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Enhancing Research in Regenerative Medicine

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Over the past decade regenerative medicine has become a highly active area of investigation with the potential to address many unmet medical needs. Hematologists have played a prominent role in advancing this emerging field because of prior expertise in stem cell and transplantation biology as well as extensive experience in related areas of translational research. Despite the impetus for growth this field has experienced, investigators continue to face numerous challenges in conducting translational and clinical research in regenerative medicine and cell-based therapy.

In response to these concerns, and at the urging of the ASH Committee on Government Affairs, we were asked by the ASH Executive Committee to co-chair an expert working group in October 2009 and develop recommendations to the Society and to the National Institutes of Health (NIH) on enhancing research in regenerative medicine. The conclusions, recommendations, and composition of the working group are outlined in an editorial in *Blood* [116: 866-7, 2010].

Workshop participants identified a number of challenges that can be broadly classified into two areas: funding and implementation. Funding research in this area is a challenge for a number of reasons. For example, pre-clinical research is difficult to fund within the usual NIH study section format because the proposals seek to validate initial findings, establish safety, and determine efficacy rather than address a hypothesis-driven aim; hence, these proposals are often noncompetitive in study section reviews. Nonetheless, the work is essential to validate clinical protocols in support of Investigational New Drug (IND)

(Cont. on page 7)

DIFFUSION

Turning Over the Rotting Log in Del(5q) Myelodysplasia

Tehranchi R, Woll PS, Anderson K, et al. Persistent malignant stem cells in del(5q) myelodysplasia in remission. N Engl J Med. 2010;363:1025-1037.

The immunomodulatory drug lenalidomide can induce striking hematologic and cytogenetic responses in patients with myelodysplastic syndromes (MDS), especially among patients whose clonal cells bear a somatic deletion of the long arm of chromosome 5q (del(5q)). Unfortunately, most patients whose cytopenias and burden of clonal cells improve during lenalidomide therapy will relapse within three years – including the approximately 45 percent of patients with lower-risk del(5q) MDS who achieve a complete cytogenetic remission.

In order to better understand the cellular basis for such relapses, a multinational team led by Sten Eirik Jacobsen serially examined flow cytometrically sorted CD34+, CD38+ hematopoietic progenitors and CD34+, CD38 undetectable or low (CD38-/low), and CD90+ multipotent stem cells (a subpopulation previously shown to be Thy1+) from seven patients with del(5q) MDS who developed red blood cell transfusion independence and also experienced a partial or complete cytogenetic response during lenalidomide therapy. Study subjects included two patients in whom del(5q) became undetectable by both conventional G-banded metaphase cytogenetics and fluorescent *in situ* hybridization (FISH) of whole bone marrow.

The investigators found that despite clearance of most or all of the del(5q)-bearing CD38+ progenitor cells during lenalidomide treatment, a small fraction of del(5q) CD38-/low stem cells remained, lurking undetected by conventional assays just as saprophytic insects can hide in the diseased core of outwardly healthy-appearing timber. These persistent drug-resistant cells served as a nidus for subsequent clonal expansion and karyotypic evolution at the time of clinically apparent disease progression.

It is well recognized that small numbers of therapy-resistant neoplastic cells, regardless of whether they exhibit a stem cell-like phenotype, can presage relapse. Clinicians are accustomed to searching for evidence of these cells – e.g., monitoring for minimal residual disease by flow cytometry in acute lymphoblastic leukemia, or repeatedly testing for persistent *BCR-ABL* positivity by polymerase chain reaction in chronic myeloid leukemia. The findings of Tehranchi et al. using serial samples from MDS patients extend these observations to a different disease state and complement a large body of clever work on human cancer stem cells using murine models or *in vitro* assays.

Precisely how that small population of stubborn stem cells managed to evade destruction during lenalidomide treatment remains unclear, in part because the critical mechanisms of action of lenalidomide, in MDS generally and in del(5q) MDS in particular, are still undefined. Several attractive hypotheses for the origin of lenalidomide's beneficial effects have been put forward, including inhibition of haplodeficient phosphatases encoded on chromosome 5q, T cell or NK cell activation, alteration of immune cell subsets (e.g., Th1 cells), anti-angiogenesis activity, and changes in the cytokine profile. Del(5q) stem cells might escape the lenalidomide poisoning to which other clonal cells are susceptible, either directly (by effluxing the drug or by activating compensatory signaling pathways) or indirectly (by evading an immune response or by "taking cover" in a protective microenvironmental niche). Greater understanding of these details will aid clinicians in designing trials specifically targeting lenalidomide-resistant cells.

This study confirms the existence of rare and phenotypically distinct lenalidomide-resistant stem cells in del(5q) MDS and suggests that a small, quiescent fraction of cells may be driving relapse in patients who appear to be responding well to therapy. Monitoring for the presence of these dangerous cells during lenalidomide treatment is straightforward, but determining how to eliminate them will be more challenging.

DAVID P. STEENSMA, MD

Dr. Steensma indicated no relevant conflicts of interest.

FEATURES

DEPARTMENTS

President's Column

Restoring Clinical and Translational Research

Recent advances in basic and translational research have set the stage for tremendous progress in clinical hematology research, but trials to pursue these opportunities run afoul of many obstacles. For example, David Dilts, Director of Clinical Research of the Knight Cancer Institute, reported last year that opening a phase III cooperative oncology group trial requires an average of 2.5 years to accommodate 118 decision points, complete more than 769 process steps, and receive approval by up to 36 separate groups or individuals. Whether many of these steps improve trial quality or patient safety is doubtful. Many approved trials never enroll a single patient and barely half are ever completed, which is a terrible waste of human and financial capital. Small wonder that Garret FitzGerald, MD, Director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania, has described our current system as "spreading dysfunction that undermines progress for the sake of managing risk." Not surprisingly, the cost of conducting trials has grown much faster than federal funding, and clinical research is fleeing for more hospitable shores. According to Kenneth A. Getz, a Senior Research Fellow at the Tufts Center for the Study of Drug Development, the number of active FDA-regulated investigators outside of the United States grew 15 percent annually between 2002 and 2007, whereas the number in the United States declined 5.5 percent annually over the same period.

The National Institutes of Health (NIH) clearly recognizes the scope of these problems, and two recent announcements describe major initiatives to reinvigorate clinical trials.

On December 23, the National Cancer Institute (NCI) publicized plans to restructure the nine groups that currently conduct adult cancer trials to make them more efficient. The proposed changes are based upon an NCI-requested April 2010 report from the Institute of Medicine, which recommended total reorganization to reduce redundancy and shift the primary focus of the NCI from oversight to facilitation of clinical trials. The protocol approval process would be streamlined through parallel, concurrent, or joint reviews. Additional measures would standardize data collection and analysis and enhance the sharing of banked specimens. These changes are expected to reduce by half the time needed to initiate new studies. In addition, trials that do not begin within two years of concept approval would be terminated, providing a strong incentive to accelerate enrollment and completion.

Of course the problems besetting clinical trials are not unique to cancer, and the NIH is poised to launch a more comprehensive countermeasure. On December 7, the Scientific Management Review Board (SMRB), which advises the NIH, voted to recommend establishing a new center to focus on translational medicine, provisionally named the National Center for Advancing Translational Sciences (NCATS). NIH Director Francis Collins has outlined plans to integrate several existing translational research programs and their educational infrastructure into this new center. For example, it would absorb the Clinical and Translational Science Awards (CTSAs), which now provide an academic home to train and mentor clinical researchers and manage clinical trials at 55 medical research institutions across the country. The proposed NCATS would have a budget of at least $650 million and could be operational as soon as October 2011.

These developments attempt to address a burning need, but the broader consequences for biomedical research, intended or otherwise, are not yet known. For example, concerns have been raised that the new translational research center could divert funds from basic research. However, Francis Collins has signaled that he will not allow such an outcome. As Garret FitzGerald puts it, this is not necessarily "a zero-sum game: the success of translation requires investment in basic science."[1] Conversely, we cannot shortchange basic research without also crippling clinical research.

These NIH proposals have started a lively discussion about the best way forward, and alternatives surely will be proposed. However these initiatives evolve, reforming the conduct of patient-oriented research should help reestablish the implicit bargain between investigators and their patients, who enroll in trials with the understanding that participation will lead to better medical care, if not for them then at least for future patients. This shared goal is frustrated when clinical trials are conceived but never approved, approved but never accrue, or accrue but never see publication. If changes underway do succeed in restoring the vitality of clinical research, they will translate directly into better, longer lives for more people.

J. Evan Sadler, MD, PhD

1. FitzGerald G. Drug development needs a new brand of science. Nature. 2010;468:869.

Dear Editor:

In "Ask the Hematologist" (Nov/Dec 2010), Dr. DiMichele incisively responds to Dr. Zora Rogers' questions about a 14-year-old with both menorrhagia and a family history of thrombophilia. With Dr. DiMichele's recommendations, young women should be spared the three years it took this patient to be optimally assessed. Dr. DiMichele outlined the appropriate evaluation that should be performed at presentation. She also gave sound counsel concerning the young woman's request for combined hormonal oral contraceptive pills, an effective treatment for menorrhagia, but complicated in this patient by the family history of thrombophilia. The wise advice here was avoidance of risk factors. The comprehensive nature of Dr. DiMichele's reply is evidenced in her noting the importance of the psychosocial, or quality-of-life, consequences for adolescents who must face these issues.

The Foundation for Women & Girls with Blood Disorders (FWGBD) is a new national, nonprofit organization focused on educating health-care providers about the range of blood disorders that impact women and girls. FWGBD is partnering with key organizations, like ASH, to be sure that state-of-the-art information, such as contained in Dr. DiMichele's "Response," reaches all physicians treating women and girls at every life stage. For more information, contact: *info@fwgbd.org*.

Sincerely,

Andra H. James, MD, MPH
Director, Women's Hemostasis and Thrombosis Clinic
Duke University

LETTERS TO THE EDITOR SOLICITATION

The Hematologist welcomes letters of up to 200 words. Please include a postal address, e-mail address, and phone number. Publication will be based on editorial decisions regarding interest to readers and space availability. We may edit letters for reasons of space or clarity. *The Hematologist* reserves the right to publish your letter, unless it is labeled "not for publication."

Letters should be sent to:
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ASH Advocacy & Policy Statement on Clinical Research and Trials

The Society has undertaken numerous advocacy efforts to remove barriers to physician and patient participation in clinical trials. Specifically:

- An ASH-supported provision was included in the health reform law to require health insurance plans to provide coverage for routine costs associated with participation in clinical trials.
- ASH works with Congress to encourage NIH, FDA, CMS, and other federal agencies to collaborate to better harmonize existing policies and regulations on clinical trial operations in order to increase the initiation of new trials and patient access to new treatments.

The ASH policy statement on clinical research and trials (available at *www.hematology.org/Advocacy/Policy-Statements/5835.aspx.*) proposes recommendations to overcome critical barriers to conducting clinical research, including:

- Lack of harmonization of existing policies and regulations on clinical trial operations
- Insufficient insurance coverage for routine patient care
- Complex consent forms and language
- Inadequate support for benign hematology and rare diseases.

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2011 Highlights of ASH® is Coming to China and Uruguay

This April, ASH is bringing clinical content from the Society's 52nd annual meeting to hematologists and hematologist-oncologists in China and Latin America. Partnering with societies based in these host regions, ASH will provide unbiased analysis of abstracts presented at the annual meeting, while offering educational content tailored specifically to local audiences.

For the first time ever, ASH, in collaboration with the Chinese Society of Hematology and the Chinese Medical Association, will offer an official Highlights of ASH meeting in China. This meeting will take place April 2-3, 2011, in Beijing. Following that meeting, the Society will host its third Highlights of ASH in Latin America, partnering this year with the Sociedad de Hemotología del Uruguay. This meeting will be held in Punta del Este, Uruguay, April 29-30. Both meetings will offer simultaneous translation. To learn more about these meetings, visit *www.hematology.org/highlights*.

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

The Hematologist – New Contributing Editors

Three new Contributing Editors have joined *The Hematologist* Editorial Board in 2011. Each is slated to serve through 2013. The new Contributing Editors are:

Xavier Leleu, MD, PhD

Associate Professor, Service des Maladies du Sang, Hôpital Huriez, CHRU
Lille, France

Dr. Leleu's areas of expertise include multiple myeloma and Waldenstrom macroglobulinemia.

