Figure

Drs. Tothova and Steensma indicated no relevant conflicts of interest.

ZuZana Tothova, MD, PhD, and David P. Steensma, MD

2013;368:1509-1518.

Antigens. These carefully designed recombinant receptors combine chimeric antigen receptors (CARs) directed at tumor-associated bioengineered T cells, which are genetically manipulated to express antitumor activity. As it turns out, “the devil is in the details” with respect to these constructs, and changes in the CAR structure can dramatically alter both clinical effectiveness and adverse event profile.

Cancer is, fundamentally, a state of immunologic failure – the unfortunate result of the inability of a patient’s endogenous immune system to recognize and eliminate neoplastic clones. The latest and most promising tool in the long history of attempts to overcome inappropriate immunologic tolerance and harness the power of the immune system to eliminate cancer cells are bioengineered T cells, which are genetically manipulated to express chimeric antigen receptors (CARs) directed at tumor-associated antigens. These carefully designed recombinant receptors combine a cell-surface binding site targeting an antigen, which does not need to be peptide processing or HLA-restricted presentation as well as a fragment of cytoplasmic signaling domains designed to enhance T-cell activation.

Since their initial development in the late 1980s, CAR T cells have undergone modifications in order to enhance both their anti-tumor activity and their persistence in vivo. The figure below depicts the evolution of CD19-specific CARs through three different generations, with the addition of co-stimulatory domains in later generations to augment antitumor activity. As it turns out, “the devil is in the details” with respect to these constructs, and changes in the CAR structure can dramatically alter both clinical effectiveness and adverse event profile.

In the summer of 2011, Carl June and his colleagues at the University of Pennsylvania reported the first successful use of second-generation, bioengineered T cells, which are genetically manipulated to express antitumor activity. As it turns out, “the devil is in the details” with respect to these constructs, and changes in the CAR structure can dramatically alter both clinical effectiveness and adverse event profile.

The same group recently reported similar results in patients with relapsed or refractory B-cell acute lymphocytic leukemia (ALL) – a disease that continues to be extremely challenging to treat effectively in spite of increased use of allogeneic stem cell transplantation and availability of novel agents such as the anti-CD22 anti-lymphocytic leukemia drug conjugate inotuzumab, and the CD3-CD19 bi-specific antibody blinatumumab. Grupp and his colleagues at the University of Pennsylvania reported the first successful use of second-generation, CAR-modified T cells expanded in the peripheral blood and bone marrow about 1,000-fold over their original engraftment levels, and their levels peaked at around day 10 after treatment. Both children achieved complete remission, but one patient relapsed with CD19-negative disease about two months after treatment. Deep sequencing of peripheral blood and marrow at IGH and TCRb loci documented molecular remission in one of the patients, with the absence of any detectable tumor cells by day 23. In contrast, the second patient was never able to clear her tumor clone, in assessed by deep sequencing, in spite of morphologic remission. Similar results have been obtained by Renier Brentjens and his colleagues in New York using an alternative version of second-generation CD19-CAR T cells (Figure).2

CAR-modified T cells are not benign; severe adverse events have been observed by all groups working with these cells and seem to correlate with the dose of the cells administered. Adverse effects reported in the study by Grupp and colleagues included acute respiratory distress syndrome, febrile neutropenia, hypotension, encephalopathy, hepatic transaminitis, and macrophage activation syndrome. In one patient, a life-threatening inflammatory response resolved following administration of anti-cytokine therapy (specifically, etanercept and tocilizumab) and corticosteroids. Other CAR T-cell constructs have had slightly different toxicity profiles, including seizures.

Use of CAR T cells is likely to be practice-changing not only in the realm of lymphoid malignancies, but also for other neoplasms. Studies are currently underway using this strategy in the treatment of plasma cell neoplasms and solid tumors, including neuroblastoma and several sarcomas. The applicability to myeloid malignancies is less straightforward, since a CAR T-cell response against most of the antigens present on malignant myeloid cells would result in severe, long-lasting neutropenia. Many questions remain with respect to CAR T-cell use in lymphoid neoplasms, such as the best and safest method of introducing CAR into T cells, the ideal number and type of costimulatory domains and specificity of scFv (Figure) for maximal anti-tumor effect, the optimal conditioning chemotherapy protocol for lymphoreduction and dose of cells to be infused, and how best to manage post-infusion cytokine storm without compromising the odds of long-term remission or cure.

This study provides exciting evidence that CD19-specific CAR T cells can induce long-lasting remission in patients with aggressive CD19+ pre-B ALL. Additional studies will be needed to determine the long-term safety and efficacy profile, how this approach will compare with the use of the new ALL antibodies, and which patients have the most potential to benefit from this novel treatment.


Baylor (Baylor College of Medicine) – clinical trials NCT01859631, NCT01858631
NCI (National Cancer Institute) – clinical trials NCT01859631, NCT01858631
MSKCC (Memorial Sloan-Kettering Cancer Center) – clinical trials NCT01840566, NCT01860937, NCT01444096, NCT00489531, NCT01495754
Penn (Abramson Cancer Center of the University of Pennsylvania) – clinical trials NCT01747486, NCT01229867, NCT01551043

Evolution of CD19-directed chimeric antigen receptors (CARs) and their use in clinical trials targeting lymphoid malignancies. All generations of CARs contain a transmembrane structural domain, as well as an extracellular single chain fragment (scFv), which is derived from a human-CD19-specific mouse monoclonal antibody – either FMC63 (lgG2a) or 2S25C1 (lgG1). First-generation CARs contain a single cytoplasmic signaling domain (CD3ζ), which links antigen recognition to intracellular signal transduction pathways. Second-generation CARs contain CD3ζ plus a co-stimulatory signaling domain, either CD28 or 4-1BB (also known as CD137, a member of the tumor necrosis factor receptor superfamily). Compared to first-generation CARs, second-generation CARs induce superior anti-tumor responses in preclinical studies and in patients with B-cell malignancies. Third-generation CARs contain two CD3ζ, CD28 and 4-1BB, in addition to signaling domain CD3ζ.
ASH as Your Partner in Quality Improvement

Improving the quality of care delivered to patients with hematologic diseases is the most important mandate for clinicians practicing in our specialty. The need for quality improvement in health care has been detailed in reports from the Institute of Medicine and oft-cited articles, such as that by Elizabeth A. McGlynn, PhD, and colleagues whose research concluded that 50 percent of recommended care is not being delivered.1 ASH has responded to these serious concerns by providing leadership in developing an array of quality-improvement efforts.

We have created guidelines for selected diseases, distilled existing guidelines into highly portable pocket guides and mobile applications, and hosted both webinars and sessions at the annual meeting on quality improvement. These efforts have been well and ably executed by the ASH Subcommittee on Quality of Care. I want to take this opportunity to thank Mary Cushman, MD, for her superb leadership of that subcommittee for the past two years.

The landscape in quality improvement is changing constantly as evidenced by 1) new Medicare and private insurance programs that tie professional reimbursement to quality guidelines and measures, and 2) the latest changes to the Maintenance of Certification programs. The most recent quadrennial ASH survey captured the importance of these changes to our membership, with clinical practice guidelines being among the products you most commonly request from the Society. With the initiation of Accountable Care Organizations and other tenets of the Patient Protection and Affordable Care Act (i.e., Obamacare) in January 2014 and onward, defining and measuring quality will have greater significance.

Given these drivers, the ASH Executive Committee charged a task force chaired by Linda Burns, MD, and Adam Caker, MD, and composed of representatives from many of ASH’s standing committees, to envision a next generation of ASH quality programs to meet member needs and proactively address quality issues in a comprehensive way. The Executive Committee wholeheartedly endorsed the task force’s recommendations to establish an ASH Quality Initiative, components of which include the following:

1. Create additional clinical practice guidelines in hematology at a faster pace. Determine the best methods to integrate standard practice, expert opinion, and other inputs when an evidence-based assessment is not available. These guidelines will be developed with the needs of busy clinicians in mind.

2. Develop “toolkits” to assist hematology practices with implementation of the guidelines. The toolkits will continue to include pocket guides, apps, and webinars as well as practice-improvement modules for certification and quality measures for pay-for-performance reporting.

3. Represent hematologists vigorously in policy discussions about tying reimbursement to quality.

ASH considers these efforts our obligation and responsibility. I encourage you to email ASH at quality@hematology.org with your thoughts about quality-improvement topics and programs that the Society should consider. Member input will be an important resource for the newly formed Committee on Quality, which includes members with both methodologic and disease-based expertise and is chaired by Mark Crowther, MD.

Janis L. Ahkowitz, MD


ASH supports an organized, graded approach to the teaching of principles of quality care and clinical competency with measurable outcomes beginning in the first year of fellowship. For an example of an approach to this process, please read the article by Dr. Meir Preis and Dr. Christian Cable on page 6 of this edition of The Hematologist.
ASH Awards Additional Bridge Grants to Support Hematology Research Threatened by NIH Budget Cuts

To combat the cuts in federal funding that are jeopardizing the state of biomedical research, the Society announced support for 12 additional investigators in the second round of competition for ASH Bridge Grants. Read the press release, including the list of recipients, at www.hematology.org/News/2013/10910.aspx.

This year and for the next two years, ASH’s will provide at least 30 one-year awards, in the amount of $100,000 each, to ASH members who applied for an NIH R01 grant or equivalent, and whose hematology-focused submissions were scored but not funded. The long-term goal of the award is to help sustain recipients’ research and to contribute to retention of outstanding investigators whose work centers on hematology.

The application deadline for the next round of Bridge Grant awards is November 1, 2013. Recipients will be announced in mid to late January 2014. For more information about the ASH Bridge Grant Program, including eligibility criteria, please visit the following website: www.hematology.org/Awards/Bridge-Grants/9669.aspx.

We reached out to a few of the inaugural recipients to get a sense of how the ASH Bridge Grant has had an impact on their research.

