A Novel Strategy to Cure OncomiR Addiction


MicroRNAs (miRs) are short, noncoding RNA molecules that regulate the expression of target genes. OncomiRs are miRs that are overexpressed in certain cancers and play a role in the onset and development of these tumors, which display oncomiR addiction. Inhibition of oncomiRs by antimiRs is therefore an attractive and evolving therapeutic strategy. Various approaches to silence the aberrantly expressed miRs have been used, including peptide nucleic acids (PNAs), which are nucleic acid analogues consisting of synthetic backbones connected by intramolecular amide bonds. The PNA backbone stabilizes the antimiR by preventing nucleicase degradation and increasing the binding affinity for the complementary target sequence.

Notwithstanding recent improvements in RNA-based treatments, the effectiveness of current antimiR therapy is hindered by non-specific organ targeting, clearance in the reticuloendothelial system, and endosomal/lysosomal trafficking. Dr. Christopher Cheng and colleagues from Yale University have overcome these drawbacks by constructing a novel antimiR delivery system, which specifically targets tumors, facilitates entry into cancer cells via a nonendocytic pathway, and avoids clearance by the liver. The researchers exploited the acidic microenvironment of tumors and the unique properties of a peptide with a low pH-induced transmembrane structure (pHLIP), which forms an α-helix under acidic conditions and facilitates translocation of membrane-impermeable molecules, such as PNA-antimiRs, into cells.

To evaluate their new delivery platform, they used a mouse model of an inducible miR-155–addicted lymphoma whereby miR-155 expression is stimulated in hematologic tissues to promote tumorogenesis, which can be reversed by adding doxycycline. They first demonstrated that pHLIP labeled with a fluorescent dye, localized to inducible lymphoid tumors in nude mice, and also localized correctly in mice with disseminated lymphadenopathy. The liver was not affected, but some of the peptide accumulated in the kidneys where it was cleared by renal excretion.

These promising results prompted the researchers to create a pHLIP-antimiR-155 to target lymphoma. The construct consisted of the pHLIP peptide linked at the C-terminus to the PNA antimiR by a disulfide bond. The acidic pH (approximately 6) of the tumor microenvironment promoted insertion of the construct into the lipid bilayer of the plasma membrane and delivered the antimiR to the intracellular cytosol where the disulfide bond was cleaved to release the free antimiR, which then targeted tumoral cells. AntimiR-155 was therefore an attractive and evolving therapeutic strategy.

The ASH Meeting on Lymphoma Biology was held August 10-13, 2014, to establish a collaborative forum for the community of lymphoma researchers, enable them to share data, and ultimately, advance the understanding of lymphoma pathogenesis and expedite new therapies. With assistance from ASH, a steering committee of lymphoma experts both organized the meeting and developed a “Roadmap for Discovery and Translation in Lymphoma,” which was recently published in Blood. In this companion article, we will summarize the current landscape of challenges, as well as advances, that provide the backdrop for the roadmap and the priorities (Table; see additional Figure in online article) at its foundation.

There are more than 80 unique subtypes of mature lymphoid malignancy, including non-Hodgkin lymphomas (NHLs), Hodgkin lymphoma (HL), and chronic lymphocytic leukemia (CLL). Many of these subtypes are rare, with 5,000 or fewer cases occurring in the United States annually. The association between some subtypes and pre-existing conditions, including immunodeficiencies, autoimmune disorders, and infections (e.g., HIV, hepatitis C virus, Epstein-Barr virus [EBV]), further complicates both categorization and treatment.

Despite this diversity, therapeutic advances in lymphoma have been critically important in cancer medicine since the administration of nitrogen mustard to a patient with NHL in 1942. Treatment of endemic Burkitt lymphoma in the 1950s was one of the first demonstrations that chemotherapy could cure cancer. Combination chemotherapy with MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone), developed by investigators at the National Cancer Institute in the late 1960s, cured more than one-half of patients with HL.

The addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for diffuse large B-cell lymphoma (DLBCL) established the paradigm for treatment of early-stage mucosa-associated lymphoid tumors (MALT) of the stomach was the first demonstration that modulation of the gut microbe can eradicate a neoplastic process. Finally, a deeper understanding of lymphoma pathogenesis has guided the development of targeted therapies such as ibrutinib and idelalisib for associated lymphoid tumors (MALT) of the stomach was the first demonstration that modulation of the gut microbe can eradicate a neoplastic process. Finally, a deeper understanding of lymphoma pathogenesis has guided the development of targeted therapies such as ibrutinib and idelalisib for...
A Call to Action on Sickle Cell Disease

ASH has many strengths, but one of its greatest abilities is its power to convene. Last month, as part of its broader global initiative, ASH used its convening power to spearhead the ASH Sickle Cell Disease (SCD) Summit: A Call to Action. This summit, chaired by ASH President-Elect Charles Abrams, was the first meeting of its kind for our Society and brought together for a full-day discussion of more than 60 experts in SCD, including clinicians and researchers, federal agency partners, representatives from industry, and other members of the SCD community, to identify the areas of opportunity and highest priorities to ultimately improve outcomes for individuals with SCD.

The issues facing SCD patients both domestically and globally are multiple. ASH realizes that it cannot effectively deal with the enormity of these issues alone. However, the Society is well positioned to facilitate, and in some cases lead, collaborative efforts to impact the lives of individuals with SCD in a positive fashion. ASH has already taken a number of incremental steps to ensure that patients with SCD receive state-of-the-art care, including releasing the ASH Priorities for Sickle Cell Disease and Sickle Cell Trait (www.hematology.org/Research/Recommendations/Sickle-Cell/), co-hosting a briefing on Capitol Hill on SCD, and developing ASH’s clinical quick-reference guides (www.hematology.org/Clincians/Guidelines/Quality/Quick-Reference.aspx) based on the National Heart, Lung, and Blood Institute’s Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. But there is still so much more we can do.

The summit set the stage for developing forward-looking initiatives. During the meeting, attendees participated in interactive discussions in which they identified progressive and provocative strategies that address all aspects of SCD, including basic, translational, and clinical research, as well as access to care issues, both in North America and around the world. The discussions identified key partners, including government agencies, patient advocacy organizations, other medical/scientific societies, foundations, and industry; the summit also identified issues ranging from the effects of reimbursement on physician specialization in SCD care, to models of community-based care, to education and training of care providers, to existing gaps in research such as in pain treatment and curative therapies.

A commonly held view of those at the summit was that ASH was to be commended for stepping forward to initiate this conversation and was in a unique position to have a positive impact due to the worldwide respect the organization commands in the areas of hematology research, advocacy, and education. Throughout the next few months, ASH will refine and prioritize the issues pinpointed during this summit and identify other stakeholders who should be involved to help advance future efforts. In the short term, the Society plans to launch a dedicated SCD page on the ASH website that will include a list of the Society’s SCD tools and resources, as well as links to federal and other philanthropic programs and funding opportunities for SCD. In the future, this webpage will also include the Society’s official call to action on SCD.

Now is the time for a comprehensive response. We look forward to working with ASH members and partners as we move forward with this critical initiative.

David A. Williams, MD

A Novel Strategy to Cure OncomiR Addiction

was suppressed. The onset of splenomegaly and the development of lymphadenopathy were also significantly delayed. Importantly, the treated mice showed no clinical signs of distress, toxicity, or renal damage, and this was confirmed by studies on healthy mice using the highest dose of pHLP-antiMIR-155. These control mice exhibited no significant impairment of liver and kidney function and had normal white blood cell counts, and body as well as organ mass. PNA antiMIRs are cleared by the reticuloendothelial system, which leads to a significant increase in splenic size and weight in mice treated with pHLP-antiMIR-155 alone.

The mechanisms of tumor induction and subsequent addiction to miR-155 are not well characterized. Similarly, the pathways that facilitate tumor regression once miR-155 has been removed are still unknown. To investigate these aspects, the researchers performed RNA sequencing on miR-155–addicted lymphoid tumors and compared the data to regressing tumors. More than 2,000 genes were significantly up- or down-regulated when miR-155 was silenced, and the majority of these have been associated with cancer or cell adhesion and migration pathways. A notable example is the BACH1 gene, which codes for a transcription factor, and which was validated as a miR-155 target in clinical studies on mouse models.

The novel pHLP-antiMIR delivery platform described in this study represents a significant advance in targeted RNA therapy. It has several advantages, including 1) specificity, since it targets the acidic microenvironment of the tumor and is ineffective in cells with a normal, neutral pH; 2) low systemic toxicity; 3) efficient delivery of the cargo antiMIR, which facilitates the use of low doses of the therapeutic construct; and 4) versatility, since delivery is not dependent on the sequence of the antimiR and the system can thus be exploited to target multiple cancer types. Additionally, this approach has therapeutic potential for other pathological conditions in which a localized acidic environment is produced, such as ischemia, myocardial infarction, stroke, tissue trauma, and sites of inflammation and infection.
ASH Releases Agenda for Hematology Research

The field of hematology has experienced a recent surge in progress thanks to novel technologies, mechanistic insights, and cutting-edge therapeutic strategies that have driven significant and meaningful advances in the quality of care. Yet today, numerous specific and critically important research questions must be answered to gain the insights needed for the field to advance to the next level of care for hematologic conditions. The 2015 ASH Agenda for Hematology Research that was released on April 29, 2015, is a set of guideposts for the prioritization of research support across the hematology community, including recommendations for dedicated resources from funding agencies and foundations that will equip researchers today and in the future to make truly practice-changing discoveries. These priorities include:

- Advancing novel therapies tailored to genetic profiles by integrating genome sequencing and analysis into the drug discovery pathway
- Fostering new studies to optimize the application of genome editing and gene therapy
- Enriching studies of epigenetic mechanisms to evaluate novel therapeutic targets and to develop new treatments that may overcome limitations of existing therapies
- Maximizing the potential of immunotherapies to eradicate minimal residual disease
- Evolving stem cell research to enhance therapeutic and diagnostic uses
- Improving the prediction, diagnosis, and treatment of venous thromboembolic disease

The agenda serves as focal point for ASH science advocacy and partnership-building efforts with organizations that fund, legislate, regulate, and/or implement hematology-related research. The ASH Committee on Scientific Affairs met with the leadership of the National Cancer Institute; National Heart, Lung, and Blood Institute; and National Institute of Diabetes and Digestive and Kidney Diseases on April 29, 2015, to discuss the research priorities outlined in the ASH research agenda.

The priorities outlined here represent some of the most promising strategies for overcoming the limitations of current therapies and for accelerating momentum to cure hematologic diseases. Dedicated research funds will enable the pursuit of these compelling opportunities and will prepare the next generation of scientists in the field to produce high-impact results and, ultimately, to introduce new standards of care. Such standards will not only transform the diagnosis and treatment of patients with hematologic diseases today, they will form the basis for continued scientific progress in hematology and other fields of medicine for years to come.

To learn more about the research agenda, visit www.hematology.org/researchagenda.

57th ASH Annual Meeting and Exposition

December 5-8, 2015, Orlando, Florida

ASH invites you to save the date for the 57th ASH Annual Meeting and Exposition in Orlando, Florida. As the premier event in malignant and nonmalignant hematology, this meeting will provide attendees with an invaluable educational experience. The call for abstracts will be posted in early May, and the abstract submission site opens June 4. Annual meeting abstracts are due August 4. Early-bird registration and housing opens July 22 for members, and registration opens August 12 for non-members.

Visit www.hematology.org/Annual-Meeting for upcoming information on abstract submission, program sessions, and what’s new at this year’s meeting.

Abstract Submission Site for Meeting on Hematologic Malignancies Opens May 5

The ASH Meeting on Hematologic Malignancies (MMH) will be held in Chicago, September 17-19. The abstract submission site opens May 5, and abstracts for the meeting are due July 1. Abstracts submitted to MMH may also be submitted to the 2015 ASH Annual Meeting. Visit the website for more information about this new clinical meeting. For more information about MMH and for details on how to register, go to www.hematology.org/MMH.

Learn more about the creation of this meeting directly from the co-chair in an informational video www.hematology.org/MMHvideo.

Help ASH Identify New Leaders

Members in good standing can nominate themselves or other members for leadership and committee positions through May 31, 2015. Vacancies on the Executive Committee for 2016 include the Vice President and two Councillor positions, including one Councillor position designated for an individual in clinical practice. The eligibility criteria for this position have recently been expanded; please visit www.hematology.org/About/Governance.aspx to learn more about the Society’s structure and governance and to explore all vacant positions.

To use the online nominations system, visit www.hematology.org/ Nominations. Self-nominations are welcome.

2014 ASH Annual Report Now Available

The digital 2014 ASH Annual Report, a celebration of the Society’s growth and accomplishments over the past year, is now available. Learn about how the Society continues to refine and expand its programs to support the science and practice of hematology, delivering new opportunities, products, and services to support members.

To view online, visit www.hematology.org/annualreport.

Editor Search for Hematology, the ASH Education Program

ASH is in the initial stage of the selection process for the next Executive Editor of Hematology, the ASH Education Program (term: 2016-2018). Qualified candidates with an MD, MD/PhD, or equivalent who demonstrate a broad and comprehensive knowledge of translational research and clinical investigation in hematology and its subspecialty areas; a distinguished research and publication record; high standing among peers; and proven editing, writing, and reviewing skills are encouraged to apply.

Nominations should be accompanied by a description of the candidate’s editorial experience and a short, informal endorsement. Nominations must be received on or before June 1, 2015. Submit a letter of intent if you are interested in the position or provide the name of a potential candidate. Please submit nominations via email, addressed to:

Editor Search Committee
Hematology, the ASH Education Program
editorssearch@hematology.org

The April 15, 2015, ASH Sickle Cell Disease Summit: A Call to Action brought together more than 60 leaders in sickle cell disease and key federal agency partners to discuss strategies to improve care for patients with the disease around the world. Left: ASH President-Elect and Summit Chair Dr. Charles Abrams reports the results of one of the day’s breakout sessions. Right: Dr. Alan Schechter discusses strategies and priorities with fellow attendees. To learn more about this event and future efforts, contact ASH Government Relations and Practice Manager, Stephanie Kaplan, at skaplan@hematology.org.

The April 15, 2015, ASH Sickle Cell Disease Summit: A Call to Action brought together more than 60 leaders in sickle cell disease and key federal agency partners to discuss strategies to improve care for patients with the disease around the world. Left: ASH President-Elect and Summit Chair Dr. Charles Abrams reports the results of one of the day’s breakout sessions. Right: Dr. Alan Schechter discusses strategies and priorities with fellow attendees. To learn more about this event and future efforts, contact ASH Government Relations and Practice Manager, Stephanie Kaplan, at skaplan@hematology.org.

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My patient has moderate renal impairment. Does that mean I cannot prescribe a DOAC? Although all DOACs depend on renal clearance more than warfarin does, renal insufficiency is not a contraindication in all cases. Indeed, an analysis of the subgroup of patients with moderate renal impairment (creatinine clearance: 30 to 50 mL/min) in the phase III clinical trials indicates that the DOACs (when dosed according to the manufacturers’ recommendations) are at least as safe as warfarin for such individuals.1 The thresholds at which dose-adjustment is required vary depending on the DOAC; most providers would avoid DOACs altogether in patients with severe renal impairment (creatinine clearance < 30 mL/min). That being said, the U.S. FDA has approved a dose adjustment for apixaban in patients on hemodialysis. Apixaban is the DOAC that depends least on renal clearance. On the other end of the spectrum of renal function, the U.S. FDA has recommended that edoxaban not be used in AF patients with excellent renal function (creatinine clearance > 95 mL/min) because of a subgroup analysis suggesting it may be less effective than warfarin to prevent stroke or systemic embolism in this subgroup.

When will antidotes for some or all of the DOACs be available? Should I avoid prescribing DOACs until antidotes reach the market? The lack of experience managing DOAC-associated bleeding is an understandable concern. However, the absence of a dedicated antidote should probably not be a major consideration in the decision to use (or not use) this class of medications. Outcome data from randomized phase III clinical trials that included more than 100,000 patients show that, although no antidote was available, the likelihood of fatal bleeding was lower among the patients randomized to a DOAC than among the patients randomized to warfarin. Furthermore, taking a DOAC (as opposed to warfarin) was not associated with a higher likelihood of death among patients who experienced a major bleed. These seemingly counterintuitive observations are probably explained by several factors:

1) Despite the availability of vitamin K and plasma products, warfarin-associated major bleeding has a very high associated mortality; 2) compared with warfarin, the DOACs cause 50 percent fewer intracranial bleeds; and 3) the short half-life of the DOACs means that in many cases of major bleeding, no antidote or “reversal agent” is needed. These observations notwithstanding, antidotes and reversal agents in late-phase clinical development are likely to reach the U.S. market within the next two to three years. The DOAC antidotes that are furthest in the development process are andexanet (a factor Xa “decoy” molecule that is intended for patients on a FXa inhibitor) and ifarucizumab (an antibody fragment targeting the direct thrombin inhibitor, dabigatran).

What should I do if consulted about a patient with DOAC-associated bleeding? Many patients with DOAC-associated bleeding will be best managed with supportive care such as red blood cell transfusions and volume support; excellent renal perfusion will maximize the rate at which the anticoagulant effect dissipates. Unless a patient has compromised renal function, the plasma DOAC concentration (and corresponding drug effect) will have decreased by more than 50 percent six to 12 hours after the last dose. In the small minority of patients with DOAC-associated bleeding who require more aggressive efforts to counteract the anticoagulant effect immediately, one could consider prothrombin complex concentrates or recombinant activated factor VII. However, the thrombosis risk associated with these interventions is not trivial, and the rationale for their use is based entirely on animal and other preclinical models.

In which patients should DOACs be avoided? In general, DOACs should be used only for approved indications. In particular, warfarin is inferior to warfarin in the only head-to-head comparative trial that has been done in this population,2 the DOACs should not be prescribed to

<table>
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<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
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<td>Hip Arthroplasty</td>
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*Edoxaban and dabigatran are approved for the acute treatment of venous thromboembolism only after an initial 5-day course of treatment with a parenteral anticoagulant (e.g., low-molecular-weight heparin, fondaparinux, heparin).

My patient taking a DOAC needs to undergo an elective procedure. How far in advance of the procedure should I stop the medication, and do I need to provide “bridge” therapy? Unlike vitamin K antagonists (VKAs), all of the DOACs have both a rapid onset of action and a relatively short half-life. DOACs induce maximal anticoagulant effect within two to three hours of the first dose and, unless renal function is impaired, will essentially disappear from the plasma 24 to 48 hours after the last dose. Therefore, perioperative anticoagulation (“bridging”) with a parenteral anticoagulant is not necessary for a patient taking a DOAC unless the patient undergoes a surgery that will preclude swallowing or gastrointestinal absorption. Patients with renal impairment will need to interrupt the DOAC (see individual prescribing information for more details), but others can safely undergo most interventions as early as 24 to 48 hours after their last DOAC dose.
patients with mechanical prosthetic heart valves. There are also subgroups of patients with (or at risk for) VTE, where routine DOAC use should also be avoided pending further evidence. Because of their highly prothrombotic tendencies, patients with active cancer, heparin-induced thrombocytopenia, and bona fide antiphospholipid syndrome are other groups for whom I do not think DOACs should be a first option. Instead, we should work hard to enroll such patients in clinical trials that will provide evidence on which we can base future practice.

Conclusion

In summary, the DOACs offer hematologists and well-selected patients four oral alternatives to warfarin and other VKAs. Important ongoing trials will tell us more about how best to manage serious DOAC-related bleeding, whether DOACs can be safely used in patients with cancer-associated VTE, and what is the safest way to combine DOACs with antiplatelet agents (e.g., in patients with previous acute coronary syndromes). In the meantime, many patients for whom these medications are indicated (and for whom cost is not a barrier) will likely choose them over warfarin because of their convenience and impressive safety profile.


Dr. Garcia indicated no relevant conflicts of interest.

Meir Wetzler, MD (1954-2015)

Dr. Meir Wetzler’s work in the field of leukemia grew from a complaint. During his 1986 residency in internal medicine at Kaplan Hospital in Rehovot, Israel, he was assigned a presentation on hypercalcemia. When he told his mentor that he found the topic boring, “he got very upset with me,” Dr. Wetzler recalled in a 2014 interview with the Roswell Park Cancer Institute (RPCI) CRS Corner newsletter. “He said, ‘if you don’t want to do your presentation on hypercalcemia, I don’t want to be your mentor anymore.’”

That conflict turned out to be fortuitous: When Dr. Wetzler asked the department chair for help in finding an alternate project, he was directed to The Weizmann Institute, where basic research was underway in the evolving field of oncogenes. Dr. Wetzler ended up studying the breast cancer oncogene Her2/neu under the direction of Dr. Joseph “Yossi” Schlessinger (now the William H. Prusoff Professor and Chair of Pharmacology at Yale University) – an experience that jump-started Dr. Wetzler’s interest in the field of oncology.

A 1980 graduate of Hebrew University’s Hadassah Medical School in Jerusalem, Dr. Wetzler later won a fellowship in medical oncology at MD Anderson Cancer Center in Houston. Before coming to the United States, he began research in the field of leukemia and immediately got hooked. He subsequently completed a second fellowship in clinical immunology/biologic therapy, also at MD Anderson.

In 1994 Dr. Wetzler moved to Buffalo, New York, to join RPCI’s Leukemia Section. His research focused on the role of the signal transducer and activation of transcription (STAT) protein in leukemogenesis; cellular and humoral immune response to leukemia-associated antigens; and cytogenetics in acute myeloid leukemia and acute lymphoblastic leukemia.

He had an overarching interest in improving the standard of care for patients with leukemia, and this fed his enthusiasm for making newer biologic and immunotherapeutic options available to his patients. He was actively involved in promising early-stage clinical trials of novel therapeutics, and at the time of his death, served as principal investigator on several clinical trials at RPCI. With Dr. Mary Reid, Director of Collaborative Research at RPCI, Dr. Wetzler co-chaired RPCI’s Scientific Review Committee (SRC). Together they helped reduce by 40 days the process of taking a protocol from SRC submission to activation.

Following Dr. Wetzler’s death on Feb. 23, 2015, Greg Stephens, Executive Director of the National CML Society, noted in a Facebook post that Dr. Wetzler “made himself available at all hours of the day and night and shared his knowledge freely and abundantly.” Comments posted on local media websites included accolades from his patients and their family members, praising his passion and compassion.

Through RPCI’s affiliation with the School of Medicine at the State University of New York at Buffalo, Dr. Wetzler mentored many young physicians and researchers. A physician now on the faculty at M.D. Anderson recalls how Dr. Wetzler “drew the BCR-ABL chromosomal translocation to teach me how CML develops, on my first visit [to RPCI] … I would not be where I am if it were not for his mentoring.”

Dr. Wetzler lived up to his assertion that every member of his team was equally valuable. “I have an outstanding team,” he previously stated. “That’s what makes me smile every morning.”

He encouraged his colleagues to fulfill their potential, and he then helped them do just that. Linda Lugten-Dunkley, Pathology Resource Technician in Dr. Wetzler’s lab, said he adjusted her work hours to accommodate her family life after the birth of her son, and he later enabled her to work a flexible schedule so she could pursue a bachelor’s degree in biology. Ms. Lugten-Dunkley will graduate in May of 2016.

Dr. Wetzler was an accomplished athlete who completed many triathlons, including the Ironman, which combines a 2.4-mile swim, a 112-mile bicycle course, and a marathon (26.2 miles), with no breaks in between. He also had a humorous and playful side, evidenced when he and his team participated in the annual Gelatin Splash to benefit the Leukemia and Lymphoma Society of Western New York. They wore themed costumes while sliding into a pool of gelatin, raising thousands of dollars in pledges. Over the years, Dr. Wetzler appeared as Superman, Shrek, Jack Sparrow from “Pirates of the Caribbean,” and, in drag, as Edna Tumbird from the film “Hairspray.”

Dr. Wetzler was a member of the CML Clinical Practice Guidelines Committee of the National Comprehensive Cancer Network and was named numerous times to the Castle Connolly Medical Ltd. list of America’s Top Doctors. At the time of his death, he was Chief of RPCI’s Leukemia Section and Medical Director of Clinical Services in the Department of Medicine.

Dr. Wetzler inspired us all in so many different ways; RPCI and the cancer community have lost a dedicated son. He had an overarching interest in improving the standard of care for patients with leukemia, and this fed his enthusiasm for making newer biologic and immunotherapeutic options available to his patients. He was actively involved in promising early-stage clinical trials of novel therapeutics, and at the time of his death, served as principal investigator on several clinical trials at RPCI. With Dr. Mary Reid, Director of Collaborative Research at RPCI, Dr. Wetzler co-chaired RPCI’s Scientific Review Committee (SRC). Together they helped reduce by 40 days the process of taking a protocol from SRC submission to activation.

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Dr. Wetzler inspired us all in so many different ways; RPCI and the cancer community have lost a dedicated son. Those of us who have had the privilege of working and interacting with him are better people for it. He will be sorely missed.

Dr. Wetzler is survived by his wife, Chana; daughters, Mor and Shira; and sons, Adam and Modi. RPCI has established the Meir Wetzler Memorial Fund for Leukemia Research in his honor. Visit http://giving.roswellpark.org/wetzler.

– Alex Adjei, MD, PhD, FACP
Professor and Chair of the Department of Medicine, Senior Vice President of Clinical Research, The Katherine Anne Gibbs Chair of Cancer Medicine, Roswell Park Cancer Institute, Buffalo, New York
In the early 1990s, Dr. James Homer Wright and colleagues observed a reduction in the “dust of the blood” (platelets) is associated with bleeding. Today we know that while their primary function is hemostasis, platelets also participate in antimicrobial host defense, inflammation, and tissue repair. Chronic inflammation is often associated with reactive thrombocytosis, and responses to acute infections may be accompanied by thrombocytosis. Thrombopoiesis is the making platelets bellwethers of health and disease. A steady platelet supply is ensured by continuous platelet production and clearance of about 1011 platelets daily. The rate of production rises sharply under conditions of platelet destruction to maintain levels of 150,000 to 400,000 platelets per microliter of blood. Platelet production and clearance per microgram of blood. Platelet production and clearance must be tightly regulated to avoid spontaneous bleeding or arterial occlusion and organ damage.

Platelet production (thrombopoiesis) is a complex process that requires differentiation of hemopoietic stem cells into specialized progenitors and a final maturation in the bone marrow microenvironment and hematopoietic cytokines. A major milestone in understanding the bone marrow microenvironment and hematopoietic stem cells is thrombopoiesis. Thrombopoietin (TPO) was first discovered in 1994. TPO is the primary regulator of platelet production, supporting the survival, proliferation, and differentiation of bone marrow megakaryocytes. Since the discovery of TPO, many molecules with mechanisms of thrombopoiesis have been identified, including the development of polyplody and pro-platelet formation, and the final fragmentation of the megakaryocyte cytoplasm to yield blood platelets. However, a primary determinant of thrombopoiesis regarding thrombopoiesis is how TPO production is regulated under steady-state and pathologic conditions.

Historically, TPO regulation has been explained by a two-step model: 1) hepatocytes are the major source of TPO, which is released into circulation in a constitutive manner; and 2) circulating plasma TPO binds to its high-affinity receptor Mpl, expressed on the surface of platelets and megakaryocytes, resulting in subsequent degradation of TPO. Thus, the removal and destruction of circulating TPO has been thought to be mediated solely by expression of Mpl on circulating platelets and large megakaryocytes. This model predicted that circulating TPO levels are clearly evident in patients undergoing bone marrow transplantation and in Mpl mice. However, several human and mouse phenotypes lend credence to the assertion that platelet TPO metabolism is not the sole determinant of plasma TPO levels. For example, serum TPO levels are lower than expected in patients with immune thrombocytopenia (ITP) and are higher than expected in patients with immune thrombocytopenia (ITP) and are higher than expected in patients with immune thrombocytopenia (ITP) and are higher than expected in patients with immune thrombocytopenia (ITP). The inflammation-induced increase in TPO expression is mediated by interleukin (IL)-6, which stimulates TPO mRNA expression both in hepatocytes in vivo and in HepG2 and Hep3B cells in vitro. Hepatic TPO regulation by IL-6 is well characterized, but the ligand-receptor pair regulating hepatic TPO production at steady state has remained elusive.

A new model that helps to explain the regulation of blood TPO levels and thrombopoiesis is the clearance of senescent, desialylated platelets via the hepatic JAM receptor (AMR), which enhances hepatic TPO production. Studies have shown that platelet surface glucan platelet clearance. Sialic acid is normally covalently bound to glycoproteins, glycolipids, or proteins; glycosylated sialic acids are presumed to be fucosylated by sialic acid residues (i.e., fully sialylated). A recent study identified loss of sialic acid as a determinant of senescent platelet removal. This study shows that platelets lose sialic acid during circulation, likely due to upregulation of platelet intrinsic sialidases. Neutrophil and monocytes. Desialylated platelets are cleared via the hepatic AMR, a transmembrane heterodimeric glycoprotein complex composed of ASGPR1 (CLEC-4H, HL-1) and ASGPR2 (CLEC4D, HL-2) subunits. This highly conserved receptor has been largely regarded as an endocytic receptor, and its regulatory role remains unclear since its discovery four decades ago. Specifically, mice lacking either the ASGPR1 or ASGPR2 subunit do not accumulate plasma proteins or lipids lacking sialic acid, which has been the predicted outcome. However, it was a surprising discovery that platelets with reduced ~2,3-linked sialic acid due to sepsis, cold storage (in vitro aging), or in mice lacking the sialyltransferase ST3GaIv, are cleared by the hepatic AMR.

The notion that loss of sialic acid determines platelet life span is not entirely novel. However, our recent study elucidates the specific mechanisms by which senescent, desialylated platelets are cleared. Our data indicate that TPO mRNA production in vivo via the AMR. This feedback mechanism presents the desialylated platelet–AMR pair as the critical control point for TPO homeostasis and shows that hepatic TPO production is regulated and not constitutive. In support of this notion, injection of desialylated platelets into rats stimulates platelet production, presumably by stimulating liver TPO secretion.

These findings led to the discovery that removal of senescent, desialylated platelets drives hepatic TPO mRNA expression via JAK2 and STAT3 phosphorylation, and translocation of the latter to the nucleus. Sequence analysis shows that the TPO promoter contains STAT3 binding sites; however, their function remains to be investigated. Interestingly, the AMR signaling cascade shares similarities with that of the IL-6 receptor (IL-6R). Binding of IL-6 to its hepatic receptor engages the signal transducing subunit gp130, leading to STAT3 tyrosine phosphorylation and activation by gp130-associated JAK1. Thus, both desialylated platelets and IL-6 lead to STAT3-mediated hepatic TPO mRNA expression downstream of the AMR-JAK2 and IL-6R-JAK1 signaling cascades, respectively. It remains to be determined whether JAK2 and STAT3 directly bind to the TPO promoter.

Hepatic STAT3 controls the transcription of mRNA for acute phase proteins. It is therefore tempting to speculate that acute phase proteins are produced in response to AMR ligation, which would establish clearance of desialylated platelets as a component of the acute phase response. Consistent with this hypothesis, the AMR-mediated removal of desialylated platelets improves the probability of host survival during sepsis. Separate studies have shown that liver regeneration following injury is promoted by platelets and requires AMR and hepatic STAT3 function. Thus, the platelet–AMR-JAK2-STAT3 signaling cascade may confer desialylated platelets to inflammatory responses.

The most compelling evidence showing that TPO expression is required for the AMR-JAK2-STAT3 pathway is the experiments using JAK1/2 inhibitors. Disruption of the AMR-JAK2-STAT3 signaling cascade by JAK1/2 inhibitors (TTD) 480, TG101348, and BMS115437 adversely affects hepatic TPO mRNA expression and secretion in hepatocytes in vivo, and in HepG2 cells in vitro. JAK1/2 inhibitors target white type and 1G17f, and are clinically used in MPNs. Common on-target JAK-inhibitor–associated toxicities include anemia and thrombocytopenia, which relate to JAK2’s essential role in red blood cell and platelet function. Our data indicate that inhibitors could additionally cause thrombocytopenia by inhibiting TPO production downstream of the hepatic AMR-JAK2 signaling cascade. Clinical studies are necessary to investigate this notion, particularly regarding plasma TPO levels in patients with MPNs following JAK1/2 inhibitor treatment.

In conclusion, recent evidence has shown that the hepatic AMR recognizes circulating desialylated platelets under steady-state conditions. Our data also show that the AMR and the AMR are the exclusive physiological ligand-receptor pair regulating hepatic TPO mRNA production, resolving the longstanding mystery of steady state hepatic TPO regulation. This feedback mechanism, which recruits hepatic JAK2 and STAT3, contributes to our understanding of the mechanisms of thrombopoiesis observed in patients with MPNs treated with JAK1/2 inhibitors.

The authors indicated no relevant conflicts of interest.

ASH Committee on Government Affairs Visits Congress to Discuss Research Funding and Physician Payment Reform

Following its March 17, 2015, meeting in Washington, DC, the ASH Committee on Government Affairs visited more than 30 congressional offices on March 18 to explain to members of Congress and their staff the impact National Institutes of Health (NIH) funding cuts have on research to find cures and treatments for patients with serious hematologic diseases. ASH Committee members also educated Congressional members and staff on the need to repeal the current Sustainable Growth Rate (SGR) formula and reform Medicare payment for physician services (see developments on SGR repeal below).

Congressional meetings are an important component of ASH’s advocacy efforts, providing an opportunity for Members of Congress and their staff to gain insight on issues of concern to hematologists. However, the Society needs the help of all members to bring issues important to the future of hematology to the attention of the U.S. Congress and other governmental agencies.

ASH strongly encourages members to let the ASH Government Relations, Practice, and Scientific Affairs Department know when you are in Washington, DC, and are available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard in the halls of Congress. You can also participate in the Society’s advocacy efforts by visiting the ASH Advocacy Center and by joining the ASH Grassroots Network. Contact ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org, or visit www.hematology.org/Advocacy for additional information on ASH’s advocacy efforts.

Legislation to Address Specialty Tier Drug Cost-Sharing Introduced in House

In late March, Representatives David McKinley (R-WV) and Lois Capps (D-CA) reintroduced the Patients’ Access to Treatments Act (H.R. 1600) in the House of Representatives. The bill, identical to legislation introduced in the last Congress by Representatives McKinley and Capps, seeks to prevent private health insurance plans from imposing higher costs for medications in the specialty drug tier (Tier IV). The legislation represents an important first step toward removing the burdens of excess cost-sharing for Americans who need high-cost, specialty-tier medications. This legislation would make critical, life-saving medications some of which can cost thousands of dollars per month affordable for patients. Instead of paying a percentage of the cost of these drugs, from 25 to 33 percent or more, patients would have a much lower, fixed co-payment. H.R. 1600 would require drugs in Tier IV to be priced as those in Tier III, typically at a $50 co-pay. Representatives McKinley and Capps are working to find sponsors for a Senate version of the bill.

ASH has been working with the Coalition for Accessible Treatments, a group of 32 patient and provider groups dedicated to ensuring that all Americans have access to critical life-changing and life-saving medications, to support the Patients’ Access to Treatments Act for the past year. The Society issued a statement applauding the bill’s introduction on March 25, 2015, and urging congressional support for the legislation.

High drug prices are a major issue facing patients with hematologic conditions such as leukemia, lymphoma, and hemophilia, and ASH will continue to advocate for passage of the Patients’ Access to Treatments Act. Additionally, as part of the Society’s efforts to ensure patient access to safe and effective hematologic drugs that are expensive and often in specialty tiers, ASH has developed a resource on its website that provides a consolidated list of resources for physicians and patients trying to access high cost hematologic drugs. The High-Cost Hematologic Drug Access webpage (www.hematology.org/Clinicians/Drugs/) includes:

- Patient assistance (drug access) program information available through patient groups, foundations, and pharmaceutical companies, with direct links to specific details and forms for obtaining each therapy
- Templates of appeal letters ASH members can download and use to justify the use of high cost drugs to insurance companies
- Links to the Consult a Colleague Program for physicians with further questions
- A callout box to ASH’s advocacy campaigns related to drug access

ASH Committee on Government Affairs Visits Congress to Discuss Research Funding and Physician Payment Reform

Congress Passes Bill to Permanently Repeal SGR, Reform Medicare Physician Payment System

In early 2015, ASH advised members on the status of the SGR, the payment formula that each year leads to potential cuts in Medicare physician payment and each year is avverted by Congressional action. Although ASH expected to again see Congressional action on a temporary fix, given the new Congress and the April 1 deadline, surprising developments eventually led to the March 19, 2015, introduction of a bill, the Medicare Access and CHIP Reauthorization Act of 2015 (H.R. 2), which would permanently address the issue. H.R. 2 repeals the SGR, a flawed formula mandating scheduled reductions in Medicare physician payments, and replaces it with a 0.5 percent annual physician pay increase for the next five years. The legislation also establishes a merit-based incentive payment system starting in 2018 that will recognize physician performance related to quality measure reporting, resource use, meaningful use of electronic health records, and clinical improvement activities. On March 26, the House of Representatives passed H.R. 2 with extraordinary bipartisan support. Upon its return from a two-week recess, the Senate cleared the bill by a 92-8 vote and sent the measure to the White House for President Obama’s signature. Visit www.hematology.org/Newsroom to read a statement from ASH President Dr. David A. Williams on the passage of the Senate bill.

ASH Committee on Government Affairs Visits Congress to Discuss Research Funding and Physician Payment Reform

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Too Many RBCs or Platelets Stall Blood Flow in Cerebral Capillaries


The demonstration by Dr. Santisakultarm and colleagues of stalled blood flow in increased percentages of cerebral capillaries in PV and ET provides a mechanism other than thrombosis for focal cerebral hypoxia and subsequent microinfarction. The abrupt, spontaneous resolution of these capillary stalls with re-established rapid blood flow may explain the frequent but transient central nervous system symptoms including headaches, dizziness, vision loss, dysphasia, and focal paresis that are associated with PV, ET, and secondary polycythemia. Stalled blood flow in cerebral capillaries may also help explain how increased hemostatic is associated with reduced perfusion and enhanced infarct size on serial MTRIs following ischemic strokes. Therefore, stalled cerebral capillary blood flow may play a role in microinfarcts and in exacerbation of ischemic damage from compromised blood flow in larger cerebral vessels.

Figure A
Sequential 2PEF images that demonstrate flowing (left panels) and stalled (right panels) capillaries in the cerebral cortex (images captured every 0.3 s for a total of 1.2 s of observation). Texas Red-dextran was intravenously injected to label blood plasma (bright), leaving the cellular components unlabeled (dark).


Ten years ago, multiple groups published groundbreaking work describing the somatic activating JAK2 V617F mutation and its central role in the pathogenesis of myeloproliferative neoplasms (MPNi).1-4 Further studies identified JAK-STAT pathway mutations in the thrombopoietin receptor (MPL) and the caleutrin gene (CALR) in JAK2-negative MPNi.5,6 The pivotal role of aberrant JAK-STAT signaling in MPN has provided the rationale for the development of JAK kinase inhibitors. The JAK1/ JAK2 inhibitor ruxolitinib was recently approved for patients with hydroxyurea-resistant or intolerant polycythemia vera (PV), which follows its initial approval for myelofibrosis (MF) in 2011. In both MF and PV, core benefits include improvement of symptomatic systems and splenomegaly. It has been observed that MPN patients have markedly elevated levels of proinflammatory cytokines, and that ruxolitinib (as well as other JAK inhibitors) is associated with a decrease of cytokine levels.7 However, the exact mechanisms by which JAK inhibitors impact the production of cytokine levels have been largely speculative. In a collaborative study originating from the Memorial Sloan Kettering Cancer Center, Dr. Maria Kleppe and colleagues use single-cell cytokine profiling of mouse models and patient samples to show that the attenuating effects of JAK inhibitors on cytokine secretion is only efficacious if it occurs in both nonmalignant and malignant cell populations.

Using two mouse models of MF (MPLW515L+bone marrow [BM] transplanted mutant mice and JAK2V617F knock-in mice), the authors show that proinflammatory cytokines are elevated in the serum and/or BM supernatant of these mice, and that short-term ruxolitinib treatment could normalize serum cytokine levels. Next, the authors performed single-cell cytokine profiling experiments that demonstrated aberrant cytokine secretion profiles of MF murine and human bone marrow cells compared to control BM cells. These findings included: 1) an increased fraction of cytokine-secreting cells, 2) increased per-cell cytokine secretion, and 3) co-secretion of multiple cytokines. The authors showed that sorted mature myeloid cells and megakaryocyte/erythroid progenitor (MEP) cells both had increased fractions of cytokine-secreting cells and increased per-cell cytokine secretion in MF compared to controls. The two cell types, however, had discrete cytokine secretion profiles: mature myeloid cells primarily secreted TNF-α and CCL3, whereas MEP were predominantly from nonmutant cells. These findings of increased and heterogeneous cytokine secretion from mutant and nonmutant cells were corroborated in a murine model of JAK2V617F-positive disease and a patient with JAK2V617F-positive primary myelofibrosis.

This work by Dr. Kleppe and colleagues sheds light on the complex interactions between malignant cells and supporting cells in the BM microenvironment of MPN. These findings may also extend to other cancers since inflammation arising from pathologic cytokine elaboration is a cardinal feature of many tumors. Numerous questions are generated from this work. For example, how do differences in cell-specific cytokine secretion profiles influence the phenotype and severity of MPNs? What role do host genetic factors versus diseases-specific variables (e.g., JAK2 mutant allele burden) play in initiating and perpetuating the aberrant cytokine storm? Given the common tendency for disease persistence to develop over time with JAK inhibition, it will be important to interrogate whether these pathways can be therapeutically exploited to improve outcomes for patients.

Multiple myeloma (MM) is a diagnosis based on the presence of a monoclonal, κ- or λ-expressing plasma cell in bone marrow or of more of the CRAB criteria including lytic lesions, renal insufficiency, anemia, and/or hypercalcemia. Until recently, the standard of care for the evaluation of MM-related bone disease had been whole-body x-ray (WBXR). The International Myeloma Working Group has revisited this definition very recently, incorporating, along with free light chain ratio and degree of marrow plasmacytosis, the results of top of local lesions on sensitive imaging techniques. In this recent consensus statement by Dr. Meletios Dimopoulos and colleagues, the International Myeloma Working Group (IMWG) has issued new evidence-based recommendations for the use of magnetic resonance imaging (MRI) for the evaluation of plasma cell disorders.

The consensus statement recommends the use of MRI to define symptomatic MM.4 This is now incorporated into the new definition of symptomatic MM.2 Evidence provided in the recent publication supports the conclusion that patients with lesions detected on MRI are at higher risk of progression to symptomatic MM4 and should be treated for MM. The statement further supports the use of MRI as the gold-standard method for the detection of bone marrow involvement by MM. MRI is also defined as the modality of choice to evaluate painful lesions, particularly in the axial skeleton, and to detect spinal cord compression. MRI is further recommended to distinguish between benign versus malignant MM-related osteoradionecrotic fractures.

A solitary plasmacytoma of the bone (SBP) is defined by the presence of a solitary bone lesion in the absence of a clonal plasma cell population on bone marrow biopsy and lack of CRAB criteria. The majority of patients with this condition will ultimately progress and subsequently require systemic therapy for the treatment of MM. MRI is a more sensitive modality for the detection of occult lesions and is now recommended as part of the staging procedure in patients with SBP. The IMWG did not change its recommendation regarding the routine work-up of monoclonal gammopathy of undetermined significance and does not recommend MRI as part of the staging. Instead, the authors of the consensus statement also highlight the role of MRI as a prognostic tool in the evaluation of MM but do not recommend the routine use of MRI for this purpose.

Historically, the use of MRI has been limited by cost, prolonged acquisition time, patient discomfort due to claustrophobia, and the exclusion of patients with metal devices. Whole-body MRI (WB-MRI), a method that does not require contrast, has been developed, circumventing or mitigating a number of these limitations. However, this technique is not widely available as of yet. The alternative to MRI when a more sensitive imaging modality is needed is positron emission tomography combined with computed tomography (PET-CT). Like, MRI, PET-CT is a more sensitive imaging modality than WBXR for the detection of active focal lesions. The recent prospective study was inferior to PET in the detection of diffuse pattern bone marrow involvement, however, head-to-head, MRI was not found to be superior to PET in the detection of focal lesions in another.8

The IMWG consensus statement provides guidelines for the judicious use of MRI in the diagnostic evaluation of MM. The use of advanced skeletal imaging to better classify patients with asymptomatic MM and SBP will refine management of these diseases. Information gathered by such testing is an excellent option with the added advantage of less radiation exposure.
Immunomodulation: An Interesting Off-target Effect of Ibrutinib


Inhibitors that can inhibit negative regulators of T-cell activation have been the subject of great interest recently, with blockade of CTLA-4 and PD-1 or of PD-L1 showing impressive results in clinical trials for a number of solid tumors, as well as Hodgkin lymphoma. There is also emerging evidence that small molecules with activity in lymphoma, such as inhibitors of phosphoinositide-3-OH kinase (PI3K) p110 delta, may have effects upon T-cell responses, raising the possibility of additive or even synergistic effects between these different classes of drugs. This study from the laboratory of Dr. Ronald Levy at Stanford University extends this idea to the Bruton tyrosine kinase inhibitor ibrutinib, which has shown activity against chronic lymphocytic leukemia, mantle cell lymphoma, activated diffuse large B-cell lymphoma and lymphoplasmacytic lymphoma, by inhibition of the signaling pathways downstream of the B-cell receptor. Ibrutinib is also an inhibitor of interleukin-2 inducible T-cell kinase (ITK), which is an important mediator of survival for Th2 cells. These investigators therefore hypothesized that ibrutinib might act as an immunomodulator by altering the balance of Th1/Th2 response to tumors.

Initial experiments established that the syngeneic lymphoma cell line A20 is insensitive to ibrutinib, both in vitro and in vivo, with no evidence of cell killing or reduced tumor growth at doses up to 10 µM. Similarly, A20 is not killed in vitro by anti-PD-L1 antibodies, despite expressing high levels of the antigen, although there was evidence of slight growth retardation in vivo. However, the combination of ibrutinib and anti-PD-L1 demonstrated much more substantial therapeutic effects in vivo, with around half the mice cured after treatment of established lymphoma. This effect was lost if the mice were depleted of T cells, suggesting an active immune response. This was confirmed by the demonstration of intracellular IFNγ staining and the appearance of anti-PD-L1 antibodies in the peripheral blood by MHC tetramer staining. Re-challenge of cured animals with further doses of 10⁶ CT26 cells demonstrated the presence of immune memory, with resistance to their engraftment.

This study adds further evidence to the view that molecules that can affect signaling pathways in malignant lymphocytes may also have potent effects upon the normal cells of the immune system. This that could be shown in a tumor model where the malignant cells lack any Btk expression is particularly interesting, and it suggests that ibrutinib may be able to augment weak T-cell responses in tumors that respond less well to immunomodulating antibodies. The translation of this idea to clinical investigation is appealing, though previous experience of severe liver toxicity when vemurafenib was combined with Gilumumab highlights the risks of uncontrolled autoimmune and the need for caution in trial design with this class of agents.

2. Ali K, Soond DR, Piñeiro R, et al. Inactivation of PI(3)K p110 delta, may have effects upon T-cell responses, raising the possibility of additive or even synergistic effects between these different classes of drugs. This study from the laboratory of Dr. Ronald Levy at Stanford University extends this idea to the Bruton tyrosine kinase inhibitor ibrutinib, which has shown activity against chronic lymphocytic leukemia, mantle cell lymphoma, activated diffuse large B-cell lymphoma and lymphoplasmacytic lymphoma, by inhibition of the signaling pathways downstream of the B-cell receptor. Ibrutinib is also an inhibitor of interleukin-2 inducible T-cell kinase (ITK), which is an important mediator of survival for Th2 cells. These investigators therefore hypothesized that ibrutinib might act as an immunomodulator by altering the balance of Th1/Th2 response to tumors.

Further experiments confirmed similar findings with the ibrutinib-insensitive J558 myeloma cell line and with two solid tumor cell lines: 4T1, a triple-negative breast cancer; and CT26, a colon cancer, neither of which express Bruton tyrosine kinase. The in vivo therapeutic effect was more impressive with the CT26 model, which is known to express a murine leukemia virus antigen AH1. In mice treated with the ibrutinib/anti–PD-L1 combination, AH1-specific CD8 cells were detectable in the peripheral blood by MHC tetramer staining. Re-challenge of cured animals with further doses of 10⁶ CT26 cells demonstrated the presence of immune memory, with resistance to their engraftment.

This demonstration of a humanized mouse capable of being infected with the human variant of Ebola Zaire. To accomplish this model, the research team took advantage of an immunodeficient mouse strain, NSG, and irradiated and subsequently transplanted these mice with human CD34+ cells. After eight to 12 weeks post-transplantation, these mice then had a functioning human hematopoietic system with fully differentiated human lymphocytes and myeloid cells. Depending on the individual transplantation, mice varied in their degree of human chimerism, and were separated into a “low” engraftment group (20% to 40% human chimerism) and a “high” engraftment group (>40% human chimerism). These groups of mice were infected with the human Ebola Zaire virus, resulting in death in 75% of the low group and 100% of the high group. Both groups of infected mice had high viremia, with blood viral titers of up to 10⁵ focus-forming units (FFU)/mL at the peak of disease. Intriguingly, necropsies of infected mice showed liver steatosis, and in one animal, the authors observed areas of focal hemorrhage and necrosis in the liver. Splenomegaly was also seen in the Ebola-infected mice, along with considerable lymphocyte infiltrates in the spleen and lipid droplet deposits in the liver.

This demonstration of a humanized mouse capable of being infected with human Ebola Zaire represents the first small animal model of the disease that reproduces the typical features of Ebola infection in humans, including viremia, cell damage, liver steatosis, signs of hemorrhage, and lethality. This study adds to the growing list of humanized mouse models to study infections, including the humanized BLT (bone marrow, liver, and thymus) mouse now used for HIV research, which will help to reduce the amount of expensive and limited NHP research typically used in these fields. Given the presence of a human immune system capable of being infected with the human virus, this new model of mouse Ebola disease may serve as a viable research tool for preclinical development of novel antivirals and vaccines to combat this deadly epidemic.

Antibody Therapy for the Treatment of Relapsed ALL

**STUDY TITLE:** Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 100135, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT0121853

**SPONSOR:** National Cancer Institute

**COORDINATOR:** Children’s Oncology Group

**PARTICIPATING CENTERS:** Multiple sites in the United States and other countries

**ACCRUAL GOAL:** 598 patients

**STUDY DESIGN:** A risk-stratified randomized phase III trial will test whether the incorporation of blinatumomab into a multiagent chemotherapy regimen improves disease-free survival (DFS) for patients with a first relapse of B-lymphoblastic leukemia (B-ALL). Patients aged one to 30 years are risk-stratified based on the site and timing of relapse and the presence of MRD ≥ 0.1%. Blinatumomab has also been investigated as a single-agent therapy in highly refractory patient populations, achieving a second remission in 43 percent of patients treated with stepwise dosing for up to five cycles (Gore L, et al. 2016;59:3-17). Blinatumomab is a bispecific T-cell engager (BiTE®) single-chain antibody construct that directs CD3-positive T cells to CD19-expressing leukemic blasts to effect cell lysis. Preliminary results with this agent have been promising, with a greater number of marrow B-ALL relapses, refractory B-ALL, and non-overlapping toxicity profiles. This has prompted efforts to incorporate novel agents into traditional treatment regimens, including several new classes of immuno-oncologics (Barth M, et al. 2012;159:3-17; Ai J. Br J Haematol. 2015;168:471-480). Potential advantages of this class of agents include their unique mechanisms of action and non-overlapping toxicity profiles.

**RATIONALE:** While outcomes for pediatric patients with newly diagnosed B-ALL have improved dramatically in recent decades, outcomes for relapsed disease remain poor. This has prompted efforts to incorporate novel agents into traditional treatment regimens, including several new classes of immuno-oncologics. Blinatumomab is a bispecific T-cell engager (BiTE®) single-chain antibody construct that directs CD3-positive T cells to CD19-expressing leukemic blasts to effect cell lysis. Preliminary results with this agent have been promising, with a greater number of marrow B-ALL relapses, refractory B-ALL, and non-overlapping toxicity profiles. This has prompted efforts to incorporate novel agents into traditional treatment regimens, including several new classes of immuno-oncologics (Barth M, et al. 2012;159:3-17; Ai J. Br J Haematol. 2015;168:471-480). Potential advantages of this class of agents include their unique mechanisms of action and non-overlapping toxicity profiles.

**TREATMENT OBJECTIVES:** Although outcomes for pediatric patients with newly diagnosed B-ALL have improved dramatically in recent decades, outcomes for relapsed disease remain poor. This has prompted efforts to incorporate novel agents into traditional treatment regimens, including several new classes of immuno-oncologics. Blinatumomab is a bispecific T-cell engager (BiTE®) single-chain antibody construct that directs CD3-positive T cells to CD19-expressing leukemic blasts to effect cell lysis. Preliminary results with this agent have been promising, with a greater number of marrow B-ALL relapses, refractory B-ALL, and non-overlapping toxicity profiles. This has prompted efforts to incorporate novel agents into traditional treatment regimens, including several new classes of immuno-oncologics (Barth M, et al. 2012;159:3-17; Ai J. Br J Haematol. 2015;168:471-480). Potential advantages of this class of agents include their unique mechanisms of action and non-overlapping toxicity profiles.

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** Clinicians Corner **

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**STUDY DESIGN:** This is a phase III randomized trial, with a two-to-one randomization to the ibrutinib arm (arm A) of 346 patients and to the FCR control arm (arm B) of 173 patients.

**ACCRUAL GOAL:** 519

**STUDY DESIGN:** This is a phase III randomized trial, with a two-to-one randomization to the ibrutinib arm (arm A) of 346 patients and to the FCR control arm (arm B) of 173 patients.
treatment include anemia, thrombocytopenia, symptomatic or progressive lymphadenopathy or hepatosplenomegaly, weight loss, moderate fatigue, fever, and night sweats. Exclusion criteria include active hematologic anemia, corticosteroids orally, active prior malignancy with certain exceptions, major surgery or radiation therapy within four weeks, active hepatitis, pregnancy, cardiac disease, or a cerebrovascular accident. Treatment: Treatment A consists of oral ibrutinib with IV rituximab for seven cycles, then continuous oral ibrutinib until disease progression; treatment B consists of six cycles of fludarabine and cyclophosphamide IV daily for three days and rituximab on day 1 of each cycle except split dosing on days 1 and 2 for cycle 1.

The primary objective of the trial is to assess the ability of ibrutinib-based induction therapy to prolong progression-free survival (PFS) as compared with FCR, the standard chemomunotherapy regimen. Secondary objectives include evaluation of overall survival (OS), relative toxicity, quality of life (both short and long term), correlation of pretreatment characteristics with outcomes, longitudinal evaluation of minimal residual disease (MRD), genetic examination and monitoring of clonal evolution, examination of T-cell function, and signaling networks downstream of the BCR. The trial is expected to incorporate clinical and biologic characteristics will be used to predict PFS and OS. Laboratory specimens will be collected for biomarker and diagnostic analysis, and relapse specimens will be collected to analyze for mechanisms of resistance.

Rationale: FCR has exhibited a high response rate – 95 percent overall with a 72 percent complete response (CR) – and an excellent duration of response with median time to progression of 80 months, especially for patients who achieve a CR without MRD, for whom the median time to progression is 80 months (Tam CS, et al. Blood. 2008;112:975-980). In two meta analyses of upfront regimens for CLL, FCR has been the leader in terms of PFS and OS (Messner A, et al. Ann Hematol. 2015 [Epub ahead of print] Lodyzynski P, et al. Cancer Treat Rev. 2015;41:77-83). However, FCR is an intensive regimen, with a high rate of serious adverse events, such as cytopenias and infections. In particular, FCR can be toxic to the elderly patients (Shah N, et al. Leuk Lymphoma. 2014;55:1-12 [Epub ahead of print]), and as 70 is the average age at diagnosis of CLL, the regimen is perceived as too toxic for many individuals. Moreover, prolonged cytopenias (19 years last three months; Tam CS, et al. Blood. 2008;112:975-980), and therapy-related myelodysplastic syndrome/acute myeloid leukemia are ever present concerns (Benjamin O, et al. Leuk Lymphoma. 2014 [Epub ahead of print]).

Ibrutinib, a Bruton tyrosine kinase inhibitor, has been a successful therapy for several B-cell malignancies, and it has received U.S. Food and Drug Administration approval for mantle cell lymphoma (MCL) with at least one prior treatment, CLL with at least one prior treatment, upfront CLL with del17p, and Waldenström macroglobulinemia. These approvals have been in rapid succession between November 2013 and January 2015, with impressive results even as a single agent.
A survey of practice-based hematologists that was recently commissioned by ASH’s Committee on Practice highlighted the changing nature of clinical hematologic care. Fellows completing their training will inevitably encounter a dynamic landscape as they enter the workforce. With this in mind, it is worth examining the unique opportunities and challenges that hematology fellows face during this transition, and how fellows may be modifying their clinical training in response to these changes.

Workforce Shortage Predictions and Job Opportunities

In ASH’s Committee on Practice survey, one in four respondents (24%) indicated that they were considering retirement in the next five years. Over the next 10 years, the physician retirement rate, combined with changing population demographics and Medicare use patterns are estimated to increase the overall demand for hematology and oncology services by 40 percent, whereas the supply of full-time equivalent hematologist-oncologists may only grow by 25 percent.1 Additionally, with the implementation of the Affordable Care Act, approximately 25 million Americans will gain insurance coverage by 2017.2 These newly insured individuals are projected to increase demand for hematology-oncology services by 500,000 visits in 2025 alone.3

Though practicing physicians have voiced concern that physician shortages will lead to demands for increased physician productivity, recent fellows completing training view the open job market as one with increasing employment opportunities and job security. In fact, 42 percent of physicians responding to ASH’s survey indicated they are actively recruiting new hematologists into their group.4 While practices owned by academic medical centers are the most active in recruiting new physicians, 40 percent of fellows training at academic institutions are choosing to pursue diverse opportunities in private practice, industry, and government.5

Blurred Lines and Practice Changes

Interest in alternative career paths may not only be driven by decreased federal research funding, but also by the fact that the distinctions in academic and nonacademic practice careers is becoming less clear. Opportunities for both research and patient care can now be found throughout traditional private practice, industry, and academic settings. In fact, an impressive 95 percent of practice-based hematologists participate in clinical research.3 Fellows considering careers in practice-based hematology are more likely take note of declining reimbursements for medical services, increasing costs related to running private practices, and the trend toward practice affiliation with larger institutions when contemplating practice-based careers. In response to these changes, fellows are not only adapting their career decisions, but also choosing to modify their training environment.

Who is the Hematology Fellow?

The average hematology fellowship graduate enters the workforce having spent a minimum of 10 years in graduate training (four years of medical school, three years of internal medicine or pediatric residency, and three years of fellowship training). A small subset will have advanced degrees, including PhDs, and will enter training much older than their counterparts. Most fellows commencing training are in their mid-30s, and many have young families. The degree of educational debt varies, but one nationwide study found that 37 percent of hematology-oncology fellows have more than $100,000 of debt.6 Women make up 48 percent of fellows in hematology-oncology training programs, and international medical graduates comprise 43 percent.7

Factors influencing career paths are a function of individual factors: personal goals, expectations of personal time, financial obligations, and mentorship. Some fellows prioritize financial compensation, restricted call duties, predictable work hours, and time for leisure activities, while others may choose job opportunities based on their desire to teach, interest in research, or perception of academic prestige.8,9

Emerging Trends in Post-Fellowship Career Choices

Despite the diversity of factors that influence fellows’ career paths, there appear to be several emerging trends. Most fellows (69%) report that geographical location is one of the most important factors informing subsequent career choices.9 While job openings are available throughout the United States, perceived reliability and compensation vary considerably. At present, there is a greater demand for jobs within large metropolitan hubs where the job market is relatively saturated. As a result, fellows are often seeking jobs in higher-cost-of-living environments with a paucity of opportunities, rather than less-densely populated areas where compensation and demand may be higher.

Interestingly, the factors of relative compensation and/or loan burden may not be as strong in influencing post-fellowship career choices as previously thought. One study conducted by Dr. Leora Horn and colleagues demonstrated that a higher percentage of fellows with an interest in academic careers had cumulative debt loads of greater than $100,000 when compared to their counterparts pursuing nonacademic careers.4 Beyond compensation, it appears that many new job seekers are increasingly conscious of controllable lifestyle factors. In fact, when the American Society of Blood and Marrow Transplantation polled fellows asking whether increased compensation or improved work-life balance (WLB) would motivate their move into the field, it was apparent that WLB was a more potent factor in driving career decisions.5 The priority that fellows place on WLB should come as no surprise since many have spent the preceding five years of training working 60 to 80 hours a week while concurrently raising children, caring for aging parents, and investing time in personally meaningful activities. Various studies have shown that fellows suffer higher rates of burnout and emotional exhaustion when compared with population control samples, so it is natural for these factors to influence post-fellowship career plans.

Fellows are Changing Their Training in Response to This Changing Landscape

Given these changes in the hematology workforce, fellows are modifying their training agendas. With the knowledge that mentorship is critical to optimizing future career fit, fellows are seeking mentors with whom they not only share professional interests, but who are also able to model balance in their personal lives. Engaging in “team-based” science is one method to increase efficiency and productivity while still protecting personal time. To achieve this, fellows may align themselves with mentors who are able to provide connections with productive collaborative groups. Similarly, on the clinical side, fellows are recognizing the need to balance organizational pressure for increased productivity with the maintenance of WLB. To that end, in programs throughout the United States, fellows are learning how to work collaboratively with advanced practice providers to deliver team-based care.

Fellowship is a privileged time during which trainees have the flexibility to augment and diversify their marketable skill set. In this regard, fellows’ pursuit of advanced degrees or classes in education, epidemiology, pharmacology, and clinical research is now commonplace. For example, the University of Washington created a Clinical Biostatistics class that incorporates expert teaching from both academic and industry settings. Industry has likewise created training opportunities; for example, Genentech’s Clinical Fellows Program provides a one-year training grant that allows fellows to complete their own clinical research project, while obtaining training in decision-making about novel therapeutics.10

Persistent Challenges

The current training experience offered by most hematology programs provides minimal exposure to less traditional career choices. Additionally, fellows often complete their training without sufficient knowledge of the administrative and business demands of practice—promotion requirements for distinct career paths, and funding requirements. Without this exposure, fellows may underestimate the demands of their chosen careers and subsequently experience significant career dissatisfaction.8,11

To address these shortcomings, the ASH Trainee Council, working with the Committee on Training, has developed a number of tools and programs to help fellows during this period of transition. During the ASH annual meeting, both early and later-career speakers from academia, industry, government, and community-based practice provide didactics and break-out sessions that focus on mentoring, the diversity of career tracks, early career development, and job-seeking strategies. The Council has also created Career Development Timelines (www.hematology.org/Career/Timelines) tailored to the unique needs of MDs and MD-PHDs to help them transition from training to their first job. Additionally, the Council maintains a Grants Clearinghouse list on the ASH website (www.hematology.org/Fellows/Grants2015) to highlight funding opportunities during and after the fellowship period.

The role of social media and networking could be further developed to help fellows find their ideal work niche. Online professional networking hubs such as Doximity and LinkedIn could be used to connect fellows not only to jobs, but to more formal mentoring as well. Online social networks and media have the advantage of overcoming geographical barriers to showcase the diversity of career opportunities in hematology—from newly minted hematologists to medical students contemplating future careers.

Epilogue

Fellows are entering the workforce during a time when the demand for physician productivity will skyrocket due to major shifts in population demographics and insurance coverage. How fellows choose to practice hematology will ultimately be a function of their ability to understand the changing landscape. It is therefore imperative that fellows are provided with, and actively seek, opportunities to decipher the social, economic, and political forces currently affecting practice. With such insight, fellows, working together with their local training...
Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal disorder associated with intravascular and extravascular complement-mediated hemolysis. Intravascular hemolysis is effectively controlled by eculizumab, but there are few data reflecting monitoring of the effect of the drug. In this week’s Blood, Dr. Régis Péfatul de Latour and colleagues report that effective complement blockade can be monitored quite simply by assessment of 50 percent hemolytic complement activity, which correlates with lactate dehydrogenase levels and need for breakthrough transfusions. This should prove an invaluable method for monitoring effectiveness of eculizumab and distinguishing inadequate dosing from other causes of breakthrough hemolysis, notably extravascular hemolysis.


Telomere biology disorders (TBDs) are a heterogeneous group of syndromes caused by germline mutations in genes required for telomere biology. Manifestations of TBDs range from isolated bone marrow failure to multisystem disorders. The frequent development of aplastic anemia (AA) has been attributed to telomere attrition in hematopoietic stem cells. In this week’s Blood, Dr. Arun Balakumaran and colleagues demonstrate that skeletal stem/progenitor cells from patients with TBDs are unable to support hematopoiesis and give rise to a marrow that mirrors some histologic features of AA marrow. They suggest that telomere dysfunction in bone progenitors may also contribute to AA through dysfunction of the bone marrow microenvironment.

Dr. Bharind indicated no relevant conflicts of interest.

3. Adapting to Changes in Practice-Based Hematology. ASH Clinical News. Available at http://ahsclinicalnews.org/

FEBRUARY 19, 2015

The V600E kinase-activating mutation of BRAF profoundly shapes the distinct identity of hairy cell leukemia (HCL) among B-cell neoplasms. BRAF V600E acts as a defining and driving mutation in this form of chronic leukemia. The plenary paper by Dr. Valentina Petriossi and colleagues in this week’s Blood explores the mechanistic basis and molecular impact of target inhibition in hairy cell leukemia. The investigators demonstrate the significance of the BRAF-MEK-ERK pathway in the biology of HCL, and give further credence to the potent antileukemic activity of clinically available BRAF and MEK inhibitors in this disease.

FEBRUARY 26, 2015

The poor outcome of acute myeloid leukemia (AML) in elderly patients is partly attributed to an increased incidence of underlying myelodysplasia, but outcomes are also often poor in elderly patients with de novo AML. In this week’s plenary paper in Blood, Dr. R. Coleman Lindley and colleagues provide critical insight into this observation. In an elegant targeted mutational analysis of secondary AML (s-AML), treatment-related AML, and unselected AML, they confirm that mutation in one of eight genes (SRSF2, SF3B1, U2AF1, ZNF644, ASXL1, EZH2, BCR, or STAG2) predicts for secondary AML. In the 67 cases of de novo AML in the unselected series, 42 patients were over age 65, and one third of them had s-AML mutations. These patients had the predicted poor prognosis; perhaps more important is the observation that those patients without these mutations treated with standard AML therapy had a response that mirrored that of younger de novo AML patients. This important study will lead the way to a better understanding of AML heterogeneity and inform the appropriate choice of therapy.


The mainstay of treatment for primary central nervous system lymphoma (PCNSL) has been high-dose methotrexate (MTX), often in combination with high-dose cytarabine. This has improved survival of the disease, which with supportive care has a median survival of less than four months, to about 40 to 50 percent at three years. In this week’s Blood, Dr. Antonio Omuro and colleagues report results of a phase II trial combining MTX and rituximab-based combination therapy with high-dose therapy and autologous stem cell transplantation in newly diagnosed PCNSL. Two-year progression-free survival was 79 percent, and overall survival was 81 percent. Furthermore, they document that there was little or no detectable neurotoxicity associated with this regimen. These highly encouraging results suggest that a phase III trial is warranted and is likely to change the standard of care for this devastating disease.


Although platelet transplants are generally thought to be relatively contraindicated in patients with thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT), their safety has been a focus of ongoing controversy. In this week’s Blood, Dr. Ruchika Goel and colleagues report on a survey of the Nationwide Inpatient Sample to evaluate a potential association between platelet transplant and thrombosis in 10,624 hospitalizations for TTP. Of 5,334 patients receiving platelet transfusions, 79 percent developed thrombosis, and overall survival was 57 percent. There was a significant association between platelet transplant and arterial and thrombotic events and mortality in the setting of HIT and TTP, but no such association was seen with ITP. These results support the traditional caution regarding platelet transplant in the setting of platelet consumption disorders.

MARCH 5, 2015

Many of the inherited platelet bleeding disorders affect the formation of specialized storage compartments within platelets, termed lysosome-related organelles. In two parallel publications in this issue of Blood, Dr. Ronghua Meng et al. and Dr. Anish Sharda and colleagues use the Hermansky-Pudlak syndrome (HPS) as a model to show that ADP released by dense granules serves as an autocrine signal to promote platelet release of α-granule and lysosome cargo and protein disulfide isomerase (PDI), all of which serve to stabilize thrombus formation. Thus, the authors of these papers present evidence that the dense granule is the source of an autocrine signal. These data provide critical insights into the pathogenesis of defective thrombus formation in HPS and also furnish a novel perspective on understanding hemostasis in general.


Dr. Franços Bermaidun et al. identify the rate of acute anemic events and extracranial internal carotid artery stenosis as risk factors for silent cerebral infarction (SCI) in children with sickle cell disease. Although these “silent” permanent brain lesions do not produce obvious focal neurologic deficits, they can cause neurocognitive impairment and poor academic performance and also portend overt stroke. SCI occurs as early as in the first year of life, and its prevalence increases with age. The study published in this week’s Blood establishes the rate of acute anemic events and extracranial internal carotid stenosis as significant and independent risk factors for silent cerebral infarcts.

As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), and find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster).

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See below for the latest recorded events, and visit https://ashondemand.org/webinars to start viewing!

Choosing Wisely: Examples of Stewardship Initiatives in Hematology
Speakers: Dr. Lisa Hicks (Moderator), Dr. Ravi Sarode, Dr. John Freedman, Dr. Scott Weingarten

The unspoken challenge of the Choosing Wisely campaigns is how to move from words to action. How can physicians and other health-care workers encourage adoption of the Choosing Wisely recommendations? This webinar will explore three different examples of quality improvement and stewardship initiatives in the hematology arena. Presenters will review how they developed and implemented their initiatives, the impact they have had, and challenges they have encountered along the way.

The Medicare Oncology Care Model: What It Is and What It Means for Practice
Speakers: Dr. Steven L. Allen (Moderator), Dr. Ron Kline, Dr. Heidi Schumacher, Brian Whitman

The Center for Medicare and Medicaid Innovation recently announced a new payment model initiative focusing on cancer care. This webinar will help practices to understand what is required in order to receive the care management fee and how their resource use will be calculated. Questions about the role of blood cancers, bone marrow transplants, and specialized centers will also be addressed.

Chimeric T-Cell Antigen Receptor Therapy in Leukemia and Lymphoma
Speakers: Dr. Cynthia Bollard (Moderator), Dr. Michel Sadelein, Dr. James Kochenderfer

This webinar will discuss the development of non-human leukocyte antigen-restricted chimeric antigen receptors (CARs) as a strategy to target leukemias and lymphomas using gene transfers, plus various clinical trials underway utilizing CAR-C19 therapies for both autologous and allogeneic transplant settings. CAR technology involves the genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by tumor cells.

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