Hematopoietic Stem Cells: Nature’s Unpredictable Child


To maintain the enormous daily hematopoietic cell output (approximately 1 x 10^12 cells/day), terminally differentiated blood cells are continually produced from highly proliferative but short-lived progenitors, which in turn arise from a rare population of quiescent hematopoietic stem cells (HSCs). Understanding how individual HSCs contribute to blood cell formation throughout a lifetime has remained a subject of debate. In this paper, McKenzie and colleagues studied individual human HSCs and found substantial variation in proliferation kinetics and self-renewal capacity implying that HSC fate is unpredictable before they enter the more rigid downstream developmental programs.

Hematopoietic cell repopulation following sublethal irradiation of the nonobese diabetic-severe combined immunodeficiency (NOD-SCID) mouse has emerged as the “gold standard” surrogate assay for studying human HSCs. The human cells that repopulate these mice are functionally defined as “SCID mouse-repopulating cells” (SRCs), SRCs express CD34 and are lineage-negative (Lin-), and distinct SRC activities can be found in the CD34+ and CD34- subfractions. McKenzie and colleagues generated more than 600 individual human SRCs from placental and umbilical tissues that were transduced with a lentivirus to track the clonal ancestry of the human cells after injection and evaluated their repopulating activity and self-renewal over a seven-month period of analysis in serially transplanted NOD-SCID mice. Primary transplant recipients showed that only a subset of clones in the injection site (right femur) were also present in other bones, indicating that only some SRCs divided and migrated to other hematopoietic tissues. Individual SRCs collected from primary recipients were heterogeneous in terms of self-renewal, with some clones making substantial yet fluctuating contributions over time to all hematopoietic territories and cells of secondary mice, and others not engrafting after serial transplantation. Evidence that clonally related daughter cell pairs have distinct and unpredictable repopulation kinetics provides the strongest support favoring this stochastic model for hematopoiesis.

The paper by McKenzie and colleagues successfully brings together a wide range of experimental methodologies to now address the key issue of how human HSCs act in vivo. The considerable heterogeneity among stem cell fate and self-renewal implies that this unpredictability likely arises through HSC interactions with as-of-yet undefined extrinsic properties (i.e., HSC niche occupancy and cytokine exposure) or intrinsic properties (i.e., asymmetric distribution of intracellular proteins and alterations of signal transduction pathways). If HSC self-renewal and proliferation kinetics are governed by probabilistic elements, then the current strategies to identify a molecular stem cell signature by profiling global gene expression of pooled yet static HSC populations may prove unreliable. Also, as the resemblance between normal and malignant stem cells deepens, the understanding of how stem cell behavior can be modulated by extrinsic and intrinsic factors will identify novel targets for cancer therapeutics.
The Hematologist: ASH News and Reports

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ASH™/EHA POLICY FORUM: ROADMAPS?
WE NEED GPS NAVIGATION!

WILLIAM G. WIERDA MD, PhD
Dr. Wierda is Assistant Professor of Medicine in the Department of Leukemia at the University of Texas M.D. Anderson Cancer Center.

At the Plenary Policy Forum during the 2006 ASH™ Annual Meeting, we had the pleasure of hearing presentations from two of the most prominent health officials in science and medicine, Colin Blakemore FMedSci, FRS, Chief Executive of the Medical Research Council since 2003, and Elias Zerhouni, MD, Director of the National Institutes of Health since 2002. During the forum, Dr. Zerhouni described the current NIH funding crisis as “The Perfect Storm.” The bottom line for me was that it is our responsibility to enlighten our House Representatives, Senators, and the President and educate our patients and the public to do the same. This is the only way for us to make lawmakers aware of our funding crisis and biomedical research’s dismal outlook for the future, given the current level of NIH funding.

Dr. Zerhouni knows the recent great advances in biomedical research — he reviewed many of them with the Senate Appropriations Subcommittee when he made his 2007 budget request. Dr. Zerhouni should be frustrated by the budget restrictions and reductions and probably is uneasy when he speaks to large groups such as the ASH/EHA Plenary Policy Forum. Yet, his testimony to the Senate Subcommittee on Labor-HHS-Education Appropriations regarding the FY2007 budget request was surprising. He spent a significant amount of time describing the tangible and unprecedented advances in cardiovascular disease, stroke, cancer, HIV/AIDS, influenza, and diabetes. However, he made no mention of a need to expand the research basis and funding — owing to the new research opportunities that came out of these advances — nor did he mention the record number of new grant applications to the NIH, or the decline in the rate of new grant application funding from 31 percent in 2003 to the current projection of 19 percent for 2007. To someone with pedestrian political interests, this seems like it would have been an opportune time to make our lawmakers aware of our needs; however, Dr. Zerhouni requested the same level of funding for 2007 as for 2006, without even a request to keep up with inflation.

He also spoke of making medicine predictive, personalized, and preemptive. These are goals that, in my humble opinion, will only be realized with continued growth and support. This is why we must, ourselves, educate the House, Senate, President, and the public in order to see that our funding needs are met.

In 1999, Congress initiated and followed through with a bipartisan goal to double the NIH budget over five years. As a result, significant progress and advances were made during those years. For example, the human genome sequencing was completed, the importance of epigenetic regulation of gene expression in aging and disease was realized, advances were made in understanding the role of micro-RNAs in cancer pathogenesis, and new techniques were developed for biologic imaging and computing, to name only a few. With recent advances, whole new fields of basic and applied research were discovered for study. Certainly, new and added resources are required to fully capitalize on this growth and discovery.

Since 2003, there has been no budgetary growth — in fact, there has been reduction and contraction. NIH’s budget in 2004 and 2005 failed to keep up with the inflationary cost of doing biomedical research. In 2006, it was cut for the first time in 36 years, by $62 million. This has demoralized established and experienced investigators and discouraged young investigators from pursuing a career in biomedical research.

In this era, biomedical research must be a global effort. With technology and the availability of information, we must consolidate, organize, and thoughtfully tackle an agenda for biomedical research, including our agenda for hematology research. We, as hematologists, must partner with NIH. In turn, NIH must partner with the MRC and other national bodies. ASH and EHA must double their efforts to search for a more profound way to impact and influence how government funds are allocated for biomedical research.
EDITOR SEARCH ANNOUNCEMENT

The American Society of Hematology is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist (term: 2009-2011).

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

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

The Hematologist: ASH News and Reports

c/o Molly Polen, Managing Editor

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Hematology 2006 and the Program and Abstracts Book

Did you miss the 2006 ASH™ Annual Meeting? Check your mailbox — all ASH members who were not able to attend the annual meeting will be receiving a copy of Hematology 2006, the American Society of Hematology’s Education Program Book.

Need an extra copy? Additional copies of both Hematology 2006 or the 2006 Program and Abstracts Book (the abstract issue of Blood) can be ordered from the online ASH store. Hematology 2006 includes review articles from the 2006 ASH Annual Meeting Education Program — each chapter relates to a session presented. The 2006 Program and Abstracts Book contains all of the abstracts submitted for the 2006 annual meeting as well as speaker, exhibit, award, and general ASH information.

If you have questions about the 2006 Program and Abstracts Book or the Education Program Book, e-mail customerservice@hematology.org.

A two-day workshop on “MicroRNA in Cellular Development and Hematopoiesis,” sponsored by the Hematology and Endocrine Biology Programs of NIDDK at the National Institutes of Health, will be held at The Historic Inns of Annapolis Conference Center, on April 23 and 24, 2007. This workshop will review current information on the biogenesis and function of miRNAs and on how miRNA-mediated post-translational regulation influences organ and tissue development and function, with a particular focus on hematopoiesis. For information about registration and abstract submission, contact Amy Amerson of The Scientific Consulting Group at 301-870-4980 or aamerson@scgcorp.com.

