ASH TO RAISE AWARENESS OF BLOOD DISEASES WITH EDUCATIONAL CAMPAIGN AND DOCUMENTARY FILM TO PREMIERE ON DISCOVERY HEALTH

KENNETH KAUSHANSKY, MD
Dr. Kaushansky is president of ASH.

In 2007, ASH conducted a national survey to determine the public’s level of awareness of blood disorders and hematology. Survey results revealed that Americans have low awareness of hematology, blood diseases, and health risks. When asked to name a common blood condition, only a small minority were able to identify common conditions like anemia, blood clotting, hemophilia, and deep-vein thrombosis, and only one in five people could define hematology. These results underscore the public’s need for easy-to-understand resources on blood disorders and guidance on the role of hematologists in the health-care team.

To address this need and help people understand just how important blood is to their overall health, ASH has launched Blood: The Vital Connection, a public education campaign that provides credible information on many different blood diseases as well as risk factors, prevention strategies, and treatment options. An exciting component of this campaign is a documentary on hematology produced by award-winning filmmaker Joseph Lovett and supported by ASH, NHLBI, NIDDK, NCI, and NCRR. “Blood Detectives” shows the vital role hematologists play in treating complex medical conditions and in conducting basic research that leads to life-saving treatments. Mark your calendar to catch the film’s premiere on the Discovery Health cable network on December 19 at 7:00 p.m. ET/PT, and look for more details at this year’s annual meeting.

As we all know, millions of Americans are affected by blood disorders each day, and more and more are using the Internet as their primary source of information. We encourage you to refer your patients to the Blood: The Vital Connection Web site at www.bloodthevitalconnection.org for reliable information on anemia, bleeding and clotting disorders, blood cancers, and women’s blood-related health issues. The site also provides information about participating in clinical trials and a “Find a Hematologist” tool, which allows patients or their health care providers to search for a hematologist by location or specialty. (If you are an ASH member and wish to have your name added to this searchable database, contact lstark@hematology.org.)

We need your help getting the word out about the important resources at www.bloodthevitalconnection.org. Please join us in raising awareness about blood diseases and the important work hematologists do by sharing this site with your patients, family, and friends.

The site also includes valuable career resources for medical students, and, over the coming weeks, we plan to add blood disease animations, short videos, and more details about the documentary.

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BLOOD MOVES TO WEEKLY PUBLICATION IN 2009

Blood, the journal of the American Society of Hematology (ASH), will change from a semimonthly to weekly schedule effective with the January 1, 2009, issue.

Blood publishes original articles describing novel and precedent-setting laboratory, translational, and clinical investigations in the field of hematology and related areas of research. Editorial content also includes Inside Blood, succinct summaries of cutting-edge research; focused topical reviews; and clinically focused “How I Treat” articles from respected leaders in clinical hematology worldwide.

Most importantly, the shift of the journal to weekly publication will get research to members more quickly. Chair of Journals Committee Joel Anne Chasis, MD, said that the schedule change will provide several additional benefits for members and subscribers, including increased portability of the print journal due to more convenient size, greater visibility for ongoing and new content features, enhanced content, and distribution of a weekly e-Table of Contents.

Blood’s Editor-in-Chief Cynthia Dunbar, MD, notes that the journal will increase the solicitation and publication of Review articles, Perspectives, and “How I Treat” articles to ensure sufficient material of interest to the Blood readership. The number of primary research articles will remain stable. The entire table of contents will be reorganized as of the January 1 issue to better reflect the balance of articles being published and to help readers find articles of interest more easily.

With a weekly publication schedule, an almost-immediate online prepublication, and a seven-week average time from acceptance to print publication, Blood will deliver high quality content that leads the world in reporting basic and clinically relevant hematology research.

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4 MAINTENANCE OF CERTIFICATION – Dr. Charles Abrams outlines the certification process.

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See You in San Francisco, December 2008
developed in the 1960s, but today, after new combinations of drugs were developed in the 1970s. A diagnosis of acute lymphoblastic leukemia was fatal for every child who received a death sentence, and have been pioneers in the fields of bone marrow transplantation and gene therapy.

By the NIH’s own estimates, the overall five-year survival rate for childhood cancers rose to nearly 80 percent during the 1990s from under 60 percent in the 1970s. A diagnosis of acute lymphoblastic leukemia was fatal for every child who developed it in the 1960s, but today, after new combinations of drugs were developed by hematology researchers, and aggressive treatment of the brain and spinal fluid were incorporated, approximately 80 percent of children with the disease are cured.

NIH also notes that the emergence of new, more precise ways to treat cancer, such as drugs that target abnormal proteins in cancer cells, have contributed to a dramatic increase in the average life expectancy for Americans. Again, hematologists have been at the forefront of these discoveries.

APL was once described as the most malignant form of acute leukemia. Today, the treatment of APL has become a model for treating cancer with targeted therapy. In combination with chemotherapy, targeted treatment has significantly improved survival in patients with APL and raised remission rates to about 85 percent.

In the 1950s, the only treatment for CML was radiation of the spleen, granting patients about 30 months of survival. Analysis of the CML-specific chromosomal translocation allowed the development of imatinib, a gene-targeting drug that is the paradigm for a new generation of “smart” drugs that allow disease-specific therapy. Using this nontoxic oral drug, more than 75 percent of patients diagnosed with CML achieve a durable, complete cytogenetic remission.

I have consistently fought for increases to NIH annual budget, and will continue to do so to ensure that hematologists and researchers around the nation continue to have the resources necessary to lead in new fields of biomedical investigation and translate new scientific discoveries into improved diagnostic, therapeutic, and preventive strategies.

Again, I salute the American Society of Hematology for a magnificent first 50 years. With continued NIH funding, I am confident that hematologists will have even greater successes in treating and eliminating blood diseases over the next 50 years.

FURTHER READING
To read previous congratulations from Senator Arlen Specter and Representatives Michael Castle and Jesse Jackson Jr., head to www.hematology.org/about/50thanniversary.

Hematology and Glycobiology

To the Editor:

Earlier this year, the NHLBI convened a working group workshop on the roles of glycans in hemostasis, inflammation, and vascular biology. The Working Group Report has just been published in Glycobiology (2008; 18(10):747-8; www.ncbi.nlm.nih.gov/pubmed/18621991). Given the extensive scientific overlaps between the fields of hematology and glycobiology, this report could be of interest to many of your readers. The hope is that it will not only potentially result in new NHLBI funding initiatives, but also enhance collaborations between hematologists and glycobiologists.

Best wishes,

Ajit Varki, University of California, San Diego [Chair]
Linda Baum, University of California, Los Angeles [Co-Chair]
Susan Bellis, University of Alabama, Birmingham [Co-Chair]
Rita Sarkar, National Heart, Lung, and Blood Institute [Convener]

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.”

Letters should be sent to: Karen Learner, Managing Editor
The Hematologist: ASH News and Reports
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ASH Leadership Election Results

Vice President
J. Evan Sadler, MD, PhD

Dr. Sadler, from the Washington University School of Medicine in St. Louis, MO, was elected vice president of ASH and will serve as vice president in 2009, becoming president-elect in 2010 and then president in 2011.

Secretary
Charles S. Abrams, MD

Dr. Abrams, from the University of Pennsylvania, School of Medicine, will serve a four-year term.

Councillor
David A. Williams, MD

Dr. Williams, from Children's Hospital Boston, will serve a four-year term.

Councillor
Elaine A. Muchmore, MD

Dr. Muchmore, from the VA San Diego Health Care System, will serve a two-year term.

ASH Appoints New Editor-in-Chief of The Hematologist

PETER D. EMANUEL, MD
Dr. Emanuel has served as Editor-in-Chief of The Hematologist from 2005 - 2008.

The Hematologist was inaugurated in January 2004 under the energetic leadership of Dr. Andrew Schafer as the founding editor-in-chief. It began as a quarterly publication with the Diffusion articles as its foundation. When Dr. Schafer was elected ASH vice president at the 2004 annual meeting, he had to relinquish his role as founding editor. I was selected as the next editor-in-chief and took over with Volume 2, Issue 2. My term as editor will come to a more routine end this December. On behalf of the entire editorial staff, I am proud of our accomplishments. Some aspects of The Hematologist have changed, while others have remained the same. The Diffusion articles, as written by our exemplary contributing editors, remain the firm foundation of this publication. A couple of these editors have been with The Hematologist from the start, Joe Prchal and Roy Silverstein. The Hematologist is now published every other month, and has cemented itself as a mainstay in the fabric of ASH. I feel quite privileged to have been part of the start of a new tradition.