Margaret Ragni, MD, MPH

Professor of Medicine, Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, and Director, Hemophilia Center of Western Pennsylvania
Pittsburgh, PA

Dr. Ragni's areas of expertise include hemostasis, thrombosis, hemophilia, von Willebrand disease, and congenital bleeding disorders.

David P. Steensma, MD

Associate Professor of Medicine, Harvard Medical School; Clinical Faculty, Adult Leukemia Group, Dana-Farber Cancer Institute; Attending Physician, Brigham & Women's Hospital
Boston, MA

Dr. Steensma's areas of expertise include myelodysplastic syndromes, AML, sideroblastic anemias, hematopoietic growth factors, and myeloproliferative neoplasms.

Correction

The table on Page 5 of the Jan/Feb 2011 issue should read "Contact Cascade," not "Constant Cascade."

Ask the Hematologist

JOHN SWEETENHAM, MD, FRCP

Professor of Medicine, Vice-Chair for Clinical Research, Taussig Cancer Institute, Cleveland Clinic

(Editor's Note: The original question was submitted to Dr. Sweetenham through Consult a Colleague. He expanded his answer for print.)

The Question

A previously healthy 72-year-old male presented with a new diagnosis of clinical stage IVB diffuse large B-cell lymphoma (DLBCL), with maxillary sinus involvement and involvement of multiple bony sites. His ECOG performance status was 0 and his International Prognostic Index (IPI) score was 3 based on his age, clinical stage, and involvement of multiple extranodal sites, all of which are adverse factors in the IPI. A biopsy from the maxillary sinus confirmed DLBCL by morphology and was positive for cyclin D1. Since cyclin D1 expression in DLBCL is reported to have a poor prognosis, should this patient be treated with CHOP-rituximab or should he receive a more intensive regimen such as dose-adjusted EPOCH-rituximab?

My Response

This clinical case raises several important questions regarding the management of advanced DLBCL, partly related to diagnostic criteria and to the optimal treatment regimen, but also regarding the broader issue of whether different immunophenotypic or molecular subtypes of DLBCL should be treated differently.

Cyclin D1 is a nuclear protein with a well-defined role as a regulator of cell cycle progression from G1. Its deregulation is central to the pathogenesis of some B-cell neoplasms, especially mantle cell lymphoma (MCL), where it is over-expressed in about 90 percent of cases, as well as in myeloma and hairy cell leukemia. In the vast majority of MCLs, cyclin D1 over-expression is associated with the t(11;14), whereas this association is much less common in other B-cell neoplasms.[1]

Reports of the expression of cyclin D1 in DLBCL have been conflicting, partly because different methodologies are used for detection of cyclin D1 and partly because the morphologic distinction between DLBCL and the blastoid variant of MCL can be problematic, particularly since other immunophenotypic characteristics of DLBCL and MCL can sometimes overlap. Despite these challenges, there are several case reports and some larger series that describe the presence of cyclin D1 in cases of DLBCL that are negative for CD5 but have other classical markers of DLBCL, such as bcl-6 and MUM-1.[2]

As indicated by the questioner, there is a suggestion from the limited literature that patients with cyclin D1-positive DLBCL have a worse prognosis. In the largest published series, nine of 10 patients had died from progressive disease after a median of 29 months from diagnosis.[2] However, these data are anecdotal, and if this represents a true clinicopathologic entity, there are insufficient data to indicate whether it has a meaningfully different prognosis from other cases of DLBCL.

In contrast, other immunophenotypic and molecular features of DLBCL have been shown to have defined predictive and prognostic value. Examples include the adverse prognostic effect of bcl-2 expression and lack of bcl-6 expression, both of which can apparently be overcome by the addition of rituximab to standard chemotherapy regimens such as CHOP (cyclophosphamide, doxorucibin, vincristine, and prednisone). Gene expression profiling studies have identified two major molecular subtypes of DLBCL; one has a gene expression profile (GEP) consistent with germinal center B-cells (GCB-like), and one has a profile consistent with activated peripheral B-cells (ABC-like). Molecular subtyping by GEP has also been shown to have prognostic value, as patients with ABC-like GEPs have poorer progression-free and overall survival rates independent of the IPI. This difference in prognosis is seen for patients treated both with CHOP and with CHOP-rituximab.[3]

The clinical utility of these findings has been limited by the lack of routine availability of suitable tissue and resources for conducting GEP studies. As a result, several groups have explored the use of immunohistochemical (IHC) surrogates to assign GCB and ABC subtypes.[4] Since the correlation between cell of origin identified by GEP and IHC is high, these algorithms are gaining widespread use as a method of risk stratification in clinical trials.

Although the prognostic significance of cell of origin (GCB versus ABC) in DLBCL is well established, the question of whether this or any other biologic predictor of outcome should be used to direct therapy for DLBCL is unknown. The dose-adjusted EPOCH-R regimen mentioned by the questioner uses infusional drug scheduling and pharmacodynamic dosing based on hematologic toxicity to exploit tumor proliferation as a target mechanism. Phase II studies of this regimen have shown impressive results and, interestingly, no difference in progression-free or overall survival according to GCB or non-GCB cell of origin.[5] As a result, this regimen is now being compared directly with CHOP-rituximab in a randomized, prospective intergroup study led by the CALGB, which includes an analysis of cell of origin by GEP. The results of this study will not be available for several years, so for now, CHOP-rituximab remains the standard regimen for first line therapy of DLBCL, irrespective of cell of origin or expression of other biomarkers.

Early results from some recent studies suggest that this is likely to change. Two recent studies have suggested that the addition of bortezomib to standard chemotherapy-rituximab combinations for DLBCL produces improvements in response rates and progression-free survival rates, which may be restricted to patients with the ABC subtype.[6,7] Additionally, data are emerging to suggest that some recently identified therapeutic targets such as Bruton's tyrosine kinase (Btk) are differentially expressed in ABC- versus GCB-like DLBCL, providing a rationale for limiting trials of these agents to those patients with specific molecular subtypes.

Future progress in the treatment of DLBCL is likely to emerge from further characterization of specific molecular targets. In the meantime, CHOP-rituximab should be regarded as standard, first-line therapy for all patients with DLBCL outside clinical trials.

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Dr. Sweetenham receives research funding from Novartis, Millennium, Seattle Genetics, Aegera, and Celgene.

Dabigatran: An Important New Option for Chronic Anticoagulation

LAWRENCE LEUNG, MD

Maureen Lyles D'Ambrogio Professor of Medicine, Stanford University School of Medicine and VA Palo Alto Health Care System

It is well known to hematologists that managing patients who require chronic anticoagulation is a cumbersome task, and until very recently, warfarin, a vitamin K antagonist, has been the only available oral anticoagulant. Warfarin treatment requires regular monitoring with prothrombin time testing, and, since it has multiple interactions with food and drugs, frequent dose adjustments are necessary. Despite regular monitoring by either patient self-management or hospital-based anticoagulation clinics, patients fall outside the desired therapeutic range about one-third of the time. So the recent FDA approval of the orally active direct thrombin inhibitor (DTI) dabigatran etexilate has been welcome news.

DTIs are a new class of anticoagulants that function by direct interaction with the active site of thrombin and do not require the natural physiological inhibitor antithrombin, so they are mechanistically distinct from heparin, low-molecular-weight heparin, and fondaparinux (Figure). Three parenterally administered DTIs (lepirudin, bivalirudin, and argatroban) are currently used in the acute treatment of heparin-induced thrombocytopenia (HIT).

Dabigatran etexilate is the second oral DTI. The first, ximelagatran, was found to be effective as an antithrombotic in a variety of clinical situations. However, the drug was not approved by the FDA for concerns of associated hepatotoxicity and its distribution was discontinued in Europe.

Dabigatran etexilate is a prodrug that is rapidly converted to its active metabolite, dabigatran, by a ubiquitous, non-specific plasma esterase, and reaches its peak plasma anticoagulant effect ~0.5-2 hours after oral administration.[1] Drug clearance is completed primarily by the kidney, with a plasma half-life of ~12-17 hours. Metabolism of dabigatran does not involve the hepatic cytochrome P450 system, so it has minimal drug-drug and drug-food interactions and does not require regular monitoring, thus fulfilling the criteria for an oral anticoagulant to replace warfarin — rapid onset of action, ease of use, and no need for regular monitoring.

Dabigatran has been tested extensively for venous thromboembolism (VTE) prophylaxis in high-risk patients undergoing orthopedic surgery and has demonstrated either superiority or noninferiority to enoxaparin with no significant hepatotoxicity. Dabigatran is approved in Europe for VTE prophylaxis at an oral dose of 220 mg once daily, with the first dose given as a half-dose between one and four hours after surgery for a total of 10 days after total knee replacement and for 28-35 days after total hip replacement. For patients older than 75 years and those with creatinine clearance of 30-50 ml/minute, the total daily dose is reduced to 150 mg once daily. Dabigatran is contraindicated in patients with creatinine clearance less than 30 ml/minute.

The RE-LY trial addressed the efficacy of dabigatran versus warfarin to prevent stroke or systemic embolism in moderate- to high-risk patients with atrial fibrillation.[2] Dabigatran dosed at 110 mg twice daily is equivalent to warfarin in efficacy but is associated with lower rates of major hemorrhage (2.7 % vs. 3.4 % per year), while dosing at 150 mg twice daily has a reduced stroke and systemic embolism rate (1.1 percent vs. 1.7 percent), with similar major hemorrhage rates. The FDA has approved dabigatran for this indication.

The RE-COVER trial showed that dabigatran (at 150 mg twice-daily dose) and warfarin (with INR targeted to 2-3) were equivalent for the treatment of acute VTE after an initial 5-10 day treatment with an injectable anticoagulant.[3] A phase III trial testing the long-term efficacy of dabigatran in patients with recurrent VTE is ongoing, and, given the prior positive clinical trial results with ximelagatran, dabigatran is expected to be effective in the long-term treatment of VTE.

Patient convenience, safety, and clinical efficacy of dabigatran have now been demonstrated, but the treatment cost will likely be substantially higher than for warfarin. Based on the pricing in the United Kingdom and the data from the RE-LY trial, dabigatran has been estimated to be cost-effective compared to warfarin in the prevention of stroke in high-risk patients with atrial fibrillation.[4] A similar conclusion has been reached in the use of dabigatran in VTE prophylaxis as compared to enoxaparin.[5] Whether this applies to patients who require chronic anticoagulation for prevention of recurrent VTE remains to be seen.

Dabigatran, similar to the parenteral DTIs, does not have an effective antidote, and management of serious bleeding complications or acute reversal of anticoagulation for urgent surgery can be problematic. This remains a potential limitation for this new class of anticoagulants.

In addition to oral DTIs, oral factor Xa inhibitors have demonstrated clinical efficacy in prophylaxis against VTE in orthopedic surgery.[6] Rivaroxaban has been approved in Canada and Europe for this indication. The anticipated approval of the oral factor Xa inhibitors should further broaden the armamentarium for anti-thrombotic therapy, and further competition may lead to more cost-effective treatment options for patients with VTE.

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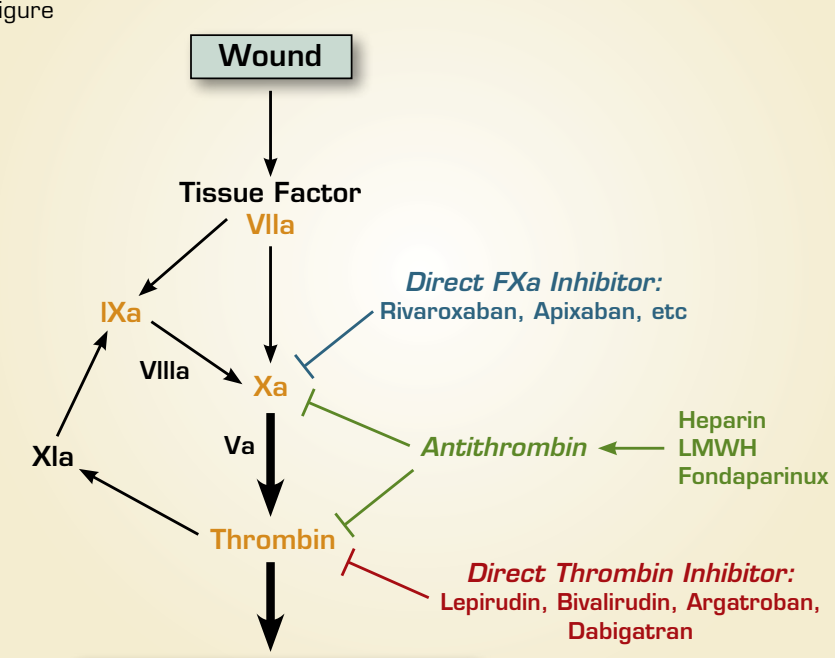
Figure



At the site of a vascular wound, tissue factor is exposed, which acts as a physiological cofactor for Factor VIIa, and the tissue factor/FVIIa complex activates the clotting cascade. Tissue factor/FVIIa activates factor X either directly or indirectly through the activation of factor IX, and the resultant factor Xa activates prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and also activates platelets, resulting in the formation of a fibrin-platelet thrombus. Thrombin can also activate factor XI, and factor XIa in turn activates FIX, thus serving as a tertiary pathway of thrombin generation. Warfarin is a vitamin K antagonist and targets prothrombin, factor VII, factor IX, and factor X (Red), with factor X and prothrombin being the main targets. Heparin, low-molecular-weight heparin (LMWH), and the synthetic pentasaccharide fondaparinux serve as anticoagulants by activating antithrombin, a plasma serine protease inhibitor that functions as the major physiological regulator of the clotting cascade; antithrombin then inhibits factor Xa and thrombin. Both the direct thrombin inhibitors and the direct factor Xa inhibitors inhibit their respective targets directly without the need of antithrombin.

