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DIFFUSION

Designer Babies?

Liang P, Xu Y, Zhang X, et al. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell. 2015;6:363-372.

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.[1] 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*[2] 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 2015 "Year's Best" edition of *The Hematologist*.[3]

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 amount of media coverage. One CBS news report on the manuscript referred to the study as the "Designer Baby Controversy"[4] – a similar sentiment in many other media outlets.

The researchers took advantage of the relatively new gene-editing tool, CRISPR/Cas9.[5,6] 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.[8-10] Unlike zinc finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), where the protein specifically recognizes 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).[5,11] This has opened the door of genome editing to a much broader group of scientific teams than the previous technologies.

(Cont. on page 3)

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Dr. Hoggatt indicated no relevant conflicts of interest.

Therapy-Related AML and MDS: Who Really Has It?

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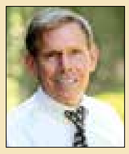
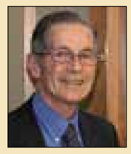
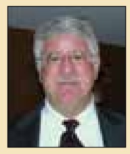

> *"Imagination is more important than knowledge."*
> –Albert Einstein

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 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.[1] 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.[2] 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 postexposure.

(Cont. on page 5)

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Dr. Gotlib has no relevant conflicts of interest to disclose.

President's Column

ASH as a Global Organization

For many years ASH has had a strong international presence — actively engaging hematologists around the world through our annual meeting, *Blood* journal, international Highlights of ASH meetings, and programs such as the International Consortium on Acute Leukemia and the Visitor Training Program. But what does it mean to be a truly "global" organization? The ASH leadership has spent considerable time examining this question over the past two years.

You may be surprised to learn that 22 percent of the ASH membership is now international (non-North American). Just over 50 percent of *Blood* manuscripts are submitted from outside of North America, and 41 of the 98 Blood Editorial Board members are international as well. In 2014, 50 percent of annual meeting attendees and 58 percent of abstract submissions were international. Yet, the Society's governance focus has been primarily domestic, and only residents of North America can be Active members.

For ASH to attract the best science to the annual meeting and *Blood*, improve the care of patients with blood diseases around the world, and promote international research collaborations, the officers and Executive Committee feel that it is critical for ASH to evolve as a global society. By that I mean that the context in which we develop, deliver, and evaluate our programs and services needs to reflect the reality of our global strengths. For instance, we'll need to consider developing our programs and educational materials in multiple languages and formats that offer broader worldwide applicability. But more importantly, we must become "boundary-less" in our perspectives, and we must deliberate many issues within a context that transcends North American borders in order to achieve our goal of "helping hematologists conquer blood diseases worldwide."

This past year, I chaired a working group that examined the future of many aspects of ASH's global efforts. Among these, the Executive Committee unanimously voted to continue the evolution of ASH's global presence. For ASH to effectively embrace this new mindset, the Society's governance structure must be more welcoming of International members. To that end, later this fall ASH members will be asked to approve a bylaws amendment already approved by the Executive Committee that will give International members the right to vote and give the Nominating Committee the flexibility to nominate international candidates to run for a Councillor position, as appropriate for the needs of the Society, at any given time. A second proposed bylaws amendment would create a new membership category for International Associate members, allowing trainees outside of North America to join and enjoy a member benefits package similar to Associate members in North America.

I urge you to support these changes in governance and membership structure as the logical next steps in ASH's advancement as a global organization. At the same time, I would like to assure our Active members that funding for current programs, including all our advocacy and educational efforts in North America, will not be reduced in order to fund new international programs or member benefits. ASH continues to thrive and grow, and the leadership's commitment to its core membership and existing programs is stronger than ever. For example, for the second year in a row, the Executive Committee recently approved an additional commitment of $1 million to the Scholar Awards program, above and beyond the current level (approximately $3.8 million). In addition, ASH continues to vigorously advocate on behalf of hematology researchers and clinicians before Congress and has plans to develop a number of new practice guidelines as well as tools to help our practicing members maintain their hematology certification in an increasingly challenging regulatory environment.

More information about these bylaws amendments will be mailed to Active (North American) members in the fall, and the formal vote will occur during the Business Meeting at this year's annual meeting. I hope you will join me in support of this critical and historic vote on site in Orlando.

David A Williams M.D.

David A. Williams, MD

IN MEMORIAM

Gerald J. Robbins, MD (1951-2015)

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 hematology practice occurs – in a vibrant, successful community-based practice caring for patients with both hematologic and oncologic disorders. Through his leadership, his 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. Despite his diagnosis of glioblastoma multiforme and the debilitating side effects of therapy, he continued to serve on numerous committees and remained very involved. His commitment was recognized by the ASH Committee on Practice in 2013 with the presentation of a plaque acknowledging his lifetime contributions to hematology and, even more importantly, his being a friend, colleague and mentor to so many of us.

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?

(Cont. from page 1)

Using CRISPR/Cas9 editing, Dr. Liang and colleagues set out to determine whether they could edit a portion of the human *β-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 percent of the time during *in vitro* fertilization (IVF) programs. The triploid zygotes are not able to develop normally and do not result in births, 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 *β-globin* gene (found in prescreens in a cell line), the mRNA for Cas9 nuclease, green fluorescent protein (GFP) mRNA, and a ssDNA oligo, which was a template for the corrected *β-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 mosaic, containing multiple 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 pre-implantation 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 policies against similar research in human embryos.[12] The authors themselves may have outlined the larger question of embryo gene editing when they mentioned preimplantation genetic testing, 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 were edited would be normal – their DNA would have been forever altered for no reason."[13] Attention on gene editing should be focused at this time on therapies in somatic cells to treat children and adults with genetic diseases. Researchers exploring somatic cell gene editing for blood disorders are pioneering this field, and the hematologic scientific community should help inform the public about the differences between these ongoing efforts and those related to germline modification.

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Earn CME Credit at the Free Summit "Improving MDS Outcomes from Diagnosis to Treatment: A Multidisciplinary Approach"

ASH, in collaboration with the American Society of Clinical Pathology and The France Foundation, is offering complimentary summits to improve the diagnosis and care of patients with myelodysplastic syndrome (MDS). "Improving MDS Outcomes from Diagnosis to Treatment: A Multi-Disciplinary Approach" includes case-based tumor board discussions and interactive breakout sessions on identifying the new role of molecular testing in MDS, distinguishing morphologic mimics from MDS, assessing low- and high-grade MDS, and applying new prognostic scoring systems to patients. Participants can earn up to six *AMA PRA Category 1 Credits*™.

This event is designed for a wide range of specialists including general pathologists, hematopathologists, medical oncologists, hematologists, pathologists' assistants, hematology and oncology nurse practitioners, physician assistants, and medical laboratory scientists. The program uses a multidisciplinary approach through team-based learning activities. The summits will be held in the following locations:

- Chicago, IL, September 17, 2015 – Fairmont Hotel (just prior to the ASH Meeting on Hematologic Malignancies)
- New York, NY, October 9, 2015 – Lowes Regency
- Tampa, FL, October 16, 2015 – Center for Advanced Medical Learning and Simulation (CAMLS)

More information on the MDS Summits can be found at *www.pathologylearning.org/mds/summits*. This is a free program and space is limited.

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 care 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 initiative is led by Dr. Mark A. Crowther (ASH Committee on Quality chair), Dr. Adam Cuker (Guideline Coordination Panel chair), and Dr. Holger Schünemann (guideline methodology lead). For any questions about these and other ASH guidelines, contact Rob Kunkle, Senior Manager of Practice Guidelines, at *rkunkle@hematology.org*, or visit *www.hematology.org/Clinicians/Guidelines-Quality*.

A Presenter's POV: ASH Meeting on Hematologic Malignancies

The ASH Meeting on Hematologic Malignancies (MHM) takes place September 17-19 in Chicago and features top experts on hematologic malignancies, discussing the latest developments in clinical care and answering some of the most challenging "How I Treat" patient care questions in leukemia, lymphoma, myelodysplastic syndromes, myeloma, and myeloproliferative neoplasms, among other core malignancies. We interviewed four of these experts to see how they believe this meeting's format will be most helpful to attendees and which speakers they are most looking forward to hearing. Drs. Bob Löwenberg (BL), Irene Ghobrial (IG), Ross Levine (RL), and Wendy Stock (WS) share their expectations below.

Q: MHM is shaped around "How I Treat" presentations from top experts. How will this format help attendees to apply 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 hematologic neoplasms have inspired new avenues of diagnostic and therapeutic development and has furnished opportunities for a personalized treatment approach. I expect MHM to offer useful 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 MHM. I think this is probably one of the best opportunities to hear the experts give their opinions on how to make decisions in treating cases and what options to choose in clinical practice. We have a unique opportunity in this meeting to meet with some of the best experts in hematologic 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 hematologic 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 MHM. Who are the experts from whom you are most looking forward to hearing, and why?

