Newly Redesigned ASH Website Offers Improved Search Capability and Access to Most-Viewed Content

If you have visited the ASH website in the past few weeks you may have noticed some significant changes. A new site design was launched on April 4 as part of a multi-year effort to upgrade the Society’s technology platforms. ASH President Linda J. Burns, MD, explained, “The ASH leadership felt the time had come to invest in a strategy that will better serve the Society’s membership by bringing ASH’s digital offerings in closer alignment with member needs.” These offerings include not only the Society’s website, but also mobile apps, e-books, and other forms of electronic communication.

The first step in the process entailed months of research to better understand why ASH’s key audiences visit the website, the specific tasks they are trying to accomplish, and how successful they are. “By using software to track where users tend to click most often throughout ASH’s website, we learned that many of the navigational headings designed to help users find information quickly were not being utilized,” said Michael Mersky, ASH’s Web Manager. “So we employed a number of user testing exercises to find out what terms our users would choose to name and find on the website.

To better understand why ASH’s key audiences visit the website, the specific tasks they are trying to accomplish, and how successful they are, the Society employed a number of user testing exercises. These included user research, which involved software that tracked where users tend to click most often throughout ASH’s website. The research revealed that many of the navigational headings designed to help users find information quickly were not being utilized. By using this information, ASH’s Web Manager, Michael Mersky, was able to identify areas for improvement and make changes to the website to better serve the Society’s membership.

A Hereditary Bleeding Disorder Reveals a New Cog in the Coagulation Mechanism

What is the differential diagnosis in a 35-year-old male with a lifelong history of easy bruising, epistaxis, and prolongation of both the prothrombin time (PT) and the activated partial thromboplastin time (APTT)? So began the evaluation by Dr. Shao-Qing Kuang et al. in the laboratory of Dr. Dianna Milewicz at the University of Texas Health Science Center in Houston, Texas. The family history revealed an autosomal bleeding disorder in an east Texas kindred consisting of 46 family members spanning four generations. Surprisingly, coagulation factor assays for fibrinogen and factors II, V, VII, VIII, IX, X, XI, and XII were normal. Linkage analysis demonstrated that the factor V (FV) gene (F5) mapped to the disease interval. Sequencing of the F5 gene revealed an A2440G mutation in exon 13 at position 2440, predicting a βS66G mutation in the B domain of FV. However, because FV levels were normal, the mutation was considered an unlikely cause of the bleeding diathesis.

The cause of this mysterious bleeding disorder remained unknown for more than another decade until it was elucidated by Dr. Lisa Vincent and colleagues from the laboratories of Dr. Milewicz in Houston and Dr. Björn Dahlbäck of Lund University Hospital in Malmö, Sweden. The authors began by looking for abnormalities in the plasma FV in the kindred by Western blotting. Full-length FV is 330 kDa procofactor that is proteolytically activated by thrombin or factor Xa. During this process, the large, central B domain is removed (Figure). The product, FVα, is a heavy chain/light chain heterodimer that is a cofactor for factor Xa in the prothrombinase complex. Analysis of 36 family members revealed that in addition to full-length FV, plasma from affected family members contained a prominent 250 kDa variant, which they named FV-short. FV-short was also identified in much smaller amounts in unaffected family members.

RT-PCR analysis of whole blood from affected family members using primers spanning exon 13 identified an expected 2946 bp product and, additionally, large amounts of a smaller 840 bp product. The 840 bp fragment was also found in unaffected family members but, as with FV-short protein, in much smaller amounts. Sequencing of the 840 bp product revealed that the F5 gene variant produces an in-frame deletion of 2,106 base pairs, resulting in the deletion of nearly 85 percent of the B domain (Figure).

A thrombin generation assay was used as a potentially more sensitive method to detect abnormalities in the tissue factor-initiated extrinsic coagulation pathway in the kindred. Despite having normal coagulation factor levels, all affected family members demonstrated decreased thrombin generation. The addition of recombinant FV-short to immunodepleted FV-deficient plasma resulted in normal thrombin generation, indicating that the abnormality was not due to an intrinsic procoagulant defect in FV-short per se. However, addition of affected plasma to unaffected plasma resulted in decreased thrombin generation, revealing the presence of a coagulation inhibitor in affected plasma.

To identify the inhibitor, the authors took advantage of the recent discovery by Dr. Connie Duckers et al. that FV binds to tissue factor pathway inhibitor α (TFPIα). This finding was a result of the clinical observation that patients with severe FV deficiency often only have a mild bleeding disorder. This finding suggests that FV deficiency produces a secondary deficiency of a coagulation inhibitor with which it is associated. Dr. Duckers et al. made the key observation that plasma levels of TFPIα, a candidate coagulation inhibitor, is decreased in FV deficient individuals. They then demonstrated that TFPIα binds FV in a purified system.

These observations led Dr. Vincent et al. to the hypothesis that the inhibitor in affected family members is TFPIα and that the greater inhibitor activity must be a consequence of the high concentration of FV-short. The addition of anti-TFPIα antibodies to affected plasma increased thrombin generation to normal levels, indicating that TFPIα is the culprit producing the coagulant abnormality in the kindred. Furthermore, addition of anti-TFPIα antibodies to affected plasma removed FV-short, but not full-length FV, suggesting a stronger association of TFPIα with FV-short. This interpretation was confirmed by a semi-quantitative immunoprecipitation assay showing that TFPIα binds with higher affinity to FV-short than to full-length FV. The authors also found that TFPIα levels are increased several-fold in affected

(Cont. on page 2)
Training the Next Generation

As a fellowship program director for the past 18 years, I marvel at the changes that have been introduced into the training environment. From managing mandated reductions in duty hours of fellows to documentation of competency measures, it seems those of us in the educational space have not had a moment’s rest!

I’m proud of the Society’s long history of partnering with medical educators in hematology to advance scholarship in our subspecialty by tackling head-on the challenges we’ve all had to face. From practical approaches such as training guidelines, to advocating for evidence-based medical education, to creation of tools for educators, to awarding of grants to trainees, ASH has stood by those of us on the front lines of our medical schools and teaching hospitals. Several new initiatives aim to continue this tradition:

1. As has been reported in this publication, in ASH NewsLink, and on the ASH website, the Committee on Training, chaired by Gary Schuller, MD, is interested in developing an ASH Medical Educators Institute. This program, modeled on ASH’s Clinical Research Training Institute, will provide guidance to dedicated hematology educators who are aiming both to improve individual teaching skills and to enhance learning opportunities at their home institution. The committee and I would be interested in your thoughts on crafting this program and count on your enthusiastic volunteerism in making this new initiative a success.

2. A working group, organized by the Committee on Training and led by Elaine Muchmore, MD, is in the process of developing milestones for fellows in hematology training programs. Creation of these milestones is a critical element necessary to meet the requirements of the Accreditation Council for Graduate Medical Education’s Next Accreditation System (ACGME NAS). For those of you who have yet to hear of this sweeping new program, NAS began phase implementation in July 2013 and represents the culmination of a multi-year process of restructuring ACGME’s accreditation system based on educational outcomes in clinical competency.

3. The Teaching Cases Subcommittee, which has responsibility for developing and maintaining the ever-popular medical student cases on the ASH website, has been diligently developing new cases and researching new approaches to make the cases more interactive and engaging. This program is strongly supported by the Society as evidenced by its prominent place on the agenda of the upcoming ASH Executive Committee Meeting.

4. Last spring, the Society launched the Fundamentals for Hematology Fellows Program that provides a bundle of ASH resources to fellows in hematology-related training programs. This initiative has exceeded our expectations by adding more than 1,000 additional fellows to our Associate member category. The program not only provides a connection from ASH to the trainee, but also makes participants eligible for ASH programs such as the Clinical Research Training Institute.

These new efforts join a panoply of continuing programs, including the Research Training Award for Fellows, annual meeting events such as the Hematology Course Directors’ Workshop, and services such as the Hematology In-Service Examination, designed to address hematology training from the perspective of the learner, the educator, and the training environment. I hope every educator in hematology knows about these programs and uses them to their best advantage. Please contact training@hematology.org with any questions about ASH’s educational programs.

Our goal at ASH is to enthusiastically support medical educators in hematology and, together with this dedicated group, to continue improving training in our subspecialty by developing new initiatives and sustaining ongoing programs that focus on the needs of faculty and fellows.

Linda J. Burns, MD

A Hereditary Bleeding Disorder Reveals a New Cog in the Coagulation Mechanism

(Cont. from page 1)

plasmas compared with unaffected plasmas. They proposed that free, 40 kDa TFPIx is cleared by kidneys, and that this clearance is prevented when TFPI is bound in a high-molecular-weight complex with FV or FV-short. Thus, the increased association of TFPIx with FV-short leads to higher plasma levels.

The authors speculated that the normal levels of FV and other coagulation factors in affected plasmas are due to the strong procoagulant stimulus in coagulation assays (tissue factor in the PT and activated partial thromboplastin in the APTT). Accordingly, the rapid production of high concentrations of Factor Vila and Factor Xa would overwhelm TFPIx, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhelm TFPI, even when its concentration is elevated in affected plasmas. In contrast, thrombin generation assays were prevented when TFPIx would overwhel...

An A2440G mutation in exon 13 of the F5 gene results in increased usage of an alternative splice-donor site, leading to production of a previously undetected protein, FV-short. Alternative splicing and expression of FV-short also occurs in the absence of the mutation, albeit to a lesser extent. TFPIx binds to full-length FV and FV-short, but with higher affinity to the latter. The association of TFPIx with FV-short reduces the clearance of TFPIx by preventing renal filtration. The resulting increase in TFPIx produces a bleeding diathesis due to an increased inhibition of Factor Vila and Factor Xa. The results of this study have identified an important new mechanisms underlying FV and TFPIx biology in the regulation of coagulation.

The Hematologist: ASH News and Reports

2014 ASH Annual Meeting and Exposition

December 6-9
Moscone Center, San Francisco, CA

The American Society of Hematology (ASH) invites you to save the date for the 56th ASH Annual Meeting in San Francisco, CA. As the premier hematology event, this meeting will provide attendees with an invaluable educational experience and the opportunity to:

- Review more than 3,000 scientific abstracts.
- Interact with the global community of more than 20,000 hematology professionals from every subspecialty.
- Attend the Education and Scientific Program sessions that feature lectures by leaders in the field.
- Develop collaborations with clinical and basic investigators who share your research interests.
- Share the experience with friends and colleagues in a collegial, stimulating atmosphere in one of America’s great cities.

