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Looking Backward but Moving Forward – ASH Annual Meeting 2011

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Editor-in-Chief, *ASH News Daily* 2011

For more than 50 years, ASH has hosted the largest and most influential meeting for those interested in the basic and clinical science of hematology. Every year, for four packed days, individuals from all over the world meet to review and discuss the latest research in the field and its implication for patients with blood diseases. Indeed, attendance this year was the second highest on record with more than 22,000 participants (representing 71 countries) registered for the meeting. (The 50th ASH Annual Meeting in 2008 was the highest attendance on record.) Furthermore, more than 6,000 abstracts were submitted, of which 1,032 were selected for oral presentations and 3,198 were presented as posters.

This past meeting, held in "not always sunny" San Diego, was a fascinating merger of past and present; we looked back at great accomplishments and saw both how they have shaped the standards of the present and how they will surely enhance the discoveries of the future. Here is the executive summary. (Cont. on page 14)

DIFFUSION

Searching for Second Events in Follicular Lymphoma: A New Target for Therapy

Oricchio E, Nanjangud G, Wolfe AL et al. The Eph-receptor A7 is a soluble tumor suppressor for follicular lymphoma. Cell. 2011;147:554-564.

Although the pathognomonic t(14;18) translocation has long been characterized as necessary but not sufficient for malignant transformation in follicular lymphoma (FL), there remains a good deal of uncertainty about the nature of the other molecular events that result in the full malignant phenotype, and more still about the processes that underlie transformation to diffuse large B-cell lymphoma. Classical cytogenetics have revealed the common occurrence of abnormalities on the long arm of chromosome 6, but no one consistent region of gain or loss has been implicated, and most of the changes are hemizygous, leaving a large number of potential gene candidates to be examined.

The group at Memorial Sloan-Kettering Cancer Center has taken a combined approach to this problem, using the results of array-comparative genomic hybridization analysis to define the main regions of loss on 6q and constructing a library of short hairpin RNAs (sh-RNAs) designed to knock down expression of the genes from the most commonly deleted regions. By transfecting the shRNAs into a B-cell line dependent on IL-3, they were able to identify genes whose inhibition rendered the cells relatively immune to IL-3 deprivation, indicating that the inhibited genes functioned as tumor suppressors. Among the genes identified by this screening procedure were A20, already known to be the target of deletions in B-cell lymphoma, and the ephrin receptor A7 (*EPHA7*), whose silencing had previously been found to be associated both with aberrant methylation in lymphoma and with epithelial malignancies such as those of the stomach, colon, and prostate.[1] Suppression of *EPHA7* by shRNA knockdown in a spontaneous mouse-lymphoma model resulted in accelerated lymphoma development, at a rate equivalent to that observed with knockdown of *p53*. Further studies confirmed that translation of *EPHA7* was lower in most FL than in normal germinal-center B cells, and that 72 percent of FL tested by immunohistochemistry had absent or weak staining for EPHA7 protein. In contrast, control studies showed that EPHA7 was abundant in the cytoplasm of normal tonsillar B cells. Much of the loss of expression in EPHA7 in FL appears to be the result of epigenetic silencing through promoter methylation, an effect that was reversible in B-cell lymphoma lines using the methylation inhibitor, 5-azacytidine.

Ephrin receptors mediate cell-cell interactions, embryonic development, neural development, and angiogenesis signaling through several different kinase pathways. A truncated form of EPHA7 protein, EPHA7TR, is expressed in normal B cells and is found in lymphocyte-conditioned media and in normal human serum where it may act as a growth inhibitor. The group showed that a tagged EPHA7 ectodomain protein could bind to the homologous EPHA2 receptor on B cells thereby blocking receptor-mediated oncogenic signaling as evidenced by inhibition of downstream phosphorylation of ERK, STAT3, and a variety of SRC family kinases. Studies in B-lymphoma xenograft models showed that soluble EPHA7TR protein had a suppressive effect on tumor growth, especially when administered locally at the injection site. Importantly, a fusion protein of anti-CD20 antibody and EPHA7TR showed a growth inhibitory effect upon Raji xenografts when given systemically, with the fusion protein having significantly greater potency than EPHA7TR alone. These experiments suggest a mechanism for targeting EPHA7TR to B cells through binding to CD20.

This study once again confirms the power of functional genomics as a method for identifying important events in the pathogenesis of lymphoma, and in this case, it appears that loss of *EPHA7* expression may constitute a point of vulnerability in a surprisingly high proportion of FL. Inhibiting lymphoma growth by restoring the tumor suppressive effect of EPHA7 using a recombinant form of the protein appears promising, and the potential efficacy of EPHA7 delivered selectively by antibody targeting (through anti-CD20 in the case of FL) is appealing as a clinical approach to treatment. As a novel route to combined epigenetic and somatic targeting of treatment, it would be interesting to see whether simultaneous restoration of natural expression of EPHA7 by demethylating agents would enhance the efficacy of the targeted, exogenously delivered protein.

1. Dawson DW, Hong JS, Shen RR, et al. Global DNA methylation profiling reveals silencing of a secreted form of Epha7 in mouse and human germinal center B-cell lymphomas. Oncogene. 2007; 26:4243-4252.

PETER JOHNSON, MD
Dr. Johnson indicated no relevant conflicts of interest.

FEATURES

DEPARTMENTS

Welcome to Year #9 of The Hematologist

I have been a fan of *The Hematologist* since its inception in 2004. The mixture of news and educational features presented in a variety of lively, concise formats filled a previously unmet need of the Society for a publication that is reader-friendly but respected for scholarship based on the standing of the members of the editorial board and guest contributors. Over the past eight years, both the vitality and the mission of the newsletter have been maintained while new, innovative features have further enlivened the publication.

I have been honored to be part of the editorial board as a contributing editor since January 2008 and more recently to be coordinating editor for the Clinical Trials Corner section. In the former role, I contributed articles to the Diffusion section of *The Hematologist*. These articles are brief reviews of scholarly articles that address issues of fundamental importance to hematologists or that are seen as particularly creative or imaginative. The idea is to provide an amount of background information on the subject sufficient for the non-expert reader to understand the hypothesis being addressed and then to communicate the author's perspective on why the publication is noteworthy. The Diffusion section is the heart and soul of *The Hematologist* and participating in this endeavor along with 12 other outstanding contributing editors under the guidance of the Editor-in-Chief Roy Silverstein was particularly rewarding.

In my more recent role as coordinating editor, I worked with Roy and Karen Learner, managing editor, on developing the Clinical Trials Corner feature. This initiative (first appearing in the July/August 2010 issue) resulted directly from reader feedback asking for information on ongoing clinical trials. Synopses of important trials are solicited from the contributing editors. We developed a format for the Clinical Trials Corner designed to encourage the contributing editors to use their insight and experience to enliven their review so that the reader will understand why they chose a particular clinical trial. In particular, we wanted the reviews to be more than just an outline of the nuts and bolts of the trial; rationale and comments sections were incorporated into the format to be used by the contributors to develop their personal position on the study.

The current format of *The Hematologist* accurately reflects the aims of the publication to provide news of special interest to members of the Society in both the academic and clinical arenas and to deliver educational pieces that encompass the broad, integrated interest of basic and clinical researchers and practicing hematologists. *The Hematologist* is an official publication of ASH and, as such, is one of the voices of the Society. It is this official standing that gives the publication its impact and mandates the highest standard of editorial integrity.

Although *The Hematologist* is a publication of the American Society of Hematology, the Society includes many international members, and nearly 40 percent of those who attend the annual meeting are from countries other than the United States. There is much to be learned from our international colleagues. Currently, Drs. Peter Johnson from Southampton, UK, and Xavier Leleu from Lille, France, are members of our board, and *The Hematologist* will continue to solicit regularly guest contributions from leading hematologists outside of the United States.

Our fellows are the future of the Society, and they should feel included from the beginning of their careers. In addition, fellows have interests that are unique to their group. These interests include training regulations that impact on board eligibility and certification, career options and choices, and opportunities for specialty training and entry-level research funding. Contributions from fellows, training program directors, and relevant policymakers will remain regular features of *The Hematologist*.

We will also continue to feature profiles of both distinguished members of ASH and more junior colleagues whose careers illustrate the aspirations of the Society to encourage scholarship among its members. We feel strongly that advocacy among our readers should be promoted, and *The Hematologist* will provide a forum for the Society to inform members of ongoing and planned advocacy efforts.

I am honored to be the fourth editor-in-chief of *The Hematologist*, following in the footsteps of my respected predecessors Andrew Schafer, Peter Emanuel, and Roy Silverstein. Their dedication and vision have turned a stranger of uncertain intent into a trusted friend whose visit every couple of months we now welcome. At the Editorial Board Meeting in December, we said goodbye to Michael Linenberger (University of Washington) and Steven Grant (Virginia Commonwealth University); both served consecutive terms on the board. Their insightful contributions will be missed. At the same time, we welcomed Mark Koury and Peter Kurre. Mark is professor of medicine at Vanderbilt. He has a longstanding interest in erythropoiesis and has made important contributions to the field over three decades. He brings with him a wealth of laboratory and clinical experience. Peter is associate professor in the Departments of Pediatrics and Cell & Developmental Biology at Oregon Health and Sciences University. He is interested in bone marrow failure syndromes and gene therapy. As a pediatric hematologist, Peter will represent an important contingent of our readership.

The Hematologist exists to serve our readers. In his Commencement Address to the Stanford University Class of 2005, Steve Jobs gave a nod to the counterculture of the 60s and 70s that had so profoundly influenced him by quoting from the *Whole Earth Catalog*, imploring the new graduates to "Stay hungry. Stay foolish." Foolish in this case did not mean unwise or silly, but rather its use in this context was intended to convey the idea of taking a playfully irreverent approach to dealing with dogma, and, in so doing, to open the way for creative, innovative thinking. To a greater or lesser degree, reality sullies many of our ideals, but I suspect that most readers of *The Hematologist* are still excited by new concepts and different ways of thinking about things. We will do our best to keep the publication fresh and invigorating, and in turn we ask you, the reader, to stay curious, stay engaged.

–Charles Parker, MD
Editor-in-Chief, 2012-2014

President's Column

ASH: Continuity and Renewal

I feel extraordinarily privileged and humbled to address you in this forum. I am really optimistic about the future of hematology! I declare this view despite the challenges facing our field, especially in benign hematology; but, at the same time, I believe that meeting these challenges successfully will be the basis for our continued growth. I am struck both by the vitality of the field and by its diversity, characteristics that are due in large part to the field's long history of basic and translational research that has led to remarkable advances in clinical medicine that extend well beyond the traditional boundaries of hematology. The natural relationship between laboratory and clinical hematology is one of hematology's greatest strengths.

But as clinicians and scientists in hematology, we have another huge advantage in meeting the challenges of the future — the American Society of Hematology.

One of the *many* remarkable things about ASH is its capacity to respond both to the interests and aspirations of its members and to the hematology community at large, while remaining focused on its basic mission of "promoting research, clinical care, education, training, and advocacy in hematology."

A current example of ASH's responsiveness is the role of the Society in support of the field of regenerative medicine. Hematologists have been leaders in many cutting-edge areas of medicine, including targeted therapy, clinical genomics, and personalized medicine, but our specialty has had a particularly important role in the development of cell-based therapy. As a result, hematology has an enormous amount to contribute to the burgeoning field of regenerative medicine. After all, hematologists were largely responsible for its precursor, blood and marrow transplantation. Consequently, ASH has been active in promoting research in regenerative medicine. In 2009, ASH held an agenda-setting workshop on regenerative medicine to develop recommendations on measures to enhance research in the area. The proceedings from the workshop were published in 2010 in *Blood* in an editorial titled "Enhancing Research in Regenerative Medicine." ASH also adopted a Policy Statement on Regenerative Medicine (*www.hematology.org/Advocacy/Policy-Statements/5101.aspx*) that both describes the current challenges facing researchers and offers suggestions to advance the field.

Several recommendations from the ASH Policy Statement on Regenerative Medicine were addressed by NIH this year, including the establishment of a trans-institute NIH Intramural Center for Regenerative Medicine and an initiative to create a world-class center of excellence in stem cell technology on the NIH campus. A focus of the stem cell cell center will be generation of induced pluripotent stem cells (iPS cells). These remarkable cells (that are a testament to the power and beauty of science) are anticipated to have an array of applications ranging from uncovering disease mechanisms to drug testing to cellular therapy. A major goal for the Center for Regenerative Medicine is to use existing NIH expertise in combination with investments in stem cell research to advance translational studies and, ultimately, to develop and initiate cell-based treatment studies at the NIH Clinical Center. According to the recently appointed director, Mahendra Rao, MD, PhD, the center will also serve as a resource for the scientific community, providing stem cells along with supporting protocols and standard operating procedures that can be used by investigators to derive, culture, and differentiate cells. ASH has already met with Dr. Rao to discuss ways in which the Society can support and collaborate with the Center (*www.hematology.org/News/2011/6934.aspx*).

With ASH at our side, you can see why I'm confident and excited about the future of hematology.

Armand Keating, MD

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ASH Members Elected to Membership of the Institute of Medicine of the National Academies of Science

The Institute of Medicine (IOM) has announced the election of 65 new members, including three ASH members. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

The three ASH members elected to the IOM are:

Carlo M. Croce, MD

John W. Wolfe Chair in Human Cancer Genetics; Chair, Department of Molecular Virology, Immunology, and Medical Genetics; and Director, Institute of Genetics, The Ohio State University Medical Center

George Q. Daley, MD, PhD

Investigator, Howard Hughes Medical Institute; Samuel E. Lux IV Professor of Hematology, Division of Hematology/Oncology, Children's Hospital Boston; Professor of Biological Chemistry, Molecular Pharmacology, and Pediatrics, Harvard Medical School

Yuet Wai Kan, MD

Louis K. Diamond Professor of Hematology, Departments of Medicine and Laboratory Medicine, University of California San Francisco Medical Center, San Francisco

ASH Executive Committee Election Results

VICE PRESIDENT

Linda J. Burns, MD

Professor of Medicine, Division of Hematology, Oncology and Transplantation (HOT); Senior Fellowship Program Director, Department of Medicine; Fellowship Program Director, Division of HOT; Director, Inpatient Blood and Marrow Transplant (BMT) Unit; Director, Hematologic Malignancy BMT Interdisciplinary Site-Specific Teams; Attending Physician, BMT Program, University of Minnesota in Minneapolis

Dr. Burns will serve as vice president in 2012, president-elect in 2013, and the president in 2014.