At the recommendation of the Editor Search Committee of ASH, Roy L. Silverstein, MD, has been named the new editor-in-chief of The Hematologist and will take over with Volume 6, Issue 1. His term will extend through 2011. Dr. Silverstein is chairman of the Department of Cell Biology and vice chair for Translational Research in the Lerner Research Institute of Cleveland Clinic Foundation as well as professor of molecular medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Dr. Silverstein holds the Jan Bleeksma Endowed Chair in Vascular Biology at Cleveland Clinic. His clinical interests are thrombosis and bleeding disorders. He currently directs an NHLBI-funded Specialized Center of Clinically Oriented Research (SCCOR) in thrombosis and is funded by four different grant programs from NHLBI.

Dr. Silverstein served as a contributing editor for The Hematologist from 2004-2007 and has been “shadowing” me over much of 2008. He also was on the editorial board of Blood from 1997-2002. His other editorial board experience includes an advisory editor position with the Journal of Experimental Medicine from 2004-2008, consulting editor of the Journal of Clinical Investigation from 2003-2010, and member of the Editorial Advisory Board of Current Immunology Reviews. His other responsibilities within ASH have been numerous, including serving as chair of the Government Affairs Committee from 2005-2008.

Dr. Silverstein stated that he is “committed to the concept of data-driven decision making” and believes “that the driving force of the publication should remain the Diffusion pieces.” Given that Dr. Silverstein has been involved with The Hematologist from the start, I feel confident that I’m leaving the publication in good hands.
As a hematologist, and the recently elected Chair of the American Board of Internal Medicine (ABIM) Hematology Board, I thought I would explain what is required to remain board certified in our subspecialty. Although maintaining ABIM certification is not mandatory, it is an important marker of standard training and professional and clinical competence. In fact, many hospitals not only require initial certification in your practicing subspecialty, but also require ongoing participation in the maintenance of certification (MOC) program in order to maintain admitting privileges.

Personally, I’ve been through recertification once before — renewing my certification in hematology in 2005. Although I am currently certified through 2015, I have decided to begin to fulfill my MOC requirements now, rather than wait until one or two years before my certification expires. This is because I have seen some of my colleagues rushing to fulfill all of the requirements in that final year, or perhaps waiting until the last minute to schedule the exam, only to find that the examination dates do not match their schedules. Even though the requirements of MOC can be completed within one year, it is certainly a tougher and more stressful way to complete the process. By enrolling now, I plan to complete all of the requirements over the course of the next seven years without feeling rushed.

You can take the recertifying examination any time beginning in the sixth year of certification or recertification. In my situation, this will be some time after 2011. While 86 percent of the hematologists who took the MOC exam over the past five years passed on their first attempt, some physicians did need to retake the examination in order to ultimately pass. It is reassuring to know that 96 percent of those who had at least three opportunities to take an MOC exam ultimately passed. These pass rates are another reason to take the exam a few years before your certificate expires. Taking the exam early allows you the time to retake the test, if necessary, without endangering your status of uninterrupted certification in hematology.

In addition to passing the exam, recertification requires taking several open-book ABIM self-assessment tests directly related to the practice of hematology, including hematology knowledge modules. Alternatively, ASH members can complete the ASH-SAP/MOC product, which has been designated by ABIM for 70 points of MOC credit. It is worth noting that hematologists can meet all of the MOC requirements through the ABIM and ASH program without paying any additional fees.

Finally, the MOC process requires at least one Practice Improvement Module (PIM). PIMs are Web-based tools, worth 20 to 40 points each, that enable you to examine your practice and identify ways in which it can be improved. Available ABIM PIMs include Communication with Referring Physicians, Communication with Patients, and Osteoporosis (for physicians prescribing chronic steroid therapy). In addition, ASH offers PIMs related to the diagnosis and treatment of myelodysplastic syndrome, multiple myeloma, and idiopathic thrombocytopenic purpura that also fulfill MOC point requirements.

Once you have enrolled and paid the one-time MOC fee, you can meet all of the ABIM program requirements, including your ABIM modules and one exam, without additional charges from ABIM. The self-assessment points can be applied to more than one certification, and they last for 10 years. So, if you are dual-certified in hematology and medical oncology, your self-assessment points can be applied toward both certifications. You will, however, still need to take both exams. In addition, physicians participating in MOC can earn Category 1 CME credits for completing medical knowledge modules and PIMs, and for preparing for the exam.

The best source for information about MOC, including registration periods and exam dates, is the ABIM Web site, www.abim.org. To enroll in MOC, visit www.abim.org and select “Physician Login” at the top of the page.

HOW MANY POINTS DO YOU NEED?

You need to earn 100 points — with a minimum of 20 points in medical knowledge, and 20 points in practice performance. The additional 60 points can be from either or both categories. You do not need to complete the 100-point requirement before you take the recertifying exam, but you do need all of the points before your certification is set to expire.

The ASH Subcommittee on Quality has developed a pocket-sized, laminated Quick Reference summarizing key points of “Von Willebrand Disease (VWD): Evidence-Based Diagnosis and Management Guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report [USA].”

This evidence-based tool helps guide the diagnosis, laboratory evaluation, and management of VWD. Principles of laboratory testing and interpretation are summarized. Treatment recommendations cover general management and are tailored for major or minor bleeding episodes. Approaches to prophylaxis for surgery are also presented for patients at risk for minor or major bleeding. Questions to help assess the risk of bleeding in patients are also included in the pocket guide.

This Quick Reference supports ASH’s efforts to provide clinicians with high-quality, easily accessible resources as they see patients. The Quick Reference is also available online at www.hematology.org. The Quick Reference on VWD will be distributed in the annual meeting registration bags and will also be available at the Practice Forum (see page 6) and the ASH booth (#637) in the exhibit hall. After the annual meeting, the VWD Quick Reference will be on the ASH Web site.

ASH is pleased to collaborate with NHLBI to broadly disseminate this information to hematologists.
MicroRNAs in Acute Myeloid Leukemia

MICHAEL D. RADMACHER, PHD, CLARA D. BLOOMFIELD, MD, AND GUIDO MARCUCCI, MD

Dr. Radmacher is Senior Clinical Biostatistician at The Ohio State University Medical Center. Dr. Bloomfield is Professor at The Ohio State University, Senior Advisor at The Ohio State University Comprehensive Cancer Center, and an OSU Cancer Scholar. Dr. Marcucci is Associate Professor of Medicine at The Ohio State University.

Introduction

Acute myeloid leukemia (AML) is a malignant disease characterized by proliferation with maturation arrest of myeloid blasts in bone marrow and blood.1 Mounting evidence supports the notion that this disease is constituted by a group of distinct entities that are being recognized and categorized based on clinical, cytogenetic, and molecular features.2 Despite recent progress in our understanding of the leukemogenic mechanisms of AML and the use of intensive therapeutic approaches, the prognosis for these patients remains suboptimal, underscoring the critical need for novel diagnostic, risk-stratification, and therapeutic approaches. To achieve this goal it is imperative to dissect the biologic differences that determine the outcome of distinct clinical, cytogenetic, and molecular subsets of AML. The expectation is that the understanding of such differences will allow implementation of “personalized” molecularly targeted therapeutic programs according to the genetic make-up of the disease for each individual patient.

Recent structural and numerical chromosomal aberrations have been identified as one of the most important prognostic factors in AML.3 Approximately half of AML patients, however, present with a normal karyotype. Cytogenetically normal (CN) patients are typically classified in an intermediate-risk prognostic category.

Subsequent studies showed that microRNA signatures are capable of distinguishing not only between different leukemias but also between cytogenetic subtypes of AML.

Two microRNA expression profiling studies indicate that t(8;21), inv(16), and t(15;17) have unique microRNA expression signatures capable of distinguishing them from other subtypes of AML.4,14 As is common with expression profiling studies, there is not a perfect concordance between the signatures derived from the two studies, but there are some commonalities, including the up-regulation of microRNAs in genes transcribed from genes at the 14q32 region in t(15;17) and the down-regulation of miR-133a in t(8;21). Patterns of microRNA expression associated with t(1q22), trisomy 8, and CN-AML have also been reported.13

MicroRNA expression associated with morphological and molecular characteristics

Aberrant microRNA expression patterns associated with morphological and molecular characteristics have been identified in AML, some within particular cytogenetic subtypes.