Key Dates

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<th>Event</th>
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<td>Abstract submission site opens</td>
<td>June 5</td>
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<tr>
<td>Advance member registration &amp; housing</td>
<td>July 24</td>
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<tr>
<td>Advance registration for non-members</td>
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Register to Attend the New ASH Meeting on Lymphoma Biology

August 10-13, 2014
The Broadmoor, Colorado Springs, Colorado

Get a comprehensive update on the most recent discoveries in lymphoma biology and interact with world-class experts in the field. During this three-day forum, keynote speaker Klaus Rajewsky, MD, will discuss immune regulation and cancer, and attendees will hear about the most recent progress in basic and translational lymphoma research, share their findings with colleagues, and exchange ideas with experts on how to move the field forward.

What to Expect

- Informal setting with networking opportunities to share ideas and establish collaborations
- Presentations by invited experts on topics including:
  - B-cell receptor signaling
  - Germinal center biology
  - Epigenetics of lymphoma
  - Immune evasion
  - Lymphoma genetics
  - Metabolism
  - T-cell lymphoma
  - Panel discussions
- Oral presentations of the top-rated abstracts
- Poster sessions and interactive workshops

For more information about the meeting and to register, go to www.hematology.org/Lymphoma-Biology.

ASH and ASCO Present New Seminar on Hematology for the Oncologist

ASH is partnering with the American Society of Clinical Oncology (ASCO) to present a Hematology for the Oncologist symposium, May 29-30, 2014, in Chicago, IL, as part of ASCO’s Pre-Annual Meeting Seminars. Lectures will focus on hematologic issues that medical oncologists commonly encounter in a consultative practice. Experts in the field will discuss clinical aspects of bleeding and clotting disorders, novel oral anticoagulants, iron replacement therapy, and other benign hematology topics. Question-and-answer periods will be incorporated into the sessions to encourage discussion and ensure maximum interaction between faculty and participants.

To learn more about the symposium, go to http://am.asco.org/hematology-oncologist-seminar.
Ask the Hematologist

JANET L. ABRAM, MD
Professor of Medicine, Harvard Medical School; Division of Adult Palliative Care, Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute

The Case

The patient is a 54-year-old woman with IgA lambda multiple myeloma, receiving dexamethasone, lenalidomide, and bortezomib therapy. She was healthy before her diagnosis but had mild hypercalcemia and mild renal insufficiency at diagnosis, both of which have resolved with treatment.

She is about to begin her third treatment cycle, but reports painful (pain score of 7/10) numbness and paresthesias in her fingers and feet. The former problem causes clumsiness when using her touch-screen tablet and phone because she cannot accurately feel her fingers touch the screens, and she needs the light on at night because she cannot reliably feel when her feet touch the floor. Her Zubrod (eCoG) performance status is 1. She has had similar, but less severe, symptoms at the beginning of her last chemotherapy cycle, but she did not mention them to anyone for fear that treatment would be delayed or discontinued.

During her exam, she was anxious, alert, and oriented. She denied both spine pain and bowel or bladder incontinence. Her exam was unremarkable except for the neurologic examination. She had impaired proprioception, decreased vibration and light touch in her hands to the wrists and feet to the ankles, 4/5 hand grip and finger strength bilaterally, and 4/5 ankle strength. Her ankle deep tendon reflexes (DTRs) were absent (flaccid).

Laboratory studies showed normal potassium, BUN, creatinine, glucose, calcium, and magnesium. B12 concentration and thyroid function studies were normal. Her paraprotein concentration showed a continuing decrease in response to treatment.

The Question

What is your approach to assessment and management of patients with chemotherapy-induced peripheral neuropathy?

My Response

Presentation/Physical Findings

The patient’s presentation is typical of chemotherapy-induced peripheral neuropathy (CIPN) that is characterized by tingling (71%), numbness (58%), and paresthesias or dysesthesias (45%), or spontaneous burning, cramping, or aching pain (40%) that is usually symmetric, begins peripherally and progresses proximally. Patients often report dysesthesias (45%), or spontaneous burning, cramping, or aching pain (40%) that is caused by a mild to painful stimulus. The mechanisms of axonal nerve injury vary by agent and include damage to mitochondria (bortezomib, platinum compounds, vincristine, paclitaxel), glial cells and macrophages (bortezomib, oxaliplatin, vincristine, paclitaxel), vasa vasorum (thalidomide, paclitaxel), endoplasmic reticulum (bortezomib), or microtubules (bortezomib, taxanes, and vinca alkaloids).

CIPN induced by vinca alkaloids causes numbness, not pain, and loss of DTRs, proprioception, and motor impairment, such as foot drop. Patients receiving thalidomide, bortezomib, or platinum have a mainly sensory neuropathy, which may include loss of vibration, proprioception, and DTRs. Taxanes cause both a sensory neuropathy and proximal weakness. Only CIPN induced by thalidomide is irreversible.

Evaluation

In a patient whose CIPN appears only after chemotherapy, the evaluation should include laboratory testing for B12 deficiency, hypothyroidism, hypocalcemia, hypomagnesemia, and hyperglycemia (Figure 1). Because patients with leptomeningeal carcinomatosis or venous sinus thrombosis may have CIPN, the evaluation should include imaging of the brain and spinal cord. Neurovascular imaging and/or intravenous contrast is helpful in identifying alternative diagnoses. The patient’s neurologic examination and history should be reviewed for evidence of other diagnoses that may cause CIPN, such as leptomeningeal carcinomatosis or venous sinus thrombosis. The patient’s clinical history should be reviewed for evidence of other diagnoses that may cause CIPN, such as leptomeningeal carcinomatosis or venous sinus thrombosis.

Diagnosis of CIPN is clinical, and nerve conduction studies, EMGs, and skin biopsies are not needed for diagnosis or management. Chemotherapy doses are generally adjusted for patients with grade 3 or greater neuropathy based on NCI common terminology criteria (CTC) for adverse events.

NCCI-CTC for Neuropathy

Peripheral Sensory Neuropathy

Grade 1: Asymptomatic or loss of deep tendon reflexes or paresthesia

Grade 2: Moderate symptoms limiting instrumental activities of daily living (ADL)

Grade 3: Severe symptoms limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death

Peripheral Motor Neuropathy

Grade 1: Asymptomatic clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate symptoms limiting instrumental ADL

Grade 3: Severe symptoms limiting self-care ADL, assistive device indicated

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death

The patient under discussion had grade 2 sensory neuropathy by these criteria, which underestimated her disability and functional losses. The NCCI-CTC are not as sensitive to patient-reported symptoms or functional loss as are some other scoring systems, but no consensus has yet been reached on a standard for grading neurotoxicity.

Quality-of-life scales may be more relevant (e.g., the CIPN 20 or FACT/GOG-Ntx).

Treatment

Dose reduction or drug discontinuation is the only specific therapy for most CIPNs; patients may tolerate higher doses of bortezomib if the drug is given by a subcutaneous injection rather than by IV infusion. Symptomatic therapies for CIPN are limited (Figure 1). Of the adjuvant agents effective for patients with neuropathic pain, only duloxetine (30-60 mg/day) has clearly shown efficacy for the CIPN induced by taxanes and platinum.

Despite the lack of proven efficacy of other agents in CIPN, insurance companies usually require that patients first fail a trial of gabapentin or pregabalin before authorizing duloxetine. Occupational therapy or physical therapy is recommended for patients with a grade 2 sensory or motor toxicity to improve function and quality of life. Patients should also be assessed for depression, which often accompanies uncontrolled chronic pain.

While vitamin E, vitamin B6, magnesium, calcium, acetyl-L-carnitine, glutamine, glutathione, n-acetyl cysteine, omega-3 fatty acids, alpha lipoic acid, and cannabinoids each have shown efficacy in non-randomized, non-placebo-controlled trials, none can be recommended yet as standard therapy.

Amitriptyline does not prevent or ameliorate chemotherapy-induced neuropathy from vinca alkaloids, platins, or taxanes. Venlafaxine, gabapentin, the N-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan, the oral anesthetics mentamine and mexiletine, and low-dose continuous capsaicin treatment are also ineffective.

Opioids are recommended for CIPN patients with severe pain. Patients will usually require a long-acting agent to provide basal pain relief (e.g., sustained-release morphine or a fentanyl patch) and short-acting opioids for breakthroughs. Methadone (Figure 2) is particularly helpful for basal pain relief. Methadone includes d- and l-isomers that act as opioid-receptor agonists and NMDA receptor antagonists. Because NMDA antagonizes the activity of the opiate receptors, blocking NMDA receptors enhances the analgesic effect of externally administered opioids. Methadone also inhibits the reuptake of serotonin and norepinephrine; therefore, it functions as a serotonin-norepinephrine reuptake inhibitor (SNRI).

Methadone is usually given orally laid to tid. Dose adjustment is needed for hepatic failure but not for renal failure. The steady state is not reached until 72 hours after the initial dose or after a dose increase. Therefore, short-acting opioids should be used to control symptoms in the interim. If pain level falls below 3 within the first 24 to 48 hours of initiating methadone, reduce the dose by half immediately to avoid excessive sedation and respiratory depression that may otherwise occur in the next 24 hours. This delay in reaching steady-state plasma levels, along with potential cardiac toxicity (prolongation of the rate corrected QT [QTC] interval) and its interactions with inducers and inhibitors of the cytochrome P450 system, CYP1A2, CYP3A4, and CYP2D6, make using methadone safely somewhat complex. Palliative care specialists can be helpful in managing initiation or adjustment of methadone doses or for consulting on patients with seemingly refractory pain syndromes.
Evidence-Based Algorithm for Evaluation and Symptomatic Treatment of Patients with CIPN

Patients who, at baseline, have a prolonged QTc interval, or who need high doses of methadone, have developed cardiac arrhythmias (torsades de pointes; polymorphic ventricular tachycardia). Fatalities have been reported but were associated with doses of >600 mg per day. Common drugs used in hematology patients that also prolong the QTc include the quinolone antibiotics (especially levofloxacin), typical and atypical antipsychotics (such as haloperidol and olanzapine), selective serotonin reuptake inhibitors (SSRIs) (but not SNRIs), and metoclopramide.

