients who are eligible for stem cell transplantation, essentially all CML patients ultimately progress and die. This often reflects the development of Bcr/abl mutations or other forms of resistance. There is also speculation that while imatinib and other kinase inhibitors may eradicate the large majority of CML cells, they may permit CML stem cells to survive. This notion is supported by preclinical evidence that various clinically relevant Bcr/abl kinase inhibitors do not efficiently induce cell death in the most primitive CML stem cell compartment.[1]

Such considerations have prompted intense interest in the development of strategies specifically designed to eradicate CML stem cells. Some of these efforts have focused on disruption of developmental pathways. For example, recent studies suggest that, unlike imatinib, pharmacologic or genetic interruption of the hedgehog signaling pathway depletes CML stem cells,[2] raising the possibility that a combined approach using Bcr/abl kinase inhibitors to eliminate the bulk of the leukemic cells with agents capable of eradicating CML stem cells may lead to improved therapeutic efficacy.

This article from the laboratory of Atsushi Hirao at Kanazawa University suggests an alternative and potentially complementary approach to eliminate CML stem cells. Akt is an important Bcr/abl downstream signaling molecule which promotes survival by negatively regulating Foxo family transcription factors. Using a murine syngeneic transplantation model, Naka et al. showed that leukemia-initiating cells (LICs) displayed diminished phosphorylation of Akt and increased nuclear localization of Foxo3A. Transgenic mice deficient in Foxo3A exhibited a significant impairment in the ability of LICs to induce disease, suggesting that Foxo3A plays a critical role in the maintenance of CML LICs. In addition, they showed that TGF-β negatively regulated Akt activation and thus promoted Foxo3A nuclear localization. An approach combining pharmacologic TGF-β inhibition and imatinib in the setting of Foxo3A deficiency was highly effective in eliminating CML stem cells and eradicating disease *in vivo*.

These findings could have significant implications for efforts to elucidate mechanisms responsible for failure of conventional therapies to eradicate CML stem cells and may also provide important insights into new therapeutic strategies to overcome this problem. It is particularly interesting that activation of Akt, which is generally thought to contribute to Bcr/abl-mediated survival signaling, may paradoxically limit the maintenance of CML stem cells by suppressing Foxo3A. If validated, this could explain why standard Bcr/abl kinase inhibitors display a very limited capacity to eliminate the most primitive CML progenitor cells. Another important implication of these findings is that in order to achieve durable responses, and possibly cures, a multi-pronged approach targeting both stem cells and their more differentiated progeny may be necessary. For example, future chemotherapeutic approaches to this disease might involve co-administration of a Bcr/abl kinase inhibitor, particularly one active against cells bearing imatinib mesylate-resistant mutations, in conjunction with inhibitors of pathways required for CML stem cell maintenance. In this context, Hedgehog inhibitors have recently entered the clinical arena, and plans for such combination regimens are currently underway. Although inhibitors of the TGF-β/Foxo pathway are not yet in the clinic, studies such as the one by Naka et al. provide a strong rationale for their development. Their arrival is awaited with much anticipation.

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Dr. Grant indicated no relevant conflicts of interest.

Platelet Kindling on the Fire: Another Example How Hemostasis and Inflammation are Linked

Boilard E, Nigrovic PA, Larabee K, et al. Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. Science. 2010;327:580-83.

Over the last several years, studies in vascular endothelial biology have highlighted the intricate linkage between inflammation and thrombosis. Inflammatory stimuli alter the procoagulant and proinflammatory balance in the endothelium to support development of a matrix for interactions between blood cells and adhesion molecules which retard bleeding and recruit inflammatory cells. Platelets promote the chemo-attraction of leukocytes through a variety of molecules, including platelet activating factor, IL-1 β, soluble CD40 ligand, macrophage inflammatory protein 1α, RANTES, PDGF, TGF-β, serotonin, PF-4, P-selectin, etc.[1,2] Platelet microparticles released upon activation can promote thrombosis[3] and attract additional leukocytes. Clinically, atherosclerosis best reflects this biology as postulated by the late Russell Ross.[4] However, other inflammatory conditions including lung disease, Crohn disease/ulcerative colitis, and rheumatoid arthritis suggest an incendiary role for platelets. From the laboratory of David Lee at Brigham and Women's Hospital, Eric Boilard et al. show that platelets can make ankles in mice with inflammatory arthritis "red hot." This amplified response is due to shed platelet microparticles which stimulate synoviocytes to dump activating cytokines into the joint space.

