Stabilizing a Mutant Enzyme: A Potential Therapeutic Strategy for Günther Disease


Congenital erythropoietic porphyria (CEP), also called Günther disease, is an autosomal recessive porphyria caused by deficiency of the heme biosynthetic enzyme uroporphyrinogen III synthase (UROS) that converts linear hydroxymethylbilane (HMB) to cyclic uroporphyrinogen III (Figure). Unlike amino-levulinic acid and porphobilinogen, the two intermediates that precede UROS in the heme biosynthetic pathway and that accumulate in patients with acute intermittent porphyria, HMB is unstable. Consequently, HMB is not detected in excess in the plasma or urine of patients with CEP. Rather HMB cyclizes non-enzymatically to uroporphyrinogen I and coproporphyrinogen I (Figure). These two porphin isomers are not substrates for downstream enzymes of the heme biosynthetic pathway (uroporphyrinogen III synthase and coproporphyrinogen III oxidease), and, hence, they accumulate in erythroid elements, plasma, urine, feces, teeth, eyes, bones, and skin. Clinical manifestations (primarily hemolysis due to ineffective erythropoiesis and marked dermatological photosensitivity) may begin in early infancy. Although phenotype varies, disease-related morbidity, including disfiguring facial scarring, hypertrichosis, and skin discoloration, can be debilitating. Standard treatment is largely supportive and includes protection from sunlight, proper dental care, and careful management of anemia. Complete resolution of biochemical, hematologic, and cutaneous abnormalities has been reported in a small number of children who have undergone allogeneic hematopoietic stem cell transplants. Gene therapy would be ideal, but remains hypothetical.

The genetic basis of CEP is heterogeneous with gene rearrangements, splitting mutations, and single-base substitutions having been reported, including missense mutations affecting any of the 10 coding exons of UROS. Missense mutations may lead to a functional decrease in enzyme activity, but Fortier et al.1 described a UROS missense mutation that altered protein folding, resulting in reduced protein stability without alterations in intrinsic enzymatic activity. In the current paper, Jean-Marc Blouin and colleagues in the laboratory of Emmanuel Richard in Bordeaux, France, demonstrate that a proteasome inhibitor (bortezomib) can retard degradation of two UROS mutants (Figure), thereby preserving cellular enzyme activity. Two UROS missense mutations, C73R and P248Q, found in CEP patients were shown to cause structural changes that resulted in rapid degradation of the mutant proteins. Blouin et al. reported that treatment with proteasome inhibitors, but not with lysosomal inhibitors, retarded degradation of UROS C73R and UROS P248Q. In a murine model of CEP (UROS C73R/P248Q), bortezomib treatment increased enzyme expression 30- to 53-fold and significantly reduced uroporphyrin accumulation in RBC. While bortezomib did not cure the hemolytic disease in these mice, photosensitivity was ameliorated.

This paper emphasizes the importance of determining the mechanism by which a genetic abnormality causes disease. In this case, the missense mutations spared protein catalytic activity but diminished the total cellular content of the protein because the structurally abnormal protein undergoes rapid proteasomal degradation. Blouin and colleagues demonstrate how this observation translated into a targeted approach to therapy. Notably, proteasome inhibition has been used successfully to treat other genetic diseases, including muscular dystrophy, in which disease pathology involves rapid proteasomal degradation of the mutant protein. Another approach that targets protein-folding abnormalities in genetic disease is pharmacologic chaperone therapy in which molecular chaperones assist in folding of mutated proteins, thereby preserving catalytic activity while preventing premature protein degradation (Figure). Whether bortezomib can be adapted to treat CEP requires further investigation. In the porphyric animal model, bortezomib was injected intraperitoneally every 48 hours, a schedule that likely would be tolerated poorly by human bone marrow and peripheral nervous tissue. Nonetheless, the studies of Blouin and colleagues serve as proof of principal that aberrant protein catabolism can be approached pharmacologically and suggest a novel approach to therapy for a subset of patients with CEP.

Challenges? Yes, But Also a Vision

Having just returned from the 55th annual meeting, the excitement of scientific advances and networking with colleagues has not yet subsided as I look forward to 2014 and the honor of serving as president of ASH.

In this first column of the New Year, I wish to share with you the vision that I, and other leaders of ASH, have for tackling the challenges we, as hematologists clinicians and researchers, continue to face. I touched on these issues during an interview with ASH News TV that took place in conjunction with the annual meeting. (It can still be viewed at www.hematology.org/Meetings/Annual-Meeting/General/11729.aspx.) We are committed to addressing the needs of our members and patients in the critical areas of research, education and teaching, and clinical practice.

At the top of our agenda is research funding. Research is the foundation of our field, and I and the rest of the ASH Executive Committee are painfully aware of the hardships that confront us as a consequence of inadequate funding. I know you share my concern not only that we are at risk for losing the next generation of scientists but also that the careers of our established scientists who have made and continue to make numerous contributions to the advancement of hematology are in jeopardy. ASH will continue to advocate for research funding with our legislators, and we urge you to learn more by visiting the ASH Advocacy Center at www.hematology.org/Advocacy. At the same time, we will invest ASH resources in supporting the research pipeline. ASH has a number of grants, awards, and scholarships for the career continuum from medical students to junior faculty. However, equally important to providing funding for new investigators is the retention of established researchers. A new mechanism of support was introduced this past year in the form of the ASH Bridge Grant Program for established physician scientists. Established to help our talented scientists sustain their vital research programs, the bridge grants are now entering the third of six planned award cycles. We have awarded grants to assist and associate as well as full—professors confirming how critical the need is for research support, even for our most senior scientists.

In addition to research, other challenges fill our busy agenda for 2014. As the fellowship program director at the University of Minnesota, I also reach out to undergraduates, medical students, and residents to introduce them to the exciting field of hematology. It is imperative that we not only recruit and train hematologists, but we must also provide opportunities for academic advancement and support of our hematology educators. I am also a clinician who cares for patients on a daily basis. Clinicians face their own set of challenges with ever-increasing regulatory requirements, demanding that we not only provide high-quality care, but do so in a timely and cost-efficient manner. With these new and ever-increasing demands on our time, ASH is committed to providing guidelines and tools to aid busy clinicians. Furthermore, hematology is a field with few procedures that are suitably compensated; therefore, we must also advocate for appropriate reimbursement for our intellectual contributions to medical decision making and best practices.

I recall attending my first ASH meeting as a fellow in 1985, sitting in a vast auditorium and thinking about how I hoped to present my own research someday. Eventually I did, with my trembling hand causing the laser beam to ramble all over the slide! But I also recall the excitement and the feeling of being part of something much larger. As president of ASH, I hope I can impart to you that same excitement of being part both of the field of hematology and the Society that I have enjoyed and benefited from so much. Yes, we have challenges, but with valued colleagues with a common vision, we will find a way forward. Please join me in our efforts and share in our successes.

Challenges? Yes, But Also a Vision

Paper President’s Column

Correction: In the November/December 2013 issue, we inadvertently did not include Donald Metcalf’s title. It should have read:

“Donald Metcalf, MD, Professor Emeritus, University of Melbourne; Carden Fellow in Cancer Research, Division of Cancer and Hematology, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.”
The Hematologist Board of Contributing Editors

At the December 2013 meeting of the Editorial Board of The Hematologist, we said goodbye to five contributing editors: John Byrd, Rob Flaumenhalt, David Steensma, Margaret Ragni, and Xavier Leleu. All have been outstanding Board members. We are grateful for the years that they unselfishly dedicated to The Hematologist. In particular, John and Rob served consecutive three-year terms (sounds penal, but it’s not!). We very much appreciated Rob’s Diffusion contributions that dealt largely with coagulation and platelet biology. He chose to review papers that featured cutting-edge science, and his precision writing made complex concepts accessible to the non-expert. John’s focus on CLL was particularly valuable over the past three years as great progress has been made in that area recently, and his lab made important primary contributions to the field. He fulfilled his duties to The Hematologist despite the many demands on his time, including serving as director of the Division of Hematology at Ohio State. John reaffirmed his commitment to ASH by accepting the call to join the Board of Blood as Associate Editor. Maggie generated many insightful Diffusion articles on management of hemophilia that were well received by our readers. You’ll be hearing more from Maggie as she is Education Program Co-Chair for the 2014 ASH Annual Meeting. David has been an outstanding contributor whose lucid, engaging writing style energized The Hematologist. We are pleased that David was chosen as the Education Program Co-Chair for the 2015 ASH Annual Meeting. Xavier has kept our readers abreast of developments in myeloma, and his perspectives on the newsletter. Theresa is co-director of Witwatersrand Research Institute for malaria and associate professor at Witwatersrand University. She is a PhD scientist who has an interest in inherited hemolytic anemias in addition to malaria. Theresa has been active in ASH and is a member of the International Members Committee serving as a liaison to the Health Volunteers Overseas (HVO)-ASH Steering Committee. David is professor of medicine at the University of Washington, Seattle, WA. His clinical research interest is hemostasis/thrombosis, and he has a strong bent toward medical education. This is an exciting and fast-moving time in clinical hemostasis/thrombosis, and we are confident that our readers will benefit from his extensive experience in the field. Adam is assistant professor of medicine and of pathology and laboratory medicine. He is also associate director of Clinical Research, Penn-CHOP Blood Center for Patient Care and Discovery. In addition to hemostasis/thrombosis, Adam has a special interest in quality measures in medicine, and he has served ASH as a co-chair of the Quality Task Force, and as a member of Committee on Quality.

