BCL-2 Is an Effective Target in Chronic Lymphocytic Leukemia


The past decade has seen remarkable improvements in therapeutic options for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). These include the approval of ibrutinib and idelalisib, small molecule inhibitors directed at components of the B-cell receptor pathway, and the novel CD-20 directed antibodies obinutuzumab andofatumumab. Drs. Joe Selby and Michaela Liedtke describe their approach to AL with cardiac involvement.

Dr. Andrew Roberts and colleagues have published results of the first phase I study of the oral drug venetoclax in relapsed or refractory CLL/SLL. Fifty-six patients were treated in the dose-escalation portion of the study (150 mg to 1,200 mg), with an expansion phase in 60 patients at a target dose of 400 mg. The patients were heavily pretreated with a median of three prior therapies (range, 1–11). Thirty and 27 percent of patients harbored deletions in chromosomes 17p and 11q, respectively, and 45 percent of patients had unmuted immunoglobulin heavy chain (IGHV).

In the initial dose escalation phase, 10 of 56 patients experienced tumor lysis syndrome (TLS) – three with clinical TLS and the remaining seven with biochemical TLS. Seven patients developed TLS after the initial dose (range, 50–200 mg) and three individuals with an increase in the dose (from 150 mg to 1,200 mg). One patient experienced sudden death, and a second required hemodialysis. In total, nine patients resumed therapy. As a result of TLS, the protocol was modified such that the dose of venetoclax was slowly escalated on a weekly basis from a starting dose of 20 mg daily. Additionally, patients were hospitalized for close observation and TLS prophylaxis upon initiation of therapy, and for dose escalation in those patients at high risk for TLS. In terms of other toxicities, the most common adverse events were mild nausea and diarrhea as well as neutropenia (grade 4 in 28% of patients). The most common serious adverse events were febrile neutropenia (6%) and pneumonia (4%). A maximum tolerated dose was not identified in doses up to 1,200 mg per day. Additionally, patients who relapse following these therapies, including those with deletions in chromosome 17p, continue to have a poor prognosis.

CLL is characterized by increased expression of the antiapoptotic protein BCL2. Targeting BCL2 using BH3-mimetics was initially tested using the drug navitoclax. In a phase II study, approximately 35 percent of patients achieved a partial remission. The drug, however, was associated with thrombocytopenia related to on-target inhibition of Bcl-xL. The second-generation BCL2 inhibitor, venetoclax, is a more potent inhibitor of BCL2 and has less activity against Bcl-xL. Preclinical data in CLL cell lines and xenograft models demonstrated promising activity.

VENETOCLOX SCHEDULES, PHARMACOKINETIC RESPONSE, AND ACTIVITY AGAINST CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) OR SMALL LYMPHOCYTIC LYMPHOMA (SLL).

(A) Administration schedule for the 58 patients in the dose escalation cohort. (B) Administration schedule for the 60 patients in the expansion cohort. (C) Plasma levels of venetoclax at steady state, grouped according to the dose at the time of collection. (D–F) Activity of venetoclax against CLL or SLL in blood (D), lymph nodes (E), and bone marrow (F), which are shown as normalized changes from baseline. From New England Journal of Medicine, Roberts AW et al, “Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia,” Volume 374, Page 314, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

MINI REVIEW – Drs. Yang and Press summarize the very latest in next-generation DNA sequencing in myeloid malignancies.

ASK THE HEMATOLOGISTS – Drs. Gregory Kaufman and Michaela Liedtke describe their approach to AL with cardiac involvement.

PROFILE – Drs. Joe Seby and Julie Panepinto chat with ASH about the mission and impact of PCORI.

PROFILES IN HEMATOLOGY – Dr. John M. Bennett reflects on his career, with former protégé Dr. Jane Liesveld.

THE AMERICAN SOCIETY OF HEMATOLOGY
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Observations on the Moonshot

Each year, when the President of the United States rolls out a budget proposal, it can be a time of tension and uncertainty as well as high hopes and excitement. Back in February, we applauded the 2017 fiscal year budget proposal of President Barack Obama, which included $331 billion in funding to the National Institutes of Health (roughly $2 billion more than the 2016 request), which would provide roughly 10,000 new research grants, as well as $755 million in mandatory funds for a project known as the “National Cancer Moonshot.” In late March 2016, we also heard that there is a promised influx of private dollars to help move the initiative forward. So what is significant about the Moonshot, and how will it impact research, policy, and the care of patients with hematologic malignancies?

The goal of the National Cancer Moonshot is to harness the advancements in cancer therapy that are currently underway, with the ultimate goal of taking big, bold steps toward researching and eradicating cancer. To launch the next phase of discovery, the initiative will begin investing in cancer-related activities throughout a number of agencies and institutes. These activities include prevention and cancer vaccine development, early cancer detection, cancer immunotherapy and combination therapy, genomic analysis of tumor and surrounding cells, enhanced data sharing, and other programs. (Learn more at www.whitehouse.gov/the-press-office/2016/02/01/fact-sheet-investing-national-cancer-moonshot.)

To date, the “Moonshot” has garnered praise from numerous experts, including within our own community of hematologists. But it has also invited a number of questions surrounding investment, and the feasibility of such a sweeping project in a contentious political environment. In the midst of all this, hematologists who specialize in malignant disorders might be contemplating what a concerted effort on the part of societies and advocacy groups like ASH might actually look like, and how they could become involved. How do we ensure hematology’s seat at the table, and how do we work with the administration and policy leaders to keep these actions focused and progressing? In an election year, these questions need to be asked so that Moonshot can remain viable and extend beyond a hotly contested sprint for The White House.

The time is right for us as a society and as a community at large to define and express the value of our input in this important conversation and in subsequent discussions and actions. In the coming year, ASH will continue to meet with key officials steering the initiative. One way that we hope to influence the dialogue is through the ASH Agenda for Hematology Research (www.hematology.org/ResearchAgenda), which was created to help agencies to navigate, prioritize, and build consensus around the most promising areas in hematologic research. This kind of alignment will not only assist the Moonshot initiative in maintaining its focus, but it will help guide decision-making to ensure that reasonable, sustainable investment choices are made. For example, emerging immunologic therapies and genomic profiling are two key priorities in which Moonshot and the ASH Research Agenda find direct alignment. With this in mind, ASH has prepared recommendations for the Moonshot on specific action items such as funds appropriation, creating incentives for data sharing, and identifying opportunities to increase collaboration and access to clinical trials.

During times of great promise and rapid change, we can’t stress enough the importance of making sure our voices are heard. Through advocacy and outreach with the public, ASH members can be instrumental in educating both the public and political leaders about current hematology research and its rich history of contributions to cancer treatment as a whole. This Moonshot opportunity is no different. Stay tuned to this publication and to www.hematology.org for ways to stay informed and involved.

BCL-2 Is an Effective Target in Chronic Lymphocytic Leukemia

(Cont. from page 1)

in the expansion cohort). Five percent of patients had no evidence of minimal residual disease on flow cytometry. The estimated durability of response was 75% at 15 months, and response duration was longer in patients with a CR versus a partial response. For patients with 17p deletion, 71 percent of patients responded, with 18 percent achieving CR. The ORR for patients with 11q deletion was 82 percent (11% CR); the respective ORRs for IGHV unmutated versus mutated patients were, respectively, 76 percent (17% CR) versus 94 percent (29% CR). At 15 months, the progression-free survival for the 400 mg target dose groups was 69 percent. Disease progression ultimately occurred in 41 patients (35%), including Richter’s transformation in 18 patients (16%).

Venetoclax is another potent tool in our armamentarium of effective therapies for patients with CLL/SLL, including those with poor risk features. Although generally very well tolerated, the drug causes rapid destruction of tumor cells and will, therefore, need to be used with great caution, in slowly escalating doses, to prevent TLS. Future studies will, no doubt, delineate combination strategies and indicate how best to sequence therapy with other agents.
The Hematologist

The Hematologist

very important. I would strongly recommend spraying clothes with permethrin (available at a variety of
the outbreak of Zika virus, and Arequipa is high and dry. However, prevention of mosquito bites is

time, Lima and the Amazon.

including a city tour of Arequipa, Colca Canyon, Cusco, Machu Picchu, and, if one takes additional

volcanoes. It is a beautiful city, called

Tell us a bit about your experience with Arequipa in general?

What is the status of hematology care in Arequipa, Peru, and what sort of disease burden are they dealing with?

Hematologists in Arequipa are very well trained and well read; they are very hard working and
dedicated physicians. The majority of their inpatients have acute lymphocytic leukemia on both the
pediatric and adult services, as well as lymphomas and aplastic anemia. They are the referral center for
the southern part of Peru and have approximately 400 adult and 240 pediatric inpatients per year, as
well as 8,000 adult and 4,000 pediatric outpatient visits per year, so they are very busy! They also have
25 ambulatory chemotherapy chairs (with oncology) that are filled daily.

What are the main issue areas that ASH volunteers can focus on to help improve hematology care in Arequipa?

This is almost the only postgraduate training available to the hematology staff and residents.
In addition to ALL, they are interested in improving their interpretations of blood smears and bone
marrows, as well as flow cytometry, blood banking, and hematopathology. Algorithms for the diagnosis
and treatment of other areas of malignant and nonmalignant pathology are of interest as well.

How was your working relationship with the on-site hematologists and other staff during your visit?

The hematologists in Arequipa are enthusiastic about our program and make a concerted effort to make
sure our volunteers have an impact on their staff as well as a gratifying experience. Dr. Mariela Fuentes,
the director of hematology, has been particularly supportive and helpful. Some of the attendings and
residents speak English quite well; the medical students are required to know English, and although
they can read English, they have varied speaking abilities. A working knowledge of Spanish is helpful
but not required. Fortunately, Dr. José Malaga, one of the senior hematologists, was a tour guide during
medical school. His English is excellent, and he is especially helpful translating slides in conference!
We have a new affiliation with Catholic University, one of the two medical schools there, and we hope
some of our volunteers can participate in their programs as well.

