Hematopoiesis, Umbilical Cord Blood, Health-Care Reform, and Mosquitoes: ASH 2010

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As we return from another wonderful ASH meeting in Orlando, FL, we reflect on the meeting and some of the highlights. Just like our host site of Orlando, with diverse attractions from the sea, space, wizards, and mice, our ASH meeting and attendees represent a heterogeneous population. This year, there were 112 registered attendees from approximately 97 countries. Equally distinctive were the presentations at this year’s meeting. Here are a few highlights for all to remember from the meeting.

This year’s Ham-Wasserman Lecture featured Dr. Tsvee Lapidot, the current Edith Aronoff Stem Professorial Chair in Stem Cell Research at the Weizmann Institute in Rehovot, Israel. His career has focused on the mechanisms of hematopoietic stem and progenitor cell movement. He

Targeting Methylation in Mantle Cell Lymphoma

The application of gene profiling to hematologic malignancies has the potential to provide prognostic information while simultaneously guiding therapy. For example, the molecular signature of the activated B-cell subtype (ABC) of diffuse large B-cell lymphoma (DLBCL) in contrast to the germinal center subtype (GC) is characterized by increased expression of genes associated with activation of the NFκB pathway.1 Notably, patients with the ABC form of DLBCL have a substantially worse prognosis than their GC counterparts and are more likely to respond to agents (e.g., bortezomib) that interrupt NFκB signaling. More recently, evidence has emerged that in addition to such genetic profiles, epigenetic signatures could also have important prognostic and possibly therapeutic implications. In this context, a recent study demonstrated that patients with acute myelogenous leukemia exhibiting specific gene expression profiles may be segregated according to their DNA methylation patterns.2

Until now, parallel studies had not been performed on patients with mantle cell lymphoma (MCL), a form of non-Hodgkin lymphoma associated with specific genetic abnormalities (e.g., t(11:14) translocation, cyclin D1 overexpression, etc.). However, this situation has now changed with the report by Leshchenko et al. from the Pares laboratory at Albert Einstein Medical Center in New York. These investigators analyzed genome-wide methylation in MCL patients using the HELP assay and identified multiple genes, including CD37, exhibiting aberrant methylation patterns (i.e., either hypo- or hyper-methylation) associated with expected changes in mRNA levels. Interestingly, exposure of MCL cell lines to hypomethylating agents (i.e., decitabine) reversed the aberrant methylation and greater-than-additive effects were observed when decitabine was combined with an HDAC inhibitor (vorinostat). In addition, targeting CD37 with an immunopharmaceutical resulted in a striking loss of viability of MCL cells. The authors concluded that in MCL aberrantly methylated genes can be targeted with therapeutic intent.

The results of this study have potentially important implications for MCL and possibly other hematologic malignancies. In the distant past, prognostic information was derived primarily from morphologic and anatomic criteria. Subsequently, the presence or absence of specific chromosomal abnormalities or mutant tyrosine kinases were incorporated into the equation, and in some cases, such as AML with FLT3 mutations, the oncogene has been targeted directly. Recently, gene profiling has revealed specific disease subcategories in which prognosis may be independent of morphologic features, chromosomal abnormalities, or the presence of mutant proteins. The significance of the present as well as recent related reports is that epigenetic abnormalities, particularly methylation-induced gene silencing, may provide yet another level of disease categorization and segregation. In the case of MCL, the concept of combining epigenetic strategies involving hypomethylating agents and HDAC inhibitors, a strategy that has shown promise in other disorders (e.g., AML and MDS), has been minimally explored, but based on the results of the Leshchenko report, certainly warrants further investigation into this disorder. Clearly, future prospective studies will be necessary to validate the prognostic and potentially therapeutic significance of aberrant methylation profiles in MCL, a task that now seems to be eminently feasible.


DR. GRANT indicated no relevant conflicts of interest.
Ten Ways for Trainees to Stay Connected With ASH After the Annual Meeting

ROBYN DENNIS, MD, AND NICHOLAS BURWICK, MD

The ASH annual meeting brings together trainees from around the world and provides them with endless opportunities for networking, developing new research ideas, and honing their clinical skills. Trainees leave the annual meeting inspired and motivated, but commonly ask, “How can I remain an active member of ASH outside of the annual meeting?” Whether you are a medical student, resident, or fellow, there are a number of opportunities throughout the year for you to stay involved as an ASH Associate member. Below are ways for trainees to remain active members of the ASH community during the course of their training. The more you stay involved, the richer your experience as a hematologist trainee will be.

#1: Make connections and keep them: Trainees are savvy social networkers, and it is helpful to use these skills to keep in touch with colleagues you meet at the ASH annual meeting. The value of your connections may not be immediately evident, but your colleagues, even if separated by distance, may one day be a valuable resource or mentor to you.

#2: Be an advocate: You do not need prior legislative experience to be an advocate for hematology. For example, trainees can become members of the ASH Grassroots Network, where they can stay up-to-date on the latest advocacy campaigns. It is also an opportunity to meet like-minded fellows or faculty, and you may even find yourself on Capitol Hill together.

#3: Write an article for Trainee News and/or The Hematologist: The ASH Trainee Council publishes a quarterly electronic newsletter called Trainee News, which is a major source of communication from ASH to its trainees. The Hematologist also publishes articles directed toward early-career hematologists. If you would like to submit an article suggestion, e-mail training@hematology.org.

#4: Be a mentor: Share your enthusiasm and knowledge of hematology with junior trainees such as residents, medical students, or graduate students. Junior trainees may have limited exposure to hematology during their training and are often looking for guidance from senior trainees. Encourage them to help with case reviews or abstract write-ups. Mentorship is a rewarding experience for both the mentor and the mentee, and it can happen at any stage of training.

#5: Recruit new members: Recruiting new trainee members to join ASH improves the diversity of the trainee membership. Consider preparing a brief synopsis of your experience as an ASH trainee, and be ready to share it with your colleagues. If you have enjoyed being a member of ASH, chances are they will, too!

#6: Regularly check the ASH trainee page on the ASH website: The ASH Trainee Council maintains a resource-packed page on the ASH website (www.hematology.org/Training) to help guide trainees at every stage in their career. The website provides career-development timelines, grant opportunities, job postings, case presentations, and more.

#7: Apply for ASH awards and workshops: ASH provides several career-enhancement awards focused on helping hematologists establish and advance their work early in their careers. ASH also provides formal research training programs for trainees involved with clinical or translational research. Trainee members should be well versed in the opportunities ASH provides and take advantage of them! Refer to the following page on the ASH website for more information: www.hematology.org/Awards.

#8: Volunteer for committees: Senior hematologists know that serving as volunteers for ASH extends beyond the annual meeting with working groups, conference calls, and committee updates going on throughout the year. Junior faculty are welcome to nominate themselves or their colleagues for standing committee roles. Those trainees who have particular research experience may be good candidates to serve as abstract reviewers and subsequently as members on scientific committees. For more information about volunteering, go to www.hematology.org/About-ASH/2654.aspx.

#9: Propose new trainee projects: If you don’t see a project of interest but you have a good idea for ways to get trainees involved, send the Trainee Council your ideas. We hope to encourage all trainees to remain active members of the ASH community during the course of their training.

#10: Join the ASH Trainee Council: The ASH Trainee Council is a committee of fellows across the field of hematology that is focused on providing opportunities and resources for the advancement of trainee education through ASH. As a member of the ASH Trainee Council, you will have the opportunity to interact directly with the ASH executive leadership to promote new initiatives for trainees. Six new council members are selected each year, for a two-year term, with 12 members in total. More information about the Trainee Council, including the application and details about the application process, are available on the ASH website at www.hematology.org/Training/Trainees/2675.aspx.

For more information, visit the ASH website at www.hematology.org or contact the Trainee Council at training@hematology.org.

The U.S. economy is suffering, job growth is inadequate, unemployment continues at 9.8 percent, and voters clearly want the situation to change — the mid-term elections have shifted the landscape dramatically. Approximately 35 new members of the House and four senators have not previously held any elected office — numbers not approached since 1948 — and they are bound to shake things up.

What does the nation expect and want? Historically, support for biomedical research has always been strong and funding for it has been protected by all previous administrations, but the new Congress may change direction in response to demands by new Members of Congress for smaller budget deficits and less government spending. For example, we’ve heard proposals to decrease non-defense discretionary spending by 20 percent, to 2008 levels, which represents a decrease of about $180 billion. Disbanding the National Science Foundation (NSF) has been mentioned as one of component of this package, and the National Institutes of Health (NIH) is prudently preparing for substantial budget reductions. Most agree that such cuts would have a trivial impact on budget deficits. Even so, the desire to appear fiscally responsible could overwhelm the traditional bipartisan enthusiasm for basic research. Given the widespread financial hardship affecting so many citizens, the resulting damage to biomedical research may not garner much attention.

