For us hematologists, the first full weekend in December is typically blacked out on our calendars. During this sacred time, ASH hosts its annual meeting for anyone interested in the basic science, clinical research, education, or industry of hematology. This year’s meeting in San Francisco filled every Starbucks in a two-mile radius with a record attendance of greater than 26,000 participants from around the world. To accommodate the masses and the numerous sessions, ASH made use of five buildings and partnered with more than 65 hotels. The annual meeting always reinvigorates the blood lust for hematology, and the 2014 edition, which showcased 5,600 abstracts, did not disappoint. Indeed, the meeting focused on all things genetic, genomic, and epigenetic. If we weren’t talking about which gene mutations cause blood diseases, we were focusing on exciting new therapies that fix them. The following are some highlights from the meeting.

Setting the rhythm on the first day, the education session “Insights from Pediatric Malignancies” (also known by its reference in ASH News Daily “Do These Genes Make My Cancer Look Bad”) presented new developments in genome-wide profiling of acute lymphoblastic leukemia. From Friday’s Scientific Workshop on Hematology and Aging, to learning about the clinical impact of genetic abnormalities in the acute myeloid leukemia education session chaired by Dr. Gail Roboz, 2014 proved that “one size fits none” is true for jeans, genes, and chemotherapy. Similarly, the education session “Genetics of Chronic Lymphocytic Leukemia and Lymphoplasmocytic Leukemia” echoed the importance of a comprehensive genetic evaluation at diagnosis, as well as the promise of new targeted therapies such as ibrutinib and idelalisib. These medications were further highlighted at the inaugural Special Education Session “Newly Approved Drugs.” This symposium included didactic presentations and a question-and-answer forum that provided audience members with an opportunity to ask the hematologist,elderly patients with AML – Dr. Bruno Medeiros answers with his approach.

Looking Backward, Moving Forward
JASON GOTLIB, MD, MS, Editor-in-Chief
A recurrent refrain I hear about The Hematologist from ASH members is how much they enjoy receiving it in the mail and reading it from cover to cover in their office or before they retire to bed. I know this to be true because I have done the same since my instructor days in 2004, the inaugural year of the publication.

The Hematologist weaves together different missions of the Society. Core departments such as Diffusion, Ask the Hematologist, Mini Reviews, and the Clinical Trials Corner educate about basic and clinical research advances; Headlines from Washington communicates advocacy efforts; News and Reports provides Society updates on topics from career development programs to new funding initiatives; and additional perspectives, in the form of Features, Profiles, and OpEds, speak to the interests of international members as well as community- and academic center–based practitioners. This mosaic of features and departments reflects the cumulative stewardship of four successive editors-in-chief (Dr. Andrew Schaler, Dr. Peter Emanuel, Dr. Roy Silverstein, and Dr. Charles Parker) as well as the dedication of ASH’s communications staff. As I begin my editor-in-chief role, this is...
Channeling Our Strengths in the New Year

As I assume the Presidency of ASH, I would like to acknowledge the outstanding leadership that Linda Burns has provided over the past year. Indeed, Linda has contributed in the same outstanding fashion in various leadership roles within ASH for more than a decade. Her contributions in numerous spheres have been both substantive and critical for the progress of the Society in many important areas.

I recently returned from our annual meeting in San Francisco, which set a new record for attendance. The meeting continues to be an outstanding mixture of basic, translational, and clinical talks. I was very impressed with the progress made in harnessing the immune system to eliminate tumor cells, the development of new targeted compounds in myeloma and leukemia, and new treatments for hemophilia. I attended my first ASH annual meeting in 1976 in Boston during the nation’s bicentennial year. I had just completed my first year of medical school at Indiana University and delivered an oral paper on alveolar macrophages to a packed room. I was both extremely nervous and immensely impressed with the science in that meeting. The experience cemented my choice of training both in hematology and in scientific investigation, which became a major component of my career. Science, education, and networking remain the key elements of the success of our meeting, which continues to be the premier hematology meeting in the world.

In the upcoming year, ASH will focus on several priorities including advocacy for increased National Institutes of Health (NIH) funding and reimbursement policies that will allow us to serve our patients in the best possible manner. In addition, as a long-time fellowship director, I feel strongly that ASH needs to focus additional efforts on facilitating the careers of young trainees. There are noteworthy recent examples of these ongoing efforts, including the decision by the ASH Executive Committee to expand funding for the ASH Scholar Awards Program that supports hematology trainees and junior faculty in the critical years between training and their first independent NIH grant. Additionally, the new ASH Junior Faculty Symposium was held for the first time at the meeting in San Francisco.

Our strengths as a society include our superb professional staff and the commitment of the outstanding volunteers. One recent example in which these strengths shine is the launch of the new ASH Meeting on Hematologic Malignancies. The inaugural meeting will be held in Chicago from September 17 to 19, 2015 and will feature premier educators from the Society. The meeting is designed for participants to discuss with top experts in the field the latest in clinical care and the most challenging patient care questions.

I am extremely proud and honored to serve as president of this outstanding society, which serves a broad representation of both practice and academic communities and both domestic and international members.

David A. Williams, MD

Looking Backward, Moving Forward

(Cont. from page 1)

a good opportunity to thank Roy and Charles for their guidance during my five years as a contributing editor. In particular, Charles’ mentorship during the last few months made my transition seamless. The contributing editors, as well as the ASH staff who support this publication, merit special recognition for their steadfast commitment. Together, these individuals bear witness to the axiom that producing each issue of The Hematologist is a “team sport.”

We have recast this January/February issue as a “Year’s Best” review of 2014’s most compelling breakthroughs in hematology. The selections were generated and ranked by our board of contributing editors. In turn, we emailed a survey to ASH members so they could also cast their choices for the most influential discoveries. In this issue, we provide the results of the reader survey as well as reviews reflecting the Contributing Editors’ choices, led by the number-one-ranked “Targeted Therapy in Lymphoproliferative Disorders,” followed by several noteworthy honorable mentions. Such end-of-the-year lists often fuel controversy; in the least, we hope that ours sparks conversation. Notwithstanding the number of pages available to us, we are unable to acknowledge every game-changing breakthrough. However, we hope that our synopsis will capture the essential flavors of hematology in 2014 much like a tasting menu at a ballet as the people who produced it. This kind of symbiosis holds equally true as in which these strengths shine is the launch of the new wards Program that supports hematology trainees and junior faculty in the critical years between training and their first independent

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In the coming months, I look forward to working with ASH President Dr. David Williams and with Dr. Mikael Selenker, editor-in-chief of our sister publication, ASH Clinical News, to deliver topical and complementary content. Additionally, having the publication tap into the speed and multiplicative effects of social media is a powerful means by which The Hematologist can maintain its responsiveness to the voices of ASH members. Furthermore, we plan to diversify the way The Hematologist communicates content by adding podcast and video features, while the print publication. ASH’s website, and a future app for the publication will serve as the primary delivery channels.

Author Fran Lebowitz commented that one of the major reasons that the New York City Ballet reached spectacular heights during the era of George Balanchine and Jerome Robbins was because the audience pushed it toward perfection. The audience had immensely high standards and knew as much about ballet as the people who produced it. This kind of symbiosis holds equally true for The Hematologist.

LETTER TO THE EDITOR

In the September/October issue of The Hematologist, Dr. Alison Bertuch and Dr. Peter Kurre highlighted some unique issues related to acquired aplastic anemia (AA) in children. This was based on a comprehensive survey performed by the North American Pediatric AA consortium. This group should be commended for performing such an important study which can pave the way for advancing the outcome of children with AA. Interestingly, one must acknowledge that issues raised in children are actually very similar to those facing the adult population, where diagnosis of bone marrow failure syndromes, infection prophylaxis, the use of growth factors, duration and management of immunosuppressive and posttransplantation therapy, and use of stem cell transplantation are still a matter of debate. While we agree with the authors that matched-unrelated donor transplantation is increasingly used with favorable outcomes, it is important to mention that the use of T-cell replete haplotransplantation is increasingly being considered, especially with the use of cyclophosphamide postgraft infusion. The benefit of cyclophosphamide for tolerance induction after haplotransplantation and its potential direct efficacy in AA makes this option very attractive. Finally, with the advent of chimeraprog, it is likely that the treatment paradigm of AA will significantly evolve in the next few years, both in the transplant and nontransplant settings.

