HEMATOLOGY PROGRAM DEBUTS IN 2010

LINDA BURNS, MD

Dr. Burns is Associate Professor of Medicine and Fellow in the Hematology, Oncology, and Transplantation Program at the University of Minnesota. She is also Treasurer of ASH.

In response to increasing demand from European researchers to focus on translational research, ASH and the European Hematology Association (EHA) have collaborated to create the Translational Research Training in Hematology (TRTH) program. The program will provide promising translational investigators an opportunity to undertake intensive training in the pathogenesis, diagnostics, and experimental treatment of hematologic disorders from some of the most recognized names in the field. Modeled after ASH’s successful Clinical Research Training Institute, the inaugural TRTH will bring 20 early-stage scientists to southern Europe on March 20-26, 2010. This rigorous one-week course will allow participants to concentrate on projects directly focused on the use of human samples or involving in vitro and/or animal studies close to translation to studies in human subjects. Leaders in the areas of biostatistics and biomarkers, ethics, clinical studies, and genetic and molecular biology will foster personalized mentoring.

Didactic sessions will help researchers prepare to conduct hypothesis-driven research, design phase I and II clinical trials, use animal models for translational research, and employ diagnostics and biomarkers in translational research. Practical sessions will focus on career development, featuring career retrospectives from hematology pioneers in addition to expert opinions.

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Hemoglobin’s Holy Grail


At the genetic level, sickle cell disease is unambiguous, resulting from mutation of a single nucleotide (A→G) that introduces an amino acid substitution [valine for glutamic acid] in the β subunit of hemoglobin. At the clinical level, however, the disease is phenotypically diverse, ranging from asymptomatic to debilitating. An important determinant of clinical severity is the patient’s level of fetal hemoglobin (HbF; α2γ2) as the γ subunit of HbF competes with sickle β for binding to the α chain. Normally, in a process called hemoglobin switching, synthesis of the γ-chain is stopped approximately six months after birth, at the same time that β-chain synthesis is initiated. A group of rare conditions called hereditary persistence of fetal hemoglobin (HPFH) are characterized by continued synthesis of high levels of HbF in adult life. Patients with both sickle cell disease and HPFH have been identified, and as anticipated, they have a clinically benign phenotype (those with at least 25% HbF are neither anemic nor subject to vaso-occlusive complication). Moreover, no deleterious effects are observed in patients who are homozygous for HPFH, even when 100 percent of the hemoglobin produced is HbF. This observation indicates that preventing or reversing hemoglobin switching would be a safe approach to treating sickle cell disease (and β-thalassemia). For this reason, determining the molecular mechanisms that regulate expression of HbF has been the ultimate quest for a number of investigators.

Interestingly, elevated levels of HbF are seen in otherwise normal individuals, and epidemiological studies have shown that adult HbF expression is inherited as a quantitative trait. The field of HbF investigation has been invigorated by two recent genome-wide association studies that identified three major loci that account for ~20 percent of the variation in HbF levels and predict the clinical severity of sickle cell disease and β-thalassemia.1 The sequence variant with the greatest effect was located in an intron of BCL11A on chromosome 2p15, and the product of the gene is a zinc-finger protein. Through a series of rigorous, compelling experiments, Sankaran, et al., from Stuart Orkin’s lab at Children’s Hospital Boston, showed that the HbF-high BCL11A genotype is associated with reduced expression of the gene and that expression of full-length forms of BCL11A (apparently influenced by sequence variants) is restricted to adult erythroid cells. In vitro experiments demonstrated that down-regulating BCL11A expression in primary adult erythroid cells leads to enhanced HbF expression. Finally, Sankaran, et al. produced the “smoking gun” by showing that BCL11A occupies several discrete sites in the β-globin gene cluster, indicating a direct role for BCL11A in globin gene regulation.

In Arthurian legend, the Holy Grail is the cup or platter used by Jesus at the Last Supper. Obtaining it was the ultimate quest because of its religious significance and miraculous power. Over time, the grail has come to represent other more prosaic things, but finding it is always the highest goal, worthy of the pursuer’s best effort. Have Sankaran, et al., informed by the powerful genome-wide association studies,1 come into possession of the hemoglobin grail (i.e., the basis of hemoglobin switching)? If not, the hemoglobin grail appears to be within reach, and finding it brings with it the possibility of developing strategies for ameliorating the severity of diseases (sickle cell disease and β-thalassemia) that affect millions worldwide.

Moving Beyond the “A” in ASH

I hope that by this time in the New Year your resolutions have not completely waned and that you are still inspired by the possibilities for great things in 2009. I continue to bask in the glow of our historical inauguration and its promise for renewed collaboration and civil discourse. The unprecedented national and international media coverage of the inauguration underscores again how small our world has become, and so it seems especially appropriate that this year at ASH should be marked by new global initiatives that will strengthen our ties with the international hematology community.

ASH has approximately 3,950 international members who hail from 96 countries and account for approximately 24 percent of our total membership; this number increases annually. More than 60 percent of the submissions to Blood come from non-North American hematologists. Furthermore, our international members’ participation is a critical contribution to our annual meeting, with attendees at the 2008 annual meeting coming from 109 countries.

The mission of ASH is to promote the best science and patient care in hematology around the world. A major goal of the Executive Committee is to consider new ways to enhance the experience of our international members, authors, and attendees in the Society. Over the past year we have launched a global initiative aimed at meeting this challenge. We hope to strengthen our relationships with our international colleagues through shared educational, scientific, and clinical programs. Our global strategy is still a work-in-progress, but this year will be marked by the inauguration of several new projects, with the expectation of more to come.

Here are a few of the global projects in the works:

ASH will hold a Highlights of ASH* meeting in Latin America in May in conjunction with the Asociación Brasileira de Hematologia e Hemoterapia (SBHH/CBH). At Highlights of ASH, leading experts will discuss the latest scientific and clinical discoveries presented at the 50th ASH Annual Meeting last December. We are delighted to initiate this annual event in partnership with the hematology associations of Argentina, Chile, Mexico, Peru, and Uruguay. ASH will support two trainees from each of our partner associations to attend the meeting.

ASH will collaborate with the European Hematology Association (EHA), with whom we have a collegial relationship, to launch the Translational Research Training in Hematology (TRTH) award program in 2010. This unique program, which is modeled after the Clinical Research Training Institute, will offer personalized training in translational hematology research and opportunities for networking and mentoring. The first one-week course will be held in southern Europe in March 2010. To learn more about TRTH, read the cover story in this issue of The Hematologist.

ASH will also be collaborating with the Japanese Society of Hematology in presenting a joint symposium on hematopoietic stem cells at their annual meeting in Kyoto in October. I will also be giving a lecture at the meeting. And ASH officers and staff will be meeting with several training directors from Mexico to better understand their hematology training program. I will also be speaking at the 50th anniversary of the Mexican Society of Hematology (Agrupación Mexicana para el Estudio de la Hematología AC [AMEHAC]), in Morelia, Michoacan, Mexico. The meeting is scheduled for April 29 - May 3, 2009.

In this year, as the country re-commits itself to responsibility as a global citizen, I am excited to see ASH’s own global initiatives grow. Over the next several months, you will hear about more these initiatives and programs, and I hope the membership will embrace our commitment to international collaboration.
DON'T FORGET TO CLAIM YOUR CME CREDITS

March 31 is the deadline for claiming CME credits for the 2008 ASH Annual Meeting. For more information, go to http://reg.ipagog.com/ashcm08/cme.

A NEW DOCTOR IN TOWN

Navy Captain Brian Monahan, MD, a member of ASH, was nominated to take over as the attending physician for Congress. Dr. Monahan is currently the deputy attending physician for Congress. The Office of Attending Physician, established in 1928, provides free medical care and medications to the 435 members of the House, the 100 members of the Senate, and the nine Supreme Court justices.

Highlights of ASH® in Latin America

May 15 - 16, 2009
São Paulo, Brazil

For the first time, ASH will be holding the only official Highlights of ASH meeting in Latin America in conjunction with the Associação Brasileira de Hematologia e Hemoterapia (SBHH/CBH). In addition, organizations in the following countries are co-sponsoring this meeting: Argentina, Peru, Uruguay, Mexico, and Chile.

