**Uncertainty at the NCRR**  
NIH Plans Controversial Transition of NCRR Programs to NCATS and Other Institutes

On December 7, 2010, the National Institutes of Health (NIH) Scientific Management Review Board (SMRB) approved a recommendation to create a new center – the National Center for Advancing Translational Science (NCATS) – at the NIH focused on translational medicine and therapeutics. This decision follows the Obama Administration’s growing concern with the slowing rate of new drug production by the pharmaceutical industry. NIH Director Francis Collins believes that consolidating NIH’s translational research programs in the new Center will help attract the pharmaceutical industry’s attention and help drive production of new therapeutics – small molecules, biologics, and devices – for common as well as rare and neglected diseases. Dr. Collins believes that the new Center will approach the drug development pipeline as a scientific problem ripe for experimentation and process engineering in a systematic way.

Although the mission of the proposed NCATS, “to advance the discipline of translational science and catalyze the development of novel diagnostics and therapeutics across a wide range of human diseases and conditions,” is generally supported by the research community, some stakeholders question whether the NIH should get involved in research aimed at attracting the pharmaceutical industry, whether the new Center will be able to actually leverage outcomes of the translational research programs funded by the NIH, and whether this shift of focus toward translational science for creation of therapeutics will negatively affect investigator-initiated basic science research.

(Cont. on page 13)

**Non-Linear Evolutionary History of All Stem Cells**


The concepts of cancer stem cells in general, and leukemia stem cells in particular, have themselves undergone a significant evolution over the last decade. Initially, clonal evolution of stem cells was thought to represent a fundamentally linear process in which an initiating genetic aberration was complemented by one or more “driver” mutations, including copy number alterations (CNAs). This model suggested that if such stem cells could be identified and their genetic abnormalities characterized, specific targeted therapies could be designed to eradicate the initiating clones, leading to disease regression. However, over the last several years, multiple groups have described findings that are difficult to reconcile with the linear clonal evolutionary model of cancer (or leukemia) stem cells. These findings include the genetic and phenotypic heterogeneity of such cells, as well as their disparate growth patterns in immunocompromised mice.

Two recent studies involving acute lymphoblastic leukemia, results of which have recently been reported in *Nature*, highlight these issues and place them in an essentially new perspective. A group led by Dr. Mel Greaves of the Institute of Cancer Research, Sutton, United Kingdom, examined a series of pediatric acute lymphoblastic leukemia cases characterized by the *ETV6/RUNX1* fusion gene in relation to the presence of CNAs. Using techniques capable of single cell analysis, these investigators observed highly heterogeneous and diverse clonal architectures, most consistent with a branching, non-linear evolutionary history of leukemogenesis. Significantly, CNAs occurred in various subclones in no particular order and reiteratively at various stages of the disease. Leukemia cells propagating in immunodeficient mice also showed heterogeneous genetic alterations and proliferative capacities. In a parallel study by Dr. John Dick and colleagues from the Ontario Cancer Institute that investigated CNAs in patients with *BCR/ABL1* lymphoblastic leukemia, the authors observed very similar findings most consistent with a non-linear, branching, multi-clonal model of leukemogenesis. Of note, patients whose cells exhibited a deletion of *CDKN2A/B* had a particularly poor prognosis in that study.

The notion that putative leukemia stem cells are considerably more complex in their genetic makeup and biologic behavior than previously appreciated is sobering, yet it offers a theoretical foundation for future attempts to develop effective stem-cell-directed therapies. At one level, the concept of a heterogeneous, branching, non-linear evolution of leukemia stem cells could help to reconcile conflicting reports in the literature attempting to explain their origin and predict their behavior. At a second level, these insights could have important translational implications for the leukemia stem cell field. Although it would be comforting to think of leukemia-initiating cells in a monolithic way, it is becoming apparent that such a view represents a gross oversimplification and that individualized therapy may be necessary to eradicate multiple stem cell clones. This is undoubtedly a daunting task, but the present findings provide a rational basis for beginning this important quest.

ASH Highlights Continual Commitment to Basic Hematology Research by Establishing a New Committee on Scientific Affairs

The American Society of Hematology has always been committed to supporting basic hematology research, which is the foundation for progress in translational and clinical research. During his term as President last year, Dr. Hal Broxmeyer was instrumental in highlighting the need for ASH to be more active in fostering the participation of basic scientists in the core activities of the Society: to encourage the presentation of the best research at the ASH annual meeting and to promote its publication in Blood. We have significantly increased the resources devoted to these goals, most recently by establishing a new standing Committee on Scientific Affairs to serve as the Society’s strategically oriented scientific council.

The Committee on Scientific Affairs is responsible for developing strategic priorities in scientific areas of interest to ASH membership. To this end, it will provide a coordinated channel for our members and 17 scientific committees to advise the Society on setting these priorities. The Committee will periodically evaluate the scope of existing scientific committees and review proposals for new ones. In addition, the Committee on Scientific Affairs will make recommendations to the Nominating Committee for scientific committee membership. This process will allow ASH to stay at the forefront of leading-edge hematology research by adapting the expertise of its scientific committees to the changing scientific landscape.

One of the Committee’s major responsibilities is to ensure that ASH annual meeting addresses the needs of basic scientists, and several initiatives will help to achieve this goal. For example, the Committee is developing a process for real-time peer-review of 2011 Scientific Program Sessions to make sure that we deliver the best possible science at the annual meeting. A recent member survey indicated that scientists would appreciate more opportunities for informal networking, and the Committee is planning to extend the Q&A period after scientific sessions at the annual meeting so that trainees and junior scientists can interact with Scientific Program speakers. In addition, members of ASH Scientific Committees and the Program Committee, as well as the Scientific Program speakers, can now interact at a new Scientific Program reception at the annual meeting.

To promote the field of hematology, the Committee on Scientific Affairs will expand the role of scientific committees in ASH advocacy for biomedical research. To make sure the voice of scientists is heard in these discussions, the Committee will exchange liaison members with the Committee on Government Affairs. In addition, members of the Committee on Scientific Affairs will join our delegations that visit Capitol Hill every spring and attend other meetings with members of Congress, the NIH, other federal agencies, and public, patient, and professional organizations throughout the year.

The Committee on Scientific Affairs includes basic, translational, and clinical scientists that represent diverse areas of hematology. Its members include past scientific committee chairs and members, past Scientific Program Co-Chairs, ASH Scholars, and ASH Scholar Award Study Section members. The Committee’s inaugural Chair and 2010 Scientific Program Co-Chair, Rob Hromas of the University of Florida, has already begun to deftly navigate a packed agenda for this summer. The committee’s first item of business is to work closely with the scientific committees to update ASH’s Agenda for Hematology Research (www.hematology.org/Advocacy/Policy-Statements/1460.aspx). This publication identifies and prioritizes the most fertile areas of research in hematology and is a focal point for advocacy efforts with our colleagues at the NIH and members of Congress.

The Committee on Scientific Affairs will be instrumental in providing a forum for discussion of issues important to the Society’s membership. It is designed to serve as a voice of the ASH scientific community within and outside of the Society. We encourage all of you to make use of this new body established to represent ASH scientists.

For additional information on the ASH Committee on Scientific Affairs, please contact ASH Senior Manager for Scientific Affairs Ulyana Desiderio, PhD, at udesiderio@hematology.org.

J. Evan Sadler, MD, PhD
Save the Date: 2011 ASH State-of-the-Art Symposium

The 2011 ASH State-of-the-Art Symposium on “Recent Advances in Hematologic Malignancies Including a Special Focus on Plasma Cell Disorders” will take place September 23-24 in Chicago, IL. This clinically focused event will provide the same high-quality educational content for which the ASH annual meeting is known and give you a first look at the latest research developments in the field. Join your colleagues and discuss new treatment approaches and solutions for your day-to-day cases.

www.hematology.org/sas

Visit the ASH Store

The ASH Store is your destination for quality educational resources that allow you to stay current with the latest advances in the rapidly progressing field of hematology. Don’t get left behind – visit the ASH Store online to find valuable products to use as your personal learning and reference tools, or share them with your colleagues and students.

New products recently added include:
• 2011 Highlights of ASH Program Book and DVD
• 2010 Abstract Book
• Hematology 2010 (the Education Program Book)

Visit www.hematology.org/store to browse all ASH products online.

New Pocket Guide Available for ITP

In May, ASH will introduce the latest in a series of pocket-sized Quick Reference Guides. The new pocket guide, on the “Evaluation and Management of Immune Thrombocytopenia (ITP),” is based on the clinical practice guideline that was recently published in Blood. This handy reference for clinicians can be downloaded from the ASH website at www.bloodjournal.org/ITPguideline, and hard copies will be available at upcoming ASH meetings (including Highlights of ASH and the State-of-the-Art Symposium) for those who stop by the ASH booth. Look for announcements about a downloadable version of the pocket guide for mobile phones and tablets to be launched soon!
The Question
A 48-year-old man taking warfarin long-term for recurrent venous thromboembolism asks during his annual follow-up clinic about switching to dabigatran. He has had fluctuating INRs requiring testing approximately every two weeks and states that he is tired of dealing with frequent dose adjustments and clinic visits. He has tried to stabilize his INR by taking a daily 100 mcg vitamin K tablet for the last three months and switching from generic warfarin to brand-name Coumadin®, with no beneficial effects. Would you switch him to dabigatran? What would be your management strategy if major bleeding were to occur while taking dabigatran?