Having served in Peru as an ASH volunteer and project director, what advice would you give an ASH member considering a volunteer assignment in Arequipa?

Although we prepare lectures in advance, we have to be flexible so that we can adjust to the local
staff’s schedules and their clinical material. Although they have limited resources at times, we can try
to help them achieve the best possible outcomes. In general, they do not have Macs available, so all
presentations should be prepared in Word or converted to PDF.

Tell us a bit about your experience with Arequipa in general?

Arequipa is the second largest city in Peru, with approximately 1 million people living in the metropolitan
area (Lima has approximately 10 million), at 7,600 feet above sea level, and surrounded by inactive
volcanoes. It is a beautiful city, called Ciudad Blanca, because the buildings are made of sillar, a
porous white volcanic stone, in Spanish colonial style. It was declared a UNESCO World Heritage
site in 2000. The people are very friendly, with a mix of Indian and Catholic cultures. The food is tasty,
and there are many well-priced restaurants. There are many interesting things to do for sight-seeing,
including a city tour of Arequipa, Colca Canyon, Cusco, Machu Picchu, and, if one takes additional
time, Lima and the Amazon.

Potential travelers should know that Peru is one of the few countries that has not been affected by the
outbreak of Zika virus, and Arequipa is high and dry. However, prevention of mosquito bites is
very important. I would strongly recommend spraying clothes with permethrin (available at a variety of
department and sporting goods stores, as well as online), which lasts for two weeks or six washings,
prior to packing, and using industrial DEET (>30%, e.g., ultrathon).

ASH partners with Health Volunteers Overseas (HVO), a nonprofit organization dedicated to improving
global health through education, to bring hematology consultation and training to hospitals in low-
resource areas that care for hematology patients with a wide range of disorders. ASH member
volunteers provide on-site training in the form of rounds in the clinics, bedside consultations, classroom
lectures, training in the laboratories, and training in blood banking and transfusion medicine. The
objective is sustainable improvement of hematology patient treatment at these institutions. Volunteer
assignments generally range between two and four weeks.

Emeritus member Dr. Susan Harris serves as the project director for volunteer sites in Arequipa, Peru,
at Carlos Alberto Sequin Escobedo Hospital and Catholic University of Santa Maria. Below is an
interview with Dr. Harris, who visited local hematologists at these sites in June 2015 to determine areas
where ASH volunteers could make the greatest impact through on-site training and consultation.

Health Volunteers Overseas: On Site in Peru

Abstract Submission Site for 2016 Annual Meeting Opens June 1

This year’s meeting will take place December 3-6, 2016, in San Diego, California, and will
provide attendees with the opportunity to learn about the latest breakthroughs in hematology and connect with the global
hematology community. Visit the ASH website for the most up-to-date information on abstract submission, program sessions,
and new events and activities. Registration and housing for ASH members will open on July 20 at 11:00 a.m. Eastern Time.

Visit www.hematology.org/abstracts and submit your abstract before October 5, 2016. Online abstract submission is
required. A call for posters will announce a call for papers during the

Conversations with Innovators

Don’t miss this issue’s “What’s on the Web” spotlighting Conversations with Innovators – the new video series from
The Hematologist. See page 16 for more information.

ASH Expands Family of Blood Journals with Blood Advances

In December 2016, ASH will launch an open-access journal, Blood Advances, which will offer a unique focus on
scholarly and educational content that both complements and expands on topics addressed in Blood. Robert S.
Negrin, MD, professor of medicine at Stanford University and associate editor of Blood, has been named founding
editor-in-chief. By accepting manuscripts deemed to be either novel or definitive, Blood Advances will publish
important studies believed to be of great interest to the ASH membership. Furthermore, the journal’s online
platform will facilitate active interaction between readers and authors and will use a variety of visuals.

Blood Advances will announce a call for papers during the summer of 2016, and the first issue will launch at the 58th
ASH Annual Meeting in San Diego, December 3-6, 2016.
involvement are frequently deemed ineligible for this with multiple myeloma, patients with AL and cardiac Drug Administration–approved drugs for AL. While high-
to achieve hematologic response with standard light-chain suppressive therapy. A clinical study evaluating sequential activity of the serum amyloid P component (SAP)—clearing molecule CP-104, and an SAP-antibody did not include patients with cardiac AL, but demonstrated rapid clearance of amyloid deposits from patients with hepatic AL. Other fibril-reactive antibodies, including 11-IF4, are also in development and have shown promising organ responses even in dose-elevation cohorts. The optimal strategy for incorporating anti-fibril-based treatments with light chain suppressive therapy (in combination or sequential) is uncertain. Their promise, however, underscores the importance for all AL patients to be evaluated at a tertiary referral center as early in their disease course as possible.

Clinical Features and Diagnostic Work-up

At the time of initial hematology referral, the diagnosis of AL with cardiac involvement is often highly suspected on the basis of typical features such as the low-voltage echocardiogram, characteristic patterns seen on echocardiography including interventricular septal thickening or ventricular strain pattern, and evidence of increased serum-free light chains. Every suspected diagnosis requires confirmation by tissue biopsy (endomyocardial biopsy or biopsy of a surrogate site such as the aortoiliac artery with long red staining and amyloid subtyping by immunohistochemistry or mass spectrometry. In addition to serum and urine monoclonal protein studies, a bone marrow biopsy is undertaken to identify the underlying clonal plasma cell disease (or rarely, other light-chain–producing B-cell neoplasm). A detailed history and physical examination focusing on cardiac and other possible AL organ involvement should be performed, including assessment of volume status, orthostatic hypotension, and neurologic examination. Baseline measurements of 24-hour urinary protein, N-terminal of the prohormone brain natriuretic peptide (NT-ProBNP), cardiac troponin-T, alkaline phosphatase, and nerve conduction studies if there is concern for peripheral nerve involvement, should be considered standard of care. The revised Mayo cardiac staging system, which assigns points based on binary cutoffs of three variables at time of diagnosis (differential free light chains ≥ 18 mg/dL, NT-ProBNP ≥ 1,800 pg/mL, and troponin-T ≥ 0.10 μg/L), is useful for risk stratification and prognostic counseling.

Management

A multidisciplinary team approach to supportive care, with the involvement of experienced cardiologists and a heart failure team focusing on cardiac AL, is essential for management of fluid status and arrhythmias, adherence to salt restriction and support stockings, pharmacologic management of autonomic neuropathies, and selection of patients who may benefit from advanced heart failure interventions including cardiac transplantation.

Light-chain-suppressive therapy directed at treating the underlying clonal plasma cells relies on approved drugs for multiple myeloma as there are currently no U.S. Food and Drug Administration–approved drugs for AL. While high-dose therapy (HDT) with melphalan and autologous stem cell transplantation is commonly used upfront for patients with multiple myeloma, patients with AL and cardiac involvement are frequently deemed ineligible for this approach based on cutoffs in troponin-T and NT-ProBNP that predict high transplant-related mortality. Furthermore, there is no prospective randomized clinical trial evidence showing that upfront HDT is superior to novel-agent– induction regimens with regard to hematologic or organ response rates or to overall survival. We therefore consider upfront HDT in selected qualifying patients and use an individualized approach, taking into account patient preferences and individual risk.

The goal of any light-chain–directed therapy is a rapid and deep hematologic response defined by consensus guidelines. Cardiac response is also defined by consensus guidelines (Table 4) with improvement in survival. While it is clear that patients achieving hematologic response are more likely to achieve cardiac response, predicting which patients will achieve cardiac responses is difficult. Combination novel agent induction regimens, similar to those used in multiple myeloma are used in the treatment of AL. In cohorts of patients with advanced cardiac AL, bortezomib, cyclophosphamide, and dexamethasone (VCD) has been shown to produce hematologic very good partial response (VGPR), or better, rates of 43 percent, and cardiac response rates of 32 percent. Similarly, an upfront approach with lenalidomide in combination with cyclophosphamide and dexamethasone (RCD) produced VGPR or better hematologic response rates of 43 percent and cardiac response rates of 26 percent in a prospective phase II trial. For patients failing to achieve adequate responses or with relapsed disease, single-agent carfilzomib has been shown to produce hematologic responses in 78 percent of patients. There are also prospective data to support the use of pomalidomide and bendamustine with dexamethasone, respectively, in relapsed AL.

Consideration for clinical trial enrollment is always a priority for newly diagnosed or relapsing/refractory patients with cardiac AL, but when initially treating patients not as part of a clinical trial on cardiac AL, we will typically use a combination regimen such as VCD or RCD, assessing markers of hematologic and organ response as well as tolerability on a cycle-to-cycle basis. In addition to this physician-directed care, we also suggest exploration of complementary services including guidance for nutrition and exercise as well as specialty local and national support groups for patients with amyloidosis to provide another level of psychosocial support and engagement (for example, www.ourc.org and www.amyloidosis.org).

The Future

Novel approaches with anti-fibril activity are currently being evaluated in clinical trials of AL. Among the 14 patients with cardiac involvement included in the phase III study of the anti-fibril antibody NEOD001, median NT-ProBNP was 1,103 μg/L, all subjects met criteria for achieving cardiac response. Ongoing studies of NEOD001 (VITAL and PRONTO), are evaluating this agent as part of upfront combination therapy and also in patients with persistent cardiac dyskinesis despite achieving hematologic response with standard light-chain suppressive therapy. A clinical study evaluating sequential activity of the serum amyloid P component (SAP)—clearing molecule CP-104, and an SAP-antibody did not include patients with cardiac AL, but demonstrated rapid clearance of amyloid deposits from patients with hepatic AL. Other fibril-reactive antibodies, including 11-IF4, are also in development and have shown promising organ responses even in dose-elevation cohorts. The optimal strategy for incorporating anti-fibril-based treatments with light chain suppressive therapy (in combination or sequential) is uncertain. Their promise, however, underscores the importance for all AL patients to be evaluated at a tertiary referral center as early in their disease course as possible.