The clinical practice of hematology also faces uncertainty. Congress still must find and agree to a long-term solution to physician payment. Practices must now adapt to new health-care delivery models, such as Accountable Care Organizations and Patient-Centered Medical Homes. There will also be increased pressure on physician practices to reduce costs and increase quality of care.

Despite these concerns, there never has been a more promising time for hematology research, whether basic, translational, or clinical. Thanks to advances in the past few decades, the tools available today make it possible to address fundamental questions that once could barely be stated, and the pace of discovery has been astonishing. Few would deny that basic research is the engine of discovery and that preeminence in such discoveries underlies our country’s dominance in biotechnology and other health-related industries. Faced with tough budgetary choices, we should not inadvertently cede our leadership in medical discovery, which is the foundation for advances in medical care.

What can ASH do? Of course we can sustain our support for research and clinical training at all levels, continue disseminating advances in hematology research in Blood and through our portfolio of scientific meetings, and meet with leaders at NIH to develop promising avenues for future research. But the critical decisions about national priorities are made on Capitol Hill and by voting citizens. ASH is engaged at this frontier as well, through the Committee on Government Affairs and the Grassroots Network, to inform Congress and the public. The influx of so many new faces at all levels of government adds a new challenge: we’re strangers to each other. If you know these new legislators, whatever their political affiliation, get involved — we need your help to ensure that ASH remains a trusted resource to inform policy decisions on hematology research and patient care.

To join the Grassroots Network and the Society’s advocacy efforts, please contact grassroots@hematology.org or visit http://grassroots.hematology.org/blood/home.
Highlights of ASH® Meetings in North America

January 21 - 22, 2011
Dallas, TX
Vancouver, Canada

January 28 - 29, 2011
San Francisco, CA

February 4 - 5, 2011
New York, NY
San Diego, CA

Did you miss the 2010 ASH Annual Meeting and want to catch up on the excitement of the meeting or simply need a recap of the meeting's highlights? If so, the only official Highlights of ASH in North America is a great alternative to access the unbiased analyses of annual meeting abstracts, evolving therapies, the latest treatment options, and their clinical applications.

Taking place in six locations on three different dates, these clinically focused meetings are a convenient way for practicing hematologists, fellows, academicians, and allied health professionals to discuss real patient cases with expert leaders in the field.

ASH is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This program is approved for a maximum of 10 AMA PRA Category 1 Credits™ for physicians.

For more information, visit www.hematology.org/Highlights.

Highlights of ASH® Expands Its Global Reach

Highlights of ASH has expanded yet again. This year ASH will partner with two different international hematology societies to offer a more robust set of international “Highlights” meetings. The programs will provide hematologists unbiased analysis of research presented at the ASH annual meeting, while offering educational content tailored specifically to local audiences.

For the first time ASH will offer Highlights of ASH in China, a collaboration with the Chinese Society of Hematology and the Chinese Medical Association, which is scheduled for April 2-3, 2011 in Beijing.

ASH will also host Highlights of ASH in Latin America, this time moving from Brazil, which hosted the first two Latin American meetings, to Uruguay. The 2011 meeting, held in partnership with the Sociedad de Hematologia del Uruguay, will take place in Punta del Este, Uruguay, April 29-30.

Discussions at these meetings will include topics on hematologic malignancies, hemostasis and thrombosis, myelodysplastic syndromes, anemia, and more. Special sessions will include "How to Prepare a Manuscript for Blood" and "How to Prepare an Abstract for Submission to ASH".

Both meetings will offer simultaneous translation. Highlights of ASH in China will offer translation from English into Mandarin, and Highlights of ASH in Latin America will offer translation from English into both Portuguese and Spanish.

Registration for both of the international Highlights of ASH meetings is now open. To learn more about these meetings and register, visit www.hematology.org/highlights.

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

A 34-year-old woman had mesenteric vein thrombosis during her last pregnancy in 2007 and two prior second trimester spontaneous fetal losses. She now presents at 13 weeks of pregnancy after being started on low-molecular-weight heparin (LMWH) by another hematologist 14 days prior. Her baseline platelet count was 160,000, but today it is 80,000. A PF4 antibody assay sent to rule out heparin-induced thrombocytopenia (HIT) was positive. Is it reasonable to stop the LMWH and put her on warfarin, since she has completed the first trimester? Danaparoid is not available, and fondaparinux is not on the American College of Chest Physicians’ list for HIT treatment.

My Response

HIT is uncommon during pregnancy. In a retrospective cohort study of 488 heparin-treated women (244 pregnant), there were no cases of HIT in the 10 pregnant women who became thrombocytopenic, but 10 cases in the 26 thrombocytopenic non-pregnant women.1 A study of 31 pregnant women receiving LMWH found that none were positive for anti-heparin/PF4 antibodies or developed antibodies when followed prospectively throughout their pregnancies.2 However, case reports and clinical experience document the occurrence of HIT with and without thrombosis during pregnancy. Although HIT may be less common in patients treated with LMWH versus unfractionated heparin (UFH), it can occur and must be considered in pregnant women receiving LMWH who have a > 50 percent decrease in platelet count.

In choosing an anticoagulant for a pregnant woman with HIT, one has to consider the effects on both the woman and the fetus. Concerns with anticoagulants that cross the placenta include teratogenicity and bleeding. Data are limited and mostly reflect predictions based on drug characteristics and/or animal studies. Danaparoid, the drug with which there is the most experience in pregnancy, is unavailable in the United States. Fondaparinux, argatroban, and lepirudin have been reported in treatment of pregnant women with HIT.3,4 All are FDA Class B, indicating that animal studies have not shown harm in pregnancy, but there are no data from human studies. Outside the setting of pregnancy, fondaparinux, unlike argatroban and lepirudin, is not FDA-approved for HIT, but there are reports of its use in this setting.3 Patients who receive this drug may develop anti-heparin/PF4 antibodies, but it is not clear that these are associated with the development of HIT.

Fondaparinux is a pentasaccharide that, with antithrombin, inhibits factor Xa. An advantage of this drug is its long half-life (~17 hrs.) allowing once-daily dosing. Disadvantages include managing a drug with a long half-life around delivery. Also, the drug has been shown to cross the placenta in vivo. N Engl J Med. 2000;343:1305-1311. However, case reports and clinical experience document the occurrence of HIT with and without thrombosis during pregnancy. Although HIT may be less common in patients treated with LMWH versus unfractionated heparin (UFH), it can occur and must be considered in pregnant women receiving LMWH who have a > 50 percent decrease in platelet count.

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When a pregnant woman develops HIT, the heparin should be discontinued; she should be evaluated for thrombosis by vascular ultrasound studies, and, unless contraindicated, alternative anticoagulation should be initiated. This patient needs continued anticoagulation because of the history of mesenteric vein thrombosis and her increased risk of thrombosis in the setting of HIT. As in non-pregnant patients, warfarin should not be started in the setting of acute HIT. The patient could be transitioned to warfarin later after the acute HIT resolves. Teratogenic effects have not been demonstrated when warfarin is ingested after 12 weeks gestation; however, it does cross the placenta and complications related to fetal hemorrhage have been reported. Two new oral anticoagulants, dabigatran and rivaroxaban, will not be useful alternatives, as both demonstrated reproductive toxicity and excretion in breast milk in animals.7

Given the need for continued outpatient anticoagulation, it is reasonable to switch her to fondaparinux, recognizing the need to discontinue the drug in anticipation of labor given its long half-life. In a patient on prophylactic therapy without a recent thrombotic event, it may be possible to stop the drug three days prior to scheduled induction or cesarean section. Epidural or spinal anesthesia could be given if an anti-Xa measurement demonstrates drug clearance. A woman at higher risk for thrombosis could be transitioned to an intravenous short-acting DTI, but since there will be anticoagulant effects in the mother and possibly the fetus, it should be discontinued in anticipation of a scheduled delivery to prevent bleeding complications. The best approach to delivery should be carefully considered in collaboration with maternal fetal medicine specialists.

After delivery, anticoagulation should be re-initiated with either fondaparinux or a DTI with transition to warfarin. Fondaparinux is excreted in breast milk in animals, while argatroban, bivalirudin, and lepirudin are not predicted to be excreted in breast milk. Data from one lactating woman on therapeutic doses of lepirudin demonstrated no measurable drug in her breast milk. Thus, if the patient plans to breast feed, lepirudin with transition to warfarin, which also is not excreted in breast milk, may be the best post-partum option.

While HIT in pregnancy is rare, it does occur and management requires knowledge of disease and drug effects on the mother and developing fetus, although data to inform these decisions are limited. Potential risks and benefits of different approaches should be discussed with the patient and her other health-care providers.8

References


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To most, the complement system resides in one of the dark corners of hematology, occasionally dimly illuminated when the direct antibody test is reported as “positive” for C3 in a patient with autoimmune hemolytic anemia. Undeniably, the complement system, with its three overlapping pathways (classical, alternative, and lectin), is complex, but the development of new and emerging targeted therapies for complement-mediated diseases necessitates understanding of this arcane system. The purpose of this article is to shine a light into that shadowy corner of hematology in which complement resides by reviewing three diseases (atypical hemolytic uremic syndrome [aHUS], paroxysmal nocturnal hemoglobinuria [PNH], and hereditary angioedema [HAE]) in which inherited or acquired mutations that affect complement system proteins underlie or contribute to disease pathophysiology. A comprehensive review of the biochemistry and pathobiology of the complement system is beyond the scope of this report; however, an excellent one can be found in the first reference.

