At the risk of publishing another essay in the first person, I am taking the opportunity in this issue to introduce two new features to *The Hematologist*. The first is our very first “No-data Zone.” As I described in the January/February issue, this recurring department will explore clinical situations that are both 1) commonly encountered and 2) lack adequate clinical research for clinicians to make data-driven decisions. The goal is to provide an overview of what guidance does exist and to describe how collaborative projects might result in a clinical trial to answer the unresolved questions. In this issue, Drs. Donald Arnold and Amaris Balitsky have taken up the reins and submitted a fascinating discussion on the use of anticoagulation for thrombocytopenia (page 5). The authors examine the cases of a 75-year-old woman with immune thrombocytopenia and a 34-year-old man who develops deep-vein thrombosis following stem-cell transplantation. They explore the landscape of available data (or lack of it), and propose a path forward for future research that will help carry us “out of the zone” for this particular clinical scenario.

A second department, which I hope will be recurring, will be called “Off the Shelf.” The concept is to carve out some space for readers to reflect on what calls us to the practices of science and medicine, and on what makes work sustainable and enjoyable. With “Off the Shelf” we invite readers to submit short essays recommending choices for nonmedical reading. I am most interested in hearing about books, essays, poetry, and other literature that has changed the way that hematologists approach their day-to-day work. These may be books or writings that may have altered the filter through which you see your patients or your research, tweaked your perspective, or helped salve the scars that this kind of profession inevitably inflicts.

Because good conversations often begin with self-disclosure, I will go first. I considered numerous candidate options for this initial essay. As a fellow, my mentor Dr. Wendy Stock recommended I read Victor Frankl’s staggering work *Man’s Search for Meaning*. I found this book to be a tremendous resource and comfort during my first year as an attending physician — one of the most difficult years of my career(s). Another option was C.S Lewis’ *A Grief Observed*, which, if you have never picked it up, is a poetic, raw, and articulate account of losing a loved one. Lewis’ writing helped me feel closer to the experiences of my patients and their families.

However, the book I would like to highlight for this first feature is a small volume I received from my brother-in-law two Christmases ago. *Seven Brief Lessons on Physics* is just that — a small handful of a book written by the Italian physicist Carlo Rovelli with the kind of love-of-subject that one only gets from a passionate educator and lover of language.

The essays are indeed brief, in some cases punctuated by small sketches to illustrate a point. Yet, they tackle fundamental questions of our natural world: the theory of relativity, quantum mechanics, the origins of the universe, and the concept of time, among others. The essays are written for an audience without a physics background and with the clarity, patience, and respect of a sophisticated and practiced teacher.

How did reading this alter my practice and affect my day-to-day work-life?

First, I think they reminded me of something that I have recognized since I was a child; namely that contemplating the big bang, refilled me with optimism. It reminded me of standing on a beach as a child with my father, staring out into the night sky over Nags Head, North Carolina. “It’s okay to feel small, isn’t it?” he said as his arm swept along the bright big bang, refilled me with optimism. It reminded me of standing on a beach as a child with my father, staring out into the night sky over Nags Head, North Carolina. “It’s okay to feel small, isn’t it?” he said as his arm swept along the bright

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Seizing the Moment for Sickle Cell Disease

In recent years, ASH has taken action to address the burden of sickle cell disease (SCD) through a multifaceted initiative in the United States and globally. Some might ask: Why SCD? Why ASH? Why now?

Among hemoglobin disorders, SCD stands out as a condition where our wealth of knowledge has done little to advance patient care. As ASH represents the corpus of modern hematology, it is uniquely positioned to convey the challenges and the potential that require ongoing investments in research and clinical care. This is the first time ASH has undertaken such an effort to support a single disease, and many achievements to date are a testament to a succession of ASH leaders who boldly took on various aspects of this extraordinary task — leaders such as Dr. Jan Abbkowitz, who championed the ASH policy on sickle cell trait testing for collegiate athletes that helped frame the public discourse on a controversial issue (www.hematology.org/Advocacy/Statements/2650.aspx); and Dr. Linda Burns who led the establishment of the current ASH research priorities for SCD and sickle cell trait. Tackling these research priorities is a big step toward finding cures in the future (www.hematology.org/Research/Recommendations/Sickle-Cell). Dr. David Williams oversaw a multidisciplinary SCD summit to help identity areas where ASH could have the greatest impact, and formed the basis of the State of Sickle Cell Disease: 2016 Report, while Dr. Charles Abrams presided over the launch of the Sickle Cell Disease Coalition (http://scdccolalition.org), which has become the town square for more than 50 diverse organizations to engage constructively, amplify the voice of the SCD community, and promote joint action. Finally, Dr. Ken Anderson helped crystallize efforts to power a research-driven interactive data repository for all of hematology, starting with multiple myeloma and SCD.

SCD has also been an important component of ASH’s many advocacy efforts, and in late February, the U.S. House of Representatives passed the Sickle Cell Disease Research, Surveillance, Prevention, and Treatment Act (H.R. 2410). A companion bill was then introduced in the U.S. Senate (S. 2465), sponsored by Senators Tim Scott (R-SC) and Cory Booker (D-NJ) — legislation for which ASH has advocated over the course of many months. ASH will continue to encourage support for the bill and provide updates as it advances through Congress (www.hematology.org/Advocacy/Campaigns/8373.aspx).

Creation of a body of resources to guide clinicians, researchers, and advocates is a critical next step. Our collection of clinician-focused educational resources includes webinars, the release in 2019 of ASH’s new clinical practice guidelines on the management of acute and chronic complications of SCD, and a forthcoming resource on hydroxyurea for adults with SCD.

We could not realize the overarching mission of ASH without considering how we might make a difference in those parts of the world where the burden of SCD is most profound. ASH is ramping up a global initiative related to SCD that is focused on reducing mortality and promoting newborn screening and early intervention in sub-Saharan African countries. We hope to have made some critical steps in this area by the time of this year’s annual meeting in San Diego.

ASH is deeply committed to helping those who treat SCD patients provide quality care, continue their professional development, and enhance their knowledge and expertise. I hope you will all not only stay abreast of the SCD initiative, but also take action, as so many have, by joining our advocacy, education, and other efforts. We have an extraordinary opportunity to shape the political, medical, and scientific trajectory to improve outcomes for individuals with SCD. This process will require the best minds in the field, support for the most cuttedge science, and crucial conversations with community leaders and lawmakers.

ASH continues to be a force for collaborative and meaningful change. We should all be proud of what we have accomplished and what we plan to achieve in making a difference in SCD.

Sincerely,

Alexis A. Thompson, MD

Off the Shelf

(my day and my patients with hope, purpose, and humility. When Tait Shanafelt, the oncologist who has provided so much valuable research on self-care for physicians, talks about resilience among health care providers, he discusses the role of belonging to something bigger than oneself: family, faith, or community. It seems to me that the stars should count.

The second way this book helped me with my work was by reminding me of the power of the written word to teach. I can only understand a small fraction of the physics that Rovelli addresses in his work, but he has brought me along despite that limitation. His language is simple, and as a reader, you feel respected, like an ally. Once I completed it, I thought about his feat of taking a physics novice and leading me through these sophisticated, intimidating scientific theories. What if I was able to teach that way? What if I was able to recontextualize the complex in such a way for patients and trainees? The bar has been raised for me, personally, by Rovelli’s words, his clarity, and his respect for his readers.

So, here is the formal invitation: We would like to publish your words or so), and we will publish these articles once or twice per year. Given that this is an open invitation, I don’t know that we’ll be able to publish all of the submissions (or if we’ll even get any), but our hope is that each of us will expand the stacks that sit next to our beds as we share creative insights on the work that we do and the scope of the missions that we have undertaken.

From Rovelli’s essay on Probability, Time, and the Heat of Black Holes

“. . . our experience of the passage of time does not need to reflect a fundamental aspect of reality. But if it is not fundamental, where does it come from, our vivid experience of the passage of time?”

I think the answer lies in the intimate connection between time and heat. There is a detectable difference between the past and the future only when there is the flow of heat…”
ASH-EHA Translational Research Training in Hematology Award

This yearlong training and mentoring program is a joint effort of ASH and the European Hematology Association (EHA) that focuses on helping junior researchers build successful careers in translational hematology research. Twenty early-career scientists are selected each year to participate in the program, which covers topics including biostatistics and biomarkers, genetics and molecular biology, ethics, and phase I clinical study design. Submit your letter of intent by July 21; full applications are due October 1. For more details, visit www.hematology.org/TRTH.

Save the Date for These Upcoming ASH Meetings

ASH Meeting on Lymphoma Biology

This ACCME-accredited meeting, taking place August 2-5, 2018, at the Westfields Marriott near Washington, DC, consists of didactic sessions, abstract presentations, interactive workshops, and panel discussions that will address an unmet need in the lymphoma community by serving as the only U.S.-based forum specifically focused on basic and translational science relevant to lymphoma and chronic lymphocytic leukemia. The meeting will bring together experts to discuss the latest lymphoma science, address current challenges in the field, establish the highest priorities for investigation, and develop novel therapeutics. Visit www.hematology.org/Lymphoma-Biology/ for additional information, to register, and to submit an abstract by May 22.

ASH Meeting on Hematologic Malignancies

Join colleagues in an intimate, small-group setting to hear experts present cutting-edge scientific data and provide their own treatment approaches through “How I Treat” presentations. Interact with your peers to answer challenging patient care questions during topic-based panel discussions, and engage in stimulating conversations on specific disease topics. The meeting takes place September 7-8, 2018, at the Marriott Marquis Chicago and will provide exciting updates in each of the core hematologic malignancies including leukemia, lymphoma, myelodysplastic syndromes, myeloma, and myeloproliferative neoplasms. Visit www.hematology.org/Malignancies for more information.

