Targeting Regulators of Hemoglobin F

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Hemoglobin F (also known as fetal hemoglobin or HbF, \( \alpha_2^f \gamma_2^f \)) is a major contributor to the clinical heterogeneity observed in patients with the major \( \beta \)-globin disorders, sickle cell disease (SCD) and \( \beta \)-thalassemia. HbF is the major hemoglobin produced during fetal life but is largely replaced by adult hemoglobin (HbA, \( \alpha_2^a \beta_2^a \)) following a “switch” around birth. By substituting for polymerization-prone \( \beta \)-globin or absent \( \beta \)-globin, increased \( \gamma \)-globin expression can ameliorate the clinical severity of SCD or \( \beta \)-thalassemia, respectively. Therefore, augmentation of HbF production has served as a longstanding goal. The development of target-based therapeutics has been confounded by limited understanding of molecular mechanisms of globin gene expression. However, recent discoveries of regulators of HbF level represent a major advance and provide opportunities for novel rational therapeutic strategies.

Transcriptional Regulation of HbF

Breakthroughs have initiated largely from human genetic studies.1 Residual HbF expression in adulthood is a heritable quantitative trait. Genome-wide association studies (GWAS) demonstrate that polymorphisms in three loci account for about half of the heritable variation in HbF level. These loci include the \( \beta \)-globin cluster itself, an intergenic interval between the HBS1L and MYB genes, and the BCL11A gene. Subsequent studies have demonstrated that BCL11A is a zinc-finger transcription factor that functions as a developmental stage-specific repressor of HbF expression.2 It cooperates with other transcription factors to directly silence HbF expression in human erythroid precursors and controls globin switching in mice and humans by binding discrete regions of the \( \beta \)-globin cluster.1

A recent linkage study of a family with hereditary persistence of fetal hemoglobin identified mutations in the KLF1 (previously known as EKLF) gene associated with increased HbF.5 Additional studies have demonstrated that a variety of KLF1 mutations lead to derepressed fetal/embryonic globin gene expression in humans and mice.6,7 Interestingly, KLF1 is a DNA-binding transcription factor that functions as a developmental stage-specific repressor of HbF expression.2,3 It cooperates with other transcription factors to directly silence HbF expression in human erythroid precursors and controls globin switching in mice and humans by binding discrete regions of the \( \beta \)-globin cluster.1

Molecular analysis of the globin switch has also revealed the crucial roles of epigenetic modifiers in regulating HbF expression. The \( \gamma \)-globin genes become methylated in the adult stage and are occupied by multiprotein repressive chromatin complexes including DNA methyltransferases and histone deacetylases. Studies focusing on the biochemical characterization of the globin genes have identified a repertoire of trans-acting regulators of HbF expression (Figure), although few of these nuclear factors have yet been fully validated as robust regulators of HbF in vivo.

(Cont. on page 5)
Save the Dates for Highlights of ASH® 2012

<table>
<thead>
<tr>
<th>Month</th>
<th>City</th>
<th>City</th>
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<tbody>
<tr>
<td>January 20-21</td>
<td>Austin, TX</td>
<td>Orlando, FL</td>
</tr>
<tr>
<td>January 27-28</td>
<td>Atlanta, GA</td>
<td>Las Vegas, NV</td>
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<tr>
<td>February 3-4</td>
<td>New York, NY</td>
<td>San Francisco, CA</td>
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</table>

Held a few weeks after the annual meeting, these smaller, clinically focused meetings provide another opportunity to hear leading experts discuss the most practice-changing scientific findings and the latest treatment options that were presented during the annual meeting, but in a more intimate setting.

Attendees will be able to discuss some of the most rapidly evolving developments in the field with experts as well as colleagues. The limited attendance, panel discussions, evening reception, and "Breakfast With the Experts" will provide numerous opportunities to discuss real patient cases with leaders in the field, network with colleagues, and gain knowledge that can impact practice strategies.

Online advance registration for all Highlights of ASH in North America meetings will open October 10. Go to www.hematology.org/Meetings/Highlights for more information. Also coming up in 2012: Highlights of ASH in Asia (March 3-4) and Highlights of ASH in Latin America (May 18-19).

Professional Society Membership and Career Development – Join Early

The American Society of Hematology has done a great job of encouraging people to join. At some point in their careers, most hematologists get around to attending the American Society of Hematology annual meeting, and many of them – 14,000 worldwide at present – go on to join ASH so they can enjoy the benefits of membership. These perks include publications (Blood, The Hematologist, ASH NewsLink, and Hematology, the ASH Education Program Book), discounted "earlybird" annual meeting registration, and access to members-only hotels. The net savings compared with non-member registration fees more than covers the cost of dues.

Members can sponsor meeting abstracts and Scholar Award applications, review meeting abstracts, chair sessions, and participate in ASH education, scientific, and advocacy activities.

Most of our members appreciate these benefits. But for one member category, Associate members, joining ASH is an even better deal. Associate members live in North America and are hematologists or oncology fellows or postdoctoral scientists (PhD or equivalent) working in a hematology or oncology-related field. They can remain Associate members until the December after their fellowship or for four years, whichever comes first. After that, Associate members automatically become Active members; Associate members comprise about 10 percent of total membership. Associate members receive the usual benefits of membership but at an even steeper discount. No matter how you slice it, if you attend the ASH meeting, then ASH membership saves money.

In addition, Associate members have a few opportunities uniquely appropriate to their stage of career development. Associate members have early access to the limited number of slots for the Trainee Day event at the annual meeting. They are eligible for funding through Research Training Awards and Scholar Awards and for participation in the Clinical Research Training Institute or Translational Research Training in Hematology.

Keep in mind that Associate members can be nominated to attend the new ASH Advocacy Leadership Institute, the first of which is scheduled for October 12-13 in Washington, DC. Participants will receive intensive training in policy-making process and advocacy, with speakers from Congress, the Administration, NIH, and other health agencies. This short course is ideal for members interested in health policy and advocacy who want to become more involved in ASH activities.

The tangible benefits of membership are a good value, but the intangible benefits are even more important professionally. Most of us have enough time and energy for meaningful participation in one major professional society, sometimes two. I encourage my trainees to join ASH and get involved in it as deeply as they want, because ASH best represents their natural affinity group, whether for research or patient care, and participation is very rewarding. Reviewing abstracts, serving on Scientific Committees, and working on education or advocacy initiatives with NIH and Congress all teach important skills that can’t be learned otherwise. These shared experiences establish relationships with colleagues that last an entire career.

I’ve been a member of ASH for 26 years, my entire time as a faculty member, and would have joined as a fellow except that the Associate membership did not exist then. For those of you now in fellowship or postdoctoral training, you can still apply in time to gain valuable experiences establish relationships with colleagues that last an entire career.

For more information, check out the Training section (www.hematology.org/Training) and the career-development awards (www.hematology.org/Awards).

LETTERS TO THE EDITOR

SOLICITATION

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

Letters should be sent to:
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The Hematologist: ASH News and Reports
2021 L Street, NW, Suite 900
Washington, DC 20036
klearn@hematology.org

Join ASH Today

Applications for Associate membership are considered on a rolling basis. Those who are eligible include postdoctoral fellows with an MD or equivalent medical degree who reside in Canada, Mexico, or the United States and are enrolled in a hematology or oncology training program accredited by the Accreditation Council for Graduate Medical Education. Trainees with a PhD degree, who are within four years of having attained the PhD and are in a postdoctoral position or a training program in a hematology and/or oncology-related field are also eligible. Associate membership concludes the December following completion of the fellowship program or after a maximum of four years, whichever comes first. The Associate membership is automatically converted to the Society’s Active member status. Associate membership dues are $55 annually. For more information, including the application, go to www.hematology.org/Membership/Categories.aspx.
Submit an Abstract for the National Conference on Blood Disorders in Public Health

ASH, in partnership with the Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention; the Maternal and Child Health Bureau, Health Resources and Services Administration; the Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, National Institutes of Health; and Hemophilia of Georgia, will host the second National Conference on Blood Disorders in Public Health on March 12-14, 2012, in Atlanta, GA. The purpose of this conference is to promote the adoption and full integration of evidence-based and evidence-informed public health functions that can improve outcomes among people with a blood disorder. Abstract submission for the conference is now open through September 18. To learn more about the conference and the abstract submission process, visit the conference website at http://blooddisordersconferences.com.

Election Ballots Due October 31

Materials for this year’s ASH leadership election for Vice President, Councillor, and Councillor in Practice will be disseminated by October 1 to Active members in good standing. The results of the election will be announced on the ASH website in November.

ASH Deputy Executive Director Receives Highest Honors for Exceptional Leadership

Matthew Gertzog, MBA, CAE, received one of the American Society for Association Executives’ (ASAE) highest honors for exceptional leadership, the Professional Performance Award, which recognizes invaluable contributions made by association executives who are at the top level within their organizations but are not CEOs.

In addition, Mr. Gertzog was recently promoted to deputy executive director of ASH; his primarily responsibilities include overseeing the day-to-day operations of the Society and working closely with the executive director in the strategic management of the organization. Mr. Gertzog joined the ASH staff in March 2003 as its first chief operating officer.