**The Question**

What is your approach to newly diagnosed patients with immunoglobulin light-chain amyloidosis (AL) with cardiac involvement?

**Our Response**

AL is a protein deposition disease resulting from toxicity of the abnormal light chain with long red staining and amyloid subtyping by immunohistochemistry or mass spectrometry.
Since 2012, when the Patient-Centered Outcomes Research Institute (PCORI) first began funding research, its vision and mission were clear: to fund studies on practical health-care questions — issues that are not only important to patients and their health-care providers, but also not adequately addressed by other major funding programs. Authorized by the U.S. Congress in 2010, PCORI is overseen by an independent, 21-person, Government Accountability Office–appointed board. The institute is a private, non-profit, independent research funding organization that represents the entire health-care community.

Dr. Joe V. Selby has been PCORI’s Executive Director from its start. “We fund studies that will give patients and those who care for them the information needed to choose the health-care options that may work best for them given their personal situations and preferences,” he says. “We share these results in ways that patients, clinicians, and others will find useful.” The studies PCORI funds are best described as comparative clinical effectiveness research (CER) — studies comparing how different approaches to care work (Table 1). “We are a ‘stakeholder-driven’ research funder,” Dr. Selby asserts, explaining that the institute’s research questions don’t come only from the scientific community or from the manufacturers. Instead they emerge from patients, clinicians, delivery systems, and insurers. Another one of the hallmarks of PCORI research is that rather than placing focus on the “average” patient or the average PCORI research is that rather than another one of the hallmarks of science, and insurers. Instead they emerge from patients, clinicians, delivery systems, and insurers.

Yet another hallmark of PCORI research is that rather than placing focus on the “average” patient or the average difference between two treatments, PCORI research emphasizes how treatment effectiveness varies among particular patient subgroups. A further point of importance is the inclusion of outcomes that other studies might not address. “In comparing drugs to treat multiple sclerosis, for example,” Dr. Selby proposes, “we don’t focus just on how two drugs impact changes on an MRI or CT image, but on how the treatments compare for reducing pain, stiffness, balance, fatigue, depression, or cognitive impairment.”

Dr. Julie Panepinto with Medical College of Wisconsin has a unique perspective on PCORI study selection, not only as a hematologist, but as a reviewer of grant applications to the institute. “PCORI is interested in comparative effectiveness studies, not efficacy studies,” she says. “I like to think of efficacy trials as studies that attempt to answer the question ‘can it work?’ as with a typical phase III-type study, whereas effectiveness studies attempt to answer the question ‘does it work?’” It is the “does it work” question that gets to the core of real-world settings, where studies are designed to test two equally efficacious interventions against each other to determine which treatment is better, and especially, which is better at improving patient-centered outcomes such as physical functioning.

Dr. Selby and Panepinto stress that it is these varieties of outcomes that offer patients a clearer idea of what works better for people like themselves. This emphasis on the patient perspective is key: PCORI-funded studies involve patients in the development of the research projects, governance and oversight, and dissemination strategy.

Patients are the not only the only valued resource in PCORI’s bold efforts to improve health care. Caregivers, patient organizations, clinical specialty organizations, payers, and employers are also demonstrating increasing engagement. They are becoming more involved as powerful “non-researcher” partners, who rely on more substantive evidence for their day-to-day activities. These stakeholder groups help ensure that PCORI identifies the right questions, studies them in appropriate ways, interprets the data in light of all the available information, and disseminates and implements the findings widely when studies suggest that practice should change. “We’re seeing that these patients and other stakeholders partner with scientists in choosing research questions, as well as in designing and conducting studies to answer those questions, they make it more likely that the results will be relevant to them and incorporated into daily practice,” says Dr. Selby.

To make sure that studies are well informed by these diverse stakeholders, PCORI hosts workshops convening participants from every sector. Dr. Panepinto represented ASH during a recent workshop on sickle cell disease (SCD). “There were SCD physicians, nurses, patients, representatives from pharma, the head of the National Institute for Children’s Health Quality, and representatives from the American Academy of Pediatrics and the Sickle Cell Disease Association present.” Among the goals of such events is to collaboratively shape high-level research questions that would lend themselves to specific proposals and more specific research questions.

PCORI has funded several research areas that focus on hematologic diseases, especially SCD, of which a few examples are summarized in Table 2. But what are the characteristics of a successful application? Dr. Panepinto points to three common themes: 1) evidence that the efficacy of different interventions (e.g., a therapeutic solution or procedure) that were then compared head-to-head in order to test effectiveness; 2) involvement of patients in a capacity that fits well with the overall mission of PCORI; and 3) measurement of outcomes that matter to patients, such as patient-reported functioning.

Looking ahead, the time appears to be ripe for hematologists to engage with programs such as PCORI. “I think any field that has several different acceptable methods to treat patients lends itself well to PCORI research,” notes Dr. Panepinto. For more information or to get involved, visit www.pcori.org.

Table 1. PCORI National Priorities for Research

<table>
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<tr>
<th>Priority</th>
<th>Description</th>
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<tbody>
<tr>
<td>Assessment of Prevention, Diagnosis, and Treatment Options</td>
<td>Comparing the effectiveness and safety of alternative prevention, diagnosis, and treatment options to see which ones work best for different people with a particular health problem.</td>
</tr>
<tr>
<td>Improving Health-Care Systems</td>
<td>Comparing health-system-level approaches to improving access, supporting patient self-care, innovative use of health information technology, coordinating care for complex conditions, and deploying workforce effectively.</td>
</tr>
<tr>
<td>Communication and Dissemination Research</td>
<td>Comparing approaches to providing comparative effectiveness research information, empowering people to ask for and use the information, and supporting shared decision making between patients and their providers.</td>
</tr>
<tr>
<td>Addressing Disparities</td>
<td>Identifying potential differences in prevention, diagnosis, or treatment effectiveness, or preferred clinical outcomes across patient populations, and the healthcare required to achieve best outcomes in each population.</td>
</tr>
<tr>
<td>Accelerating Patient-Centered Outcomes Research and Methodological Research</td>
<td>Improving the nation’s capacity to conduct patient-centered outcomes research, by building data infrastructure, improving analytic methods, and training researchers, patients, and other stakeholders to participate in this research.</td>
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</tbody>
</table>

PCORI makes an effort to include studies of rare conditions that may be overlooked and underfunded, studies that address improving care and outcomes for patients with multiple chronic conditions, and studies centering on the burden of specific illnesses, as measured by their frequency, their severity, the availability or lack of other treatments, and their costs to society.

Table 2. Examples of PCORI-Funded Hematology Projects and Studies

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Lead/Principal Investigator (Organization)</th>
<th>Objective</th>
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<tbody>
<tr>
<td>Tennessee Sickle Cell Disease Network</td>
<td>Dr. Michael DeBaun (Vanderbilt University)</td>
<td>To build the readiness capacity of individuals living with SCD throughout Tennessee for patient-centered outcomes research and to obtain a population-based representation for patient-centered outcomes research–based initiatives.</td>
</tr>
<tr>
<td>Comparing Patient-Centered Outcomes in the Management of Pain between Emergency Departments and Dedicated Acute Care Facilities for Adults with Sickle Cell Disease</td>
<td>Dr. Sophia Larzaron (Johns Hopkins)</td>
<td>To compare patient-centered outcomes, including pain management processes and patient experiences of care delivery, for patients with sickle cell disease (SCD) seeking treatment for pain due to a vaso-occlusive crisis in an emergency department compared to an infusion center.</td>
</tr>
<tr>
<td>Patient-Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease</td>
<td>Dr. Lakshmanan Krishnamurti (Emory University)</td>
<td>To help determine which individualized interventions, such as virtual clinic visits or video-based therapy via cell phone, will improve adherence to hydroxyurea (HU) treatment. It will also measure the impact of adherence with HU on clinical and patient-reported outcomes.</td>
</tr>
<tr>
<td>Comparative Effectiveness of a Decision Aid for Therapeutic Options in Sickle Cell Disease</td>
<td>Dr. Lakshmanan Krishnamurti (Emory University)</td>
<td>To develop and test a web-based decision aid for patients with SCD for determining treatment options.</td>
</tr>
<tr>
<td>Individualized Care Plans for Hematopoietic Cell Transplant Survivors</td>
<td>Dr. Elizabeth Murphy (National Marrow Donor Program)</td>
<td>To develop a survivorship care plan (SCP) for post-transplant care that incorporates the experiences of past transplant patients and to compare outcomes of transplant patients who receive the SCP with those of patients who do not.</td>
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</table>
The rapid adoption of next-generation (massively parallel) DNA sequencing (NGS) methods into clinical diagnostic laboratories has created an incredible opportunity to profile the many actionable driver genes in patients with known and/or suspected myeloid malignancies. The clinical availability of this abundance of information now presents practicing hematologists with several unique genomic-era challenges that could not have been imagined in the "single-gene" era of only a few years ago. Toward the goal of unifying all of this information into a unique comprehensive framework of NGS-based testing, this review will address some common practical questions that arise regarding "hotspot" gene mutation panels for myeloid malignancies. The same generic issues are equally applicable to other hematologic malignancies as well as nonhematopoietic solid tumors. This discussion will not touch on the use of gene panels in the context of clonal hematopoiesis of indeterminate potential, idiopathic cytopenias of undetermined significance, idiopathic dysplasia of undetermined significance, or clonal cytopenias of undetermined significance, which are extensively reviewed elsewhere,14 and which are becoming a very common diagnostic outcome after gene panel workups for cytopenia.

Acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN) are clonal disorders of hematopoietic stem cells. The simultaneous NGS-enabled detection of somatic mutations in dozens or hundreds of genes as markers of the neoplastic clone, can provide "actionable" information in four broad clinical utility categories, as outlined in the Table: 1) diagnostic, 2) prognostic risk stratification, 3) eligibility for targeted therapy, and 4) minimal residual disease (MRD) detection and monitoring.

Diagnostic Utility
A common diagnostic dilemma that is often favorably informed by NGS-based mutation profiling is the evaluation of a cytopenic patient for possible MDS. The presence of a pathologic MDS-associated driver mutation (Table) can establish the existence of clonal hematopoiesis and thus support an MDS diagnosis versus a nonclonal benign cause of cytopenia.15 The overwhelming majority of patients with MDS (approximately 70%-90%) will have one or more oncogenic mutations identified by NGS. Other common scenarios in which NGS can be diagnostically informative (Table) include distinguishing clonal MDS from benign pathologic mimics (by detecting JAK2, CALR, or MPL mutations) and detecting a particular genetic alteration that has a high positive predictive value for a specific diagnostic entity (often with a specific targeted therapy). One example is detection of the CSF3R T618I mutation that is found in approximately 80 percent of patients with chronic neutrophilic leukemia (and more rarely in atypical CML); ruxolitinib is now being tested in these patients since CSF3R signals through JAK2.

Prognostic Utility
The presence of certain recurrent somatic mutations in myeloid malignancies can provide useful prognostic risk stratification and inform optimal treatment (Table). In cytogenetically normal AML, consensus risk stratification recommendations include the use of gene panel testing to guide the assessment of mutations in the FLT3 (poor risk), NPM1, and CEBPA (favorable risk) genes to inform treatment decisions, including the use of hematopoietic stem cell transplantation.16 In patients with a normally favorable risk core binding factor (CBF) AML, the presence of a Kit mutation conveys a relatively poorer prognosis, such that targeted therapy is currently considered intermediate risk.17 Less mature data might suggest the concomitant use of other molecular markers for AML risk stratification, including TP53, IDH1/2, DNMT3A, TET2, and RUNX1 (all conferring poor risk).18 Multigene sequencing panels are also often used to stratify risk in MDS, with several common gene mutations conferring a poor prognosis (DNMT3A, IDH1/2, ASS1, RUNX1, EZH2, NRAS, and TP53).19,20 (Otherwise-low-risk MDS patients by International Prognostic Scoring System criteria, but with an EZH2 or TP53 mutation, have a worse prognosis than expected.

Therapeutic Utility
Perhaps the most direct patient benefit of multigene sequencing panels is the detection of specific mutations that define a likely response (or nonresponse) to a targeted therapy, either with an approved drug, or one being evaluated in an ongoing clinical trial. Proven or promising examples include JAK2 inhibitors in JAK-STAT pathway-activated MPN,21 second-generation FLT3 kinase inhibitors in FLT3/ITD positive AML,22,23 inhibitors to the mutant IDH1/2- generated onco-metabolite in AML,24,25 Braf inhibitors in hairy cell leukemia,26 hypomethylating agents in TET2/DNMT3A/ ASS1 associated mutant MDS,27 and many other examples in ongoing clinical trials (Table).

MRD Utility
Another promising area of clinical utility for NGS-based profiling is monitoring the persistence of AML-associated mutations ("minimal residual disease") after therapy. The persistent detection of these pathogenic mutations after standard AML induction chemotherapy is predictive of future relapse,28,29 and may indicate the need for more aggressive therapy.

Gene Test Selection and Sensitivity
The mutation profiling tests available within clinical laboratories are predominantly NGS-based "hotspot" panels interrogating all exons or selected commonly mutated regions within 10 to 50 different "cancer genes." The label-specific practice of gene targets and correlated tumor types is heterogeneous and must be carefully assessed by the referring clinician. Assays specific for "hematopoietic malignancies" or "myeloid malignancies" are the common consequence of such decisions. The typical analytical sensitivity (lower detection limit) for such NGS-based tests is typically a variant allele fraction (VAF) of 1 to 10 percent (depending on sequencing depth and other laboratory mutations), and the truly actionable mutations thus risk being "lost in the weeds." Although the search for actionable mutations or "likely benign" mutations is not always straightforward, in most cases the mutant allele fraction is greater than some defined threshold (typically 1%). Otherwise uncharacterized variants at a germline-compatible 50 percent or 100 percent allele frequency can often be clarified as "likely benign" genetic variants.

Determining the "pathogenicity" of a particular variant is a much more difficult process, requiring rigorous investigations into 1) the association of the variant (how frequently?) with the tumor of interest (or other tumors); 2) in vitro or animal studies of variant function (onco/normalcy); 3) in silico tools for predicting the biochemical function (of the variant); and 4) clinical trials of possible targeted therapies. Invaluable database/tools for these variant annotation tasks include COSMIC (catalogue of somatic mutations in cancer), ClinVar, and many other expert curation efforts.

Although all NGS-based diagnostic reports will include a list of prefiltered variants/mutations, their annotation with respect to clinical "actionability," whether the mutation is likely to directly impact patient care with respect to diagnosis, prognosis, or therapy, is highly variable.30 This assessment of actionability requires a manual (or semiautomated) review of published literature (PubMed); professional guidelines; and comprehensive clinical, genetic, biochemical, and functional database searches (detailed above). Although real-world heterogeneity in the art and science of mutation interpretation and reporting remains a substantial, stakeholders in the pathology, hematology, and oncology communities are advocating for and drafting a standardized system of discrete categories of actionability evidence. These four to live actionability categories may ultimately include terms such as: "actionable," "potentially actionable," "variant of unknown significance (VUS)," and "benign/likely benign." Although any such "actionable" variant should, of course, be emphasized in the final report, many pathologists do not report benign or likely benign variants. The grey-zone VUS category presents a particular challenge to both laboratories and pathologists ("should we report it?" and clinicians ("what does it mean?"). In our opinion, however, a reportable mutation list that is a little too short (i.e., includes VUS but not benign variants) is usually preferable, given that a "VUS" with today’s knowledge may become an "actionable" mutation in the future. The contrary opinion, to keep reports short and clinically focused, is certainly respected, particularly when the presence of mutations is long, and the truly actionable mutations thus risk being "lost in the weeds." However, since the search for actionable diagnostic or MDS mutation is now widely available in academic medical centers, commercial laboratories, and large community hospitals. However, since all of these NGS-based diagnostic and MDS mutation panels are non-FDA approved, some "laboratory developed tests," the technical details of each test — genes and tumors covered, mutation detection limits, reporting

Table: Categories of Actionable Mutations

<table>
<thead>
<tr>
<th>Actionable Categories</th>
<th>Mutated Genes</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td></td>
<td></td>
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<tr>
<td>Diagnostic panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF3R</td>
<td></td>
<td>Diagnostic marker for chronic neutrophilic leukemia (and more rarely atypical CML)</td>
</tr>
<tr>
<td>MYD88 L265P</td>
<td></td>
<td>Diagnostic marker for lymphoplasmaic lymphoma/ Waldenstrom macroglobulinemia</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td></td>
<td>Diagnostic marker for hairy cell leukemia</td>
</tr>
<tr>
<td>JAK2 (V617F or exon 12, CALR (exon 9), MPL)</td>
<td></td>
<td>Distinct clonal myeloproliferative neoplasm from benign myelodysplasia</td>
</tr>
<tr>
<td>NPM1, CEBPA</td>
<td></td>
<td>Favorable risk in AML (without a FLT3 mutation)</td>
</tr>
<tr>
<td>RUNX1</td>
<td></td>
<td>Independently associated with a poor prognosis in MDS and AML</td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td>Independently associated with a poor prognosis in MDS and AML</td>
</tr>
<tr>
<td>DNMT3A</td>
<td></td>
<td>Adverse effect on outcome in cytogenetically normal AML</td>
</tr>
<tr>
<td>ASXL1</td>
<td></td>
<td>Independently associated with a poor prognosis in MDS and CML</td>
</tr>
<tr>
<td>KIT</td>
<td></td>
<td>Poor prognosis in CBF AML</td>
</tr>
<tr>
<td>U2AF1</td>
<td></td>
<td>Associated with a poor prognosis in MDS</td>
</tr>
<tr>
<td>ZRSR2</td>
<td></td>
<td>Associated with a poor prognosis in MDS</td>
</tr>
<tr>
<td>FLT3</td>
<td></td>
<td>Tyrosine kinase inhibitors in phase II clinical trials for AML (midostaurin, quizartinib, gilteritinib, crizotinib, quizartinib, quizartinib)</td>
</tr>
<tr>
<td>Therapeutic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kit</td>
<td></td>
<td>Tyrosine kinase inhibitors in clinical trials for AML (midostaurin, quizartinib, gilteritinib)</td>
</tr>
<tr>
<td>BRN4</td>
<td></td>
<td>Venetoclax</td>
</tr>
<tr>
<td>Minimal Residual Disease</td>
<td>Any driver mutations identified in the diagnostic specimen</td>
<td>Mutation persistence after therapy predicts future relapse</td>
</tr>
</tbody>
</table>
ASH Committee on Government Affairs Visits Congress to Discuss Research Funding and Sickle Cell Disease

Following its March 22, 2016, meeting in Washington, DC, the ASH Committee on Government Affairs visited more than 40 congressional offices on March 23 to advocate for sickle cell disease (SCD) legislation and funding for the National Institutes of Health (NIH). ASH advocates encouraged House and Senate offices to support comprehensive SCD legislation to enhance federal government activities in SCD research, training, and services.

The group also urged the offices to recognize the value of biomedical research by investing in the NIH and supporting at least $3.45 billion in funding for the NIH in fiscal year 2017.

That same day, ASH Vice President Dr. Alexis Thompson presented ASH’s 2015 Public Service Award to Representative Danny K. Davis (D-IL) for his work in co-founding the Congressional Sickle Cell Caucus. The caucus is working to bring public and congressional awareness to the unique needs of the SCD community.