Dr. Leung indicated no relevant conflicts of interest.

HEADLINES FROM Washington

House Leadership Plans to Cut Federal Spending; Advocacy Needed to Protect NIH Funding

House Republican leaders are planning to cut future federal spending down to fiscal 2008 levels for discretionary spending outside of military programs and are headed for a showdown with Senate Democrats over the fiscal year (FY) 2011 and 2012 funding laws.

As this issue of *The Hematologist* went to press, President Obama was preparing to release his proposed FY 2012 budget, which represents the opening bid in a lengthy federal budget process. Although precise details of the FY 2012 were not yet known, the Obama Administration had previously announced plans to freeze all federal non-security discretionary spending, a promise that, if kept, would make it extremely difficult for Congress to provide any increase in funding for NIH.

Further complicating the process is the fact that the FY 2012 budget and appropriations process has gotten underway even as the FY 2011 process is still being finalized. Because Congress was unable to come to an agreement on FY 2011 funding bills before it adjourned last December, the federal government has been operating under a temporary funding measure, known as a Continuing Resolution (CR). The CR is set to expire March 4, requiring Congress to resolve differences about FY 2011 or shut down the government.

With the current budgetary climate, grassroots advocacy will become more important than ever. The Society strongly encourages all ASH members to visit the online Advocacy Center (*www.grassroots.hematology.org*) for the latest information on NIH funding and information on how to easily contact their Members of Congress to support NIH.

The Urgency of Health Reform – Testimony by Nathan Wilkes About the Problem of "Underinsurance" for His Son and Family Because of Hemophilia

In January, the U.S. House of Representatives passed legislation to repeal the Patient Protection and Affordable Care Act (PPACA), the health reform law enacted last year. As this issue of *The Hematologist* went to press, congressional committees were preparing for a series of hearings to examine the current law and propose alternatives, talk radio throughout the country continued to debate the issue, and the courts were reviewing the law's constitutionality. In the midst of all of this noise, voices from patients, including those with hematology-related diseases, are rising up to share their perspectives on the urgency for health reform and their appreciation for the new law's elimination of several discriminatory insurance practices such as pre-existing condition exclusions and lifetime and annual caps on benefits.

Below is an excerpt from congressional testimony presented by Nathan Wilkes. Nathan's son, Thomas, was born with hemophilia in 2003. At the time, he and his family had great insurance through the high-tech telecommunications company that he helped found, but when the insurance company saw Nathan's claims (ranging from a few thousand dollars to $750,000 a year for his son), they started to increase the premiums for all the employees and their families. Nathan testified to the difficult decisions his family faced to stay covered when their insurer announced a $1 million lifetime cap.

Mr. Wilkes told the Committee on Energy and Commerce's Subcommittee on Oversight and Investigations:

The introduction of the cap for the 2006 plan-year started a timer that couldn't be reversed. I recognized that when, not if, we hit the cap, I would have to make critical decisions related to my work, family, and lifestyle. To go without insurance for even a few months would put us into a "pre-existing condition" category due to my son's hemophilia and our access to insurance would be severely compromised.

I knew I would have to find some way to maintain private insurance coverage. Over the next few months we considered our options:

1. *Quit my job and work for a larger company or the government with a larger risk pool, where my claims would not be noticed as quickly.*
2. *Have my wife go to work and shift our children to her new employer's plan. We felt that this would only shift the problem temporarily and we would then need to put our three children into childcare, which was costly and something we did not want to do.*
3. *Turn to Medicaid for Thomas. By all accounts, Colorado is one of the most difficult states in which to get on to Medicaid. Since we "earn too much money," the only option would be through a waiver program. We did start this process but his qualification was not certain and the waitlist at the time was around five years. A wait of five days would be a problem for us – five years was out of the question.*
4. *Get divorced and have my wife – earning no income – qualify for Medicaid. A social worker told us that others have done this in order to provide health insurance for their children.*
5. *Put Thomas on our state's high-risk pool, CoverColorado, which has a $1 million cap. At the current rate of claims, this would have been a short-term fix, where we would likely hit the cap in six to 18 months.*
6. *Start my own consulting business as an employer of two, thus falling into the small group insurance category.*

…Maintaining health insurance has been a struggle for our family, but it has allowed me to provide my son with the lifesaving treatment he needs. Thomas is now seven and very healthy, but without reforming the private insurance system in this country this struggle will continue for me. Health reform is critically important to me and the many other individual and families that face high health care costs due to chronic conditions.

Mr. Wilkes testified before the health reform law was enacted. The new law eliminates lifetime limits, places restrictions on annual limits, and prevents insurance companies from denying children coverage based on pre-existing conditions.

Comparative Effectiveness Institute Ramps Up Work

The Patient-Centered Outcomes Research Institute (PCORI) is the new institute responsible for funding comparative effectiveness studies established by the health reform legislation enacted last year. In January, it indicated that it is gearing up to begin work by announcing the members of its Methodology Committee that will shape the way the studies will be conducted. The Committee is charged with developing and updating methodological standards and guidance for comparative clinical effectiveness research, and its members include physicians, academics, and representatives of groups that conduct comparative effectiveness studies.

The health reform law established PCORI as a nonprofit organization to assist patients, clinicians, purchasers, and policy makers in making informed health decisions by carrying out research projects that compare medicines, devices, or methods of delivering care. However, PCORI and comparative effectiveness studies became somewhat controversial during the health reform debate because some critics feared that federal officials might decide to limit coverage for treatments that are shown in studies to be less effective than alternatives. Proponents, meanwhile, argue that PCORI will accelerate the uptake of innovations by being able to rapidly identify which patients will benefit the most from different types of care. Once research priorities are announced, PCORI expects to distribute funding for comparative effectiveness studies in the coming months.

The Perpetual Fellow — Extending Fellowship Training in Hematology: The Trainee Perspective

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"But I'm already 34, and I feel like I have been training forever!" remarked the character in an introduction video played at this year's ASH annual meeting trainee reception. This sentiment resonates for many trainees, as post-graduate medical education has lengthened considerably since the creation of the first U.S. residency program in 1889. Current trainees wishing to pursue an academic career feel increasing pressure to obtain additional clinical and research training beyond their hematology/oncology fellowship in the form of "fourth-year options," additional fellowships, or advanced degrees. Trainees also face rising debts from medical education and the need to support their families, while shouldering the cost of caring for their aging parents, following in the footsteps of the "sandwich generation." Increasing financial constraints, prolonged training, reduced grant funding, delayed retirement savings, and deferred investment opportunities can greatly affect a hematology/oncology fellow's career choices and could potentially drive fellows out of academics.

Career Options	First-Year Earnings	Net Income After Projected Expenses
Academics (3 years of fellowship training) (deficit projected for 3 years)	$200,000†	-$12,000 for first year
Academics (5 years of fellowship training) (deficit projected for 5 years)	$200,000	-$23,000 for first year
Private Practice (3 years of fellowship training)	$306,000*	+$26,000 for first year

† Academic salaries varied greatly depending on region and career track. $200,000 is an average of salaries based on a survey of recent fellow experiences.

* Based on MGMA 2009 Physician Compensation and Production Survey.

Despite what appears to be an increasing number of trainees extending fellowship, there is a dearth of literature describing its personal, financial, and societal impact. We therefore informally calculated the economic ramifications of pursuing a career in academic hematology, using basic financial planning techniques and previously published assumptions.[1] These assumptions included starting fellowship at age 30, average medical student debt of $162,500, a home mortgage of $250,000, two children with associated college savings expenses, industry-recommended retirement savings parameters, and other average expenses based on the Bureau of Labor Statistics data for a professional cohort. A similar analysis focusing on primary-care careers was recently published in Academic Medicine (reference below), which includes the rationale for the assumptions, possible limitations, and a supplemental online calculator for individualized modeling. For our model, the parameters that differed between the career cohorts were time to starting one's career and salary.

The primary drivers for these budgetary deficits are rising medical student debt and delayed savings and investing expenses.

Besides the financial impact on trainees, prolongation of subspecialty training can have a substantial impact on patients. It is projected by the American Association of Medical Colleges that there will be a shortage of 27,000 internal medicine subspecialists by the year 2020. The American Society of Clinical Oncology estimates a shortage of 2,550 to 4,080 oncologists, including hematology/oncology specialists, by 2020. This estimation has not taken into account the potential shortage of non-malignant hematologists. If trainees choose to prolong subspecialty training, it will likely intensify the shortage.

The decision to pursue academics is often stimulated by a drive and desire to advance the field. Additional research training helps young investigators develop their ideas and drive discovery, and opportunities for additional training are rare outside of a fellowship setting. However, the harsh financial reality that many fellows face, particularly in regard to medical education debt and declining grant opportunities, can make a career in academic hematology untenable and drive them into more lucrative career options. Prevalent prolongation in subspecialty training may also intensify an already-looming physician shortage and create an unacceptable environment for patients requiring hematology care. Addressing these issues through research and coordinated policy development is necessary to ensure the recruitment and retention of hematologists to meet society's growing health-care needs. Expanding medical student debt forgiveness programs and assisting residents and fellows with financial planning could help to alleviate some of the financial challenges that a career in academics and extended training pose.

1. Palmeri M, Pipas C, Wadsworth E, et al. Economic Impact of a Primary Care Career: A Harsh Reality for Medical Students and the Nation. Acad Med. 2010;85:1692-1697.

Regenerative Medicine

(Cont. from page 1)

applications. Other challenges include the considerable expense of conducting phase I trials, a lack of participation by industry, and the possibility that the applications may cross the jurisdictions of individual Institutes within NIH.

To address these and other challenges that were identified during the meeting, workshop participants recommended that a new grants panel/study section be established with broad expertise in translational and clinical research, including matters related to cell manufacturing under Good Manufacturing Practice (GMP) conditions. It was suggested that an NIH Center for Regenerative Medicine be established to champion and coordinate NIH activities in this area.

Recommendations to the general scientific community focused on the need to improve communications between basic and clinical scientists in regenerative medicine and to obtain consensus on the most appropriate design of clinical trials, including not only trials methodology but also cell characterization, cell and tissue banking, long-term follow-up of the recipients of the cell therapy (potentially utilizing a national database), and identification of the most relevant pre-clinical animal models for safety and efficacy testing.

The workshop recommendations to ASH included the need to meet with the leadership of other learned societies interested in regenerative medicine to promote education and research across disciplines. There was agreement that ASH was particularly well placed to foster such interactions. ASH members, as experts in stem cell biology and blood and marrow transplantation, were in an excellent position to assume a leadership role in the field of cell therapy and regenerative medicine. This leadership could extend to developing educational material on a range of topics relevant to regenerative medicine, including guidance on the risks of traveling to other countries for unapproved clinical interventions utilizing stem cells (stem cell tourism) and recent developments with reprogramming of somatic cells to stem cells, termed induced pluripotent stem (iPS) cells. It should also be extended to leadership in developing a consensus on efficacy, safety, and cell product release criteria. Specific short-term recommendations to ASH included forming an *ad hoc* scientific committee on regenerative medicine and including a session on regenerative medicine at its annual meeting.