In clinical studies, the investigators showed that synovial fluids from rheumatoid arthritis patients contained 0.2-1.0 micron diameter CD41 (GPIIb) expressing vesicles, while 19/20 osteoarthritic patients had no such particles. Interestingly, no intact platelets were detected in the synovial fluids; CD45-positive leukocytes seemed to be carrying microparticles into the joint. In a K/BxN serum transfer mouse model of inflammatory arthritis, platelet depletion, but not blockade of the ADP receptor P2YR12 by clopidogrel or absence of thromboxane or GPIIb, cooled the joint flames. Local rather than systemic platelet activation seemed to play a role as fibroblast-like synoviocytes and their extracellular matrix-associated proteins triggered microparticle release. Platelet GPVI and its associated gamma chain of the Fc receptor proved essential in microparticle release responding to collagen and collagen-related peptides. Mechanistically, platelet microparticles could elicit a range of cytokines including IL-6 and IL-8 from fibroblast-like synoviocytes. The activation of these cells (so abundant in the rheumatoid pannus) by platelet microparticles was related to platelet-associated IL-1 (Figure).

This article suggests that inhibiting platelet GPV1 may be useful in treating rheumatoid arthritis. One would think that IL-1 antagonism would be very efficacious, but apparently platelet microparticle-associated IL-1 is difficult to antagonize. As Zimmerman points out in an accompanying article,[5] we usually don't think about platelets playing a significant role in rheumatoid arthritis. Since intact platelets are not found in the rheumatoid arthritis joint space, how do the microparticles get there? Could they be hitchhiking on transmigrating white cells? Boilard et al. propose that platelets release infiltrating microparticles after GPVI activation when they contact collagen. The microparticles enter the joint space via fenestrations in permeable subsynovial capillaries (Figure). This manuscript adds to the evidence for the critical role of platelets in inflammation and spurs me to speculate whether excessive platelet transfusions may be providing kindling for inflammatory fires in our thrombocytopenic patients.

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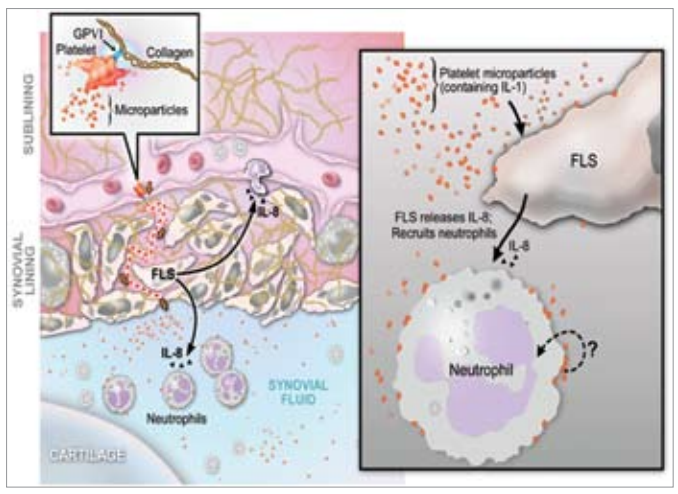
Proposed pathway for GPVI-dependent participation of platelets in arthritis via microparticles



GPVI-expressing platelets activated by collagen produce copious amounts of IL-1-rich microparticles (MPs) (left panel and inset). The precise anatomic location of platelet activation and the route by which microparticles enter the joint (dotted red line in the left side of the figure where the microparticles are going across the synovial lining) remain unknown. Platelet MPs (~0.2-1 µm in diameter), detectable at high levels in inflammatory synovial fluid, interact with tissue cells including fibroblast-like synoviocytes (FLS) and synovial fluid leukocytes (right panel). This interaction elicits further inflammatory effector functions from target cells, thereby amplifying synovitis. In the case of FLS, platelet MPs promote elaboration of IL-8 and other mediators that are capable of leukocyte chemoattraction to the joint (right panel). Platelet microparticles attached to neutrophils, as found in diseased synovial fluid, may also stimulate neutrophil effector functions, although this remains to be established (question mark, right panel). Figure courtesy of S. Moskowitz and D. Lee

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Dr. Vercellotti indicated no relevant conflicts of interest.

