DIFFUSION

Non-Ablative Allogeneic Transplant Demonstrates Promising Long-Term Outcome in Relapsed Patients With CLL


The past decade has brought forward a multitude of new therapies for chronic lymphocytic leukemia (CLL). A combination of these treatments as part of chemo-immunotherapy has improved the response rates, remission durations, and overall survival of patients with this disease. Despite these advances, no currently available therapy is a cure for CLL. Also, many patients with CLL eventually become refractory to traditional treatment modalities, including chemo-immunotherapy, and, ultimately, die as a direct consequence or complication of the disease. Identification of strategies that offer curative intent for CLL would represent a major advance for this disease.

The recent publication by Sorror and colleagues provides more conclusive evidence that non-ablative allogeneic stem cell transplant may represent one such therapy in CLL. Application of ablative allogeneic transplant in the past has been associated with significant treatment-related mortality and has only been applicable to the fewer than 5 percent of patients younger than 50 who develop refractory CLL. Adaptation of non-ablative approaches has broadened the age group of CLL patients eligible for this approach, making it more applicable to the large population of individuals with this disease. Multiple early reports have been published documenting feasibility and surprisingly low early treatment-related mortality as compared to previously published ablative allogeneic stem cell transplant in CLL. More importantly, graft-versus-leukemia was clearly documented with meaningful responses observed, even in patients with measurable CLL at time of transplant. While problems with chronic graft-versus-host disease (GVHD) clearly arise using the non-ablative allogeneic approach, significant excitement across the field exists for this treatment in patients with refractory CLL. The report by Sorror and Maloney provided what all CLL investigators have been looking for — extended follow-up showing that a large minority of patients undergoing this procedure remain disease-free and fully functional at five years. While the authors identified chronic GVHD as problematic early on, this eventually burned out in the majority of patients allowing them to be free of immunosuppressive medication.

Given the five-year 50 percent overall survival and 39 percent progression-free survival with a low risk of late relapse in this heavily treated CLL population, we must now consider non-ablative transplant as an option for patients with relapsed CLL. On a practical level, these findings should decrease the commonly identified insurance denial or delay in approval by select insurers that ultimately prevent many individuals from pursuing this potentially curative therapy. Documentation of long-term follow-up of this large cohort of CLL patients receiving non-ablative transplants with very favorable results provides convincing data to support this modality as a standard, and, thus, a research-based therapy for select patients with relapsed CLL.

Can we improve further on what has been achieved in non-ablative transplant for CLL? Several important questions remain to be answered from the report by Sorror and Maloney and other non-ablative transplant series in CLL.

These include:

1) What proportion of high-risk [i.e., del(17p13.1) or complex karyotype] patients are salvaged with non-ablative approaches, and should this treatment be applied earlier in the disease process?

2) Can moderate-intensity regimens or addition of other immune-modulating agents post-transplant afford the same morbidity observed by Sorror and colleagues but diminish the risk of relapse in patients with bulky lymph nodes?

3) Are unrelated donors actually better for transplantation in the CLL population?

To fully pursue these questions and further improve this modality, we require well-controlled clinical trials building upon the successes already documented with non-ablative transplants in CLL. Many trials are being initiated to address these questions that hopefully would afford even better outcomes for patients with this disease.

JOHN BYRD, MD
Dr. Byrd indicated no relevant conflicts of interest.

REVISED PHRMA CODE GOES INTO EFFECT: SUNSHINE OR MORE OF THE SAME? — Drs. Kenneth Kaushansky and Roy Silverstein review changes to the ethics code guiding pharmaceutical companies.

ASK THE HEMATOLOGIST — Dr. Joseph M. Connors responds to a question regarding a young woman with stage IVB Hodgkin lymphoma.

MINI REVIEW: CORD BLOOD TRANSPLANTATION — Dr. Hal E. Braselmyer chronicles notable advancements in the 20 years since the first CB transplant.

WHAT DO THE RESULTS OF THE NOVEMBER ELECTIONS MEAN FOR ASH? — Dr. George Weiner offers a medical perspective on the recent election results.

LIFE AT THE SUBDUCTION ZONE: HEMATOLOGY AND CERTIFICATION OF ELECTRONIC HEALTH RECORDS — Dr. Lawrence A. Solberg Jr. discusses reasons for the slow adoption of electronic health records.

THE MEANING AND IMPACT OF THE ASH SCHOLAR AWARD — Dr. D. Gary Gilliland reflects on how his career has benefited from the ASH Scholar Award.

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I am honored to serve as the third editor of this publication, which is now in its sixth year as both a print and online publication. The Hematologist was originally conceived as an informative and educational year-round vehicle to enhance communication for ASH membership. Given the broad constituency of ASH, which includes laboratory-based and translational scientists, clinical investigators, practicing clinicians from the disciplines of adult and pediatric hematopathology and oncology, pathology and laboratory medicine, transfusion medicine, and vascular medicine, as well as trainees in both the clinical and laboratory arenas, this is a daunting charge. Nevertheless, all are dedicated to improving the lives of those with blood disorders and, thereby, are part of a marvelous and vibrant community.

The “heart” of The Hematologist will continue to be the Diffusion pieces. In a research-driven field like ours, we will continue to see movement toward more and more sub-specialization, both at the bench and bedside. The Diffusion articles, by providing brief but cogent and clinically relevant summaries of the “hottest” publications in hematology, serve as outstanding tools to help ASH members keep up with the most important basic, translational, and clinical research advances.

As we begin our second half-century as a society, we are likely to see unprecedented transformations. We hope to expand The Hematologist’s role in communicating important developments in our discipline related to practice, research, public policy, government affairs, training, education, and career development, as well as occasionally highlighting significant personal achievements of ASH members. Communications from ASH officers and standing committee chairs will appear on a regular basis, as will discussions of important controversies in our field. We also recognize that the “American” Society of Hematology is an international society, and we will make every effort to address the needs and interests of our non-North American members.

The Hematologist was developed to serve. Our aim is to keep it lively and informative and relevant to the entire spectrum of ASH membership. As editor, I am committed to the traditions of our previous editors, Drs. Andrew Schafer and Peter Emmons, which include frequent review and assessment based on solicited and unsolicited input from ASH membership.

—Roy L. Silverstein, MD

Recently, we have seen heightened attention by government officials and news media on financial relationships between physicians and manufacturers of pharmaceuticals and medical devices. A few notable cases of physicians and surgeons receiving six- or seven-figure “consulting” fees to promote drugs and devices often with little or no public disclosure have heightened interest. In this context, the Pharmaceutical Research and Manufacturers of America (PhRMA) have revised their “Code on Interactions with Healthcare Professionals” for the first time since 2002. The updated voluntary Code, which went into effect in January, is part of an ongoing effort to reassure the public that pharmaceutical marketing practices comply with ethical standards. It reaffirms that interactions between company representatives and health-care professionals “should be focused on informing health-care professionals about products, providing scientific and educational information, and supporting medical research and education.”

The revised Code prohibits distribution of non-educational items (e.g., pens, mugs, and other “reminder” objects) to healthcare providers and their staff and goes beyond previous rules by stating that companies should not provide any entertainment or recreational benefits (e.g., restaurant meals, theater and sports tickets, etc.) to health-care professionals. The Code still allows reps to provide occasional meals in physician offices and restaurants in conjunction with informational presentations and at national and regional medical society meetings.

The Code also includes new provisions related to disclosure and employee education. Companies must ensure that their representatives are sufficiently trained in applicable laws, regulations, and industry codes of practice, including the Code, that govern interactions with healthcare professionals. Companies are also asked to assess their representatives periodically and to take appropriate action if they fail to comply with relevant standards of conduct.

Companies must also state their intention to abide by the Code and that their CEOs and Compliance Officers will certify each year that they have processes in place to comply, a system patterned after the Sarbanes-Oxley regulations. Companies are encouraged to obtain periodic external verifications that they have processes in place to foster compliance with the Code. PhRMA will post on its Web site a list of all companies that announce their pledge to follow the Code, contact information for company compliance officers, and information about their annual compliance certifications.

Other additions to the Code include more detailed standards regarding the independence of continuing medical education (CME), principles on the responsible use of non-patient-identified prescriber data, and additional guidance for speaking and consulting arrangements with health-care professionals, including disclosure requirements for health-care providers who are members of committees that set formularies or develop clinical practice guidelines and who also serve as speakers or consultants for a pharmaceutical company.

Questions remain about implementation of a number of aspects of the new Code. Although manufacturers are required to set limits on consulting and speaking fees, the limits are not actually defined, and public disclosure of consulting and speaking relationships is not mandatory. It is also important to note that the Code applies only to Big Pharma; device manufacturers and blood products industries have their own trade organizations and have chosen not to follow suit with their own codes of conduct.