ASH has already made progress on two fronts in response to the workshop recommendations. First, a scientific session on regenerative medicine is being planned for inclusion at the 2011 annual meeting. Second, the hard work of the Committee on Government Affairs, armed with the workshop recommendations, has led to incorporation of language recommended by ASH in the U.S. Senate Appropriations Committee report to the full Senate. The Senate Committee language reads in part:

The field of regenerative medicine represents a unique approach to treating diseases and disorders by enabling the body to repair, replace, restore and regenerate damaged or diseased cells, tissues and organs. The Committee believes that the NIH should carefully and deliberatively consider how best to organize and undertake research in this promising field, with input from experts in multiple disciplines. The Committee urges the Director to develop a plan that would: assess current research; identify research gaps including research methodologies; develop a mechanism to allow for the coordination of research between Institutes; consider the development of a separate study section; and in coordination with FDA, develop clinical trial methodologies and measures to assure the safety and efficacy of therapies, including data and sample registries. The Committee requests a response in the fiscal year 2012 congressional budget justification.

It is highly gratifying that, in a remarkably short time, the ASH workshop recommendations have led to the same recommendations by a Senate committee to the NIH. It is now up to the ASH membership to take a leadership position on regenerative medicine in the scientific community at large.

Clinical Anti-Myeloma Activity of Aminobisphosphonates

Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010;376:1989-1999.

Bisphosphonates have demonstrated an ability to reduce skeletal-related events (SRE), including bone pain, pathologic fracture, spinal cord compression, and need for radiation to bone. As approximately 80 percent of patients with multiple myeloma (MM) have bone disease, the use of bisphosphonates has transformed the paradigm for supportive care in MM. With their long-term use, attendant complications such as renal compromise and osteonecrosis of the jaw occur in a small percentage of cases. As a result, guidelines now recommend use of aminobisphosphonates for two years in MM patients, with further use predicated upon the presence of active MM and ongoing bone disease. Importantly, bisphosphonates are now standard practice, since the benefits of their use to reduce bone-related complications and pain and improve quality of life and performance status is overwhelming.

In addition to this clinical benefit, preclinical studies in laboratory models show that bisphosphonates can induce MM cell apoptosis and inhibit cytokines including IL-6. Moreover, decreased tumor cell growth with prolonged host survival has been observed after aminobisphosphonate treatment in xenograft murine models of human MM. Prior smaller clinical studies have suggested anti-MM activity when aminobisphosphonates were added to conventional therapies for newly diagnosed MM, relapsed and refractory disease, or MM with high bone turnover. However, whether aminobisphosphonates confer clinical benefits, aside from reducing bone complications, remains controversial.

In this study by Dr. Morgan and colleagues from the United Kingdom, patients received either intensive chemotherapy (if they were candidates for high-dose therapy) and stem cell transplantation, or non-intensive chemotherapy (if they were not candidates), and were subsequently randomized to receive either zoledronic acid or clodronic acid. The primary endpoints were to determine anti-MM clinical benefits assessed by progression-free and overall survival, as well as overall response rate. Compared with clodronic acid, zoledronic acid prolonged median progression-free survival by two months and overall survival by 5.5 months, and reduced mortality by 16 percent. However, the extent and frequency of response within the intensive and non-intensive chemotherapy arms, assessed by response rates (complete/very good partial/partial), did not differ with zoledronic versus clodronic acid treatment. Adverse events were uncommon, although osteonecrosis of the jaw was more frequent with zoledronic acid (3%) than with clodronic acid (< 1%) treatment.

This study provides the strongest evidence to date of a clinically significant anti-MM effect of zoledronic acid. Zoledronic acid also reduced the proportion of patients with SRE, further confirming the benefit of aminobisphosphonates in reducing bone-related disease and complications in MM. The early separation of the survival curves in favor of zoledronic acid, coupled with the prolonged survival with zoledronic acid even after adjusting for time to first SRE, further supports its anti-MM activity. The lack of differences between zoledronic versus clodronic acid treatment in extent or frequency of response within either treatment cohort, coupled with prolonged progression-free and overall survival in both settings, is consistent with zoledronic acid's benefit as a maintenance therapy. Both direct and indirect (targeting angiogenesis or cytokines, modulating immunity) anti-tumor effects may be contributing to this clinical outcome. In this study, patients took bisphosphonates until progression; however, they received bisphosphonates for an average of approximately one year. Since current guidelines recommend bisphosphonate therapy for two years, further studies examining duration and frequency are necessary to establish their optimal use. Importantly, the only novel therapy used in the intensive or non-intensive cohorts was thalidomide. Given that novel agents targeting the tumor cell in its bone marrow microenvironment (such as bortezomib) can also have an impact on bone, it is not surprising to confirm that therapies targeting bone such as zoledronic acid may also favorably impact MM. In the future, it will be critical to incorporate novel agents for MM with novel agents targeting bone to determine their optimal use as both induction and maintenance therapies.

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Dr. Anderson indicated no relevant conflicts of interest.

A Role for TET2 Dysregulation in Myeloid Malignancies

Ko M, Huang Y, Jankowska AM, et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant *TET2*. Nature. 2010;468:839-843.

Aberrant methylation of DNA, particularly hypermethylation of tumor suppressor genes, occurs frequently in many cancers, including hematopoietic malignancies. This has prompted the development of agents capable of reversing hypermethylation, such as DNA methyltransferase inhibitors. These agents have yielded encouraging results both alone and in combination with other epigenetic agents (e.g., histone deacetlyase inhibitors) in patients with myelodysplastic syndrome (MDS) and some acute leukemias. However, the endogenous factors regulating the hypermethylated state have not been fully elucidated.

The α-ketoglutarate-dependent TET2 gene is closely related to TET1, whose protein product is responsible for conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in DNA. Somatic mutations in TET2 occur with significant frequency in patients with certain myeloid malignancies, including MDS, acute myeloid leukemia (AML), myeloproliferative neoplasms, and chronic myelomonocytic leukemia (CMML). Until recently, however, the physiologic implications of TET2 dysregulation and its relationship to DNA methylation patterns were unknown.

This has now changed, with a recent report by Dr. Ko and colleagues from Children's Hospital Boston and Cleveland Clinic. The team of investigators characterized the functional implications of dysregulation of TET2 in myeloid malignancies in relation to hematopoietic cell behavior, DNA methylation patterns, and levels of 5hmC. They found that TET2 mutations were associated with low levels of 5hmC compared with healthy controls. Moreover, shRNA knockdown of TET2 in a murine model resulted in a pronounced shift toward monocytic/macrophage development. An unexpected finding was that TET2 dysregulation was associated with hypomethylation, rather than hypermethylation, of differentially regulated CpG islands. The authors concluded that TET2 plays an important role in normal myelopoiesis, and that a strong association exists between myeloid malignancies and the loss of TET2 catalytic function. They further proposed that levels of 5hmC in the cells of patients with myeloid malignancies may have independent prognostic significance and could potentially provide a basis for future targeted therapeutic interventions. Interestingly, in human AML, mutations in the citrate metabolism genes isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) have recently been shown to act in part by interfering with TET2 function.[1]

The results of these studies have a number of implications for myeloid malignancies. Although the clinical implications of TET2 mutations remain the subject of debate, diminished levels of 5hmC may nevertheless serve as a prognostic indicator in these disorders, particularly in circumstances in which epigenetic forms of therapy are employed. These studies also provide a possible link between genetic aberrations and the metabolic dysregulation characteristic of cancer cells. For example, mutations in metabolism-related genes such as *IDH1/2* and *TET2* may modify gene expression by altering DNA methylation patterns and, in doing so, could contribute to leukemic transformation. Although the relationships between these events will undoubtedly prove to be highly complex, further insights could lead to novel therapeutic paradigms and possibly more individualized treatments for patients with myeloid malignancies.

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Dr. Grant indicated no relevant conflicts of interest.

Not Too Little, Not Too Much, Just the Right Amount of Hepcidin Can Limit Iron Overload in β-Thalassemic Mice

Gardenghi S, Ramos P, Marongiu MF, et al. Hepcidin as a therapeutic tool to limit iron overload and improve anemia in β-thalassemic mice. J Clin Invest. 2010;120:4466-4477.

Remarkable advances in the care of β-thalassemic patients over the past 40 years have prolonged lives and prevented organ dysfunction due to iron overload through the use of parenteral and oral iron chelators. Iron overload occurs in β-thalassemia because ineffective erythropoiesis and frequent RBC transfusions over-enhance iron absorption. It is a curious phenomenon that, in the presence of a globin chain synthesis mismatch, excess heme, erythroid hyperplasia, and anemia, the body still signals the intestine to increase iron absorption as if more iron might solve the problem. We now know that levels of hepcidin, the key regulator of iron absorption and recycling, are low in patients with thalassemia. Hepcidin is made in the liver and controls ferroportin (the "iron door"), which is found on the surface of duodenal enterocytes, macrophages, and hepatocytes. In thalassemia, hepcidin levels are lower than normal for the degree of iron overload, presumably reflecting the fact that hepcidin production decreases in the presence of increased erythropoiesis … even if that erythropoiesis is ineffective. Dr. Gardenghi et al. in Stefano Rivella's lab at Weill Cornell Medical College provide insight into how controlling iron intake and hepcidin itself may add to the therapeutic options available to limit iron overload in organs and improve anemia in patients with β-thalassemia.

In β-thalassemic mice a moderate increase in expression of hepcidin limits iron overload, decreases formation of insoluble membrane-bound globins and reactive oxygen species, and improves anemia. Mice with increased hepcidin expression also demonstrated an increase in the lifespan of their red cells, reversal of ineffective erythropoiesis and splenomegaly, and an increase in total hemoglobin levels. A low dietary intake of iron in thalassemic mice also positively affected erythropoiesis while reducing tissue iron levels in the liver, spleen, kidney, and heart. Interestingly, on the low iron diet, hepcidin levels decreased while erythropoietin levels increased, suggesting that hepcidin expression is more sensitive to the suppressive effect of iron restriction in states of increased erythropoiesis. Even after five months on a low iron diet, hemoglobin levels did not drop and spleen size diminished in the thalassemic mice. When very high hepcidin levels were tested, hemoglobin levels were very low and spleen iron levels were six-fold higher, suggesting that very high levels of hepcidin can inhibit release of iron from macrophages, leading to inhibition of red cell production.

According to these data, therapeutics that can increase hepcidin levels or act as hepcidin agonists might help treat the abnormal iron absorption in individuals with β-thalassemia and related disorders. However, the hepcidin level has to be just right. Supportive evidence comes from a recent report by Dr. Li et al., which showed that transferrin injections can increase hepcidin expression and improve anemia in β-thalassemic mice.[1] As discussed in an accompanying commentary by Drs. Bartnikas and Fleming,[2] promising new agents are in development for use in modulating hepcidin levels and possibly in iron overload states or chronic disease-related anemia in humans. Clearly, restricting iron intake as severely as was done in these mouse studies is impractical, but new iron chelators combined with "just right" amounts of hepcidin may improve organ function and prolong the lives of individuals with β-thalassemia.

1. Li H, Rybicki AC, Suzuka SM, et al. Transferrin therapy ameliorates disease in beta-thalassemic mice. Nat Med. 2010;16:177-182.
2. Bartnikas TB, Fleming MD. A tincture of hepcidin cures all: the potential for hepcidin therapeutics. J Clin Invest. 2010;120:4187-4190.

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Dr. Vercellotti indicated no relevant conflicts of interest.

Is There a Path to Quality of Life for Elderly Patients Treated for Myeloma?

Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol. 2010;11:934-941.

The treatment of elderly patients with newly diagnosed symptomatic multiple myeloma has improved since the era of melphalan plus prednisone, the standard treatment for more than 30 years. Current regimens still include melphalan plus prednisone as a backbone for combination regimens that contain newer agents, such as bortezomib, lenalidomide, or thalidomide therapy. Despite remarkable response rates and survival benefits, none of these combinations has freed patients and physicians from the anxiety of various side effects. Aside from constipation and somnolence, thalidomide shares thromboembolic events and fatigue with lenalidomide, and peripheral neuropathy with bortezomib. Bortezomib is also marked by gastrointestinal symptoms, most notably diarrhea. In the VISTA study [Velcade as Initial Standard Therapy in Multiple Myeloma] that supported the approval of bortezomib in newly diagnosed elderly patients with multiple myeloma, grade 3 or worse peripheral neuropathy was described in 13 percent of patients and grade 3 or worse gastrointestinal symptoms in 19 percent.[1] Still, patients must receive some kind of treatment without delay, since myeloma can rapidly lead to renal failure, bone lytic lesions and fracture, severe bone pain, and spinal cord compression, among other complications.