At this meeting, leading experts will discuss the latest scientific discoveries presented at the 50th ASH Annual Meeting, held in December 2008, and the clinical applications of this new research. Presentation topics will include adult and pediatric hematology, oncology, and transfusion medicine. In addition, the interactive panel discussions and social events will provide many opportunities to discuss your challenging patient cases with the expert speakers and your colleagues. Presentations will be delivered in English and simultaneously translated into both Portuguese and Spanish.

Program materials will be available in English only.

Apply for the Trainee Research Award

The Trainee Research Award provides an award of $4,000 for approximately three months of research support for a relevant hematology research project and $1,000 for travel to the Society's annual meeting. The program is open to undergraduates, medical students, and residents. Please note that fellows are ineligible for this award. Applications are due March 16. For more information, including a copy of the application, visit www.hematology.org/education/awards/trainee.cfm.

LETTERS TO THE EDITOR

SOLICITATION

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

Letters should be sent to:
Karen Learner, Managing Editor
The Hematologist: ASH News and Reports
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A 22-year-old woman is referred for persistent elevated platelet count. She is well and her past history is negative. Physical examination is notable for splenomegaly (palpable 2 cm below the costal arch). Current CBC shows platelet count of 900,000/µl with normal hematocrit and WBC count. The diagnostic workup, including bone marrow histology, was consistent with JAK2V617F mutated essential thrombocythemia (ET). Counseling for pregnancy planning is also requested.

**RISK STRATIFICATION**

Age (patients older than 60) and a history of previous thrombotic event(s) are the most important predictors of thrombosis in patients with ET, whereas a clear association between platelet count and thrombotic events has never been demonstrated. Peculiarly, a very high platelet count (>1500 x 10^9/L) is a risk factor for bleeding rather than thrombosis, probably due to the impairment of von Willebrand factor multimerization found both in patients with ET and in those with reactive thrombocytosis. Recently, leukocytosis and the presence of the V617F JAK2 mutation have been recognized as risk factors for thrombosis. Remarkably, JAK2 mutation is associated with increased leukocyte and platelet activation, platelet-leukocyte interactions, and expression of tissue factor and fibrinogen on leukocyte surfaces. These alterations might play a role in the pathogenesis of thrombosis in ET, but further studies are required to ascertain whether such findings should modify the risk classification of patients. To date, a young, asymptomatic woman should be considered “low-risk,” irrespective of her platelet and leukocyte count or JAK2 mutational status.

**MANAGEMENT OF “LOW-RISK” PATIENTS**

Avoiding cytoreduction is generally recommended for low-risk ET patients. The natural history of these patients left untreated was prospectively evaluated in a controlled study that compared 65 patients fulfilling the criteria for low risk for thrombosis and 65 age- and sex-matched normal controls. After a median follow-up of 4.1 years, the incidence of thrombosis was similar in both groups (1.9% vs 1.3% per patient-year) and no major bleeding was observed. Thrombotic deaths are rare in low-risk ET patients, and there are no data indicating that fatalities can be prevented by starting cytoreductive drugs early. Therefore, withholding chemotherapy is justifiable in young, asymptomatic individuals with a platelet count below 1500 x 10^9. If cardiovascular risk factors together with ET are identified (e.g., smoking, obesity, hypertension, hyperlipidemia, diabetes, and other thrombophilic factors), specific management of such situations is recommended. Aspirin at doses ranging from 30 to 500 mg/day has been found to control microvascular symptoms, such as erythromelalgia and transient neurological and ocular disturbances including dysarthria, scintillating scotoma, amaurosis fugax, migraine, and seizure. However, the benefit of low-dose aspirin (100 mg daily) as primary prophylaxis of vascular events in asymptomatic individuals has not been demonstrated by appropriate clinical trials.

**PREGNANCY IN ET**

Pregnancy is a challenging event in young women with ET. No controlled studies addressing the management of pregnancy in ET have been published, and current recommendations are based on pooled data from small cohort studies and clinical expertise. In the literature, about 400 pregnancies in about 200 women are reported. First-trimester abortion is the most frequent complication, occurring in about one-third of pregnancies. Interestingly, the incidence of maternal complications is relatively low: 3 percent for major thromboembolic and 2 percent for major bleeding events. The presence of the JAK2V617F mutation seems to be an independent predictor of pregnancy complications. Pregnancy in ET should be stratified according to underlying risk factors in low-, high-, and highest-risk pregnancies. Risk factors include: previous major thrombotic or bleeding complications, previous severe pregnancy complications (>3 first-trimester or >1 second- or third-trimester losses, birth weight <5th percentile of gestation, preclampsia, intrauterine death, or stillbirth), and platelet count >1500 x 10^9/L. Women with low-risk pregnancies are treated with low-dose aspirin, whereas women with high- and highest-risk pregnancies may benefit from low-dose aspirin plus interferon alpha ± low-molecular-weight heparin throughout pregnancy and for at least six weeks post-partum. Although interferon alpha does not appear to cross the placenta, it is probably excreted in breast milk and thus breast-feeding is contraindicated. Analgesic and hydroxyurea should be avoided in pregnancy due to the risk of teratogenic effects, though successful pregnancy outcomes have been reported.

**FURTHER READING**


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HARNESSING THE RESOURCES OF THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD PROGRAM TO ADVANCE HEMATOLOGY

BARRY S. COLLER, MD

Dr. Coller is David Rockefeller Professor of Medicine, The Rockefeller University. Dr. Coller is also Principal Investigator, Rockefeller University Clinical and Translational Science Award.

The Clinical and Translational Science Award (CTSA) program is the centerpiece of NIH’s Roadmap initiative to “reengineer the clinical research enterprise.” The product of the recommendations of multiple advisory committees under Dr. Zerhouni’s leadership, it was designed to address the limitations of the General Clinical Research Centers (GCRC) program, which it succeeded. Twelve CTSA programs were awarded in 2006, 12 in 2007, and 14 in 2008, bringing the current total to 38. Ultimately, the program is expected to have 60 centers.

The CTSA program provides significant resources that can be used to advance the discipline of hematology. Below are descriptions of some of those resources and a primer on how they can be harnessed to meet the goals of the hematology programs at both CTSA and non-CTSA institutions. CTSA programs provide tremendous support for investigators nationwide and worldwide. For example, at Rockefeller, the lead biostatistician has extended methods based on U-statistics to structured multivariate data, which are particularly valuable for integrating gene expression data and clinical data. Software based on this methodology is being made available to all investigators from CRAN (http://CRAN.r-project.org), and access to a grid of PCs, which provides the computational resources to apply this methodology to genome-wide association and expression studies, is available through the Rockefeller Web server (http://musat.stat.rockefeller.edu).

As a result of my interest in hemostatic disorders, with CTSA support, I have been developing an electronic bleeding history form for research purposes. This is part of a larger human phenotyping initiative that we are developing to complement the enormous amount of genetic, proteomic, and gene expression data that are now becoming available, so as to better understand the gene-gene, gene-environment, and stochastic phenomena that affect the clinical expression of disease. The goal of our project is to make this research tool available to the entire academic community so that it can be used by investigators anywhere in the world. We hope that this will make it easier for junior physician scientist investigators to get started in careers in hemostasis research. Moreover, if multiple investigators use this same questionnaire, we hope to move to the next, and more ambitious, phase of the project by encouraging investigators to upload their de-identified data into a common database where the data can be pooled. This has the potential to strengthen statistical power and thus enhance the likelihood of successfully identifying the effects of modifying genetic and environmental influences. We are also part of an International Society on Thrombosis and Haemostasis group that is developing a much shorter bleeding history questionnaire as a clinical tool. We plan to also use our CTSA resources to convert that to an electronic format and to host it on the Rockefeller University server. When that questionnaire is complete, we will make it available to all ASH members.

