Human embryonic stem (ES) cells are derived from early embryos and are capable of differentiating into all tissues. Although they are excellent tools for research and have broad therapeutic promise, their procurement, manipulation, and use raise major ethical issues.

The International Society of Stem Cell Research (ISSCR) accepted the challenge of analyzing these concerns and of writing guidelines for the conduct of human ES cell research. Their thoughtful document was reviewed by ASH’s Scientific Committee on Stem Cells and its Committee on Government Affairs, and has been formally endorsed by the Executive Committee. It is available online at www.isscr.org/guidelines/index.htm and as a link from the ASH Web site.

Human ES cell research may lead to novel therapies for genetic, malignant, and degenerative disorders. Theoretically, one could construct replacement cells for blood, skin, pancreas, or other tissues. Also, studies of ES cell lines derived from diseased embryos could provide new insights into the pathophysiology of immune diseases.

The current method for matching these haplotypes is defined by interrogating only about 18,000 base pairs and therefore cannot define extended haplotypes (the intervening genes between the HLA alleles). However, the whole MHC region contains more than 400 genes within the 7.6 million base pairs that have immune-related functions and the total numbers of transplantation antigens encoded in this region is unknown.

In this paper, Petersdorf et al. describe a novel DNA microarray method to isolate DNA strands extending across two million base pairs of the MHC to determine the physical linkage of HLA-A, B, and DRB1. The hope was that this method could identify genes that influence transplantation outcomes if the extended haplotypes of the unrelated donor and recipient could not be defined. Two hundred and forty-six HCT recipients and their donors who were HLA matched by current methods were patients with hematologic malignancies and myelodysplasia.
Despite the tremendous progress in basic hematologic research, there is a shortage of trained hematologists, especially in adult medicine, to care for patients with non-malignant blood disorders. Ellen Werner, PhD, Acting Deputy Chief of the Blood Diseases Branch who oversees these awards, recalled the origins of this K12 program. “The articles by Todd et al. in Blood 2003 and Bob Handin in ASH News Spring 2002 certainly caught our attention. They helped validate our concern about the ‘small numbers of trainees who…pursue careers in non-malignant hematology.’ In consultation with Harvey Lukensenburg, MD, a BBDR Medical Officer and hematologist, we took the concept for this program to the NHLBI Board of Extramural Advisors and Advisory Council for their approval. Both agreed that basic research findings in hematology are ready for translation, but there are insufficient numbers of non-malignant hematologists who can apply these findings in clinical settings and research.”

The program defines non-malignant hematology broadly. For example, it includes aplastic and hemolytic anemias, hemoglobinopathies, disorders of hemostasis or thrombophilia, myeloproliferative disorders, and myelodysplastic syndromes. Although myeloproliferative disorders and myelodysplastic syndromes are pre-malignant, and could be considered “malignant,” they are included as disorders for which a hematologist would usually be consulted. The program combines specialized clinical training and coursework in clinical research methodologies with a mentored clinical research project, over two or three years. At many of the participating centers, the coursework can be applied toward a Master of Science degree in clinical investigation, epidemiology, or a related field. The Program Directors have flexibility to customize the curriculum, depending on the experience and training of each Scholar.

The centerpiece of the program is the mentored clinical research experience, which allows Scholars to develop their clinical research skills with oversight by two faculty mentors. With this foundation of experience and publications, graduates are expected to be strong applicants for independent research funding through the NIH Mentor Patient-Oriented Research Career Development (K23) or Research Project Grant (R01) mechanisms.

Eligible candidates include physicians in the later years of fellowship training, or newly appointed faculty, who are U.S. citizens or permanent residents. Non-physicians with a PhD degree also may apply if they have previous clinical hematologic research experience. Funding includes salary support of up to $75,000 plus fringe benefits and $30,000 annually for research expenses, travel, and tuition. In addition, Scholars are assured of being able to participate fully in clinical research — at least 75 percent of their time must be devoted to the program. Mentors also receive 5 percent salary support and funds to travel to an annual grantees’ meeting at NIH. Financial support for faculty mentors is a unique feature of this K12 program.

“This allocation shows NHLBI’s commitment to mentorship,” says Dr. Werner.

Across the country the program has so far enrolled eight Scholars with diverse backgrounds that include prior experience in adult or pediatric hematology-oncology and transfusion medicine. Another round of applications will be reviewed this fall, to start the program in January or July of 2008. Approximately six new Scholars will be accepted each year. Meanwhile, plans are being finalized for the first annual grantees’ meeting at NIH, which will include Program Directors, current Scholars, mentors, and NHLBI staff to hear about ongoing clinical research and share information.

The impact of this career development program won’t be known for some time, but it seems likely to increase the visibility of academic careers in non-malignant hematologic research. Many young physicians find traditional hematologic very interesting but often have difficulty visualizing a career in the field in comparison to other directions of specialization. The program provides more structure to the transition between fellowship training and faculty appointment, which should help to attract scientists who otherwise would have taken a different path. If successful, the program may reduce the mismatch between the relatively small number of trained hematologists and the many opportunities for research and clinical care in non-malignant hematologic.

Participating institutions and Program Directors are: Washington University (J. Evan Sadler, MD, PhD), Harvard University (Ellis Neufeld, MD, PhD), Duke University/University of North Carolina at Chapel Hill (Marilyn J. Telen, MD), Johns Hopkins University (James F. Casella, MD), University of Washington (Janis L. Abkowitz, MD), and University of Pennsylvania (Barbara A. Konkle, MD). Several of the programs have Web sites that provide more information.

References cited by Dr. Werner:


Handin RI. Whither the practice of hematology? Or should it be wither? ASH News Spring 2002; 2-4.
Online Early-Bird Registration and Housing for the 49th ASH Annual Meeting

ASH members who have paid their dues for 2007 are eligible for online early-bird registration from July 17 - August 6. This member benefit allows ASH members in good standing to register for the 2007 annual meeting and make hotel reservations online via the ASH Web site (www.hematology.org) before the general public. Please note that one must register for the annual meeting before making a hotel reservation.

Online Early-Bird Registration Fees
ASH Members (Active and International): $195
ASH Associate Members : $90
Honorary/Emeritus: No charge

On-Site Registration Fees
ASH Members (Active and International): $275
ASH Associate Members : $90
Honorary/Emeritus: No charge

Deadline Approaching for the EHA-ASH International Fellowship Award

The EHA-ASH International Fellowship Award is a partnership between the American Society of Hematology (ASH) and the European Hematology Association (EHA) that gives hematologists early in their training or in their careers the opportunity to establish new collaborations and experience research (both clinical and laboratory-based) in a different environment. The letter-of-intent deadline for the 2007 award is September 4. To learn more about this program, including eligibility requirements, visit the ASH Web site at www.hematology.org.

ASH Members Elected to The National Academy of Sciences

Brian J. Druker
Investigator, Howard Hughes Medical Institute, and JELD-WEN Chair of Leukemia Research, Oregon Health & Science University

David Ginsburg
Investigator, Howard Hughes Medical Institute, and James V. Neel Distinguished University Professor, University of Michigan Medical School

Leadership Election
Ballots to Mail in August

Active members in good standing should look to receive election materials by mail in late August for this year’s ASH leadership election for Vice President and two Councillors. Ballots are due by September 30, and the results of the election will be announced in the November/December issue of The Hematologist.