Given public interest in relationships between physicians and pharmaceutical companies, the revised Code will not close the book on the conflict-of-interest issue, or put a halt to continued government and media scrutiny. As physicians, we may ask what role industry should play in setting our own professional standards of behavior. What role should our professional societies play, and for those of us in academic medicine, what role should our employers play?

Among the medical professional societies, ASH has been at the forefront in dealing with conflicts of interest by developing detailed policies that preserve the scientific integrity of the discipline while allowing productive interactions with industry. ASH’s mission does not include marketing of pharmaceutical or biomedical products, yet opportunities exist for purchase of space for commercial displays at the annual meeting and other smaller meetings, and for purchase of advertising in Blood. ASH mandates that revenues generated from these activities be devoted to the support of the Society’s mission and that advertisers have absolutely no role in determining the scientific or educational content of the journal or any ASH meeting or CME activity. ASH uses disclosure and peer review to identify potential conflicts and encourages hematologists to question speakers if they suspect that the information provided is in any way biased. Commercial support for CME is acknowledged publicly, and attendees are always provided with a formal opportunity to report on their perceptions of any possible bias. To ensure transparency and compliance, every ASH committee has a conflict-of-interest compliance officer, and all of the many professional volunteers who provide leadership to ASH by serving as officers, members of standing committees, editors of ASH publications, or faculty in ASH-sponsored educational activities must provide a detailed conflict-of-interest disclosure. A centralized, Web-based, conflict-of-interest registry for ASH will be online no later than 2010.

ASH has not taken a position on the interactions of its members with industry outside of ASH-sponsored activities. Should it? Tell us what you think. We also encourage your feedback on the revised PhRMA Code and current ASH conflicts of interest policy. Please send your comments to klearner@hematology.org.

For More Information

ASH’s policies and practices were formulated by the ASH Executive Committee during its spring meeting. On May 22, 2008, Dr. Kaushansky presented oral testimony to the Institute of Medicine (IOM) on conflicts of interest between medical societies and the pharmaceutical industry and the policies that ASH has implemented to safeguard against introducing bias into ASH’s meetings, publications, and positions. To read the written testimony, go to www.hematology.org/policy/testimony/IOM.pdf.
**Meeting of the Co-Sponsors of Highlights of ASH in Latin America**

For the first time, ASH will be holding a Highlights of ASH meeting on May 15 - 16, 2009, in Latin America in conjunction with the Associação Brasileira de Hematologia e Hemoterapia (SBHH/CBH). During the SOOH annual meeting, the presidents of the co-sponsoring organizations, ASH President Dr. Nancy Berliner, and Dr. Carlos Chiattone, of SBHH/CBH, met with the leaders of Latin American hematology associations from Argentina, Mexico, Peru, and Uruguay to discuss planning and registration.

**Attention Training Program Directors: Apply for the ASH Alternative Training Pathway Grant**

The Alternative Training Pathway Grant is intended to foster the development and implementation of creative new curricula for trainees in clinical and clinical/translational hematology and related fields. A growing number of trainees are expressing an interest in pursuing hybrid careers [e.g., medicine/pediatrics] and/or a desire to become trained in both clinical care and laboratory medicine [e.g., transfusion medicine or directing hemostasis laboratories]. The Alternative Training Pathway Grant is designed to allow training program directors to develop a curriculum that meets these new demands. Grants of up to $50,000 will be awarded to support the development and implementation of novel hematology-related training programs as an alternative to traditional training programs. The award may be expended over a one- to two-year period of time.

To be considered for this award, prospective applicants must submit a letter of intent via e-mail by February 2, 2009. For more information, visit [www.hematology.org/education/awards/training_pathway.cfm](http://www.hematology.org/education/awards/training_pathway.cfm).

**ASH Minority Medical Student Award Program (MMSAP) Application Available**

The MMSAP is an eight- to 12-week summer research experience for first- and second-year minority medical students. The benefits of this program include the guidance of two mentors, a $5,000 research stipend ($2,500 at the start and $2,500 at the completion), and a $2,000 allowance for travel to the ASH annual meeting. The deadline to request ASH’s assistance to match an applicant with a host institution and research mentor is February 2, 2009. For more information, please contact Elisa Shea, Awards Manager, at eshea@hematology.org or visit the ASH Web site at [www.hematology.org/education/awards/mmsap.cfm](http://www.hematology.org/education/awards/mmsap.cfm).

**Call for Honorific Award Nominations**

ASH members are invited to submit nominations for the William Dameshek Prize, Henry M. Stratton Medal, E. Donnall Thomas Lecture and Prize, and the Wallace H. Coulter Award for Lifetime Achievement in Hematology for 2009. Nominations must include the nominee’s full name, institution, current bio-sketch, or CV, and a brief paragraph summarizing his or her contributions to hematology. Nominations are due by February 2, 2009, and should be sent by postal mail to the American Society of Hematology, Attn: Elisa Shea, 1900 M Street, NW, Suite 200, Washington, DC 20036, or via e-mail to eshea@hematology.org. More information and nomination forms can be found at [www.hematology.org/education/awards/honorfic.cfm](http://www.hematology.org/education/awards/honorfic.cfm).
Atlantic City, to the colossal 24,000-attendee convention center gathering last month, the ASH meeting has grown over the past half-century to become the essential international meeting focused on hematology research and practice.

This past year’s meeting set a high-water mark in terms of the number of attendees, total number of submitted abstracts (6,362), and breadth of educational offerings. But even more important than the annual meeting’s size, scale, or venue (how can one not enjoy San Francisco?) is the important role it plays in advancing the field of hematology and furthering the goals of the Society. Fundamentally, this year’s 50th anniversary meeting accomplished four important tasks: 1) It provided a venue for the highest-quality educational offerings — an up-to-the-minute summary of the current state of diagnosis and management of hematologic disease; 2) it was a time for intense discussion and scrutiny of new scientific observations; 3) there were plenty of opportunities to discuss and critique therapeutic trials, including the first presentations of numerous novel therapies; 4) physicians and scientists representing broad and diverse disciplines relevant to hematology met for discourse, planned collaborations, and celebrated the past, present, and future of our field.

Learning Hematology: A Lifelong Pursuit

Staying up-to-date in any field of medicine is increasingly challenging, and this is particularly true in our own specialty area. Rapid application of scientific observations to the diagnosis or management of hematologic diseases means that there can be significant changes in the state of the art, even over the course of a single calendar year. This year’s program spanned the diversity of hematology, with 72 different time slots (38 for education topics and 34 for scientific committee sessions), each of a quality and scope to rival any independent continuing medical education program. More intimate discussion opportunities were offered through 40 different limited-access Meet-the-Expert Sessions, or one of six special sessions in which participants had a chance to interact with the “Pioneers in Hematology,” Robert Kyle, MD, known as the “father of myeloma” to many, received the Wallace H. Coulter Award for his intimatediscussion opportunities were offered through education topics and scientific committee sessions, planned collaborations, and celebrated the past, present, and future of our field.

Vetting New Therapies: Improving Treatments for Our Patients

Although we all read a myriad of journal articles and rely upon the data in the (now weekly) editions of Blood, nothing matches the ASH meeting for the spirited discussion and vetting of clinical trial outcomes. The Plenary Session included several high-profile trial results, describing improved outcomes with the addition of rituximab to dexamethasone for treatment of immune thrombocytopenia purpura (Dr. Francesco Zaja), responses induced by a new oral inhibitor of the tyrosine kinase spl (fostamatinib disodium) in patients with lymphoid neoplasms (Dr. Jonathan Friedberg), and results of a multicenter trial (PROTECHT) of nadroparin for prophylaxis of cancer patients against thromboembolic events (Dr. Giancarlo Agnelli). Many questions echoed through the large halls of the Moscone Center: How effective are the JAK2 inhibitors for the myeloproliferative disorders? What is current status of the oral thrombopoietin agonists? Which patients with chronic lymphocytic leukemia need to be treated, and what’s the best way to do it? For every question the meeting sessions answered, two more arose in their place. Nothing beats the animated discussion in the lecture or poster hall after a trial is presented to highlight the trial’s strengths and weaknesses, applicability, and most likely follow-up steps.

Hematology — Past, Present, and Future

For the hematologist, the ASH meeting marks the transition to a new year. The annual meeting is a time to present the fruits of one’s past year’s efforts and plan for next year’s experiments or clinical trials. In addition to the official events, the meeting is a time to meet with friends and colleagues from around the world and to gather for early morning investigator breakfasts or late night drug-development-pipeline dinners. This year’s meeting added a special wrinkle: an anniversary reflection on where we have been as a field and where we are going. Capping the wonderful yearlong 50th Anniversary Review series in Blood, the meeting was filled with historical vignettes, ranging from the development of the Society’s logo to the Nobel Prize of E. Donnall Thomas for bone marrow transplantation. The halls echoed with interviews of ASH presidents from years past, to placards of the myriad of major accomplishments that the field can boast. I am sure I speak for many of my colleagues when I say I was filled with tremendous pride over the accomplishments of our field both for science and for patients. I was impressed by the vigor and strength of our Society, and I look with optimism toward our next 50 years.