I hope this brief description of CTSA resources will encourage you to make contact with CTSA leaders in your institution or, if you are not in an institution with one, to search for CTSA-developed resources available to non-CTSA investigators. Finally, CTSA leaders served as a nucleus to create a new broad-based Society for Clinical and Translational Science (SCTS) for all translational investigators. This society is specifically designed to complement the role of ASH and other subspecialty societies by focusing on the process of clinical and translational research rather than the results of investigations in any particular research area. SCTS will also focus on the interdisciplinary teams needed to conduct clinical and translational research and the need to partner with industry and governmental agencies. It will be exciting to explore the many ways in which SCTS and ASH can work together on common goals.
NRC RECOMMENDS SECURITY OVER REPLACEMENT OF CESIUM CHLORIDE RADIATION SOURCES

In September 2008, the Nuclear Regulatory Commission (NRC) held a workshop on the security and continued use of cesium-137 chloride (CsCl) sources. CsCl sources are widely used in irradiators to sterilize human blood, in biomedical and industrial research, and for calibration of radiation instrumentation and dosimetry. Gamma-ray irradiation of lab animals by CsCl-containing devices is widely used in hematology, immunology, and stem cell biology research.

CsCl sources have come under scrutiny from a security standpoint because cesium is a compressed powder that is highly soluble in water and dispersible as an aerosol. Alternatives such as x-ray irradiators and cobalt-60 irradiators could be used in some cases, but not all; and the cost of switching to these alternatives would be financially prohibitive to most users.

During the September workshop, the NRC solicited comments from stakeholders on a draft paper that discussed alternative CsCl sources and technologies, a phase-out of CsCl, additional enhanced security measures, and other potential future requirements. ASH submitted comments urging the Commission to consider how the elimination of CsCl sources would compromise care and research that leads to development of clinical treatments for patients. ASH also shared these concerns with the staff of Representative Edward Markey (D-MA) who has sponsored legislation that would give the NRC authority to further regulate radiation sources such as CsCl.

In November 2008, NRC staff submitted a memorandum outlining three possible options for the Commission’s consideration regarding the continued use and security of CsCl sources. The option recommended by NRC staff for approval, and for which ASH advocated, suggests maintaining current CsCl use in blood irradiation, biomedical research, and calibration, while also advocating for developing enhanced security systems for new and existing units and for developing a Commission policy statement. This option also acknowledges that significant impediments exist to any potential phase-out of CsCl and states that there is insufficient information available to develop a technical basis for rule-making.

ASH was pleased that the NRC staff’s analysis and conclusions echoed the Society’s concerns. ASH will continue to monitor this issue and keep members updated on any future developments.

Headlines From WASHINGTON

Obama Administration Continues to Take Shape

Although Barack Obama has officially taken office as president of the United States, a number of key positions within his administration had not yet been announced as this issue of The Hematologist went to press. Former Senator and Majority Leader Tom Daschle (D-SD) withdrew from consideration as secretary of the Department of Health & Human Services (HHS) on February 3, leaving who would fill the position in question as of press time. Daschle had also been expected to lead the administration’s efforts to reform the nation’s health-care system by serving as director of the newly created White House Office of Health Reform. However, health-care reform is expected to remain near the top of President Obama’s agenda.

Several other key appointments within HHS have also yet to be named and will likely not be chosen until after the Senate has confirmed an HHS secretary. Among the other positions yet to be named are director of the National Institutes of Health (NIH), commissioner of the Food and Drug administration (FDA), director of the Centers for Disease Control and Prevention (CDC), and administrator of the Centers for Medicare and Medicaid Services (CMS). Interim personnel are in place for these positions and will remain until the Obama administration appoints individuals to these leadership positions and the Senate confirms them. For a final listing of these appointments, please visit www.hematology.org.

Congress Considers Health Provisions in Economic Recovery Legislation

As this issue of The Hematologist went to press, Congress was in the midst of finalizing economic recovery legislation. Conference from the House and Senate agreed to provide $10 billion in total additional funding for NIH to fund extramural research grants and improve facilities at NIH and research facilities across the nation. Additionally, each bill contained significant funding for a variety of health-care programs, including helping states cope with rising Medicaid costs, helping people who have lost their jobs keep their employer-provided health insurance under a program known as COBRA, and facilitating universal adoption of electronic medical records.

Congressional leaders hoped to have an economic stimulus bill finalized and ready to be signed into law by President Obama before President’s Day in mid-February.

NIH Unveils New Research, Condition, and Disease Categorization (RCDC) System

NIH unveiled the new Research, Condition, and Disease Categorization (RCDC) system, which offers scientists and the public a quick and easy way to get a complete list of research projects funded in 215 specific research areas, diseases, or conditions. Established as part of a mandate set forth in the NIH Reform Act to improve how NIH presents information to the public, RCDC is a computerized process that NIH will use at the end of each fiscal year (beginning with fiscal year 2008) to sort and report the amount of research it funded. RCDC reports will provide detailed information within each category, including the total dollar amount for research projects, the name(s) of the principal investigator(s) and institution conducting the research, and the NIH Institute or Center supporting the research. For more information, including detailed instructions on using RCDC, go to http://report.nih.gov/rcdc.

TAKE ACTION

As this issue of The Hematologist went to press, Congress was set to address funding for the NIH through a variety of avenues, including an economic recovery package, finalization of fiscal year (FY) 2009 funding levels, and the beginning of the FY 2010 appropriations process. It is critical for all ASH members to contact their senators and representatives to help ensure that Congress gets the message that hematologists and their patients want Congress and the Obama administration to include more funding for NIH research.

Advocacy by the research community can make a difference in securing funding for NIH. ASH members are encouraged to visit the ASH Advocacy Center (www.hematology.org/takeaction) to participate in ASH’s advocacy efforts to increase federal funding for NIH. The ASH Advocacy Center makes advocacy easy by providing a sample letter with ASH’s message and allowing visitors to contact their congressional delegation with a few simple clicks of a computer mouse.

The Hematologist: ASH NEWS AND REPORTS
Training to become an effective clinician and researcher in hematology has become an extremely lengthy and complex activity. Currently, 1,348 Associate members of ASH include physicians enrolled in programs leading to certification in multiple hematology-related clinical disciplines as well as non-physicians enrolled in pre- and post-doctoral research training programs. One goal of the ASH Trainee Council is to assist this increasingly diverse set of trainees in navigating through the complex pathways of their career development by defining and tracking specific milestones. The Council has recently completed an extensive enhancement of Web-based resources for this purpose on the ASH Web site (www.hematology.org/training, under Career Planning). This updated section can be used by clinical and non-clinical trainees and their mentors to plan their specific educational objectives and to mark important milestones in their progression through training.

A "Career Timeline for MD Trainees" aids fellows by breaking down their education and research objectives according to the clinical year of training. "Continuous priorities" (those relevant throughout the training period) such as frequent mentoring meetings and participation in research and writing opportunities, are detailed. First-year priorities, including identifying a research mentor and outlining and refining research opportunities, are subsequently outlined. The second-year objectives focus on initiating research opportunities and identifying possible grant prospects, including the ASH Research Training Award for Fellows. The third-year page focuses on continuing research and the need to prepare an objective review of the fellow's clinical and research activities. This tool is organized around the three "classical" phases of training revolving around the qualifying exam. On the pre-examination page, numerous suggestions are made regarding course work and identifying the optimal mentor — the most important part of a student's career. Links to critical questions that trainees need to ask of possible mentors and additional suggestions for screening prospective research laboratory prospects are provided. Near the time of the qualifying examination, PhD candidates should also be actively focusing on conducting research and identifying collaborations that will extend their reach well beyond the confines of their primary laboratory. Suggestions are made to prepare students for their exam and to enhance their research experience. Finally, after successful completion of the qualifying exam, trainees can focus on enhancing and finalizing their thesis research project, publishing their results, and beginning the hunt for post-doctoral positions while writing their dissertations. A number of links, including a direct link to the ASH Grants Clearinghouse, which allows direct access to information on more than 80 awards for both clinical and non-clinical trainees, provides helpful advice and recommendations for optimal career development.