Methadone’s drug interactions are listed on websites including www.drugs.com or www.qtdrug.org. Fluconazole, voriconazole, fluoxetine, and fluvoxamine raise methadone levels. Drug levels of desipramine (or other tricyclic antidepressants) (e.g., venlafaxine) do not. Additionally, grapefruit juice and acute alcohol ingestion can increase methadone levels. SSRIs may raise methadone levels in CyP2D6 rapid metabolizers but SNRIs do not. Additionally, methadone increases the levels of methadone and have precipitated withdrawal symptoms.


To safely prescribe methadone, monitor the QTc. If the QTc is prolonged, correct contributing metabolic abnormalities or discontinue agents that can prolong the QTc. If the patient requires concomitant therapy with a CYP3A4 inhibitor (such as voriconazole), use lower doses of methadone. See text for other agents that require adjustments of methadone doses. Increase methadone doses no more than every 72 hours.

Conclusion
The patient continued therapy, but bortezomib delivery was switched from IV infusion to SQ injection. Her pain symptoms fell to tolerable levels on 2 mg tid of methadone such that breakthrough pain was controlled and she was able to work, and her functional level was further enhanced by participation in an occupational therapy program.

CIPN can be a disabling complication of chemotherapy. Patient education that encourages reporting relevant symptoms, chemotherapy dose adjustment, occupational therapy, physical therapy, and symptomatic therapy using duloxetine and opioids, including methadone, can often help patients maintain or regain function and minimize pain and disability.

First, exclude spinal or leptomeningeal metastases and pleocystathies and correct vitamin or hormone abnormalities, if present. For patients who have NCI-CTC grade ≥ 3 CIPN, follow standard protocol guidelines for dose adjustments of ant-neoplastic agents. Use duloxetine for patients with unacceptable pain levels who are receiving other platinum or taxanes. For refractory pain, add an opioid. If standard opioids are not effective, or if they cause excessive sedation, myoclonus, or other side effects, consider using methadone as the “basal” opioid, and use the standard opioids for breakthrough pain.

*Despite the lack of proven efficacy, insurance companies may require that patients first fail a trial of gabapentin or probabidin before authorizing duloxetine.

www.drugs.com

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www.drugs.com
categorize various pieces of Web content, and we used those findings to develop a more intuitive navigational scheme.”

Along with the upcoming Blood website redesign, more changes will be introduced in the coming months, as standalone sites such as the ASH Academy, an eLearning platform for hematologists, are brought into alignment with the look and feel of the new website. In addition, both the functionality of the ASH Store and the account management section of the ASH website will be enhanced throughout 2014. In the meantime, please visit Hematology.org to explore the new design. We encourage you to share your feedback by emailing webmaster@hematology.org.

ASH staff will continue to engage in ongoing user testing to refine the website user experience. ASH members who are interested in being part of this process are encouraged to email webmaster@hematology.org to sign up for the Website Users Group. Members of this informal group will be invited to act as beta testers and to provide feedback prior to the rollout of new website features.

(Cont. from page 1)

Newly Redesigned ASH Website

Website organized around most-accessed resources – The site has been reorganized to showcase the content that is most popular with users. This content includes Blood, educational resources such as clinical practice guidelines, and information about ASH’s upcoming meetings, which are now front and center.

Top 5 Website Changes You Should Know About:

➔ Improved Search – Not only has ASH invested in a state-of-the-art search engine that provides far superior results compared with the previous search function, but users are now able to search across all ASH websites without leaving Hematology.org. In addition, users will see suggestions for related searches when the item they search for is not found.

➔ Enhanced viewing of The Hematologist online – Readers will now be able to quickly get to their favorite sections and view collections of articles written by specific authors.

➔ Responsive Design – The new website design adjusts automatically for optimal viewing from smartphones and tablet devices.

➔ Consistent Navigation – Later in 2014, all auxiliary ASH websites will have a consistent navigational structure for a more unified experience across sites.

➔ Website Organized Around Most-Accessed Resources – The site has been reorganized to showcase the content that is most popular with users. This content includes Blood, educational resources such as clinical practice guidelines, and information about ASH’s upcoming meetings, which are now front and center.

Consistent navigation – Later in 2014, all auxiliary ASH websites will have a consistent navigational structure for a more unified experience across sites.
Congress Moves Forward with FY 2015 Budget Process

In early March, President Obama kicked off the fiscal year (FY) budget and appropriations process with the release of his FY 2015 budget proposal. While noting that “biomedical research contributes to improving the health of the American people,” the President’s proposed budget seeks $310.2 billion for the National Institutes of Health (NIH), a slight increase over the amount provided for NIH in the final FY 2014 budget passed by Congress in January. The proposed budget requests small increases in funding for all of the Institutes of interest to hematology, including NHLBI, NCI, and NIDDK and estimates that this proposed increase in funding “would support about 650 additional new grants” NIH-wide.

It is important to remember that the President’s nonbinding budget proposal merely sets forth the Administration’s priorities and is just one step in a lengthy federal budget process. Announced a month later than expected, and after the House and Senate had already established FY 2015 spending blueprints, the President’s budget begins a new round of congressional negotiations on annual spending bills. Obama Administration representatives have begun to testify before Congress on the President’s proposals, and the House and Senate Appropriations Committees are in the midst of drafting legislation establishing actual federal spending levels for FY 2015.

As the FY 2015 budget process continues, lawmakers need to understand the impact that unplanned funding shortages will have on federal medical programs. These cuts in funding should be encouraged to acknowledge the value of biomedical research by maintaining the nation’s investment in NIH. Visit the ASH Advocacy Center (www.hematology.org/Advocacy) to read the latest news on NIH funding and to send a message in support of research funding to your elected officials.

ASH Provides Hematologists with Resources to Prepare for ICD-10 Conversion

On October 1, 2015, all health-care business transactions in the United States must convert from the use of the ninth version of the International Classification of Disease (ICD-9) to the 10th version (ICD-10). This change entails a complete restructuring of the diagnosis codes used by hematologists every day. The transition will take place on a single day, so there will not be any time to try the new diagnosis codes. ASH will be helping members to prepare for this transition, primarily by giving examples of the changes in hateology diagnosis coding. Twice a month, a new disease category will be released, comparing the ICD-10 codes with those in ICD-9. This review will provide clinicians with real examples so that they can understand the effect of the changes on their individual practices. Visit www.hematology.org/ICD10 to learn more about the ASH resources. If you have any questions about the implementation of ICD-10 or ASH’s resources, please contact Brian Whitman, ASH’s Senior Manager for Policy and Practice, at bwhitman@hematology.org or 202-776-0544.

General Accountability Office Releases Report on Drug Shortages

In February, the General Accountability Office (GAO) issued a report titled, “Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability,” which was called for in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. The report points to the combination of production lapses due to quality concerns and constrained manufacturing capacity as being the main cause of the large number of drug shortages experienced by the hematology community over the last several years. Encouragingly, the report states that the FDA has made progress over the past two years in preventing shortages by improving its recognition of and responsiveness to impending supply chain disruptions. GAO recommends that FDA further strengthen internal controls over data gathering that can alert the agency to a potential drug shortage and conduct periodic analyses to systematically assess drug shortage information so as to proactively identify drug shortage risk factors. Visit ASH’s drug shortage information page (www.hematology.org/DrugShortages) to access information about current hematologic drug shortages and to learn about ASH’s advocacy efforts and resources for physicians dealing with shortages.

ASH Committee on Government Affairs Takes to Capitol Hill to Discuss Research Funding

In April, while Congress was beginning the FY 2015 budget process in earnest, the ASH Committee on Government Affairs conducted a Hill Day to discuss with congressional offices the importance of biomedical research and the need to protect NIH from funding cuts. These meetings with Congress are an important component of ASH’s advocacy efforts, providing an opportunity for Members of Congress and their staff to gain insight into issues of concern to hematologists. However, the Society needs the help of all members to bring issues important to the future of hematology to the attention of the U.S. Congress and other governmental agencies.

ASH strongly encourages members to let the Government Relations, Practice, and Scientific Affairs staff know when you are in Washington, DC, and available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard in the halls of Congress. You can also participate in the Society’s advocacy efforts by visiting the ASH Advocacy Center and by joining the ASH Grassroots Network. Contact ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org, or visit www.hematology.org/Advocacy for additional information on ASH’s advocacy efforts.

Update on the 2013 ASH Choosing Wisely Initiative

LISA K. HICKS, MD, MS:
Staff Hematologist, St. Michael’s Hospital; Assistant Professor, University of Toronto; Chair of the Choosing Wisely Task Force

Choosing Wisely is an initiative led by the ABIM Foundation in partnership with professional societies across the country (www.choosingwisely.org). This medical stewardship campaign aims to encourage physicians and patients to question the necessity of common medical tests and treatments. ASH released its first Choosing Wisely list at the ASH annual meeting in December 2013, and the full list and methodology that was used to develop the recommendations are available at www.hematology.org/choosingwisely. In brief, the ASH Choosing Wisely campaign suggests the following: 1) use the minimum number of red blood cell transfusion units to treat symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dl in stable, non-cardiac inpatients); 2) do not perform thrombophilia testing in patients with a provoked venous thromboembolic event (VTE); 3) do not use inferior vena cava (IVC) filters in the routine management of patients with a VTE; 4) do not use plasma to reverse the activity of vitamin K antagonists in non-emergency situations; and 5) limit CT surveillance for aggressive lymphoma in asymptomatic patients in complete remission.

After the release of the ASH Choosing Wisely List, the ASH Choosing Wisely Task Force was inundated with feedback from ASH members. The vast majority of feedback was positive and two major themes emerged. First, many members told us they want tools that will aid them in sharing the ASH Choosing Wisely message with their home institutions through teaching and continuing education sessions. In an effort to meet this request, ASH has developed a public-access Choosing Wisely slide deck. The slide deck summarizes the list, identifies the underlying evidence, and describes the methodology used to generate each of the ASH Choosing Wisely recommendations. The slide deck is available at www.hematology.org/choosingwisely. We encourage all members to use it, and pass it on. ASH is also developing a Choosing Wisely pocket guide that will be available on the same Web page.