Finally, I would like to express my gratitude to the dedicated ASH News Daily authors, Drs. Rafa Abenour, James Foran, Michael McDermott, Bart Scott, and David Steensma.

From top to bottom: 1) Commemorative banners mark the halls of the Moscone Center. 2) Bob Löwenberg, MD, PhD, discusses AML during the Ham-Wasserman Lecture. 3) Attendees listen to Martin Tallman, MD, during a Meet-the-Expert Session. 4) An impromptu discussion ensues at the Late-Breaking Abstracts Session.
ASK THE HEMATOLOGIST

JOSEPH M. CONNORS, MD

Dr. Connors is Clinical Professor and Chair of the Lymphoma Tumor Group at the British Columbia Cancer Agency.

(Notaely: The original question was submitted to the Consult-a-Colleague Program and was adapted for print by Dr. Connors.)

CLINICAL PROBLEM

A 24-year-old woman with stage IVB Hodgkin lymphoma was severely ill with pain, nausea, vomiting, weight loss, and massive retroperitoneal disease. She did not have pulmonary function testing performed at baseline despite being advised to do so. After four cycles of ABVD (therefore eight doses of bleomycin 10 U/m²), she is totally asymptomatic (no cough, no dyspnea), but her carbon monoxide diffusing capacity (DLCO) is now approximately 50 percent of the normal predicted value, with the other pulmonary function tests in the normal range. Her doctor felt the best course of action was to give her another two cycles, including bleomycin, if she is clinically well and then retest her pulmonary function tests. He then asked:

1. Would you consider dose reduction of bleomycin at this time? If so, by how much? Would you consider 20 percent dose reduction going forward unless her pulmonary function tests deteriorate further or she becomes symptomatic?

2. Would you consider stopping chemotherapy after six cycles based on current data? I will certainly repeat her PET/CT scan after six cycles for any evidence of residual disease. I want to save the option of a marrow transplant if she needs it in the future.

MY RESPONSE

The management of this patient nicely demonstrates the major challenge confronting each clinician treating Hodgkin lymphoma: how best to balance maximizing the likelihood of curing the disease while minimizing acute and late toxicity. I will address two of these issues: when to drop bleomycin from the chemotherapy and how to decide how many cycles of chemotherapy are necessary. Neither has been directly addressed by randomized clinical trials, so we must rely on clinical experience and reasonable extrapolation from past observations.

I have found the measurement of carbon monoxide diffusing capacity (DLCO) to be of limited use in monitoring for bleomycin toxicity. Even after correction for hemoglobin level, which is usually necessary in patients receiving chemotherapy, the correlation between DLCO and acute or chronic bleomycin toxicity is poor and unreliable, with very low sensitivity (<20%) and specificity (~80%). Taking a careful history and monitoring the plain chest radiograph are much more reliable. My personal approach is to ask patients specifically about the presence of a persistent cough at the time of each visit and to perform a plain chest radiograph with every other cycle of chemotherapy. I do not routinely perform pulmonary function testing. If either an otherwise unexplained cough or fine streaking in the peripheral lung fields develop, I stop the bleomycin. By using this approach, at least three-fourths of patients complete their planned course of ABVD receiving full doses of bleomycin. Even when bleomycin is dropped, patients have usually received more than half of the full planned total dose.

Following such an approach for the approximately 80 patients we see each year, my colleagues and I in British Columbia have seen severe bleomycin toxicity in less than 1 percent of patients. Of course, one should not lightly drop a potentially important agent from curative chemotherapy, because doing so risks reducing the effectiveness of the treatment. However, limited observations support the hypothesis that omission of bleomycin from the latter courses of chemotherapy for Hodgkin lymphoma has little impact on outcome. Fortunately, randomized trials addressing the necessity of including bleomycin in ABVD are currently being conducted.

How many cycles of chemotherapy are enough? Three bodies of evidence are relevant. First, over the past four decades randomized trials have demonstrated that the total number of cycles of chemotherapy for advanced-stage Hodgkin lymphoma can be reduced to six to eight without compromising effectiveness. Second, other randomized trials have shown that adding further treatment, such as radiation or even high-dose chemotherapy and hematopoietic stem cell transplantation (HDC/HSCT), after a complete response has been obtained does not improve long-term outcome. Finally, functional imaging with positron emission tomography (PET/CT) has been shown to reliably distinguish between residual fibro-necrotic masses and persistent viable Hodgkin lymphoma. Thus, once a complete response has been clearly established, further chemotherapy is unnecessary, provided a minimum of at least six cycles have been delivered, and we now have a tool that allows reliable identification of complete response.

WHAT DO I RECOMMEND FOR THE DESCRIBED PATIENT?

Continue the bleomycin only if, on direct questioning, the patient has no cough and the chest radiograph shows no new fibrotic streaking in the peripheral lung. Have a low threshold for omitting it. Perform a PET/CT scan after six cycles of the ABVD, along with other planned reassessments. If there is no persistent lymphoma, I would stop treatment. If the PET/CT scan is still abnormal, other measures, including: observation, if the PET/CT results are indeterminate; radiation, if disease appears limited in extent; or HDC/HSCT, if persistent disease is documented by biopsy, need to be considered.


ASH NEWS AND REPORTS

ASH Highlights of ASH

New this year – ASH is offering three meetings!

Plan to attend one of the three Highlights of ASH® meetings!

January 30 – 31, 2009
Phoenix, AZ

February 6 – 7, 2009
Miami, FL

May 15 - 16, 2009
São Paulo, Brazil

These exceptional educational opportunities will feature leading hematology experts who will present unbiased analysis of the annual meeting abstracts and sessions, evolving therapies, and the latest treatment options and their clinical applications. The meeting is the only “Highlights” meeting produced by ASH in collaboration with the ASH Program Committee.

The program format is designed to allow practitioners, fellows, academicians, and allied health professionals to discuss some of the most rapidly evolving developments in the field with experts as well as colleagues. The limited attendance, panel discussions, evening reception, and "Breakfast With the Experts," will provide numerous opportunities for attendees to discuss real patient cases with leaders in the field, network with colleagues, and gain knowledge that can change practice strategies. The program has also been approved for AMA PRA Category 1 Credits™ for physicians. For more information, visit www.hematology.org/meetings/highlights.
T H E  H E M A T O L O G I S T  A D V O C A T E

PRACTICE FORUM AND GRASSROOTS NETWORK BREAKFAST

Clockwise from top left: 1) Malik Juweid, MD, addresses the audience, while Philip R. Greipp, MD, looks on. 2) Practice Forum attendees learn about health advocacy opportunities. 3) An audience views the short film “Research Saves Lives” at the ASH Grassroots Network Breakfast. 4) ASH Practice Committee Chair Lawrence Solberg Jr., MD, PhD, speaks with a meeting attendee.

WASHINGTON

Obama-Biden Administration
Transition Moving Forward

As this issue of The Hematologist went to press, the Obama-Biden administration transition team was in the process of making several announcements of new agency heads and senior-ranking federal officials. Of note, former Senator and Majority Leader Tom Daschle (D-SD) was chosen to be Secretary of Health & Human Services, an appointment that many policy-makers predict will greatly help with efforts to overhaul the health-care system. ASH has been sharing concerns and information about priority issues to the Society with the transition team. All ASH members are encouraged to share their ideas about issues the new administration and Congress must address with the Society by contacting grassroots@hematology.org.

Health Reform a Top Priority for New President and Congress

Because health reform was a central component of the Obama campaign and exit polls indicated that health care ranked in the top three most important issues cited by voters, it is expected that health reform legislation will be a priority of the new president and Congress. Even before the 111th Congress was sworn in, the chairmen of the Senate committees with jurisdiction over health reform released details of their proposed plans and House leaders began meeting on the issue. Of note, Democratic leaders are making an effort to include Republicans in the planning process, as they recognize the importance of bipartisanship on this issue, despite the Democrats’ vastly expanded majority. A major point of contention with the Republicans is how lawmakers will find funding for the package.

Senators Propose Legislation Linking Medicare Payment to Hospitals to Quality

Senate Finance Committee leaders are working on bipartisan legislation that would link the level of Medicare payment to hospitals to the quality of medical care rather than the number of services provided. Many lawmakers and health-care analysts have expressed support for the idea of linking Medicare reimbursement to the quality of care provided, also known as “pay for performance,” as a way to improve health-care quality and lower its cost. The senators’ proposal would start the value-based purchasing program in fiscal year 2012, phasing it in over five years with full implementation beginning in fiscal year 2016. Payment levels would gradually increase from 1 percent in fiscal year 2012 to 2 percent by fiscal year 2016. The program would be budget-neutral and any savings would be kept in the hospital payment system in the form of increased payments to other hospitals.