Hematology 2010 at Deeply Discounted Sale Price

Purchase your copy of Hematology 2010: The ASH Education Program Book today. This is a comprehensive publication that presents summaries of the topics covered during the Education Program sessions at last year’s ASH annual meeting. Each chapter corresponds with a session. Visit the ASH store online (http://store.hematology.org) for ordering information.

Members $23
Non-Members $38

Registration Open for Antiphospholipid Antibody Syndrome Webinar

ASH will be hosting a series of informative webinars during 2011 and 2012. These sessions have been designed to spotlight universal issues facing practicing hematologists and will address the most up-to-date techniques in patient care. Additionally, the sessions will feature presentations from experts in the field and an interactive question-and-answer period. The series is available to ASH members and nonmembers, and registration is free.

Registration is now open for the first webinar, Antiphospholipid Antibody Syndrome (APS), which will be held on September 6 at 8:00 p.m. and moderated by Wendy Lim, MD, of McMaster University. APS is a hypercoagulable condition related to venous and arterial thrombosis. This webinar will concentrate on laboratory testing related to venous and arterial thrombosis. The webinar will be followed by an interactive question-and-answer period. The series is available to ASH members and nonmembers, and registration is free.
The Question

A 48-year-old man with factor XI deficiency (2% activity) was first diagnosed at the age of 17 during evaluation for a prolonged aPTT. He underwent extraction of wisdom teeth without plasma or topical support uneventfully. Periodontal surgery led to oozing for which he was successfully treated with oral aminocaproic acid. He now needs arthroscopic surgery on his left shoulder for repair of a torn rotator cuff. Does he need factor replacement prior to surgery and afterward?

My Response

Inherited deficiency of factor XI was first described in 1953 as a mild to moderate bleeding disorder. Factor XI deficiency exhibits an autosomal inheritance pattern with a variable clinical penetrance, as described below. It has been described in a wide variety of population groups but is most common in Ashkenazi Jews. In this particular group, it is estimated that one in eight individuals are heterozygous and one in 190 are homozygous for mutations in the factor XI gene.

Spontaneous bleeding, except for menorrhagia, is uncommon in patients with factor XI deficiency. Most bleeding episodes occur following surgical procedures or trauma. In contrast to patients with hemophilia A or B, the correlation between clinical bleeding and the baseline factor XI clotting activity is poor. For example, some patients with severe factor XI deficiency (factor XI level < 10-20 IU/dL) exhibit no increase in hemorrhage, whereas other individuals with levels that are only moderately below the lower limit of the normal range develop bleeding complications after surgery.

Rates of hemorrhagic complication have also been shown to vary depending on the type of surgery being performed. In particular, procedures involving sites with increased fibrinolytic activity, such as the oral mucosa, nose, and genitourinary tract, are more frequently associated with excessive bleeding compared to procedures involving tissues not expressing fibrinolytic activity, such as bones or muscles. This study included six patients who underwent trauma surgery and one total knee replacement, but none of the patients underwent an arthroscopic procedure. The implication from these observations is that conservative use of replacement therapy in patients with even severe factor XI deficiency undergoing certain types of surgery is possible.

Management of bleeding episodes and prevention of bleeding in relation to surgery is not straightforward and needs to be tailored to the individual patient. In many patients with factor XI deficiency, antifibrinolytic therapy alone may be sufficient to prevent bleeding in most surgical settings. Factor XI levels can be raised with fresh frozen plasma, but relatively large volumes may be required. The hemostatic level of factor XI activity to target is debated, but a level of 30 to 45 IU/dL is probably sufficient in patients with severe deficiency. Factor XI concentrates have been associated with an increased thrombotic risk in certain patients and are not available in the United States.

Good hemostasis helps to maintain arthroscopic visual clarity during surgery and is essential for the successful completion of the procedure. A variety of strategies have been used to control arthroscopic bleeding, including using electrocautery or a radiofrequency thermal probe, adding epinephrine to the inflow irrigation solution or increasing the irrigation fluid inflow pressure, and applying direct pressure via the shaver blade. Relatively limited information is available describing therapeutic arthroscopy of the shoulder in patients with clotting disorders. A single case series describing the management and outcomes of five patients undergoing a total of six shoulder arthroscopic procedures included one patient with a mild factor XI deficiency (baseline level of 60 IU/dL) who underwent arthroscopic subacromial decompression. This patient was treated with a combination of intravenous and oral tranexamic acid without any bleeding complications.

Although shoulder arthroscopy is performed in a tissue not considered to have high fibrinolytic activity, the impact of even a minimal increase in bleeding during a surgical procedure in an enclosed space can be significant. The severely decreased factor XI activity level in this patient, and the fact that he had previously required antifibrinolytic therapy for periodontal surgery, are concerning for an increased bleeding risk. Consequently, it was recommended that the patient receive fresh frozen plasma to supplement the factor XI level prior to the procedure. Post-operatively, depending on the factor XI activity levels and clinical outcome of the procedure, additional fresh frozen plasma could be administered or antifibrinolytic therapy could be substituted instead.
Targeting Regulators of Hemoglobin F

**Optimal Characteristics of a Target**

The identification of a new set of regulators has therapeutic implications for directed reactivation of HbF. A crucial task will be to place these factors into a hierarchy to prioritize the most promising leads for further target-based clinical development. To define the “optimal” characteristics of a target, it is important to consider a number of features including quantitative effect on globin expression, non-globin effect on erythropoiesis, impact outside of the erythroid lineage, and feasibility of therapeutic modulation. Of note, reactivation of HbF expression would be required for the lifetime of the patient to achieve desired benefit; therefore, any cumulative toxicity would be undesirable.

While some of the HbF regulators are ubiquitously expressed, others are more restricted to the erythroid lineage. Many of the factors influencing globin gene transcription have general importance in hematopoietic or erythroid differentiation, thereby complicating their use as possible targets for therapeutic manipulation.

Inhibition of epigenetic activities has been a longstanding focus for HbF induction and has been reinvigorated by chemical screens “rediscovering” their potential efficacy.9 DNA hypomethylating agents, such as 5-azacytidine and decitabine, have been used successfully to induce HbF expression in animal models and patients.10-13 Inhibitors of histone deacetylases, such as butyrate and its derivatives, have also been shown to increase HbF synthesis and continue in clinical development.14 Increased understanding of the regulatory pathways in HbF silencing may reveal additional epigenetic modulators as potential targets. Furthermore, next-generation epigenetic modulators with increased specificity for particular isoforms or protein–protein interfaces may minimize “off-target” effects. However, the broad role of many chromatin regulators both within and beyond the erythroid lineage raises concern about the achievability of an adequate therapeutic window.

Recently identified transcription factors participating in HbF regulation also serve as attractive targets for future therapeutics (Table). BCL11A controls HbF expression in a robust and dose-dependent manner, has few erythroid non-globin targets, and is dispensable for erythropoiesis. One concern is that BCL11A is expressed in the developing central nervous system and is essential for normal B-lymphocyte development, suggesting inhibition of BCL11A might have an impact on other cell lineages. In contrast, KLF1 expression is highly erythroid-restricted, and the dual role of KLF1 in globin regulation makes it an appealing target. However, this “master regulator” has numerous target genes and coordinates multiple aspects of terminal erythroid differentiation. Of note, a variety of erythroid phenotypes have been observed in patients carrying KLF1 mutations. An improved understanding of these genotypic-phenotypic correlations could help predict how KLF1 could be targeted to specifically result in HbF reactivation.

**Opportunities and Challenges**

Despite intensive investigation in the past two decades, combination therapy consisting of two or more modulators, each with a different mechanism of action, may be the most effective strategy for the induction of very high levels of HbF while limiting adverse effects. There is actually historical precedence for this; combined therapy with hydroxyurea and recombinant erythropoietin elevates HbF levels more so than hydroxyurea alone in SCD patients.15 By gaining an increased mechanistic understanding of globin gene regulation, it is anticipated that targeted, mechanism-based therapeutic approaches for efficient HbF induction can be developed.

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**Table. Important criteria in evaluation of potential targets for therapeutic induction of HbF**

<table>
<thead>
<tr>
<th>Effect on HbF</th>
<th>BCL11A</th>
<th>KLF1</th>
<th>Epigenetic regulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-globin erythroid functions</td>
<td>Minimal influence on erythropoiesis</td>
<td>“Master regulator”; mutations associated with a variety of erythroid phenotypes</td>
<td>Not fully explored, but potentially with broad roles</td>
</tr>
<tr>
<td>Non-erythroid roles</td>
<td>Expressed in the central nervous system; required for B-cell development</td>
<td>Exclusive erythroid expression</td>
<td>Often widely expressed or with similar non-erythroid activities</td>
</tr>
<tr>
<td>“Druggability”</td>
<td>Challenging to target transcription factors</td>
<td>Challenging to target transcription factors</td>
<td>Enzymes can make excellent small molecule targets</td>
</tr>
</tbody>
</table>

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The complexity of the mechanisms of HbF regulation suggests that combination therapy consisting of two or more modulators, each with a different mechanism of action, may be the most effective strategy for the induction of very high levels of HbF while limiting adverse effects. There is actually historical precedence for this; combined therapy with hydroxyurea and recombinant erythropoietin elevates HbF levels more so than hydroxyurea alone in SCD patients. By gaining an increased mechanistic understanding of globin gene regulation, it is anticipated that targeted, mechanism-based therapeutic approaches for efficient HbF induction can be developed.