Hematology practice and research are becoming increasingly multi-disciplinary in nature, and training programs have necessarily become ever more complex. The new ASH Career Timelines attempt to detail critical milestones that trainees should concentrate on during their academic careers. We have highlighted important events and opportunities during each cycle of the training, so that both clinical and basic science students can plan for and succeed in their chosen field. The ASH Trainee Council has created these Web pages for the trainee, but encourages both students and those who mentor them to visit the site when constructing a training roadmap. By preparing for and maintaining a steady progression throughout training, today doesn’t have to be the tomorrow you worried about yesterday.

FOR MORE INFORMATION
ASH Research Training Award for Fellows:
www.hematology.org/education/awards/training_fellows.cfm
The Grants Clearinghouse:
www.hematology.org/education/training/grants_clearinghouse.cfm
The Hematologist
ASH NEWS AND REPORTS

The Paradox of the Anti-Inflammatory Immunoglobulin


In 1890, von Behring and Kitasato described the presence of "antitoxins," which we now call antitoxin antibodies, in the sera of animals immunized with preparations of diphtheria or tetanus toxin. The following year von Behring successfully treated a child with diphtheria with a preparation of the antitoxin antibody and in 1900 founded Behringwerke to commercialize the use of passive and active immunization to treat infectious diseases. Subsequently, intravenous preparations of IgG (IVIG) derived from pooled human plasma were used to extend the passive immunization approach to treat patients with antibody deficiency. In 1981, Imbach et al. made the surprising observation that children with refractory immune thrombocytopenic purpura (ITP) could be treated successfully with IVIG. Their rationale was the earlier observation that thrombocytopenia had resolved in two patients with congenital agammaglobulinemia being treated with IVIG and a 1964 case report of a child with chronic ITP who responded to IVIG. IVIG is approved by the FDA as an anti-inflammatory agent for the treatment of ITP and Kawasaki disease and is used off-label in several autoimmune disorders.

The mechanism underlying the paradoxical anti-inflammatory effect of IVIG has been the subject of considerable investigation. The Y-shaped immunoglobulin G (IgG) molecule consists of two antigen-binding arms and a stem that contains the Fc domain. Fc domains mediate binding of IgGs to cellular receptors, which links antigen recognition to cellular responses. Both the antigen-binding regions and the Fc domain have been implicated in the anti-inflammatory action of IVIG. Ligation of activating Fc receptors for IgGs (FcγRs) mediates pro-inflammatory responses, such as phagocytosis and tumor-cell killing as well as auto-inflammatory responses in systemic lupus erythematosus, rheumatoid arthritis, and other disorders. However, inhibitory FcγRs, including FcγRIIB in mice, have been identified that mediate anti-inflammatory responses.

Previously, Ravetch and co-workers identified Fc fragments that demonstrated efficacy in several murine inflammatory disease models. Subsequently, they identified anti-inflammatory activity in a small subpopulation of IVIG. This subpopulation consisted of IgG with N-linked glycan at Asn297 that contained a terminal sialic acid in α2,6 linkage to the penultimate galactose. In the present study, the authors explored the mechanism of the anti-inflammatory activity of 2,6-sialylated Fc. To do so, they used an inflammatory disease model in which mice were injected with sera from K/BxN mice, which spontaneously develop antibody-mediated arthritis and soft-tissue inflammation. K/BxN sera produces quantifiable paw swelling that can be used to measure the therapeutic effect of IVIG. Initial experiments indicated that splenic macrophages were necessary for the efficacy of IVIG in this model. Then the authors searched for a receptor for 2,6-sialylated Fc among candidate macrophage cell surface carbohydrate-binding proteins. The central observation of the paper was that antibodies to the lectin SIGN-R1 inhibited the anti-inflammatory properties of IVIG. Furthermore, IVIG was ineffective in mice lacking SIGN-R1. Additionally, sialylated Fc bound poorly to a macrophage cell line lacking SIGN-R1 compared to a cell line expressing SIGN-R1. Adaptive transfer of splenocytes from normal (C57BL/6), IVIG-treated mice to SIGN-R1 knockout mice protected against K/BxN sera challenge. However, adoptive transfer was ineffective in mice lacking FcγRIIB. This result indicates that macrophages containing FcγRIIB are the effector cells in the anti-inflammatory response mediated by IVIG.

Humans do not have SIGN-R1, but express a related molecule, DC-SIGN, which contains a carbohydrate recognition domain that is homologous to SIGN-R1. In contrast to SIGN-R1, which is expressed on macrophages, DC-SIGN is expressed in dendritic cells. Heterologous expression of SIGN-R1 or DC-SIGN in Chinese hamster ovary cell lines resulted in saturable binding of sialylated Fc. This binding was inhibited by mannan, which is consistent with the proposal that Fc binding by SIGN-R1 and DC-SIGN includes recognition of the penultimate mannose in the sialylated glycan.

The results of this study provide new insights into the anti-inflammatory properties of IVIG and identify a novel pathway that potentially could be targeted in the treatment of autoimmune diseases.


PETE LOLLAR, MD
Dr. Lollar indicated no relevant conflicts of interest.
Resistance Is Not Futile


Relapse is the primary hurdle of leukemia therapy. This remains true despite more complex therapy, more aggressive treatment schedules, and newer, targeted therapy. In acute leukemia (AML and ALL), most patients will obtain a first remission, but many will subsequently relapse. Once relapse occurs, cure is difficult, if not impossible, with chemotherapy alone.

Sometimes relapsed leukemia cells are different from those of the initial diagnostic sample. Changes can be detected at the level of cytogenetics, single genes (e.g., AML patients with a ras or FLT3 mutations at diagnosis can relapse without the mutation, or vice versa), or surface phenotype (e.g., the antigen expression pattern detected on flow cytometry). These are important observations, as they suggest potential clonal complexity of disease at presentation and thus have implications for treatment strategy.

This new study by Mullighan, et al., from James Downing’s lab at St. Jude, investigated genetic evolution and relapse in pediatric ALL. They studied 61 cases, focusing on the detection of genomic copy number abnormalities (CNAs) as a measure of the leukemia “fingerprint.” CNAs were determined by arraying DNA on high-density chips designed to detect single nucleotide polymorphisms across the genome. From these assays, the number of gene copies (increased or decreased) could be assessed and compared between paired diagnostic and relapsed samples.

The results may be an underestimate of the genetic complexity of diagnostic and relapsed samples, since other types of genetic lesions (mutations, translocations) are not necessarily detected by this method. Nonetheless, the analysis reveals some interesting and exciting features about relapse in ALL.

At diagnosis, approximately 10 CNAs were detected per case with more in B-cell than T-cell ALL. Further, more CNAs were found at relapse than diagnosis; the mean in B-ALL, for example, was 11 at diagnosis, compared to 14 at relapse. The bulk of these additional CNAs were new deletions.

Comparing the diagnostic samples to the relapse samples, four patterns emerge (see Figure). First and most unusual (<10%) were relapse samples that shared no commonality to the diagnostic samples. These genetically distinct leukemias may have arisen from an early progenitor without detectable CNA marker or represent an altogether independent, secondary leukemia. The second pattern, also seen in <10 percent of cases, is one in which there was identical CNA at diagnosis and relapse. A related third category, comprising ~30 percent of cases, is one showing a clear evolution from the diagnostic sample. (Note, the aforementioned group might fall into this group if one looked closely at other genetic mutations such as point mutations, etc.). The remaining majority (>50%) of cases at relapse shared some CNAs with the initial sample but also had additional CNAs not found in the diagnostic sample. The most likely interpretation is that, in this situation, the leukemia cells at relapse shared a common ancestor with the cells at initial presentation, but independent lines of evolution, with different accumulated CNAs, led to the original disease and relapse.

The authors developed sensitive polymerase chain reaction (PCR) assays for a group of genetic alterations commonly found at relapse and used them to probe for these alterations in the diagnostic samples. They found evidence that the relapsed clone was present at a very low level at the time of diagnosis in many patients. Multiple genes and pathways were associated with relapsed CNAs, though many mapped to cell-cycle control and B-cell differentiation. Curiously, drug metabolism genes were not commonly found to be involved in relapse.