Increasing Awareness — The Clinician-Educator Track in Academic Medicine

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During the two to four years generally needed to complete a demanding hematology or hematology/oncology fellowship, trainees are expected to partake in academic endeavors that will position them for success in their specific career path — be it academia, community practice, industry, or any combination of the three. This decision, like many before it in medical education, may be based on limited knowledge or exposure to a particular practice environment or area of study.

For those of us who believe we are fit to carve out a niche for ourselves in the competitive world of academic medicine, we must first decide what it is about academic medicine that we find attractive. If drawn to laboratory research or clinical investigations at an institution where there is high-quality mentorship available, a young investigator may decide to pursue a career as a clinician-scientist or clinical investigator with relative ease. Academic medical centers support new discoveries using the strength of laboratory/clinical research programs and attainment of grant support to claim their place among the nation's elite institutions. In addition to research, the mission statements of the esteemed centers reflect a commitment to patient care and medical education. At last year's ASH Trainee Day, which took place during the annual meeting, Dr. Kenneth Kaushansky, chair of the Department of Internal Medicine at University of California, San Diego (UCSD), discussed a career pathway in academic medicine that merges these latter two critical elements: the clinician-educator track. Trainees who strive to provide world-class patient care and are devoted to the tutelage of their junior colleagues may be well suited for the clinician-educator pathways in academia.

As clinician-educators in academic medical centers, physicians will devote their time to caring for patients in both inpatient and outpatient settings and supervising medical students and residents.[1] Depending on the institution, a clinician-educator may split his or her time evenly between patient treatment and education or alternately up to 80 to 90 percent of his or her time devoted to patient management.[2] His or her salary will generally come from revenue generated by services rendered, without emphasis on grant support. Students, residents, and faculty members often recognize clinician-educators as outstanding physicians and role models.[3]

According to two Association of American Medical Colleges (AAMC) reports, there are ample opportunities for clinicians to pursue academic appointments in these tracks. Dr. George Richard, director, Careers in Medicine Program for AAMC, and Michelle Sullivan, Vanderbilt University School of Medicine, presented research on faculty career options for the AAMC on November 4, 2008. They collected data online from 75 U.S. allopathic medical schools and found that 26 schools outlined at least one specific education-based track; three schools had two clinical-educator tracks. Common titles included academic educator, teaching scholar, and clinician-teacher. Of the 29 tracks discovered, 11 were eligible for tenure. The majority of U.S. medical schools will have clinically based tracks with educational components despite there not being a direct emphasis on education. According to a 2005 AAMC report,[4] 100 American medical colleges have such tracks. There are ample opportunities to pursue this career track, but there is significant variation among institutions regarding eligibility for appointment to clinical-educator tracks and even more variation, with some controversy, regarding promotion of clinical-educators. Several health-care organizations have data regarding physician career tracks available online. According to Dr. Kaushansky, UCSD has a Clinical Professor of Medicine track for physicians who desire to be largely committed to patient care and education, while still being involved in scholarly activity. At the time of appointment, candidates are expected to have completed a recognized training program and display excellence in basic clinical skills as evidenced by recommendation letters from program directors and colleagues. A scholarly plan is required that may include such efforts as participation in collaborative research and publication of case reports, book chapters, reviews, and articles for lay audiences. Candidates will participate in training house staff and students through clinical activity. Assuming completion of the fourth-year appraisal, advancement to associate professor requires independent clinical excellence with distinction in teaching house staff, as documented in teaching evaluations and letters. At the associate professor level, scholarly activity, as listed previously, with documented continued productivity and presentations at national/local meetings, including CME, is expected. At this level, service to the university is also required through hospital/institutional committee membership. With continued momentum in the areas mentioned, full professorship is attainable.