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**Figure**

The switch from fetal (HbF) to adult (HbA) hemoglobin is regulated by various transcription factors and cofactors. Regulators of this process constitute potential therapeutic targets for patients with the major hemoglobin disorders. Positive and negative interactions are denoted by pointed and blunt arrows, respectively. Dotted lines indicate the physical interactions between BCL11A and other cofactors. The dashed line indicates relationship with a lower level of experimental support.

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Drs. Xu, Bauer, and Orkin indicated no relevant conflicts of interest.
Debt Deal Sets Up New Spending Challenges for NIH and Medicare Physician Payment

President Obama and Congress reached agreement on legislation to raise the nation’s debt limit and reduce the national deficit just prior to the August 2 deadline. While the passage of the “Budget Control Act of 2011” ends one of the most litigious legislative periods in contemporary congressional history, new difficulties lie ahead. Another deadline looms September 30 for passage of the fiscal year (FY) 2012 spending bill or a funding extension resolution that will impact funding for the National Institutes of Health. Beyond FY 2012 funding comes action by the Budget Control Act’s new special congressional panel, assigned to find $1.5 trillion in additional reductions and possible Medicare cuts on top of the scheduled 29.5 percent physician payment reduction beginning in January. The panel is required to report its recommendations to the Congress by a majority vote no later than November 23, 2011. Congress is required to vote on the recommendations by December 23, 2011. If the panel finds at least $1.5 trillion in savings and its recommendations are enacted by Congress, the debt ceiling will be raised by $1.5 trillion. If the panel fails to produce a bill, its bill is not enacted, or it produces less than $1.2 trillion in savings, the debt limit will increase by $1.2 trillion and across-the-board cuts known as “sequestration” will be triggered to achieve $1.2 trillion in savings. For the latest information about the Budget Control Act and how it will impact hematologists, please visit the ASH website at www.hematology.org.

Meanwhile, progress on most fiscal year (FY) 2012 spending bills was slowed significantly due to the deficit negotiations. With both the Senate and House adjourned until early September, it remains unlikely that the appropriations process will be completed by the start of the new fiscal year on October 1. As a result, Congress would have to implement what is known as a continuing resolution that would simply fund the government at current levels to avoid a government shutdown.

In lieu of the finalization of the FY 2012 budget, the Society encourages all members to visit the ASH Advocacy Center (www.hematology.org/takeaction) to take action to urge support for NIH funding. To obtain the latest information about the FY 2012 budget and its impact on NIH, please visit www.hematology.org.

Update on Hematologic Drug Shortages:
ASH Advocacy and Resources for Physicians

The United States continues to experience severe shortages of drugs used to treat patients with hematologic malignancies, including leukemia and lymphoma. An increasing number of physicians have been forced to take their patients off therapies mid-treatment, delay treatment, choose alternative therapies that are less effective, and ration their remaining supplies of these therapies. ASH members have reported severe shortages of carmustine (BiCNU), bleomycin injection, cytarabine (Ara-C), daunorubicin, leucovorin, and thiopeta.

The Society has taken a number of steps to provide its membership and the patients they serve with the most up-to-date information to assist them during this critical time while working with policymakers on possible solutions. Information about specific drug shortages (including what is causing the delays and when the drugs will become available) is posted on the ASH website (www.hematology.org) as it becomes available. ASH has also alerted the Food and Drug Administration (FDA) to the hematology/oncology drug shortages and requested an official response to the matter.

ASH also continues to work with policymakers on legislation to address this problem. Members of the ASH Committees on Government Affairs and Practice, along with ASH Vice President Dr. Armand Keating and Dr. Samuel Silver, chair of the ASH Reimbursement Subcommitte, met with congressional officers to garner support for legislation (S. 296 and H.R. 2245, the Preserving Access to Life-Saving Medications Act) that seeks to take the first steps toward addressing the critical shortages of certain hematology-related chemotherapy and other lifesaving drugs. The Society requested that a congressional hearing on the problem of drug shortages take place, where the FDA’s ability to address this problem, as well as how future shortages may be prevented, will be discussed.

Update on Health Reform Implementation: Opportunities for Patients with Pre-Existing Conditions

The Patient Protection and Affordable Care Act enacted last year created a new program that provides a health coverage option for individuals who have been uninsured for at least six months, have a pre-existing condition, and have been denied coverage (or offered insurance without coverage of the pre-existing condition) by a private insurance company. This program will provide coverage until 2014 when such individuals will have access to affordable health insurance choices through an exchange and can no longer be discriminated against based on a pre-existing condition.

The U.S. Department of Health and Human Services (HHS) is trying to increase enrollment in this program for people with pre-existing medical conditions by reducing premiums and easing application requirements. HHS announced on May 31 that an applicant for the Pre-existing Condition Insurance Plan (PCIP) will be able to qualify in part by submitting a letter from a physician, physician assistant, or nurse practitioner stating that the patient has or has had a pre-existing medical condition, disability, or illness. The department previously had required PCIP applicants to submit a letter of denial from a health plan before qualifying.

HHS also is lowering plan premiums by up to 40 percent in 18 states and notifying other states that they can enact similar premium reductions. The application and premium changes became effective July 1. The federal government is running the program in the following states: AL, AZ, DC, FL, GA, HI, ID, IN, KY, LA, MA, MN, MS, ND, NE, NV, SC, TN, TX, VA, VT, WV, and WY. The remaining states are running their own programs.

HHS has posted information about the program and brochures or to share with patients at www.healthcare.gov/center/brochures/pcip_toolkit_news.html.

Take Action Today

Help effect change! Go to http://grassroots.hematology.org to read about ASH’s latest advocacy efforts on issues that impact hematology, find resources to help you get in contact with your legislators, and sign up for the ASH Advocacy Update, a monthly electronic newsletter concerning ASH advocacy news and information.
Stay Connected While at the Meeting

ASH offers a number of ways for you to stay connected with other attendees while you are at the meeting. The Message Center stations located at ASH Central provide a place for you to check email. In addition, free WiFi will be offered throughout the convention center. Users of the annual meeting mobile app can send messages through the app to other attendees (provided they have opted in). You can also follow ASH on Twitter (@ash_hematology) to get the latest news and announcements. Use hashtag #ASH11 to join the conversation about the meeting.

In addition to electronic communications, there are plenty of opportunities for in-person networking. ASH Central provides comfortable seating areas for informal meetings and conversation, while trainees are invited to visit the Trainee Lounge to relax and connect with their peers. Please also see the listing of receptions on the ASH website for other opportunities to interact with colleagues.

Planning Your Schedule While At the Meeting

ASH offers a number of resources to help you plan your schedule.

- **The Online Program Planner** allows you to search for sessions and access the abstract text from your mobile device.
- **The Abstract Book**, which contains the full text of all the presented abstracts, is now available on flash drive as well as in print. During the registration process, attendees are asked to indicate whether they want to receive a print copy of the book on site. All attendees will receive the abstracts on flash drive. The annual meeting abstracts will also be available online in early November.
- **The Program Book** provided on site contains a detailed schedule as well as session descriptions. One thing to keep in mind when planning which sessions to attend is that some sessions are repeated (Education and Scientific Sessions) while a number of sessions are recorded and available via webcast or on DVD (available for purchase after the meeting). Please note that neither the Scientific Committee Sessions nor the abstract-driven sessions are repeated (Education and Scientific Sessions) while a number of sessions are recorded and available via webcast or on DVD (available for purchase after the meeting).
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### New to the Annual Meeting?

As a first-time attendee, you might be overwhelmed by the scope of the ASH annual meeting. With approximately 20,000 attendees and hundreds of sessions, posters, and exhibits – not to mention dozens of special receptions and events – planning your schedule can be a challenge.

#### Basic Structure of the Meeting

The meeting sessions fall into two basic categories: the invited program and abstract-driven sessions. The invited program sessions are planned by the ASH Program Committee early in the year and feature the top experts in the field of hematology. They include the Education and Scientific Sessions, special lectures and symposia, Education Spotlight Sessions, Meet the Expert, Special-Interest Sessions, and trainee sessions.

The abstract-driven sessions include the Plenary Scientific Session (oral presentations of the top-rated abstracts), oral sessions (talks timed to occur simultaneously at 15-minute intervals to allow attendees to move back and forth to different sessions to hear specific presentations of interest), and posters (visual presentations of abstracts that can be viewed throughout the day; posters are available for informal Q&A during specific times). These presentations are selected by the Program Committee, through an extensive peer-review process, from among thousands of abstracts submitted each year. Poster sessions are offered Saturday through Monday, while the oral abstract presentations kick off with the Plenary Scientific Session on Sunday and continue throughout the latter half of the meeting.

The general and special-interest sessions, which include named lectures and award presentations, are spread throughout the four days of the meeting. For more information, go to [www.hematology.org/Meetings/Annual-Meeting/General/3749.aspx](http://www.hematology.org/Meetings/Annual-Meeting/General/3749.aspx).

### For Your Convenience

For your convenience, the Preliminary Program (in PDF format) and detailed session and scheduling information are available on the ASH website ([www.hematology.org](http://www.hematology.org)). This information will be updated in real time, so be sure to check the site for any changes to the program that may have occurred since the Preliminary Program went to press in July.