**aHUS**
Hematologists encounter patients with aHUS when they are asked, along with their nephrology colleagues, to evaluate a patient with the triad of severe thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. The clinical features suggest a thrombotic microangiopathy. With supportive care, patients who develop typical diuretic-positive HUS have a favorable prognosis, with spontaneous resolution of the classic disease triad in approximately 90 percent of cases (although temporary dialysis may be required). For patients who present with the diuretic-negative form of the disease (aHUS), however, the prognosis is bleak with 50 percent developing end-stage renal failure and 25 percent dying from complications of the disease.

Recently, new insights into the etiology of aHUS have emerged, with studies by a number of investigators demonstrating that aberrant regulation of the amplification C3 convertase of the alternative pathway of complement (APC) predisposes to disease acquisition (Figure). Molecularly defined abnormalities have been identified in approximately half of the cases. Specifically, complement factor H is mutant in approximately 30 percent of cases, membrane cofactor protein (MCP, CD46) in approximately 10 percent, and complement factor L in approximately 10 percent. In another 10 percent, auto-antibodies against factor H have been identified. Disease penetrance, however, is variable, as risk polymorphisms may be required for development of aHUS. New DNA sequencing technology will likely solve the current problems of both time delay and expense required to identify the genetic basis of the disease in an individual patient. Moreover, these techniques will reveal novel genetic mechanisms that underlie the pathobiology in the 50 percent of patients who do not have mutations in APC C3 amplification convertase components.

Understanding the molecular basis of aHUS has important prognostic and therapeutic implica-
tions, as disease penetrance, response to plasma exchange, immunosuppressive therapy, and kidney transplant are influenced by the mutational status of the patient. Plasma exchange appears to be more efficacious in patients with mutant factor H than in those with mutant factor I, whereas 80 to 90 percent of patients with mutant MCP remit spontaneously without plasma exchange. Long-term dialysis-free survival has been observed in 60 to 70 percent of patients with auto-antibodies to factor H who are treated with a combination of plasma exchange, immunosuppressant drugs, and rituximab. Anecdotial reports of responses to the comple-
ment inhibitory drug, eculizumab, led to initiation of two multicenter, open-label clinical studies for both adult (NCT01194973) and pediatric patients (NCT01193348). Except for patients with mutation in MCP (a cell surface protein, Figure), kidney transplant for patients with aHUS is unsatisfactory because the other APC C3 amplification convertase components are plasma proteins that are produced in the liver. And while kidney/liver transplantation is feasible, procedure-related morbidity and mortality are daunting.

**PNH**
PNH has a special place in hematology and complementology, as identification of the molecular basis of the intravascular hemolysis that is the clinical hallmark of the disease led to a remarkable number of discoveries that helped identify and characterize the APC and define the physiology and pathophysiology of the complement system in humans. The discoveries began with the seminal observations of Thomas Hale Ham in the late 1930s and led ultimately to the development of the first successful targeted therapy for a comple-
ment-mediated disease when eculizumab was approved for treatment of PNH in 2007.

PNH is an acquired disorder that arises as a consequence of somatic mutation in one or more hematopoietic stem cells of PGK1, a gene located on the X chromosome that is required for synthesis of the glycosylphosphatidylinositol (GPI) moiety that anchors some proteins to the cell surface (Figure). Consequently, all GPI-anchored proteins (GPI-APs) are deficient on the hematopoietic stem cells and their progeny. The complement-mediated intravascular hemolytic anemia and the resulting hemoglobinuria that are the clinical hallmarks of PNH are a consequence of deficiency of the GPI-anchored complement regulatory proteins, CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis). The intravascular hemolysis of PNH can be controlled with eculizumab, a humanized monoclonal antibody that disrupts formation of the cytolytic membrane attack complex by binding to the fifth component of complement (C5) (Figure). PNH has been the subject of recent com-
prehensive reviews published in *The Hematologist* and *Blood*.

**HAE**
Unlike aHUS and PNH, the defining clinical features (episodic, nonurticarial, nonpuritic subcutaneous, and submucosal swelling affecting primarily the upper respiratory and gas-
trointestinal systems) of HAE are non-hematologic. As a result, hematologists are usually not involved in the initial diagnosis of the disease. HAE displays an autosomal dominant inheritance pattern and is due to mutation of C1 inhibitor, a serine protease inhibitor that binds irreversibly to target enzymes of the classical and lectin pathways of complement, the intrinsic pathway of coagulation, and the contact pathway involved in endothelial cell activation (Table). Once suspected, based on recurrent angioedema without urticaria, recurrent abdominal pain and vomiting, laryngeal edema, and a positive family history, the diagnosis can be made by measuring plasma concentrations of C1 inhibitor and comple-
mant C4. A number of treatment options are available, and these have been the subject of four recent publications in *The New England Journal of Medicine*. Notably, two of the inhibitors (ecalantilide and icatibant) specifically target the contact cascade, with no direct effect on either the complement or coagulation cascade, indicating that disease pathobiology is primarily the result of endothelial cell activation rather than a consequence of deregulation of the coagulation or complement cascades (Table).


Dr. Parker indicated no relevant conflicts of interest.
A Quick Look at the 112th Congress

As a result of the November elections, there will be significant changes to the new Congress. In the House of Representatives, the Republicans have reclaimed the majority; John Boehner (R-OH) will replace Nancy Pelosi as Speaker of the House, and the Republican leadership is focused on cutting discretionary funding, advancing a conservative agenda, and rolling back some of the changes that Congressmen and President Obama accomplished during the 111th Congress. In the Senate, the Democrats’ majority was weakened. What is less well known is that the new Congress has a dearth of representation by scientists, MDs, and PhDs. Of the 435 members of the House, only four have PhD and 20 have MD degrees. In the Senate, there are four physicians but there are no researchers or PhDs.

Congress Needs Scientists

Of 435 Congressional districts, only 4 have representatives with a science PhD.

The Senate is dominated by lawyers and business people; there are four physicians, but there are no researchers or PhDs.

U.S. House of Representatives

Attorney 56
Business 27
Career Public Official 7
Physician 4
Educator 4
Farmer 2
Journalist 2
Social Worker 2
Veterinarian 1
Naval Officer 1
Wiler/Comedian 1

Washington

Teach Your Congressional Representative About NIH

George Weiner, MD
Chair, Committee on Government Affairs

We have heard it many times before — “contact your Congress.” This time, we really need to do it. In fact, we need to do more than contact, we need to teach.

All hematologists know that research supported by the National Institutes of Health (NIH) is responsible for many major advances in hematology and clinical medicine in general. This research takes place at medical centers across the country and is selected through a highly competitive peer-review process. Funding from NIH serves as an economic engine for many communities and is an outstanding example of the “promote the general welfare” referenced in the Constitution. Indeed, NIH has been called the “crown jewel” of the federal government.

Nevertheless, support for NIH is in greater danger now than at any time in recent memory. Our current elected body, with a large number of new Members of Congress are leading to consideration of a major rollback in NIH funding. This is because many in Congress, particularly newcomers, know little to nothing about NIH. They do not know that a vast majority of NIH funds are spent in medical centers across the United States, that NIH funding is distributed based on a highly competitive peer-review system and is not “pork,” and about the major and positive economic impact NIH funding has on many congressional districts and on our ability to remain competitive internationally in biomedicine.

As hematologists, we apply research advances to our care of patients every day. We pride ourselves on being excellent teachers of both patients and trainees. We, therefore, are in an excellent position to teach Members of Congress about the vital importance of NIH. Write to your Representative or Senators (http://grassroots.hematology.org/blood/home). If you are in Washington, set up a time to visit them in their offices. Better yet, invite them when they are back in the district for a tour of your office, hospital, or lab, and bring along a patient who is of like mind and can speak about the importance of research advances made possible by NIH.

NIDDK: 60 Years of Hematology Research and Counting

Daniel G. Wright, MD, and Terry Rogers Bishop, PhD

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2. Hematology Program Director, DKUHD, NIDDK, National Institutes of Health

In 2010, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) celebrated its 60th anniversary.

Sixty years ago, the “Omnibus Medical Research Act” of 1950 established a new Institute at NIH to support basic and clinical research relevant to a broad range of medical subspecialty areas, including hematology. In the early 1950s, this new Institute, the National Institute of Arthritis and Metabolic Diseases (NIAMD), began to award grants for support of research on “erythrocyte production, turnover, and metabolism; erythropoietic regulation and erythropoietin; hemoglobin; iron, B12, and folate metabolism; hematopoiesis and bone marrow grafts; transplant immunology; immune-hematology; and leukocyte cell biology.” In 1972, the Institute’s name was changed to the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), and, subsequently in 1986, as NIH grew and new institutes were established, its name changed again to the National Institute of Diabetes and Digestive and Kidney Diseases. However, throughout its history, the Institute maintained its commitment to support leading-edge hematology research in areas of interest defined at the time the Institute was originally established.