As a second example, Duke University has a clinician-teacher track in which 75 percent or more of a candidate's time is spent on clinical undertakings.[5] Although physicians are to be judged most heavily on clinical activity, participation in the academic community is considered in the promotion process. Teaching is obviously required and evaluated, and research and scholarly publications that enhance the candidate's regional/national reputation as a master clinician are encouraged, but are considered as secondary measures of performance. Promotion from assistant to associate professor is primarily based upon clinical excellence and attaining a regional or national reputation with a wide referral base. The rank of professor is awarded to those who have become nationally or internationally renowned for clinical excellence.

These examples of clinician-teacher tracks represent two similar but varied approaches to the clinical-educator pathway in medicine. This pathway is a viable option for those that love to teach and embrace patient care with a desire to excel. The current state of affairs would generally require willingness to accept a non-tenured position and an understanding that, despite a heavy clinical and teaching load, if a program stipulates a need for a national reputation in order to gain full professorship, a significant number of publications and presentations may be necessary. The days of the academic physician as a triple threat are coming to a close. As our colleagues in the laboratories continue to break ground at the molecular level, there will be an increasing need for exceptional clinicians to employ state-of-the-art patient management strategies and educate the next generation of physicians.

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Use of ESAs

(Cont. from page 7)

the historical control.[6] In the ECOG study, no significant treatment-related increase in incidence of either cardiovascular or thrombotic events occurred in the ESA arm.[4] Thus, published data do not show a negative impact of these drugs for treatment of MDS.

Given these findings, the NCCN MDS Practice Guidelines Panel endorsed its prior recommendations supporting judicious ESA use in the management of symptomatic anemia in lower-risk MDS patients but with a change in the target hemoglobin level to ≤12 gm/dl.[7]

ASH continues to seek further clarification from the FDA about how the REMS will apply to MDS patients, including clarification about the frequency required to provide *Medication Guides*. Physicians who have questions about how the REMS will apply to your MDS patients are encouraged to contact the ASH Government Relations & Practice Department at *grassroots@hematology.org*.

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C. Lockard "Lock" Conley, MD (1915 – 2010)

Each day we witness the passing of another member of the "Greatest Generation" that guided us through the dark days of World War II. In much the same way, this decade is relentlessly taking from us the architects of the "greatest generation" of academic hematology. These remarkable scholars transformed hematology during the 1950s through 1970s from a largely descriptive field to a discipline where advances in clinical care were driven by scientific discoveries. Sadly, we have now lost another true giant of this generation, C. Lockard "Lock" Conley, who succumbed to Parkinson's disease at the age of 94 on January 30 at his home in Maryland. Throughout his life and career, Lock Conley was one of those rare individuals who inspired awe and respect for his brilliance and incredible accomplishments and admiration, affection, and gratitude for his caring ways; his gentle mentorship; and his teaching of generations of physicians and hematologists. He will be missed as much for who he was as for what he accomplished.

Lock Conley was born in Baltimore and received his bachelor's degree in 1935 from Johns Hopkins and his medical degree from Columbia University in 1940. He served during World War II at the Air Corps' Maxwell Field General Hospital in Alabama and after the war returned to Johns Hopkins, joining the faculty in 1946. He was named the first director of the Division of Hematology in 1947. At the time, an inviolate rule at Hopkins was that only heads of departments would be elevated to the rank of full professor. Because of his brilliance as an investigator, clinician, and educator, Lock was the first person for whom that rule was altered: He was made a full professor in the School of Medicine in 1956 while still a division chief. Lock was named the University Distinguished Professor of Medicine in 1976. The long list of honors and distinctions he received do not capture fully the character or the distinct mix of clinical and laboratory scholarship underpinning his extraordinary contributions to the field. Of the 70 fellows Lock supervised during his 33 years as head of hematology, a dozen became hematology division heads or medicine department chairs.