COUNCILLORS

Joseph M. Connors, MD

Clinical Professor, Department of Medicine, Division of Medical Oncology, University of British Columbia; Clinical Director, BC Cancer Agency Centre for Lymphoid Cancer, Vancouver, BC

Dr. Connors will serve a four-year term.

John C. Winkelmann, MD

Physician, private practice, Oncology Hematology Care, Cincinnati, Ohio

Dr. Winkelmann will serve a four-year term.

2012 International Highlights of ASH®

This year, ASH brings the most influential and clinically relevant research from the 53rd ASH Annual Meeting to Latin America and Asia. The official Highlights of ASH international meetings will feature leading experts in hematology presenting evolving therapies, the latest treatment options, and their clinical applications. The program formats will allow local practicing hematologists and oncologists at all career levels to talk about their patient cases during panel discussions and in small-group settings with their colleagues and speakers. Register at *www.hematology.org/highlights*.

March 3-4

Highlights of ASH Asia

Singapore

Online registration ends February 3.

Following last year's successful "Highlights" meeting in China, ASH continues to provide clinically focused educational content to physicians in Asia. This year, the Society has partnered with the Cancer Science Institute of Singapore, National University of Singapore (CSI, NUS) to bring 2012 Highlights of ASH to Singapore, a conveniently located destination for medical professionals in the Asia-Pacific region.

May 18-19

Highlights of ASH Latin America

Foz do Iguaçu, Brazil

Online registration ends April 12.

For the fourth consecutive year, the Highlights of ASH program will be presented in Latin America. Partnering with the Associação Brasileira de Hematologia e Hemoterapia (ABHH), ASH will bring the meeting to Foz do Iguaçu in 2012. The city is home to one of the world's natural wonders – Iguaçu Falls – and is located on the borders of Argentina, Brazil, and Paraguay, making it a great location for the meeting. Simultaneous translation into Portuguese and Spanish will be provided.

Please note that *AMA PRA Category 1 Credits*™ will not be available for international meetings.

Ask the Hematologist

KENNETH A. BAUER, MD

Professor of Medicine, Harvard Medical School, Boston, MA

(Editor's Note: This question was submitted through the Consult-a-Colleague program. Dr. Bauer was asked to respond.)

The Question

How do you manage a patient with heparin-induced thrombocytopenia (HIT) being treated with argatroban who has persistent thrombocytopenia? The patient is a 45-year-old man with laboratory evidence of HIT (positive serotonin release assay) without thrombosis who has been treated with argatroban for 10 days. The platelet count was 52,000 per microliter at the time of diagnosis and increased to 95,000 per microliter during the first five days of therapy. However, over the past five days, no significant increase in the platelet count has been observed.

- Is there a platelet threshold at which you recommend starting warfarin? If so, what evidence supports that determination? Would your recommendation change if the patient had HIT with thrombosis (HITT)?
- If the recommended platelet threshold is not reached, is there a point at which you feel it is safe to start treatment with warfarin? For example, in this patient who has been on argatroban for 10 days, is it acceptable to start warfarin even though his platelet count is less than 100,000 per microliter? Would your recommendation change if the patient had HIT with thrombosis?
- Does fondaparinux play a role in management of HIT in this setting?
- Is there a role for the new oral anticoagulants (dabigatran and rivaroxaban) in this setting?

My Response

HIT is a clinical-pathological syndrome that is typically characterized by the onset of thrombocytopenia (≥50% fall from baseline) within five to 10 days of drug initiation. The mean platelet count in patients with this disorder is 60,000 per microliter. Thrombosis occurs in approximately 50 percent of patients and clusters in the first few days following onset of thrombocytopenia (termed HITT). It is mediated by antibodies against platelet factor 4 (PF4)-heparin complexes that activate platelets leading to excessive thrombin generation. Prompt recognition and appropriate treatment of HIT is required to reduce the risk of serious thrombotic events and complications including limb loss. Paradoxically, a major problem with HIT today is its over-diagnosis. Enzyme immunoassays (EIAs) for antibodies against PF4-heparin complexes are currently widely applied for making the diagnosis of HIT; while highly sensitive (>99%), only some antibodies have strong platelet-activating properties in the serotonin-release assay, one of the "gold standard" platelet-activation assays used for diagnostic confirmation. As results of serotonin release assays are rarely available for clinical decision making early in the course of HIT, it is best not to order ELISA tests in patients with low pretest probability scores for HIT (4T score: **T**hrombocytopenia, **T**iming of platelet count fall, **T**hrombosis, o**T**her causes of thrombocytopenia).[1] Also, many labs do not report the optical densities (OD) of positive EIAs; in such instances, it is useful to request this information, as it can be useful diagnostically since the strength of a positive EIA (OD) predicts for a positive SRA.[2]

After stopping heparin administration in patients with HIT, the median time to achieving a platelet count of >150,000 per microliter is about four days. However, in patients with more severe HIT, the platelet count can take longer (up to two weeks or more) to recover. It is important to keep in mind, however, that patients with HIT often have concurrent medical problems or are on other medications contributing to thrombocytopenia. The recommendation in the 8th Edition of the *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* is as follows[3]: "For patients with strongly suspected or confirmed HIT, we recommend against the use of vitamin K-antagonist (VKA) therapy until after the platelet count has substantially recovered (i.e., usually to at least 150 × 109/L) over starting VKA therapy at a lower platelet count (Grade 1B); that VKA therapy be started only with low, maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) rather than with higher initial doses (Grade 1B); and that the non-heparin anticoagulant (e.g., lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the INR has reached the intended target, and after a minimum overlap of at least five days between non-heparin anticoagulation and VKA therapy rather than a shorter overlap (Grade 1B)."

Despite a platelet count that has only risen to 95,000 per microliter, I would transition this patient with HIT without thrombosis (termed isolated HIT) off a parenteral direct thrombin inhibitor (i.e., argatroban) after 10 days of therapy. Management options for this patient include: 1) initiation of warfarin carefully under the cover of continued IV argatroban; 2) initiation of fondaparinux alone at therapeutic doses (provided the patient's creatinine clearance is greater than 30 mL/min) in lieu of argatroban; or 3) initiation of an oral direct thrombin or factor Xa inhibitor (either dabigatran etexilate or rivaroxaban) at therapeutic doses.

The initiation of warfarin causes a rapid decline in protein C levels and a slower decline in the levels of longer-lived vitamin K-procoagulant factors (especially prothrombin) augmenting the preexistent hypercoagulable state due to HIT. This mechanism is contributory to the development of venous limb gangrene, which is estimated to occur in 12 percent of patients with HITT[4]; its frequency is likely less in patients with isolated HIT. Fondaparinux, a synthetic pentasaccharide that selectively inhibits factor Xa after binding to antithrombin, has an attractive profile for the treatment of HIT based on *in vitro* studies; it is administered subcutaneously once daily. Small case series indicate generally favorable outcomes with initial use of this agent in HIT; in a recent retrospective series of 16 patients with the diagnosis confirmed by serotonin-release assay, nine of whom had thrombosis, none developed new or recurrent thrombosis.[5] However, fondaparinux is not approved for this indication; it is approved in the United States for the prophylaxis of VTE following major orthopedic and general surgery and the initial treatment of VTE.

If the continuation of argatroban is the only reason for continued hospitalization, I would employ fondaparinux alone at this juncture provided the patient could self-inject the medication and drug acquisition was not a problem (i.e., inability to gain insurance approval or prohibitive out-of-pocket cost). The total duration of anticoagulant treatment has not been defined by prospective studies, but I would treat isolated HIT for a minimum of six weeks given the high risk of thrombosis within the first 30 days after diagnosis. The use of fondaparinux to complete treatment would obviate the use of warfarin entirely and the burden of INR monitoring with attendant dose adjustments. Alternatively, warfarin could be initiated after the platelet count had risen to more than 150,000 per microliter under the cover of fondaparinux overlap for a minimum of five days until the INR reached the target range of 2-3. This would also circumvent complexities relating to INR monitoring during argatroban therapy if this option were chosen.[3] For patients with HITT, I would treat with anticoagulation for three to six months.

It should be pointed out that the efficacy of non-heparin anticoagulants for HIT and their approval by the U.S. FDA was not based on prospective, randomized controlled clinical trials. Vitamin K antagonists have been used for the treatment of HIT for many years and adopted by evidence-based guidelines after initial treatment with a non-heparin anticoagulant, as they have up until recently been the only class of oral anticoagulants available. Based on our mechanistic understanding of venous-induced limb gangrene in HIT, a strong case can be made that we should be moving away from using warfarin in the initial phase of HITT (and HIT) treatment (up until 30 days after diagnosis) given that alternative oral anticoagulants that do not lower protein C levels are available.[6] These oral agents selectively target thrombin or factor Xa, have a rapid onset of action, and do not require coagulation monitoring; however, there is not yet any reported experience with these agents in this patient population, and they have no specific antidote. Dabigatran and rivaroxaban have gained FDA approval for stroke prevention in atrial fibrillation[7, 8] and rivaroxaban is approved for the prophylaxis of VTE following total hip or knee replacement[9]; they have shown promising result for the treatment of symptomatic VTE but have not yet been approved for this indication in the United States. Thus, caution should be exercised if either dabigatran or rivaroxaban is used in a patient such as this; if chosen, they should be used at therapeutic doses and limited to adult patients with satisfactory renal function (creatinine clearance > 30 mL/min). Furthermore, given that HIT can result in serious complications including limb loss and subsequent litigation against health-care providers, hematologists choosing to use any of the new anticoagulants (dabigatran, rivaroxaban, or fondaparinux) should carefully document in the medical record their rationale for choosing the new agent.

Both the infrequent occurrence of HIT confirmed by validated platelet-activation assays and the clinical heterogeneity of affected patients make it difficult to perform trials of new agents in HIT. It is therefore unlikely that the new oral anticoagulants will be studied in controlled trials so as to gain FDA approval for management of this disorder in the near future. Hopefully, the reporting of well-characterized cohorts of patients with HIT (or HITT) treated with these agents will lead to favorable outcomes that will improve, as well as simplify, management of this disorder.

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Dr. Bauer has served as a consultant to GSK, Bayer Healthcare, and Johnson & Johnson.

Surprising Splicing: The New Most Frequent Class of Genetic Alteration in Myelodysplastic Syndromes

DAVID P. STEENSMA, MD

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Of all the molecular processes that a biologist-detective might interrogate for the cellular crime of promoting malignant behavior, surely pre-mRNA splicing — i.e., knitting together coding information-bearing exons and discarding "useless" introns to produce a mature gene transcript, ready for translation into protein — must rank among the least likely suspects.

There has been, admittedly, circumstantial evidence pointing toward at least an accomplice rap for RNA splicing in cancer promotion: Aberrantly and alternatively spliced transcriptional isoforms are commonly found in the transcriptome of neoplastic cells, and transformed cells often selectively express specific transcripts (e.g., encoding more active kinase isozymes) that can confer a growth or survival advantage. But almost all metazoan genes are multi-exonic, and ~95 percent of eukaryotic multi-exonic genes are alternatively spliced using the same highly conserved splicing machinery (Figure 1A). So how could that basal splicing machinery itself possibly be deranged without causing catastrophic cellular consequences? The mRNA splicing process itself is so fundamental to normal cell behavior that any serious defect in the small nuclear ribonucleoproteins (snRNPs) or the >100 associated protein factors comprising the spliceosome that catalyzes splicing should be lethal.

Many investigators presumed that cancer-associated alternative splicing resulted from cis-acting DNA mutations in conserved intron/exon boundary recognition sites (Figure 1B), or another local phenomenon, such as a specific epigenetic pattern favoring one splicing isoform over another (since splicing is co-transcriptional). All previously known mutations in *trans*-acting splicing factors appeared to have only cell-specific effects, such as the germline pre-mRNA processing factor (PRPF) mutations underlying certain forms of autosomal dominant retinitis pigmentosa.

But now, new incontrovertible evidence has surfaced — the oncologic equivalent of a smoking gun or a bloody glove that fits. Several ongoing next-generation sequencing projects (ironically, whole-exome resequencing) have identified a high frequency of somatic mutations in core splicing components in myelodysplastic syndromes (MDS) and in secondary acute myeloid leukemia (AML, either post-MDS or therapy-related); the same mutations are also found at a low rate in numerous other neoplasms.[1-3]

At least eight different splicing components — SF3B1, SRSF2, U2AF35, ZRSR2, SF3A1, PRP40B, SF1, and U2AF65 — are somatically mutated in patients with MDS, always heterozygously and almost always mutually exclusively.[2] Collectively, mutation in one of the components of the spliceosome is found in 45 to 85 percent of MDS and chronic myelomonocytic leukemia (CMML) cases. The most frequently abnormal gene, *SF3B1*, is mutated in 20 to 45 percent of MDS cases generally and, notably, in 65 to 85 percent of MDS cases associated with ring sideroblasts — a striking morphologic-genetic correlation.[1,2] Acquired mutations in these same splicing factors are also found at least occasionally in a series of other neoplasms, including 9 to 15 percent of chronic lymphoid leukemia (CLL);[4,5] 3 to 9 percent of myeloproliferative neoplasms and *de novo* AML;[1,2,6] and rare cases of breast, renal, and adenoid cystic carcinomas – and probably other tumor types as well.[1]

In MDS, several groups have reported that splicing mutations are associated with longer overall survival and leukemia-free survival,[1,7,8] though a Mayo Clinic series suggests that the presence of a splicing mutation may not be independent of known MDS prognostic features such as morphology or the International Prognostic Scoring System (IPSS) score.[9] In CLL, in contrast, SF3B1 mutations are associated with poorer prognosis that correlate with ATM mutations and deletion of chromosome 11q.[4]

Strangely, all eight of the known mutated splicing factors are involved in recognition of the canonical 3' DNA splice element and its nearby polypyrimidine tract, while no mutations have yet been described in 5' elements (e.g., U1snRNP components). Even more peculiarly, mutations in SF3B1 and mutations in DNMT3A, which encodes a DNA methyltransferase and is associated with poorer outcomes in MDS, appear to co-associate more frequently than would be expected by chance alone.[7] It is not clear why this should be the case.