2007 ASH Abstract Submission Deadline

Abstracts for the 2007 ASH Annual Meeting are being accepted through August 21. To review the submission rules and submit your abstract, visit the ASH Web site and use the electronic submission program. All abstracts submitted by August 21 will be considered for presentation at the meeting, being held December 8-11, 2007, in Atlanta, GA.

Visit the ASH Web site www.hematology.org to note the changes to the abstracts process and get the most up-to-date information on the 49th ASH Annual Meeting and Exposition.
ASH Endorses Ethical Guidelines for Human Embryonic Stem Cell Research

(Cont. from Page 1)

Fanconi anemia, thalassemia, sickle cell disease, and other genetic disorders, or be used to test drug therapies. This promise has led to both excitement and unrealistic expectations since many scientific obstacles remain. For example, we need methods to ensure that the mature cells generated in vitro have normal function and retain genetic integrity before these applications are feasible.

Furthermore, there are major ethical obstacles to human ES cell research since ES cells derive from the inner cell mass of blastocysts (an early embryo). If left in situ, adjacent to the trophoectoderm, these cells could implant in the uterus and develop into a fetus and child. However, when removed at this early stage, they lose this fate and if transplanted can only give rise to teratomas (a disorganized differentiating cell body). For an investigator, it is often difficult to navigate the hype, scientific reality, political reality, and ethical issues implicit in human ES cell research.

The goal of the ISSCR guidelines was to clearly articulate principles and rules of behavior and thus to facilitate the ethical conduct of this research.

The guidelines specifically state that scientific trainees and technical staff with conscientious objection to human ES cell research should not be required to participate in the research or cell procurement. They prohibit human reproductive cloning (defined as seeking to establish a pregnancy and birth by the transfer into the uterus of human embryos derived from nuclear transfer or nuclear reprogramming). In addition, they prohibit the culture of human embryos beyond 14 days or the time of formation of the primitive embryonic streak, the step that triggers organogenesis.

One important strength of the guidelines is the authors’ insistence that all terms are precise and accurate. Because of this, the position and intent of the document are clear. The accompanying glossary of terms is written in simple, accurate language. This and the answers to frequently asked questions (FAQ, www.isscr.org/public/index.htm) may also be helpful to ASH members.

The ISSCR guidelines are comprehensive. They cover aspects of human ES cell research ranging from establishment of human ES cell lines, the distribution and sharing of materials among scientists, the need for informed consent at the time of donation and not afterwards, and the understanding that consent must be voluntary, explicit, and free of financial inducement or other coercion to facilitate the ethical conduct of this research.

Sample consent forms for the donation of oocytes, embryos, somatic cells, and sperm are provided. To facilitate the exchange of research materials among scientists, sample material transfer agreements are also provided.

The ISSCR guidelines were written by scientists, lawyers, and ethicists from 14 countries. It is not surprising that ASH members had prominent roles. George Daley, MD, PhD (Children’s Hospital, Boston), chaired the ISSCR guidelines committee and authored the accompanying manuscript in Science that discusses the differences between these guidelines and recent documents by the U.S. National Academy of Sciences and the California Institute for Regenerative Medicine. The current president, immediate past president, and vice president of the ISSCR are ASH members.

It is likely that the ISSCR guidelines will be an excellent resource for ASH members. It should be a useful document for investigators and for institutions involved in the oversight of human ES cell research as it is comprehensive and pragmatic. It is also excellent reading for a concerned practitioner who wants a clear, conceptual understanding of the ethical challenges of human ES cell research to share with family, friends, or patients.

References:

VENOUS THROMBOEMBOLISM (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs with an annual incidence of about 1 in 1,000 adults. The rates increase after the age of 45 years and are slightly higher in men than in women. Major risk factors for VTE include exogenous factors (such as surgery, immobility, trauma, pregnancy and the puerperium, and hormone use) as well as endogenous factors (such as cancer, obesity, and congenital or acquired thrombophilic disorders). Each year, it is estimated that approximately two million Americans have a DVT episode, which is complicated by PE in about 600,000. The PE is fatal in over 200,000 each year. Therefore, the annual mortality rate from VTE is higher than that for breast cancer and AIDS combined.

At least 50 percent of the cases of VTE occur in hospitalized patients, or in those who were in the hospital in the past three months. Half of these patients are hospitalized with medical problems, while the surgical population accounts for the remainder. Particularly susceptible are the elderly, patients in intensive care, and those with cancer or previous VTE. Most episodes of PE arise from DVT in the legs, which is often clinically silent. Therefore, prevention is critical. Although VTE is the third most common cause of death in hospitalized patients, it is the number one preventable cause of death in these individuals.

WHAT ARE WE DOING TO INCREASE AWARENESS ABOUT VTE, OPTIMIZE PREVENTION, AND IMPROVE TREATMENT?

Advances have occurred on all three fronts. First, building on a two-day workshop convened in May 2006 by the Surgeon General’s office and the National Heart, Lung, and Blood Institute, there will be a Call-to-Action paper from the National Heart, Lung, and Blood Institute, there will be a Call-to-Action paper from the Surgeon General. A major impetus behind this call to action is a push for increased VTE awareness among healthcare workers and patients. This initiative also is likely to provide new opportunities for research into the pathogenesis, prevention, and treatment of VTE.

WHAT IS HAPPENING TO OPTIMIZE PREVENTION OF VTE?

The National Quality Forum has developed national consensus standards for VTE prevention in healthcare settings. These include standardized VTE risk assessment for all hospitalized patients and utilization of risk-appropriate thromboprophylaxis. Coupled to these recommendations is a framework for measuring the effectiveness of VTE prophylaxis, developed through the Joint Commission on Accreditation of Healthcare Organizations (see www.jointcommission.org). Hospital reimbursement will be linked to performance, and performance measures for each hospital will be posted on accessible Web sites, such as those of the Leapfrog Group (www.leapfroggroup.org).

Finally, what advances have occurred in the treatment of VTE? Management of VTE in cancer patients has been streamlined through the recent FDA approval of dalteparin for extended treatment. Cancer and its treatment place patients at risk for VTE. Warfarin can be problematic in this setting because hepatic metastases, concomitant medications, and gastrointestinal disturbances complicate dosing, whereas limited venous access renders coagulation monitoring difficult. Interruption of treatment for invasive procedures or because of chemotherapy-induced thrombocytopenia further complicates warfarin treatment. Finally, recurrent VTE can occur in up to 20 percent of warfarin-treated cancer patients despite a therapeutic INR.

In the CLOT trial, cancer patients with symptomatic VTE were all treated with dalteparin (at a once-daily dose of 200 U/kg) for at least five days. They were then randomized to continued dalteparin (at a once-daily dose of 200 U/kg for the first month and 150 U/kg thereafter) or to warfarin (with doses adjusted to achieve a target international normalized ratio of 2 to 3) for six months. The risk of recurrent VTE was significantly lower with dalteparin than with warfarin (9 percent and 17 percent, respectively; p = 0.002), while the risk of major bleeding was not significantly different (6 percent and 4 percent, respectively).