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Available Now Online: CML Interactive Patient Cases

Management of chronic myeloid leukemia (CML) is becoming increasingly complex, and according to data from the American Cancer Society, CML accounts for 15 to 20 percent of leukemias in adults. To address these complexities, ASH and The France Foundation have partnered to create CML Interactive Patient Cases: An Immersive Simulated Learning Experience. These interactive, on-demand cases will give health care professionals a simulated learning environment to help users narrow the growing knowledge gap and improve care for CML patients. Faculty include Drs. Jessica Altman (Northwestern University), Jorge Cortes (M.D. Anderson Cancer Center), Elizabeth Hexner (University of Pennsylvania), and Kendra Sweet (Moffitt Cancer Center). On successful completion, receive a maximum of 3.5 AMA PRA Category 1 Credits™, and 3.5 MOC points. Visit www.ashacademy.org or email cme@hematology.org for more information.

The Hematologist App Is Now Available

Download ASH’s newest app to get on-the-go access to the Society’s official member newsletter. Save articles to read offline, take notes in-app, listen to podcasts, and more. The app supports both smartphones and tables and is available in the App Store for iOS and on Google Play for Android devices. Visit www.hematology.org/Thehematologist/App/ to learn more about features and to download it.

Multimedia

Conversations With Innovators Video Series

A new video from the Conversations With Innovators series is now available on YouTube. Dr. Stella T. Chou discusses her and her colleagues’ findings on the innovative use of induced pluripotent stem cells to help identify complex RBC antibodies. In another video, Dr. Daniel DeAngelo discusses the work of his lab, exploring the highly potent and KIT-specific, oral inhibitor BLU-285 to treat patients with advanced systemic mastocytosis. View this new video and more multimedia from The Hematologist at www.hematology.org/Thehematologist/Multimedia.

The Hematologist Podcasts

Stay up to date with the latest news and views with The Hematologist podcast. Add this podcast to your favorite RSS feed and follow us on SoundCloud and iTunes. Find all podcasts by visiting www.hematology.org/Thehematologist/Multimedia/.
Transfusion services live, and many in our communities roll up their sleeves to donate blood and platelets. Patients benefit from these altruistically motivated donations when they are administered appropriately. Randomized controlled trial results, clinical guidelines, patient blood management, and Choosing Wisely programs demonstrate favorable outcomes when patients receive fewer transfusions than given a decade ago.1,2

Blood collection and red cell transfusions peaked during 2008.3,4 By 2013, 13% of hospitalized patients received transfusions plummets.5 In 2015 (the most recent year for which comprehensive data are available), collections and red cell transfusions declined by 27.2% and 24.4 percent, respectively, compared to 2008 levels (Figure). Some reports indicate additional utilization decreases of 2.2 percent and 4.38 percent in 2016 and 2017, respectively, with expectations for continued contraction. Consequently, hospitals have achieved significant cost savings. Assuming a blood center charge of $200.00 per red cell unit and a decline of 3.67 million red cell transfused units between 2008 and 2015 (and blood center revenues) declined by more than $700 million in 2015 alone.6

Due to long-standing payment and coverage practices, there is no direct link between hospital reimbursement and payment to blood centers. Hospitals recover costs for blood products through bundled payment reimbursement from insurers or the U.S. Centers for Medicare & Medicaid Services (CMS), not a per-unit charge. In turn, hospitals pay blood centers for blood products through negotiated contracts. For years, this arrangement permitted blood centers to recover costs and undertake improvements, but it faltered following hospital consolidations, mergers, and acquisitions that shifted the negotiating power from smaller regional blood centers to larger hospital groups. Blood centers also consolidated, merged, or aligned with group purchasing organizations to achieve efficiencies and economies. However, the significant infrastructure expenses remained, resulting in blood center budgetary shortfalls. Larger blood centers paid a greater proportion of a dwindling market by offering lower prices to hospitals. Blood charges declined, blood centers distributed fewer units, the blood center faced financial uncertainty, and blood centers were threatened with possible closures.

In September 2015, the U.S. Department of Health & Human Services (HHS) contracted the RAND Corporation to assess blood supply system instability. The HHS Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) provided guidance for reviewing the report. In November 2016, RAND presented its findings and recommendations in a report titled, “Toward a Sustainable Blood Supply in the United States.”7 Represented predominantly by hematologists and oncologists and based on limited data, RAND’s conclusion was that the system functioned effectively through these challenges to date. They also conceded that continued stress on blood centers could lead those centers to reduce their investments in research, innovation, and surge capacity, causing shortages, especially during emergencies. RAND saw price competition between blood centers as an incentive for reducing fixed costs (i.e., fewer blood centers) and indicated that the current system was not conducive to private investments in innovation and suppliers to blood centers face significant uncertainty.8

 RAND recommended “targeted policy intervention,” collecting more data about blood use and financial arrangements, developing pricing to account for appropriate surge capacity levels and emergency response plans, paying blood centers for maintaining surge capacity, and paying direct incentive payments to the private sector. As there is no private business case for adoption. Subsequently available data indicate that more than 90 percent of blood donors’ expenses exceeded revenues in 2016.9

In its more global analysis, ACBTSA thought that RAND overstated the economic benefits of competition and price reductions while underestimating risks to the blood system. In its report to the Assistant Secretary for Health, ACBTSA stated, “Public blood centers face the dilemma of non-renumerated blood donors. Simple supply and demand economic principles do not fully address the societal value of this critical national resource. . . There is an urgency that requires a near-term solution — the resiliency of the blood system is at risk.”10 ACBTSA recommended that the U.S. government explore direct payments to blood centers for the infrastructure costs of maintaining adequate blood supplies for the public good and examine future policy making that includes all stakeholders in the vein-to-vein process from blood donor recruitment to bedside infusion.

Action on these recommendations remains in abeyance pending additional data collection in support of the tweaks suggested by RAND, or the more “crisis”-oriented interventions suggested by ACBTSA and a recent New England Journal of Medicine article.11 That article, authored by seasoned, transfusion medicine leaders, eloquently describes these events and provides supplementary background information. The authors conclude that “allowing [the U.S. blood] system to function

shortages elucidate difficulties with ramping production capacity and maintaining redundancy.”12 Hospitals also face decisions about pathogen reduction technology-treated platelets, point-of-care testing, or alternative strategies to reduce platelet transfusion-transmitted agent detectable in 1:4,000-1:9,000 apheresis platelets; reported platelet-associated sepsis in 1:108,000.13 Additionally, transfusion-transmitted Babesia microti infections represent a red cell transfusion hazard.14 For this agent represents another decision point.14

The obstacles described in this article represent possible cost increases for hospitals or additional financial pressures for blood centers if they absorb the associated costs. Although recent observations indicate that total blood center revenues (+3.6% per hospital account investments) exceeded expenses by approximately 1.7 percent during 2017,15 a more granular assessment reveals that aggregated operating expenses exceeded revenues. Hospitals face cost-containment restraints, and insurers and CMS seek reimbursement reductions. As such, it is obligatory that informed hematologists/oncologists and their patient care colleagues become actively involved and advocate for a sustained, safe, and adequate blood system.

Trends in RBC distributions and transfusions. Red cell collections and transfusions peaked in 2008 at approximately 17,286,000 units collected, 17,159,000 units distributed, and 15,014,000 units transfused. By 2015, collections, distributions, and transfusions declined dramatically, by 12,581,000, 12,028,000, and 11,349,000 units, respectively. Note the narrowing of the distribution and transfusion curves, possibly representing diminished resiliency and surge capacity. Reprinted by permission from John Wiley & Sons, Ltd: Transfusion doi: 10.1111/trf.14165, copyright 2017.


Dr. Menitove indicated no relevant conflicts of interest.
The need for anticoagulation in patients with thrombocytopenia is a common, vexing problem and a scenario in which clinicians have to commit to therapy without the benefit of solid trial data. Instead, the decision to administer or withhold anticoagulation depends on the assessed risks of thrombosis and bleeding. To make an informed decision, patients and clinicians must consider the clinical context, the presence of additional risk factors, and the potential consequences of thrombosis and bleeding. Management decisions result in a trade-off since administration of anticoagulation will increase the risk of bleeding, and omission of anticoagulation will increase the risk of thrombosis. In addition to balancing the absolute risks for individual patients, several principles should be considered when deciding on anticoagulation in the setting of thrombocytopenia: 1) a low platelet count does not protect from thrombosis; and 2) in general, thrombotic complications are more dangerous than bleeding complications.

PATIENT 1

A 75-year-old woman with immune thrombocytopenia (ITP) develops atrial fibrillation with a CHADS2 score of 3. Her platelet count is 19 x 10⁹/L. You contemplate administering anticoagulation.

As the population ages, the incidence of atrial fibrillation in patients with ITP will continue to increase. In addition, as the management of stroke prevention becomes more aggressive, the need for anticoagulation in patients with ITP will become a more common occurrence. In general, older ITP patients have an increased annual risk of bleeding compared with younger patients: 10.4 percent in those older than 60 years compared with 0.4 percent in those younger than 40 years. In a systematic review of adults with ITP, the overall risk of severe bleeding was 9.6 percent (95% CI, 4.1-17.1%) and the risk of intracranial hemorrhage was approximately 1 to 2 percent. Conversely, ITP patients may have an increased risk of thrombosis compared with age-matched controls and some ITP treatments, including intravenous immune globulin and thrombopoietin receptor agonists, have been associated with an increased thrombotic risk.

Data on the use of anticoagulation in ITP are lacking; thus, treatment decisions should be based on the best available evidence, typically from studies in nonthrombocytopenic patients and patient values. For this patient, stroke prevention would likely take priority at the expense of bleeding, especially since the risk of thrombosis (including stroke) may be particularly high in patients with ITP. The bleeding risk can be mitigated by improving the thrombocytopenia. For patients with normal platelet counts and a CHADS2 score of 3, the annual risk of stroke is 5.9 percent (95% CI, 4.6-7.3). In the context of ITP and ITP treatments, that annual risk might be approximately twofold higher. With full-dose anticoagulation (e.g., apixaban) in non-ITP patients, the annual risk of stroke is reduced to 1.3 percent; however, the risk reduction is likely to be similar or greater in patients with ITP. The risk of major bleeding with apixaban is approximately 2.1 percent for nonthrombocytopenic patients. Add to that the risk of bleeding attributable to thrombocytopenia (approximately 10%), and the risk of major bleed may increase for this patient might be closer to 15 percent; however, raising the platelet count above 30 to 50 x 10⁹/L would partially mitigate her risk of bleeding.