During his quarter-century tenure as chief, Lock kept his Division at the absolute leading edge of the most exciting period in the development of the field of academic hematology. During that time, hematology became a

C. Lockard Conley, MD

very broad yet highly focused and scientifically based discipline, evolving into many highly specialized and technical sub-disciplines. Many areas were advanced by landmark contributions by Lock or his protégés. These include establishing that clotting factors were plasma proteins, the association of thrombosis with the lupus anticoagulant, the description of homozygous hereditary persistence of fetal hemoglobin and its interaction with sickle cell anemia, and crucial contributions to the use of vitamin B12 in pernicious anemia.

A common feature of all of Lock's contributions was the matching of precise and rigorous descriptions of the clinical condition (now popularly called "phenotyping") with elegant application of the most up-to-date laboratory technologies. This invariably produced important insights about the molecular or cellular abnormalities responsible for those conditions. Lock articulated many ideas about the pathophysiology of blood disorders. Many of these approaches remain in place today, buttressed by decades of even more precise molecular and cellular analysis.

People point to the development of protein electrophoresis, first applied to the study of hemoglobin disorders, by Linus Pauling in 1947 as the beginning of the era of "molecular medicine." It was Lock and a young associate, Ernest W. Smith, however, who developed a simple device that could accomplish almost equivalent separation of hemoglobin variants. While Pauling showed how it could be done, it was Lock and Smith who devised a way that hundreds of laboratories could actually study millions of patients and open the field of hemoglobinopathy research.

Around the world, Lock was known as an extraordinary hematologist and internist. At Johns Hopkins, he will also be remembered as a gentle and caring educator, mentor, and caregiver and for his unique combination of personal traits, brilliance, and dedication. He was a role model for many students and trainees, influencing generations extending even beyond the 70 highly accomplished graduates of the hematology fellowship program that he led. In a recent remembrance in the *Johns Hopkins University Gazette*, colleagues and friends captured Lock's unique combination of personal traits, brilliance, and dedication.[1]

Dr. Conley was predeceased by his wife of 61 years, Edith, who died in 2004. He is survived by two daughters, Anne Weaver, a pediatrician in Amherst, MA, and Jean Alexander, a horticulturist in Silver Spring, MD, two grandchildren, and four great grandchildren.

We note his passing with sadness but also with gratitude, both for his enormous contributions to the understanding and treatment of hematologic disorders and for his nurturing of so many hematologists who will carry the work forward.

Edward J. Benz Jr., MD
George Dover, MD
Chi V. Dang, MD, PhD

1. Grauer NA, The JHU Gazette, February 8, 2010.

Out With the Old and in With the New

The human leukocyte antigens (HLA) system is the major histocompatibility complex (MHC) in humans. These proteins are encoded by a large set of genes (alleles) and are essential elements for immune function. Thus, they play an important role in the success of solid organ and hematopoietic progenitor cell transplantation. When HLA nomenclature was adopted in 1987, it was thought that the naming convention put in place could accommodate all of the HLA alleles likely to be sequenced. Since then, new additions to the original code have been added to extend the use of the nomenclature system.

As the science of HLA matching has advanced and more and more allelic variation discovered, the capacity to name newly discovered alleles by the current HLA naming convention has been exceeded. As a result, a new version of HLA nomenclature was launched on April 1, 2010. The World Marrow Donor Association (WMDA) and National Marrow Donor Program (NMDP) are working with organizations and suppliers from around the world to ensure that worldwide systems are prepared for the new version of HLA nomenclature.

The current convention has been revised in three ways. First, with the ever-increasing number of HLA alleles, it has been decided to introduce colons (:) into the allele names to act as delimiters of the separate fields. It will be mandatory to include the leading zeros currently included in the alleles; this will help to lessen any confusion in the conversion to the new style of nomenclature, but no further leading zeros will be added to allele names.

Second, the "w" has been removed from the HLA-C allele names, but will be retained in the HLA-C antigens' names, to avoid confusion with the factors of the complement system and epitopes on the HLA-C molecule often termed C1 and C2 that act as ligands for the killer-cell immunoglobulin-like receptors.