My Response
Background Information on Dabigatran
Dabigatran (Pradaxa®), a new oral anticoagulant, is a synthetic direct thrombin inhibitor that does not require monitoring of its anticoagulant effect by blood tests and is not influenced by dietary vitamin K intake. It was approved by the FDA in October 2010 for the prevention of stroke and systemic arterial thromboembolism in patients with atrial fibrillation based on a large trial showing that, at the approved dose (150 mg twice daily), it was more effective than warfarin in preventing stroke and systemic embolism, and equally safe.1

Dabigatran Use in DVT and PE
Dabigatran is not FDA-approved for the prevention or treatment of venous thromboembolism (VTE), so any such use would be considered off-label. However, a key phase III trial of 2,539 patients with acute deep-vein thrombosis (DVT) or pulmonary embolism (PE) showed that dabigatran (150 mg twice daily) taken for at least six months after a diagnosis of acute DVT or PE was as effective and safe as warfarin.1 These solid data make me comfortable considering off-label use of dabigatran for VTE treatment. It is important to realize, though, that in this trial dabigatran was not given as first-line treatment in patients with newly diagnosed VTE, but rather only after at least five days of a parenteral anticoagulant. Therefore, if I were to use dabigatran in patients with VTE, I would not use it first-line in the first few days after an acute clot. I would feel comfortable, however, switching from warfarin to dabigatran in the non-acute setting in select patients.

In Which Patients Might I Consider Off-Label Dabigatran Use?
Some patients tolerate warfarin quite poorly and/or dislike the therapy to such a degree that they would consider stopping treatment and accepting a significant risk of recurrent VTE. Reasons include: (a) wide fluctuations of INRs creating stress and need for frequent dose adjustments; (b) significant side effects (hair loss, fatigue); (c) decreased quality of life due to need for frequent blood tests, dietary restrictions, fear of bleeding, or recurrent thrombosis when non-therapeutic; and (d) cost of anticoagulation management, including clinic visits and INR testing. For these patients, I would consider a switch to off-label dabigatran.

In patients tolerating warfarin well and having stable INRs I would not yet consider a switch to dabigatran. It is a relatively new drug, and even though it has been used in a large number of patients (more than 20,000 in the phase III VTE1 and atrial fibrillation3 trials), I would like to see more real-life experience with the drug, more published data in the peer-reviewed literature on optimal management of major bleeding complications, and a comprehensive FDA review of the VTE trial data during the approval process for the VTE indication.

Management of Major Bleeding
One major reason for me not to prescribe dabigatran more frequently off label in VTE patients is that neither a reversal agent nor an established evidence-based strategy exist for management of major bleeding. In patients on warfarin who have a major bleed, established treatment options include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant factor VIIa, depending on the degree of bleeding. For bleeding on dabigatran, suggested management strategies are based on ex vivo plasma mixing studies, rat-tail bleeding models, or limited studies on healthy volunteers, and are mostly published only in abstract form.4,5 I am not aware of any peer-reviewed, full-length, patient-data-based publications on management of major bleeding in patients on dabigatran. Major bleeding occurred at rates of one in 32 patients and one in 63 patients in the atrial fibrillation1 and VTE trial3, respectively. It would be helpful to have data from these trials reporting how major bleeding was managed and what the clinical outcomes were, so that clinicians would have at least some clinical data to go by in their decisions about how to manage such patients.

In the event of bleeding in patients on dabigatran, management strategies should be individualized according to the severity and location of the bleed. Dabigatran is predominantly (80%) cleared by the kidney. It has a plasma half-life of 13 hours (range 11-22 hours) in individuals with normal renal function (creatinine clearance greater than 80 mL/min). This increases to 18 hours (range 13-23 hours) and 27 hours (range 22-35 hours) in patients with creatinine clearances of 30-50 mL/min and less than 30 mL/min,6 highlighting the need to maintain good renal output and consider hemodialysis in cases of major and life-threatening bleeding. Supportive measures, such as mechanical compression, surgical intervention, and fluid replacement, should of course be employed. Beyond that, treatment options include activated charcoal to prevent absorption of residual drug if the last drug intake was within two to four hours; PCCs with or without additional FFP, activated PCCs, recombinant factor VIIa, or antifibrinolytic drugs (aminocaproic acid or tranexamic acid). As major bleeding is likely to occur in some patients taking dabigatran, emergency departments and hematologists may want to proactively establish a management strategy for their institutions. To assist in the development of these approaches, I have provided suggestions for drug selection and dosing through Clot Connect (www.clotconnect.org), the educational resource of the University of North Carolina Blood Clot Education Outreach Program.5


Dr. Moll has consulted for OrthoMcNeil.
Stem Cell Transplantation for Adults and Children with Sickle Cell Disease: Progress at a Different Pace

MITCHELL E. HORWITZ, MD
Associate Professor of Medicine, Duke Adult Stem Cell Transplant Program, Duke University Medical Center

The first successful allogeneic stem cell transplantation (SCT) for sickle cell disease (SCD) was reported in 1984, establishing the procedure as the only curative option for the disease.1 However, widespread adoption of this treatment modality has been slow to evolve. There are multiple reasons for this, most important of which are the complex risk-versus-benefit considerations.

The risks of allogeneic SCT are well known, yet important advances in the field during the past decade have helped mitigate these risks. The ability to risk-stratify SCD patients has also improved recently. Patients with SCD are characterized as high-risk if they have central nervous system pathology (clinical or subclinical stroke, seizures), recurrent severe acute chest syndrome, chronic kidney disease, or chronic unremitting retinopathy, or some of the end organ damage such as pulmonary hypertension. The appropriateness of SCT can be more firmly established in the presence of these high-risk features.

When taken together, these advances have helped to clarify the role of allogeneic SCT in the management of SCD. But despite this, the procedure remains under-utilized and the pace of development is uneven among both adult and pediatric populations.

Allogeneic SCT for Pediatric Patients with SCD

The published results of allogeneic SCT for pediatric patients with SCD are excellent. The four largest series reported in the literature describe outcomes of more than 250 children, all with a median age of less than 10 years.2-4 With rare exception, a high-risk population of patients was targeted and the donors were HLA-identical siblings. All patients received fully myeloablative bone marrow conditioning. Graft rejection ranged between 7 and 18 percent, which is higher than what might be expected from a comparable group of patients transplanted for hematologic malignancy. However, overall survival was an impressive 93 to 100 percent. These studies established the fact that successful allogeneic SCT not only eliminates the sickle-cell-induced vaso-occlusive symptomatology, but also leads to reversal of some of the end organ damage that occurred prior to the procedure.

Use of a non-myeloablative conditioning regimen prior to allogeneic SCT reduces treatment-related toxicity, so this approach holds great appeal for the treatment of patients with non-malignant disorders. Yet efforts to employ non-myeloablative conditioning for transplantation of pediatric patients with SCD have been largely unsuccessful due to high rates of graft rejection.5 6 Thus, current opinion is that children with high-risk SCD and a suitably matched donor should be offered allogeneic SCT using a conventional myeloablative conditioning regimen.

Allogeneic SCT for Adult Patients with SCD

The risk-versus-benefit considerations surrounding adult patients with SCT are, in many ways, more complex than those in pediatric patients. The risks of the disease become quite apparent in many severely affected adults, and the toll on quality of life is often more dramatic. Yet for these very same reasons, risks of the SCT are amplified. Recent efforts have focused on reducing the risks of the transplant procedure by developing the non-myeloablative approach, and while published reports are few in number and small in size, they appear to demonstrate feasibility. Dr. Biernacki and colleagues recently reviewed published reports on the use of non-myeloablative SCT for SCD.7 Twenty-four patients were identified. With a median follow-up of 2.5 years, the overall and disease-free survival was 95 percent and 85 percent, respectively. While clearly compromised by reporting bias, the study demonstrates considerably more promise for this approach in adult patients compared with that in children. A multicenter phase II protocol of non-myeloablative SCT for adult SCD is in development and expected to begin accrual in 2011.

Mixed chimerism (presence of both donor and recipient hematopoiesis) is a frequently observed outcome of non-myeloablative SCT. Immunologic tolerance that characterizes mixed chimerism has been associated with a reduced frequency of severe graft-versus-host disease, but in recipients with underlying malignancies, it has also been associated with an increased risk for tumor recurrence. Donor lymphoid and myeloid chimerism is often discordant due to the significantly different lifespan of the cells in the lineage. In contrast, myeloid and erythroid cells share a relatively short lifespan, resulting in concordant chimerism. Furthermore, these lineages reflect the degree of donor stem cell engraftment. However, hemoglobinopathy transplant recipients with mixed chimerism typically display greater than 90 percent donor peripheral blood red cell chimerism, irrespective of the degree of donor leukocyte chimerism (Figure).8 9 10

The tremendous survival advantage afforded to normal erythroid cells is a consequence of ineffective host erythropoiesis, and there are significant clinical implications of this phenomenon. First, it provides a strong rationale for further development of a reliable non-myeloablative SCT approach that fosters stable mixed chimerism. In addition, it suggests a promising role for gene therapy in SCD patients for whom high-level gene correction of stem cells is difficult to obtain, but might not be necessary for therapeutic benefit.