National Sickle Cell Disease Scientific Meeting

The combined 3rd Annual Sickle Cell Disease Research and Educational Symposium & Grant Writing Institute (GWI) and Annual National Sickle Cell Disease Scientific Meeting is scheduled for February 15 - 20, 2009, in Hollywood, FL. For more information about the meeting, visit www.hematology.org/calendar.cfm.

TAKE ACTION

Urge Congress to Support Economic Recovery Package Containing NIH Funding

Because of a shortened congressional schedule due to the elections, Congress was not able to complete work on the fiscal year (FY) 2009 spending bills before the end of the 2008 fiscal year on September 30. Consequently, Congress passed a continuing resolution (CR) that allows the federal government to continue operating at their FY 2008 spending levels through March 6, 2009. By March, it will be up to the new Congress and administration to resolve funding issues and develop a funding measure for the rest of the 2009 fiscal year, in addition to beginning work on funding bills for FY 2010.

Last November, in an effort to provide NIH with additional funding, Senate Majority Leader Harry Reid (D-NV) and Senator Robert Byrd (D-WV) introduced a $100.3 billion economic recovery package that included $1 billion for the National Institutes of Health for FY 2009. This important funding would build upon the $150 million in additional FY 2008 funding for NIH that congressional supporters were able to secure earlier this year and would represent an important step toward reversing NIH’s downward funding trend and setting it on a new course by providing enough funding for an estimated 5,000 additional research grants.

As this issue of The Hematologist was going to press, it was expected that an economic stimulus package would be one of the first pieces of legislation the 111th Congress debates. All ASH members are encouraged to visit the ASH Advocacy Center (www.hematology.org/takeaction) to join ASH’s advocacy efforts to increase NIH funding by contacting your senators and representative and urging them to support increased funding for NIH in the stimulus package.

HAL E. BROXMEYER, PhD

Dr. Broxmeyer is Distinguished Professor, Chairman and Mary Margaret Walther Professor of Microbiology/Immunology, and Professor of Medicine at the Indiana University School of Medicine. He also serves as the Scientific Director of the Walther Oncology Center. He is also the President-Elect of ASH.

An international conference on cord blood (CB) cells, organized by Eliane Gluckman, MD, was held October 16-19, 2008, in Mandelieu, France, celebrating the 20th anniversary of the first CB transplant and 10th anniversary of NETCORD. The first CB transplant was performed in Paris on October 6, 1988, under the pioneering direction of Dr. Gluckman, with advice from me. Donor CB was tested, frozen, and stored in my laboratory as an ongoing proof of principle CB bank. Since then, more than 400,000 CB units have been collected and stored in more than 100 CB banks, and more than 14,000 cord blood transplants have been performed for a wide range of disorders, mainly with unrelated cells.

A highlight of the meeting was the opening ceremony in which many of the pioneers in the field offered brief reminiscences. Speakers included Mr. Farrow, recipient of the first CB transplant, and Drs. Gluckman, Arleen Auerbach, Joanne Kurtzberg, Pablo Rubinato, Marcela Contreras, Peter Wernet, Paolo Rebulla, Jon Van Rood, and John Wagner. I also spoke during the meeting. This elicited fond memories of the international collaborative efforts that culminated in the first and subsequent CB transplants. The meeting covered CB hematopoietic stem cells (HSCs) and other stem cells, banking, and clinical transplantation. A webcast from this conference will soon be available via www.eurocord.org, www.esb.org, and www.eurocord.org, and summaries of selected presentations are provided below.

Dr. Vanderson Rocha noted that 2,000 to 3,000 CB transplants per year have been performed in the last four years, and since 2005 more adults than children have received transplants. The driving forces for these trends are comparable outcomes between unrelated marrow and CB in adults, use of reduced-intensity conditioning (RIC), and double CB transplants. Improved outcome for adult transplants with single CB reflect better donor choice, better definition of indications, modifications in conditioning regimens, and better graft-versus-host disease (GVHD) prophylaxis. Dr. Wagner shared encouraging results with use of two CBs. Dr. Juliet Barker presented updates on RIC/non-myeloablative transplantation and discussed approaches to ensure engraftment, differences in efficacy in specific disease entities, and guidelines for patient selection. Dr. Kurtzberg reported CB as a source of cells for treatment of children with liposomal storage diseases, with correction of damage to non-hematopoietic tissue. Dr. Kurtzberg noted that post-thaw hematopoietic progenitor cell (CFU) analysis correlates best with engraftment and survival, and should be considered a measure of banked CB potency.

New biological insights were presented by Dr. Irwin Bernstein, who noted that Notch signaling in HSC-enriched populations is mediated primarily by Notch 2. Induction of signaling in CB CD34+ cells with the Notch ligand Delta 1 expands CD34+ cell number and provides accelerated engraftment in HSC transplantation. Dr. Elizabeth Shpall described ex vivo expansion of HSCs by co-culture of CB mononuclear cells with bone marrow-derived mesenchymal stem/stromal cells. Using this approach, the first six patients recovered neutrophils and platelets in 14.5 and 30 days, respectively. She also presented preclinical studies in NOD/SCID and NOG mice in which pretreatment of human CB progenitors with fasudil/transferase-VI reversed the homing defect of these cells.

New developments in stem cell biology were reported by Dr. Mariusz Ratajczak, who discussed very small embryonic/epiblast-like stem cells (VSELs). These cells, which are smaller than erythrocytes, are CD133lin CD45+ and express high levels of aldehyde dehydrogenase, SSEA-4, and Oct4. Freshly isolated VSELs only show hematopoietic activity after co-culture on OP-9 stromal cells. Routine CB processing strategies lead to 60 percent loss of VSELs. Dr. Mervin Yoder noted that human circulating endothelial progenitor cells (EPCs) continue to be difficult to isolate and characterize. Populations of circulating progenitors previously reported to contain EPCs are devoid of endothelial differentiation and in vivo vessel formation, and enriched in HSCs. Newer multiparameter fluorescence activated cell sorting (FACS) approaches may define the relatively abundant progenitor cells (previously called EPCs) and extremely rare, true EPCs. Dr. Paul Simmons described development of new biomarkers such as angiotensin-converting enzyme as a characteristic of human CB SCID repopulating cells (HSC). A subpopulation of CB CD34+ cells expressed uPARAP/Endo180/CD280, a cell adhesion molecule with homology to selectins. A proportion of CB CD34+ cells expressed endoglycan, but not podocalyxin, members of the CD34 family.

Dr. Frederik Falkenburg reported that a major difference between adult blood and CB is that adult blood contains both memory and naive T cells, while CB contains only naive cells, presumably because CB has not been exposed to allo-antigens (except perhaps maternal antigens). After mismatched transplant, the memory compartment contributes to GVHD. Dr. Dominique Charron described immune reconstitution as a key prognostic factor in predicting outcome of HSC transplantation. After CB transplantation, reconstitution of the T-cell repertoire, although slightly delayed, is fully complete and diverse, while it remains incomplete and skewed after adult stem cell transplantation. This may explain the lower incidence of GVHD after CB transplantation. In anticipation of the decline in stem cells with age, Dr. Charron proposed collection and cryopreservation of CB leukocytes as a bioresource for restoration of immunity and development of adoptive immunotherapies, particularly in aging populations.

Dr. Tsvee Lapidot discussed physiological interactions governing bone remodeling, HSCs, and evolving niches via neurotransmitter signaling, creating a regulatory “brain-bone-blood” triad to the HSC niche. I presented mechanistic insights into engraftment through an SDF-1/CXCL12-CXCR4 and CD26/dipeptidyl peptidase IV axis, in which SDF-1/CXCL12 control of migration, homing, and survival of HSCs was negatively modulated by CD26. Moreover, CD26 negatively modulates actions of selected colony-stimulating factors (CSFs). Inhibition of CD26 enhances the activities of these CSFs — effects that may allow enhanced engraftment and recovery of hematopoiesis after cytotoxic conditioning and/or transplantation. I also discussed a role for SIRT1, a deacetylase, in regulation of maintenance of stemness and in differentiation of HSCs.

This meeting, along with the 6th International Cord Blood Transplantation conference in Los Angeles, CA, in June (www.cordbloodforum.org), which also celebrated the 20th anniversary of the first CB transplant, was a welcome celebration of the past, a confirmation of how far we have come in the 20 years since the first transplant, and how much more we have yet to learn.
Gfi1: Dual Functions as Oncogene and Inducer of Differentiation


The studies in this manuscript significantly contribute to the solution of two scientific puzzles. They elucidate the mechanism of the (surprisingly) essential role of growth factor independence 1 (Gfi1), which was originally identified as an oncogene, in neutrophil differentiation; and by dissecting the mechanism by which a mutant form of Gfi1 leads to severe congenital neutropenia (SCN), they generate the long sought-after mouse model for this human disease, hopefully leading to further understanding and treatment.