AWARD OPPORTUNITIES AT ASH

ASH has 10 award opportunities to help hematologists throughout their careers. Members can access the 2007 applications for the Trainee Research Award, Clinical Research Training Institute (CRII), and Mentor Award applications online.

- The Trainee Research Award is open to medical students, residents, and selected undergraduates and provides monetary support for a three-month research project and travel to the ASH annual meeting. Applications must be submitted by March 15, 2007.

- The prestigious CRII provides mentoring, career development, and research project protocol refinement to 20 hematology fellows and junior faculty each year through the year-long program. Applications must be submitted by March 30, 2007.

- Through the ASH™ Mentor Award you can say “thank you” to someone who has dedicated his or her time and attention to teaching the next generation or who has personally made an impact on your career development. Applications must be submitted by May 4, 2007.

For more information or to download an application, visit the ASH Web site at www.hematology.org/education/awards.
Highlights of 2006 ASH Annual Meeting

(Cont. from Page 1)

Elliott discussed the results of trials using inhibitors of vascular endothelial growth factor (VEGF). Dr. Shahin Rafii discussed the role of angiogenesis inhibitors in hematologic conditions, and Dr. Brian Kini discussed the results of trials using anti-angiogenesis agents in solid tumor malignancies.

On Sunday, the inaugural ASH Mentor Awards were announced (see articles on pages 12 and 13). This was followed by the Plenary Scientific Session, highlighting the top six abstracts submitted to the meeting. After being introduced by Dr. J. Evan Sadler, Dr. Harumt Weiler from the Blood Research Center of Milwaukee delineated mechanisms, described in abstract #1, for mortality reduction of activated protein C (APC) in sepsis in a mouse model. He reported that the cellular effects of APC can be distinguished from the anticoagulant effects — and that the latter do not appear to be required for the survival benefit in sepsis.

Introduced by Dr. Dieter Hoelzer, Dr. Jacob M. Rowe from Rambam Medical Center in Haifa, Israel, presented abstract #2, the final results of the international AML trial (MRC UK ALL AII/E COG E2993), which randomized patients with ALL in first complete remission to consolidation with allogeneic stem cell transplant, autologous stem cell transplant, or conventional chemotherapy. He reported superior survival for patients who received allogeneic transplant, but, surprisingly, this benefit was limited to those with standard risk disease. Moreover, survival was superior for all patients in the conventional chemotherapy arm compared to the autologous transplant arm.

After being introduced by Dr. Nancy Andrews, George C. Shaw, a medical student in the lab of Dr. Barry Paw at Brigham and Women's Hospital in Boston, presented abstract #3. Shaw and colleagues found that the mitoferrin (MFRN) protein was aberrantly spliced and non-functional in children with erythropoietic protoporphyrin (EPP) who did not have the more common mutation in ferrochelatase. These findings underscore the importance of mitochondrial processing in heme synthesis.

Dr. Mark Minden introduced Dr. Richard F. Schlenk from the University of Ulm in Ulm, Germany, who presented abstract #4. Dr. Schlenk's group examined patients from four separate clinical trials with AML in the "intermediate risk" category with no apparent cytogenetic mutations for presence of several specific molecular markers. They found improved outcomes with the NPMI+ / FLT3-ITD and CEBPA mutations in patients less than 48 years of age, indicating that it may be possible to individualize treatment approaches for AML patients.

Abstract #5, presented by Dr. Alessandro M. Vannucchi from the University of Florence, Italy, reported a tight correlation between the proportion of mutant JAK-2 allele in patients with polycythemia rubra vera at diagnosis and major clinical events. Dr. Vannucchi’s abstract was introduced by Dr. Kenneth Kauhansky.

Finally, after being introduced by Dr. Jeffrey I. Weitz, Dr. Henry R. Buller from Academic Medical Center in Amsterdam, The Netherlands, presented abstract #6, the results of the trial conducted by the Van Gogh Investigators comparing once-weekly idraparinux with heparin and vitamin K antagonists for treatment of venous thrombosis. In results that surprised almost everyone, idraparinux was the winner in the DVT trial over heparin and vitamin K antagonists, but the roles were reversed in the PTE trial. The confounding variable was a lower than expected incidence of recurrent thrombosis in patients receiving heparin and vitamin K antagonists. This will require additional studies.

Dr. Aaron Ciechanover from the Israel Institute of Technology, recipient of the 2004 Nobel Prize in Chemistry, delivered the Ham-Wasserman Lecture on Monday. Dr. Ciechanover described how research on protein degradation and the ubiquitin-proteasome system has changed our understanding of multiple basic cellular processes and treatment of diseases such as cancer and neurodegenerative disorders.

The theme of the Presidential Symposium on Tuesday was microRNAs (miRs), naturally-occurring RNAs that regulate gene expression by causing degradation of complementary mRNA. Of note, the 2006 Nobel Prize in Medicine was awarded to Drs. Andrew Fire and Craig Mello for their discovery of gene regulation by this naturally-occurring RNAs that regulate gene expression by causing degradation of complementary mRNA. Dr. James Dahlberg led off the symposium by describing specific miRs associated with poor-prognosis lymphomas. Dr. Chang Zheng Chen described the miRs involved in hematopoietic lineage differentiation and maturation. Finally, Dr. Carlo Croce discussed the importance of miRs in leukemogenesis, highlighting his work on correlations between expression of specific miRs and subtypes of AML. During the Presidential Symposium, Dr. Kanti Rai also presented the William Daneshek Prize for recent outstanding contributions to the field of hematology to Dr. Ricardo Dalla-Favera of the Institute for Cancer Genetics and Herbert Irving Comprehensive Cancer Center at Columbia for his seminal work on the understanding of abnormalities of specific genes in the leukemias. The Hematology Society of Wisconsin over a career was presented to Dr. Jack Hirsh for his work on thrombosis and antithrombotic agents.

Would you like to learn more about what was presented at this year’s ASH meeting? Mark your calendar for the second annual Highlights of ASH, taking place on February 9-10, 2007, at the Ritz Carlton in Marina Del Rey, CA. This meeting is geared toward practitioners and is the only "Highlights" meeting that is produced by ASH in collaboration with the original researchers.

The educational program will include expert analysis of ground-breaking research from abstracts presented at the 2006 ASH Annual Meeting. Attendees will not only hear expert analysis, but will discuss real cases with leading experts in the field.

For more information, visit www.hematology.org/meetings/highlights.
THE PATIENT

A 74-year-old African-American woman was found to have a serum ferritin concentration of 2012 µg/L and transferrin saturation of 33 percent on screening blood tests. She was on anti-hypertensive and cholesterol-lowering medications and multivitamins with iron, but had no history of blood transfusions or blood donations. She did not drink alcohol. Repeat blood testing revealed ferritin 2012 µg/L, transferrin saturation 34 percent, hemoglobin concentration 13.2 g/dL, and mean corpuscular volume 91 flL. Testing for hepatitis B surface antigen, antibody to hepatitis C, the C282Y and H63D mutations in the HFE gene, and the Q248H mutation in the ferroportin gene was negative. Apart from a slightly elevated gamma glutamyl transferase concentration of 43 U/L, liver function tests were normal. A diagnostic needle liver biopsy revealed grade 3 hepatocellular iron in a perportal distribution, the presence of macrophage iron, minimal portal inflammation, and otherwise normal hepatic architecture. The patient was advised to discontinue multivitamins with iron and to undergo a weekly phlebotomy program with the endpoint of serum ferritin <20 µg/L, but the patient complied with the program only sporadically.

WHAT IS THE DIFFERENTIAL DIAGNOSIS OF AN ELV EATED SERUM FER RIT IN CONCEN -

TRATION?