Mateos et al. from the Spanish Myeloma Group reported the results of a phase III trial in which 260 patients with untreated multiple myeloma, 65 years of age and older, were randomly assigned to receive six cycles of bortezomib plus melphalan and prednisone (VMP) or bortezomib plus thalidomide and prednisone (VTP) as induction therapy. The first cycle of bortezomib was given at maximum intensity per cycle (twice per week for six weeks) followed by five cycles of reduced intensity bortezomib (once per week for five weeks). Patients were then randomized to maintenance therapy.

This approach was associated with similar response rates and slightly better progression-free survival than VISTA, although the two approaches were never directly compared in a randomized study. More importantly, this approach was associated with a reduction in the incidence of grade 3 or worse peripheral neuropathy (8% of patients) and gastrointestinal symptoms (4%). The frequency of peripheral neuropathy might be further decreased if the dose of bortezomib was reduced to 1.0 mg/m^2.

This study reported use of a novel and less intensive bortezomib-based treatment regimen with two objectives: to maintain efficacy and reduce toxic effects compared with the regimen used in VISTA. This study shows that bortezomib-based regimens using an intensive dosing schedule of bortezomib twice per week in the first cycle to obtain rapid debulking activity, followed by less intensive weekly dosing, are not only well-tolerated but are also an active approach for elderly populations. These changes could not only provide a more safe and convenient treatment for patients, but may also reduce early discontinuations, which eventually lead to decreased efficacy. In the present study, 28 infusions of bortezomib within 31 weeks were as good as 32 infusions within 24 weeks in the VISTA study. Similar results were confirmed in other studies published and ongoing. For example, low-dose dexamethasone was as good as high-dose dexamethasone because it was less toxic.[2] The race to develop the most effective novel agents and to determine the most intensive regimens has escalated since 2000, and yet the most striking observation in recent years has been that "more is better" only in a less intensive manner in elderly patients with multiple myeloma.

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2. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11:29-37.

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Dr. Leleu indicated no relevant conflicts of interest.

Gene Therapy for Wiskott-Aldrich Syndrome: Benefits and Risks

Boztug K, Schmidt M, Schwarzer A, et al. Stem-cell gene therapy for the Wiskott-Aldrich syndrome. N Engl J Med. 2010;202:1918-1927.

An international team headed by Dr. Christoph Klein in Germany has reported clinical improvement after gene therapy in two children with Wiskott-Aldrich Syndrome (WAS), a disease caused by mutation of the gene encoding Wiskott Aldrich syndrome protein (WASp). In patients with this condition, the lack of functional WASp, which plays a critical role in actin polymerization in blood cells, leads to thrombocytopenia as well as immunodeficiency with recurrent infections and a tendency toward development of autoimmune diseases. WAS is a promising candidate disease for gene therapy, because the mutated gene is expressed uniquely in hematopoietic cells, and previous animal studies have shown that WASp-corrected cells have a survival advantage over non-corrected cells. Thus, even low levels of corrected cells may produce clinical benefit.

The study included patients over one year of age with documented severe WAS. After receiving a nonmyeloablative dose of busulfan (4 x 4 mg/kg), the children underwent autologous transplantation of gene-corrected cells. Prior to transplantation, CD34+ G-CSF mobilized peripheral blood stem cells were infected *in vitro* with a retrovirus encoding the normal *WASp* gene, with a five-fold multiplicity of infection (number of virus particles per cell), such that some cells would likely be infected with more than one copy of the retrovirus. The final CD34+ dose in these patients was 13 and 18 million CD34/Kg, with approximately 50 percent transduction efficiency.

Both patients in the study showed functional immune reconstitution and significant increases in platelet counts from below 20,000 to 80,000-200,000 per microliter. Within six months of transplantation, both children had significant levels of WASp+ blood cells with 80 to 90 percent of their T cells (CD4, CD8, and Treg) expressing WASp, and these increases were maintained for the length of follow-up (three years). Clinically, both patients experienced fewer and less severe infections and bleeding episodes. Both had decreased autoimmunity (autoimmune anemia and eczema, respectively) and normalized immunoglobulin levels, and after immunization each developed effective titers against tetanus, diphtheria, and H. flu.

With retroviral gene therapy, retroviral DNA permanently inserts into the genome, usually near promoters of active genes. The biggest safety concern in these WAS patients is that permanent insertion may occur in or near an oncogene to promote leukemia. Retroviral insertion into the LMO2 locus in children with X-SCID severe combined immunodeficiency was associated with development of leukemia after gene therapy.[1] The investigators therefore performed extensive insertion site analyses in the bone marrow cells and found increased representation of cells having insertions near genes critical for cell proliferation, including LMO2.

In this published report, there were no adverse effects and the clinical benefits persisted. At the 2010 ASH annual meeting, Dr. Klein reported on results from 10 children treated with this protocol. Of these patients, nine (including the two published) showed clinical improvement after gene therapy. One patient failed treatment due to low CD34+ cell counts and instead underwent haploidentical transplantation. One patient developed acute lymphocytic leukemia; this patient, like those patients with X-SCID who developed leukemia after gene therapy, had a leukemia clone with retroviral insertion near the LMO2 gene.

This work accentuates the need for safer gene therapy vectors that will not activate oncogenes. Ongoing efforts to make gene therapy safer include: 1) assuring that the inserted virus does not activate adjacent genes by removing all promoter activity except for that which drives expression of the therapeutic gene; 2) insulating expression of the transgene from the surrounding genomic DNA; and 3) targeting integration to "safe" genomic regions – meaning that they lack genes that could promote cancer either by activating (oncogenes) or inactivating (tumor suppressor) adjacent genes.

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Dr. Krause indicated no relevant conflicts of interest.

The Flavors of MPNs: Is STAT1 the Key Ingredient?

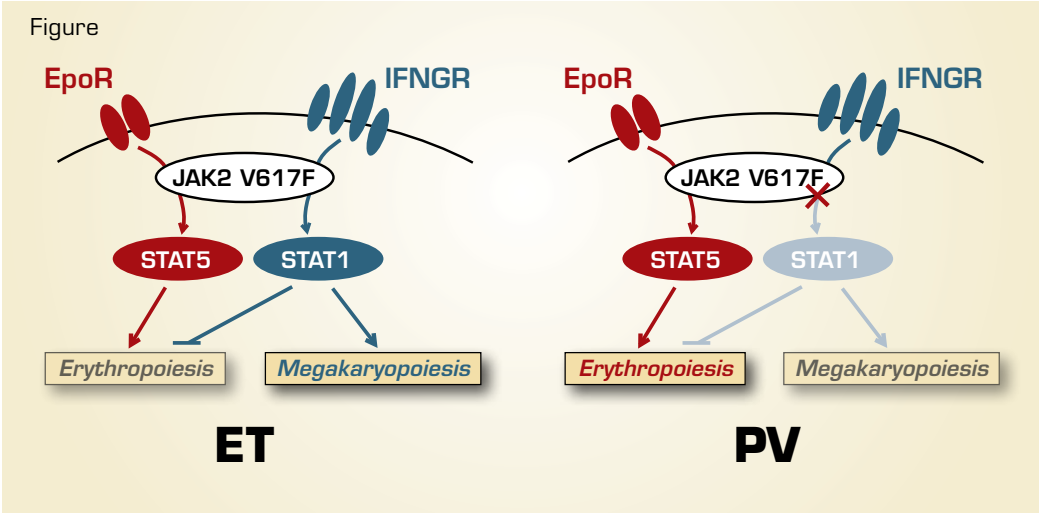
Chen E, Beer PA, Godfrey AL, et al. Distinct clinical phenotypes associated with *JAK2V617F* reflect differential STAT1 signaling. Cancer Cell. 2010;18:524-535.

A lingering question in the study of myeloproliferative neoplasms (MPNs) is how the singular *JAK2* V617F mutation results in distinct clinical presentations. The mutation is identified in more than 95 percent of patients with polycythemia vera (PV) and 50-60 percent of patients with essential thrombocythemia (ET) and primary myelofibrosis. In addition to host genetic modifiers, higher *JAK2* V617F allele burden and/or homozgyosity for mutant *JAK2* in PV compared to ET has been invoked as one mechanistic basis for this difference in phenotypic diversity. However, the application of several experimental techniques has not yet convincingly demonstrated biologic differences in the activated signaling pathways downstream of *JAK2* V617F between PV and ET. Such results may be partly confounded by analyses of samples intermixed with varying proportions of wild-type (WT) and mutant *JAK2* clones, as well as other patient variables.

In order to sidestep this "clonal confusion," Dr. Chen and colleagues from Anthony Green's laboratory in the U.K. cultured and genotyped thousands of erythroid colonies from PV and ET patients, each derived from a WT or mutant *JAK2* erythroid progenitor cell. Pooled WT and heterozygous *JAK2* V617F erythroid colonies were subjected to biologic assays, including expression arrays, flowcytometry, and immunocytochemistry. Expression profiling revealed the surprising finding that *JAK2* mutant colonies were more closely related to WT colonies from the same individuals than to mutant colonies from other patients. The profiling also revealed that interferon (IFN)-regulated genes were significantly up-regulated in ET compared to PV mutant erythroblasts. Increased expression of phosphorylated STAT1 was identified in ET, but not PV erythroblasts, a finding consistent with its essential role in IFNγ receptor signaling. Further, the expression of constitutively active STAT1 in K562 cells or $CD34^+$ cord blood cells enhanced megakaryocytic differentiation and reduced erythroid differentiation. Conversely, inhibition of STAT1 signaling via introduction of a dominant negative form of STAT1 in $CD34^+$ progenitors from ET patients resulted in a PV-like phenotype, with increased numbers of erythroid clones and reduced numbers of megakaryocytic clones.

These data highlight the power of using clonal analysis to unmask differences in intracellular signaling that arises from a specific somatic mutation in related diseases. Preferential activation of STAT1 constrains erythroid differentiation and promotes megakaryocytic development, leading to an ET phenotype (Figure). In contrast, a reduced phospho-STAT1 response to JAK2 V617F promotes erythroid differentiation, as observed in PV. The finding that JAK2 V617F induces only minor effects on global gene expression (compared to WT JAK2) within the same patients serves to highlight the relative importance of inter-patient genetic variation as a contributor to disease diversity. This study raises several important questions, including what the biologic basis is for differential activation of STAT1 in ET versus PV, and how the marked differences in interferon signaling between PV and ET patients can be reconciled with the beneficial effects of interferon-α in both MPN subtypes. It will be of interest to evaluate whether changes in STAT1 activation herald the dynamic evolution between ET and PV observed in some patients.

Figure



JASON GOTLIB, MD, MS

Dr. Gotlib indicated no relevant conflicts of interest.

Membrane Phospholipid Scrambling by TMEM16F

Suzuki J, Umeda M, Sims PJ, et al. Calcium-dependent phospholipid scrambling by TMEM16F. Nature. 2010;468:834-838.

The plasma membrane of animal cells contains a phospholipid bilayer; the outer leaflet largely contains phosphatidylcholine and sphingomyelin and the inner leaflet is mainly composed of phosphatidylserine (PS) and phosphatidylethanolamine (PE). This lipid asymmetry is maintained by an ATP-dependent enzyme called the aminophospholipid translocase. Scrambling of membrane phospholipids leading to dissipation of lipid asymmetry was originally observed during platelet activation[1] and subsequently has been identified in other important processes, including apoptosis and the release of neurotransmitters and microvesicles. PS is a component of the surface for assembly of the prothrombinase and intrinsic pathway factor X activation complexes, which are necessary for normal blood coagulation. In 1979, a female with a history of excessive surgical bleeding was identified with platelets displaying impaired procoagulant activity.[2] This rare bleeding disorder, called Scott syndrome after this patient, is associated with defective phospholipid scrambling in platelets and other blood cells.

Dr. Suzuki et al. in the laboratory of Shigekazu Nakata in Kyoto have identified a protein known as TMEM16F, which participates in the scrambling of PS in plasma membranes. The authors used a mouse B-cell line, Ba/F3, which exposes PS on its cell surface after treatment with a calcium ionophore. A Ba/F3 subline with considerably increased PS exposure compared to the parental cell line was isolated by repetitive fluorescence-activated cell sorting. A complementary DNA library was then constructed from this subline and was introduced into the parental cell line. After repetitive sorting and expansion, the team isolated a cell line, designated LD-PS4, that constitutively exposed PS in the absence of calcium ionophore. The cDNA of the LD-PS4 was compared to the GenBank database revealing the gene encoding TMEM16F, which has a predicted polypeptide molecular mass of 106 kDa and eight transmembrane segments. Compared to wild-type TMEM16F, LD-PS4 TMEM16F contains an A-to-G mutation at nucleotide 1226 in codon 409, leading to an aspartate to glycine (D409G) replacement. LD-PS4 cells also constitutively expressed PE, consistent with scramblase activity. Inhibiting endogenous TMEM16F expression in Ba/F3 cells with a TMEM16F short hairpin RNA resulted in a significant decrease in the rate of calcium ionophore-induced exposure of PS and PE. RT–PCR analysis of TMEM16F in a B-cell line from a patient with Scott syndrome revealed the absence of exon 13 and a frameshift producing premature termination of exon 14, caused by a homozygous G-to-T mutation at the splice-acceptor site in intron 12. These results strongly indicate that TMEM16F is an essential component of the entire composition of a phospholipid scramblase.