This year’s diverse program will include many special lectures. Peter Carmeliet, MD, PhD, will deliver the Ham-Wasserman Lecture, “Angiogenesis in Health and Disease,” to open this year’s meeting. Here he will discuss the fundamentals and medical relevance of angiogenesis and address original approaches and molecular drug targets aimed at tackling resistance to anti-angiogenic therapy. George Q. Daley, MD, PhD, will present the E. Donnell Thomas Lecture, “Hematopoietic, Embryonic, and Induced Pluripotent Stem Cells: Diseases, Myths, and Medicines,” which will explore the possibilities and obstacles surrounding the use of genetically modified human embryonic stem cells and personalized induced pluripotent cells derived from patients by somatic cell reprogramming.

The Ernest Beutler Lecture, “Chronic Myeloid Leukemia (CML): A Success Story from Chromosomes to Effective Therapy,” will be delivered by Prizes recipients Janet D. Rowley, MD, and Brian J. Druker, MD, and will highlight their achievements in CML research and treatment. In addition, ASH offers a number of resources to help you plan your schedule.

#### Planning Your Schedule

- **The Online Program Planner** allows you to search for sessions and access the abstract text from your mobile device.
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One thing to keep in mind when planning which sessions to attend is that some sessions are repeated (Education and Scientific Sessions) while a number of sessions are recorded and available via webcast or on DVD (available for purchase after the meeting). Please note that neither the Scientific Committee Sessions nor the abstract-driven sessions are recorded.
Coagulation's Contact Activation System Again Stands Accused


P tourkallikrein, factor XII, and high-molecular-weight kinogen are members of the contact activation system of coagulation. Despite decades of research, the contact activation system has been enigmatic. Although deficiencies of the contact activation factors result in prolongation of the activated partial thromboplastin time, they are not associated with a bleeding diathesis. However, thrombosis models using factor XII-deficient and high-molecular-weight-kinogen-deficient mice have suggested that these two proteins contribute to thrombosis.1

Additionally, there has been a resurgence of interest in the study of the contact activation system because of its possible roles in a variety of platelet processes, including binding to preplatelet regulation, cell proliferation, angiogenesis, apoptosis, and inflammation.2 Now Liu et al. from the laboratory of Edward Feener at Harvard Medical School have reported results using rat and murine models that suggest that kallikrein may play a pathogenic role in stroke.

The path that led to this observation is an example of how a logical direction can lead to unexpected turns in the laboratory. In an earlier study of carbonic anhydrase-dependent edema following intracerebral hemorrhage (ICH) in rats, the Feener laboratory became interested in kallikrein because of the association between deficiency of C1 esterase inhibitor, which inhibits kallikrein, and hereditary angioedema.3 They found that antibodies to kallikrein inhibited retinal edema and proposed that the effect was due to the well-known production of the proedematous peptide bradykinin following proteolytic cleavage of high-molecular-weight kinogen by kallikrein.

In the present study, Liu et al. addressed the clinical observation that diabetes mellitus and hyperglycemia are associated with ICH in stroke patients. They found that ICH expansion following intracerebral infusion of autologous blood was increased in diabetic rats and non-diabetic hyperglycemic rats. Intracerebral injection of purified kallikrein increased ICH expansion, which was blocked by antibodies to kallikrein. In an analogous murine model, ICH expansion was decreased in prekallikrein-deficient mice. Surprisingly, bradykinin receptor antagonists had no effect on ICH expansion in rats. Searching for a possible anti-hemostatic role of kallikrein, they found that it inhibited collagen-induced rat platelet aggregation in vitro, but not ADP- or thrombin-induced platelet aggregation. Continuing to search for an association between hyperglycemia and ICH, they found that glucose enhanced the inhibitory effect of kallikrein on collagen-stimulated platelet aggregation. Additionally, using surface plasma resonance spectroscopy, they found that kallikrein binds collagen, suggesting that kallikrein binds to exposed subendothelium and prevents platelet adhesion and activation. Consistent with this finding, they observed that kallikrein bound to de-endothelialized rat aorta, and that binding increased with increasing concentrations of glucose.

On the platelet membrane surface, collagen binds to glycoprotein (GP) VI, whose expression depends on its association with the FcRγ chain. Liu et al. found that administration of a neutralizing monoclonal anti-GPVI antibody to mice increased ICH expansion. Additionally, ICH expansion was increased in FcRγ-deficient mice. They also observed that hyperosmolar mannitol and sodium chloride produced effects similar to glucose on the binding of kallikrein to collagen, inhibition by kallikrein of collagen-stimulated platelet aggregation, and kallikrein-dependent ICH expansion. These findings suggest that mannitol, which is used to reduce intra-cerebral pressure and edema in individuals with stroke, may also have adverse effects.

Liu et al. propose a novel mechanism in which inhibition by kallikrein of collagen-induced platelet aggregation contributes to ICH following stroke, thus implicating another member of the contact activation system in thrombotic pathology. They additionally propose that kallikrein is a potential macromolecular target. As the authors note, their findings are limited to rodents ICH models that may have important differences from stroke settings in humans. Nonetheless, their findings should stimulate further investigation into the possible roles of the contact activation system in thrombosis, including hemorrhagic stroke, and in platelet function.


Into Thin Air: New Insights Into the Role of Hypoxia-Inducible Factor in Cancer and Ischemic Diseases


The normal cellular response to low oxygen state and tissue ischemia includes activation of hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor that shifts metabolism toward non-oxidative glycolysis and triggers adaptive mechanisms that affect cell survival, migration, adhesion, and extracellular signals. Notably, many cancer cells preferentially utilize glycolytic metabolism, even in oxygen-abundant states, and this feature serves as the mechanistic basis of positron-emitting tomography imaging of glucose-avid tumors with FDG. Otto Warburg hypothesized in 1924 that cancer cell glycolysis (referred to as the “Warburg effect”) underlies a critical pathobiological function in tumorigenesis. Indeed, activation of HIF-1 in cancer cells induces genes encoding proteins involved in invasion, metastasis, and angiogenesis. Despite this growing knowledge of HIF-1, many key molecular interactions remain undefined.

Two publications from the laboratory of Gregg Semenza at the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins provide important new insights into HIF-1-associated dysregulation in tumor cells and biochemical approaches of manipulating HIF-1 in angiogenic cells to enhance their ability to salvage ischemic tissue.

Luo and colleagues explored the regulatory pathways responsible for the Warburg effect in cultured tumor cell lines. Because the M2 isof orm of pyruvate kinase (PK), the enzyme responsible for the final step of glycolysis, is preferentially expressed in tumor cells, they focused on how PKM2 interacts with the oxygen-regulated HIF-1α subunit of the HIF-1 heterodimer and on HIF-1 transcriptional activity. In a series of elegant biochemical experiments they showed that PKM2 is a HIF-1 target gene, PKM2 directly interacts with HIF-1α to enhance DNA binding and HIF-1α transcriptional activity, and PKM2 interacts with prolyl hydroxylase-3 to further increase PKM2 coactivator function. Together, these promote a feed-forward mechanism that drives the reprogramming of cancer cells to glycolytic metabolism. Rey and colleagues investigated methods of manipulating HIF-1 activation to optimize the homing, retention, survival, and tissue-sparing effects of bone marrow-derived angiogenic cells (BMDACs) in a mouse model of limb ischemic injury. This model includes local injection of an HIF-1α-encoding recombinant adenovirus.1 They observed that pretreatment of BMDACs from young and old mice with dimethylxalylglycine, which potentiates HIF-1 activation and induces the Warburg effect, allows these cells to survive longer than untreated BMDACs in low oxygen and low pH states and to significantly reduce ischemic tissue damage and motor impairment caused by femoral artery ligation.

The observations in these two papers emphasize the value of understanding HIF-1 activity in normal physiology and disease states. The complex PKM2 interactions delineated by Luo et al. reveal potential therapeutic targets against cancer cells that have co-opted the HIF pathway to utilize glucose for basal metabolism and tumors growing in hypoxic conditions. The outcomes observed by Rey et al. in a murine model that combines local HIF-1α gene therapy with BMDACs primed for glycolytic metabolism by HIF-1 activation raise the hope that similar manipulations might be useful for cell-based therapies in patients with severe tissue ischemia. These findings also have broader relevance, as it is now recognized that many HIF-1-mediated regulatory pathways modulate homeostasis in tissues with low-oxygen microenvironments, such as the bone marrow.


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Drs. Cheng and Linenberger indicated no relevant conflicts of interest.

PETE LOLLAR, MD

Dr. Lollar indicated no relevant conflicts of interest.
Spectrin Plays a Critical Role in Platelet Formation


This study from the laboratory of Dr. Joseph Italiano in Boston demonstrates that intact spectrin tetramers are critical for normal megakaryocyte maturation and platelet formation. While a critical role for spectrin is known for red blood cells and for platelet activation, it has not been shown previously that spectrin may also play a role in platelet biogenesis.