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 MHM 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 but also how to manage the difficult cases and how to make decisions in treating those patients."

RL: "I am excited to hear from everyone, including Bob Löwenberg 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 hematologic 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 to clinicians."

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

Ask the Hematologist

ROBERT J. KREITMAN, MD

Chief, Clinical Immunotherapy Section, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD

The Question

What is your management approach to patients with relapsed/refractory hairy cell leukemia?

My Response

Hairy cell leukemia (HCL) is an indolent B-cell malignancy, originally with a median survival of approximately four years.[1] Single-agent purine analog therapy with pentostatin or cladribine achieves complete remission (CR) rates of 70 to 90 percent and median relapse-free survivals in excess of 15 years.[2-4] However, minimal residual disease (MRD) often remains, and may be associated with relapse, particularly in young patients with longer follow-up.[5] Thus, in the past 25 to 30 years, many patients have neither died nor been cured, leading to the increasingly common question of how to treat relapsed and refractory patients. The answer requires accurate diagnosis, understanding the history of response and toxicity to prior agents, and a strategy for prioritizing options including exciting new targeted therapies.

Diagnosis of HCL and Recognition of Variant Disease

HCL diagnosis today is most accurately made by flow cytometry showing strong expression of B-cell antigens CD20 and CD22; strong CD11c; and positive CD25, CD103, and CD123.[6] Bone marrow immunohistochemistry is positive for CD20, tartrate-resistant acid phosphatase (TRAP), annexin 1A (Anxa1), and for the V600E mutated form of *BRAF*.[7] Variant HCL (HCLv) has a similar immunophenotype but lacks CD25, Anxa1, CD123, and TRAP.[6] Additionally, *BRAF* is wild type. HCLv is more aggressive, with worse splenomegaly, malignant lymphocytosis rather than cytopenias, and exhibits a poor response to single-agent purine analog; it also may require adding rituximab. Although classified in 2008 by the World Health Organization as a separate disorder, HCLv is also discussed here. Another aggressive variant is characterized by an immunophenotype of HCLv or classic HCL, but with the IGHV4-34 type of immunoglobulin rearrangement that is more than 98 percent homologous (unmutated) to its germline sequence.[8] Even with the classic immunophenotype, these patients resemble those with HCLv with malignant lymphocytosis, purine analog resistance, and wild-type *BRAF*.[8,9] By shipping blood samples and unstained bone marrow slides to an expert center, accurate diagnosis is also possible without travel. Treatment should only be initiated after accurate diagnosis is established.

Treatment of Patients in First Relapse

With some exceptions, remission rates are lower after second-line versus after first-line purine analog therapy[3,4]; however, if the length of the first remission is at least two to four years, many will recommend repeating the initial purine analog. The shorter the treatment-free interval, the greater the risk of overlapping toxicity. Patients relapsing after shorter intervals often receive the anti-CD20 MAb rituximab alone in four to eight weekly doses. While single-agent rituximab can achieve response without overlapping chemotherapy toxicity, response rates are relatively low in patients with prior purine analog therapy who have cytopenias requiring treatment. A more effective strategy is to combine a purine analog with rituximab. Elimination of MRD, detectable by immunohistochemistry of the bone marrow biopsy, as well as by flow cytometry of the blood or bone marrow aspirate, is possible with rituximab one month after cladribine.[10] We treat once-relapsed HCL/HCLv with rituximab, starting immediately with cladribine to effect synergy,[11] or delayed at least six months so MRD status can be determined.

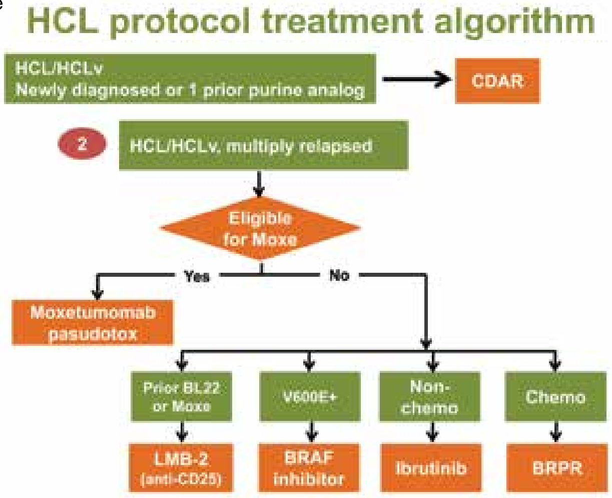
Therapy of Multiply Relapsed HCL

Several options are being tested for multiply relapsed HCL. In order to avoid chemotherapy toxicities, but to retain cytotoxic power, we use recombinant immunotoxins containing an Fv fragment of a Mab 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,[12] 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 moxetumomab pasudotox achieved CRs in approximately 50 percent of patients with multiply relapsed HCL, many without MRD.[13] Another strategy to achieve MRD-negative CR is to use six cycles of either pentostatin plus rituximab,[4] or bendamustine plus rituximab.[14] 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 moxetumomab 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 ibrutinib, 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.

Figure



Newly diagnosed HCL patients typically receive a purine analog, most commonly cladribine in five daily doses, less commonly pentostatin in six to 12 biweekly doses. Newly diagnosed or once-relapsed patients may receive repeat courses of single-agent purine analog, but at MD Anderson and the NIH, are also eligible for protocol treatment with rituximab and cladribine (CDAR). At the NIH, multiply relapsed HCL/HCLv patients eligible for moxetumomab pasudotox receive that option (also available in other centers), while ineligible patients may receive LMB-2, BRAF inhibition, ibrutinib, and BRPR (bendamustine-rituximab vs pentostatin-rituximab) in that order of priority. Common off-protocol options for multiply-relapsed HCL include repeat courses of single-agent purine analog, single-agent rituximab, and pentostatin-rituximab. Splenectomy and even splenic radiation can have palliative benefit at least for a limited period of time.

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 after 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, moxetumomab 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 immunotoxins (BL22 or moxetumomab pasudotox) but need additional therapy, we target CD25 with recombinant immunotoxin LMB-2. For patients ineligible for moxetumomab pasudotox or LMB-2, we use BRAF or BRAF/MEK inhibition, 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 ibrutinib protocol or our protocol using rituximab combined with either bendamustine or pentostatin. Ibrutinib 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 moxetumomab pasudotox) of not needing therapy for many years. Further 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.

Dr. Kreitman is the co-inventor on the NIH patent for Moxetumomab pasudotox.

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Therapy-Related AML and MDS: Who Really Has It?

(Cont. from page 1)

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.[3] 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.[4] 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.[5,6] 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 without scientific merit. This is because the relationship between an exposure and risk of developing therapy-related AML or MDS is uncertain in most instances. Some cases of AML and MDS are therapy related, especially in persons with a genetic predisposition.[7] However, we typically have insufficient data to designate a specific person as having therapy-related AML or MDS. One limitation is that for most drug exposures, there are no specific risk estimators. The consequence is that risk estimates from exposures to the anticancer drugs are qualitative rather than quantitative. Phrases such as "reasonably expected to be associated," "likely to be associated," or "possibly associated" are used rather than numerical risk estimators. This poses a huge obstacle to precise risk estimation. Given these considerations, it is surprising that the World Health Organization (WHO) classification of AML includes the category "acute myeloid leukemias and myelodysplastic syndromes, therapy related (t-AML and t-MDS)."[8] Even more amazing, the WHO classification goes on to specify two types: alkylating agent/radiation therapy related and topoisomerase II inhibitor related and gives a 10- to 15-point detailed description of each. How this is possible is a mystery to us. How is anyone supposed to know with reasonable certainty who has therapy-related AML or MDS?

Prior radiation exposure differs from drug exposure in that quantitative risk estimators are available.[9,10] However, calculating probability of causation requires knowing several exposure- and subject-related variables. Consequently, although attributable risk from radiation exposures can be more precisely estimated than risk after drug exposures, the data needed for this calculation are seldom available to hematologists.

Given these considerations, it is unlikely or impossible that a hematologist can accurately estimate whether a case of AML or MDS in a person who received prior cancer therapy is therapy related. How important is precise estimation? Probably not very important, but it is important to have a qualitative estimate such as "likely," "unlikely," or "uncertain." Boundaries to these estimates might be less than 30 percent, 30 to 70 percent, or more than 70 percent. This process can be considered somewhat analogous to the more precise expression of uncertainty incorporated in a confidence or credibility interval.

Many things flow from a reasonably accurate estimate of whether a person's AML or MDS is therapy-related. For example, deciding whether to give induction chemotherapy, hypomethylating drugs, or low-dose cytarabine may be influenced by this estimate. Another example is whether to consider a hematopoietic cell transplant. For each of these therapies and others, an imprecise or incorrect estimate of whether AML or MDS is therapy related can result in under- or over-treatment.