Infectious and other inflammatory processes, hepatic disorders such as alcoholic and viral hepatitis and non-alcoholic steatohepatitis, increased body-iron stores resulting from multiple blood transfusions, anemias characterized by ineffective erythropoiesis, and mutations in HFE or other iron pathway-related genes are all potential causes of increases in serum ferritin concentration. In addition, any acquired anemia that is not due to blood loss or iron loss is associated with an increase in macrophage stores and serum ferritin, because iron formerly present in hemoglobin enters storage during development of anemia. Inflammatory processes are typically characterized by reduced transferrin saturation in association with increased serum ferritin concentration. On the other hand, patients with elevated iron stores or hepatic disorders tend to have transferrin saturations above the population mean in association with increased serum ferritin concentration.

HOW OFTEN ARE PRIMARY INCREASES IN BODY IRON STORES DUE TO CONDITIONS OTHER THAN HFE MUTATIONS?

Homozygosity for HFE C282Y, the most commonly recognized cause of primary increases in body-iron stores in persons of European ancestry, has a prevalence of about 440/100,000 in Caucasians but only 14/100,000 in African-Americans. About 90 percent of male and about 55 percent of female C282Y homozygotes have elevated serum ferritin concentrations, at least to a mild degree, but the occurrence of organ damage is far lower. The ferroportin Q248H mutation seems to be unique to persons of African ancestry. Heterozygosity for ferroportin Q248H occurs in about 10 percent of African-Americans and has been associated with increased iron stores in a minority of individuals. Mutations in a number of other genes, including those for transferrin receptor 2, hemosiderin, and hepcidin, are associated with increased iron stores but rare in the population. Iron overload on a dietary basis is well described in sub-Saharan Africa and may be associated with an as-yet-undefined genetic predisposition. Whether taking multivitamins with iron contributed to increased iron stores in the patient presented here is not clear. Frequently, increased iron stores, usually of mild degree, are documented in patients of various ethnic groups without a history of blood transfusions and without the presence of HFE mutations. In a recent analysis, serum ferritin concentration >200 µg/L for women or >300 µg/L for men in combination with transferrin saturation >29 percent for women or >35 percent for men occurred in 6.7 percent of more than 27,000 African-American primary care patients ≥25 years of age, and these patients were at increased risk for elevated body iron stores and/or liver disease.

HOW SHOULD THE PATIENTS WITH INCREASED IRON STORES BE MANAGED?

Clearly, heavily iron-loaded patients are at risk for cirrhosis, hepatoma, and heart failure and iron should be removed by phlebotomy therapy if anemia is not present and by iron chelation if phlebotomy is not possible. Heavy iron loading associated with these complications occurs in only a small minority of HFE C282Y homozygotes, ferroportin Q248H heterozygotes, and patients with primary increases in iron stores of undetermined etiology. Mild increases in iron stores are associated with symptomatic purpura cutanea tarda, and some studies suggest such elevations may be associated with a general increased risk of cancer, the development of hepaticellular carcinoma in the absence of cirrhosis, and an increased risk of diabetes mellitus. Further studies of the proper management for various degrees of iron overload are needed. At present, we believe that in general it is prudent to remove excess body iron of even mild or moderate degrees.

FURTHER READING


Dr. Gordeuk has received consulting fees from Amgen in the past year. Dr. Onyekwere indicated no relevant conflicts of interest.
As most of us are now aware, the November elections have drastically changed the political landscape in Washington. After more than a decade with the Republican Party in control of Congress, the Democrats have gained control of both the Senate and the House of Representatives. However, in addition to changing the face of power in Washington, these elections also stand to impact a number of issues of concern to ASH membership, including NIH research funding, Medicare payments to physicians, and stem cell research.

This month, as Congress reconvenes, the Democratic Party will be setting the congressional agenda in both the House and Senate for the first time since 1995. This change in leadership will have the impact of establishing a new set of priorities. Already, several incoming congressional committee chairs and Democratic leaders have indicated that a number of health-related issues will top their agendas for the upcoming year.

With health and research advocates such as Senator Edward Kennedy (D-MA) and Representative John Dingell (D-MI) ascending to the chairmanships of some of the most influential committees in Congress, issues of importance to hematologists and other health advocates are on the table. There are concerns that the most influential committee chairmen, such as the new leadership in the House and Senate, will not give health-related issues the same attention and funding as they did in the past. In addition, the new Congress will face pressure to continue to allocate funding for health-related issues, such as the war in Iraq and homeland security.

Perhaps the issue reaping the greatest amount of attention in the wake of the congressional elections is that of stem cell research. A deciding factor in several recent congressional races across the nation, the issue of expanding federal funding for stem cell research will likely once again be at the forefront of the congressional agenda. In her plan for the first 100 hours of the 110th Congress, Speaker of the House Nancy Pelosi (D-CA) promised that Congress will “promote stem cell research to offer real hope to the millions of American families who suffer from devastating diseases.” While the expansion of federally funded stem cell research enjoys bipartisan support in both the House and the Senate and easily passed both chambers in the 109th Congress, the Bush Administration remains opposed to such an expansion and has developed quality measures for hematologists to be used in a future pay-for-performance program. A detailed analysis of the new legislation is available on the ASH Web site at www.hematology.org.

As for Medicare, Congress staved off scheduled physician payment cuts this year, but it is unclear if it will be able to fix the problem permanently. While the Democrats have been sympathetic to repealing the Medicare payment cuts for doctors, the new leadership has focused more on the Medicare drug benefit, and it is not clear how the Democrats will find enough money to resolve all of these expensive problems.

With key congressional committees undergoing changes in membership and leadership, it is important for ASH members to know on which committees their own Representatives and Senators serve and to continue their advocacy efforts locally and in Washington. The ASH Government Affairs Committee will continue to promote the ASH legislative agenda and advocate for ASH members to participate in the Grassroots Network and ASH advocacy campaigns to ensure that the new Congress listens and responds to our concerns. For more information about the Grassroots Network, visit www.hematology.org/takeaction.
Uniparental Disomy in Polycythemia Vera and Other Malignancies

MARIILIZ R. MOJICA-HENSHAW, MD, PHD, AND JOSEF T. PRCHAL, MD

Dr. Mojica-Henshaw is Research Associate at the University of Utah School of Medicine. Dr. Prchal is Professor of Medicine at the University of Utah School of Medicine.

The identification of somatic and germline genetic lesions of hematologic malignancies has contributed to our understanding of the biology of cancer. Further elucidation of the molecular mechanisms in cancer should eventually provide dramatic clinical benefits, just as the understanding of the molecular impact of the BCR/ABL translocation has fundamentally changed the prognosis and therapy of chronic myelogenous leukemia.

Tumor suppressor genes limit unregulated cell proliferation and maintain normal differentiation. Classically, they act in a dominant fashion such that a single normal allele is enough to avoid malignant transformation. Heterozygosity is having two dissimilar alleles at a locus. If this is at a tumor suppressor locus and one of these alleles is normal and one mutant, it will still result in normal differentiation and maturation.

Loss of heterozygosity (LOH) is the reduction from two dissimilar alleles to, effectively, only one. LOH through loss of DNA occurs through deletions or partial or complete chromosome loss resulting in hemizygosity, or only a single copy of the locus. Conversely, LOH without loss of DNA can be a result of mitotic recombination or gene conversion resulting in homozygosity, or two copies of the same allele. Functional LOH represents expression of only a single allele with no change in the DNA. This is through epigenetic mechanisms such as DNA methylation, histone acetylation, or changes in subnuclear localization, all of which can affect the transcriptional activity of the affected gene(s).