A host of new questions are raised by these findings.[10] First, what are the molecular consequences of splicing machinery gain-of-function or loss-of-function mutations? Although there is considerable allelic heterogeneity, SF3B1 K700, and H662 represent high-frequency recurrent mutation sites. Other detected mutations are less deleterious than would be predicted if the mutations occurred randomly, and null mutations are rarely if ever observed.[2] These observations, that mutations are not simple loss of function but instead lead to aberrant spliceosomal properties, suggest that perhaps neomorphic alleles result from the mutations in a manner analogous to the AML-associated IDH1 R132H mutation.

Second, why are mutations only found in 3' splicing elements in MDS, CLL, and other diseases? Is there something special about 5' elements; would changes there be lethal to the cell?

Third, a similar question arises as that raised by ribosomal defects in MDS (particularly in relationship to the 5q- syndrome) — does a splicing mutation result in a clonal advantage in the marrow milieu, and if so, how? Initial experimental results do not suggest that mutant spliceosome components confer a proliferative or survival advantage; transfection of mutant U2A35 into HeLa and TF-1 cell lines reduced the cells' proliferative potential and increased apoptosis compared to cells transfected with wild-type U2A35, while mutant-transduced murine stem cells exhibited compromised reconstitution capacity in lethally irradiated mice.[2] (*SF3B1* cDNA is challenging to work with and results of transfections have not yet been reported.) Interactions with the polycomb repressor complex suggest a possible non-splicing role for SF3B1.

Fourth, why are splicing mutations so tightly associated with ring sideroblasts? Is there a gene already associated with sideroblastic anemia, such as *ABCB7*, *SLC25A38*, or *ALAS2*, mis-spliced in a consistent way? Transfection of mutant splicing factors into cells increased generation of unspliced RNA species with a premature stop codon and induced nonsense-mediated decay, but no specific altered transcript of interest was observed.[2] Clearly, there is much work still to be done to characterize these mutations functionally.

Finally, is there any way disordered splicing could be a therapeutic target? There are several compounds that can alter splicing patterns, but it is too early to predict whether any of these reagents might have clinical utility.

(Cont. on page 7)

Figure 1A

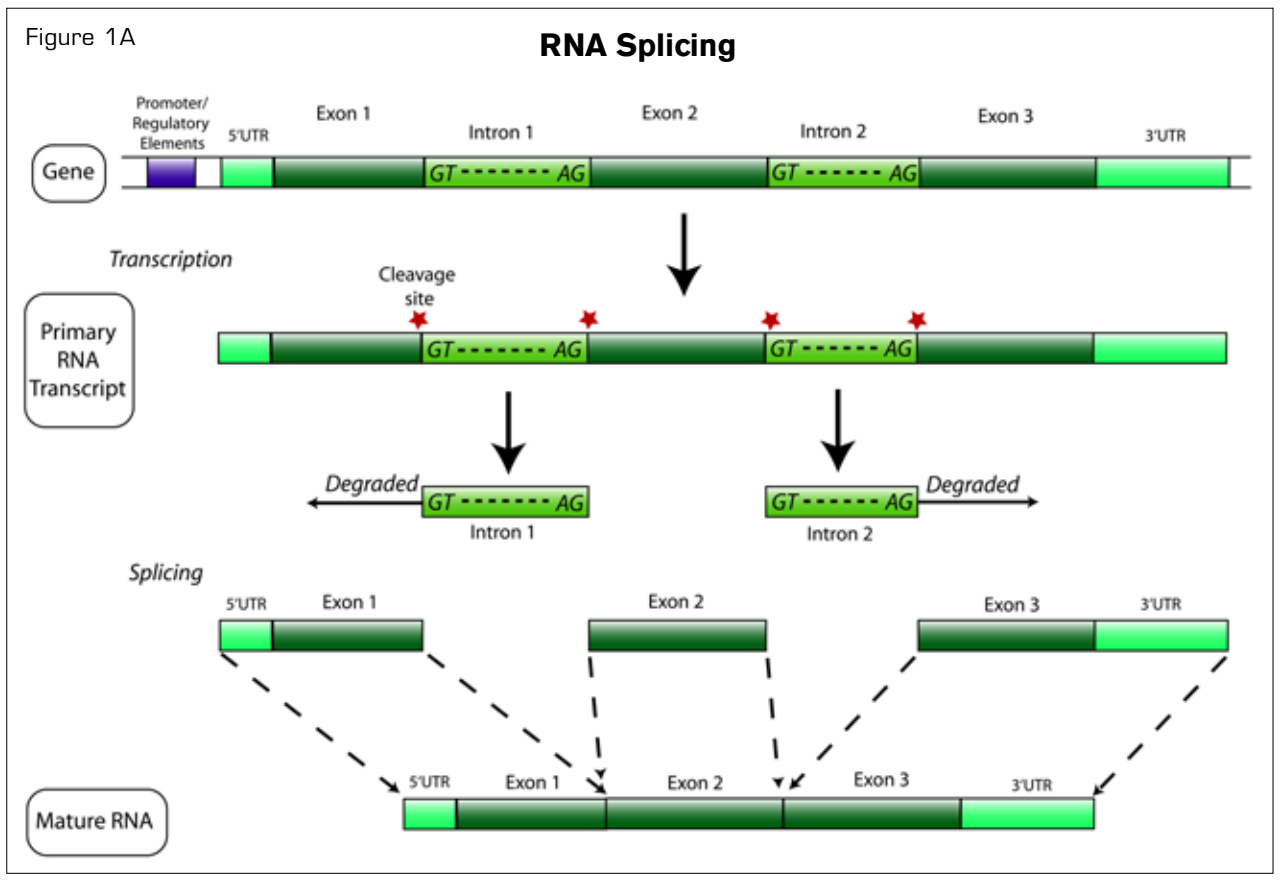
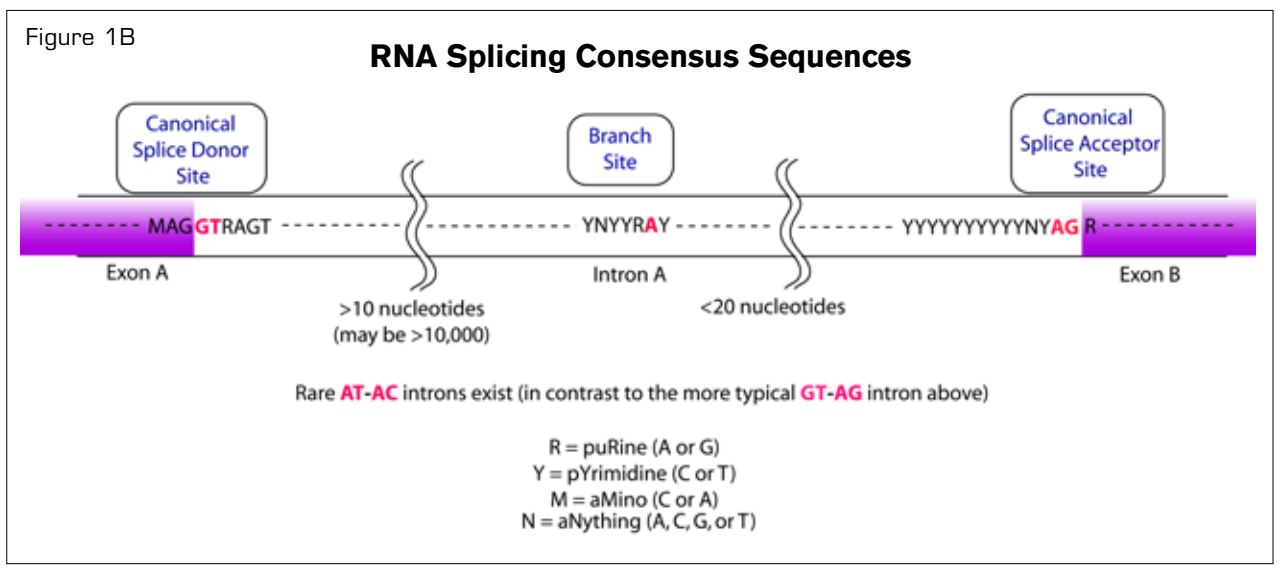


Figure 1B



HEADLINES FROM Washington

Congress Passes Final FY 2012 NIH Funding Bill

In late December, two-and-a-half months into fiscal year (FY) 2012, Congress cleared a final FY 2012 spending package that included funding for the National Institutes of Health (NIH). For NIH, the agreement appropriates $30.69 billion, an increase of $1.7 million over FY 2011. However, NIH and many other federal programs are subject to across-the-board cuts, which, when applied, will mean that NIH will receive only a fraction of that increase in FY 2012.

The agreement reduces the salary cap on extramural grants from Executive Level I ($199,700 in 2011) to Executive Level II ($179,700). The package also includes language to implement the creation of the National Center for Advancing Translational Sciences (NCATS) and eliminate the National Center for Research Resources (NCRR), transferring the various NCCR programs to other institutes and centers. The agreement also provides NCATS with up to $10 million for the Cures Acceleration Network.

NIH Appoints Interim NCATS Leadership

National Institutes of Health Director Francis Collins, MD, PhD, has designated Thomas Insel, MD, as the acting director and Kathy L. Hudson, PhD, as acting deputy director of the newly created National Center for Advancing Translational Sciences (NCATS). Drs. Insel and Hudson have been deeply involved in establishing NCATS and will lead the process of bringing the Center into being and getting its programs underway while NIH conducts a nationwide search for the first NCATS director.

Dr. Insel has served as director of the National Institute of Mental Health (NIMH) at NIH since 2002. Dr. Hudson has served as deputy director for Science, Outreach, and Policy at NIH since October 2010. Drs. Insel and Hudson will continue to serve in their current roles while serving in these acting positions at NCATS.

Congress Reaches Last-Minute Agreement to Temporarily Avert Medicare Physician Payment Cuts

In a dramatic turn of events, Republican leaders in the House of Representatives bowed to pressure from President Obama, Senate Democrats, and some in their party and passed a legislative package of two-month extensions that would, among other things, block the 27.4 percent Medicare payment cut to doctors otherwise set to begin January 1, 2012.

The deal marked the end of weeks of uncertainty over the fate of Medicare physician payments in 2012 and was a striking retreat for House Republicans who previously rejected a bipartisan proposal passed by the Senate that would block the 27.4 percent Medicare payment cut to doctors and give a two-month extension for unemployment benefits for the long-term unemployed and for a Social Security payroll tax reduction.

Although both the House and Senate agreed on the need to avert the physician payment cuts, at issue were differences over the length of the extensions as well as how to pay for the measure. The Senate limited the provisions to two months because it could not find ways to fund a longer fix. House Republicans, however, insisted on a longer-term package and initially refused to vote on the Senate-passed measure, making it appear unlikely that an agreement would be reached prior to January 1 when the cuts were scheduled to begin.

The agreement means that Medicare physician payment rates are extended until March 1, 2012, and congressional negotiators will need to consider a long-term extension when they return to Washington after their holiday recess. For updates on this issue, please go to *www.hematology.org/practice*.

ASH Calls on Congress to Take Immediate Action to Prevent Drug Shortages; Obama Administration Issues Interim Final Rule

As part of the Society's efforts to combat drug shortages, ASH urged a number of congressional committees to expand authority of the Food & Drug Administration (FDA) and provide economic incentives to manufacturers of low cost generic drugs to prevent drug shortages.

In response to ASH advocacy, on December 15 the Obama Administration issued an interim final rule that will help prevent prescription drug shortages. The rule will require manufacturers that are the only producer of certain critical drugs to report to the FDA all interruptions in manufacturing of products. The rule builds on recommendations ASH made on the importance of early notification by manufacturers of disruptions in drug production. For more information about hematology drugs in shortage, please visit the ASH website at *www.hematology.org/News/2011/7389.aspx*.

President Obama Nominates Marilyn Tavenner for CMS Administrator

President Obama has nominated Marilyn Tavenner to become administrator of the Centers for Medicare & Medicaid Services (CMS). Ms. Tavenner, who has served as principal deputy administrator since joining CMS in February 2010, began serving as acting CMS administrator December 5. Ms. Tavenner's nomination will be considered by the Senate Finance Committee. The Committee's chairman, Max Baucus (D-MT), has been noncommittal about a confirmation hearing date.

Members of ASH Participate in Inaugural Advocacy Leadership Institute

ROY L. SILVERSTEIN, MD

The Linda and John Mellowes Professor and Chairman, Department of Medicine, Medical College of Wisconsin

In mid-October, 22 ASH members and associate members from 19 institutions across the country gathered in Washington, DC, for the first ASH Advocacy Leadership Institute. Participants brought a range of interests and perspectives to the two-day workshop, including those of clinicians involved in patient care covering the entire range of hematologic disorders affecting both children and adults, laboratory and clinical investigators (both MD and PhD), trainees, educators, and leaders. During the first day of the workshop, held at ASH headquarters, attendees were introduced to the important role of advocating to government officials in support of both biomedical research and issues relevant to the training of hematologists and the practice of hematology. They also toured ASH headquarters and learned about opportunities to get involved in programs and activities sponsored by ASH.

Mila Becker and Suzanne Leous, ASH staff from the Government Affairs and Practice departments, described how the federal legislative and regulatory process works and how ASH develops positions on key policy issues, such as stem cell research. Participants were then treated to remarks by former Congressman Michael Castle (R-DE) who explained that Members of Congress take letters and phone calls from constituents very seriously and how impressive it is when busy physicians and scientists take the time to visit their home offices or their offices in Washington to share concerns. He assured participants that individual voices matter and re-affirmed his strong support for biomedical research.