Spectrin is a cytoskeletal protein that supports cell structure by forming a latticework that is attached to the inner side of the plasma membrane. Humans have two alpha (α) and five beta (β) spectrin genes. Mature tetrameric spectrin consists of two α/β spectrin dimers joined head to head. In red blood cells, α1 and β1 are the primary spectrins, and mutations in these erythroid spectrins cause RBC abnormalities including hereditary spherocytosis and elliptocytosis. While many nonhematopoietic cells, including neurons, express spectrins, they are usually non-erythroid spectrins. The investigators in this study demonstrated that megakaryocytes express α1 and α2 as well as β1 and β2 spectrins. However, the erythroid (α1, β1) spectrins are expressed at much lower levels, and their proportion decreases during platelet biogenesis suggesting that α2 and β2 are the key spectrins in platelets.

Using a novel spectrin tetramer-disrupting protein, Patel-Hett and colleagues demonstrated a requirement for intact spectrin tetramers at multiple stages of platelet biogenesis. Depending on when the disrupting reagent was introduced into the cells, effects were assessed on a) megakaryocyte cytoplasmic maturation, b) pro-platelet extension, and c) transition from the proplatelet to the preplatelet to mature platelets (Figure). During megakaryocyte maturation, an extensive invaginated membrane system forms. Without intact spectrin tetramers, megakaryocytes lack this extensive membrane structure. However, the alpha and dense granules, which are essential for functional platelets, did not seem to be affected. When tetramers were disrupted after megakaryocyte maturation, then effects on proplatelet extension could be assessed. Treated megakaryocytes showed far fewer proplatelet extensions, and those that were present were blunted. Similarly, when proplatelet/preplatelet interconversion was assessed using time-lapse microscopy, disruption of spectrin tetramers led to a dramatic change in cell shape, with the cell rounding up becoming unable to form/release mature platelets.

The clinical implications of these findings are not yet clear. In general, patients with spectrinopathies have not been reported to have platelet function abnormalities. However, detailed platelet function studies have not been determined in a rigorous manner. In one oft-cited report, Jarolim et al. present a case report of severe hemolyis and red cell fragmentation caused by the combination of a spectrin mutation with a thrombotic microangiopathy.1 Perhaps in such cases there are mutations in the non-erythroid spectrins that affect platelet biogenesis/function in addition to RBC structure.


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**Figure**

Disruption (red arrows) of spectrin tetramers disrupts multiple stages of megakaryocyte maturation and platelet formation. After disruption, megakaryocytes fail to form a normal invaginated membrane system, proplatelets that started to elongate retract, and proplatelet “barbells” lose their structure and fail to form platelets. Yellow indicates supporting spectrin skeleton.
Malaria, Sickle Hemoglobin, and Heme Oxygenase-1: How Heme Can Induce Tolerance to Cerebral Malaria in Mice


 Although the morphologic and immunophenotypic profile of hairy-cell leukemia (HCL) is well characterized, the disease has thus far been bland with respect to the identification of recurrent cytogenetic or molecular abnormalities. With costs plummeting and increasing sophistication of bio-informatic approaches to distinguish sequencing errors from somatic variants, the prime time has arrived for entire genome or exome (whole-exome) sequencing for genetically obscure diseases such as HCL. Such approaches have already been applied to acute myeloid leukemia,1 chronic lymphocytic leukemia,2 and multiple myeloma.3

In a multicenter collaboration led by investigators from the University of Perugia in Italy, massively parallel sequencing (Illumina platform) of the whole exome was performed in an HCL patient using purified CD19-positive leukemic cells at the time of diagnosis and on non-tumor CD19-negative cells after treatment. Using a filtering program, five somatic variants unique to the tumor population were identified and confirmed as heterozygous by Sanger sequencing: Braf, Csmd3, Slc5a1, Cntn6, and Or8j1.

Because it is a frequently mutated serine/threonine kinase in multiple cancers (Figure), investigators focused on a mutational hotspot in exon 15 of the BRAF gene in which a T→A transversion results in a glutamic acid for valine at position 600 (V600E). The mutation was not only identified in the index patient, but in all 47 additional HCL patients analyzed. In 30 patients for whom zygosity could be tested, Braf/V600E was found to be heterozygous in 26 individuals and homozygous in four patients. The mutation was not identified in more than 200 patients with other B-cell leukemia/lymphomas, including splenic-marginal zone lymphoma, the HCL variant, and splenic red-pulp small B-cell lymphoma.

The BRAF V600E mutation results in constitutive activation of BRAF kinase activity as well as increased phosphorylation of the downstream MEK/ERK signaling pathway. Immuno-histochemical and immunofluorescence studies confirmed the presence of phosphorylated MEK in paraffin-embedded core biopsy samples as well as purified HCL cells. In vitro incubation of primary leukemic cells with the BRAF inhibitor PLX-4720 led to a decrease in phosphorylated MEK and ERK, whereas cells treated with vehicle alone did not exhibit reductions in MEK or ERK phosphorylation.

The invariable presence of BRAF V600E in HCL and its absence in other peripheral B-cell lymphomas strongly implicates this protein kinase mutation as a relevant driver of disease pathogenesis. However, its ubiquitous presence in various solid and hematologic neoplasms begs the question of how a singular mutation contributes to such diverse phenotypes. This same question has arisen with the JAK2 V617F mutation that occurs in related, but clinically distinct, myeloproliferative neoplasms. Allele burden, host genetic background, additional disease-modifying mutations, and the cell of hematopoietic origin in which these molecular lesions arise may influence such genotype-phenotype relationships. From a therapeutic standpoint, although the majority of HCL patients enjoy durable remissions with purine nucleoside analogues, BRAF inhibitors may be particularly useful for relapsed/refractory disease or augment the quality of responses in conjunction with standard frontline therapies. Quantitative PCR assays of BRAF V600E to monitor minimal residual disease may also be an avenue to explore.

E
ccess bleeding is noted in up to 25 percent of patients with severe aortic stenosis. The associated platelet dysfunction, detected by prolonged platelet function analyzer (PFA-100) closure times, which measures hemostasis under shear, resolves after valve replacement surgery. Previous investigators hypothesized that bleeding in patients with aortic stenosis (AS) was related to the high shear force of a stenotic aortic valve. The shear associated with a high aortic valve gradient of severe AS leads to stretching and unfolding of von Willebrand factor (vWF), facilitating cleavage by ADAMTS13 within the A2 domain, which leads to acquired von Willebrand disease (vWD) with loss of the largest vWF multimers. Although several studies have confirmed the inverse relationship between the aortic valvular gradient and vWF multimer size, the problem remains that some patients with severe AS and bleeding have no decrease in large vWF multimers.

Further evidence suggests that the conformational changes required for vWF binding to platelets are found not only in high-molecular-weight multimers, but also in lower-molecular-weight multimers, indicating that the loss of large vWF multimers might not be the sole explanation for this process. Moreover, platelet activation correlates with valvular pressure gradient even in patients with mild or moderate AS, suggesting the potential importance of platelet activation in bleeding in AS patients.

Hulsette and colleagues from Utrecht in the Netherlands measured vWF activation (i.e., platelet-bound vWF activity) in the plasma of patients with various thrombocytopenias and/or thrombotic disorders and proposed an alternate explanation. They reasoned that increased shear in severe AS decreases vWF multimer size, and, since high-molecular-weight vWF multimers preferentially bind the platelet glycoprotein Ibα (GP Ibα) receptor, there is less available "active" platelet-bound vWF. This accounts for the platelet dysfunction and potential bleeding in AS patients.

To determine whether "active" vWF (vWF in platelet-binding GP Ibα conformation) is decreased in AS, the investigators tested plasma samples from 62 adult patients using a recombinant antibody fragment (AU/vWF-11)-based ELISA. Among severe AS, defined as mean valve area of 0.6 cm² and mean gradient 60 mm Hg, they found that vWF activation was reduced. In fact, there was a strong negative correlation between vWF activation and aortic gradient: vWF activation decreased as valvular gradient increased. The proportion of vWF able to bind the GP Ibα in patients with severe AS was significantly lower than in those with less severe AS.

vWF activation in these patients was also negatively correlated with PFA-100. Specifically, vWF activation levels decreased with increasing prolongation of PFA-100 closure times. Closure times were also strongly correlated with valve gradient, with longer closure times noted at higher aortic valve gradients (Table).

So, what are the implications for the bleeding patient with AS? While the novel findings of Hulsette et al. suggest clinical bleeding with AS arises from a decrease in vWF A1 binding to platelet GP Ibα receptor, not a decrease in vWF multimers, management of such patients would still require vWF concentrates to reduce clinical bleeding. With demonstrated depletion of vWF stores, neither DDAVP nor platelets would be expected to help. In the home "stretch," that is, before valve surgical repair, one wonders whether a pharmacologic agent, such as an aptamer, that can alternately turn on (promote) or off (block) vWF-platelet interaction might provide a novel approach.


In the Home Stretch: GP Ibα Runs Away With VWF


Can We Treat Myeloma at Early Stages?


In this review, Landgren and colleagues from NCI updated our knowledge of monoclonal gammapathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), focusing on advances in their definition and pathogenesis, with clinical implications. Specifically, they described the evolution in the definition of these entities by the International Myeloma Working Group (IMWG) as well as of distinct subtypes and their clinical sequelae. They focused on predictive models for progression to active MM, based upon parameters such as serum M protein concentration, lg isotype, and free light-chain ratio, as well as multiparameter flow cytometric evaluation of normal versus aberrant bone marrow (BM) plasma cell ratio. Finally, they outlined the clinical implications of these advances, including opportunities for clinical trials to block progression and related complications.