During the past 60 years, the NIDDK Hematology Research Program has worked in parallel with blood diseases programs at the National Cancer Institute (NCI), National Heart Institute, which evolved into the National Heart, Lung, and Blood Institute (NHLBI) of today, and the National Institute of Allergy and Infectious Diseases (NIAID). Although NIDDK’s footprint of support for hematology research has been smaller than that of NCI and NHLBI, it has been an important part of support for seminal, basic hematology research that not only has advanced the understanding of blood diseases and laid foundations for improved treatment of these diseases, but also has led to advances in cell and molecular biology generally, informing current understanding of cell structure and function, genomics and proteomics, signal-response coupling in cells, regulation of gene expression and cellular development, and stem cell biology. During its history, the NIDDK Hematology Research Program has been privileged to provide long-term support for the research and training activities of a large number of distinguished academic and research leaders in hematology, including 23 ASH presidents.

ASH honored NIDDK’s 60th anniversary year at its recent 52nd annual meeting in Orlando, FL, with a special symposium. This symposium highlighted seminal advances and future opportunities for progress in three key areas of hematologic research supported by NIDDK during its 60 year history: hematopoiesis, hemoglobin, and iron. The symposium was introduced by Dr. Griffin P. Rodgers, ASH member and current director of NIDDK, and included talks by three distinguished NIDDK grantees: Drs. Kenneth Kaushansky, Alan N. Schechter, and Nancy C. Andrews. Read more about this symposium in the ASH News Daily article, “Inquiring at Age 60: The NIDDK is One to Follow” (http://ashnewsdaily.ash/NewsDaily/2010/0620.aspx), and listen to the webcast from this symposium (http://ash.eventmediasite.com).

On behalf of NIDDK, we wish to express our gratitude to ASH for its interest and enthusiasm in helping us celebrate NIDDK’s 60th anniversary. The NIDDK Hematology Research Program has been and remains an important source of research support for leading-edge basic and translational hematology research. This long-standing role tends to be overlooked by the hematology research community because (as we sometimes say in jest) the “H” for Hematology, is silent in NIDDK.
Reflections on the James B. Herrick Sickle Cell Symposium

ALEXIS THOMPSON, MD
A. Watson and Sarah Armour Endowed Chair for Blood Diseases and Cancer; Head, Hematology Section; Division of Hematology Oncology; Transplantation; Director, Comprehensive Thalassemia Program; Children’s Memorial Hospital; Chicago, IL

“This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer.” — JAMES B. HERRICK, MD

The National Institutes of Health (NIH) marked the 100-year anniversary of the first published case report of sickle cell disease with the James B. Herrick Symposium on November 16 and 17 on the Bethesda campus. The symposium highlighted key milestones in our understanding of sickle cell disease since this initial description (see above), including contributions of sickle cell research toward the advancement of molecular medicine, ongoing challenges in clinical care, and directions of future sickle cell research. National and international experts provided historical and cultural perspectives. The crossroads of race and sickle cell disease were explored by a diverse panel of historians and medical and social scientists. The point of view of the patient was at the forefront of the program, beginning with acknowledgment of Walter Clement Noel, the West Indian dental student who was the subject of Herrick’s paper, and including presentations by adults with sickle cell disease and representatives from sickle cell advocacy groups.

Dr. Francis S. Collins, director of NIH, summarized how programs at NIH represent opportunities to advance the field of sickle cell research, particularly stem cell processing and collection, and the potential to change the mechanics of bone marrow transplantation, particularly stem cell processing and collection, which may continue to improve outcomes for our patients undergoing this therapeutic strategy.

To dovetail the Ham-Wasserman lecture, the Presidential Symposium reflected on transplantation — from the viewpoint of the evolution of the field of umbilical cord blood transplantation (UCBT). The symposium presented the state of cord blood transplantation and the microenvironment are continuing to be described. Future understanding has the potential to change the mechanics of bone marrow transplantation, particularly stem cell processing and collection, which may continue to improve outcomes for our patients undergoing this therapeutic strategy.

The Hematologist: ASH News AND Reports

November 16 and 17 on the Bethesda campus.

The National Institutes of Health (NIH) sponsored a joint symposium in which Dr. Emanuel spoke about the historical significance for health-care reform and the Patient Protection and Affordable Care Act. He also recommended ways in which physicians can prepare for the provisions of the new law, including implementing electronic medical records in their practices and developing quality indicators and treatment guidelines for their specialties. He touched on how all of this is germane not only to the United States but to our foreign colleagues as well. During the question-and-answer session, Dr. Emanuel validated and appreciated ASH representatives’ willingness to volunteer aid in this time of change. This session underscored the changing times of health care as we have come to know it and be ready for what the future will bring.

This ASH meeting was wonderful to cover and bring to you as it had so much to offer. ASH News Daily’s coverage would not have been possible without the diverse expertise of this year’s writing team — Drs. William Blum, Mark Fratini, Stephen Hunger, Jason Mendler, Chris Porter, Naveen Manchanda, and Erin Gourley Reid — whose intelligence, knowledge, and esoteric references and puns made for a quality product. Special thanks to Dr. David Steensma who created our crossword puzzle for the second year in a row. The articles from ASH News Daily 2010 can be found on the ASH website at www.hematology.org/Publications/ASH-News-Daily/2010/5970.aspx. We are always looking for feedback.

We are looking forward to 2011 and another exciting meeting in San Diego, nicknamed America’s finest city!

Reflections on the James B. Herrick Sickle Cell Symposium

ASH 2010

(Cont. from page 1)

illustrated the complexity of the homing process and the many systems involved in this process. The sections of this intricate choreography between chemokines, bone turnover mechanistic overviews of the systems and the microenvironment are continuing to be described. Future understanding has the potential to change the mechanics of bone marrow transplantation, particularly stem cell processing and collection, which may continue to improve outcomes for our patients undergoing this therapeutic strategy.

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Changing the Signals for a New Treatment in B-Cell Lymphoma


Events downstream of the B-cell receptor (BCR) appear to be critical not only for the normal functions of humoral immunity but also in the life of many malignant B-cells. Circumstantial evidence of this comes from the constitutive activation of the BCR pathway in a variety of lymphomas. This has been highlighted recently by the observation in an interference screen that short hairpin RNAs directed against Bruton tyrosine kinase (Btk) were selectively lethal to lymphoma cell lines and the finding of specific patterns of glycosylation on the idiotype in follicular lymphoma, suggesting a selection pressure mediated by the interaction of the BCR with lectins.1 There is a growing sense that hijacking of the normal activation pathways in B cells, either endogenously by mutation or exogenously through cell-cell interactions, may be key events in lymphoma pathogenesis.

A research group at Stanford University and Pharmacycluss Inc. has previously identified potent inhibitors of Btk that act by binding covalently to a cysteine residue in the active site, and in this paper they present the results of applying this to B-cell lymphoma lines, mice with programmed autoreactivity, and dogs with spontaneous B-cell lymphoma. The selectivity of the lead compound, PCI-32765, was tested by synthesis of a fluorescent-tagged derivative, which was shown to bind to wild-type Btk or a catalytically inactive mutant but not to a version lacking the crucial cysteine residue. Immunoprecipitation from the DoHH-2 lymphoma cell line showed that the fluorescent derivative migrated with Btk with a high degree of specificity. Analysis of the effects upon signaling in DoHH-2 cells showed inhibition of phosphorylation of Btk and its substrate PLCγ, as well as of the downstream kinase ERK at nanomolar concentrations of PCI-32765. Normal, non-malignant B cells stimulated with anti-IgM demonstrated that the inhibitor blocked activation at doses as low as 10nM, while Fccell activation by CD3/CD28 beads was unaffected, even at high concentrations.

In vivo experiments showed suppression of collagen-induced arthritis in DBA/1 mice after 11 days oral dosing at 3.125 mg/kg, while the MRL-Fas(L) model of lupus nephritis, with the promise of limited off-target effects. The first results of phase I clinical testing have been reported in an earlier publication, the Rafii lab showed that sinusoidal endothelium of the bone marrow provides essential support for proliferation of hematopoietic stem cells, in part through vascular endothelial growth factor (VEGF) and its receptors.1 Here, the authors hypothesized that VEGF receptor-expressing SECs play a critical role in the regenerative response to partial hepatectomy. Evidence is presented supporting a model in which LSECs elaborate “angiocrine trophogens,” inducing hepatocyte proliferation within the first four days after partial hepatectomy. Over subsequent days, the LSECs themselves proliferate, providing needed vessels within the new liver mass.