Dr. Griffin Rodgers, a sickle cell disease researcher and long-time ASH member who now serves as director of the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) at NIH, echoed his support for advocacy and described how his Institute

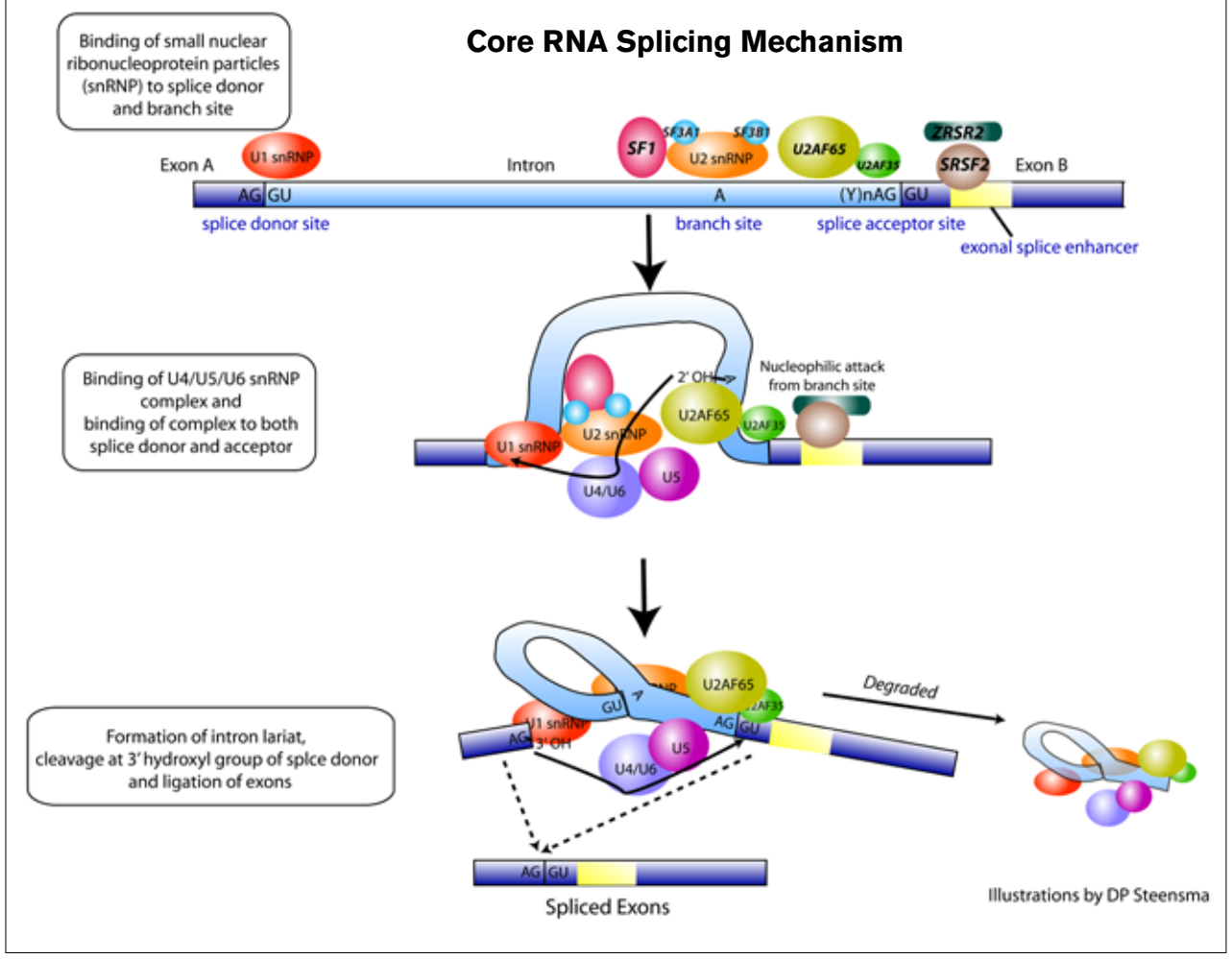
Surprising Splicing

(Cont. from page 5)

The MDS splicing story rings a personal note. In 2007, puzzled by the frequency of expressed aberrant spliceoforms of genes such as *CDC25C* and *ATRX* without any correlating genomic changes in canonical splicing elements,[11,12] I submitted an R01 grant application proposing to look for mutations in spliceosome components in MDS primary cells (proposal R01 CA136631-01). The suspicious biologist-detectives of the Cancer Molecular Pathobiology study section were appropriately skeptical of my application, and the proposal was triaged without a score. One reviewer commented that splicing was an implausible target in MDS – and besides, if disordered splicing were truly important, more well-established labs would surely already be working on the problem.

As a relatively callow young scientist, I lost confidence in my ideas, assumed the study section was correct and that I was barking up the wrong tree, shut down my lab, and moved to a clinical job at a new institution. Four years later, to see MDS-associated splicing mutations become *Nature* and *New England Journal of Medicine* papers and an ASH annual meeting plenary session makes me happy for friends and colleagues involved, and glad progress is being made, yet disappointed not to be part of the action – and kicking myself for giving up too soon. Erstwhile independent U.S. Presidential candidate H. Ross Perot once said, "Most people give up just when they're about to achieve success. They quit on the one yard line. They give up at the last minute of the game, one foot from a winning touchdown." The take-home message for young investigators: Don't let that be you, too.

Figure 2



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Dr. Steensma indicated no relevant conflicts of interest.

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maintains open communication lines with its constituents, including ASH. He also reviewed the major efforts and commitments the Institute has made to hematology research over the past 50 years.

Over a working lunch, participants took part in a round-table discussion of current "hot" topics in Washington, led by Brent Jaquet and Ellen Riker from Cavarocchi Ruscio Dennis and Associates, a consulting firm that works with ASH in Washington. Conversation focused on both the generally pessimistic outlook for NIH funding attributed to pressures from deficit reduction hawks and the uncertainty of the economic impact of health-care reform.

Breaking into small groups, ASH staff then reviewed tools and strategies for making effective visits to congressional offices. Participants had done homework prior to the workshop to create personalized NIH funding fact sheets showing the specific economic impact of NIH-sponsored research in their home congressional districts and states. These sheets were reviewed and finalized in preparation for a visit to Capitol Hill that was arranged for day two of the workshop.

The next morning groups of four to five participants, each accompanied by an experienced ASH staff member, went to Capitol Hill and met with Members of Congress and Senators and/or their legislative staff from the home districts and states of the participants. Because of the emphasis on unemployment and the deficit in the current Congress, most of the discussion focused on the economic impact as well as the medical impact of NIH-supported research. Copies of the personalized NIH fact sheets along with specific information about ASH and hematology research were left with each office.

As a former member and chair of the ASH Government Affairs Committee with many years of advocacy experience, I was delighted to serve as chair of the workshop. It was extremely gratifying to see the growing excitement and enthusiasm of the workshop participants as the sessions unfolded. Thanks to the efforts of Ulyana Desiderio, PhD, who organized the workshop, and other ASH staff, the inexperienced group quickly became comfortable with the process. Successful advocacy is all about "telling a story," and participants soon realized that ASH members have a compelling story to tell about their patients and the role of that research plays as the engine that drives improvement in health care.

Participants of the Advocacy Leadership Institute took part in a graduation ceremony during the Grassroots Network Breakfast at the 2011 ASH Annual Meeting. Participants included Drs. Roy Silverstein (Chair), Gregory Abel, Martha Arellano, Latorya A. Barber, Thomas P. Bradley, Jeffrey S. Buzby, Rachel Cook, Laura M. De Castro, Sherine Elsawa, Jonathan Hoggatt, Krishna Komanduri, Jose F. Leis, Troy Lund, Ines Macias-Perez, Navneet Majhail, Manali Patel, Naveen Pemmaraju, Lindsay Peterson, Jonathan Thon, Ramon Tiu, Nicole Hasbrouck Verdun, and Ann Woolfrey.

Gene Correction in Patient iPS Cells Without a Trace

Yusa K, Rashid ST, Strick-Marchand H, et al. Targeted gene correction of α_1-antitrypsin deficiency in induced pluripotent stem cells. Nature. 2011;478:391-394.

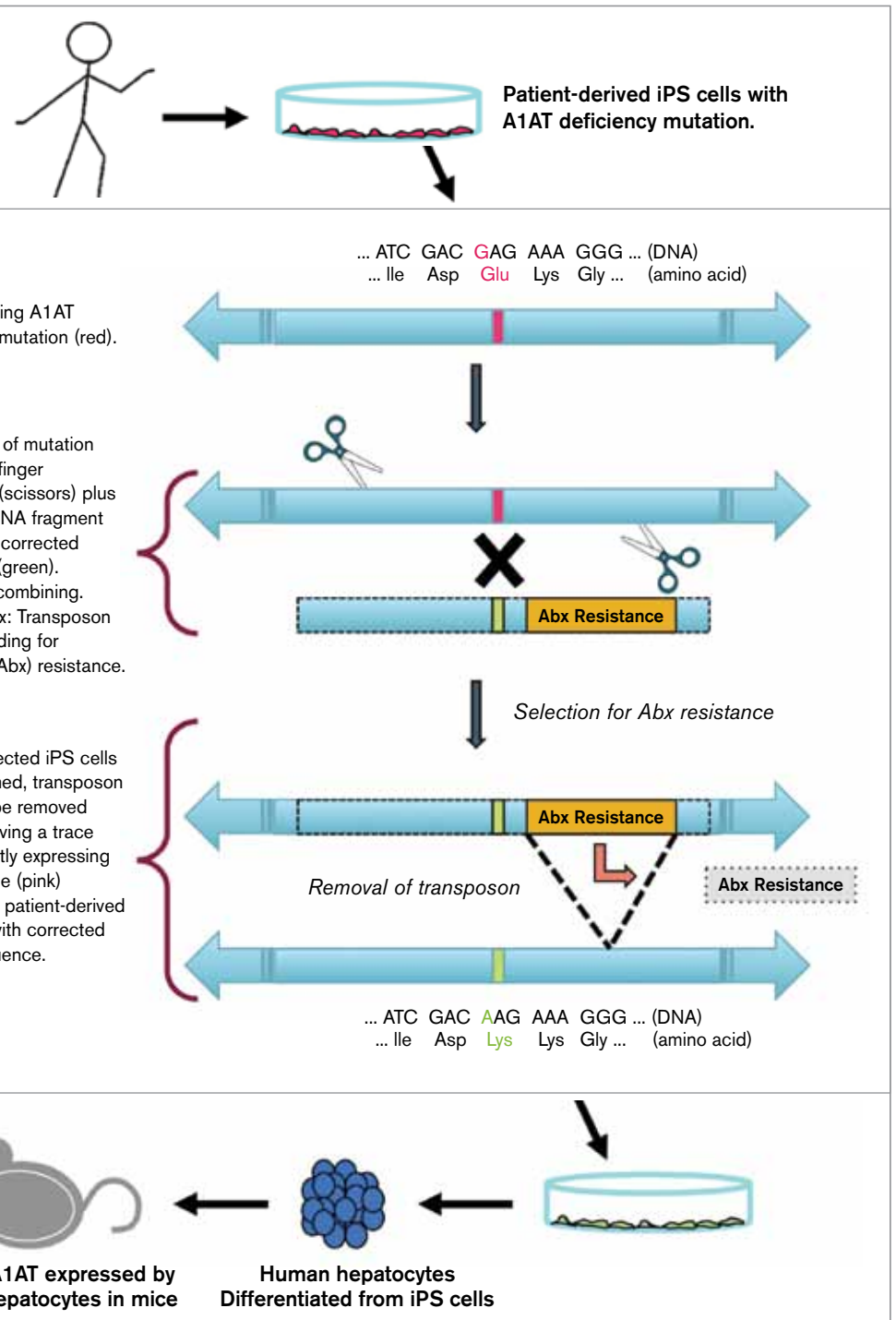
Alpha-1 anti-trypsin is a protease inhibitor that protects cells from enzymatic digestion. Mutations in the *A1AT* gene cause liver disease or emphysema, depending on the specific mutation. The *A1AT* mutation most frequently associated with liver disease (known as "PiZZ") results in the substitution of glutamate for lysine. The PiZZ form of A1AT polymerizes and accumulates inside liver cells, interfering with their normal function and leading to irreversible injury. The only effective therapy for cirrhosis due to A1AT deficiency is liver transplantation, but this potentially curative procedure is not an option for all patients due primarily to limited organ availability. In the current study, investigators aimed to develop a novel treatment for liver disease caused by *A1AT* mutation by using gene-corrected autologous cells.

The investigators succeeded in bringing together multiple technologies to correct the *A1AT* mutation without leaving any trace of the manipulations used to achieve this correction (Figure). First, they reprogrammed cells from patients with PiZZ-associated A1AT deficiency into induced pluripotent stem cells (iPSCs), taking advantage of the properties of these cells that allow them to grow indefinitely in culture. Next, they used two novel approaches to correct the mutation in the iPSC: 1) zinc finger nucleases (ZFNs) and 2) transposons. ZFNs are engineered proteins with both a customized domain that confers binding to specific DNA sequences and a nuclease domain that nicks DNA. In order to target the *A1AT* gene, two ZFNs (scissors in Figure) were designed – one that binds specifically upstream of the *A1AT* mutation and the other that binds immediately downstream. By nicking the DNA flanking the mutation, these nucleases promote exchange of mutant DNA for the correct sequence. Transposons are unique in that they have evolved to enter and then exit the genome without leaving a trace. A transposon (orange box in Figure) was used in this study to confer antibiotic (Abx) resistance upon the iPS cells that also receive the corrected *A1AT* sequence. Once these cells were selected based on their capacity to grow in the presence of the antibiotic, the transposon was removed without leaving behind a trace of its presence.

An overriding concern with both iPSC and gene therapy technologies is that these complex procedures can introduce other mutations into the DNA, potentially leading to unpredictable growth and possibly oncogenesis. The investigators performed extensive analyses of the corrected clones to identify those that had not undergone additional mutations. Although none of the corrected iPSC populations were entirely free of mutations, several had only a few small changes to their DNA. These corrected iPSCs were differentiated into hepatocytes that were then transplanted into immunodeficient mice and shown to be functional.

This research provides proof of principle that gene-corrected iPSCs can be engineered successfully using gene-specific, "customized" zinc-finger proteins and transposon DNA. Gene-corrected iPSCs can be differentiated to a desired cell type in culture (hepatocytes in this example) and transplanted to treat A1AT disease. In addition to ensuring safety of iPSC-derived cell therapy, efficient protocols for hepatocyte transplantation and therapeutic repopulation will need to be developed in order for this approach to be applied clinically. This remarkable feat of scientific engineering has wide application for the treatment of genetic diseases, including, for example, those affecting patients with inherited bone marrow failure syndromes.