Disruption of the wildtype allele by genetic or epigenetic changes in the regulatory or coding regions may expose either loss- or gain-of-function in the other allele. Conventional cytogenetics (karyotyping), comparative genomic hybridization, and fluorescence in situ hybridization (FISH) can detect more substantial chromosome architectural abnormalities but cannot detect more subtle genetic changes, since these techniques do not have sufficiently high resolution or cannot detect LOH without loss of genetic material (epigenetic changes).

Recently, another mechanism by which LOH can occur has been identified — uniparental disomy (UPD) created by mitotic recombination. In this case, the consequences of LOH can be substantially different from those described above in which loss of function is the pivotal event. In UPD, the mitotic recombination of a heterozygous cell with one mutant allele results in daughter cells that are homozygous for the mutant allele or contain two copies of the wildtype alleles (Figure). Thus, UPD is a condition wherein both homologues at a particular chromosomal region, or alleles at a particular locus, are derived from the same parent. If the cell homozygous for the mutant allele has a growth advantage, this leads to clonal expansion and clonal dominance. Some types of LOH can be identified by comparing normal and abnormal tissues from an individual with cancer and demonstrating the presence of heterozygosity at a particular genetic locus in normal tissue and the LOH in abnormal tissue. This is often done using polymorphic markers such as microsatellites and single nucleotide polymorphisms (SNPs); however, these DNA-based studies will not identify epigenetic LOH.

Using genome-wide microsatellite markers, our laboratory identified three genomic regions that had LOH in patients with polycythemia vera (PV). The most frequently observed segment of LOH (33 percent of PV patients) covered a region of 40 megabases on the short arm of chromosome 9 (9pLOH). Cyto genetic analysis in these patients did not detect any deletion, while more detailed laboratory studies confirmed the presence of two copies of the same alleles in the 9pLOH region, suggesting that the LOH arose through mitotic recombination resulting in UPD. The JAK2 gene, found within this 9p region, plays a crucial role in erythropoietin signaling. However, our laboratory missed the possible causative role of this gene in genesis of PV because we concentrated only on the tyrosine kinase domain of this gene.2 However, it is certainly not limited to hematologic malignancies. It has also been described in cancers of the breast, colon, lung, liver, gallbladder, and skin.3,4-6 This may be responsible for 9pLOH (and the acquired UPD in cancers) occurring in a non-random fashion. There is growing evidence that the evolutionary conserved JAK/STAT signaling pathway may be responsible for PV, but the acquired JAK2 V617F mutation has occurred1,7,8,9.

REFERENCES
Primary CNS Lymphoma: Progress and Caveats

The treatment and outcomes for primary CNS lymphoma improved in the 1990s with the incorporation of high-dose methotrexate-based regimens. These gains were in part offset by neurotoxicity associated with the use of whole brain radiation therapy (WBRT), usually manifest as impaired cognitive function or overt dementia. Gavrilovic and colleagues now update the extensive Memorial Sloan-Kettering Cancer Center experience with follow-up of a consecutive non-randomized series of 57 patients treated from 1992-98 with high-dose methotrexate (MTX), procarbazine, vincristine, cytarabine, and intrathecal MTX (per Ommaya reservoir). WBRT 45 Gy was also included, although after 1995 patients > 60 years of age did not receive RT due to recognition of neurotoxicity being pronounced in this age group. Overall, 17 patients (30 per cent) remain alive at the time of analysis (December 2005), 13 of whom were < 60 years at the time of initial therapy (Table).

<table>
<thead>
<tr>
<th>Induction Regimen</th>
<th>Chemo/RT &lt; 60 yo</th>
<th>Chemo/RT &gt;/= 60 yo</th>
<th>Chemo only</th>
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<tr>
<td>n</td>
<td>19</td>
<td>12</td>
<td>26</td>
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<tr>
<td>Relapse</td>
<td>7</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>5</td>
<td>8</td>
<td>3*</td>
</tr>
<tr>
<td>Alive</td>
<td>13 (68%)</td>
<td>9</td>
<td>4 (15%)</td>
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<tr>
<td>Median survival</td>
<td>Not reached</td>
<td>29 mo</td>
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* includes two patients with neurotoxicity after WBRT at relapse

Primary CNS lymphoma remains a significant clinical challenge. While it occurs with increased frequency among individuals with congenital or acquired immunodeficiency, it also occurs in those who are immunologically intact. Spread outside the CNS is unusual, although ocular, spinal cord, and leptomeningeal involvement may occur. As demonstrated in this long-term follow-up study, improved outcomes as compared with historical experience were realized using a combined modality regimen incorporating high-dose methotrexate and WBRT, albeit at the cost of neurotoxicity and neurocognitive decline, especially in patients > 60 years of age. The authors note that they likely underestimated the rate of neurotoxicity, as formal neuropsychiatric testing was not performed. WBRT is now deferred in many patients, especially in the older age group. Future studies will need to incorporate cognitive testing and utilize recently developed standardized staging and response criteria.

Newer therapeutic strategies include the use of rituximab and temazolamide, which have activity in recurrent disease; these agents have been incorporated into up-front therapy ongoing trials. Recent reports have also suggested benefit for stem cell transplantation as part of initial therapy in younger patients.

LEF-1 Expression in Congenital Neutropenia


Congenital neutropenia (CN) is associated with mutation of a number of genes including elastase, G-CSF receptor, GFI-1, and WASP; however, in many cases the underlying defect is not established. In this manuscript, the focus shifts to analysis of L-EF-1, whose role as a transcription factor that is important in lymphocyte proliferation and differentiation is well established. The authors compare mRNA expression patterns in CD33+ cells from patients with congenital neutropenia to those from normal donors, as well as those with neutropenia from other causes, and found that there was a marked reduction in expression of L-EF-1 in cells from patients with CN, but not those with other forms of neutropenia or normal neutrophils. Although half of the 13 patients with CN in this study had mutations in the ELA2 gene, all had reduced levels of L-EF-1 and maturation arrest. The differences in expression level were evident beyond the blast stage and were most dramatic in the promyelocyte. Expression of L-EF-1 in progenitor cells from patients with CN enables differentiation. The investigators propose that regulation occurs through the β-catenin-independent action of L-EF-1 and is likely due to a balance between proliferative and apoptotic factors.

The work here not only characterizes factors that may be important in cyclic neutropenia, but also establishes a role for the transcription factor L-EF-1 in myelopoiesis. An earlier report by Li et al. demonstrated that L-EF-1 was expressed in bone marrow cells and myeloid cell lines and identified a L-EF-1 binding domain that was mutated in two patients with severe chronic neutropenia. Of interest is that L-EF-1 binding to the promoter is enhanced by the mutation that was uncovered in both of the patients described and results in increased elastase production. In contrast, in the patients studied in this manuscript, diminished L-EF-1 expression — and thus activity — are thought to be critical for the maturation arrest, diminished proliferation, and decreased cell survival that is observed in these patients. Here, the investigators used two techniques to confirm that L-EF-1 expression was necessary for maturation of myeloid precursors — expression in progenitors from patients with CN enabled differentiation; and disruption of its expression by small hairpin RNAs resulting in maturation arrest, diminished proliferation, and decreased cell survival. In probing for mechanisms, L-EF-1 overexpression enhances CEBP expression independently of G-CSF that normally regulates its expression. Of note is that G-CSF had little effect on L-EF-1 levels under "physiologic" concentrations but is hypothesized to upregulate its expression at pharmacologic doses. This manuscript characterizes a group of patients with congenital neutropenia that have diminished L-EF-1 expression. It remains to be seen whether this finding is consistent among a larger cohort of patients. Nonetheless, the data presented here demonstrate that its expression level plays a role in myeloid cell differentiation and implicate it in neutropenia. Since analysis of the promoter region L-EF-1 has not identified a potential mutation site, the next step will be to determine the post-transcriptional regulatory step that may be altered in these patients.