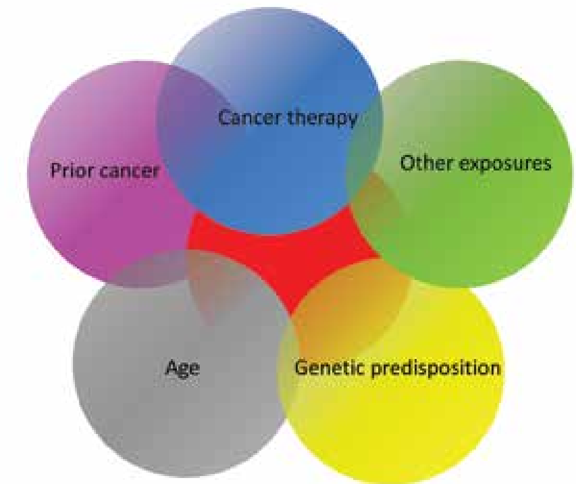
Where does this leave us? We suggest that hematologists be more cautious in saying a person has therapy-related AML or MDS. They need to try to ascertain precise details of prior exposures and consider possible confounders, especially the normal steep age-related increases in AML and MDS. They also need 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 and indicate 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." Adopting 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.

Note 2: Cases are associated with the baseline risk for persons of like age and gender and, ideally, with the same disease history but not exposed to potentially leukemogenic drugs and/or ionizing radiations.

Figure

Variables confounding accurate diagnosis of therapy-related AML or MDS (red circle).



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NEWS AND REPORTS

Abstract Submission for the 2015 ASH Annual Meeting is Now Open

Now is the time to consider presenting your research at the world's premier hematology event. Abstract submission for the 57th ASH Annual Meeting & Exposition is now open, and ASH is accepting submissions across 60 scientific and clinical categories, spanning the entire field of hematology. The submission deadline is August 4, 2015, at 11:59 p.m. PDT. Visit the ASH website for more information on attending as well as presenting at this year's meeting in Orlando, Florida. Please also note that early-bird registration and housing (ASH members only) opens on July 22, 2015, at 11:00 a.m. EDT.

For more information about this year's meeting, visit *www.hematology.org/Annual-Meeting*. To learn more about ASH's call for abstracts, visit *www.hematology.org/amsubmitabstracts*.

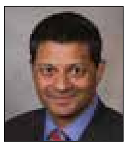
Program Genealogies: Myeloma at Mayo

S. VINCENT RAJKUMAR, MD,[1] WITH PERSONAL REFLECTIONS FROM ROBERT A. KYLE, MD[2]

1. Edward W. and Betty Knight Scripps Professor of Medicine, Mayo Clinic, Rochester, MN
2. Professor of Medicine, Laboratory Medicine & Pathology, Mayo Clinic College of Medicine, Rochester, MN

Editor's Note: I'm not a foodie, but I am a fan of chef Anthony Bourdain's "Parts Unknown," a weekly globe-trotting series that transports viewers to local cultures and culinary delights. I was particularly drawn to an episode from Lyon, France since most of my father's side of the family has resided in that city for more than 75 years. Lyon is famous for having been the epicenter of "the System," which employed a high-pressured, militaristic system of grooming Master Chefs. "The System" was borne of a fascinating genealogy of female cooks, Les Mères, and most famously La Mère Brazier (the first chef to attain six Michelin stars for two restaurants), who dominated the culinary scene between and during the World Wars to fill vacancies left by men serving in the military. La Mère Brazier was the mentor of Chef Paul Bocuse, a living legend and ambassador of French nouvelle cuisine. Importantly, Bocuse and his contemporaries trained and inspired successive generations of chefs and restaurateurs who have dispersed beyond France's borders to share their disciplined techniques and ground-breaking dishes with an international clientele.

The Lyon episode made me ponder the genealogy of successful programs in hematology, and made me want to learn more about their historical roots. Who are our Paul Bocuses? What "systems" have been developed to fertilize the growth and prominence of specific programs over time? Are there characteristics of an institution or its faculty that help foster a unique culture or enduring legacy of achievement? This new feature "Program Genealogies" is a twist on the individual profiles we've highlighted in past issues of *The Hematologist* and is meant to explore the aforementioned questions. Besides taking a walk back in time, it is my hope that these pieces can inform how success may be duplicated elsewhere. We are delighted to have Drs. Vincent Rajkumar and Robert Kyle inaugurate this series with a look at Mayo Clinic's Multiple Myeloma Program. –Jason Gotlib, Editor-in-Chief



The Mayo Clinic is one of the largest academic medical centers in the world, with more than 2,500 physicians and scientists contributing their 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 to focus on one rare cancer, representing just 1 percent of all malignancies. How does one maintain academic 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 one of us, Dr. Bob Kyle, joined the institution as a fellow. In 1959, Dr. Kyle stared at 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 100 became 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, or amyloidosis), while those with a lower ratio had polyclonal processes (chronic, active hepatitis, rheumatoid arthritis, or other inflammatory diseases).

After 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 William Terry learning the technique of immunoelectrophoresis – a more sensitive and specific test that was needed to confirm and type abnormal monoclonal proteins detected on standard electrophoresis. Against all odds and obstacles, Dr. Kyle obtained permission from the leaders of the Mayo Clinic to spend two hours each day in the laboratory performing immunoelectrophoresis. Although it meant adding extra patients to his already busy clinical practice, Dr. Kyle realized that to understand the new laboratory findings, he had to see and follow all patients he identified with abnormal monoclonal proteins. The number of tests performed in the laboratory increased rapidly, and the practice grew accordingly.

Perhaps the most seminal event was Dr. Kyle's foresight to establish a serum bank in the early 1960s to save any remaining samples. A close second was the establishment of a database at around the same time, which contained clinical and laboratory data from all patients with a monoclonal plasma cell disorder. The database consisted of IBM punch cards with a maximum limit of 80 entries per patient. The third key element was the establishment of the program as a *separate* unit within the Division of Hematology, dedicated to the diagnosis and treatment of multiple myeloma and related plasma cell disorders.

Dr. Kyle *was* 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. Morie Gertz. These three pillars of the program attracted residents and fellows like magnets. Fellows understood that the myeloma program was vibrant and that it offered exceptional opportunities for research and career development. Key recruits in the ensuing years were Drs. Thomas Witzig, John Lust, Martha Lacy, Angela Dispenzieri, Rafael 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, Dr. Leif Bergsagel and Dr. A. Keith Stewart. Yes, they came to be known as the three musketeers.

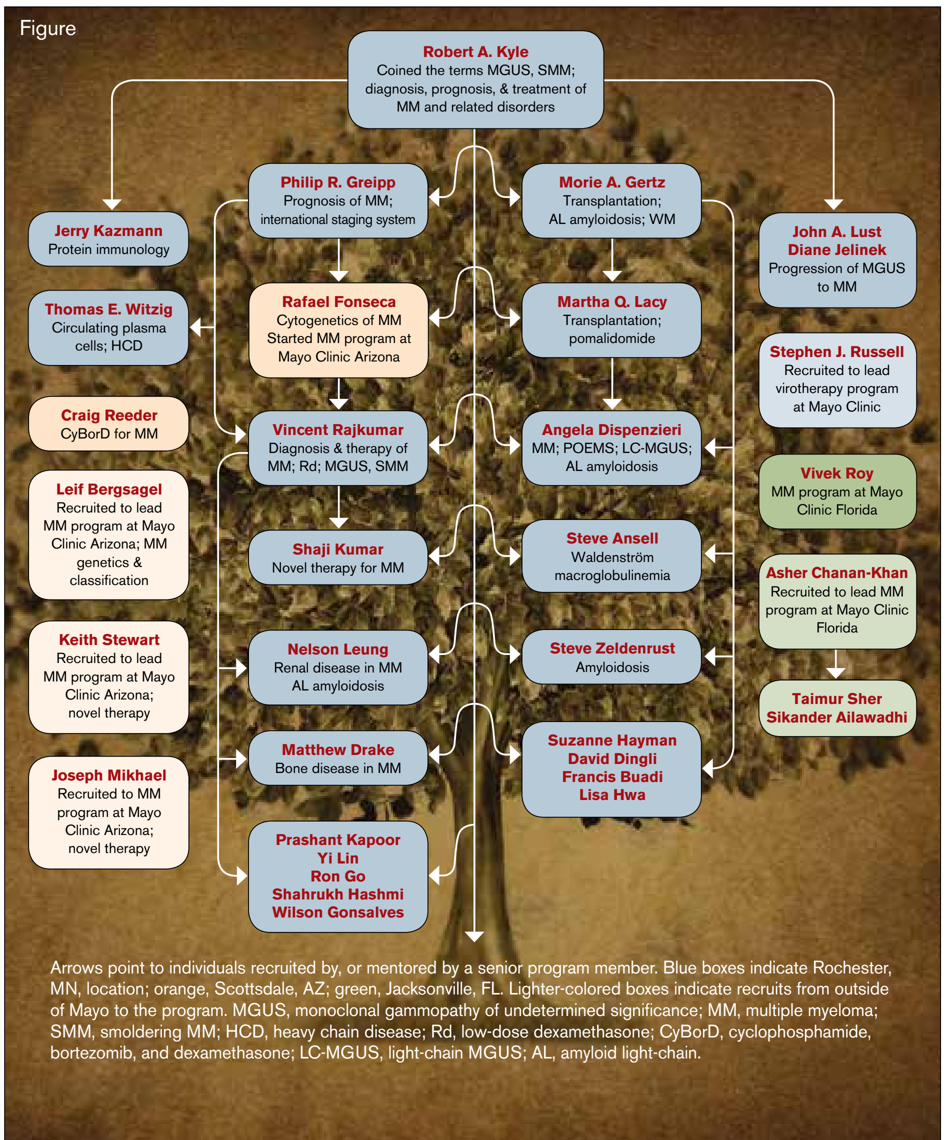
Today, 40 years later, the growth and transformation of the Mayo Clinic Multiple Myeloma Program is astonishing. The serum bank has more than 250,000 samples; the database now contains almost 50,000 patients. The IBM punch cards are long gone, replaced by the most modern of statistical systems, which can be interrogated to answer simple and complex questions. 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 individually and collectively are 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 defined and characterized monoclonal gammopathy 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 amyloidosis, while Dr. Dispenzieri described light-chain MGUS 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. Witzig 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 the very best in the ensuing years. Dr. Asher Chanan-Khan built the Jacksonville myeloma program. Dr. Shaji Kumar has become one of the finest clinical trialists in myeloma. Dr. Stephen Ansell has taken on the challenge of Waldenström macroglobulinemia. Dr. Stephen Russell has developed virotherapy from bench to manufacturing to bedside, culminating in the measles virus trials for relapsed/refractory myeloma. Dr. Craig Reeder developed the CyBorD regimen, one of the most commonly used treatments in myeloma. Dr. Joseph Mikhael has become a leader in education. The genealogy of the Mayo Myeloma program (Figure) has deep roots with many branches, including many alumni who have gone elsewhere to play a major role in the field; notably, Dr. Brian Durie, founder of the International Myeloma Foundation, who developed the Durie-Salmon Staging system in 1976.