-Mohamad Mothy, MD, PhD, Hôpital Saint-Antoine, University Pierre & Marie Curie, Paris, France

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Welcome and Adieu to The Hematologist Board of Contributing Editors

At the ASH annual meeting, the yearly convening of The Hematologist Editorial Board marks a time of transition. This past December in San Francisco, we said goodbye to three contributing editors: Drs. Peter Kurre, Pete Lollar, and Greg Vercellotti, the latter two of whom served consecutive three-year terms. During his term, Oregon Health and Science University’s Peter Kurre elegantly communicated pediatric research developments involving the intersection of inherited and acquired bone marrow failure syndromes, gene therapy, and hematopoietic stem cell transplantation (HSCT). Pete Lollar’s career in pediatric hematology at Emory University has focused on hemophilia and Factor VIII/inhibitory antibodies. Pete crafted insightful Diffusion articles for The Hematologist that doubled as concise master classes in hemostasis and thrombosis. And although Greg’s research interests at the University of Minnesota encompasses vascular biology, inflammation, and sickle cell disease, he tackled many diverse topics as contributing editor, often taking readers on a historical journey to contextualize current breakthroughs. The passion and energetic writing of these editors will be missed.

To fill the vacancies left by the departure of Drs. Kurre, Lollar, and Vercellotti (and my transition to Editor-in-Chief), the Executive Committee unanimously approved the appointment of four Contributing Editors: Drs. Tracy George, Jonathan Hoggatt, Elizabeth Raetz, and Noopur Raje.

Dr. George is associate professor of pathology at the University of New Mexico School of Medicine. In addition, she serves as division chief of hematopathology and director of the Hematopathology Fellowship Program. Her research interests are myeloproliferative neoplasms, with a focus on mastocytosis, reactive lymphadenopathies, and laboratory hematology. She has served in several education and leadership roles with the College of American Pathologists, and is a member of ASH’s Image Bank task force.

Dr. Hoggatt is assistant professor of medicine at the Cancer Center and Center for Transplantation Sciences at Massachusetts General Hospital and Harvard Medical School. His research investigates the regulation of hematopoietic stem and progenitor cells, and he is interested in developing methods that facilitate engraftment and mobilization for HSCT. He serves on ASH’s Committee of Government Affairs and is a liaison to the Communications Committee.

Dr. Raetz is professor in the Division of Pediatric Hematology-Oncology at the University of Utah/Huntsman Cancer Institute. She is director of their High-Risk Leukemia and Lymphoma Program. Her research mission is centered on clinical trials in acute lymphocytic leukemia. She holds several leadership positions within the Children’s Oncology Group.

Dr. Raje is associate professor of medicine at Harvard Medical School and director of the Multiple Myeloma Center at Massachusetts General Hospital. She spearheads a translational research program evaluating novel therapeutics in myeloma with a special interest in the biology of myeloma bone disease. Dr. Raje is a member of the International Myeloma Working Group and NCCN Clinical Practice Guidelines Committee for Multiple Myeloma.

We are excited to bring new perspectives on hematopathology, hematopoiesis, pediatric hematology/oncology, and plasma cell dyscrasias with the respective additions of Tracy, Jonathan, Elizabeth, and Noopur. Over the years, our editors have infused the pages of The Hematologist with creative and crisp narratives of the latest clinical and scientific advances that have transformed our profession and our patients’ lives. However, we are always looking to engage topics that are increasingly relevant to the dynamic membership of ASH. Please reach out to us – we welcome your feedback and ideas.

– Jason Gotlib, MD, MS, Editor-in-Chief

ASH Foundation Run/Walk

The ASH Foundation and Development Committee is delighted to share an update on the second annual ASH Foundation 3K – 5K Run/Walk. The success of the 2013 event allowed the foundation to establish a very ambitious second-year goal: to register 600 participants and raise $80,000.

Thanks to the overwhelming support from corporate sponsors and the enthusiastic participation of meeting attendees, there were 940 registered participants, and the foundation raised more than $95,000 to help with the goal of doing more for hematology research, education, and quality care.

Top Fundraisers
• Janssen Oncology Joggers
• AbbVie
• Team Novartis

Top Individual Fundraisers
• Kevin Imrie – Sunnybrook Health Science Center
• James Bradner – Dana-Farber Cancer Institute
• Hetty Caraway – Cleveland Clinic
• Carrie Dandy – ARIAD Pharmaceuticals
• Mary Eapen – Medical College of Wisconsin

Large Teams
• Janssen Oncology Joggers
• ARIAD Pharmaceuticals
• Team Novartis

Large Institution Teams
• National Institutes of Health/National Heart, Lung, and Blood Institute
• ASH Trainee Council
• H. Lee Moffitt Cancer Center

Participants enjoyed running and walking with their friends and colleagues on a beautiful Sunday morning along the Embarcadero, and team fundraising was the story of the day. There were 11 teams, and a third of all registrants belonged to a team. Participants were cheered on by volunteers that included the ASH President, the Chair of the ASH Foundation and Development Committee, and current and past participants from ASH award programs.

The Committee would like to thank all who took part in this event and helped to make it a success. Visit www.hematology.org/RunWalk to view the Run/Walk video, final results, and photos.

The ASH Foundation thanks 2014 3K – 5K Run/Walk Sponsors AbbVie, Incyte, Millennium: The Takeda Oncology Company, and Seattle Genetics. To learn more and to donate to the ASH Foundation, visit www.hematology.org/foundation.
investigators developed a simplified early death score and non-aml covariates that predict early outcomes, a criterion of "functionally older" aml patients ineligible for ag- aging. Comorbidity, nutritional status, and geriatric syndromes. for age based on functional status, comorbidities, polypharmacy, and performance status at diagnosis, age, platelet count, albumin, sAML, white blood cell count, percentage of peripheral blood blasts, and serum creatinine (cstagging.fhcrc-research.org/TDM/Default.aspx). Interestingly, removal of age as covariate had minimal impact on the predictive power of this model. Similarly, investigators from the Study Al- liance Leukemia demonstrated that the risk of induction mortality and the chance of complete remission could be predicted in older patients with AML using a combination of pre-treatment covariates, including age, hemoglobin, platelet count, fibrinogen, type of AML, karyotype and limited molecular abnormalities at diagnosis (eAMLscore. org). These data suggest that age alone is a poor predictor of treatment intent and outcomes, and is likely a surrogate for other covariates associated with inferior prognosis.

The Future is Now: The Rise of Targeted Therapies

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness." This opening sentence from A Tale of Two Cities describes the sentiment of hematologists regarding the current state of manage- ment of AML in older patients. While our understanding of the molecular alterations responsible for leukemogenic transformation has flourished in recent years, none of these discoveries has yet translated into approved treat- ment strategies for patients beyond "7+3" conventional induction chemotherapy. However, characterization of the mutational landscape of AML has accelerated development of targeted therapeutics that may soon be within the reach of patients. Activating mutations in signaling pathways, including FLT3, KIT, RAS, and others, have been described in roughly 60 percent of AML patients. Clinical trials test- ing the activity of FLT3, KIT and MEK inhibitors (as single agents or in combinations) are available in most academic centers and may reshape treatment strategies for these patients. Mutations in the JAK/STAT and TET2 genes have been linked to increased sensitivity to hypomethylating agents. Examples of novel agents in clinical develop- ment include small molecule inhibitors of mutant IDH1 and IDH2, DFT1-L inhibitors for patients with MLL rearranged acute leukemia, novel epigenetic modulators such as the bromodomain (BRD4) inhibitors, and development of second-generation anti-CDD3 conjugated monoclonal antibodies. Also, addition of multikinase (sorafenib) or aurora kinase inhibitors to conventional induction chemother- apy is associated with promising antileukemic activity and improved survival. Finally, improved patient selection (genomic profile, AML-MRD, or adverse-risk karyotype) or combination with novel agents (pracinostat or pevonedistat) may optimize the clinical benefit of DNA methyl- transferase inhibitors such as azacitidine.