Susceptibility to Oxidative Stress: A Leukemic Cell's Achilles' Heel?


In a recent study published in Cancer Cell, Trachootham et al. reported that expression of mutant oncogenic proteins, including Bcr/Abl in the context of lower concentrations, or H-Ras in the case of epithelial tumors (i.e., ovarian cancer), not only induced transformation but also triggered an increase in levels of reactive oxygen intermediaries (reactive oxygen species - or ROS). As a consequence, cells expressing these mutant oncogenes were significantly more sensitive to the lethal effects of agents that disrupted cellular oxidative injury defense mechanisms than their normal counterparts. Specifically, exposure to β-phenylethyl isothiocyanate (PEITC), a compound which disables the GSH anti-oxidant system, caused significantly more apoptosis in transformed versus wild-type cells. The authors conclude that oncogenic transformation may be accompanied by perturbations in redox homeostasis, and that this phenomenon could represent the tumor cell’s “Achilles heel,” rendering it selectively vulnerable to therapeutic intervention.

If validated, these findings could have particularly important implications for the treatment of hematologic malignancies. It has long been known that tumor cells may display higher levels of ROS than their normal counterparts. Interpretation of the significance of this phenomenon has been complicated by evidence that ROS play a diverse and, on occasion, opposing roles in cellular survival and behavior. For example, at high concentrations, ROS damage DNA and lipid membranes and induce mitochondrial dysfunction culminating in apoptosis. However, at lower concentrations, ROS can act as signaling molecules and may contribute to cell proliferation among other functions. In the case of Bcr/Abl hematopoietic malignancies [e.g., CML], ROS induced by the Bcr/Abl oncoprotein have been implicated in the induction of mutations responsible for disease progression or drug resistance. Thus, the net effect of ROS generation may depend upon multiple factors, including cell context, the degree of oxidative injury, and perhaps the nature of the inciting stimulus.

The possibility that transformed cells display greater susceptibility to oxidative damage takes on added significance in view of emerging insights into the mechanisms of drug resistance. Thus, the currently underdeveloped strategies for the therapeutic selectivity. In this context, histone deacetylase inhibitors (HDACis), which are currently undergoing extensive evaluation in the treatment of hematologic malignancies, are known to kill leukemic cells through the selective induction of oxidative injury. In addition, proteasome inhibitors like Bortezomib, which in preclinical studies preferentially kill transformed cells, can also exert their lethal effects through induction of ROS. Other studies involving agents like 2-methoxyestradiol, arsenic trioxide, or the tyrophostin adaphostin, administered alone or in combination with other targeted agents, point to oxidative injury as a basis for therapeutic selectivity.

The possibility that the Bcr/Abl kinase or dysregulated RAS, which is frequently mutated in hematopoietic malignancies, might predispose cells to oxidative injury-induced cell death has very obvious clinical implications, particularly in diseases like leukemia. It raises the possibility that a) certain agents might preferentially induce ROS in leukemic cells, and b) leukemic cells may be intrinsically less capable of surviving these insults. It also suggests that strategies combining novel agents, each of which may preferentially induce ROS in transformed cells, might be a particularly appropriate strategy in this setting. In view of ongoing efforts to develop such clinical strategies, answers to these questions should begin to emerge in the near future.


The association between long-distance travel and pulmonary embolism has been recognized for over half a century. The mechanism for the linkage between these two events is unclear. In addition to stasis of blood caused by immobility while in the economy class compartment of the plane, investigators have speculated that the unique air travel environment makes long-distance air travel particularly risky. In a study published in Lancet earlier this year, F.R. Rosendaal and colleagues compared changes in parameters of coagulation and fibrinolysis in subjects during an eight-hour plane flight, eight hours of sitting while watching a cinema marathon, or eight hours of normal activities. In that study, thrombin-antithrombin complex levels (a measure of activated coagulation) increased significantly only in the subjects while they traveled by air. The changes in thrombin-antithrombin complexes were almost exclusively identified in the subgroup of subjects who were predisposed to thrombosis (i.e., Factor V Leiden carriers who were not on anticoagulation therapy). This study suggested that airplane travel per se, rather than mechanical confinement, activated the coagulation system contributing to the thrombosis.

Since reduced oxygen tension and cabin pressures are potential environmental risk factors that could affect the coagulation system, W.D. Toff et al. analyzed subjects before and after eight seated hours in a hypobaric and slightly hypoxic chamber. These subjects did not have any known prothrombotic risk factors. Again, changes in parameters of coagulation and fibrinolysis were assayed including thrombin-antithrombin complex levels. In seeming contrast to the Lancet study, these authors did not find any effect of hypobaric hypoxia on the coagulation system. The potential discrepancy between these two studies may be explained by an environmental factor encountered during air travel that is not due to low oxygen tension or cabin pressure. Alternatively, the effect of these conditions on coagulation may be so subtle that it is only detectable in subjects who are already mildly pro-coagulable.

In 1940, Keith Simpson, an Assistant Lecturer in Forensic Medicine in London, noted a recent six-fold increase in lethal pulmonary embolisms (see Case Report from Lancet December 14, 1940, page 744). Dr. Simpson speculated that prolonged sitting on deck chairs in public air-rail shelters contributed to this epidemic. He was further convinced that providing bunks, instead of chairs, would help alleviate this early example of ‘economy class syndrome.’ Since that time, the association between confinement and thromboembolic disease has been recognized during car trips, air flights, and train travel. The death of David Bloom, a NBC reporter who suffered a pulmonary embolism while riding in an armored car, has been recognized during car trips, air flights, and train travel. The death of David Bloom, a NBC reporter who suffered a pulmonary embolism while riding in an armored car, has been recognized for over half a century. The mechanism for the linkage between these two events is unclear. In addition to stasis of blood caused by immobility while in the economy class compartment of the plane, investigators have speculated that the unique air travel environment makes long-distance air travel particularly risky. In a study published in Lancet earlier this year, F.R. Rosendaal and colleagues compared changes in parameters of coagulation and fibrinolysis in subjects during an eight-hour plane flight, eight hours of sitting while watching a cinema marathon, or eight hours of normal activities. In that study, thrombin-antithrombin complex levels (a measure of activated coagulation) increased significantly only in the subjects while they traveled by air. The changes in thrombin-antithrombin complexes were almost exclusively identified in the subgroup of subjects who were predisposed to thrombosis (i.e., Factor V Leiden carriers who were not on anticoagulation therapy). This study suggested that airplane travel per se, rather than mechanical confinement, activated the coagulation system contributing to the thrombosis.

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Graft-Versus-Host Disease: Finding THE Cell Subset!

Why is this study not just another rodent model with poor clinical implications? Two main reasons, at least from my point of view:

1. Identification of selective drug targets within the GVHD memory stem cell could be used for eradicating ongoing GVHD and thus break the deadly circle of donor T-cell activation against the host target cells, while sparing a T-cell subset engaged against infectious agents (viral and fung.

2. Discovery of such a cell subset has much broader applications and implications beyond just GVHD. Memory stem cells will be important targets for understanding and influencing diverse chronic immune reactions, including autoimmune diseases and solid organ transplant rejection.

So now what are the obstacles to overcome from a clinical perspective before moving from the bench to the bedside?

1. The first objective must surely be to identify and characterize whether these memory stem cells actually do exist in humans.

2. The relationship of this subset of cells to other cells responsible for the graft-versus-leukemia (GVL) observed after allogeneic HSCT is of major importance. Does the memory stem cell identified in this model setting differ from the cell that is responsible for the GVL effect both in rodent models and, most importantly, in human beings?