Clonal relationship of diagnosis and relapse samples in ALL. The majority of relapse cases have a clear relationship to the diagnosis leukemic clone, either arising through the acquisition of additional genetic lesions or, more commonly, arising from an ancestral [prediagnosis] clone. In the latter scenario, the relapse clone acquires new lesions while retaining some but not all of the lesions found in the diagnostic sample. Lesion-specific back-tracking studies revealed that in most cases the relapse clone exists as a minor subclone within the diagnostic sample before the initiation of therapy. In only a minority of ALL cases does the relapse clone represent the emergence of a genetically distinct and thus unrelated second leukemia.


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Why is this study important? First, it expands on previous work in ALL, AML, and CML, suggesting that genetic evolution is a relatively common feature of relapse. Thus, chemotherapy may act as a selective force to foster outgrowth of rare resistance clones or outgrowth from the spawn of a more primitive, ancestral [pre]-leukemia cell. The understanding of the diverse paths to resistance, and the genes recruited in this task, may eventually expose the therapeutic targets to control or abort relapse.

JERALD RADICH, MD
Dr. Radich indicated no relevant conflicts of interest.
Dr. Socié indicated no relevant conflicts of interest.

Immune-mediated eradication of leukemias, the so-called graft-versus-leukemia (GVL) effect, is a major beneficial effect observed after allogeneic hematopoietic cell transplantation (HCT). Patients with graft-versus-host disease (GVHD), especially chronic GVHD, have a lower risk of relapse compared with patients without GVHD. In 1990, Mary Horowitz and coworkers at the International Bone Marrow Transplant Registry (IBMTR) published a seminal paper addressing whether donor HLA-DPB1 functions as a classical transplantation antigen in preventing leukemia recurrence after bone marrow transplantation. Of the 2,254 subjects in their study with HLA-identical sibling bone marrow transplants for acute myelogenous leukemia (AML) in first remission, acute lymphoblastic leukemia (ALL) in first remission, and chronic myelogenous leukemia (CML) in first chronic phase, they observed fewer relapses in recipients of non-T-cell-depleted allografts with acute, chronic, and both acute and chronic GVHD, as compared with those without GVHD. These data support an anti-leukemic effect of GVHD. AML patients who received identical twin transplants had an increased probability of relapse compared with allograft recipients without GVHD, suggesting a GVL effect independent of GVHD. CML patients who received T-cell-depleted transplants with or without GVHD had higher probabilities of relapse than recipients without GVHD, suggesting that the anti-leukemic effect independent of GVHD is altered by T-cell depletion. This highly cited study has since been confirmed by many other clinical papers and the curve derived from this analysis used in thousands of lectures on GVL (see Figure).

Investigators from the IBMTR have now revisited this clinical concept to ask whether patients benefit from an unrelated donor (URD) transplant because of a stronger GVL effect. The authors analyzed 4,099 patients with AML, ALL, and CML undergoing a myeloablative allo-HCT from an URD (8/8 HLA-matched, n=341) or HLA-identical sibling donor (n=3158). In multivariate analysis, URD transplant recipients with AML had a higher risk for transplant-related mortality and relapse than those receiving transplants from HLA-identical sibling donors. This difference was not seen in patients with ALL or CML. Chronic GVHD was associated with a lower relapse risk in all diagnoses. Leukemia-free survival (LFS) was decreased in patients with AML without acute GVHD receiving URD transplant, but was comparable to those receiving HLA-identical sibling transplants in patients with ALL or CML. In patients without GVHD, multivariate analysis showed similar risk of relapse, but decreased LFS for URD transplant recipients for all three diagnoses. The authors concluded that the risk of relapse was the same (ALL, CML) or worse (AML) in URD transplant recipients compared to HLA-identical sibling transplant recipients, suggesting a similar GVL effect.

The GVL effect has not been evaluated as frequently in URD transplants as in sibling transplants. Today, approximately one-third of patients in need of HCT have an available HLA-identical sibling donor. The growth of donor registries worldwide has improved the overall chance that a patient who lacks a family donor will have a suitable URD. In a previous Diffusion selection (The Hematologist March/April 2008 issue), I discussed two major studies relevant to this subject. One by Lee and coworkers clearly highlighted the fact that there is a 10 percent loss of survival with any mismatch (although of marginal significance for HLA-DQ), but that classical risk factors including patient age, race, disease stage, and CMV status were as predictive of survival as donor HLA matching. The other by Shaw and coworkers confirmed in a large number of patients that DPB1 functions as a classical transplantation antigen. The increased risk of GVHD associated with HLA-DPB1 mismatching was accompanied by a lower risk of relapse.

Thus the study by Ringden and coworkers basically confirms the strong anti-leukemic effect of GVHD. However, even if transplant with URD is associated with more GVHD, this does not seem to translate to better leukemic control. The caveat of this study is the fact that authors included only 8/8-matched URD [HLA-A, -B, -C, -DRB1 matched]. Thus, they exclude DPB1, which is the allele reported by Shaw and coworkers to be linked to lower relapse and GVL effect.


A Picture is Worth a Thousand Words


Fig.1

A major advantage of this novel approach is that the interactions between the stem/progenitor cells and the niche can be visualized in vivo. The hematopoietic stem cells localized to areas in close proximity to the osteoblasts in microvessels were dynamic and nonrandom. Different hematopoietic cell subsets localized to distinct locations, depending on the stage of differentiation and guided by nonautonomous factors. When expansion or engraftment was studied, the hematopoietic stem cells localized to areas in close proximity to the osteoblasts.

These initial studies provide direct visualization of previously observed colocalization of hematopoietic stem cells with the osteoblasts, defining one of the bone marrow niches. These technologies will allow for further studies of hematopoietic stem/progenitor cells and open up new ways of understanding hematopoiesis and malignancies. For example, single mutations that affect hematopoiesis can now be tracked in vivo. Malignant cells can also be studied in this manner and their associations with the osteoblasts or the vascular niche, and other immune cells that are found in the marrow cavity can also be analyzed in their responses to antigenic challenge.

YouTube will be busy.

Nelson Chao, MD
Dr. Chao indicated no relevant conflicts of interest.
Therapeutic Potential of Targeting the Immunoproteasome

Kuhn DJ, et al. Targeted inhibition of the immunoproteasome is a potent strategy against models of multiple myeloma that overcomes resistance to conventional drugs and non-specific proteasome inhibitors. Blood. 2008. [Epub ahead of print]

Kuhn and colleagues report on the novel strategy of targeting the immunoproteasome to overcome bortezomib resistance on the one hand, and avoid side effects on the other. The core proteasome (20S) protease complex is composed of α and β subunits; the β1, β2, and β5 subunits mediate caspase-like (C-L), trypsin-like (T-L), and chymotrypsin-like (CT-L) activities. The corresponding interferon-inducible subunits of the proteasome are the β1i, β2i, and β5i subunits of the immunoproteasome, which enhance the generation of antigenic peptides for MHC Class I presentation. In this study PSI-CD1, a selective inhibitor of β1i, is shown to overcome resistance to proteasome inhibitor bortezomib in preclinical models. Moreover, the data suggest that neuropathy may not be induced by this more selective β1i inhibitor, providing the framework for clinical trials of selective immunoproteasome inhibitors to improve outcome and lessen toxicity in multiple myeloma (MM).