Definition of “Elderly” in Patients with AML

Older patients can be classified into three categories of chronological age: 1) young-old patients are 65 to 75 years of age; 2) old patients are 76 to 85 years of age; and 3) oldest-old patients are older than 85 years. In AML, clinical outcomes worsen with advancing age. Recognizing this relationship between older age and outcomes, contemporary AML treatment protocols have typically used an arbitrary cutoff of 55 to 65 years to distinguish between younger and older subjects. However, chronological age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. Comprehensive geriatric assessments (CGA) are multi- disciplinary, in-depth evaluations designed to assess life expectancy and attendant morbidity and mortality risks in older patients. CGAs include tools to predict the functional age based on functional status, comorbidities, polypharmacy, nutritional status, and geriatric syndromes. For this reason, pre-treatment CGAs or more focused geriatric assessment tools may replace chronologic age as an iden- tifier of “functionally older” AML patients ineligible for ag- gressive treatment approaches.

AML and Non–AML-Related Factors Influencing Treatment Decisions

Recent studies suggest that age may be a suboptimal sole criterion for allocation to intensive AML treatment proto- cols, and that additional variable may improve the ability to predict toxicity and outcomes. Population-based data demonstrate that older age was only one of the several covariates (including history of antecedent hematologic disorder [sAML], higher comorbidity score, poor perfor- mance indicators, marital status, and lower household incomes) associated with lack of antileukemia therapy in newly diagnosed older patients with AML. A retrospective analysis showed that a pre-treatment geriatric assessment, focused on cognitive and physical function, improved the prediction of survival among older adults with AML treated with conventional induction chemotherapy. Two large retrospective studies have identified several AML and non-AML covariates that predict early outcomes, such as induction mortality and likelihood of complete remission, following intensive chemotherapy. In the first, investigators developed a simplified early death score with moderate discriminatory power that incorporates per- formance status at diagnosis, age, platelet count, albumin, sAML, white blood cell count, percentage of peripheral blood blasts, and serum creatinine (cstagging.fhcrc-research.org/TDM/Default.aspx) 1. These data suggest that age alone is a poor predictor of treatment intent and outcomes, and is likely a surrogate for other covariates associated with inferior prognosis.

The Question

What is your approach to the treatment of elderly patients with acute myeloid leukemia?

My Response

Acute myeloid leukemia (AML) is not a significant public health hazard, accounting for less than 2 percent of all cancers diagnosed yearly in the United States. The American Cancer Society estimates that 18,860 new cases of AML were diagnosed in 2014. Nonetheless, AML is second only to chronic lymphocytic leukemia as the most common subtype of leukemia in adults. The median age at diagnosis is 67 years, and more than 60 percent of newly diagnosed patients are older than 60 years. The management of elderly patients with AML poses unique therapeutic challenges. These individuals disproportionally account for greater than 75 percent of AML deaths yearly. In addition, recent data from the Surveillance, Epidemiology, and End Results (SEER) Program demonstrate that 50 to 60 percent of newly diagnosed AML patients older than 65 years do not receive any form of antileukemia therapy.

ASH does not recommend or endorse any specific tests, physicians, products, procedures, or opinions, and disclaims any representation, warranty, or guaranty as to the same. Reliance on any information provided in this article is solely at your own risk.
Donald Metcalf, MD (1929-2014)

Donald Metcalf was born in Mittagong, a small country town in the southern highlands of New South Wales, Australia. The son of schoolteachers, he grew up in New South Wales during the time of the Great Depression and World War II. Always inquisitive, Dr. Metcalf (Don to those who knew him) became a conscientious student and obtained a scholarship to study medicine at the University of Sydney. While completing his degree, Dr. Metcalf undertook his first scientific studies into the ectromelia virus, an experience he would regard as incredibly formative. He graduated in 1953 with a Bachelor of Medicine and Surgery and began his medical residency, where he met his future wife, Jocypa, forming a partnership that would last a lifetime.

Dr. Metcalf’s interest in blood cell and leukemia development took precedence over his medical career when he was awarded the Garden Fellowship to work at the Walter and Eliza Hall Institute of Medical Research in Melbourne. Under the directorship of the eminent virologist Sir Macfarlane Burnet, Dr. Metcalf spent two years working on the vaccinia virus. Ever the renegade and true to the terms of his fellowship, Dr. Metcalf conducted experiments that branched out to investigating thymus biology and the role of this organ in leukemia development. To further his skills in cancer research, Dr. Metcalf undertook a post-doctoral fellowship at Harvard University with the Hungarian-born Dr. Jacob Furth, whose ideas on cancer development as an imbalance of cell regulators would significantly influence Dr. Metcalf’s thinking.

Dr. Metcalf returned to the Walter and Eliza Hall Institute keen to identify regulators controlling blood cell formation. In 1965, Dr. Ray Bradley, a scientific collaborator of Dr. Metcalf’s at the University of Melbourne, showed Dr. Metcalf small cellular colonies, which had serendipitously been grown from mouse bone marrow in semi-solid agar. They realized that the growth of these colonies, each derived from a single cell, required the addition of something to the medium in culture. These were proposed as soluble “factors” that supported the survival and growth of clonogenic myeloid bone marrow and spleen blood cell colonies in tissue culture. Dr. Metcalf and Dr. Bradley termed these “colony-stimulating factors” (CSFs).

This semi-solid agar system would allow not only the growth of blood cells in vitro, but also provide a method of detecting and quantifying the concentrations of the proposed but yet undiscovered CSFs. Much would hinge on this astute observation, which was also made contemporaneously by a group in Israel. Optimizing this clonogenic culture system laid the groundwork for the purification and genetic cloning of the CSFs. In addition, this culture system provided Dr. Metcalf with the method he would use to explore the hierarchy of blood cell development in great detail throughout his career, beginning with what he regarded as the apex of progenitor cell development – the multipotential blast colony–forming cell. Together with Dr. James Till and Dr. Ernest McCulloch, Dr. Metcalf was a pioneer in the understanding of the hematopoietic hierarchy.

Ultimately, it was amino acid sequencing and the development of molecular biology techniques that allowed the cloning of the murine and human genes for CSFs. It speaks to Dr. Metcalf’s fastidiousness that he was only convinced that a pure CSF had been discovered when the gene encoding it has been identified. Dr. Metcalf’s leadership ushered in the era of molecular hematology, which ultimately made possible the efficiencies of scale required for CSF production for research and clinical applications. The Parkville group obtained extensive amino acid sequence for murine CSFs, and, in addition, this culture system provided Dr. Metcalf with the method he would use to explore the hierarchy of blood cell development in great detail throughout his career, beginning with what he regarded as the apex of progenitor cell development – the multipotential blast colony–forming cell. Together with Dr. James Till and Dr. Ernest McCulloch, Dr. Metcalf was a pioneer in the understanding of the hematopoietic hierarchy.

At the center of this maelstrom of activity and honors stood Dr. Metcalf. He was a brutally honest but giving collaborator, with a profound work ethic and exacting scientific observations to the point of obsession, he remained at the laboratory bench and beside his beloved microscope for his entire career.

We will miss him dearly.

—Douglas Hilton, PhD, Director of The Walter and Eliza Hall Institute of Medical Research
—Warren Alexander, PhD, Head of the Division of Cancer and Haematology, The Walter and Eliza Hall Institute of Medical Research
—Nicos Nicola, PhD, Head of the Division of Cancer and Haematology, The Walter and Eliza Hall Institute of Medical Research
—Ashley Ng, PhD, Postdoctoral Scientist, Division of Cancer and Haematology, The Walter and Eliza Hall Institute of Medical Research

Donald Metcalf was an extended family to him. Known for his formidable work ethic and exacting scientific observations to the point of obsession, he remained at the laboratory bench and beside his beloved microscope for his entire career.

We will miss him dearly.
Mature blood cells have a limited life span, necessitating the need for constant tissue regeneration. The standard model to explain the ability to maintain lifelong production of blood is based on the “hematopoietic tree,” in which a few numbers of hematopoietic stem cells (HSCs) go through a series of progressively lineage-restricted divisions to produce mature blood cells. For more than 50 years, HSCs and their progeny have been studied to explore this remarkable ability to regenerate a highly dynamic tissue system without exhaustion and only relatively rare cases of neoplasia.