VTE remains a common and largely preventable healthcare problem. Increased awareness, better use of appropriate thromboprophylaxis for hospitalized patients, and improved treatment for cancer patients with VTE will help to reduce the disease burden.

REFERENCES:


PQRI Begins with a Bonus Payment for Medicare Fee Schedule Services

The Centers for Medicare and Medicaid Services (CMS) will begin implementing the Physician Quality Reporting Initiative (PQRI) on July 1. This program provides a financial incentive for physicians to participate in a voluntary quality reporting program. Eligible professionals who successfully report a designated set of quality measures on claims for dates of service from July 1 to December 31, 2007, may earn a bonus payment from Medicare — subject to a cap — of 1.5 percent of total allowed charges for covered Medicare physician fee schedule services. Four hematology-related performance measures developed by ASH are included in the 74 measures for the 2007 program.

While physicians do not need to register for this program, to participate and file claims physicians must have a National Provider Identifier (NPI). The NPI is a unique identification number for covered health-care providers. Covered health-care providers and all health plans and health-care clearinghouses will use the NPIs in the administrative and financial transactions adopted under HIPAA. The NPI is a 10-position, intelligence-free numeric identifier (10-digit number). This means that the numbers do not carry other information about health-care providers, such as the state in which they live or their medical specialty. Beginning May 23, 2007 (May 23, 2008, for small health plans), the NPI must be used in lieu of legacy provider identifiers in the HIPAA standards transactions.

ASH has developed special online resources to help guide practitioners through the PQRI, including obtaining an NPI, which are available on the ASH Web site at www.hematology.org/policy/resources/pqri. This includes specific information about:

- What measures are available for hematologists
- How to report measures
- What the reporting requirements are
- How to receive the incentive payment

Checklist for Hematologists to Participate in PQRI

- Get your NPI
- Bookmark ASH’s PQRI resources Web page (www.hematology.org/policy/resources/pqri)
- Check it often
- Understand the measures
- Educate office billing staff

ASH NEWS AND REPORTS

Kerry Weems Nominated to Head Medicare Agency

On May 3, President Bush nominated Kerry Weems to head the Centers for Medicare and Medicaid Services (CMS). Weems has been with the Department of Health and Human Services for twenty-four years and currently serves as the agency’s deputy chief of staff. The current Acting Administrator of CMS, Leslie Norwalk, Esq., said that she had asked early on not to be considered to permanently replace CMS’s previous director, Dr. Mark McClellan, who left the agency in October. In a statement, HHS Secretary Michael O. Leavitt said that Weems “understands the large fiscal challenges facing Medicare and Medicaid and what it will take to strengthen and sustain those programs for the future.”

Congress Moves Forward with Funding Bills; ASH Continues Efforts to Increase Funding for NIH in FY 2008

ASH, along with the biomedical research community, continues to advocate for an increase of 6.7 percent for FY 2008 over the final FY 2007 levels, despite a proposed budget from the White House for FY 2008 that includes cuts totaling $310 million for the National Institutes of Health (NIH). ASH co-signed a letter with several hundred other organizations to the Chairmen of the House and Senate Appropriations Committees requesting increased funding in FY 2008 for federal health programs.

As a result of these efforts and grassroots advocacy from within the biomedical research community, support within Congress to increase funding for NIH continues to gain momentum. A letter to the House Labor-HHS Appropriations Subcommittee in support of this 6.7 percent increase for NIH was cosigned by 182 members of the House. An identical letter to the Senate Appropriations Committee generated the support of 48 Senators.

As this issue of The Hematologist went to press, Congressional leaders in the House remained hopeful that the House would be able to consider all 12 of the annual spending bills by the end of June, while the Senate hoped to complete action on its versions of the bills prior to the month-long August congressional recess.

ASH will continue its NIH advocacy efforts on Capitol Hill in the FY 2008 budget debate. With a very tight year expected for the entire federal budget, continued grassroots support for NIH funding is critical to gain any traction in the budget process. Please visit the ASH Web site at www.hematology.org for the most up-to-date information about NIH funding.

Medicare Proposes Coverage Policy for ESAs

ASH submitted comments to the Centers for Medicare and Medicaid Services (CMS) and local carriers concerning the development of a Medicare coverage policy for darbepoetin alfa and epoetin alfa after recent studies linked the treatments with increased risk for serious side effects. Of particular concern to ASH are potential restrictions in the use of ESAs for treatment of anemia in patients with hematologic malignancies who are not undergoing chemotherapy. ASH’s comments indicate that there are data to support the use of ESAs in patients with anemia associated with low-risk myelodysplasia. ASH also recommended further studies into the use of ESAs to treat anemic patients with hematologic malignancies, and in the meantime recommended that coverage of these patients should be decided on a case-by-case basis. ASH also presented comments to the FDA’s Oncologic Drugs Advisory Committee (ODAC) on May 10, 2007.

CMS Revises Medicare Clinical Research Policy

The Centers for Medicare and Medicaid Services (CMS) has proposed new rules to govern Medicare coverage of services provided to beneficiaries enrolled in clinical research studies. Since the September 2000 issuance of a National Coverage Decision, Medicare has paid for the routine costs of beneficiaries enrolled in qualifying clinical trials. The revised policy would, among its many provisions, pay for investigational treatments and services if they are covered by Medicare or the beneficiary’s clinical trial or are required in order to manage the patient’s health within the study.

ASH’s comments focused on concerns about the new requirements for public release of research study information, the generalization of studies to the Medicare population, and self-certification and deeming.

It is expected that CMS will issue a final version of the revised Clinical Research Policy by mid-July. For more information, see the article, “Changes Afoot for the Medicare National Clinical Research Policy” on page 15.
Exploiting the Innate Antitumor Properties of γδ-T Cells for the Immunotherapy of Human Cancers

RICHARD LOPEZ, MD

A number of reports have since established that human γδ-T cells can recognize and kill human malignant cells of epithelial origin including breast, prostate, ovarian, colorectal, and renal cell carcinomas. It has also been established that human γδ-T cells can recognize and kill malignant cells of hematolymphoid origin. These and related findings have provided the pre-clinical and clinical rationale for the design of studies to examine how human γδ-T cells might be exploited for the treatment of a wide range of cancers.

In Vitro Antitumor Activity of Human γδ-T Cells

A number of reports have since established that human γδ-T cells can indeed recognize and kill human malignant cells of epithelial origin including breast, prostate, ovarian, colorectal, and renal cell carcinomas. It has also been established that human γδ-T cells can recognize and kill malignant cells of hematolymphoid origin. These and related findings have provided the pre-clinical and clinical rationale for the design of studies to examine how human γδ-T cells might be exploited for the treatment of a wide range of cancers.