In addition to requests for tools to help disseminate the Choosing Wisely message, the Task Force received numerous emails suggesting that ASH produce a second Choosing Wisely list. In collaboration with the ABIM Foundation, ASH has already started working on a second list. Similar to the first ASH list, the second will be evidence-based and will prioritize tests and treatments that have limited benefit but a recognized risk of harm; the Task Force is aiming to release the second list at the annual meeting in December.

The Choosing Wisely Campaign has a formal partnership with Consumer Reports and other consumer groups to both facilitate outreach to patients and direct dissemination to consumers. ASH has been working with Consumer Reports to produce an article geared toward patients, focusing on ASH’s recommendation to avoid routine use of IVC filters. We anticipate that this resource will be available in mid 2014. It will be posted on both the ASH Choosing Wisely landing page, (www.hematology.org/choosingwisely) and at www.consumerreports.org.

The future challenges for the ASH Choosing Wisely Task Force are effective implementation and measurement of outcomes of the recommendations. How can we encourage the implementation of Choosing Wisely recommendations, and how can we determine if Choosing Wisely recommendations are leading to beneficial changes in patient care? These two related objectives are likely to be the most exacting aspects of this project. As yet, we on the ASH Choosing Wisely Task Force don’t have the answers to these questions, but we look forward to updating ASH membership as we tackle these issues.
Time to Retire the Old IMID Mechanism of Action Slide


(Original data: Published in this paper were presented in abstract form by Dr. Krönke at the Late-Breaking Abstract Session during the 2013 ASH annual meeting in New Orleans.)

The publication of thalidomide’s remarkable and unanticipated anti-myeloma activity in 1999 heralded the anti-cancer successes of its more potent analogs, lenalidomide and pomalidomide, over this past decade. The reemergence of these therapeutics, known as immunomodulatory drugs (IMiDs), as effective treatment for myeloma and other hematologic malignancies is a bookend to thalidomide’s tragic beginnings, which are inexorably linked to phocomelic infants born to women who took the drug to mitigate emesis gravidarum. How thalidomide’s teratogenicity interdigitates with its biologic activity in various malignancies has been a focus of intense investigation for more than 20 years. Early illustrations depicting the mechanism of action of thalidomide and lenalidomide highlighted autocrine and paracrine interactions between myeloma cells and stromal cells of the surrounding marrow microenvironment. An array of imaginative artistic techniques were used to propose mechanisms of action that involve anti-angiogenic and immunomodulatory pathways, induction of oxidative stress, and modulation of cytokines, including down-regulation of tumor necrosis factor-α and up-regulation of interleukin-2, which stimulates T-cell production (Figure 1).

The first major breakthrough in understanding the mechanism of action of thalidomide and its derivatives occurred when thalidomide was shown to bind to cereblon, a critical component of an E3 ubiquitin ligase complex (Figure 2). This report tied the teratogenic effects of thalidomide to inhibition of ubiquitination and toxic accumulation of proteins that led to cell death. In the current reports published in Science, two independent groups have identified targets of lenalidomide that account for its therapeutic effect in multiple myeloma. Dr. Gang Lu and colleagues from the laboratory of Dr. Benjamin Ebert, Cancer Institute, Boston, MA, and Dr. Jan Krönke and colleagues from the laboratory of Dr. Benjamin Ebert, Brigham and Women’s Hospital, Boston, MA, report that treatment with lenalidomide, and other agents in the treatment of del (5q) MDS, it is unclear how these two targets is sufficient to induce cytotoxicity. Notably, Dr. Lu and colleagues observed resistance to lenalidomide-induced cytotoxicity in a number of myeloma cell lines. This unresponsiveness appears to be the result of low-level expression of cereblon in the resistant cells, supporting the concept that the cytotoxic effects of lenalidomide are cereblon-dependent through its action on expression of IKZF1 and IKZF3 (Figure 2).

A number of other purported mechanisms for lenalidomide’s activity in multiple myeloma have been reported, including down-regulation of expression of interferon regulatory factor 4 (IRF4) and up-regulation of expression of interleukin-2 (IL-2). The authors of both papers tied the decrease in IRF4 to the decrease of IKZF1 and IKZF3 induced by lenalidomide, while Dr. Krönke et al. demonstrated a marked decrease in IKZF1 and IKZF3 protein levels in T cells treated with lenalidomide that was accompanied by a coincident increase in IL-2 expression. Based on these observations, it appears that these previously reported effects of lenalidomide (IRF4 down-regulation and IL-2 up-regulation) are downstream effects of a lenalidomide-induced decrease in IKZF1 and IKZF3 (Figure 2).

Selective inhibition of transcription factors, molecules otherwise considered undruggable, represents a novel therapeutic paradigm that has emerged from the story of the relationship between IMiDs, cereblon, and IKZF1/IKZF3. Data derived from these studies also provide a foundation for exploring these interactions to design new therapeutics and to develop strategies for overcoming resistance to IMiDs. However, important issues remain unexplained. The finding that the activity of IMiDs relies on targeting transcription factors for proteasomal degradation seems incongruous with the highly effective clinical response observed when IMiDs are combined with proteasomal inhibitors in the treatment of patients with myeloma. This paradox, and the contrasting roles of Ikaros transcription factors in different disease contexts (e.g., as tumor suppressors in acute lymphocytic leukemia, and as anti-neoplastic targets in myeloma), require better understanding. Further, while several mechanisms of action have been proposed to account for the therapeutic activity of lenalidomide in the treatment of del (5q) MDS, it is unclear whether targeted ubiquitination and destruction of specific transcription factors underlies the efficacy of lenalidomide in this disease.


Unlocking the Mysteries of AITL

Although angioimmunoblastic T-cell lymphoma (AITL) is a rare disease, it is one of the more common subtypes of peripheral T-cell lymphoma in the Western world. Patients typically present with advanced-stage disease and systemic symptoms, and associated autoimmune manifestations of the disease are common. Histologically, AITL is characterized by a proliferation of malignant T cells in a mixed background of polyclonal plasma cells, eosinophils, histiocytes, and B cells, often harboring the Epstein-Barr virus (EBV). In an expanded network of follicular dendritic cells with increased numbers of high endothelial venules. The pathogenesis of the disease is poorly understood and recurrent genetic abnormalities have not been systematically characterized. Using targeted exon capture and next-generation sequencing, Dr. Orofie Odejide and colleagues in the laboratory of Dr. David Weinstock at Dana-Farber Cancer Institute in Boston examined a panel of 219 genes that were identified as mutated in other hematologic malignancies and correlated the findings with demographic and clinical data in 85 cases of AITL (Figure).

The median overall survival for patients was 18 months and was significantly inferior in patients over the age of 70. Mutations were identified in the coding regions of 80 genes, 34 of which were altered in two or more cases. The genetic changes did not differ according to the presence of EBV. Mutations in TET2 were present in 65 patients (76%), and 43 of 65 harbored two or three mutations in that gene. Twenty-eight patients (33%) had alterations in TP53, of which 15 also harbored TET2 mutations (Figure). Notably, alterations in TET2 and DNMT3A, which function as epigenetic modifiers of DNA, and in IDH2, a mitochondrial enzyme that when mutated produces the presumed oncometabolite 2-hydroxyglutarate, are commonly found in myeloid neoplasms, and in contrast to many other lymphoid malignancies, alterations in TP53 were identified in only four cases. Given recent evidence suggesting that mutations in TET2 or DNMT3A may be derived from CD34+ progenitor cells, the investigators examined cellular subsets from a peripheral blood stem cell collection from a patient with AITL in remission whose tumor cells had been shown to harbor a TET2 mutation. That mutation was identified only in the lineage-negative CD34+ fraction of cells and not in the patient’s CD34+ positive cells or in cells with an immunophenotype similar to that of the patient’s AITL cells. The authors used the same experimental design to characterize the origin of the mutant cells in a patient with histology that overlapped AITL and peripheral T-cell lymphoma. In contrast to the prior case in which the mutation arose in a lineage-negative subpopulation, mutations in this case were acquired within lineage-committed progenitors. Additional investigation is needed to understand the origins of AITL.

The prognosis of AITL is poor. The optimal management of the disease has not been well defined, and outcomes following anthracycline-based chemotherapy are dismal. Although a small minority of patients will achieve long-term disease control following stem cell transplantation, the vast majority of patients die of progressive disease. The work of Dr. Odejide and colleagues, identifying recurrent and overlapping mutations in TET2, DNMT3A, and IDH2, as well as recent reports demonstrating frequent alterations in RHOA, a small GTPase that regulates diverse biologic processes, raise the exciting possibility of novel therapeutic approaches in this disease. Studying drugs that work through epigenetic control over transcription, as well as investigating the efficacy of inhibitors of IDH2, may provide critically needed advances in the management of AITL.


Distribution of mutations in 85 cases of AITL. Common mutations and demographic and clinical factors across the cohort are shown. Each column represents a single patient. IPI = International Prognostic Index; ECOG PS = European Cooperative Oncology Group Performance Status.


ANN LACASCE, MD, MSc
Dr. LaCasce indicated no relevant conflicts of interest.
The Fate of Hematopoietic Nuclei: Major Roles for Lamins Before and After Marrow Release

Marrow hematopoietic cells comprise a semi-solid tissue that differentiates into various mature cell types that then populate the peripheral blood, a fluid tissue. The transition from marrow to blood requires that the mature blood cells acquire viscoelastic properties that allow them to pass through apertures as small as three microns as they traverse capillaries and narrow fenestrations in the marrow vascular endothelium, in the splenic red pulp, and in lymph nodes. Now, in an elegant series of experiments, Dr. Jae-Won Shin and colleagues in Dr. Dennis Discher’s laboratory at the University of Pennsylvania demonstrate that, depending upon hematopoietic lineage, expression of nuclear lamins plays differing roles in determining both the fate of hematopoietic progenitor cells and the viscoelastic properties of mature nucleated blood cells.