These questions aside, this paper nevertheless opens the door of a new and highly exciting era in the field of GVHD in particular, and in the world of immunology in general.
Targeting Protein Homeostasis in Novel Therapeutics

The ubiquitin proteasome pathway is a major system for degradation of proteins, and the proteasome inhibitor, Bortezomib, has now been FDA-approved for treatment of relapsed as well as relapsed and refractory multiple myeloma. In spite of its remarkable activity, some patients do not respond, and those who do respond eventually acquire resistance. Moreover, clinical activity outside of myeloma has been limited. We are now beginning to uncover clues to address this problem. Specifically, an alternative mechanism for degradation of ubiquinated proteins is via the aggresome/lysosome/autophagy pathway. In this cascade, histone deacetylase (HDAC) 6 binds to ubiquinated protein on the one hand, and to dynein microtubule complexes on the other, thereby shuttling the ubiquinated protein to its degradation via the aggresome/lysosome/autophagy mechanism. The relative roles of these two pathways of protein degradation, both in normal and cancer cells, as well as their substrate specificities, are not yet defined. Previous studies in myeloma have shown that blockade of the aggresome cascade with tubulin deacetylase inhibitor tubacin triggers a compensatory increase in proteasomal degradation of ubiquinated proteins, whereas inhibition of proteasomal degradation of ubiquinated proteins with Bortezomib induces increased aggresomal activity. Importantly, inhibiting both aggresomal and proteasomal activity with tubacin and Bortezomib, respectively, triggers synergistic myeloma cell cytotoxicity, associated with significant accumulation of polyubiquinated proteins.

In this study, Catley and colleagues move this concept from bench to bedside toward a derived clinical trial. They show that the novel hydroxamic acid derivative histone deacetylase inhibitor LBH 589 induces apoptosis of myeloma cells resistant to conventional and novel therapies, as well as tubulin hyperacetylation, at clinically achievable concentrations. Conversely, Bortezomib triggers increased aggresome formation. When used in combination, both Bortezomib-induced aggresome formation and LBH 589-induced α-tubulin hyperacetylation are augmented. Importantly, combined LBH 589 and Bortezomib treatment induces synergistic cytotoxicity against myeloma cell lines and patient cells, including those sensitive and resistant to conventional and novel therapies.

This study provides insight into the mechanisms of synergistic cytotoxicity of combined Bortezomib and LBH 589 in myeloma. Excitingly, it suggests that either intrinsic or acquired resistance to Bortezomib may be overcome by addition of LBH 589, thereby broadly expanding the spectrum of myeloma patients who respond. It is not at present clear to what extent ubiquinated protein degradation via the aggresome/lysosome/autophagy mechanism mediates resistance to proteasome inhibitors in cancers outside of myeloma. However, Nawrocki and colleagues have recently shown that Bortezomib induces aggresomes in pancreatic cancer cells, and that Bortezomib-induced aggresome formation was inhibited by either HDAC 6 small interfering RNA or HDAC inhibitors, resulting in synergistic cytotoxicity. Importantly, the therapeutic index of LBH 589, Bortezomib, and combined use is favorable, since normal cells are not dependent on multiple mechanisms of ubiquinated protein degradation. Clinical trials of LBH 589 in myeloma are beginning, with trials of combined LBH589 and Bortezomib to quickly follow, based upon this study. Targeting protein homeostasis in this fashion therefore has great potential to improve outcome, not only of patients with myeloma, but those with solid tumors as well.

This year, ASH honored not only those who have achieved great prominence in hematology, but also those who help people get started. With the ASH Mentor Award, the Society seeks to recognize the important role mentors play in helping to advance science.

Mentors can play many significant roles in the lives of others. They can advise, advocate, teach, criticize, or “simply” serve as a good role model. All these qualities and more are honored with this new award, given for the first time at the annual meeting in December. Two award winners were chosen — one an outstanding mentor in the basic sciences and the other an outstanding clinical investigator mentor.

The inaugural ASH Mentor Award winners are Samuel E. Lux, IV, MD, of the Children’s Hospital of Boston, for mentorship in clinical investigation, and Deane F. Mosher, MD, of the University of Wisconsin-Madison, for mentorship in basic science.

**THE GOOD MENTOR** - DR. DEANE F. MOSHER

Dr. Murphy-Ullrich is Professor of Pathology at the University of Alabama at Birmingham and Co-Director of the BioMatrix Engineering and Regenerative Medicine Center.

**M E N T O R  A W A R D**

Good scientific mentoring is akin to good parenting. When you start your career, your mentor must be there to meet your constant demands, assure your insecurities, and pick you up, all the while showing you how to move forward by example. The good mentor must encourage your development, give you the ability to make some mistakes along the way, and know how to turn these “failures” into learning opportunities. The good mentor must know when it is time to leave the nest and give you the support and confidence to take that frightening step. The good mentor should also be willing to be a colleague as your career progresses.

Deane F. Mosher, MD, is a rare and truly remarkable person. I am most fortunate to have known Deane for nearly 27 years, practically all of my scientific career. He has an impressive legacy of mentoring successful basic scientists and clinician scientists, particularly women. Deane is clearly deserving of the ASH Mentor Award as he exemplifies the characteristics of the good mentor.

I first met Dr. Mosher when I was a second-year graduate student in the Department of Pathology at the University of Wisconsin. One of my classmates was a student in Deane’s lab. Deane was a new assistant professor, fresh from his fellowship work in Helsinki where he made some key early discoveries regarding the important extracellular matrix molecule, fibronectin. I would spend time in Deane’s lab while visiting my classmate - although I was not his student, he always took the time to chat and to explain the workings of his lab. When I decided to focus on extracellular matrix for my thesis work, I asked Deane to be on my thesis committee. As my thesis was on the renal consequences of autoimmune responses to fibronectin, Deane was an important member of my committee. We generated several forms of chemically-modified fibronectin for this project — Deane’s expertise in the protein chemistry of the fibronectin molecule was essential. Even though he was not my thesis mentor, Deane was exceedingly generous with his time, knowledge, advice, and laboratory resources. One of his post-docs trained me in several techniques and I regularly used his lab equipment. He helped me with manuscript writing as well.

When it came time to choose a post-doctoral fellowship, it was clear to me that it would be hard to find a more intelligent and giving mentor than Deane Mosher. In 1983, I started my post-doctoral fellowship in his lab. It was a rather unusual setting in retrospect, critically important environment. At that time, all of Deane’s post-docs, graduate students, and most of his technicians were women. Many of them were married and one had a young child. It seems hard to remember what it was like for women in science nearly 25 years ago, but there were few role models for women scientists who wanted both a career and a family. I learned from my colleagues in Deane’s lab how to be effective at both career and family. Deane provided the supportive atmosphere that allowed people in his lab to work flexible schedules and he never tallied hours or created unreasonable demands or structures that competed with family duties. The quality of one’s science was the sole determinant of one’s success in Deane’s lab. I think that Deane’s tacit assumption that his “hyphenated” women scientists were simply the best gave us all the confidence to pursue this difficult course. In fact, all of my post-doctoral fellow contemporaries in the lab are now in senior faculty positions at major research institutions. He provided first-rate mentoring in how do outstanding, critical, and innovative science in a supportive, collegial atmosphere. Deane was also well ahead of his time in recognizing the importance of the clinical relevance of basic science pursuits — something that today we call translational science.

In 1986, it was time to move on and I accepted a research associate position at UAB. During this time, I maintained frequent contact with Deane. He generously provided thrombospondin protein to me for years while I was getting started on my independent career. He read my grants and greatly assisted me when I was writing my first R01 application in 1989. He provided me with his typically sage advice on what constitutes a good grant - the freestyle Olympic figure skating program analogy. Deane remarked that my draft R01 read like a legal brief and that no reviewer would be able to follow it. He likened a good grant to an Olympic figure skating program — you have a limited number of opportunities to impress the judges and the transitions must be seamless. I still have the letter in which he wrote this and I have passed on this advice to all of my students and post-docs.