Gfi1 derives its name from its identification as an oncogene by an insertion-al mutagenesis screen. Gfi1 was found to be over-expressed in T-cell lymphomas, suggesting that Gfi1 should be down-regulated during normal hematopoietic differentiation. However, as with many other genes, it’s not that simple. Gfi1 functions as an oncogene in some cell types, while promoting differentiation in others. The discovery that Gfi1 knockout mice have many developmental defects, including severe neutropenia, prompted the identification of mutations in this gene in patients with SCN. Gfi1 is a transcriptional repressor, which binds to its specific target DNA sequences via its 5 zinc finger domains. The SCN-associated Gfi1N382S mutation (the asparagine at position 382 is replaced by a serine) occurs in the 5th zinc finger and completely prevents DNA binding.

Zarebski, et al. validate and further elucidate the mechanism by which wild-type Gfi1 promotes, and mutated Gfi1N382S inhibits, granulocytic differentiation. Previously published data show that Gfi1 is required for normal terminal differentiation of granulocytes. Myeloid cells lacking Gfi1 are blocked at an abnormal stage of differentiation wherein they have features of both neutrophils (Gr1 expression and the ability to mount a respiratory burst) and macrophages (Mac1 expression and phagocytosis), but lack secondary granules and do not adequately respond to bacterial infection. In their manuscript, Zarebski, et al. show that, as expected, enforced expression of exogenous Gfi1 in hematopoietic progenitor cells leads to an increase in neutrophils and a decrease in monocytes, while Gfi1-null progenitors differentiate predominantly into monocytes and a “neutrophil-monocyte mix cell” but no neutrophils. Expression of the mutant Gfi1 (N382S) fails to correct the null phenotype and mimics the null phenotype when overexpressed in wild-type progenitors, demonstrating that it is a dominant negative mutation. Zarebski, et al. identified several potential target genes of Gfi1 that may mediate this effect, but only colony stimulating factor-1 (CSF-1) fulfilled two criteria making it a likely candidate gene in SCN. Its expression is downregulated by Gfi1, and it is de-repressed (i.e., ultimately up-regulated) by Gfi1N382S. To demonstrate the importance of CSF-1 as a target gene, Zarebski, et al. showed that hematopoietic progenitor cells from CSF-1 null mice undergo normal granulocytic differentiation even when induced to express Gfi1N382S.

These results clarify that inhibition of Gfi1’s inhibition (inhibition + inhibition = de-repression) of monocyte differentiation by a mutant dominant negative Gfi1 plays a role in the pathogenesis of SCN and suggest that inhibition of CSF-1 activity in vivo could provide therapeutic benefit. How Gfi1 promotes terminal differentiation of granulocytes beyond the “biphenotypic” fate decision of granulocyte/monocyte precursors is not yet clear. Perhaps identification of additional Gfi1N382S targets in the future will lead to the development of therapies that fully promote functional granulocytes in patients with SCN.

SNPing Away at Risk Factors for Deep-Vein Thrombosis


Both acquired and genetic factors contribute to deep-vein thrombosis (DVT). It is estimated that the contribution of genetic factors is ~60 percent. DVT is a complex multigenic disorder; while several heritable risk factors have been identified, many remain to be determined. The earliest identified inherited abnormalities associated with DVT included several that were relatively uncommon but imparted a substantial increase in risk of DVT (e.g., heterozygosity for protein C, protein S, or antithrombin III deficiency). Subsequently, genetic variants that are more common, but demonstrate more moderate increases in DVT risk, were identified (e.g., factor V Leiden, prothrombin gene mutation). Although the odds ratio associated with these more common variants is smaller, they carry a greater risk to the overall population (e.g., a genetic polymorphism that is associated with a moderate but demonstrably increased risk of DVT). Can we further improve our understanding of the heritable contributions to DVT by identifying genetic variants that are even more common, but difficult to detect because of their subtle phenotype?

Bezemer, et al. have identified several such gene variants by studying single nucleotide polymorphisms (SNPs) in large populations of patients with DVT. SNPs are variants in the genetic code that are relatively common in the population (frequency ≥1%) and occur at a rate of approximately 1 per 1,000 base pairs. Bezemer, et al. screened 19,862 SNPs located in 10,887 genes (e.g., nearly half the genome) using SNPs selected for their potential to affect gene function or expression. They evaluated 3,155 patients with DVT and 5,087 controls in three distinct groups, enabling confirmation of results. The objective was to identify SNPs that occurred at an increased frequency in patients with DVT compared with controls.

Three SNPs that are consistently and significantly associated with DVT were found in genes for antithrombin (SERPINC1), glycoprotein VI (GP6), and a cytochrome P450 family gene (CYP4V2). That variants in antithrombin III, an essential natural anticoagulant, and glycoprotein VI, a platelet receptor required for normal thrombus formation, could contribute to DVT is physiologically plausible. CYP4V2 may be linked to a nearby causal gene, such as F11 (factor XI). SERPINC1, GP6, and CYP4V2 variants were associated with relatively weak odds ratios, ranging from 1.15 for the GP6 variant to 1.29 for the SERPINC1 variant. However, the frequencies of alleles associated with DVT were high, ranging from 0.10 for the SERPINC1 variant to 0.48 for the GP6 variant. When considering such a common allele over an entire population, even these relatively weak odds ratios become important. For example, the population-attributable risk associated with the GP6 variant is similar to that of factor V Leiden.

The studies of Bezemer, et al. demonstrate a means whereby genome-wide association studies can assist in elucidating the many subtle inheritable factors that contribute to DVT. By identifying high-frequency gene variants, such as those in antithrombin and glycoprotein VI, these studies detect small but common DVT risks. These newly identified common risk factors for DVT will need to be verified as thrombophilic in non-northwestern European populations. Once confirmed, results such as those described in this study could be combined with those of other genome-wide association studies and gene-centric genotyping studies to provide the basis for a profiling screen, consisting of a battery of SNPs, to assess DVT risk. Ultimately, the results of such individual profiling could guide clinical decisions in thrombosis management.

Moving Toward Personalized Therapies in Myeloma


Multiple attempts have been made to define clinical and laboratory parameters that have prognostic significance in myeloma. The Durie-Salmon Myeloma Staging System has recently been replaced by the International Staging System, a system that is based on serum b2-microglobulin and serum albumin. Assessment of chromosomal abnormalities, such as deletion of 13q and 17p, can further define adverse subgroups. Most recently, multiple patient prognostic subgroups have been defined using DNA array comparative genomic hybridization and RNA profiling. Importantly, these prognostic signatures are relevant only in a clinical context. For example, del 13 and t(4;14) do not predict for adverse response to bortezomib. Additionally, achievement of complete remission after aggressive therapy with high-dose chemotherapy, stem cell transplant, and thalidomide (Total 2) predicts survival only in the gene expression profile (GEP)-defined high-risk groups, but not the GEP-defined low-risk groups. Ultimately, genetic profiling will allow for selection of those patients most likely to respond to given therapies and allow for individualized therapies.

Decaux and colleagues have used GEP to define a gene signature predictive of outcome in 250 patients uniformly treated with high-dose melphalan and autotransplantation therapy protocols of the Intergroupe Francophone du Myélome (IFM). Specifically, 15 genes were used to calculate a risk score to define high-risk versus low-risk with 47.4 percent versus 90.5 percent survival at three years, respectively.

Importantly, this survival model was validated in a test set of 68 patients and three independent cohorts totaling 853 patients with both newly diagnosed and relapsed myeloma, who were treated with high-dose therapy and autotransplantation, as well as novel therapies including bortezomib. This is critical to assure that its value transcends specific treatments or stages of disease. It is also important, as new signatures are identified, to determine their independent prognostic value versus overlap with other published signatures. Interestingly, when compared with the University of Arkansas School of Medical Sciences' (UAMS) 17-gene prognostic model, this new 15-gene model did not remain an independent significant prognostic variable for UAMS patients treated with total therapy, but did remain independently prognostic for the other two patient cohorts examined. Conversely, the UAMS model did identify high-risk patients in IFM clinical trials. In this study, serum b2-microglobulin >5.5mg/L and/or t(4;14) identified subsets with distinct survival within the 15 gene-defined high- and low-risk groups, stressing the potential added value of conventional genetics supplementing GEP-based models. Moreover, gain of 1q and t(4;14) versus hyperdiploidy were associated with the high- versus low-risk groups. Finally, GEP-defined prognostic models can yield important discoveries in myeloma biology and pathogenesis. For example, in this study overexpression of regulators of chromosomal segmentation was identified in the high-risk group, consistent with dysfunction of mitosis in myeloma leading to chromosomal instability and aneuploidy. These are the hallmarks of aggressive myeloma and suggest potential utility of anti-mitotic therapies.