Since the original recognition of benign monoclonal gammapathy by Waldenström and of MGUS by Kyle, long-term clinical annotation has allowed for more precise definitions of MGUS and SMM. Specifically, the most recent iteration by the IMWG defines MGUS as serum M protein < 3 g/dL; BM clonal plasma cells < 10 percent; and absence of end-organ damage including hypercalcemia (> 11.5 mg/dL), abnormal creatinine (> 2.0 mg/dL), or creatinine clearance (< 40 mL/min); normochromic normocytic anemia (Hb < 10 g/dL); bone lesions (lytic lesions, osteopetrosis, pathologic fractures); recurrent bacterial infections (< 2 in 12 months); amyloidosis; or symptomatic hyperviscosity. Moreover, distinct non-IgM, IgA, and light-chain subtypes evolve to MM, Waldenström macroglobulinemia, and light-chain lymphoproliferative diseases, respectively. In parallel, SMM is characterized by serum M protein of > 3 g/dL and/or clonal BM plasma cells > 10 percent without end-organ damage. Such uniform definition is essential to assure that epidemiologic and interventional studies evaluate similar patient populations and likely will continue to evolve, as does active MM, into genomic subtypes.

Having uniformly defined these entities, it is then essential to identify factors predictive of progression both in preclinical and clinical studies. It now appears that all MM evolves from precursor MGUS, but the genetic or epigenetic correlates remain to be defined. To date, most genetic subtypes and abnormalities defined in active MM appear to be present in MGUS, and no common genetic signature correlates with progression to active disease. Moreover, although epigenetic (i.e., IL-6 transcription and secretion from the BM milieu) or host (i.e., immune effector cells) factors have been correlated with progression, no causative factors are identified as of yet. Since the disease does not progress to active MM in many patients with these precursor conditions even over a long period of time, defining host factors that control proliferation of clonal cells has great promise.

Although current treatment guidelines include expectant follow-up in most cases, the ability to define patients at high risk to progress to active MM, coupled with the advent of novel therapies with acceptable adverse side effect profiles, is now making it possible to evaluate treatment strategies directed to prevent progression to active disease. These interventions include immunomodulatory drugs or other efforts to enhance anti-tumor immunity and must be evaluated not only for their ability to delay time to progression, but also on their ultimate capacity to extend overall survival. Moreover, such treatments may be long-term, and a particular focus on complications of chronic therapy must be balanced against any potential benefits. Nonetheless, the opportunity to intervene earlier in the disease course and ultimately prevent the development of complications attendant to active MM is now a real possibility to be evaluated in ongoing and future clinical trials.
**Notch Notches a New Leukemia on Its Belt**


The Notch cell signaling pathway – named for its contribution to Drosophila wing indentations, which were first described in 1914 by John Dexter, a college biology professor who spent several summers working with legendary geneticist Thomas Hunt Morgan at the Marine Biology Laboratory in Woods Hole, MA – is a highly conserved signal transduction cascade present in all metazoan organisms, critical for normal embryological development and definitive hematopoiesis. Although Notch pathway activity is dysregulated in several cancers and congenital disorders, hematologists know Notch best from T-cell acute lymphocytic leukemia (T-ALL), where constitutively activating mutations of NOTCH1 are detectable in more than 50 percent of cases.1 The more recent identification of recurrent activating mutations in NOTCH1 in 12 percent of patients with chronic lymphocytic leukemia (CLL), particularly among the poor prognosis subset of patients with unmutated immunoglobulin heavy chain genes, highlighted NOTCH1's status as an oncogene and underscored the relevance of the Notch pathway in human lymphoid neoplasia.2

Recently, experiments designed to explore the role of the Notch pathway in hematopoiesis unexpectedly revealed another face of Notch signaling: a tumor suppressive effect. Apostolos Klinakis and Iannis Atlantis from Athens, Greece, led an international group of investigators who knocked out one of the few non-redundant members of the Notch pathway, nicastrin, in hematopoietic cells in a murine model. Nicastrin is a member of the γ-secretase enzyme complex that normally cleaves an intracellular domain from cell-surface Notch receptors upon ligand-receptor binding; the cleaved Notch intracellular domain then migrates to the nucleus, where it modifies the expression of a broad range of genes via interactions with several DNA-bound factors and recruitment of mastermind-like (MAML) proteins. Notably, none of the mice with nicastrin loss lived more than 20 weeks, and all developed monocytosis, splenomegaly, and myeloid proliferation suggestive of human chronic myelomonocytic leukemia (CMML). Furthermore, deletion of either Notch1 or Notch2 receptors (but not Notch3) in murine hematopoietic cells resulted in a similar CMML-like proliferation, whereas forced Notch1 expression rescued the nicastrin knockout phenotype. The hematopoietic effects of Notch disruption were cell-autonomous and mediated by the MAML1 transcriptional co-activator and Hes1 transcriptional repressor.

The relevance of these findings to human CMML was confirmed when the investigators discovered inactivating mutations in Notch pathway members in five of 42 patients with CMML. These patients had heterozygous somatic mutations in one of four Notch pathway genes: NCSNT (encoding nicastrin), APPH1 (anterior pharynx-defective 1, a member of the γ-secretase complex), MAML1, or NOTCH2. Additional polymorphisms that might be somatic mutations were detected in other patients with CMML; the possibility of epigenetic silencing was not explored. Transcriptional reporter and in vitro differentiation assays confirmed that the MAML1 and NCSNT mutations were either null or dominant negative. Notch pathway mutations were not present in 47 patients with polyclonemia vera or primary myelofibrosis. The five CMML patients with Notch cascade signaling mutations also had mutations in other genes previously described in myeloid neoplasia, including JAK2, KRAS, ASXL1, and TET2, suggesting that these mutations may be cooperative and are not mutually exclusive.

The discovery of inactivating Notch pathway mutations in a human myeloid neoplasm provides evidence of a novel pathobiological role for deregulated Notch signaling. Notch-based experimental therapeutics in lymphoid leukemia have thus far focused on reducing pathologically upregulated Notch signaling, primarily by inhibition of γ-secretase. The discovery that Notch pathway members might act as tumor suppressors rather than oncogenes suggests that augmenting Notch signaling might also have therapeutic benefit; it also indicates that effects on non-lymphoid leukocyte subsets should be monitored during longer-term Notch pathway inhibition in lymphoid leukemias.


**Reaching a Consensus on the Definition of Complete Response in Myeloma**


Complete response (CR) remains the optimal objective in front-line treatment of myeloma to improve survival. The definition of CR has evolved in recent years from normalization of serum protein electrophoresis and bone marrow morphology with negative immunofixation, to normal serum free light-chain ratio test (stringent CR), and more recently to normal immunophenotype (IR). However, neither is achieved when the malignant plasma cell signature is undetectable using multiparameter flow cytometry (MFC) at a sensitivity level of 10−4 to 10−5.

Paiva and colleagues from Salamanca, Spain, have investigated the impact of IR versus CR and stringent CR in 260 newly diagnosed elderly (> 65 years) patients with multiple myeloma. They compared patients in the PETHEMA/GEM 05 trial (Programa para el Estudio de la Terapéutica en Hemapatas Malignas/Grupo Espanol de Mieloma) Forty percent of patients achieved CR, 30 percent achieved stringent CR, and 30 percent achieved IR. The patients in IR showed significantly increased three-year rates of progression-free survival (PFS) and time to progression (TTP) as compared with those in stringent CR or CR – 90 percent versus 69 percent and 60 percent, and 96 percent versus 71 percent and 68 percent (p < .001), respectively. On a multivariate Cox regression analysis for PFS, only IR status was an independent prognostic factor (relative risk, 4.1; 95% CI, 1.4 to 12.0; p < .01). Some discrepancies between the three techniques were seen, however; the patients displaying IR also had stringent CR and CR. Interestingly, patients in stringent CR plus IR compared with those in stringent CR but with persistent malignant plasma cells by MFC showed a significantly longer PFS (median not reached; 95% at three years vs. 35 months, respectively; p < .02) and TTP (p<0.003). Identical results were observed with MFC-positive patients who were immunofixation negative (CR) who showed a tendency toward early reappearance of the M-component (median, 3 months).

The authors accurately concluded that these techniques provide complementary information, and thus an effort should be made to refine response criteria in myeloma. The plot thickens, though. Ladetto et al. recently evaluated the impact of minimal residual disease (MRD) during the consolidation in 32 patients with myeloma following autologous transplantation. They monitored MRD every six months after consolidation. Tumor shrinkage was evaluated by immunofluorescence (IR)-PCR using specific DNA probes for immunoglobulin heavy-chain rearrangements. Molecular CR was defined as a negative PCR with a sensitivity threshold of 10−6. The CR rate increased from 15 percent to 49 percent after the consolidation courses, while 15 percent of the patients achieved molecular CR. Interestingly, none of the patients who reached molecular CR relapsed, with a median follow-up of 29 months. Consistently, patients with detectable MRD had significantly poorer outcome and higher risk of relapse. Although further investigations are needed to consider MRD evaluation as a decision-making tool in myeloma, these results provide another argument for the relevance of reaching a consensus on the definition of complete response. On the road to technical progress, today’s complete response might well be tomorrow’s partial response. One might agree on the use of the term “minimal residual disease” in place of complete response.