The ability to experimentally evaluate HSCs is based largely on animal models of bone marrow transplantation. As part of their educational materials, the National Institutes of Health (NIH) defines an HSC as “a cell isolated from the bone or bone marrow that can renew itself, can differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo proliferation and differentiation.” To begin to define the regulation of native hematopoiesis, to the clonal output from an individual HSC (or progenitor cell) was recently monitored in humans without the need for transplantation. The authors tracked the output of individual clones due to a rare mutation of the phosphatidylinositol 3-kinase gamma subunit (PIK3CG), which is a hallmark of PIK3CG-deficient diffuse large B-cell lymphoma. They found that the vast majority of blood output from an individual HSC, particularly those contributing to granulocytes, was lineage restricted. These data, like that of the Camargo study in mice, suggest that human blood production at steady-state may come predominately from lineage-restricted progenitors rather than the classical multilineage, transplantable HSC.

Expanding the Sleeping Beauty model to settings of hematopoiesis, the authors found that the vast majority of blood output from an individual clone, particularly those contributing to granulocytes, was lineage restricted. These data, like that of the Camargo study in mice, suggest that human blood production at steady-state may come predominately from lineage-restricted progenitors rather than the classical multilineage, transplantable HSC.

To begin to define the regulation of native hematopoiesis, a new work published by the Camargo laboratory describes clonal dynamics of hematopoiesis in mice using a novel cellular barcoding system. Mice were engineered with Sleeping Beauty Transposase, which is an enzyme that mediates the insertion of a DNA element into a genome. The transposon results in a readable DNA sequence being randomly inserted into a unique position within each individual cell, and their subsequent progeny will have the same insertional site. This stable genetic tag allowed the researchers to then track blood production from individual clones, without the need for transplantation like prior lentiviral barcoding experiments.

While tracking the mice approximately every six weeks for a period of more than 40 weeks after in situ genetic tagging, researchers found that the vast majority of granulocytes were produced by myeloid clones that were only present at a single time point. This suggests that native granulopoiesis is supported by a large number of successive clones that “awaken” at different time points throughout the lifetime span of the organism, supporting the “clonal succession” model of hematopoiesis. When determining the potential of lymphoid clones, about half of the clones 10 months after genetic tagging were also present in myeloid cells, demonstrating that a myeloid clone of blood can be a pool of multipotent stem or progenitor cells. Remarkably, when evaluating genetic tags in granulocytes, very few of the genetic tags found in granulocytes were also found in lymphoid cells. These data suggest that the bulk of clones producing granulocytes are myeloid-lineage-restricted and call into question the role of multipotent HSCs in the production of blood in the absence of transplantation.

Since prior work has relied on transplantation to evaluate HSCs, the authors used their mouse model in a transplanta-
A Snapshot of the 114th U.S. Congress

In last year’s midterm elections, the Republican Party won control of the Senate and added members to its majority in the House. Republicans now control both houses of Congress for the first time since the 109th Congress during President George W. Bush’s presidency. With Senator Mary Landrieu’s (D-LA) loss to Representative Bill Cassidy (R-LA) in a December 6 runoff election, Republicans now hold a 54-46 majority in the Senate. Republicans also retained control of, and added 12 seats to, their majority in the House of Representatives (Republicans now have a 244-188 majority in the House). Republican leadership has stated it will continue to focus on cutting discretionary funding and advancing a conservative agenda, including continuing to attempt to repeal the Affordable Care Act (ACA). However, Republicans may face hurdles in keeping control of the Senate in two years. In 2016, 24 Republican-held seats will be up for re-election while only 10 Democrat-held seats will be at stake.

Both House Democrats and House Republicans voted to restate their leaders in the 114th Congress. Representative John Boehner (R-OH) will remain Speaker of the House, and Representative Kevin McCarthy (R-CA) will remain Majority Leader. Representative Nancy Pelosi (D-CA) will remain Minority Leader. Minority Whip Steny Hoyer (D-MD) was also re-elected by his party. Senator Mitch McConnell (R-KY) will serve as Senate Majority Leader opposite Minority Leader Harry Reid (D-NV).

A new Congress also brings new committee chairs and ranking members. Representative Harold Rogers (R-KY) and Representative Nita M. Lowey (D-NY) will remain Chairman and Ranking Member of the House Appropriations Committee. Representative Tom Cole (R-OK) will chair the Labor, Health and Human Services, and Education Subcommittee, which determines funding for many health programs including the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC). Senator Barbara Mikulski (D-MD) will remain the top Democrat on the Senate Appropriations Committee, and Senator Thad Cochran (R-MS) is expected to become chair of the committee.

Representative Paul Ryan (R-WI) will replace Representative Dave Camp (R-MI) as the House Ways and Means Committee Chairman. Representative Sander Levin (D-MI) will remain the committee’s ranking member. This powerful committee has jurisdiction over Medicare (including physician reimbursement), the ACA, and tax policy. The Senate Finance Committee – the Senate counterpart to Ways and Means – will see its leadership flip. Current Ranking Member Senator Orrin Hatch (R-UT) will become chairman, and current Chairman Senator Ron Wyden (D-OR) will serve as ranking member.

Also of interest, the 114th Congress will see a reduction in physician members. In all, there will be 14 physicians in the House of Representatives and three in the Senate (down from 20 physicians who served in the 113th Congress).

Sustainable Growth Rate – Where Do We Go from Here?

As the 113th Congress wound down, it became clear that this group of legislators would not be remembered as the one that permanently addressed the issues associated with Medicare physician payment. Since 1998, annual updates to Medicare physician payment have been governed by a formula known as the Sustainable Growth Rate (SGR), a complicated formula tied in part to the growth in the economy. In 2002, for the first time, this formula governed a payment cut of 4.8 percent for physicians. Since that time, a payment cut has been triggered each year, but these cuts have never occurred due to direct Congressional action. Instead, Congress has chosen to go back and forth, choosing a short-term fix to a period of days. Even the landmark ACA, which touched every facet of health care in the United States, did not include permanent SGR relief.

The SGR in the 113th Congress

The 113th Congress started with unprecedented action toward permanently addressing what was broadly agreed to be a significant problem. Early in 2013, the two committees with jurisdiction in the House – Ways and Means, and Energy and Commerce – announced a plan to work together on a draft to address the issue. This plan actually came to pass, with a draft framework released for comment and a full committee mark-up section in which members could address issues with individual elements. The chances of repeal seemed better than ever, especially with news that the cost of addressing the SGR, which had always been the biggest barrier to repeal, had been reduced substantially due to updated projections on the growth in spending in the physician fee schedule.

The reduced cost and the cooperation of the committees took the bill further than any previous effort but not far enough. In the end, the partisan divide over how to pay for a permanent fix made it impossible to pass a bill through Congress.

The SGR in the 114th Congress

While Republicans will control both the House and Senate in the 114th Congress, a Democratic president remains, and the Senate rules allow for significant influence by the minority party. In addition to the changes in party control, the leadership of the committees of jurisdiction has changed in almost all circumstances. With this change, some of the technical policy will need to be addressed again. And some of the elements of the bill that were agreed to in 2013 have been adopted by other legislation or are no longer as relevant.

With all of these factors in place, it appears that Congress will have to start over to some degree to address this issue. With a March 31, 2015, deadline approaching, Congress will have little time to create all new policy and may have to again turn to a short-term patch. Although it appears that many changes may need to take place to the bills, the underlying framework may not change as much.

What ASH will be doing in 2015

ASH commented extensively on the elements contained in the bill agreed to by the committees of jurisdiction in the 113th Congress. The Society will continue to work with those who are crafting a new version of a bill to ensure that hematologists are in the best position to treat Medicare patients with blood diseases. Addressing the SGR remains a top legislative priority, but it is important to ensure that the solutions do not undermine other priorities as well.