Now as a senior faculty member, I still value my interactions with Deane. We collaborated in the mid 1990s on important studies from my lab defining key sequences in thrombospondin that activate latent TGFβ, on use of his recombinant thrombospondin fragments of the N-terminal domain in signaling of cell survival, and on some exciting collaborative efforts with a third investigator on thrombospondin transactivation of a growth factor receptor. To this day, I am still impressed with the depth and breadth of his knowledge and his keen insights. I still feel that I have much to learn from him. Yet, he is never overbearing and he never positions himself as the senior scientist, something that would be well justified.

Despite his success over the years, Deane remains humble and I am sure this award is a source of embarrassment as well as pride. But this too is part of his charm and strength as “the good mentor.”
CALL FOR AWARD NOMINATIONS

ASH members are invited to submit nominations for the William Dameshek Prize, Henry M. Stratton Medal, and E. Donnall Thomas Lecture and Prize for the year 2007. Letters of nomination must include a brief paragraph summarizing the nominee’s contributions to hematology as well as a current bio-sketch or curriculum vitae. Nominations are due by February 1 and should be sent by postal mail to American Society of Hematology, Attn: Courtney Krier, 1900 M Street, NW, Suite 200, Washington, DC 20036, or via e-mail to cknier@hematology.org.

To submit a nomination for the ASH Mentor Award, simply complete a nomination package by May 4 and send it by postal mail to ASH Mentor Award, Attn: Joe Basso, 1900 M Street, NW, Suite 200, Washington, DC 20036. More information can be found on the ASH Web site at www.hematology.org/education/awards/mentorship.cfm.

DR. SAMUEL LUX ON MENTORING

The Hematologist asked Dr. Samuel Lux to answer a few questions about being honored with the ASH Mentor Award. His responses follow.

What does this award mean to you?

This award means more to me than any other I’ve received. My previous awards were all individual achievement awards, teaching or science, but this award reflects not only my own success, but the success of the many men and women I’ve had a chance to work with over my career. That’s the unique joy of mentoring. You gain pleasure from the success of others. It’s like having grandchildren. You can recognize the successful mentor because they can’t help bragging about their protégés.

How important is mentoring for trainees?

I think it is vital. I suppose it’s possible to forge a successful career on your own but it is surely harder, and I would bet less fun. Most of us owe a large measure of our success to the efforts of others. Certainly, I do. I would never have chosen pediatrics or Children’s Hospital Boston except for a chance meeting with my own mentor, David Nathan, and my success is due in large measure to his unflagging attention to my career.

What advice would you give others about mentoring?

I usually summarize a mentor as an advocate, coach, teacher, guide, role model, valued friend, door opener, benevolent authority, available resource, cheerful critic, and career enthusiast. It’s all those roles and more. I see mentoring as a continuum with recruiting and advising. I think it’s something that starts very early in your career, the first time someone comes to work for you, and continues for a lifetime. As advice, I would say to first be a friend and an interested colleague of your mentees — someone they can come to whenever they do something interesting. Second, focus on their strengths — emphasize those in career choices. Make them shoot high and do high quality work, but be a cheerful and constructive critic. Third, be their advocate in getting important trips, talks, session chairmanships, and the other little plums of academic life. Offer their name for important jobs, even when you desperately don’t want them to leave. Fourth, protect their time but make sure they take on responsibilities that are necessary for the careers they desire. Someone who aspires to be a division chief or a department chair needs to hone clinical and teaching skills as well as do research. Fifth, don’t try to make them a clone of yourself. This is, I think, one of the biggest mistakes. And, sixth, stick with them. Being a mentor is a lifetime responsibility, even after they move on to other institutions. We have brought our alums together at ASH for something we call the Vampire Dinner for more than 30 years. We do it in part to see old friends, but also to remind our alums that they are still a very important part of our lives and that we are extremely proud of them.
In recent years, reduced trends in the funding of young biomedical research scientists have raised serious questions about the future of life sciences research. As federal funding sources have become more competitive, young investigators must constantly seek new opportunities. Unfortunately, navigating the alphabet soup of National Institutes of Health (NIH) and non-profit funding opportunities is a challenge for the uninstructed.

Briefly, there are three main categories of NIH grants for young investigators: 1) The National Research Service Awards (NRSA) — "T" grants, 2) "F" grants, and 3) "K" awards. The "T" (training) grants are generally awarded to institutions that train residents and post-doctoral fellows. These grants are primarily used to promote the education of our future researchers. The "F" (fellowship) grants are typically awarded to individuals, either pre-doctoral or particularly promising post-doctoral fellows, to promote diversity in health-related research. Many of these awards are granted to those who demonstrate the potential to become independent investigators. The "K" (career development) awards are granted to individuals during the mentored phase of their careers. These awards focus on enhancing career development while providing protected time to selected investigators.

The American Society of Hematology (ASH) has always recognized the need to foster young trainees — offering numerous resources to hematologists interested in advancing their careers. In an effort to de-mystify this application process, the ASH Trainee Council recently revised their educational Trainee Career Center Web page. A key feature has been the addition of the recently unveiled Grants Clearinghouse — a comprehensive list of research grants for hematology trainees in various stages of training (both MDs and PhDs). The Grants Clearinghouse provides a multitude of hematology-related research grant opportunities available through ASH, NIH, and other federal agencies, as well as award opportunities from selected patient groups. Each grant entry included in the Grants Clearinghouse (available to all ASH members as a downloadable Excel file) provides a brief description of the grant award, the sponsoring organization, eligibility and citizenship requirements, award amounts and duration, and the most recent deadline and Web link information.

The newly revised Training section of the ASH Web site also contains other valuable features for young investigators. These features include: an article titled “Making Sense of NIH Funding Opportunities,” a primer on various NIH-funded grant opportunities; a PowerPoint presentation on “Preparation for Life After Fellowship,” which includes suggestions to guide fellows in preparation for life after training; and a “Career Development Timeline for Trainees,” a generalized framework for the career development of trainees at various stages. We invite you to explore these newly added features as well as take advantage of the numerous opportunities afforded through ASH membership at www.hematology.org.

Looking for $$$$? Postdoctoral Fellow Funding Opportunities

Mona D. Shah, MD

Dr. Shah is a Postdoctoral Clinical Fellow in the Department of Pediatrics, Division of Hematology/Oncology at Texas Children’s Hospital, Baylor College of Medicine.

NIH is Reauthorized in the Wee Hours of the Morning Before Congress Adjourns

Roy Silverstein, MD

Dr. Silverstein is Chairman of the Department of Cell Biology and Vice-Chairman for Translational Research at the Lerner Research Institute of Cleveland Clinic. He is also Chair of the ASH Committee on Government Affairs.
FDA STAFF AND MYELOMA EXPERTS MEET TO DISCUSS CLINICALLY RELEVANT ENDPOINTS AND NEW DRUG APPROVALS FOR MYELOMA

KENNETH ANDERSON, MD

Dr. Anderson is Kraft Family Professor of Medicine, Harvard Medical School, Chief, Division of Hematologic Neoplasia and Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute

The ASH®/FDA Workshop on Clinical Endpoints in Multiple Myeloma was held in Washington, DC, on October 26, 2006. The workshop began with James N. George, MD, Past President of ASH, welcoming participants and citing the successful ASH/FDA Workshop on Acute Leukemia, which provided the framework for this collaborative workshop on multiple myeloma (MM). These workshops were initiated because the FDA wanted to participate in an informed discussion with leaders in the field regarding emerging endpoints that might be used to support claims of efficacy for products with potential utility in the treatment of hematologic diseases. ASH agreed to provide the leadership and to host a discussion that could provide useful material to the FDA and that could be used in the FDA's formal presentations to its Oncology Drugs Advisory Committee (ODAC). Chaired by Richard Pazdur, MD, Director, Office of Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), and myself, this workshop brought together FDA staff and myeloma experts to provide guidance for definition of clinically relevant endpoints that could potentially expedite new drug approval for multiple myeloma. The format of the workshop was informal, with participants seated around a large U-shaped table. This facilitated active discussion and debate following each presentation. In addition to panel members, an audience of 175 physicians and scientists from academic and pharmaceutical institutions participated in the public afternoon session.