Current Challenges and Future Directions

Access remains the major limitation to the broader use of SCT for treatment of severely affected patients with SCD, due to lack of private and government-funded insurance coverage. However, powerful pharmacoeconomic data demonstrating the advantage of early, definitive therapy for SCD versus lifelong supportive care may help improve coverage for SCT. In addition, the rarity of both unaffected HLA-identical sibling and matched unrelated donors severely limits accessibility of SCT therapy. Ongoing efforts to improve outcomes of umbilical cord blood and haploidentical transplantation for SCT may one day address this problem as well.


Comparison of lineage-specific chimerism in recipients of allogeneic SCT in patients with hemoglobinopathy. Data drawn from three separate studies.8 9 11 Figure adapted from Hsieh et al.12

Dr. Horwitz indicated no relevant conflicts of interest.
Congressional Showdown Over Government Shutdown; Battle Over 2012 Budget Just Beginning

As this issue of The Hematologist went to press, Congress was preparing to vote on a compromise deal on a final fiscal year (FY) 2011 spending bill. The FY 2011 plan was unresolved until an hour and a half before the government was scheduled to shut down. Overall, the deal included approximately $39 billion in cuts from previous spending levels but dropped most of the controversial policy provisions proposed by House Republicans.

The federal government has been operating under a temporary funding mechanism known as a Continuing Resolution (CR) since the start of FY 2011 on October 1, 2010. Because the CR, which provided flat funding for the National Institutes of Health (NIH), was set to expire April 8, Congress needed to pass a funding bill for the remainder of the fiscal year to avoid a government shutdown. However, negotiations between the House of Representatives, the U.S. Senate, and the White House had been stalled over major disagreements over not only spending cuts, but also 65 policy provisions that conservatives in the House wanted, including stopping the implementation of the 2010 health-care overhaul law and blocking funding for Planned Parenthood.

The compromise slices $13 billion from Labor-HHS-Education provisions but preserves $500 million for biomedical research at the National Institutes of Health originally set to be cut. Spending restrictions on the health-care overhaul law funding, included in an earlier House-passed spending bill (HR 1), were eliminated in exchange for studies on the impact of the law’s mandates. There continue to be controversial issues that are likely to meet strong resistance in Congress and will require Democrat and Republican leaders to persuade rank-and-file lawmakers to finally pass the deal. Once those votes occur, attention will focus on the FY 2012 funding bill in which NIH will once again be a target for budget cuts.

Further threatening NIH funding, the Congressional Budget Office (CBO) released a report titled “Reducing the Deficit: Spending and Revenue Options.” The CBO regularly produces a compendium of options for lawmakers to consider for altering federal spending and revenues, and Congress frequently refers to CBO options when considering changes in spending or revenue.

Included in the report are more than 100 options for altering federal spending or revenues, including an option that would “reduce or constrain” funding for NIH, suggesting two possible funding alternatives:

1. Restrict the rate of growth of the NIH appropriations to 1 percent per year, an amount less than recent annual biomedical inflation rates, or around 3 percent.
2. Reduce NIH’s FY 2012 appropriation to the FY 2003 funding level (which would mean a cut of about 13 percent); after that, funding would increase at the rate of inflation assumed in CBO’s baseline projections.

ASH will continue to advocate for support of the NIH. The Society has already participated in multiple coalition efforts as well as individual advocacy campaigns, Capitol Hill Days, and a communications strategy involving publishing letters to the editor in newspapers around the country. In the coming weeks and months, ASH will again be asking members for help in making the case for NIH and advocating for appropriate NIH funding in the upcoming FY 2012 budget. It is critical that members of the medical research community contact their Representative and Senators to inform them about the benefits of NIH-funded research and the threats posed by NIH funding cuts. Please take action by visiting the ASH Advocacy Center at www.grassroots.hematology.org to send a letter to your Representative and Senators. Updated information about FY 2011 and FY 2012 funding is available on the ASH website at www.hematology.org.

ASH Partners With Medical Organizations to Call for Permanent Fix for Medicare Physician Payment System

ASH, in partnership with 130 medical organizations, has sent letters to each member of the House of Representatives and Senate requesting a bipartisan, permanent fix to the current Sustainable Growth Rate (SGR) system.

The SGR is a statutory formula that sets overall targets in order to hold down spending on Medicare Part B physician services. Payment rates are adjusted every year to reflect differences between actual spending and the target. Since 2002, spending has exceeded the target, resulting in payment cuts. Beginning in 2003, Congress has repeatedly implemented temporary measures to avert the cuts.

Without action, the SGR mandates that Medicare payments be cut by 29.5 percent starting January 1, 2012. While Congressional leaders have indicated plans to take action by that date, there has not been agreement on a permanent solution, leaving doctors with uncertainty that affects their ability to formulate business plans. In addition, because of the enormous price tag of a complete overhaul of the current payment system – several hundred billion dollars over a decade – many believe Congress will likely put off a permanent solution once again at the end of the year in favor of a less costly, short-term fix.

Although it appeared a few years ago that both Democrats and Republicans were ready to include the costs of a comprehensive overhaul into the deficit, the rise of Tea Party activists makes that unlikely any time soon. The excuse at the end of this year for another short-term fix may be that the issue will be handled as part of eventual legislation overhauling the Medicare entitlement.

ASH continues to be active in working with the Congress to identify a permanent solution and will keep members apprised of developments.
ASH Announces Changes to Honorific Awards

GEORGE DOVER, MD
Given Professor and Director, Department of Pediatrics,
Johns Hopkins University

ASH Honorific Awards, the Society’s most prestigious awards, are presented during the annual meeting each year to recognize significant contributions to the field of hematology. For many years, there were only three awards — the E. Donnall Thomas Lecture and Prize, the William Dameshek Prize, and the Henry M. Stratton Medal. However, as the field of hematology has grown, so has the need for additional recognition. By 2009, the Ernest Beutler Lecture and Prize and the Society’s highest honor, the Wallace H. Coulter Award for Lifetime Achievement in Hematology, were added to the awards portfolio, which also includes the Mentor Award, established in 2006 to honor outstanding mentors in the hematology community. The Ernest Beutler Lecture and Prize recognizes major translational advances related to a single topic, while the Wallace H. Coulter Award for Lifetime Achievement in Hematology acknowledges an individual’s lifetime commitment and outstanding contributions to hematology — specifically one who has made a significant impact on education, research, and/or practice.

The field of hematology continues to be on the leading edge of targeted therapies and serves as a paradigm for the movement of knowledge from the bench to the bedside. Exponential growth in clinical research in recent years has resulted in further progress within the field of hematology. To capture the full breadth of the field, and to recognize colleagues at all stages of their careers, the Society decided to expand the portfolio of honorific awards even further, while at the same time redefining the descriptions of some of the existing awards.

In recognition of the work being done by both basic science researchers and clinical researchers, the Henry M. Stratton Medal will now be awarded to two individuals annually — one in basic science and one in clinical research. Furthermore, the Society wanted to recognize hematologists at all stages of their independent careers. As of the 2012 award cycle, the Stratton Medal will be awarded to mid-level and senior investigators (older than 50 years of age) and the William Dameshek Prize will be awarded to early-career investigators no more than 50 years of age. The criteria for the Wallace H. Coulter Award for Lifetime Achievement in Hematology, Ernest Beutler Lecture and Prize, and the E. Donnall Thomas Lecture and Prize will remain the same.

The changes to the honorific awards are meant to encourage a diverse pool of nominations, reflecting the evolving field of hematology and the researchers doing the work.

The nomination cycle for the 2012 honorific awards is now open, and the deadline to nominate a colleague is July 1, 2011. Please see the updated descriptions and submit a nomination by visiting the ASH website at www.hematology.org/awards/honorific/2239.aspx.

ASH NEWS AND REPORTS

OBITUARY

Ernest McCulloch
(1926 – 2011)

Ernest Armstrong McCulloch, a giant in the field of hematopoiesis, died in Toronto on January 20, 2011, at the age of 84. Together with his long-time colleague, Dr. James Till, he is especially recognized for the discovery of hematopoietic stem cells in the 1960s.

The work arose out of a study of the radiation sensitivity of normal bone marrow cells and led to the discovery of the spleen colony-forming unit (CFU-S) in the mouse. “Bun,” as he was affectionately known by his colleagues, and Jim Till showed that a spleen colony arose from a single cell and helped to define the criteria for a stem cell. Together with others at the Ontario Cancer Institute in Toronto where they worked, they were able to show that CFU-S had the capacity to self-renew and also to differentiate along multiple lineages. Their studies laid the groundwork for defining the properties of stem cells and provided a rationale for bone marrow transplantation. Dr. McCulloch extended these fundamental studies to acute myeloid leukemia and demonstrated the hierarchical organization and cytokine dependence of the clonal disorder, paving the way for the current focus on cancer stem cells as therapeutic targets.

Dr. McCulloch was the recipient of many awards throughout his career, including membership in the Royal Society of London, the Gairdner Foundation International Award, the Thomas W. Eadie Medal, and the Order of Canada. He delivered ASH's prestigious Henry M. Stratton Lecture in 1982 and, most recently (together with Jim Till), was presented with the Albert Lasker Award.