Up-regulation of miR-155 in patients with an internal tandem duplication (ITD) of the FLT3 gene has been independently reported by two groups.13,16 This observation fits well with the reported high-blast proliferation and poor survival duration in FLT3-ITD+ AML, since it has also recently been shown using a mouse model that miR-155 can drive granulocytic/myeloid expansion and result in pathological features characteristic of myeloid neoplasia.12

Mutations of the NPM1 gene also have a characteristic microRNA expression signature, including the up-regulation of miR-10a, -10b, and -196a.15 Interestingly, these microRNAs reside in the genomic cluster of the homologous HOX genes, and up-regulation of HOX genes is a prominent feature of myeloid neoplasia.12

In CN-AML, with high risk molecular characteristics (i.e., FLT3-ITD+ or NPM1 wild-type, or both), we have recently identified a microRNA expression signature associated with event-free survival and validated its prognostic significance.15 The prominent feature of this signature was increased expression of miR-181a and -181b associated with decreased risk of an event. One of the particular features of this report was the integration of the genetic and microRNA expression profile with gene expression in the attempt to identify genes that are micro-RNA-regulated and contribute to leukemogenesis in high molecular risk CN-AML.

Expression levels of 452 genes significantly correlated with the prognostic microRNA signature. We showed that genes involved in mechanisms of innate immunity,25 including genes encoding Toll-like receptors (TLR2, TLR4, TLR8), interleukin-18, and its regulators (IL1B, CARD8, CARD12 [NLRC4], CARD15 [NOD2], ASC, [PYCARD], CASP1), were overly represented in the microRNA-dependent gene expression signature. Some of these genes have already been reported to sustain growth and proliferation of AML blasts and may represent therapeutic targets.26,28

Conclusion

Altogether, the current studies suggest that microRNA expression is associated with cytogenetics, molecular and morphological alterations, and clinical outcomes in AML. We are only beginning to unravel the functional relationships that exist between microRNAs and these other factors, but there is great opportunity for gaining biological insights by studying altered microRNA expression in AML. Furthermore, it will be interesting to see if altered microRNA expression can serve as a valuable prognostic marker that adds information beyond the current collection of cytogenetic and molecular abnormalities.

References

ASH PRACTICE FORUM TO FOCUS ON THE UNEXPECTED RESULTS HEMATOLOGISTS ENCOUNTER

LAWRENCE A. SOLBERG JR., PHD, MD
Dr. Solberg is Chair of the ASH Committee on Practice.

For those hematologists primarily engaged in practice, the Practice Forum on Saturday, December 6, is where you’ll want to be. The Practice Forum, “The Patient, The Hematologist, and the Unexpected,” will be from 6:00 to 7:30 p.m. followed by a special reception for practitioners from 7:30 to 8:30 p.m. Among other benefits, the forum and reception are a great opportunity for trainees who are entering practice to meet senior members of well-established hematology practices and members of the practice committee.

With changes in health information technology, patient demographics, the quality industry, and even the forthcoming change in the administration, ASH remains committed to represent the interests of patients and practitioners in this complex environment, and the Practice Forum and reception are a great place for one to participate in this dialogue.

The focus of the forum this year is on two areas of unexpected results encountered commonly enough to raise the interest of the community of practitioners who are members of ASH. Dr. Philip Greipp will discuss some selected dilemmas of incidental findings and monoclonal proteins. Dr. Malik Juweid will discuss instances in which a follow-up PET scan for lymphoma displays an abnormality inaccessible to simple biopsy yet the patient has a normal CT scan. In addition, ASH will provide a brief legislative update and tips on what to expect from the new U.S. president and Congress.

Mark Your Calendar: ASH Practice Forum
6:00 p.m., Saturday, December 6
San Francisco Marriott, Yerba Buena, Salons 4-6

SNAPSHOT

Below, photos from the sixth annual ASH State-of-the-Art Symposium (SAS), held in Chicago on September 12-13. If you missed the 2008 SAS, you can purchase both the Program Book and DVD of the meeting through the ASH Store at https://store.hematology.org.

FY 2009 Funding for NIH Held at FY 2008 Level

At this issue of The Hematologist went to press, congressional leaders had just finalized a stopgap spending bill to keep federal programs and agencies funded and in operation through the first part of fiscal year (FY) 2009. With FY 2009 having begun on October 1 and the annual appropriations bills to fund federal agencies still not close to being approved and finalized, Congress passed a continuing resolution (CR) to continue funding the federal government and various federal programs, including the National Institutes of Health (NIH), at FY 2008 levels through March 6, 2009 — nearly halfway through the 2009 fiscal year. President Bush signed the CR into law on September 30.

House and Senate Appropriations Subcommittees approved spending bills earlier this summer with slight increases for NIH above the current year’s funding level and President Bush’s FY 2009 budget. However, because of a shortened congressional schedule due to the national elections, Congress was not able to complete work on these bills before the end of the 2008 fiscal year on September 30.

Continuing with the FY 2008 funding levels in FY 2009 provides significant budget restrictions at NIH and will be detrimental to federally funded biomedical research. Individual Institutes have announced expected decreases in paylines.

ASH worked with the biomedical research community to support the inclusion of additional funds for NIH in the CR and will continue to work on increasing funding with the new administration and Congress. ASH encourages all members to visit the ASH Advocacy Center at www.hematology.org/takeaction to help influence the budget process and find the most up-to-date information about NIH funding.

Surgeon General Issues Call to Action to Prevent and Reduce Deep-Vein Thrombosis and Pulmonary Embolism

Acting U.S. Surgeon General Steven K. Galson released a Call to Action on Deep-Vein Thrombosis (DVT) and Pulmonary Embolism (PE) on September 15. The Call to Action seeks to raise public awareness of this blood condition; increase research on the causes, prevention, and treatment of DVT and PE; and share evidence-based practices.

ASH applauded the Office of the U.S. Surgeon General for releasing the announcement and increasing public attention regarding research, prevention, and treatment in this area.

ASH participated in an initial Surgeon General workshop that instigated the government’s decision to launch a Call to Action. The Society also continues to lead efforts to understand the impact of this condition and has conducted two Society-sponsored workshops on thrombosis. The first, held in 2006, focused on thrombosis in the elderly, and the more recent June 2008 workshop focused on thrombosis surveillance.

ASH is also encouraging Congress to support the development of a national thrombosis surveillance system at the CDC and continues to support funding at NIH, CDC, the Agency for Healthcare Research and Quality (AHRQ), and other federal agencies to enable research into prevention, treatment, and cures of DVT and PE.

NIH Director Elias Zerhouni Resigns

On September 24, NIH Director Elias Zerhouni, MD, announced that he would be leaving his position at the end of October. Dr. Zerhouni’s departure will allow the newly elected president to appoint his nominee for this position after he assumes office in January 2009. Because the transition process can often take many months, NIH’s current Deputy Director Raynard Kington is expected to serve as Interim Director until the new president’s nominee can be confirmed.

Following the November elections, it is customary for federal agency heads to submit their resignations as the new president-elect will be working with a transition team to identify new leadership and political appointees.
A Q&A WITH W. KEITH Hoots, MD

On January 5, 2009, Dr. Hoots will assume the position of Senior Advisor to the Director of Blood Diseases at NHLBI. He will serve as liaison to NHLBI’s Division of Blood Diseases and Resources (DBDR). We asked him to share his thoughts about this new role and provide insight into the future of the Blood Division at NHLBI.

Q: Why did you accept this position?
A: I accepted this position because of the challenge it presents to preserve and extend our nation’s established role in doing research into the pathogenesis of diseases that manifest as abnormalities of the bone marrow and blood. In addition, having participated as a clinician scientist during the early days of HIV disease in the hemophilia and blood recipient populations, I have an abiding commitment to the safety of blood and blood components for transfusion therapy. Further, having spent my entire career in academic medicine, I appreciate the need to maximize training opportunities for the next generation of hematologists.

Q: What are the most immediate issues facing the Blood Division? What are your plans for the immediate future?
A: In my opinion, the highest priorities for DBDR (in no particular order) are to maintain (and extend if new funding becomes available) investigator-initiated research grants (e.g., RO1s, PO1s), support stem cell research including therapies utilizing stem cells, energize investigation into sickle cell anemia and hemoglobinopathies, enhance research in venous thrombosis/vascular injury states, explore new models of collaboration for translational research into rare hematologic diseases, and recruit more of the next generation of clinicians/scientists into hematologic.

My plans for the immediate future, upon my arrival in Bethesda, are to work with existing leadership and staff to learn the operational nuances of the NIH and the breadth and depth of existing programs, to recruit new scientists and administrators into key vacant positions at DBDR, and to begin intramural and extramural dialogues with scientists across the United States and abroad to explore opportunities for collaboration.