Take Action in Support of Hematology

This year, and throughout the 114th Congress, ASH will continue its advocacy efforts on several important research and practice-related issues, such as:

• Seeking increased federal funding for research
• Responding to changes in physician reimbursement
• Ensuring access to safe and effective hematologic drugs
• Supporting legislative initiatives concerning sickle cell treatment and research

The Society needs the help of all ASH members to bring issues important to the future of hematology to the attention of the U.S. Congress and other U.S. governmental agencies. Members of the ASH Grassroots Network receive action alerts and information about issues in which they indicate interest. At times, Grassroots Network members are also invited to represent hematology in activities such as visits to Capitol Hill, with NIH leadership, and with other regulatory agencies. Visit the ASH Advocacy Center at www.hematology.org/takeaction to take action on the Society’s advocacy campaigns and to join the ASH Grassroots Network.
### Targeted Therapy in Lymphoproliferative Disorders (excluding CAR T cells)

**ANN LACASSE, MD, MSC,** 1 **PETER JOHNSON,** 2 AND **JASON GOTLIB, MD, MS**

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**Chronic Lymphocytic Leukemia and Lymphomas**

More than 70,000 new cases of non-Hodgkin lymphomas were diagnosed in the United States during the past year. Despite the introduction of rituximab nearly two decades ago, the majority of patients with lymphoma and chronic lymphocytic leukemia (CLL) who require treatment receive cytotoxic chemother-apy. Recent advances in the understanding of the pathobiology of B-cell lymphoproliferative disorders have led to the identification of multiple therapeutic targets and the development of rational novel agents.

In CLL and mantle cell lymphoma (MCL), Bruton’s tyrosine kinase (BTK), a critical enzyme in the B-cell receptor signaling axis (Fig-ure), mediates the proliferation and survival of malignant lymphocytes through multiple downstream signaling pathways. Ibrutinib, an oral, covalent inhibitor of BTK, received accelerated approval in MCL in late 2013 and in CLL in early 2014. In the pivotal phase II study in relapsed or refractory CLL, the overall response rate (ORR) was 71 percent with a two-year progression-free sur-vival (PFS) of 75 percent. ¹ A subsequent randomized study compar-ing brontinib to flutamide confirmed the drug’s activity with significant improvements in both median PFS and one-year overall all survival.² The activity of brontinib was independent of adverse prognostic indicators, including 17p deletion. In mantle cell lymphoma, brontinib yielded an ORR of 68 percent, and activity was similar regardless of prior bortezomib exposure.³ The median PFS was 13.9 months, and duration of response was 17.5 months. Additionally, recent preliminary data in both CLL and MCL demon-strated improved activity with the addition of rituximab to brontini-b.⁴ In terms of toxicity, common adverse events included mild gastrointestinal toxicity and cytopenias. A risk of bleeding, par-ticularly in patients on anticoagulation, and atrial fibrillation, which appears to be related to on-target inhibition of BTK and related kinases in the myocardium, have been reported.⁵-⁶

Idelalisib, an oral inhibitor of the delta isoform of PI3 kinase, another critical enzyme in the BCR signaling pathway in B-cell lymphomas (Figure), received full approval for use in combination with rituximab in patients considered appropriate for treatment with single-agent rituximab, as well as accelerated approval in relapsed follicular and small lymphocytic lymphomas (SLL). Based on a 72 percent ORR in the phase I study in CLL, a phase III study was conducted comparing rituximab plus delalasib or placebo in patients with decreased renal function or other major comorbidities.⁷ The ORRs were 81 percent and 13 percent, with 12-month OSs of 92 percent and 80 percent, respectively. In patients with indolent B-cell lymphomas, the majority of whom had follicular lymphoma (FL) or SLL, the single-agent activity in disease refractory to both rituximab and alkylating agents was 57 percent, with 6 percent complete remissions (CRs). The median PFS and duration of remission were 11 and 12.5 months, respectively.⁸ Therapy was well tolerated, with the most common serious adverse events being neutropenia, transaminis, diarrhea, and pneumonia.⁹-¹⁰

Moving forward, combining these agents with monoclonal anti-bodies, as well as immunotherapy, will advance the goal of increasing the duration of remissions and OS. In addition, un-derstanding mechanisms of resistance, including the substitution of serve to cytotoxic at rate ≤4.1% of the BTK active site, will lead to improved inhibitors.¹¹

In parallel to the arrival in the clinic of new targeted agents, more data have emerged on underlying driver events in lympho-magenesis, particularly from genome-wide sequencing studies of sequential biopsies. Examination of a series of FL showed that in many cases, early driver mutations were present in chromatin regulator genes such as CREBBP, EZH2, and KMT2D (MLL2).¹² This opens the way to novel therapies such as inhibi-tors of EZH2, with the hope that these agents may be able to deplete the lymphoma progenitor cell pool that gives rise to recurrence.

Modulation of the cellular immune response using checkpoint-blocking antibodies such as anti–PD-1 and anti–CTLA-4 has

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been successful in numerous epithelial cancers and is now the subject of studies exploring their potential in lymphoma. Two studies of the use of the anti-PD-1 antibody pidilizumab in FL in combination with rituximab,12 and in diffuse large B-cell lymphoma after high-dose therapy14 suggested that this was feasible, but the strongest data to emerge was in Hodgkin lymphoma (HL). In a phase II study in 23 patients with relapsed and refractory HL, most of whom had previously undergone high dose therapy and/or had received brentuximab vedotin, subjects received rilumivab 3 mg/kg every two weeks.15 The response rate in this difficult group was 87 percent, with 86 percent progression-free survival at 24 weeks, 22 percent grade 3 toxicity, and only two withdrawals for this. Although at an early stage, this represents a promising new approach to the treatment of lymphoma, especially in those types such as HL and primary mediastinal lymphoma which are characterized by dysregulation of the PD-1/PD-1 ligand pathway. Finally, in individuals with high-risk characteristics who are refractory to conventional therapies,16 and who previously had responded to conventional therapies,17 research into the use of CAR T cells targeting B-cell malignancies has been promising.18-20 Subsequently, in 2014, the same group of investigators, Drs. LaCasce, Johnson, and Gotlib indicated no relevant conflicts of interest.

Drs. LaCasce, Johnson, and Gotlib indicated no relevant conflicts of interest.

Drs. Park and Brentjens indicated no relevant conflicts of interest.

Meta-analysis of Bleeding Complications with Direct Oral Anticoagulants

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Looking back at 2014, several published articles related to non-malignant hematologic conditions were significant because of their potential to influence clinical practice. Leading authors such as Dr. Claire Chai-Adisaksopha and colleagues, “The Impact of Bleeding Complications in Patients Receiving Target-Specific Oral Anticoagulant Reversal and Meta-Analysis.” By pooling data from 12 phase III randomized, controlled trials involving more than 100,000 patients, the authors compared the direct oral anticoagulants (DOACs) – apixaban, dabigatran, edoxaban, and rivaroxaban – with more traditional anticoagulation strategies such as warfarin. While many hematologists are aware that the DOACs have proven effective in the treatment of venous thromboembolism (VTE) and in the prevention of atrial fibrillation–related stroke, the power to examine the relative safety of DOACs vs. warfarin has been limited by the small number of serious events (e.g., fatal bleeding) that occur in any single trial. The finding from this meta-analysis that fatal hemorrhage occurred less frequent (risk ratio, 0.53; p<0.001) among patients randomized to DOACs may seem surprising because there is no “antidote” for DOACs, while factor replacement and vitamin K can be used to correct warfarin–associated coagulopathy. However, the message from these pooled data is not that the ability to “reverse” warfarin did not translate into fewer bleeding-related deaths.

The Forrest plot (Figure) is particularly compelling because the point estimates for relative risk from the individual studies are very consistent: Even one suggests a lower risk of fatal bleeding with the DOACs. Part of this difference is explained by the lower risk of intracranial bleeding associated with DOACs, but the lower risk of fatal bleeding is probably also attributable both to the relatively short half-life of DOACs and to the well-documented grave prognosis associated with major bleeding that occurs on warfarin. Regardless of the explanation, the findings of Dr. Chai-Adisaksopha et al. indicate that for patients with an approved treatment indication, the lack of an antidote for DOACs should not be a rationale for choosing warfarin.

While the evidence about the relative safety of DOACs is encouraged by the “Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis” study reminds us that the search for strategies with even lower bleeding risk continues, our experiments with animal models and outcome data from humans with congenital factor XI (FXI) deficiency had previously indicated that FXI may be a low levels of FXI activity activity appear to protect against thrombosis while not increasing the risk of spontaneous bleeding. In this phase II randomized trial of primary VTE prevention after knee replacement surgery, the FXI antisense oligodeoxynucleotide (ASO) compared very favorably to a more standard approach with enoxaparin. While this study is too small to permit any definite conclusions about relative safety and efficacy, a critical concept was proven: If given by subcutaneous injection, starting approximately one month prior to surgery, the FXI ASO can migrate to the hepatocyte, decrease FXI synthesis, and provide substantial protection against VTE while conferring a very low risk of major postoperative bleeding.