Therefore, this study is a harbinger of the future in myeloma, and cancer more generally, where genetic profiling will allow for effective personalized and targetted treatments on the one hand and advance understanding of basic disease pathogenesis on the other.


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The Hematologist: ASH News and Reports
Down-Regulation of PML: A Wake-Up Call for Leukemia-Initiating Cells


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Mother Knows Best


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Minor histocompatibility antigens (mHAgs) are formed by polymorphic peptides located in the helical grooves of the major histocompatibility complex (MHC) molecules. These mHAgs are recognized by T-lymphocyte clones and provoke T-cell immune responses, thus playing an important clinical role in mediating both the graft-versus-host disease and graft-versus-leukemia effects of allogeneic hematopoietic stem cell transplantation. Although they can be expressed ubiquitously on tissues throughout the body, several recently discovered mHAgs are expressed selectively on hematopoietic cells. Until now, all of these hematopoietic-specific mHAgs have been identified on MHC class I molecules, with recognition by CDB+ T cells. However, Spaapen and colleagues have discovered the first hematopoietic-restricted mHAg on an MHC class II molecule, with recognition by CD4+ T cells, a discovery that offers tremendous opportunity for developing selective cytotoxic responses in cancer immunotherapy.

The identification of mHAg peptides and the genes encoding them is an important step in deciphering the role of individual mHAgs and their specific T-cell clones. However, discovering these genes has traditionally been a laborious and time-consuming process. Spaapen, et al. have not only identified an mHAg clone from a multiple myeloma patient and performed a genome-wide, two-point linkage analysis to identify a large region of interest on chromosome 16. Then, using a novel genetic strategy termed “zygosity-genotype correlation analysis,” they were able to correlate the zygosity of a given individual with previously identified SNP genotypes on chromosome 16, which allowed them to precisely map the genetic locus of this antigen to a single nucleotide substitution within the third exon of CD19. Further testing, including reactivity with CD19-specific T-cell clones, confirmed that this class II mHAg is encoded by the CD19 allele.

CD19 is a cell surface receptor that is expressed on normal lymphocytes from the earliest stages of pre-B-cell development through terminal differentiation into plasma cells, as well as on B-cell malignancies. Because this class II mHAg is not present on myeloid lineage cells or pluriptotent stem cells, it presents an attractive potential target for directing an mHAg-specific T-cell clone against B-cell malignancies. And functional testing did reveal that these mHAg-specific CD4+ T cells demonstrated anti-tumor effects by directly lysing CD19-positive tumor cells in vitro.

Minor histocompatibility antigens are important potential targets for future immunotherapeutic treatments, and the identification of the polymorphic genes encoding mHAgs is an important step in directing the anti-tumor activity of mHAg-specific T-cell clones. Applying their zygosity-genotype correlation analysis using the complete genome-wide set of HapMap SNPs, the authors were able to precisely map the genetic locus of a wide range of previously identified mHAg clones using the data from only 23 individuals, showing the broad clinical applicability of this novel genetic strategy. The discovery of hematopoietic lineage-restricted responses within the T-cell receptor and the ability to precisely and easily locate the genetic locus of these mHAgs should provide new opportunities to manipulate these responses in a wide range of hematologic diseases.

**Targeting the Lipid Rheostat in Leukemia**


Lipid mediators have long been known to play important roles in diverse cellular processes in both normal and neoplastic cells, particularly regulation of survival and cell death. For example, the lipid second messenger ceramide has been implicated in promoting leukemic cell death, including that triggered by conventional cytotoxic agents, including ara-C and anthracyclines, as well as that induced by novel targeted agents, including histone deacetylase inhibitors. Alterations in lipid signaling pathways have also been invoked to explain certain forms of drug resistance in leukemia (e.g., anthracycline resistance). Such considerations have prompted intense interest in agents that modulate lipid signaling pathways in transformed cells and lower the apoptotic threshold.

Sphingosine-1-phosphate (S1P) is a lipid mediator, derived from the precursor sphingosine and ceramide, which exerts potent anti-apoptotic effects. The sphingosine/ceramide rheostat is regulated in part by the enzyme sphingosine kinase 1 (SphK1), which is up-regulated in several malignant diseases including leukemia. Efforts to target this enzyme, and the pathways it regulates, have been complicated by the fact that most SphK1 inhibitors developed to date are relatively non-specific (i.e., they also target SphK2, an enzyme that exerts certain actions that may oppose those of SphK2). For example, safinogol and dimethylsphingosine (DMS) have been shown to induce leukemic cell death, but as both agents inhibit SphK1 and K2, the mechanism by which these agents act is unclear.

New insights into this question have emerged from a recent study by Paugh and colleagues. Through a broad screening approach, they identified a highly specific, water-soluble inhibitor of SphK1, designated SK1-I, which potently induced apoptosis in human leukemia cell lines and primary blasts, and inhibited the growth of leukemic cells in nude mice, but was relatively sparing to normal hematopoietic cells. Notably, SK1-I diminished expression of S1P, while reciprocally increasing expression of its pro-apototic precursor ceramide. Significantly, SK1-I lethality was sharply attenuated by S1P, arguing that modulating the ceramide/S1P rheostat played a clear functional role in triggering leukemic cell death. The authors conclude that SphK1 activation is important for leukemia cell survival and that targeting this protein warrants attention as a novel anti-leukemic strategy.

The significance of this study is that while targeting signaling pathways implicated in leukemogenesis, such as those related to mutated receptor-tyrosine kinases (e.g., FLT3), have received considerable attention, efforts to disrupt critical lipid signaling survival pathways remain relatively unexplored. However, this situation appears to be changing. For example, several recent studies have suggested a role for the S1P kinase and protein phosphatase 2A (PP2A) activator FTY720, an immunosuppressant, in CML and CLL. Whether specific agents such as SK1-I will offer therapeutic advantages in leukemia compared to agents such as FTY720, which are considerably more pleiotropic in their actions, remains to be determined. Whatever the answer to this question, the development of new and selective inhibitors of critical lipid signaling pathways could potentially add potent new weapons to the expanding therapeutic armamentarium in acute and chronic leukemia.


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Drs. Gilbert and Prchal indicate no relevant conflicts of interest.

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Dr. Grant indicates no relevant conflicts of interest.
that increased blood flow correlates negatively with the fractional saturation of hemoglobin by oxygen rather than with dissolved oxygen tension suggested that the biochemical pathways that regulate blood flow are contained within the red cell itself and led to the hypothesis that oxygen delivery is matched to metabolic demand by allosteric coupling of hemoglobin deoxygenation to stimulation of vasodilation. It has been more than 12 years since Jia, et al. published their seminal paper suggesting a central role for S-nitrosylated hemoglobin (SNO-Hgb) in hypoxic vasodilation, and over the ensuing years, this concept has been extended such that SNO-Hgb is viewed by some as the principal mediator of the essential physiological coupling of increased blood flow to hypoxia. According to this model [see Figure], as red cells become oxygenated in the lungs, a nitric oxide (NO) group is covalently bound to the highly conserved Cys93 residue in the β-chain of hemoglobin. In this high oxygen affinity state [the relaxed, R-state], SNO-Hgb is unreactive, but upon Hgb deoxygenation in the periphery and the consequent transition to the low oxygen affinity state [the tense, T-state], SNO-Hgb can react with red cell thiols [e.g., glutathione (GSH) or anion exchanger-1 (AE-1)] via transnitrosation and thereby transmit a vasodilatory signal (RSNO) out of the red cell. Over the past decade, experimental data have accumulated, suggesting that disturbances in the SNO-Hgb pathway lead to a variety of systemic vascular and pulmonary diseases and contribute to the pathology of diabetes, congestive heart failure, and the untoward consequences of transfusion of stored blood.1-3

Despite the elegance of the paradigm and an abundance of supporting experimental data, several key elements of the SNO-Hgb hypothesis have been challenged, including the allosteric nature of both SNO-Hgb dependent vasodilation and transnitrosation reactions, quantitation of in vivo SNO-Hgb concentration, the presence of physiologic arterial-venous SNO-Hgb gradients, and mechanisms of SNO-Hgb formation.

To investigate the importance of the conserved B(Cys93) specifically the role of SNO-Hgb in regulation of blood flow, Isbell, et al. generated two transgenic mouse strains in which the α and β chains of murine hemoglobin were replaced with their human counterparts, either with or without an alanine substitution at the B(Cys93) residue (HbC93A). Unexpectedly, only minor phenotypic differences were observed between the two strains under either basal physiological or exercise-stress conditions. Moreover, crucial ex vivo experiments indicated that SNO-Hgb was not required for red cells to simulate hypoxic vasodilation. The authors concluded that SNO-Hgb is not an essential physiological regulator, although they recognized the possibility that the humanized mouse model may have masked a pathophysiologic effect of B(Cys93) substitution.