Lastly, the level of resolution achieved by many of the HLA-typing technologies employed today does not always allow for a single HLA allele to be unambiguously assigned. For some purposes, it is helpful to provide codes that aid the reporting of certain ambiguous alleles "strings." To this end, codes have been introduced to allow for the easy reporting of both HLA alleles that encode for identical peptide-binding domains and HLA alleles that share identical nucleotide sequences for the exons encoding the peptide binding domains.

Lists of old and new allele names will be made available through the IMGT/HLA Database *(www.ebi.ac.uk/imgt/hla)*. HLA allele code information is available at *http://bioinformatics.nmdp.org/HLA/Ver3_Nomenclature_Allele_Codes.* For general information about this transition, visit *www.marrow.org/hla.*

Career-Defining Opportunities Through ASH

NEIL A. GOLDENBERG, MD, PhD

Assistant Professor of Pediatrics and Medicine (Hematology); Associate Director, Hemophilia and Thrombosis Center; Co-Director, Pediatric Thrombosis and Stroke Programs at the University of Colorado Denver and The Children's Hospital; and Director of Venous Thromboembolism Trials, the Colorado Prevention Center

ASH has played a critical part in my career development, beginning with a memorable experience early on as a medical student at McGill University. I was given a pivotal opportunity: to submit a proposal to perform a clinical research project in lieu of the "back to the classroom" module in my fourth year. The proposal was selected and involved the investigation of plasma levels of angiogenic factors and coagulation markers in cancer-associated venous thromboembolism (VTE) in adults, through a three-hospital, cross-sectional study. My mentors at the time, ASH members Drs. Susan Solymoss and Susan Kahn, had me present the study to each site's Ethics Committee, pitch it to the faculty in the relevant hospital departments, carry a study pager 24/7 for potential subjects with acute VTE, and perform study coordinator and laboratory assistant responsibilities on the study, until returning to the United States for Med/Peds residency. In 2000, I presented the findings in poster format at my first ASH meeting. The meeting was an eye-opening experience, and I immediately knew that ASH would become a professional home for me. After several rounds of revision, the manuscript was published in 2002, my first year of pediatric Hem/Onc/BMT fellowship at the University of Colorado.

Another career-defining opportunity came in the summer of 2002, when my application to the first ASH Clinical Research Training Institute (CRTI) was accepted. CRTI provided access to a network of leading clinical/translational physician-scientists and committed mentors in the discipline, with whom I have maintained contact and had subsequent productive collaborations. CRTI also solidified my interest in a clinical research career in non-malignant hematology. At the same time, my mentors in fellowship, ASH members Drs. Marilyn Manco-Johnson and Bill Hathaway, impressed upon me that, despite my orientation toward a future in clinical trials in thrombosis, one must have command of the laboratory aspects of coagulation medicine in order to be a strong clinician and clinical scientist in this area. Indeed, this helped build a foundation for translational science, which can offer added value atop the basic design of observational clinical research and clinical trials.

Encouraged by CRTI faculty, in 2004 I successfully competed for an ASH Scholar Award in Clinical/Translational Research stemming from my CRTI project. The CRTI experience and the applied clinical/translational research training focus of the Scholar Award inspired me to complete a PhD in clinical science at the University of Colorado, as well as to pursue a one-year practicum in the conduct and management of clinical trials through a University of Colorado-affiliated academic research organization, the Colorado Prevention Center. The ASH CRTI and Scholar Award also provided academic currency that helped me obtain a five-year K23 Career Development Award from the National Heart, Lung, and Blood Institute. My K23 focuses on clinical investigation in pediatric VTE — specifically, conduct of the Kids-DOTT trial (Multicenter Evaluation of the Duration of Therapy for Thrombosis in Children) and associated translational investigation of prognostic markers in pediatric VTE.