What do we think are the main factors responsible for the remarkable success of the program? The first is the setting. It is indeed easier to succeed when there is a patient-centered organization such as the Mayo Clinic behind you. The breadth of expertise in the institution also helps the program work at a high level with other related fields, especially imaging, nephrology, endocrinology, and cardiology. Second are the unique program resources, specifically the biobanks and the database, started decades ago. They enable us to address questions that would take years to answer if we had to start now. Third is the people. Clearly we have been fortunate to attract and retain (our retention rate is almost 100%) the best and brightest in the field. It took a lot of effort to build the program, and a lot more work is needed to maintain its standards and integrity. Fourth is the ability to forge consensus. Despite philosophical differences, we have been able to synthesize the best available data and come up with a consensus approach to clinical practice (*www.msmart.org*), which is essential not only for teamwork and excellence in patient care, but also for generating the next research questions. Finally, perhaps the most critical element of our success is independence. Each investigator in the program has the freedom to be a leader in the field. There is no hierarchy, and members of the myeloma group are encouraged to pursue their own interests and not become cogs that help one or two senior people to succeed. People speak their minds openly without fear of retribution. We know we can offer more to the field by working together. Additionally, there is an unbelievable amount of trust; and for any program, trust, ultimately, is everything.

The authors indicated no relevant conflicts of interest.

Figure



Arrows point to individuals recruited by, or mentored by a senior program member. Blue boxes indicate Rochester, MN, location; orange, Scottsdale, AZ; green, Jacksonville, FL. Lighter-colored boxes indicate recruits from outside of Mayo to the program. MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering MM; HCD, heavy chain disease; Rd, low-dose dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; LC-MGUS, light-chain MGUS; AL, amyloid light-chain.

HEADLINES FROM Washington

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 Washington, DC, and 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 or 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.

Drs. Marsha Kinney and Paul Shaughnessy discuss oral parity with Rep. Will Hurd (R-TX).

Drs. Steven Allen, Steven Kroft, and Kenneth Adler in front of the U.S. Capitol during the ASH Committee on Practice Hill Day.

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*.

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. On the second day, participants will visit their respective congressional delegation on Capitol Hill to apply what was learned on the first day.

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.hematology.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).

On April 29, 2015, 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 to discuss hematology research priorities. The members (pictured L to R) are Drs. Debra Newman, Charles Mullighan, Pavan Reddy, David Williams, David Bodine, Kenneth Anderson, Willem Fibbe, and David Motto.

New Light on an Old Drug

Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol. 2015;33:1235-1242.

As 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 a 3.9-fold increased risk of relapse with less than 90 percent adherence to MP in a multiracial cohort of children.[4] Finally, another line of evidence regarding the importance of MP in maintenance therapy is that activating mutations in *NT5C2*, which confer resistance to thiopurines, are among the most common mutations noted at the time of disease recurrence.[5,6]

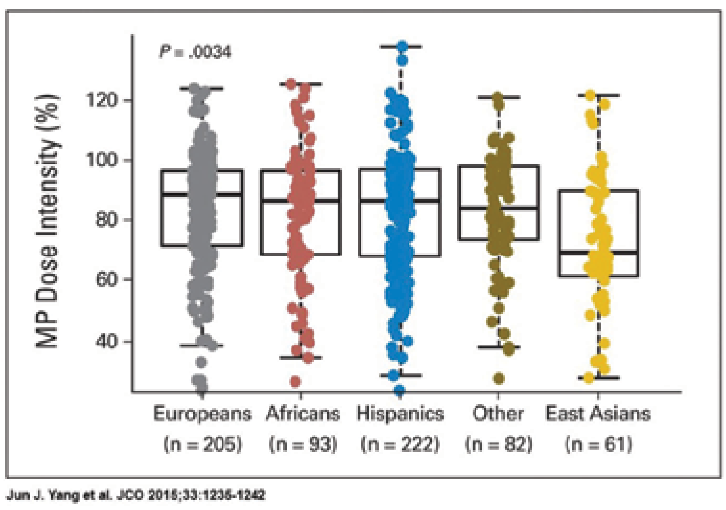
Tolerance to the adverse effects of MP is another important factor for optimizing treatment delivery. Protocols commonly specify dosing modifications for myelosuppression, and achieving adequate MP dosing without frequent treatment interruptions, which can negatively impact outcomes, can be a challenge for some patients. Previous studies have demonstrated that genetic variation in thiopurine methyltransferase (TPMT) is a major contributing factor to MP intolerance.[7,8] 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 thio-dGTP 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.[9] 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.

Figure

Mercaptopurine (MP) dose intensity and genetic ancestry.



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/m^2 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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Dr. Raetz indicated no relevant conflicts of interest.