Despite his international prominence and formidable demeanour (the inevitable bow tie), Dr. McCulloch was a gentle and modest man. He was a wonderful teacher and an outstanding mentor. He was very interested in ensuring that all the graduate students, postdoctoral fellows, and junior faculty with whom he interacted were able to attain their highest possible level of scientific development. He inspired several generations of researchers who will remember his passion for science, his integrity, and his ability to think well beyond the immediate project. Although he leaves a remarkable legacy, his wisdom and perspective will be greatly missed.

— Armand Keating, MD

The Hematologist: ASH NEWS AND REPORTS
Histone Deacetylase Inhibitors Block Platelet Production

This study from the laboratory of Dr. Ricky Johnstone in Australia is focused on the underlying cause of the profound thrombocytopenia that occurs in about 80 percent of patients taking histone deacetylase inhibitors (HDACi). This thrombocytopenia is often the dose-limiting toxicity with all types of HDACi, including panobinostat (a pan-HDACi), romidepsin (HDAC1/2-selective), and vorinostat.

HDACs regulate chromatin structure by deacetylating histones that form the cores of nucleosomes around which DNA wraps. Deacetylation of histones is associated with more tightly wrapped chromatin and transcriptional repression. Because cancer cells are known to silence tumor suppressors, HDACi are thought to have anti-tumor activity by reactivating expression of these genes that normally prevent cell transformation. This is likely an oversimplification, because some genes are downregulated after exposure to HDACi and HDACs may also deacetylate non-histone proteins.

HDAC inhibitors are effective in many types of cancer including Hodgkin lymphoma, T-cell lymphoma, and multiple myeloma. Although their molecular mechanisms are thought to be known, it is not yet clear how their anti-tumor effects are mediated. Because the histone targets are spread throughout the entire genome, the effects of HDACi are considered to be quite broad, so specific genes whose reactivation is induced by these drugs in each different malignancy have not been identified. Similarly, the mechanism by which these relatively nonspecific drugs cause thrombocytopenia has not been identified.

In this study, the investigators show that multiple HDACi used in the clinic can also induce thrombocytopenia in mice, and they use this murine system along with cell lines to determine a mechanism for the thrombocytopenia. They show that, unlike the thrombocytopenia that occurs with conventional chemotherapy, HDACi do not have anti-mitotic or pro-apoptotic effects on hematopoietic stem and progenitor cells, and that both thrombopoietin levels and megakaryocyte numbers are elevated. Thus, they pursued studies to determine why thrombocytopenia occurs despite normal cellularity with increased megakaryocytes in the marrow.

Culturing the cells in vitro, they visualized a defect in proplatelet formation by megakaryocytes from mice that had been treated with HDACi. Proplatelet formation, which occurs when multiple long projections extend out from the megakaryocytes, is required for release of functional platelets and requires the coordinated action of actin and tubulin cytoskeletal elements. The mediators of these complex cytoskeletal changes are the G proteins Rac, Rho, and CDC25. In order for proplatelets to form, myosin light chain 2 was maintained in a highly phosphorylated form, presumably due to alterations in the network of proteins that regulate RhoA activity.

Importantly, the investigators could prevent HDAC inhibitor-induced thrombocytopenia in the mice by administering a mouse-specific thrombopoietin-mimetic (AMP-4), which returned the platelet count to levels similar to those in untreated controls. AMP-4 is the murine version of the FDA approved thrombopoietin-mimetic romiplostim (AMG-531).

These studies begin to answer the question of why thrombocytopenia occurs in response to HDACi, but it remains to be determined how HDACi promote RhoA stimulation. These findings may also be relevant to the thrombocytopenia that can occur in patients treated with the anti-epileptic drug valproic acid, which also functions as an HDACi. Seemingly not directly related to the findings regarding RhoA activation, this study also shows that thrombopoietin mimetics may be clinically useful for preventing HDACi-induced thrombocytopoenia even in the setting of elevated levels of endogenous thrombopoietin, thus allowing HDAC inhibitors to be more widely used as anti-tumor agents.

DIANE KRAUSE, MD, PhD
Dr. Krause indicated no relevant conflicts of interest.

Rusting Vessels: How Inflammation and Iron Can Promote Atherogenesis

Over 30 years ago, Dr. Jerome Sullivan hypothesized that the differences in incidence of heart disease between the sexes could be attributed to differences in stored iron. He suggested that phlebotomy to deplete iron might be a reasonable clinical experiment to test a potential role of iron in this risk factor. Dr. Zarcharski proposed the feasibility of such a study in 2000 and then demonstrated correlations between levels of ferritin, inflammatory biomarkers, and mortality in a subset of patients with peripheral arterial disease. However, this hypothesis has been challenged by studies in hemochromatosis patients with HFE mutations, which have failed to demonstrate an association with coronary artery disease. So Dr. Sullivan recently described the “hepcidin” hypothesis to reconcile this paradox. In most patients with HFE mutations and iron overload, hepcidin levels are low. Atherosclerosis is an inflammatory process, and cytokines such as IL-6 can increase hepcidin, which in turn can regulate macrophage iron content.

Valenti et al. from Milan now enter this debate by demonstrating that hepcidin and macrophage iron correlate with both MCP-1 release and vascular damage in high-risk individuals with metabolic syndrome, including hyperlipidemia, Type 2 diabetes, and hypertension. Patients with nonalcoholic fatty liver disease (NAFLD)/metabolic alterations and elevated ferritin levels were compared to patients with C282Y HFE homozygosity or heterozygosity with C282Y or H63D. The researchers used monocyte activation, serum hepcidin, and carotid artery intima media thickness to determine the extent of vascular damage. In response to iron, monocytes with HFE genotypes had a partial defect in iron retention. Iron treatment increased MCP-1 and IL-6 in normal monocytes, especially those in patients with advanced carotid vascular disease, but not in monocytes with HFE mutations. Hepcidin and iron added to normal monocytes, which blocked ferroportin and allowed monocyte iron accumulation, progressively increased MCP-1 mRNA and protein. In 130 patients with NAFLD, hepcidin levels correlated with serum ferritin and MCP-1 levels. In addition, serum MCP-1 levels were higher in patients with carotid artery wall than in those without such plaques. In multivariate analysis, the presence of carotid plaques was significantly associated with ferritin and MCP-1 serum levels, independent of classic risk factors and HFE mutations.

There is a strong association between NAFLD and cardiovascular risk with metabolic syndrome. The role of inflammation and oxidative stress underpins this risk and suggests the rationale for antioxidant or cytokine therapies. Most of these patients have elevated serum ferritin, suggesting that iron may be driving oxidative stress. In Dr. Valenti’s study, patients with NAFLD/metabolic syndrome and iron overload related to the presence or absence of HFE mutations were phlebotomized. Should the Sullivan and Zarcharski hypotheses regarding phlebotomy in certain patients with iron overload in the absence of HFE mutations be revisited? Would drugs lowering hepcidin levels be beneficial in NAFLD? Do patients with homozygosity for C282Y with inflammation or NAFLD have an even greater risk of cardiovascular disease? In plaques, there are frequently hemorrhaging red cells that can provide heme-derived iron, but is heme-derived iron in the artery wall more atherogenic? Although not resolved, the possibility that iron promotes rusting of vessels remains intriguing.

2. Depalma RG, Hayes VW, Chow BK, et al. Ferritin levels, inflammatory biomarkers, and mortality in peripheral arterial disease: a substudy of the iron (Fe) and atherosclerosis study (FeAST) trial. J Vasc Surg. 2010;51:1498-1503.

GREGORY M. VERCELLOTTI, MD
Dr. Vercellotti indicated no relevant conflicts of interest.

The Hematologist: ASH NEWS AND REPORTS
Immunosuppression in Myelodysplastic Syndrome: Where Do We Go From Here?


Four therapies are currently FDA-approved for myelodysplastic syndromes: azacitidine, decitabine, lenalidomide, and deferasirox for iron overload. These success stories are notable exceptions along the historical highway of MDS treatment, which has been littered with numerous underwhelming investigational agents. Antithymocyte globulin (ATG) and cyclosporine (CSA) have been studied in MDS based on the premise that a subset of patients experience cytopenias due to suppression of hematopoiesis by cytotoxic T cells, similar to the mechanism seen in aplastic anemia. In the current National Comprehensive Cancer Network (NCCN) guidelines for MDS, immunosuppressive therapy with ATG and CSA is recommended as an option in low-intermediate-1 risk international prognostic scoring system (IPSS) patients in whom the serum EPO level is greater than 500 mU/ml and who have a good probability of response. In addition to lower-risk disease, younger age, hypoplastic marrows, HLA-DR15, shorter duration of disease or red blood cell transfusion dependence, and PNH clone positivity have been identified as predictors of response.