**The Hematologist: ASH News and Reports**

**Xavier Leleu, MD, PhD**

Dr. Leleu indicated no relevant conflicts of interest.
Pointed Questions: Targeted Strategies for Prophylactic Anticoagulation in Cancer Outpatients

STUDY TITLES:
1. A Randomized Controlled Trial of Enoxaparin Thromboprophylaxis in Cancer Patients With Elevated Tissue Factor-Bearing Microparticles (MicroTEC)
2. A Study of Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients (PHACS)

COORDINATORS:
1. Principle Investigator: Jeffrey Zwicker, Beth Israel Deaconess Medical Center, Boston, MA
2. Principle Investigator: Charles Francis, University of Rochester, Rochester, NY

SPONSORS:
1. NHLBI, Sanofi
2. NHLBI, Eisai

REFERENCES:

StudY DESIGN:
1. MicroTEC is a phase II, randomized, three-arm study for patients with advanced cancer (pancreatic, colon, non-small-cell lung, gastric) within four weeks of initiating first-line or second-line chemotherapy. Following measurement of microparticles, those with elevated levels are randomized to enoxaparin, 40 mg subcutaneous daily, or dalteparin or observation in cancer patients starting first-line or second-line chemotherapy. Following a defined target population, the efficacy of prophylaxis in patients with cancer may be improved beyond that observed in unstratified patient populations.

The Hematologist: ADH News and Reports

Ready, Set, Go: Stratification of Diffuse Large B-Cell Lymphoma in Real Time Based on Gene Expression Profiling

STUDY TITLE: A Randomized Evaluation of Molecular Guided Therapy for Diffuse Large B-Cell Lymphoma With Bortezomib (REMO-ALL-B); ISRCTN 51837425.

COORDINATORS: The UK National Cancer Institute Lymphoma Clinical Studies Group in collaboration with the Swiss Group for Clinical Cancer Research and the Haematological Malignancy Diagnostic Service (HMDS). St James’s University Hospital, Leeds, through the University of Southampton Clinical Trials Office, Southampton, UK

STUDY DESIGN: Patients newly diagnosed with diffuse large B-cell lymphoma (DLBL) will undergo full staging and commence treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). During the first 21-day cycle (i.e., cycles 2-6), a gene expression profile will be generated from each patient’s original diagnostic tissue sample. To ensure uniformity, all samples will be processed and analyzed at HMDS. The molecular data will be used to assign cases to either germinal center B-cell (GCB) or activated B-cell (ABC) types, and beginning with the second treatment cycle, patients will be randomized either to continue conventional R-CHOP or to also receive bortezomib at 1.3 mg/m2 (R-CHOP-B) on days 1 and 8 of each subsequent 21-day cycle (i.e., cycles 2-6).

Initially, all patients will be randomized, but an iterative design will allow closure of randomization for GCB lymphomas if there is evidence of detriment in outcomes after 55 such patients treated with R-CHOP-B have been followed for at least six months. According to the protocol, patients in the GCB group will no longer receive R-CHOP-B if the interim analysis shows that the six-month progression-free survival (PFS) for that group is < 80 percent. A second analysis will be performed for futility in the GCB group after 73 of those patients have been randomized to receive R-CHOP-B and followed for one year. If the estimate of one-year PFS is < 85 percent, further exploration of the value of bortezomib in this group of patients is not warranted based upon data from retrospective series using molecular profiling. Because of these potential interim modifications and allowing for failure of RNA extraction and unclassifiable gene expression profiles in some cases, the total number of patients taking part in the trial may vary between 567 and 940. The study aims to randomize a minimum of 260 ABC-type lymphomas to allow for detection of a statistically significant improvement in 30-month PFS of 10 percent in the R-CHOP-B arm.

RATIONALE: Gene expression profiling of fresh frozen tissue samples has provided new insights into the biology of DLBL. Unsupervised hierarchical clustering identified two distinct subgroups of the disease: one with GCB-like and one with ABC-like patterns of gene expression. These molecular subgroups had distinct clinical outcomes after R-CHOP chemotherapy, with the ABC-like lymphomas having an inferior three-year PFS of 40 percent, compared with 75 percent PFS in the GCB group. Several oncogenic mechanisms distinguish the two subgroups. In particular, the constitutive activation of the nuclear factor-kappa B (NF-kappa B) signalling pathway appears central to cell survival in ABC-like lymphomas. The induction of the NF-kappa B pathway may suppress the apoptotic effect of cytotoxic chemotherapy, and this mechanism could contribute to the observed differences in outcome. This effect might be mitigated through the use of bortezomib, which, among other actions, can reduce proteosomal degradation of the natural NF-kappa B inhibitor, I-kappa B.

Attempts have been made to simplify molecular subclassification of DLBCL by using immunohistochemistry (IHC) methods, but to date, no such approach has proven sufficiently reproducible among laboratories or even among expert hematopathologists. Consequently, this trial uses the more technically complex array technology as the basis for stratification of the two subgroups.

COMMENT: This is the first study to use prospective gene expression profiling in lymphoma as a means of stratifying randomization of DLBCL subgroups between treatment with R-CHOP or R-CHOP-B. The goal of the trial is to determine if there is a subset of lymphomas in which bortezomib improves outcome. Additionally, the study affords an opportunity to analyze the clinical utility of several IHC algorithms in distinguishing subgroups of DLBCL, using the expression array data as the standard of comparison. The results of this aspect of the study will become increasingly important as more targeted therapies, requiring a reproducible means of identifying the appropriate subset of patients to treat, emerge.

–Peter Johnson, MD

Dr. Johnson is the chief investigator for this study, which is supported by an unrestricted grant from Janssen-Cilag.
The Modern Era of Transfusion Medicine

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Transfusion medicine (TM) is an important part of the broad field of hematology, and members of the TM research and practice communities participate actively in ASH programs and leadership. In response to the general lack of knowledge among trainees about TM as a career pathway in hematology, manifest recently as low attendance at the TM career-development event at the 2010 ASH meeting, the ASH Trainee Council conducted a series of interviews with leaders in the TM field to learn more about this potential career path.

The field of TM has transformed in the last 20 years from one led by hematologists to an independent subspecialty in pathology, medicine, and pediatrics. Available career options for TM specialists are in government, academics or private institutions and can involve a combination of administrative, public health, laboratory, clinical practice, and research responsibilities. TM specialists are drawn into the field by the exciting cutting-edge complexity of immunohematology (the study of humoral and cell-mediated immune reactions in the pathogenesis and clinical manifestations of blood disorders), the ability to combine laboratory and clinical practice, the relationship to public health, the close bedside-to-bench connection, and the feasibility of combining practice with research.

As Dr. Christine Cserti-Gazdewich from Toronto General Hospital described, “[T]M is a complex and dynamic field of medicine, which simply gives the illusion of stability by virtue of its culture of (necessary) procedural regimentation and quality assurance;quality control.” In other words, TM is a field dominated by process and procedures.

TM is often incorrectly thought of as a laboratory-based subspecialty, isolated from all other branches of clinical medicine. In fact, TM specialists interact with patients and medical staff on a daily basis and work with clinicians by managing transfusion reactions, hemovigilance (examination of the safety of blood supply covering the entire transfusion chain), hemostasis, blood product utilization, and apheresis. As a result of these interactions, TM specialists are well connected to their colleagues. Dr. Jacob Pendergrast, also from Toronto General Hospital, described the blood bank as “the circulatory system of a hospital.” TM specialists respond and circulate out their goods, to the sickest and most complex patients ... In this sense, they have their fingers on the pulse of ... the hospital.”

Most TM practitioners are initially exposed to TM during hematology fellowship or pathology residency, after which they enter a one-year (U.S.) or two-year (Canada) specialized TM training program. Canada also accepts trainees from anesthesia or critical care medicine. Training typically consists of rotations in cellular therapeutics, apheresis, immunohematology, product utilization, coagulation, donor clinics, and hemovigilance.

Because of the intimate connections between TM and blood bank operations, TM training program and practice administration has largely migrated from hematology to pathology/laboratory medicine. As a result, most hematology trainees do not receive much exposure to the field. In the United States, remuneration in non-malignant hematopathology and TM are significantly lower than malignant hematopathology and medical oncology, possibly contributing to the diminished interest among hematology trainees in TM. Creative strategies are needed to overcome this “pipeline” problem and to recruit more hematology trainees into this unique and exciting field of medicine. Addressing remuneration, improving mentoring, exposing trainees to TM early in their careers, and developing novel, mixed training pathways combining TM with non-malignant hematopathology practice and research are all on the ASH radar screen. The goal is to attract TM-trained hematologists to influence a large number of trainees by virtue of their dual connection with the laboratory and clinical aspects of training.