Current State of γδ-T Cell-Based Immunotherapy for Cancer

It is now recognized that either synthetic phosphoantigens or aminophosphonomocates can stimulate human γδ-T cells leading to their expansion and activation in vitro and in vivo. Importantly, human γδ-T cells exposed to these compounds appear to retain potentially clinically useful antitumor activity against human cancer cells. As recently reported, SCID mice harboring human cancer cells were found to have reduced tumor burdens and prolonged survival when treated with human γδ-T cells first expanded ex vivo using the aminophosphonate alendronate (Fosomax®). These and related findings have since led others to initiate early-phase clinical trials to assess how aminophosphonates and related compounds might be used to activate and/or expand tumor-reactive human γδ-T cells for clinical use. Additional approaches designed to ex vivo expand γδ-T cells are also being actively developed and will soon be examined in phase I clinical trials at our institution.

Open Questions for Future Investigation

From an immunotherapy perspective, a number of unanswered questions remain. Presuming that large numbers of autologous γδ-T cells can reliably be obtained from patients, will re-infusing these cells restore or augment immune responses against tumor? More precisely, will the reintroduction of large numbers of autologous γδ-T cells have any moderating effect on tumor growth or progression — or likelihood of relapse if used in an adjuvant setting? Should γδ-T cells be utilized alone or will they best be utilized in conjunction with standard chemothera-py or radiation-based treatments? Which diseases respond best to γδ-T cell-based therapies? These and related questions can only be addressed in ongoing or future clinical trials.

In addition, while the above discussion focuses on the adoptive transfer of autologous (patient-derived) γδ-T cells as a form of immunotherapy for malignancies, from a conceptual point of view, the transfer of allogeneic tumor-reactive γδ-T cells must also be considered. This is especially important if it is found that in patients with malignancies, tumor-reactive γδ-T cells expand poorly — or function poorly — in all but those with early stage disease, thereby precluding the widespread use of autologous γδ-T cell reconstitution strategies. Indeed, it has been reported that significant numeric and functional deficits may exist within the peripheral blood γδ-T cell compartment of patients with certain cancers.

Conclusion

Although the potential promise of γδ-T cell-based immunotherapies is great, major obstacles remain to be negotiated in order for clinical trials to be designed and performed in a feasible and practical manner. Particularly for studies involving the adoptive transfer of γδ-T cells, significant regulatory issues must be addressed as cellular products must be produced and administered in accordance with FDA standards. Related to this point is the requirement that cGMP grade reagents must be used in the expansion and/or purification of γδ-T cells for adoptive transfer making such trials extraordinarily expensive. Nevertheless, despite these challenges, the use of human γδ-T cells for the treatment of cancer is a fertile area for basic and clinical research directed at developing novel immunotherapy-based strategies for the primary or adjuvant treatment of a variety of human malignancies.

Casting the NET to Trap Bacteria

Activation of neutrophils during bacterial sepsis plays a role both in defense against offending organisms and in tissue damage. In this paper, the investigators demonstrate that the interaction of platelets contributes to the untoward effects of neutrophils in this process. More specifically, the investigators establish a role for TLR 4 on platelets through its interaction with ligands that are released during sepsis. Although others were not able to see expression of activation markers or aggregation as a result of TLR 4 expression on platelets, the investigators here demonstrated that LPS does indeed bind to platelets through TLR 4. LPS-treated platelets are able to bind to adherent neutrophils, and binding is blocked by TLR 4-specific antibodies and specific antagonists to the receptor ligand complexes. Plasma from septic patients induced platelet-neutrophil interactions. This could be recapitulated in a mouse model of endotoxemia where neutrophils localized to post sinusoidal venules and platelet-co-localized only when neutrophils were bound. LPS-treated platelets induced neutrophil degranulation and the release of DNA to outside of the cell. This resulted in formation of neutrophil extracellular traps (NETs) that are resistant to shear flow and can trap bacteria under shear flow. The investigators went a step beyond to demonstrate that binding of LPS-activated platelets to neutrophils, but not activation of neutrophils alone, caused endothelial cell injury. Organ damage, as measured by a reduction in liver sinusoid perfusion, was induced by platelet-neutrophil complexes and could be reduced by depletion of neutrophils and, less dramatically, platelets from the site.

The work here addresses several key components in innate immunity that are responsible for tissue damage during sepsis and include the interaction of platelets with neutrophils and the dependence on the deposition of neutrophil extracellular traps (NETs). The investigators show evidence that platelets play a key role in endothelial damage and that this occurs through LPS interaction with platelet TLR 4. This is exciting because the role of TLR 4 expression on platelets was not thought to be an active one since treatment with LPS did not result in upregulation of activation markers or aggregation. It is not platelets alone but rather their TLR 4-induced interaction with neutrophils that appears to be critical in this process. Although phagocytosis remains a central component of neutrophil function during bacterial infection, it appears that, at least in part, TLR 4-dependent platelet binding results in neutrophil degranulation and the release of both DNA and proteolytic enzymes. The combination of neutrophil platelet binding resulted in rapid release of NETs that extend well beyond the neutrophil boundary. Unfortunately, as much as NETs may enhance bacterial trapping, their formation contributes to damage in the liver microcirculation. Further exploration for TLR 4 ligands that may play a role in sepsis may help refine tools to disrupt the platelet-neutrophil interaction through TLR 4, a critical and tractable component in this process during bacterial sepsis.

LILU PETRUZZELLI, MD, PHD

Dr. Petruzzelli indicated no relevant conflicts of interest.

Initial Therapy of Follicular Lymphoma: Another Option


Therapeutic approaches to follicular lymphoma (FL) continue to evolve via the incorporation of immunotherapy, novel chemotherapeutics, and stem cell transplantation. The East German Study Group enrolled patients with previously untreated follicular lymphoma in a prospective phase III multicenter trial of MCP (mitoxantrone, chlorambucil, and prednisolone) versus rituximab-MCP. Only the results for the FL patients are reported, with all patients being stage III-IV, grade 1 or 2, and in need of therapy based on “B” symptoms and disease volume or progression. Virtually all patients had intermediate- or high-risk FLIPI prognostic scores. Treatment was administered in 28-day cycles with a total of eight cycles for patients in complete (CR) or partial remission (PR) following cycle 6. All responding patients received interferon alfa-2a thrice weekly as maintenance therapy, continued until relapse. FL patients treated with R-MCP (n = 105) versus MCP (n = 96) had higher overall response (92 percent versus 75 percent, p = .0008) and CR rates (50 percent versus 25 percent, p = .0004), as well as improved progression-free survival (PFS; median not reached versus 29 months). Median overall survival (OS) was not reached for either group, but the four-year OS rates were significantly increased for R-MCP (87 percent) versus MCP (74 percent, p = .0096). Patients receiving R-MCP experienced more frequent grade 3-4 neutropenia, but without increased infectious episodes. To date, no patients have developed MDS or AML.