Figure



The investigators 1) created induced pluripotent stem cells (iPSCs) from patients with PiZZ-associated A1AT deficiency; 2) designed zinc finger nucleases to specifically nick the DNA flanking the mutation in the *A1AT* gene; 3) replaced the region of genomic DNA containing the mutation with a fragment of DNA containing not only the corrected gene sequence, but also a transposon, which allows for selective growth of corrected iPSCs; 4) removed the transposon without leaving a trace; 5) assessed for corrected clones that had not undergone additional mutations during the procedures using deep sequencing, genome hybridization, and other approaches; and 6) differentiated the iPSCs into functional hepatocytes that were transplanted into immunodeficient mice, where they functioned to produce human albumin and the corrected A1AT protein.

DIANE KRAUSE, MD, PhD, AND E. SCOTT SWENSON, MD, PhD

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

ON

Cardiac Amyloid: It's All in the Genes

Perfetti V, Palladini G, Casarini S, et al. The repertoire of λ light chains causing predominant amyloid heart involvement and identification of a preferentially involved germline gene, *IGLV1-44*. Blood. 2011. [Epub ahead of print]

The most common form of systemic amyloidosis is light chain disease (AL amyloid) that is a consequence of secretion of pathologic monoclonal immunoglobulin light chains (LC) by a clonal population of plasma cells. Tissue deposition of these misfolded proteins results in progressive organ damage and, in some cases, sudden death as a result of cardiac involvement. Diagnosis can be challenging, requiring histology confirmation and specialized testing to determine disease subtype. Kidney and heart are the most frequently involved organs, with the extent of cardiac disease being the most important prognostic factor. The current goal of treatment is eradication or reduction of the monoclonal plasma cell mass, thereby eliminating or reducing the production of pathologic light chains. Such treatment leads to a decrease in amyloid deposits with corresponding improvement in organ function and added survival time. However, to hasten organ recovery and to enhance survival further, there is a need to increase the rate at which AL amyloid deposits are cleared, especially in cases in which cardiac involvement is extensive. To this end, recent studies have focused on the genetics of AL amyloid with a goal of understanding the properties of the pathological proteins that account for their diverse clinical manifestations.

In a case-control study, Perfetti and colleagues from the University of Pavia characterized the repertoire of the variable region of germline genes of λ LC that preferentially target the heart and compared it with that of LC lacking cardiac tropism (the control group). They found that the repertoires were highly restricted, showing preferential use of the same few germline genes, with a different frequency of Vλ family usage. A five-fold increase in the odds of being associated with heart-dominant disease was observed for a single gene, *IGVL1-44*, while cardiac involvement was absent when the monoclonal LC was a product of *IGVL6-57*. LC expression in the control population was dominated by the VλIII family (involved in 46% of cases), with the VλII and VλVI families each accounting for approximately 20 percent of LC expression and the VλI family involved in 11 percent of cases. In contrast, the heart-dominant group was characterized by even distribution of LC expression by VλI, VλII, and VλIII families (equally contributing ~30% of sequences) and under-representation of the VλVI family (this latter family is known to be preferentially expressed in cases with kidney involvement). Based on these comparisons, the frequency of involvement by the VλI family was almost three times greater in the heart-dominant group (odds ratio 3.48, 95% CI 1.08-13.17), suggesting biased expression at the level of germline genes.

The results of this interesting study support the hypothesis that LC genetics play an important role in organ targeting. Study of the characteristics of IGVL1-44 LC may lead to an understanding of the mechanisms that mediate interactions between this light chain and cardiac tissues, thereby providing insight into the basis of organ damage and potentially identifying new approaches to therapeutic interventions that enhance the rate of clearance of amyloid deposits. In the same way, investigating the properties of LC derived from IGVL6-57 may suggest an approach to ameliorating renal dysfunction in patients with AL amyloid with kidney involvement.

XAVIER LELEU, MD, PhD
Dr. Leleu indicated no relevant conflicts of interest.

Heparin: Pure and Simplified

Xu Y, Masuko S, Takieddin M, et al. Chemoenzymatic synthesis of homogeneous ultralow molecular weight heparins. Science. 2011;334:498-501.

In 1916, Jay McLean, a second-year medical school student walked into the office of William H. Howell, his research professor at Johns Hopkins University, placed a beaker of cat's blood on a table and asked Howell to tell him when the blood clotted. McLean had added to the blood an extract prepared from liver that he called heparphosphatide. Instead of behaving like a thromboplastin and accelerating coagulation like most tissue-derived substances did, the heparphosphatide-treated blood "never did clot."[1] This substance, subsequently named heparin by Howell and Luther E. Holt, immediately became the subject of an active investigation into its chemical, biosynthetic, physiologic, and pharmacologic properties that has continued to this day.

Crude preparations of heparin were first used clinically as an antithrombotic in 1935, followed by commercial preparation of unfractionated (UF) heparin from porcine intestine or bovine lung, and, much later, by low-molecular-weight (LMW) and ultralow-molecular-weight (ULMW) heparins. Animal-derived heparin is a polysaccharide containing variable amounts of a disaccharide-repeating unit of either iduronic acid or glucuronic acid residues linked to a glucosamine residue. Each of these residues is variably sulfated within the polysaccharide chain. Both the variation in polysaccharide sequence and length and the variation in the degree of sulfation result in an extremely heterogeneous population of molecules that collectively is called heparin. UF heparin and LMW heparin, prepared through chemical or enzymatic degradation of UF heparin, contain an average of ~40 and ~14 monosaccharide units, respectively, leading to average molecular weights of 14,000 and 5,000 daltons, respectively. Fondaparinux sodium is a ULMW pentasaccharide that has a molecular weight of 1,508 daltons. In contrast to animal-derived UF and LMW heparins, fondaparinux is a synthetic heparin.

The identification of contaminated heparin formulations in 2007 that produced severe hypersensitivity-type reactions has increased the motivation to develop synthetic heparins to replace animal-derived heparins.[2] However, the only commercial synthetic heparin, fondaparinux, is produced by a difficult manufacturing process involving approximately 50 steps. The lengthy chemical synthesis is necessitated by the introduction and removal of protecting groups and results in a yield of only ~0.1 percent. Partly as a result, fondaparinux is the most expensive heparin.

Now Xu et al., working in the laboratory of Jian Liu at the University of North Carolina at Chapel Hill, describe the scalable synthesis at ~40 percent yield of two ULMW heparins with molecular weights of 1,778 and 1,816 daltons, respectively (Figure). The method centers on the use of enzymes that are involved in the biosynthesis of heparan sulfate, a polysaccharide that is closely related to heparin. The chemoenzymatic synthesis includes the use of four sulfotransferases that add sulfo groups at specific sites in the polysaccharide chain. The size of polysaccharide starting material and intermediates, the sequence of sulfo group addition, and improved purification protocols were critical to the optimization process.

Heparin functions as an anticoagulant by binding to antithrombin and accelerating its capacity to inhibit factor Xa and thrombin. Xu et al. report that both of the new ULMW heparins bind antithrombin with affinities similar to that of fondaparinux. Additionally, the capacity of the new ULMW heparins to promote the inhibition of factor Xa by antithrombin is indistinguishable from that of fondaparinux as is the pharmacodynamic behavior of both constructs in rabbits as measured by anti-factor Xa activity.

The chemoenzymatic approach to the manufacture of synthetic heparins as described by Xu and colleagues is a potentially cost-effective process that may lead to safer antithrombotic drugs. Additionally, synthetic heparins could serve as chemically defined starting materials for development of novel polysaccharide-based drugs with new or improved pharmacologic properties.

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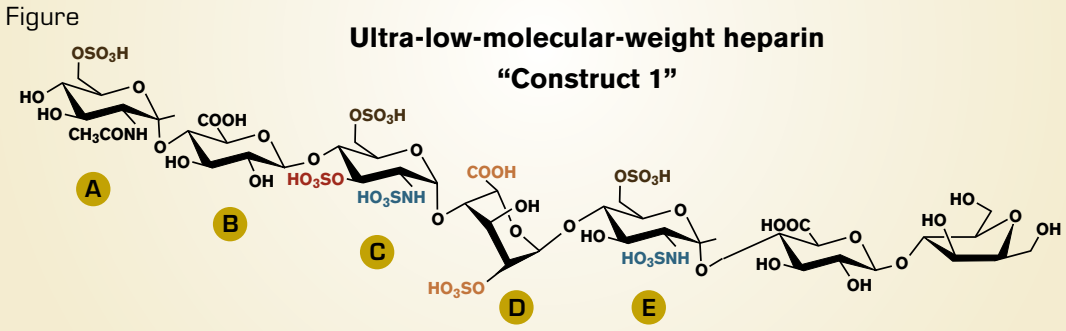
Figure

Ultra-low-molecular-weight heparin "Construct 1"



PETE LOLLAR, MD
Dr. Lollar indicated no relevant conflicts of interest.

Hep, Hep Hooray!

Preza GC, Ruchala P, Pinon R, et al. Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload. J Clin Invest. 2011;121:4880-4888.

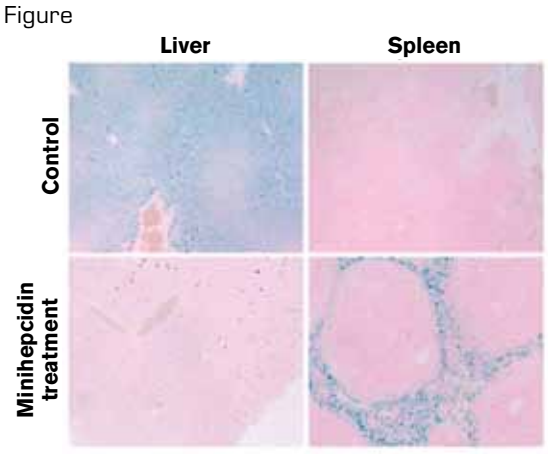
The protean clinical manifestations of iron overload observed in patients with either primary or secondary hemochromatosis reflect the toxic effects of excess-free iron that cause end-organ damage through oxidative injury to lipids, proteins, and DNA. Phlebotomy and iron chelators are effective in preventing and, in some cases, reversing end-organ damage caused by iron overload. However, not all patients are good candidates either for phlebotomy because of anemia or for iron chelators because of adverse effects or expense. Therefore, new approaches to preventing and treating iron overload are needed, and understanding the fundamentals of iron metabolism and the pathophysiology of iron overload is of paramount importance if novel therapies are to be developed successfully.

Recent studies from a number of investigators (many of whom are ASH members) have delineated how nature handles iron. The story of hepcidin, a peptide hormone that mediates iron homeostasis, is among the most fascinating investigative triumphs in hematology. By inducing endocytosis and degradaton of its receptor, ferroportin, the "door" through which cells export iron, hepcidin controls plasma-iron concentration by inhibiting both dietary iron absorption and release of recycled iron from macrophages. Hepcidin deficiency underlies or contributes to iron overload in hereditary hemochromatosis, thalassemia, and a number of other disease states. Several investigations have suggested that replacement of hepcidin would be a rational approach to the prevention and treatment of iron overload in these disorders.[1-3] However, the use of recombinant hepcidin as a replacement therapy in hepcidin-deficient conditions has major limitations. Generation of a correctly folded, full-length hepcidin protein is challenging and expensive as the 25 amino acids molecule has four disulfide bonds that are required for maintenance of its tertiary structure. Further the protein's molecular mass of 2.7 kDa limits GI absorption, and *in vivo*, the half-life of the renally excreted protein is short. Based on structure/function studies of hepcidin/ferroportin, Preza et al. in the laboratories of Elizabeth Nemeth and Tomas Ganz at UCLA developed a series of seven- to nine-amino-acid peptides, "minihepcidins," that mimic the activity of hepcidin in cell-based bioassays and in mice. Their findings establish the feasibility of small, drug-like hepcidin mimetics for the treatment of iron overload disorders due to hepcidin deficiency.

The investigators targeted the extracellular loop of ferroportin that is involved in hepcidin binding. By identifying hepcidin residues critical for binding to ferroportin, computer modeling allowed the design of minihepcidins, seven to nine amino acids long. The capacity to induce ferroportin degradation was used to screen the synthesized peptides for functional activity. Aromatic and hydrophobic side chain interactions and cysteine thiols necessary for disulfide exchange with ferroportin were necessary for maximal activity. Pegylation increased solubility and use of unnatural D-amino acids enhanced resistance to proteolysis. These minihepcidins given intraperitoneally or orally by gavage after conjugation to bile acids or palmitate caused hypoferremia in mice, and they prevented hepatic iron overload in hepcidin-1 knockout mice (Figure).

These careful, rigorous studies support the therapeutic utility of minihepcidins to block hyperabsorption of dietary iron in patients with hemochromatasis. It is not clear whether minihepcidins would "unload" iron from affected organs in patients with hemachromatosis, but conceivably, they could redistribute iron from parenchymal cells to macrophages. Such redistribution is potentially therapeutic as macrophages are more resistant to the toxic effects of iron than organ tissues such as hepatocytes and cardiac myocytes that are commonly affected in patients with hemochromatosis.[4] These promising results, based on understanding nature's way of handling iron, may bring to the clinic new agents for treating iron overload by locking and degrading the "iron door."

Figure



Minihepcidin treatment prevents hemochromatosis phenotype in hepcidin knockout mice. In hereditary hemochromatosis, because of hepcidin deficiency, iron is excessively exported into plasma, both from enterocytes, which absorb dietary iron and from macrophages, which recycle iron from old red blood cells. This process results in iron overload of hepatocytes in the liver and iron-deficient spleen macrophages, as shown in the top row of the figure for knockout mice treated with solvent only. In the bottom row, two weeks of daily minihepcidin injections prevented liver iron accumulation and caused normalization of iron stores in spleen macrophages.

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Dr. Vercellotti indicated no relevant conflicts of interest.

Combined Histone Deacetylase and Proteasome Inhibitor Therapy in Myeloma

Harrison SJ, Quach H, Link E, et al. A high rate of durable responses with romidepsin, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma. Blood. 2011:118;6274-6283.

In this study, Harrison and colleagues report the results of a clinical trial that examined the combination of romidepsin, bortezomib, and dexamethasone in patients with relapsed multiple myeloma (MM). Using a novel accelerated dose-escalation trial strategy, they established the maximum tolerated dose in a 28-day cycle to be bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; dexamethasone 20 mg on days of and after bortezomib; and romidepsin 10 mg/m^2 on days 1, 8, and 15. Grade > 3 thrombocytopenia and neuropathy occurred in 64 percent and 8 percent of cases, respectively. Remarkably, the overall response rate was 72 percent, with 8 percent complete responses, 28 percent very good partial responses, and 24 percent partial responses. Moreover, time to progression was 7.2 months and median overall survival was 36 months. These data provide the rationale for further evaluation of this regimen.