This year marks the beginning of the second decade of publication of The Hematologist. Look for changes on the revamped ASH website (to be introduced this spring) that will enhance the visibility of The Hematologist, and more details will be forthcoming in a future issue. Our editorial goals are communication, education, and scholarship, and we are pleased that the Society continues to make this publication a member benefit. We encourage (and appreciate) reader input. Let us hear from you.

—Charles Parker, MD, Editor-in-Chief

ASH Members Elected to Institute of Medicine of the National Academies of Science

The Institute of Medicine (IOM) has announced the election of 70 new members, including four ASH members, two of whom are past presidents of ASH, Janis L. Ackbowitz, MD, and J. Evan Sadler, MD, PhD. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

The four ASH members elected to the IOM are:

- Janis L. Ackbowitz, MD
  - Clement A. Finch Professor
  - Head of Division of Hematology
  - Department of Medicine
  - University of Washington, Seattle

- Frederick R. Appelbaum, MD
  - Executive Vice President and
  - Deputy Director, Fred Hutchinson Cancer Research Center;
  - President and Executive Director, Seattle Cancer Care Alliance, Seattle

- James R. Downing, MD
  - Executive Vice President,
  - Scientific Director, and Deputy Director, St. Jude Children’s Research Hospital

- J. Evan Sadler, MD, PhD
  - Professor of Medicine,
  - Department of Medicine,
  - Washington University School of Medicine, St. Louis

The Hematologist Editor Search Announcement

The American Society of Hematology is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist (term: 2015-2017). Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills. Members of ASH are invited to submit the names of potential candidates, accompanied by a short, informal endorsement and a brief description of the candidate’s editorial experience. Self-nominations are also welcome. Please send materials to:

The Hematologist: ASH News and Reports

c/o Karen Learner, Managing Editor

American Society of Hematology

2021 L Street, NW, Suite 900
Washington, DC 20006

klearer@hematology.org

Deadline to receive applications is February 28.
Gumbo, ASH Style

Gumbo is the official cuisine of the state of Louisiana, tracing its roots back to the 1800s when the culinary practices of the French, Spanish, native American tribes, and enslaved Africans were combined to form a hearty dish using readily available ingredients. Gumbo is thought to be based on cuisines found in West Africa or to derive from French bouillabaisse. The name “gumbo” probably derives from the Bantu word for okra that is commonly used as a thickener in preparing the dish. Like a good pot of New Orleans gumbo, the recent annual meeting in New Orleans provided nourishment for its attendees who numbered over 22,000. For gumbo, you need a large, sturdy pot with the capacity to hold all of the ingredients and with sufficient additional space to allow the dish to simmer throughout the day without boiling over. For the annual meeting, the gumbo pot was the Ernest N. Morial Convention Center.

ASH Members Share Their Passion for Hematology with New Orleans Students

Prior to the annual meeting, Dr. Marc Kahn, ASH News Daily editor (and a resident of New Orleans), and I worked on designing a program that would stimulate local interest in science and spread our passion about careers in medicine and hematology. The program was three-pronged: ASH members visited students at both a local high school and a New Orleans university and brought together trainees and faculty from three local fellowship programs to discuss challenging cases in a grand rounds style format.

ASH members Dr. Neil Shah, University of California, San Francisco, and Dr. Matt Ulrickson, Banner/MD Anderson Cancer Center, Arizona, visited Benjamin Franklin High School, a local magnet school with a well-respected science department. Bright and inquisitive students who were enrolled in the school’s advanced placement curriculum were introduced, through interactive lectures, to the biology of hematopoiesis, blood cell morphology, and molecular diagnostics, focusing on the Philadelphia chromosome and CML. Next, pre-imatinib CML therapies were reviewed with the participants. Students were told that such therapy was suboptimal and they were asked to “design” a more effective approach to treatment based on what they had learned from the preceding lectures. This challenge led to a discussion about targeted drug therapy, tyrosine kinase inhibition, drug development, and clinical trial design. The students were next asked to consider the perplexing problem of how economic issues affect medical care. This discussion was framed by asking them to consider how income disparity might have an impact on access to life-saving but expensive medications such as tyrosine kinase inhibitors, thinking both of uninsured residents of New Orleans and of impoverished patient populations worldwide.

To reach undergraduate college students, ASH members Dr. Alexis Thompson, Northwestern University, Chicago; Dr. Benjamin Kim, University of California, San Francisco; and Dr. Joe Fouche, Tulane University, visited premedical students at Xavier University. These highly motivated students, who were also in the midst of final examinations, watched the ASH videos “What is Hematology?” and “Why Choose Hematology?” Next, Dr. Thompson, Dr. Kim, and Dr. Fouche shared stories about how they decided to become physicians and hematologists, provided insights into careers in academic medicine, and answered questions about opportunities in medicine and hematology and the difficulties of balancing family life with demanding careers.

Although trainees from different fellowship programs don’t often interact, ASH was able to make it happen in New Orleans. Hematology fellows and faculty from Tulane, Oschner Medical Center, and Louisiana State University were invited to gather at Tulane where they presented patient cases to ASH members and lymphoma experts, Dr. John Leonard, Weill Cornell Medical College in New York, and Dr. Sonali Smith, University of Chicago. Controversies concerning the management of intravascular lymphoma and aggressive HIV-associated lymphoma were reviewed. The presentations were stimulating, and the atmosphere was collegial.

The generosity of the Society and the unselfish dedication of the participating ASH members, created a unique experience for these New Orleans high school and undergraduate students and for the local hematology fellows.

Dr. Joe Fouche, Tulane University, New Orleans, LA, talks with pre-medical students at Xavier University.
Everyone this year in San Francisco. Of course the Golden

Although the ASH annual meeting wouldn’t pass for an

being encumbered by the burden of parental responsibility.

adults so that they could continue to celebrate without

directed at the children, fais do-do was used by raucous

in southern Louisiana. The term "fais do-do" derives from

New Orleans make a habit of celebration. This

hematology.org/highlights

for more details.

Additionally, Highlights of ASH in Latin America will be held April 25 and 26 in Florianopolis, Brazil. Certainly, these meetings will be more flavorful

in a casual, comfortable setting.

Of course, the best thing about cooking a large pot of

time to mix and simmer, leftovers are often better than the

incorporated into the annual meeting.

After most of the ingredients are added, the gumbo is left to

Similarly, the information absorbed from the research presented at the meeting simmered in the minds of attendees. The four days of the meeting allowed for networking and for the admixture of knowledge and ideas to percolate. To assist in this process, Hematology MeetUp spaces were provided throughout the convention center so that colleagues could discuss their impressions of a provocative presentation or just catch up with one another in a casual, comfortable setting.

Of course, the best thing about cooking a large pot of gumbo is that there are always some leftovers, and with
time to mix and simmer, leftovers are often better than the original batch. The second serving of this year’s annual meeting comes in the form of the 2014 Highlights of ASH® meetings. In North America, the remainder of the meetings will be held January 31 and February 1 (Miami and Seattle). Additionally, Highlights of ASH in Asia will take place March 29 and 30 in Singapore and Highlights of ASH in Latin America will be held April 25 and 26 in Florianopolis, Brazil. Certainly, these meetings will be more flavorful given the advantage of time for topics to simmer and stew in the minds of the presenters. Be sure to visit www.hematology.org/highlights for more details.