For patients with advanced FL who require treatment, prospective phase III studies have shown improved outcomes for patients receiving rituximab plus chemotherapy as compared with chemotherapy alone, including R-CVP, R-CHOP, and, as shown in the present study, R-MCP. While CR, PFS, and OS are improved with these rituximab-containing regimens, none is curative, and the relative long-term benefit of incorporating doxorubicin or mitoxantrone up front remains uncertain. Potential adverse effects could include late cardiac or other toxicities and loss of some treatment options in the event of histologic transformation, although recent reports have suggested a decreased risk of transformation when an anthracycline is utilized with initial therapy. The ongoing PRIMA trial, comparing four different induction regimens — R-CVP, R-CHOP, R-FCM, and R-MCP — with post-induction randomization to maintenance rituximab versus observation, will be of considerable importance in addressing these treatment options. Correlative analyses of clinical, phenotypic, and molecular markers of response and resistance collectively and with each regimen will be of interest.

MICHAEL WILLIAMS, MD

Dr. Williams has received research funding from BingenDEC and Genentech, and serves on CME speakers’ bureau sponsored by the two companies.
Multiple myeloma (MM) is a genetically and clinically heterogeneous disease, and many attempts over the years have sought to define staging systems or identify individual prognostic factors to predict patient outcome to conventional and high-dose therapies. In this paper, Mayo Clinic investigators classified patients as high-risk versus low-risk based upon cytogenetic abnormalities and then formulated ed treatment parameters and transplant-eligible versus transplant-ineligible patients in these two groups. This is a laudable effort and an important first step to tailor therapies for those most likely to respond, but there are several important caveats. First, there have been remarkable advances in oncogenomics, which have already provided for RNA- and DNA-based-prognostic classifications of MM, as well as a changing treatment paradigm using targeted therapies. Second, since MM remains incurable and there are numerous novel agents, all patients should have access to treatment protocols whenever possible. Third and most importantly, these risk stratifications are only one of several outcome of conventional and high-dose therapy that does not necessarily reflect the current use of three recently FDA-approved drugs, namely bortezomib, thalidomide, and lenalidomide. Each agent was shown to have activity alone or in combination in relapsed disease refractory to conventional and high-dose therapies, and has then been combined with dexamethasone for transplant-eligible patients and with melphalan and prednisone for transplant-ineligible patients as initial therapy. In each case, overall response has been 60-100 percent, with complete and very good partial response rates of up to 50 percent using bortezomib and lenalidomide-based treatments. Although the data is limited, bortezomib and lenalidomide seem to overcome the adverse prognosis conferred by cytogenetic deletion 13q and FISH translocation 4; 14, supporting their use in patients defined here as high risk. This does not, however, justify restricting the use of novel drugs only to high-risk groups and not standard-risk patients, where outcome could be improved. In fourth, each agent is being integrated into the transplant paradigm by cytoreduce MM pre-transplantation, as well maintenance therapy to prolong progression-free and overall survival post transplant. Finally, these investigators show that lenalidomide and dexamethasone achieve complete and very good partial responses in 67 percent of patients with newly-diagnosed MM, with 74 percent and 91 percent two-year progression-free and overall survival, respectively — randomized data confirm impressive survival and less toxicity when lenalidomide is combined with low, rather than high-dose dexamethasone. This regimen is highly likely to transform treatment of newly diagnosed patients.

Future translational research in MM will build upon these platforms and focus on the development of molecularly based combination therapies to achieve high frequency, extent, and duration of responses in the majority of patients, while minimizing toxicity. As we move towards this goal, collaborative science studies will redefine the features predicting a response and allow for selection of patients most likely to benefit from particular combination therapies.


Any blood centers in the U.S. are unable to maintain a minimum three- to five-day reserve of blood group O red blood cells (RBCs). Moreover, because only 5 percent of non-Asians are group AB (i.e., the “universal recipient”), the majority of blood donors are group B, and the more common group A donor RBCs produce a significant fraction of the group O RBCs. Group O RBCs have been generated from group B erythrocytes modified with PEG or other nonimmunogenic surface molecules, thereby facilitating the management of individuals who are heavily alloimmunized, such as patients with sickle cell disease. Although erythrocytes modified with PEG or other nonimmunogenic surface molecules could theoretically create truly “universal donor” RBCs that avoid antibodies against ABO/Rh antigens, minor red cell antigens, and autoantigens (Figure), considerable progress must be made before that technology is ready for evaluation in clinical trials. 

This paper by Liu et al. describes the isolation and in vitro properties of novel recombinant bacterial glycosidases that specifically generate ECO RBCs from group B, AB, and subgroup A1 and A2 erythrocytes. The ECO cells produced by these methods express normal H antigens, as characterized by licensed typing reagents, cytotoxicometric assays, and biochemical analyses. Membrane glycoproteins, such as group P antigens, are not altered. Of significance, only small amounts of the recombinant GalNAc-ase and Gal-ase enzymes are required to efficiently and selectively hydrolyze 200 mL of packed RBCs during a 30-minute reaction within a neutral pH buffering system. Thus, large-scale automated processing should be feasible and affordable.

While these data suggest that the major technical barriers to ECO RBC generation have been largely overcome, systematic functional assays and comprehensive human studies are still needed to assess the safety and efficacy of these cells for transfusion. If this methodology proves clinically beneficial, blood centers will be able to supplement their inventory of group D RBCs by producing ECO units from non-D products (Figure). In addition, an expanded supply of ECO RBCs could be prepared from donors who lack certain minor antigens, thereby facilitating the management of individuals who are heavily alloimmunized, such as patients with sickle cell disease. Although erythrocytes modified with PEG or other nonimmunogenic surface molecules could theoretically create truly “universal donor” RBCs that avoid antibodies against ABO/Rh antigens, minor red cell antigens, and autoantigens (Figure), considerable progress must be made before that technology is ready for evaluation in clinical trials.


2. Kruska MD, Aubuchon JP, Anthony KY, et al. Transfusion to blood group A and O patients of group B RBCs that have been enzymatically converted to group O. Transfusion 2000; 40:1290-8.
The survival of hematopoietic cells is governed by the complex interplay between members of the Bcl-2 family of pro- and anti-apoptotic proteins. This family has been divided into multi- and BH3 domain-only members. Certain multi-domain members such as Bak and Bax promote apoptosis by interfering with mitochondrial integrity, whereas others, such as Bad, act indirectly by blocking the actions of multi-domain anti-apoptotic proteins (i.e., Bcl-2 or Bcl-xL). BH3 domain-only proteins such as Bid and Bim act either directly to activate Bax or Bak, or, as recently suggested, indirectly by neutralizing multi-domain anti-apoptotic proteins.

Bcl-2 Proteins Control Platelet Life Span In Vivo: A Potential Target for New Approaches to Treat Thrombocytopenia


Previous studies have shown that mice deficient for Bak, a “pro-apoptotic” Bcl-2 family member known to bind to Bcl-xL, had the opposite phenotype — they were thrombocytotic with prolonged platelet survival. Importantly, Bak deficiency “rescued” the thrombocytopenic phenotype of the Bcl-xL mutants. The investigators thus propose that platelets are genetically programmed to die by Bak-mediated apoptosis. In “young” platelets this is held in check by Bcl-xL, which binds and neutralizes Bak. Since the Bcl-xL protein is less stable than Bak, as platelets age in the circulation Bcl-xL levels drop, eventually to the point where Bak inhibition is lost and cell death is triggered. In essence, Bcl-xL instability serves as a molecular clock ticking down towards the inevitable destruction of the circulating platelet.