TMEM16F is a member of the TMEM16 family, which consists of 10 members in both humans and mice. The original member of this family, TMEM16A, is a calcium-dependent chloride channel, suggesting that TMEM16F may bind to and be regulated by calcium. The constitutive activity of the D409G mutant may be due to an increased affinity for calcium and binding at endogenous calcium levels.

The results of this study indicate that TMEM16F is an essential component of the long sought-after phospholipid scramblase. This finding opens the door for studies of the diverse biological processes that are regulated by phospholipid membrane composition, including hemostasis, apoptosis, and neurotransmission.

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2. Weiss HJ, Vicic WJ, Lages BA, et al. Isolated deficiency of platelet procoagulant activity. Am J Med. 1979;67:206-213.

PETE LOLLAR, MD

Dr. Lollar indicated no relevant conflicts of interest.

Take This One for a Test Drive: It Looks Like a HIT

Cuker A, Arepally G, Crowther MA, et al. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost. 2010;8:2642-2650.

Heparin-induced thrombocytopenia (HIT) is a thrombotic disorder, occurring in 3 percent or more of individuals exposed to heparin, in which antibodies to platelet factor 4-glycosaminoglycan complexes form on platelet surfaces, leading to thrombi, which can be life-threatening. Diagnosis of this disorder can be difficult because the clinical picture may be confusing and assays are limited by poor specificity and lack of availability in real time.

To tackle this problem, a multi-institution team of investigators constructed a HIT-test clinical scoring model based on the expert opinions of 26 physicians who regularly diagnose and manage HIT. The experts, who are participants in the NHLBI-funded Transfusion Medicine Hemostasis (TMH) Clinical Trials Network, were asked to rate the diagnostic importance of each of eight HIT clinical findings selected from the literature, ranging from -3 (strongly against a diagnosis of HIT) to +3 (strongly for a diagnosis of HIT). The median ratings for these variables were used to derive the pre-test probability model, the HIT Expert Probability (HEP) score. The model was then validated in 50 consecutive patients referred for HIT testing at a single reference laboratory at the University of Pennsylvania, with tests including a polyspecific HIT antibody ELISA and an in-house serotonin release assay. Clinical information on the 50 patients was obtained at baseline testing and then by phone interview at 30 days post-testing. A panel of three experts determined whether HIT was likely or unlikely in the patients, and two hematology fellows rated each patient independently using the HEP score, the 4 Ts,[1] (a diagnostic method using four criteria to determine a HIT probability score), and a third system, the Lillo-Le Louët model,[2] (a diagnostic score using three criteria to determine a HIT probability score following cardiopulmonary bypass) to determine inter-observer agreement.

As compared with the standard 4 Ts pre-test system, the eight-criteria HEP score showed better inter-observer agreement, better correlation with HIT laboratory tests, and better agreement with a HIT diagnosis by the expert panel. Further, the HEP score showed better specificity and was better able to distinguish patients with a positive serotonin release assay than the 4 Ts system. The authors conclude, based on these findings, that the HEP score reduced the number of false positive diagnoses by 40 percent, thereby reducing the unnecessary use of direct thrombin inhibitors in parallel.

The new pre-test probability score for HIT appears to be innovative and impressive, considering the fact that it is based on the expert opinion of 26 busy hematologists who agreed to complete the questionnaire. The score is straightforward, as it is based on standard clinical and laboratory features of HIT, and will likely be test-driven by hematologists in the coming year. Before the scoring system can be implemented, however, a few critical issues need to be considered. For example, it will be important to determine how the HEP score model works when not all data are available, which was the case in 10 percent of the validation group. It will also be critical to validate the scoring system in surgical, medical, and critical-care HIT patients, who constituted fewer than half of the cases in the validation group. Finally, as the score was tested with patients from a single institution, it will be important to assess the HEP score at other institutions and with different serotonin release assays and cutoffs. Notwithstanding these caveats, as the HEP score is tested in the field, it should be noted that *hematology fellows with no prior experience* were able to apply the score and closely reproduce the findings of the expert panel.

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	HEP Score	4 Ts	p-value
Clinical Features	1. Fall (%) in platelets 2. Timing of platelet fall 3. Nadir platelet count 4. Thrombosis 5. Skin necrosis 6. Acute systemic reaction 7. Bleeding 8. Other causes	1. Thrombocytopenia 2. Timing of platelet fall 3. Thrombosis or skin necrosis or acute reaction 4. Other causes	
Inter-Observer Agreement (Correlation Coefficient)	0.88	0.71	
Concordance with Lab, Panel (AUROC)	0.91	0.74	p=0.017
Mean Score in ITP	1.98	4.09	
Sensitivity	1.00	1.00	
Specificity	0.60	0.44	
PPV	0.29	0.23	
NPV	1.00	1.00	
Score in SRA(+)	5.4	1.3	p=0.0003
Score in SRA(-)	4.5	4.0	p=0.33

AUROC is area under the receiver operating curve; SRA is serotonin release assay

MARGARET V. RAGNI, MD, MPH

Dr. Ragni indicated no relevant conflicts of interest.

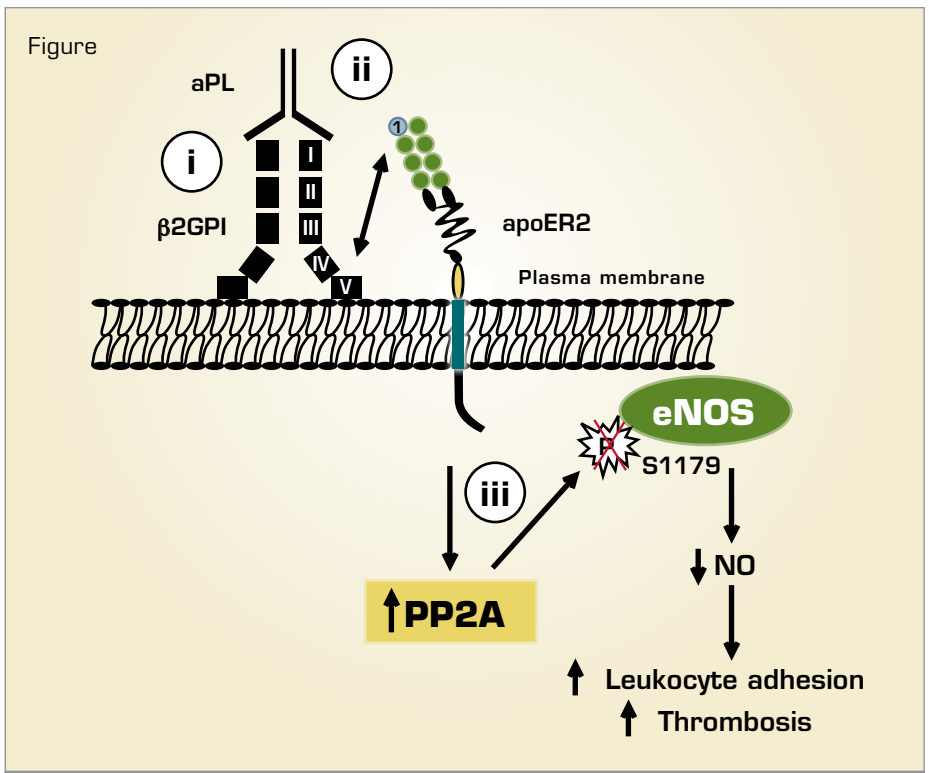
Antiphospholipid Antibodies Do NO Wrong

Ramesh S, Morrell CN, Tarango C, et al. Antiphophsolipid antibodies promote leukocyte–endothelial cell adhesion and thrombosis in mice by antagonizing eNOS via β2-GPI and apoER2. J Clin Invest. 2010. [Epub ahead of print]

The underlying molecular events responsible for antiphospholipid antibody syndrome (APS) have been difficult to pinpoint. Characterization of causative antibodies has demonstrated that they are not actually directed at phospholipids, but rather directed at plasma proteins that bind phospholipids. β2-glycoprotein I (β2-GPI) is an important antigen in this regard, but despite its high plasma concentration and central role in APS, the function of β2-GPI in normal physiology remains poorly defined. One function that has been observed is the binding of dimerized β2-GPI to members of the LDL receptor family on endothelial cells, yet the significance of this interaction is unclear. A group led by Dr. Chieko Mineo at Southwestern Medical Center now describes an antiphospholipid antibody-mediated signaling pathway involving β2-GPI and apolipoprotein E receptor 2 (apoER2) that leads to inhibition of endothelial NO synthetase (eNOS). This pathway induces leukocyte-endothelial interactions and thrombus formation *in vivo*.

The investigators found that incubating cultured endothelial cells with antiphospholipid antibodies isolated from patients with APS led to decreased eNOS activity and increased adhesion of monocytes. Their studies demonstrated a pathway in which dimerization of β2-GPI by antiphospholipid antibodies enabled binding to and activation of apoER2, leading to activation of the phosphatase PP2A. PP2A then elicited dephosphorylation of eNOS, with a resulting decrease in NO production and increase in leukocyte-endothelial cell interactions (Figure). The investigators performed several experiments to demonstrate that this pathway was operative *in vivo* as well. They used intravital microscopy to demonstrate that the leukocytes adhered to the endothelium following infusion of antiphospholipid antibodies into mice, noting that antiphospholipid antibody-mediated leukocyte adhesion was impaired in mice lacking eNOS or ApoER2. Thrombus formation was also evaluated, and the reduction in closure time following infusion of antiphospholipid antibodies was absent in mice lacking eNOS or ApoER2, indicating a role for this pathway in antiphospholipid antibody-mediated thrombosis.

The prevalence of antiphospholipid antibodies in the general population is approximately 1 to 5 percent. These antibodies can contribute to both venous and arterial thrombosis as well as recurrent pregnancy loss. How these antibodies elicit vascular disease has been a recondite puzzle, and, although some pieces of the puzzle have been identified during the past three decades, a coherent picture of the molecular mechanism by which they elicit thrombus formation has been slow to emerge. The article by Dr. Ramesh and colleagues now fits these pieces together into a cohesive pathway. While the β2-GPI/ApoER2-dependent eNOS inactivation by antiphospholipid antibodies may not be the only operative pathway that mediates vascular disease in APS, the *in vivo* data indicate that it is an important one. Understanding the molecular mechanism of APS could redirect drug development programs to focus on more proximal events in the pathway, potentially leading to therapies with fewer side effects than traditional anticoagulation.



Pathway for antiphospholipid antibody-induced thrombosis.
(i) Antiphospholipid antibodies (aPL) bind to β2GPI causing dimerization.
(ii) Dimerized β2-GPI binds to and activates apoER2. (iii) This interaction results in increased activation of PP2A. PP2A decreases eNOS activity. The ensuing decrease in bioavailable NO results in increased leukocyte adhesion and increased thrombosis.

ROBERT FLAUMENHAFT, MD, PhD
Dr. Flaumenhaft indicated no relevant conflicts of interest.

CT Scans in Response and Follow-Up Assessment of CLL: Can We Eliminate Their Use?

Eichhorst BF, Fischer K, Fink AM, et al. Limited clinical relevance of imaging techniques in the follow-up of patients with advanced chronic lymphocytic leukemia: results of a meta-analysis. Blood. 2010. [Epub ahead of print]

Chronic lymphocytic leukemia (CLL) is a disease characterized by blood lymphocytosis, cytopenias, bone marrow infiltration, lymph node enlargement, and hepatosplenomegaly. Prior to the availability of modern imaging studies, the Rai or Binet Staging systems employed a routine blood test and physical exam to predict patient outcomes at diagnosis. When treatment was initiated, response criteria included documentation of partial improvement in cytopenias (if present), resolution of blood, lymph node, and spleen/liver disease for a partial response, and complete resolution of these events with bone marrow clearance for a complete response. Computed tomography (CT) studies of internal lymph nodes, liver, and spleen were not included, as this technology was not yet developed. Over time, CT scans were rapidly adopted for lymphoma staging, and, in the absence of supporting data, the use of CT scans was empirically adopted for staging and therapy response of CLL as well. This empiricism in using expensive CT scans has evolved into a requirement by regulatory agencies for registration of new therapeutic agents for CLL and has become part of response guidelines for clinical trials. In a time of concerns about the costs of health care and unnecessary exposure to radiation by such imaging studies, the question of where the evidence for this mandated imaging approach is derived should be asked.