Several important articles raised doubts about the benefit of three clinical interventions often considered or recommended by hematologists. From the TIPPS trial, we learned that women with thrombophilia such as protein S deficiency or activated protein C resistance do not benefit from daily prophylaxis with low-dose heparin. The multicenter, open-label, randomized trial enrolled 289 women who had a personal history of either thrombosis or pregnancy complications in addition to thrombophilia. The finding that the primary outcome of thrombosis, small-for-gestational-age infant, pregnancy loss, or VTE occurred with similar frequency in both groups (dailyparin 17.1%; 95% CI, 11.4%-24.2% vs. low-dose heparin 18.9%; 95% CI, 12.8%-26.3%) corroborates other evidence and suggests that women with thrombophilia should not be prescribed low-molecular-weight heparin (LMWH) to prevent these complications unless further research indicates that LMWH is beneficial in this setting. Thanks to SOX, a randomized controlled trial to prevent post-thrombotic syndrome in patients with leg deep vein thrombosis, we now know that an elastic compression stocking fitted to achieve 30-40 mmHg pressure at the ankle does not reduce the likelihood that a patient will suffer from venous insufficiency more than six months after anticoagulant treatment is begun. Finally, 2014 brought us important insights about the challenges of “individualized medicine.” Because of its complex metabolism and its narrow therapeutic index, pharmacogenomic-guided warfarin dosing has been studied extensively ever since genetic variants that impact the pharmacokinetics of vitamin K antagonists were identified. Since individual trials have been small and yielded inconsistent results, it had been difficult to establish whether routinely testing patients for commonly occurring polymorphisms might reduce the risk of clinically important events. After pooling data from nine randomized trials involving 2,812 patients, Dr. Kathleen Stergiopoulos and Dr. David Brown found no benefit from adding pharmacogenetic testing to dosing algorithms that did not use this information: Compared with clinical dosing, the risk ratio for an international normalized ratio (INR) greater than 4 was 0.92 (95% CI, 0.83-1.05) when pharmacogenetic information was added, and the risk ratios for major bleeding and thromboembolic events were 0.60 (95% CI, 0.29-1.20) and 0.97 (95% CI, 0.46-2.00), respectively. Based on these observations, it is difficult to justify the addition of pharmacogenetic testing to close follow-up with INR-based dose adjustments.

Mutation of the Calreticulin (CALR) Gene in Myeloproliferative Neoplasms

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The discovery of mutations in exon 9 of the calreticulin (CALR) gene in the majority of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) came out of left field.1 This breakthrough dominated the management landscape of these hematopoietic stem cell disorders and led to the development of CALR-targeted therapies.2,3 However, the clinical utility of detecting CALR mutations in patients with ET, PMF, and less frequently, refractory anemia with ring sideroblasts (RARS-T) is consistent with Dr. Alessandro Vannucci and colleagues’ observation that CALR immunostaining primarily highlights megakaryocytes in narrow specimens from patients with these diagnoses.4 Together with the detection of mutation CALR in hematopoietic stem cells,5 these data define CALR mutated MPNs as stem cell–derived neoplasms with aberrant and preferential expansion of the megakaryocyte lineage. A retrospective mouse model of mutant CALR phosphorylations

human disease and should be a useful platform for evaluating new treatments.3

What is the profile of the “typical” MPN patient with a CALR
mutated clone? Patients with JAK2/MPL mutations and
CALR-mutated ET patients are more commonly male,
and they exhibit lower white blood cell and hemoglobin levels,
higher platelet counts, and a lower risk of thrombocytosis than
the disease. The mean steady-state levels of various
factors in the MPN clone. Most MPN patients exhibit
disease persistence that has been attributed to transactivation
of JAK2 by JAK family kinase members JAK1 and TYK2.11
The laboratory of Dr. Ross Levine at Memorial Sloan Kettering Cancer Center presented preclinical data on the type II JAK
inhibitors that effectively block the inactive conformation of
JAK2.12 The drug showed impressive activity in JAK inhibitor
persistent cells as well as murine models of MF and polycy-
thermia vera. These data portend a wave of promising second-
generation JAK inhibitors in MF.

Follow-up pilot data were presented at the ASH annual meet-
ing on the telomerase inhibitor imetelstat. The agent elicited
partial or complete remissions in seven (21%) of 33 patients
with intermediate-2/high-risk MF.13 All patients with complete remission and off therapy for 6 to 12 months developed
a lower risk of thrombosis, but no clear
trend in survival.14

While CALR is a clonal marker that can provide diagnostic
certainty in cases of ambiguous thrombocytemia, it does not have a bearing on therapeutic decisions in established cases of ET
or MP. For example, modification of CALR does not alter the
international prognostic score for predicting the risk of throm-
bus in ET.1 Similarly, MF patients with mutant CALR exhibit
responses to JAK inhibitor therapy.15 For the individual patient,
the prognostic import of mutated CALR needs to be weighed in the context of refined genotyping systems that layer additional prognostic information such as
cytogenetic abnormalities (especially poor-
risk mutations in AXL, E2H3, SRSF2, IDH1/2) on top of the
clonal and labile components that comprise the DIPSS-PLUS
prognostic score. Such dynamic prognostic schemes are par-
cially relevant to decision making about hematopoietic
stem cell transplantation.

At the end of the 2014, the ASH annual meeting featured an
eeclectic collection of studies. Current JAK inhibitors, which are type I inhibitors, only bind to the active conformation of
the JAK2 kinase. These agents effectively reduce spleno-

galy and symptom burden in patients with MF but exhibit modest effects on the MPN clone. Most MPN patients exhibit

No inhibitor formation occurred in patients treated with either
long-acting factor concentrate.

Half-life prolongation of factor VIII has proven more difficult.
Recombinant factor VIII (FVIII) fusion protein, the first long-acting
factor VIII molecule to receive FDA approval (in June 2014),
has a terminal half-life of 1.9 hours and requires admin-
istration every three to five days for prophylaxis in most
patients.4 As honorable mentions for best of 2014, it is worth highlight-
ing the work of Dr. Cuker and colleagues on age-adjusted D-dimer cutoffs to rule out pulmonary embolism: the ADJUST-PE study. JAMA.
2015;313:119-123.

Growing evidence suggests that perioperative bridging antico-
agulation is overused in clinical practice and associated with
increased bleeding. In the PERIOP-2 trial, patients on warfarin
for atrial fibrillation or mechanical heart valves who require
interruption of anticoagulation for an invasive procedure are
randomized to postoperative low molecular weight heparin
bridging or placebo. The primary outcome is thromboembolic
risk at 90 days and bleeding and other safety outcomes are also assessed.

Long-Acting Factor Concentrates for Hemophilia

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Regular prophylactic factor infusion reduces bleeding,
improves joint health, and has be-
come standard of care in the management
of patients with severe hemophilia A and B.
However, the inconvenience of frequent intra-
venous dosing limits the long-term compliance and
costs of prophylaxis. These factors, along with
the patient dissatisfaction and nonadherence. Most patients must
infuse two to three times weekly to maintain hemostatic
trough levels due to the relatively short half-lives of factor VIII (12
hours) and factor IX (12 hours). The arrival of long-acting fac-
tor concentrate has been anxiously anticipated as a means of
enhancing the convenience of, and adherence to, therapy. In
2014, long-acting factor IX concentrate became available.

In a phase III study, two prophylactic regimens of a recombi-
nant factor IX Fc fusion protein (efitrenonacog alfa; Alprolix)
were tested. Group 1 received a starting dose of 100 IU/kg every
3 weeks, and group 2 received a starting dose of 100 IU/kg every
3 weeks and dosing intervals of 3 to 5 days for prophylaxis in most
patients.4 In the ATTRACT trial, patients with acute proximal DVT are randomized to PCDT plus stan-
ard care (anticoagulation and elastic compression stockings) or
standard care alone. The primary outcome is development of
PTS within two years. Bleeding and other safety outcomes are also assessed.

No inhibitor formation occurred in patients treated with either
long-acting factor concentrate.


ection of JAK2 by JAK family kinase members JAK1 and TYK2. 


activation as a mechanism of persistence to JAK2 inhibitor therapy. 


with N-WASP/HDH2886 Reverse Type I JAK Inhibitor Permeability 

and Demonstrates Increased Efficacy in MPN Models [abstract]. 


13. Venetsakis S, Klajdn JG, Grievesharm M, et al. Results of a prophylactic, randomized, placebo-controlled phase III trial of 

ruxolitinib (RUX) in polycythemia vera (PV) patients resistant to or intolerant of hydroxyurea (HU). The RESPONSE trial [abstract]. 


Dr. Cuker indicated no relevant conflicts of interest.


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Dr. Gotlib receives research funding, serves on an advi-
sory board, and receives honoraria from Inotec. He also 
receives research funding from Gilead and Promedior.
As hematologists we provide much of the medical care for patients with sickle cell disease (SCD), so we need to remain cognizant that SCD is a truly multisystem disease that affects most tissues and organs beyond the blood and bone marrow. For example, the brain is at ongoing threat of ischemic injury in SCD. The risk of overt stroke in children with SCD (without primary stroke prophylaxis) is more than 200-fold higher than the general population, and the burden of stroke may be even higher in adults with SCD.2 As if overt stroke were not worrisome enough, a far more common form of brain injury is silent cerebral infarction (SCI). SCI refers to generally small, permanent brain lesions that do not produce focalizing neurologic signs (Pseudoneuritis). The lack of localizing signs should not reassure us, however, because the brain is more than a motor strip. Indeed, SCI is a misnomer because these small strokes are often not “silent.” SCI is a morbid condition associated with neurocognitive impairment, poor academic performance, neurologic soft signs, and an increased risk of subsequent overt stroke. SCI can occur as early as the first year of life, and its prevalence increases with age. Approximately 40 percent of adolescents with SCD have SCI, and adults probably continue to acquire new or enlarged SCI lesions.4,5 Despite the high frequency and morbidity of SCI, we have had no randomized clinical trials (with SCI as the primary outcome) to inform medical therapy for patients with SCI, until now.

Among the most important clinical advances for hematologists in 2014, especially those who care for patients with SCD, is the report by Dr. Michael DeBaun and colleagues of the results of the Silent Cerebral Infarct Transfusion Trial (SIT Trial). In the SIT Trial, children (ages five to 16 years) with SCD and SCI were randomly allocated to three years of chronic transfusion therapy or observation. Children at high risk of overt stroke were excluded. Chronic transfusions provided a 58 percent relative risk reduction in new or progressive cerebral infarction compared with observation, with a number needed to treat (NNT) of 13. Chronic transfusions also decreased the incidence of other vaso-occlusive complications, but the trade-off was an increased incidence of transfusional iron overload. Given that chronic transfusions can be burdensome and several severe iron overload develops in patients who receive inadequate chelation therapy, some clinicians, perhaps put off by the NNT, may balk at implementing this therapy as standard clinical practice. When the Prevention Study for Primary Stroke Prevention in Sickle Cell Anemia (STOP) was published in 1998 with a NNT of seven,6 many hematologists then also balked at implementing chronic transfusions for primary stroke prevention, but now it is considered the standard of care. How broadly the SIT Trial results will be implemented by hematologists remains to be seen, but we now have high-quality data from randomized trials to inform the therapy for patients with SCI, which is still more than can be said for the treatment of most other complications of SCD.

There were many other noteworthy publications in the field of SCD in 2014. Among these, Dr. Matthew Hsieh and colleagues reported that adults with severe SCD, who are typically deemed ineligible for hematopoietic stem cell transplantation (HSCT), can often safely tolerate a nonmyeloablative regimen with a human leukocyte antigen–matched sibling donor and achieve stable mixed-donor chimerism. These quite promising results with low morbidity and mortality, although not fully mature, suggest that more patients with SCD will be eligible for curative therapy with HSCT in the near future. Two other noteworthy reports highlight novel aspects of the hematopoietic pathophysiology of SCD that mechanistically links hemolysis and vaso-occlusion. Dr. Grace Chen and colleagues4 showed that neutrophil extracellular traps (NETs) and soluble NET components are present in a murine model of SCD, are induced by exposure to free heme, and contribute to vaso-occlusion. Dr. Belcher and colleagues demonstrated that free heme triggers signaling through Toll-like receptor 4, promoting vaso-occlusion through degradation of Weibel-Palade bodies and expression of adhesion mol-ecules. A final noteworthy report by Dr. Robert Carter and colleagues21 analyzed genomic strains of pneumococci isolated from children with SCD. These investigators identified 60 noncapsular pneumococcal genes (e.g., encoding virulence determinants) that were under differential selective pressure in SCD hosts compared with strains from non-SCD hosts. For example, virulence determinants were distinct from pneumococcal strains isolated from children with SCD with high-quality clinical evidence for a new indication for an established therapy (chronic transfusions for SCI), expanded the eligibility criteria for a curative therapy using new techniques (nonmyeloablative HSCT), identified targets for developments of novel drugs for SCD (heme and Toll-like receptor signaling), and informed the development of new vaccines for a potentially fatal complication of SCD (pneumococcal sepsis). The array of work presented at the recent 2014 ASH Annual Meeting indicates that 2015 will also be an exciting year for SCD, with perhaps two to 10 years after infusion: more about the role of hydroxyurea for primary overt stroke prophylaxis and the potential role of MEK inhibition in SCD.

In summary, 2014 provided hematologists and individuals with SCD with high-quality clinical evidence for a new indication for an established therapy (chronic transfusions for SCI), expanded the eligibility criteria for a curative therapy using new techniques (nonmyeloablative HSCT), identified targets for developments of novel drugs for SCD (heme and Toll-like receptor signaling), and informed the development of new vaccines for a potentially fatal complication of SCD (pneumococcal sepsis). The array of work presented at the recent 2014 ASH Annual Meeting indicates that 2015 will also be an exciting year for SCD, with perhaps two to 10 years after infusion: more about the role of hydroxyurea for primary overt stroke prophylaxis and the potential role of MEK inhibition in SCD.
Gene Therapy by Insertion, Editing, or Ablation

1. GENE INSERTION
   - Vector Delivery of Normal cDNA

2. GENE EDITING
   - Genes are present in the cell.

3. GENE ABLATION
   - Gene is deleted.

At the 2014 ASH Annual Meeting, two abstracts reported the use of a third type of vector, a lentivirus, to correct β-thalassemia. The replication-defective, self-inactivating lentiviral vector contains an engineered β-globin gene (βAT707) and is called Lentibeta-MD. Both studies reported that some study subjects no longer needed red blood cell transfusions.

2014 also witnessed innovation in preclinical studies in the methodology for gene editing, including not only the ability to correct in situ defective mutant genes, but also the ability to disrupt gene function. Gene editing is accomplished using engineered nucleases that can be targeted to specific regions of DNA to excise mutated region(s) and replace them with a normal sequence, or to disrupt genes to alter or eliminate undesirable gene function. The former technique was used to correct replicating hematopoietic stem cells from a child with XCI-CRIS.

Dr. Xi-Kai and colleagues from the University of California, San Francisco corrected induced pluripotent stem cells from patients with β-thalassemia using the endonuclease system CRISPR (clustered, regularly interspaced, palindromic repeats) associated protein 9 (Cas9) and the piggyBac cassette containing normal parts of the gene. The CRISPR/Cas9 endonuclease system was also used to disrupt two clinically relevant genes in primary human hematopoietic cells: 1) β2-microglobulin as the accessory chain of the major histocompatibility gene class I molecules in order to produce hypomunogenic cells for transplantation, and 2) GCRS, the main co-receptor for certain strains of HIV that could potentially interfere with viral entry.

These reports represent key milestones in gene editing technology that augur well for future success in the clinic.

Pre-Leukemic Hematopoietic Stem Cells in Human Acute Myeloid Leukemia

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Patients with de novo acute myeloid leukemia (AML) typically come to clinical attention with symptoms of bone marrow failure in the absence of any prior hematologic condition. In many such patients, the diagnosis is sudden and unexpected, without any significant prodrome.

The generally poor prognosis of AML and the decades-long impasse in generating effective therapeutic strategies other than conventional anticoagulant and cytotoxic-based (“3+7”) induction chemotherapy has spurred intense investigation of its molecular and cellular origins. Pioneering work by numerous investigators led to an early understanding of the genetic mechanisms of AML, particularly the identification of recurrent chromosomal abnormalities and mutations in the genes FLT3 and NPM1. However, it is only with the recent implementation of massively parallel next-generation DNA sequencing technology that the full spectrum of mutations in AML has been defined. These genome and exome sequencing efforts have determined that there are five core mutations on average in an individual case of de novo AML. This observation raises the important question of how many mutations accumulate in a single lineage of cells?

More than a decade ago, Weissman and colleagues hypothesized that since hematopoietic stem cells (HSCs) are the only long-lived self-renewing cells in the myeloid lineage, mutations must be serially acquired in clones of HSC. In 2012, we reported direct evidence supporting this model from studies of rare, residual HSCs at the time of AML diagnosis. In a small cohort of patients, we demonstrated that residual HSCs could be prospectively isolated from diagnostic AML samples. Through targeted deep sequencing, HSCs were found to harbor some, but not all, of the mutations present in the same patient’s leukemia cells. Moreover, through analysis of single cells, we showed that mutations were serially acquired in successive clones of HSCs, formally proving our model described above. We termed these cells pre-leukemic HSCs that harbored pre-leukemic mutations.

During the last year, this work was extended further by studies from the laboratory of Dr. John Dick and our own group. Dr. Dick and colleagues focused on AML that was resistant to therapy in patients who had relapses in DMN73A and identified this as an early mutation occurring in pre-leukemic HSCs that were capable of contributing to both lymphoid and myeloid progeny in patient samples both at the time of diagnosis and in clinical remission. They further showed that these DMN73A-mutant HSCs outcompeted normal HSCs in xenotransplantation assays, establishing them as pre-leukemic. Finally, they reported evidence that IDH2 mutations could also be identified in pre-leukemic HSCs. Our own work investigated patterns of mutational acquisition in AML, determining that early pre-leukemic mutations occur primarily in genes that regulate the epigenome, while later mutations are enriched for genes involved in proliferative signal transduction. Like Dr. Dick and colleagues, we also demonstrated that pre-leukemic HSCs persist in remission where they contribute to normal lymphoid and myeloid progeny. Finally, we showed that there are multiple clonal paths to relapse, including the possible acquisition of novel mutations by pre-leukemic HSCs. Collectively, these studies established the existence of pre-leukemic HSCs that undergo clonal evolution resulting in de novo AML and raise a number of important clinical issues.

First, there is currently great interest in developing targeted treatments against specific AML mutations; however, this approach is limited by the possibility of leukemic subclones that do not carry that specific mutation. Pre-leukemic HSCs are likely to be contained in all AML cells and are therefore the best therapeutic target. Second, the possibility that pre-leukemic HSCs may acquire novel mutations that lead to related disease suggests that curative therapies will not only need to target frankly leukemic cells but also pre-leukemic HSC. Third, the use of highly sensitive sequencing methods to detect specific mutations as a measure of minimal residual disease (MRD) is an area of active biomarker research; however, as pre-leukemic HSCs persist in clinical remission, detection of such pre-leukemic mutations may lead to false-positive assessments of MRD. Finally, the existence of clinically silent pre-leukemic HSCs raises the possibility of early detection prior to the development of frank AML. In fact, several large population-based studies have recently been published reporting that mutations found to be recurrent in hematologic malignancies, including DMN73A and TET2, can be detected in the peripheral blood of patients with no history of hematologic disease. Indeed, long-term follow-up of such individuals indicates that they have a much higher future risk of developing a hematologic disease. Thus, it is possible that population-based screening might identify such individuals, eventually paving the way for AML prevention strategies.

Dr. Majeti indicated no relevant conflicts of interest.

Myeloma Highlights of 2014

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A number of publications from 2014 that impact our understanding and treatment of multiple myeloma (MM) have appeared. First, insights into the mechanism of action of thalidomide and its analogues came fast and frequently. It was previously shown that thalidomide induced ceramide. This drug-protein interaction is critical for both the teratogenicity that gave thalidomide its notoriety and also the surprising ability of thalidomide and its newer analogues lenalidomide to treat MM. Using complementary approaches, two groups described another critical link by demonstrating that the transcription factors IKZF1 and IKZF3 are selectively blocked by ceramide. Interestingly, by binding these, immunomodulatory drugs activate cerobin, resulting in rapid degradation of Ikars and Aiolos. This is important because Ilars and Aiolos are regulators of B- and T-cell lymphoid development and are critical for normal plasma cell development in mice. This discovery highlights that all of the immune modulators use the same basic mechanism of action, albeit with increasing potency. These findings also raise the possibility of using biomarkers to predict drug response and exploring new targets to target these pathways.

With more direct therapeutic relevance, the results of the Phase III ASPIRE clinical trial were published. This trial tested the hypothesis that thalidomide and lenalidomide would result in a higher remission rate in relapsed MM. The trial compared carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) and met its primary endpoint for high-risk patients who had a significantly extended progression-free survival (PFS) by 8.7 months (263 months with KRd vs. 176 months with Rd). The overall response rate was 87 percent with KRd and 66.7 percent with Rd. In the KRd and Rd groups, 31.8 percent versus 9.3 percent of patients achieved a complete response, respectively (p<0.0001). Perhaps most importantly, KRd consistently improved Global Health Status/Quality of Life compared to Rd over 18 cycles of treatment. The study also was reassuring with respect to toxicity, as treatment discontinuation due to an adverse event occurred in 15.3 percent of patients and 17.7 percent of the patients. In each group, 7.7 percent versus 8.5 percent of patients died while still on study treatment. The significance of this study is that it confirms that a more aggressive approach with three drugs is tolerable and dramatically improves outcome for relapsed MM patients. Use of this or similar combinations should now be the standard of care in relapsed disease.

Finally, a randomized trial reconfirmed the role of transplantation in MM patients younger than 65 years. This trial also highlighted that using combinations of drugs for longer as maintenance results in the longest PFS period for patients. All patients received four cycles of alternating lenalidomide and carfilzomib. Six cycles of lenalidomide and dexamethasone (MPR), or to high-dose melphalan and autologous transplantation. All patients received four cycles. The study met its primary end point by demonstrating that KRd significantly improved progression-free survival (PFS, 43 vs. 22.4 months [p<0.001]; four-year overall survival, 81.6% vs. 65.3%; p=0.02). Median PFS was significantly longer with lenalidomide (MPR), or to high-dose melphalan and autologous transplantation in the longest PFS period for patients. All patients received four cycles. The study also was reassuring with respect to toxicity, as treatment discontinuation due to an adverse event occurred in 15.3 percent of patients and 17.7 percent of the patients. In each group, 7.7 percent versus 8.5 percent of patients died while still on study treatment. The significance of this study is that it confirms that a more aggressive approach with three drugs is tolerable and dramatically improves outcome for relapsed MM patients. Use of this or similar combinations should now be the standard of care in relapsed disease.

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30-31 Highlights of ASH
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February

14 Applications available for the Translational Research Training in Hematology program
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20 Application deadline for 2015 ASH HONORS Award
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28 – Mar. 1 Highlights of ASH in Asia
Bangkok, Thailand www.hematology.org/meetings

March

10 Application deadline for the 2015 Minority Medical Student Award Program
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12 Application deadline for the 2015 Clinical Research Training Institute in Latin America
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20 Application deadline for the 2015 Latin American Training Program
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27 Application deadline for ASH Clinical Research Training Institute**
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April

6 Nomination Packages Due for the 2015 ASH Mentor Award
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10 Deadline to submit nomination package for ASH Mentor Award
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14-16 Thrombosis & Hemostasis Summit of North America
Chicago, IL www.thsna.org

17 Deadline to claim CME credits and print a CME certificate for the 56th ASH Annual Meeting
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18-22 American Association for Cancer Research Annual Meeting
Philadelphia, PA www.aacr.org/meetings

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