The proteasome inhibitor bortezomib achieves remarkable frequency and extent of response when used as initial therapy for MM or to treat relapsed/refractory disease. Moreover, based upon preclinical mechanistic studies showing that combination therapies can achieve additive or synergistic cytotoxicity, bortezomib has been combined with other classes of targeted therapies with some of these combinations producing striking clinical efficacy. For example, the combination of bortezomib, lenalidomide, and dexamethasone triggers dual apoptotic signaling *in vitro* and achieves responses in the majority of patients whose MM is refractory to any of these agents alone. Moreover, near universal response is observed when this combination is used as initial therapy for MM. *In vitro* studies have shown that perifosine (an inhibitor of Akt and PI3 kinase) blocks bortezomib-induced activation of Akt, suggesting a mechanism by which this drug can increase sensitivity to or overcome clinical resistance to bortezomib. Previous studies have shown that bortezomib down-regulates class I histone deacetylase (HDAC) activity and that the class I HDAC inhibitor romidepsin enhances histone H3 and H4 hyperacetylation induced by bortezomib.[1] Therefore, the remarkable clinical responses to romidepsin, bortezomib, and dexamethasone observed in the present study may be related, at least in part, to greater class I HDAC inhibition. It is also possible that inhibiting class I HDACs is efficacious because such treatment results in reduced expression of cytokine genes that mediate the growth, survival, and drug resistance of MM cells within the bone marrow microenvironment. Importantly, although targeting the proteasome with bortezomib results in multiple sequelae affecting the MM cell directly, the tumor-host interaction in the bone marrow milieu is also affected. The primary effects of proteasome inhibition, however, are a consequence of blocking the degradation of substrate proteins by the proteasome. Proteasome inhibition also triggers compensatory up-regulation of the alternative aggresomal pathway for degradation of ubiquitinated proteins *in vitro*, and dual blockade of both the proteasome with bortezomib and the aggresome with HDAC inhibitors triggers synergistic MM cytotoxicity.[2] Specifically, HDAC 6 (a class II b family member) binds to ubiquitinated proteins on the one hand and to dynein motility complexes on the other to shuttle proteins for degradation via the aggresomal pathway. Importantly, combination therapy either with broad class I, II HDAC inhibitors (e.g., panobinostat, vorinostat), or with an HDAC 6 selective inhibitor (e.g., ACY 1215) blocks bortezomib-induced up-regulation of this alternative aggresomal pathway and mediates synergistic MM cell death *in vitro*.

Clinical trials combining bortezomib with an HDAC inhibitor in MM are demonstrating promise, even in the setting of bortezomib resistance. However, compared with more selective agents, broad class I, II HDAC inhibitors appear to be associated with more or worse adverse events (e.g., fatigue, thrombocytopenia, and diarrhea), especially when used in combination with bortezomib. Ongoing and future studies will therefore identify the optimal spectrum and extent of HDAC class I and/or II inhibition needed to achieve maximal clinical benefit while maintaining a favorable therapeutic index and safety profile.

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Dr. Anderson indicated no relevant conflicts of interest.

The Bloody Problem With VTE Prophylaxis

Qaseem A, Chou R, Humphrey LL, et al. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011;155:625-632.

Prophylaxis against VTE has become routine in the hospital setting. Yet the benefits and risks of this practice are nebulous. While bleeding that complicates prophylactic anticoagulation is generally mild, significant morbidity or even mortality can result when the central nervous system is involved. The American College of Physicians (ACP) Clinical Guidelines Committee recently reviewed VTE prophylaxis to develop practice guidelines.[1] This committee systematically analyzed both randomized clinical trials and reviews of VTE prevention identified through MEDLINE and Cochrane Library searches published from 1950 to 2011.

Analyses of 10 trials comparing heparin prophylaxis to no VTE prophylaxis in 20,717 medical patients without stroke showed a reduction in pulmonary embolism, RR=0.69 [95% CI, 0.52-0.90] but no decrease either in the incidence of DVT or mortality, but significantly more bleeding in the heparin-treated patients compared with no prophylaxis, RR=1.34 [95% CI, 1.08-1.66]. In eight trials that involved a total of 15,405 patients with acute stroke, meta-analysis showed that compared with no VTE prophylaxis, heparin prophylaxis resulted in no statistically significant reduction in PE, DVT, or mortality, but a statistically significant increase in major bleeding was observed, RR=1.66 [95% CI, 1.20-2.28].

When LMWH prophylaxis was compared with unfractionated heparin (UFH) prophylaxis in nine trials of 11,650 subjects, there was no difference in mortality, pulmonary emboli, or major bleeding events. Among 2,785 acute stroke patients in five trials, compared with UFH, LMWH prophylaxis resulted in no statistically significant difference in mortality, PE, symptomatic DVT, or major bleeding.

Comparing the use of mechanical devices (i.e., compression stockings) in 2,518 subjects in one clinical trial and evidence from three reviews, there was no statistically significant difference in mortality, PE, or symptomatic DVT, as compared with no stockings. There was, however, a greater risk of skin damaged with stockings, RR=4.02 (CI, 2.34-6.91].

In a trial of 6,085 hospitalized medical patients classified as immobile, LMWH prophylaxis was given for 10 days and patients were randomized subsequently to stop prophylaxis or to continue heparin for an additional 28 days. Those randomized to continue LMWH had a significant reduction in symptomatic VTE and a significant increase in major bleeding, but not in mortality, as compared with those randomized to no additional heparin prophylaxis.

The Table compares the ACP VTE prophylaxis recommendations for hospitalized patients with those previously published by the American College of Chest Physicians (ACCP).[1-3] Both place emphasis on individualized assessment of the risk of thrombosis versus the risk of bleeding; however, some differences are noted. For example, in contrast to the ACCP guidelines, the ACP guidelines suggest no reduction in the incidence of DVT for patients on prophylactic anticoagulation. Additionally, while bleeding risk is downplayed in the ACCP guidelines, it is a focal point of the ACP analysis. Stroke patients are grouped separately in the ACP analysis but not in the ACCP recommendations. The ACP focused on studies using compression stockings, while the ACCP recommendations featured a more general category of mechanical prophylaxis. Of note, recommendations related to mechanical prophylaxis are based on relatively sparse data from a small number of trials (Table), underscoring the need for prospective studies designed to establish benefit and risk of anticoagulant-independent DVT prophylaxis.

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Table: Comparison of VTE Prophylaxis Guidelines

American College of Physicians (ACP) (2011)[1]	American College of Chest Physicians (ACCP) (2008)[3]
Thromboprophylaxis 1) Assess bleeding and clotting risk before initiating VTE prophylaxis. 2) Initiate prophylaxis for VTE in medical patients, unless bleeding outweighs risks.*	**Thromboprophylaxis** 1) Thromboprophylaxis (LMWH, low-dose unfractionated heparin, or fondaparinux) is recommended for acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease (Grade 1A).†
Mechanical Propylaxis 1) Avoid mechanical prophylaxis (compression stockings) for VTE prevention.§	**Mechanical Prophylaxis** 1) Optimal use of mechanical prophylaxis is recommended for medical patients with risk factors for VTE and for whom there is a contraindication to anticoagulant thromboprophylaxis. (Grade 1A).¶ 2) Mechanical methods of thromboprophylaxis are recommended primarily in patients at high risk of bleeding (Grade 1A), or possibly as an adjunct to anticoagulant-based thromboprophylaxis (Grade 2A).

** In hospitalized medical patients, heparin prophylaxis decreases PE but not mortality or DVT and increases bleeding risk.*

† Randomized trials conducted over the past 30 years provide evidence that thromboprophylaxis prevents DVT and PE and reduces hospital cost. Data from meta-analysis and blinded, randomized clinical trials demonstrate little or no increase in rates of clinically important bleeding with thromboprophylaxis.

§ Mechanical compression does not improve clinical outcomes but damages lower extremity skin.

¶ Mechanical thromboprophylaxis has not been studied in a large enough sample size to determine reduction in risk of death or PE. Potential advantages include reduction in leg swelling and lack of increase in risk of bleeding. Potential limitations include lack of clinical trials of mechanical devices; lack of established standards for size, pressure, and physiologic features; lack of blinding in most mechanical thromboprophylaxis trials; poor compliance by patients and staff; and unknown effects on PE and death.

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Dr. Ragni indicated no relevant conflicts of interest.

The Value of Specialty Care in Malignant Hematology

Shanafelt RD, Kay NE, Rabe NE, et al. Cancer. 2011. [Epub ahead of print]

Among colleagues who recently returned from the 2011 ASH Annual Meeting in San Diego, a common discussion point has been how much and how rapidly management of each disease entity in hematology changes as both diagnostic and therapeutic options grow in mass and complexity. For those of us who are specialists in a given disease, we marvel at how general hematologists and hematologist/oncologists strive to stay current with this information explosion while integrating the new developments with the "experience/art" component of specialty practice to provide outstanding patient care. And as a corollary, as specialists we have come to suspect that, for those areas of hematology outside of our focus, our ability to provide state-of-the-art care may be suboptimal. Until recently, however, there have been no objective studies addressing this issue. Now, a paper by Shanafelt and colleagues that retrospectively examined management of chronic lymphocytic leukemia (CLL) patients by "CLL specialists" and by other "hematology specialists" at the Mayo Clinic supports our intuitive impressions by showing that survival is greater for patients under the care of a hematology specialist.

The study by Shanafelt and colleagues showed that patients treated by CLL specialists were statistically more likely to undergo prognostic testing at diagnosis and more likely to experience a longer period of observation before beginning therapy (9.2 vs. 6.1 years [$p < 0.001$]). Patients treated by the CLL specialist were more likely both to receive purine analog-based therapy and to enroll in prospective clinical trials. The median overall survival for the group treated by a CLL specialist was 10.5 years compared with 8.8 years for those treated by non-CLL-specialist hematologists ($p=.002$). While there were slight differences in the characteristics of the patients assigned to each group of physicians, these differences are considered insufficient to account for the reported findings. Of note, in neither group was there a difference in outcome when comparisons were made between patients managed by an attending and fellow in training together compared with those managed by the attending alone, suggesting that the current model of training new hematologists does not adversely affect how patients fare.

The retrospective findings of Shanafelt and colleagues may have bearing both on allocation of resources and on the practice of hematology in academic medical centers as, unlike other studies that examined outcome of patients at small treatment centers to the outcome of patients at larger treatment centers, this study involved physicians within a single, well-respected academic institution. Based on both univariate and multivariate analysis, CLL/SLL patients benefit from specialty management. But important issues surrounding these findings need to be addressed. First, the results need to be prospectively validated, ideally in a separate medical center where specialists in CLL are prevalent but where patients with CLL are also managed by non-CLL/SLL-specialist hematologists. Secondly, the impact of similar specialty care on outcome in other diseases such as chronic myeloid leukemia, other lymphoproliferative disorders, and acute leukemia must also be assessed. Such prospective studies might choose to examine how often guidelines (e.g., those from NCCN) are followed to better understand how differences in outcome might emerge. Finally, as the study of Shanafelt et al. did not include comparison of outcomes involving either true general hematologists or hematologist/oncologists with those of the CLL specialist, the results should not be extrapolated to those two groups of physicians.

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Dr. Byrd indicated no relevant conflicts of interest.

The Mystery of the Gray Platelets: Solved

Gunay-Aygun M, Falik-Zaccai TC, Vilboux T, et al. NBEAL2 is mutated in gray platelet syndrome and is required for biogenesis of platelet α-granules. Nat Genet. 2011;43:732-734.

Albers CA, Cvejic A, Favier R, et al. Exome sequencing identifies NBEAL2 as the causative gene for gray platelet syndrome. Nat Genet. 2011;43:735-737.

Kahr WH, Hinckley J, Li L, et al. Mutations in NBEAL2, encoding a BEACH protein, cause gray platelet syndrome. Nat Genet. 2011;43:738-740.

In 1971, Dr. Giovanni Raccuglia published a curious case of an 11-year-old boy with a bleeding tendency out of proportion to his thrombocytopenia.[1] His platelets appeared large, gray, and agranular upon Wright staining. The plot thickened over the next 40 years, as several dozen patients were found to be affected by the syndrome. The tell-tale signs of the disorder were large platelets with a distinct deficiency of α-granules. In contrast to other known platelet granule abnormalities, such as Hermansky-Pudlak syndrome and Chédiak-Higashi syndrome, the dense granules in victims of gray platelet syndrome remained unaffected. These findings led investigators to ask what gene was responsible for this syndrome and how the defect impaired α-granule formation without affecting the formation of dense granules. The mystery spawned a multi-national search for the defective gene. Approximately one year ago, the search intensified as a team of Israeli and American investigators narrowed the location of the causative gene to a small piece of chromosome 3p, a region that contained 165 gene suspects.[2] A second team confirmed this location and narrowed the lineup of suspects.[3] The precise identity of the culprit gene, however, remained unknown. Now, after decades of searching, the gene responsible for gray platelet syndrome (the BEACH domain-encoding gene, *NBEAL2*) has been finally apprehended.

In an unusual twist to a genetic caper, the identity of *NBEAL2* as the causative gene in gray platelet syndrome was identified by three investigative teams using three different experimental strategies and published simultaneously. The U.S.-Israeli group performed genome-wide linkage analysis and homozygosity mapping of 25 individuals with gray platelet syndrome. Sequencing of exons in 15 unrelated affected individuals demonstrated mutations in *NBEAL2*. In a British-French collaboration, whole-exome sequencing of four unrelated patients was performed. Previously observed variants and those not likely to affect platelet function were filtered. All four subjects demonstrated two mutations in *NBEAL2*. A third team, including investigators from the United States and Canada, used next-generation RNA sequence analysis of platelets from an individual with gray platelet syndrome to identify atypical transcripts derived from genes located in a 2.7 MB region previously identified by this group to be linked to gray platelet syndrome. This analysis demonstrated intron retention in transcripts of *NBEAL2* in affected subjects. Sequencing of genomic *NBEAL2* in the affected individual and two other families with gray platelet syndrome confirmed that *NBEAL2* was the affected gene. Together, these studies provide irrefutable evidence of the role of *NBEAL2* in gray platelet syndrome.