Given the risks of bleeding and stroke in the patient, the treatment approach was to increase the platelet count to 90 x 10⁹/L (starting with low-dose corticosteroids) until it is above 50 x 10⁹/L, and then to administer anticoagulation.

The Use of Anticoagulation in Patients With Thrombocytopenia

AMARIS K. BALITSKY, MD, MSC,1 AND DONALD M. ARNOLD, MD, MS2

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PATIENT 2

A 34-year-old man who recently underwent relapsed diffuse large B-cell lymphoma develops deep vein thrombosis in his right leg. His platelet count is 15 x 10⁹/L. You contemplate administering anticoagulation.

Cancer-associated thrombosis is common, occurring in up to 19 percent of patients depending on the tumor type and cancer treatments. Anticoagulation is required to improve immediate and long-term symptoms and to reduce the risk of recurrence. In patients without cancer, the risk of recurrence after unprovoked venous thromboembolism (VTE) is 5 percent at one year.1 The risk of recurrence is higher in patients with cancer — 20.7 percent (95% CI, 15.2-25.5%) at one year as reported in one study. However, risk estimates are limited because anticoagulation is rarely stopped, and life expectancy is reduced in this patient population. On the other hand, the risk of bleeding on anticoagulants in patients with cancer is also increased — up to 12.4 percent (95% CI, 6.5%-18.2%) at one year2 and even higher due to the severe thrombocytopenia.

In terms of management approach, in this patient, his one-year risk of VTE recurrence is likely higher than his risk of bleeding, the thrombocytopenia is anticipated to be short-lived, the consequences of thrombosis are more dangerous than bleeding in general, and his platelet counts and bleeding symptoms can be closely monitored, the decision was to administer a platelet transfusion and start anticoagulation once the platelet count is greater than 50 x 10⁹/L. Low-molecular weight heparin (LMWH) is recommended for patients with cancer-associated thrombosis3 and the dose can be adjusted for severe thrombocytopenia.4 Data from a recent randomized trial supported the use of the direct oral anticoagulant edoxaban for patients with cancer-associated VTE; however, patients with thrombocytopenia were excluded from that trial and the generalizability of those data is limited.

Future Research: Clinical trials are needed to address pressing clinical questions related to the use of anticoagulation in patients with thrombocytopenia. For example, in patients with ITP (platelets <50 x 10⁹/L) and atrial fibrillation, what is the risk of severe bleeding with full-dose anticoagulation? In designing a trial to address this question, patients could be stratified by the severity of the thrombocytopenia (bleeding risk) and CHADS2 score (thrombotic risk); the intervention could be to administer or withhold anticoagulation; and the primary outcome could be bleeding (as assessed by an ITP-specific bleeding tool).5 While a randomized trial design could be used, the feasibility and buy-in from clinicians and patients would be important limitations. An alternate approach could be a prospective longitudinal registry, where the decision to administer or withhold anticoagulation is made by the clinician and patient as per clinical practice, and bleeding and thrombotic outcomes can be captured over time. Registries and other well-designed observational studies are needed therefore to inform these difficult management scenarios.
Translational Research Training in Hematology

JEAN SOULIER, MD, PhD,1 AND DAVID M. BODINE, PhD2
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2. Co-director TRTH 2015, Chief, Genetics and Molecular Biology Branch, National Institute for Human Genome Research, Bethesda, MD

In 2009, ASH and the European Hematology Association (EHA) jointly announced a pioneering venture known as the Translational Research Training in Hematology (TRTH) program. The goal of TRTH is to provide expert training to a select group of 20 trainees (10 from Europe and 10 from North America) engaged in research into the mechanisms of hematologic disorders and experimental treatments. The program was designed to establish a network of talented trainees and dedicated mentors available to provide scientific input as well as career development advice.

The “translational research” component of the program’s name can be misinterpreted to mean that TRTH is not designed for trainees engaged in “basic” research, which is not the case. A perusal of the trainees and their projects throughout the past nine years demonstrates that TRTH welcomes all trainees engaged in all aspects of discovery and translational research in hematology. In fact, TRTH only excludes trainees engaged in clinical trials research, who are directed to the Clinical Research Training Institute (CRTI) and Clinical Research Training in Hematology (CRTH) programs, run by ASH and EHA, respectively. Most of the trainees selected for the CRTI and CRTH programs as well as the faculty are MDs. In contrast, the nine classes of TRTH participants thus far have nearly equal representation of PhDs (28%), MD/PhDs (39%), and MDs (32%), which is proportional to the overall distribution of the applications received. Likewise, the TRTH faculty includes PhDs, MD/PhDs, MDs, and DVMs.

TRTH is a yearlong experience. Each year the selected trainees meet in March at a European location (currently Milan, Italy) for an intensive week of training. The meeting includes an in-depth review and discussion of each trainee’s research project, intertwined with didactic faculty presentations on ethics, biostatistics, model organisms, and the pharmaceutical industry, as well as grant- and paper-writing workshops and a mock grant-review study section. Afternoons are typically devoted to small-group discussions involving five trainees and three faculty members and on-demand sessions. Evenings are dedicated to social events that include dinner speeches by the faculty and a successful trainee from a previous class describing their career paths. The group reconvenes at the EHA Annual Congress in June and has a final group meeting at the ASH annual meeting the following December.

A major value of TRTH is the establishment of a network of talented trainees and dedicated mentors that is designed to support each trainee throughout their career. It is expected that the trainees and faculty members will continue to interact over many years. Indeed, this has overwhelmingly been the case. More than 95 percent of TRTH trainees have maintained contact with their classmates and faculty. (For validation of the value of the TRTH experience one may visit the “What to expect” page on the http://ehaweb.org site to read some of the many testimonials and the list of present and previous TRTH trainees.)

The alumni of TRTH have become highly successful in hematology. More than 34 percent of the TRTH alumni now run their own laboratories, and this number will continue to rise as recent classes transition to independence. The 115 participating trainees prior to 2018 have collectively published more than 2,220 articles, including almost 900 as first authors. Additionally, more than 90 percent of the TRTH alumni have been successful in obtaining funding from a variety of governmental and philanthropic sources. The enduring benefits of TRTH can be seen in the fact that more than 50 percent of trainees who are engaged in active collaborations with their TRTH classmates and/or TRTH faculty members.

The eligibility requirements for North American and European TRTH applicants are broad, reflecting the diversity of hematology research and the people engaged in that research. There are no specific degrees included or excluded; the only requirement is a demonstrated commitment to hematology research. The complete eligibility requirements can be found at www.hematology.org/TRTH.

The application process begins with a letter of intent (LOI) that is due July 21, 2018. We hope that all interested trainees will explore applying.

Author’s Note: We thank the EHA and ASH staff for sharing information about the TRTH trainees. Special thanks to Dr. Donna Neuberg for compiling detailed follow-up of each TRTH trainee.

A Real Nose-Pinner

YI LI, MD,1 AND ANNETTE S. KIM, MD, PhD2
1. Associate Professor of Pathology, Harvard Medical School/Brigham and Women’s Hospital, Boston, MA
2. Hematopathology Fellow, Harvard Medical School/Brigham and Women’s Hospital, Boston, MA

A 68-year-old man with a history of polycystic kidney disease presented five months postcadaveric renal transplantation with new-onset neutropenia and anemia, as well as a rising creatinine (0.59 mg/dL the prior week) with no other significant symptoms. A concurrent complete blood count showed the following:

- White blood cell count 2.25 K/μL (absolute neutrophil count 0.71 K/μL)
- Hemoglobin 7.9 g/dL
- Hematocrit 24.9%
- Mean corpuscular volume 86.2 FL
- Platelet count 160 K/μL

A 95-genome next-generation sequencing myeloid panel identified no pathogenic variants or copy number alterations. Metaphase cytogenetics revealed a normal karyotype. Two images from the peripheral blood smear and one image of the bone marrow biopsy are shown in Figures 1 and 2.

Figure 1. Peripheral blood smear.

Figure 2. Bone marrow biopsy.

What is the likely cause of this patient’s neutropenia?
A) Congenital Pelger-Huët anomaly
B) Infection
C) Myelodysplastic syndrome
D) Medication (mycophenolate mofetil/tacrolimus)
E) Autoimmune disorder

For the solution to the quiz, visit The Hematologist online, www.hematology.org/Thehematologist/Image-Challenge.

Dr. Li and Dr. Kim indicated no relevant conflicts of interest.

Put your fellow readers to the test, and send us your Image Challenge submissions! Email case descriptions and image files to the Managing Editor at jllorens@hematology.org.
ASH Advocates Visit Congress to Urge Support for Issues Important to Hematology

Earlier this spring, following their business meetings in Washington, DC, the ASH Committee on Government Affairs and ASH Committee on Practice visited more than 65 congressional offices to advocate for issues of importance to hematology, including funding for the National Institutes of Health (NIH), issues related to physician reimbursement, and sickle cell disease (SCD) legislation. ASH advocates encouraged congressional officials to recognize the value of biomedical research by providing NIH with sustained and predictable funding increases in fiscal year (FY) 2018 and FY 2019 and urged legislators to cosponsor SCD legislation.

Congressional meetings are important components of ASH’s advocacy efforts, providing an opportunity for members of Congress and their staff to gain insight on issues of concern to hematologists. However, to continue to gain support for these issues, the Society needs the help of all members in bringing issues to the attention of Congress and other governmental agencies. ASH strongly encourages members to let the ASH Government Relations and Practice Department know when you are in Washington, DC, and are available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard in the halls of Congress. You can also participate in the Society’s advocacy efforts by visiting the ASH Advocacy Center and joining the ASH Grassroots Network. Contact ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org, or visit www.hematology.org/Advocacy for additional information.

Congress is now beginning to turn its attention to the FY 2019 budget. In February, the president released his budget proposal outlining his priorities for the year. Like the previous year’s proposal, the president’s new budget includes dramatic cuts to critical public health programs. While the proposal seeks to increase overall funding for NIH above FY 2017 levels, it falls short of the FY 2018 levels that were recently passed by Congress. The Society has expressed grave concerns with the proposed levels and has called on members of congress to increase support for scientific innovation and public health programs.

It is important to remember that the president’s nonbinding budget proposal merely sets forth the administration’s priorities and is just one step in a lengthy federal budget process. Ultimate authority on setting annual spending levels for programs and agencies rests with Congress. Throughout the remainder of the spring and into early summer, administration representatives will be called to testify before congress on the president’s proposals, and the House and Senate Appropriations Committees will begin drafting legislation establishing actual federal spending levels for FY 2019.

As this process continues, ASH encourages you to contact your elected officials about the need for sustained federal funding for NIH and its importance for your research and the patients you treat. Visit www.hematology.org/Grassroots to send your elected officials an email urging support for sustained and predictable NIH funding.

ASH Secretary Joins Senator Booker to Introduce SCD Legislation in the Senate

On February 28, ASH Secretary Dr. Robert Brodsky participated in a roundtable discussion hosted by Senator Cory Booker (D-NJ) following the introduction of SCD legislation in the U.S. Senate. The Sickle Cell Disease Research, Surveillance, Prevention and Treatment Act (S. 2465), sponsored by Senators Tim Scott (R-SC) and Booker, reauthorizes SCD prevention and treatment grants awarded by the Health Resources and Service Administration (HRSA) and authorizes the CDC to award SCD surveillance grants to better understand the prevalence and distribution of SCD and its associated health outcomes, complications, and treatments. ASH and 66 other organizations have endorsed the Senate bill in a joint sign-on letter. Similar legislation (H.R. 2410) sponsored by Representatives Danny Davis (D-IL) and Michael Burgess (R-TX) passed the U.S. House of Representatives in late February.

In the past several years, ASH members have made numerous visits to congressional offices and participated in congressional briefings to raise awareness of SCD. These steadfast advocacy efforts were critical in the introduction of this legislation. ASH looks forward to continuing the fight to move this bill through the Senate and ultimately have it signed into law. Your legislators need to hear from you about why this bipartisan legislation is needed to help understand this devastating disease. Visit the ASH Advocacy Center at www.hematology.org/Advocacy to take action and tell your senators to cosponsor S. 2465.

Register for the 2018 ASH Advocacy Leadership Institute

ASH is now accepting nominations for the eighth annual Advocacy Leadership Institute (ALI) taking place September 24-25, 2018. ALI is an intensive two-day program during which ASH members learn about advocacy, health policy, and the legislative process, and start engaging with the Society’s activities. Nominations are due by June 1. The first day of ALI focuses on the legislative process and health policy. Participants hear about the major issues facing the field of hematology and see first-hand how Congress can impact research and practice. On the second day, participants meet with their congressional delegations on Capitol Hill, to turn their knowledge into action in support of hematology.

For more information, email ASH Government Relations Coordinator Foster Curry at fcurry@hematology.org or visit www.hematology.org/ALI.

Congress Finalizes FY 2018 Budget for NIH and Other Federal Programs, Begins Work on FY 2019

Nearly six months into the FY that began on October 1, 2017, Congress passed final FY 2018 spending levels on March 23. The omnibus spending package included funding for NIH and other federal agencies and programs. The final spending bill included a $3 billion increase (8.8%) in NIH funding for a total level of just more than $37 billion, a larger increase than either the House or Senate originally proposed. The Centers for Disease Control and Prevention (CDC) also received an increase of $1.1 billion, for a total funding level of approximately $8.3 billion for FY 2018.

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**Management of Heavy Menstrual Bleeding on Anticoagulation**


Heavy menstrual bleeding (HMB) is a well-known adverse effect of anticoagulant therapy. As women do not necessarily spontaneously report their menstrual bleeding patterns and physicians may not inquire about them, HMB may be missed during clinical visits, and potentially useful treatment options may therefore not be considered, discussed, and implemented.

In this current context, the published work by Dr. Kochawan Boonyawat and colleagues, while not presenting any original data, is a welcome summary of the experience and perspectives of experts in respect to the optimal anticoagulant treatment of women with HMB. This is important because anticoagulants are frequently used in women of childbearing age, and the impact of anticoagulant use on menstrual bleeding has been noted to be variable, with some studies showing an increase in menstrual bleeding while others do not find differences.

**Table. Treatment Options for Heavy Menstrual Bleeding on Anticoagulants**

- Progesterin intrauterine device
- Combined estrogen-progestin contraceptive
- Endometrial ablation procedure (if no further pregnancies desired)
- Tranexamic acid at times of menstrual flow
- Decrease in anticoagulant drug dosing (mesorobomin 10 mg once daily; aspirin 2.5 mg twice daily; lower target INR for anticoagulation; lower INR targeted for stroke prevention; switch to a different anticoagulant)  

The main management points in the female patient of childbearing age on anticoagulation for a VTE include specifically asking about the degree of menstrual bleeding during the clinic visit; having a low threshold to order a complete blood count (CBC) and a serum ferritin level; recommending a progesteron IUD if the woman is considering having children in the future; discussing a progesteron IUD or endometrial ablation procedure in the woman who does not plan to have further children; considering decreasing the DOAC dose after the initial three months of full-dose anticoagulation; and keeping in mind other potential treatment options such as a combination of estrogen-progestin contraceptive (preferred) or a progestin (if second or fourth-generation pill), higher-dose oral progestins as per gynecologic recommendations, and use of tranexamic acid.

In addition to identifying a link between the JAK2 mutation and induction of PD-L1 expression in myeloproliferative neoplasms (MPNs) as seen in patients with myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs), we also identified a link between the JAK2 mutation and induction of PD-L1 expression in MPNs as seen in patients with myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). This is important because anticoagulants are frequently used in women of childbearing age, and the impact of anticoagulant use on menstrual bleeding has been noted to be variable, with some studies showing an increase in menstrual bleeding while others do not find differences. Therefore, while anticoagulants are important for preventing thromboembolic events, they may also have adverse effects on menstrual bleeding, which can be managed with these treatment options.

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**JAK2V617F Mutations Promote PD-L1 Expression to Mediate Immune Escape in Myeloproliferative Neoplasms**


Programmed death ligand 1 (PD-L1) and PD-L2 engage the programmed death 1 (PD-1) on T cells and induce T-cell exhaustion. Pharmacologic blockage of PD-1 signaling has resulted in numerous therapeutic advances for patients with cancer and may be particularly relevant in the subset of patients with a high mutational burden such as melanoma and non–small-cell lung cancer. In contrast to these tumor types, however, most hematopoietic malignancies have a lower mutational burden, and consequently, many patients with refractory leukemias and lymphomas do not seem to benefit from blockade of PD-1. One notable exception to this paradigm is Hodgkin lymphoma. For classical Hodgkin lymphoma (cHL), the PD-1–blocking antibodies pembrolizumab and nivolumab have received U.S. Food and Drug Administration approval for patients who have relapsed or progressed after autologous hematopoietic stem-cell transplantation.1,2 This sensitivity is thought to be due to the fact that Reed–Sternglass cells of cHL are characterized by genomic amplification of the Pdcd4 gene, leading to overexpression of PD-L1 and PD-L2. Interestingly, the kinase Jak2 is also encoded at aPdcd4, approximately 22kb upstream of PD-L1.3,4 So, does upregulation of Jak2 activity also contribute to immune escape, or is Jak2 inhibition simply a “byproduct” of being adjacent to PD-L1?

In the article by Dr. Alessandro Prestipino and colleagues, the authors identify that expression of constitutively active Jak2 mutations as seen in patients with myeloproliferative neoplasms (MPNs) upregulates PD-L1 expression and confers responsiveness to PD-1 targeting in preclinical MPN models. To understand if there was a relationship between constitutively active forms of Jak2 and PD-1 expression, the authors tested PD-1 expression in cell line models with overexpression of wild-type Jak2 or Jak2V617F, mouse models with knock-in of constitutively active (preferentially somatic) or knock-out Jak2 mice, and cells from patients with Jak2V617F-mutant MPNs versus healthy controls. This effort led to the consistent observation that the Jak2V617F mutation was associated with increased PD-L1 expression. Prior work has suggested that the transcription factor Stat3, and possibly Stat5, which are activated by Jak2, may directly bind to the promoter of PD-L1 and promote its expression. Consistent with this hypothesis, expression of a constitutively active Stat3 (Stat3Y640F) also upregulated PD-L1 expression.

While the above results are exciting, it is important to note that other frequently mutated kinases that have been linked to STAT3 activation did not seem to be associated with PD-L1 expression. For example, FLT3 internal tandem duplications or tyrosine kinase domain mutations, alterations in PDGFR (the FIP1L1-PDGFRα translocation), and EGFR mutations (Del19, L858R) did not seem to upregulate PD-L1 protein expression in systems. Even more curiously, mutations in CALR, which are mutually exclusive with Jak2 mutations in MPN and are found in the majority of MPN patients lacking the Jak2V617F mutation,5,6 were associated with increased PD-L1 expression. Thus, further mechanistic work to understand the precise relationship between Jak2-mediated Bacl expression and PD-L1 expression is clearly needed.

These data raise interest in evaluating the efficacy of PD-1 inhibition in MPNs. This is the subject of several ongoing clinical trials testing the effects of PD-1 inhibition in advanced MPNs (for example, the phase 2 trial, ClinicalTrials.gov identifier: NCT03065400). It is important to note that patients with frank acute myeloid leukemia, however, lacked PD-L1 expression in this study. Moreover, the study by Prestipino and colleagues evaluated PD-L1 expression on mature cell types in MPN patients (monocytes, neutrophils, platelets, and myeloid-derived suppressor cells), but it is not yet clear if PD-L1 is also upregulated in the cells that serve as MPN-initiating cells (such as CD34+ cells and their subpopulations). Thus, further efforts to evaluate the efficacy of PD-1 inhibition in MPNs, alone and together with Jak2 inhibition, at the chronic phase versus blast phase, and transformation of MPNs, will be critical.


**References**

Targeted Therapy to Trigger GVL: A Case for the Prosecution in FLT3-ITD–Mutant AML


FLT3-ITD–mutant acute myeloid leukemia (AML) is associated with a high rate of relapse post allograft, and outcomes for patients who relapse are very poor.1 Empirically, this has prompted trials of "maintenance therapy" with inhibitors of FLT3 such as sorafenib following allogeneic transplantation. While the jury may still be out on whether such therapy should be routine, some patients who relapse post allograft can be rescued with sorafenib therapy if there is induction of graft-versus-host disease (GVHD) and associated graft-versus-leukemia (GVL). Having evidence to explain how responses and apparent cures are achieved and why only some patients benefit would certainly strengthen the case for further exploration of this approach.

Dr. Nimitha R. Mathew and colleagues have sought to understand how treatment with sorafenib may trigger an allo-immune response. Using sophisticated mouse models and primary samples from patients in vitro and in vivo, they dissected how each of the constituent elements of the system (targeted inhibitor, T cells, cytokines, AML cells, and FLT3-ITD mutation) contribute to leukemia control in an allosetting. First, in a model setting, they demonstrated that long-term control of leukemia postallograft requires both treatment with sorafenib and allogeneic T cells — neither was effective alone, nor was the combination of sorafenib with syngeneic T cells. This dual requirement was consistently observed in several models, including a humanized model using primary human FLT3-ITD–mutated AML (Figure 1). Furthermore, the cure of leukemia could occur without lifelong GVHD. Second, this effect was driven specifically by increased IL-15 production, with increased levels observed in sera. When IL-15 was blocked, no antileukemic effect was observed, and sorafenib did not directly influence production of other cytokines. Importantly, the increased IL-15 production was from the FLT3-ITD–mutant AML cells, not from the donor cells. While systemic treatment with exogenous IL-15 could replace the production from leukemia cells, this resulted in severe GVHD and increased lethality. The authors suggest that as the GVL effect extinguishes the AML, the source of the instigating IL-15 production is removed, eliminating a driver for unrestrained GVHD. Third, CD8+ T cells were the effector cells for the allo-immune response. While sorafenib had no direct effect on T cell activation in vitro, sorafenib-treated AML-bearing mice generated more CD8+ CD107a+ IFN-γ+ T cells, which could impart long-term leukemia control if transplanted into secondary recipients with the same leukemia (but not a third-party leukemia). Fourth, this sorafenib-induced allo-immune response was not observed in models where AML cells lacked the FLT3-ITD mutation. Indeed, when AML cells were engineered with a variant of FLT3-ITD that was resistant to sorafenib inhibition, no sorafenib-induced IL-15 production or leukemic protection was observed.

Consistent with these model findings, when patients with FLT3-ITD–mutant AML relapse postallograft were treated with sorafenib and donor lymphocyte infusions (DLI), serum IL-15 and IFN-γ levels at day 8 of sorafenib therapy were only increased in patients who ultimately demonstrated a clinical response (Figure 2). The investigators elegantly demonstrated that induction of IL-15 production required sorafenib-induced inhibition of mutant FLT3-ITD. Constitutive signalling from the mutant receptor leads to production of the transcription factor ATF4. Inhibition of FLT3-ITD signalling reduces ATF4 levels, which then reduces repression of IRF-7 activation. Increased IRF-7 activation in turn increases IL-15 transcription (Figure 3). When FLT3-ITD is resistant to sorafenib, there is no change in IL-4 levels, IRF-7 activation, or IL-15 production by the leukemia cells, and hence, no downstream allo-immune effect and no clinical response. Finally, while sorafenib can inhibit other kinases, this effect was specific to its ability to inhibit FLT3 and was recapitulated by other more specific FLT3 inhibitors.

In summary, Dr. Mathew and colleagues have convincingly elucidated a mechanism by which a small molecule inhibitor targeting a leukemia-specific kinase mutation can trigger an effective CD8+ T cell–mediated allo-immune response that leads to durable leukemia control. The detailed experiments conducted by these investigators highlight that the clinical responses observed with DLI and sorafenib are probably not due to nonspecific allo-immune responses or due to direct cytotoxicity by sorafenib. Rather, they reflect specific inhibition of FLT3-ITD with consequent upregulation of IL-15 production by the leukemia cells themselves, which then fuels a GVL effect with immune memory. With ongoing randomized studies of planned maintenance therapy with FLT3 inhibitors postallograft for patients in remission (as opposed to relapsed disease), it is interesting to speculate as to the mechanism by which these drugs may add benefit; will it be via a direct cytotoxic effect or by enhancing GVL? The discoveries described in this article provide strong support for ongoing efforts to advance the DLI-sorafenib combination and similar combinations with other FLT3 inhibitors as a therapeutic option. This new concept also highlights the importance for hematologists to understand how targeted agents are working when they are combined with immunotherapy.

Eupenic aberrations are commonplace in cancer, and the past decade has seen the identification of a wide range of pathogenic variants in numerous epigenetic regulators in neoplasms, including myeloid neoplasms. Genes involved in histone modification in particular are targeted frequently by mutation. Histone modification marks include acetylation, methylation, ubiquitination, sumoylation, and phosphorylation, and these marks can be "written," "erased," or "read" by various enzyme complexes. Bromodomains are "readers" of histone acetylation of lysine tails. BRD4 is a ubiquitous member of the bromodomain and extra terminal (BET) family of bromodomain proteins and plays a key role in transcriptional elongation through its recruitment of P-TEFb. It targets key enhancers and superenhancers that regulate critical genes involved in tumorigenesis. Accordingly, BET inhibitors represent an enticing class of experimental anticancer drugs.

Recently, Dr. Hui Yang and colleagues created excitement in the discussion of BET inhibitors with their dramatic finding that pathogenic variants in ASXL1 result in a truncated protein that binds directly to BRD4 to induce transcription of genes that confer a hematopoietic stem-cell (HSC) advantage. Pathogenic variants in ASXL1 are seen recurrently in nearly all diagnostic categories of chronic and acute myeloid neoplasms, associated with poor prognosis. Additionally, these variants may also be seen in age-related clonal hematopoiesis and are associated with higher risk of progression to a subsequent myeloid neoplasm. All proven pathogenic variants in ASXL1 are truncating. These nonsense or frameshift variants occur in exons 11 and 12, resulting in loss of the C-terminal PHD domain (residues 1479-1539), even though the transcript is still expressed. Dr. Yang and colleagues have now demonstrated that the truncated protein has distinct altered function through its interaction with BRD4 from that of the wild-type protein, opening up new therapeutic avenues for targeted therapy in ASXL1-mutated myeloid neoplasms.

Using a transgenic mouse model engineered with an ASXL1-truncation mutation (a common recurrent nonsense mutation seen clinically), Dr. Yang and colleagues demonstrated that this truncated form can enhance the expression of key genes involved in stem-cell maintenance and myeloid differentiation. The results are summarized on Figure 1, wherein the protein product interacts with key developmental genes such as CDCA9/tenascin enhancer binding proteins as well as PPARγ. Their data suggest that ASXL1 mutation plays key roles in hematopoietic colony formation and stem-cell expansion through increased transcription of Prom116. Significantly, the truncated ASXL1, but not the WT protein, binds to BRD4 to reorient phosphorylated RNA polymerase II (RNAPII-pSer2) and acetylated H3K122 (H3K122Ac) to the promoter region of Prom116 (Figure 1) as shown by reciprocal immunoprecipitation studies. Thus, ASXL1 truncation mutations result not in a loss of function or dominant negative function, but rather in specific gain of altered function.

This gain of altered ASXL1 function generates enhancement of the HSC pool with increases in Lin-Sca-1+c-kit+ (LSK) cells, both long- and short-term HSCs, colony formation and repopulating ability, and the ability to reconstitute the recipient marrow of recipient mice in transplantation studies. Additionally, differentiation of the HSCs is also affected by this ASXL1 truncation, with a shift from erythroid and megakaryocytic differentiation to increased myeloid differentiation morphologically, immunophenotypically, and in gene-expression profiling studies.

This ASXL1 truncation model mimics many of the features of a variety of myeloid neoplasms. The mice had shorter mean survival (P < 0.01), relative neutropenia (P = 0.017), increased platelets (P = 0.048), relatively decreased lymphocytes (P = 0.005), and decreased hemoglobin and red blood cells (P = 0.004 and 0.007, respectively). In keeping with the clinical observations of ASXL1 mutations, the transgenic mice expressing the truncated ASXL1 protein progressed to a wide range of myeloid malignancies involving the bone marrow, blood, and spleen with features consistent with acute myeloid leukemia, myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), or MDS/MPN. Somewhat counterintuitively, based on differentiation studies in mice, the MPN and MDS/MPN cases were characterized by significant thrombocytosis with megakaryocytic hyperplasia. As megakaryocytes are known to produce a wide range of profibrotic cytokines, this finding is concordant with the clinical association of histomorphology, immunophenotypically, and in gene-expression profiling studies.

In summary, Dr. Yang and colleagues have provided the critical link between ASXL1 truncation mutations and a novel therapeutic avenue employing BET bromodomain inhibitors through their demonstration of gain of altered ASXL1 function. As ASXL1 mutations are amongst the most common alterations seen throughout all chronic and acute myeloid neoplasms, these discoveries are especially impactful. This work also points to the potential of synergetic targeted therapies as downstream interactions such as with PPARγ. With this single study, ASXL1 has taken from a phenomenological association with myeloid neoplasms to a mechanistic understanding that points toward the potential of directed targeted therapy for a large number of patients with otherwise poor prognosis.


BETtong on Targeted Therapy for ASXL1-mutated Myeloid Neoplasms


Professionalism and the Written Word: Attitudes and Words Matter in Medical Care for Adults With SCD


For hematologists providing care for children and adults with sickle cell disease (SCD), we frequently must consult our colleagues not to use terms that are considered pejorative, such as sickler or frequent flyer when describing individuals with SCD. Individuals with SCD consider the term sickler to be derogatory, particularly because the term reduces their existence to a disease. Based on the belief that such terms dehumanize the individual with SCD, the SCD community has worked hard to limit their use. There are data to support such care with terminology: Dr. Jeffrey Glassberg and colleagues conducted a survey of 655 emergency department physicians from 49 U.S. states. The results serve as compelling evidence that the term sickler is associated with negative physician attitudes and lower adherence to evidence-based guidelines for acute care in the emergency department.

In a randomized controlled trial of medical students and residents (n=143), Dr. Anna P. Goddio and colleagues tested the hypothesis that after reading a medical record note using stigmatizing language, trainees would treat the patient more less aggressively than trainees who read a chart note using neutral language. The definition of stigmatizing language was defined as having any one of the following three features: 1) casting doubt on the patient’s pain (e.g. “insisting that his pain is 'still a 10' when it has 10/10 pain”); 2) portraying the patient negatively (with irrelevant or unnecessary indicators of lower socioeconomic status such as “hanging out with friends outside McDonald’s”); and 3) implying patient responsibility with references to uncooperativeness (e.g., “he refused his oxygen mask vs. he is not tolerating the oxygen mask”). Reading the stigmatizing language in the medical record resulted in a hypothetical, less aggressive management. The patient’s pain was compared to reading a note that was neutral but that contained the same pertinent medical information (5.56 stigmatizing vs. 6.22 neutral; p=0.003) when using two multiple choice questions (complain of intensity of pain treatment). Reading the stigmatizing language was also associated with more negative attitudes about the patient with SCD in acute pain (20.6 stigmatizing vs. 19.6 neutral; p=0.001) when using the validated Positive Attitudes towards Sickle Cell Patients Scale (range, 7-35).

In summary, the results of the randomized controlled trial by Dr. Goddio and colleagues provide evidence that derogatory written words in the medical records likely result in less-than-optimal treatment of acute vaso-occlusive pain in adults with SCD. An equally important but nuanced message from the trial is the undue influence of medical attendings who elect not to correct the written and oral language stigmatizing children and adults with acute vaso-occlusive pain. Rarely in medicine do we have clear messages of teaching opportunities that make a true difference in how we manage acute vaso-occlusive pain, but we have one now. When stigmatizing language is used among our peers and families, we should not relegate the oral and written language disapprovingly. We should also reinforce the proper use of oral and written language when referring to individuals with not only SCD, but any disease, and highlight this strategy as a component of compassionate medical care. Studies like this highlight that being a good physician is not just about choosing the right medication, but also about selecting the right words.


Micheal DeBaun, MD, MPH
Dr. DeBaun indicated no relevant conflicts of interest.
The Importance of Genomic Testing in Children With Complex Autoimmune Cytopenias: Precision Medicine Is Not Just for Cancer


Patients with Evans syndrome (ES) is defined as the idiopathic autoimmune destruction of at least two hematopoietic cell types, including destruction of erythrocytes (autoimmune hemolytic anemia), platelets (autoimmune thrombocytopenia), and neutrophils (autoimmune neutrophilic defect). ES is a diagnosis of exclusion, and when a patient is diagnosed with ES, it is important to exclude rheumatologic disease, infection, malignancy, and immune deficiency. Historically, these diagnoses that mimic ES were often made clinically or with functional testing, and they only represented a small proportion of patients presenting with multiple autoimmune cytopenias. Based on the hypothesis that ES is a heterogeneous disease, patients with ES are typically treated with nonspecific medications that are commonly used to treat other idiopathic autoimmune cytopenia syndromes including coagulopathies, intravascular hemolysis, and thrombocytopenia.

Multiple reports demonstrate that a large fraction of patients with ES have comorbid benign lymphoproliferative disease (lymphoproliferative or hematoproliferative), and a small fraction develop secondary malignancies. Based on these comorbid features, it was hypothesized and established that a fraction of patients with ES have a genetic syndrome termed autoimmune lymphoproliferative syndrome (ALPS) that distinguishes ES from ALPS is important because rituximab and splenectomy are relatively contraindicated in ALPS, but are commonly used to treat ES. Additionally, multiple studies have demonstrated that mycophenolate mofetil (cellcycle arrest effective (amyloidosis)) is not effective in ALPS. Recent work has established dysregulated mTOR signaling drives the autoimmune disease and lymphoproliferation in ALPS, suggesting mTOR inhibitors are a targeted therapy for ALPS.

Recently, Dr. Caroline Bensard and colleagues hypothesized that a large percentage of children diagnosed with ES may have other underlying genetic disorders. They evaluated 48 patients with ES throughout an 18-year period. Twenty-four had ALPS, and the authors performed sequencing on the remaining 18 children. Subjects who did not have mutations in ALPS-causative genes (PAS, FAS, or CASP10) or CTLA4 had whole-exome sequencing.

Seven of 18 of the children were found to have genetic defects with mutations in CTLA4 (n=3), LRBA (n=1), STAT3 (n=1), and KRAS (n=1). These important results highlight the significant clinical implications of many of these conditions that have targeted therapies. CTLA4 haploinsufficiency with autoimmune infiltration (CHA) and LRBA deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy (LATAIE) are recently described disorders characterized by profound autoimmunity. These patients also develop severe autoimmune neurologic disease and inflammatory bowel disease. As LRBA regulates CTLA4, patients with CHA and LATAIE have been shown to benefit from the CTLA4 agonist, abatacept.

In summary, several recent studies have established it is crucial that children and young adult patients with multilocal autoimmune cytopenias or chronic single-lineage autoimmune cytopenias with either recurrent infections, lymphoproliferation, or autoimmune disease in other organ systems receive comprehensive genomic profiling if functional, immunologic, and clinical testing fail to identify a definitive diagnosis. These patients need genetic counseling and often benefit from a precision medicine approach with targeted therapies.

4. Bode JL, Vincent T, Smith-Whitley K, et al. Immunodeficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy (LATAIE) is a recently described disorder characterized by profound autoimmunity. These patients also develop severe autoimmune neurologic disease and inflammatory bowel disease. As LRBA regulates CTLA4, patients with CHA and LATAIE have been shown to benefit from the CTLA4 agonist, abatacept.

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Immunotherapy in Multiple Myeloma: The Era of CAR T Cell Therapy


For more than a decade, the standard of care for treating multiple myeloma included novel therapeutic agents with the use of immunomodulatory drugs (IMIDs) and proteasome inhibitors along with autologous hematopoietic cell transplantation (AUTO or ASCT).1 However, recent advances in immunotherapy have paved the way to develop novel agents that re-educate the immune system to effectively target the tumor clone. Chimeric antigen receptor (CAR) T cell therapy2-5 reprograms the patient’s T cells to target tumor-associated antigens such as CD19 as in the case of the recently U.S. Food and Drug Administration-approved CAR T cell therapies.6-8 Tiag-srcelcecel for recurrent pediatric acute lymphoblastic leukemia (ALL) and axacatigene ciloleucel for certain recurrent adult B cell lymphomas.

After the great success of CAR T cell therapy in ALL, more research is currently underway to extend this treatment to other hematologic malignancies, including chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). There are currently 27 registered CAR T clinical trials, 20 of which are specific for MM and 16 of which are in the United States alone.9 Similar to other hematologic malignancies, CAR T cell therapy in MM began with targeting CD19, which unfortunately did not yield a sustained clinical response following ASCI7 likely because of the low expression of CD19 on the surface of MM cells. Similarly, targeting CD138,10 and the kappa light chain of plasma cells led to modest responses owing to low potency and inability of plasma cells to retain surface expression of immunoglobulins, respectively.

Current studies and clinical trials are focused on targeting BCMA, a TNF receptor superfamily 17, that is exclusively upregulated in B cells differentiating into plasma cells.11 After the first BCMA CAR T cell therapy clinical trial was conducted with promising outcomes,9 other trials targeting the same antigen followed suit. A single-arm clinical trial on BCMA CAR T cell therapy in relapsed/refractory MM presented its results at the 2017 American Society of Clinical Oncology (ASCO) meeting indicating that 19 patients with a median infusion number of 4.7 (0.6-7.0) × 10^6/kg, achieved complete remission (CR) throughout a median follow-up of 208 (62-321) days, with the majority (14 of 19) experiencing manageable cytokine release syndrome (CRS).12

Most notable perhaps, is the recent phase I clinical trial published by Dr. Jesus Berdeja and colleagues, which revealed that 15 (71%) of 21 MM patients who failed a median of seven lines of treatment experienced CRS following CAR T cell infusion. In this study, the authors used bb2121, a novel CAR that incorporates an anti-BCMA single-chain variable fragment, a 4-1BB costimulatory motif, and a CD3-zeta T cell activation domain. Moreover, from 16 of 18 patients who received a fixed infusion dose, a good treatment response was observed in 17, with achieving CR at a median follow-up of 40 weeks. This sparked the launch of the phase II KarMMa trial to investigate the difference in response to an infusion of 150 versus 300 million CAR T cells.

From there, mechanisms of relapse and resistance to anti-BCMA CAR T cell therapy, and the possibility of devising a potent combination of CAR T cells and a chemotherapeutic regimen require further study. Another study presented at the 2017 ASH Annual Meeting compared the response of high refractory MM patients with high-risk cytogenetics to CAR T cells at different infusion dosages with and without lymphodepletion with cyclophosphamide.13 Indeed, they found that a lower infusion dose led to lower response rates and efficacy, while the addition of cyclophosphamide to CAR T cell therapy led to a significant peak expression of MM-specific CAR, which supported a partial or better response. Furthermore, another pilot trial of eight patients simultaneously used both anti-CD19 and BCMA CAR T cells in addition to cyclophosphamide.13 While this study demonstrated clinical benefit and collateral toxicities (CRS and cytokine release syndrome) similar to other trials, the small patient number and short follow-up of four weeks prevents them from drawing concrete conclusions at this point. Yet, this study addresses a main concern, which is the possibility of CAR T–BCMA-mediated immune editing whereby residual MM cells decrease their BCMA expression following CAR T cell infusion, enabling immune evasion. Therefore, using a dual- or even triple-targeting CAR could potentially overcome this problem and enhance the response rate to CAR T cell therapy. To address the issue of CRS, which has been the most significant side effect in all trials, another study presented at the 2017 ASH Annual Meeting demonstrated the possibility of generating CD8+ anti-BCMA CAR T cells via mRNA transfection rather than viral gene transduction that causes uncontrollable and uncontrolled expansion of permanently modified CART cells. The idea was to generate a transgenic and neuroblastoma (SkN) cell line that mimics the desired neuroblastoma cell dependent efficacy in a disseminated human MM model as well as a reduced secretion of interferon-g, a key cytokine in CRS.

The field of immunotherapy in MM is gaining momentum in the direction of CAR T cell therapy, as more preclinical and clinical studies are initiating to study different infusion dosages and drug combinations, as well as single versus multiple CAR specificities. The rare event that we are witnessing a substantial treatment response to CAR T cell therapy in groups of those who have failed a median of six or more lines of treatment predicts the possibility of a revolutionary breakthrough in treatment in MM. It would not be surprising to see this promising treatment being administered in the next few years to treatment-naive newly diagnosed MM cases with high risk features and poor prognosis with current standard of care.

mostly translocation factors (QFAT2, RUNX1, MECOM/EVI1), in 21 (24.4%) of 86 patients. A third cluster included genes primarily involved in ribosome assembly (UB5D1, SPRTP2, DNAJC21, and RPL5) in 12 (14.0%) of 86 patients. DNA damage response genes (ERCC6L2, LIG4, and ATM) were mutated in 11 patients (12.8%).

The authors also correlated the genetic findings with available clinical data and compared this to reports described in the literature associated with the corresponding gene. Many patients found to have causal or likely causal germline mutations in known inherited bone marrow failure syndrome genes lacked prototypical clinical findings of the disorders. Additionally, 23.3 percent of patients found to have causal or likely causal germline mutations initially presented with hematologic signs as adults (20/86 were ≥ 18 years of age). These findings underscore that predicting genotype based on clinical information alone is unreliable. Germline mutations in the SAMD9 and SAMD9L genes, located in tandem on chromosome 7, are associated with a clinical spectrum of autosomal recessive disorders including the MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy), LIG4 ataxia-pancytopenia syndrome, and myelodysplasia and leukemia syndrome with monosomy 7. In the current work, patients with mutations in SAMD9 and SAMD9L typically experienced overt onset severe bone marrow failure with frequent dysplastic features characterized by a monosomy 7 karyotype. Strikingly, in many of these individuals, the cytopsins improved and the monosomy 7 karyotype resolved over time in patients who acquired a somatic mutation leading to replacement of the mutated allele by the wild-type allele, confirming earlier reports of this important finding.

This work extends our understanding of the inherited genetic underpinnings of marrow failure and hematologic malignancy predisposition. The findings affirm that these disorders are indeed heterogeneous, involve mutations in a broad number of genes, and can present in both pediatric and adult patients without classical syndromic findings. Importantly, the data provide clinical rationale to screen broadly for these disorders. The work extends the list of genes more commonly implicated in these inherited disorders to include SAMD9, SAMD9L, MECOM, and ERCC6L2, which were not sequenced in a number of earlier large studies. In this study, variants classified by the American College of Medical Genetics and Genomics criteria as of uncertain significance could be reclassified as “causal or likely causal” based on clinical acumen (roundtable sessions involving bioinformatics specialists, scientists, biologists, and physicians trained in germline syndromes that predispose to hematopoietic malignancies), raising a concern for the reproducibility of variant classification and providing strong support for ongoing efforts in the field to more systematically collate inherited variants conferring risk to myeloid malignancies. An additional clinical pearl to take away from this meaningful work is the importance of a constitutional DNA source for testing and parental testing in these disorders to exclude the possibility of hematopoietic reversion (observed in patients with mutations in SAMD9 and SAMD9) or somatic mutations.


Production of Chimeric Antigen Receptor T Cells

cells, monocyttes, and neutrophils, but in much lower numbers. In the presence of B-ALL and tumor antigen, there is a resultant proliferation of these anti-CD19 CAR T cells with high-level expression of the anti-CD19 CAR. Using a luciferase reporter, CAR T cells were visualized within the spleen by day 3 and in the bone marrow and lymph nodes shortly thereafter. CAR T cell levels peak between days 6 and 12. Both the MTAS/NSL peptides and transposon/ transposase elements were necessary for these findings. In contrast to the CAR T cells that are generated, only 1 percent of off-target cell populations express the anti-CD19 CAR, and this fraction decreases throughout the first 12 days following infusion while CAR T cell levels are increasing.

While the ability to generate CAR T cells in vivo is an elegant and incredibly innovative way to overcome the potentially rate-limiting manufacturing times needed for the current ex vivo technologies, it needs to maintain, or improve upon, the efficacy of conventional CAR T cell technologies to become a meaningful clinical therapy. Dr. Smith and colleagues were able to demonstrate antitumor efficacy in mouse models of B-ALL using their anti-CD19/4-1BB CAR, similar to that seen with conventional CAR T cell treatment, with both groups yielding significantly improved survivals compared with negative controls. What remains to be seen is whether this technology will be effective in generating CAR T cells in humans, whether the response rates and durability of responses will be comparable to those seen with conventional CAR T cell therapies, and whether there is an unforeseen safety issue due to off-target nanoparticle binding and CAR expression. If successful, however, in phase I clinical trials, this technology would be transformative, allowing for the immediate treatment of patients, greatly expanding the applicability of this technology to patients in whom progression during manufacturing would otherwise be rendered too sick for eventual therapy.

Together Not Apart: Combining Ibrutinib and Venetoclax Therapy in Chronic Lymphocytic Leukemia

**Study Title:** CLARITY: Assessment of Venetoclax (ABT-199) in Combination With Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia

**ISRCTN Number:** ISRCTN13751862

**Sponsor:** University of Birmingham, United Kingdom

**ACCRUAL GOAL:** 55

**PARTICIPATING CENTERS:** Eight centers within the United Kingdom

**STUDY DESIGN:** This was a single-arm study for patients with relapsed or refractory chronic lymphocytic leukemia (CLL), defined as failure to respond to, or relapse within six months of, a purine analogue alone or with chemotherapy; relapse within three years after Budaarzine, cyclophosphamide, and rituximab or bendamustine and rituximab; or with del(17p) and failed at least one line of therapy. Patients must not have had previous treatment with Bruton tyrosine kinase (BTK) inhibitor (BTKi) or venetoclax (VEN). Treatment consists of eight weeks of IBR monotherapy (420 mg/day) followed by the addition of weekly escalating doses of VEN from 10 mg/day until a final dose of 400 mg/day.

**PRIMARY ENDPOINT:** Eradication of minimal residual disease (MRD) within bone marrow (BM) defined as less than 0.01 percent CLL cells in BM after 12 months of treatment.

**SECONDARY ENDPOINTS:** BM MRD after six and 24 months, overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events/serious adverse events (AEs/SAES).

**RATIONALE:** Eradication of MRD is associated with improved outcome in chronic lymphocytic leukemia (CLL) and, importantly, this is observed regardless of the therapy used to achieve it. Ibrutinib, which inhibits the BTK enzyme, and VEN, an oral Bcl-2 inhibitor, are both highly active in CLL and are used typically in sequential fashion. Although the drugs have different primary mechanisms of action, IBR also reduces the level of anti-apoptotic molecules and might potentiate the effect of VEN. This trial aims to test this hypothesis by combining ibritnib with venetoclax. Researchers want to see whether the combination is superior to historical experience of either drug alone in patients with relapsed/refractory CLL.

**COMMENT:** Treatment of CLL has been transformed within the past five years. Although combination treatment with chemotherapy and an anti-CD20 antibody remains the first-line option for most patients, the development of ibritnib, idelalisib, and venetoclax has led many hematologists to wonder how long they must continue to prescribe chemotherapy. Nevertheless, these new agents have almost always been used as monotherapy in combination with the anti-CD20 antibody rituximab. The CLARITY trial, which is part of the Trials Acceleratingand Prolonging Survival funded by the charity Bloodwise, uses the oral agents ibritnib and venetoclax in combination.

This principle would seem to make a lot of sense. Ibrutinib rapidly reduces nodal disease and redistributes CLL into the peripheral blood, whereas venetoclax leads to depletion of CLL in circulation and in the bone marrow. Ibrutinib’s effect on molecules such as MCL1 may also theoretically potentiate the effect of venetoclax. Additionally, venetoclax is associated with a risk of tumor lysis syndrome, and the CLARITY trial introduces ibritnib at full dose of 420 mg/day for eight weeks prior to the introduction of venetoclax. Venetoclax is then increased weekly from an initial 20 mg/day dose to the full dose of 400 mg/day, in its typical “ramp up” regimen.

As currently tested, ibritnib must be taken continuously, which is both costly and challenging for patient compliance. This study has the advantage of, in certain patients, allowing for discontinuation—a benefit with downstream cost savings. Venetoclax is also highly effective for many patients but is most effective in combination therapy. Its use with ibritnib offers the potential to avoid the need for anti-CD20 monoclonal antibodies and attendant visits to the day unit. A combination of two novel oral agents may also serve as an exciting platform for next-generation protocols.

Academic arguments aside, how did this combination therapy perform in clinical practice? The answer is that it performed very well indeed, and the results augur positively for future therapy.

The primary endpoint in the study was the clearance of MRD. Not many centers currently use MRD to guide the management of CLL, but this is likely to change as evidence accumulates about its predictive power. The two main technologies for measuring MRD are eight-color flow cytometry and polymerase chain reaction, and the former was used in this study with a sensitivity of one tumor cell per 10,000 cells.

Assessment after the first six months of combination therapy in 38 patients was reported at the 2017 ASH Annual Meeting. All patients showed a response, and complete responses were seen in 47 percent, with the remaining partial remissions reflecting only residual modest lymphadenopathy. Importantly, 32 percent of patients were MRD-negative within the bone marrow at that time.

Venetoclax was given for a maximum of two years, and ibritnib continues for those who remain MRD-positive after this period. However, both drugs are stopped if patients can achieve MRD negativity; the study incorporated a novel stratification based on the time taken for individual patients to reach MRD.

Specifically, after reaching MRD, patients continue dual therapy for the same duration of time as it took them to achieve it. For instance, those who are MRD-negative after six months have three months of combination ibritnib and venetoclax. This group also observed that MRD-negative within the bone marrow at that time.

In relation to side effects, biochemical tumor lysis syndrome was noted in two patients as a rise in phosphate level and resolved with short-term venetoclax discontinuation, before escalation to full dose. Neutropenia is a recognized side effect of venetoclax, but although grade 3 or 4 suppression was observed in around 40 percent of patients, this did not translate into a high incidence of infectious complications.

Similar findings have been reported by Dr. Nitin Jain and colleagues from the MD Anderson Cancer Center, who also noted that 8 percent of patients became MRD-negative after only three months of combination therapy. This group also included a cohort of treatment-naive patients, and although patient numbers are currently modest, they observed a rate of 80 percent MRD negativity after nine months of therapy. Obinutuzumab will also be sidelined, and combination therapy with either venetoclax or ibritnib/venetoclax is achieving impressive MRD rates in treatment-naive patients.

Data of this sort are now encouraging combination therapy with ibritnib and venetoclax for large-scale studies for first-line therapy of CLL. It is likely that relatively short-term treatment will drive patients into a deep MRD, and the ultimate hope is that this may translate into effective “cure” of disease. Whether the immune system can then suppress such low levels of disease, or whether relapse remains inevitable, are important questions to consider. Nevertheless, in the 57 years since David Galton reported on the first use of chlorambucil in CLL, this once relatively unflattering area of hematology is now chasing chronic myeloid leukemia toward eradicate the use of chemotherapy.

**2017 Annual Report: A Year of Growth and Innovation for ASH**

**You can now read the 2017 ASH Annual Report, “A Year of Growth and Innovation,” online. This year’s annual report is delivered in a multimedia format that can be browsed from any computer, smartphone, tablet, or other mobile device.**

The 2017 report explores ASH’s accomplishments in uniting a global community in the shared mission to conquer blood diseases worldwide. ASH encourages all members to delve into this easy-to-use online publication that highlights a wide range of ASH’s successes in 2017, including:

- The development of a patient registry, new guideline development, and the strengthening of the Society’s role regarding precision medicine and immunotherapies.
- The continued success of the Society’s annual meeting and publications such as Blood and Blood Advances.
- ASH’s work with policymakers to advocate for the interests of hematologists.
- ASH’s continuing commitment to supporting trainees and increasing the diversity of the hematology workforce.
- The distinguished recipients of ASH’s honorific and career-enhancement awards.

Lastly, ASH thanks the many generous donors for supporting the Society during 2017. These contributions make it possible to continue to expand efforts to help hematologists conquer blood diseases worldwide.

The full report is available on the ASH website at www.hematology.org/Annual-Report/2017.
Editors’ Choice

FEBRUARY 22, 2018


While it is known that hepcidin increases the ubiquitination and degradation of ferroportin (Fpn), Dr. Sharraya Aschemeyer and colleagues elucidate a novel second mechanism by which hepcidin inhibits Fpn. They demonstrate that hepcidin binding sterically inhibits Fpn’s function as an iron exporter.

FEBRUARY 1, 2018


This study addresses a major gap in our knowledge about the timing of the treatment of patients with relapsed light-chain (AL) amyloidosis. The investigators identify a set of criteria that define hematologic progression with adverse outcomes.


Hepatitis C virus (HCV) infection frequently causes B-cell lymphoproliferative disease and mixed cryoglobulinemia (MC) that can progress to non-Hodgkin lymphoma (NHL). In these studies, the investigators examine B cells in these patients and show that B-cell clonal expansion is common in HCV patients, likely representing a precursor stage to the development of MC and NHL.

FEBRUARY 15, 2018


In a plenary paper that is also this month’s CME article, Dr. Olivier Bluteau and colleagues report whole-exome sequencing on 179 patients with suspected inherited bone marrow failure and identify a diverse range of known and novel mutations.

JANUARY 25, 2018


Both severe congenital neutropenia and Shwachman-Diamond syndrome (SDS) are associated with the development of acute myeloid leukemia (AML). Dr. Jun Xia and colleagues used exome sequencing to demonstrate that clonal hematopoiesis does not reflect an increase in total somatic mutations, but rather the clonal selection of cells carrying specific mutations. They report that over half of patients with SDS carry somatic mutations in TP53, suggesting that acquisition of TP53 mutations is an early event in AML development.

MARCH 15, 2018


This plenary paper changes the approach to the study of the role of protease activated receptors in vivo. The investigators describe the generation of two mouse lines with distinct point mutations in protease-activated receptor 1 (PAR1) that prevent the cleavage of the receptor by either thrombin or activated protein C.

MARCH 22, 2018


In this consensus document, the authors discuss the complex technical issues and scientific challenges of optimizing the use of measurable residual disease (MRD) to prognosticate outcomes in acute myeloid leukemia (AML).


Dr. Elena Tholouli and colleagues report excellent outcomes with reduced-intensity conditioning (RIC) transplantation in four patients with GATA2 mutations complicated by life-threatening infections and respiratory complications, suggesting that RIC transplant should be considered even in patients without myelodysplastic syndrome or AML.

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Featured content from Blood Advances, Volume 2, Issue 7

Defective RAB1B-related Megakaryocytic ER-to-Golgi Transport in RUNX1 Haplodeficiency: Impact on von Willebrand Factor (vWF)

In this article, the authors address the hypothesis that RAB1B is a transcriptional target of RUNX1 and that RAB1B regulates ER-to-Golgi transport in MC cells. Chromatin immunoprecipitation studies and electrophoretic mobility shift assay using PMA–treated human erythroblastemia cells revealed RUNX1 binding to RAB1B promoter region RUNX1 consensus sites, and their mutation reduced the promoter activity. RAB1B activity and protein expression were inhibited by RUNX1 siRNA and enhanced by RUNX1 overexpression. These indicate that RAB1B is a direct RUNX1 target, providing a mechanism for decreased RAB1B in patient platelets. Vesicle trafficking from ER to Golgi in PMA-treated human erythroblastemia cells was impaired along with Golgi disruption on siRNA downregulation of RUNX1 or RAB1B. The effects of RUNX1 knockdown were reversed by RAB1B reconstitution. Trafficking of vWF was impaired with RUNX1 or RAB1B downregulation and reconstituted by ectopic RAB1B expression. Platelet vWF was decreased in patients with RUNX1 mutations. Thus, ER-to-Golgi transport, an early critical step in protein trafficking to granules, is impaired in megakaryocytic cells on RUNX1 downregulation, secondary to decreased RAB1B expression. Impaired RAB1B mediated ER-to-Golgi transport contributes to platelet α-granule defects in RUNX1 haplodeficiency.

Key Dates and Deadlines for the 2018 ASH Annual Meeting

This year’s meeting will take place December 1-4, 2018, at the San Diego Convention Center, and will feature the latest breakthroughs in hematology while connecting and convening the global hematology community. Numerous key dates for abstract submission and registration are right around the corner. See below for more information, and mark your calendar!

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<th>Event</th>
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<tr>
<td>Abstract submission site opens</td>
<td>June 5, 2018</td>
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<tr>
<td>ASH Foundation Run/Walk registration opens</td>
<td>July 5, 2018, 11:00 a.m. Eastern time</td>
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<td>Member-only registration and housing opens</td>
<td>July 18, 2018, 11:00 a.m. Eastern time</td>
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<tr>
<td>Abstract submission deadline</td>
<td>August 1, 2018, 11:59 p.m. Pacific time</td>
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<td>Advance registration and housing opens for ASH members and non-members</td>
<td>August 8, 2018, 11:00 a.m. Eastern time</td>
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<td>Call for late-breaking abstract submissions</td>
<td>October 22-31, 2018</td>
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<tr>
<td>Advance registration deadline</td>
<td>October 31, 2018, 11:59 p.m. Pacific time</td>
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<td>Abstracts available online</td>
<td>November 1, 2018, 9:00 a.m. Eastern time</td>
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Visit the www.hematology.org/Annual-Meeting for the latest information on abstract submission, registration information, and details about new events and activities forthcoming in San Diego.

ASH News Daily Call for Authors

ASH is in search of the next team of authors for the 2018 ASH News Daily. If you are an ASH member (MD or PhD) who has a passion for writing as great as your love for hematology, you may be just the right fit. Ideal candidates are proficient, published writers (please send at least two clips) who are curious about, and willing to cover, areas outside their comfort zone. You must be able to attend the annual meeting in December, as well as one in-person board meeting in late September.

We are also seeking those who:
- Have a flexible schedule at the annual meeting and are great at time management
- Enjoy science writing and can also apply a creative approach to it
- Are cognizant of timelines and are dependable with schedules and firm deadlines
- Enjoy networking and doing author outreach
- Are mid-career professionals interested in becoming more involved with ASH.

If this sounds like you or a colleague you wish to nominate, please email Managing Editor Juana Llorens (jllorens@hematology.org).

Required materials include a letter of interest, two writing samples, and a CV. Materials are due by June 15, 2018. For more information on ASH News Daily, visit (www.hematology.org/Annual-Meeting/AND.aspx).