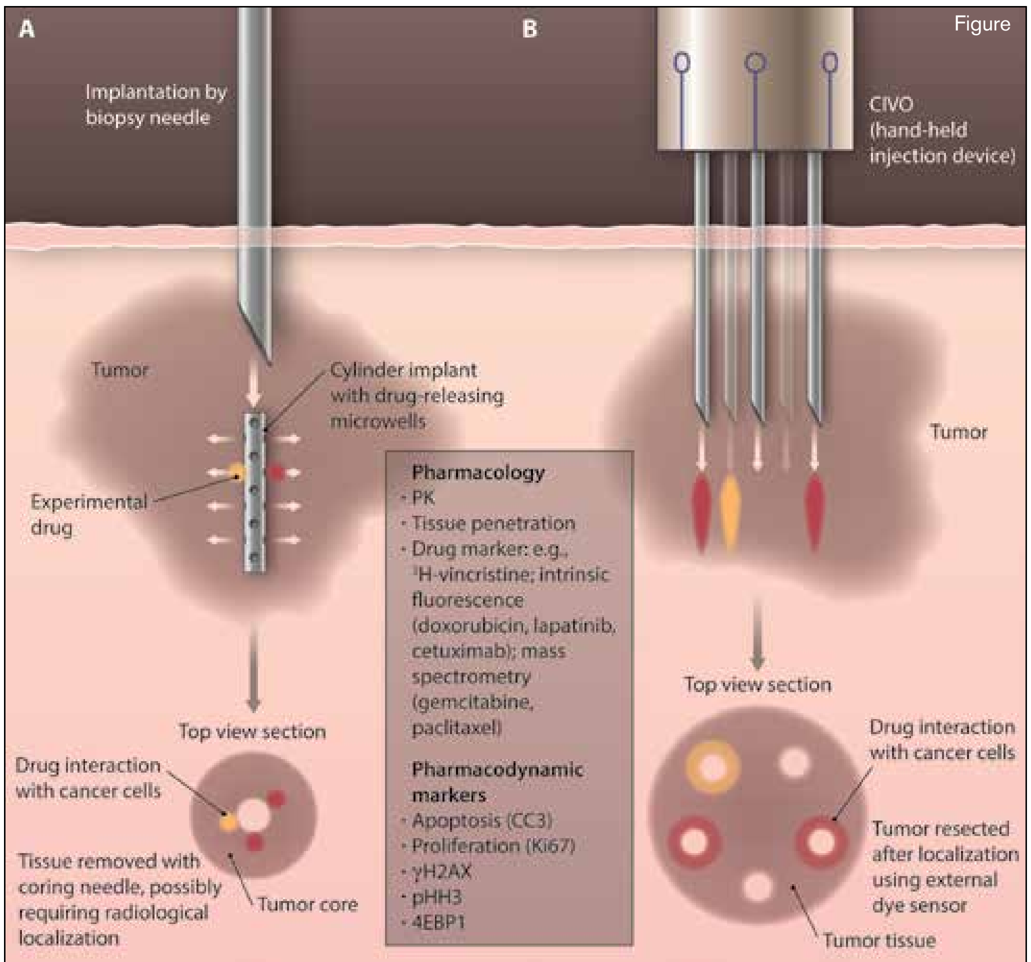
USION

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

Klinghoffer RA, Bahrami SB, Hatton BA, et al. A technology platform to assess multiple cancer agents simultaneously within a patient's tumor. Sci Transl Med. 2015;7:284ra58.

Jonas O, Landry HM, Fuller JE, et al. An implantable microdevice to perform high-throughput in vivo drug sensitivity testing in tumors. Sci Transl Med. 2015;7:284ra57.

"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 not to undertreat patients by administering drugs to which their cancer isn't sensitive, and not to over-treat, 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.



Individualized drug sensitivity testing. Two different devices are illustrated that allow for in vivo drug sensitivity testing and biomarker analysis in patient tumors. (A) The Jonas et al. device is implantable and can test up to 16 different drugs simultaneously. (B) The Klinghoffer et al. device called CIVO microinjects up to eight different drugs or drug combinations before tumor sampling and has been tested in rodent and canine models and in human subjects. Various pharmacologic and pharmacodynamic markers were evaluated in both studies to demonstrate that the results correlated with clinical response to therapy. Reprinted with permission from Coombes RC, et al. Drug testing in the patient: toward personalized cancer treatment. Sci Transl Med. 2015:7;284ps10.

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, at Seattle Children's Hospital, 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 3, 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 sunitinib, 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.

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Dr. Becker indicated no relevant conflicts of interest.

Circulating Tumor-Specific DNA: A Promising Biomarker in Diffuse Large B-Cell Lymphoma

Roschewski M, Dunleavy K, Pittaluga S, et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. Lancet Oncol. 2015;16:541-549.

Current approaches to assess response to therapy and disease recurrence in diffuse large B-cell lymphoma (DLBCL) have many limitations. The detection of minimal residual disease by positron emission tomography (PET) and/or computed tomography (CT) requires a sufficient volume of disease, and false positives are common. Frequent imaging is very costly and is associated with exposure to ionizing radiation and the risk of secondary malignancies. Identifying minimal persistent lymphoma or early recurrence using assays for disease-specific circulating tumor DNA may offer a safe and effective means of disease assessment.

In their recent study published in *Lancet Oncology*, Dr. Mark Roschewski and colleagues retrospectively evaluated the utility of circulating DNA to identify persistent and recurrent disease in patients with DLBCL. Previously untreated patients with DLBCL, treated on three clinical trials using EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), with or without rituximab, underwent CT imaging with concurrent serum collection at baseline, during therapy, and at the end of chemotherapy. Surveillance was performed every three, four, and six months during years one, two, and three, respectively, then annually during years four and five. Available pretreatment formalin-fixed paraffin-embedded biopsy specimens were analyzed for tumor-specific immunoglobulin gene rearrangements using next-generation sequencing of VDJ gene sequences, which were then quantified. For patients without available tissue, circulating tumor DNA was isolated from serum.

One hundred twenty-six patients had identifiable tumor specific clonotypes, with 94 isolated from 109 patients with available diagnostic tissue, and 32 isolated from 86 patients with banked serum specimens. The concentration of baseline circulating tumor DNA correlated with tumor burden as reflected by the International Prognostic Index, stage, and lactate dehydrogenase. After two cycles of therapy, 108 patients underwent interim assessment of circulating DNA. The five-year progression-free survival of patients with detectable versus undetectable DNA was 42 percent versus 80 percent, respectfully, yielding a positive predictive value of 63 percent and a negative predictive value of 80 percent.

Thirty-six patients experienced disease progression. Twenty-five patients relapsed early, at less than six months from treatment, and 11 patients relapsed late. Of the patients with early progression, those who recurred earliest did not clear circulating tumor specific DNA. At the completion of frontline chemotherapy, none of those with late relapse had measurable tumor DNA. Ten of 11 patients subsequently developed detectable levels – eight had no concurrent clinical evidence of disease. Seven patients who had clinical progression did not have measurable circulating tumor DNA – four had localized mediastinal lymphoma with a small area of residual disease by PET, and one had an isolated central nervous system disease. Of the 98 patients who remained in remission, only two had low-level detectable circulating tumor DNA measurable on one assessment, which was not reproduced. Overall, the positive predictive values and sensitivity of circulating tumor DNA were both 88 percent, and the negative predictive value and specificity were 98 percent. Circulating tumor DNA was detectable at a median of 3.5 months prior to the appearance of clinical disease and was earlier for patients with primary refractory disease or early recurrence.

Monitoring circulating tumor DNA in patients with DLBCL has a number of important advantages over imaging-based strategies, including accuracy, cost, and safety. Although no clear evidence to date demonstrates an improvement in survival for patients treated for asymptomatic relapse detected on imaging, many patients and providers are uncomfortable with clinical follow-up exclusively. Additionally, following serum disease-specific DNA has great potential for application in the design of novel clinical trials. PET-driven risk-adapted studies in DLBCL have been difficult to interpret given the low positive predictive value of interim scans. Using slow clearance of circulating tumor DNA to select those patients for whom to intensify therapy, while reducing treatment in early complete responders, may improve outcomes and limit toxicity. Lastly, using serum tumor DNA as a predictive biomarker may lead to more rapid assessment of the efficacy of novel agents and combinations.

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Dr. LaCasce indicated no relevant conflicts of interest.

Less Autophagy in Myeloid Precursors Boosts Neutrophil Counts

Rožman S, Yousefi S, Oberson K, et al. The generation of neutrophils in the bone marrow is controlled by autophagy. Cell Death Differ. 2015;22:445-456.

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. Sasa Rožman and colleagues in the laboratory of Dr. Hans-Uwe Simon report 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 neutrophilic precursor cells of *Atg5*, which encodes a protein required for the formation of the autophagosome, these investigators found an approximately 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 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. With this *in vitro* granulocytic differentiation system, Dr. Rožman and colleagues also showed by inhibitor studies that the p38 MAPK-mTORC1 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.[2] 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[3] – 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. Rožman and colleagues demonstrate that inhibiting autophagy by activating the p38 MAPK-mTORC1 pathway can increase 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.

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Dr. Koury indicated no relevant conflicts of interest.

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

Crescenzo R, Abate F, Lasorsa E, et al. Convergent mutations and kinase fusions lead to oncogenic stat3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015;27:516-532.

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^+ anaplastic large-cell lymphoma (ALCL), where translocations yield 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 Rabadan 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 copy 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. Conversely, no mutations in these genes were seen in *ALK*-positive ALCL or in other types of peripheral T-cell lymphoma. The cases with mutations were all found to express nuclear phosphorylated STAT (pSTAT) by immunohistochemistry, with some nonmutant cases also showing this pattern, suggesting that alternative mechanisms of STAT3 upregulation may also exist. Similar increases in pSTAT 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. Mutant *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 transphosphorylation, 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 *NPM-ALK* chimeras of the type found in ALK^+ ALCL.

Investigating the potential for targeted therapy based on these findings, the authors tested inhibitors of the pathway for their effects in cell lines and preclinical models. Although the *STAT3* inhibitor niclosamide showed limited activity in cells bearing mutations, an *ALK*-negative ALCL-derived xenograft showed growth inhibition with clinically relevant concentrations of the JAK1/JAK2 inhibitor ruxolitinib. In the cells bearing translocations such as *NFkB2-ROS1*, 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-ROS1*–bearing 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.

Fresher Blood is Not Necessarily Better Blood

Lacroix J, Hébert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. N Engl J Med. 2015;372:1410-1418.

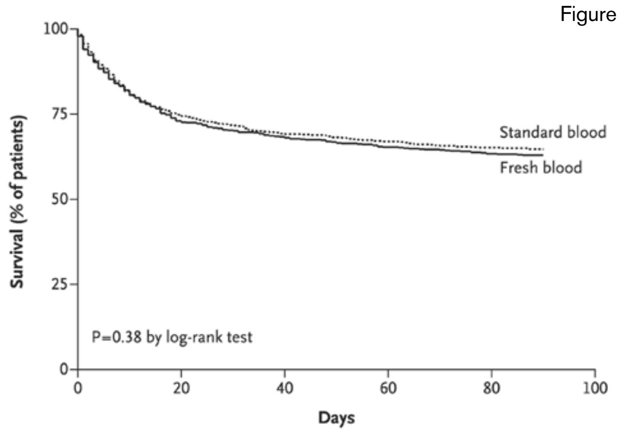
Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015;372:1419-1429.

Red 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 and rheologic changes as well as changes in metabolism, and oxygen affinity/delivery, commonly referred to as the RBC "storage lesion."[1] Multiple observational and retrospective analyses have been performed examining the effects of RBC storage age on patient outcomes. The results of these studies have been mixed and complicated with bias.[1] 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 issue 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 two groups with respect to major illnesses; duration of respiratory, hemodynamic, or renal 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 outcomes 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.

Figure



Kaplan–Meier survival analysis of time to death in the intention-to-treat population. The intention-to-treat population included 2,430 patients. The hazard ratio in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9-1.2).

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.[2] 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.

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

Chan SM, Thomas D, Corces-Zimmerman MR, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. Nat Med. 2015;21:178-184.

Acute myeloid leukemia (AML) is a heterogeneous disease presenting with various clinical subtypes. A broad spectrum of cytogenetic 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 misssense 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-hydroxyglutarate (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, explored an alternative approach of synthetic lethality to target mutant cells. This concept exploits the fact that malignant cells rely on a non-oncogenic pathway for their survival. They used AML cell lines that had been engineered to express either the wild type *IDH1* or the mutant $IDH1^{R132H}$ together with a green fluorescent protein marker under the control of a doxycycline-inducible promoter. They performed a large-scale RNA interference study by transducing the cells with a lentiviral shRNA library and identified two synthetic lethal genes, *BCL-2* and *BCL-W*, which are members of the antiapoptotic *BCL-2* family. Knockdown of *BCL-2* decreased the viability of $IDH1^{R132H}$ cells compared with wild-type cells, and the level of knockdown correlated with the degree of apoptosis, consistent with an on-target effect. Further experiments showed that increasing the intracellular levels of 2-HG by treatment with octyl-R-2-HG, sensitized cells to apoptosis. Subsequent studies were facilitated by the availability of a highly specific, clinically available *BCL-2* inhibitor, ABT-199, which was used to recapitulate the synthetic lethal phenotype. *In vitro* studies on the engineered AML cell lines, as well as *ex vivo* experiments on blasts from AML patients, showed that cells expressing mutant IDH were more sensitive to the effects of ABT-199. Transplant and xenotransplant experiments in mice demonstrated further that the drug targeted $IDH1^{R132H}$ AML cells, as well as leukemic stem cells *in vivo.*

These results prompted the researchers to investigate the mechanism of the synthetic lethal effect. The antiapoptotic BCL-2 protein binds to the BH3 domain of proapoptotic proteins BAX and BAK, which prevents them from initiating apoptosis by permeabilizing the outer mitochondrial membrane and triggering the release of cytochrome c into the cytosol. ABT-199 is a BH3 mimetic, which could disrupt the BCL-2/BAX/BAK interaction and induce apoptosis. Treatment of mutant *IDH* cells or cells with experimentally elevated levels of 2-HG exhibited increased levels of cytochrome c 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 data 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*.

THERESA L COETZER, PhD

Dr. Coetzer indicated no relevant conflicts of interest.

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

Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA. 2015;313:1627-1635.

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).[1] 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.[2]

The Prévention 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 removed within three months of insertion. Slightly more than half of the enrolled patients were older than 75 years, and approximately two-thirds had some evidence of right ventricular dysfunction or myocardial injury. Only about 9 percent of enrolled patients had iliocaval 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 relative risk estimate for the primary endpoint in patients with filter (vs. no filter) was 2.00 (95% CI, 0.51-7.89; $p = 0.50$). 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.

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Table 1. Included patients had to have at least one of these factors, chosen by the authors because they correlate with PE severity.
Age > 75 years
Active cancer
Chronic cardiac or respiratory insufficiency
Ischemic stroke with leg paralysis within the last six months
Deep vein thrombosis that involved the iliocaval segment or was bilateral
At least one sign of right ventricular dysfunction or myocardial injury

Table 2. The most common complications observed among the 193 patients who received an IVC filter
Retrieval failure due to mechanical reasons (5.7%)
Access site hematoma (2.6%)
Filter thrombosis (1.6%)

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Dr. Garcia indicated no relevant conflicts of interest.

Health-related Smartphone Apps: Status Update for Hem-Onc Practitioners

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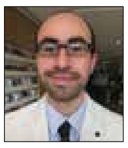

In the last few years, there has been a tremendous increase in the availability of smartphones, tablets, and computers in the United States and worldwide. Smartphones are the most commonly used personal computer and have revolutionized the communication landscape in our personal and professional lives. In the current rapidly growing technology era, 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."[1]

Experts studying mobile health market trends have estimated that 500 million smartphone users worldwide, including health-care professionals and patients, will be using a health-care application by 2015.[2] 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.[3] 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 reported daily use of mobile applications.[4] 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 all adults in the United States have owned a smartphone. Ownership was slightly more common in males (61%) than females (57%). The majority of African Americans (59%), Hispanics (61%), and whites (53%) owned a smartphone.[5] 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 on their phones when compared with non-owners (6%).[6] 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, smartphone owners and women aged 30 to 64 years are more likely to sign up to get health text alerts. While smartphones enable individuals to use different apps to help monitor and manage their health, only 19 percent of 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 (298) 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 comprised the majority 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 nonmedical, and/or those with unclear purposes. Only a minority of hematology and oncology apps were disease-specific, and most journals in the field had more apps available in Apple iTunes. Hematology or oncology 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.[7-9]

Potential Benefits

Mobile devices and health-related apps offer many benefits to health-care providers, trainees, and patients. Some medical 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.[10] Additionally, there are several apps that help patients to self-manage their lifestyle, specifically weight and exercise. Users can also track a chronic condition and even report symptoms to their health-care providers. Therefore, mobile apps use can facilitate bidirectional physician-patient communication in different settings.

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.[11-12] Concerns about patient safety, accountability, 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.[12] In addition, an app developed to identify and manage skin cancer was found to be accurate in identifying only 11 percent (10 of 93) of high-risk melanoma cases when tested against images from the National Cancer Institute and Fitzpatrick's Dermatology in General Medicine,[13] urging caution 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 and app developers is critical to ensuring that regulations are followed and unforeseen pitfalls are avoided.[14] Advances in the technological landscape outpace 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 (HIPPA) 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.[15] HIPPA privacy rules apply to any health-care provider that transmits health-care information electronically and uses health-related apps within a health-care setting.[16] 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 liability, which may or may not 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 private health apps have full control of app content and functionality, 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.

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's focus is primarily on 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 or performance of traditional medical 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. Policing 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 technology 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.

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Table. Popular Hematology and Oncology Apps

App Name	Platform	Developer	Purpose	Comments
Miniatlas Hematology	iOS	EC-Europe	Patient education	Good-quality detailed medical illustrations that can be e-mailed to patients
Hematology Outlines	iOS	Dr. Hooman H. Rashidi and Dr. John C. Nguyen	Medical education	Multiple interactive options showing normal and abnormal hematologic entities; atlas, and glossary components
CancerRx	iOS	MedPage Today and CollabRx	Clinical decision support	Physicians can enter patient data and receive a list of suggested therapies with references from UpToDate website
Calculate by QxMD	iOS, Android	QxMD Medical Software Inc.	Calculations and formulas	Includes hematology and oncology specialties; physicians can enter data to derive disease-specific staging results and prognostic scores
PubMed On Tap	iOS	ReferencesOnTap	Journal articles	Users can search PubMed or PubMed Central, as well as their library's collection after entering an organization or university's unique proxy URL in the app's settings
NCCN Guidelines®/ NCCN Guidelines® for Smartphone	iOS, Android	National Comprehensive Cancer Network	Guidelines and reimbursement resource	Guidelines are listed in alphabetical order; icons for chosen guidelines can appear on the homepage. Physicians, patients, or payers can view and download content.
inPractice for Specialists	iOS, Android	Clinical Care Options	Clinical decision support	Includes a search interface that is able to retrieve results in three main buckets: Guidelines, PubMed, and Clinical Trials.

blood® Editors' Choice

Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding *Blood* articles that have appeared either in print or online during the two-month interval between issues of *The Hematologist*. The goal is to underscore the remarkable research that is published in *Blood* and to highlight the exciting progress that is being made in the field.

MARCH 26, 2015

Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. Blood. 2015;125:2062-2067.

The Bruton's tyrosine kinase inhibitor ibrutinib has had a dramatic impact on the treatment of patients with relapsed chronic lymphocytic leukemia (CLL). However, Dr. Preetesh Jain and colleagues present a sobering report on the outcome of patients who discontinued ibrutinib for progressive disease, transformation, transplantation, or adverse events. The outcome of these patients is extremely poor, with a median survival of 3.1 months following drug discontinuation. Nearly all the patients had high-risk features; nevertheless, their extremely poor outcome is somewhat surprising and will likely be the basis for the next series of investigations aimed at improving the long-term survival of CLL patients.

APRIL 2, 2015

Guida C, Altamura S, Klein FA, et al. A novel inflammatory pathway mediating rapid hepcidin-independent hypoferremia. Blood. 2015;125:2265-2275.

A decrease in circulating iron levels, hypoferremia, is a common response to systemic inflammatory conditions. Hypoferremia 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 hypoferremia in response to inflammatory stimuli. These findings have direct implications for our pathophysiological understanding of anemia of inflammation.

Wang TF, Squizzato A, Dentali F, et al. The role of thrombolytic therapy in pulmonary embolism. Blood. 2015;125:2191-2199.

Pulmonary embolism (PE) has an incidence of 60 to 100 per 100,000 patients per year, with a 30-day case fatality rate of 10 to 30 percent. The standard of care for PE has been anticoagulation, but the beneficial effects of the addition of thrombolysis have remained controversial. Questions include, "When and how to use thrombolysis in PE?" and "Why do the results of several recent studies on thrombolysis in PE differ so markedly?" Dr. Tzu-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.

APRIL 9, 2015

Airoldi I, Bertaina A, Prigione I, et al. $\gamma\delta$ T-cell reconstitution after HLA-haploidentical hematopoietic transplantation depleted of TCR-$\alpha\beta$+/CD19+ lymphocytes. Blood. 2015;125:2349-2358.

HLA-haploidentical transplantation has emerged as a potential therapy for patients requiring hematopoietic stem cell transplantation (HSCT) who do not have an HLA-matched donor. However, these transplants have 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 $\alpha\beta$ 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, $\gamma\delta$ 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 zoledronic acid. These results strongly support further efforts to move this approach forward for wider use in HSCT.

APRIL 16, 2015

Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125:2497-2506.

This study by Dr. John Byrd and colleagues provides an important update on the prolonged use of the single-agent Bruton's tyrosine kinase inhibitor ibrutinib in patients with CLL or SLL who have been followed for a median time of three years from start of treatment. The study adds new observations on the efficacy and toxicities of ibrutinib. High rates and remarkably long durations of responses are noted, particularly in treatment-naive patients.

APRIL 23, 2015

Hoban MD, Cost GJ, Mendel MC, et al. Correction of the sickle cell disease mutation in human hematopoietic stem/progenitor cells. Blood. 2015;125:2597-2604.

Dr. Megan Hoban and colleagues report on the use of gene 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 into human marrow 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.

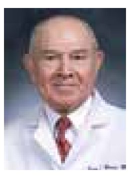
MAY 7, 2015

Popat U, Mehta RS, Rezvani K, et al. Enforced fucosylation of cord blood hematopoietic cells accelerates neutrophil and platelet engraftment after transplantation. Blood. 2015;125:2885-2892.

Delayed engraftment is a major limiting factor in the widespread adoption of cord blood transplantation (CBT). Slow engraftment may be a result of limiting stem cell numbers but may also reflect defective homing of CB cells to the marrow, which appears to be secondary to decreased fucosylation of cell surface P- and E-selectin ligands. Dr. Uday Popat and colleagues address this deficit by performing *ex vivo* fucosylation of CB cells prior to transplantation. They demonstrate improved neutrophil and platelet engraftment when a treated unit was infused with a second untreated unit. These promising data suggest a novel means to improve engraftment efficiency in the setting of double CBT.

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 anointed a Pharmacist'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 Phosphatides: 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 used widely for evaluating blood coagulation in patients.

These studies took place in a narrow, instrument-crammed laboratory at the VA New York Harbor Healthcare System, where he became Chief of Hematology-Oncology in 1958. In 1973, he was appointed Professor of Medicine at Weill Cornell Medical College and joined its Specialized Center of Research in thrombosis.

His immersion in platelet biology led Dr. Marcus to vascular eicosanoids and then to eicosanoid mediation of platelet-endothelial cell interactions. He created a new discipline that he called "transcellular metabolism." "We now call this 'systems biology' and consider it a cutting-edge approach to scientific discovery," notes Dr. Roy Silverstein, who worked with Dr. Marcus early in his career.

By the early 1990s, Dr. Marcus's focus had shifted to an enzyme on the surface of endothelial cells that he and his team–including longtime colleagues Drs. Joan Drosopoulos and Johan Broekman–identified as CD39/NTPDase1. CD39 rapidly metabolized ADP and ATP released from activated platelets, and Dr. Marcus soon proposed that it represented the main control system for blood fluidity. His subsequent studies explored its antithrombotic, anti-inflammatory, and cardioprotective effects. In a final paper published this year (*FASEB J. 2015;29:61-69*), Dr. Marcus demonstrated how CD39 in cardiac nerve terminals modulated local renin release, angiotensin formation, and ischemic arrhythmias. "It was a privilege to share authorship on Aaron's very last papers," remembers Dr. Roberto Levi, a longtime colleague at Weill Cornell.

As a scientific investigator, Dr. Marcus was notable for his sheer longevity and unquenchable curiosity – he was the longest continuously funded National Institutes of Health grantee, and garnered a new 10-year National Heart, Lung, and Blood Institute MERIT award at age 80. "He lived and breathed hemostasis," recalls Dr. Ralph L. Nachman, another comrade-in-arms. "He was on a constant search for new therapeutic agents designed to combat human thrombotic disease." Dr. Marcus also took the role of mentor very seriously. In fact, he considered it a crucial part of his job. "He had a natural penchant for training generations of eager young investigators," say close friends and Weill Cornell colleagues Drs. Katherine Hajjar and David Hajjar. Dr. Charles Serhan (Brigham and Women's Hospital), who worked in Dr. Marcus's lab as a graduate student, concurs: "His curiosity was infectious and his talent for zeroing in on the most critical and burning questions was unusual, and one of the most important for an effective mentor." Dr. Andrew Schafer, former colleague and ASH past president, adds, "Aaron was one of my most influential mentors and a firm believer that being a mentor and being a mentee were lifetime responsibilities."

Among his many honors, Dr. Marcus received the Henry Stratton Lectureship and "Pioneer in Hematology" award

Pharmacomechanical Catheter-Directed Thrombolysis: An Attractive Option for Prevention of Post-Thrombotic Syndrome?

STUDY TITLE: **Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT)**

CLINICALTRIALS.GOV IDENTIFIER: NCT00790335

COORDINATOR: Washington University School of Medicine

FUNDING SOURCE: National Institutes of Health. Additional support is provided by four companies (Bayer Healthcare, BSN Medical, Covidien, and Genentech), who play no role in study design, execution, or analysis.

PARTICIPATING CENTERS: 58 participating centers throughout the United States.

ACCRUAL GOAL: 692

STUDY DESIGN: The ATTRACT study is a phase III, multicenter, randomized, open-label, assessor blinded, parallel two-arm, controlled clinical trial. Adults (aged 16 to 75 years) with acute proximal deep vein thrombosis (DVT) are randomized to standard therapy (anticoagulation and elastic compression stockings), with or without adjunctive pharmacomechanical catheter-directed thrombolysis (PCDT) with recombinant tissue plasminogen activator. Patients who are pregnant, have active malignancy, recent major surgery or obstetrical delivery, an intracranial lesion, or preexisting post-thrombotic syndrome (PTS) are excluded. Randomization is stratified by anatomic extent of DVT and clinical center. Subjects return for follow-up at 10 days and 30 days, and at six, 12, 18, and 24 months. The primary efficacy outcome is development of PTS (defined as a score of ≥ 5 using the Villalta PTS scale or venous ulceration) within the 24-month follow-up period. Secondary outcomes include bleeding, quality of life, relief of acute DVT symptoms, and cost-effectiveness (*Vedantham S et al. Am Heart J 2013;165:523*).

RATIONALE: PTS develops in approximately 40 percent of patients after a first episode of proximal DVT. Clinical manifestations include chronic pain, swelling, heaviness, skin changes, and ulceration of the affected limb, resulting in disability and reduced quality of life. Options for preventing PTS are limited. Elastic compression stockings did not reduce PTS compared with placebo stockings in a recent randomized controlled trial (*Kahn SR et al. Lancet. 2014;383:880*).

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, added 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 extensive proximal DVT (*Jaff MR et al. Circulation. 2011;123:1788; Vedantham S et al. J Vasc Interv Radiol. 2006;17:435*), whereas the American College of Chest Physicians guidelines suggest anticoagulation alone over catheter-directed interventions (*Kearon C et al. Chest. 2012;141:e419S*). The CaVenT trial showed a 26 percent relative risk reduction in PTS at two years among patients with proximal DVT who underwent catheter-directed therapy (*Enden T et al. Lancet. 2012;379:31*). The study was small (189 subjects) and was conducted at just four centers in Norway, limiting the strength and generalizability of the evidence.

Perhaps the most important limitation of the ATTRACT trial is the open-label design. Knowledge of treatment assignment could bias assessment of the primary outcome, particularly because it relies on a subjective tool (i.e., the Villalta Scale). To minimize such bias, all clinical outcome evaluators and event adjudicators are blinded to 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 provide a definitive answer to whether PCDT is an effective means of preventing PTS.

–Adam Cuker, MD, MS

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**

CLINICALTRIALS.GOV IDENTIFIER: NCT02400242

SPONSOR: Acetylon Pharmaceuticals, Inc.

PARTICIPATING CENTERS: Six centers in the United States

ACCRUAL GOAL: 60 patients, depending on number of dose levels

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 one line of prior therapy; 2) at least two cycles of lenalidomide; and 3) at least two cycles of a proteasome inhibitor (either as separate therapy or in the same line of treatment). ACY-241 is given orally daily on days one to 21 on a 28-day schedule for the first cycle, and subsequently in combination with pomalidomide and dexamethasone.

RATIONALE: Histone deacetylase inhibitors (HDACi) such as vorinostat (Zolinza) and now panobinostat (Farydak) are an important new class of cancer therapeutics. By increasing histone acetylation, HDACi modulate the transcriptional profile of cells and other nuclear events. There are several classes of HDACi, and there are also nonhistone substrates of HDACi in the cytoplasm through which HDAC inhibitors exert manifold effects on protein degradation (via the aggresome), protein-protein interactions, and protein localization.

In MM, preclinical work targeting both proteasomal and aggresomal protein degradation systems with proteasome inhibitors and HDACi respectively, showed accumulation of polyubiquitinated proteins, followed by activation of apoptotic cascades and synergistic cytotoxicity (*Pei XY et al. Clin Cancer Res. 2004;10:3839-3852*; *Richardson PG et al. Leuk Res. 2013;37:829-837*; *Santo L et al. Blood. 2012;119:2579-2589; Mishima Y et al. Br J Haematol. 2015;169:423-434*). This motivated the clinical development of HDACi as part of MM combination therapy, beginning with vorinostat, a pan-HDACi. VANTAGE 088 was a phase III trial of vorinostat in combination with bortezomib, compared to bortezomib alone on a 21-day schedule in relapsed/refractory MM with one to three prior lines of therapy (*Dimopoulos M et al. Lancet Oncol. 2013;14:1129-1140*). While this study showed statistically significant improvement in progression-free survival (PFS), the difference was only 0.8 months and was not clinically meaningful.

Panobinostat (LBH589) is a newer oral pan-HDACI that was recently approved for the treatment of relapsed/refractory MM. PANORAMA1 was a phase III trial comparing panobinostat, bortezomib, and dexamethasone to bortezomib and dexamethasone in a similar patient population as VANTAGE 088 with one to three prior lines of therapy (*San-Miguel JF et al. Lancet Oncol. 2014;15:1195-1206*). This study enrolled 768 patients, and the median PFS was significantly longer in the panobinostat arm (11.99 months) versus the control arm (8.08 months; p<0.0001). The overall response rate (ORR) trended higher in the panobinostat arm, 60.7 percent versus 54.6 percent (p=0.09). However, similar to the VANTAGE 088 trial, there was more grade 3-4 diarrhea in the panobinostat arm (25%) than in the control arm (8%). Deaths due to other causes besides progressive disease were also higher in the panobinostat arm (7% vs. 3%). Given some of these concerns, the U.S. Food and Drug Administration (FDA) in November 2014 deferred accelerated approval of panobinostat as second-line therapy.

Panobinostat was re-evaluated earlier this year as third-line therapy. In a pre-specified subgroup analysis of 193 patients who received prior treatment with both bortezomib and an immunomodulatory drug, the improvement with panobinostat was significantly greater. The median PFS was 10.6 months in the panobinostat arm versus 5.8 months in the control arm, and the ORR was also higher: 59 percent versus 41 percent, respectively. Given the benefit in this more challenging-to-treat patient population, the FDA gave panobinostat accelerated approval in February 2015 in patients who have received at least two prior lines of therapy, including bortezomib and an immunomodulatory drug. However, the drug has a black-box warning of diarrhea, cardiac events, and arrhythmias. Some of the toxicity may reflect its inhibition across all HDAC classes.

Targeting of specific HDACs may be better tolerated than pan-HDAC inhibition. In particular, HDAC6 regulates acetylation of α-tubulin and the aggresome degradation pathway, and myeloma cells are vulnerable to HDAC6 inhibition (*Hideshima T et al. Proc Natl Acad Sci U S A. 2005;102:8567-8572*). Ricolinostat (ACY-1215) is an oral HDAC6-selective inhibitor that synergistically increases the apoptosis of myeloma cells when combined with lenalidomide or pomalidomide (*Quayle SN et al. 2015. AACR Abstract 5380*). In addition, this combination was found to further reduce expression of the transcription factors MYC and IRF4, which are implicated in myeloma progression. Ricolinostat is currently in phase I and II clinical trials in combination with bortezomib (NCT01323751), lenalidomide (NCT01583283), or pomalidomide (NCT01997840). Preliminary data from these trials show promising efficacy and an improved toxicity profile. ACY-241 has similar activity as ricolinostat against HDAC6, but has the advantage of availability as a tablet instead of ricolinostat's liquid formulation. These findings set the stage for evaluating ACY-241 in combination with pomalidomide and dexamethasone.

COMMENT: Given that myeloma is a relapsing illness, patients need newer agents for their next line of therapy. The results of the PANORAMA1 study and the FDA approval of panobinostat are major advances for patients with MM. However, panobinostat is associated with significant toxicity, which likely reflects its activity across all HDAC classes. Selective inhibition of HDAC6 may be a means of enhancing the efficacy of HDAC inhibition, while improving tolerability. The trial of the oral HDAC6 inhibitor ACY-241 will test this therapeutic approach.

–Andrew J. Yee, MD, and Noopur S. Raje, MD

Dr. Yee and Dr. Raje indicated no relevant conflicts of interest.

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 endearingly 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 provocative and challenging ideas." Dr. Nachman similarly commends his old colleague's "spontaneous humor and warm friendship," and the "jazz and operatic pearls that poured from his 10-foot stereo speakers" on convivial occasions. "We shared a dual reverence for Arturo Toscanini," says Dr. Levi, and indeed, one of Dr. Marcus's 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

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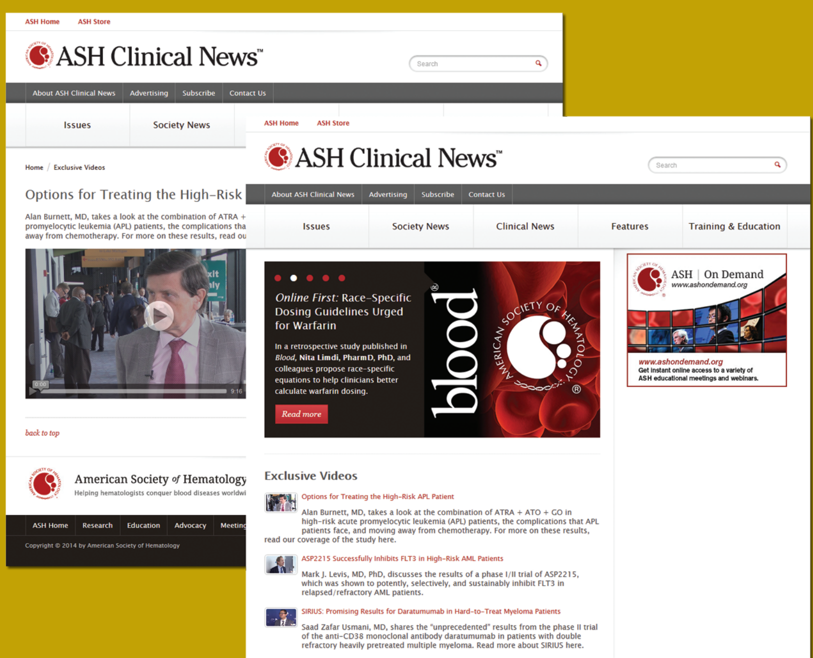

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