Gray platelet syndrome is a rare, autosomal, recessive disorder characterized by the absence of α-granules. The identification of *NBEAL2* as the affected gene in this syndrome will provide a means to definitively diagnose this disorder. Determination of the causative gene of gray platelet syndrome also provides a new direction in the study of α-granule biogenesis. NBEAL2 encodes neurobeachin-like protein 2, a member of a family of proteins containing a BEACH domain. These domains were originally identified in LYST, the protein that is mutated in Chédiak-Higashi syndrome, in which dense granules are deficient. These proteins are known to function in vesicle trafficking and membrane dynamics. Further studies will be required to determine the role of neurobeachin-like protein 2 in packing and sorting platelet α-granules.

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Dr. Flaumenhaft indicated no relevant conflicts of interest.

Responding to a Nuclear Catastrophe: A Report from the Radiation Injury Treatment Network State-of-the-Science Workshop on Radiation, Medical Countermeasures, and Treatment

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Editor's Note: Dr. Chao was president of the American Society of Blood and Marrow Transplantation when he worked with the National Marrow Donor Program to found the Radiation Injury Treatment Network (RITN). Currently, he serves as co-chair of RITN.

It seems that these days the only thing that is certain is uncertainty. The threat of a nuclear catastrophe is real given both the increase in activity of global terrorist organizations and the lax security of nuclear material in some countries that has led to a rise in illicit trafficking of radioactive materials. Additionally, failure of safeguards in one of our nuclear reactors could result in a national tragedy of the same or greater magnitude as that which followed the earthquake and tsunami in Japan in March 2011. The Radiation Injury Treatment Network (RITN) was established in 2006 as a joint effort of the American Society of Blood and Marrow Transplantation and the National Marrow Donor Program with support from the Office of Naval Research. RITN serves to assist with the medical and logistic concerns of the hematology community in response to a mass casualty event involving radiation exposure. If a nuclear disaster occurred today, hematologists would be key figures in the response effort. Such a central role is logical in that the bone marrow is highly sensitive to radiation, and hematologists are experienced in dealing with the complications of bone marrow failure. Additionally, transplant physicians have expertise in managing patients who have received ablative doses of radiation. Accordingly, their experience would be invaluable in determining the need for hematopoietic stem cell support and in caring for patients with multi-organ damage associated with high-dose radiation exposure. Physician members provide the RITN with the expert advice needed both to marshal and to allocate resources properly. In the event of a nuclear emergency, the response effort would be coordinated by RITN, which has a memorandum of understanding with the Office of the Assistant Secretary for Preparedness and Response under the Department of Health and Human Services (HHS). Following activation by HHS, RITN would be responsible for coordinating the care of affected individuals, utilizing the resources of medical centers across the country or abroad if necessary.

This past October, RITN hosted a State-of-the-Science Workshop titled "Radiation, Medical Countermeasures and Treatment." The program included such topics as radiation biology, biodosimetry, supportive care, hematopoietic and immune reconstitution, and specific organ toxicity. With funding support from the National Institutes of Allergy and Infectious Diseases through its Centers for Medical Countermeasures Against Radiation, investigators reported the results of studies aimed at identifying methods for assessing and ameliorating radiation toxicity. Among the highlights of the workshop were reports of the progress made in the area of biodosimetry, especially the development of automated techniques and the use of genetic signatures. Automation now allows for two established manual assays that measure absorbed doses of radiation to be done in a mechanical fashion so that several thousand analyses can be performed in parallel. Further, by taking advantage of state-of-the-art molecular techniques, gene array chip signatures that are useful in quantifying the dose of radiation exposure have been developed. Data from rodents and from non-human primates demonstrate conclusively the utility of providing rapid, supportive-care measures in the form of intravenous fluids, antibiotics, blood products, and hematopoietic growth factors. Two available drugs (human growth hormone and insulin-like growth factor 1) that stimulate hematopoiesis were shown to improve outcomes after irradiation. Novel agents that showed promise in pre-clinical studies or in phase I trials include flagellin, pleotrophin, meloxicam, thrombopoietin receptor agonists, Notch ligand stimulators, and GS-Nitroxide. Moreover, a number of strategies for enhancing immune reconstitution following radiation are under investigation. For example, both animal and limited human data suggest that IL-7, keratinocyte growth factor, and sex steroid inhibition with leuprolide have efficacy in this setting. Others have been investigating cell-based approaches to radiation injury including the use of mesenchymal stromal/stem cells and myeloid progenitors. An issue that generated considerable debate because of the Fukushima experience was the role of banking hematopoietic stem cells of radiation first-responders. In the end, a global consensus statement sponsored by the World Health Organization concluded that evidenced-based medicine supported a strong recommendation for the use of myeloid colony-stimulating factors and a weak recommendation for both erythropoiesis-stimulating agents and hematopoietic stem cell transplantation in the management of patients with radiation injury.

While it appears that we are still far away from a magical drug, or drugs, for the management of exposed individuals, the consensus from the attendees was that we have come a long way in re-invigorating research in this important public health area that had fallen into neglect with the end of the Cold War. Still, much needs to be done and important questions need to be answered. Foremost, we need to develop agents that can unequivocally mitigate radiation toxicity. The list of potentially effective agents is extensive, and while the basic science is interesting, there is a sense of urgency that these agents be tested *in vivo* according to the "two animal rule" and Good Laboratory Practices so as to generate data sufficient for FDA approval for use in humans. Nonetheless, the RITN workshop can be counted a success as it established a foundation for future research, articulated clear questions to be addressed by the field, and set uniform standards for comparing research going forward.

Is Less More? Combination Biologics in Elderly AML

STUDY TITLE: Azacitidine Plus Lenalidomide Combination in Elderly Patients with Previously Treated AML and High-Risk MDS (VIREL2 Trial)

COORDINATOR: Principal Investigator: Bruno Carneiro de Medeiros, Stanford University, Stanford, CA

CLINICALTRIALS.GOV IDENTIFIER: NCT01442714

PARTICIPATING CENTER: Stanford Cancer Institute (Celgene, Inc. is the provider of azacitidine and lenalidomide for this investigator-initiated trial.)

ACCRUAL GOAL: This trial uses a Simon two-stage mini-max design with a total enrollment goal of 53 patients.

STUDY DESIGN: This is a phase II, non-randomized, open-label study. Patients are eligible if they meet the following disease-specific criteria: 1) age > 60 and not an immediate candidate for allogeneic stem cell transplantation; 2) *de novo* or secondary AML or high-risk myelodysplastic syndrome (HR-MDS); 3) prior treatment with hypomethylating agents for AML or HR-MDS, or lenalidomide for del(5q) and non-del(5q) HR-MDS. Prior cytotoxic chemotherapy is not permitted. Patients receive azacitidine 75 mg/m^2 daily SC or IV on days 1-7 followed by lenalidomide 50 mg PO on days 8-28 of a 42-day cycle. If a complete response (CR), CRp, partial response, hematologic improvement, or stable disease is documented after six total cycles, patients continue treatment until evidence of disease progression, provided they are tolerating treatment. Patients with progressive or relapsed disease after the sixth cycle are discontinued from the study, and patients with excessive toxicity at any time are removed from the trial. The primary objective is to determine overall response rate. The secondary objectives are: 1) 42-day survival rate, and 2) duration of remission. Safety and tolerability of the combination will also be assessed.

RATIONALE: AML primarily afflicts older individuals (median age at diagnosis in the mid-60s). In this population, standard induction chemotherapy elicits a complete remission rate of ~40 percent with a higher early death rate compared with younger patients. In addition, median survival is one year or less, and long-term overall survival is observed in only 5 to 10 percent of patients. Because there is no standard of care for such patients, participation in a clinical trial is the treatment recommendation of the National Comprehensive Cancer Network for most patients with AML over the age of 60.

In older AML patients who were considered poor-risk candidates for induction chemotherapy, single-agent azacitidine exhibited a CR rate of 20 percent and a median survival over 15 months in responders (*Sudan et al. Cancer, 2006*). The CR rate for single-agent, high-dose lenalidomide in elderly patients with AML was 30 percent (*Fehniger et al. Blood, 2011*). In 18 high-risk MDS patients who received both azacitidine and lenalidomide, the CR rate was 44 percent (*Sekeres et al. J Clin Oncol, 2010*). Investigators of this current highlighted trial recently published a phase I study of sequential combination of azacitidine plus lenalidomide in 18 previously untreated, elderly AML patients (*Pollyea et al. Leukemia, 2011*). A maximum tolerated dose was not reached. Ten patients responded (56%), and the rate of CRs or CRs with incomplete recovery of blood counts (CRi) among evaluable patients was 44 percent (7/16). The median response duration was 6.2 months. These data provide an impetus for studying the combination of azacitidine plus lenalidomide in patients who have failed prior therapy for MDS or AML with either one of these agents.

COMMENT: Poor outcomes related to high rates of both disease- and treatment-related mortality plague the experience with intensive chemotherapy in elderly patients with AML. This trial of combination biologic therapy with sequential azacitidine and lenalidomide therapy in previously treated patients is one example of several studies (Table) that aim to address basic questions about the role of biologics in elderly AML induction. The aggregate data that develop from these trials should help clarify whether "less is more" for older patients with AML who have traditionally been steered toward either cytotoxic chemotherapy or supportive care.

–Jason Gotlib, MD, MS

Dr. Gotlib indicated no relevant conflicts of interest.

Table: Trials of Azacitidine Plus Lenalidomide Induction Therapy for Elderly AML

Patient Population	Agents	Principal Investigator/Sites	Clinicaltrials.gov Identifier
Newly diagnosed AML age ≥ 60 years, *de novo*, secondary to prior therapy, or transformed from MDS (except M3 AML) Relapsed AML age ≥18 years, (except M3 AML) with CR < 1 year post first induction chemotherapy	Phase I: Azacitidine 25, 50, or 75 mg/m^2 days 1-5 and lenalidomide 50 mg PO daily days 1-28 Phase II: Azacitidine MTD mg/m^2 days 1-5 and lenalidomide MTD mg PO daily days 1-28	Ravi Vij, MD Washington University School of Medicine, St Louis, MO	NCT01016600
Relapsed or refractory AML (>30% blasts, FAB) with monosomy 5 or del(5q) or MDS (including therapy-related MDS) INT-2 or HIGH IPSS with monosomy 5 or del(5q) either previously treated or untreated	Azacitidine 75 mg/m^2 SC days 1-5 every 28 days for a maximum of 8 cycles; lenalidomide 10 - 25 mg PO days 6-19 every 28 days for a maximum of 8 cycles	Uwe Platzbecker, MD Germany sites: Dresden, Düsseldorf, München, Frankfurt	NCT00923234
Patients of any age with refractory or relapsed AML and MDS (bone marrow blasts >/= 10%); or untreated patients older than 60 years of age with AML or MDS (marrow blasts >/= 10%) who refuse or are not eligible for frontline chemotherapy	Azacitidine 75 mg/m^2 IV daily x 5 days on days 1 to 5; lenalidomide 10 mg PO daily x 5 days on days 6 to 10	Guillermo Garcia-Manero, MD M.D. Anderson Cancer Center, Houston, TX	NCT01038635

ASH Annual Meeting 2011

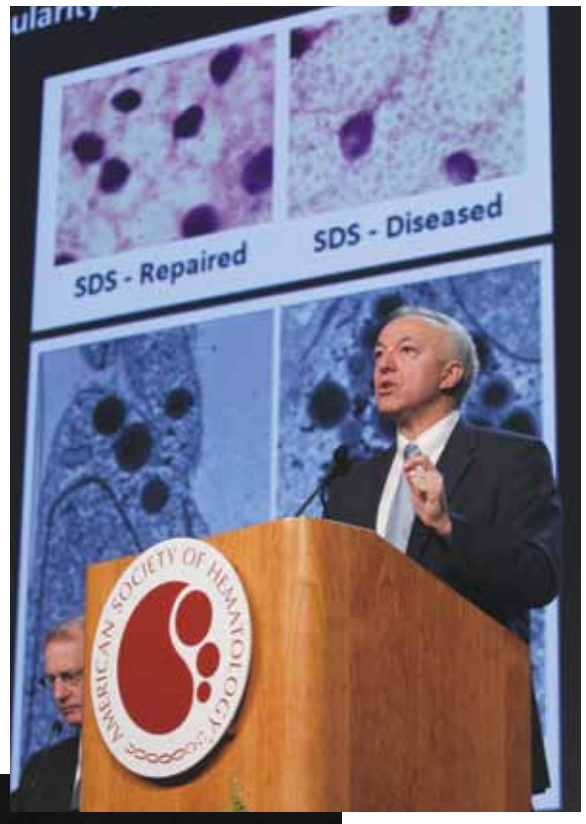
(Cont. from page 1)

The Past

The rich history of our specialty was represented at the meeting. The Ham-Wasserman Lecture is given annually by an investigator from outside of the United States who has made important contributions to hematology. This year's iteration addressed the subject of angiogenesis and was masterfully presented by Dr. Peter Carmeliet, Katholieke University of Leuven, Belgium. Dr. Carmeliet delivered an inspiring overview of 30 years of dedicated investigation that has led to an appreciation of the importance of the biology and pathobiology of angiogenesis. And from his unique perspective, Dr. Carmeliet provided an overview of how an understanding of angiogenesis currently affects patient care and how this knowledge may lead to new therapeutic options for treating neoplastic diseases.

Stem cell biology was the subject of the E. Donnall Thomas Lecture, as the career of Dr. George Q. Daley, Children's Hospital Boston and Howard Hughes Medical Institute, was profiled. His lecture, "Hematopoietic, Embryonic, and Induced Pluripotent Stem Cells: Diseases, Myths, and Medicine," was a stirring recounting of the history of stem cell research. Dr. Daley elegantly reviewed the scientific accomplishments and the political implications that have kept this complex subject in the forefront of biomedical research for more than a decade. Finally, he tantalized us with how his group and others are using "disease in a dish" technology (i.e., the creation of induced pluripotent of stem cells from patients with genetic disorders) to develop novel approaches to the treatment of inherited diseases such as congenital bone marrow failure syndromes.