The two most common A-type lamins, lamin-A and lamin-C, are alternatively spliced products of one gene, while the two B-type lamins, B1 and B2, are products of separate genes. The lamin proteins form a mesh-like network, progenitor cells and the viscoelastic properties of mature nucleated blood cells. The two most common A-type lamins, lamin-A and lamin-C, are alternatively spliced products of one gene, while the two B-type lamins, B1 and B2, are products of separate genes. The lamin proteins form a mesh-like network, progenitor cells and the viscoelastic properties of mature nucleated blood cells.

Dr. Shin and colleagues used mass spectrometry-calibrated intracellular flow cytometry to determine amounts and ratios of A-type and B-type lamins in normal human marrow and in nucleated blood cells. Using data from such analyses, the investigators developed a method for distinguishing early-stage hematopoietic cells from their mature progeny by plotting the content of A-type and B-type lamins versus the ratio of A-type:B-type lamins (Figure). In other experiments, they perturbed expression of lamins in hematopoietic progenitors using specific interfering RNAs or transcription factors. These interactions can influence gene expression, nuclear shape, and nuclear deformability. Mutant A-type lamins are associated with myopathies, neuropathies, and progeria. In murine models, germ-line mutations in B-type lamins result in death early in embryogenesis, while mutant membrane receptors for B-type lamins are associated with progressive lamination.

In humans, mutations in B-type lamin receptors cause the hyposegmentation of neutrophils that characterizes the Polger-Huet anomaly.

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In humans, mutations in B-type lamin receptors cause the hyposegmentation of neutrophils that characterizes the Polger-Huet anomaly.

Megakaryocytes contained the most total lamins, which increased with increasing ploidy, whereas the erythroid cells had the highest A-type:B-type lamin ratio, which increased with differentiation. The high lamin content of megakaryocytes and the nuclear rigidity associated with the high lamin A:A lamin B ratio in erythroblasts make these marrow cell types least likely to migrate through the marrow vascular endothelium as they are the laminae that produce anucleate blood cells through proplatelet formation in the case of megakaryocytes and undergo nuclear extrusion prior to entering the circulation in the case of erythroblasts. Altered expression of A-type and B-type lamins also affected the differentiation of myeloid progenitor cells that increased lamin A-expression and/or decreased lamin B-expression enhanced erythroid progenitor development but decreased granulocyte-monocyte progenitor growth. Lamin A overexpression was also associated with increased megakaryocytic differentiation, while decreased lamin A-expression inhibited erythroid progenitor differentiation and enhanced granulocyte-monocyte progenitor development.

With decreased lamin A:A lamin B ratios compared with erythroid nuclei and decreased lamin amounts compared with megakaryocytic nuclei, lymphocytic and myeloid nuclei had greater nuclear deformability, consistent with the distribution of the mature nucleated cells in bone. During differentiation, the lamin A:A lamin B ratio increased in granulocytic-monocytic cells, but their total lamin content decreased. Nuclear lamins, granulocytic monocytes as well as lymphocytes readily migrated through three micron pores to simulate transcytosis across capillary endothelium.

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Dr. Shin and colleagues demonstrated a role for nuclear lamin A in both differentiation of marrow hematopoietic cells, and in the nuclear flexibility required by mature nucleated blood cells to enter and remain in circulation. These results suggest that increased lamin A content contributes both to the loss of circulating lymphocytes in lamin A receptor-deficient mice and to the impaired chemotactic migration associated with the Polger-Huet anomaly that is a consequence of mutant lamin B receptors in humans.

The findings also suggest mechanisms that could account for the leukostasis observed in acute leukemias with high numbers of circulating blasts. The hypothesis in this case is that nuclei of the leukemic blast are more rigid than nuclei of normal mature granulocytic-monocytic cells. Further, although nuclear rigidity may contribute to the development of microvascular occlusions that complicate sickle cell anemia.


Dr. Johnson indicates no relevant conflicts of interest.
Elastics compression stockings (ECSs) and intermittent pneumatic compression (IPC) devices have been used in a variety of medical settings, usually with the goal of restoring or maintaining normal venous return from the legs. Two recent publications provide important evidence about the effectiveness of these modalities in two different settings.

The first study was a double-blinded, randomized, controlled trial of graduated ECSs (30 to 40 mm Hg at the ankle) versus placebo stockings (<5 mm Hg compression at the ankle). The trial was designed to test the hypothesis that ECSs reduce the risk of post-thrombotic syndrome (PTS), a chronic complication of arm or leg deep-vein thrombosis (DVT). At 24 different North American centers, the “SOX” investigators enrolled 806 patients (mean age 55 years; 60% men) with a first, proximal DVT. Patients were included only if they 1) had a life expectancy > 6 months, 2) did not receive up-front thrombolytic therapy, and 3) had no contraindication to compression stockings. One year after randomization, the proportion of patients with PTS (as defined by validated, pre-specified scoring systems) was 14 percent in the ECS arm and 13 percent in the “placebo stockings” arm. Similarly, overall quality of life (as measured by the SF-36 questionnaire) was not statistically different between the two groups.

The second study was an unblinded, primary, VTE prevention trial, involving 2,876 patients (mean age 55 years; 59% women) from 199 centers in the United Kingdom who were both hospitalized for acute stroke (ischemic or hemorrhagic) and immobile. Patients in the CLOTS 3 trial were randomly assigned to receive either bilateral thigh-length IPC (n=1438) or no IPC (n=1438). Individuals with subarachnoid hemorrhage or leg problems (e.g., skin ulcers or severe edema) were excluded. Sequential compression was continued in the intervention group for 30 days or until the patient became independently mobile, was discharged, declined further use, or had adverse events. All outcomes were evaluated 30 days after enrollment. The primary outcome (symptomatic or asymptomatic proximal DVT) occurred less commonly in the group assigned to IPC (9.6% vs. 14%; p=0.001). Symptomatic DVT, a key secondary endpoint, also occurred less frequently in the intervention group (4.6% vs. 6.3%; p=0.045). The rate of pulmonary embolism was not statistically different between the groups, but the numeric trend favored IPC (2.0% vs. 2.4%; p=0.453). IPC increased skin breaks (3.1% vs. 1.4%; p=0.002). A strong, but statistically non-significant, trend toward lower 30-day mortality favored the IPC group (22 vs. 25%, p=0.057).

Much can be learned from these two important prospective trials. The SOX trial is probably practice-changing. Until now, VTE experts have recommended that most patients with proximal leg DVT wear ECSs (30–40 mm Hg at the ankle) because two previous studies had indicated that ECS use could decrease the risk of PTS by 50 percent. However, neither of these often cited studies was blinded. The PTS score, which is the key outcome measure of all these trials, depends heavily on subjective assessments by both clinicians and patients; thus the possibility of bias in unblinded comparisons is significant. By using “placebo” stockings in the comparator arm, the SOX investigators eliminated this kind of bias and found no benefit from ECSs. More evidence is needed about how we might reduce the risk of PTS before it occurs. While ECSs may still be worth trying as a palliative measure in the 10 to 15 percent of patients who develop moderate to severe PTS, the SOX trial suggests we will need to look beyond ECSs if we hope to prevent PTS in the first place.

The CLOTS-3 trial is by far the largest and most rigorously designed study that shows that IPC devices can substantially reduce the risk of VTE in a non-surgical population of hospitalized patients. Hematologists are often asked to comment on the risks and benefits of VTE prevention. For some populations (e.g., patients admitted for acute leukemia or hematopoietic cell transplantation), pharmacologic modalities are less costly than compression stockings and allow for easier patient mobility, thereby reducing length of hospital stay. However, for patients with acute or subacute thromboembolic disease who do not have contraindications, the choice is clear that IPC devices are the preferred treatment for preventing PTS. More research is needed to determine how to best use IPC devices in the various settings in which they can be applied. The CLOTS-3 trial is by far the largest and most rigorously designed study that shows that IPC devices can substantially reduce the risk of VTE in a non-surgical population of hospitalized patients. Hematologists are often asked to comment on the risks and benefits of VTE prevention. For some populations (e.g., patients admitted for acute leukemia or hematopoietic cell transplantation), pharmacologic modalities are less costly than compression stockings and allow for easier patient mobility, thereby reducing length of hospital stay. However, for patients with acute or subacute thromboembolic disease who do not have contraindications, the choice is clear that IPC devices are the preferred treatment for preventing PTS. More research is needed to determine how to best use IPC devices in the various settings in which they can be applied.

Genome Forensics Reveal Origins and the Mechanism That Drives t(12;21) Childhood B-ALL


At times, one of the most fundamental issues in human biology have appeared inaccessible to direct experimental investigation and have consequently been relegated to study using model systems. The origin of childhood precursor-B cell acute lymphocytic leukemia (B-ALL) was included in that group until the discovery 15 years ago of the prenal origin of the t(12;21) translocation that generates the ETV6-RUNX1 fusion gene found in 25 percent of childhood ALL. In a succession of studies using blood samples from twin pairs, neonatal blood spots from archived Guthrie cards, and stored cord blood units, investigators showed that the ETV6-RUNX1 fusion gene developed in utero at an astonishing frequency of one percent. Clearly, 1 percent of children do not develop B-ALL. Thus, events acting in concert with t(12;21) are necessary for leukemogenesis.

During the Ham-Wasserman Lecture at the 2009 ASH annual meeting, Professor Mel Greaves, who had pioneered work in this area, made a compelling case for incorporating Darwinian evolutionary principles into a conceptual framework for understanding ALL leukemogenesis. But at the time, the genetic events underlying clonal evolution of ETV6-RUNX1 expressing cells were speculative. Was the process merely stochastic, or was it connected mechanistically to t(12;21)? The expanding use of genome-scale technology over the past several years only added to the confusion by identifying many seemingly random genetic abnormalities. Now, the current study, led by Prof. Greaves from the Institute for Cancer Research in London and by Professor Peter Campbell from the University of Cambridge, Cambridge, UK, reports identification of the mechanism that underlies clonal expansion in B-ALL expressing ETV6-RUNX1.