Q: What is your vision/long-term plan for the Blood Division?
A: My long-term plans for DBDR include creating new opportunities for leveraging existing and new resources (funding and creative initiatives). These include public-private partnerships, intra-governmental collaborations, inter-Institute initiatives, and international joint ventures (particularly for rare hematologic diseases often precluded from statistically powered translational/clinical trials). I also want to partner with all stakeholders to maximize the likelihood that the next generation of hematologists is the best and the brightest to ensure that the number of practicing hematologists is sufficient to meet our national needs and priorities.

Q: Is there anything else you would like to share with ASH in regard to your new position?
A: I and the staff at DBDR are actively seeking to extend our dialogue with members of the hematology community. We will need your insight, advice, and camaraderie in order to utilize most fully the resources that the citizens of the United States have placed in our trust. I pledge to try to create expanded opportunities for this dialogue to occur. Thank you for the opportunity to initiate my part of this conversation here.

Q: Please talk about important issues facing the blood research community in the next five years.
A: As I alluded to in previous questions, I see the greatest challenges for NIH/NHLBI/DBDR in the next five years to be the following:

• To maintain and extend funding to meet the research needs of existing and evolving science as it relates to blood
• To ensure that we have adequate clinician scientists in our subspecialty to meet national needs
• To foster through funding and intellectual investment continued expertise in stem cell biology and therapeutics
• To make greater strides in the treatment of sickle cell disease and other hemoglobinopathies
• To invest so that hematology continues to be one of the scientific “homes” for vascular biology and endothelial injury investigation
• To continue the long-acknowledged worldwide excellence of DBDR in being an essential engine for investigation into the blood organ and its diseases

Q: What do you see as the role for professional organizations (such as ASH) in the Blood Division?
A: I believe that ASH provides an essential international face and voice for hematologists. As a non-governmental organization, it can undertake actions on behalf of the community of hematologists and scientists investigating the “biology of blood” that are both essential and sometimes unique. Some examples include lobbying Congress concerning important hematologic issues, crossing arbitrary disciplinary lines, and serving as the “keeper of the collective history/memory” of our subspecialty. The Blood Division can play none of these roles. Further, ASH and other professional organizations keep the international dialogue in hematologic vibrant and open. Without the latter, I doubt that many of the ambitions for research sharing that I envision would be feasible. Finally, ASH and other professional organizations (and hopefully DBDR) play prominent roles in nurturing and helping to create learning opportunities for our young scientists.

Q: Is there anything else you would like to share with ASH in regard to your new position?
A: I and the staff at DBDR are actively seeking to extend our dialogue with members of the hematology community. We will need your insight, advice, and camaraderie in order to utilize most fully the resources that the citizens of the United States have placed in our trust. I pledge to try to create expanded opportunities for this dialogue to occur. Thank you for the opportunity to initiate my part of this conversation here.

MORE INFORMATION ON THE ROLE OF DBDR

The mission of the Division of Blood Diseases and Resources (DBDR) of NHLBI is to provide leadership for a national program in diseases of blood and blood resource management. In this role, DBDR plans and directs basic, translational, and clinical research and research training on the caus es, treatment, and prevention of blood diseases and disorders. Areas of emphasis include:

• Stem cell biology
• Sickle cell disease and hemoglobinopathies
• Medical management of blood/bone marrow diseases of a destructive or pre-malignant nature
• Cell-based therapies
• Tissue repair and regeneration
• Pathogenesis and clinical management of diseases of bleeding and clotting
• Transfusion biology and medicine

The DBDR also assumes a major responsibility for improving the adequacy and safety of the nation’s blood supply. It consists of three branches: Blood Diseases, Thrombosis and Hemostasis, and Transfusion Medicine and Cellular Therapeutics.
A Supersize BiTE into Cancer. A New Era of Immunotherapy?


I t has been decades since immunotherapy of tumors was proposed, but the initial excitement was rapidly dampened by failure to find tumor-specific antigens as these potential targets were shared with normal tissues. Furthermore, administration of antibodies against these antigens has been frequently followed by antigen modulation resulting in rapid refractoriness of the tumor and the need for a relatively large concentration of antibodies. While cell-mediated immunotherapy based on in vitro expansion of antigen-trained T cells and dendritic cells have been more promising for EBV-initiated tumors such as certain lymphomas and Hodgkin lymphoma, this laborious and expensive approach has been limited to a few specialized centers, and clinical studies of other therapies designed to elicit a T-cell response, such as vaccination and anti-CTCL4 therapy, have thus far been disappointing.

T cells lack an Fc receptor and thus cannot be recruited or activated by conventional antibodies. Bispecific T-cell Engagers (BiTE) are a novel construct of single-chain bispecific antibody-like molecules with one end having specificity for a tumor-expressing antigen and the other for a T-cell antigen. As shown in the Figure, a BiTE antibody tethers T cells to a target cell determined by its tumor-expressing antigen specificity, and this direct engagement elicits cytotoxicity. Blinatumomab is a BiTE antibody that has dual specificity for the T-cell CD3 antigen and the universal B-cell antigen CD19. Bargou and coworkers from Germany describe the first human trial of a BiTE antibody. The authors treated 38 patients with various B-cell non-Hodgkin lymphomas at increasing dose levels of blinatumomab in this phase I/II study. The majority of patients had follicular lymphoma (41 percent) or mantle cell lymphoma (38 percent). All had received prior therapy, with a median of three prior therapies (range 1 to 12). Eighty-seven percent had received rituximab. Blinatumomab was administered as a continuous intravenous infusion over four to eight weeks at dose levels of 0.0005 to 0.06 mg/m². There were four complete and seven partial responses, all of which occurred at doses of 0.015 mg/m² or higher. All seven patients treated at the highest dose level (0.06 mg/m²) responded. The majority of tumor regression occurred during the first four weeks of therapy. The longest duration of CR was 13+ months in a patient with mantle cell lymphoma and three additional patients had responses lasting longer than six months. The most common toxicities were fever, chills, lympho- and leukopenia, and increased C reactive protein levels. These side effects were most common in the first week of treatment. Eight patients discontinued therapy due to adverse events. Five of the eight had central nervous system events, including confusion, cerebellar symptoms, and seizures, but all symptoms were reversed with discontinuation of therapy. CD19 positive cells rapidly vanished from the peripheral blood and remained undetectable during therapy. Peripheral T-cell numbers also initially vanished but then returned to baseline and in some patients were increased.

This report by Bargou, et al. may radically change the applicability and efficacy of cell-mediated immunotherapy of cancer. The BiTE antibody approach bypasses many of the mechanisms cancer cells use to evade cytotoxic T cells. Binding to CD3 activates cytotoxic T cells and effectively recruits additional T cells to tumor tissue. In addition, the cell kill is limited to the cells with the target antigen. Thus, low levels of BiTE antibody should be effective, and indeed the amount of blinatumomab associated with response in this trial was an amazing 5-log-fold lower than the amount of rituximab required for response. Additional work in a larger number of patients will be required to ascertain the response rate and duration of response. In addition, potential toxicities of this therapy will need to be better defined; for example, the drastic decline of B cells would be expected to lead to the usual complications of immunosuppression. A more convenient schedule of administration would also be desirable. However, this is indeed a very promising new therapy, and BiTE antibodies to other antigens, including CD33 and CEA, are already in the process of development.

**Figure 1:** The Fab of conventional antibodies bind to their target cells but do not bind to T cells as T cells lack a receptor for the Fc portion of the antibody. BiTE antibody-like molecule is a single-chain polypeptide consisting of a binding site for the target antigen and a CD3 binding site that binds to CD3. **Figure 2:** BiTE antibody binds to the target cell and to the CD3 antigen on T cells. **Figure 3:** This, in turn, activates T cells.
Size Is Not the Only Thing That Matters


Although the importance of the terminal region of the chromosome in maintaining genome integrity had been recognized in the 1930s and 1940s by Hermann Muller (who coined the term telomere) and Barbara McClintock, it was the pioneering work of Elizabeth Blackwell, Jack Szostak, and Carol Greider in the 1970s and 1980s that led both to detailed characterization of the structure of telomeres and to discovery of the enzyme complex (telomerase) that is responsible for maintaining telomeric structure. Basic and medical research focused on telomerase and on the properties of telomeres has remained vibrant, and the achievements of Drs. Blackwell, Szostak, and Greider were recognized with the 2006 Albert Lasker Award for Basic Medical Research.