Chronic myeloid leukemia (CML) was the focus of the Ernest Beutler Lecture and Prize. Named for a former ASH president and prototypical physician-scientist, this award recognizes excellence in an area that bridges basic and clinical sciences. Dr. Janet Rowley, University of Chicago Medical Center, and Dr. Brian Druker, Knight Cancer Institute, Oregon Health & Science University, recounted one of hematology's great stories — from discovery of the Philadelphia chromosome to development of oral therapy for CML. Indeed, Dr. Rowley's work on "personalizing" cancer therapy led to breakthroughs that were developed further by Dr. Druker and others into tyrosine kinase inhibitors that target CML. We dream that this pattern of developing targeted therapy could be repeated in all cancers!



Top: Dr. George Daley talks about stem cell research during the 2011 E. Donnall Thomas Lecture. Above: During the Ernest Beutler Lecture, Dr. Janet Rowley shares her work on personalizing cancer therapy.

The Society's highest honor, the Wallace H. Coulter Award for Lifetime Achievement in Hematology, was bestowed on Dr. David Nathan, Dana-Farber Cancer Institute and Children's Hospital Boston. His seminal work on the use of hydroxyurea for treatment of patients with sickle cell disease and on iron chelation to reduce the morbidity of iatrogenic hemochromatosis in patients with thalassemia has improved the lives of thousands of patients. His career is a model for all of us, not only in the depth of the science, but also in the commitment to patients, colleagues, and mentees.

The Present

The heart of the meeting remains the educational and scientific sessions. Covering all major areas of basic science and clinical hematology, these sessions present the most up-to-date information in our field. Nearly 30 Education Program sessions addressed benign, malignant, adult, and pediatric hematology. Attendees were provided with expert insight into basic mechanisms of disease and their therapeutic implications by nearly 100 lecturers. To ensure that these lectures will be available for future reference, the essence of each presentation (authored by the lecturer) is available in manuscript form in *Hematology 2011*, the Education Program Book.

The Education Program was complemented both by the Scientific Program, with sessions representing each of the 17 scientific subcommittees, and Education Spotlight Sessions that highlight controversial and "hot" areas of hematology.

Looking at the sessions as a whole, it is remarkable how far we have come in the last decade in hematology. Diseases that were previously characterized by an aggressive, rapidly fatal course have been made chronic, our understanding of the mechanisms of disease has deepened, and therapeutic targets have been accurately hit.

The Future

The pace and volume of research continues to expand (in a seemingly exponential fashion). The oral and poster abstracts presented at this meeting demonstrate how rapidly hematology is evolving, and how different the near future will be from the past and present.

Six of the highest rated abstracts, comprising the Plenary Scientific Session, were presented to a large, enthusiastic audience. I have had the privilege of attending the Plenary Session for the last 12 years and have yet to see crowds of similar size. Dr. Claudio Anasetti summarized the results of a trial of marrow versus filgrastim-mobilized peripheral blood as the source of stem cells for patients undergoing unrelated donor transplant. A higher incidence of graft-versus-host disease was noted with the filgrastim-mobilized stem cell source, but no survival difference was observed between the two treatment arms after three years of observation. These findings may encourage greater use of bone-marrow-derived stem cells for patients undergoing unrelated donor transplant.

Dr. Amit Nathwani presented groundbreaking work in treatment of hemophilia. Six patients with hemophilia B who underwent a trial of gene therapy showed a reduction in the grade of their hemophilia from severe to either mild or moderate. This trial represents, at minimum, the first step in downgrading the severity of this life-threatening chronic disease.

Other presentations included a report on the development of an immortalized megakaryocyte cell line that suggested the possibility of creating a source of unlimited platelets of recipient origin; a report on somatic mutation in patients with sideroblastic anemia of a gene (*SF3B1*) involved in RNA splicing, an elegant abstract presentation that dealt with identification of the earliest genetically characterized pre-leukemic cell; and a report that suggested a survival advantage for patients with acute leukemia who received, as part of their induction regimen, gemtuzumab ozogamicin (a drug that was withdrawn from the U.S. market in 2010).

The increasing presence of trainees and trainee events at the annual meeting makes me proud to be a part of this Society. Over the last decade, we have seen the formation of the Trainee Council, Trainee Day, sessions devoted to trainees, and workshops on career development and grant writing. This year's meeting was no exception. Outstanding sessions included "The Secret to Getting Funded," "Drug Development: Bench to Bedside and Beyond," and "How to Publish a Manuscript in a Peer-Reviewed Journal."

Suffice it to say the future looks bright.

This report only scratches the surface of the meeting. There were numerous other sessions, meetings, receptions, and activities, all of which contribute to the success of the ASH annual meeting. This was the most "connected" annual meeting ever with free WiFi throughout the convention center, a new ASH annual meeting mobile application, an electronic *ASH News Daily*, and live Twitter updates. Consequently, the reach of the meeting went far beyond San Diego.

A critical aspect of the meeting that I have to mention is the social one. Not only is the meeting a great opportunity for professional and mentorship networking (that leads to international collaborative efforts), but it is also a lot of fun. Many a good meal was had in the Gaslamp District, and I hope many were able to enjoy the "outdoor" sessions that included a beautiful, refreshing view of the ocean. It was difficult to pass up the opportunity to slip outside between sessions and soak up the weather and culture of San Diego.

I would like to thank all of those who contributed to *ASH News Daily* for their hard work in making the publication such a success. With headlines such as "Platelet Pandemonium," "Chocolate, Vanilla or Both: Making Choices in Myeloma," and "Bone Marrow Harvest Time: Are We Going Back to the OR?," we trust you found the articles both informative and entertaining. You can still access them online at *www.hematology.org/Meetings/Annual-Meeting/*. The authors were Drs. Michael Bishop, Amanda Brandow, David Garcia, Shari Ghanny, Heather Landau, Julie Panepinto, Barbara Pro, and Michael Rosenzweig. Special thanks to the ASH staff; it was such a delight to work with the whole team.

I hope you are already making plans for Atlanta in 2012.

Annual Meeting Materials

To purchase a copy of the 2011 Annual Meeting Education Program DVD, go to the ASH Store (*http://store.hematology.org*). Look for the annual meeting webcast in early February.

Honest, There's a Silent "H" in NIDDK

GRIFFIN RODGERS, MD, MACP

Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

It often seems like only yesterday that I was growing up in New Orleans, where I witnessed the interaction of genetics and the environment around the city's diverse neighborhoods. I saw a range of people suffering from obesity, diabetes, and other ailments resulting from a poor diet and lack of exercise.

These experiences pointed me toward science as a career, but something else stoked my passion for hematology: I saw three of my close friends suffer unbearable, unimaginable pain from sickle cell disease. And I was helpless to do anything about it. Then, two of them died while I was still in high school. The third died several years later. When you're a teenager, you're not supposed to bury your friends. But that's what sickle cell does. That's the toll it takes. And that's how I was drawn into hematology.

During medical school at Brown University and beyond, I pursued my passion for hematology research. Eventually, I was fortunate to be part of the team that contributed to the development of the first and only FDA-approved therapy for sickle cell disease, hydroxyurea. More recently, colleagues in my lab reported on a modified blood stem cell transplant regimen that has reversed sickle cell disease in adults and is associated with relatively low toxicity. Mere words cannot describe how good it feels to see people live longer and better lives.

And now, as director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I'm privileged to work with an extraordinarily talented team of scientific and administrative managers who work tirelessly to support our own scientists and grantees and who are searching for cures and better methods for preventing and managing illnesses that rank among America's greatest public health challenges.

I'm often asked how NIDDK, with its broad scope of seemingly unrelated interests, happened to get into the hematology business. It dates back to 1950, when NIH Institutes were fewer and further between. What is now NIDDK was established as the National Institute of Arthritis and Metabolic Diseases (NIAMD) by the Omnibus Medical Research Act. The newly created NIAMD incorporated and expanded the laboratories of the pre-existing Experimental Biology and Medicine Institute, which had been handling nearly all internal medicine research outside of cardiology — a *de facto* "Institute of Internal Medicine," although not in name. The NIAMD's mission included clinical investigation in rheumatic diseases, diabetes, anemias, and various metabolic and gastrointestinal diseases. This was logical at the time, as hematology was considered an integral component of internal medicine rather than its own specialty as we know it today.

Also in the early 1950s, NIAMD started to award hematology research grants, focused on the following general areas within the field: erythrocyte production, turnover, aging, and metabolism; erythropoietic regulation and erythropoietin; hemolytic anemias; hemoglobin; B12 and folate; iron metabolism; hematopoiesis and bone marrow grafts; transplant immunology; immunohematology; and leukocyte cell biology.

As part of one of those very first NIDDK research grants — number 0002 to be exact — NIH-supported researchers, led by legendary hematologist the late Dr. Max Wintrobe, helped to pioneer many ground-breaking discoveries that resulted in a clearer understanding of red cell metabolism and how hereditary disorders can lead to several debilitating diseases.

In the 1960s, the discovery and characterization of the human leukocyte antigen (HLA) system shed important light on the immune response and molecular differentiation between "self" and "non-self" cells and tissues.

In the 1980s, our scientists helped to develop techniques for cloning of genes for human hematopoietic cytokines, for expression of these cytokines as recombinant proteins, and for successful introduction of these biological therapies — EPO and G-CSF — into clinical

> ***Mere words cannot describe how good it feels to see people live longer and better lives.***

practice. The clinical availability of EPO, now in various forms, has had a major impact on the management of anemia associated with renal failure. G-CSF is now widely used to hasten the recovery of circulating neutrophils following myelosuppressive chemotherapy, and equally important, to release hematopoietic stem and progenitor cells from the bone marrow into the circulation where they can be harvested by apheresis for use in autologous and allogeneic transplantation. These so-called "G-CSF mobilized" hematopoietic stem cells (HSC) support much more rapid hematopoietic recovery in transplant recipients than that achieved by HSC harvested directly from the marrow, greatly reducing the early toxicity and risks of these transplants.

As the 1990s approached and throughout that decade, we contributed to detailing immunophenotyping of human blood cell subtypes with murine monoclonal antibodies specific for cell surface molecules. This procedure has allowed for major advances in understanding cellular immune responses, in diagnosing and classifying leukemias and lymphomas, and in isolating, through immunophenotypic recognition, transplantable HSCs. Further, this research has led to the production of various recombinant "humanized" murine monoclonal antibody preparations that are now widely used clinically both to prevent platelet aggregation and restenosis following cardiac bypass surgery or arterial stenting and to treat B-cell malignancies.

Scientists have made many other remarkable discoveries revealing genetic associations with diseases. Pertaining to hematology, understanding these genes is important in at least the following three areas of research:

- The basic mechanisms involved in hematopoiesis and in regulating the expression of genes relevant to normal blood cell maturation and function
- The metabolism, storage, and transport of iron and disorders resulting from disturbances in these processes, including hemochromatosis and iron-restricted anemias
- The basis of acquired and congenital disorders of erythropoiesis, including anemias, thalassemias, and sickle cell disease resulting from disturbances in the production or function of hemoglobin

As NIDDK reflects on the past 60 years of supporting and conducting research, it is clear that the scientific progress achieved during that time period has been remarkable. Looking to the future, NIDDK will continue to build on the landmark scientific discoveries of the past to foster new research breakthroughs. Paramount to this effort is the continued vigorous support of basic, pre-clinical, and clinical research, as well as the development of educational materials to disseminate important new research findings to patients, their families, and health-care providers. To inform research directions in hematology, NIDDK will continue to solicit input from the broad scientific community through forums such as scientific workshops and conferences. In addition, strategic planning, with broad external input, will continue to guide future research directions. To view a poster that illustrates the long, productive research experience that NIDDK's hematology grantees have had, visit *www2.niddk.nih.gov/Funding/OnTheRoad/OnTheRoad_2011_ASHematology.htm*.

Moving forward, NIDDK is hopeful that its research portfolio will continue to provide scientific insights and improvements in patient care. As always, an important component of the Institute's support for biomedical research is its strategic planning. Often, initiatives and funding solicitations emerge from opportunities identified through this planning process, which reflect both broad scientific review and input from key stakeholders. Planning may occur in an *ad hoc* process or may be organized under the auspices of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, and sometimes involves partnering with professional and/or patient advocacy groups. Through these efforts, NIDDK seeks to steer the research enterprise in a way that follows science while maximizing the return on the Institute's investment in order to improve the lives of patients and their families.

WHAT'S ON THE WEB

The ASH website offers a convenient way for members to find information about upcoming Society events and provides easy access to many valuable products and services.

PQRI*wizard*SM

A new ASH-sponsored Web-based tool to help hematologists obtain PQRS incentive payments

ASH has launched a new Web-based tool to help hematologists obtain the 1 percent incentive payment for reporting quality measures on Medicare patients during calendar year 2011. The ASH-branded registry, PQRI*wizard*SM, will assist hematologists in satisfactorily reporting data on quality measures under the Centers for Medicare & Medicaid Services (CMS) Physician Quality Reporting System (PQRS). The PQRI*wizard*SM is similar to online tax preparation software and will make reporting easier.

The PQRI*wizard*SM features 25 quality measures in the areas of hematology, oncology, and general medicine, including ASH's four hematology measures on myelodysplastic syndrome, acute leukemias, multiple myeloma, and chronic lymphocytic leukemia. Satisfactorily reporting 2011 data on quality measures for covered services furnished to Medicare beneficiaries before February 17, 2012, ensures eligibility for the 1 percent incentive payment. The cost of PQRI*wizard*SM is $299 per provider.

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

Mark Your Calendar

January

20-21 **Highlights of ASH**
Austin, TX — *www.hematology.org*

Highlights of ASH
Orlando, FL — *www.hematology.org*

27-28 **Highlights of ASH**
Atlanta, GA — *www.hematology.org*

Highlights of ASH
Las Vegas, NV — *www.hematology.org*

February

3-4 **Highlights of ASH**
New York, NY — *www.hematology.org*

Highlights of ASH
San Francisco, CA — *www.hematology.org*

March

3-4 **Highlights of ASH in Asia**
Singapore — *www.hematology.org*

25-28 **New Directions in Leukaemia Research Conference**
Queensland, Australia — *www.ndlrconference.com*

April

13 **Deadline to obtain CME credit for the 53rd ASH Annual Meeting**
Washington, DC — *www.hematology.org*

25-28 **2012 World Congress of Hematology**
Cancun, Mexico — *www.hematology2012.com*