One small study of our own institution's retrospective experience with flavopiridol-treated patients demonstrated no difference in using clinical exam and labs versus adding a CT scan assessment when examining progression-free (PFS) and overall survival. In a recent, much larger retrospective study, Dr. Eichorst and colleagues from the German CLL group examined the impact of CT scans in 1,372 patients receiving first-line therapy in clinical trials and demonstrated that these imaging studies added no benefit when following patients for evidence of relapse after treatment. For those patients receiving modern chemoimmunotherapy, no benefit was observed in using CT scans post-therapy to better predict PFS. Finally, the presence of bulky lymph nodes (> 5 cm) was not shown to be predictive of patient outcomes. It was only with chemotherapy-based treatments that CT scans improved prediction of PFS over that of routine clinical response assessment. Collectively, these authors recommend that CT scans not be used for CLL staging or follow-up outside of clinical trials, as supported by the current IWCLL guidelines.

This article provides even more important evidence that CT scans for CLL are not required outside of select circumstances. These include evaluation of symptoms referable to areas not adequately visualized by exam, the rare setting of follow-up post-therapy when the only site of disease is in the abdomen or chest and not measurable by exam, and in those patients participating in clinical trials. It is unclear why the authors did not take their recommendations further to question why these CT scans are needed at all as part of clinical trials. The current requirement for CT scans remains problematic to interpreting new study results, as essentially all prior CLL clinical trials did not include CT scans. More importantly, these imaging tests add significant cost and potential morbidity to the very special patients who volunteer to be part of clinical trials exploring new treatment approaches. Reconsideration of the CT requirement in the setting of implementing detailed lymph node and spleen physical exams might offer an opportunity to match our new clinical trial approaches to methods best supported by evidence-based tumor assessment.

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

Polycythemia Vera

STUDY TITLE: Randomized, Open Label, Multicenter Phase III Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 Tablets Versus Best Available Care (The RESPONSE Trial)

COORDINATOR: The study is sponsored by Incyte Corporation in collaboration with Novartis Pharmaceuticals.

CLINICALTRIALS.GOV IDENTIFIER: NCT01243944

PARTICIPATING CENTERS: 48 medical centers in North America.

ACCRUAL GOAL: 300 patients.

STUDY DESIGN: This phase III, randomized, open label, multi-center trial will compare the JAK inhibitor INC424 to best available care. Eligiblity criteria are as follows: adults with a diagnosis of polycythemia vera for at least 24 weeks who have splenomegaly with leukocytosis and/or thrombocytosis, who are resistant to or intolerant of hydroxyurea, and who have undergone at least two phlebotomies over a 24-week period preceding enrollment. The randomization ratio is 1:1. Best available therapy is selected by the investigator for each subject and may include hydroxyurea (at a tolerated dose), anagrelide, interferon, or an immunomodulatory agent (e.g., lenalidomide or thalidomide). After week 32, subjects are allowed to cross over from best available therapy to INC424.

The trial's primary outcome measure is the proportion of clinical responses to INC424 by week 32 compared with best available therapy. Clinical response criteria are the absence of phlebotomy, a 35 percent or greater reduction in spleen volume, or both. Secondary objectives include comparison of both the proportion of patients who attain a complete hematologic response by week 32 and the proportion of subjects who obtain a response by week 32 and maintain that response for a total duration of 48 weeks.

RATIONALE: Phlebotomy and low-dose aspirin are accepted as the initial standard of care for patients with low-risk polycythemia vera. However, many patients eventually require treatment with hydroxyurea because of poor tolerance of phlebotomy, progressive splenomegaly, or high risk of thrombotic complications. But treatment with hydroxyurea can result in unacceptable myelosuppression or other intolerable side effects, such as lower extremity ulcers, and the therapeutic index of second-line drugs including anagrelide, interferon, and immunomodulatory agents is suboptimal. Therefore, development of alternative therapeutic agents is warranted. More than 95 percent of polycythemia vera cases are positive for JAK2 activating mutations. The JAK2 inhibitor INC424 has demonstrated clinical response rates of ~45 percent and a favorable toxicity profile in phase II testing in patients with advanced myeloproliferative neoplasms regardless of JAK2 mutational status.

COMMENT: The RESPONSE trial is a pivotal study as a favorable outcome will expand the therapeutic options for patients with polycythemia vera who are resistant to or intolerant of hydroxyurea. Ongoing studies comparing hydroxyurea to pegylated interferon as initial treatment of patients with high-risk polycythemia vera, however, could influence the sequence in which available therapeutic agents are used. A number of JAK2 inhibitors are in various stages of development, and well-designed clinical trials are required to define optimal use of these agents (including INC424) for the treatment of polycythemia vera and other neoplasms in which aberrant activation of the JAK-STAT pathway underlies disease pathophysiology.

–Bart Scott, MD, and Michael Linenberger, MD

Dr. Scott is the local site investigator for this trial at the University of Washington Medical Center.

Transfusion Independence in MDS Patients Treated with Lenalidomide

STUDY TITLE: A Study of Lenalidomide Versus Placebo in Subjects With Transfusion Dependent Anemia in Low Risk Myelodysplastic Syndrome (MDS) Without Del 5Q (MDS-005)

COORDINATOR: The study is sponsored by Celgene, the manufacturer of lenalidomide.

CLINICALTRIALS.GOV IDENTIFIER: NCT01029262

PARTICIPATING CENTERS: This international trial is being conducted at more than 70 medical centers in 14 countries, including nine centers in the United States and Canada.

ACCRUAL GOAL: 375 patients.

STUDY DESIGN: The study is a phase III, double-blind, randomized, placebo-controlled trial of lenalidomide in patients with International Prognostic Scoring System (IPSS) low- or intermediate-1-risk MDS who do not have del(5q), have not responded to erythropoiesis-stimulating agent therapy and require regular red blood cell transfusions. Patients with severe neutropenia or thrombocytopenia are excluded. Enrolled patients are being randomized (2:1) to receive either 10 mg of lenalidomide daily or placebo for up to four years. The primary endpoint of the study is transfusion independence; secondary endpoints include safety and health-related quality of life. An ancillary study is assessing the capacity of an erythroid differentiation gene expression signature (based on microarray analysis) to predict treatment response.

RATIONALE: Lenalidomide was approved in December 2005 by the Food and Drug Administration for the treatment of patients with transfusion-dependent anemia due to IPSS low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities. Approximately two-thirds of such patients will become transfusion-independent during lenalidomide therapy. Some patients with MDS lacking del(5q) also respond to lenalidomide, but transfusion independence in this group is uncommon and rarely durable (e.g., 26 percent transfusion independence rate and 41-week median response duration in the MDS-002 phase II study). The characteristics of responding non-del(5q) patients are poorly understood. In 2008, the European Medicines Agency refused marketing authorization for lenalidomide for the treatment of MDS-associated anemia, citing lack of randomized data and limited safety information. The MDS-005 randomized study, like the similarly designed and recently completed MDS-004 study in del(5q) patients, will provide additional safety and efficacy data, including controlled information on disease progression.

COMMENT: Lenalidomide is an expensive drug, and most MDS patients without del(5q) do not benefit from it. This study may give additional insight into which patients without del(5q) are most likely to respond favorably to lenalidomide, allowing for more cost-effective drug use. In addition, some investigators are concerned that lenalidomide may, in some cases, selectively suppress a slow-growing, indolent clone in the marrow of patients with lower-risk disease, thereby allowing a more aggressive clone (e.g., with a p53 mutation) to expand, precipitating clinically apparent disease progression. While this placebo-controlled study would be difficult to accrue to in the United States, where lenalidomide is widely used off-label in the non-del(5q) population, most of the study sites are located in countries where lenalidomide is not available.

–David P. Steensma, MD

Eugene Goldwasser 1922 – 2010

ASH Emeritus member Eugene Goldwasser, PhD, of the University of Chicago, died on December 17, 2010, at his home in Chicago, IL, of complications of prostate cancer. He was 88. Known as "the father of Epo," Dr. Goldwasser, the Alice Hogge and Arthur A. Baer Professor Emeritus of Biochemistry and Molecular Biology, was the first scientist to isolate and purify erythropoietin, or Epo, in the late 1970s. Dr. Goldwasser and his team produced a purified sheep form of erythropoietin in 1971, followed by the human variety in 1977. The first successful clinical trial took place in 1985. By 1986, mass production of Epo had begun. As a result of Dr. Goldwasser's revolutionary discovery, millions of dialysis patients and anemic patients with other diseases are able to live longer and more productive lives. "The enormous success of Epo still astonishes me," Dr. Goldwasser wrote in a 1996 biographical essay.[1] "It is still gratifying to me to see how effective Epo is in correcting the anemia of dialysis patients, and how it spares them repeated transfusions."

Read more about how Dr. Goldwasser's discoveries helped advance the treatment of anemia in *The Story of Erythropoietin* by John W. Adamson, MD, part of ASH's 50 Years in Hematology series at *www.hematology.org/Publications/50-Years-in-Hematology/4726.aspx*.

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ASH Program Successful in Promoting Minority Careers

MICHAEL DEBAUN, MD, MPH

Professor of Pediatrics and Medicine, JC Peterson Endowed Chair in Pediatrics, Vice Chair for Clinical Research, Pediatrics, and Director, Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease, Vanderbilt University Children's Hospital

Five years ago, ASH entered into a partnership with the Harold Amos Medical Faculty Development Program (AMFDP) of the Robert Wood Johnson Foundation in an effort to increase the number of underrepresented minority scholars receiving academic and research appointments in the field of hematology. Although the AMFDP has been supporting minority scholars for more than 25 years, ASH's funding of the joint ASH-AMFDP Award helps to ensure that deserving applicants in the field of hematology receive the support they need. Since the new award was launched in 2006, five scholars, one per year, have been accepted into the program, which is a remarkable accomplishment considering that the AMFDP accepts applications from all specialties and funds only eight to 12 scholars per year.

ASH is currently the only subspecialty society to partner with the AMFDP, which recognizes ASH's Minority Medical Student Program (MMSAP) as a model program for providing medical students with research experiences and considers the MMSAP the pipeline to the ASH-AMFDP scholars program.

Christopher R. Flowers, MD, MS, the first ASH-AMFDP Award recipient, describes the profound impact the award has had: "This funding provided the groundwork for my future career goals with training in information management with regard to clinical trials, research design, and statistical modeling; it has strongly supported my desire to pursue a career in academic medicine."

In addition to remaining committed to developing careers in academic medicine, ASH-AMFDP recipients are equally as committed to serving as role models for students and faculty of similar backgrounds and giving back to the Society. A number of the current ASH-AMFDP recipients have served as research and career-development mentors to MMSAP participants, and ASH-AMFDP awardees and alumni come together annually at the Promoting Minorities in Hematology Reception at the ASH annual meeting to support the careers of the MMSAP participants.

"The ASH-AMFDP award has really been a huge jumpstart to my career. It enabled me to secure my own lab space and devote more time to my research. I am hoping that the data accrued during my award will serve as the basis for my R01 application," said 2008 recipient Seth Rivera, MD, PhD.

The ASH-AMFDP award not only provides dedicated time for scholars to obtain academic and research appointments, but also fosters leaders within ASH and the hematology community at large. Formerly known as the Minority Medical Faculty Development Program, the AMFDP program was expanded in 2006 in honor of Harold Amos, PhD, the first African-American to chair a department, now the Department of Microbiology and Medical Genetics, at Harvard Medical School. Thirteen Active ASH members have been recipients of the award. They include Alexis Thompson, MD, MPH, currently an ASH Councillor, and Griffin Rodgers, MD, Director of the National Institute of Diabetes and Digestive and Kidney Diseases at NIH.