Because DNA polymerase can function only in the 5'-to-3' direction, the antiparallel structure of the two strands of duplex DNA (one strand being oriented 5'-to-3' and the other 3'-to-5') poses a problem for replication. Nature has largely solved this problem by using a series of RNA templates that anneal to the parental DNA (called the lagging strand) that is oriented 5'-to-3' with respect to the direction of the replication fork. These RNA templates serve as primers for DNA polymerase, and, consequently, the lagging strand is replicated discontinuously and backward with respect to the replication fork. After the RNA primers are removed, DNA polymerase fills in the resulting gaps, and replication is complete except for the sequence to which the most 3' RNA primer was annealed. Left unresolved, this end-replication problem would result in continuous shortening of the 3'-end of the chromosome with each cell division. Chromosomes with truncated ends are unstable and are subject to recombination, end-to-end fusion, and recognition as damaged DNA. This latter process activates the ATM-p53 DNA damage pathway, leading to cell cycle arrest or cell death. The end-replication problem is solved by telomerase, an enzyme complex that uses an RNA template (TERC) and reverse transcriptase (TERT) to elongate the 3'-end of telomeric DNA and thereby seal the ends of chromosome so as to maintain structural integrity. The telomerase complex is made up of components in addition to TERC and TERT including dyskerin, a pseudouridine synthase that is a component of a box H/ACA ribonucleoprotein particle required for stability of the telomerase complex.

Bone marrow failure is a common clinical feature of patients with mutations in telomerase components and in dyskerin, and in some domains of TERC cause the syndrome of dyskeratosis congenita (see Table).1 As anticipated, short telomeres are characteristic of all patients with mutations in dyskerin, TERC, and TERT, but whether mutations in telomerase components affect cell viability independent of telomere shortening has been speculative. Now, through a series of rigorous genetic experiments in mice, Gu and colleagues have shown that mutant dyskerin induces the ATM-p53 pathway of DNA damage recognition in a telomerase-dependent process that is independent of telomere length. Laboratory mice are particularly good models for studying the effects of mutations in telomerase components that occur independent of telomere length because they have long telomeres that, even in the absence of telomerase activity, do not become critically short for several generations. The mouse model developed by Gu, et al. carried a dyskerin (Dkc) deletion mutation similar to one identified in a family with X-linked dyskeratosis congenita. Male mice hemizygous for mutant Dkc showed no signs of bone marrow failure, nail dystrophy, skin pigmentation problems, or other stigmata of human dyskeratosis congenita. Due to X-chromosome inactivation, females have only one functional X-chromosome in somatic tissues, and, therefore, females that are heterozygous for the mutant Dkc gene are mosaic with cells expressing either wild-type Dkc or the mutant Dkc. Gu and colleagues took advantage of this mosaicism to demonstrate that cells with mutant Dkc have a proliferative disadvantage that was more apparent in cells from organs with a higher growth rate (spleen, thymus, and bone marrow) compared to those with lower cell turnover (brain and liver) and was dependent on telomerase integrity but not on telomere length.

Further studies showed that Dkc mutant cells have enhanced DNA damage response mediated by the ATM-p53 pathway with damage foci localized to telomeric ends. Together, these experiments demonstrate that mutations affecting the telomerase complex can induce DNA damage independent of telomere length, although telomere shortening appears to be required for full manifestation of the clinical phenotype (see Table).

OK, so no more jokes about guys with short telomeres.


CHARLES PARKER, MD
Dr. Parker indicated no relevant conflicts of interest.

Table: Phenotypes of patients with mutations in telomerase components

<table>
<thead>
<tr>
<th>Affected Component</th>
<th>Phenotype</th>
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| Dyskerin (DKC1)    | • X-linked dyskeratosis congenita (bone marrow failure, abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia)
| Telomerase RNA Component (TERC) | • Autosomal dominant dyskeratosis congenita
| Telomerase Reverse Transcriptase (TERT) | • Aplastic anemia later in life without physical stigmata of dyskeratosis congenita
|                   | • Aplastic anemia later in life without physical stigmata of dyskeratosis congenita

† Usually fatal.
‡ Mutations in the 3'-end of TERC affecting the box H/ACA domain that associates with dyskerin produce the dyskeratosis congenital phenotype as do mutations affecting the CR7 domain of TERC.
§ Mutations in the 5' region of TERC (the pseudoknot and CR4-CRS domains) are associated with late-onset bone marrow failure but not with physical stigmata of dyskeratosis congenita.
¶ Missense mutations affecting one allele result in haploinsufficiency of the telomerase reverse transcriptase. Some adult family members of probands have TERT mutations and short telomeres but no hematologic abnormalities.1
Platelet Production From Stem Cells: Shedding a Barrier


More than 10 million units of platelets are transfused in the United States annually. Platelet supplies presently rely on volunteer donations, which are subject to regional and seasonal variation and shortages. Cold storage of platelets dramatically reduces their half-life in the circulation. Since they cannot be refrigerated, donated platelets can only be stored for five days owing to the risk of bacterial contamination from transfusion. Alternative sources of platelet production include large-scale expansion of CD34+ cells and platelet production from embryonic stem cells (ESCs). An advantage of using ESCs for purposes of generating platelets is that these cells have the potential to proliferate indefinitely in culture. Since platelets are anucleate, they can be irradiated before transfusion to prevent transfusion of undifferentiated ESCs. The theoretical potential is limitless. However, technical barriers to generating functional platelets from ESCs have so far prevented widespread implementation of this technology.

Nishikii, et al. have addressed a significant difficulty in platelet production from ESCs. They described a two-stage approach for producing platelets from mouse ESCs. During the first stage, ESCs were induced for embryoid body formation in liquid culture. Selected cells were subsequently co-cultured with stromal cells in the second stage. Culture supernatants contained proplatelets and platelet-sized particles that displayed an open canalicular system as well as multiple dense α-granules. Evaluation of major surface proteins on ESC-derived platelets demonstrated αIIbβ3, GPIbα, and GPIbβ expression, indicating that metalloproteinase-mediated shedding caused loss of these surface proteins during cell culture. Inhibition of metalloproteinase activity improved several aspects of ESC-derived platelet function. Signaling through αIIbβ3 was enhanced in ESC-derived platelets cultured in the presence of GM6001 compared with those that were not. Thrombus formation occurring when whole blood flowed over a collagen matrix at physiological shear rates was markedly enhanced in ESC-derived platelets incubated with GM6001. In addition, incubation with GM6001 substantially increased the survival of ESC-derived platelets when infused into recipient mice. These results demonstrate the importance of inhibiting platelet surface receptor shedding in producing functional ESC-derived platelets.

The demand for platelet transfusion has continued to rise, prompting efforts to devise novel strategies of platelet production and storage. Production of platelets from ESCs offers a theoretically limitless supply of platelets. Yet considerable technical barriers hinder the progress toward efficient production of functional ESC-derived platelets. Nishikii, et al. demonstrate that metalloproteinase activity that occurs during co-culture results in loss of critical platelet surface proteins. Inhibition of metalloproteinase activity results in the production of platelets with enhanced functionality and longer survival in vivo. Although these studies do not solve all the technical problems associated with large-scale production of functional ESC-derived platelets, they do shed an important barrier to accomplishing this objective.

Of Men and News


Regenerative medicine is one of the new buzzwords in science. The therapeutic promise is just too good to pass up. The concept that, for humans, science could one day reproduce the feats of a newt in regenerating a new limb is the stuff of science fiction. Yet, the potential and progress continue to astound us. We have moved from somatic nuclear transfer in the 1990s, to transdifferentiation, cell fusion for adult pluripotent cells, and, most recently, the ability to program mouse and human differentiated cells into induced pluripotent cells (iPS) by the expression of a defined set of factors (Oct4, Sox2, c-Myc, KLF4). All of these findings have been surprising in that the dogma was that the adult cells follow a series of sequential, unidirectional, developmental steps that were thought to be irreversible. The concept has been that the “attaining maturity” process leads to terminally differentiated cells.