“I applied for the Bridge Grant because my start-up funds were pretty much dried-up, and I had not yet been able to secure sustained support for a project that I think has quite a bit of merit. I had received a good, but ultimately unfunded, score on my first R01 application that was aimed at studying the cell cycle checkpoint protein, Wee1, as a therapeutic target in AML, and I wanted to maintain the momentum of the project. Receipt of the Bridge Grant has allowed us to do that by providing funds for costly in vivo experiments that were necessary to challenge our hypothesis. Fortunately, the resubmission was scored at the 6th percentile, so the Bridge Grant mechanism has served its purpose exceedingly well.”

–Christopher C. Porter, MD, Assistant Professor, Pediatrics, University of Colorado School of Medicine & Center for Cancer and Blood Disorders, Children’s Hospital Colorado

“I have been involved in experimental hematopoiesis research for almost 25 years. As is the case in most labs, our budget is tight, so whatever source is available, I will look into it. As a basic science investigator, NIH funding is the lifeline of my career and without it, the future viability of my research program is in jeopardy. I applied for the ASH Bridge Grant in order to try to sustain an ongoing project in my laboratory that was scored by an NIH study section but was not funded because of the limitation of the current NIH budget. With funds from the Bridge Grant, I continue to work on the same project and collect more data to further support my argument, thereby giving me the opportunity to reapply with a more competitive proposal. This project is a collaborative effort; I am working with four other investigators who are also faculty at Indiana University, so this support has a synergistic effect.”

–Edward F. Srour, PhD, Robert J. and Annie S. Rohn Professor of Leukemia Research, Professor of Medicine, Pediatrics, Microbiology & Immunology; Director, Flow Cytometry Resource Facility, Indiana University School of Medicine

ASH Receives NCI R25E and NHLBI R13 Awards in Support of the Clinical Research Training Institute

The Society recently learned that it is the recipient of a National Cancer Institute R25E (cancer education grant program) award in support of the ASH Clinical Research Training Institute (CRTI). The R25E project, titled "Training and Mentorship of Hematologic Oncologists," received five years of support with total costs in excess of $1.4 million. Grant funds will be instrumental in allowing ASH to secure the future of the program, conduct regular, comprehensive evaluations of CRTI, and both broaden the scope of the summer workshop and enhance the experience of the trainees throughout the rest of the program year. Information on the grant (1R25CA168526-01A1) can be found on the NIH Reporter website.

ASH would like to thank co-Principal Investigators Dr. Linda Burns and Dr. Lillian Sung for their dedication to the program and for preparation of this application. ASH would not have received this grant without their diligence and willingness to serve in leadership roles on this project. ASH would also like to thank Dr. Scott Goldin and Dr. John Byrd for their invaluable work in conceiving, organizing, writing, and reviewing ASH’s initial submission. And all of the CRTI directors and faculty are to be thanked for contributions including agreeing to be listed as faculty on the grant application, writing letters of support, and providing insights and comments on the application process.

In related news, the Society is pleased to report that the R13 (conference support) application it submitted to the National Heart, Lung, and Blood Institute requesting support for the 2013 CRTI Summer Workshop was funded in the amount of $40,000. ASH would like to thank Dr. Julie Panepinto for her work as Principal Investigator on that grant application. Information on the R13 (1R13HL120372-01) is also available on the NIH Reporter website.

Avoid Medicare PQRS Penalties; PQRS PRO Coming Soon

Physicians must meet requirements for the Physician Quality Reporting System (PQRS) in 2013 to avoid a 1.5 percent reduction in Medicare payments in 2015. The Centers for Medicare and Medicaid Services developed a fact sheet detailing with the 2015 PQRS Payment Adjustment, which helps physicians understand how to avoid payment penalties in the PQRS system. In mid-September, a new Web-based tool, PQRS PRO, will help hematologists meet requirements both for obtaining the incentive pay that accrues from properly reporting quality measures on Medicare patients during calendar year 2013 and for avoiding future penalties that are levied for incomplete or inaccurate reporting.

Exhibit Hall Product Theaters

Product Theaters are designed to provide exhibitors with a forum to present new research findings on products, provide product details, and give demonstrations to small groups of annual meeting attendees within the Exhibit Hall. ASH members are encouraged to visit the Product Theaters while in the Exhibit Hall. Details about the presentations will be included in the Program Book, in the annual meeting app, and posted on signage outside of the Product Theaters each day. The Product Theater sessions offered at the times listed below will be solely promotional in nature; therefore, continuing medical education credits will not be offered.

Product Theater Session Times

- Saturday, December 7
  11:30 a.m. – 12:30 p.m.
- Sunday, December 8
  11:30 a.m. – 12:30 p.m.
- Monday, December 9
  12:15 p.m. – 1:15 p.m.
The Hematologist: ASH News and Reports

Ask the Hematologist

CHARLES T. QUINN, MD, MS
Associate Professor of Pediatrics
Cincinnati Children’s Hospital Medical Center

The Question

What criteria do you use for selecting patients with sickle cell anemia (SCA) for allogeneic hematopoietic stem cell transplantation (HSCT)?

My Response

About 40 years ago, only half of the children born with SCA in the United States were expected to live long enough to reach adulthood. Now, however, as a result of the high quality of care available in comprehensive sickle cell centers, disease-related mortality during childhood has been reduced to 1 to 2 percent.1,2 This remarkable improvement in survival stems mainly from interventions aimed at preventing early deaths from infection and splenic sequestration, as well as the greater use of disease-modifying therapies (e.g., hydroxyurea and chronic transfusions). No current U.S. statistics are available, but in a study published in 2001, the median lifespan for individuals with SCA in a Jamaican cohort was estimated to be more than 50 years.3 Not reflected in these improving survival data, however, is the burden of SCA-related chronic organ injury acquired in early childhood that becomes especially manifest in young adulthood, adversely affecting the quality and duration of the remaining life of the patient. The burden of morbidity and mortality in SCA has not simply shifted to adults, and the period after transplantation to adult medical care is associated with a particularly high risk of death, especially from acute chest syndrome and multi-organ failure syndrome.4

HSCT is the only available cure for SCA, and more than 500 transplants for SCA have been reported to international registries. Although usually successful and curative, the widespread use of HSCT is still limited by the lack of sufficient suitable donors and concerns about regimen-related morbidity and mortality. HSCT is safest when an HLA-matched sibling donor is available, but only about 10 percent of transplant candidates will actually have such a donor. Current estimates place regimen-related mortality for myeloablative transplantation using an HLA-matched sibling donor at about 5 percent, with a concomitant 9 percent risk of graft rejection and a 15 percent risk of chronic graft-versus-host disease (GVHD) (Table).5,6 There are additional late effects of transplantation not tabulated here, including infertility, endocrinopathies, premature cardiovascular disease, and possibly cancer. One can argue that SCA-related morbidity during childhood (in patients cared for in comprehensive centers in developed nations) is now lower than the regimen-related mortality of HSCT, but this comparison does not integrate the lifelong risk of progressive morbidity, impaired quality of life, and early mortality due to SCA. Of course, there is no randomized comparison of transplantation versus no transplantation that accurately quantifies the relative lifetime risks of morbidity and mortality from SCA and HSCT, but life after a successful transplant — the event-free survival (EFS) of a full-sibling donor myeloablative HSCT is approaching 90 percent (Table) — is arguably better than a life with SCA. An important caveat, however, is that the definition of EFS differs by study and often does not include chronic GVHD, which may be worse than SCA, so EFS rates that are meaningful to patients are usually lower than reported (70-80% vs. 95%, respectively).

Expert panels and professional societies provide differing sets of clinical indications for HSCT as a treatment option for SCA, but common recommendations include recurrent vaso-occlusive complications (acute chest syndrome and painful events), usually despite hydroxyurea therapy, and overt cerebrovascular disease. Other indications have been proposed and used, such as abnormal transcranial Doppler velocities and silent cerebral infarction, despite much less agreement among experts and very limited data. Some hematologists now also advocate that a diagnosis of SCA itself is an indication for HSCT, justified by the knowledge that complications of SCA are often unpredictable, and most individuals with SCA will have progressively severe morbidity and early mortality. In my clinical practice, I do not compare a fixed list of indications for HSCT with an ongoing tabulation of the number and type of SCA-related complications experienced by the patient. Rather, I initiate (or continue) the discussion of HSCT in three main clinical scenarios.

The first usual scenario is planned. I ensure that all patients with SCA and their parents know about the possibility of cure by HSCT. I include discussion of the option of HSCT as part of the comprehensive, ongoing education about SCA starting with the very first visit after diagnosis (usually the result of newborn screening). I also recommend tissue typing of all unaffected siblings, including those with sickle trait, to know if there is an HLA-matched donor. If there is a matched-sibling donor, I offer dedicated clinic visits for frank discussions about the risks and benefits of myeloablative HSCT compared with life with SCA, as well as the risks and benefits of hydroxyurea therapy and chronic transfusions. If there is continued interest in pursuing HSCT, then I arrange formal consultation and counseling with the HSCT team. This multi-step process does not lead to HSCT for most patients, but they are at least aware and knowledgeable about the option, and I support them with decision-making.

The second scenario is a direct inquiry about HSCT by a patient or parent, often times as a result of something heard or read about on the Internet. Recent immigrants from Africa also tend to ask commonly about transplantation.

The third scenario occurs when a patient suffers a particularly serious complication, such as overt stroke. In these instances, I follow the same general process outlined above in counseling patients and their families about HSCT.

In essence, I consider every patient with SCA (here I include both HSsS and sickle/β-thalassemia) who has an HLA-matched sibling donor to be a potential candidate for myeloablative HSCT. Honest discussions about the risks, benefits, and alternatives are needed, regardless of the “severity” of a patient’s disease, and the decision to pursue HSCT is a lengthy and patient- and family-centered process. Once a decision to perform HSCT is made, I recommend that it be done during early childhood. My opinions and practices are based upon the assumption that my patient’s HSCT will be performed in a center with substantial experience in transplantation for SCA and, ideally, as part of a clinical research study. The use of alternative donors (unrelated, mismatched, or haploidentical) and stem cell sources (unrelated umbilical cord blood) for children carries a much higher risk of transplant-related morbidity, mortality, and graft rejection and should be performed only as part of a carefully designed investigational study.