New Orleanians make a habit of celebration. This characteristic is evident in the tradition of “lais de-do-do,” an all night dance party made famous by the Cajuns who live in Southern Louisiana. The term “lais de-do-do” derives from the Cajun French term for “go to sleep.” As an admonition directed at the children, bais de-do-do was used by rascous adults so that they could continue to celebrate without being encumbered by the burden of parental responsibility. Although the ASH annual meeting wouldn’t pass for an authentic “lais de-do-do,” it was nonetheless a wonderful celebration of education, science, and camaraderie. We happy NOLA denizens with an annual meeting attendees health and good fortune, and we look forward to seeing everyone this year in San Francisco. Of course the Golden Gate is beautiful, but alas, “New Orleans, je t’aime.”

ASH Advocacy Influences FDA’s Action to Address Drug and Biologic Shortages

On December 30, ASH submitted comments to the U.S. Food and Drug Administration (FDA) in response to its proposed rule requiring all manufacturers of certain medically important prescription drugs and biologic products to notify the FDA of a permanent discontinuance or a temporary interruption of manufacturing that is likely to disrupt supply. ASH’s comments on the proposed rule, issued on October 31, underscored the Society’s support for the inclusion of biologics in the advanced notification requirements and urged the agency to also apply the requirements of the final rule to biosimilars. Additionally, the comments noted ASH’s support for the inclusion of blood and blood components for transfusion in the proposed rule, but requested clarification on how the provision would be implemented, as well as how FDA plans to address potential shortages of blood and blood components not included in the reporting requirements. ASH’s ongoing advocacy to combat drug and biologic shortages was instrumental in ensuring the inclusion of biologics in the proposed rule, as well as in formulating FDA’s strategic plan contained in the Food and Drug Administration Safety and Innovation Act of 2012, which outlines FDA’s plans to enhance its response to preventing and mitigating shortages of drugs and biologics.

Visit the drug shortage information page on the ASH website (www.hematology.org/drugshortages) to read the Society’s full comments on this critical matter and to access additional information about current hematologic drug shortages, ASH’s advocacy efforts, and resources for physicians dealing with shortages.

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Getting the Word Out on the Genetic Information Nondiscrimination Act

CONGRESSWOMAN LOUISE M. SLAUGHTER

Discrimination, real or perceived, based on any factor, is unacceptable in our society. As the Human Genome Project began in the early 1990s, I recognized that sequencing and characterizing the genome would further our understanding of human health and disease, but it could also create the potential for discriminatory use of genetic information. Thus, I began working on legislation banning genetic discrimination. After a 14-year-long effort, my bill, the Genetic Information Nondiscrimination Act (GINA), was passed into law. My good friend, the late Senator Ted Kennedy, described it as the first major civil rights bill of the 21st century.

My desire was to quell public fear of losing one’s job or health insurance due to discrimination based on their genetic makeup and to encourage participation in research that would eventually lead to new treatments and medical breakthroughs. I first introduced GINA in 1995 with the hope that science and policy would develop hand in hand, as it rarely does. Our goal was to have the bill passed prior to the completion of the Human Genome Project, which happened in 2003. Regrettably, the task of educating my peers on Capitol Hill about the need for the protections offered by GINA took a bit longer, but in 2008, President George W. Bush signed it into law.

GINA stipulates that it is illegal for any health insurance company to deny coverage to, or charge higher premiums to, a healthy individual based on his or her genetic information. It also protects the privacy of family genetic information and prohibits insurance companies from requesting specific genetic tests. GINA also prohibits employers from hiring, firing, promoting, or assigning based on the genetic information of an employee or potential employee.

Because of GINA, people can get genetic testing to determine their risk of diseases such as breast cancer, Huntington’s disease, and Alzheimer’s disease, without fear that the information gained from those tests will be used in employment or health insurance decisions. Hematology was one of the earliest adopters of genetic testing, using available technology to aid in the diagnosis and management of leukemias and lymphomas, beginning with the identification of the Philadelphia chromosome to diagnose chronic myeloid leukemia (CML) through the development of imatinib, a targeted treatment for this disease. This early success story for personalized medicine will no doubt be repeated in the years to come.

Although GINA has been the law of the land for five years, the public is largely unaware of its provisions. Many Americans still fear that if they undergo genetic testing or participate in research, employers and insurance companies can obtain the results and use such information to raise their rates or fire them. This lack of understanding does not apply only to the general public, unfortunately. A recent study indicated that 55 percent of family physicians were unaware of the GINA-based protections that exist.

It is the duty of both public officials and doctors to inform American citizens about their choices, options, and rights. We need your help. I encourage you to talk to your patients – and your colleagues – about the benefits and necessity of genetic testing, as well as the rights and protections secured by GINA. Ensuring that patients are informed about their medical decisions and free from the fear of discrimination is an essential component of health care.

The National Coalition for Health Professional Education in Genetics (NCHPEG) has resources for physicians wishing to speak to their patients about genetic testing and GINA. Go to: www.nchpeg.org

1. A 2010 survey by Cogent Research titled “Cogent Genomics: Attitudes and Trends: 2010” found that 77% of Americans surveyed were unaware of any laws protecting the privacy of their genetic information.


Jane Desforges, MD (1921-2013)

Dr. Jane Desforges, an eminent member of the hematology community and former ASH president (1984-1985), died in Melrose, MA, on September 7, 2013, at the age of 91.

Dr. Desforges, the daughter of a graduate, graduated from Wellesley College in 1942 and from Tufts University School of Medicine in 1945. She studied hematology with Dr. Max Wintrobe in Salt Lake City from 1947 to 1948 and then returned to Boston, where she worked for 25 years at the Boston City Hospital. During that time, she rose from medical resident to become director of laboratories at Boston City Hospital and professor of medicine at Tufts University. In 1973, Dr. Desforges joined the Hematology-Oncology Division of the New England Medical Center (now Tufts Medical Center) and remained there until her retirement in 1995.

She served on numerous ASH committees as well as on the editorial board of Blood. Additionally, she was associate editor of the New England Journal of Medicine and was a member of numerous advisory boards and committees, including those of the National Institutes of Health, the U.S. Food and Drug Administration, and the American Board of Internal Medicine. In recognition of her many contributions to the field, Dr. Desforges was elected a member of the Institute of Medicine in 1990. These are the bare facts of the long career of an illustrious physician, but the achievements listed in her curriculum vitae do not reveal the real Jane Desforges. When she joined the Hematology-Oncology Division of Tufts Medical Center, I was technically her boss. In reality, however, I was her student. I learned much from Jane during our 25-year association, but the most important lessons were the value of empathy for the sick, especially when treatment wasn’t working; acceptance of the frailty of the human condition; and equanimity despite personal adversity.

Jane was much loved by her patients, students, and colleagues. Medical students an astonishing 13 times and, in 2007, was the first woman to receive the Distinguished Teaching Award from the American College of Physicians. Jane’s patients adored her because they knew that she insisted on the best that a physician could offer patients, even if it meant the doctor’s personal sacrifice. After explaining a complex treatment for Hodgkin disease to a patient, she would return later that day or early the next day to be sure that her patient understood the situation and to probe for more questions or doubts. I can recall standing by her side on the hematologist-in-patient ward while she explained to a family that their elderly father with relapsed acute myeloid leukemia had severe pneumonia. Do they want her to administer antibiotics or simply make an old man with a soon-to-be fatal disease as comfortable as possible without treatment? All clinical hematologists have faced this dilemma, but the delicacy and love emanating from Jane could not and cannot be matched.

Jane was an inspiration to the generation of women in medicine that followed her. When asked about their goal in medicine, so many women who were medical students or trainees in hematology told me, “I want to be like Dr. Desforges.” This response is a foundational element in her wonderful legacy.

It was not easy for a woman to become a physician in the 1940s, and it was not easy for a woman to rise to the top of academia. She was one of five women in her Tufts medical school class of 104 students, and as a woman, she was barred from entering the urologic ward of Boston City Hospital. Still, the slights that she endured failed to deter her — indeed, she seemed to have gained from them.

Jane’s clinical skills were legendary, her knowledge of hematology was encyclopedic, and she could reliably provide an instant answer while the hematology fellow was still looking for it in the index of Wintrobe. She could find the cause of fever in a boy with sickle cell anemia that was missed by every other physician who had examined the child. She taught her patients hematology because she wanted them to understand the disease they had and what her task was. Jane was wonderfully straightforward and honest. There was no hidden agenda, no judging, no excusing, and no self-promotion. She expected you to meet and even exceed her high standards. In a Hematology-Oncology Division that was home to an extraordinary group of research stars, Jane Desforges topped the list of luminaries simply by being herself.

—Robert Schwartz, MD, Professor of Medicine Emeritus, Tufts University School of Medicine
Janet Davison Rowley, MD (1925-2013)

Dr. Janet D. Rowley died at her home in the Hyde Park neighborhood of Chicago on December 17, 2013, from recurrent ovarian cancer. She was 88 years old. Dr. Rowley, the Blum-Reise Distinguished Service Professor at the University of Chicago, was one of the most renowned scientists of the 20th century for her transformative contributions to the understanding of cancer biology and the development of novel approaches to cancer treatment. She was internationally recognized for her studies of chromosome abnormalities in human leukemia and lymphoma, leading directly to more precise diagnoses, to better risk stratification, and to specific therapies for these malignancies. Her work set in motion the current era of cancer genetics, revolutionized thinking about the pathogenesis of cancer, and led to novel therapies such as imatinib for chronic myeloid leukemia (CML).

As a trainee in hematology in 1980, my first recollection of Janet is a memory of her wearing hiking boots and a heavily laden backpack, climbing up and down the back staircase in the Franklin McLean Institute at the University of Chicago. She was training to hike the Inca Trail from Cuzco to Machu Picchu with her husband Donald. She approached her science with equal vigor, determination, and persistence. In addition to her independent scientific contributions, Dr. Rowley was an exceptional role model and mentor. She was known for her kind and energetic guidance of her colleagues, and she was an inspiration to dozens of young physician-scientists, especially women.

Janet was born in New York City in 1925 and moved to Chicago when she was two. At the age of 15, she was granted a scholarship to an advanced placement program at the University of Chicago Laboratory Schools, which combined the last two years of high school with the first two years of college. She received her Bachelor of Philosophy degree in 1944 and was accepted into the University’s medical school, although her enrollment was delayed a year because the quota of women—three in each class of 65—had already been filled.

She received her MD in 1948 at the age of 23 and married Donald Rowley, also a physician, the very next day. She spent most of the next two decades raising their four children while working part time as a physician at a clinic for children with developmental disabilities, including Down syndrome. The 1959 report by J.J. Lejeune describing trisomy 21 in Down syndrome sparked her interest in cytogenetics.

Janet was a pioneer in what is now called “translational research,” applying laboratory studies to the understanding and treatment of human disease. In 1962, after spending a year at Oxford learning cytogenetics, while Donald, a pathologist, was on a sabbatical, Janet returned to the University of Chicago as a hematology research associate. Dr. Leon Jacobson, a colleague and mentor, suggested she apply her knowledge to the study of chromosomes from patients with leukemia. He offered some laboratory space, a microscope, and a salary of $5,000 a year. For the next decade, she labored over the microscope, searching amid the seeming genetic chaos for consistent chromosome abnormalities.

In 1972, Dr. Rowley discovered the first consistent chromosome translocation in any human cancer, namely the t(8;21) translocation in acute myeloid leukemia (AML). In a landmark paper published in Nature in 1973 (Nature; 1973;243:290-293), Janet described the t(9;22) translocation in CML. At that time, the distinctive Philadelphia chromosome was thought to result from the loss of DNA from either chromosome 21 or 22, but Janet showed that it was due to a balanced translocation. Subsequently, she identified more than a dozen different recurring translocations in children and adults with leukemia and lymphoma, including t(14;18) seen in follicular lymphoma, t(15;17), the pathognomonic signature of acute promyelocytic leukemia, and chromosome 11 translocations affecting the MLL gene that contribute frequently to the pathobiology of lymphocytic and myeloid leukemias. Working closely with hematopathologists James W. Vardiman and Daina Variojiokis and with Harvey M. Golomb, her clinical collaborator, she was able to link these recurring chromosomal abnormalities with distinctive phenotypes, clinical characteristics, and treatment outcomes. Janet was a pioneer in what is now called “translational research,” applying laboratory studies to the understanding and treatment of human disease. Her discoveries changed the prevailing view of cancer researchers who had considered chromosomal abnormalities in cancer to be an epiphenomenon with little biologic or clinical significance.

“Janet has been a mentor for her colleagues as well as her trainees and an ongoing example of scientific wisdom and imagination combined with impeccable professional and personal style,” colleague Michelle Le Beau, PhD, director of the University of Chicago Medicine Comprehensive Cancer Center, said. “She received just about every imaginable honor. Yet she remained breathtakingly humble, giving most of the credit to her colleagues, her students, and luck.”

Janet’s contributions to hematology were recognized by ASH with the William Dameshek Prize in 1983 and the Henry M. Stratton Medal in 2003. In 2011, she shared the Ernest Beutler Lecture and Prize with Dr. Brian J. Druker. She was elected to membership of numerous scientific and honorary societies including the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society, and the American Academy of Arts and Sciences. President Jimmy Carter appointed her to the National Cancer Advisory Board (1979-1984). President Bill Clinton awarded her the National Medal of Science (1998). From 2002 to 2009, she served on President George W. Bush’s Council on Bioethics, and, in 2009, she stood next to President Barack Obama when he lifited the federal moratorium on funding for stem cell research. She was also the recipient of many prestigious awards for her work—among them, the 1998 Albert Lasker Clinical Medicine Research Prize for her work on chromosomal translocation, the Presidential Medal of Freedom in 2009, and the Gruber Prize in Genetics.

Outside of the lab, she was an avid biker. She was also well known for her gardening skills. Her husband, Donald, an emeritus professor of pathology at the University of Chicago, died in early 2013. Her legacy is the impact she has had on the thousands of patients who benefited from her discoveries, the worldwide community of cancer cytogeneticists and leukemia investigators, and the students and trainees she mentored.

—Richard A. Larson, MD, Professor of Medicine, Section of Hematology/Oncology, University of Chicago
The MLL gene is located at chromosome 11q23 and encodes a protein with epigenetic activity. The product of the gene is an enzyme that modifies chromatin by methylating lysine 4 on histone H3 (Figure). The SET domain of MLL that bestows this methyl transferase activity is deleted by the chromosomal translocations that occur in MLL-rearranged acute leukemias, and consequently, aberrant epigenetic functions that contribute to disease pathophysiology are acquired (Figure). MLL-rearrangement is observed in subsets of both myeloid and lymphoid acute leukemias that are characterized by an aggressive clinical course and a poor prognosis.

In the context of acute leukemia, MLL is promiscuous in that rearrangements involve a variety of partner genes that generate leukemogenic fusion proteins with various functional properties that mediate disease by driving proliferation, enhancing survival, or inducing differentiation arrest. At least 70 translocations involving MLL have been documented, including those that partner with lens epithelium-derived growth factor; the histone methyltransferase, DOT1L (Figure); chromobox homolog 8; histone demethylase KDM1A; and bromodomain-containing 4. These fusion proteins activate key regulatory pathways to contribute to leukemia pathogenesis (Figure). With so many different fusion partners, it seemed unlikely that the pathobiologic process underlying leukemia involving MLL rearrangement would converge on a common mechanism, but now, Kuo and colleagues report that activation of the IKK/NFκB pathway is a critical component of the neoplastic process in MLL-rearranged leukemias (Figure).

The transcription factor NFκB has a fundamental role in cancer pathogenesis, through its effects on cell proliferation, its anti-apoptotic properties, and its contributions to drug resistance and metastasis. The transcription factor complex has two forms: NFKB1, which drives the canonical pathway and consists of RELA/p50; and NFKB2, which drives the non-canonical pathway and consists of RELB/p52. The canonical pathway affects cell proliferation, survival, and self-renewal (Figure). The activity of NFκB is tightly controlled by an inhibitory protein (IkB) that binds and sequesters the canonical RELA/p50 complex in the cytoplasm (Figure). NFκB becomes active when IkB is phosphorylated by the IKK complex (Figure). Consequently, IkB is degraded and RELA/p50 is free to translocate to the nucleus and enable transactivation of target genes (Figure). For example, transcriptional activation of two key target genes, HOXA9 and MEIS1, by NFKB1 contributes to the self-renewal capacity of leukemia stem cells (Figure).

To identify proteins that underlie neoplastic transformation in MLL-rearranged leukemia, a lentiviral-based, shRNA-knockdown approach was used by Kuo and colleagues to examine the effect of 211 candidate stem cell kinases or pathways that contribute to disease pathogenesis (Figure). With so many different fusion partners, it seemed unlikely that the pathobiologic process underlying leukemia involving MLL rearrangement would converge on a common mechanism, but now, Kuo and colleagues report that activation of the IKK/NFκB pathway is a critical component of the neoplastic process in MLL-rearranged leukemias (Figure).

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Together, these rigorous studies demonstrate that NFκB signaling is critical for propagation and maintenance of MLL-associated leukemias and for implementation of the epigenetic programs directed by the MLL fusion proteins. This enlightening publication highlights NFκB as the final common pathway for the MLL-rearranged leukemias and, in so doing, reveals new targets for therapy of these aggressive, often refractory, hematologic malignancies. As an example, a selective amino-nucleoside inhibitor, EPZ-5676, which targets the DOT1L complex consisting of DOT1L, a histone methyltransferase (Figure), and MLL fusion partners such as AF9, ENL, and AF10, has been studied in preclinical models, and a phase I clinical trial using EPZ-5676 is ongoing.


For most new leukemia patients, the initial clinical symptoms include some combination of fatigue, bleeding, and infection—all the result of deficits in blood cell production. The diagnostic bone marrow at presentation often shows near-complete replacement of hematopoietic tissue by infiltrating leukemic blasts. Intuitively, the peripheral cytopenias that reflect the loss of normal hematopoietic function are seen as a manifestation of unrestrained leukemic expansion resulting in “over-crowding” of the bone marrow by malignant cells. However, this straightforward notion of passive loss of hematopoietic tissue is called into question by the observation that cytopenias are a common feature of patients in early relapse when the bone marrow leukemia burden is low. Schepers et al. now provide evidence that the loss of hematopoietic function is an active process, where the bone marrow stromal cells are reprogrammed by invading neoplastic cells to promote both leukemic expansion and HSC suppression.

Like other organs, the bone marrow microenvironment functions as a unit where the complex interplay of the different cell types sustains normal organ function (hematopoiesis in the case of the bone marrow). Multipotent stromal cells (MSCs) and their osteoblastic progeny (osteoblastic lineage cells, OBCs) provide critical support for the maintenance of normal hematopoietic stem cell (HSC) homeostasis. In the current study, Koen Schepers and colleagues in the laboratory of Emmanuelle Passegué at the University of California, San Francisco, used a transgenic mouse model of chronic myeloid leukemia (CML) to investigate the effects of leukemogenesis on the function of the bone marrow niche. Experimental animals, expressing inducible BCR/ABL that drives leukemic expansion, developed a florid myeloproliferative neoplasm (MPN) within six weeks. Bone marrow analysis showed preferential expansion of the OBCs, and subsequent experiments demonstrated that the expanded population was derived from MSCs that had been induced by leukemic stem cells to overproduce OBCs. Thus, the overproduction of OBCs was orchestrated by the MPN cells. Subsequent experiments suggested that thrombopoietin, CCL3, and cell-cell interactions drove the expansion of OBCs. Examination of the bone marrow showed morphologic features (fibrosis and trabecular bone thickening) reminiscent of those observed in patients with MPNs. The process was both reversible (upon eradication of leukemia cells) and transplantable (sublethally irradiated wild-type mice transplanted with leukemic cells from the bone marrow) and transplantable (sublethally irradiated wild-type mice transplanted with leukemic cells from the bone marrow). Overproduction of OBCs was orchestrated by the MPN cells. Subsequent experiments suggested that thrombopoietin, CCL3, and cell-cell interactions drove the expansion of OBCs. Examination of the bone marrow showed morphologic features (fibrosis and trabecular bone thickening) reminiscent of those observed in patients with MPNs. The process was both reversible (upon eradication of leukemia cells) and transplantable (sublethally irradiated wild-type mice transplanted with leukemic cells from the bone marrow).

The study by Schepers and colleagues describes an active process in which reprogramming of niche components by neoplastic cells favors leukemic proliferation while compromising normal hematopoiesis. Microenvironmental contributions to leukemic drug resistance have long been appreciated, and the current work suggests that, similarly, leukemia-associated bone marrow dysfunction is an elegantly orchestrated component of the leukemic process rather than a simple case of physical competition for available space and resources within the bone marrow. The systematic dissection of events that convert the bone marrow from a nurturing environment to a hostile niche may hold important translational value for the treatment of hematopoietic neoplasms.

Ironing Out the Problem: Targeting Hepcidin to Treat the Anemia of Inflammation


Hepcidin is a small peptide hormone produced by the liver that is the master regulator of iron homeostasis. Hepcidin mediates this function by impairing the export of iron from macrophages, duodenal enterocytes, and hepatocytes by binding to ferroportin, thereby driving internalization and degradation of this key transmembrane iron exporter (Figure). Consequently, hepcidin regulates both intestinal absorption of dietary iron and reutilization of iron derived from recycling of the hemoglobin of senescent red blood cells. A Diffusion article that I wrote last year (“Irons in the Fire: Developing New Therapies for Iron Overload,” The Hematologist, March/April 2013) focused on aberrant suppression of hepcidin expression, which leads to iron overload. The current article discusses the converse – enhanced expression of hepcidin that underlies the anemia of inflammation by limiting iron availability.

Hepcidin is an acute-phase reactant that is strongly induced by inflammation. Indeed, hepcidin was initially identified in a search for innate antimicrobial peptides. Chronic infections and other inflammatory diseases, including rheumatologic diseases and cancer, and chronic kidney disease, which results in decreased urinary clearance of hepcidin, are associated with abnormally high plasma concentrations of hepcidin. Consequently, the absorption and reutilization of iron is impaired, leading to the iron-restricted anemia of inflammation. This anemia is resistant to treatment with supplemental iron and erythropoiesis-stimulating agents (ESAs). Therefore, effective treatment options are needed to aid in the management of symptomatic anemia of inflammation.

Cooke and colleagues, building on previous work with mouse monoclonal antibodies, developed a fully human, high affinity, hepcidin-neutralizing antibody (12B9m). This antibody was tested in a mouse model of anemia of inflammation where it was found to successfully treat ESA-refractory anemia. Antibody treatment increased plasma hemoglobin concentration in this model both by improving the hemoglobin content (“hemoglobinization”) of red blood cells and by stimulating production of reticulocytes. Antibody-mediated neutralization of hepcidin was shown to increase serum iron concentration in both mice and monkeys. There was no evidence that antibody treatment improved the anemia by modulating inflammatory status, as the production of cytokines and erythropoietin was unchanged following anti-hepcidin treatment. The antibody was found to be most effective when given simultaneously with an ESA compared with being given either two days before or two days after ESA treatment. Pharmacodynamic studies showed that weekly dosing was effective at modulating serum iron concentration and that a dose of 300 mg/kg achieved complete neutralization of hepcidin activity.

Cooke and colleagues have developed an antibody that alleviates the anemia of inflammation in animal models by blocking hepcidin, thereby improving the availability of serum iron and increasing both the reticulocyte count and the hemoglobin content of red blood cells. A short-term practical offshoot of this research explored by the authors is the use of this antibody in a sandwich ELISA assay for the laboratory measurement of plasma hepcidin concentration. The ultimate goal of this research is to develop a pharmacologic reagent that can be used to modulate iron metabolism for the treatment of human disease, particularly the anemia of inflammation. This research provides cautious optimism for development of both a reliable and broadly available clinical test for quantifying hepcidin concentration (which would be a valuable aid in characterizing diagnostically challenging anemias) and a targeted therapy for anemia of inflammation, especially when the underlying cause of inflammation cannot readily be eliminated or controlled.
Take Me to the Liver: New Insights on Antibody Mechanisms


M any studies have shown that rituximab exerts its effects on B-cell lymphoma through host effector mechanisms, particularly antibody-mediated cellular effects in the form of either antibody-dependent, cell-mediated cytotoxicity or antibody-dependent cellular phagocytosis. Although we know that these mechanisms are dependent upon interaction with Fc receptors on the surface of effector cells, we have little information about the exact process that takes place in vivo. Now, Montalvo and colleagues at the Institut Pasteur in Paris report that liver macrophages (i.e., Kupffer cells, KCs) are the key effectors of antibody-mediated B-cell destruction.

Initial studies of B-cell depletion kinetics in different organs following anti-CD20 treatment in mice showed that this process took place most rapidly in the liver and, furthermore, that partial hepatectomy (but not splenectomy) reduced the rate and extent of B-cell depletion. Pre-treatment of B cells with pertussis toxin, which prevents their sequestration in lymph nodes and the splenic white pulp, resulted in even more rapid depletion, supporting the concept that liver-mediated B-cell destruction is the dominant mechanism of action of anti-CD20 therapy and that depletion from other organs is not the result of direct intra-organ cytotoxicity but rather a consequence of redistribution of antibody-targeted B cells to the liver. This interpretation was further supported by the results of experiments that used intravital imaging of B cells labeled with a fluorochrome. Those studies showed rapid accumulation of anti-CD20-treated B cells in the liver sinusoids, followed by local destruction, and this effect was blocked by liposomal sirolimus, which is toxic to KCs.

A series of elegant experiments were performed using transgenic mice expressing a fluorescent reporter, which selectively highlights KCs and monocytes/macrophages, allowing direct visualization of phagocytic cells during intravital imaging of the liver. This experimental approach confirmed that normal B cells were rapidly trapped and engulfed by KCs in the liver sinusoids following anti-CD20 treatment, an observation that was replicated when malignant B cells were tested in the same system.

We have known for some time that Fc receptor-dependent effects are central to the action of rituximab and other type 1 anti-CD20 antibodies such as obinutuzumab, but it has not previously been clear which compartment mediates this action. There was an assumption that lymphohematopoietic sequestration by macrophages mediated this process, but the studies of the Paris group show that KCs are the primarily agents of antibody-mediated B-cell destruction, at least in the mouse. It also appears that anti-CD20 treated B cells resident at other sites, such as the spleen and lymph nodes, traffic to the liver for destruction rather than being eliminated in situ. These observations have implications for the use of antibodies in the clinic and may provide an explanation for the preferential effect of anti-CD20 therapy on circulating B cells as opposed to those in lymphoid or other organs, where the process of depletion is less rapid. These findings also suggest that type 1 anti-CD20 antibodies may be optimized by targeting Fc receptor engagement on KCs, whereas the type 2 antibodies such as obinutuzumab appear to act through a different mechanism, at least in part by inducing B-cell apoptosis.

For the future, this type of in vivo imaging experiment provides a powerful tool for dissecting the mechanisms of action of antibodies and other complex biotherapeutics, although evidence that the situation in humans is similar to that in the mouse is needed. These experiments have given a strong indication that we should seek this evidence in the liver.

The Hemostatic Mechanism and Allergy


T oil-like receptor 4 (TLR4) is most commonly known as a receptor for lipopolysaccharide (LPS, endotoxin). Indeed, the gene encoding TLR4 was identified by positional cloning using LPS-resistant C3H/HeJ mice.1 Subsequently, many ligands for TLR4 have been identified, including tauro, heparan sulfate, and hyaluronate.2 TLR4 is expressed by several types of cells, including monocytes, macrophages, dendritic cells, mast cells, and B cells. Ligation of TLR4 initiates signaling via MYD88- and TRIF-dependent pathways, which leads to activation of innate immune system functions. The innate immune system is an ancient set of mechanisms brought into play by several classes of TLRs in response to microbial infection. While necessary for control of specific microbial agents, as witnessed by susceptibility to infection associated with genetic defects in TLR-dependent pathways, the flip side of TLR activity is involvement in autoimmunity and allergy. For example, TLR4 is involved in Type 1 T-helper cell (Th1)-dependent allergic responses, including asthma and other inflammatory disorders.

Allergic responses to pollen, dust mite antigens, and fungi are associated with proteinase-dependent and proteinase-independent Th2 cell-mediated events. To study the role of TLR4 in allergic inflammation, Millen et al. in the laboratory of David Corry, Baylor College of Medicine, Houston, Texas, subjected mice to intranasal challenge with several known allergens, including a proteinase derived from Aspergillus, live conidia (spores) from Aspergillus niger, and ovalbumin. Wild-type (wt) mice developed airway hypersensitiveness, eosinophilia, and other findings consistent with allergic asthma when exposed to the immunogens. These responses were significantly attenuated in TLR4−/− mice. Consistent with its dual role in allergy and immunity, TLR4+− mice were also defective in detecting A. niger following inhalational challenge. In contrast, there was no difference between wt and TLR4−/− mice in Th2-dependent pulmonary IL-4 secretion and IgE levels. This result indicates that TLR4 does not produce a Th2-dependent process, but rather is involved in the response to a Th1-mediated process.

Exposure of murine bone marrow-derived macrophages (BMDMs) or alveolar macrophages to LPS, or fungal proteinase, resulted in upregulation of several genes that are involved in serum-dependent fungistasis. They produced fibrinogen cleavage products (FCPs) by adding thrombin to purified fibrinogen and found that FCPs could substitute for fungal protease and serum as a fungistatic agent. FCPs also induced the expression of mRNA for IL-13 and the airway mucin gene Muc5ac, which are components of allergic responses, including inflammation, TLR4–/– mice were also defective in clearing fungal infection. For example, TLR4−/− BMDMs were used, FCPs or the combination of fungal proteinase and serum did not produce fungistasis. Intranasal challenge of mice with FCPs did not produce airway hyperresponsiveness or pulmonary IL-4 secretion, consistent with the hypothesis that TLR4 mediates, but does not drive, Th2-dependent responses. However, hirudin, a specific thrombin inhibitor, attenuated both fungal proteinase- and ovalbumin-mediated experimental asthma.

These findings support a model in which airway proteinase activity, possibly primarily mediated by thrombin, leads to formation of fibrin and/or fibrin degradation products that are ligands for TLR4. TLR4 activation then “licenses” innate immune cells to respond to Th2 cells, resulting in the development of allergic airway disease. Interruption of the FCP-dependent TLR4 signaling may be an approach to treating common allergic airway disorders, including asthma, allergic rhinitis, and chronic rhinosinusitis.

John M. Goldman, DM (1938-2013)

John M. Goldman, emeritus professor at Imperial College London, was a leader in studies of leukemia for the last 40 years. He focused on chronic myeloid leukemia (CML), an invariably fatal disease when he began his research in 1971.

John was born in 1938, was educated at Westminster School where he was a superior student, and sang in the choir that performed at the coronation of Queen Elizabeth II. He studied medicine at Magdalen College, Oxford, where he was also a classics scholar, and he completed his medical training at St. Bartholomew Hospital, London. He then moved to the University of Miami and later to Harvard University.

In 1971, John joined the renowned department of hematology at Hammersmith Hospital, which included Sir John Dacie, Sir David Galton, Professor Victor Hoffbrand, and Professor Daniel Catsovsky, among others. There he focused on CML where he pioneered the use of bone marrow transplantation and helped establish the Anthony Nolan Trust Donor Registry, which now includes more than 500,000 volunteers and is used to find donors for recipients in the United Kingdom and worldwide.

In the 1990s, John promoted promising preclinical research, conducted by Dr. Brian Druker, using imatinib to treat CML. Despite working miraculously, no drug company was interested in developing the drug. Much like the story of Florey and Chain who developed penicillin, but had to travel to the United States to find a drug company willing to travel to the United States to find a drug company willing to produce it, Goldman flew to Basel, Switzerland, to persuade Novartis to produce imatinib. He succeeded, and imatinib and successor drugs are now given to thousands of people worldwide.

John was a founder and served as president of several professional organizations that promoted research and collaboration in blood diseases and transplantation, including the European Hematology Association and the European Bone Marrow Transplant Group. From 1998 to 2002, John was chair of the Center for International Blood and Marrow Transplant Research. He also created the Leukemia and Lymphoma Society, a charity to raise money to fund leukemia research, and founded the widely read journal Bone Marrow Transplantation.

Following his retirement from Hammersmith Hospital in 2004, John focused on global health issues. He developed a particular interest in the impact of sunburn and sunlamp use in the study of skin cancer.

While ultraviolet (UV) radiation exposure has been inversely associated with Hodgkin lymphoma risk, reporting has been inconsistent, sparse, and without attention to Hodgkin lymphoma heterogeneity. The authors of this study conducted a pooled analysis of Hodgkin lymphoma risk focusing on type and timing of UV radiation exposure and on disease subtypes stratified by age, histology, and tumor-cell Epstein-Barr virus (EBV) status. Four case-control studies contributed 1,320 Hodgkin lymphoma cases and 6,381 controls. After adjustment for lifetime, adulthood, and childhood UV radiation exposure and history of sunburn and sunlamp use in the study of skin cancer.

subjects, investigators observed statistically significant inverse associations between childhood and adulthood UV radiation exposures, suntan history, and sunlamp use with Hodgkin lymphoma risk but did not find significant dose-response relationships. Risks were significant only for EBV-positive Hodgkin lymphoma. Increased UV radiation exposure may protect against Hodgkin lymphoma and particularly against EBV-positive Hodgkin lymphoma. Plausible mechanisms involving UV radiation induction of regulatory T cells or the cellular DNA damage response suggest opportunities for new disease prevention targets.


A seminal study in Blood reports the first determination of the crystal structure of the prothrombinase complex, providing insights into both the architecture and the mechanism of action of one of the most important enzyme complexes in coagulation. Lechtenberg and colleagues solved the crystal structure of Pseutarin C, an intrinsically stable prothrombinase complex reassembled in the venom gland of the Australian Eastern Brown snake (Pseudonaja textilis). This complex is homologous to the human prothrombinase complex, composed of the protease factor (f)Xa and cofactor IVa, that converts prothrombin into thrombin by specific, sequential cleavage at two sites. Insufficient thrombin generation is the root cause of hemophilia and excessive thrombin production results in thrombosis. Thus, with this discovery, we can now understand how factor Va, Va, and prothrombin assemble to produce active thrombin. The long-sought-after elucidation of this structure is not only a scientific milestone but is also clinically relevant, as it will serve as the foundation for future drug development.

Putting Rituximab in Its Place

**STUDY TITLE:** Rituximab in Auto-Immune Hemolytic Anemia

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01181154

**SPONSOR:** Assistance Publique-Hôpitaux de Paris

**COLLABORATOR:** Hoffmann-La Roche

**LOCATION:** Henri Mondor University Hospital, Créteil, France

**ACCRUAL GOAL:** 34

**STUDY DESIGN:** This is a phase III, double-blind, randomized, placebo-controlled trial. Patients with newly diagnosed, primary (not associated with lymphoid neoplasms, lupus erythematosus, etc.) warm autoantibody-mediated, autoimmune hemolytic anemia (AIHA) within six weeks of diagnosis, who are being treated with prednisone (1 mg/kg/day, maximum daily dose 100 mg) and who are not responding to this treatment will be enrolled. Patients will be randomized 1:1 to receive either 375 mg/m² of rituximab or placebo on days 1 and 15. Prednisone will be tapered based on evidence of response. Patients will participate in the study for three years. The primary endpoint is remission rate (complete + partial) at one year. Secondary outcomes include comparisons between the two groups for two-year remission rates, cumulative prednisone doses, red blood cell transfusions, and requirement for splenectomy, or immunosuppressive therapy.

**RATIONALE:** Retrospective clinical data suggests that the remission rate at one year will be greater in the rituximab arm (80%) than in the placebo arm (20%). Rituximab, a bioengineered chimeric mouse/human monoclonal antibody that binds CD20, an antigen expressed on B lymphocytes, has been extensively studied and used in the treatment of human lymphoid neoplasms as a single agent and, more commonly, as part of standard chemotherapy regimens. B lymphocytes mediate autoimmune diseases through several actions including antibody production, antigen presentation, and enhancement of T-cell function and dendritic cell differentiation. Therefore, rituximab has been used to treat a variety of autoimmune hematologic disorders including immune thrombocytopenia purpura (ITP), acquired hemophilia A, thrombotic thrombocytopenic purpura, and Evans syndrome, as well as AIHA, both warm-antibody and cold-agglutinin types (Diericks D et al. Am J Hematol. 2011;86:278-291 and Barcellini W et al. Eur J Intern Med. 2011;22:220-229).

**COMMENT:** Until the advent of the use of rituximab, treatment of warm-antibody AIHA followed a familiar algorithm: a corticosteroid, usually prednisone, was first-line treatment, splenectomy was second-line therapy, and an immunosuppressive medication such as azathioprine, cyclophosphamide, or cyclosporine constituted the third line of treatment. About 20 percent of patients who achieve remission with corticosteroids can be tapered off steroids successfully. Among the remaining 80 percent, 20 percent are primarily unresponsive and 60 percent fail the steroid taper. Splenectomy is successful in the majority of patients who are refractory or who require unacceptably high doses of steroids to maintain an adequate response. But relapse is common among splenectomized patients. About third therapies are often unsuccessful and associated with significant adverse effects, rituximab found a place in the clinician’s treatment armamentarium for this difficult-to-manage group. And due to the requirement for an operative procedure and concerns about long-term sequela associated with splenectomy, rituximab soon became an alternative second-line modality.

Results, emanating from small, uncontrolled studies of high remission rates in patients with AIHA treated with rituximab after failing corticosteroids, have led to its use in combination with steroids as both primary and secondary therapy. However, controlled studies such as NCT01181154 are required to establish the place of rituximab in the hierarchy of AIHA therapy. Rituximab is not entirely benign therapy as it can worsen chronic viral infections such as hepatitis C, CMV, and Herpes zoster. Progression multiscalar leukoencephalopathy is a rare but potentially fatal viral illness associated with rituximab therapy. Further, many patients successfully treated with rituximab for autoimmune diseases have subsequent relapses at lengths of time varying from months to years. Some patients with such relapses respond to additional courses of rituximab, but splenectomy may offer a more durable long-term remission. In light of these observations, the secondary endpoints of remission status at two years and frequency of splenectomy will be of particular interest. Notably, an abstract presented at the recent ASH annual meeting reported that patients with ITP who received rituxan in conjunction with corticosteroids after failing monotherapy with corticosteroids had a higher complete response rate at 24 weeks compared with patients in the placebo control arm, but no difference was observed between the two groups either in the rate of splenectomy or in the number of subjects reaching the criteria for splenectomy by week 78 of the study (Ghazvini W et al. Blood. 2013;122:449). The current AIHA trial will likely be one of multiple controlled trials required to put rituximab in its place in the treatment hierarchy of warm-antibody AIHA.

~ Mark J. Koury, MD

Dr. Koury indicated no conflicts of interest with this article.
A Life in Hematology

DAVID G. NATHAN, MD, DSc (Hon)
Center for Pediatric Hematology and Oncology of the Boston Children’s Hospital and Dana-Farber Cancer Institute;
Robert A. Stranahan Distinguished Professor of Pediatrics and Professor of Medicine, Harvard Medical School

I assumed my duties as a fourth-year Harvard medical student on the Internal Medicine wards of the then Peter Bent Brigham Hospital in the fall of 1954 and almost immediately met the late E. Donnall Thomas, a recent chief resident and the acting hematologist. He talked to me about his hopes to create a safe and effective approach to bone marrow transplantation. I knew in an instant that I wanted to be a doctor like him. (Soon thereafter he moved to Cooperstown, NY, where he could carry out the canine studies that began his illustrious career.)

A year later, I became an intern on that service and struggled with my career options. Should I continue on the path that I thought I would follow—to be a subspecialist internist with an interest in liver disease, or should I establish a group practice in a poor area of Cambridge, MA, as I thought I would when I was a Harvard undergraduate? The Korean conflict settled the issue. I was invited to join the U.S. Public Health Service in the nascent clinical research program at the National Cancer Institute (NCI), which was led by the late Gordon Zubrod, a thorough gentleman. Alternatively, I could go to Korea in the Army. With a lovely wife and two children and another on the way, I wisely chose the former and was immediately ordered into experimental hematology by my appointed supervisor, then Captain (four stripes) the late Nathaniel I. Berlin. I had only two stripes on my sleeve, so hematology was my “choice.” I shared a lab with my Harvard classmates, Sherman Weissman and Tom Waldman. The late Dan Nathans was next door. George Brecher and Fred Stohlman were there to teach me. It was a remarkable environment, and I have been intensely loyal to the National Institutes of Health ever since.

Three years later, in 1959, I completed my senior residency in medicine at the Brigham and launched into a career in adult hematology under the watchful eye of the late Frank H. Gardner, a superb clinician. I decided to investigate thalassemia and the congenital hemolytic anemias because the patients fascinated me. I wanted to understand the pathophysiology of those diseases, and my work at NCI had given me some decent tools with which to explore the disorders. That work led me to establish many international friends, the most exciting of whom was and remains David Weatherall. David was knighted for his fine work, but has yet to introduce me to the Queen—a failing that he refuses to acknowledge.

In those years I labored in the Brigham lab with some wonderful colleagues like Chester Alper, Phin Cohen, Sergio Piomelli, Tom Gabuzda, Y.W. Kan, and Stanley Yachnin. All of us wanted to be clinical investigators examining patients and learning lessons about disease in the laboratory. Our goal was to be elected to membership in the American Society of Clinical Investigation. While working at the Brigham, I was greatly assisted by the late William Castle and his incredibly strong group at the then Thorndike Memorial Laboratory of the Harvard Service at the Boston City Hospital. The Thorndike was clearly the apex of hematology at Harvard and was one of the leading experimental hematology laboratories in the world. I learned something about myself in those years. I realized how much I needed to admire the leader of the unit to which I was assigned. Castle was the type of leader that I needed in my life. His advice, probity, and wisdom about patient-oriented research made my daily life in the lab and the clinic seem important. I came to realize that I would always need to build my research around my patients; I was motivated by a desire to understand the physiologic and chemical bases of their illnesses and to try to define better approaches to diagnosis and treatment. I was less interested in biology for its own sake.

In the early to mid 1960s, I met the late Frank Oski, a developing pediatric hematologist at Boston Children’s Hospital (Children’s), who introduced me to one fascinating patient after another. Later we combined our efforts to initiate our textbook titled *The Hematology of Infancy and Childhood*. That book is now entering its eighth edition under the leadership of Stuart Orkin. My efforts with Frank Oski made me realize that the future of hematology surely lay in genetics and that pediatrics was indeed “genetics on the hoof.” Then suddenly in 1966, the late Charles A. Janeway came into my life. He was the chief of the Department of Medicine at Children’s and was searching for a successor to the late Louis K. Diamond who was retiring from his position as chief of hematology at Children’s. I deeply admired Janeway who had many of the characteristics of William Castle. I took that job because I knew that pediatrics had the patients who would fascinate me and advance my career, and I wanted to report to Janeway. In those days, there were far fewer rules. I had my boards in Internal Medicine, and after a few years I took the quiz and the oral exam and became board certified in Pediatrics. In fact, I served as chair of Janeway’s department at Children’s from 1985 to 1995. I never took hematology boards because I didn’t believe in them and still don’t. I firmly hold that a hematologist is someone who gains the approval of William Castle, Louis Diamond, Maxwell Wintrobe, or Carl Moore and their ilk. I suppose that view is now unacceptable. Despite my subspecialty board deficiency, I ran the Hematology/Oncology Division for 20 years and served as president of Dana-Farber Cancer Institute from 1995 to 2000. No one cared about the subspecialty boards; neither do I.

I have been at Children’s and then its close collaborating institution, Dana-Farber, since 1966. I first focused on the development of a pediatric hematology training program at Children’s and then a joint pediatric hematology and oncology program at Children’s and Dana-Farber.

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I have known David Nathan for more than 35 years and been proud to serve as the first incumbent of the David G. Nathan Professorship at Harvard Medical School. Each of us who has trained or worked with David Nathan has special reminiscences of his prowess as a clinician, clinician-teacher, and leader, and builder of academic institutions. Through an intent trainee in adult hematology, he developed an extraordinary combined pediatric hematology and oncology program between Children’s and Dana-Farber and led the Department of Medicine (Pediatrics) at Children’s for a decade. During his tenure as department chair at Children’s, he garnered Howard Hughes Medical Institute support for the hospital, paving the way for its remarkable research presence over the past three decades. When called to serve as president at Dana-Farber at a challenging time in its history, he stabilized the institution and expanded both its research and clinical activities to better position it as a premier academic cancer center.

Despite these professional accomplishments, or perhaps in light of them, I most admire David’s humanism and humanity. Humanism places concern for human interests, values, and dignity at the center of care of the sick. Fueling David’s enthusiasm and passion in all aspects of academic medicine is his unwavering commitment to improving the lives of patients with potentially devastating illnesses. For him, a palpable connection between the laboratory and disease is what captures his attention and imagination and gives hope for improved therapies. David’s humanity is reflected in his loyalty and fairness in his interactions with trainees, colleagues, and patients. He embodied a steadfast mentor long before the practice of mentoring became a recognized academic exercise. For David, the person is always the focus.

As he nears his 85th birthday, we all marvel at his enthusiasm and engagement in all aspects of life. I can barely think of David however, without also thinking of his wife Jean. There is a remarkable love story. While choosing to remain in the background in David’s professional endeavors, Jean has given David her total support and made his family life a source of inestimable pleasure. We should all thank Jean for generously sharing David with us in the world of hematology.

Dr. Gene Orringer is a hematologist and a distinguished clinician-scientist. His research activities and clinical practice at the University of North Carolina at Chapel Hill have focused on red blood cell disorders with an emphasis on sickle cell disease. Dr. Orringer was a leader in the NIH-funded studies that culminated in FDA approval of hydroxyurea for treatment of sickle cell disease. From 1983 to 1987, Dr. Orringer was the chair of the NIH NHLBI Sickle Cell Disease Advisory Committee, and he remains an active member of that Committee. His many contributions to the field have led to lasting improvement in the care of two generations of patients with sickle cell disease.

As a pediatrician at Children’s Hospital Boston, Dr. Orringer trained many of the greatest names in pediatric hematology/oncology and mentored many pediatric hematology/oncology trainees to return to each other (and me) stories about “the old days.”

Yes, I was ordered into hematology. I don’t like orders very much, but that one was the best command I’ve ever received. I’ve been the recipient of some wonderfully exciting awards like the ASH Wallace H. Coulter Award (Read more about Dr. Nathan receiving the Wallace H. Coulter Award for Lifetime Achievement in 2011, www.hematology.org/ Awards/Honorable/6492.aspx) and an honorary degree from Harvard. But the greatest honor has been the privilege of working with those bright young people and seeing their careers flourish. That has truly been the greatest academic joy of all.

But my most profound happiness has come from my family. All these years, my wife Jean has stood by me and tolerated my love of academic hematology. In addition to our three children (one a musician, another an educator, and the third an attorney), we have been blessed with two marvelous sons-in-law and six exciting grandchildren. One of the grandchildren is a superb pediatric nurse at Children’s, another is going to medical school, and the four others include two musicians, a budding cellist, and a budding engineer. We are grateful that he is still available to guide the next generation. We must, and will, repay his efforts by continuing the work he started.

As a clinician-scientist, Dr. Orringer remains a profound, positive force in the careers of basic and clinical researchers who trained with him at Chapel Hill. Those of us who have been fortunate enough to work with Gene know and appreciate the depth of his investment in us, in hematology, and in his patients. We are grateful that he is still available to guide the next generation. We must, and will, repay his efforts by continuing the work he started.

--Julia E. Brittain, PhD, Associate Professor, Vascular Biology Center, NCIBM Southeastern Exploratory Sickle Cell Center of Excellence, Georgia Regents University/ Medical College of Georgia
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January

31- Feb. 1 Highlights of ASH
Miami, FL www.hematology.org/meetings

Highlights of ASH
Seattle, WA www.hematology.org/meetings

February

4 Applications available for the ASH-Harold Amos Medical Faculty Development Program (AMFDP) Award
Washington, DC www.hematology.org/awards

14 Applications available for the Translational Research Training in Hematology program
Washington, DC www.hematology.org/awards

21 Application deadline for ASH HONORS (Hematology Opportunities for the Next Generation of Research Scientists) Award
Washington, DC www.hematology.org/awards

March

3 Abstract submission site opens for ASH Meeting on Lymphoma Biology
Washington, DC www.hematology.org/meetings

10 Application deadline for the ASH Minority Medical Student Award Program (MMSAP)*
Washington, DC www.hematology.org/awards

14 Application deadline for the ASH-Harold Amos Medical Faculty Development Program (AMFDP) Award
Washington, DC www.hematology.org/awards

28 Application deadline for ASH Clinical Research Training Institute**
Washington, DC www.hematology.org/awards

29-30 Highlights of ASH in Asia
Singapore www.hematology.org/meetings

April

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

4 Deadline to submit nomination package for ASH Mentor Award
Washington, DC www.hematology.org/awards

10-12 Thrombosis & Hemostasis Summit of North America
Chicago, IL www.thsna.org

11 Deadline to claim CME credits and print a CME certificate for the 55th ASH Annual Meeting
Washington, DC www.hematology.org/meetings

25-26 Highlights of ASH in Latin America
Florianópolis, Brazil www.hematology.org/meetings

29 Abstract deadline for ASH Meeting on Lymphoma Biology
Washington, DC www.hematology.org/meetings

*In order to submit an application for the MMSAP, you must have requested a mentor by January 6, 2014.

**In order to submit an application for the Clinical Research Training Institute, you must have submitted an eligibility review by January 8, 2014.

For additional meeting dates and award deadlines, go to www.hematology.org/Calendar.