Proteasome inhibition has achieved remarkable anti-tumor activity and can overcome cell adhesion-mediated drug resistance to conventional therapies in both in vitro and in vivo models of MM cells in the bone marrow microenvironment. Moreover, remarkable extent and frequency of response in MM were observed in phase I clinical trials. Based upon durable responses with associated clinical benefit and with reduced refractoriness, relapsed, and newly diagnosed MM, bortezomib was FDA-approved for treatment in these settings in 2003, 2005, and 2008, respectively. However, its use is associated with neuropathy and thrombocytopenia. Moreover, not all patients respond, and those that do eventually develop resistance. Acquired mutations in proteasome subunits have been associated with bortezomib resistance. Carfilzomib and CEP-18770 both more potently inhibit the CT-L activity, as does bortezomib, whereas NPI0052 inhibits the T-L activity as well as the T-L and CT-L activities. All can overcome bortezomib resistance in preclinical studies and are undergoing clinical evaluation. Alternatively, heat shock protein 90 inhibitors, Akt inhibitors, histone deacetylase inhibitors, and each have been combined with bortezomib to overcome bortezomib resistance in preclinical and early-phase clinical trials; these combinations are each now undergoing evaluation in randomized phase III clinical trials for FDA registration. Finally, we have seen in preclinical models that combinations of proteasome inhibitors bortezomib and NPI0052, even at doses which are ineffective alone, can achieve synergistic cytotoxicity with a very favorable side effect profile.

Of note, carfilzomib, CEP-18770, and NPI0052 all inhibit both constitutive and immunoproteasome activities; and we have shown that bortezomib inhibits β5 and β1 constitutive as well as immunoproteasome subunit activities to a similar extent in MM cells. Therefore, whether the more selective inhibition of the immunoproteasome activity, as reported here, will overcome clinical bortezomib resistance remains to be determined. Importantly, immunoproteasomes are restricted to hematologic cells, suggesting a more favorable therapeutic index than these inhibitors of the constitutive proteasome activities. However, whether inhibition of the immunoproteasome confers immunosuppression needs to be a particular focus of clinical trials. Importantly, fluorogenic substrates are now available to evaluate both the constitutive and immunoproteasome activities in MM cells before and after treatment to correlate the extent of qualitative and quantitative inhibition of the constitutive versus immunoproteasome activity with tumor response versus side effect profile. These studies will provide the rationale for next-generation, more potent and less toxic, single-agent or combination inhibitor approaches, thereby expanding the spectrum of patients benefiting from proteasome inhibitor therapeutic strategies.

Sequence of Therapy in Leukemia: An Ever-Recurring Question Now Relevant to CLL


The initial use of chemotherapy for CLL has evolved over the past 15 years from alkylator-based monotherapy to fludara- bine and then to fludarabine/cyclophosphamide (FC) based upon well-designed randomized phase III studies demonstrating improved overall response (OR), complete remission (CR), and progression-free survival (PFS) with successive treatment regi- mens. Several phase II studies adding rituximab to the fludarabine regimens demonstrated further promising incremental increases in CR rates and durations of PFS as compared to historical trials. At the 2008 ASH meeting, two large randomized phase III trials demonstrated that FC plus rituximab (FCR) was better than FC alone with respect to OR, CR, and PFS. All of the large phase III combination studies of FC or FCR to date have administered the therapeutic agents together based upon multiple preclinical studies suggesting synergistic benefit between each. FCR is based upon pre-clinical work, disadvantages to concurrent therapy include the inability to deliver dose intensity of each agent and also the potential of enhanced toxicity, such as secondary acute myeloid leukemia.

Lamanna, et al., from the Memorial Sloan-Kettering Lymphoma Program, have now reported promising data with sequential use of standard-dose fludarabine, high-dose cyclophosphamide, and consolidation rituximab (FCR+R) for previously untreated CLL where they demonstrate similar response, CR, and PFS as observed with the FCR-based regimens. This regimen was well tolerated despite a high proportion of advanced Rai stage patients, as compared to most other trials reported for CLL. This group rightfully calls attention to their previous study of sequential fludarabine followed by cyclophosphamide (FC+R) and a randomized phase II study comparing sequential versus concurrent rituximab with fludarabine that all demonstrated no obvious disadvantage to sequential treatment with respect to PFS but improved tolerability for patients. It is only through a randomized phase III trial that this will be adequately evaluated, and this study suggests that performing such a trial should be considered in the future.

Of note, carfilzomib, CEP-18770, and NPI0052 all inhibit both constitutive and immunoproteasome activities; and we have shown that bortezomib inhibits β5 and β1 constitutive as well as immunoproteasome subunit activities to a similar extent in MM cells. Therefore, whether the more selective inhibition of the immunoproteasome activity, as reported here, will overcome clinical bortezomib resistance remains to be determined. Importantly, immunoproteasomes are restricted to hematologic cells, suggesting a more favorable therapeutic index than these inhibitors of the constitutive proteasome activities. However, whether inhibition of the immunoproteasome confers immunosuppression needs to be a particular focus of clinical trials. Importantly, fluorogenic substrates are now available to evaluate both the constitutive and immunoproteasome activities in MM cells before and after treatment to correlate the extent of qualitative and quantitative inhibition of the constitutive versus immunoproteasome activity with tumor response versus side effect profile. These studies will provide the rationale for next-generation, more potent and less toxic, single-agent or combination inhibitor approaches, thereby expanding the spectrum of patients benefiting from proteasome inhibitor therapeutic strategies.
Breaking the Barrier: Molecular Basis of the Blood–Brain Barrier


That vital organ, the brain, is protected by the blood–brain barrier (BBB), which is composed of both a physical barrier formed by tight junctions between brain capillary endothelial cells (ECs) and a selective active transport system, including a multiple drug resistance transport system that precludes some drugs and chemicals from entering the brain. The integrity of the BBB is essential to prevent noxious substances from entering, while allowing passage of oxygen, glucose, and other essential nutrients. Disruption of the BBB occurs in brain ischemia, malignancies, and neurodegenerative disorders including Alzheimer disease. Some proteins involved in the tight junction complex, such as claudins (Cldn) and occludins, are essential for BBB maintenance; claudin 3 (Cldn3), in particular, has brain-specific expression. However, the mechanisms by which the BBB is formed and maintained have not been understood. Recent complementary reports by Liebner, et al., and Stenman, et al., suggest a crucial role for Wnt signaling in this process.

The Wnt signaling pathway is involved in many aspects of normal cell behavior, such as morphogenesis, cell differentiation, and proliferation. Wnt proteins, named for their ability to bind to Wnt receptors, also known as Frizzled proteins, to produce a variety of intracellular events, one of which is stabilization of the protein β-catenin. β-catenin, in turn, activates expression of many genes by binding to several transcription factors. The Wnt pathway is active in brain development, but it was not previously known that it is also important for vascular development.

Liebner and colleagues, from Elisabetta Dejana’s lab in Germany, showed that the Wnt/β-catenin signaling pathway is active in mouse brain ECs during embryogenesis, but declines after birth and is present in very small amounts in adult mouse brains. They hypothesized that this pathway is necessary for the formation and maintenance of the BBB. Inactivation of β-catenin in ECs was associated with decreased levels of Cldn3 and increased levels of Cldn5, which is found in non-barrier types of endothelium, while the reverse was found with activation of β-catenin. These data suggest that β-catenin controls the formation of the tight junctions. In vitro treatment of brain ECs by one of the Wnt proteins, Wnt3, activated β-catenin and increased Cldn3 expression and BBB formation.

Stenman and colleagues, from Andrew McMahon’s lab at Harvard, almost concomitantly reported that the developing neuroepithelium expresses Wnt7a and Wnt7b proteins and that the surrounding ECs respond to these signals. The ECs begin expressing glucose transporter (GLUT1), an essential component of the BBB, and GLUT1 expression ceases in neuroepithelial cells. Deletion of Wnt7a and Wnt7b in neuroepithelial progenitor cells or deletion of β-catenin in ECs results in similar vascular defects of abnormal vascular sprouting and central nervous system (CNS) hemorrhage in mouse embryos. These data nicely complement the data described by Liebner, et al.

Wnt signaling appears to be crucial for formation of the highly specialized neuro-vascular interaction that comprises the BBB. This work also suggests a role for Wnt signaling and β-catenin activation in BBB maintenance by affecting the expression of proteins that make up the tight junctions. Although the details remain to be elucidated, these findings should open new pathways to explore in order to explain defects in the BBB caused by disease, as well as to design new therapies for disorders with impaired BBB.