Adults with SCA tolerate myeloablative conditioning regimens poorly, likely because of the cumulative burden of chronic organ injury acquired during childhood. However, there is very promising early experience with a non-myeloablative conditioning regimen (including total-body irradiation, almtuzumab, and sirolimus) in severely affected adults with SCA that can produce stable, mixed donor-recipient chimerism that effectively cures the disease.7 These outcomes have been achieved without chronic GVHD or mortality and with a low rate of graft rejection. The mixed chimerism appears to persist after discontinuation of immunosuppression.8 In the future, adults may no longer be summarily excluded from HSCT. Until then, all transplants in adults should be performed as part of a clinical research study with the indications being dictated by the eligibility criteria of the particular study. While the experience with adult recipients and alternative donors matures, research needs to focus on reducing transplant-associated morbidity, especially sterility, in young patients undergoing reduced-intensity conditioning regimens.

Ongoing studies will continue to expand access to HSCT for both children and adults, and the next “Ask the Hematologist” question on this topic might also include the option of gene therapy.


*Four of 11 patients had mild, chronic GVHD of the skin that resolved completely after steroid therapy.

Table. International Studies of Myeloablative HSCT for SCA Using Matched-Sibling Donors†§

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=11</td>
<td>100</td>
<td>94</td>
<td>86</td>
<td>85</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>N=67</td>
<td>100</td>
<td>94</td>
<td>86</td>
<td>85</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>N=276</td>
<td>100</td>
<td>94</td>
<td>86</td>
<td>85</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

1. Data compiled from tables in Locatelli et al. and Laciarelli et al.
2. Values are shown as the percentage of the N for the corresponding study.
3. Abbreviations: OS, overall survival; RRM, regimen-related mortality; cGVHD, chronic graft-versus-host disease; EFS, event-free survival.
4. Four of 11 patients had mild, chronic GVHD of the skin that resolved completely after steroid therapy.
Erythropoietic Protoporphyria: Multiple Pathways to a Common Phenotype

JAMES P. KUSHER, MD,* AND JOHN D. PHILLIPS, PhD†

1. Maxwell W. Winthrop Distinguished Professor of Medicine, Emeritus, Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine
2. Associate Professor, Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine

Abnormalities affecting the function of the FECH (ferrochelatase) complex and delivery of FECH’s substrates are responsible for a group of disorders known as erythropoietic protoporphyria (EPP). Although the heme biosynthetic pathway is active in all cells, the excess protoporphyrin of EPP is derived from erythroid precursors. This situation differs from that observed in the acute porphyrias (acute intermittent porphyria, hereditary coproporphyria, variegate porphyria) where excess porphyrin and porphyrin precursors originate in the liver.

The heme biosynthetic pathway involves eight enzymatic reactions partitioned between the mitochondria and the cytosol (Figure 1). FECH, a homodimer associated with the matrix side of the inner mitochondrial membrane, catalyzes the final step in the pathway, the insertion of iron into protoporphyrin (Figure 1). Each monomer of FECH contains a 2Fe-2S iron-sulfur cluster, which is required for enzymatic activity (Figure 1). The human FECH gene maps to chromosome 18q21.3. FECH is synthesized in the cytosol and targeted to mitochondria by sequences in the leader peptide. Recent evidence suggests that FECH functions as part of a multi-enzyme complex associated with the inner mitochondrial membrane (Figure 1). Two members of the complex are required to deliver substrates to FECH, protoporphyrinogen oxidase (PPO) to deliver protoporphyrinogen and mitotetrin 1 (Mtr1) to deliver iron (Figure 1). A third member, ABCB10, stabilizes Mtr1 and likely has additional undefined functions (Figure 1).

EPP was characterized and named by Magnus et al. in 1961. Those investigators described a 35-year-old man who manifested an unusual reaction to sun exposure that had begun in childhood and was characterized by intense discomfort, redness, and swelling of exposed skin that developed within five minutes of sun exposure. The reaction was termed solar urticaria. High levels of protoporphyrin were found in feces, plasma, and red cells; and narrow erythroid precursors fluoresced. Notably, the patient had a history of cholesteatoma for treatment of a symptomatic gallstone.

The clinical description of EPP has been verified and expanded by many investigators over the past 50 years. The photosensitivity is quite different from that seen in other types of cutaneous porphyria (e.g., congenital erythropoietic porphyria and porphyria cutanea tarda) in that bullous lesions, scarring, and pigment changes do not occur. Instead, the skin of sun-exposed areas (primarily facial skin) develops a leathery appearance that mimics premature aging. A mild, microcytic anemia is common, but it is not a uniform finding. Ringed sideroblasts are occasionally noted. Gallstones occur in about 10 percent of EPP patients and usually develop early in life. The liver takes up protoporphyrin from plasma and transfers it to bile where solubility of bile components is altered. There is a vigorous enterohepatic recirculation of biliary protoporphyrin, which further magnifies plasma porphyrin values and adds to the amount of protoporphyrin taken up by the liver. Cholestasis, severe enough to cause progressive and lethal liver disease, occurs in about 5 percent of cases.

Autosomal Recessive EPP

The discovery of loss-of-function (LOF) FECH mutations coupled with family studies initially suggested that EPP was transmitted as an autosomal dominant trait with variable penetrance, but clinically affected heterozygotes consistently showed FECH activity of only 15 to 20 percent of normal. A dominant negative effect was proposed, but the discovery of a hypomorphic FECH allele established that most cases of EPP represent an autosomal recessive disorder. An intragenic polymorphism (IVS3-48C) in intron 3 of the FECH gene favors the use of a cryptic acceptor splice site yielding an aberrantly spliced mRNA that is rapidly degraded. The result is a lower steady-state level of wild-type FECH mRNA. More than 90 percent of clinically evident cases of EPP are due to coinheritance of the hypomorphic (hypo) FECH allele in trans to a LOF mutant allele (genotype FECH/hypo/FECH LOF). The frequency of the hypomorph allele varies widely in different populations and relates to the observed differences in the prevalence of EPP. EPP is pan-ethnic, but it is extremely rare in individuals of African descent. A rare exception to the FECH hypo/FECH LOF genotype is inheritance of two FECH LOF alleles (genotype FECH LOF/FECH LOF). This form of EPP carries a higher risk of severe cholestatic liver disease.

X-Linked EPP

The application of FECH gene sequencing and the concentration of porphyrin patients in centers in the United States, Europe, and South Africa revealed that 5 to 10 percent of patients with EPP have no FECH mutations. Whatley et al. studied eight families in the United Kingdom with “mutation-negative” EPP. They displayed a dominant pattern of inheritance with an absence of father-to-son transmission, a finding suggestive of X-chromosome linkage. The EPP phenotype was also observed in females due to skewing of X-chromosome inactivation. Erythocyte protoporphyrin concentrations were higher in EPP patients with FECH mutations, and the percentage of the zinc chelate (i.e., zinc protoporphyrin) was markedly higher (median 44% vs. 8% in the FECH mutant group). The cause of the EPP phenotype in these families proved to be mutations affecting the carboxy-terminus of the erythropoietic specific form of δ-aminolevulinic acid synthase (ALA-S2). The mutations resulted in an increase in specific activity compared with wild-type ALA-S2. The increased production of ALA leads to an increase in flux through the pathway and generates protoporphyrin in excess of the capacity of FECH to produce heme. The large amounts of zinc-protoporphyrin suggested that the metal chelating properties of FECH have not been exceeded and that delivery of iron to the active site of FECH limits heme synthesis.

Others have confirmed the findings of Whatley et al., and a total of five ALA-S2 gain-of-function mutations have been identified, all involving the carboxy-terminus. The carboxy-terminus of ALA-S2 forms a “flexible” loop over the active site of the enzyme. The “open” position favors release of ALA and likely increases access of substrates to the active site. Both eNOS result in increased enzymatic activity. The carboxy-terminus also enhances the stability and activity of ALA-S2. A carboxy-terminal mutation that abolishes the seryl motif of ALA-S2 binding site causes LOF changes in ALA-S2 and X-linked sideroblastic anemia. Surprisingly, one gain-of-function mutation (Q548K) does not bind seryl-CoA synthase. Collectively, the data suggest that conformational changes associated with the carboxy-terminus are the main mechanism determining the specific activity of ALA-S2.

Acquired EPP

Over a dozen late-onset cases of EPP associated with myelodysplastic and myeloproliferative disorders have been reported, many of which displayed partial or complete loss of chromosome 18 in the affected clone. A late-onset case of X-linked EPP has also been reported. The acquired gain-of-function mutations in the abnormal hematopoietic clone (Q548K) had previously been detected in an inherited case of X-linked EPP.

Other Causes of EPP

A handful of individuals with the EPP phenotype do not have detectable mutations in FECH or ALA-S2. Abnormal Mtr1 expression and low FECH activity were detected in one such case, but potential defects in iron-sulfur cluster assembly and transport, iron chaperones, transcription factors, translational regulators, and factors required for assembly of multi-enzyme complexes remain unexplored.

Treatment

The therapy of EPP is focused on minimizing the harmful effects of exposure to sunlight and on managing the hepatotoxic effects of protoporphyrin. As with other photosensitizing porphyrias, protective clothing and opaque sunscreens are helpful. Reference to sunlight can be further enhanced by inducing carotenemia with β-carotene and darkening skin color with an o-melanocyte stimulating factor (Continued on page 14)
Developing a Treatment Plan as a Core Competency of Hematology Training

Diffuse large B-cell lymphoma (DLBCL) is one of the most common lymphoid malignancies worldwide. The incidence increases steeply with age and half of the cases occurring in patients older than 65 years. The elderly frequently have co-morbid conditions, rendering the intensive treatment required for cure inapplicable for many of them. Consequently, a treatment plan for an elderly patient can pose a challenge, but developing such a plan has significant educational value for hematology trainees.

Formulating a treatment plan for a patient with a hematologic disorder is a core medical-knowledge competency issue of hematologic training. Prescribing cytotoxic chemotherapy should be regarded as an educational opportunity to be vigilantly taught, and trainee competency should be evaluated and tested on an ongoing basis. We suggest a methodical approach to conceiving, implementing, and adjusting a treatment plan to accompany patient engagement. We also suggest methods to evaluate and provide feedback to trainees based on level of training.

Let’s look at the case of an 80-year-old woman with advanced-stage DLBCL and a good performance status (Figure). Given her advanced age and the potential for treatment-related toxicity, it is imperative to clarify with the patient and her family the goals of care. Since elderly patients may have a good performance status, it is reasonable to discuss the use of cytotoxic chemotherapy with curative intent in this subset. The following steps are recommended to formulate a treatment plan.

**Step 1: Choosing the chemotherapy regimen**

The introduction of rituximab to the backbone of the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) for the treatment of DLBCL resulted in significantly better treatment outcomes in elderly patients (age 60-80) that included a 10 to 13 percent improvement in overall survival. The recommended frequency of chemotherapy cycles (every 14 vs. 21 days) and the number of cycles (6 vs. 8, respectively) can vary among treatment centers. The NCCN task force category 1 recommendation is for six cycles of R-CHOP. The data from the LNH03-68 GELA study suggest that a 21-day cycle (R-CHOP21) trends toward higher efficacy and lower toxicity than a 14-day cycle in elderly patients, although no randomized controlled trial has been done to compare the two. It is a common practice to use R-CHOP-21 for six cycles in DLBCL patients.

**Step 2: Dose modification**

Multiple factors affect treatment outcome in the elderly, including comorbidities, functional status, and support systems. Although age is an important prognostic factor in DLBCL, it should not be used as the sole criteria to determine eligibility for treatment. Over the last decade, geriatricians have developed tools for functional assessment that can be implemented for treatment decisions in cancer patients. Comorbidities can be assessed by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). This scoring system can help guide dose modification or inform about deletion of drugs that would improve tolerability (e.g., omitting vincristine in patients with neuropathy). The Activities of Daily Living (ADL) scale includes items that assess the performance of basic self-care activities (e.g., bathing). The Instrumental ADL (I-ADL) assesses higher levels of physical and cognitive function (e.g., shopping). ADL and I-ADL should be used to help determine dose modification and assessment of patient needs. A recent study showed that applying these scales in elderly patients with DLBCL to determine the chemotherapy regimen and dose adjustment was associated with a complete response rate of 81 percent.

According to the National Cancer Database, the addition of rituximab was found to improve overall survival, but it demonstrated that racial and socio-economic disparities are likely affecting outcomes in elderly African-American patients. In addition, gender and weight can influence the metabolism of rituximab. Rituximab clearance is significantly reduced in females with half-life of 30 days compared with 24 days in males. This pharmacokinetic difference was associated with a decreased response in elderly men, and further studies need to clarify whether dose modification is needed for this population. Many elderly patients have decreased cardiac function that may limit the use of doxorubicin. Etoposide substitution for doxorubicin can achieve a similar response rate with decreased myocardial toxicity and should be considered in patients with mild to moderate myocardial impairment. Additional factors that should be taken into consideration when deciding on a treatment plan are decrease bone marrow function and altered drug metabolism due to aging. These factors are difficult to quantify and integrate, but they are the subject of ongoing research in this expanding population. A recent phase II study tested the R-miniCHOP regimen that includes upfront reduction by ~50 percent of the cytotoxic drugs cyclophosphamide, doxorubicin, and vincristine in fit patients older than 80 years of age. The overall response rate was 73 percent, and complete response or unconfirmed complete response rate was 62 percent. Treatment-related mortality was 8 percent, and the median survival was 29 months.

**Step 3: Supportive care**

Elderly patients are at an increased risk for treatment-related toxicity. Hematologic toxicity (primarily neutropenia and thrombocytopenia) is the most common adverse effect in these patients. The risk of febrile neutropenia and infection is greater in the elderly, resulting in unplanned hospitalization and suboptimal treatment delivery. The use of growth factor support and consideration of prophylactic antibiotics in high-risk patients can decrease the incidence of febrile neutropenia. Patients with DLBCL are at risk for tumor lysis syndrome, and elderly patients with poor renal function are particularly vulnerable. A careful hydration plan should be implemented, and prophylactic use of xanthine oxidase inhibitors (allopurinol), or recombinant urate oxidase (rashburicase) should be considered to prevent acute urate nephropathy.

**Step 4: Considering support systems**

Malnutrition and lack of social support often influence treatment outcomes in the elderly and therefore should be part of the treatment plan, including the use of visiting nurses. Many centers have support groups that can help elderly patients cope with the emotional part of this
difficult illness. Finally, detailed, written instruction and close follow-up can provide patients with the needed reassurance to cope with treatment-related toxicities.

The Teaching Perspective

The steps outlined above parallel a trainee’s development and competency in prescribing chemotherapy. Expert faculty members likely do not follow a step-by-step approach, but rather integrate the methodology unconsciously when seeing individual patients. However, it is necessary for faculty to break down the process when teaching novice hematologists. During the first year of hematology training, the task is to recognize standard therapy (step 1), and to learn from the parent specialty a completely different language. Frequent use of chemotherapy drug books and NCCN guidelines should be encouraged. Intermediate trainees should incorporate supportive care practices and be able to recognize that guidelines and regimen books represent average populations of patients. In individual patients require individualized approaches (steps 2-3). A senior trainee is preparing to enter unsupervised practice and should recognize the systems implications of care, including caregiver engagement and recruitment of multidisciplinary teams to share the management of special patient groups (step 4).

Fellows benefit from frequent feedback, ideally on a weekly basis. Prescription of chemotherapy in hematology is a high-risk and complex task. Competency in this area can and should be taught and evaluated in a systematic way. Why not present these general steps in the first continuity clinic and provide feedback with the first patient checkout? By recognizing and assessing treatment planning as a core medical-knowledge competency, we hope to improve patient care and the standard for teaching and evaluating fellows.

Activating G-CSF Receptor Mutations in Neutrophilic Leukemias


Crystalline activation of tyrosine kinases (TKs) and related signaling pathways has become the pathogenetic sine qua non of myeloproliferative neoplasms (MPNs). This theme is exemplified by the BCR-ABL fusion oncogene in chronic myeloid leukemia; the JAK2 V617F mutation in polycythemia vera, essential thrombocytemia, and primary myelofibrosis; KIT D816V in systemic mastocytosis; and rearranged PDGFRα/B and FGFR1 in myeloid (and sometimes lymphoid) neoplasms associated with eosinophilia. CML and eosinophilic neoplasms with activated PDGFRα/B are emblematic of the successful application of small molecule inhibitors (e.g., imatinib), especially in the earlier phase of illness when a singular genetic lesion is the predominant driver of the disease. In intermediate- to high-risk myelofibrosis where increasing genetic complexity supervenes, the benefits of JAK inhibitors are more palliative in nature and are typically characterized by mitigation of splenomegaly and disease symptoms without hematologic or molecular remissions. The basis for these more modest responses also partly relates to the fact that JAK inhibitors are not specific to mutant JAK2, as they also inhibit the wild-type protein.

Chronic neutrophilic leukemia (CNL) is a very rare MPN that is characterized by leukocytosis (>50,000/mm³) and a differential consisting of >80 percent neutrophils and band forms. Exclusionary criteria include the finding of BCR-ABL or PDGFRα/B and reactive causes of neutrophilia. Non-specific cytogenetic abnormalities have been described in CNL, and mutations such as JAK2 V617F have been described in a few cases. CNL may show overlapping clinical and laboratory features with MDS/MPNs such as atypical (BCR-ABL negative) CML and chronic myelomonocytic leukemia (CMML), but the presence of dysplasia or prominent myeloid immaturity or monocytosis mitigates against the diagnosis. The prognosis of CNL is generally poor, with death usually resulting from bleeding, infection, or evolution to acute myeloid leukemia. Conventional chemotherapeutics (e.g., hydroxyurea) may produce temporary disease control, but they do not modify the natural history of the illness. Given its rarity and the absence of a disease-defining therapeutic target, CNL has remained an esoteric myeloid neoplasm compared with its more visible MPN cousins.

Jeffrey Tyner and Julia Maxson and colleagues from the Oregon Health and Sciences University led a multi-institutional study to identify unknown molecular targets in primary leukemia samples, with a focus on CNL and aCML given the paucity of mutation data in these diseases. They utilized a combined approach of deep sequencing and panels of leukemia samples, with a focus on CNL and aCML, gauging the paucity of mutation data in these diseases. They utilized a combined approach of deep sequencing and panels of tyrosine kinase-specific, small interfering RNAs (siRNAs) and small molecule inhibitors to assess the inhibition of cell viability from patient samples. For example, cells from a patient with CNL, who was ultimately found to have a truncating frameshift mutation (S783fs) affecting CSF3R (the G-CSF receptor), exhibited decreased viability with siRNAs against tyrosine kinase nonreceptor 2 (TNK2) and the SRC kinase FGR, and cells from that patient were potently inhibited by dasatinib. Such CSF3R truncation mutations have been previously reported in patients with severe congenital neutropenia, especially at time of leukemic transformation.1,2 Cells from another patient with CNL exhibited sensitivity to the JAK inhibitor ruxolitinib, but no inhibition with dasatinib, with sequencing revealing a membrane proximal CSF3R T618I mutation. Ultimately, of 27 CNL and aCML patients evaluated, 16 (59%) harbored either membrane proximal or truncation CSF3R mutations, with a few patients exhibiting compound mutations of either class. In contrast to their high frequency in CNL and aCML, CSF3R mutations were rare in AML (3/292 cases), and except for one of three cases of early T-cell precursor T-cell ALL, they were not identified in 49 additional cases of B- or T-cell ALL.

Both classes of mutations were able to transform Ba/F3 cells to interleukin-3-independent growth, although the membrane proximal mutations were the more efficient. Ba/F3 cells expressing a truncation mutant expressed high levels of TNK2 and phosphorylated FGR, whereas Ba/F3 cells transfected by CSF3R T618I induced high levels of phosphorylated STAT3 and JAK2, validating the results from the siRNA and drug inhibitor assays. Cells with the S783fs mutation demonstrated higher expression levels of CSF3R, a finding consistent with prior studies showing that truncation mutants result in blockade of receptor internalization. Notably, treatment of a CSF3R T618I-mutated CNL patient with ruxolitinib, 15 mg twice daily, resulted in a marked decrease of neutrophilic leukocytosis and normalization of the platelet count that still persisted a year later.

Use of an integrated functional and genetic sequencing strategy has unmasked highly recurrent, druggable CSF3R mutations in CNL and atypical CML. The role of the G-CSF–CSF3R axis in promoting the growth, differentiation, and survival of myeloid cells is consistent with the finding of neutrophilic leukocytosis in hematologic malignancies with activating CSF3R mutations. Truncation mutations result in increased levels of CSF3R, signal predominantly through SRC kinases, and exhibit drug sensitivity to SRC kinase inhibitors such as dasatinib. In contrast, CSF3R membrane proximal mutations strongly activate the JAK/STAT pathway and are sensitive to JAK kinase inhibitors such as ruxolitinib (Figure). Clinical responses and CSF3R genotype will need to be prospectively validated in a larger cohort of patients. Undoubtedly, CSF3R mutation status will be incorporated into World Health Organization diagnostic criteria for CNL and atypical CML, and should help dissect the clinical basis of neutrophilias whose etiology is unclear.

Global Warming: Hematologists Warm up to Global Thrombin-Based Assays


Thrombin provides the momentum for clot formation. As little as 1 percent of the total thrombin generated during the coagulation process is needed to activate all of the components of the system, including platelets, clotting factors (fibrinogen and factors V, VIII, and XII), and the anticoagulant, protein C. Increasingly, assays of thrombin generation, the so-called “global” assays, are being recognized as more precise measures of coagulation that offer qualitative and quantitative information about clot formation that is more integrative than the standard, one-dimensional aPTT and PT clotting assays. These global assays, which include thrombin generation and thromboelastometry (ROTEM), yield results that correlate more precisely with clinical bleeding phenotypes than assays that are in clinical use currently. So what exactly do the thrombin generation and the ROTEM assays measure, and how do the findings apply to the management of clinical bleeding disorders?

In the current paper, Young and colleagues provide an overview of the application of global assays to clinical management of congenital hemophilia. While it has long been recognized that the correlation between disease severity based on clotting factor assays and clinical bleeding phenotype is imprecise, management is nonetheless determined largely using data generated by such assays. Further, because of the lack of correlation between factor assay results and bleeding propensity, clinical trial outcomes in patients with hemophilia are based on patient-reported bleeding. Clearly, more objective outcome measures are needed. Thrombin generation measures the lag time to clot formation, the peak thrombin generated, and the endogenous thrombin potential (ETP) as determined by the area under the curve (Figure, blue line). In a patient with severe hemophilia A, all three parameters are abnormal, with delayed lag time and greatly reduced peak thrombin generation and ETP observed (in this case, the thrombin generation assay plot appears as a nearly flat line). (Figure, red line) After factor VIII treatment, all three parameters improve. By comparing the parameters of thrombin generation post-infusion with those of a normal control, the dose of factor VIII that most closely simulates normal thrombin generation for a given hemophilia patient can be determined. Using this approach, hemophilia management can be individualized (Table). Thrombin generation assays can also be used to monitor hemostatic efficacy in hemophilia patients with acquired inhibitors who require bypass agents such as recombinant factor VIII or factor eight inhibitor bypass activity (FEIBA) to manage bleeding complications or to provide hemostasis support peripheratively (Table). By conducting a series of spiking experiments with increasing concentrations of recombinant factor VII or FEIBA, it is possible to determine the minimal dose of the optimal bypass agent required to attain peak thrombin generation for a given inhibitor patient. This information could be used to determine the dose and frequency of bypass therapy required to maintain peak thrombin generation throughout the management period. Lack of clinical availability of such an assay is a particularly pressing issue, as currently there are no approved laboratory methods by which the efficacy of bypass therapy can be measured. Similar spiking experiments with clotting factor concentrates, anti-fibrinolytic agents, and anticoagulants can also be conducted by using the ROTEM assay. Thromboelastometry measures time to clot initiation, clot propagation, and clot firmness. By adding different activators, the ROTEM assay can be adapted to measure clot stability after treatment with various products. For example, tissue plasminogen activator can be added to induce fibrinolysis to measure the effects of treatment of a hemophilia patient with tranexamic acid.

The thrombin generation and ROTEM assays provide the means both to gain insight into the basis of the heterogeneity of clinical bleeding phenotypes and to improve management of patients with hemophilia. These assays will also be valuable in providing objective data upon which to base measurement of outcomes in clinical trials. Standardization is the primary issue that must be addressed before these global assays can be implemented for routine clinical use. Encouragingly, an international study is underway to resolve this issue.


Table: Potential Future Applications of “Global Assays” in Hemophilia Management

<table>
<thead>
<tr>
<th>Potential Use of Global Assays</th>
<th>Role</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease severity and phenotype</td>
<td>Use global assays to predict bleeding risk for each severity of hemophilia</td>
<td>Determine in whom prophylaxis should be initiated early</td>
</tr>
<tr>
<td>Personalized prophylaxis</td>
<td>Use global assays to determine peak and trough thrombin generation in product-sampled patient plasma samples</td>
<td>Provide individualized dose regimens based on thrombin generation values</td>
</tr>
<tr>
<td>Efficacy of bypass therapy</td>
<td>Use global assays to determine optimal dose and to monitor coagulation induced by rVIIa or activated prothrombin complex concentrates</td>
<td>Tailor dose and monitor hemostasis in inhibitor patients undergoing surgery</td>
</tr>
<tr>
<td>Efficacy of long-acting factors</td>
<td>Use global assays to assess thrombin generation induced by long-acting clotting factors</td>
<td>Determine optimal dosing and monitoring parameters for long-acting factors</td>
</tr>
</tbody>
</table>
Pesky, Long-Lived Plasma Cells in ITP


Immune thrombocytopenia (ITP) is a disorder caused by autoantibody-mediated platelet destruction and decreased platelet production. GPlibll is an immunoregulatory antigen in ITP, although other platelet surface proteins are frequently targeted. Approximately 40 percent of ITP patients respond to treatment with rituximab, a monoclonal antibody directed against CD20 on the surface of B cells, although the response is transient in a significant number of these patients. Most patients who fail rituximab are cured by splenectomy, indicating that the spleen is the major site of autoantibody production in ITP.

During the humoral response to an antigen, B cells differentiate and proliferate in germinal centers of secondary lymphoid organs such as the spleen. B-cell differentiation involves a branched pathway that leads to the formation of antibody-secreting plasma cells (PCs) or memory B cells (Figure). PCs are non-proliferating and lack CD20. Plasmablasts (PBs) are PC precursors that also lack CD20 and secrete antibody, but are distinguished from PCs by their capacity to proliferate. Additionally, they contain surface immunoglobulin and greater amounts of HLA-DR than PCs.

Matthieu Mahévas et al. in the laboratory of Claude-Agnès Reynaud at Paris Descartes University analyzed B cell populations in splenectomy samples from 10 ITP patients who did not respond to treatment with rituximab and five ITP patients who were rituximab-naive. Additionally, they analyzed normal spleens obtained from patients who had died of stroke. They found that in contrast to normal spleens, spleens from rituximab-naive ITP patients contained numerous active germinal centers. They used the proliferation marker Ki67 and HLA-DR to discriminate PBs from PCs by flow cytometry. Compared with normal spleens, PBs, but not PCs, were significantly increased in the spleens from rituximab-naive ITP patients. In four of the five rituximab-naive ITP spleens, anti-GP1blla antibody-secreting cells were identified by ELISPOT assay.

The rituximab-treated ITP patients had been splenectomized within the six months after the last rituximab infusion. B cells were barely detectable in peripheral blood of these patients, consistent with previous reports on the duration of response to rituximab. In the contrast sample, the spleen samples in these rituximab-treated ITP patients showed significant numbers of PCs. Memory B cells were rare, and PBs were not observed. Additionally, anti-GP1blla antibody-secreting cells were identified in seven out of the 10 patients by ELISPOT assay.

The lack of PBs and the small numbers of memory B cells in rituximab-treated ITP patients suggested that the observed antibody-secreting cells were long-lived PBs that were produced before treatment with rituximab. Seven out of 10 of these patients responded to splenectomy, suggesting that autoreactive, long-lived PCs in ITP are often restricted to the spleen. To test this hypothesis, the authors performed transcriptional analysis on PCs and PBs that were sorted from rituximab-naive and rituximab-treated ITP spleens and from normal spleens using HLA-DR expression as a discriminatory marker. Compared with PBs from rituximab-naive ITP patients, PCs from rituximab-treated ITP patients displayed a gene expression profile consistent with a quiescent, long-lived phenotype. This phenotype included overexpression of anti-apoptotic genes, negative regulators of the cell cycle, including members of the Kruppel-like factor family, and genes related to the unfolded protein response and underexpression of genes involved in positive regulation of the cell cycle and activating molecules (e.g., toll-like receptors).

In contrast, PCs from normal spleens displayed an intermediate expression profile, including some anti-apoptotic genes shared with long-lived PC and some cell-cycle genes expressed by PB. This observation was confirmed by single-cell expression analysis. At the single-cell level, PCs from rituximab-naive ITP patients also displayed an intermediate expression phenotype. Because the spleen is an inflammatory milieu in rituximab-naive ITP patients, the authors suggested ITP spleen does not favor the formation of long-lived PCs, per se.

Splenectomy performed in patients with ITP represents a unique opportunity to study the cell population in an autoimmune process. The results of the study by Mahévas et al. indicate that the spleen is the site of an active B-cell response in patients with ITP. The authors identified antibody-secreting, evidently long-lived PCs that survived in the absence of germinal center B cells, dividing memory B cells, and PB. The results suggest that treatment with rituximab may paradoxically lead to the formation of long-lived splenic PCs in some ITP patients.

Genetic Evolution Promotes Progression and Drives Relapse in CLL


Chronic lymphocytic leukemia (CLL) is generally an indolent process, but about 20% of patients succumbing within one to two years of diagnosis as a result of aggressive, treatment-refractory disease. Like many other types of cancer, CLL is genetically heterogeneous, and specific chromosomal abnormalities have been shown to correlate with survival. For example, loss of the TP53 locus as a consequence of deletion affecting chromosome 17p has been shown to correlate with survival. For example, loss of the TP53 locus as a consequence of deletion affecting chromosome 17p has been shown to correlate with survival. For example, loss of the TP53 locus as a consequence of deletion affecting chromosome 17p has been shown to correlate with survival.

In the current study, Landalu and colleagues have addressed these issues by investigating intratumoral genetic heterogeneity using whole-exome sequencing and single-nucleotide polymorphism analysis in a large cohort of patients with CLL. Together, the results of the experiments reported by Landalu and colleagues provide new insights into the heterogeneous nature of patterns of clonal evolution in CLL. How treatment impacts the clonal evolution that drives cancer relapse, and the association between subclonal mutations and adverse clinical outcomes. This study also underscores the potential of next-generation sequencing to identify mutations and monitor disease progression at the molecular level.

The rapid development of more accurate, less expensive technology, greater sequencing depth may become available and provide a means for reliably detecting somatic mutations at very low frequencies, and sequencing of DNA derived from a single cell may allow for an even more sensitive approach by which subclonal tracking can be developed. Looking to the future, this technology may be used to identify the best available therapy for individual patients and thereby bring us closer to the goal of truly personalized medicine.


Chemotherapy-Induced Neuropathy Pains the Marrow Stem Cell Niche


ver the past half-dozen or so years, the surprising contribution of the sympathetic nervous system (SNS) to control of hematopoiesis at the level of the hematopoietic stem cell (HSC) has come to be recognized. It is now well established that the SNS regulates hematopoietic stem cell self-renewal and differentiation, and that this influence includes both neurotoxicity and myelosuppression. Now, a report by Lucas and colleagues from the laboratory of Paul Frenette at Albert Einstein College of Medicine in New York provides new insights into the basis of the marrow insufficiency sustained after chemotherapy by demonstrating that drugs that cause sensory neuropathy also induce a defect in innervation of the marrow, thereby altering the cellular architecture of the hematopoietic stem cell niche.

This pivotal paper demonstrates that the integrity of the SNS is critical for maintaining the structure and function of the HSC niche and, as such, participates in both blood cell recovery after chemotherapy and progenitor cell mobilization. As the same drugs that were used in the animal experiments, i.e., cisplatin and vincristine, are routinely used during standard chemotherapy in patients (e.g., vincristine in CHOP) or in regimes that have dual roles in salvage/mobilization (e.g., cisplatin in ESHAP, DHAP, VD(O)RIT/PACE), we should consider the potential clinical consequence of neuropathy on marrow function. With this issue in mind, neuroprotectant drugs could restore marrow function and mobilization and promote recovery. Drugs that do not cause neuropathy might be helpful and consider that the effect of a damaged SNS on marrow function. With this issue in mind, we should consider the potential clinical consequence of neuropathy on marrow function. With this issue in mind, neuroprotectant drugs could restore marrow function and mobilization and promote recovery. Drugs that do not cause neuropathy might be helpful and consider that the effect of a damaged SNS on marrow function. With this issue in mind, we should consider the potential clinical consequence of neuropathy on marrow function. With this issue in mind, neuroprotectant drugs could restore marrow function and mobilization and promote recovery. Drugs that do not cause neuropathy might be helpful and consider that the effect of a damaged SNS on marrow function. With this issue in mind, we should consider the potential clinical consequence of neuropathy on marrow function. With this issue in mind, we should consider the potential clinical consequence of neuropathy on marrow function.
An Anecdote Leading to an Antidote

Anecdotes for anti-coagulants have been sought ever since a dairy farmer named Ed Carson walked into the laboratory of Karl Paul Link at the University of Wisconsin with a dead cow. This encounter led to the discovery of dicumarol and the synthesis of warfarin (patented in 1945 and named in recognition of the support provided by the Wisconsin Alumni Research Foundation) and the rest is history. Every clinician is familiar with the bleeding risk that accompanies warfarin therapy. Fortunately, warfarin-induced hemorrhage can be effectively treated with vitamin K, fresh frozen plasma, or coagulation factor concentrates. Likewise, unfractionated heparin can be neutralized with cationic protamine, which can also partially inhibit the activity of low-molecular-weight heparins (LMWHs) such as enoxaparin, but not the short, synthetic heparin derivatives such as the pentasaccharide fondaparinux. In case of severe hemorrhage in patients being treated with LMWHs and synthetic heparin derivatives, fresh frozen plasma, prothrombin concentrates, or recombinant FⅦa can be used to support hemostasis while awaiting metabolism of the offending anticoagulant. Now with the approval of the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban, we have entered a new era of anticoagulation. These agents have been enthusiastically embraced, especially for management of patients with atrial fibrillation, as they are administer orally at a fixed dose, have a rapid onset of action, and require no monitoring of anticoagulant activity. A major criticism of these agents, however, is that reversal of their anticoagulant activity is problematic. Recombinant FⅦa, 3- or 4-factor-activated prothrombin complex concentrates, anti-fibrinolytic agents such as tranexamic acid, and dialysis (in the case of dabigatran) have been used to control hemorrhage induced by the novel oral anticoagulants (NOACs). The relatively short half-life of the NOACs also works in the favor of patients who experience bleeding complications.

The Hematologist: ASH NEWS AND REPORTS

Hodgkin Lymphoma: Antibody-Drug Conjugate Tested in the Front Line

STUDY TITLE: ECHELON-1: A Randomized, Open-Label, Phase III Trial of A-ADV Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma

CLINICAL TRIALS.GOV IDENTIFIER: NCT01724980

SPONSOR: Millennium Pharmaceuticals

COLLABORATORS: Seattle Genetics (USA) and Millennium Takeda (worldwide)

PARTICIPATING CENTERS: More than 100 centers worldwide

ACCRUAL GOAL: 1,110 patients

STUDY DESIGN: Adult patients with histologically confirmed classic Hodgkin lymphoma who are treatment-naïve have Ann Arbor III or IV disease staged by FDG-PET/CT, have bi-dimensional measureable disease; and have an ECOG performance score of ≤ 2 are randomized 1:1 (stratified by geographic region and prognostic factor score) to receive either conventional ABVD, or ADV plus brentuximab vedotin 1.2 mg/kg on days 1 and 15 of each 28-day cycle. After two cycles, patients undergo reassessment with P ET/CT, and those with FDG uptake not markedly above that of the liver (Deauville scores 1-4) continue the same therapy to complete six cycles, while those with markedly FDG-avid disease (Deauville score 5) are eligible to receive alternative salvage therapy. Further PET/CT assessment is performed at the end of therapy. Radiotherapy is permitted to sites of PET-positive residual disease at the discretion of the investigator. Follow-up with CT assessment is performed every three months in year one, and every six months subsequently.

The primary endpoint is modified progression-free survival (mPFS) obtained with brentuximab vedotin plus ADV versus that obtained with ABVD. The modification is to include, as an event, the receipt of chemotherapy or radiotherapy for patients not in complete remission at the end of initial treatment. Overall survival is the secondary endpoint, and the study will also include brentuximab vedotin pharmacokinetics, tumor biomarkers for response and drug clearance, fertility assessment, and analyses of patient-reported outcomes for lung toxicity.

Planned enrollment is 1,104 patients, which will give the power to detect a hazard ratio in the three-year mPFS of 0.67 with 90 percent power at a significance level of 0.025. This outcome measure would correspond to a change in mPFS from 75 percent to 82.5 percent in the experimental arm.

RATIONALE: Brentuximab vedotin, an immunomunomab that targets CD30 on Reed-Sternberg cells with a payload of monomethyl auristatin E (MMAE), a spindles poison, has been a notable success. High response rates were seen after single-agent therapy in relapsed and refractory Hodgkin lymphoma (Younes A et al. J Clin Oncol. 2012;30:21839), and a strikingly high response rate on FDG-PET scanning was observed in a phase IIb combination study with chemotherapy (Ansell SM et al. Blood ASH Annual Meeting Abstracts. 2012;120:788). In most subjects, toxicity has been confined to a cumulative peripheral neuropathy, thanks to a stable linker between the antibody and the toxin that minimizes systemic exposure to MMAE. There was, however, an important note of caution that came from the combination study: brentuximab vedotin given concomitantly with ABVD produced severe pulmonary toxicity, with two deaths among 25 patients. Based on these observations, use of brentuximab in combination with bleomycin is not recommended. Thus, the experimental arm in the current study uses ADV concomitantly with brentuximab, a combination that was shown to be tolerable, and without apparent additive neurotoxicity.

COMMENT: Although the outcomes of chemotherapy for patients with advanced Hodgkin lymphoma are generally good, about 25 percent of patients are not cured by initial therapy with ABVD. This proportion can be reduced by...
about 5 to 10 percent with the use of much more intensive escalated BEACOPP therapy, but this treatment carries the risk of significant short- and long-term morbidity, and alternative approaches to maximize control of the lymphoma are still being sought. The demonstration that brentuximab vedotin can be given safely in combination with AVD, and that this combination results in a high rate of metabolic remission, provides a sound basis for testing the combination in first-line therapy.

This study should determine whether a higher response rate will translate into superior PFS without the toxicity that attends the intensification of conventional cytotoxics. The increasing role of interim PET/CT scanning is reflected in the re-assessment after two months of treatment, with the opportunity to switch to salvage protocols for the small proportion of patients with persistently FDG-avid disease, although some investigators may feel that all subjects with uptake higher than that of the liver (Deauville score 4 as well as 5) are at a relatively high risk of treatment failure, and this concern may be a source of imbalanced early protocol withdrawals. Another important consideration will be the long-term toxicity of the immunomodulator in a patient group that has a high expectation of cure and many years of life ahead. To date, there are very limited data available addressing this issue, and there are theoretical concerns over the depletion of T-cell memory that may result from targeting CD30. So far, T-cell depletion has not resulted in clinically significant sequelae, although a small number of cases of progressive multifocal leukenoencephalopathy have been reported in patients treated with brentuximab. Accordingly, this serious adverse event requires continuing vigilance.

–Peter Johnson, MD

Dr. Johnson has received payments for consultancy and speaker fees from Millennium Takeda.

Oh, What a Relief It Is

STUDY TITLE: Polycythemia Vera Symptom Study Evaluating Ruxolitinib Versus Hydroxyurea in a Randomized, Multicenter, Double-Blind, Double-Dummy, Phase III Efficacy and Safety Study of PatientReported Outcomes

CLINICALTRIALS.GOV IDENTIFIER: NCT01632904

SPONSOR: Incyte Corporation

PARTICIPATING CENTERS: 61 sites in the United States and Europe

ACCRUAL GOAL: 110 patients

STUDY DESIGN: This is a phase III, multicenter, double-blind, placebo-controlled, randomized study. Disease-specific eligibility criteria include the following: 1) patients with symptomatic polycythemia vera (PV) age > 18 years who have received a stable dose of hydroxyurea (HU) for at least 12 weeks; 2) no palpable splenomegaly or no more than one phlebotomy in the prior six months; and 3) the hematocrit has to be controlled within the range of 35 to 45 percent before randomization. Subjects are randomized (1:1) to two treatment arms: ruxolitinib and HU-placebo or HU and ruxolitinib-placebo. Subjects in either arm are eligible to transition to open-label ruxolitinib after week 16, and the study ends when the last patient reaches week 48 of treatment. The primary outcome measure is the proportion of patients with a > 50 percent reduction in the platelet count and reduction in the serum lDH concentration. Secondary outcome measures are as follows: 1) the number of relapses, defined as a de novo event that occurs later than 30 days after the last plasma exchange, during a 12-month follow-up; 2) the time to first relapse of TTP; 3) the number of exacerbations that occur during therapy after the last plasma exchange; and 4) the time to first exacerbation.

RATIONALe: The major cause of TTP is deficiency of the metalloprotease ADAMTS13, resulting either from a hereditary mutation of the ADAMTS13 gene or from an acquired inhibition of an antibody inhibitor directed against the enzyme. ADAMTS13 cleaves high-molecular-weight multimers of vWF. When ADAMTS13 is deficient, unprocessed large (UL)vWF complexes, capable of spontaneously binding to the platelet cell surface receptor GP1b, circulate in the bloodstream. Platelets decorated with ULvWF become caught in the microvasculature and occlude the circulation, resulting in thrombocytopenia, microangiopathic hemolytic anemia, and ultimately the end-organ failure that characterizes TTP.

Nanobodies are 12 to 15 kDa recombinant proteins modeled after the heavy-chain-only antibodies found in members of the Camelidae family (e.g., camels, llamas, alpacas). They consist of an antigen-binding variable domain that retains complete antigen-binding capacity. Nanobodies have advantages over conventional antibodies in that they are relatively easier to manufacture and have greater stability. ALX-0681 is a bivalent humanized nanobody that targets the A1 domain of vWF, the region of the protein responsible for binding to platelet surface receptor GP1b. ALX-0681 prevented development of laboratory abnormalities in a baboon model of TTP in which thrombocytopenia and hemolytic anemia was induced by infusion of 3H9, an antibody directed against ADAMTS13 (Callawert et al. Blood 2012;120:3603-3610). Further, ALX-0681 was shown to be efficacious when infused subsequent to induction of TTP by 3H9.

COMMENT: Plasma exchange has been the mainstay of TTP treatment for nearly four decades and has reduced mortality from >90 percent in the era prior to plasma exchange to ~20 percent in the plasma exchange era. Immunosuppressive therapy with corticosteroids or rituximab may be used in conjunction with plasma exchange. Yet 10 to 20 percent of patients will have an inadequate response to plasma exchange, and relapse remains a major concern. Much has been learned about the pathophysiology of TTP since plasma exchange for treatment of TTP was introduced, yet there are still no drugs specifically approved for TTP. Development of therapy driven by an understanding of molecular underpinnings of the thrombotic process could further improve response rates and reduce the incidence of relapse. Agents targeting the AI domain of vWF represent a new strategy for ameliorating the progression of TTP. In the baboon model of TTP, ALX-0681 demonstrated excellent efficacy without inducing bleeding (Callawert et al. Blood 2012;120:3603-3610). Similar preclinical results using the same animal model were obtained using GBR600, a conventional antibody directed at the AI domain of vWF (Feyts HB et al. Blood 2012;120:3611-4). Together, these studies provide compelling evidence of the efficacy of inhibiting binding of vWF to platelets as a strategy for treatment of TTP. 3H9-induced TTP, however, models the earlier stages of the disease (thrombocytopenia and microangiopathic hemolytic anemia) without eliciting end-organ changes such as renal insufficiency or neurological complications. Thus, the efficacy of ALX-0681 in the prevention or amelioration of these life-threatening sequelae of TTP remains to be proven. TITAN will be important for determining whether interference with vWF binding to platelets is an effective strategy in a clinical setting as an adjunct to plasma exchange. Although TITAN is designed to test the efficacy of ALX-0681 in conjunction with plasma exchange, success could provide the first steps on a path to replace plasma exchange with therapies that are directed at the underlying thrombotic process of the disease.

–Robert Flaumenhaft, MD, PhD

Dr. Flaumenhaft indicated no relevant conflicts of interest.

TITAN: Using Nanobodies to Defeat TTP

STUDY TITLE: Study to Assess Efficacy and Safety of Anti-von Willebrand Factor Nanobody in Patients With Acquired Thrombotic Thrombocytopenic Purpura (TTP) (TITAN)

CLINICALTRIALS.GOV IDENTIFIER: NCT01151423

SPONSOR: Ablynx

PARTICIPATING CENTERS: This is a multinational trial that includes 51 participating centers.

ACCRUAL GOAL: 110 patients

STUDY DESIGN: TITAN is a phase II randomized, placebo-controlled trial designed to determine the efficacy of a nanobody (ALX-0681) directed against von Willebrand factor (vWF), as an adjunct to plasma exchange in the treatment of patients with TTP. Patients randomized to the experimental arm of the study will receive a 10 mg IV infusion of ALX-0681 prior to plasma exchange followed by 10 mg subcutaneous injections once or twice a day for a maximum of 90 days. The primary outcome measure for this study is time-to-recovery marked at completion of plasma exchange and defined by improvement in the platelet count and reduction in the serum lDH.
MAY 30, 2013


Large granular lymphocytic (LGL) leukemia is characterized by clonal expansion of cytotoxic T cells or natural killer cells. The STAT molecules have a major role in intracellular signaling. Recently, somatic mutations in the STAT5B gene were discovered in 30 to 40 percent of LGL leukemia patients. In this paper, investigators screened a remarkably large cohort of LGL patients for STAT5B mutations. By exome and transcriptome sequencing of two STAT5B-exonation negative LGL leukemia patients and, subsequently, by targeted amplicon sequencing of 211 LGL leukemia patients, the authors identified four patients with recurrent, somatic missense mutations (Y659F and N642H) in the SH2 domain of the STAT5B gene. The Y659F and N642H mutant constructs increase both the transcriptional activity of STAT5 and the level of tyrosine (Y694) phosphorylation. The clinical course of the disease in patients with the N642H mutation is aggressive and fatal, clearly different from typical LGL leukemia, which has a relatively favorable outcome. This is the first time somatic STAT5B mutations have been discovered in human cancer. These findings further emphasize the important role of STAT family genes in the pathogenesis of LGL leukemia.

MAY 24, 2013


Yuan and colleagues elucidate the role of RNA splicing in tissue-specific expression of von Willebrand factor (vWF) protein. This study confirms that the presence of the first intron of vWF is required for endothelial cell, but not megakaryocyte, expression of vWF. Interestingly, the intron could be replaced by heterologous introns without eliminating expression. In addition, the presence of the intron affected protein levels, not RNA levels. These discoveries suggest that the splicing process itself is important for post-transcriptional, tissue-specific expression of vWF. These fascinating insights into the molecular events regulating vWF expression may also provide clues to the pathogenesis of von Willebrand disease in patients who have divergent loss of expression between endothelial and platelet vWF.

The Blood Journal Video Library on the Blood website now offers new videos including one on how to get published in a peer-reviewed journal, featuring Dr. Cindy Dunbar, past Blood editor-in-chief, and additional Meet the Editors videos. Check these out at http://bloodjournal.hematologylibrary.org/site/media/videoLibrary.xhtml.

The Hematologist: ASH news and reports

Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The citations are annotated to provide readers both with a concise description of the thrust of the article and an explanation of why the paper is particularly important. 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.

July 25, 2013


Long-term engraftment of allogeneic cells necessitates eluding immune-mediated rejection and is currently achieved by the combination of matching for human leukocyte antigen (HLA) expression and immunosuppression. Torikai and colleagues developed designer zinc finger nucleases (ZFNs) to selectively eliminate HLA expression as an approach to circumventing immune-mediated clearance of target cells. The novel approach of genetic engineering for altering HLA expression on T cells or embryonal stem cells may ultimately prove useful in the development of banks of T cells or primitive stem cells that can be transplanted without being susceptible to clearance by alloreactive T cells. Thus, the results provide a foundation whereby universal cells from one donor can be used for immunotherapy or stem cell transplant in multiple recipients.


Strategies to increase fetal hemoglobin (HbF) levels have the potential to ameliorate symptoms and improve the lives of β-hemoglobinopathy patients. While most studies have focused on induction of γ-globin gene expression, in the present study, the authors investigated whether increasing eukaryotic initiation factor 2a (eIF2α) phosphorylation, a key regulator of protein translation, could enhance HbF post-transcriptionally in human primary erythroid cells. Their results provide convincing evidence that fetal hemoglobin production can be significantly increased through translation, a mechanism that has not previously been targeted. Importantly, the increase in HbF observed was accompanied by a decrease in HbA. The magnitude of this effect of combined translational and transcriptional approaches can produce levels of HbF sufficient to significantly benefit most patients with β-hemoglobinopathies.

June 13, 2013


While adult T-cell leukemia (ATL) has a poor prognosis, the immune effect of allogeneic stem cell transplantation is potentially curative. However, an effective target for anti-ATL immunotherapy has yet to be defined. In the June 13 issue of Blood, investigators demonstrate for the first time that human telomerase reverse transcriptase (hTERT), a leukemia-associated antigen, is a promising target at which to aim genetically programed T cell to selectively recognize and kill ATL tumor cells. This paper provides proof of concept of the feasibility of developing selective immunotherapy for ATL by genetically redirecting antigen targeting of T cells.

The Blood Journal Video Library on the Blood website now offers new videos including one on how to get published in a peer-reviewed journal, featuring Dr. Cindy Dunbar, past Blood editor-in-chief, and additional Meet the Editors videos. Check these out at http://bloodjournal.hematologylibrary.org/site/media/videoLibrary.xhtml.

Dr. Kushner and Dr. Phillips indicated no relevant conflicts of interest.
Promising Med Students Devote Their Summer to Hematology Research

Each year, the ASH Minority Medical Student Award Program (MMSAP) provides a group of bright minority medical students with the opportunity to design and implement a hematology-related research project during an eight-to-12-week summer program. Each student participant is paired with both a research and career-development mentor who assist them with the execution of their projects and offer career guidance throughout medical school and beyond. Medical students conduct research alongside their mentors. At the end of the research experience, students present their findings at the Promoting Minorities in Hematology Reception at the ASH annual meeting. After the research year, the students remain involved with ASH throughout medical school and residency to keep them engaged in the study of hematology and to help them gain experience in the field.

This career-development award program, offered to first- and second-year medical students from the United States and Canada in their DO, MD, or MD/PhD programs, is designed to spark minority medical students’ interest in the field of hematology. It is one of several initiatives under ASH’s Minority Recruitment Initiative, a program committed to increasing the number of minority medical scholars in hematology.

What interested you in this program; what made you apply? I was attracted to the ASH MMSAP program by the immense variety of options available. The only requirement was that the research be in hematology. Hematology is such a broad field that almost anyone can find some aspect that interests them. The freedom to choose where I could do my research was another big plus.

Joy Morgan
Howard University College of Medicine
Research Project: MicroRNA expression profiles in sickle cell disease
Research Mentor: James Taylor, MD
National Institutes of Health

Jamai Wnangaji-Enwerem
Harvard Medical School
Research Project: Creating a mammalian erythroid cell line to biochemically characterize sideroflexin-4 and its role in megaloblastic anemia and mitochondrial disease
Research Mentor: Barry H. Paw, MD, PhD
Bingham and Women’s Hospital

Osarihemi Omwamghe
University of Illinois at Urbana-Champaign
Research Project: Habitual physical activity and exercise patterns in children with sickle cell disease
Research Mentor: Robert Liem, MD
Northwestern University School of Medicine

Manuel Ozambela
Harvard Medical School
Research Project: Use of glycoconjugate-programmed stereosubstitution (GPS) to improve targeted stem cell therapies in models of traumatic brain injury
Research Mentor: Robert Backstein, MD
Harvard Medical School

Lauren Patrick
University of Rochester School of Medicine and Dentistry
Research Project: The role of bone marrow stroma in acute lymphoblastic leukemia cell dormancy during maintenance chemotherapy
Research Mentor: Craig Mullen, MD, PhD
University of Rochester Medical Center

Necrisa Roach
The Ohio State University College of Medicine
Research Project: Targeting the PRMT5 enzyme in sickle cell anemia
Research Mentor: Robert Baicich, MD, PhD
The Ohio State University College of Medicine

Returning Participant

Hewan Belete
University of Minnesota
Research Mentor: Muta Arora, MD
University of Minnesota

Research Project: Predicting transplantation-related toxicity in older adults following HCT

In Her Own Words

What do you hope to gain at the end of this experience? My career goal is to become an academic physician where I will have the flexibility of integrating a scientific question with patient care. Therefore, by participating in this program, I believe that I can learn more about the field of hematology and what clinical research entails. I hope it will strengthen my understanding of basic science concepts and my ability to formulate well thought-out scientific questions.

How did you go about selecting this year’s research project, and how is it different from last year’s research proposal? I loved my previous year’s research project. I participated in a project that investigated the role of omega-3 fatty acid in sirolimus-induced hyperlipidemia. I worked with Dr. Linda Burns, who has been an amazing mentor and supporter. This year, I am working with Dr. Muta Arora (who was my career mentor last year). We are working on a project that looks at toxicity in older adults following autologous hematopoietic stem cell transplantation. This year’s project involves more subjects and more data collection on my part. I will continue to participate in the project further (beyond the summer) and possibly explore publishing opportunities. Dr. Muta is amazing.

First-Time Participants

Gilbert M. Acevedo
University of Colorado School of Medicine
Research Mentor: Jorge D. Paicoc, MD
University of Colorado School of Medicine and Children’s Hospital Colorado

Research Project: Role of Asl FC in platelet inhibition

Karen C. Manotas
University of Utah
Research Project: Long- and short-term outcomes of allo-immune thrombocytopenic mothers and neonates treated with IVG 2x/week plus prednisone

Research Mentor: James B. Bussel, MD
Cornell University, New York Presbyterian Hospital

In Her Own Words

How is the experience so far? My experience working with Dr. Bussel on neonatal allo-immune thrombocytopenia (NAIT) has been an unforgettable one. Not only have I learned a tremendous amount about clinical research, this hematology condition, and its treatment, but I also had the opportunity to work with an outstanding group of mentors and physicians at Weill Cornell Medical College that I hope to be able to stay in contact with for years to come.

What do you hope to gain from this summer research experience? I hope to carry the skills I have learned as a student researcher with me and apply them to future experiences in this field. In addition, I hope to be able to stay in touch with the people who had an invaluable role in the enrichment of my clinical research experience and to my growth as a physician in training, namely Dr. Bussel and his wonderful research team.

Reelin I. Moore
Indiana University
Research Project: The effect of CD26/DPP 4 on the functional activity of MIP-1α for inhibition of proliferation of hematopoietic progenitor cells
Research Mentor: Hail E. Bromeyer, PhD
Indiana University

In His Own Words

How is the experience so far? Although things started off slowly, as the lab was working hard on experiments with very near deadlines, things have picked up in the past few weeks. I am enjoying learning new techniques while gaining an understanding of how scientists have to come to know all of the minute details about how cells interact with each other. Also, I am surrounded by very interesting and kind people who make every day enjoyable and make me feel very comfortable asking questions. They are invaluable to my learning.

How did you go about selecting your research project? Dr. Bromeyer was highly recommended as an ideal research mentor. I met with him to discuss his recent work, and together, we came up with a topic that would both contribute to his lab’s work and allow me to practice many useful techniques and procedures.
Launched in June, around the time that the American Board of Internal Medicine (ABIM) announced that changes in recertification will become effective in January 2014, ASH Academy is a unified Web-based platform designed to provide hematologists with easy-to-use options for knowledge testing (for both maintenance of certification [MOC] and continuing medical education [CME] purposes), for completing practice-improvement modules (PIMs), and for evaluating and claiming CME credit for ASH meetings attended. The decision to develop ASH Academy was driven in part by these anticipated changes to ABIM’s process of MOC, which will affect not only hematologists certified by ABIM but pediatric hematologists and hematopathologists as well. The ASH Academy will also provide hematologists with accessible and clinically relevant options for MOC Part II (self-evaluation of medical knowledge) and Part IV (self-evaluation of practice performance).

The Academy now features two PIMs, one for non-Hodgkin lymphoma and one for myelodysplastic syndromes. The cost for each module is $25 for associate members, $75 for regular members, and $250 for non-members. For more information, please visit www.ashacademy.org.

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

**WHAT’S ON THE WEB**

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

**MARK YOUR CALENDAR**

**September**

1 | Application deadline for ASH Physician-Scientist Career-Development Award<br>Washington, DC | www.hematology.org/awards

1 | Application deadline for Translational Research Training in Hematology*<br>Washington, DC | www.hematology.org/awards

27 | ASH Consultative Hematology Course<br>Chicago, IL | www.hematology.org/meetings

27-28 | ASH State-of-the-Art Symposium in Chicago<br>Chicago, IL | www.hematology.org/meetings

**October**

11-12 | ASH State-of-the-Art Symposium in Los Angeles<br>Los Angeles, CA | www.hematology.org/meetings

22 | ASH annual meeting late-breaking abstracts submission site opens<br>New Orleans, LA | www.hematology.org/meetings

22-23 | ASH Advocacy Leadership Institute<br>Washington, DC | www.hematology.org/ALI

29 | Deadline to submit late-breaking abstracts for the ASH annual meeting<br>New Orleans, LA | www.hematology.org/meetings

**November**

6 | ASH annual meeting advance registration ends<br>New Orleans, LA | www.hematology.org/meetings

7 | ASH annual meeting late/on-site registration begins<br>New Orleans, LA | www.hematology.org/meetings

**December**

7-10 | 55th ASH Annual Meeting and Exposition<br>New Orleans, LA | www.hematology.org/meetings

*In order to submit an application for the Translational Research Training in Hematology program, you must have submitted a letter of intent by June 29, 2013.

For additional meeting dates and award deadlines, go to www.hematology.org/Calendar.