As might be anticipated, these studies generated some lively correspondence from leaders of the SNO-Hgb field suggesting that the conclusions were erroneous because of flaws in experimental design, including the possibility that the presence of even small amounts of prenatal mouse hemoglobin could normalize responses in the HbC93A mice. While the criticisms appeared well reasoned and were thoughtfully presented, Patel and Townes, writing for the authors of the original study, provided equally cogent counter arguments.

Indirectly, all of the participants in the discussion suggested that a human model of B(Cys93) deficiency might resolve the dilemma; however, humans who are homozygous mutant for B(Cys93) have not been reported. Stamler and colleagues argued that the absence of documented homozygous human B(Cys93) mutations suggests that humans cannot survive loss of the nitrosylation site at B(Cys93). Patel and Townes countered with the argument that humans who are homozygous for B(Cys93) mutations have not been identified because they have no clinical phenotype and, therefore, do not come to the attention of physicians. Where does this debate leave us? For my part, I am still unsure about the physiological relevance of SNO-Hgb, but the provocative studies of Isbell, et al. have enlivened further an already lively debate and provided a valuable model for further investigation of the functional significance of the highly conserved B(Cys93).

Stay tuned.


WHAT DO THE RESULTS OF THE NOVEMBER ELECTIONS MEAN FOR ASH?

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S
ince the November elections, ASH Headquarters has fielded numerous calls from members with questions about what the election results may mean for stem cell research, health-care reform, funding for NIH, and other issues important to ASH and its members. These are difficult questions to answer, other than to say that the changes resulting from this election will lead to what promises to be a “most interesting” 111th Congress.

As we all know, November elections swept Senator Barack Obama into the White House and significantly widened the Democratic party’s majorities in both chambers of Congress. The Democrats will command a unified government in Washington for the first time since 1994. In the U.S. Senate, Democrats gained enough seats to get within shouting distance of the magic number 60 (the number of votes needed to bring legislation to the floor), while in the House of Representatives, they captured enough new seats to get close to the margins they had over 14 years ago.

Democrats will be firmly in control, yet will face multiple monumental challenges, including a failing economy, a financial crisis, a collapsing auto industry, and wars in Iraq and Afghanistan. The new president and Congress will need to manage competing priorities while trying to remain unified behind a consensus agenda. Will reform of health care and health policy be the top priority on that agenda? Will federal support for biomedical research be identified as an excellent way to build infrastructure or stimulate the economy? We do not know, since, in this climate, statements of understanding and support for issues important to ASH may not translate into policy as other issues of higher priority receive attention.

Despite this uncertainty, some educated guesses are possible based on President-Elect Obama’s prior statements and long-held positions. One of his first executive orders will be to allow expansion of federally funded embryonic stem cell research. The transition team and congressional leaders have also acknowledged that the State Children’s Health Insurance Program (S-CHIP), which is set to expire April 1, will need to be reauthorized. Fixing physician payment in Medicare is also recognized as a priority, although there continue to be some disputes over financing. It is also expected that one of the first pieces of legislation before the new Congress will be a stimulus package and that Democratic congressional leaders will likely try to include additional funding for the National Institutes of Health in the package.

Comprehensive health reform is considered a priority by President-Elect Obama and Congressional leaders. Health reform was a central aspect of President-Elect Obama’s campaign, and exit polls indicate that health care ranked in the top three most important issues cited by voters. The chairmen of the two Senate committees with jurisdiction over health reform, Senator Ted Kennedy (D-MA), chair of the Senate Health, Education, Labor, and Pensions Committee, and Senator Max Baucus (D-MT), chair of the Senate Finance Committee, have each released details of their proposed plans for comprehensive health reform. Both plans include universal coverage, reducing costs, reforming the delivery system, and increasing the focus on prevention and public health. Both Senators plan to hold multiple public hearings next year and are seeking input from a variety of stakeholders. Legislative activity on health reform in the House is more likely to follow an incremental approach.

What is ASH doing during the transition? The ASH Committee on Government Affairs and staff in the Society’s government relations department have been tracking developments in the Obama-Biden transition team and identifying transition team members who are responsible for reviewing all federal agency activities and reporting back to the president-elect. Not surprisingly, there are several team members with whom ASH has worked closely in the past and who are receptive to our offers to provide input. The Society has updated its “Agenda for Hematology Research,” which identifies top hematology research priorities, and will be sharing it with policymakers. ASH is also developing briefing documents that outline the legislative issues of greatest concern to the society.

In addition to calls from ASH members asking “what changes mean for ASH,” we have received calls from ASH members saying they know new members of Congress from their state delegation or agency officials who are likely to play major roles in the new administration. Such calls are always welcome, as personal relationships can be key to helping ASH advance our agenda. ASH strongly encourages all members to participate in its grassroots advocacy efforts and to share their ideas about issues the new administration and Congress must address. Please e-mail ASH at grassroots@hematology.org. We certainly will remain in close contact with our membership as these events evolve.

ASH CONVENES MDS RESEARCH WORKSHOP

D. GARY GILLILAND, MD, PhD, AND ALAN F. LIST, MD

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Earlier this year, ASH introduced the idea of hosting a research agenda-setting workshop into MDS. Several NIH institutes expressed an interest in working with ASH—individually and together—to further explore the research needs for MDS. As a result, the ASH Workshop on Myelodysplastic Syndromes (MDS) was convened in Washington, DC, on November 20.

We had the privilege of jointly chairing the one-day workshop that assembled a group of more than 20 participants, including representatives from each of the relevant Institutes at NIH. The workshop was patterned after the model used for recent ASH research agenda-setting workshops concerning anemia and the elderly, thrombosis in the elderly, and sickle cell disease, and focused on four areas: identifying questions that need to be answered in this area, determining where gaps exist in the research, pinpointing the windows of opportunity in investigation of this topic, and establishing a list of priorities that may form the basis for a sustainable MDS research program at NIH.

Topics discussed at the workshop focused on improving the understanding of the biology and pathogenesis of MDS, and expert participants examined research priorities in areas that included the role of senescence in the predisposition to MDS, the genetic and epigenetic changes associated with MDS, therapeutic targets and strategies in MDS, the immunobiology of MDS, and the relationship between normal stem cells and MDS stem cells.

A workshop writing committee is developing a summary of the meeting’s deliberations and will produce a report identifying research priorities, recommendations, and next steps. Once finalized, the document will be shared with the ASH membership and NIH.
LIFE AT THE SUBDUCTION ZONE: HEMATOLOGY AND CERTIFICATION OF ELECTRONIC HEALTH RECORDS

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Dr. Solberg is Professor of Medicine in the Department of Hematology/Oncology at the Mayo Clinic in Jacksonville, FL. Dr. Solberg is also Chair of the ASH Committee on Practice.

The subduction zone arises where geological tectonic plates collide—a reasonable metaphor for the collision of health information technology (HIT), finances, and medical practice. The adoption of electronic health records (EHRs) in general medical practice has been slow but is likely to accelerate in part due to its potential to improve patient safety and to promote evidence-based medicine. A recent survey of 5,000 physicians randomly selected from an AMA physician database by DesRoches, et al. (N Engl J Med 2008;359:30-60) revealed that only 4 percent of the respondents have access to what an expert panel determined would be a fully functional electronic-based system, and only 13 percent had access to even a basic system. Why has there been such a slow roll-out despite the near universal acceptance by experts in quality improvement that HIT improves quality of care? Perhaps the answer lies in inherent conflicts at the subduction zone. For the HIT experts whose world revolves around large scale health-care systems and their economics, the critical issues are the concepts of “functionality,” “interoperability,” “security,” “reliability,” “financial incentives for adoption,” “harmonization of standards,” and “measuring performance and errors.” The community practicing physician has other concerns related to more direct personal engagement (i.e., cost of acquisition and maintenance, steepness of learning curve, inherent conflicts at the subduction zone). For the physician, the HIT story has to carefully weigh a different set of financial implications, medication management incentives, administrative gains and costs, and oncology-specific features. “The Oncology Electronic Health Record Field Guide” published by the American Society of Clinical Oncology is a good resource to guide practices in selecting oncology EHRs. While this resource is helpful for the limited purpose of identifying a system that can handle oncology information, you may want to purchase an electronic system that will not have to be upgraded or replaced if you want it to interact with systems outside of your office.

Since many physicians have concerns about the viability of an electronic record, it is not surprising that an accrediting agency has emerged that is designed to validate the utility of various systems. That agency is the Certification Commission for Healthcare Information Technology (CCHIT). CCHIT is an independent, non-profit, federally authorized certification body for EHR products. Having a certifying authority, free of conflict of interest, to help assure hematologists that the EHR system they use or purchase has necessary functionality, security, reliability, and interoperability is a commendable goal. Additional impetus for CCHIT certification comes from national HIT policies. In 2006, the Department of Health and Human Services began to spur universal adoption of EHRs by creating a safe harbor for entities such as hospitals to assist small practices in acquiring systems. The safe harbor allows participants to cooperate without violating federal anti-kickback statutes or the Physician Self-Referral Law (Stark Law). A requirement of this safe harbor exception was that any such software had to be certified as being interoperable by a certifying body, such as CCHIT. On June 10, 2008, the HHS secretary announced 12 communities that have been selected to advance the use of EHRs in the first-ever national demonstration project estimated to affect 3.6 million patients. Embedded in this pilot is an offer of bonus payments to physician practices that adopt a certified EHR and use it to measure and improve quality.