Drs. Richard Pazdur and Robert Kane of the FDA first outlined the regulatory basis for marketing authorization, types of approval, drugs approved for MM, and study designs and endpoints supporting drug approval. Qing Young, Program Director for the Multiple Myeloma Research Foundation (MMRF), next described two prior MMRF/FDA workshops defining the framework for new drug approval in MM, as well as sponsored novel drug trials ongoing in the context of MMRF and the Multiple Myeloma Research Consortium. Dr. Brian Durie, Chairman of the Board of Directors of the International Myeloma Foundation, described the International Myeloma Working Group (IMWG) criteria for classification of myeloma and related disorders, as well as the recently proposed IMWG international uniform response criteria for multiple myeloma. I then cited the examples of recent new drug approvals in myeloma, including thalidomide, lenalidomide, and bortezomib, and the need for early endpoints that could potentially expedite new drug approval for multiple myeloma, including thalidomide, lenalidomide, and bortezomib, and the need for early partnership of industry, academia, the FDA, the National Cancer Institute, and patient advocates in order to expedite novel drug development in myeloma.

Panels next examined appropriate clinical trial design and endpoints for new drug approval for stages of disease including monoclonal gammopathy of unclear significance (MGUS)/smoldering multiple myeloma (SMM), newly diagnosed myeloma, maintenance therapy, relapsed myeloma, and relapsed and refractory myeloma. Within the MGUS/SMM panel led by Robert A. Kyle, MD, of the Mayo Clinic, the importance of defining a population at high risk of progression to MM was paramount, with progression to MM the most clinically relevant endpoint. Within the newly diagnosed myeloma panel chaired by Vincent Rajkumar, MD, of the Mayo Clinic, rate and extent of response are primary endpoints, with associated clinical benefit. Within the transplant candidate population who go on to receive high-dose therapy and stem cell transplantation, response assessment is done prior to transplantation, and it is therefore not possible to assess the durability of response to initial therapy. However, in the non-transplant population, time-to-progression, progression-free survival, and overall survival are measures of clinical benefit, in addition to response extent and frequency.

There are no standard maintenance therapies to prolong the duration of response in myeloma, and the maintenance therapy panel led by Keith Stewart, MD, of the Mayo Clinic felt that clinically relevant endpoints for evaluation of a novel maintenance therapy would include prolongation of event-free survival and overall survival, as well as improvement in response. Within the relapsed myeloma panel, chaired by Donna Weber, MD, of the M.D. Anderson Cancer Institute, clinically relevant endpoints for new drug approval included extent and rate of response and durability of response, with time to progression as a surrogate for overall survival.

Finally, the relapsed and refractory myeloma panel, led by Paul Richardson, MD, of Dana-Farber Cancer Institute, identified this patient population, which remains an important unmet medical need in MM and therefore offers an opportunity to rapidly demonstrate benefit. Assessment of the clinical benefit of novel agents in this subgroup should include response rate and extent, as well as assessment of duration of response and time to progression. More information as well as slide presentations from the workshop can be found at www.hematology.org/policy/news/fda_workshop__multiple_myeloma.cfm.

ASH Members Awarded Membership in the Institute of Medicine of the National Academies

Nancy C. Andrews, MD, PhD
George R. Minot Professor of Pediatrics, Division of Hematology/Oncology, Children’s Hospital Boston

Chi Van Dang, MD, PhD
Johns Hopkins Family Professor of Oncology Research, Professor of Oncology, Cell Biology, Oncology, and Pathology, Vice Dean for Research, Johns Hopkins University School of Medicine

Rudolf Jaenisch, MD
Professor of Biology, Massachusetts Institute of Technology, Founding Member, Whitehead Institute for Biomedical Research

Joseph Loscalzo, MD
Harvey Professor of the Theory and Practice of Physcics, Harvard Medical School, Chair, Department of Medicine, Brigham and Women's Hospital

Ajit P Varik, MD
Distinguished Professor of Medicine and Cellular and Molecular Medicine, Department of Medicine, University of California, San Diego

Kimberly Stegmaier, MD, first recipient of the Joanne Levy, MD, Memorial Award for Outstanding Achievement, presents her abstract, “Modulating AML1-ETO with Signature-Based Small Molecule Library Screening,” at the annual meeting in December. This award is given to the current ASH Scholar with the highest scoring abstract for the ASH annual meeting as determined by the appointed abstract reviewers.
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.


Earn CME CREDITS (https://reg.jspargo.com/ash06cme/cme) from the 2006 ASH Annual Meeting by completing the online meeting evaluation by March 31, 2007.

Register for HIGHLIGHTS OF ASH (www.hematology.org/meetings/highlights) to hear expert analysis of the top abstracts of 2006, discuss real cases with leaders in the field, and network with colleagues while earning category 1 CME credits.

Read through HEMATOLOGY 2006 (www.asheducationbook.org), the ASH Education Program Book.

Complete the new MULTIPLE MYELOMA PRACTICE IMPROVEMENT MODULE (PIM) (www.hematology.org/education/recertification/pims.cfm) to gain 20 points toward ABIM recertification.

Search through job listings or post your own open position on the ASH JOB BANK (www.hematology.org/education/jobs/index.cfm).

Begin planning what to do in a disaster with the EMERGENCY PREPAREDNESS PAGE (www.hematology.org/policy/emergency_preparedness.cfm), stocked with resources that can assist you in developing your own emergency preparedness plan.

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**MARK YOUR CALENDAR**

### JANUARY

**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

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### FEBRUARY

**1**

Nominations due for ASH Honorific Awards

Washington, DC  
www.hematology.org

**8 – 12**

2007 Blood and Marrow Transplantation Tandem Meetings

Keystone, CO  
www.asbmt.org

**9 – 13**

48th Annual Meeting of the American Society for Cell Biology

San Diego, CA  
www.ascb.org

**15**

Minority Medical Student Award Program deadline to request ASH’s assistance to match applicant with a host institution and research mentor

Washington, DC  
www.hematology.org

**17 – 20**

Scripps Cancer Center’s Annual Conference: Clinical Hematology and Oncology

San Diego, CA  
www.scripps.org

**21 – 23**

First Annual Sickle Cell Disease Research and Educational Symposium

Hollywood, FL  
www.memorialregional.com

**28 – MARCH 3**

47th Annual Conference on Cardiovascular Disease Epidemiology and Prevention

Orlando, FL  
www.americanheart.org

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### MARCH

**23**

Deadline for ASH-AMFDP Award applications

Washington, DC  
www.hematology.org

**20 – 24**

31st Annual Congress of the International Society of Hematology

Punta del Este, Uruguay  
www.2007ish.org

**24 – 27**

56th Annual Scientific Session of the American College of Cardiology

New Orleans, LA  
http://acc07.acc.org

**24 – 30**

96th Annual Meeting of the United States and Canadian Academy of Pathology

San Diego, CA  
www.uscap.org

**25 – 28**

33rd Annual Meeting of the European Group for Blood and Marrow Transplantation

Lyon, France  
www.ebmt.org