In their detailed genetic analyses, Dr. Papaemmanuil and colleagues studied samples from 57 ETV6-RUNX1 positive ALL patients. Using both exome and low-coverage whole-genome sequencing, they found an average of 11 somatically acquired structural variations per case, mostly deletions, with half being highly recurrent. Notably, deletions mostly affected genes involved in B-cell differentiation. When the authors analyzed the nucleotide sequence of the structural variants, they observed a striking frequency of recombination signal sequence (RSS) motifs spanning breakpoint junctions. This finding suggested that recombination-activating endonucleases (RAG)-1 and -2 were involved in creation of the structural variants. RAG-1 and -2 are essential components of the process involved in generating antibody and T-cell receptor diversity through mediation of V(D)J gene recombination. This process involves DNA cleavage and the addition of non-template nucleotide bases, which incidentally leaves a genomic fingerprint of RAG activity. The authors found that 40 percent of the analyzed structural variants had RAG recognition sequence (RSS) motifs and that 70 percent had inserted non-template sequence. Two other intriguing findings were the unexpectedly high incidence of structural variants that localized within promotor and enhancer regions, many of them coinciding with RSS motifs, and identification of mutations in two previously unrecognized tumor suppressor genes, ATIP7 and MGA. Interpreted as a whole, the mutational pattern suggests successive inactivation of genes that would otherwise promote differentiation, stalling the ETV6-RUNX1 expressing cells in a stage of early B-lineage differentiation. Sustained high RAG activity would then drive clonal evolution, converting a pre-leukemic cell into a malignant clone.

This rigorous study provides a detailed genetic fingerprint of ETV6-RUNX1 B-ALL, revealing RAG-mediated deletions as the driver of leukemogenesis. The contribution of this process to leukemogenesis in other subtypes of ALL will be the subject of future studies. The authors hope in understanding leukemic evolution is, of course, the possibility of translation of that understanding into development of effective treatment. Knowing the mechanisms at work, and the genomic fingerprints that signal progression to full-blown disease versus regression, might not only allow for development of targeted therapy, but perhaps suggest an approach to preemptive intervention. This study is also noteworthy for identification of novel immunosuppressor genes and for the interventional use of existing databases with innovative bioinformatics. The authors’ genome forensics focused on t(12;21) ALL, but their experimental design strategies may help gain insight into other pediatric and adult malignancies.

Lessons From the Liver: Rebalanced Hemostasis in Immune Thrombocytopenia


Immune thrombocytopenia (ITP) is another disorder in which a laboratory abnormality (low platelet count) does not necessarily predict the risk of bleeding, especially for the individual patient. A single focus on the platelet count in ITP can cause a clinician to make the treatment for ITP worse than the disease itself. Two childhood ITP patients with normal versus elevated von Willebrand factor (vWF) had elevated vWF antigen levels (218%, S.D. 104%) when adjusted for their blood group type. Thromboelastography parameters were within the normal range for most patients. A subgroup analysis compared patients with normal versus elevated vWF. Those with elevated vWF were older and had longer duration of ITP, the clot formation time (CFT) was shorter, and the angle between vWF and platelet function was increased. In general, the α-angle was larger in those with elevated vWF. The CFT and α-angle were sensitive to platelet number and function and fibrinogen level and polymerization. So, higher vWF levels were associated with better thrombosis and improved coagulation compared with low vWF, which had elevated vWF antigen levels (218%, S.D. 104%) when adjusted for their blood group type. Severe bleeding did not occur in any patient, but four patients had minor bleeding (3 in the normal vWF group).

The study by Dr. Kim and colleagues was small and many aspects of the hemostatic system were not measured, but they did document evidence for “rebalanced hemostasis” in ITP. The main finding was an association between high vWF antigen levels in ITP patients and improved thromboelastographic measurements that might account for a decreased tendency toward bleeding. Although these results are intriguing, they cannot yet be taken at face value. Hopefully, further research can more completely explain why some patients with ITP bleed and some do not. Possible explanations include the effects of the autoantibody on platelet function and a rebalancing of hemostasis analogous to that of liver disease. Whatever the answers, we clearly need better laboratory assessments to understand the global hemostatic consequences of ITP, which would also not. Possible explanations include the effects of the autoantibody on platelet function and a rebalancing of hemostasis analogous to that of liver disease. If interpreted in isolation, these laboratory abnormalities appear to indicate a tendency for the patient to bleed. Consequently, clinicians often transfuse blood products in an attempt to normalize these laboratory abnormalities, especially before invasive procedures. In recent years, there has been an increasing understanding of a “rebalancing” of the hemostatic system in liver disease, whereby hemostatic changes that promote bleeding can be counterbalanced by hemostatic changes that promote thrombosis. Thus, the platelet count, αPTT, and PT, although commonly ordered, fail to reflect the globally rebalanced hemostasis of liver disease, which can lead to unnecessary and possibly harmful treatments. Indeed, preoperative “correction” of these laboratory abnormalities does not necessarily reduce bleeding and may actually promote it.

Dr. Won Ho Kim and colleagues from Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, sought evidence for a rebalancing of hemostasis in ITP, a disorder that proposed for arguing purposes, which could explain the frequent disconnect between the platelet count and the occurrence of bleeding. They built upon prior observations that a global hemostatic change occurred despite treatment to raise the platelet count. One possible explanation could be that there are hemostatic differences beyond the platelet count that predispose to severe bleeding.

Another Reason to Eat More Apples and Whole Grain: How Inflammation and Hemopoiesis Are Affected by Dietary Fiber and GI Microbes


Dietary fiber changed the gut and lung microbiota by enhancing bacterial diversity, especially in the proportion of bacteroidaceae and bifidobacteriaceae, both potent fermenters of fiber into SCFAs. Both serum and oral acetate and propionate levels were higher in the high-fiber fed animals. To show that increased SCFAs mediate the protective effect of fiber against inflammation, mice were fed acetate or propionate. One day after mice were given an intranasal house mite challenge, inflammation was similar in control- and propionate-fed mice, but after two days, eosinophils and cytokine levels in the lung were reduced in SCFAs-treated mice. This protective effect was dependent on G-protein coupled receptor 41 (also called free fatty acid receptor 3). There was impaired Th2 differentiation and decreased dendritic cell (DC) activation in SCFAs-treated mice four days after the challenge. Other experiments showed that propionate enhanced hemopoiesis, increasing both common DCs and macrophage DCs in the bone marrow.

This study demonstrates the impact that dietary fermentable fibers have on the intestinal microbial milieu and influence the barrier functions of the bowel, and the effects on GVHD of interventions ranging from gut bacterial decontamination, to protective environments, to the addition of certain bacteria into the gut are the subjects of ongoing investigation. Prof. Burkitt’s hypothesis has proven prescient, and continued study of the relationship between dietary fiber intake, the intestinal microbiome, systemic immuno/inflammatory processes, and bone marrow function is warranted to further explore the wide spectrum of associated disease pathophysiology and to identify new therapeutic targets.

Not Just for GIST: A New FLT3 Inhibitor Active in Kinase Domain Mutated AML

STUDY TITLE: A Phase II Study of Crenolanib in Relapsed/Refractory Acute Myeloid Leukemia Patients With FLT3 Activating Mutations

CLINICAL TRIALS.GOV IDENTIFIER: NCT01657682

COORDINATOR: ArQ Pharmaceuticals LLC
PARTICIPATING CENTER: MD Anderson Cancer Center

ACCRUAL GOAL: 41

STUDY DESIGN: This is a phase II study of a new Fms-like tyrosine kinase 3 (FLT3) inhibitor (crenolanib) in relapsed or refractory acute myeloid leukemia (AML). The study includes two cohorts: one with relapsed/refractory AML without prior FLT3 tyrosine kinase inhibitor (TKI) treatment, and one with relapsed/refractory AML with prior FLT3 TKI treatment. The primary endpoints are response rate after the first 28-day cycle and at best response and safety. There is a stopping rule that will be applied if there is more than a 95 percent chance that the toxicity rate exceeds 30 percent, with toxicity defined as a grade 4 or greater non-hematologic adverse event. The secondary endpoints are duration of clinical response and progression-free and overall survival. Pharmacodynamic markers, including phospho-FLT3, will be assayed in blood and marrow blast samples, and pharmacokinetic studies will be performed to determine the relationship of drug concentration to response and toxicity. Patients in each cohort receive the same dose of crenolanib besylate (200 mg/m²/day) divided into three daily doses, preferably every eight hours, taken orally at least 30 minutes before or after a meal. Concurrent hydroxyurea (maximum 5 mg total daily dose for 14 days) is permitted during the first 28 days of study therapy.

RATIONAL: AML patients with FLT3 internal tandem duplications (ITD) have a poor prognosis. Several FLT3 TKIs have been studied in clinical trials, and the results have been disappointing to date because of lack of efficacy and treatment-related toxicity (Serce H et al. J Clin Oncol. 2013;31:3110-3118). Crenolanib was initially found to have activity against the imatinib-resistant PDGFRα-mutant kinases that drive gastrointestinal stromal tumors (GIST) (Henrich MC et al. Clin Cancer Res. 2012;18:4375-4384). In addition, it is not only a potent inhibitor of FLT-ITD, but it is also active against FLT3 with gain-of-function mutations in the tyrosine kinase domain (TKD), including D835H/Y.

COMMENT: About 30 percent of AML patients have FLT3-ITD mutations, and another 8 percent have FLT3-TKD mutations. Studies of sorafenib, one of the early TKIs tried in AML patients with FLT3-ITD, did not show appreciable benefit despite early reduction in blasts (Serce H et al. J Clin Oncol. 2013;31:3110-3118). This ultimate lack of efficacy was explained by near uniform development of drug resistance, by 72 days on average, attributed to platelet count recovery (defined as platelet count > 150 x 10^9/L or recovery to platelet count at the time heparin was initiated). The primary outcome is new symptomatic venous or arterial thromboembolism at day 30. Secondary endpoints include major bleeding and time to platelet count recovery. In addition to local testing, serum from all subjects will be analyzed for platelet activating antibodies in a central laboratory (McMaster Platelet Immunology Laboratory) using a serotonin release assay (SRA).

RATIONAL: Drugs licensed for the treatment of HIT (e.g., argatroban, danaparoid, lepirudin) are associated with important drawbacks, including parenteral administration, need for intensive laboratory monitoring, limited availability (in the case of danaparoid and lepirudin), high cost, and incomplete efficacy. These agents decrease thromboembolism by 50 to 65 percent but do not reduce HIT-associated amputations or mortality. Transitioning from argatroban to warfarin is challenging because of the effect of argatroban on the INR and added length of hospital stay.