The investigators found that LSECs from mouse livers express VEGF receptor 3 (VEGF-R3) and -receptor 2 (-R2) but lack expression of CD34, which is expressed on many, but not all ECs. Within the adult mouse liver, VEGF-R2 and VEGF-R3 were restricted to LSECs. In the first four days after partial hepatectomy, hepatocytes proliferated rapidly, while LSECs did not. However, following the initial burst of hepatocyte replication, LSECs underwent “proliferative angiogenesis” in the regenerating remnant liver.

Using generalized and endothelial-specific gene deletion strategies, VEGF-R2 and VEGF-R3 were shown to be key players in this process. Differences in LSEC gene expression between normal and regenerating liver were investigated and Id1, a transcriptional regulator, was found to be upregulated after partial hepatectomy. Mice in which the Id1 gene is knocked out had defective regeneration after partial hepatectomy. The failure of Id1-null livers to regenerate normally could be rescued by transplantation into the portal circulation of wild-type LSECs. The investigators determined that Id1-null LSECs express much less hepatocyte growth factor (HGF) and Wnt2 than controls, while other factors such as thrombomodulin were unaffected. Restoration of HGF, Wnt2, or both into Id1-null LSECs partially restored hepatocyte-induced regeneration, with the combination of HGF and Wnt2 being more effective than either alone.

Thus, LSEC-derived HGF and Wnt2 are critical for liver regeneration after partial hepatectomy. This raises the intriguing possibility that LSECs or the angiocrine factors they produce might be exploited for therapeutic purposes in patients undergoing liver resection for tumor or organ donation or in patients receiving an inappropriately small liver allograft. Whether LSECs or their angiocrine factors play a similar role in repair after different types of liver injury is unknown. One of the most remarkable findings of the two studies from the Rafii laboratory is that ECs from the bone marrow and liver produce different growth factors in response to local damage. Hence, endothelial cells in different organs sense tissue damage and how they become specialized to provide unique factors remains a mystery.


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

The Blood Vessels of Prometheus


The ability of the liver to repair itself is well known, as the myth of Prometheus so evocatively demonstrates. However, the mechanisms required for liver repair are not yet well understood. Ding et al. from the laboratory of Shahin Rafii at Weill Cornell Medical College have shown that endothelial cells play a critical role in liver regeneration. Not only do they line the blood vessels and expand when needed for vascularization, but liver sinusoidal endothelial cells (LSECs) also promote hepatocyte growth in tissue repair by secreting critical factors.

Surgical resection of 70 percent of mouse liver (3 lobes) rapidly induces compensatory hypertrophy and proliferation in the remnant lobes. Nearly all of the remnant hepatocytes undergo one or two cell cycles within the first three to four days, followed by replication of remnant bile duct cells and vessels, including the sinusoidal endothelium. In contrast to diffuse toxic liver injury, the remnant liver after partial hepatectomy is relatively free of inflammation or cellular damage.

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E. SCOTT SWENSON, MD, PHD, AND DIANE S. KRAUSE, MD, PHD
Dr. Swenson and Krause indicated no relevant conflicts of interest.
Hemostatic and Inflammatory Networks and NETs


The anti-microbial defense provided by neutrophils includes phagocytosis of microbes into phagolysosomes and degranulation with release of anti-microbial molecules at the site of infection. Recently, an additional defense mechanism was discovered—the formation of neutrophil extracellular traps (NETs), which are produced following the release of the nuclear contents of the neutrophil into the extracellular space. NETs have been identified in all vertebrate lineages and function in innate immunity. They are composed of chromatin components, including histones, and neutrophil antimicrobial proteins. Microbes are trapped in NETs, where they encounter high concentrations of anti-microbial proteins.

Both activation of the hemostatic mechanism and inflammation are vertebrate responses to infection, and there has been an increasing awareness of crosstalk between these two systems. Now, an association between hemostasis and NETs has been identified by Fuchs et al. in the laboratory of Denisa Wagner at Harvard Medical School. The authors produced NETs in vitro and studied their interaction with whole blood or platelet-rich plasma under conditions of flow at both arterial and venous shear rates. NETs aligned in the direction of flow; platelets adhered to them rapidly and aggregated. Additionally, red cells adhered to NETs. NETs dissolved in the presence of heparin, which, as a negatively charged sulfated polysaccharide, is known to bind positively charged histones. Interestingly, histones H3 and H4 directly bind to NETs, and the presence of fibrinogen resulted in thrombin-dependent fibrin deposition. NETs also were studied in a baboon model of deep-venous thrombosis produced by catheter occlusion of the iliac vein. Thrombus formation resulted in elevated plasma levels of DNA with kinetics that mimicked the elevation of fibrinogen D-dimer that occurs in this model. Post-mortem analysis of the injured vein revealed nuclear DNA and histones in the thrombus as well as VWF.

The results of this study indicate that the association of NETs with fibrin may serve to organize the structure of the thrombus and influence platelet activation (in part through histones acting as agonists), fibrin formation, and fibrinolysis. At a site of infection, the anti-microbial and prohemostatic functions of NETs may function to prevent or limit sepsis by local containment and killing. However, extracellular histones may contribute to endothelial dysfunction and exacerbate the pathological sequelae of sepsis. The beneficial and pathological effects of the linkage between NETs and the hemostatic system remain to be established.


Rituximab Chemoimmunotherapy Transforms Old Treatment Paradigms for CLL by Improving Overall Survival


Therapy for chronic lymphocytic leukemia (CLL) over the past five decades has included different types of chemotherapeutic treatment including alkylator agents (chlorambucil and cyclophosphamide) and nucleoside analogs (fludarabine, cladribine, and pentostatin). While these non-targeted chemotherapies have effectively palliated symptoms of CLL, no impact on improving overall survival of CLL patients has been appreciated. The early introduction of the anti-CD20 chimeric antibody rituximab with chemotherapy-based approaches has significantly improved the outcome in patients with CLL. Rituximab plus chemotherapy enabled higher response rates, prolonged progression-free survival, and longer overall survival. However, this combination was associated with a high risk of serious infections and was less effective in patients with high-risk disease. The addition of rituximab to fludarabine and cyclophosphamide in patients with high-risk but asymptomatic disease might also improve CLL survival further. This question is now being studied by the German CLL Study Group, and we will anxiously await the answer of this second study.

The importance of this paper is that it is transforming to the field of CLL. The finding of a targeted agent rituximab prolonging survival in CLL has not been appreciated with any other chemotherapeutic agent examined prior to this time. Moving forward, it provides strong justification to improve on the properties that make the anti-CD20 rituximab antibody effective against CLL and also for the development of alternative agents that might target pathways influenced by rituximab. It also opens the question about whether applying such therapy earlier in the course of the disease in patients with high-risk but asymptomatic disease might also improve CLL survival further. This question is now being studied by the German CLL Study Group, and we will anxiously await the answer of this second study.
How is Bortezomib Best Used in Myeloma?


Thalidomide (T), bortezomib (V) and lenalidomide, all were initially shown to be efficacious to treat relapsing refractory myeloma, then relapsed myeloma, and now are used routinely to treat newly diagnosed myeloma. In particular, each has been added to melphalan and prednisone (MP) as initial therapy for elderly patients and increased overall and extent of response, as well as PFS and OS, compared to MP alone. Similarly, each has been combined with dexamethasone as initial therapy for transplant-eligible patients and achieved increased overall and extent of response both before and after high-dose melphalan and autotransplantation, setting the stage for ongoing trials evaluating novel therapies with and without transplantation. Finally, each has been examined as maintenance therapy. For example, lenalidomide maintenance therapy has prolonged PFS in both newly diagnosed elderly patients treated with MP lenalidomide, as well as in younger patients who have undergone high-dose melphalan and autotransplantation therapy.

In the current trial reported by Palumbo et al. from Torino, Italy, two very important questions are asked. First, is a four-drug combination VMPT followed by maintenance VT better than a three-drug VMP without maintenance in terms of both efficacy and toxicity for non-transplant patients with newly diagnosed myeloma? The overall rate and extent of response, as well as progression-free survival (PFS) were superior in patients treated with VMVT/VT (38% vs. 24% CR rate and 56% vs. 41% estimated three-year PFS), but no differences were yet seen in overall survival (89% vs. 87%). Importantly, adverse events were more frequent and severe with VMVT/VT, with 38 percent versus 28 percent grade ≥ 3 neutropenia, 10 percent versus 5 percent cardiologic events, and 5 percent versus 2 percent thromboembolic events, so additional studies are clearly needed prior to recommending four-drug induction combination therapy. The incidence of treatment-related death was similar in both groups (4% vs. 3%). In this study, it is impossible to evaluate the independent value of VT maintenance therapy since there were two variables, four-drug and maintenance VT in one arm, versus three-drug VMPT without maintenance in the other cohort. Nonetheless, this study does provide further support to a Spanish trial, which showed that VT maintenance was superior to VP maintenance post VP therapy. The second important question of this study is the relative efficacy and toxicity of once-versus twice-weekly bortezomib treatment. Indeed, the most important finding of this study is that bortezomib can be given weekly (three-year PFS of 50% vs. 47% compared to twice weekly), thereby markedly reducing overall and severe adverse events without significantly compromising efficacy. Thus, the therapeutic index of this therapy was greatly improved, with ≥ grade 3 non-hematologic adverse events reduced from 51 percent to 36 percent (p=0.003) and ≥ grade 3 sensory peripheral neuropathy reduced from 16 percent to 3 percent with the once weekly regimen. Other trials such as cytorexan, bortezomib, and dexamethasone now further support these benefits of weekly bortezomib, and additional studies are ongoing. Thus, this study has modified the paradigm to weekly bortezomib treatment, assuring that it can be given to a broader spectrum of patients for longer durations and markedly expanding its therapeutic benefits.