Recent discoveries have challenged many longstanding beliefs about platelet function and biology. For example, we now know that even though platelets do not have nuclei, they contain RNA and have the machinery to process it and translate it, and may thus contribute to inflammation and thrombosis in manners not previously appreciated. Furthermore, platelets express many of the components of the apoptotic machinery, including caspases and Bcl family members. These components have been postulated to play a role in platelet fragmentation from some marrow megakaryocyte precursors and their presence in circulating platelets thought perhaps to be a relic from the parent megakaryocyte. It is now clear, however, that while platelets are incapable of undergoing “classic” apoptosis in that they do not have nuclei to condense or DNA to fragment, they are capable of undergoing a form of programmed cell death. In this important manuscript, the authors used a sophisticated genetic approach to discover that pro-apoptotic platelet death is regulated by the balance of pro- and anti-apoptotic proteins Bak and Bcl-xL, and that this balance determines the limit on circulating platelet life span. The ability to manipulate this balance pharmacologically to extend platelet lifespan holds considerable promise for future treatment of thrombocytopenic conditions and for storage of platelets for transfusion.

Pharmacologic Recapitulation of the Cell Death Program


ABT-737 has displayed impressive in vitro and in vivo activity against murine and human tumours of both hematopoietic and non-hematopoietic origin. One theoretical barrier to the effectiveness of ABT-737 stems from its failure to bind to and inhibit Mcl-1, a protein known to play a critical role in the survival of malignant hematopoietic cells.

In this context, several groups have recently reported that first, Mcl-1 expression does in fact represent a critical determinant of ABT-737 activity, and second, multiple interventions that reduce Mcl-1 expression by disparate means dramatically increase the sensitivity of malignant cells, including leukemia cells, to this novel agent. Such interventions include the use of CDK inhibitors such as roscovitine, which act as transcriptional repressors and downregulate expression of short-lived proteins such as Mcl-1, or alternatively, inhibitors of MEK1/2 (mitogen-activated protein kinase kinase 1/2), which promote Mcl-1 degradation. Interestingly, the simultaneous administration of pharmacologic Bcl-2/Bcl-xL antagonists like ABT-737 and agents that downregulate Mcl-1 expression in essence recapitulates the pro-death actions of more physiologic inhibitors of Bcl-2/Bcl-xL (i.e., Bad) and Mcl-1 (i.e., Noxa). This phenomenon may reflect coordination between Bcl-xL and Mcl-1 in tethering/inactivating the multi-domain pro-apoptotic protein Bak, which cooperates with Bax to trigger mitochondrial injury and apoptosis.

The significance of these findings is that, just as the combination of multiple conventional cytotoxic agents has proven active in the clinic, the rational combination of BH3 mimetics and targeted agents may be similarly effective. This could be particularly pertinent in the case of agents which specifically target separate but interrelated arms of the apoptotic machinery. With the possible exception of diseases such as CML, which are characterized by a pronounced dependency upon a critical oncoprotein (i.e., Bcr/Abl), redundancy of tumor cell survival pathways make it unlikely that single interventions employing targeted agents will prove sufficient. The findings described above raise the possibility that the rational targeting of multiple arms of the apoptotic machinery, an approach that offers the prospect of restoring the physiologic death process in leukemic and other neoplastic cells, may be eminently feasible.


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Dr. Silverstein indicated no relevant conflicts of interest.

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Dr. Grant indicated no relevant conflicts of interest.
Is There a Common Pathway for Maintenance of Adult and Embryonic Stem Cells?


Galan-Caridad et al. demonstrate that the zinc finger protein zfx plays a role in the self-renewal of both murine hematopoietic stem cells (HSCs) derived from adult bone marrow and murine embryonic stem cells (ESCs). These data suggest that very different types of stem cells may share a regulatory pathway for maintaining survival of self-renewing stem cells.

The data show that when the zfx gene is knocked out, both murine ESCs and HSCs lose their capacity for self renewal. Surprisingly, the loss of zfx does not promote differentiation nor does it inhibit the ability of the cells to proliferate, either of which one might have considered to be a key role of any gene specifically required for stem cell maintenance. Without zfx, ESCs gradually die off in culture. However, until they die, the cells maintain their undifferentiated phenotype, suggesting that zfx is not critical for maintaining the undifferentiated pluripotent state, but rather that it maintains cell viability by inhibiting apoptosis and/or senescence of self-renewing cells. zfx is not needed for differentiation of ESCs. When zfx-null ESCs are added to a blastocyst-stage embryo in order to make a chimeric mouse, they contribute normally to all cell types in the adult mouse except hematopoietic cells. One might expect that if zfx were needed for survival of all types of stem cells, then zfx-null cells derived from ESCs would not be able to contribute long-term to tissues such as the GI tract and skin, which are constantly renewed by adult stem cells. Thus, zfx is not needed for self-renewing adult stem cells of organs outside of the hematopoietic system.

Similar to ESCs, when zfx is knocked out of murine HSCs, the HSCs are gradually lost in vivo due to apoptosis, while more differentiated hematopoietic progenitors are able to proliferate and terminally differentiate to maintain hematopoiesis for up to two months. Without functioning HSCs, however, the hematopoietic system is eventually lost. Therefore, as with ESCs, zfx confers to HSC resistance to apoptosis/senescence, but has no effect on the ability of the progeny of zfx-null HSC to proliferate and differentiate into functional blood cells.

Several investigators have assessed whether there is a “stem cell signature” of gene expression that can confer “stem-ness”1-3. Although several studies published constellations of genes that were expressed in multiple stem cell types, there was very little concurrence between the different groups, suggesting that the “stem cell signature” hypothesis is too simplistic. However, zfx was among the genes jointly expressed by HSCs, neural stem cells, and ESCs in two of these studies1,2.

By highlighting the unique pro-survival role of zfx in both ESCs and HSCs (though not all adult stem cell types), these fascinating findings demonstrate a new level of complexity that must be considered in stem cell biology. In order for stem cells to be able to self-renew and maintain their undifferentiated state, active pathways that appear to be unique to stem cells are needed to maintain survival. Relevant to hematology, an increased understanding of how genes such as zfx are regulated could a) lead to a greater understanding of HSCs self renewal, b) improve our ability to expand HSCs ex vivo for clinical purposes, and c) provide insight into leukemogenesis.