Many of these studies have worked primarily with cells in tissue culture. A recent report suggests that it may not be necessary to reach back to the level of an iPS. Perhaps adult differentiated cells can be used and such reprogramming can be done in vivo. The investigators of this manuscript identified adult reprogramming factors by re-expressing multiple embryonic genes in living adult animals. The specific goal was to reprogram adult pancreatic exocrine cells into cells that resemble the islet beta cells, thereby potentially curing diabetes. A group of nine transcription factors was used initially in a mixture after which several were systematically removed so that the least number of transcription factors that could still give rise to the desired phenotype were used. A specific combination of three transcription factors, Ngn3, Pdx1, and Mafa, could reprogram pancreatic exocrine cells in adult mice into cells that closely resembled the beta cells of the islets in size, shape, and ultrastructure. Moreover, these cells express the genes that are essential for beta-cell function and could ameliorate hyperglycemia (although not completely) by producing and secreting insulin. Surprisingly, the reprogramming did not require proliferation and occurred rapidly with the first insulin-positive cells seen within three days. However, these reprogrammed cells did not organize into islets, and further studies are needed to understand how to aggregate these cells, thereby potentially optimizing their response to hyperglycemia. More studies are also necessary to ascertain that these cells do not become malignant.

The ability to generate iPS is very exciting since other mammalian tissue could be developed by first converting a skin cell into an iPS and then guiding these cells to become the tissue of interest. This approach raises the possibility of generating patient-specific human embryonic stem cell lines for therapy. There is also great interest in treating hematologic patients by developing iPS from the patient that could lead to reseeding of the marrow to restore all the blood elements. Moreover, for hematologists in particular, mature B cells have been reprogrammed into macrophages or pro B cells. This study takes this concept one step further by using transcription factors and targeting mature adult cells. The data confirm the regenerative potential by reactivation of embryonic regulators and suggest a possible paradigm that direct cell programming may be possible without necessarily reverting to a pluripotent stem cell state.

Profiling AML Stem Cell Active Agents


In recent years, targeting cancer stem cells (CSCs) has become the focus of intense interest in diverse malignancies, including those of hematopoietic origin, and particularly AML. CSCs are capable of continuous regeneration and, as a consequence, may serve as an unlimited reservoir to restore the bulk population of cells following ablation (e.g., by chemotherapy). Significantly, AML stem cells appear to be relatively resistant to conventional cytotoxic agents, such as ara-C or daunorubicin, which very effectively kill bulk populations of AML blasts, raising the possibility that failure to eradicate AML stem cells (AML SCs) may be responsible for or contribute to treatment failure in this disease. On the other hand, evidence has emerged that certain targeted agents, particularly inhibitors of the NF-κB pathway, may be particularly effective in eliminating AML SCs. One such agent, the sesquiterpene lactone parthenolide, has been shown to induce AML SC death in association with NF-κB inactivation and induction of oxidative injury. Such findings have prompted efforts to identify other compounds with similar characteristics.

In a recent study, Hassane, et al. describe a novel genetic approach specifically designed to achieve this aim. Using the multi-institutional Gene Expression Omnibus (GEO) as a platform, they hypothesized that compounds capable of eradicating AML SCs would exhibit a gene profile array similar to that of parthenolide. In silico screening of this public database by two separate search procedures yielded two compounds, celastrol and 4-hydroxy-2-nonenal (HNE), whose signatures mimicked that of parthenolide. Interestingly, both of these terpenoid compounds shared with parthenolide the ability to ablate the bulk, progenitor, and SC populations of leukemic cells, disrupt NF-κB signaling, and induce oxidative stress. The authors concluded that mining of large, public, gene array databases may provide an extremely valuable resource for drug discovery by helping to classify both new and old drugs according to their genetic perturbations that they produce. More specifically, in the case of AML such computational tools may help in identifying the relatively small subset of agents likely to be effective against the AML SC, rather than the bulk population of blasts.

While the concept of employing sophisticated computation-al methods in conjunction with large genetic databases to discover new agents is clearly an exciting one, the ultimate success of this strategy in the context of AML will depend upon multiple factors. First, while it seems intuitive that agents capable of abating both AML SC and bulk populations should prove superior to agents that only ablate bulk populations, this hypothesis has not yet been formally tested. In this regard, the entry of the parthenolide analog LC-1 into the clinical arena, including studies involving AML, should begin to address this question. The possibility also exists that specific genetic perturbations may primarily yield agents mimicking the pharmacodynamic properties of the index compound. Nevertheless, the novel drug discovery approach described here clearly has tremendous potential, and its validation over the years to come is awaited with great interest.


Never-Ending Debates on the Role of Allogeneic Stem Cell Transplantation in Multiple Myeloma


Although allogeneic hematopoietic stem cell transplantation (HSCT) has been performed for the treatment of multiple myeloma since the early 1980s, its place (if any) has been, and is still, highly debated. Conventional allogeneic HSCT following myeloablative conditioning has been associated with cure through a graft-versus-myeloma effect, but its development has been greatly hampered by an unacceptable transplant-related mortality. Recently, non-myeloablative conditioning has led to a resurgence of allogeneic HSCT, and several phase II trials have been associated with more acceptable rates of transplant-related mortality, opening the door for its use in older, mostly relapsed, patients. Thus, the next logical step was to test allogeneic HSCT within the therapeutic schemes of first-line therapy.

The PETHEMA group set up a randomized trial in which 110 patients with multiple myeloma failing to achieve at least near-complete remission after a first autologous HSCT were scheduled to receive a second autologous transplant (BS patients) or an allograft with reduced-intensity conditioning (Allo-RIC) (25 patients), depending on the HLA-identical sibling donor availability. They reported a higher CR rate (40% vs. 11%; p=0.001) and a trend toward a longer progression-free survival (PFS) (median 31 months vs. not reached; p=0.08) in favor of Allo-RIC. In contrast, it was associated with a trend toward higher transplant-related mortality (16% vs. 5%; p=0.07), a 66 percent chronic graft-versus-host disease incidence and no statistical difference in event-free survival and overall survival. They stated that "although the PFS plateau observed with Allo-RIC was encouraging, Allo-RIC is associated with a high morbidity and mortality, and, therefore, it should be still considered investigational and restricted to well-designed prospective clinical trials." Of note, of 752 patients who received a first autologous HSCT, 280 failed to achieve CR or nearly CR, but there was a very high drop-out rate since 170 patients did not undergo the pre-planned second transplant.

Many trials testing the same hypothesis are currently underway, but two major trials asking a similar question as the PETHEMA group have been published and reached different conclusions. The first study, by the Intergroup François de Myélome (IFM),1 included 65 patients in the autologous/allogeneic group and 219 patients in the autologous/autologous group. Based on an intention-to-treat analysis, there was a significantly better median overall survival in the autologous/autologous group than in the autologous/allogeneic group. If patients who actually received treatment were analyzed, there was still a significantly superior overall survival in the tandem autologous transplant group over the autologous allogeneic group. This study included only high-risk patients younger than 65, with high serum beta-2 microglobulin and deletion of chromosome 13. The RIC was busulfan plus fludarabine and ATG, and thus some form of T-cell depletion.

The second series by Bruno, et al.2 showed a superior overall survival for patients who underwent autologous-allogeneic transplantation. In this study, 245 patients were treated and included a tandem autologous transplantation followed by reduced intensity conditioning, as the first treatment. Whether analyzed according to the intent-to-treat (i.e., whether allografting was performed), or based on actual treatment administered, there was a significant advantage of undergoing an auto-allo transplantation. It is interesting to note that the deviation in the survival curves to the advantage of the auto-allo transplantation approach regimen was seen only after about two years of follow-up.

Thus, these three trials (although not strictly identical) shared the same problem of significant drop-out with only a portion of the patients receiving the allocated treatment. We still face the unanswered question of the place [if any] of allogeneic HSCT with RIC in the management of newly diagnosed myeloma. Further, during the period when these trials were conducted, significant advances have been made in the treatment of myeloma with better description of the disease severity using cytogenetics and with the advent of new drugs including bortezomib, lenalidomide, and thalidomide.

Incorporating Novel Agents into Upfront Myeloma Therapy


Ikaros and Ph+ ALL


The Philadelphia (Ph) chromosome stems from a reciprocal translocation between chromosomes 9 and 22. On a gene level, this rearrangement places upstream domains from the Bcr gene from chromosome 22 in juxtaposition with the downstream tyrosine kinase domains of Abl, from chromosome 9. The Ph chromosome is found in virtually all cases of chronic myeloid leukemia (CML) and approximately 5 percent of pediatric and 25 percent of adult acute lymphoblastic leukemia (Ph+ ALL). An intriguing mystery is how Bcr-Abl causes both a myeloid (CML) and lymphoid (Ph+ ALL) leukemia, and why does chronic-phase CML usually progress to myeloid blast crisis, but sometimes to lymphoid blast crisis?

In the mid-1990s, researchers described the gene Ikaros, a member of a family of zinc-finger-containing transcription factors. Like many such genes, it possessed DNA domains involved in forming homo- and heterodimer formation, with internal DNA domains coding for zinc fingers. Ikaros undergoes several splice variations, and it is thought that the mix of these splice variants influences Ikaros function. It appears that in these various isoforms, certain exons serve essential for normal lymphocyte development, whereas a shift in splicing was associated with lymphoid malignancy.1,2

Previously, in vitro experiments suggested that Bcr-Abl induction causes a shift in Ikaros splicing, encouraging the non-DNA binding isoforms. However, a more recent elegant paper highlights the role of DNA structural changes and the expression bias of Ikaros isoforms, demonstrating that actual deletions occur in the gene, eliminating the key DNA-binding domains. In a genome-wide screen of deletions and additions in ALL, Mullighan, et al. found an exceptional ly high loss of the IKZF1 gene (coding for Ikaros) in Ph+ ALL cases. Of the 43 Ph+ cases studied, 35 (84 percent) had the IKZF1 deletion. In 19 cases, the deletion was restricted to the region coding Ikaros exons 3-6 (designated the ik6 variant), which code for the DNA binding domain. The authors then examined 159 ALL cases looking for ik6 mRNA expression, and found it only in cases that harbored the exons 3-6 deletion, strongly suggesting that ik6 expression was based on DNA structural changes, rather than a splicing variation. Chronic-phase CML was free of alterations in the IKZF1 site. However, four of 15 blast crisis samples showed a IKZF1 deletion, including two/three lymphoid blast crisis. Sequence analysis of the IKZF1 deletion suggested that exons 3-6 were possibly deleted by aberrant work of the lymphoid RAG-mediated recombination machinery, which functions normally in differentiation to create VDJ rearrangements. Thus, the study implicates non-DNA-binding Ikaros variants associated with the pathogenesis of Ph+ lymphoid malignancy.

A complementary paper by Iacobucci, et al. suggests that the ik6 variant may be important in understanding the resistance of Ph+ ALL to tyrosine kinase inhibition. At diagnosis, nearly 50 percent of Ph+ ALL expressed only the non-DNA binding ik6 isoform. In vitro studies in cell lines suggested that the ik6 variant was associated with an impaired apoptotic response to TKI exposure, increased DNA synthesis, and more robust colony growth.

These studies suggest an important role of Ikaros in the pathogenesis of Ph+ lymphoid malignancies. Many interesting questions remain. What is the link between Bcr-Abl and Ikaros? If the ik6 isoform causes a loss of Ikaros transcription regulation, what genes are deregulated? Would their correction be therapeutic? One suspects that this Ikaros has wings that can withstand the heat of investigation [sorry, readers, I couldn’t resist].

2008 Honorific Award and Mentor Award Recipients

E. Donnall Thomas Lecture and Prize

Created in 1992, this lecture was named after Nobel Prize laureate and past ASH President E. Donnall Thomas, MD. The E. Donnall Thomas Lecture and Prize recognizes a scientist whose pioneering research achievements in hematology have been sustained and have had a significant and lasting impact.

The 2008 Thomas Lecture will be given by Dr. Neal Young of the National Heart, Lung, and Blood Institute. Dr. Young has been a pioneer in the field of bone marrow failure syndromes; his lecture, scheduled for Monday, December 8, from 9:30 to 10:30 a.m., will focus on the pathophysiology of bone marrow failure.

Henry M. Stratton Medal

The Stratton Medal was named for the late Henry M. Stratton, a co-founder of the publishing house of Grune and Stratton, to honor an individual whose contributions to hematology are well recognized and have taken place over a period of several years.

The 2008 Henry M. Stratton Medal goes to Clara D. Bloomfield, MD, of The Ohio State University, for her remarkable achievements in the area of hematologic malignancies, especially AML, over more than three decades. Dr. Bloomfield has been a major contributor to the understanding of the biology of these diseases and the practical use of biologic information in diagnosis, classification, and determining prognosis and selection of curative therapeutic approaches. Dr. Bloomfield will receive her award on Tuesday, December 9, at 9:30 a.m.

Wallace H. Coulter Award for Lifetime Achievement in Hematology

The Coulter Award is named for Wallace Henry Coulter, a prolific inventor who made important contributions to hematology and to ASH. During his lifetime, Mr. Coulter was a strong supporter of ASH; to date, he is the only person to receive the American Society of Hematology Distinguished Service Award for his enormous contribution to the field of hematology. The Wallace H. Coulter Award for Lifetime Achievement in Hematology is bestowed on an individual who has demonstrated a lifetime commitment and outstanding contribution to hematology, and who has made a significant impact on education, research, and/or practice.

This year’s award goes to Robert Kyle, MD, of the Mayo Clinic in Rochester, MN, for his contributions to multiple myeloma, monoclonal gammopathies, amyloidosis, and related plasma cell disorders. Over his entire 50-year career as a physician-researcher, educator, and consultant, he has focused on defining these diseases; understanding their pathogenesis, presentation, and prognosis; and designing and evaluating therapeutic approaches. Dr. Kyle will receive his award on Sunday, December 7, at 1:30 p.m.

William Dameshek Prize

The William Dameshek Prize was named for the late Dr. William Dameshek, a past president of the Society and the original editor of Blood, to recognize a recent outstanding contribution to the field of hematology.

Kenneth Anderson, MD, of the Dana-Farber Cancer Institute in Boston, MA, is being awarded the Dameshek Prize for his contributions to the treatment of myeloma. Dr. Anderson has advanced the field by establishing a new paradigm focused not only on the malignant cell, but also on the microenvironment for the identification of molecularly targeted therapies. See Dr. Anderson receive his award on Tuesday, December 9, at 9:30 a.m.

Mentor Award — Clinical Investigation

Dr. Buchanan is a pediatric hematologist at the University of Texas Southwestern Medical Center. He is the Children’s Cancer Fund Distinguished Chair in Pediatric Oncology and Hematology, and the director of the Barrett Family Center for Pediatric Oncology. Believing that a mentor should identify and foster talent in its earliest stages, Dr. Buchanan has mentored everyone from high school students to senior investigators.

Mentor Award — Basic Science

Dr. Ley is an associate director for basic science at the Alvin J. Siteman Cancer Center, Washington University, St. Louis, MO. He is known as someone who sets an extremely high standard of personal integrity and scientific rigor, and passes that on through his commitment to his trainees and his advocacy of scientific education.

Drs. Buchanan and Ley will be formally presented with their honors prior to the Plenary Scientific Session on Sunday, December 7, at 1:30 p.m. in the Moscone Center.

Look for articles on the four honorific and two mentor award winners in ASH News Daily, the on-site, daily, annual meeting newspaper.
Hematology research has historically been on the front lines of scientific discovery aimed at seeking answers to fundamental biological questions. Many breakthroughs in the field of hematology have been translated into advances in diagnosis, treatment, and prevention of blood disorders, as well as a wide variety of other human diseases. For example, sickle cell disease was the first disorder to be characterized at the molecular level, and research on hemoglobin led to the current understanding of the relationship between human gene structure and function. Stem cells of the hematopoietic system were the first adult stem cells to be described, and they still provide the best model for understanding the biology of stem cells in other tissues. Hematopoietic stem cell transplantation continues to drive forward clinical research on other forms of stem cell therapy. Fundamental studies of thrombosis and hemostasis have had a major impact on our understanding and treatment of cardiovascular disease. These are just a few of the examples of the distinguished tradition of hematology fostering groundbreaking innovations in biomedical research.

In recognition of this role, ASH began a strategic planning initiative in 2006 to define and promote the leading areas of active endeavors in hematologic research. The ASH Agenda for Hematology Research: 2006 received extensive input from all members of the Society’s 17 scientific committees and the Executive Committee. This year, the Society undertook a similar process to update the agenda. The ASH Agenda for Hematology Research: 2009-2011 reflects current trends in hematologic research and celebrates the 50th anniversary of ASH. Although many aspects of our research priorities remain unchanged, the 2008 revision describes the latest advances in the field, including breakthroughs in stem cell research, and reinforces the commitment to improved understanding of sickle cell disease, as well as disorders of hemostasis and thrombosis.

The ASH Agenda for Hematology Research: 2009-2011 is organized into two parts. First, the highest priority scientific themes are described; they contain a wide range of comprehensive topics that are considered to be the most promising and exciting directions in hematology research. They include: hematopoietic stem cells; normal and pathological hematopoiesis; sickle cell disease; hematologic malignancies; targeted, cellular, and genetic therapies; immunobiology; thrombosis and vascular biology; and health care delivery and patient outcomes. Second, the Agenda recommends the most important priorities for development of research infrastructure in order to facilitate all areas of hematology research, with a particular focus on the needs for training and core facilities.

The ASH Agenda for Hematology Research: 2009-2011 is expected to be an important tool in promoting the recognition and importance of hematology research to the scientific community, funding agencies, political and legislative bodies, philanthropic organizations, patients and their advocacy groups, and the American public. The Agenda will be distributed to all participants at the annual meeting in San Francisco and will be available for download on the ASH Website in December.

ASH UNVEILS AN UPDATED AGENDA FOR HEMATOLOGY RESEARCH

NANCY BERLINER, MD

Dr. Berliner is the President-Elect of ASH.

Dr. Beutler pursued his work with extraordinary intellectual power. Both the breadth of his research and the fluency of his writing were incomparable. He always pursued both basic and patient-centered research, finding inspiration in the clinical problems he witnessed firsthand. At times, however, his achievements seemed to materialize out of thin air.

Dr. Beutler’s major scientific work began with the discovery that G6PD deficiency was responsible for hemolysis in primaquine-sensitive individuals. Aware that G6PD is encoded by an X-linked gene, he began to ponder the mechanism of dosage compensation in mammals, which in turn led him to deduce and prove the principle of random embryonic X-chromosome inactivation. With this, he identified the first example of stochastic epigenetic silencing in humans, and showed that human females are mosaics of X-chromosome activity. This, in turn, led to the strongest evidence that neoplastic diseases are, for the most part, clonal. Indeed, he foresaw the importance of epigenetics years before most of the scientific community fully understood it.

Over the years, Dr. Beutler made many other seminal contributions to science, and foremost to our understanding of red cell enyz-

O B I T U A R Y

Ernest Beutler, MD (1928 – 2008)

Ernest Beutler, past president of ASH, died on October 5, 2008, at 80 years of age. Only a few months ago, Dr. Beutler’s immense contributions to hematology were summarized in the May/June 2008 and January/February 2008 issues in The Hematologist in two articles: a brief biography and an acknowledgment of his receiving the Wallace H. Coulter Award for Lifetime Achievement in Hematology. (See links to these articles below.)

Read the two Hematologist articles:
• 50th Anniversary Profile in Hematology: www.hematology.org/publications/hematologist/MJ08/profiles.cfm
• Wallace H. Coulter Award for Lifetime Achievement in Hematology: Inaugural Award Winner Ernest Beutler, MD: www.hematology.org/publications/hematologist/JFOB/news.cfm#D

ASH EXTENDS ITS THANKS

Drs. Frank Bunn, Marshall Lichtman, and Wendell Rosse graciously agreed to coordinate with The Hematologist to present the 50th anniversary profiles starting in late 2007 through the end of our anniversary year. We would like to say thank you to Drs. Bunn, Lichtman, and Rosse for all their exemplary work.

They put forth their time and effort to give readers the opportunity to learn more about these extraordinary individuals. Because of the quality and popularity of these articles, we will be extending this series into 2009. To view the profiles, go to www.hematology.org/education/legends.
Clement Finch: A Unique Man at a Unique Time

JOHN W. ADAMSON, MD

Dr. Adamson is Clinical Professor at the University of California, San Diego. He is also a past president of ASH.

Clement (Clem) Alfred Finch, MD, was born on July 4, 1915, in upstate New York. With a father and grandfather who were physicians, and occasionally joining his father on evening house calls, Dr. Finch decided to follow in their footsteps. After his second year at the University of Rochester Medical School, Dr. Finch was offered the Dean’s Fellowship to work with Nobel Prize winner George Whipple — a pillar at the school. Although Dr. Finch didn’t feel he “accomplished anything [in] particular,” his first paper, on hemoglobin regeneration in dogs that had been bled, was published in the Journal of Experimental Medicine, which was not bad for a second-year student. Also, in Rochester he came into contact with Paul Hahn, who was working on iron metabolism, and, to a lesser extent, Joe Ross, whom Dr. Finch would later join in Boston. He began to feel that academic life could be fun!

After graduating in 1941, Dr. Finch went to the Brigham in Boston, where he encountered many of the leaders in American medicine, including Soma Weiss. In those days, house officers lived in the hospital, and, if they wanted to get married, they had to ask for permission! Dr. Finch married after one year. Dr. Weiss said, “Congratulations, but when you come back, act like you’re not married.” Dr. Finch felt that when he was at the Brigham the most important thing in his life was being a good clinician. The Brigham spirit was one of viewing each patient as a research subject. Patient loads were light; inquiry was fostered. There was ample contact with stellar physicians, such as Eugene Stead and Charlie Janeway.

After his clinical training, Dr. Finch accepted a fellowship with Joe Ross at Boston University. It was Dr. Ross who really introduced Dr. Finch to academic medicine, teaching, and research-oriented division. LA was smoggy; Seattle was clean. At six feet, five inches, Dr. Finch was conspicuous going between hospitals on his Vespa. In an attempt to carve out more hours for his science, Dr. Finch worked two days devoted to Education Sessions, admired with the programs of the Scientific Committees, and the very useful ASH Education Book.

By 1948, Dr. Finch felt it was time to go. Having grown up in the Adirondacks and loving the outdoors, Dr. Finch always thought of moving to a place with mountains. In 1948, he was invited by Bob Williams, the new Chair of Medicine in Seattle, to look at a position there. John Lawrence (from Rochester) tried to recruit Dr. Finch to the UCLA faculty but Dr. Finch decided on Seattle, where he could build a new division from scratch in his own vision of an integrated clinical, teaching, and research-oriented division. LA was smoggy; Seattle was clean and fresh, according to Dr. Finch. Seattle was a new medical school; it opened in 1946. With Dr. Finch’s spirit of adventure, three technicians also made the move into his office. Occasionally, on his forays into the woods, he would bring back mushrooms — as John Huff, a young faculty person at Harborview, discovered when he went to take a preparation of tobacco mosaic virus off the lyophilizer only to find that Dr. Finch was drying mushrooms!

Dr. Finch lived life a bit differently. He loved the outdoors and climbing in the Cascades. He put his skills to the test one day when, having forgotten his keys, he scaled the outside of the Health Sciences Building to get into his office. Occasionally, on his forays into the woods, he would bring back mushrooms — as John Huff, a young faculty person at Harborview, discovered when he went to take a preparation of tobacco mosaic virus off the lyophilizer only to find that Dr. Finch was drying mushrooms!

At six feet, five inches, Dr. Finch was conspicuous going between hospitals on his Vespa. In an attempt to carve out more hours for his science, Dr. Finch worked all night, every other night. The reduced-sleeping routine lasted for about a week. And, he may be the only faculty person at the University of Washington targeted by the Medical Executive Committee, who ruled that hospital rounds were not to be made wearing lederhosen.

As I look back on my time with Dr. Finch in Seattle, anything was possible intellectually. There was a wonderful faculty doing truly meaningful clinical research and a hematology program built on rigor and collaboration. Not a bad model.
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.

Refer your patients to a resource they can trust: BLOOD: THE VITAL CONNECTION (www.bloodthevitalconnection.org). The site includes:

- Hematologist-approved information on various blood disorders and issues:
  - Bleeding and clotting
  - Anemia
  - Cancer
  - Blood-related women’s health issues
- Tips for how patients can communicate effectively with their doctors
- A guide to clinical trials
- Major medical advances in hematology
- “Find a Hematologist” — patients can search for a hematologist by location or specialty

Additionally, the site includes a career resources section for medical students who want to learn more about hematology. Please help ASH promote this valuable resource by directing your patients to www.bloodthevitalconnection.org.

Participate in ASH’S 50TH ANNIVERSARY and learn more about the rich history of ASH and hematology by visiting www.hematology.org/about/50thanniversary. On this Web page you can meet legends in hematology and read their oral histories, in which they reflect upon their careers. Check out the latest additions of Drs. Louis K. Diamond and Leon Jacobson in the Legends of Hematology section at www.hematology.org/education/legends.

Register for the 2009 official HIGHLIGHTS OF ASH® taking place in two countries, on three different days! Mark your calendar to attend the Highlights of ASH meeting in Phoenix, AZ, on January 30-31; in Miami, FL, on February 6-7; or in São Paulo, Brazil, on May 15-16. For more information, go to www.hematology.org/meetings/highlights.

Get up-to-date ANNUAL MEETING information at www.hematology.org/meetings/2008. Join ASH in San Francisco for its 50th anniversary celebration.

Read THE HEMATOLOGIST ONLINE (www.hematology.org/publications/hematologist) and catch up on the latest news in the field of hematology right on your desktop.