Venous Thromboembolism in the Hospital: Prediction With Padua Precision


Phlebitic anticoagulation to prevent venous thromboembolism (VTE) in hospitalized medical patients has been implemented at most institutions as standard of care. Despite this, there is significant interest in developing risk stratification models to help predict those at highest risk of VTE to help prioritize patient selection for prophylaxis, and, thereby, potentially reduce the risk of bleeding complications. Although models predicting VTE risk have been developed, some are biased by high rates of cancer patients or suboptimal control selection, and, thus, none has been validated for predicting VTE risk in hospitalized patients; that is, until the model developed by Barbar and colleagues from the University of Padua, Italy.

In a prospective cohort study, these investigators assessed VTE risk for 1,180 inpatients admitted over a two-year period between January 2007 and December 2008, using a risk assessment model (RAM), the Padua Prediction Score, they developed. Individual risk scores were assigned based on a 20-point quantitative scoring system of risk factors, including cancer, myocardial infarction, stroke, congestive heart failure or respiratory failure, trauma, surgery, mobility, acute infectious or rheumatologic disease, thrombophilic condition, obesity (BMI ≥ 30), or hormone use. Renal disease, thrombocytopenia, major or recent bleeding, or pregnancy were exclusions. A total of 469 (39.7%) patients had a RAM score of 4 or greater, considered indicative of “high-risk” while the remaining 711 (60.3%) had RAM scores of less than four and were considered “low-risk.”

Among the 469 high-risk patients, only a minority, 186 (39.7%), received thromboprophylaxis with unfractinated heparin, low-molecular-weight heparin, or fondaparinux during hospitalization. Of these, 2.2 percent (4) developed confirmed VTE over the next 90 days. In contrast, 11.8 percent (31) of the high-risk patients not receiving thromboprophylaxis developed VTE. Among the 711 low-risk patients, 52 (7.3%) received pharmacological thromboprophylaxis and only two (0.3%) developed confirmed VTE. Bleeding complications, including gastrointestinal, intramuscular, and cerebral, occurred in three (1.6%) of the 469 high-risk patients but were non-fatal.

Comparing these results to a previous scoring system revealed that the Padua Score identified twice as many high-risk patients (469 vs. 243). Among these additional subjects, nine (3.7%) developed VTE, indicating the Padua Score affords greater predictive value and protection against VTE.

Several findings merit mention. First, it is of interest that even after thromboprophylaxis was discontinued after hospital discharge, the protection continued; that is, none developed recurrence. Although not immediately apparent, the authors surmise this is because correction of factors precipitating hospitalization provided protection. Further, it is of note that two of 17 (11.8%) high-risk patients continuing VTE prophylaxis post-hospitalization developed bleeding complications. This finding supports the importance of a risk-benefit assessment for decisions regarding long-term anticoagulation. Second, it is also of interest that only 40 percent of patients determined to be high-risk received VTE prophylaxis. In many hospitals in the United States, including mine, the rate would have been higher, as the electronic medical record admissions orders require VTE prophylaxis for all medical patients unless a reason is provided to avoid it. Quantitative risk assessment tools, such as the Padua Score, offer a potential alternative to “all-inclusive” prophylaxis strategies for which ultimate risk-benefit, specifically bleeding complications, remain to be seen. Furthermore, with approval of newer safer oral anticoagulants (e.g., dabigatran, rivaroxiban) prophylaxis strategies will likely continue to evolve.


Padua Risk Assessment Model*  

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<tr>
<td>1</td>
<td>≥70, CHF, AMI, ischemic CVA, BMI ≥30, hormones, other*</td>
</tr>
<tr>
<td>2</td>
<td>Trauma or surgery in past month</td>
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<tr>
<td>3</td>
<td>CA, past VTE, mobility, thrombophilic condition</td>
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Prospective Cohort Study

| Patient Groups | Group A | Group B | Group C  
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MARGARET V. RAGNI, MD, MPH  
Dr. Ragni indicated no relevant conflicts of interest.
Aulus Cornelius Celsus (born ca 25 B.C.) in De Medicina is credited with recording the cardinal signs of inflammation: rubor, calor, dolor, and tumor. A practitioner of Greek medicine, he believed in careful observation of nature and minimal interference with the healing process. For example, fever was an effort to defend the body against some sinister imbalance of nature and should not be hindered. McDonald et al. in the laboratory of Paul Kubes in Calgary, Canada, elegantly observe how neutrophils get to an area of dead cells to begin the healing process without destroying viable tissue to restore nature’s balance. These innate effector cells clear debris in areas of necrosis, but an over exuberant response can deliver lethal oxidants and proteases destroying organ function, as demonstrated in acute myocardial infarction. The intricate signaling described for guiding these inflammatory cells to sites of sterile organ injury provides a rational basis for why certain therapies to control the cardinal signs of inflammation may do more harm than good, disrupting homeostasis.

A murine model of focal hepatic necrosis was induced by localized thermal injury on the surface of the liver, followed by subsequent use of spinning disk video confocal microscopy to visualize the response of fluorescence-tagged neutrophils. Neutrophils adhered to the microvascular endothelium via leukocyte integrin Mac1 binding to endothelial ICAM-1 and accumulated within the area of necrosis. There was directional chemotaxis toward the necrotic tissue, ultimately infiltrating the area of cell death. Remarkably, the majority of neutrophils migrated via the intravascular route, which was often a less-direct course than transmigrating out of the vessel into the tissue. Purinergic danger signals such as ATP released from damaged cells directed neutrophils to sites of necrosis by activating the Nlrp3 inflammasome, including inflammatory cytokines such as interleukin (IL)-1b. Selective inhibition of P2X7 receptors resulted in reduced neutrophil recruitment in response to tissue injury. The CXCL2 chemokine, macrophage inflammatory protein 2 (MIP-2), immobilized on the luminal endothelial surface directed intravascular chemotaxis toward foci of damage, confirming that neutrophil chemotaxis is directed by a functional gradient of intravascular chemokines. The intravascular gradient of MIP-2 was consistently observed to abruptly end at the border of necrotic tissue. It was hypothesized that necrotic cells released an independent chemo-attractant or “necrotaxis” signal, which directs neutrophil migration beyond the intravascular chemokine gradient. Necrotic cells release damage-associated molecular patterns or DAMPs, including formylated peptides from mitochondria. In vitro, blockade of neutrophil formyl-peptide receptor 1 (FPR1) with inhibitory antibodies or the selective antagonist cyclosporine H (CsH) significantly attenuated neutrophil chemotaxis toward necrotic cells. FPR1 signals controlled only directionality within the necrotaxis zone.

The authors conclude that intravascular danger sensing and recruitment mechanisms have evolved to limit collateral damage during responses to sterile injury by allowing neutrophils to migrate intravascularly as they navigate through healthy tissue to sites of injury. Necrotaxis signals promote localization of neutrophils directly into existing areas of injury to focus the innate immune response on damaged areas and away from healthy tissue, providing an additional safeguard against collateral damage during sterile inflammatory responses. This allows the innate immune system to clean up the dead without killing the living. Observing nature, as Celsus advised, really does provide us with the clues to heal. To really appreciate these findings check out the videos in the paper at: www.sciencemag.org/content/330/6002/362/suppl/DC1.
Lost in Translation: Pulling the Switch on p53 Production in Dyskeratosis Congenita


A number of inherited bone marrow failure syndromes (IBMFSs) are associated with altered ribosome biogenesis or function. A common thread among many of these disorders is impaired hematopoiesis and a predisposition to malignancy. Patients with dyskeratosis congenita (DC), a heterogeneous disorder caused by defects in components of the telomerase complex, have a 200-fold increased incidence of AML and a thousand-fold increased incidence of squamous cell cancer of the head and neck. The X-linked form of DC (X-DC) is caused by mutations in DKC1 that encodes dyskerin, a multifunctional RNA-binding protein involved in both telomerase complex activity and pre-ribosomal RNA modification and processing. The genetically engineered DKC1 hypomorphic mouse (DKC1m) shares many DC phenotypic features, but, notably, half of early generation mice develop tumors of various histologies without associated telomere shortening. Impaired dyskerin function alters the translation of mRNAs that utilize an internal ribosome entry site (IRES) element, and IRES-mediated translation is important in cell-cycle control, hypoxia, and apoptosis. Thus, understanding the tumorigenic roles of dysregulated rRNA processing and mRNA translation in X-DC may provide important insights into mechanisms of cancer predisposition in other IBMFSs.