To characterize cellular and extrinsic interactions in leukemia-associated marrow niches, Colmone, et al., from Dorothy Sipkins’ lab at the University of Chicago, performed live-animal tracking studies in severe combined immunodeficient (SCID) mice engrafted with fluorescently labeled normal human CD34+ HPCs and a human pre-B ALL cell line [Nalm-6]. Homing and migration of xenografted cells were assessed by confocal and multi-photon microscopy imaging of calvarial bone marrow. Colocalization to vascular and perivascular niches was determined by fluorescent labeling for stromal cell-derived factor-1 (SDF-1), an important HPC chemoattractant and supportive molecule. They observed that both normal CD34+ HPCs and Nalm-6 cells predominantly homed to SDF-1-rich vascular niches. However, SDF-1 expression was down-modulated over time in established leukemic infiltrates, and normal HPCs that were either freshly injected or previously co-engrafted migrated to and lodged in the SDF-1-negative leukemic niches. Aberrant relocation to leukemic niches was followed by compromised HPC maintenance and mobilization with granulocyte colony-stimulating factor (G-CSF) and AMD3100 [an antagonist of the SDF-1 receptor, CXCR4], suggesting that the leukemic microenvironment entraps and poorly preserves the CD34+ cell pool. Additional studies implicated leukemia cell-derived stem cell factor (SCF), an HPC growth factor and chemoattractant, as the major stimulator of HPC migration. Indeed, anti-SCF antibodies blocked HPC exodus from normal marrow niches and maintained their survival in mice co-engrafted with Nalm-6 tumors. Similar results were observed in an SCID-idiodeficient mouse model, the non-obese diabetic (NOD)-SCID line, when co-transplanted with normal CD34+ HPCs and primary human ALL or AML cells. Moreover, histochemical analyses identified high levels of leukemia-associated SCF expression in marrow biopsies from patients with pre-B ALL, suggesting that this mechanism is clinically relevant.

This elegant study proposes an intriguing mechanism of hematopoietic suppression associated with ALL and AML. In model, leukemia cell-derived SCF out-competed SDF-1 to induce normal HPCs to migrate from a nurturing vascular niche into a relatively inescapable and unsupportive tumor niche. If confirmed in further patient studies, therapeutic interventions targeting this pathway may be beneficial. However, these will likely need to focus on inhibiting leukemia cell SCF production, rather than blocking SDF interactions in the microenvironment, given the importance of SCF in maintaining normal hematopoiesis. On a broader scale, it will be of interest to determine whether competing tumor microenvironments are relevant mechanistic paradigms in the hematopoietic suppression and immunosuppression associated with non-Hodgkin lymphoma and multiple myeloma — diseases for which critical elements of the tumor niche are rapidly being elucidated.
Unmasking the Serine Protease TMRSS6: Its Role in Regulating Iron Metabolism


At the 2007 ASH annual meeting in Atlanta, Ernest Beutler was scheduled to present another amazing hematologic breakthrough during the plenary session. Because of his ill health, his son Bruce presented pictures of a semi-hairless mouse with anemia, microcytosis, iron deficiency, and high hepatic levels of hepcidin mRNA transcripts. In response to high doses of iron, they grew hair. (Some iron-deficient humans have hair loss.) This so-called “mask” mouse could not absorb iron from the gut (most likely due to the high hepatic levels) and had a mutation on chromosome 15 in a gene encoding a transmembrane serine protease of unknown function, TMRSS6 or matriptase-2. Dr. Beutler's team demonstrated that the protein encoded by the normal TMRSS6 gene suppressed hepatic hepcidin expression induced by bone morphogenic protein (BMP), hemojuvelin (HJV), SMAD-1, and IL-6, while the protein encoded by the mutated mask allele or a mutated protein with an inactive protease domain did not suppress. They concluded that TMRSS6 is required to sense iron deficiency, but its sensing mechanism remained speculative.

Now, Silvestri, et al., from Clara Camaschella’s group in Milan, report that matriptase-2 inhibits hepcidin activation by cleaving membrane HJV, thus interfering with primary hepcidin signaling in the hepatocyte. To review, hepcidin levels are regulated by body iron levels. Inflammation and cytokines such as IL-6, erythroid factors such as growth differentiation factor 15 (GDF15), and hypoxia via hypoxia-inducible transcription factors all play roles in modulating hepcidin synthesis. Hepatic hepcidin regulation by iron is regulated by HJV, which acts as a co-receptor for BMP to the BMP receptor, signaling a cascade to SMAD-4 translocation to the nucleus and hepcidin transcription. HFE, TFR2, and transferring are critical to this process.

In an elegant set of studies, Silvestri, et al. demonstrate that matriptase-2 cleaves membrane HJV releasing proteolytic fragments and disrupts the HJV/BMP complex binding to the BMP receptor, inhibiting hepcidin signaling (see Figure). The mask mutant matriptase-2 and a partially mutated matriptase-2 from a family with refractory iron deficiency did not cleave HJV and, when expressed in zebrafish, caused anemia. Soluble HJV cleaved in vitro by furin (distinct from membrane HJV) can act as a decoy receptor competing for membrane HJV, thus decreasing hepcidin. Matriptase-2 does not cleave soluble HJV.

These studies are relevant in both iron deficiency and iron overload. Two recent publications reported mutations in the TMRSS6 gene associated with familial iron deficiency refractory to oral iron. Thus, these translational studies extend our understanding of iron metabolism. Unmasking the role of this protease, matriptase-2, adds another brick in the foundation of hematology that our late ASH president, Ernest Beutler, had so importantly helped build.


Figure

A) Schematic representation of a model of matriptase-2 activity in iron deficiency. On the left, the serine protease cleaves m-HJV releasing soluble fragments (here simplified by the black boxes). The cleavage sites of matriptase-2 are unknown. The question mark indicates uncertainty on fragments’ function. The resulting hepcidin inhibition is shown. The complementary effect of s-HJV, produced by furin cleavage, to sequester BMP is shown on the right.

B) Lack of hepcidin inhibition in the presence of matriptase-2 mutations. m-HJV acts as BMP co-receptor and permits hepcidin production in iron deficiency; the effect of s-HJV cannot down-regulate hepcidin in the presence of m-HJV.

In 2006, the European Society of Hematology (EHA) and ASH introduced the EHA-ASH Research Exchange Award, a groundbreaking award for both clinical and laboratory-based researchers in training or early in their careers. This award offers them an opportunity to experience research in a different environment and to establish new collaborations with established scientists from around the world. We are pleased to announce the 2009 EHA-ASH Research Exchange Award recipients are Freda Passam, MD, PhD, and Carmen Schweighofer, MD.

Dr. Passam is currently a research fellow in the Hematology Department at the University Hospital of Crete, Medical School of Crete in Greece. Dr. Passam began her hematology training under home mentor, Michael Alexandrakis, MD. As her mentor, Dr. Alexandrakis supported Dr. Passam’s basic research project at St. George Hospital in Australia under the supervision of Steven Krilis, PhD, a world leader in the antiphospholipid syndrome. As a result of this research experience and her clinical experience from training in the routine coagulation laboratory, Dr. Passam developed a strong interest in the field of hemostasis and thrombosis. Dr. Passam’s eventual goal is to organize a Thrombosis Section at the University of Crete; however, since the opportunities for research in hemostasis and thrombosis are limited in Crete, Dr. Passam will need experience in an international research center. In July, this award will enable Dr. Passam to take her research project, “Role of the thiol isomerase ERp5 in thrombus formation,” to the Research Center of Thrombosis and Hemostasis at the Beth Israel Deaconess Medical Center in Boston, MA, to develop under the guidance of Bruce Furie, MD.

Dr. Carmen Schweighofer comes from the University of Cologne in Germany. Dr. Schweighofer earned her degree in medicine, graduating with honors, at the Ludwig-Maximilians-University Medical School in Munich, Germany. She began her residency and fellowship in internal medicine and hematology/oncology at the University of Cologne under home mentor Michael Hallek, MD. During her fellowship, Dr. Schweighofer began serving as a trial investigator within the German CLL Study Group, where she gained extensive clinical experience and a strong understanding of clinical and translational needs and challenges. It is her overall goal to serve as a liaison between basic and clinical research in CLL, and, therefore, she is motivated to continue to pursue intensive training in laboratory-based research, specifically cytogenetic studies. Dr. Schweighofer will be taking her research project, “Genomic aberrations predict outcome in patient with chronic lymphocytic leukemia (CLL) treated with frontline FCR chemoimmunotherapy,” to M. D. Anderson Cancer Center under the mentorship of Lynne Abruzzo, MD, PhD. The host laboratory of Dr. Abruzzo is focused on molecular cytogenic features of CLL and lymphoma and offers a unique opportunity for basic research in a scientifically diverse and clinically well-grounded environment, which will benefit not only Dr. Schweighofer, but also the University Hospital of Cologne.

ASH and EHA are pleased to support the research of these promising young investigators through this unique award. For more information about this program, visit the ASH Web site at www.hematology.org/education/awards/ifae.cfm.
William J. Williams, MD, has left a unique stamp on the field of hematology through his exemplary patient care and research, and he also wrote “the book” on the field, editing what became for most of the 1970s and 80s one of the two most familiar English-language hematology textbooks. The book, originally called *Hematology* remains in wide use along with an expanding group of other excellent texts.

To honor his contributions as founding editor the name of the book was changed to *Williams Hematology* beginning with the fifth edition.

Dr. Williams has an established history of leadership, serving as dean of the College of Medicine and vice president for Biomedical Sciences at SUNY Upstate Medical University from 2002 to 2004. He was named a Distinguished Service Professor by the State University of New York in 2002, and he remains an inspiring teacher today, grounding students in both the science and art of medicine.

During teaching rounds, he frequently says, “Just because someone knows how to physically take care of a patient doesn’t mean that person will automatically have a good doctor-patient relationship. Some of this is instinctual, but it also must be taught and explained to students — we can’t just expect they will pick it up by observing.” Through his guidance of the medicine department, Dr. Williams was known as the man with the bow tie and gentle smile who added a humanistic touch to a competitive field. He knew each trainee well and would occasionally surprise them with a T-shirt, a book, or a personal gift.

Dr. Williams was born in a small town in New Jersey, where he first acquired his desire to go into medicine. His family doctor, whom he described as a “hero,” suggested that he consider a career in medicine. While reading the Sinclair Lewis novel *Arrowsmith* in college, he acquired an interest in academic research, seeking to emulate the book’s hero, Martin Arrowsmith, who chose a research career. Arrowsmith was all the things Williams wanted to be, and he vowed to follow this new role model. While an apprentice seaman in the Navy in 1945, he was assigned to the hematology laboratory at the U.S. Naval Hospital in Philadelphia, even though he had originally asked to go into the chemistry lab. While he was working daily in the hematology lab, he was able to see the close association between the laboratory and clinical problems. With this, a career was born.

He was soon transferred to the medical school at the University of Pennsylvania, from which he graduated in 1949. In fact, he remained there until 1969, serving as chief of the Hematology Section and professor of medicine, except for the 18 months he spent at Washington University of Saint Louis, working with Carl Moore and William Harrington. He also spent a year at Oxford University with R. G. Macfarlane and M. Peter Enoiu. He did research on the biochemical mechanisms of blood coagulation, specifically the initiation of blood clotting by Russell’s viper venom and tissue factor. He also participated in projects on methylmalonic acid excretion in vitamin B12 deficiency, carbon monoxide production as a measure of hemolysis, and phospholipid metabolism in platelets and leukocytes. Later he studied peripheral blood stem cells and spent a sabbatical working with Donald Metcalf at the Walter and Eliza Hall Institute of Medical Research.

When he joined the faculty of the State University of New York Upstate Medical Center in 1969, he became the Edward C. Reifenstein Professor of Medicine and Chairman of the Department of Medicine, where he served for 22 years. In his early years, he attracted excellent faculty members including Arlan Gottlieb, Robert Comis, and Kenneth Zamkoff, who were the leaders of hematology-oncology at that time, and their legacy continues to this day.

He began working on *Hematology* in the mid-1960s, in collaboration with Ernest Beutler, Allen Ersliev, and Wayne Rundles, who was replaced by Marshall Lichtman after the second edition. Dr. Williams continued as editor-in-chief through the fourth edition, when the name was changed to *Williams Hematology*. The book is currently in its seventh edition.

Many residents were attracted to Syracuse because of his textbook, and they remained on the faculty because of his outstanding leadership, vision, and support of research and academic growth. But, most of all, those who know him remember best his big heart and his penchant for looking after them.

From top to bottom: 1) Drs. David Duggan, Chairman of Internal Medicine at SUNY Upstate Medical Center, and William Williams. 2) From left to right: Drs. Maxwell Wintrobe, William Dameshek, Thomas Hale Ham, William Williams and Fraser Mustard (in the back) at the American Society of Hematology annual meeting in 1965.
The ASH Web site 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.

The HEMATOLOGY LIBRARY, available at www.hematologylibrary.org, provides access to the wealth of information available from ASH. The site serves as an entry point to ASH's various publications and allows users to easily search across multiple resources, including Blood, the annual meeting abstracts, the ASH Image Bank, and Hematology, the ASH Education Program Book.

Submit clinical questions to your ASH colleagues. The ASH CONSULT A COLLEAGUE PROGRAM is expanding. ASH members can now seek consultation on clinical cases related to lymphomas, multiple myeloma, and other lymphoproliferative disorders, as well as leukemias and hemostasis/thrombosis. ASH members interested in taking advantage of this exclusive benefit should visit www.hematology.org/policy/resources/consult.cfm.

Trainees: Access the new ASH CAREER TIMELINES. This new section, created by the ASH Trainee Council, includes an “ASH Career Development Timeline for MD Trainees” and an “ASH Career Development Timeline for PhD Students.” To learn more about this new section, turn to page 7 to read the article by Dale Bixby, MD, PhD.

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Trainees: Access the new ASH CAREER TIMELINES. This new section, created by the ASH Trainee Council, includes an “ASH Career Development Timeline for MD Trainees” and an “ASH Career Development Timeline for PhD Students.” To learn more about this new section, turn to page 7 to read the article by Dale Bixby, MD, PhD.

MD TRAINEES: www.hematology.org/education/training/timeline_md

PhD STUDENTS: www.hematology.org/education/training/timeline_phd

Mark Your Calendar

MARCH

1
New ASH membership applications due

10
ASH membership renewal payments due

12
Deadline for submitting MMSAP applications

12
Deadline for submitting ASH-AMFDP applications

16
Deadline for submitting Trainee Research Award applications
      Washington, DC  www.hematology.org

23 – 25
7th International Symposium on Targeted Anticancer Therapies
      The Netherlands  www.nddo.org

27
Deadline for submitting ASH Alternative Training Pathway Grant applications
      Washington, DC  www.hematology.org

29 – 31
58th Annual Scientific Session of the American College of Cardiology
      Orlando, FL  www.acc09.acc.org

29 – APRIL 1
35th Annual Meeting of the European Group for Blood and Marrow Transplantation
      Göteborg, Sweden  www.akm.ch/ebmt2009

31
Deadline for submitting ASH Clinical Research Training Institute applications
      Washington, DC  www.hematology.org

31
Deadline for claiming CME credits for the 2008 ASH Annual Meeting
      Washington, DC  www.hematology.org

APRIL

22 – 25
22nd Annual Meeting of the American Society of Pediatric Hematology/Oncology
      San Diego, CA  www.aspho.org

24
Blood in Motion 2009: Symposium on Thrombosis and Hemostasis
      Pittsburgh, PA  www.asghcme.org

29 – MAY 1
American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology Annual Conference
      Washington, DC  www.americanheart.org

MAY

7 – 9
10th National Conference on Anticoagulant Therapy
      San Diego, CA  www.acforum.org

18 – 20
Preservation of Cells, Tissues, and Gametes
      Minneapolis, MN  www.me.umn.edu/education/shortcourses/preservation

18 – 22
100th Annual Meeting of the American Association for Cancer Research
      Denver, CO  www.aacr.org