AMFDP Recipients	
Griffin Rodgers, MD	1983
David Diuguid, MD	1985
José Lopez, MD	1985
Arturo Molina, MD	1986
Felipe Samaniego, MD	1987
Faith Young, MD	1987
Betty Pace, MD	1990
Alexis Thompson, MD, MPH	1992
Richard Lopez, MD	1994
Michael DeBaun, MD, MPH	1995
Olubunmi O. Afonja, MD	1999
Kenneth Cooke, MD	2000
Andrew Campbell, MD	2005
J. Anthony Graves, MD, PhD	2009
ASH-AMFDP Recipients	
Christopher Flowers, MD, MS	2007
Seth Rivera, MD, PhD	2008
Alejandro Gutierrez, MD	2009
Alison Walker, MD	2010
Adrienne Phillips, MD, MPH	2011

Current and past AMFDP Scholars gathered at the Promoting Minorities in Hematology reception during the 2010 ASH Annual Meeting in Orlando, FL. Pictured left to right: Back Row: Christopher Flowers, MD, MS (2007); José López, MD (1985); James Gavin, III, MD, PhD (AMFDP Director); Andrew Campbell, MD (2005); David Diuguid, MD (1985); J. Anthony Graves, MD, PhD (2009); Arturo Molina, MD, MS (1986). Front Row: Nina Ardery (AMFDP Deputy Director); Alexis Thompson, MD, MPH (1992); Adrienne Phillips, MD, MPH (2011).

As an MMFDP alumnus, I am honored to be chairing the Committee on Promoting Diversity that oversees this program in addition to the other programs under the Society's Minority Recruitment Initiative. This partnership is a testament to the Society's commitment to increase the diversity of scholars in the field of hematology.

Alejandro Gutierrez, MD, received the award in 2009 and is excited for the work yet to come. "During the remaining years of my award, I hope to translate my findings into novel therapeutic strategies leading to clinical trials in patients with relapsed or high-risk T-cell acute lymphoblastic leukemia, which I hope will improve outcomes for this subgroup of patients. Outcomes are poor with currently available therapy," he said.

This year's ASH-AMFDP Award application deadline is March 16. Interested applicants should visit the ASH website, *www.hematology.org/awards*, to learn more and to apply online.

The ASH Scholar Award: Just the Beginning

DAVID MOTTO, MD, PhD

Assistant Professor of Internal Medicine and Pediatrics, Division of Hematology, Oncology, and Blood & Marrow Transplantation, University of Iowa

The day I received the e-mail informing me that I was a recipient of the 2005 ASH Scholar Awards for fellows is fondly and forever etched in my memory. At the time, I was a postdoctoral fellow in David Ginsburg's laboratory at the University of Michigan. We were just about to begin the practice session for our upcoming platform presentations at the ASH annual meeting, which was in San Diego that year, and just around the corner. I quickly printed the critiques, went downstairs to the conference room, and read them with a big smile on my face as everyone filtered in and got their lunches. That was quite literally the very first time I had read anything positive about my postdoctoral research project, which had already been underway for three years.

At the Ginsburg laboratory, researchers study the physiology and genetics of blood clotting disorders, with a long-standing focus on von Willebrand Factor (VWF). Just prior to my arrival, Gallia Levy had identified the gene responsible for the familial form of thrombotic thrombocytopenic purpura (TTP) as *ADAMTS13*, which encoded a protease responsible for the proper processing of VWF in the plasma. This was a major breakthrough in the field, and it became my project to develop a mouse model for this important human disease. Although I was ultimately successful (with the help of many others), this project proved to be much more difficult than merely "knocking out" ADAMTS13 in mice.

We and other colleagues have since used this model to investigate the pathophysiology of TTP and have identified a number of environmental triggers and genetic modifying factors for this disease, including a previously unknown pathogenic link between TTP and the clinically similar thrombotic microangiopathy hemolytic-uremic syndrome (HUS). Now at the University of Iowa, my laboratory continues to study the pathophysiology of thrombotic microangiopathies, focusing on the roles that VWF, complement, and the endothelium play in these disorders. More recently we have developed new techniques to visualize and investigate in detail the clot formation and endothelial damage that occur as a result of thrombotic disorders.

Thinking back to my clinical pediatric hematology/oncology fellowship at Michigan, I realize that I was extremely fortunate to have been trained by many outstanding physician-scientists, including three former ASH Scholars. However, it was from my most influential clinical mentor, Dr. Larry Boxer, that I acquired my interest in rare and intriguing hematologic disorders. So it is with great pleasure that I have been able to incorporate these clinical interests into my research program. Regarding my postdoctoral mentoring, I could not have been more fortunate to have trained in David Ginsburg's laboratory. I would choose to do so again without hesitation, which definitely is not the case with many of the other decisions I made since then.

I remain thoroughly committed to a career in academic hematology medicine and research, in very large part due to the mentorship of ASH members like David and Larry and to the recognition and funding from sources like the ASH Scholar Awards. I remain especially proud of my first Scholar Award, and I was fortunate to receive a second Scholar Award after starting my lab at Iowa. Apart from the many obvious tangible benefits, these awards also enabled me to become more involved with the Society, which I have been privileged to serve in a number of ways, including: writing for the first year of *ASH News Daily*, speaking in the Education Program, co-chairing oral abstract sessions, reviewing abstracts for the annual meeting, and serving on the study sections for the Research Training Award for Fellows, the EHA-ASH Research Exchange Award, and, most recently, the Scholar Award study section.

I am extremely grateful for everything that the American Society of Hematology has given to me and my career. It will be my great pleasure to continue to serve within the Society, and I hope to have a positive impact on young ASH members. I look forward to the day when one of my own trainees may receive an ASH Scholar Award of his or her own.

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THE HEMATOLOGIST ADVOCATE

NIH Plans to Dissolve NCRR and Create New Center for Translational Science

The NIH Scientific Management Review Board issued recommendations to dissolve the National Center for Research Resources (NCRR) and create a new National Center for Advancing Translational Science (NCATS). This decision follows the Obama Administration's growing concern with the slowing rate of new drug development by the pharmaceutical industry. With the rising costs for developing and marketing new drugs, the industry's research productivity has been slowing for the last decade. According to NIH Director Francis Collins, the new Center will help attract the pharmaceutical industry's attention by doing some of the exploratory and "discovery" research that was previously done by the industry within the NIH structure.

The proposed reassignments include:

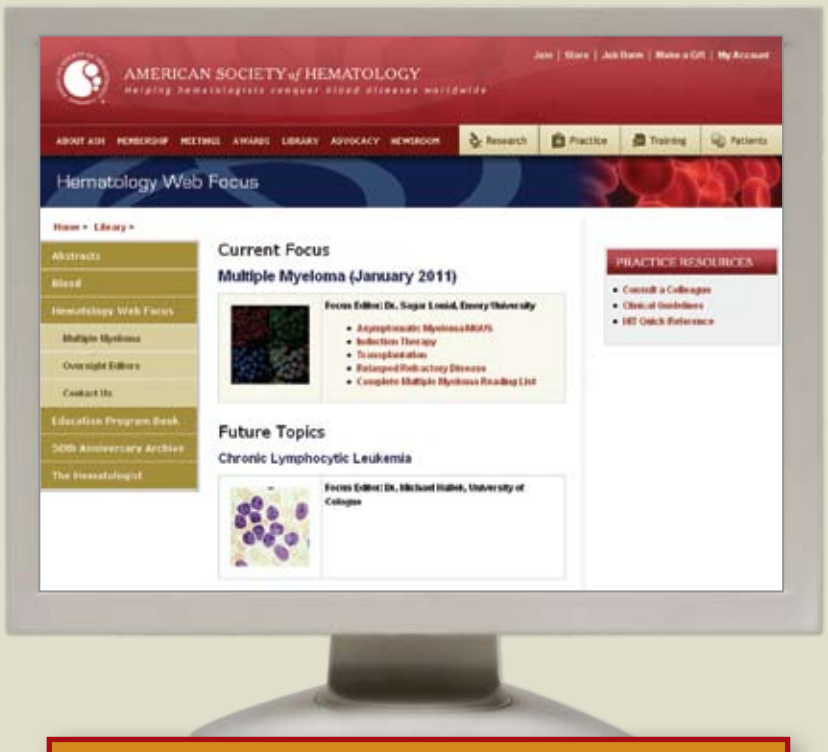
1. The Clinical and Translational Research Awards (CTSA) program would be transferred to NCATS.
2. Non-primate model organism programs, beam line and mass spectrometry P41 grants, Shared Instrumentation Grants, and High-End Instrumentation grants would be transferred to National Institute of General Medical Sciences (NIGMS).
3. Imaging P41 grants would be transferred to the National Institute of Biomedical Imaging and Bioengineering (NIBIB).
4. The Research Centers in Minority Institutions (RCMI) program would be transferred to the National Institute on Minority Health and Health Disparities (NIMHD).
5. Primate model organism programs, remaining P41 grants, other biomedical technology programs, Institutional Development Awards, Science Education Partnership Awards, and Construction would be transferred to an interim infrastructure unit within the Office of the Director (OD).

NIH Wants Your Opinion

The NIH has created a "straw model" of the proposed reassignments of current NCRR programs and is seeking comments from the public regarding the proposed changes. To view the NIH site and/or comment, visit *http://feedback.nih.gov.*

WHAT'S ON THE WEB

Early in 2011, ASH launched **Hematology Web Focus**, an online **resource for clinicians** to help keep them apprised of the latest **treatments options** for their patients. Each Web Focus provides a **concise overview** of a hematologic disorder written by an expert in the field, with convenient **links to timely, relevant articles** that serve as a reference for developing effective treatment strategies. This resource is **free to ASH members and *Blood* subscribers**.



The **first Web Focus, on Multiple Myeloma**, covers the following topics, each with its own **reading list**:

- Asymptomatic Myeloma/MGUS
- Induction Therapy
- Transplantation
- Relapsed/Refractory Disease

Future Web Focus topics will include Acute Lymphocytic Leukemia, Chronic Lymphocytic Leukemia, and von Willebrand Disease.

Visit *www.hematologywebfocus.org* for more information, to log in, and to begin using this resource today. If you have any questions, please contact 866-828-1231. International callers dial +1-202-776-0544.

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

March

18 – 20 **The 2nd International Hematologic Malignancies Conference "Bridging the Gap 2011"**
Singapore City, Singapore *www.asiapacifichematology.org*

23 – 26 **7th Annual Conference of the Hematology/Oncology Pharmacy Association**
Salt Lake City, UT *www.hoparx.org*

April

2 – 3 **Highlights of ASH® China**
Beijing, China *www.hematology.org*

2 – 6 **102nd Annual Meeting of the American Association for Cancer Research**
Orlando, FL *www.aacr.org*

4 – 6 **51st Annual Scientific Meeting of the British Society for Haematology**
Brighton, United Kingdom *www.bshconferences.co.uk*

7 – 9 **Internal Medicine 2011**
San Diego, CA *www.acponline.org/meetings*

7 – 10 **Stem Cell Engineering & Cell-Based Therapies Meeting**
Cold Spring Harbor, NY *http://meetings.cshl.edu/meetings/celleng11.shtml*

13 – 16 **24th Annual Meeting of the American Society of Pediatric Hematology/Oncology**
Baltimore, MD *www.aspho.org*

14 – 16 **10th International European Bone Marrow Working Group Course on Bone Marrow Pathology**
London, United Kingdom *https://sites.google.com/site/bonemarrowcourse/home*

15 **Deadline to Obtain CME Credit for 52nd ASH Annual Meeting**
Washington, DC *www.hematology.org*

29 – 30 **Highlights of ASH® Latin America**
Punta del Este, Uruguay *www.hematology.org*

May

6 – 8 **XXIVth International Symposium on Technological Innovations in Laboratory Hematology**
New Orleans, LA *www.islh.org*

18 – 21 **11th International Symposium on Myelodysplastic Syndromes**
Edinburgh, United Kingdom *www2.kenes.com/mds/Pages/Home.aspx*

18 – 21 **14th Annual Meeting of the American Society of Gene & Cell Therapy**
Seattle, WA *www.asgt.org*

18 – 21 **17th International Society for Cellular Therapy Annual Meeting**
Rotterdam, Netherlands *www.celltherapysociety.org*

June

1 – 4 **American Society for Apheresis 2011 Annual Meeting**
Scottsdale, AZ *www.apheresis.org*

3 – 7 **Annual Meeting of the American Society of Clinical Oncology**
Chicago, IL *www.asco.org*

9 – 12 **16th Congress of the European Hematology Association**
London, United Kingdom *www.ehaweb.org*

15 – 18 **9th Annual Meeting of the International Society for Stem Cell Research**
Toronto, Canada *www.isscr.org*