To explore these potential mechanisms, Bellodi and colleagues in the laboratory of Davide Ruggero at the University of California, San Francisco, evaluated IRES-mediated translational responses to oncogene-induced senescence (OIS) and genotoxic stress in the DKC1m mouse model and in primary X-DC cells. They demonstrated that RAS-mediated OIS, which is associated with increased p53 via a switch from cap- to IRES-dependent mRNA translation, was impaired in DKC1m mouse embryonic fibroblasts. DKC1m cells maintained higher proliferative rates and clonogenic potential compared to RAS-transfected wild-type (WT) cells. RAS-induced p53 mRNA levels were similar in DKC1m and WT cells; however, production of p53 protein was blunted in DKC1m cells due to alterations in polyribosomal association with p53 mRNA and depressed IRES-mediated translation. Similarly, reduced p53 translation and cell senescence were observed after exposure of DKC1m cells to etoposide in vitro or to \( \gamma \)-irradiation in vivo. Deregulated p53 translational control was also demonstrated in etoposide-treated human X-DC lymphoblasts and early-passage fibroblasts.

This important study advances our understanding of stress response and molecular pathogenetic mechanisms of cancer predisposition in X-DC that are independent of telomere-related genomic instability. Recent observations have further implicated reduced dyskerin with impaired p53 activation in breast carcinomas and altered p27 expression in pituitary tumors, suggesting that acquired defects in translational control might promote sporadic malignancies. Hematologists are well versed in the biology of p53, and it is common practice to look for p53 deletions or mutations in certain hematologic malignancies. Deregulated translation of p53, and/or other tumor suppressors, represents a different enemy, but one that might theoretically be targeted by agents that can restore polyribosomal association and IRES-mediated translation during genotoxic and oncogenic stress (Figure). The practical take-home message and reminder from this study is that DNA-damaging agents are often poorly tolerated and potentially tumorigenic in individuals with IBMFS and ribosomal dysfunction. Therefore, caution should be exercised when contemplating such drugs for patients with undiagnosed cytopenias.

Hodgkin Lymphoma

**STUDY TITLE:** A Randomized, Double-Blind, Placebo-Controlled Phase III Study of SGN-35 (brentuximab vedotin) and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Patients at High Risk of Residual Hodgkin Lymphoma (HL) Following Autologous Stem Cell Transplantation (ASCT) (The AETHERA Trial)

**SPONSOR:** Seattle Genetics, Inc.

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01100502

**PARTICIPATING CENTERS:** This is an international trial with a goal accrual of 322 patients (~161 patients randomized per treatment arm) with approximately 50 trial sites in the United States, Europe, and the Russian Federation.

**STUDY DESIGN:** Eligibility criteria include patients ≥18 years of age with ECOG performance status of 0 or 1 and with high-risk classical HL who have received ASCT in the previous 30 to 45 days. Patients at high risk of residual HL post-ASCT are defined as follows: 1) a history of refractory HL (defined as patients progressing on or failing to achieve a complete remission following frontline standard chemotherapy or a combined modality therapy); 2) relapsed or progressive HL that occurs <12 months from the end of frontline standard chemotherapy or combined modality treatment; and 3) extranodal involvement at time of pre-ASCT relapse. Patients are randomized in a 1:1 manner to receive SGN-35 1.8 mg/kg or placebo administered via outpatient IV infusion on day 1 of each 21-day cycle for a maximum of 16 cycles. The primary objective is to compare the progression-free survival of SGN-35 and BSC versus placebo and BSC. Secondary study objectives include comparison of overall survival between the two treatment arms, evaluation of the safety and tolerability of SGN-35 compared to placebo, and characterization of the incidence of anti-therapeutic antibodies.

**RATIONALE:** HL and anaplastic large-cell lymphoma commonly express the CD30 antigen. SGN-35 is an anti-CD30 antibody conjugated to the anti-tubulin agent monomethyl auristatin E (MMAE) in order to enhance its anti-tumor activity. In a phase 1, single-arm, open-label, dose-escalation study of SGN-35 in which the study population consisted primarily of patients with refractory/relapsed HL (including 73% with prior ASCT), the maximum tolerated dose was 1.8 mg/kg administered every three weeks. Tumor regression was observed in 36/42 (86%) evaluable patients, including 11 complete remissions (Younes A et al. New Engl J Med. 2010;363:1812-1821).

**COMMENT:** The five-year event-free survival rates for HL patients with intermediate- or high-risk disease is less than 30 percent post-ASCT, with the majority of relapses occurring within the first two years. Currently, there is no standard of care for HL patients who have received ASCT and are at high risk for disease relapse. Such patients may benefit from an agent that targets CD30 expressed on Reed-Sternberg cells. A similar strategy has been used in patients with relapsed/refractory follicular lymphoma where addition of rituximab maintenance after chemotheraphy resulted in better overall survival than in patients who did not receive the antibody (Vidal L et al. J Natl Cancer Inst. 2009;101:248-255).

– Jason Gotlib, MD, MS

Dr. Gotlib has disclosed no relevant conflicts of interest.

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**OBITUARY**

Alan Gewirtz – A Zest for Life
1949 – 2010

On November 17, 2010, we lost one of our most distinguished and beloved colleagues, Dr. Alan M. Gewirtz. Alan dedicated his career to the development of novel therapeutics for the treatment of leukemia. He was the C. Willard Robinson Professor in Medicine and Pathology at the University of Pennsylvania (Penn) and headed the Hematologic Malignancy Program at the Abramson Cancer Center. It was during his hematology fellowship at Yale when Alan developed a love affair with hematopoiesis that never ended. Alan was an early advocate of the use of interfering RNA oligonucleotides in leukemia, and he was a pioneer in the field of therapeutic gene targeting. He was a faculty member at Temple University before moving to Penn, where Alan spent the last two decades. Alan was a leader in the field of stem cell biology and engineered therapeutics. Not only did Alan have an impact on the world of science, but he also had an impact on all of those whom he taught. He was a tireless advocate for basic science research and for promoting the careers of young scientists.

Alan’s noteworthy scientific contributions were published in the most esteemed journals and were recognized by the American Society of Hematology, Doris Duke Foundation, Leukemia and Lymphoma Society, American Society for Clinical Investigation, and the Association of American Physicians. He also served on the editorial boards of such publications as Experimental Hematology and the Journal of Clinical Investigation. Alan was a member of the Board of Trustees of the Leukemia and Lymphoma Society and a recipient of the Doris Duke Charitable Foundation’s Distinguished Clinical Scientist Award, and he was awarded an honorary doctorate from the Pomeranian Medical University in Szczecin, Poland. He was also the holder of nine patents.

Alan’s reach was both worldwide and universal, and he showed grace and ease both on the ground and aloft. He was not only a passionate pilot, but he was even funded by NASA to study hematopoiesis in outer space. Alan’s dedication, commitment, and contributions to ASH were boundless and remarkable. Alan was the editor of the ASH Education Book since 2007 and continued working on the 2010 book right up to the time of his passing. He was also scientific co-chair for two annual meetings, and he served with distinction on numerous ASH committees.

However, more important than Alan’s outstanding career and his scientific contributions, is the way in which he led his life. He had that perfect and enviable balance, which allowed him to excel without taking himself or life too seriously. He would not hesitate to debate with you, while Sparky, his dog, dutifully remained by his side. Not only was he brilliant and indefatigable, he was also caring, funny, and kind. He had an endless zest for life and learning. Alan was that bright light that will forever live on in the hearts of all those around the world whom he touched.

For those who wish to make a donation to ASH in memory of Dr. Alan Gewirtz, please visit www.hematology.org/makeagift.

– Charles S. Abrams, MD
From Uganda to Boston and Back

On a blustery Boston afternoon last October, Derrick Bengo wrapped his coat around him as he shook the hands of ASH members Drs. Walter “Sunny” Dzik and Aliyah Sohani. Having come from the equatorial nation of Uganda, Mr. Bengo was unprepared for Boston’s chilly autumn. Mr. Bengo came to Boston for six weeks to study with Drs. Dzik and Sohani at Massachusetts General Hospital (MGH) as part of ASH’s Visitor Training Program (VTP). The program funds opportunities for doctors and scientists in developing countries to train on a specific topic or technique under the mentorship of an ASH member anywhere in the world. When the participants finish their training, they return to their home countries to implement and share the skills they have learned.

Mr. Bengo applied to learn about the interpretation of peripheral blood smears and differentiation of leukemias by histochemical staining of peripheral blood smears. His goal for the training was to gain proficiency in interpretation of peripheral blood smears and the correlation of peripheral blood smear findings with multi-parameter CBC results and, when indicated, with bone marrow findings.

“I first met Sunny in 2007, when the ASH teams from Health Volunteers Overseas came to visit Mulago Hospital,” said Mr. Bengo, referring to the main referral hospital in Kampala, Uganda, where he is a senior laboratory technologist. Dr. Dzik and his colleagues at MGH returned to Uganda in 2010 and encouraged Mr. Bengo to apply for the VTP. Mr. Bengo had high expectations for himself and the program. “My dream is to become a good hematologist for all of these children down here in Uganda, so I have to learn to fly with the eagles. It’s a golden opportunity to have hands-on experience on the hematologic techniques that we just read about and can’t actually perform. With these new skills, I’ll be able to teach laboratory technologists in Uganda, since I’m the main trainer for the laboratory training schools.”

As Mr. Bengo’s host mentor at MGH, Dr. Dzik was responsible for working with Mr. Bengo to prepare the training proposal and budget. After Mr. Bengo was accepted into the program, Dr. Dzik worked with Mr. Bengo to secure housing, airfare, and his visa.

The benefits of the program extend not only to the participant, but also to the hosts who gain valuable insight into facets of hematology they would not have had without the cross-cultural interaction. Dr. Sohani worked with Mr. Bengo each day in the lab and describes their interaction as a learning experience for her just as much as it was for Mr. Bengo.

“Derrick’s morphological skills were incredibly strong; it was eye-opening for the lab techs to see how important such skills are in settings where there is no easy access to flow cytometry or molecular genetic studies. Derrick’s visit to MGH made us appreciate how much we all can learn and benefit from others whose background and set of experiences differ from our own.”

Mr. Bengo left Boston with a renewed sense of dedication to his work at Mulago Hospital. He will continue to report back to Drs. Dzik and Sohani to demonstrate how he is implementing the skills he learned at MGH.

The Visitor Training Program is open to medical professionals in developing countries. ASH also encourages members to volunteer as host mentors. The application and mentor volunteer forms are both available on the ASH website at http://hematology.org/Awards/Visitor-TrainingProgram/2196.aspx.

Association of American Medical Colleges Awards National Recognition to Two ASH Members

During the Association of American Medical Colleges’ 2010 annual meeting in early November, ASH members Drs. George Buchanan and David Ginsburg were awarded national recognition for their outstanding contributions to academic medicine.

Dr. George Buchanan, professor of Pediatrics and director, Pediatric Hematology-Oncology at the University of Texas Southwestern Medical Center, received the 2010 Arnold P. Gold Foundation Humanism in Medicine Award. This award honors a medical school faculty physician who exemplifies the qualities of a caring and compassionate mentor in the teaching and advising of medical students.

Dr. David Ginsburg, James V. Neel Distinguished University Professor and Warner-Lambert/Parke-Davis Professor, Departments of Internal Medicine, Pediatrics, and Human Genetics, Life Sciences Institute, University of Michigan Medical School, received the 2010 Award for Distinguished Research in the Biomedical Sciences. This award honors outstanding clinical or laboratory research by a medical school faculty member related to health and disease who has contributed to the substance of medicine.
What Do You Want to Be When You Grow Up?

KIMBERLY STEGMAIER, MD
Assistant Professor of Pediatrics, Harvard Medical School, Associate Member, The Broad Institute

For some, this is a question answered with conviction in childhood. For others, it is a journey peppered with path-altering interjections. For me, one such career-altering influence was the ASH Fellow Scholar Award in Clinical Translational Research.

From a relatively young age, I contemplated two dichotomous paths — that of a physician or ballerina. At Duke University I completed the necessary pre-medical requirements and thought I would become a general pediatrician. A research career was not in my range of sight with no scientists in my family and no prior laboratory-based research experience. The earliest seed of change was planted when I applied to medical school. One of my interviewers was David Sabiston, then the chief of surgery at Duke University Medical Center. After the interview, he called me to follow up on our discussions and urged me to consider a physician-scientist career. I was shocked by his genuine interest in my career and intrigued by his suggestion.

As a student at Harvard Medical School, I found myself drawn to the field of hematology-oncology and, with the seed planted three years prior, embarked on a Howard Hughes Medical Institute (HHMI) Medical Student Research Fellowship. It was a year like no other. I worked in the laboratory of Dr. Gary Gilliland and managed to continue to pursue my passion for ballet, dancing with Ballet Theatre of Boston. I was mentored at the bench by Dr. Todd Golub, then a pediatric hematology-oncology postdoctoral fellow. Dr. Golub had recently cloned the ETV6 (TEL) gene in a TEL-TELGFRI rearrangement in CML. What then followed was his cloning of leukemia-related TEL-ABL and TEL-AML rearrangements and our discovery of frequent TEL abnormalities in children with ALL. I was hooked. When I was searching for laboratories, one of the medical students working in Dr. Gilliland’s laboratory raved about his mentoring and the overall laboratory environment. She was most certainly correct. I could not have asked for a more outstanding environment in which to learn. This year was transformative. I often wonder where I would be today if it were not for the magic of that first year in the laboratory.

After completing a pediatric residency at the Children’s Hospital of Boston and the first year of a pediatric hematology-oncology fellowship at the Dana-Farber Cancer Institute and Children’s Hospital, I faced the challenge of selecting a laboratory. I gravitated toward Dr. Golub and the promise of genomics for cancer-related discovery. Since my training in Dr. Gilliland’s laboratory, Dr. Golub had become a principal investigator at Dana-Farber and the director of the cancer program at the Broad Institute of Harvard and MIT. During my postdoctoral training, we developed an approach to small-molecule discovery using gene expression signatures and applied it to the identification of chemical modulators of AML differentiation. At this point, the idea of a physician-scientist career continued to be affirmed. However, the leap from postdoctoral fellow to independent investigator seemed to span a deep ravine.

What inspired the vault despite the possible plunge? For me, a critical issue was truly remarkable mentoring from both Drs. Gilliland and Golub. To this day, they continue as my two primary career mentors, even as my network of mentors has grown. A second was the outstanding support that I received at Dana-Farber Cancer Institute, Children’s Hospital Boston, and the Broad Institute, where numerous individuals encouraged my efforts and guided my path toward a physician-scientist career. A third was the external validation that I could succeed in this path. The ASH Fellow Scholar Award in Clinical Translational Research came at just the right time. This award was pivotal in my career transition. It affirmed, by an external group of senior scientists, a confidence in my ability to succeed in this path and welcomed me into the greater community of ASH. It funded some of the earliest efforts in my laboratory to develop gene-expression-based high-throughput screening and its application to leukemia. This work was recognized with the ASH Joanne Levy, MD, Memorial Award. (Joanne Levy was also an ASH Scholar Award recipient.) This award was an incredible honor and inspiration to continue my studies.

I currently lead a laboratory-based research effort at the Dana-Farber Cancer Institute and am an associate member of the Broad Institute. My research focuses on the integration of new genomic approaches for both target and small-molecule discovery for the acute leukemias and other malignancies affecting children. I also provide clinical care to children with cancer at Dana-Farber and Children’s Hospital Boston. ASH is an ongoing lifeline for my work. It is a rich source of mentors and collaborators. I have also enjoyed the opportunity to develop ASH-related educational materials, to serve on abstract review and scientific committees, and to both chair sessions and share our work at the annual meeting.

One of the great joys of a physician-scientist career is the mentoring of trainees. As I develop my research program, I now have the pleasure of sharing in the excitement of my students and postdoctoral fellows as they win ASH-related training awards and present their work at the annual meeting. As a nucleus for fomenting collaboration, encouraging innovative science, connecting student with mentor, and empowering early investigators, ASH is a critical force in the future of hematologic research.

Drs. Gary Gilliland and Todd Golub, Dr. Stegmaier’s mentors, are also past ASH Scholar Award recipients. This program has had obvious impact on hundreds of careers. ASH is a 501(c)(3) charitable and educational organization. The Society seeks annual donations for several programs, one of which is the ASH Scholar Awards. If you would like to contribute to the ASH Scholar Awards program to support the next generation of promising hematologic researchers, please visit www.hematology.org and click on “Make a Gift.” If you have donation questions, please e-mail development@hematology.org.

The ASH Fellow Scholar Award in Clinical Translational Research came at just the right time. This award was pivotal in my career transition. It affirmed, by an external group of senior scientists, a confidence in my ability to succeed in this path and welcomed me into the greater community of ASH.
The ASH website offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH.

### Spotlight on: Annual Meeting

Even though the 2010 ASH Annual Meeting is over and the focus now turns to the 2011 annual meeting in San Diego, CA, on December 10-13, the ASH website still serves as a valuable source for meeting-related information and resources.

Visit [www.hematology.org/Meetings/Annual-Meeting](http://www.hematology.org/Meetings/Annual-Meeting) to:
- Obtain CME credits or certificate of attendance
- Access webcasts of select meeting sessions
- View annual meeting abstracts
- Read the daily annual meeting newspaper ASH News Daily
- Peruse the Education Program Book online
- Order the following items:
  - Annual Meeting Sessions DVD
  - Education Book
  - Abstract Book
- Get preliminary information about the 2011 annual meeting

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