Does this mean that hematologist/oncologists should buy a CCHIT-certified product? No. Most hematology-oncology applications, including some of the largest and most widely used, have not been submitted for certification and, as CCHIT declares on its Web site, “Purchasers should not interpret a lack of CCHIT certification as being of significance for specialties and domains not yet addressed by CCHIT criteria.” CCHIT has not yet established an oncology-specific work group, even in its 2009 activities, but in time is expected to do so. It is prudent, however, for hematologists engaged in evaluating or purchasing EHRs to be familiar with this evolving certification story.
The Meaning and Impact of the ASH Scholar Award

D. GARY GILLILAND, MD, PhD

Dr. Gilliland is a Professor of Medicine at Harvard Medical School and an Investigator at the Howard Hughes Medical Institute. He is also an ASH councilor.

2009 marks the 25th anniversary of the ASH Scholar Award program. Since 1985, the American Society of Hematology has supported many great researchers through this program. The ASH Scholar Awards are designed to support hematologists who have chosen a career in research by providing partial salary or other support during that critical period required for completion of training and achievement of status as an independent investigator. In recognition of this anniversary, The Hematologist will be highlighting past and present award winners throughout 2009. We are starting with Dr. D. Gary Gilliland, who was a recipient in 1991.

The ASH Scholar Award was a life-changing event for me. Were it not for this award, I almost certainly would have done something else with my life, rather than pursuing an academic career focused on developing better treatments for hematologic malignancies based on insights into the genetic basis of disease.

I had only dared in my wildest imaginings to dream that I might be a productive physician-scientist … and no one, including me, knew whether I had such potential. The ASH Scholar Award gave me the confidence that I might actually be able to make it work.

I received my PhD in microbiology in 1980 from the University of California, Los Angeles (UCLA) in John Collier’s lab, where we attempted to redirect the potent diphtheria and ricin toxins to cancer cells using monoclonal antibodies. Based on this experience, I became interested in cancer biology and cancer therapy and elected to pursue medical training to further inform my understanding of cancer. I trained in a wonderful clinical environment at the University of California, San Francisco (UCSF) as a medical student, and subsequently at the Brigham and Women’s Hospital (BWH) as a resident and chief resident. I completed my fellowship training at the BWH in hematology and at the Dana-Farber Cancer Institute in medical oncology. But, when I completed that training, I still did not know whether I would have what it takes to make significant contributions to our understanding of the molecular genetics of hematologic malignancies and to try to translate those insights into better therapies.

I was very fortunate to be mentored and supported by Dr. Frank Bunn as a hematology fellow. In his laboratory, he gave me broad breadth for investigation and fostered and nurtured my interest in hematologic malignancies. He is the consummate physician-scientist and continues as a role model to this day. I have no way of repaying the debt that I owe to Dr. Bunn, except to thank him for selfless support of my career development. It was Dr. Bunn who suggested that I apply for the ASH Scholar Award to study myelodysplastic syndrome — the start of a wonderful journey in understanding molecular pathogenesis of myeloid malignancies.

At the time I applied for the ASH Scholar Award, in 1990, I had very little preliminary data and no track record of publication apart from graduate school publications while at UCLA. I believe that having a mentor like Frank Bunn made all the difference in my application, and ultimately in my being selected for the ASH Scholar Award. And receiving the award helped convince me that I should pursue this challenging career path. It was an honor like no other.

It has been a very exciting era of disease allele discovery and development of targeted therapy in myeloid malignancies, and it has been a thrill for me from a scientific, clinical, and personal perspective to see the remarkable advances that we have made as a community of investigators since 1990. I am currently a professor of medicine at Harvard Medical School with a lab full of graduate students and postdoctoral fellows who (thankfully) are much smarter than I am, so my scientific and clinical life remains exciting and invigorated. And the torch gets passed on. My trainees benefit from my understanding from Frank Bunn of how important it is to be generous and provide support early in career development. Many of them, in turn, have been recipients of the ASH Scholar Award in support of their career development and have gone on to their own independent academic labs and careers.

I view the ASH Scholar Award in the way we think of the Notch pathway in development as a cell fate determinant. The ASH Scholar Award was my fate determinant. It persuaded me to pursue this academic career path. The award program has continued to support development of promising young investigators and ensures the future for our efforts to develop cures for leukemias and other cancers.

“I had only dared in my wildest imaginings to dream that I might be a productive physician-scientist … and no one, including me, knew whether I had such potential. The ASH Scholar Award gave me the confidence that I might actually be able to make it work.”

GENERAL TIMELINE TO APPLY FOR THE ASH SCHOLAR AWARD

Letter of Intent due: Early May 2009

Application available for those who successfully submit a letter of intent by the deadline: June 2009

Full proposal due: Late August 2009

The Hematologist: ASH NEWS AND REPORTS 15
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.

In December, ASH launched three new areas of the ASH Web site that provide easy access to an array of various resources and tools for the Society’s main constituencies.

The **RESEARCH** page was designed with the scientist in mind. It includes quick links to information of most interest to researchers, including:

- Research news
- Grants and awards (from ASH, the federal government, and advocacy groups)
- ASH research agenda setting workshops
- The ASH Advocacy Center
- Blood
- Meetings of interest

The **PRACTICE** page was designed with the clinician in mind. It includes the following:

- Practice news
- Resources for treating patients
- The ASH Advocacy Center
- CME opportunities (meetings and publications)
- Maintenance-of-Certification resources
- Quality care information
- Reimbursement information

The new **TRAINING** page was created for both the trainee and the educator. It includes the following:

- Resources for trainees
- Career planning
- Grants and funding
- Finding a mentor
- Preparing a journal club presentation
- Resources for training program directors
- ASH training awards
- Curricular resources

**BLOOD: THE VITAL CONNECTION** ([www.bloodthevitalconnection.org](http://www.bloodthevitalconnection.org)) is a site of the American Society of Hematology that provides hematologist-approved information on various blood disorders and issues. The site aims to raise awareness about blood disorders and is targeted at patients and medical students. In addition to providing information about common blood conditions, risk factors, preventive measures, and treatment options, it also includes colorful and easy-to-understand blood disease animations on:

- Blood and its components (red cells, white cells, platelets, and plasma)
- Anemia (including sickle cell disease and hereditary spherocytosis)
- Bleeding
- Clotting (deep-vein thrombosis)
- Cancers

Three short films are featured on the site that:

- Explain what hematology is and what hematologists do
- Highlight the importance of biomedical research funding
- Inspire medical students to consider a career in hematology

Visitors can also find information about:

- How to communicate effectively with their doctors
- Navigating clinical trials
- Major medical advances in hematology

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**MARK YOUR CALENDAR**

**JANUARY**

30 – 31
Highlights of ASH
Phoenix, AZ  [www.hematology.org/meetings/highlights](http://www.hematology.org/meetings/highlights)

**FEBRUARY**

2
Deadline to Nominate a Colleague for an Honorific Award
Washington, DC  [www.hematology.org](http://www.hematology.org)

2
Letter-of-Intent Deadline for the ASH Alternative Training Pathway Grant
Washington, DC  [www.hematology.org](http://www.hematology.org)

5 – 6
Active Communications International’s National Conference on Successful Strategies for Genetic and Molecular Diagnostic Testing
Orlando, FL  [www.hematology.org/calendar.cfm](http://www.hematology.org/calendar.cfm)

6 – 7
Highlights of ASH
Miami, FL  [www.hematology.org/meetings/highlights](http://www.hematology.org/meetings/highlights)

14 – 17
Scripps Cancer Center’s 29th Annual Clinical Hematology and Oncology Conference
San Diego, CA  [www.scripps.org/clinicalhemoncCME](http://www.scripps.org/clinicalhemoncCME)

15 – 20
National Sickle Cell Disease Scientific Meeting
Hollywood, FL  [www.hematology.org/calendar.cfm](http://www.hematology.org/calendar.cfm)

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**ASH Members Awarded Membership to the Institute of Medicine of the National Academies**

**Elaine S. Jaffe, MD**
Chief, Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

**Olufunmilayo F. Olopade, MB**
Walter L. Palmer Distinguished Service Professor in Medicine and Human Genetics and Director, Center for Clinical Cancer Genetics, University of Chicago, Chicago, IL

**Charles L. Sawyers, MD**
Investigator, Howard Hughes Medical Institute; and Chair, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY