ASH™ APPOINTS NEW EDITOR-IN-CHIEF OF BLOOD
EDWARD BENZ, MD
Dr. Benz is President of the Dana-Farber Cancer Institute and Richard and Susan Smith Professor of Medicine, Professor of Pediatrics, Professor of Pathology, at Harvard Medical School.

Cynthia Dunbar, MD, senior investigator at the National Institutes of Health (NIH), has been selected as the next Editor-in-Chief of Blood, the world’s leading hematology journal. Working on the Blood team is nothing new to Dr. Dunbar. She has been an associate editor of the journal for nearly nine years, and has served on the editorial boards of other journals, including Molecular Therapy, Cancer Gene Therapy, and Stem Cells, making her an ideal choice for the position.

During the interview process, the New Editor Search Committee (which made recommendations to the ASH Executive Committee), chaired by myself and including Nancy Andrews, MD, PhD, Kenneth Kaushansky, MD, J. Evan Sadler, MD, PhD, and Bradford Schwartz, MD, was particularly impressed by Dr. Dunbar’s energy, enthusiasm, and practiced eye for scientific quality.

As Editor-in-Chief, she will succeed Sanford J. Shattil, MD, who considers his proudest accomplishments on the journal to be recruitment and retention of world-class associates, navigating an ongoing and popular review series in translational hematology, and expansion of the well-received “Inside Blood” section, which provides digests of the most cutting-edge articles in each issue.

In a word, Dr. Shattil’s goal for the journal was “balance” — balance between basic science and clinical hematology and balance among the many different subcategories in hematology. Dr. Dunbar agrees and says her foremost goal for the journal will be maintaining “the incredible quality of scientific and clinical research in Blood.”

(Cont. on Page 4)

Contagious Cancer

Cancer is generally considered a private disease which arises in an individual with inherited, spontaneous, or induced genetic changes that predispose to malignant transformation. However, there are rare examples of transmissible cancers in non-human species. It has been appreciated for 130 years that canine transmissible venereal tumor (CTVT) spreads among dogs through sexual and oral contact. Living histiocytic tumor cells pass from one individual to another and establish new tumors in the recipient. In this paper, Murgia and colleagues present evidence that cases of CTVT in diverse dog breeds and geographic locations are descendants of a single rogue tumor estimated to have arisen between 200 and 2500 years ago. The investigators took advantage of modern DNA analysis to show that tumors in 40 dogs on five continents over 20 years all had the same genetic signatures. Although the tumors could be assigned to two subclades, they appear to have arisen from the same ancestral tumor, which gave rise to the subclades early after its establishment as a transmissible malignant parasite. All carry a characteristic insertion of a LINE DNA repetitive element close to the c-myc proto-oncogene. They share other distinct genetic markers that distinguish the tumor from its hosts. The authors conclude that the CTVT cells represent the oldest mammalian cell line in continuous propagation — the widely used HeLa cell line is quite young by comparison.

There are several important lessons to be learned from this study. First, the relative genomic stability of CTVT is surprising — although aneuploid, the karyotype is unexpectedly preserved. This may be relevant to its success as a parasitic tumor. CTVT regresses spontaneously and does not kill its hosts, suggesting that there is selective pressure on the tumor cells to maintain their immortality by ensuring that they can continue to be transmitted to others. However, it is unlikely that the tumor cells must propagate asexually suggests that, over a long enough time, they will acquire deleterious mutations that will impair their viability. Second, the tumor has escaped from the normal allo-recognition mechanisms of its MHC-incompatible hosts. The authors raise the interesting notion that the highly polymorphic MHC system may have evolved to protect animals from transmissible tumors as well as infectious agents. But they point out that MHC antigens are suppressed by many types of tumors, raising the interesting questions of why transmissible allograft tumors have not emerged more frequently and why they have not (yet?) been observed in human populations.

NANCY ANDREWS, MD, PhD
Dr. Andrews indicated no relevant conflicts of interest.

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NEW ORLEANS: ONE YEAR LATER

MARC KAHN, MD

Dr. Kahn is Associate Dean of Admissions and Student Affairs at Tulane University Health Sciences Center.

August 29, 2005, the day that Hurricane Katrina made landfall, is a day that no New Orleans resident will ever forget. It was the day that changed lives forever. Within three-and-a-half weeks following the storm, the Tulane School of Medicine administration, with the help of Baylor College of Medicine and an alliance of Texas medical schools including Texas A&M, UTMB Galveston, and UT Houston, re-established the school 350 miles from home. Unfortunately, this was just in time for Hurricane Rita, which delayed the school’s opening by an additional week.

ASH has been terrific in the face of these disasters. Though the hurricane forced ASH to relocate its 2005 annual meeting from New Orleans to Atlanta, the Society remained committed to New Orleans. Through the ASH Katrina Relief Fund, the Society supported the city’s convention bureau, restaurant, and tourism workers, and supported our fellowship program financially. They also provided funding to Louisiana State University Health Sciences Center. Importantly, they replaced books lost in the flood waters, waived dues for folks in affected areas, and provided financial assistance to attend the annual meeting.

It has now been more than a year since Hurricanes Katrina and Rita. New Orleans remains a “tale of two cities.” Parts of the city, including the French Quarter, remain unscathed and look like they did before the storms. Other parts have not changed since the storms and look as desolate and damaged as postwar cities. Many patients are finding doctors, but health care for the poor remains fragmented. We are seeing patients with more advanced malignancies as they have not been able to find health care providers. There is also a severe shortage of mental health providers in town. The number of available hospital beds is increasing every day, but Charity Hospital remains closed (although it is due to reopen this fall) and there are no mental health beds in the city.

We now see patients at several different hospitals that have not been used by Tulane before. There has also been a much smaller clinic volume than before the storms as a result of displaced folks. We did manage to keep all of our fellows in the program, but it is more difficult to recruit new fellows and residents.

At this point, New Orleans is not “better.” It will take years for health care to get back to where it was pre-Katrina. However, each day new businesses open, debris is removed, and storm damage is repaired. Importantly, people are returning home. To quote Dickens, “remember to the last, that while there is life, there is hope.” New Orleans is still alive; it is just a little under the weather.
Discover New Possibilities at the ASH Booth

You know about the groundbreaking science at ASH’s annual meeting and you’ve read the world’s leading hematology journal, Blood, but have you explored all the opportunities that the Society has to offer? At the ASH booth, you can learn how to honor a mentor, nominate an institution for participation in the International Outreach Initiative, purchase a copy of the ASH-SAP, or apply for funding for a cross-cultural experience conducting research abroad. For more information on the ASH annual meeting, visit the ASH Web site at www.hematology.org/meetings/2006.

Annual Meeting Advance Registration Available Online

Avoid lines at on-site registration counters and benefit from a discount by registering for the meeting prior to November 6, 2006. ASH encourages meeting attendees to register online, but registration can also be made by faxing the ASH registration form with credit card payment to 888-273-5708 (U.S. and Canada toll-free number) or 703-631-6288. The registration form may also be mailed along with the appropriate fees to the ASH Registration Center. For more information, visit the ASH Web site at www.hematology.org.

ASH™ UPDATES CONFLICT-OF-INTEREST REQUIREMENTS FOR ALL ANNUAL MEETING SPEAKERS AND POSTER SESSION PRESENTERS

ARMAND KEATING, MD

Dr. Keating is the Secretary of ASH.

This year, ASH has updated its conflict-of-interest requirements for annual meeting speakers and poster session presenters to remain in compliance with guidelines set forth by the Accreditation Council for Continuing Medical Education (ACCME), the accrediting body that allows ASH to provide continuing medical education (CME) credits to its attendees. The ASH leadership feels that it is imperative to continue to offer CME opportunities to physicians, and therefore finds it necessary to strengthen the Society’s policy on conflict of interest.

The Society now requires that all annual meeting speakers, session chairs, and moderators (including both invited speakers and abstract presenters) provide an oral disclosure and display a disclosure slide at the start of their presentations. If the speaker has no conflicts to report, a statement to that effect will be included on the conflict-of-interest disclosure slide. To make sure that the audience has time to absorb this information, disclosure slides must be shown for a minimum of five seconds. To ensure compliance, an audio-visual technician will advance both the title slide and disclosure slide for each presentation; after this, the technician will return control of the slides to the speaker for the rest of the presentation.

Beginning this year, all poster presenters must list conflict-of-interest information for themselves and all co-authors at the bottom of their poster. Again, if there are no conflicts to report, that will be indicated on the poster. In order to offer CME credits for the ASH Poster Sessions, all posters must include this conflict-of-interest disclosure.

The Society would like to thank all those presenting at the annual meeting for their understanding of the need for these updated conflict-of-interest requirements.
New Editor-in-Chief of Blood

(Cont. from Page 1)

She also feels that it is important to show the NIH and others involved the value of peer review in journal publishing. As chair of the NIH Assembly of Scientists, she actively participates in discussions regarding issues such as Public Access, conflicts of interest, and clinical research ethics — possible flashpoints in the current biomedical publishing world.

Even outside the realm of hematology, Dr. Dunbar feels that the research presented in Blood is of value, stating, “Hematology is at the crossroads of science and medicine. In hematology, you can study the biology of human disease and tissue. Hematology is a paradigm for other areas of medicine.”

“When I first started as Associate Editor, there were around 2,500 submissions to Blood. Now, each year, there are more than 5,000, which shows a huge increase in interest in hematology during the last 10 years.”

Dr. Dunbar graduated magna cum laude with a degree in History of Science from Harvard University and received her doctorate from Harvard Medical School. She currently heads the Molecular Hematopoiesis Section of the National Heart, Lung, and Blood Institute.

Dr. Dunbar will be the first female Editor-in-Chief of Blood, which was first published in 1946, and she feels that her appointment sends a positive message to the many other women active in hematology. Dr. Dunbar hopes to increase the diversity of the pool of associate editors during her tenure.

During the next year, Dr. Dunbar will assume increasing responsibilities under Dr. Shattil’s guidance, and her five-year term will officially begin with the January 1, 2008, issue of Blood. In Dr. Shattil’s words, “The journal will be in wonderful hands.”

ASH™ has developed an agreement with the National Institutes of Health (NIH) that creates a new option for authors to comply with the NIH policy on enhanced access. All Blood authors that publish NIH-funded articles from May 2005 forward have no obligation to submit manuscripts to the NIH archive. Blood will do this on their behalf. ASH estimates that approximately 800 articles (from May 2005 to September 2006) will be deposited into the archive in this manner.

The new option, the PMC (NIH Portfolio) Archive Program, is the result of efforts by ASH and a group of nonprofit publishers to help authors improve compliance with the current NIH public access policy while maintaining the publisher-mandated access embargoes. The pilot project will provide NIH with final articles representing NIH-funded research for an internal-use archive at NIH.

The new program will achieve NIH’s goals of managing its research portfolio and developing a digital research archive, as well as increasing compliance with its submission policy, which was previously less than 4 percent. The program will also protect the integrity of the journal article of record, maintain business models that enable the Society to fund numerous educational and research programs, and, significantly, relieve Blood authors from the burden of submitting manuscripts to NIH.

ASH believes the PMC Archive program provides a better alternative for authors and journals than a mandated policy with a shorter embargo period. For more details, visit the Blood Web site at www.bloodjournal.org.
DIAGNOSIS MYELOFIBROSIS: WHAT DO YOU DO NEXT?

Myelofibrosis with myeloid metaplasia, or simply myelofibrosis (MF), is also known as chronic idiopathic myelofibrosis, according to the World Health Organization classification system for chronic myeloid neoplasms. MF is currently classified with polycythemia vera (PV) and essential thrombocythemia (ET) as a BCR-ABL-negative classic myeloproliferative disorder (MPD). Pathogenetic mechanisms in MF include 1) stem cell-derived clonal myeloproliferation, 2) reactive bone marrow stromal changes including collagen fibrosis, and 3) extramedullary hematopoiesis. However, the primary cytogenetic event(s) has not been identified, although much attention has been given to recently described gain-of-function mutations involving the JAK2 tyrosine kinase (JAK2V617F) and thrombopoietin receptor (MPLW515L/K).

THE PATIENT

A 55-year-old woman presented with fatigue and dyspnea on exertion. Over the last three months, she had developed left upper quadrant discomfort, early satiety, night sweats, and weight loss despite good appetite. Physical examination revealed pallor and marked splenomegaly. Complete blood count disclosed anemia, thrombocytopenia, and left-shifted leukocytosis. Peripheral blood smear examination showed myelophthisis (i.e., presence of nucleated red blood cells, immature granulocytes, and dacryocytes). Bone marrow examination yielded a “dry tap” and biopsy was read out as showing myelofibrosis. How should the clinician approach the patient, henceforth?

STEP 1: CONFIRM ACCURACY OF DIAGNOSIS

Neither myelophthisis nor bone marrow fibrosis is specific to MF and one has to entertain and exclude other conditions that could mimic MF in their clinical presentation. In this regard, the therapeutically most relevant distinction is between MF and chronic myeloid leukemia. Therefore, cytogenetic studies and/or fluorescent in situ hybridization/RT-PCR for BCR-ABL are highly recommended during the initial evaluation of MF. I also recommend mutation screening for JAK2V617F as part of the initial workup. The presence of JAK2V617F excludes the possibility of reactive bone marrow fibrosis associated with infections, inflammatory processes, lymphoid disorders, or metastatic cancer. However, JAK2V617F is detected in only ~50 percent of patients with MF and can also occur in other myeloid disorders, including myelodysplastic syndrome and acute myeloid leukemia. Therefore, bone marrow histological review by an experienced clinical pathologist is required to distinguish MF from the latter disorders.

STEP 2: DEFINE PROGNOSIS FOR THE INDIVIDUAL PATIENT

Survival in MF is substantially affected by the presence or absence of risk factors that have been used to construct several prognostic scoring systems (PSS). At my institution, we use a modified Dupriez PSS, henceforth referred to as the Mayo PSS, that considers four adverse prognostic features: a platelet count of <100 x 10^9/L, hemoglobin level of <10 g/dL, leukocyte count of <4 or >30 x 10^9/L, and an absolute monocyte count of >1 x 10^9/L. In the absence of any of these four poor prognostic indica-
ASH ADVOCATES FOR FAIR PHYSICIAN REIMBURSEMENT; NEW MEDICARE RULES TO BE IMPLEMENTED JANUARY 1

Dr. Silver is Professor, Department of Internal Medicine, and Director, Cancer Center Network, at the University of Michigan.

As this issue of The Hematologist went to press, final rules concerning the physician fee schedule and the hospital outpatient payment system for 2007 were pending. These reimbursement rules are in addition to changes previously announced in a proposed rule, which incorporated changes in the practice expense methodology and revisions resulting from the five-year review of physician work values.

Proposed changes from the accepted reimbursement rules will be implemented January 1, 2007. Last-minute legislative changes are possible and could significantly alter how proposed changes actually are finalized. In addition, there has been significant interest on Capitol Hill in enacting changes in the cost of the Medicare program by tying Medicare reimbursement to reporting on various quality measures. The concept of such pay-for-performance (P4P) or “value-based purchasing” programs has been gaining acceptance and momentum across federal and private payers alike.

Unless Congress legislates changes, Medicare payments to physicians will decrease by 5.1 percent. The reduction is largely attributable to the fact that physician spending substantially exceeded the target rate established by the Sustainable Growth Rate system (SGR). The SGR is a formula that is universally considered flawed by organized medicine, as well as many members of Congress and CMS. ASH and other specialties have urged Congress and CMS to repair the flawed formula. While a couple of legislative proposals have been circulated, action is stalled in part due to the price tag and in part because increasing physician payment will cause an increase to the beneficiary Part B premium—a concept not popular, particularly right before the November elections.

Hematology-oncology is expected to see an increase in total relative values for 2007 of about 2 percent, so combined with the scheduled decrease, the specialty overall could expect about a three-percent reduction in Medicare reimbursement. Actual amounts will vary across practices, depending on the mix of services rendered. Rural states, such as Montana, North Dakota, South Dakota, and Wyoming can anticipate further cuts of up to three percent due to changes in the Geographic Practice Cost Index.

On the outpatient side, Medicare has proposed tying full outpatient reimbursement to compliance with inpatient reporting on quality measures. If hospitals fail to report on inpatient quality measures, the outpatient reimbursement may be reduced by up to 2 percent. This is another indicator of the Agency’s intent to move to a reimbursement model based on P4P.

Overall, hospital outpatient departments will receive a 3.4 percent increase in the update for inflation. Significant payment changes are proposed including increases of 20 percent for spheres codes 36515 and 36516 as well as photopheresis code 36522. Bone marrow harvesting, biopsy, and transplant codes are either kept about 20 percent for apheresis codes 36515 and 36516 as well as photopheresis code 36522. Bone marrow harvesting, biopsy, and transplant codes are either kept about 20 percent for apheresis codes 36515 and 36516 as well as photopheresis code 36522. Bone marrow harvesting, biopsy, and transplant codes are either kept about 20 percent for apheresis codes 36515 and 36516 as well as photopheresis code.

ASH has actively campaigned for Medicare to fairly reimburse physicians. This has included lobby days and advocacy campaigns to prevent the physician payment cuts and the development of hematology performance measures to be used in future P4P programs.

A complete update on the final physician payment rules and status of P4P will be presented at the ASH Practice Forum, “Pay-for-Performance: Are You Ready?” on Saturday, December 9, from 6:00-7:30 p.m. at the annual meeting in Orlando.

From left to right: ASH Vice-President Kenneth Kaushansky, MD, ASH President Kanti Rai, MD, ASH Executive Director Martha Liggitt, Esq., and ASH President-Elect Andrew Schafer, MD, meet at ASH headquarters to prepare for their visit to NIH to discuss the 2006 ASH Agenda for Hematology Research.

NEWS HEADLINES FROM WASHINGTON

Analysis of Mid-Term Elections

This issue of The Hematologist went to press prior to the November elections. Visit the ASH™ Web site (www.hematology.org) for an analysis of what the election results may mean for ASH’s legislative agenda.

House Energy and Commerce Committee Passes NIH Reauthorization Bill

The House Committee on Energy and Commerce approved by a vote of 42-1 a reauthorization bill that would reform the National Institutes of Health (NIH) and increase its funding. The legislative proposal would boost annual NIH funding by 5 percent, would create a “common fund” to promote cross-agency research, and would establish an electronic catalog of all agency research activities. It also would create a Scientific Management Review Board to review NIH’s structural organization every seven years. The Senate committee with jurisdiction over NIH had not taken up reauthorization legislation, so it is likely that new legislation will have to be introduced at the start of the next Congress in January.

Medicare Premiums Begin to Vary in 2007

Beginning in 2007, wealthier Medicare beneficiaries will pay higher Medicare premiums. A surcharge will be added to the basic premium, with higher surcharges for higher-income beneficiaries. The surcharge will be phased in between 2007 and 2009. For beneficiaries with incomes over $200,000, the monthly Medicare premium is expected to exceed $375 by 2009.

New Acting Medicare Administrator Named

On October 15, Mark McClellan, MD, PhD, stepped down from his position as Medicare Administrator. Dr. McClellan was Administrator of CMS from March 2004 through October 2006, and was instrumental in the development and implementation of Medicare Part D, the prescription drug benefit. U.S. Health and Human Services Secretary Michael O. Leavitt has named Leslie Norwalk, Esq., the new Acting Administrator for the Centers for Medicare and Medicaid Services (CMS) and Herb Kuma Acting Deputy Administrator.

Congress Heads to “Lame Duck” Session

Because the U.S. House and Senate were unable to complete action on several pieces of legislation, including the FY 07 NIH funding bill, the Congress will convene a “lame duck” session and return to Washington after the November elections. Visit the ASH Advocacy Center (www.hematology.org/takeaction) to take timely action on legislative issues affecting hematologists.

To read more about ASH’s government relations efforts, please see:

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NEWS AND REPORTS

CMS, P4P, PIMs, ABIM, ASH, and YOU .......... p.13
The Why, Which, When, and How of Azacytosine Nucleosides in Myeloid Malignancies

STEVEN D. GORE, MD

Dr. Gore is Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University.

The approval by the Food and Drug Administration (FDA) of 5-azacitidine (5AC) in 2004 and 2-deoxy-5-azacytidine (decitabine, DAC) in 2006 as two of the first three drugs approved for the treatment of myelodysplastic syndromes (MDS) represented landmarks in the study of these clonal disorders. Despite the commercial availability of 5AC for approximately two years, the optimal utilization of this agent remains unclear. The recent availability of decitabine has left many clinicians uncertain about the relative merits of these two agents and has likely increased the calls on physicians' offices by representatives of two pharmaceutical companies. From the perspective of a tertiary referral center, many clinicians continue to struggle with the appropriate use of these agents.

Why?

5AC and DAC comprise the most active class of drugs for the treatment of unselected patients with MDS. Randomized trials of each agent compared to observation have firmly established meaningful hematologic responses, ranging from well-documented single lineage hematologic improvement, which can provide important palliation of anemia, thrombocytopenia, and neutropenia, to less common complete hematologic, and at times, cytogenetic remissions1,2. While the median duration of response in these studies (15 months for DAC trial of 10 months for 5AC) was less than optimal, both agents prolonged the time-to-progressive-disease or death (progressive disease in these cases defined as the development of 30 percent marrow blasts). While this endpoint did not achieve statistical significance in the DAC study, most likely due to under-treatment of patients (see ‘Which’), the observation of this trend in the latter study strengthens the conclusion from the former study that DNA methyltransferase inhibitors positively impact the natural history of MDS.

Despite the toxicities of these drugs, treatment with 5AC has resulted in improved quality of life compared to observation3. Comparison of the phase III studies is difficult. The DAC study included fewer patients with low-risk disease and administered no greater than eight cycles of therapy. In the 5AC study, patients achieving complete response (CR) were treated with three cycles of therapy beyond CR; patients achieving responses less than CR received ongoing treatment until progression. The median number of cycles of treatment administered in the DAC study was three. Importantly, previous studies had shown that both agents require a minimum of four cycles to demonstrate hematologic response. The median time to exit from the 5AC arm in that trial was nine months. Given these important differences in study design and execution, response rate and duration were superior in the 5AC study, while toxicity was significantly less (<1 percent mortality versus 10 percent). The reasons for the apparent under-treatment in the DAC study included disease progression (32 percent), death (23 percent), adverse events (2 percent), persistent cytopenias (21 percent), withdrawal of consent in four patients (9 percent), and physician choice (6 percent). Thus, it seems likely that the dose and schedule of DAC investigated and now FDA-approved may be more toxic and difficult to administer than the approved dose schedule of 5AC. A recent randomized phase II trial of three dose schedules of decitabine (100 mg/m² total dose administered over five days) suggests a lower toxicity rate and higher response rate, with 95 percent confidence intervals around the response rate in the “best” schedule ranging from 27 – 51 percent (reported CR rate 40 percent). This important single-center phase II study will require confirmation in a multicenter setting2.

When?

Many clinicians appear to believe that azacytosine nucleosides should be reserved for high-risk or progressive MDS. However, the Silverman CALGB study of 5AC enrolled patients with all FAB subtypes, including approximately 60 percent with low-or intermediate-1-risk MDS classified by the International Prognostic Scoring System (IPSS)8. Thirty percent of the patients on the randomized trial of DAC had lower-risk disease. In both studies, eligibility required hematologic impairment sufficient to potentially benefit from therapeutic intervention. Given that these agents are active in lower-risk disease and appear to retard progression of the disease, it does not seem appropriate to limit the use of these drugs to patients with higher-risk disease. Demonstrating change in natural history in response to these agents in lower-risk disease would require randomized trials specifically in that patient population. Both agents clearly have significant single-agent activity in AML; ongoing studies will be exploring the optimal application of these drugs for that indication. Regardless of the timing of the decision to commence therapy with an azacytosine analogue, a commitment to administering a minimum of four to six cycles of drug must be made, since it may require many cycles to see the first evidence of hematologic improvement. There is currently no evidence suggesting benefit of ongoing therapy if no objective response develops within that first six-month window. Several authors advocate the administration of azacytosine analogues on schedule despite persistent or worsening cytopenias during the first four cycles of treatment2. At Hopkins, we have delayed therapy only if patients begin treatment with greater than 500 neutrophils and/or or greater than 20,000 platelets and have failed to recover to that baseline4. Responses clearly develop in patients with critical neutropenia and thrombocytopenia. Indeed, these drugs may be critically important for such patients.

How?

Based on their ability to inhibit DNMT and reverse aberrant methylation in vitro, both agents are frequently referred to as “hypomethylating agents.” It is important to note that while reversal of aberrant methylation in malignant cells has been reported associated with treatment with 5AC and DAC10, it remains unclear whether this mediates or is required for response. Administration of 5AC to patients with MDS and AML has resulted in the unexpected induction of histone acetylation4. DAC induces expression of phosphorylated histone H2AX, closely associated with double-stranded breaks in DNA (Fanday and Gore, unpublished data). Dissection of the operant molecular mechanisms responsible for the clinical responses to azacytosine analogues is critical both for the development of more active congeners and for the rational development of appropriate combination therapies.

REFERENCES

The importance of JAK2 in erythropoiesis, specifically in erythropoietin/erythropoietin-receptor signaling and in modulation of receptor expression, has been highlighted after the seminal role of the JAK2 mutant in myeloproliferative disorders (JAK2V617F) was described. The JAK/STAT pathway is evolutionarily conserved and plays an important role in cell proliferation and organism development. In this paper, Shi et al. used a Drosophila melanogaster hematopoietic tumor model to show that the role of JAK/STAT in tumorogenesis is mediated by suppression of epigenetic gene silencing, suggesting yet a third possible mechanism of action for mutated JAK2. D. melanogaster possesses a single JAK, known as Hopscotch (hop), and a single STAT, which are similar to JAK2 and STATS in higher organisms. Interestingly, a hyperactive mutant of hop, known as Tumoral lethal (Tum-l), displays a leukemia-like phenotype with hematopoietic tumors manifested as blood cell aggregates in the body cavities of drosophila and globally disrupts heterochromatome. Shi and colleagues found that several enhancers of heterochromatin (decondensed chromatin) in euchromatin were actively transcribed and deacetylated and demethylated, and, as a result, genes located in the heterochromatin area of chromosomes are less accessible to the transcription machinery of the cell. Heterochromatin, mediated by histone deacetylase, and methylation by Su(var)3-9 with subsequent binding of HP1, play an important role in the stabilization of D. melanogaster heterochromatin structure and the silencing of genes. A similar array of enzymes and nuclear chromatin-binding proteins are involved in the epigenetic silencing of genes in higher organisms. The findings of Shi et al., which identify a role for the JAK/STAT pathway in "global" reversal of heterochromatome gene silencing, are significant because they show a direct link between signaling events and gene expression. The tumorogenesis seen in the gain-of-function JAK mutant (hopTum-l) might be due to removal of the epigenetic silencing of tumor suppressor genes, a removal that could be reversed in D. melanogaster by overexpression of the heterochromatin stabilizing protein HP1. The existence of a similar mechanism in JAK2V617F-induced myeloproliferative disorders is a tantalizing possibility that demands further investigation. The work of Shi and colleagues might also explain the phenotype that is seen in cells transfected with JAK2V617F. Perhaps, wild-type JAK2 signaling counteracts the epigenetic changes induced by JAK2V617F and reverses the phenotype of cells carrying both wild-type and mutant JAK2 back to normal. Further, the mutagenesis-promoting properties of hyperactive JAK such as JAK2V617F may explain the frequent mitotic crossover in PV [present in 30 percent of PV patients] resulting in uniclonal translocations with high rate of homozygosity for somatic JAK2V617F mutation.


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**Down the Slippery Slope: Neutrophils Suppress T Cells by Depletion of Arginine**


**Why do some patients seem to accumulate large numbers of medical problems while others stay essentially healthy?** Is it genetics, is it what they eat, or does one problem directly trigger the next? In particular, why do patients with chronic inflammatory conditions seem to be at higher risk for cancer and for poor prognoses after cancer diagnosis? Does the inflammatory process promote cancer through increased oxidative damage or direct suppression of anti-tumor immune responses?

In this paper, Munder et al. show that activated human neutrophils directly suppress the ability of T cells to be activated through the T-cell receptor. This brake occurs because of a sudden depletion of the local T-cell milieu of the amino acid arginine, which is caused by the local release of arginase from neutrophil granules. Not only is overall T-cell metabolism and cell proliferation repressed, but the \( \zeta \) chain of CD3 is specifically downregulated, so that no T-cell activation signals are delivered from the cell surface after antigen binding. So in a locally inflamed environment, T cells are essentially paralyzed. One could easily imagine that local or chronic generalized inflammation would lead to depressed T-cell responses, including both response to infectious pathogens and tumor antigens.

This link to arginase secretion had been previously detected in the mouse, but many mouse cells secrete arginase, including macrophages and dendritic cells. So not in humans, where arginase production is strictly limited to neutrophils. Munder and colleagues demonstrate every step of the arginase-T-cell paralysis link in human neutrophils. In addition, by showing that neutrophils from a patient with congenital arginase deficiency do not suppress T cells, they show that arginase is specifically required for this T-cell paralysis. This is important because it suggests that specific pharmacologic inhibitors of arginase activity could be developed to specifically disrupt inflammation-induced T-cell anergy. For now, it suggests yet another reason why aspirin and anti-inflammatory homeopathic interventions might be of real benefit to our patients. And of course, this reinforces the lesson that basic scientists would be well served to closely consider folk wisdom for possible unsuspected physiology, if we are to truly uncover nature's mysteries.


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**Does Janus Have Three Faces?**

**PTEN Scores a “10” in Stem Cell Discrimination**


**It’s About Time: A New Prognostic Tool for Acute Graft-Versus-Host Disease**


Dr. Emanuel indicated no relevant conflicts of interest.

**Dr. Emanuel indicated no relevant conflicts of interest.**
A n optimal therapeutic strategy for initial treatment of follicular lymphoma remains undefined. In this paper, Press and colleagues have updated the findings of the SWOG 9911 study of sequential CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) followed by radioimmunotherapy (RIT) with the anti-CD20 131I-tositumomab regimen (Bexxar™). Ninety eligible patients were treated with six cycles of standard-dose CHOP followed by restaging four to eight weeks after cycle six. RIT was then administered for those achieving a partial or complete response, using the standard 131I-tositumomab treatment protocol. Ninety-six percent of patients had stage III-IV disease, 27 percent had “B” symptoms, 23 percent had bulky adenopathy > 10 cm, and 65 percent had intermediate- or high-risk FLIPI scores. Eighty-six of the patients completed CHOP therapy, and 77 (90 percent) of these completed RIT 1. The complete response rate improved from 39 percent following CHOP to 69 percent following RIT; 22 percent achieved partial response. With 5.1 years median follow-up, the estimated five-year progression-free survival rate is 67 percent and overall survival is 87 percent. Acute toxicities included expected levels of transient cytopenias following each phase of therapy. Late toxicities have included elevated TSH in 9 percent of patients (despite the use of Lugol’s solution or potassium iodide to block thyroid uptake of 131I), one patient with myelodysplasia (MDS) 1.4 years after trial registration, and three patients with second cancers (3 percent, said to approximate the expected rate for the study age group).

Follicular lymphoma, a highly prevalent subtype of non-Hodgkin lymphoma, remains incurable for the vast majority of patients. The clinical course historically has been typified by response and later progression following various cytotoxic therapies. However, the advent of chemoimmunotherapy approaches in the past decade appears to have changed the natural history and improved survival for the disease. The updated results presented by Press and colleagues show that progression-free and overall survival represent “the best ever observed in a study of FL by the SWOG,” according to the authors. The low rates of late toxicities observed to date, including MDS and second cancers, is reassuring. Nonetheless, it remains important for hematologists/oncologists to enroll eligible patients in the ongoing SWOG/Intergroup S0016 trial comparing the CHOP→RIT regimen with CHOP-rituximab to prospectively verify these findings. Other front-line strategies currently being tested in high-priority clinical studies include the ECOG 4402 indolent lymphoma trial of front-line rituximab followed by scheduled maintenance rituximab vs. observation and rituximab retreatment at progression. The European PRIMA study includes randomization to a four-arm rituximab-chemotherapy induction regimen followed by a second randomization of responders to rituximab maintenance therapy vs. observation. Correlative analyses of clinical risk parameters such as the FLIPI score, and biomarkers of higher- or lower-risk disease promise to further refine our ability to provide risk-adapted treatment approaches and improved outcomes for these patients.


Dr. Williams indicated no relevant conflicts of interest.
Heparins – Is the Lite Stuff Really Healthier?

Low-risk patients with thromboembolic disease can be safely treated with low-molecular-weight heparin — a more expensive cousin of standard unfractionated heparin. It is true that the cost of low-molecular-weight heparin is high. However, this approach does save money since it saves on the even higher cost of inpatient hospitalization and monitoring required for treatment with unfractionated heparin. In this paper, Kearon et al. analyzed whether a fixed dose of weight-adjusted subcutaneous unfractionated heparin was as effective as low-molecular-weight heparin for treating thromboembolic disease in outpatients. The purpose of this trial was to ascertain whether patients could be safely treated as outpatients with a fixed dosage of unfractionated heparin without adjusting the prescribed amount to aPPTT results.

In this multi-institution trial, 708 patients were randomized to receive a fixed dose of unfractionated heparin subcutaneously (333 U/kg initial dose followed by 250 U/kg every 12 hours) or low-molecular-weight heparin (100 IU/kg every 12 hours). Nineteen percent of the patients in both treatment groups had pulmonary embolisms at enrollment into the trial. After a few days of treatment, all patients were transitioned to standard warfarin therapy for three months. Approximately 70 percent of patients in either arm of the trial remained as outpatients for the entire length of the study. Recurrent thromboembolism occurred in 3.8 percent of the 345 unfractionated heparin-treated patients, and in 3.4 percent of the 352 low-molecular-weight heparin-treated patients. This met the non-inferiority primary objective of the study. The rate of major bleeding was also similar in the two treatment strategies (1.1 percent in those treated with unfractionated heparin, and 1.4 percent in those treated with low-molecular-weight heparin). There were no patients who developed heparin-induced thrombocytopenia in this study. Therefore, in this one trial, it appears that a fixed dose of unfractionated heparin (not monitored for aPPTT) was as efficacious and safe as low-molecular-weight heparin.

Metaanalysis of multiple trials has demonstrated that subcutaneous administration of unfractionated heparin is actually superior to the more commonly used intravenous delivery. However, these previous trials adjusted the dosage of subcutaneous heparin based on aPPTT monitoring. The need to monitor the aPPTT several times a day has prevented the widespread use of subcutaneous unfractionated heparin for outpatient treatment of thromboembolic disease. However, there is substantial literature that suggests that aPPTT results do not correlate well with either recurrent thromboembolism or bleeding. This implies that a fixed dosage of subcutaneous unfractionated heparin might be appropriate for the initial treatment of deep vein thromboses or pulmonary embolisms. Consistent with this idea, a few small trials have suggested that fixed doses of subcutaneous unfractionated heparin can lead to good outcomes. However, it is notable that all of these trials (including the recently published JAMA article) converted the subcutaneous therapy to oral warfarin within a few days. Therefore, it is not known whether prolonged administration of a fixed dose of subcutaneous unfractionated heparin is either safe or effective.

There is now an ever-increasing variety of pharmacologic products that may be appropriate for the outpatient treatment of thromboembolic disease (Figure). Low-molecular-weight heparin and fondaparinux can easily be used for this indication. There is a small amount of data supporting the use of subcutaneous direct thrombin inhibitors (such as hirudin) for outpatient anticoagulation. Oral inhibitors of Factor IIa (such as dabigatran etexilate) and Factor Xa (such as Rivaroxaban) appear to be promising antithrombotics. The data by Kearon and colleagues suggests that standard unfractionated heparin may be able to compete with these pricey alternative agents. Does this mean that we can all use a heparin preparation that is approximately one-twentieth the cost of low-molecular-weight heparin? Not yet, but there may still be another life left for our old friend unfractionated heparin.


CHARLES ABRAMS, MD
Dr. Abrams has served as an ad hoc consultant to GlaxoSmithKline and Portola Pharmaceuticals.
Somatic cell mutation of the gene that encodes PIGA results in the loss of formation of GPI-anchored proteins and is associated with PNH. In this paper, the investigators describe an autosomal recessive disease that results in GPI deficiency. In uncovering the etiology of childhood thrombosis and seizures in two unrelated families (but each consanguineous), a HAM test was found to be positive. GPI expression was reduced in both patients in some but not all hematopoietic cells. By homozygosity mapping and SNP analysis of the two families, they closed in on the PIGM gene as the possible culprit. Cell lines were isolated from the affected patients and their parents and radiolabeled glycolipids were isolated and analyzed. The products reached the GlcN acyl PI stage (Figure), but the cell lines failed to add additional mannose and PETN residues — implicating either PIGM or PIGX as the defective step. The combination of genetic information with the biochemical findings pointed to PIGM as the mutated gene.

The analysis put forth by this group to explain the clinical course of two families with children who presented with thrombosis at a young age is not only an admirable piece of detective work but also a lesson in the application of biochemical insight into their genetic findings. Although it would be attractive to place the defect that the investigators uncovered in the context of more general clinical application, the thoroughness of their studies (which enabled them to discern a cellular defect) is the major take-home lesson from this work. The mutation is not in the expressed enzymatic portion of the gene, but rather in the upstream promoter that binds the transcription factor Sp-1. In explaining why a gene, PIGM, that is important in development, may lead to only mild neurological defects, acetylation status of the PIGM locus is suggested to play a role in promoting sufficient biosynthesis of the PIGM product to overcome the defect in Sp-1 binding. Alternatively, other promoters were detected (e.g., GATA) that may induce expression in a more tissue-restricted manner. Since these enzymatic pathways play a critical role in development across a number of tissues, it is difficult to surmise whether other defects will be uncovered to explain some similar thrombotic complications or whether this enzymatic step is at the threshold of sustaining development but still yields clinically significant findings when affected.

LILLI PETRUZZELLI, MD, PhD
Dr. Petruzzelli indicated no relevant conflicts of interest.
Bleeding Disorders in Women:
A Damself in Distress

MARGARET RAGNI, MD, MPH

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von Willebrand disease (VWD) is the single most common congenital bleeding disorder—it is also probably the single most difficult to diagnose. The problem is that the variability of symptoms and the lack of a single diagnostic test lead to underdiagnosis, significant morbidity, and poor quality of life, thereby constituting a major public health problem.

Type 1 VWD, which constitutes over three-fourths of all cases, occurs in up to 1 percent of the population and in up to 20 percent of women with menorrhagia. It is caused by a partial quantitative deficiency of von Willebrand factor (VWF), a multifunction protein that plays a key role in hemostasis—specifically platelet adhesion in platelet plug formation and factor VIII binding to prevent its degradation in the circulation. An autosomal disorder with variable penetrance, type 1 VWD is characterized by mucosal bleeding of variable severity and frequency, including menorrhagia, epistaxis, postpartum, and postoperative bleeding. Although genetic defects have been identified in some cases of VWD (usually these are primarily single-amino-acid substitutions leading to defective VWF secretion or clearance), the genetic defects underlying most forms of type 1 disease are less well defined than in more severe type 2 and 3 disease.

According to the VWD Subcommittee of the International Society of Thrombosis and Hemostasis, diagnosis is based on the presence of bleeding symptoms and low VWF activity (based on ristocetin platelet aggregation, VWF:RCOF, or collagen binding, VWF:CB), low VWF antigen (VWF:Ag), low FVIII activity (FVIII:C), and normal VWF multimers. These laboratory assays, however, may be variable and may also be affected by extragenic factors (hormones, exercise, ABO blood group). Further, they are difficult to perform and affected by sampling and storage conditions. Although in general the lower the VWF activity the greater the bleeding tendency, the diagnosis is difficult in those (the majority) with mildly decreased to borderline VWF levels that overlap with those in the normal control group. Further, the natural history of the disease is not well known and treatment remains suboptimal. Current therapies are invasive, of short-duration, and, if plasma-based, costly and subject to potential infectious agent risk. Among VWD women with menorrhagia, hormonal therapy is the primary treatment choice, but it is nonspecific and ineffective in the majority.

Because of the clinical and laboratory variability, it has been argued that VWD is not truly a disease but rather a marker of bleeding tendency. Although the specificity of symptoms and laboratory assays for type 1 VWD are low, the lack of a test of significance by hope, specificity is not sufficient to deny the existence of type 1 VWD. According to Webster’s unabridged dictionary, type 1 VWD fulfills the definition of a disease, as “an impairment … that interrupts or modifies the performance of the vital function… being a response to… genetic anomalies.” Denying the existence of a disease on that basis is potentially dangerous for the female patient and the health-care system caring for her. Without a diagnosis, which constitutes the focal point of prescribing medical therapy and communicating with physicians and affected patients, management would be difficult at best. Shepherding a patient through the current health care system without a diagnosis could severely jeopardize her health care, leading to delays in treatment, difficulty in obtaining insurance referral, refusal of medical reimbursement, and potentially alternative incorrect diagnoses—in a word, chaos in her health care.

Yet there is room for hope. First, a new quantitative bleeding scoring system has been developed with high sensitivity and specificity for VWD. The application of such a scoring system in, for example, the preoperative clinic could identify individuals who require VWD testing and hematology consultation, potentially averting bleeding complications. Second, several large multi-center phenotype-genotype studies of VWD kindreds in Europe and the U.S. are seeking to determine the relationship of clinical and genetic markers of VWD. This will hopefully improve our understanding of the pathophysiology and diagnosis of VWD. Finally, clinical trials of new hemostatic agents are underway, including a phase II study of interleukin-11, which has shown promise in the VWD dog model. Future research studies to determine the optimal diagnostic and management algorithms for VWD are essential. Better approaches to the diagnosis of VWD in children, who are not yet developed bleeding symptoms, are greatly needed. Recombinant VWF should be a treatment option for individuals unresponsive to standard therapy and should not be dictated by the size of the affected population requiring it. Finally, optimization of patient-physician communication and empowerment of those with bleeding disorders is essential to assure their success in navigating a health-care system that doubts not only their symptoms, but also their diagnosis.

Editor-in-Chief’s Note:

Clearly, the subject of whether VWF is a diagnostic test for type 1 VWD versus whether it is a marker or risk factor for bleeding tendency is a controversial one. We welcome comments (both for and against) to be submitted to The Hematologist. Additionally, we want to remind our readers aware this and other topics will be the subject of a special symposium at 2006 ASH Annual Meeting entitled, “Bleeding Disorders in Women’s Health.” Be sure to attend on Saturday, December 9, from 2:00 – 3:30 p.m., in Halls F3-F4 of the West Building, Orange County Convention Center.
Not since 1987 has there been a Match for the selection of fellows in adult hematology and/or oncology. In early 2004 the Committee on Training Programs for ASH and the ASCO Training Programs Committee proposed a return to the Match, beginning with the 2006 recruiting year. The proposal was endorsed by the respective executive committees of ASH and ASCO, setting the stage for a renewal of the Match for adult hematology, oncology, and combined training programs. The driving interest in establishing the Match was to broaden the pool of applicants to each participating program and to ensure that positions are presented to applicants in the most fair and equitable fashion.

The process began in the fall of 2005 with a concerted effort by a joint ASH/ASCO task force, led by Dr. Linda Burns (ASH) and Dr. William Gradishar (ASCO), to obtain commitments from at least 75 percent of hematology and oncology programs. The efforts of the task force were successful with commitments from 94 percent of all training programs by November 1, 2005, the deadline for enrollment in the Match.

Applicants and programs submitted their final rank order list by June 7, 2006. Match day was June 21. As a result of the Match, 93 percent of all adult hematology programs and 98 percent of adult oncology and combined programs filled on Match Day.

The immediate effect of the Match was to increase the number of applicants to each program. There were 205 applicants for the eight participating hematology programs, 490 applicants for the 15 oncology programs, and 872 applicants for the 114 combined programs. Information about the applicant pool is also notable. The demographics of the applicant pool showed that a majority of applicants graduated from medical schools in the United States (approximately 41 percent overall), and male applicants were more common than female applicants by a 2:1 margin.

ASH and ASCO conducted a post-Match survey and found that the overall satisfaction rate was high. Of the responders, 100 percent plan to participate in the 2007 Fellowship Match. The success of the Match was a result of the programs being kept well informed about the process, and the majority of those surveyed felt that the applicants were well informed as well. The staff from ASH, ASCO, and the National Resident Matching Program can be commended on their diligence and hard work in assuring a smooth transition back to the Match.

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In research, it is often easy to become so engrossed in what you are doing that you cannot see the flaws or think beyond your current plans. However, during my week at the CRTI my tunnel-vision eyes were opened to aspects of clinical research that enhanced the project and made me and my project better than I would have thought possible. Not only did new and relevant ideas emerge through the conference, but so did new collaborations and mentor/mentee relationships. I already had a great relationship with my mentor — he has my same passion, a strong background in my area of interest and clinical research, and genuine willingness to help me in any way possible — but new personal examples displayed at the CRTI (even by my mentor) illustrated to all the trainees how to make their research even better and stronger. There were excellent faculty lectures in areas relevant to career development and clinical research in hematology/oncology. Another extremely inspirational aspect experienced throughout the week was the faculty presentations on career perspectives. The faculty shared their personal experiences in clinical medicine, research, career development, and the balance between personal and professional life. It was amazing to hear experts in our field speak about their experiences having been where I am now. Everyone involved with the CRTI wanted to be there and it showed. I could not ask for a better experience. I am so inspired by all involved in the CRTI project. It is a remarkable example for young investigators in any area of medicine. I can only imagine that the ASH CRTI, as well as my many mentor/mentee relationships, will simply improve with time.

The Mentor’s Perspective (Dr. Richard Lottenberg)

Throughout my academic endeavors I have had excellent mentors. This was particularly true for fellowship training, and my experiences have had a profound influence on how I provide guidance to fellows and graduate students. Participation in the ASH CRTI has taken the mentoring experience to a new level, and the summer workshop has become a highlight of my professional activities. The curriculum and interactive format provide an exceptional framework for enhancing research project and career development. However, it is the synergism of a faculty dedicated to clinical research training and the talented and highly motivated trainees working together that make the mentoring process so effective for all participants. The small group sessions and one-on-one interaction with trainees are particularly rewarding because of the ability to provide individual attention and to readily obtain feedback. As the week moves along, I find my contributions are amplified by the input provided to each of us by the biostatisticians, faculty, and other trainees. It is gratifying to see the refinement of each project plan progress at such a rapid pace. The workshop is only the beginning of my involvement as a mentor. I look forward to staying in contact with members of the small group to discuss research progress, as well as getting together with all the trainees at the CRTI session at the ASH annual meeting. Participation in the ongoing career development process makes it so worthwhile for me. I have certainly received more than I have given in my association with the CRTI and it has been a wonderful experience.
For over thirty years the American Society of Hematology (ASH) has recognized individuals in the field of hematology for their outstanding contributions. As two of the nominators of this year’s impressive awardees, we are pleased to highlight the winners of the Society’s Honorific Awards — the E. Donnall Thomas Lecture & Prize, the William Dameshek Prize, and the Henry M. Stratton Medal. These awards give the ASH membership a unique opportunity to step back and applaud great achievements that have lasting impacts on our field and the work we do.

In recognition of his fundamental contributions to science and his impact on the hematology field, Dr. Richard Stanley, the 2006 recipient of the E. Donnall Thomas Lecture & Prize, Dr. Stanley, the Renee and Robert A. Belfer Professor of Developmental Biology and Chairman of the Department of Developmental and Molecular Biology at the Albert Einstein College of Medicine, has made seminal discoveries in hematology research regarding the development and biology of macrophages, as well as regarding the nature of signal transduction through tyrosine kinase receptors. Specifically, Dr. Stanley isolated and identified colony-stimulating factor-1 (CSF-1) as the primary regulator of tissue macrophage and osteoclast production. He defined its receptor, physiology, and roles in development and neoplasia. He also identified and elucidated the function of several signaling molecules that act downstream of the CSF-1 receptor. Dr. Stanley has established several widely used mouse models to investigate the role of CSF-1 and the CSF-1 receptor in development and disease. These discoveries have taught us how monocytes and macrophages develop and grow, how they interact with their stroma, and how growth factors can direct the functions of hematopoietic cells. Dr. Stanley has also been an outstanding mentor to several generations of scientists. Dr. Stanley’s lecture, “Colony Stimulating Factor-1 in Development and Disease” will take place on Saturday, December 9, at 12:30 p.m. during the ASH annual meeting.

This year’s William Dameshek Prize will be awarded to Dr. Riccardo Dalla-Favera. Dr. Dalla-Favera, Director of the Herbert Irving Comprehensive Cancer Center of Columbia University and Jeremy and Percy Uris Professor and Director of the Institute for Cancer Genetics, has made seminal discoveries in the area of lymphoma biology. His discoveries in this area started with his central role in the identification of c-myc as the oncogene involved in the (t(8;14)) translocation characteristic of Burkitt’s and other lymphomas. More recently, Dr. Dalla-Favera discovered and cloned BCL6, a gene located on chromosome 3q27, which is the most frequently involved locus in diffuse large B-cell lymphomas (DLBCL). His subsequent work showing that BCL6 is a master regulator of B cell differentiation revealed a critical link between the normal functioning of the immune system and the development of DLBCL. Along these lines, Dr. Dalla-Favera found that the enzymatic machinery that generates high affinity antibodies by mutating the immunoglobulin loci in B cells often makes “mistakes.” These errors often result in the introduction of point mutations into other genes that can alter their function. Remarkably, the gene most commonly targeted in this way is BCL6, which as a consequence may become constitutively expressed. Dr. Dalla-Favera has gone on to show that this constitutive expression of BCL6 directly causes DLBCL. Taken together, much of what is known about the pathophysiology of aggressive lymphomas is due to Dr. Dalla-Favera’s seminal discoveries in this field. His impact on the field is even greater since, as a role model, he has inspired and encouraged many others. The William Dameshek Prize will be presented to Dr. Dalla-Favera on Tuesday, December 12, at 10:30 a.m. during the Presidential Symposium at the annual meeting.

The Henry M. Stratton Medal is being awarded to Dr. Jack Hirsh. A former Chairman of the Department of Medicine and the Founding Director of the Henderson Research Center, Dr. Hirsh (currently Professor Emeritus in the Department of Medicine at McMaster University in Hamilton, Ontario) established a thrombosis program at McMaster University that has been pre- eminent in thrombosis research for over three decades. He has trained scores of scientists who now head up thrombosis units throughout the world. Dr. Hirsh’s investigation of heparin and warfarin set the standards for their dosing and clinical use internationally. He also pioneered the standardization of laboratory monitoring and dosing of warfarin, thereby increasing its safety and expanding its use to patients that had been denied the benefit of this oral anticoagulant. His work elucidated the unique characteristics of low-molecular-weight heparin and uncovered its clinical advantages. Dr. Hirsh will be presented with the Henry M. Stratton Medal on Tuesday, December 12, at 10:30 a.m. during the Presidential Symposium.

If you would like to nominate an ASH member for one of these prestigious awards in 2007, visit the ASH Web site at www.hematology.org/education/awards/honorific.cfm for nomination information.
WHAT’S ON THE WEB

The ASH™ Web site offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH. At www.hematology.org you can:

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.

Learn about the ASH NEW MEMBER RECEPTION, (www.hematology.org/meetings/2006/attendee/social_events.cfm), an opportunity for new members to the Society to socialize while learning about programs and services offered by ASH.

Register (https://reg.jipargo.com/ash06) online for the 2006 ASH ANNUAL MEETING.

Access the latest annual meeting PROGRAM INFORMATION (www.hematology.org/meetings/2006).

Buy tickets for the ALL-ASH RECEPTION (www.hematology.org/meetings/2006/attendee/social_events.cfm), where all meeting attendees can enjoy dessert and dance the night away.

Learn about the ATTENDEE SERVICES (www.hematology.org/meetings/2006/attendee/attendee_services.cfm) available to all attending the 2006 ASH Annual Meeting.

Browse the TRAINEE GRANTS CLEARINGHOUSE (www.hematology.org/education/training/grants_clearinghouse.cfm), a comprehensive list of research grants for hematology trainees.

MARK YOUR CALENDAR

NOVEMBER

1, 14, AND 15
Master Classes in Hematology: Challenges in the Understanding and Diagnosis of Complement-Related Hemolytic Anemia
World Wide Web www.cmknowledge.com

4 – 8
11th International Conference on Differentiation Therapy and Innovative Therapeutics in Oncology
Versailles, France www.icdt2006.org

7 – 10
American Academy of Pediatrics National Conference and Exhibition
Atlanta, GA www.aap.org/nce

8 – 11
Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow
New York, NY www.mssm.edu/tcf

9 – 11
Neoplastic Hematopathology Update: New Insights into Old Questions
Rio Grande, Puerto Rico www.unmc.edu/hematopathologyupdate

9 – 11
Innate Immunity: Receptors, Response, Regulation
San Antonio, TX www.leukocytebiology.org

15
The Crossroads of Anemia and Aging
Dallas, TX www.anemia.org

29 – DECEMBER 3
Fifth International Congress on Autoimmunity
Sorrento, Italy www.kenes.com/autoimmunity

DECEMBER

5
2006 Leadership in the Healthcare Markets
New York, NY www.execforum.net

9 – 12
48th Annual Meeting of the American Society of Hematology
Orlando, FL www.hematology.org

9 – 13
48th Annual Meeting of the American Society for Cell Biology
San Diego, CA www.ascb.org

JANUARY

16 – 18
Stem Cell Transplantation in Children: Current Results and Controversies
San Diego, CA www.cincinnatichildrens.org

25 – 26
The Stanley J. Korsmeyer Symposium - Cell Death and Cancer: Opportunities for Therapeutic Intervention
Boston, MA www.aacr.org

25 – 27
Ninth International Symposium on Febrile Neutropenia
Valencia, Spain www.imedex.com