These experiences, from initial mentoring by ASH members and exposure to the annual meeting as a medical student, to fellowship training involving CRTI participation, PhD work in clinical science, and ASH Scholar activity, have instilled in me the passion to give back to clinical research mentorship. As an assistant professor, I am now privileged to serve as a member of the CRTI faculty. Every bit as important as the training of tomorrow's clinical investigators in hematology is the unstructured interaction, career guidance, exchange of ideas, and networking that develops among mentors and trainees. This continues to be a vibrant part of the CRTI experience, for faculty and trainees alike. Every resident or fellow interested in a career in clinical/translational research in hematology should strive to take advantage of the portfolio of ASH career-development programs, including the Research Training Award, Scholar Awards, and CRTI. The funding for and focused training in clinical investigation provided by ASH through these programs have proven instrumental in facilitating the transition toward successful, independent research in hematology for myself as well as a growing number of early-career clinical investigators in our discipline.

ALLISON KING, MD, MPH

Assistant Professor, Program in Occupational Therapy and Department of Pediatrics, Division of Hematology and Oncology, Washington University School of Medicine

In 2005, I was fortunate to attend the ASH Clinical Research Training Institute (CRTI) as a trainee. I was starting my third year as an instructor and was anxiously awaiting comments from the K23 application that I had submitted to the National Heart, Lung, and Blood Institute. I had earned a master's degree in public health during my pediatric hematology and oncology fellowship and was in Dr. Michael DeBaun's clinical research laboratory at Washington University. Despite having a strong mentor and solid training, I had never spent such an intense and focused amount of time on studying the finer points of clinical investigation. CRTI provided didactic training, small-group meetings to improve a clinical research project, and the chance to develop valuable relationships with accomplished leaders and clinical investigators in ASH. The interactions and feedback from that week greatly assisted my final K23 resubmission that was eventually awarded. In addition, I formed relationships with senior members of ASH whom I probably would never have met; these people became mentors and friends.

The week of CRTI had a positive effect on my career. After CRTI, I literally pulled out slide sets from lectures on how to write a hypothesis and how to design a clinical trial as I wrote future grants. Two of my small-group leaders wrote letters of recommendation for my promotion, and I kept in contact with my new network of friends to collaborate. In fact, the project that I worked on at CRTI (a single-center, randomized educational intervention for children with sickle cell disease) evolved as part of my K23, and in 2009 I received an ASH Scholar Award to test the feasibility of completing the intervention at a second site. My collaborator, ASH member Dr. Julie Panepinto, was a faculty member at CRTI with me in 2008.

The ASH Scholar Award, which I received in 2009, is providing the funding that I need to really test the legs of the primary aim of my K23 award. While the K23 covered a large portion of my salary, I lacked the funds to gather enough preliminary data for an independent grant for that intervention. I am hopeful that we will be able to demonstrate that a second site can conduct the same intervention so that we can pursue an independent grant.

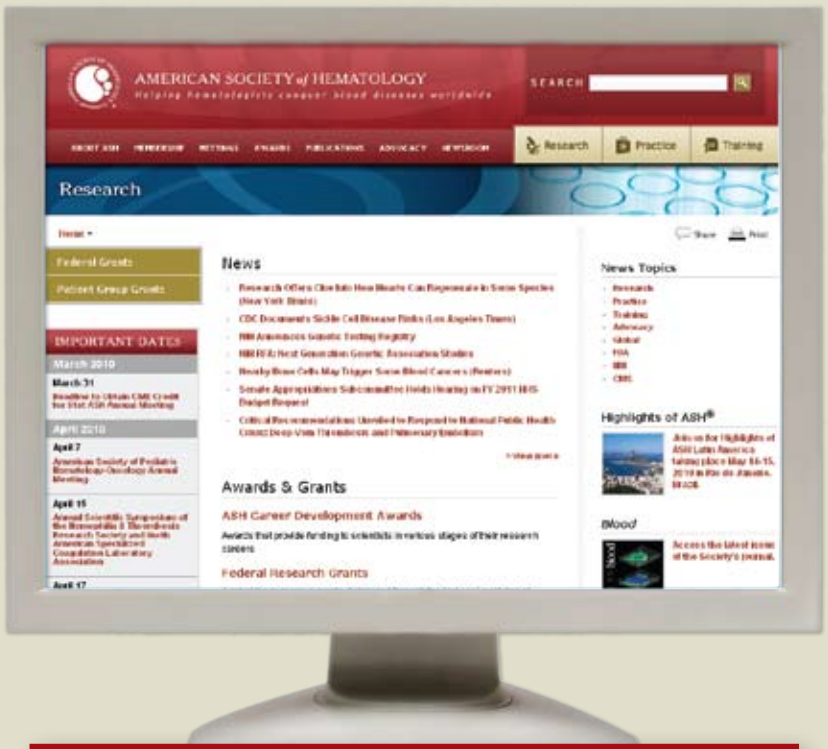
ASH is obviously a large organization with thousands of members. However, participating in the CRTI and receiving the ASH Scholar Award has allowed me to become a part of a supportive family of ASH members and staff. I have started to give back to ASH by serving on the CRTI oversight committee, serving as faculty at the CRTI, donating financially to CRTI, reviewing abstracts, and speaking at one of the educational sessions at the 2009 annual meeting. I look forward to continuing to serve ASH, so that future trainees and junior faculty can experience the same assistance that I have received.