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

You can participate in the Society’s advocacy efforts by visiting the ASH Advocacy Center and joining the ASH Grassroots Network. Contact ASH Legislative and Advocacy Manager Tracy Roades at troades@hematology.org or visit www.hematology.org/Advocacy for additional information.

ASH Vice President Dr. Alexis Thompson presenting the 2015 ASH Public Service Award to Representative Danny Davis (D-IL).

Dr. Richard L. Rovin and Dr. Jonathan Hoggatt, Dr. Rachel Cook, Representative Suzanne Bonamici (D-OR), Dr. Alan Rosmarin, and Dr. David Rizzieri during the March 23 ASH Committee on Government Affairs H4 Day.

Medicare Proposes Radical Experiment in Drug Payment Policy

On March 8, 2016, the Centers for Medicare and Medicaid Services (CMS) released a proposed change in payment policy for physician-administered drugs (https://www.cms.gov/apps/policydocuments/federalregister.gov/2016/0308pdf). This project was developed by CMS’s Centers for Medicare and Medicaid Innovation and will affect more than half the country since the policy mandates participation.

Currently, Medicare pays for physician-administered drugs at a payment rate that is equal to 106 percent of average sales price (ASP), which is calculated by the manufacturer and a least costly alternative (establishing payment rates for new equivalent drugs based on the current standards), among others. To the extent that drugs are not affected by these new payment policies, they would continue to be paid on the basis of the existing ASP policy (either 106% of ASP or 102.5% of ASP, depending on the region). The second phase would begin sometime in 2017.

This is a major policy shift for Medicare. Reducing the payment made for infused drugs is likely to have a significant effect on the viability of hematology practices, particularly those that remain in a private practice environment. The new innovative payment policies could prove cumbersome or prevent patients from receiving certain treatments.

These policies could also reduce costs for patients and steer them toward more appropriate treatment. ASH will offer comments on this proposed new payment policy before the May deadline and will continue to update members on this proposal.

ASH is responding to the proposed policies that will change Medicare payments for infused drugs in portions of the country and plans to discuss the issues of concern with officials from Medicare as well as to provide appropriate comments in response to the proposed rule. ASH will ensure that no patients are limited in their access to drugs and that new tools do not interfere with the doctor-patient relationship.

ASH Submits Comments to NHLBI on its Draft Strategic Research Priorities

In March, ASH submitted comments to the National Heart, Lung, and Blood Institute (NHLBI) on its recently released draft strategic research priorities that will inform the institute’s policy and funding decisions for the next several years. ASH’s comments were developed based on the ASH Agenda for Hematology Research (www.hematology.org/ResearchAgenda) and input from members of the ASH Committee on Scientific Affairs and ASH Scientific Committees. ASH strongly supports the NHLBI’s vision and is pleased to help shape many priorities in its draft align with the Society’s mission to further the understanding, diagnosis, treatment, and prevention of disorders affecting the blood, bone marrow, and the immunologic, hemostatic, and vascular systems. The Society appreciates the opportunity to provide comments and looks forward to working with them on implementing its vision. The full text of the Society’s comments may be found on the ASH website at www.hematology.org/Advocacy/Testimony.aspx.

Dr. Yang and Dr. Richards indicated no relevant conflicts of interest.

Minimal residual disease (MRD) in multiple myeloma (MM) reflects the persistence of chemoresistant clonal plasma cells (PCs) after treatment. The correlation between the presence of MRD and duration of remission and overall survival is now well established in MM.1 At the 2015 ASH Annual Meeting, Dr. Herve Avet-Loiseau and colleagues evaluated the presence of MRD in patients achieving a very good partial response or better after receiving lenalidomide, bortezomib, and dexamethasone induction therapy with or without autologous stem cell transplantation. Patients achieving an MRD-negative state by next-generation sequencing had significantly improved progression-free survival (PFS) when compared with those who did not.2,3 Furthermore, Dr. Avet-Loiseau demonstrated that next-generation sequencing was more sensitive than flow cytometry at detecting MRD, with a sensitivity of 10−9 versus 10−10, respectively. The greater the sensitivity of the MRD detection instrument, the more powerful the prognosticator of PFS. As MRD monitoring is incorporated into an increasing number of study designs, the exploration of the biological features of the residual PCs detected by this evaluation becomes of increasing interest and importance.

Dr. Bruno Paiva and colleagues conducted a novel evaluation of the genetic and phenotypic properties of MRD in a small cohort of patients from the GEN2010IM659 study using multidimensional flow cytometry. In this study, newly diagnosed, transplant-ineligible patients were treated with either eight cycles of VMP and lenalidomide and low-dose dexamethasone. Of the 40 newly diagnosed, transplant-ineligible patients were treated with either eight cycles of VMP and lenalidomide and low-dose dexamethasone. Of the 40 patients studied, MRD was characterized in 12 of the postinduction samples. The goal of their analysis was to compare genetic and phenotypic features of PCs from bone marrow aspirates collected before treatment to specimens obtained postinduction. To date, no biological studies have been performed in primary chemoresistant clonal PCs detected at MRD levels following front-line therapy.

Immunophenotypic protein expression profiles were generated from clonal PCs of paired samples and demonstrated upregulation of integrin (CD11a, CD11c, CD29, CD49d, CD49e), chemokine receptors (CXCR4), and adhesion molecules (CD44/CD54) in the MRD samples. This suggested that the MRD clonal PCs might represent a phenotypic subset of the whole diagnostic tumor population. To further explore this hypothesis, Dr. Paiva investigated copy number alterations (CNAs) of matched diagnostic versus MRD clonal PCs. Of the 12 sets examined, three showed identical copy number profiles. In the remaining nine, there were unique CNAs identified in at least one of the two PC populations. In some samples, CNAs detected at diagnosis were no longer present in MRD clonal PCs, whereas in others, a selected number of genetic alterations became apparent only at the MRD stage.

Gene expression profiling was performed on seven available samples and showed significant downregulation of genes related to protein processing in the endoplasmic reticulum, protein export, and α-glutamine biosynthesis in the MRD subclone. Loss of ALCAM has been linked to aggressive phenotypes in a variety of diseases. In this cohort, there was a trend toward decreased expression in the chemoresistant PCs. This deregulated gene expression profiling may contribute to plasma cell survival after multidrug therapy.

This study is a first exploration into understanding the biology of clonal PCs present in low levels or MRD states after induction therapy. These investigations provide a foundation upon which larger studies can further explore the characteristics of residual disease. Understanding the correlation between the biologic and phenotypic profiles of clonal PCs at the time of MRD and at time of relapse should lead to a better understanding of chemoresistance and ultimately better therapeutic strategies for MM.


Elegant Biology: Glycine- and Folate-correctable SLC25A38-mutated Sideroblastic Anemia


“It’s not whether you win or lose, but how you play the game.” - Babe Ruth

Sideroblastic anemia is a group of congenital and acquired bone marrow disorders with varied underlying pathophysiologies, primarily related to a heme or hemoglobin synthesis deficiency, and characterized by pathologic iron deposits in the mitochondria of erythroid precursors. Among the congenital sideroblastic anemias, the most common form is X-linked sideroblastic anemia due to mutations in β-aminolevulinate synthase 2 (ALAS2). ALAS2 is the first enzyme in the heme synthetic pathway; it catalyzes the formation of β-aminolevulinate (ALA) from glycine and succinyl-CoA and is an erythroid-specific enzyme. Most pathogenic mutations are partial loss-of-function alleles.1

Dr. Duane L. Guernsey and colleagues previously demonstrated that mutations in the erythrocyte-specific, inner mitochondrial membrane transporter, SLC25A38, cause autosomal recessive form of congenital sideroblastic anemia.2 SLC25A38 is highly and preferentially expressed in transferrin receptor positive erythroid cells and deletion of the SLC25A38 homologue in yeast causes reduced levels of heme and a defect in heme synthesis. The defect in heme synthesis can be rescued by supplementing the media with ALA or glycine. Dr. Guernsey and colleagues speculated that SLC25A38 facilitates ALA production by importing glycine into the mitochondria or by exchanging glycine for ALA across the inner mitochondrial membrane. However, the precise function of SLC25A38 remained unknown.

To determine the function of SLC25A38 and to identify potential therapies for what is emerging as a relatively common form of congenital sideroblastic anemia,3 Dr. J. Pedro Fernandez-Murray and colleagues also used yeast-deletional strains and a morpholinob-knockout zebrafish model. As previously shown,4,5 they found that yeast lacking the yeast homologue of SLC25A38 exhibit decreased heme levels. Heme synthesis was restored with expression of the human SLC25A38 protein or with ALA or glycine supplementation. They went on to establish that SLC25A38 functions as a mitochondrial glycine importer, and that cytoplasmic glycine is the main source of glycine for heme synthesis within the mitochondria (Figure). Additionally, they replicated earlier work6 showing that morpholino knockdown of both zebrafish homologues of SLC25A38 results in anemia. They demonstrated that neither ALA nor glycine supplementation in the zebrafish model could ameliorate the anemia, in contrast to their yeast model where this supplementation restored heme synthesis. To account for this finding, the authors cleverly recognized that while yeast have the capacity to synthesize folate, which is needed for cell growth, vertebrates such as zebrafish and humans require dietary folate supplementation, providing the rationale to treat the knockout morphants with glycine and folate. This combination improved hemoglobinization to near normal levels.

In humans, congenital sideroblastic anemia due to SLC25A38 deficiency typically presents as a transfusion-dependent anemia, and thus, patients are faced with the burden and complications of a lifelong, chronic transfusion program. The elegant biology carefully deciphered in this paper identifies glycine and folic acid supplementation as a simple therapy for this form of congenital sideroblastic anemia. Confirmation of its safety and efficacy in patients awaits further study.


The Hematologist: ASH NEWS AND REPORTS

References

Acquired thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy caused by autoantibody-mediated deficiency of the von Willebrand–cleaving protease, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, type 1, motif, member 13). Reduced ADAMTS13 activity results in accumulation of ultra-large von Willebrand factor (ULvWF) multimers. Via their A1 domain, ULvWF multimers bind to glycoprotein Ib-IX-V on the surface of platelets and induce formation of platelet-rich microthrombi, leading to microvascular occlusion and end-organ ischemic injury. Treatment of TTP involves daily plasma exchange (PLEX) to remove the autoanti-ADAMTS13 antibody. However, PLEX is effective in treating acute episodes, patients remain at risk for recurrent disease upon discontinuation of PLEX due to the persistent formation of autoantibodies. Thus, immunosuppression (e.g., corticosteroids, rituximab) is often added to inhibit autoantibody production.

Caplacizumab is a humanized single domain immunoglobulin that targets the A1 domain of vWF and prevents it from binding to platelets. In the phase II, single-blind, TITAN study, subjects with an acute episode of suspected acquired TTP were randomized to 10 mg/d caplacizumab subcutaneously or matching placebo during plasma exchange and for 30 days afterward. Patients with active bleeding were excluded. The primary end point was time to platelet normalization (≥150 × 10^9/L).

Seventy-five patients were assigned to the caplacizumab (n = 38) or placebo (n = 39) arms. Baseline characteristics were similar between the two groups. Two-thirds of patients were enrolled at the time of an initial episode; one-third had recurrent disease. Severe ADAMTS13 deficiency (<10%) was documented in 77% of subjects at enrollment. The ADAMTS13 level at study entry was not available in 12% of patients, and it was a 10% in 11 percent of subjects, suggesting that some patients had a thrombotic microangiopathy other than TTP. During PLEX, 91 percent of patients received corticosteroids, and 15 percent received rituximab.

Caplacizumab shortened the median time to platelet normalization compared with placebo (39% reduction, p < 0.005). Among the 69 patients in the study who did not begin PLEX until after they received the first dose of study drug, the median time to response was 3.0 days (95% CI, 2.7–3.9) in the caplacizumab arm and 4.9 days (95% CI, 3.2–6.6) in the placebo group. Exacerbation (recurrent TTP within 30 days of discontinuing daily PLEX) occurred in three patients in the caplacizumab group and in 11 patients in the placebo group. Relapse (recurrent TTP during the 12-month observation period but after day 30), however, occurred more commonly in patients assigned to caplacizumab (11 patients vs. 3 patients). Seven of the 11 relapses in the caplacizumab arm occurred within 10 days of stopping study drug. As might be expected for a drug that inhibits vWF function, bleeding-related adverse events were more common in caplacizumab-treated patients (54% vs. 39%). Most were mild or moderate in severity.

Proportion of patients free from relapse (recurrent thrombotic thrombocytopenic purpura within 30 days) or relapse (recurrent thrombotic thrombocytopenic purpura between day 30 and day 365) after discontinuation of daily plasma exchange.

Acquired TTP is a relapsing disease. Consistent with other published series, 29 (38.7%) of 75 patients in the TITAN study experienced an exacerbation or relapse within 12 months of discontinuing daily PLEX. This figure may underestimate the true incidence of relapse because: 1) a minority of patients in the study may have had a thrombotic microangiopathy other than acquired TTP based on–severely deficient ADAMTS13 levels at enrollment; 2) not all patients were followed for the full 12-month study period; and 3) late relapses beyond 12 months may occur.

PLEX is a life-saving therapy for acute episodes of acquired TTP, but it does not reduce autoantibody formation or prevent exacerbation and relapse once it is discontinued. Like PLEX, caplacizumab appears to be a temporizing measure but not a means of reducing recurrence. Patients randomized to caplacizumab in combination with PLEX responded more quickly and had lower rates of exacerbation at 30 days than patients treated with PLEX alone. However, after caplacizumab was discontinued at day 30, a “catch-up” effect was observed, with more relapses in the investigational arm than the placebo arm. By day 50, the proportion of patients free of exacerbation or relapse was no better in the investigational arm than in the placebo arm (Figure). These findings are not unexpected based on caplacizumab’s mechanism of action, but they do call into question its potential role in the treatment of acquired TTP. Caplacizumab may be useful for managing refractory patients who do not respond to or are unable to discontinue PLEX. In centers where PLEX is not available, caplacizumab could also be used as a bridge, along with plasma infusion, until the patient is transferred to a center with PLEX. But for most patients, it is unlikely that the benefit of shortening time to response by a few days will make up for the cost of the drug and its increased bleeding risk.

Corticosteroids for ITP: A Comparison of Two Approaches


Dr. Garcia indicated no relevant conflicts of interest.

Dr. Chabot-Richards and Dr. George indicated no relevant conflicts of interest.

Corticosteroids have been used for more than 30 years as a first-line treatment for adult immune thrombocytopenia (ITP). The most common regimen is oral prednisone 1 mg/kg/d, typically tapering to the lowest possible dose (based on platelet count) during a period of weeks to months. Many patients simply on the basis of convenience. For most patients who achieve an initial response, a sustained response rate of 50% vs. 98% (P = 0.001). Additionally, patients on the HD-DXM arm were permitted to continue a maintenance course of prednisone 1 mg/kg/d, slowly tapering to the lowest possible dose (based on platelet count). This created a significant difference in survival or risk of relapse compared with the presence of MRD. Patients with MRD were more likely to have the FLRT-IDT mutation or a High Medical Research Council (MRC) risk score. The presence of MRD emerged as the sole prognostic factor for relapse in a multivariate analysis. Among patients considered at high-risk due to FLRT-IDT, DNMT3A, or both, the absence of mutated NPM1 transcripts identified patients with a relatively favorable outcome with a survival rate of 78 percent. Furthermore, NPM1 mutation was in fact a stable marker of disease, and was detectable in 69 (98%) of 70 patients at the time of relapse. Notably, DNMT3A and IDT are the two most common molecular abnormalities associated with preleukemic clones, persisted at high levels in patients during long-term remission.

To further assess the use of quantitative NPM1 mutation analysis in MRD, a validation cohort of 91 patients with mutations was studied prospectively. Clinicians were informed of the results of MRD testing in this group. This analysis confirmed the association of MRD with a significantly worse outcome (two years due to increased incidence of relapse (70% vs. 31%; P < 0.001) and lower rate of overall survival at 5 years vs. 87%). A total of 21 patients were identified, of which 21 were included in 46 patients and MRD in 61 of 239 patients without MRD. The absence of MRD remained prognostic in patients receiving stem cell transplantation.

This study demonstrates the value of using highly sensitive RT-qPCR-based methods to identify MRD in patients with NPM1-mutated AML. Patients with intermediate-risk AML-based on normal karyotype, have an intermediate risk of relapse, and absence of FLRT-IDT and DNMT3A mutation are generally considered to have a better prognosis. Screening for the presence of MRD can help identify patients in this group who have a higher risk of relapse and poor outcomes. Further studies are needed in this transplantation cohort to explore the necessity of more intensive chemotherapy in these patients. Patients with intermediate-risk AML and absence of FLRT-IDT and/or DNMT3A mutation without MRD identified by the absence of intermediate-risk AML and/or DNMT3A mutation without MRD identified by the absence of intermediate-risk AML and/or DNMT3A mutation without MRD identified by transplantation or chemotherapy in these patients. These results show that in addition to its role in risk stratification, NPM1 mutation can be used for MRD monitoring.
Novel Role for Iron Transport in Immune Cell Function


A n effective immune response relies on proliferation of lymphocytes and the generation of protective immune responses. Combined immunodeficiency (CID) is a genetic disorder characterized by abnormal development or function of T and B lymphocytes; however, early hematopoietic stem cell transplantation cures the disease. The underlying mutations are heterogeneous, but in several patients, no genetic defect has been identified.

Dr. Raif Geha and colleagues investigated two families of Middle Eastern origin in which CID is dominantly inherited with selective, recurrent childhood infections, hypo- or agammaglobulinemia, intermittent thrombocytopenia, and mild anemia. Lymphocyte counts were normal, but the cells were dysfunctional, T cells failed to switch from IgM to IgG and IgE, and B-cell proliferation was also impaired. Additionally, the number of memory B cells was significantly reduced, and immunoglobulin class switching from IgM to IgG was defective. These abnormalities resulted in CID and rendered the patients susceptible to infection.

To identify the causative mutation, the research team performed whole-genome sequencing and demonstrated that two patients were homozygous for a missense mutation in the TFRC gene that codes for the transferrin receptor 1 (TR1), and the obligate carrier father was heterozygous. The mutation segregated with disease phenotype in the extended family and was also present in the CID patient from the second family. Moreover, the mutation was not present in control individuals. This strongly suggested that the mutation is not a recent mutation and that TR1 is essential for iron homeostasis whereby low iron concentrations trigger the binding of regulatory proteins to the iron-responsive element in the 3′ UTR of the TR1 mRNA, which stabilizes the transcript and leads to increased levels of TR1 protein and enhanced uptake of iron. The cytoplasmic tail of TR1 contains an internalization motif of "YTRF", and the tyrosine residue is highly conserved in vertebrates. The T+C mutation in the TFRC gene of CID patients causes substitution of the tyrosine by a histidine residue, which disrupts the internalization signal leading to defective iron homeostasis. This is consistent with the markedly increased levels of TR1 on the surface of the cells. Lymphocytes are able to take up non-transformed iron-bound iron, and in vitro supplementation with iron citrate substantially increases the transferrin molecules so that excess free iron is internalized independently of TR1. Supplementation experiments with patient cells rescued the lymphocyte defects, demonstrating that insufficient iron uptake is the cause of CID. Further evidence for the pathogenic nature of the PRMT1 mutation was provided by the generation of TR1 knock-in mice that showed the same abnormalities as CID patients.

Iron is essential for erythrocyte development and oxygen transport, and knockout mice lacking the TR1 protein die in utero, so the mild anemia in the CID patients with dysfunctional TR1 was an unexpected and intriguing finding. Supporting this observation, the expression of TR1 is increased in many patient-derived erythroid precursor cells from bone marrow was only slightly elevated, and precursor cells from knock-in TR1FL/HFL mice showed normal internalization of TR1. These findings implied that iron transport into red cells may use more than one mechanism. This prompted further research focusing on STEAP3, a conserved ferrireductase, which is highly expressed in red cell precursors but not in lymphocytes. STEAP3 co-localizes with TR1 and possesses a cytoplasmic YXXF internalization motif similar to the "YTRF" in TR1. Elegant co-immunoprecipitation and transfection experiments with wild-type and an internalization-defective mutant STEAP3 demonstrated that the interaction of TR1 and STEAP3 facilitates the entry of TR1 into erythroid precursor cells. This compensatory mechanism is only present in red cells and prevents severe anemia in the CID patients. It is tempting to speculate that the alternative mechanism of iron uptake in erythrocytes, not lymphocytes, evolved due to the absolute requirement of iron in red cells, which is essential to sustain life.

This study has revealed several important findings: 1) the first demonstration of a pathogenic mutation in the TFRC gene encoding TR1; 2) impaired iron transport as a new cause of CID; 3) new insight into the role of TR1 and iron internalization in host immunity; and 4) a new pathway for TR1 endocytosis in red cells mediated by an interaction with STEAP3.

The identification of the molecular defect in a subset of CID patients and the resultant enhanced expression of TR1 on lymphocytes has clinical relevance because it provides a useful diagnostic tool for the early detection of these patients, who may then be eligible for curative hematopoietic stem cell transplantation therapy.

**Omar Abdel-Wahab, MD, and Justin Taylor, MD**

Dr. Abdel-Wahab and Dr. Taylor indicated no relevant conflicts of interest.

**Theresa L. Coetzer, MD**

Dr. Coetzer indicated no relevant conflicts of interest.

Iron is essential for erythrocyte development and oxygen transport, and knockout mice lacking the TR1 protein die in utero, so the mild anemia in the CID patients with dysfunctional TR1 was an unexpected and intriguing finding. Supporting this observation, the expression of TR1 is increased in many patient-derived erythroid precursor cells from bone marrow was only slightly elevated, and precursor cells from knock-in TR1FL/HFL mice showed normal internalization of TR1. These findings implied that iron transport into red cells may use more than one mechanism. This prompted further research focusing on STEAP3, a conserved ferrireductase, which is highly expressed in red cell precursors but not in lymphocytes. STEAP3 co-localizes with TR1 and possesses a cytoplasmic YXXF internalization motif similar to the "YTRF" in TR1. Elegant co-immunoprecipitation and transfection experiments with wild-type and an internalization-defective mutant STEAP3 demonstrated that the interaction of TR1 and STEAP3 facilitates the entry of TR1 into erythroid precursor cells. This compensatory mechanism is only present in red cells and prevents severe anemia in the CID patients. It is tempting to speculate that the alternative mechanism of iron uptake in erythrocytes, not lymphocytes, evolved due to the absolute requirement of iron in red cells, which is essential to sustain life.

This study has revealed several important findings: 1) the first demonstration of a pathogenic mutation in the TFRC gene encoding TR1; 2) impaired iron transport as a new cause of CID; 3) new insight into the role of TR1 and iron internalization in host immunity; and 4) a new pathway for TR1 endocytosis in red cells mediated by an interaction with STEAP3.

The identification of the molecular defect in a subset of CID patients and the resultant enhanced expression of TR1 on lymphocytes has clinical relevance because it provides a useful diagnostic tool for the early detection of these patients, who may then be eligible for curative hematopoietic stem cell transplantation therapy.
It all began with a most fortuitous interview in 1946 with Dr. William Dameshek, the founder and first editor of Blood. When I was a 13-year-old student at the Roxbury Latin School in West Roxbury, Massachusetts, our class was given an assignment to interview someone famous and to present that interview to the Class of 1951. My father, a pediatrician and Tufts Medical School graduate, told me that he knew “Bill” very well and would arrange for me to interview him at his home.

I found Bill in his home office cluttered with journals and manuscripts. He told me about this new specialty that he was working on that dealt with both nonmalignant conditions and malignancies of the blood. This vivid memory remained with me for a very long time and played a significant role in my career choice.

Fast forward to 1962 when I finished my internal medicine residency at the Beth Israel Hospital (BIH) in Boston and was accepted as a hematology fellow in the Tufts/Boston City Hospital program headed by two outstanding hematologists, William Moloney and Jane Desforges. Several papers later (including a publication in the New England Journal of Medicine on acquired spherocytic anemia secondary to Costrumid wuchii bowel infection) and after a year of learning from the masters, I was back at the BIH in charge of the diagnostic hematology laboratory. At the Yamin Research Institute at BIH, I met Al Rutenberg, a surgeon working on inflammatory bowel disorders. He taught me about the histochemistry of phosphatases, which led to the publication of a new series of workshops was arranged where cases were reviewed and guidelines developed. The classification was based exclusively on the morphology of the bone marrow and peripheral blood cells in

Romanowsky-stained air-dried smears. The initial intent was to separate acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) from acute lymphocytic leukemia (ALL), into easily identifiable and reproducible subtypes. The most widely used morphologic classification of AML, ALL, and MDS in the past four decades was published in 1976, and expanded definitions were proposed by the FAB Cooperative Group in 1982.

The FAB Working Group recognized that some patients could present with a disease that bore some resemblance to AML, but that this entity, unlike AML, did not have many leukemic blasts in the bone marrow. The disease was associated with some alteration in maturation of the three major cell lines, which resulted in pancytopenia and increased risk of infection and bleeding but did not necessarily progress to acute leukemia. Different terms were applied, including dysmyelopoietic anemia. The FAB leukemia working group had its genesis from initial discussions between the two of us. Each of us identified other morphologists with whom we had some contact (Drs. Daniel Catorovsky, Marie-Thérèse Daniel, David Galton, Harvey Granlick, and Claude Sultan). A series of workshops was arranged where cases were reviewed and guidelines developed. The classification was based exclusively on the morphology of the bone marrow and peripheral blood cells in

from around the world, and lasting and warm relationships with morphologists including Drs. Jean Goasguen, Barbara Bain, Dick Brunning, Ulrich Gerning, Jim Wardman, Nuket Tuzuner, Masao Tomonaga, and Yataro Yoshida have led to many pleasant trips and continued scientific efforts. It has been wonderful to witness the coming of age of trainees and fellows who have assumed important international roles, including Drs. Torsten Haferlach, Anna-Marie Sironiolo, Jeff Lancet, Rami K Komoroski, and Jane Liesveld. I have received tremendous support from the medical center, and in particular, from Drs. Richard Burack and Jonathan Friedberg, who have allowed me to continue my interests in morphology.

As I move toward my mid-80s (with more than 560 publications under my belt) I reflect on what a wonderful and full academic career I’ve had. I have been blessed with two great physician sons and one amazingly talented publishing editor daughter, as well as nine spectacular grandchildren. My wife Carol has always been at my side on most of my travel adventures (when not there, my colleagues are upset).

Teaching, clinical research, publishing results of studies, and patient care have provided me with a full academic life and no regrets.

none other than Bill Dameshek, for a second opinion. The patient had a refractory anemia with normal iron stores, but the erythrocytes were microcytic and hypochromic. Serum iron was elevated. My resident suggested that we assay the urine for hydroxykynurenine after tryptophan loading, which was dramatically elevated. A trial of oral pyridoxine restored his hematology profile, and another loading, which was dramatically elevated. A trial of oral pyridoxine restored his hematology profile, and another
Teaching Brigade
(Cont. from page 1)

professional success among hematologists, and emphasizes developing and delivering innovative
teaching materials and methods that will excite learners and stimulate enthusiasm for our
subspecialty. Lastly, hematology educators need access to ongoing, up-to-date instruction in order
to best facilitate the acquisition of skills, knowledge, and mentoring.

ASH MEI is an intensive educational and mentoring program developed to address the needs of
clinician educators in hematology. After a rigorous selection process (currently underway as of
the writing of this article), approximately 20 participants will engage in a three-day workshop held
at ASH Headquarters this September. The workshop will involve active learning sessions dealing
with critical topics in medical education. Additionally, the on-site workshop will also allow for
mentorship of a scholarly project proposed by the participant as part of the application process.
Following the workshop, participants will return to their home institutions, engage in a scholarly
project related to their roles in education, and participate in several webinars designed to facilitate
ongoing training.

What Will Participants Learn?
ASH MEI will incorporate innovative and interactive pedagogies to teach key concepts in medical
education. Core content will include topics such as active learning in the classroom, developing a
scholarly project in hematology education, assessment and feedback, and writing multiple choice
questions. Participants will also have the opportunity to discuss ways to demonstrate value to their
institutions. For example, sessions on how to build an educator’s CV and how to get promoted as a
hematology educator will be included. Most sessions will require participants to complete required
readings prior to the workshop so that time spent in the workshop can be used to discuss and apply
key concepts and engage in interactive exercises that reinforce the core content.

Each participant will come prepared with ideas for a scholarly education project to be refined
during the ASH MEI experience. Participants will gather in small groups to nurture their medical
education projects from concept to a fully formed program. It is expected that participants will be
ready to implement these projects following the workshop and will contribute an enduring product
to ASH to share with the rest of the hematology education community.

After the in-person workshop, participants will view a series of webinars to explore additional topics
in medical education throughout the next 12 months. In so doing, they will cultivate a community of
medical educators within ASH and build a network to enable educational innovation and research.

Who Are the ASH MEI Faculty?
Experienced educators in hematology will attend ASH MEI as faculty (www.hematology.org/
Educators/4692.aspx#a2). Faculty have been carefully selected based on their expertise, scholarship,
and leadership in medical education. ASH MEI faculty will run sessions among the larger group
of participants, facilitate small group project work, and offer one-on-one mentoring to guide
participants in their career development and scholarly pursuits. Course faculty will be available to
participants throughout the year for longitudinal follow-up, providing participants with continuity in
mentorship.

How Can You Get Involved?
Academic hematology recruitment, retention, and prevention of burnout are challenging in an
era of great change in our profession. The fact that the percentage of tenured faculty in medical
school continues to decline to less than 20 percent reflects the changing work environment and
underscores a need for faculty development. We are hopeful that the ASH MEI will provide such a
resource. Thinking back to the opening vignette about Louis, the ASH MEI will enable him to develop
a sound approach to curriculum development, become facile with various strategies for learner
assessment, be exposed to numerous educational technologies and digital resources to enhance
his course, and receive expert and individually tailored advice about how to develop further as an
educator.

Sounding good? Please refer all promising educators with whom you work to visit www.hematology.
org/MEI for more information, and email ASH at training@hematology.org to offer content suggestions
or to volunteer to join our faculty.

Drs. Kesselheim and Kahn indicated no relevant conflicts of interest.
Comparing Outcomes for Young Adults with Severe SCD Treated with HLA-Ideal Sibling and Matched Unrelated HCT versus Standard Supportive Care

**STUDY TITLE:** Hematopoietic Stem Cell Transplantation for Young Adults with Sickle Cell Disease (STRIDE-2)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01955619

**FUNDING SOURCE:** National Heart, Lung, and Blood Institute, National Institutes of Health

**COORDINATOR:** Emory University

**CLINICAL SITES:** Multiple clinical centers throughout the United States

**ACCRUAL GOAL:** 180-200 patients (60 for the transplantation arm and 120-140 for the parallel comparison cohort)

**STUDY DESIGN:** STRIDE-2 will open as a multicenter trial designed to compare clinical outcomes for young adults with severe sickle cell disease (SCD) after hematopoietic cell transplantation (HCT). For a variety of reasons, a randomized clinical trial for HCT or observation is not practical. Thus, eligibility will be determined on the biological assignment of HLA-identical siblings or well-matched unrelated donors (Logan BR et al. Clin Trials. 2008;5:607-616), with those lacking an eligible donor for HCT serving as a comparison group. The eligibility criteria for STRIDE-2 include age 15 to 40 years and severe SCD. Indications for HCT in SCD were previously described (Fitzhugh CD et al. Hematol Oncol Clin North Am. 2014;28:1171-1185). The conditioning regimen will include busulfan, fludarabine, and rabbit antithymocyte globulin, and graft-versus-host-disease (GVHD) prophylaxis will include cyclosporine or tacrolimus in addition to post-transplant methotrexate. The primary outcome measure will assess overall and event-free survival (EFS) at two years from the biological assignment between the two transplant arms and the standard care arm. Comparing outcomes of the transplant cohort with standard supportive care in young adults with severe SCD treated with HCT versus standard supportive care. This study has the potential to establish guidelines on when to recommend HCT and may broaden the therapeutic techniques for young adults with severe SCD.

**COMMENT:** The STRIDE-2 trial represents the next level of research for HCT in severe SCD using HLA-Ideal siblings and unrelated donors for HCT compared with standard care due to the absence of a suitable donor. A potential challenge for STRIDE-2 includes identifying HLA-identical donors for the transplantation arm. Previous HCT trials in adults with SCD demonstrated that only 14 to 17 percent of those previously described (Fitzhugh CD et al. Hematol Oncol Clin North Am. 2014;28:1171-1185) were identified using traditional HLA-identical techniques. Thus, eligibility will be determined on the biological assignment of HLA-identical siblings or well-matched unrelated donors (Logan BR et al. Clin Trials. 2008;5:607-616), with those lacking an eligible donor for HCT serving as a comparison group. The eligibility criteria for STRIDE-2 include age 15 to 40 years and severe SCD.

**RATIONALE:** Currently, HCT is the only curative option for SCD and recently became available for the increasing population of young adults with severe SCD. Nonmyeloablative regimens have been successful with high engraftment rates of 87 percent and low mortality rates of 3 percent in a single-center trial (Hsieh MM et al. JAMA. 2014;312:48-50). The pilot study, STRIDE (NCT01955619), assessed the feasibility and safety of these donor sources using a nonmyeloablative conditioning regimen in 15 young adults with severe SCD (results pending). STRIDE-2 is the first trial dedicated to comparing outcomes for young adults with severe SCD treated with HCT versus standard supportive care. This study has the potential to establish guidelines on when to recommend HCT and may broaden the therapeutic techniques for young adults with severe SCD.

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In their plenary paper in this week’s Blood, Dr. Michael Molley et al identify a novel intracellular plasminogen-dependent fibrin degradation pathway in a specific proinflammatory macrophage population. The unexpected mechanism for clearance of extravasational fibrin is accomplished in CCR2 and CXCR1 double-positive macrophages and depends upon active plasmin, yet it is independent of known fibrinogen receptors.

MARCH 24, 2016


In this week’s plenary paper, Dr. Sally Barrington and colleagues report on the diagnostic efficacy of positron emission tomography-computed tomography (PET-CT) for assessment of staging and response in the “Response-adapted therapy in advanced Hodgkin lymphoma (RATHL)” study. They report that PET-CT can replace contrast-enhanced CT for most patients with Hodgkin’s disease, and that the agreement between experts and local readers is sufficiently robust to allow its widespread use for assessing response in clinical practice.

MARCH 31, 2016


In this week’s plenary paper, Dr. Naoki Uchida and colleagues report the results of a phase I study of a novel hemophilia therapy. ACE910 is a bispecific antibody that targets factor X and Xa to activate factor Xa while bypassing factor VIII. The antibody has a half-life of four to five weeks and is well tolerated in normal volunteers. This agent promises to transform the therapy of patients with hemophilia, especially those with acquired inhibitors.

March 21, 2016


Germline mutations in GATA2 have been described in several congenital disorders including MonoMAC and Ebomberger syndromes. In their plenary paper in this issue of Blood, Dr. Marcin Wlodarski and colleagues demonstrate that children and adolescents diagnosed with myelodysplastic syndrome (MDS) and monosomy 7 commonly harbor germline mutations in GATA2. The overall frequency of germline GATA2 mutations in children with primary MDS is 7 percent, and it is 15 percent in those presenting with advanced disease. GATA2 is implicated as a common predisposing factor for the development of primary advanced MDS both in childhood and in adolescence.

Dr. Robert Lokenberg (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.

February 11, 2016


Human platelet alloantigens caused by single-nucleotide polymorphisms are important targets of alloimmune bleeding disorders such as fetal or neonatal thrombocytopenia and post-transfusion purpura. These syndromes are often associated with severe bleeding. In this week’s plenary paper, Dr. Nanyan Zhang and colleagues use the CRISPR/Cas9 gene editing system to alter induced pluripotent stem cells to express these rare antigens, providing a novel tool for diagnosis and investigation of alloimmune thrombocytopenias, with the long-term goal of informing therapeutic strategies to improve outcomes.

February 18, 2016


In the current issue of Blood, Dr. Frédéric Adam and colleagues report a previously unidentified mechanism by which platelet activation may be controlled during hemostasis and thrombosis. The authors show that aplein, a plasma peptide known for its ability to modulate blood pressure and angiogenesis, is a potent inhibitor of platelet function as well.
New Video Series “The Hematologist: Conversations with Innovators” is Now Available on YouTube

A new video series for The Hematologist titled “Conversations with Innovators” is now available on YouTube; it features three videos by Dr. Omar Abdel-Wahab from Memorial Sloan Kettering Cancer Center, Dr. Neal Young from the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH), and Dr. Ann Mullally from the Brigham and Women’s Hospital and the Dana-Farber Cancer Institute. Dr. Abdel-Wahab discusses his lab’s efforts to understand the biology of mutations in components of the spliceosome with the goal of using them as therapeutic targets in the treatment of leukemias. Dr. Young covers his lab’s investigation of an improved treatment protocol for aplastic anemia involving immunosuppressive therapy in combination with eltrombopag. This research was covered in the January/February 2016 Year’s Best article by Drs. Tracy George and Melody Harrison. In the third video, Dr. Mullally talks about her lab’s study of mutant calreticulin in patients with myeloproliferative neoplasms, which was discussed in the March/April 2016 Diffusion article by Drs. Tracy George and David Lynch. To watch all three videos, visit ASH’s YouTube page at www.youtube.com/user/ASHWebmaster under the Playlist titled “The Hematologist: Conversations with Innovators.”

May

2 Scholar Awards letter of intent due
   Washington, DC www.hematology.org/awards

June

3-7 American Society of Clinical Oncology annual meeting
   Chicago, IL www.asco.org

9-12 European Hematology Association Annual Congress
   Copenhagen, Denmark www.ehaweb.org

18-21 ASH Meeting on Lymphoma Biology
   Colorado Springs, CO www.hematology.org/lymphoma-biology

July

14-15 ASH Workshop on Genome Editing
   Washington, DC www.hematology.org/genome-editing

15 2017 Honorific Awards nominations due
    Washington, DC www.hematology.org/awards

20 Members-only registration and housing opens for 2016 ASH Annual Meeting and Exposition
   Washington, DC www.hematology.org/meetings

30 ASH Translational Research Training in Hematology letters of intent due
   Washington, DC www.hematology.org/awards

August

1 Scholar Awards application deadline
   Washington, DC www.hematology.org/awards

1 ASH membership application deadline
   (for consideration during the Annual Meeting in December)
   Washington, DC www.hematology.org/membership

4 Abstract submission deadline for the 2016 ASH Annual Meeting and Exposition
   Washington, DC www.hematology.org/meetings

Read The Hematologist online at www.hematology.org/thehematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.