On behalf of the Swiss Group for Clinical Cancer Research and the German Myelodysplastic Syndrome Study Group, Passweg and colleagues report on a multicenter, randomized phase III trial comparing horse ATG 15 mg/kg for five days plus CSA for 180 days (n=45) versus best supportive care (BSC, n=43). BSC included transfusions, antibiotics, iron chelation, and growth factor dependence was ongoing for less than 24 months. Most enrolled patients belonged to low or intermediate-1 risk groups, but patients with higher blast counts (> 10%) were eligible if other therapy was not available. The primary endpoint was hematologic response at six months, with cross-over to the ATG plus CSA arm permitted upon disease progress or lack of response to BSC after six months. Based on an intent-to-treat analysis, there was a statistically significant higher hematologic response rate of 13/45 (29%) versus 4/43 (9%). With a median follow-up of 2.3 years, the typical qualifiers likely account for some of the differences in response across trials – study design, the IPSS risk status of patients, ATG preparation (equine vs. rabbit), and the evolution of MDS response criteria over the last 10-15 years. At this time, it is not clear whether additional trials of ATG (with CSA) will provide new or useful clinical information that has not already been gleaned. Where we go from here may rest more squarely on identifying the basis for immune-mediated marrow failure with more biologic specificity and translating these findings into novel therapeutics.

Coming of Age and Thrombosis: It’s All in the Family


Genetic risks for venous thromboembolism (VTE) are known to include factor V Leiden and prothrombin G20210A mutations, as well as deficiencies of anti-thrombin, protein C, and protein S. Only 50 percent of the variability in inherited thrombophilia is attributed to familial risk, but even standard VTE risk factors, such as age, immobilization, trauma, malignancy, and estrogen, do not explain the differences in familial VTE risk between children and adults.

Utilizing a nationwide registry, the Swedish Multigeneration Register, linked to hospital discharges, Dr. Zöller and colleagues looked for other determinants of VTE risk among families during the 20-year period of 1987 to 2007. Specifically, they compared cases of VTE (deep venous thrombosis [DVT] and/or pulmonary embolism [PE]), defined by ICD-9 and ICD-10 codes, in offspring of parents hospitalized for VTE and offspring of unaffected parents, specifically calculating the ratio of observed to expected VTE cases, known as standardized incidence ratios (SIR). Linkages were made through individual national identification numbers for each of the 45,362 patients identified on the basis of the first discharge. The ICD codes included DVT, PE, superficial venous thrombosis, and other thromboses, such as portal vein, cerebral vein, and pregnancy-related thromboses.

Parental history of VTE was a strong risk factor for VTE. Of 4,865 children, among whom at least one parent had VTE, the SIR for VTE was 2.00 (95% CI, 1.94-2.05). VTE risk was higher among males, with a SIR of 2.08 (2.00-2.16) and was higher among those in whom both parents were affected, with a SIR of 3.97 (3.40-3.61). Age-specific VTE rates were increased for offspring, with the highest VTE risk in those 10-19 years of age, with a noted SIR of 3.98 (3.13-4.94) and lowest VTE risk in those 70-75 years of age, at a SIR of 1.48 (1.17-1.84). No increase was noted in those under 10 years of age.

There are potential biases in this dataset, which include missing non-hospitalized individuals or those not identified by ICD codes, but these biases are likely to be similar between the groups studied, so the bias is not likely to be selective.

These findings have important implications. First, parental history of VTE is an important risk factor for VTE and should be an important element of clinical history. Second, the contribution of parental VTE to VTE risk decreases with age even though the overall risk of VTE increases, suggesting that familial VTE history is most important at younger ages. Third, children under 10 years of age, even in thrombophilic kindreds, have no increase in VTE risk. Because VTE risk associated with familial VTE is greatest between the ages of 10 and 50, the latter age group should be the primary focus of genome-wide association studies.

<table>
<thead>
<tr>
<th>Group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>With VTE in any parent</td>
<td>2.08 (95% CI: 2.00-2.16)</td>
<td>1.91 (95% CI: 1.84-1.99)</td>
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<tr>
<td>With VTE in father</td>
<td>2.09 (95% CI: 1.97-2.22)</td>
<td>2.03 (95% CI: 1.91-2.16)</td>
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<tr>
<td>With VTE in mother</td>
<td>2.03 (95% CI: 1.93-2.13)</td>
<td>1.80 (95% CI: 1.70-1.89)</td>
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<tr>
<td>With VTE in both parents</td>
<td>4.28 (95% CI: 3.44-5.25)</td>
<td>3.67 (95% CI: 2.91-4.57)</td>
</tr>
</tbody>
</table>

Margaret V. Ragni, MD, MPH
Dr. Ragni indicated no relevant conflicts of interest.
SNPs Tell Tales About What Myelodysplasia Is Made Of


D etection of chromosomal rearrangements in patients with myelodysplastic syndromes (MDS) is useful in several respects. To the clinical pathologist, finding a somatic chromosomal abnormality confirms the clonal nature of the patient's bone marrow failure syndrome, supporting a diagnosis of MDS or another neoplastic myeloid disorder rather than a reactive, non-neoplastic cause for the cytopenias. To clinicians, the specifics of patients' abnormal karyotypes are prognostically important, as per the familiar 1997 International Prognostic Scoring System, as well as the more recent and comprehensive cytogenetic clinical outcomes dataset from a German-Austrian MDS consortium organized by Detlef Haase and Christian Steidl.1 To the scientist interested in MDS pathobiology, recurrent somatic abnormalities indicate genetic loci worthy of further laboratory investigation. For instance, frequent loss of heterozygosity (LOH) at chromosomes 4q24 and 7q35 contributed to discovery of recurrent TET2 and EZH2 mutations, respectively, in MDS and related myeloid neoplasms.

Yet nearly one-half of patients with MDS have a normal G-banded metaphase karyotype. The mechanisms of disease in such patients remain largely obscure; some cannot even obtain a clear diagnosis of MDS, and instead may need to be helplessly labeled “Idiopathic Cytopenias of Undetermined Significance (ICUS),” and allowed expertly to pursue their clinical course. It does not mean, of course, that the patients' chromosomes are normal – counting a few hundred stainable bands on 20 or 30 metaphase preparations is an insensitive technique for chromosomal assessment, offering detection only of large translocations, or deletions and additions involving many megabases of DNA.

The first attempts to improve on metaphase karyotyping in MDS included panels of fluorescent in situ hybridization (FISH) probes targeted to common chromosomal abnormalities, such as deletions of chromosomes 5 or 7. While MDS FISH panels assess as many as 500 cells and can be useful if karyotyping fails or the patient refuses a bone marrow exam, the yield of such FISH panels in patients with a good metaphase karyotype prepared in a competent clinical laboratory is quite low, and FISH probes can only assay already-recognized abnormalities. In recent years, several groups of investigators have begun to explore newer whole-genome scanning techniques in MDS, including comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays. The latest human SNP arrays include millions of genetic markers, offering unprecedented resolution for detecting copy-number variation and LOH across the genome.

In this study, an international consortium of investigators brought together by Dr. Jaroslav Maciejewski of Cleveland Clinic assessed samples from 430 patients with MDS, acute myeloid leukemia, or myelodysplasia arising from MDS or myeloproliferative overlap syndromes. The array-based technology detected chromosomal defects in 74 percent of patients, compared to only 44 percent by metaphase cytogenetics. It also found abnormal results in patients with normal metaphase cytogenetics, as well as additional abnormalities in patients already known to have abnormal cytogenetics. Dr. Maciejewski and colleagues compared paired marrow and CD34+ selected non-clonal cells whenever possible, since it can be difficult to distinguish germline and somatic copy number variations on size criteria alone.2 Abnormal SNP array results had a negative prognostic value independent of existing risk stratification criteria. It seems, then, that SNP arrays and related techniques may offer new insights into not just what MDS might be “made of,” but also which cases are less likely to behave indolently (i.e., move like a snail) or evolve more rapidly (i.e., like a frisky puppy dog tail), and perhaps even which patients need to be treated only with “sugar and spice” versus something not quite so nice.

This study confirms the ability of array-based technology to detect prognostically important somatic chromosomal defects in patients with MDS, which may also prove to be useful diagnostically, especially in ICUS cases. While several clinical laboratories are now offering array-based whole genome scanning tests on a fee-for-service basis, more data are needed in order to understand the role that SNP arrays and related techniques might play in diagnosis algorithms and treatment planning. In the short term, whole-genome arrays will continue to be a powerful tool to improve our understanding of MDS mechanisms.


Heparin: Everything Old is New Again


H earpin, a tissue-derived glycosaminoglycan (GAG), has been widely used as a standard anticoagulant for more than 40 years. A pentasaccharide sulfation sequence within the heparin polymer binds antithrombin and mediates the anticoagulant activity. Heparin also possesses non-anticoagulant properties, and these relate to the binding, immobilization, and/or activation of proteins, growth factors, chemokines, and matrix metalloproteinases (MMPs). These alternative functions have triggered investigations of heparin-based agents in cancer and inflammation. Two recent reports explore these pleiotropic mechanisms of heparin and heparin derivatives and suggest novel therapeutic applications.