ASH Honors MMSAP Award Recipients

The 2011 MMSAP award recipients are:

**SECOND-YEAR PARTICIPANT**

**Steven Ovu**
Texas A&M Health Science Center – College of Medicine
Research Project: Study of clinical practice guidelines for the prevention and treatment of acute chest syndrome in sickle cell disease

**Maura R. Munoz**
The Ohio State University
Research Project: In vitro studies of a new bortezomib formulation against acute myeloid leukemia

**Ryannie Brown**
Baylor College of Medicine
Research Project: Characterization of the VWF-GPIbαβIII interaction under high shear stress

**Debora Zamora-Olivencia**
San Juan Bautista School of Medicine
Research Project: Evaluation of safer lentiviruses vectors for a successful sickle cell disease gene therapy

**Christopher Rombooa**
Tufts University School of Medicine
Research Project: Targeting miRNA-155 in Waldenstrom macroglobulinemia

**Hyunjoo Lee**
Stony Brook University School of Medicine
Research Project: Effect of polymorphisms in p53 pathway proteins and CLL disease progression

**Lilian Msambichaka**
University of Minnesota Medical School
Research Project: Characteristics and mechanism of pain in sickle cell disease

**Ko Ko Maung**
East Tennessee State University Quillen College of Medicine
Research Project: Structural requirements of LDB1 function in erythroid differentiation

**Nicole Diaz**
University of Illinois at Chicago
Research Project: Cell line model of refractory anemia with ringed sideroblasts developed through inappropriate iron accumulation by silencing of iron processing genes

**Yakisha Partee**
 Meharry Medical College
Research Project: Mitochondrial DNA mutations in sickle cell disease

**Oyinade Aderibigbe**
University of Pennsylvania School of Medicine
Research Project: Influenza in pediatric patients with sickle cell disease

**The Hematologist: ASH NEWS AND REPORTS**
Meet This Year’s Honorific Award Winners at the 53rd Annual Meeting

WALLACE H. COULTER AWARD
FOR LIFETIME ACHIEVEMENT IN HEMATOLOGY

The Wallace H. Coulter Award, named after the inventor of the Coulter Principle, recognizes an individual who has dedicated his or her career to the hematologic field, making outstanding contributions through education, research, and/or practice. This year, the Society will bestow its highest honor on David G. Nathan, MD, of the Dana-Farber Cancer Institute and Children’s Hospital Boston, for his outstanding contribution and dedication to mentorship over the course of his 50-plus-year career. He and his team developed the first prenatal diagnostic test for thalassemia and sickle cell anemia, were the first to introduce hydroxyurea to prevent certain sickle cell complications, and were the first to develop a successful treatment for patients who produce an excessive amount of iron, subcutaneous deferoxamine, while undergoing chronic transfusion therapy. These accomplishments have had a profound impact on the field of hematology, especially as it relates to inherited, red cell disorders. Dr. Nathan, a past president of ASH, will receive his award on Sunday, December 11, at 1:30 p.m.

E. DONNALL THOMAS LECTURE
AND PRIZE

In honor of past ASH president and Nobel Prize laureate, E. Donnall Thomas, MD, this prize and lectureship are intended to recognize research achievements that have led the way to a paradigm shift in the hematologic field. The 2011 E. Donnall Thomas Lecture will be given by George Q. Daley, MD, PhD, of the Children’s Hospital Boston and Howard Hughes Medical Institute, Boston, MA. Dr. Daley receives this prize for research that has advanced the understanding of the role of hematopoietic stem cells in disease initiation and progression. Some of Dr. Daley’s earliest findings demonstrated that a specific oncogene was responsible for chronic myeloid leukemia, findings that served as the impetus for research regarding patients who may become resistant to the highly effective drug imatinib. He also achieved the first successful application of somatic cell nuclear transfer to create customized embryonic stem cells to treat genetic disease in a mouse model of immune deficiency. Consistently at the forefront of the field, Dr. Daley has been an authoritative voice in the political and scientific discussions surrounding stem cell research. He will deliver his lecture, “Hematopoietic, Embryonic, and Induced Pluripotent Stem Cells: Diseases, Myths, and Medicines,” on Monday, December 12, at 9:00 a.m.

HENRY M. STRATTON MEDAL

This award honors an individual whose contributions to the field of hematology have been noteworthy over the course of an illustrious career. This year, the Society recognizes Ching-Hon Pui, MD, of St. Jude Children’s Research Hospital, with the 2011 Henry M. Stratton Medal for using his skill and experience as a translational researcher, pediatrician, and educator to advance the cure rate and understanding of acute lymphocytic leukemia (ALL) in children. For 30 years, Dr. Pui has been at the forefront of leukemia research, and, as a result of his findings, St. Jude’s ALL cure rate increased to 90 percent. Further, his work has shown that ALL patients can be spared from the devastating side effects of standard cranial irradiation treatment, improving their quality of life. An ASH member since 1983, Dr. Pui has served as a Scientific Program session chair at the ASH annual meeting and as a member of the Blood editorial board. He has also given numerous presentations at past annual meetings and published approximately 100 articles in Blood. Dr. Pui will receive his award on Tuesday, December 13, at 9:30 a.m.

ERNEST BEUTLER LECTURE AND PRIZE

Named after a past ASH president and renowned physician-scientist, the Ernest Beutler Lecture and Prize is a dual lectureship that recognizes major translational advances related to a single topic. This year’s Prize recipients are Janet D. Rowley, MD, of the University of Chicago Medical Center, Chicago, IL, and Brian J. Druker, MD, of the Knight Cancer Institute, Oregon Health & Science University, Portland, OR. Dr. Rowley was involved in identifying the molecular nature of the Philadelphia chromosome in chronic myeloid leukemia (CML) and in cloning the BCR/ABL oncogene. Dr. Druker led efforts to translate these discoveries to develop an astonishingly effective means of targeted therapy for CML. Their work has contributed significantly to our knowledge of cancer and its treatment. During their lecture, Dr. Rowley will discuss the discovery of the chromosome translocations and cloning of the translocation breakpoint, and Dr. Druker will discuss the pre-clinical and clinical development of ABL inhibitors, including the problem of resistance. Plan to attend their lecture, “Chronic Myeloid Leukemia: A Success Story from Chromosomes to Effective Therapy,” on Monday, December 12, at 1:30 p.m.

THE EARLY-CAREER HEMATOLOGIST

American Society of Hematology Clinical Research Training Institute
July 30 - August 5, 2011

Participants and faculty members take time out from their weekend summer session in La Jolla, CA, to pose for a photo.

During the workshop participants learned the elements of patient-oriented clinical research while having an opportunity to apply the strategies learned to further develop their own proposed research projects with the help of assigned mentors and other knowledgeable faculty.
**WHAT'S ON THE WEB**

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

### Suggested Search Results

In an effort to help visitors successfully find information they search for quickly and easily, ASH has introduced a new suggested result feature designed to better match search phrases with relevant content.

For example, a search for “ASH-SAP” in the “SEARCH” box at the top right-hand corner of any page will suggest that the user first visit the main ASH-SAP page on the ASH website for more information and will then list all other relevant results below containing the search term.

### Mark Your Calendar

#### September

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>15</td>
<td>Deadline to submit letter of intent for the ASH Research Training Award for Fellows</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<tr>
<td>21-22</td>
<td>Beaumont Hospital’s 20th Annual Symposium on Molecular Pathology</td>
<td>Troy, Michigan</td>
<td><a href="http://www.beaumont.edu">www.beaumont.edu</a></td>
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<tr>
<td>23-24</td>
<td>2011 ASH State-of-the-Art Symposium</td>
<td>Chicago, IL</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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#### October

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<tr>
<td>8-9</td>
<td>The Malacca Strait International Hematology-Oncology Symposium</td>
<td>Medan, North Sumatera, Indonesia</td>
<td><a href="http://www.photismut-aceh.com">www.photismut-aceh.com</a></td>
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<tr>
<td>12-13</td>
<td>ASH Advocacy Leadership Institute</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<tr>
<td>17-19</td>
<td>Histiocyte Society Annual Meeting</td>
<td>Vienna, Austria</td>
<td><a href="http://www.hsibonn.org">www.hsibonn.org</a></td>
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<tr>
<td>19-22</td>
<td>2011 American Society for Clinical Pathology Annual Meeting &amp; World Association of Pathology and Laboratory Medicine XXVI World Congress</td>
<td>Las Vegas, NV</td>
<td><a href="http://www.ascp.org">www.ascp.org</a></td>
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<tr>
<td>21</td>
<td>ASH annual meeting late-breaking abstracts submission site opens</td>
<td>San Diego, CA</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<tr>
<td>22-25</td>
<td>AABB Annual Meeting &amp; CTXPO</td>
<td>San Diego, CA</td>
<td><a href="http://www.aabb.org">www.aabb.org</a></td>
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<td>30-</td>
<td>HAA-ISSHAPD Annual Scientific Meeting of HSANZ, ANZSBT, and ASTH</td>
<td>Sydney, Australia</td>
<td><a href="http://www.haa-ap2011.org">www.haa-ap2011.org</a></td>
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<td>Nov. 2</td>
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#### November

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<tr>
<td>2-4</td>
<td>World Conference on Regenerative Medicine</td>
<td>Leipzig, Germany</td>
<td><a href="http://www.wrcm-leipzig.com">www.wrcm-leipzig.com</a></td>
</tr>
<tr>
<td>9</td>
<td>Deadline for advance registration for ASH annual meeting</td>
<td>San Diego, CA</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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