Rivaroxaban for the Treatment of HIT: Hit or Miss?

STUDY TITLE: Rivaroxaban for Treatment of Patients with Suspected or Confirmed Heparin-Induced Thrombocytopenia

CLINICAL TRIALS.GOV IDENTIFIER: NCT01598168

SPONSOR AND COLLABORATOR: McMaster University

PARTICIPATING CENTERS: 7 medical centers in Canada

ACCRUAL GOAL: 200

STUDY DESIGN: This is a prospective, multicenter, single-arm cohort study (Linkins LA et al. J Thromb Thrombolysis. 2014. Epub ahead of print). The target population is adult patients with an intermediate or high clinical probability (4T score ≥ 4) of heparin-induced thrombocytopenia (HIT). Patients with mechanical heart valves, severe renal insufficiency (CrCl < 30 mL/min), or moderate or severe hepatic disease (Child-Pugh B and C) are excluded. All enrolled subjects are initially given 15 mg of rivaroxaban twice daily while awaiting the results of HIT laboratory testing. If laboratory testing is negative, rivaroxaban is discontinued. In patients who test positive for HIT, rivaroxaban is continued for 30 days. The dose is changed to 20 mg daily after 21 days in patients with thrombosis, and, in patients without thrombosis, the dose is changed at the time of platelet count recovery (defined as platelet count > 150 x 10^9/L or recovery to platelet count at the time heparin was initiated). The primary outcome is new symptomatic venous or arterial thromboembolism at day 30. Secondary endpoints include major bleeding and time to platelet count recovery. In addition to local testing, serum from all subjects will be analyzed for platelet activating antibodies in a central laboratory (McMaster Platelet Immunology Laboratory) using a serotonin release assay (SRA).

RATIONAL: Drugs licensed for the treatment of HIT (e.g., argatroban, danaparoid, lepirudin) are associated with important drawbacks, including parenteral administration, need for intensive laboratory monitoring, limited availability (in the case of danaparoid and lepirudin), high cost, and incomplete efficacy. These agents decrease thrombocytopenia by 50 to 65 percent but do not reduce HIT-associated amputations or mortality. Transitioning from argatroban to warfarin is challenging because of the effect of argatroban on the INR and added length of hospital stay.

Rivaroxaban, a direct inhibitor of free and clot-bound factor Xa, is a promising agent for the management of HIT that may overcome some of these limitations. It is administered orally as a fixed dose, is less costly than parenteral agents, does not require routine laboratory monitoring, does not cross-react with HIT antibodies in vitro (Wielenga JM et al. Br J Haematol. 2008;143:92-99), and has an established efficacy and safety profile in the management of other thromboembolic disorders.

COMMENT: There is an urgent need for novel therapeutics in HIT that improve upon the efficacy, safety, convenience, and cost-effectiveness of existing options. Whether one or more of the target-specific oral anticoagulants will be able to fill this niche is unknown. This study will provide valuable preliminary information, but, due to two important limitations in its design, will not definitively address the role of rivaroxaban in the management of HIT.

First, the study lacks a control group against which rivaroxaban may be compared. Ideally, patients would have been allocated to receive either rivaroxaban or an active comparator (e.g., argatroban). However, randomized controlled trials have proven difficult to conduct in HIT; only two such trials have been published. A trial of danaparoid versus dextran 70 was completed in the 1990s prior to the advent of approved agents (Chong BI et al. Thromb Haemost. 2001;86:1170-1175). A more recent trial of desirudin versus argatroban was terminated early due to poor accrual after only 16 subjects had enrolled (Boye SW et al. Am J Ther. 2011;18:14-22). Comparisons between the rivaroxaban cohort and the pivotal single-arm studies that led to approval of argatroban and lepirudin are unlikely to be meaningful because of differences in patient population, outcome assessment, and adjunctive care.

Second, it is likely that the majority of patients enrolled in the study will not have serologically confirmed HIT. In a recent meta-analysis, HIT was corroborated using a specific washed platelet assay (e.g., SRA) in only 23 percent of patients with suspected HIT and a 4T score ≥ 4 (Cuker A et al. Blood. 2012;120:4160-4167). Thus, it can be anticipated that 50 or fewer of the 200 subjects enrolled in the study will have “true” serologic HIT. Whether this number will be sufficient for meaningful assessment of rivaroxaban for the treatment of HIT remains to be determined.

The aforementioned limitations notwithstanding, this study represents an important step forward in the investigation of HIT. It places renewed focus on a potentially devastating orphan disease with limited treatment options and no new FDA-approved therapies since argatroban received licensure 14 years ago. Despite lack of a control arm, the quality of evidence obtained from this study will undoubtedly exceed that derived from retrospective analyses cited to support off-label use of fondaparinux and bivalirudin for HIT. If results are promising, this study should pave the way for an international, randomized, controlled trial to definitively address the role of rivaroxaban for treatment of HIT.

~ Adam Cuker, MD, MS

Dr. Cuker indicated no relevant conflicts of interest.
Hematology as a Journey

John W. Adamson, MD
Clinical Professor of Medicine, Hematology/Oncology, University of California, San Diego

Awed by the physician who removed my tonsils (probably unnecessarily), I have wanted to be a doctor since the age of three. Not that there weren’t doubts along the way, as years later as a student at the University of California, Berkeley, I envisioned the road (medical school, internship, residency) that I would have to travel to reach that goal. For a time, I considered following my father’s lead, but he, a high school English teacher, straightened me out. “Don’t be stupid!” he said. “Being a teacher is fine, but you can teach at whatever you do.” Of course, he was right, and in the end, I had it both ways, as I became a physician/teacher.

When it came time to apply to medical school in 1958, there were the usual options for someone growing up in California. Stanford, the University of California, San Francisco, the University of Southern California, and the newly minted University of California, Los Angeles (UCLA). For whatever reason (likely intuitive), I chose UCLA. This decision led to my first airplane ride when I moved from Berkeley to Los Angeles. The experience at UCLA was eye-opening. Most of the lectures were given by young faculty who were deeply invested in their own research, so, predictably, part of the lectures were given by young faculty who were deeply interested in their own research, so, predictably, part of the class complained about the emphasis on science and the others enjoyed the newness of it all.

As for internships, I didn’t apply very widely, and there wasn’t anything like today’s computerized system that “matches” applicants with a particular training program. Fortunately, I wound up at Seattle at the University of Washington where I found myself among a group of remarkable biomedical researchers including Earl Davie, Clem Finch, and the nephrologist Belding Scribner, who was pioneering hemodialysis as an approach to treating kidney failure. Toward the end of my second year of residency in 1964, I was asked if I would be interested in becoming a hematologist. I don’t know why, but someone had given my name to Clem, who was head of the Division of Hematology at the time, and he approached me personally. After some thought, I accepted the invitation and “short-tracked,” entering fellowship after two years as a resident. I reasoned that if I didn’t like hematology, I would complete my third year of internal medicine training and go into practice.

Fellowship programs were so much less formulaic then. I spent most of the first two years (1964-1966) in the lab and fell in love with it. I was assigned to help develop a new assay for the elusive erythropoietic stimulating factor (i.e., erythropoietin or Epo), and I plunged in. We started with a bioassay wasn’t sensitive enough to reliably measure Epo activity in normal serum, so we had to develop a new assay for the elusive erythropoietic stimulating factor. We never got there! Rather, we engaged in the study of subpopulations of hematopoietic cells. And through the team of James Till and Ernie McCulloch at the University of California Institute (OCI) in Toronto, I was exposed to novel concepts in the new world of experimental hematology. Till and McCulloch had made seminal observations about the nature and function of stem cells and about clonality and clonal evolution. Ermie was very supportive, and I had the opportunity to visit the OCI on several occasions at a time when colony-forming assays were being developed.

When my time at NIH was up, Bob Petersdorf, chair of Medicine at Washington, offered me the opportunity to return, and I joined the faculty in 1969. I now had new tools to apply to the lines of investigation that had been started earlier. My work in the lab in Seattle linked two areas: the clonal nature of the myeloproliferative neoplasms (in collaboration with Phil Fialkow) and the potential value of Epo as a therapeutic agent (in collaboration with my close friend, Joe Eachbach). These two areas, along with ongoing studies of iron physiology led by Clem, dominated the next 20 years of my academic life in Seattle. Joe Mitchell joined the lab early on and became a good friend. It was an exciting time.

Joe and I had developed a large animal model of renal failure and convincingly demonstrated that plasma that was rich in Epo could reverse the accompanying anemia. As a result, scientists from Amedgen, then a small startup company, contacted us to see if their recombinant human Epo would work in our animal model. We never got there! Rather, we quickly initiated the first clinical trials of Epo, in which we assessed response in transfusion-dependent patients on dialysis; it was amazing to see something work so well!

To extend our work on clonal disorders, we developed a model of G6-PD heterozygosity in the cat—a model that Jan Ahlkowitz, then a fellow and currently ASH’s immediate past president—exploited brilliantly. Ken Kaushansky, also a fellow at the time, introduced molecular biology to the division in studies of hematopoietic growth factors, their receptors, and their biology. Ken’s work in this area culminated in his cloning and expression of the gene that encodes thrombopoietin (Tpo), Epo’s little sister.

My years in Seattle were interrupted by another important event—a year on sabbatical with (now) Sir David Weatherall at Oxford. The Weath lab was studying the regulation of globin chain synthesis in an attempt to better understand the pathophysiology of hemoglobinopathies. While I probably disappointed David in how little I accomplished, I became equally interested in and watching really good minds in action in a resource-restricted environment was revelatory. Through that experience, I made many friends and adopted a view of the world that I don’t believe I would have had it not been for the experience of living outside of the United States. I also came to love football, as it’s defined on the rest of the planet.

In 1989, I accepted a new challenge, moving to New York City and the New York Blood Center with a goal of expanding the research programs there. Fortunately, a very talented husband-and-wife team of scientists, Anna Rita and Giovanni Migliaccio, accompanied me, and they sustained and grew the laboratory by encouraging and supporting the work of visiting fellows and attendees. New York was a challenge, but very exciting.