A study by Dr. Ritchie et al. from University of Alabama Birmingham was prompted by the knowledge that heparanase is highly expressed in multiple myeloma (MM) and other tumor microenvironments, where it promotes growth and invasion by enhancing growth factor expression and stimulating the shedding of heparan sulfate proteoglycan syndecan-1. Using a number of murine xenograft models of MM, the team evaluated the effects of SST0001, a modified non-anticoagulant heparin with potent anti-heparanase activity, They observed that SST0001 significantly inhibits MM growth without associated adverse effects and that combination with dexamethasone augments tumor suppression and overcomes dexamethasone resistance. SST0001 reduced intratumoral CD34+ vasculature and extracellular HGF and VEGF levels, and inhibited MMP-9 expression and syndecan-1 shedding. Collectively, these data suggest that the anti-heparanase activity of SST0001 prevents downstream activation MMPs, syndecan-1 release, and other growth-promoting factors that stimulate angiogenesis and myeloma progression.

Dr. Poli et al. from Brescia, Italy, investigated whether heparin might affect liver hepcidin expression, because cell surface heparan sulfate proteoglycans are known to modulate bone morphogenetic protein (BMP) activities and BMP signaling regulates hepcidin expression. Unfractionated heparin (UFH) was found to strongly inhibit hepatic mRNA expression in cultured HepG2 liver cells, whereas low-molecular-weight heparin (LMWH) had a modest effect and the pentasaccharide anticoagulant fondaparinux had minimal effect. UFH appears to act by sequestering extracellular BMPs (mainly BMP6), which prevent BMP signaling through pSMAD1/5/8 and downstream induction of hepcidin expression. Treating mice with UFH lowered basal levels of liver pSMAD1/5/8 protein and hepatic mRNA, reduced splenic iron content, and increased serum iron levels. An exploratory study of five patients receiving prophylactic LMWH for serious infection or medical illness revealed decreased levels of serum hepcidin and C-reactive protein at 20 hours and subsequent decreases in serum iron and transferrin saturation.

If the observations of Dr. Ritchie et al. are confirmed in additional studies, SST0001 could soon move to phase I trials of patients with myeloma or other heparanase-producing tumors. The observations by Dr. Poli et al. are intriguing and suggest that rationally designed, non-anticoagulant heparin oligosaccharides with BMP-modulating activities might be useful for anemia of inflammation and other conditions with hepcidin overexpression. On a more global level, these reports complement a large body of work with other non-anticoagulant heparin derivatives, heparan sulfate-based drugs, GAG mimetics, and glycan-based inhibitors developed for metabolic, infectious, inflammatory, and malignant disorders and tissue regeneration.3,4 It is enlightening to realize that our “age-old” friend heparin has played a major role in the understanding of glycochemistry in health and disease and has facilitated drug discovery in a number of exciting directions.

Induction Combination Novel Agent Therapies in Myeloma


In this study, Cavo and colleagues from Italy report on the relative efficacy of thalidomide and dexamethasone (TD) versus bortezomib-thalidomide-dexamethasone (VTD) used both as initial therapy and as consolidation treatment after high-dose melphalan and stem cell transplantation in multiple myeloma (MM). The primary metric of efficacy was complete response (CR) or near complete response (nCR) rate after induction therapy. Importantly, the rate of CR or nCR was 31 percent after VTD versus 11 percent after TD (p < 0.0001). Moreover, rates of CR, nCR, or very good partial response (VGPR) were higher with VTD than TD after first transplant, after second transplant, and with consolidation therapy. The estimated three-year rate of progression-free survival (PFS) was greater after VTD than TD, at 68 percent versus 56 percent, respectively (p<0.006). However, the estimated three-year overall survival (OS) rate was not statistically different, at 86 percent versus 84 percent post VTD and TD, respectively (p=0.30). Grade 3 or 4 adverse events occurred in 56 percent of patients on VTD and in 33 percent of patients on TD (p<0.0001), including 10 percent versus 2 percent grade 3 or 4 neuropathy after VTD and TD, respectively, which resolved in the majority of cases.

Novel agents have now been shown to be efficacious to treat relapsed and refractory, relapsed, and newly diagnosed MM. In transplant-eligible patients, two drug induction regimens, including dexamethasone with thalidomide, lenalidomide, or bortezomib, achieve high extent and rate of response prior to transplantation, which portends improved outcomes post-transplant. In patients with relapsed MM, three drug regimens incorporating novel agents, such as VTD or lenalidomide-VD (RVD), have shown activity even in patients whose disease is resistant to either single novel-agent therapy. Excitingly, three drug regimens, such as VTD, RVD, or cyclophosphamide-VD, achieve responses in the majority of patients with newly diagnosed MM, with an unprecedented extent of response, including some molecular complete responses. Cavo and colleagues in this study for the first time report a randomized trial comparing two versus three novel drug combination therapies, not only as induction therapy prior to autologous stem cell transplantation, but also as consolidation treatment. Remarkably, at every point along the disease course, including pre-transplant, after first transplant, after second transplant, and as consolidation, there were statistically significant increases in overall and extent of response with VTD versus TD. Of note, there was an upgrade in extent of response related to consolidation VTD therapy post-transplant, as has been observed with use of lenalidomide, further confirming incorporation of novel therapy in this fashion. As in multiple previous studies, incorporation of bortezomib overcame the adverse effects of 4/14. And most importantly, molecular responses were more frequently achieved with VTD, a depth of response not previously achieved in MM except after allografting, when it portends prolonged disease-free survival. Finally, these unprecedented results achieved with incorporation of induction combination novel therapies into the transplant paradigm further support the rationale for ongoing studies to determine the contribution of high-dose therapy to this outcome.

The Mighty Platelet


The phenomenon of clot retraction has been a favorite subject of hematologists since it was first described by William Hewson in 1780. We now know that clot retraction is due to the actomyosin-dependent contractile force of platelets that are bound to a fibrin mesh. Clot retraction alters clot organization and stiffness, which are abnormal in certain pathological states such as premature coronary disease. Dr. Lam et al. working in the laboratory of Dr. Daniel Fletcher at Berkeley used atomic force microscopy (AFM) to measure the forces produced by single, thrombin-activated platelets bound to fibrinogen (see Figure). In this method a suspension of activated platelets is viewed under a conventional optical microscope and a fibrinogen-coated surface is shifted to trap a single platelet between the surface and a fibrinogen-coated AFM cantilever. Upon contact with fibrinogen, the platelet immediately begins to contract, the cantilever is pulled down, and the distance it moves is measured optically. The cantilever is then calibrated using displacements resulting from known applied forces. Thus, the displacement force caused by single platelet contraction can be calculated.

Measurements were made using cantilevers of varying stiffness, which has the physiological correlate that clot stiffness increases with fibrinogen density. Also, by moving the surface during platelet contraction to keep its distance from the cantilever constant, it was possible to measure platelet contractile force at infinite stiffness, corresponding to isometric contraction. The authors found that as cantilever stiffness increased, platelets exhibited higher contraction forces and rates of contraction. The average contractile force of a single platelet under conditions of maximum contraction was 19 nanonewtons (nN). Because a single myosin II molecule produces a maximum force of approximately 6 pN and there are approximately 12,000 myosin II molecules per platelet, the authors estimated that the maximum contractile force of a platelet is 72 nN. Thus, the mean contractile force of a single platelet is approximately 25 percent of this maximum value. This value is similar to the efficiency of force production observed in skeletal muscle cells, which, unlike platelets, have highly-ordered sarcomeres. Additionally, the force per unit area exerted by a single platelet was estimated to be more than one order of magnitude higher than produced by a single myoblast. Thus, the contractile forces generated by platelets are surprisingly high.

The authors also investigated the mechanical properties of single contracted platelets. After platelet contraction was complete, the cantilever was pulled down until adhesion to the surface or the cantilever was ruptured, which defined the adhesion strength. During the initial part of this maneuver, the ratio of force per unit area on the platelet to the cantilever constant, it was possible to measure platelet contractile force at infinite stiffness, corresponding to isometric contraction. The authors found that as cantilever stiffness increased, platelets exhibited higher contraction forces and rates of contraction. The average contractile force of a single platelet under conditions of maximum contraction was 19 nanonewtons (nN). Because a single myosin II molecule produces a maximum force of approximately 6 pN and there are approximately 12,000 myosin II molecules per platelet, the authors estimated that the maximum contractile force of a platelet is 72 nN. Thus, the mean contractile force of a single platelet is approximately 25 percent of this maximum value. This value is similar to the efficiency of force production observed in skeletal muscle cells, which, unlike platelets, have highly-ordered sarcomeres. Additionally, the force per unit area exerted by a single platelet was estimated to be more than one order of magnitude higher than produced by a single myoblast. Thus, the contractile forces generated by platelets are surprisingly high.

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The results of this study provide important new insights into platelet dynamics and the properties of blood clots. The novel experimental system developed in this study could lead to probes of platelet function in health and disease.

The Peculiarity of Mediastinal Lymphomas: A Target For Epigenetic Therapy?


The sub-classification of aggressive B-cell lymphomas has moved on steadily since just a decade ago, when gene expression profiling first suggested that molecular patterns might correspond to a specific clinical phenotype. One of the entities recognized as distinct early on was primary mediastinal lymphoma (PMBL), but to date there have been few clear indications about the driving events beyond the observation that PMBL appears to cluster with Hodgkin lymphoma (HL) rather than diffuse large B-cell lymphoma (DLBCL). One of the most frequent findings on array genome hybridization is amplification of chromosome 9p24, which was detected in 45 percent of PMBLs but in only 11 percent of activated B-cell-type and in 7 percent of germinal center B-cell-type DLBCL. This paper describes the characterization of two cooperating genes within this region of amplification that appear to play a key role in lymphomagenesis, a novel mechanism with potential for therapeutic exploitation.

Members of the Lymphoma Molecular Profiling Project consortium, based in the NCI Metabolism Branch, have carried out an elegant series of experiments using a library of short hairpin RNA molecules to knock down the function of each of the potential oncogenes within the amplicon. Their experiments have shown that suppression of three genes was selectively toxic to PMBL and HL cell lines: JAK2, a tyrosine kinase downstream of cytokine receptors; JMJD2C, a dioxygenase that can demethylate histone 3 at lysine 9 (H3K9); and RANBP6, a gene of unknown function. The involvement of JAK2 is interesting because activating JAK2 mutations are key events in myeloproliferative disorders. In this study the authors show that its overexpression leads to an autocrine growth loop via Interleukin-13 and the increased expression of a very significant proportion (16%) of the genes that characterize PMBL.

The most novel observation, however, is the cooperation between JAK2 and JMJD2C, with the former mediating tyrosine phosphorylation on histone 3 tyrosine 41 (H3Y41), and the latter demethylating H3K9, both of which lead to suppression of heterochromatin formation and transcriptional deregulation. One important effect of these events is the expression of c-MYC, a powerful driver of cell cycle and self-renewal, whose expression could be suppressed in the cell lines by a JAK2 inhibitor. However, there were many other genes potentially involved, and the add-back experiment with c-MYC did not fully reverse the effects of JAK2 or JMJD2C suppression.

These results are another manifestation of the power of functional genomics, using inhibitory RNA libraries to dissect the precise functions of different genes in malignant cell lines. The surprising finding here was that two genes on the same amplified segment worked together to modify the epigenome of lymphoma.

The findings have several potential implications for therapy. First, it is apparent that inhibitors of JAK2 may exert potent cytotoxicity in PMBL and HL, with an unusually large number of target genes apparently dependent on JAK2 for maintenance of the phenotype. Since JAK2 inhibitors are already under study in the clinic for myeloproliferative disorders, there is scope for rapid testing of this approach. Second, the presence of an autocrine growth loop also provides an opportunity for intervention, for example with antibodies to IL-13, which might be expected to suppress the continued activation of the pathway. Finally, it is increasingly clear that epigenetic modification is a potential target for lymphoma therapy, and the development of histone demethylase inhibitors may be useful pursued in the future for a variety of malignancies with 9p24 amplifications.

A NAC for Reducing vWF


V on Willebrand factor (vWF) is synthesized in megakaryocytes and endothelial cells as a precursor protein that is assembled into large multimers of greater than 20,000,000 MW. Individual vWF molecules (~275 kDa) are composed of multiple domains and attached to one another via disulfide bonds. vWF multimers are processed by the metallopeptase ADAMTS13, which cleaves vWF within the A2 domain. Congenital absence of ADAMTS13 or neutralizing antibodies directed against the metallopeptase result in excess ultra-large von Willebrand factor multimers (ULVWF), which are procoagulant and contribute to the microangiopathy of thrombotic thrombocytopenic purpura (TTP). ULVWF may represent a tractable target for new therapeutic strategies in TTP. Recombinant ADAMTS13 has been proposed as a means to treat TTP, but it has yet to be studied in human trials and may be problematic in patients with high titer anti-ADAMTS13 antibodies. Dr. Chen and colleagues working in the laboratory of Dr. Jose Lopez at the Puget Sound Blood Center in Seattle now demonstrate an alternative strategy for attacking ULVWF, by chemically reducing the disulfide bonds that are required for vWF polymerization.

Noting similarities between the overall polymeric structure of mucins and that of polymerized vWF, Dr. Chen and his colleagues posited that N-acetylcysteine (NAC) could be used to dissolve multimeric vWF in a manner analogous to its role in chronic obstructive lung disease, in which it acts as a mucolytic agent. The investigators found that adding NAC to plasma ex vivo reduced intercellular disulfide bonds that link vWF subunits, thereby decreasing the abundance of ULVWF. Similarly, infusing NAC into mice reduced ULVWF in plasma. In addition to decreasing the abundance of ULVWF, NAC reduced an intramolecular bond in the A1 domain (Gys1271-Cys1458) of vWF, required for its association with the platelet receptor glycoprotein Ib and inhibited the ability of vWF to bind platelets. Incubation with NAC dissolved platelet-vWF strings that form under flow conditions on cultured endothelial cells stimulated with histamine. The authors also performed a series of tests to evaluate the effect of NAC on platelet thrombus formation in mesenteric venules induced to secrete ULVWF by exposure to calcium ionophore. NAC reduced platelet thrombi in both wild-type and ADAMTS13-/- mice.

Despite the substantial advances in our understanding of the etiology of thrombotic thrombocytopenic purpura (TTP), the mainstay of treatment for the disease has been plasma exchange. Although plasmapheresis is effective, acute TTP is associated with a mortality rate of 20 percent and relapse is common, so there is need for new and safer treatments that leverage the considerable progress made in understanding the molecular pathophysiology of the disease. The clinical implications of the observation that NAC reduces vWF multimers and facilitates the dissolution of thrombus in vivo are compelling. The diagnosis of TTP is not always immediately apparent and plasma exchange is not always immediately available. It is easy to envision how a relatively non-toxic, inexpensive agent could be incorporated into TTP treatment algorithms, at least as a temporizing therapy. Long-term treatment at lower doses of NAC could reduce recurrence.

Whether NAC will be effective in ameliorating TTP remains to be determined. It is a relatively nonselective therapy, and effects on platelet function and other coagulation proteins have been described.1,2 NAC was not tested in a mouse model of TTP or even in a systemic thrombosis model, so its clinical utility in TTP remains to be proven. Nonetheless, the results of Chen et al. demonstrate a clever new application of an old drug with an established safety profile and provide a strong rationale for further testing of this approach in TTP.


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

Uncertainty at the NCRR

(Cent. from page 1)

Dr. Collins has tried to allay those fears by saying that the goals of creating the new Center are to “facilitate – not duplicate – efforts in developing therapeutics, to complement – not compete with – the private sector, and to reinforce – not reduce – NIH’s commitment to basic science research.”

Dr. Collins, as NIH Director, has full authority by law to create this new Center; it does not require new legislation, although the Congress has six months from the introduction of the proposal to intervene if it sees appropriate. However, because the law limits NIH to 27 Institutes and Centers (I/C), the proposal for the creation of NCATS included a recommendation to dissolve the National Center for Research Resources (NCRR). On February 23, 2011, the NIH task force established to study options for this reorganization delivered interim recommendations1 to the SMRR regarding transition of NCRR programs to the new NCATS and other I/C. The proposed reassignments include:

<table>
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<th>Proposed Placement (I/C)</th>
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<td>All other research grants for Technology Research and Development, and the SBIR/STTR and Biomedical Informatics Research Network (BRIN) network grants</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)</td>
<td>Pancreatic Islet Cell Resource Center</td>
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<td>New Permanent Infrastructure Entity</td>
<td>Non-Human Primate Research Resources</td>
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<td>Other Disease Model Resources</td>
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<td>Training and Career Development for Animal Medicine</td>
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<td>Clinical Research Resources</td>
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<td>Extramural Construction</td>
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<td>Research and Animal Facilities Improvement</td>
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<td>Shared and High-End Instrumentation</td>
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<td>Office of Director</td>
<td>Science Education Partnership Award (SEPA)</td>
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The proposed dissolution of the NCRR has generated significant discussion and controversy among the research community. The major concerns about the transition shared on the NIH feedback blog2 are: 1) accelerated timing (NCATS is supposed to be established by October 2011); 2) the lack of transparency of the reasoning behind the transition; 3) the absolute need for NCRR dissolution when the only programs transitioning to NCATS are the CTSA (about 40% of NCRR budget); and 4) potential harm to the NCRR programs while they are being transitioned to other I/Cs or a yet unnamed “Infrastructure Entity.” Dr. Collins indicated that the main motivation for creation of NCATS is the “deluge” of new discoveries of potential targets and unmet therapeutic needs of rare, neglected, and common diseases. As for the need to dissolve NCRR, Larry Tabak, chair of NCRR task force, said that after deciding to move CTSA to NCATS, the character and breadth of the remaining programs at NCRR make it difficult to sustain.

Some organizations actively support the transition. For example, patient advocacy organizations such as the Parkinson’s Action Network strongly support the creation of NCATS and the timeliness of the transition. Others are more cautious. The Federation of American Societies for Experimental Biology (FASEB) strongly advised “against creating a new center if that center would disrupt or compete with the existing I/C activities or reduce the funding available to them.” The American Association of Medical Colleges (AAMC) urged the NIH to spend necessary time in determining how to minimize potential disruption to the functionality of important programs being transitioned from NCRR, some of which could potentially be transferred in the middle of the budget cycle and program planning process. In addition, AAMC recommended that the NIH set in place evaluation mechanisms for the early stages of the reorganization to make sure that these programs continue to receive adequate resources and staff support.

All ASH members are encouraged to submit concerns or comments on this issue to ASH Senior Manager for Scientific Affairs Ulyana Desiderio, PhD, at adesiderio@hematology.org. We are especially interested in learning about the impact of this proposal on your program or institution.

Epigenetics: What Hematologists Need to Know

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Epigenetics is defined as the heritable alteration of gene expression without an accompanying change in DNA sequence. Epigenetic changes are primarily acquired through DNA methylation, which occurs at the cytosine located in a CpG dinucleotide, and post-translational histone modifications. These chromatin modifications are usually tightly regulated in development and differentiation. Generally, cancer cells exhibit global hypomethylation, which contributes to chromosomal instability, reactivation of transposable elements, and loss of imprinting. However, malignancies often demonstrate hypermethylation of many promoter-associated CpG islands and other CpG-rich regions. Hypermethylation of tumor suppressor genes (TSGs) was proposed to lead to increased cell proliferation, providing a selective advantage for cells with methylated gene promoters.

The four core histones, H2A, H2B, H3, and H4, make up the nucleosome, the main structural unit of chromatin. In recent years, numerous post-translational modifications, including methylation, acetylation, phosphorylation, and sumoylation, were identified on the “tails” of histones, a stretch of about 40 amino acids that does not directly bind to the DNA of the nucleosome. Some specific histone tail modifications, such as methylation of histone 3 lysine tail residue 4 (H3K4), are associated with activation of gene expression, while others, such as methylation of histone 3 lysine 27 (H3K27), are associated with gene repression. These marks are normally carefully controlled by the interplay of sequence-specific DNA binding transcription factors and transcriptional co-factors, many of which are histone-modifying enzymes. In this review, we will discuss recent developments in the field, and the current and future state of epigenetic therapies.

Altered Function of DNA Methyltransferases

The DNA methyltransferases (DNMTs) catalyze the conversion of cytosine to 5-methylcytosine. DNMT1 maintains DNA methylation once the cell divides, while DNMT3A and DNMT3B are de novo methyltransferases, which can add methyl groups to unmethylated DNA. Mutation of the DNMT3A gene was observed in 20 percent of acute myeloid leukemia (AML) cases and correlated with a poor clinical outcome. Surprisingly, however, DNMT3A mutations do not dramatically alter 5-methylcytosine or global DNA methylation levels in AML genomes but still may have indirect effects on gene expression. Additionally, alternative, aberrantly spliced transcripts of DNMT3B were observed in primary leukemia samples and cancer cell lines, and appear to lead to the deregulation of normal methylation patterns.

TET2 Mutations in Myeloid Malignancy

In 2009, inactivating mutations of the Ten Eleven Translocation oncogene family member 2 (TET2) gene were identified in myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPNs), AML, and chronic myelomonocytic leukemia (CMMI). Some studies suggested that TET2 mutations in myeloid malignancy conferred a better prognosis. TET2 can convert 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), which was hypothesized to be an intermediate in the demethylation of DNA. TET2 mutations can be found in combination with mutations of JAK2 in MPN, FLT3 in AML, and RAS in MDS, suggesting that they play a contributory role to the development of myeloid malignancies. TET2 levels increase during differentiation of myeloid cell lines, and depletion of TET2 in hematopoietic precursors leads to monocyte/macrophage differentiation, indicating that TET2 is important in normal myelopoiesis.

Epigenetic Signatures in AML

The methylation state of CpG-rich sequences within the promoters of genes can be profiled on mass through the use of microarray. This type of analysis of large cohorts of AML patients characterized 16 distinct patterns of gene methylation, some of which corresponded to specific AML subtypes, such as acute promyelocytic leukemia. However, patterns of gene methylation were found that were not associated with any known gene mutations or chromosomal translocation, yet were associated with a poorer prognosis. More recently, AML harboring isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations were found to display aberrant hypermethylation. These mutations led to the production of an abnormal metabolite in the cell, 2-hydroxylglutarate (2HG), which can inhibit the hydroxylation of 5-mC by TET2. It is likely, however, that IDH1/2 mutants have even more widespread epigenetic effects, since the Jumonji C class of histone is likely inhibited by 2HG.

Aberrant Histone Methylation in Hematologic Malignancy

Histone modifications, especially histone methylation, play an important role in altering gene expression in hematologic malignancies. Histone lysine methylation is generally performed by histone methyltransferases (HMT) containing the SET domain, while demethylation is generally performed by histone methyltransferases UTX, which would lead to increased H3K27 methylation, asthma in patients with MDS/MPN and myelofibrosis. Gain-of-function mutations of EZH2 that increase H3K27 methylation are seen frequently in large B-cell lymphoma, suggesting that EZH2 can act as an oncogene in this context. Furthermore, inactivating mutations of the H3K27 demethylase USP10, which would lead to increased H3K27 methylation, are found in 10 percent of cases of multiple myeloma.

Recent data indicate a link between aberrant signaling and chromatin modification in hematologic malignancy. The JAK2 kinase, which is mutated in MPN and overexpressed in Hodgkin disease and mediastinal lymphoma, is localized to the nucleus where it directly phosphorylates histone 3 tyrosine 41 (H3Y41), a modification that prevents the methylation of histone 3 lysine 9 (H3K9), which is a mark of inactive chromatin. In this way, JAK2 can bind and activate specific sets of genes that stimulate malignant growth.

Epigenetic Therapy in Hematologic Malignancies

“Epigenetic therapy” refers to the use of agents intended to target chromatin processes, but whether these agents work as they are designed is not clear. The DNA hypomethylating agents 5-azacytidine and 5-aza-2′-deoxycytidine are a class of compounds that bind to DNA and inhibit the action of DNA methyltransferases, resulting in aberrant overexpression. The HMT MMSET is a histone methyltransferase EZH2, which was identified in patients with MDS/MPN and myelofibrosis. Gain-of-function mutations of EZH2 that increase H3K27 methylation are seen frequently in large B-cell lymphoma, suggesting that EZH2 can act as an oncogene in this context.
decitabine can induce significant hematologic improvement in MDS. MDS is associated with aberrant gene hypermethylation, which can be reversed by 5-azacytidine treatment, but this has not been consistently correlated with re-expression of methylated, silenced tumor suppressor genes. 5-azacytidine treatment is associated with DNA damage and may work as a low-level cytotoxic agent. Vorinostat, a histone deacetylase inhibitor (HDAC), leads to global increases in histone acetylation in many cell types but has proven to be most efficacious in cutaneous T-cell lymphoma (CTCL) for unknown reasons. The therapeutic effects of this HDACi may be related to alteration in chromatin associated with shifts in gene expression, changes in chromatin stability and DNA damage, or even non-chromatin effects, such as alterations in HSP90 protein chaperone function.

Epigenetic therapy is becoming more sophisticated and in coming years will likely work through specific, on-target actions. For example, a highly specific inhibitor of DOT1L, the enzyme that methylates H3K79, specifically killed leukemia cells harboring MLL fusion proteins as intended. 2 JAK2 inhibitors being developed for the treatment of myelofibrosis may work in part through alteration of epigenetic histone modifications, reversing H3Y41 phosphorylation and increasing H3K9 methylation of JAK2-bound genes. There is much interest in the development of EZH2 inhibitors that may be useful for lymphoma and MMSET inhibitors for myeloma. IDH1/2 inhibitors that stop the production of 2HG are likely to affect the function of the TET enzymes and demethylases. As cancer genomes become sequenced and recurrent mutations characterized, it is clear that more epigenetic targets will emerge, many of which may be amenable to specific therapies. Hence, in the coming decade, epigenetic concepts are likely to change the clinical practice of hematology.

The Hematologist: ASH News and Reports
In April, ASH launched a new version of the ASH Image Bank, a Web-based image library that offers a comprehensive, growing collection of peer-reviewed images relating to a wide range of hematology topics. The new image bank features an improved search engine and streamlined navigation – users can filter images by category or publication date.

Visit [www.hematology.org/imagebank](http://www.hematology.org/imagebank) to:
- Search or browse more than 2,000 images
- Submit your own images (subject to review by the Image Bank Editor)
- Create and/or download unique collections of images

### May

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<tr>
<td>1</td>
<td>Deadline to submit letter of intent for ASH Scholar Awards</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<td>4</td>
<td>Deadline to submit nomination packages for the ASH Mentor Award</td>
<td>Washington, DC</td>
<td><a href="http://www.hematology.org">www.hematology.org</a></td>
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<td>6–8</td>
<td>XXIVth International Symposium on Technological Innovations in Laboratory Hematology</td>
<td>New Orleans, LA</td>
<td><a href="http://www.isfh.org">www.isfh.org</a></td>
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<td>12–15</td>
<td>Canadian Society for Transfusion Medicine Conference</td>
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<td>18–21</td>
<td>14th Annual Meeting of the American Society of Gene &amp; Cell Therapy</td>
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<td>18–21</td>
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### June

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<td>3–7</td>
<td>Annual Meeting of the American Society of Clinical Oncology</td>
<td>Chicago, IL</td>
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<td>9–12</td>
<td>16th Congress of the European Hematology Association</td>
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<td>15–18</td>
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### August

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<td>11</td>
<td>ASH annual meeting abstract submission deadline</td>
<td>San Diego, CA</td>
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<td>25–28</td>
<td>40th Annual Scientific Meeting of the International Society for Hematology and Stem Cells</td>
<td>Vancouver, Canada</td>
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