WHAT'S ON THE WEB

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

New for 2010: We will be **spotlighting one area of the ASH Web site** in each issue. With the redesign complete, we want to call attention to specific areas of the Web site, so you are able to access the information available on these pages.

Featured in the Web spotlight this month is the Research landing area of the ASH Web site, *www.hematology.org/research*. **Researchers are a key constituency of the Society,** representing a large percentage of our membership. As part of ASH's effort to keep hematology researchers informed, numerous resources are provided through the Society's Web site.



Visit the "Research" tab at *www.hematology.org* to:

- Get the latest hematology training news
- Access information about ASH's career-development awards that provide funding to scientists at various stages of their careers
- Look through the list of current research grants available from federal agencies and patient advocacy organizations
- Download the *ASH Agenda for Hematology Research: 2009 - 2011,* which identifies and prioritizes the most fertile areas of research in hematology
- View research recommendations developed from past ASH workshops on sickle cell disease, thrombosis in the elderly, and anemia in the elderly
- Access a schedule of important dates and deadlines for meetings, award applications, and more
- Peruse the latest issues of *Blood* and *The Hematologist* online

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

Mark Your Calendar

May

4 — **Deadline to submit nominations for the ASH Mentor Award**
Washington, DC — *www.hematology.org*

13 – 16 — **Canadian Society for Transfusion Medicine Annual Scientific Meeting**
Vancouver, Canada — *www.transfusion.ca*

14 – 15 — **Highlights of ASH in Latin America**
Rio de Janeiro, Brazil — *www.hematology.org*

17 – 22 — **Annual Meeting of the American Society of Gene & Cell Therapy**
Washington, DC — *www.asgt.org*

23 – 26 — **Annual Meeting of the International Society for Cellular Therapy**
Philadelphia, PA — *www.celltherapysociety.org*

June

3 – 4 — **CTBB 2010: 37th Annual Current Topics in Blood Banking**
Ann Arbor, MI — *www.pathology.med.umich.edu/CTBB*

4 – 8 — **American Society of Clinical Oncology Annual Meeting**
Chicago, IL — *www.asco.org*

10 – 13 — **15th Congress of the European Hematology Association**
Barcelona, Spain — *www.ehaweb.org*

14 — **ASH annual meeting abstract submission process opens**
Orlando, FL — *www.hematology.org*

14 — **World Blood Donor Day**
Worldwide — *www.wbdd.org*

16 – 19 — **Annual Meeting of the International Society for Stem Cell Research**
San Francisco, CA — *www.isscr.org*

July

10 – 14 — **World Federation of Hemophilia 2010 World Congress**
Buenos Aires, Argentina — *www.wfh.org*

20 — **Early-bird annual meeting registration open to ASH members**
Orlando, FL — *www.hematology.org*

25 – 30 — **Hemostasis Gordon Research Conference**
Waterville Valley, NH — *www.grc.org*

August

1 — **Deadline to submit active and international ASH membership applications**
Washington, DC — *www.hematology.org*

4 — **Annual meeting advance registration open to members and non-members**
Orlando, FL — *www.hematology.org*

12 — **ASH annual meeting abstract submission deadline**
Orlando, FL — *www.hematology.org*