Designer Babies?

The idea of a dystopic future in which mankind genetically engineers offspring for desirable traits or in order to make "super humans" has long been a focal point of many works of science fiction. At the beginning of this year, rumblings in the scientific community and media began to suggest that science fiction was quickly becoming reality. In January, a leading group of genetic scientists met in Napa, California, to discuss the implications of genomic engineering and published a joint opinion on the subject in Science in April. In that opinion, the authors recommended that steps be taken to:

"...strongly discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical applications in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations."

A similar piece was published in Nature a few days before from leading scientists at Sangamo and the Alliance for Regenerative Medicine titled "Don't Edit the Human Germ Line." Both groups cited that the technology was not yet adequately understood (particularly the long-term consequences) to warrant editing of human reproductive cells, and that public misperceptions about such efforts could undermine promising work on gene editing of somatic cells that has the potential to treat those with existing diseases. These efforts in gene therapy of adult cells, in relation to blood disorders, were highlighted in the January/February issue of The Hematologist.5

The prominent opinion pieces in Science and Nature were published in likely anticipation of a report in mid-April in the journal Protein Cell from Dr. Puping Liang and colleagues at Sun Yat-sen University in China. This was the first published report of genetic engineering of human embryos, and it garnered an intense media coverage. One CBS news report on the manuscript referred to the study as the "Designer Baby Controversy"– a similar sentiment in many other media outlets.

The researchers took advantage of the relatively new gene-editing tool, CRISPR/Cas9.6 CRISPRs (clustered regularly interspaced palindromic repeats) are short sequences in the genomes of several bacteria and archaea that act as a form of adaptive immunity against viruses and plasmids. When exposed to a bacteriophage, short phage-related spacer sequences are incorporated into the CRISPR region of the bacteria genome. Then, when the bacteria are exposed to the phage again, this spacer sequence interacts with CRISPR-associated (Cas) nucleases and, similar to RNAi, binds to the specific phage sequence and cuts the DNA. In a series of recent studies, it was determined that the "guide RNA" could be programmed to cut any portion of the genome desired,7 including in mammalian cells. CRISPR nucleases can recognize DNA and hence requires complicated protein engineering, the single Cas9 endonuclease is the only protein needed, and genome specificity is generated through the guide RNA – a relatively simple synthesis procedure (Figure, online only). This has opened the door of genome editing to a much broader group of scientific teams than the previous technologies.

(Cont. on page 3)

Therapy-Related AML and MDS: Who Really Has It?
ROBERT PETER GALE, MD, PHD, DSc (hon), FACP, JOHN M. BENNETT, MD, PHD, AND F. OWEN HOFFMAN, MD
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Einstein had it right when it comes to theoretical physics, but wrong when it comes to medicine. Sir William Osler was more on target when he said, "The science of medicine is uncertainty. The art of medicine is probability."

Most of our knowledge of a relationship between exposure to cancer therapy and developing acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) comes from epidemiological studies. So it is important to remember that epidemiology deals with associations, not cause and effect. Also, we need to avoid the logical fallacy of post hoc ergo propter hoc (after this, therefore because of this). Specifically, just because AML or MDS follows prior cancer therapy does not mean these diseases were caused by the therapy (see Note 1).

It is also important to recall that epidemiological studies typically consider the association between an exposure and an outcome in a cohort, not a person. Even exposures strongly associated with an increased risk of AML or MDS in a cohort do not allow us to impute this exposure as causative in a specific person with AML or MDS. Here we need to rely on a different calculation: probability of causation in an individual; namely, the likelihood his/her exposure caused or contributed to their developing AML or MDS. This is complicated. For example, what if the exposure did not cause AML or MDS because the person would have developed it in the absence of exposure? What if the exposure merely accelerated developing AML or MDS or made it worse? More on this later.

To accurately estimate whether a person’s AML or MDS is caused by or contributed to by a prior exposure, we need to know many variables. For example, there is a strong association between age and background incidences of AML and MDS in unexposed persons. Two people, one 20 and the other 70 years old, who develop AML or MDS 10 years after an exposure, have entirely different probabilities of causation. Also, data from survivors of atomic bomb explosions show age at time of exposure and gender are associated with risk of developing AML and MDS. We also need to consider the interval between exposure and developing AML or MDS. Several of these variables are confounded (Figure, page 5). For example, when we studied the interval to develop AML or MDS after radiation therapy of a first cancer (with or without chemotherapy), we found different latencies for males and females. Also, AML and MDS have different latencies under different exposure conditions. Latency for AML after radiation therapy can be very brief – less than two years – whereas it is generally believed to have been 10 to 15 years in atomic bomb survivors and to have lasted up to 30 years postiongression. (Cont. on page 5)
Dr. Gerald J. Robbins passed away on May 16, 2015, at age 63 years. His friends and collaborators on the ASH Committee on Practice, Task Force on Practitioner Needs, Committee on Communications, and ASH Practice Partnership knew Gerald as a true advocate for patients with hematologic conditions, and his many years of unwavering service helped to enhance the health and well-being of many.

Gerald always had a distinctive presence at meetings. He was the well-dressed, good-looking guy with the big smile and calming voice. As a member of the Committee on Practice, Gerald’s perspective and experience were embedded at the epicenter of where so much of modern hematologic practice occurs — in a vibrant, successful community-based practice caring for patients with both hematologic and oncologic disorders. Those who have worked with him, practice in New Port Richey, Florida, helped numerous patients gain access to clinical trials. His vast experience as a clinician and active involvement in medical affairs at every level — local, state, national — made his counsel highly valued. He had been a driving force in the Florida Society of Clinical Oncology (FLASCO) and was clearly a leader.

Gerald’s dedication was truly inspiring. He was a kind, soft-spoken, engaged, and accomplished colleague, and friend, devoted to his family, his patients, his community, and to the professional organizations with which he worked both in hematology and oncology.

Hematology has lost one of its most dedicated leaders all too prematurely. Those who knew him and worked with him have lost an irreplaceable friend.

–Dr. Steven L. Allen, MD, FACP
–Dr. Lawrence A. Solberg Jr., PhD, MD
Designer Babies?

Using CRISPR/Cas9 editing, Dr. Liang and colleagues set out to determine whether they could edit a portion of the human γ-globin gene, which is mutated in β-thalassemia, in preimplantation embryos. The team used tripronuclear zygotes that form as a result of two sperm nuclei in one oocyte — an occurrence that happens roughly 5% of the time during in vitro fertilization (IVF) programs. The triploid zygotes were not able to develop normally and did not result in embryos, and the team stated that these embryos were specifically chosen to avoid ethical concerns. The team then co-injected 86 embryos with an optimized guide RNA to target the γ-globin gene (found in preimplants in a cell line), the mRNA for Cas9 nucleus, green fluorescent protein (GFP) mRNA, and a sgRNA alklo, which was a template for the corrected γ-globin gene. Of the 86 zygotes, 71 were living 48 hours after injection. Of those, 59 expressed GFP, and of those, 54 were able to be amplified by polymerase chain reaction for further evaluation. Within the 54 that were genetically tested, about half (28) of them were cleaved by Cas9, and of those, only four were successfully edited with the repair template. The authors also noted several off-target mutations as a result of the editing procedure; it was incomplete, as the resulting embryos were mostly containing different versions of the same gene.

The authors conclude in their discussion:

“Because the edited embryos are genetically mosaic, it would be impossible to predict gene editing outcomes through preimplantation genetic diagnosis (PGD). Our study underscores the challenges facing clinical applications of CRISPR/Cas9.”

Despite the media reports to the contrary, it is fairly clear from this report that “designer babies” are not being created in China. This manuscript has, however, ignited discussion regarding the ethical paths forward for genome editing. Shortly after publication, NIH director Francis Collins reiterated the government and agency positions against similar human embryo experiments. The authors themselves may have outlined the larger question of embryo gene editing when they mentioned preimplantation genetic diagnosis (PGD), which is already occurring clinically. Dr. Rudolf Jaenisch, president of the International Society for Stem Cell Research (ISSCR), was quoted in the New York Times, stating that, “with gene editing, the cutting and pasting has to start immediately… given that (in most cases of genetic disease) half the embryos that are edited would be normal — their DNA would have forever altered for no reason.” Attention on gene editing should be focused at this time on therapies in invertebrates to treat children and adults with genetic diseases. Researchers exploring somatic cell gene editing for blood disorders are pioneering this field, and the hemato logic scientific community should help inform the public about the difference between these ongoing efforts and those related to germline modification.


ASH Convenes Venous Thromboembolism Guideline Coordination Panel

On June 19, 2015, ASH, in collaboration with McMaster University in Hamilton, Ontario, convened a panel of more than a dozen experts to discuss a new set of guidelines in the treatment of venous thromboembolism (VTE). While this critical topic is core to hematology, it intersects with primary and physicians in other subspecialties as well. Therefore a multidisciplinary approach will be taken in order to garner participation across a variety of specialties inside and outside of ASH’s membership.

This initiatives is led by Dr. Mark A. Crowther (ASH Committee on Quality chair), Dr. Adam Cuker (Guideline Coordination Panel chair), and Dr. Holger Schönemann (guideline methodology lead). For any questions about these and other ASH guidelines, contact Rob Kunke, Senior Manager of Practice Guidelines, at rnkunkle@hematology.org or visit www.hematology.org/Clincians/Guidelines-Quality.

Q: MHH is shaped around “How I Treat” presentations from top experts. How will this format help attendees to see what they have learned in their own clinical setting back home?

BL: “Our commitment to recommending and delivering the best treatment to a particular patient has become more challenging than ever. Recent insights into the biology of hemato logical neoplasms have inspired new avenues of diagnostic and therapeutic development and has furnished opportunities for a personalized treatment approach. I expect that this meeting will help hematologists understand the state-of-the-art directions in the therapeutic management of our patients in realistic and complex clinical situations.”

IG: “How I Treat is one of the best topics that I read in Blood so I am excited to hear these presentations in MHH. I think this is probably one of the best opportunities to hear the experts give their opinions on how to make decisions in treating patients. I am also looking at the opportunity to choose in clinical practices. We have a unique opportunity in this meeting to meet with some of the best experts in hemato logical malignancies and get their true clinical input.”

RL: “This format will help hematologists to learn the newest data on the management and treatment of patients with hemato logical malignancies and to learn how to use molecular data to inform the care of such patients.”

WS: “I focus almost exclusively on treatment of acute leukemias, so I am particularly excited to hear from my colleagues speaking about the lymphomas and multiple myeloma since it will be a wonderful way of getting “up to date” with the new treatment strategies and how they are being incorporated into frontline therapy.”

Q: There are 25 speakers at this first offering of the MHH. Who are the experts from whom you are most looking forward to hearing?

BL: “How do we keep up these days? This is a nontrivial challenge for many of us. Scientific knowledge across a broad range of hematologic malignancies is emerging at an unprecedented pace. This knowledge has a profound impact on diagnostics and therapeutics. I am looking forward to the extraordinary opportunity of MHH where world-class experts with in-depth experience will assemble and discuss illustrative clinical cases and examine their approach in clinically relevant disease settings.”

IG: “I am looking forward to hearing from all the experts. I think each topic will give us an opportunity to learn about the disease also how to handle the difficult cases and how to make decisions in the future.”

RL: “I am excited to hear from everyone, including Bob Lownberg on the overall picture in our field, Fred Applebaum on the use of transplantation, and Wendy Stock on novel therapies in acute lymphocytic leukemia, especially in the adolescent and young adult population.”

WS: “I am excited to get an expert review of the most recent advances and therapeutic approaches to treatment of hemato logical malignancies. It has also been great fun to work with my colleagues, Drs. Richard Larson and Adele Fielding to plan our session on acute lymphocytic leukemia, which will be a nice blend of advances and practical advice.”

*Reminder! There is still plenty of time to take advantage of reduced advance registration rates for MHH. Visit www.hematology.org/Malignancies for more information and to register.*
Therapy of Multipled Relapsed HCL

Several options are being tested for multiply relapsed HCL. In order to avoid chemotherapy toxicities, but to retain cytoxic power, we use recombinant immunotoxin containing an Fv fragment of a Mac and a truncated form of Pseudomonas exotoxin. High CR rates in multiply relapsed HCL were reported in 2001 using the anti-CD22 recombinant immunotoxin BL22, including patients with HCLv. Mutations were made in the VH domain of BL22 that improve its binding to CD22, and the resulting affinity-matured recombinant immunotoxin moneutemomab pasudotox achieved CRs in approximately 50 percent of patients with multiply relapsed HCL, many without MRD. Another strategy to achieve MRD-negative CRs is to use six cycles of either pentostatin plus rituximab, or bendamustine plus rituximab. Our protocol at the National Institutes of Health (NIH) prospectively evaluates and randomizes patients between both regimens and allows crossover to the other regimen if needed. Most can achieve MRD-negative CR, but with more toxicity than patients receiving non-chemotherapy approaches such as moneutemomab pasudotox.

Targeted Approaches in HCL

In the Braf pathway of normal cells, BRAF phosphorylates MEK, phospho-MEK phosphorylates ERK, and phospho-ERK leads to cell proliferation. Braf containing the V600E mutation, present in nearly half of malignant melanomas, in lower percentages of other tumors, but in nearly all cases of classic HCL, exhibits uncontrolled phosphorylation leading to the malignant phenotype. Inhibition of this mutant BRAF with vemurafenib, or with dabrafenib combined with the MEK inhibitor trametinib, is approved for malignant melanoma and is currently being tested in HCL. Oral BRAF inhibitors in HCL can rapidly reverse severe cytopenias but have not yet been reported to clear MRD and prevent relapse. The oral agent irutimub, which targets the Bruton’s tyrosine kinase pathway, is also being tested in patients with HCL and HCLv. Though most patients achieve stable disease, this can have palliative benefit, particularly for patients with HCLv.

Summary and Algorithm for Treatment Approach to Patients with Relapsed/ Refractory HCL

The Figure shows our algorithm for prioritization of clinical trials for relapsed HCL, additional options can be used off-protocol. Patients with once-relapsed HCL alter purine analog can be retreated with the same or different purine analog as a single-agent, particularly if the first remission duration was long, but we prefer combining cladribine with rituximab on study to eliminate MRD. For patients with multiply relapsed HCL, moneutemomab pasudotox is our preferred option due to its unique ability to achieve MRD-negative CR without chemotherapy toxicities. For patients who responded to anti-CD22 recombinant immunotoxin (BL22 or moneutemomab pasudotox) but need additional therapy, we target CD22 with recombinant immunotoxin LMB-2. For patients ineligible for moneutemomab pasudotox or LMB-2, we use BRAF or MEK inhibitors, provided patients are able to handle toxicities and understand that remission durations may be limited if MRD persists. For patients with HCL/HCLv ineligible for these approaches, we prefer either the irutimub protocol or our protocol using rituximab combined with either bendamustine or pentostatin. Brutinib offers oral therapy without chemotherapy toxicity, while the rituximab-chemotherapy combination offers a likely path to high MRD-negative CR rates and the potential (as in patients after moneutemomab pasudotox) of not needing therapy for many years. Follow-up and testing will be needed to determine the long-term benefit of these approaches and whether MRD-negative CR can translate into cure.

References

However, the minimal latency estimate is questionable, as there was no comprehensive follow-up of the survivors until roughly 1955. MDS seemed to begin much later, starting at about 30 years postexposure and continuing 60 years later, but there are no early data. These are only some of the variables requiring consideration. We also need to evaluate individual exposure to other known leukemia-causing agents such as benzene and cigarette smoking. One bottom-line conclusion: If a person who now has AML or MDS were exposed only to radiation therapy (not drugs) for a prior cancer, and the exposure was more than two to three years before, it is quite unlikely their AML or MDS would be caused by their prior radiation therapy exposure.

If a hematologist considers all these data, it is sometimes possible to give a best estimate value of the likelihood an exposure caused or contributed to a person developing AML or MDS. However, such best estimate values are uncertain and should be accompanied by a confidence or credibility interval indicating a range of possible values. In reality, it is often impossible from epidemiological data to distinguish between cases of AML or MDS where the exposure caused or contributed to developing the disease (etiologic cases) and cases in which the person would have developed AML or MDS anyway (see Note 2).

The process for determining probability of causation differs substantially from what hematologists do when they encounter a person with AML or MDS exposed to potential leukemia-causing drugs and/or ionizing radiation. All too often, the reaction is: “If you had cancer and were treated, and you now have AML or MDS, you must have therapy-related AML or MDS.” This is not to say hematologists do not consider other data such as whether there are cytogenetic abnormalities (such as del[5/5q] or del[7/7q]) associated with therapy-related AML or MDS. However, it is important to recall that the frequency of these cytogenetic abnormalities increases with increasing age in persons with AML or MDS, unrelated to therapy.14 And because cancer incidence increases with age, persons with suspected therapy-related AML or MDS are likely to be old. The same caveat applies to mutations thought to be associated with therapy-related AML or MDS, such as TP53. Consider recent data indicating a high frequency of TP53 mutations and even clonal hematopoiesis in older persons with no hematologic disorder.15,16 As discussed, details of prior exposures are rarely known. How often have you heard a colleague say a person with newly diagnosed AML or MDS had chemotherapy or radiation therapy for a prior cancer without knowing any details?

Statisticians and epidemiologists would likely judge our method of assigning causation in most cases of therapy-related AML or MDS to be scientifically meritorious. This is because the relationship between an exposure and risk of certain that all is uncertain.”

When does this leave us? We suggest that hematologists be more cautious in saying a person has therapy-related AML or MDS. They need to try to ascertain precise details of prior exposures and consider possible confounders, especially the normal steep age-related increases in AML and MDS. They also need to consider that older persons with AML are more likely to have had a prior cancer, whether or not their AML or MDS is therapy related, and that many persons with cancer, treated or not, are at increased risk of developing AML or MDS. Part of this may be a surveillance bias, and part may result from biological, genetic, or environmental factors. If there are insufficient data to make a reasonable best estimate value, a confidence interval in a case of AML, one should avoid using the designation therapy-related AML. However, with sufficient data, the hematologist should consider qualifying his/her estimate with terms which convey the level of certainty such as “likely,” “unlikely,” or “uncertain.” Accepting these suggestions can help prevent inaccurate attributions of causation and decrease the likelihood of inappropriate therapy decisions. As Francis Bacon said, “Without certainty, science is nothing more than seemingly sophisticated guesswork.” How we get to certainty is another issue entirely.11 To quote Blaise Pascal: “It is not certain that all is uncertain.”

Note 1: Therapy-related AML or MDS also refers to persons developing these disorders after therapy for other diseases such as rheumatoid arthritis. Sometimes it refers to persons exposed to diagnostic radiological procedures such as computed tomography or positron emission tomography scans, or radionuclides for diagnostic or therapeutic purposes and/or to persons receiving intense immune suppression. We consider these concepts similar.

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Acknowledgment
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The Mayo Clinic is one of the largest academic medical centers in the world, with more than 2,500 physicians and scientists. It is known for its expertise to almost every conceivable medical condition known to science. Within this medical enterprise, the Multiple Myeloma Program has managed to bring together more than 30 clinicians and researchers on a rare cancer, representing just 1 percent of all malignancies. How does one maintain adequate output, growth, collegiality, and trust while playing in a small sandbox? In other words, is there a recipe for the success of our program, and can it offer models that can be replicated elsewhere?

The story of the program for multiple myeloma and related disorders at the Mayo Clinic is both fascinating and instructive, and it can be traced back more than 50 years ago when Dr. Leif Bergsagel joined the institution as a fellow. In 1959, Dr. Kyle started a serum protein electrophoretic pattern for the first time. Little did he realize at that time what he was getting himself into. Soon, one pattern became 100, and 1,000, and 1,000 became countless. Within one year, a review of the more than 6,500 serum protein electrophoretic patterns performed at the Mayo Clinic led to a 1960 publication in JAMA, before the concept of monoclonal/ polyclonal gammopathies was introduced. In that paper, Dr. Kyle described that a height/width ratio greater than 4:1 was associated with plasma cell disorders (multiple myeloma, Waldenström macroglobulinemia, myeloma), while those with a lower ratio had polyclonal processes (chronic, active hepatitis, rheumatoid arthritis, or other inflammatory diseases).

Alter joining the Mayo Clinic staff in 1961, Dr. Kyle realized that to pursue the study of plasma cell disorders, he needed a laboratory and better techniques. He spent a week at the National Cancer Institute with Drs. John Fahey and J. Frank Quimby, learning about the iodine/vitamin B12 assay. Perhaps the most seminal event was Dr. Kyle's interaction with Dr. Robert Kyle, joined the Mayo Clinic Arizona; novel therapy

Dr. Kyle asked the program for years. Several discoveries (many of which have become among the most cited articles in the field) and almost 15 years later, this one-man myeloma program added a second staff consultant in 1975, Dr. Philip Greipp. This was followed in 1982 by the addition of Dr. More Gertz. These three pillars of the program attracted residents and fellows like magnets. Fellowed understood that the myeloma program was vibrant and that it offered exceptional opportunity for research and career development. Key recruits in the ensuing years were Drs. Thomas Wittg, John Lust, Martha Lacy, Angela Despenzcri, Rafeal Fonseca, and the other author, Dr. Vincent Rajkumar. Soon the program expanded to the Scottsdale, Arizona, location under the leadership of Dr. Fonseca, who promptly had the audacity to recruit two of his closest competitors in the field of myeloma genetics. Drs. Bergsagel and Dr. A. Keith Stewart. Yes, they came to be known as the three musketeers.

Today, 40 years later, the growth and transformation of the Mayo Clinic Multiple Myeloma Program is astonishing. The serum bank has more than 250,000 samples; the database now contains almost 50,000 patients. The IBM punch cards are long gone, replaced by the most modern of statistical systems, which can be replicated elsewhere. Today, there are more than 25 clinical faculty members (more than 10 at the professor level) with a career focused on myeloma and related disorders, across all three geographical sites of the Mayo Clinic (Minnesota, Arizona, and Florida; Figure). All are engaged in research, education, and practice, with each member providing a vital and different emphasis. Although the contributions of each member to the field are individually and collectively extensive, it is worth examining how, even in a small field, it is possible to divide the problem into many parts, where the whole is greater than the sum of its parts. Dr. Kyle realized that understanding the bone marrow gamopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and several other entities. Dr. Greipp developed the International Staging System. Dr. Gertz focused his attention on anyloidosis while Dr. Rajkumar described light-chain MGLS and has led research on POEMS syndrome. Dr. Bergsagel developed the first molecular cytogenetic classification of myeloma, and Dr. Fonseca identified the association between cytogenetic classification and prognosis. Dr. Lust studied mechanisms of progression. Dr. Wittg was one of the first to describe the identification and prognostic value of circulating plasma cells. Dr. Stewart identified biomarkers of resistance to immunomodulatory drugs and led the development of carfilzomib. Dr. Rajkumar led early trials of thalidomide and lenalidomide, while Dr. Lacy led most of the initial studies of pomalidomide.

With so many individuals performing at a high level, we were able to attract very high-caliber people to the Mayo Clinic Arizona; novel therapy

Center for Hematology, dedicated to the diagnosis and treatment of multiple myeloma and related plasma cell disorders.

The Mayo Genealogical tree illustrates the leadership in the program for years. Several discoveries (many of which have become among the most cited articles in the field) and almost 15 years later, this one-man myeloma program added a second staff consultant in 1975, Dr. Philip Greipp. This was followed in 1982 by the addition of Dr. More Gertz. These three pillars of the program attracted residents and fellows like magnets. Fellowed understood that the myeloma program was vibrant and that it offered exceptional opportunity for research and career development. Key recruits in the ensuing years were Drs. Thomas Wittg, John Lust, Martha Lacy, Angela Despenzcri, Rafeal Fonseca, and the other author, Dr. Vincent Rajkumar. Soon the program expanded to the Scottsdale, Arizona, location under the leadership of Dr. Fonseca, who promptly had the audacity to recruit two of his closest competitors in the field of myeloma genetics. Drs. Bergsagel and Dr. A. Keith Stewart. Yes, they came to be known as the three musketeers.

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With so many individuals performing at a high level, we were able to attract very high-caliber people to the Mayo Clinic Arizona; novel therapy

Center for Hematology, dedicated to the diagnosis and treatment of multiple myeloma and related plasma cell disorders.
ASH Committees Visit Congress, NIH in Support of Issues Affecting Hematology

Following its May 18 meeting in Washington, DC, the ASH Committee on Practice visited more than 40 congressional offices to advocate for insurance parity for oral cancer drugs, as well as for a Centers for Medicare & Medicaid Services (CMS) review of existing outpatient evaluation and management (E&M) codes for physicians who primarily treat chronically ill patients.

In both the U.S. House and Senate, committee members sought co-sponsors for the bipartisan Cancer Treatment Parity Act, which would require any health plan that provides coverage for cancer chemotherapy treatment to provide coverage for orally administered and self-injectable anticancer medications at a cost to the patient no less favorable than the cost of intravenous, port-administered, or injected anticancer medications.

Regarding the second issue, existing E&M codes do not properly describe the work performed by physicians who primarily treat chronically ill patients. Committee members asked for congressional support in urging CMS to commission the research necessary to study the E&M codes and determine where they are deficient in describing the work performed by physicians such as hematologists.

ASH advocacy efforts in support of hematology research also continue. In April, members of the ASH Committee on Scientific Affairs traveled to the National Institutes of Health campus in Bethesda, Maryland, to meet with leaders from the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). These meetings provided ASH with an opportunity to highlight a number of promising areas of hematology research, including the scientific investigation identified in the recently released 2015 ASH Agenda for Hematology Research, as well as to emphasize the need for sustained support in these areas.

These face-to-face meetings are an essential component of ASH’s advocacy efforts, providing an opportunity for NIH staff and members of congress and their staff to gain insight into issues of concern to hematologists. The strength in ASH’s advocacy, however, is the continued involvement of all members of the Society who, through their enthusiastic support, bring issues important to the future of hematology research and practice to the attention of the U.S. Congress and other governmental agencies. ASH strongly encourages members to let the Government Relations, Practice, and Scientific Affairs Department know when you are in the U.S. Capitol during the ASH Committee on Practice Hill Day.

Interested in Getting More Involved in ASH and Advocacy? Apply for the 2015 ASH Advocacy Leadership Institute

The fifth annual ASH Advocacy Leadership Institute will take place in Washington, DC, October 28-29, 2015. This two-day workshop provides an opportunity for ASH members to gain a better understanding of the Society and its activities and to learn about legislation and health policy affecting hematology research and practice.

The first day of the Institute will focus on learning about the legislative process and health policy and will include training in advocacy. Sessions will feature guest speakers from Congress, the presidential administration, and NIH, as well as other health agency officials. The selection of participants is based on a nomination process, and participation will be by invitation only. Up to 20 participants will be invited to attend the two-day workshop.

Nominations are being accepted through July 31. The ideal candidate is an ASH member who is a U.S. citizen, is interested in health policy and advocacy, and wants to become more involved in ASH activities. Self-nominations are welcome. For more information or to submit a nomination online, please visit www.asha.org/ALI

You may also send nominations to ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org. Please include the following information: nominator’s name and phone number; nominee’s name and institution (and contact information, if available); and reason for nomination (short paragraph describing the nominee’s interest in this opportunity).

House Advances “21st Century Cures” Legislation

In mid-May, the House Energy and Commerce Committee unanimously approved the 21st Century Cures Act. Although consideration of the legislation by the full House had not yet been scheduled as this issue of The Hematologist went to press, Committee Chairman Fred Upton (R-MI) has indicated he would like to see the bill on the House floor as soon as possible, and likely before the month-long August congressional recess.

The bill, which aims to “accelerate the pace of cures in America,” proposes changes to both NIH and the Food and Drug Administration (FDA), including seeking to provide significant increases in funding for NIH.

As approved by the committee, the bill would authorize a five-year, $10 billion NIH Innovation Fund, with $2 billion per year in mandatory appropriations routed through the NIH director. The bill allocates the Innovation Fund for various purposes, including a new Accelerating Advancement Program, research awards tied to specific projects or objectives, research awards for innovative scientists and early-stage investigators, high-risk high-reward research, research awards to small businesses, and the NIH intramural program. At least $500 million from the Innovation Fund must be allocated to a new Accelerating Advancement Program, which would provide matching funds to NIH institutes and centers to finance innovative research projects that could not be funded within the institute/center’s current budget, in areas including biomarkers, precision medicine, infectious diseases, and antibiotics.

Among other research related provisions, the bill:

- Requires NIH to issue a strategic plan
- Establishes a Biomedical Research Working Group to provide recommendations on how to streamline the grant process for researchers
- Includes a “sense of Congress to reiterate the importance of scientific conferences and meetings to the mission of NIH”
- Requires each NIH institute, as appropriate, to conduct or support high-risk, high-reward research
- Improves loan repayment programs for NIH researchers
- Requires NIH to establish a national pediatric research network
- Mandates a seven-year pilot project of a data-sharing system for data from clinical trials solely funded by NIH

ASH is closely monitoring the advancement of the House bill and a similar effort underway in the Senate. For the most up-to-date information on this issue and other issues impacting ASH advocacy, please visit the ASH website at www.hematology.org/Advocacy.
New Light on an Old Drug


A s excitement surrounding new agents and immunotherapy for the treatment of pediatric acute lymphoblastic leukemia (ALL) develops, there may be a tendency to overlook the importance of medications that have been a backbone of ALL therapy since effective treatments were first developed. Mercaptopurine (MP) has been a mainstay of ALL therapy since the early 1950s,1 and prolonged daily administration during the maintenance phase of treatment is routine practice. Why a prolonged maintenance phase is so critical for the cure of ALL is not understood.

In recent years, there have been several different lines of evidence highlighting the essential role of this component of ALL treatment. Namely, the prognostic importance of maintaining MP dose intensity through adequate chronic daily exposure during maintenance has been demonstrated in several studies. Low levels of active MP metabolites and dosing interruptions have been associated with relapse risk and shown to negatively impact outcomes.2,3 Dr. Smita Bhatia and colleagues also recently reported that genetic variation in thiopurine methyltransferase (TPMT) is a major contributing factor to MP intolerance.4,5 TPMT is an enzyme responsible for the methylation and inactivation of MP, and testing for inherited nonfunctional alleles has allowed MP dosing adjustments to achieve therapeutic benefit and/or to avoid excessive toxicity. While inherited deficiencies of TPMT lead to higher levels of active thiopurine metabolites and hematologic toxicity, MP intolerance is observed in many children with wild-type TPMT as well.

Following up on these observations, Dr. Jun Yang and colleagues investigated the genetic basis of inter-patient and inter-racial/interethnic variability in MP tolerance in children at the genome-wide level. A genome-wide association study (GWAS) was performed in two prospective clinical trials for childhood ALL. The discovery GWAS cohort consisted of 657 children treated on Children’s Oncology Group ALL protocols where there were specifications for dosing adjustments for myelosuppression. The replication cohort consisted of 371 children with ALL treated on St. Jude Children’s Research Hospital protocols. The authors reported that East Asian ancestry was significantly associated with lower MP dose intensity (p < 0.001; Figure). In the discovery GWAS, in addition to variants in TPMT, a germline variant in nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) was also strongly linked to MP intolerance in East Asian children. Patients with homozygous TT genotype were extremely sensitive to MP and tolerated only 8.3 percent of the scheduled MP dose. Defective NUDT15 is hypothesized to lead to accumulation of an excessive amount of the cytotoxic thiodGTP metabolite with normal doses of MP. The association of these risk alleles in TPMT and NUDT15 with MP dose intensity was confirmed in the validation cohort. Notably, the risk allele in NUDT15 varied by race and ethnicity and was most common in East Asians (9.8%), followed by Hispanics (3.9%). In contrast, it was very rare in Europeans, occurring in only 0.2 percent of cases. Taken together, the higher frequency of the NUDT15 germline variant in East Asians suggested this could be a contributory factor to higher rates of MP intolerance in this group.

Since the early inception of combination chemotherapy regimens for childhood ALL, efforts have been underway to investigate optimal delivery of MP and methotrexate during the maintenance phase.6 The study by Dr. Yang and colleagues illustrates the power of genome-wide approaches and the importance of expanding studies of the genetic basis of drug tolerance across different racial and ethnic groups. As MP is the mainstay of pediatric ALL therapy, studies such as this have the potential to impact individualization of drug delivery, a concept which underlies current efforts to practice precision medicine.

For patients enrolled onto AALL03N1 protocol, MP dose was adjusted during maintenance therapy on the basis of host toxicities (myelosuppression and infections), and dose intensity was defined as ratio of prescribed dose over protocol planned dose (75 mg/m² per day). Dose intensity was measured longitudinally over six months and is shown as a single cumulative value for the study period. Patients were grouped into five racial/ethnic categories on the basis of genetic ancestry. Genetically defined East Asians had lowest MP dose intensity (ie, most likely to be MP intolerant). p value was estimated by using Kruskal-Wallis test. Each box includes data between 25th and 75th percentiles, with a horizontal line indicating the median. Whiskers indicate maximal and minimal observations within 1.5× the length of the box.

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Precision medicine is the latest buzzword, and its goal is to individualize care based on the biology of each patient. For cancer therapy, this means taking into consideration myriad molecular and cellular features; namely, genomics, RNAseq, mRNA microarray, microRNA, proteomics, metabolomics, and others. Because each cancer appears to be unique, there might be distinct points of vulnerability that could be exploited for treatment. The ideal would be to not undertreat patients by administering drugs to which their cancer isn’t sensitive, and not to overtreat, causing excessive toxicity and the draining of unnecessary resources. The goal should be nontoxic "magic bullets" that have specific targets and are administered easily (preferably orally), with rapid action and resolution of the tumor, and ultimately, cure of the disease. This has happened previously in the field of leukemia — with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML). With several years having elapsed since the U.S. Food and Drug Administration approval of imatinib and related TKIs, it seems that we are not close to identifying comparable drugs despite ongoing efforts to sequence DNA and RNA, analyze proteins, and test tumor cells against drugs ex vivo. Additionally, all the ex vivo approaches to chemotherapy drug testing have many drawbacks, including lack of the appropriate tumor microenvironment and lack of the relevant organs that metabolize specific drugs.

**Up Close and Personal: Implanted Devices for Chemotherapy Testing of Tumors in Patients**


From this quagmire now emerge ingenious devices that fulfill the promise of how clever engineering will transform medicine. Two concurrent publications in *Science Translational Medicine* describe the parallel development of implantable devices that test a number of chemotherapy drugs simultaneously within the tumor in the living patient and permit readout of results so that the "winner" can be chosen. Even combinations can be preprogrammed and assessed.

Dr. Richard Klinghoffer and colleagues at Presage Biosciences, at the Fred Hutchinson Cancer Research Center, and at other sites developed a CIVO — a patented device that is inserted percutaneously into the tumor in a study subject in vivo. It permits evaluation of up to eight drugs or drug combinations at a time. The CIVO has an array of four to eight microinjectors for delivery (Figure). Tumor sections that are 4 µm thick at 2-mm intervals perpendicular to the injection column are examined to assess tumor response. Viable cells are marked blue with DAPI to label nuclear DNA, green with a tracking dye, and orange to identify a biomarker. Antimitotic activity of drugs is visualized by staining for phosphohistone H3, apoptosis by staining for cleaved caspase 9, and DNA damage by staining for phosphohistone H2AX. They also examined a drug-resistant tumor in their preclinical model to find an active drug among the 97 approved-drug panel from the National Cancer Institute, and they were able to identify that mTOR inhibitors had activity by observing decreased phosphorylation of the mTORC1 substrate of eIF4E-binding protein 1 (the "biomarker" for this drug). They were able to document images of every cell from each stained tissue using digital, automated, high-resolution whole-tissue scanning. The investigators reported that the results obtained by testing in a mouse tumor xenograft model correlated with results obtained by systemic drug administration. Data for four lymphoma patients tested in a pilot study were also presented, and the major side effect noted was mild grade 1 transient erythema.

Dr. Oliver Jonas and colleagues at Massachusetts Institute of Technology and their collaborators developed a different in vivo drug testing device. They deliver the 820-µm (diameter) × 3-mm (length) device via biopsy needle, and it remains in place for 24 hours. The device is a reservoir (Figure) that releases microdoses of drugs inside the tumor. A coring needle removes the relevant tissue from the tumor. Imaging of autofluorescent chemotherapy drugs such as doxorubicin, lapatinib, and suniptinib, or fluorescently labeled drugs, was by fluorescence microscopy; nonfluorescent drugs were visualized by matrix-assisted laser desorption/ionization mass spectrometry. The extracted sample is analyzed histologically for cleaved caspase 3 to identify apoptosis, Ki67 to mark proliferation, and survivin, an apoptosis inhibitor. The investigators validated that the same profiles of apoptosis were obtained whether the drugs were delivered intravenously or from the device.

The technological limitations of these promising devices include site-to-site variation within a tumor or between one site and a distant metastasis, and genomic instability that leads to acquisition of drug resistance over time by selective pressure after treatment. Moreover, the major challenges for future development of this technology will be its cost and widespread access to millions of patients with cancer. However, the current system of drug development via a series of sequential phase I, phase II, and phase III trials is fraught with exorbitant cost, time, and potential patient morbidity. The future will undoubtedly be revealed in next-generation prototypes of these devices.
Less Autophagy in Myeloid Precursors Boosts Neutrophil Counts


Autophagy is the intracellular process by which cytoplasmic contents are targeted for digestion with recycling of macromolecular constituents such as amino acids, nucleosides, and lipids. Cytoplasm and organelles such as mitochondria, endoplasmic reticulum, and peroxisomes that are destined for autophagic removal are enclosed in a double membrane structure termed the autophagosome that subsequently fuses with a lysosome, creating the autolysosome, in which the sequestered cytoplasm and organelles are degraded by lysosomal enzymes. Autophagy has important roles in differentiation of almost all lineages of hematopoietic cells, including required clearance of mitochondria during reticulocyte maturation and lymphocyte differentiation. 1 However, Dr. Sara Roszman and colleagues in the laboratory of Dr. huve Simon reported the surprising findings that autophagy inhibits terminal differentiation of murine neutrophilic granulocyte precursors, and deficient autophagy in neutrophilic precursors increases neutrophil production rates and steady-state numbers.

In mice with a conditional knockout in neutrophil precursor cells of Atg5, which encodes a protein required for the formation of the autophagosome, these investigators found an approximate 50 percent increase in circulating neutrophils and two- to three-fold increases in splenic and lymph node neutrophils, respectively, compared to wild-type mice. DNA labeling of promyelocytes and myelocytes, the last stages of granulocyte precursors that undergo mitosis, showed a peak appearance of neutrophils in the blood in Atg5-knockout mice on the third day compared with the fourth day in wild-type mice. These increases in neutrophil steady state numbers and production rates appeared to be due to increased proliferation of granulocytic precursors that was not associated with increased neutrophil granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage–colony-stimulating factor (GM-CSF) or decreased granulocytic cell apoptosis. In vitro assays demonstrated that Atg5-knockout neutrophils had similar functional capacities, including phagocytosis, reactive oxygen species generation, granule release, and bacterial killing, as did wild-type neutrophils. A murine system of granulocytic differentiation in vitro demonstrated autophagy in the promyelocytes and myelocytes that decreased markedly in metamyelocytes, bands, and mature neutrophils. Inhibition of Atg5 expression by shRNAs decreased the early-stage autophagy and increased in vitro differentiation, whereas lentivirus-mediated overexpression of Atg5 enhanced autophagy and retarded differentiation. 2 With this in vitro granulocytic differentiation system, Dr. Roszman and colleagues also showed by inhibitor studies that the p38 MAPK-TORC1 pathway, which suppresses autophagy, mediates the decreased autophagy during granulocytic differentiation.

Although the reciprocal relationship between autophagy and neutrophil differentiation is surprising when compared with the key role of autophagy in differentiation of other hematopoietic lineages, this reciprocal relationship is consistent with previous studies of neutrophilic differentiation. Primary or azurophilic granules of neutrophils, which are delivered to phagosomes or to the exterior of mature neutrophils, are formed in myeloblasts and promyelocytes. In addition to myeloperoxidase and elastase, azurophilic granules contain lysosomal enzymes. A study demonstrating qualitative differences in the membranes of the azurophilic granules and lysosomes also noted the absence of mature lysosomes in fully differentiated neutrophils 2 – a finding consistent with the decline in autophagy during terminal neutrophil differentiation. Thus, promyelocytes have active autophagy that requires lysosomes, while they are also forming the azurophilic granules, which contain lysosomal as well as other degradative enzymes. Autophagy normally decreases markedly in the later stages of neutrophilic precursor differentiation, but inhibition of autophagy beginning in the promyelocytic stage appears to hasten their differentiation and proliferation into neutrophils. Conversely, enhancement of autophagy in immature precursors retards their differentiation.

Reliable increases in neutrophil production in the clinical setting are currently limited to administration of G-CSF or GM-CSF. Dr. Roszman and colleagues demonstrate that inhibiting autophagy by activating the p38 MAPK-TORC1 pathway, which inhibits production of functional neutrophils by a mechanism other than increasing G-CSF or GM-CSF. Inhibiting autophagy may adversely affect other hematopoietic and non-hematopoietic cells, but increasing neutrophil numbers by a means independent of these granulopoietic factors would be of considerable interest to hematologists. Indeed, autophagy inhibition combined with G-CSF or GM-CSF administration has the potential to hasten recovery of neutrophils in patients with chemotherapy-induced neutropenia. Similarly, patients with congenital or acquired neutropenias, especially those who do not respond to G-CSF treatment, might benefit from suppression of autophagy, if it can be demonstrated to increase their neutrophil production.

STAT3 as a Common Pathway for Anaplastic Lymphomas: Something to Target in ALK-Negative Types?


STAT3 has already been identified as a central player in several inflammation-related malignancies, and various mechanisms, such as chronic cytokine stimulation, constitutive receptor activation, and downstream signaling, have been shown to dysregulate this transcription factor. The role of the JAK/STAT3 pathway is already recognized in ALK-negative large-cell lymphoma (ALKCL), where the translocation of a chimeric ALK gene that activates STAT3 and maintains the malignant phenotype. No such mechanism has previously been demonstrated in ALK-negative lymphoma, which lacks these translocations. However, this study from an international collaborative group led by Dr. Giorgio Inghirami and Dr. Raul Rababand of the University of Torino, Weill Cornell Medical College, New York University, and Columbia University, gives important new clues as to both the pathogenesis and potential targets for intervention.

Exome sequencing was used to investigate the frequency of somatic mutations and their number variation. Although mutations were evenly distributed across the chromosomes, it was apparent that JAK1 and STAT3 genes were recurrently mutated. This was confirmed by targeted sequencing of 88 cases of ALK-negative systemic ALCL, among which nonsynonymous mutations in JAK1 or STAT3 were found in 18 percent, with 38 percent of cases exhibiting lesions in both genes. Convergent mutations in the STAT3 genes were identified in some ALCL or in other types of peripheral T-cell lymphoma. The cases with mutations were all found to express nuclear phosphorylated STAT3 (pSTAT3) by immunohistochemistry, with some nonmutated cases also showing this pattern, suggesting that alternative mechanisms of STAT3 upregulation may also exist. Similar increases in pSTAT3 were observed in cell lines transfected with mutant STAT3 expression constructs, an effect heightened by exposure to interleukin-6. Injection of mutant STAT3 cells led to metastatic engraftment and early death in immunodeficient mice, whereas mice remained healthy after injection of the wild-type equivalent. Moreover, STAT3-expressing cell lines showed upregulation of the transcription factor ATF3 and its downstream targets. Similar observations were made using constructs with mutations in JAK1 of the type found in ALCL, but there was no synergy between the STAT3 and JAK1 mutations, which were lethal when present together in a single cell.

Further investigation of the molecular determinants of malignancy in ALCL were sought by whole-transcriptome RNA sequencing, which revealed that in some ALK-negative cases there were fusion transcripts involving tyrosine kinases such as ROS1 and TYK2, with partners which could provide dimerization domains such as NFKB2. This was shown to permit transactivation, which in turn led to phosphorylation of JAK2/JAK3 and STAT3. Transfection into mouse fibroblasts showed that these chimeric transcripts could produce transformation in vitro and tumors in vivo, albeit less efficiently than NFKB2-ALK chimeras of the type found in ALKCL.

Investigating the potential for targeted therapy based on these findings, the authors developed inhibitors of the pathway for their effects in cell lines and preclinical models. Although the STAT3 inhibitor nicosamide showed limited activity in cells bearing mutations, an ALK-negative ALCL-derived xenograft showed growth inhibition with clinically relevant concentrations of the JAK1/JAK3 inhibitor ruxolitinib. In the cells bearing translocations such as NFKB2-ROST1, crizotinib did not significantly affect signaling, but a specific anti-ROS1 small molecule did prevent transphosphorylation.

This study is interesting because it provides clues to the pathogenesis of ALK-negative ALCL, with convergence upon JAK1/STAT3 either from mutations or translocations. The role of IL-6 signaling is also notable, as it appears that IL-6 may enhance the transformative capacity of STAT3 mutations, offering a possible explanation for the occasional spontaneous regressions seen in ALCL, potentially in response to an alteration in the cytokine milieu. These data also suggest potential new treatment approaches for ALK-negative ALCL, which historically carries a very poor prognosis. Inhibitors of the JAK/STAT3 pathway may well yield significant clinical responses, though the failure of crizotinib to inhibit NFKB2-ALK in JAK3-deficient cells was unexpected, and different molecules may be required to inhibit the effects of the tyrosine kinase rearrangements. This report supports the need for detailed molecular analysis of ALCL and for the development of novel treatment protocols based on these findings.

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Dr. Johnson indicated no relevant conflicts of interest.

Freshener Blood Is Not Necessarily Better Blood


R ed blood cell (RBC) transfusion is a frequently used therapy worldwide. In many countries, including the United States, regulations permit storage of RBC units for up to 42 days; however, prolonged RBC unit storage has been associated with shape change and rheologic changes as well as changes in metabolism, and oxygen affinity/delivery, commonly referred to as the RBC “storage lesion.” Multiple observational and retrospective analyses have been performed examining the effects of RBC storage age on patient outcomes. These analyses have resulted in a divergent set of effects complicated with bias.† Two recently published randomized controlled trials, by Dr. Jacques Lacroix and colleagues (ABLE) and by Dr. Marie Steiner and colleagues (RECESS), examined the impact of RBC storage age on different patient populations and have helped shed light on this critical issue.

The ABLE trial examined the storage age of transfused RBCs in critically ill adult patients across 64 centers in Canada and Europe, with 1,211 patients assigned to receive fresh RBC units stored for less than eight days, and 1,219 patients assigned to receive standard RBC units (mean age of 22 days). No difference was observed between the two groups in the primary outcome of 90-day all-cause mortality (p=0.38), and there were no significant differences between the groups with respect to major illnesses: duration of respiratory support; length of hospital stay; and transfusion reactions (Figure). Importantly, the ABLE trial used leukocyte-reduced RBC units, and thus, could not address whether leukocytes contribute to the degradation of RBCs or have other deleterious effects associated with long-term storage. Additionally, this trial did not address the use of RBCs that are stored for longer periods of time, such as 35 to 42 days. It is noteworthy that the ABLE subjects were transfused at a mean pre-transfusion hemoglobin level of 7.7 g/dl, and likely received less exposure to RBC transfusions than patients at centers with more liberal transfusion policies.

The RECESS trial examined the storage age of RBC transfusion in 1,098 patients 12 years or older undergoing complex cardiac surgery at 33 U.S. hospitals. These patients received either RBCs stored for less than 10 days versus older RBCs stored for greater than 21 days. The fresh RBC storage median age was seven days, and the older RBC storage median age was 28 days. The number of RBC units transfused per patient and the percentage of patients who received eight or more units were similar between the two groups. No significant difference was observed between the two groups in the primary outcome of organ dysfunction at seven days, as assessed by the Multiple Organ Dysfunction Score (MODS; p=0.44). Similarly, no significant difference was observed in secondary outcome of MODS changes at 28 days, all-cause mortality at seven and 28 days, or length of stay in intensive care or the hospital. Adverse events were similar between the groups, with the exception of a significant increase in hyperbilirubinemia in those subjects receiving older blood (p<0.01). Similar to the ABLE trial, patients in the RECESS trial received leukoreduced RBCs, and the study did not address the clinical impact of RBC units toward the end of their storage life.

The results of the ABLE and RECESS trials argue that restricting RBC transfusion to units stored for a shorter period is not necessary for critically ill adults or patients 12 years of age or older undergoing complex cardiac surgery. However, these results may not be generalizable to non–leukocyte-reduced RBC units. Additionally, these studies did not address RBC units transfused close to the end of the maximum-allowed storage period. The ABLE and RECESS results echo the findings of the Age of Red Blood Cells in Premature Infants (ARIPI) trial, which also showed no significant differences in outcomes among premature and low-birth-weight infants. Collectively, these results have important implications for the blood supply, where the management of special requests (freshest blood, irradiated blood, cytomegalovirus seronegative, etc.) is complex, time consuming, and expensive. Whether there are other patient populations that may be impacted from RBC storage duration has yet to be determined.


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Dr. Lockhart and Dr. George indicated no relevant conflicts of interest.

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A Synthetic Lethal Approach to Treat Acute Myeloid Leukemia in Patients with Isocitrate Dehydrogenase Mutations


Acute myeloid leukemia (AML) is a heterogeneous disease presenting with various genetic subtypes. A broad spectrum of genetic abnormalities and molecular mutations has been documented, including mutations in genes that are involved in epigenetic regulation. The recent advances in whole genome and exome sequencing have led to the identification of several novel defects, including missense mutations that substitute arginine residues in isocitrate dehydrogenases (IDH) 1 and 2, in approximately 15 percent of patients with AML. The mutant enzymes exhibit a neomorphic gain of function effect that produces an oncometabolite, 2-hydroxylutarate (2-HG), which inhibits several enzymes that regulate the epigenetic signature of the genome.

The precise mechanisms linking these IDH1/2 mutations to AML pathogenesis have not been fully elucidated, but they are acquired very early in the multistep transformation process, which makes these enzymes attractive drug targets. Small-molecule inhibitors of the mutant enzymes have been developed, but Dr. Steven Chan from the laboratory of Dr. Ravi Majeti with colleagues from Stanford University and colleagues from the Massachusetts General Hospital identified two synthetic lethal genes, and interference study by transducing the cells with a lentiviral shRNA library and had been engineered to express either the wild type IDH1 or the mutant IDH1/2A mutant IDH1/2A together with a green fluorescent protein marker under the control of a doxycycline-inducible promoter. They performed a large-scale RNA interference study on inducing the cells with a lentiviral shRNA library and identified two synthetic lethal genes, BCL-2 and BCL-W, which are members of the antipoptotic BCL-2 family. Knockdown of BCL-2 decreased the viability of IDH1/2 mutant cells compared with wild-type cells, and enhanced mitochondrial membrane depolarization, compared to wild-type and untreated cells, confirming their hypothesis. The researchers provided evidence that the synthetic lethal effect was not due to an imbalance between pro- and anti-apoptotic BCL proteins, nor was it related to excessive oxidative stress, and it did not require epigenetic changes. They investigated the mitochondrial electron transport chain and found that 2-HG inhibited cytochrome c oxidase (COX), which correlated with a decreased activity of the enzyme in mutant IDH cells. Treatment of cells with other COX inhibitors confirmed that COX inhibition sensitized cells to ABT-199 treatment.

The researchers propose a model whereby IDH1/2 mutations cause an accumulation of 2-HG, which inhibits COX and increases the dependency on BCL-2 to bind and inactivate BAX/BAK, thereby preventing mitochondrial depolarization and apoptosis. Treatment of mutant IDH AML cells with ABT-199 disrupts the complex and triggers apoptosis.

These findings are important for several reasons. First, they demonstrate that IDH1/2 mutations may contribute to leukemia pathogenesis not only by modulating the epigenome, but also by dysregulating mitochondria. Second, the data provide evidence for the mechanism of a synthetic lethal approach of treating AML by inhibiting BCL-2, which has important therapeutic implications. Treatment of AML patients with BCL-2 inhibitors has produced encouraging results, but the response has varied widely between patients. Third, the current study indicates that patients with IDH1/2 mutations should respond favorably to ABT-199 treatment, and thus, it provides an important marker for a personalized approach to cancer chemotherapy. Fourth, these findings raise the possibility that a combination of ABT-199 with inhibitors that target COX or other enzymes of the electron transport chain may offer a novel strategy for treating AML patients who have normal IDH1/2.

The Unfiltered Truth: Anticoagulation Alone is Highly Effective, even in Patients with High-Risk Pulmonary Embolism


Evidence from at least one observational study has suggested that placing an inferior vena cava filter (IVCF) in addition to administering traditional anticoagulation therapy, might reduce the risk of death in patients with acute, high-risk pulmonary embolism (PE). At least partly because of this evidence, some critical care physicians advocate pre-emptive placement of a retrievable IVCF in patients who have a large clot burden or who have tenuous cardiopulmonary function, even if no contraindication to anticoagulant therapy exists. This practice may explain the dramatic recent increase in IVCF placement in the United States, where between the years 1985 and 2006, on average, nearly 15,000 filters were deployed annually in patients with pulmonary embolism.

The Prevention du Risque d’Embolie Pulmonaire par Interruption Cave 2 (PREPIC2) study was designed to determine whether patients with acute, high-risk PE might fare better if, instead of anticoagulation alone, they received both anticoagulation and a retrievable IVCF. To be included in this randomized, open-label trial conducted from August 2006 to January 2013, patients had to have acute, symptomatic PE associated with lower-limb vein thrombosis, plus at least one criterion for severity (Table 1). Anticoagulation was mandatory for six months in both groups, and for the patients randomized to IVCF deployment, the filter had to be advanced within three weeks of IVCF insertion. Slightly more than half of the enrolled patients were younger than 75 years, and approximately two-thirds had some evidence of right ventricle dysfunction or myocardial injury. Only about 9 percent of enrolled patients had loco-regional thrombosis. The primary outcome was symptomatic pulmonary embolism (including fatal PE) three months after enrollment. Safety outcomes included the three- and six-month rates of both major bleeding as well as all-cause mortality. Filter complications such as thrombosis, migration, and penetration of the vena cava wall were recorded. Although PREPIC2 was an open-label trial for the patients and treating clinicians, the adjudicators of outcomes were blinded to treatment assignment.

Of the 200 patients randomly assigned to IVCF placement, the filter was successfully deployed in 193 and was retrieved within three months in 153 of the 164 patients in whom retrieval was attempted. After three months, six (3.0%) of the patients who received a filter had experienced recurrent PE; all six recurrences were fatal. Throughout the same follow-up period, three patients (1.5%) from the control group were diagnosed with recurrent PE; two of these three recurrences were fatal. The primary endpoint in patients with filter (vs. no filter) was 0.00 (95% CI, 0.51-789; p = 0.50). Results were similar at six months. Thrombosis of the IVCF occurred in three individuals, and the relative risk of the primary outcome did not change when recalculated using an “as-treated” analysis. For the key secondary and safety outcomes, the two treatment groups were similar, including deep vein thrombosis, major bleeding, and all-cause death. The most common cause of death in both arms was cancer. The most common filter-related complications are listed in Table 2.

Although hematologists are often not involved in the very first clinical decisions for patients with acute, high-risk PE, the report by Dr. Patrick Mismetti and colleagues provides very important information about the optimal management of such patients. Much like previously published trials of systemic thrombolysis in this population, PREPIC2 highlights the effectiveness of simple, well-managed anticoagulation in patients with pulmonary embolism. Indeed, in this group of nearly 200 PE patients with at least one high-risk feature (two-thirds of whom had evidence of right ventricular dysfunction), treatment with standard anticoagulation alone prevented recurrences in all but 1.5 percent of individuals. PREPIC2 reminds us that anticoagulation is the mainstay of treatment for patients with high-risk PE and, unless anticoagulation is contraindicated, IVCF placement has no definite benefit, and may additionally expose patients to important complications.


Table 1. The most common complications observed among the 193 patients who received an IVCF filter

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter thrombosis</td>
<td>1.6%</td>
</tr>
<tr>
<td>Retrieval failure due to mechanical reasons</td>
<td>5.7%</td>
</tr>
<tr>
<td>Access site hemotoma</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ischemic stroke with leg paralysis within the last six months</td>
<td>3.0%</td>
</tr>
<tr>
<td>Deep vein thrombosis that involved the illocaval segment or was bilateral</td>
<td>2.6%</td>
</tr>
<tr>
<td>At least one sign of right ventricular dysfunction or myocardial injury</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

Table 2. The most common complications observed among the 193 patients who received an IVCF filter

<table>
<thead>
<tr>
<th>Age &gt; 75 years</th>
<th>Active cancer</th>
<th>Chronic bronchial or respiratory insufficiency</th>
<th>Ischemic stroke with leg paralysis within the last six months</th>
<th>Deep vein thrombosis that involved the illocaval segment or was bilateral</th>
<th>At least one sign of right ventricular dysfunction or myocardial injury</th>
</tr>
</thead>
</table>
In the last few years, there has been a tremendous increase in the availability of smartphones, tablets, and computers in the United States and worldwide. Smartphones are the most commonly used personal computer and have revolutionized the communication landscape in our personal and professional lives. In the current rapidly growing technology, there are opportunities to develop high-quality, standardized, and cost-effective health-related assessment and educational tools, which has led to the development of a growing area of health science research, known as mobile health, or mHealth. The National Institutes of Health (NIH) Consensus Group defines mHealth as “the use of mobile and wireless devices to improve health outcomes, healthcare services and health research.”

Experts studying mobile health market trends have estimated that 500 million smartphone users worldwide, including health-care professionals, will be using a mobile applications by 2015. By 2018, the number of users could rise to more than 3.4 billion. In 2012, the Association of American Medical Colleges (AAMC) reported on the rapid growth of health-related smartphone applications. A survey of training programs by the Accreditation Council for Graduate Medical Education showed that more than 85 percent of trainees used a smartphone, and more than 50 percent of them used them daily during the academic year. These data raise some basic questions: what are the demographics of smartphone use for health-related apps? Which hematology and oncology apps are available in the marketplace? How much control do we have over the quality of the content? What are the implications for our patients?

### Smartphone Ownership and Accessibility to Health Information

As of January 2014, the Pew Research Center reported that 58 percent of the American population have owned a smartphone. Ownership was slightly more common in males (61%) than in females (57%). The majority of African Americans (59%), Hispanics (61%), and whites (65%) owned a smartphone.1 Smartphone ownership was directly related to educational levels and household incomes, but it was inversely related to age. Smartphone owners (52%) were more likely to gather health information online than non-smartphone owners (6%).1 Individuals who recently had a medical emergency or an important change in their physical health were more likely to use their own phones to look for health information. Additionally, smartphones allow patients to monitor and manage their health, only 19 percent of non-smartphone owners have at least one health app on their phone, with exercise, diet, and weight apps being the most common.

### Hematology and Oncology Apps Available

We searched both Apple iTunes and Google Play for apps using “hematology” and “oncology” as keywords. We found a total of 545 oncology apps at Apple (296) and Google (247), and 308 hematology apps at Apple (95) and Google (213). Based on target audience, purpose, and other characteristics, we categorized apps into eight different groups (see online Figure). “Physician” apps are designed for professionals and included clinical guidelines, cancer staging, educational materials, imaging tools, and laboratory references. Apps classified as “Others” included those in non-English languages, those that are nonprofit and/or those with unclear purposes. Only a minority of a hematology and oncology apps were disease-specific, and most journals in the field had more apps available in Apple (iPhones). Hematologists or oncologists who search a disease-specific search terms could have resulted in more apps, but that was beyond the focus of this article. Some popular hematology and oncology apps are summarized in the Table.2

### Potential Benefits

Mobile devices and health-related apps offer many benefits to healthcare providers, patients, and other interested parties. Some mobile apps utilize innovative interactive platforms with searchable clinical resources for better, more personalized learning experiences. Other common uses among health-care providers include drug referencing, clinical decision-support, communication with patients or other colleagues, and access to electronic health records and medical education materials.3

### Worrisome Risks

The wide use of health-related apps may bring benefits, but it also carries risks. The main concerns have been related to safety, accuracy, and reliability. Medical professionals were involved in the design and development of only one third of more than 160 apps evaluated.5,6 Concerns about patient safety, accuracy, and the quality of the app content persist. For example, there are multiple apps to help with opioid conversion calculations, but inconsistencies were found in 23 such apps evaluated, which could have serious consequences.7,8 In addition, an app developed to identify and manage skin cancer was found to be accurate in identifying only 11 percent (10 of 95) of high-risk melanoma cases when tested with a health-care provider from the National Cancer Institute and Fitzpatrick’s Dermatology in General Medicine.9,10 Unclogging against apps with poor diagnostic accuracy in high-risk serious diseases, including cancer. Low health literacy and numeracy add to the complexity of safely utilizing health-related apps.

### Privacy, Security, Licensure, and Malpractice Considerations

Legal guidance for health-care providers who develop apps is critical to ensuring that regulations are followed and unforeseen pitfalls are avoided.11 Advances in the technological landscape have seen newly developed legal protections, and maintaining the privacy of patients’ health information with the use of health-related apps represents a challenge. Although Health Insurance Portability and Accountability Act (HIPAA) privacy protections have been effective in securing individually identifiable health information since its enactment in 1996; they may not apply to every situation in health-related apps.12 HIPPA privacy rules apply to any health-care provider that transmits electronic protected health information electronically and uses health-related apps within a health-care setting.13 Additionally, the privacy of data collected by health apps and stored on smartphones or tablets is threatened by the risk of a data breach if a device is lost or stolen. Application-specific passwords as well as device safeguard mechanisms, such as authentication and encryption, are necessary to secure sensitive patient data.

The regulation of cross-jurisdictional licensing, as it relates to how health-care providers use health apps to communicate and share patient information with other providers across state lines, is still unclear.14 Furthermore, physicians’ adoption of health apps for patient care as well as their recommendations for patient use have been guarded with concerns for malpractice and liability, which may be different from other already adopted technologies. However, with growing reliance on health apps, their use may become standard of care, especially if proven effective. Although developers of health apps may commit to ensuring the safety, accountability, and the quality of the app content, they are generally not at risk for malpractice claims, but other liability issues could apply, including design defect, breach of warranty, and failure to warn.

### Table. Popular Hematology and Oncology Apps

<table>
<thead>
<tr>
<th>App Name</th>
<th>Platform</th>
<th>Developer</th>
<th>Purpose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miniatlas Hematology</td>
<td>iOS</td>
<td>EC-Europe</td>
<td>Patient education</td>
<td>Good-quality detailed medical illustrations that can be e-mailed to patients</td>
</tr>
<tr>
<td>Hematology Outlines</td>
<td>iOS</td>
<td>Dr. Hooman R. Rashidi and Dr. John C. Nguyen</td>
<td>Medical education</td>
<td>Includes hematology and oncology specialties; physicians can enter data to derive disease-specific staging results and prognostic scores</td>
</tr>
<tr>
<td>CancerRx</td>
<td>MedPage Today and ColibriRx</td>
<td>Clinical decision support</td>
<td>Physicians can enter patient data and receive a list of suggested therapies with references from UpToDate website</td>
<td></td>
</tr>
<tr>
<td>Calculate by QxMD</td>
<td>iOS, Android</td>
<td>QxMD Medical Software Inc.</td>
<td>Calculations and formulas</td>
<td>Includes hematology and oncology specialties; physicians can enter data to derive disease-specific staging results and prognostic scores</td>
</tr>
<tr>
<td>NCN Guidelines / NCCN Guidelines for Smartphone</td>
<td>iOS</td>
<td>National Comprehensive Cancer Network</td>
<td>Guidelines and reimbursement resource</td>
<td>Guidelines are listed in alphabetical order; icons for chosen guidelines can appear on the homepage, physicians, patients, or payers can view and download content</td>
</tr>
<tr>
<td>InPractice for Specialists</td>
<td>iOS, Android</td>
<td>Clinical Care Options</td>
<td>Clinical decision support</td>
<td>Includes a search interface that is able to retrieve results in three main buckets: Guidelines, PubMed, and Clinical Trials</td>
</tr>
</tbody>
</table>

### FDA Regulations for Health-Related Apps

The U.S. Food and Drug Administration (FDA), which has oversight of mobile medical apps, has issued guidance based on risk and functionality.17 The FDA has set stringent app regulations to prevent apps that present a greater risk to patients if they do not work as intended, and on apps that cause smartphones or other mobile platforms to interfere with the functionality of traditional mobile devices. The FDA has no intention of requiring manufacturers to apply for FDA approval, register their company, or list their devices in the FDA’s database.18

### Conclusion

Additional studies are warranted to evaluate the clinical benefits and cost-effectiveness of health-related apps. Legal concerns related to app use need to be addressed with clearer regulations. Policymaking and tracking every single app developed is not feasible, but a more viable approach might be to educate users about the potential risks of the use of apps and to provide strategies to evaluate the quality of apps before downloading them on their personal devices. With these issues addressed, further adoption of mHealth by patients and providers will change the landscape and practice of fields such as hematology and oncology.

The authors indicated no relevant conflicts of interest.

### References

Aaron J. Marcus, MD (1925-2015)

Editor's Note: The 2015 Wallace H. Coulter Award for Lifetime Achievement in Hematology will recognize Aaron Marcus, MD, of Weill Cornell Medical College in New York. Dr. Marcus will be honored for seminal contributions to the field that spanned more than five decades and exemplified excellence in research, clinical care, and education.

Dr. Aaron J. Marcus died quietly in his sleep on May 6. Even at 89, he remained active in hematology research, directing experiments from his bedside until the very end.

Prior to entering the military in 1944, Dr. Marcus intended to be a lawyer. For bureaucratic reasons known only to the U.S. Navy, he was appointed a Pharcisian's Mate Third Class and assigned to a naval hospital in California. There he tended to the sick, emptied bedpans, pondered scientific riddles, and found his vocation.

He obtained his M.D. from New York Medical College in 1953 and spent his residency and a research fellowship in hematology at Montefiore Hospital. Already, he was zooming in on the mysteries of thrombosis that would occupy him for the rest of his long career, publishing "Platelet Phosphatases: Their Separation, Identification, and Clotting Activity" in the Journal of Clinical Investigation in 1958. The role of platelet lipids in thrombosis remained the focus of his research for several decades, and he was among the first to demonstrate how platelets were affected by aspirin. He also invented the partial thromboplastin time test, still widely used for evaluating blood coagulation in patients.

Hypoferrernia restricts iron availability to erythroid precursors and may contribute to the development of anemia of inflammation. Toll-like receptors (TLRs) act as key regulators of specific innate immune responses. Dr. Claudia Guida et al. reveal a novel role for TLR2 and TLR6 in mediating hypoferrernia in response to inflammatory stimuli. These findings have direct implications for our pathophysiologcal understanding of anemia of inflammation.


Pulmonary embolism (PE) has an incidence of 60 to 100 per 100,000 patients per year, with a 30-day case fatality rate of 0.5-5%. A novel role for PE has been anticoagulation, but the beneficial effects of the addition of thrombolytic therapy have remained controversial. Questions include, "When and how to use thrombolyis in PE?" and "Why do the results of several recent studies on thrombolyis in PE differ so markedly?" Dr. Tsu-Fei Wang and colleagues present an evidence-based focused review based on a meta-analysis of a series of studies that have evaluated fibrinolysis in patients with PE. They provide evidence-based practice recommendations regarding the use of thrombolytic therapies for PE with and without hemodynamic instability, and they assess the optimal regimen of thrombolytic therapy based on available data.


HLA-haploidentical transplantation has emerged as a potential therapy for patients requiring hematopoietic stem cell transplantation (HSCT). The lack of a fully HLA-matched donor, however, has been complicated on the one hand by high rates of graft-versus-host disease (GVHD) with T-cell replete transplants and on the other hand by increased leukemic relapse and poor immune reconstitution with extensively T-cell-depleted transplants. Dr. Irma Airoldi and colleagues present results of 27 children undergoing haplo-HSCT with or T-cell and CD19+ B-cell depletion for malignant and nonmalignant disorders, receiving transplants without post-HSCT anti-GVHD prophylaxis. They report that in these children, γδ T cells reconstitute rapidly, expand appropriately in response to cytomegalovirus, and display effective graft-versus-leukemia activity against leukemic blasts that can be enhanced with anti-CD3 monoclonal antibody. These results strongly support further efforts to move this approach forward for wider use in HSCT.


Dr. Megan Hoban and colleagues report on the use of editing to correct the sickle mutation in stem cells. They introduced a zinc finger nuclease designed to flank the sickle mutation in concert with a homologous donor template to correct human CD34 cells from a patient with sickle cell disease (SCD). This resulted in correction of the sickle mutation, albeit in only about 20 percent of the cells, the corrected cells successfully engrafted in immunodeficient mice, producing normal human β-globin.

This brings the possibility of definitive gene therapy for SCD a giant step closer.


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APRIL 2, 2015

APRIL 9, 2015

APRIL 23, 2015

MAY 7, 2015


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PCDT involves both catheter-directed administration of a thrombolytic agent directly into the venous thrombus and mechanical maceration of the thrombus using a catheter-based device. The primary objective of the ATTRACT trial is to determine whether PCDT, compared to standard therapy, reduces the incidence of PTS following an episode of acute proximal DVT.

**COMMENT:** An effective and safe strategy for prevention of PTS is urgently needed. There is equipoise as to whether PCDT may satisfy this unmet need. Clinical practice guidelines of the American Heart Association and Society of Interventional Radiology suggest consideration of PCDT for selected patients with acute symptomatic proximal DVT (Aldrik et al. J Vasc Interv Radiol. 2011;22:1745-54), whereas the American College of Chest Physicians guidelines suggest anticoagulation alone over PCDT to bias toward treatment allocation, and patients are given explicit instructions not to disclose their treatment assignment at study visits. If these maneuvers are successful in masking assessors, ATTRACT should bias towards the primary objective of whether PCDT is an effective means of preventing PTS.

- Dr. Cuker indicated no relevant conflicts of interest.

**Do We Need Another HDAC Inhibitor in Multiple Myeloma?**

**STUDY TITLE:** Study of ACY-241 Alone and in Combination with Pomalidomide and Dexamethasone in Multiple Myeloma

**STUDY DESIGN:** This is a phase I study evaluating the safety, maximum tolerated dose, and efficacy of the oral HDAC6 inhibitor ACY-241 as monotherapy and in combination with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (MM). Eligible patients include those who have received: 1) at least two cycles of lenalidomide; 2) at least two cycles of a proteasome inhibitor (either as separate therapy or in the same line of treatment); and 3) at least two cycles of a proteasome inhibitor directly anterior to study participation.

**RATIONALE:** HDAC inhibition can interact with other therapeutic regimens to reverse chemotherapy resistance and increase sensitivity to therapeutic agents. ACY-241 has similar activity as ricolinostat against factors MYC and IRF4, which are implicated in myeloma therapy resistance. Targeting of specific HDACs may be better tolerated than current HDACi therapy. We predict ACY-241 will reduce the incidence of PTS following an episode of acute proximal DVT.

**ACCURAL GOAL:** 60 patients, depending on number of dose levels

**IN MEMORIAM**

from ASH: the 1994 Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research; and Special Service Awards from the Veterans Administration for 55 years of service.

A kind and enduringly quirky man, Dr. Marcus had many nonscientific passions. "Aaron possessed an amazing capacity to remember fascinating details and spin them into interesting stories," recalls Dr. Silverstein. "He was a fountain of quotable sound bites. We talked about music, theater, literature, family, science, and people. There were never shades of gray in his opinions, but there were always pro-vocative and challenging ideas." Dr. Nachman similarly commends his old colleague’s “spontaneous humor and warm friendship,” and the “jazz and operatic arias that poured from his 10-foot stereo speakers” on occasion. “We shared a dual reverence for Arturo Toscanini,” says Dr. Levy, and indeed, one of his prized possessions was an inscribed photo of the maestro. But when it came to Dr. Marcus’s insistence that Luciano Pavarotti was merely “yodeling” during the late phase of his career, the two opera buffs agreed to disagree.

- Babette B. Weksler, Professor Emerita of Medicine, Weill Cornell Medical College
- James Marcus, Executive Editor, Harper’s Magazine

**Dr. Yee indicated no relevant conflicts of interest.**
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22  Members-only registration and housing opens for 2015 ASH Annual Meeting & Exposition
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30  ASH Translational Research Training in Hematology letters of intent due
    Washington, DC  www.hematology.org/awards

August

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5  ASH Abstract Achievement and Outstanding Abstract Achievement Awards deadline
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September

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   Washington, DC  www.hematology.org/awards

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