In 1998, I was recruited to the Blood Research Institute of the Blood Center of Wisconsin in Milwaukee, which Dick Aster had led for many years. The Institute was home to a group of extremely bright scientists including Dick, Peter Newman, Bob Montgomery, and Hardy Wieser. My time at the Blood Center provided one of the best experiences of my life, and with the support of the scientists and the Institute’s Board, we were able to recruit a number of outstanding young investigators who have gone on to success in their own right.

The final move, in 2007, completed the circle, bringing me back to California and to the University of California, San Diego (UCSD), where I rejoined Ken Kaushansky. At that time, Ken was chair of the Department of Medicine and (with some irony) my ultimate boss. The move to UCSF was in support of my wife’s career, and she now heads the Center for Hemophilia and Thrombosis here. With Sandy Shattil’s support, I try to do what I can for people (especially the fellows) that there is such a thing as benign hematology and that the study of blood should be a passion, not a pothole on the road to board certification.

As I look back, I don’t have enough fingers and toes to count all the good things that have happened to me, starting with Clem, my most influential mentor. Through hematology, I have had the opportunity to meet countless people brighter than me and to work with outstanding fellows and young scientists both here and abroad. And ASH became, and remains, an enormous part of my life.

Hematology has been a marvelous journey, and I count myself most fortunate to have been able to make the trip.
Thoughts From a Former Protégé
KENNETH KAUSHANSKY, MD
Senior Vice President for Health Sciences, Dean of School of Medicine, Stony Brook University

In 1996, Hillary Clinton penned the book It Takes a Village to Raise a Child, based on an ancient African parable. I have often hijacked that title to claim, “It takes a village to raise a physician-scientist.” While I do believe that most successful physician-scientists can name multiple mentors, there is almost always, as John puts it, “a most important mentor.” Most scholarly articles on mentorship list at least six roles a successful mentor fills: teacher, sponsor, advisor, agent, role model, and confidante. Most would also agree that the successful mentor does not have the role of cloning oneself, but rather, he/she should be an astute enough listener to help the protégé pursue their own dreams — a seventh role. There is little doubt that John Adamson is my most important mentor, as he was able to fulfill each of these roles. It is no wonder that he was the 2013 recipient of the ASH Mentor Award.

John taught me how to pen a scientific paper. When he revised and then handed back to me my very first scientific manuscript, I noticed he weighed out twice what it had when I handed it to him a few days earlier: the weight difference, of course, being that of the red ink. “Not bad for an author for whom English is a second language,” he quipped. But the weight of the red ink became less and less as time went on, as I learned not only science from John, but also how to communicate science. One of the criteria he said was essential was that I “should not be afraid to make a mistake.” I proudly pronounced that, despite not knowing which end of the pipette to use, I wanted to become a hematologic molecular biologist.

John was a terrific sponsor; he made sure I had ample protected time for research, suggesting that purifying hematopoietic growth factors would help achieve my career goals and introducing me to another mentor, Earl Davie, who greatly enhanced my scientific toolbox. John has served as a primary advisor and academic confidante throughout my career, epitomizing the principle that mentorship does not end when the student leaves the lab. John was also a terrific agent. Shortly after we cloned human GM-CSF, John was invited to present his work on erythropoietin at a Gordon Research Conference (GRC). He suggested to the meeting organizers that I present in his place. It was my very first GRC. And John epitomizes the quintessential role model, constantly exuding scientific integrity, service to one’s community, and excellence in clinical care, educational endeavors, and scholarship.

Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The citations are provided to readers both with a concise description of the thrust of the article and an explanation of why the paper is particularly important. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

MARCH 13, 2014

Both vascular inflammation and activation of coagulation contribute to the pathogenesis of sickle cell disease. In this study, Sparkenbaugh and colleagues used a mouse model of sickle cell disease (SCD) to demonstrate that inhibition of FXa with rivaroxaban and inhibition of thrombin with dabigatran decrease lung neutrophil infiltration, and that rivaroxaban, but not dabigatran, decreases IL-6 levels. These observations could translate into development of novel therapies aimed at ameliorating the clinical manifestations of SCD.


Hunter and colleagues report a major advance in our understanding of the genetic underpinnings of Waldenström’s macroglobulinemia (WM). They performed whole-genome sequencing on samples from 30 WM patients and subsequently validated findings of copy number alterations and somatic mutations in CXCR4 in independent cohorts of 147 and 30 WM patients. The most striking findings were the identification of somatic mutations in MYD88 in 90 percent of patients (including the L265P activating mutation), in CXCR4 in 27 percent, and in ARID1A in 17 percent. Notably, the somatic CXCR4 mutations identified in this study included those observed in patients with the warts, hyogammaglobulinemia, and myelokathexis (WHIM) syndrome that had previously been reported only in the germ line. These findings, in addition to other recurring mutations identified in this study, contribute to a more complete understanding of the pathogenesis of WM.

MARCH 6, 2014


Recently, recurrent somatic calreticulin (CALR) insertion/deletion mutations were discovered in the majority of patients with essential thrombocythemia and primary myelofibrosis in which neither JAK2 nor MPL was somatically mutated. In two independent studies, Rumi et al. and Rotunno et al. demonstrated that essential thrombocythemia patients with CALR mutations exhibit lower leukocyte and hemoglobin values, higher platelet counts, and a lower thrombosis risk as compared with patients with essential thrombocythemia with mutant

JA2K. These observations suggest that CALR-mutated essential thrombocythemia is a distinct entity with a more indolent natural history.

FEBRUARY 27, 2014

The prevalence of monoclonal B-cell lymphocytosis (MBL) in the general population ranges from 1 percent to 18 percent depending upon the detection method and population tested. Although a precursor to chronic lymphocytic leukemia, few people with MBL go on to develop clinically overt disease. In this study and article, Shim and colleagues report the surprising observation that 7.1 percent of healthy blood donors have MBL. Most patients had “low-count” MBL (≤ 1,000 cells/μL), but a small number had clinical MBL (> 5,000 cells/μL). Although the risk of engraftment of these premalignant cells is low, the current findings raise questions about the need to screen for MBL in donated blood. At the very least, study of the outcomes of transfusion of MBL-containing units is warranted.

FEBRUARY 20, 2014

In murine model systems, Notch appears to be a pivotal signaling molecule that promotes the maintenance of “stemness” and expansion of self-renewing HSCs. And human CD34+ cells expand in vitro in response to Notch signals. In the current study, Benveniste and colleagues address whether Notch directly affects all hematopoietic stem cells (HSCs) and whether this role is relevant in vivo. The results clarify essential effects of Notch signaling on human HSC maintenance and expansion, and reconcile discrepancies in the literature about the role of Notch signaling in HSC homeostasis. Their findings support the concept that Notch signals maintain human HSCs in vitro that have hematopoietic-reconstituting capacity in vivo and delay the appearance of two newly described progenitor cells.

FEBRUARY 13, 2014

Success in eradicating malaria hinges in part on the ability to prevent transmission of the parasite from the infected host back to the mosquito. In this article, Aguilar and colleagues reveal how complex an issue that may be. They present the first study based on quantitative polymerase chain reaction-based molecular analysis that delineates the characteristics of bone marrow and peripheral blood reservoirs of the parasite. They demonstrate that malarial sexual stages mature in the bone marrow and that hematologic manifestations (severe anemia and dyserythropoiesis) correlate with higher prevalence of mature gametocytes in the marrow. More important perhaps is the observation that mature, infectious gametocytes predominate in the peripheral blood, and that many asymptomatic anemic children harbor unexpectedly large numbers of circulating gametocytes. Studies that define quantitatively and qualitatively the host-parasite relationship are a critical first step in developing strategies aimed at eradicating the malaria parasite in nature.
As technology and the Web have evolved, so too have ASH’s online offerings. Now you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster), and visit ASH on Facebook at www.facebook.com/AmericanSocietyofHematology.

**ASH Seeks Volunteers for Website Users Group**

As was mentioned in the cover story, a new site design was launched on April 4, as part of a multi-year effort to upgrade the Society’s technology platforms. ASH staff will be engaging in ongoing user testing to refine the website user experience. ASH members who are interested in being part of this process are encouraged to email webmaster@hematology.org to sign up for the Website Users Group. Members of this informal group will be invited to act as beta testers and to provide feedback prior to the rollout of new website features.

**What’s on the Web**

Read The Hematologist online at www.hematology.org/thehematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.

**Mark Your Calendar**

**May**

1. Scholar Awards letter of intent due
   Washington, DC  www.hematology.org/awards

2. Application deadline for the ASH Visitor Training Program
   Washington, DC  www.hematology.org/awards

14-17 American Society of Pediatric Hematology/Oncology Annual Meeting
   Chicago, IL  www.aspho.org

21-24 American Society of Gene & Cell Therapy Annual Meeting
   Washington, DC  www.asgct.org

29-30 Hematology for the Oncologist Seminar
   Chicago, IL  www.asco.org

30- June 3 American Society of Clinical Oncology Annual Meeting
   Chicago, IL  www.asco.org

**June**

1. Application deadline for ASH Bridge Grant
   Washington, DC  www.hematology.org/awards

5. ASH annual meeting abstract submission site opens
   San Francisco, CA  www.hematology.org/meetings

5. Scholar Awards application available*
   Washington, DC  www.hematology.org/awards

12-15 19th Congress of European Hematology Association
   Milan, Italy  www.ehaweb.org

**July**

2. Nomination deadline for the 2015 ASH Honorific Awards
   Washington, DC  www.hematology.org/awards

24. Members-only registration and housing opens for 2014 ASH Annual Meeting and Exposition
   San Francisco, CA  www.hematology.org/meetings

**August**

1. ASH Active and International Membership application deadline
   Washington, DC  www.hematology.org/membership

1. Application deadline for Translational Research Training in Hematology
   Washington, DC  www.hematology.org/awards

1. Application deadline for Scholar Awards
   Washington, DC  www.hematology.org/awards

5. Deadline to submit abstracts for the ASH annual meeting
   San Francisco, CA  www.hematology.org/meetings

10-13 ASH Meeting on Lymphoma Biology
   Colorado Springs, CO  www.hematology.org/meetings

*In order to submit an application for the Scholar Awards, you must have submitted a letter of intent by May 1, 2014. For additional meetings dates, go to www.hematology.org/Meetings/Non-ASH.aspx.