A New Arena for the Transferrin Receptor


There is rapidly emerging evidence of dual and often unexpected functions of many human proteins. The transferrin receptor 1 (TfR1) is the essential host protein that efficiently delivers iron to erythroid progenitors and other rapidly proliferating cells. In this paper, Radoshitzky and colleagues in Choe’s laboratory uncover another such dual function protein: the piggybacking of an infectious agent onto this essential human protein. Viral hemorrhagic fevers are rare but devastating disorders that can be caused by at least five different arenaviruses. Four of these arenaviruses are classified as New World viruses, since the rodent hosts are located in the Western hemisphere. While these viruses are asymptomatic in the rodent host, when humans are infected the mortality rate can reach 30 percent. These investigators have identified the TfR1 as the protein responsible for binding and internalization of these viruses. The viral coat protein GP1 mediates the binding to the host cell surface. To identify which cell-surface protein was functioning as the viral receptor, the authors constructed a fusion protein consisting of the viral GP1 fused with the Fc portion of IgG1. This fusion protein was used to immunoprecipitate potential receptor proteins from metabolically labeled endothelial cells from African green monkeys, which are highly susceptible to these viruses. The major band immunoprecipitated by the fusion protein was characterized using mass spectroscopy and identified as TfR1. Chinese hamster ovary cells are resistant to New World arenavirus infections, but inducing expression of human TfR1 in these cells rendered them permissive for infection with the various New World viruses, confirming the essential role of TfR1. On the other hand, expression of the closely related transferrin receptor 2 did not allow viral binding and entry. Modulation of the TfR1 levels by treating the cells with iron or iron chelators showed that infectivity with the arenavirus was directly proportional to the quantity of TfR1 on the cell surface.

This paper also clarifies the previously reported low pH requirement for fusion of these arenaviruses with host cell membrane. The transferrin receptor/transferring-bound iron complex is internalized in endosomes where the low pH facilitates release of iron and transferrin from TfR1 and the recycling of the receptor to the cell surface. The same mechanism allows release of virus, modification of the viral coat, and fusion of the endosomal and viral membranes (Figure 1). The TfR1 is highly expressed on endothelial cells and at high levels on dividing macrophages and lymphocytes (which increase during infection), further facilitating infectivity and replication of the virus. Thus, arenaviruses hijacked a critical process of nutrient acquisition to provide a route of entry into the cell.

This manuscript expands our knowledge of disease states that are linked to iron metabolism and infection. These links include the association between the detrimental use of iron for an undiagnosed anemia that may worsen the outcome of bacterial and mycobacterial infections, the salutary effect of iron chelators on cancer progression, and the lipocalin-iron pathway that regulates apoptosis of certain cancers. The use of TfR1 as a viral entry receptor has also been demonstrated in other species (i.e., mouse mammary tumor virus has been shown to use TfR1 for entry, as have canine and feline parvoviruses). With the high degree of homology between the transferrin receptors, it is remarkable how species-specific the viral coat proteins are. As pointed out by the authors, the effect of iron deficiency is not clear on the infectious outcome of these viruses. While iron deficiency increases TfR1 expression and thus infectivity, the soluble TfR1 that also increases may, in fact, act as a decoy and protect the cells from viral entry. However, iron therapy during an acute infection may be beneficial by decreasing both the level of cell surface and the circulating TfR1. A novel therapeutic modality that remains to be tested — the administration of anti-TfR1 humanized antibodies (that are already being evaluated as the anti-cancer agents!) — would be expected to be beneficial in patients infected with New World hemorrhagic fever.


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Drs. Phillips and Prchal indicated no relevant conflicts of interest.
ASH Releases Third Edition of the ASH-SAP

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Dr. Gregory is Professor of Medicine at Rush University Medical Center and is the Eldia Kehm Professor of Medicine and Director of the Section of Hematology at Rush Medical College/Rush University Medical Center.

The third edition of the American Society of Hematology Self-Assessment Program (ASH-SAP) was released in May. This third edition follows in the footsteps of previous editions, which have established the ASH-SAP as the premier self-assessment program in the practice of hematology. The authors for the third edition, all of whom have significant expertise as educators and have provided representative case studies to reinforce information provided in the chapters, come from a broad range of respected institutions. The third edition includes over 200 newly constructed multiple-choice questions with critiques and references and is accompanied by a Web companion that allows for interactive learning, giving the reader the option to switch between text, questions, critiques, and references. The third edition includes a new chapter on plasma cell dyscrasias, and all of the remaining 17 chapters are either updated or completely rewritten.

Completion of the ASH-SAP counts toward 70 lifelong learning points for the American Board of Internal Medicine Maintenance of Certification Program and 50 AMA PRA Category 1 CME credits. As with previous editions, the third edition of ASH-SAP is a valuable tool for both graduates and trainees studying for certification and recertification board exams, as well as for practitioners wishing to be kept current on the latest developments in hematology. For more information about the third edition of the ASH-SAP, visit the ASH-SAP Web site at www.ash-sap.org.

Trainee Day: Building Critical Career Development Tools

The ASH Trainee Council would like to announce the creation of Trainee Day. This half-day workshop will be held in conjunction with the 2007 ASH Annual Meeting on Friday, December 7, from 7:00 a.m. to noon. The goal of this workshop is to provide trainees with critical career development tools. Sessions will be presented by established hematologists and will include The Secret to Getting Funded, Establishing a Research Career, Basic Elements of Grant Writing, and a mock study section. There will be abundant time for questions, participation, and interaction with speakers and other trainees. For more information on this new program, visit the ASH Web site at www.hematology.org/education/training/trainee_day.cfm.

Learning in Las Vegas: The ASH State-of-the-Art Symposium

MARK JUCKETT, MD

Dr. Juckett is Associate Professor at the School of Medicine and Public Health at the University of Wisconsin.

This past September, the ASH State-of-the-Art Symposium (SAS) was held in Las Vegas, NV. The Symposium was conducted in the “academically charged” Bellagio Hotel amid ornate decorations and Mediterranean trappings. In an era of so many options for CME, one might ask “what is unique about the SAS that is not available at the ASH annual meeting?” The SAS has a curriculum focused beyond a simple review of the latest studies in hematology research. The presenters at the SAS have taken on the daunting challenge of reviewing the most current research and assessing what findings are novel, mature, and relevant to current hematology practice. In an era of cost-conscious, evidence-based medicine, the assessment of new technology and research for incorporation into “prime time” clinical practice has become increasingly important. Clinicians are caught between the need to be competent in the use of an increasing number of new therapies and the duty to control costs. The incredible cost of the newer pharmaceuticals has mandated a need to recommend therapy based on clear evidence for benefit. I have always returned home from the ASH annual meeting both enthralled and overwhelmed with the new ideas presented. Always eager to improve our clinical care, we must incorporate our new knowledge into our daily practice — but what new developments are ready for “prime time?”

Enter the SAS. Whereas the presentations at the ASH annual meeting cover a vast array of creative and innovative research ideas, the SAS is intended to present the mature findings that are directly relevant for a practicing hematologist. Each speaker presents new research findings within the context of our current standards of care. In September, Dr. Charles Schiffer attempted to make some sense of the HSCT trials in AML and where to incorporate molecular testing in our risk assessment and decision support. Dr. Hagop Kantarjian discussed CML and placed in context the options for therapy with tyrosine kinase inhibitors (what was once easy has become complicated). Dr. Kant’s Kral presented a historical backdrop of the diagnosis and treatment of CLL followed by Dr. Bruce Cheson’s discussion of risk assessment and treatment. Dr. Alan List covered the new agents available for MDS treatment and provided some structure to their use.

A significant portion of last year’s two-day event was devoted to specific lymphoma entities. Drs. Arnold Freedman, John Leonard, Sandra Horning, Joseph Connors, and Stephen Forman addressed issues of upfront therapy, maintenance, and transplant strategies for follicular, diffuse B-cell, mantle cell, and Hodgkin lymphomas. Dr. Kerry Savage discussed the available evidence in support of treatment for T-cell lymphomas, and Dr. Malik Juweid gave an evidence-based approach for the use and misuse of PET scanning in lymphomas. Dr. Donna Rege attempted to make sense of the seemingly innumerable chemotherapy combinations for myeloma. More than a review of new studies, the SAS is a venue for those interested in learning about new developments that are directly relevant to the clinical practice of hematology.

ASH State-of-the-Art Symposium: Recent Advances in the Treatment of Hematologic Malignancies and Cancer-Associated Thrombosis

September 28-29, 2007
Philadelphia, PA

The 2007 ASH State-of-the-Art Symposium (SAS) will feature leading hematology experts exploring the latest research and treatment options for hematologic malignancies and cancer-associated thrombosis. This informative, clinically focused CME conference is designed to allow practitioners, fellows, and academicians to discuss some of the most rapidly evolving developments in the field with experts as well as their colleagues. Sessions will include in-depth discussions about developments in stem cell transplantation, best practices for reimbursement and pay-for-performance, and new treatment options for lymphoma, leukemia, multiple myeloma, and more.
On May 8-9, 2007, ASH held a highly successful sickle cell workshop in Washington, DC, aimed at developing a research agenda for sickle cell disease (SCD). The workshop explored the identification of risk factors in childhood that predict end-organ damage in adults, along with the development of new treatment paradigms to ameliorate complications or prevent them altogether. The authors chaired the workshop, assembling a group of 20 ASH members nationally recognized for their expertise in sickle cell disease and particularly in identification of risk factor measurement, treatment of organ injury, and prevention approaches at rather short notice (with the valuable assistance of Stephanie Kart, ASH Government Relations & Practice Specialist).

The meeting was a huge success. Fruitful discussion centered on the lungs, heart, kidneys, and brain as the primary target organs known to suffer from dysfunction in adult patients, despite many of them being relatively spared during childhood. Methods to measure and then monitor organ function were debated, and clinical events and laboratory tests, novel biomarkers, and genomic approaches were analyzed and prioritized. Issues concerning the prevention and management of pain were also given high priority.

Workshop participants work to develop a research agenda for sickle cell disease.

The final segment of the two-day meeting emphasized standard interventions, such as chronic transfusion, hydroxyurea, and stem cell transplantation, as well as novel approaches, including gene therapy and new agents that might be used to raise fetal hemoglobin. In order to facilitate the design and execution of the research agenda, a key recommendation of the workshop participants was the assembly of an NIH-funded multi-institutional collaborative clinical research group that would include a large number of academic centers demonstrating the ability to conduct the required studies. This national research group would be charged with, among other tasks, developing a patient registry that includes retrospective and prospective clinical data and is linked to a DNA repository and repeatedly analyzing biomarkers of disease severity and treatment efficacy. Such a clinical trials consortium would be tightly connected with peer-reviewed basic and translational investigations.

The workshop’s final report identifying key unanswered research questions in SCD was presented at the American Society of Pediatric Hematology-Oncology’s Sickle Cell Disease Summit: From Research Disparity to Action in June, shared with NIH officials, and subsequently distributed to the entire ASH membership.

**Changes Afoot for the Medicare National Clinical Research Policy**

Patients on clinical trials have had a problematic history with insurance carriers. President Clinton signed an executive memorandum in 2000, “authorize[m Medicare] payment for routine patient care costs. . .and costs due to medical complications associated with participation in clinical tri- als.” Under this memorandum, the clinical trial services that qualify for coverage include those that have therapeutic intent and are “deemed” trials. Those trials that are automatically qualified include:

1. Trials funded by federal agencies or their centers or cooperative groups;
2. Trials conducted under an investigational new drug application (IND); and
3. Drug trials that are IND-exempt.

Covered routine costs of a qualified trial included all items and services that are otherwise generally available to Medicare beneficiaries including:

- those provided absent a clinical trial (e.g., conventional care);
- those required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent);
- those required for the clinically appropriate monitoring of the effects of the investigational item or service, or the prevention of complications; and
- those needed for reasonable and necessary care, for the diagnosis or treatment of complications

Services not covered include:

- the investigational item or service itself;
- items and services:
  - for which there is no Medicare benefit category or that are statutorily excluded;
  - furnished solely to satisfy data collection and analysis
  - customarily provided by research sponsor
  - provided solely to determine eligibility

Recently, the Centers for Medicare and Medicaid Services (CMS) released a proposed revised national coverage decision for the Clinical Trial Policy. ASH has sent comments to CMS regarding some of the important changes in the proposed NCD (www.hematology.org/policy/testimony/clinical_trails_comment_letter_050907.pdf).

These new proposals (in italics), followed by ASH’s comments, include:

- “The research study protocol specifies and fulfills the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early.”

ASH believes in the peer-review publication process to verify the scientific legitimacy of the results. However, the timeline for the public release of a study in a peer-reviewed journal is difficult to determine because of the peer review process itself. In addition to peer-reviewed publications, we suggest that an alternative mechanism for sharing of information would be a summary paragraph linked to ClinicalTrials.gov.

- “The research study protocol contains a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention.”

ASH believes that a Medicare beneficiary eligible for the study, even though he/she may be in the minority, should not be denied coverage for standard of care items because the study did not meet this proposed standard. ASH proposes amending the proposed standard to allow the researcher to state the reasons why a particular study may not be generalizable to the entire Medicare population.

- “ASH commented that institutions that have received the new NIH Clinical Translational Science Award should be given delegated authority to deem studies.”

- “CMS proposes to remove IND-exempt studies as automatically qualified trials. ASH believes that the exclusion of most IND-exempt studies would be an impediment to much useful research. ASH recommends developing criteria for self-certification which include establishing local Protocol Review Committees whose membership would consist of clinical investigators, biostatisticians, and basic scientists.”

There are many additional issues that are detailed in the ASH comment letter. Members of the Committee on Government Affairs, the Committee on Practice, and the Executive Committee helped draft the ASH comment letter. We will now wait to see how CMS responds.
In 2004, ASH launched the Minority Medical Student Award Program (MMSAP) as part of the Society’s overall Minority Recruitment Initiatives. Each year ASH awards up to 10 medical students from the United States and Canada in their early years of training the opportunity to participate in an eight- to 12-week summer research experience. The following individuals have been selected for the 2007 MMSAP and the Society congratulates them on their success.

1. Abisola Ayodeji  
   Virginia Commonwealth University School of Medicine, Richmond, VA
2. Ashanti Franklin  
   University of Southern California Keck School of Medicine, Los Angeles, CA
3. Awet Abraha  
   Wayne State University School of Medicine, Detroit, MI
4. Emily McElveen  
   Brown Medical School, Providence, RI
5. Jennifer Robles  
   Case Western Reserve University School of Medicine, Cleveland, OH
6. Johnaca Biggins  
   Ohio State University College of Medicine, Columbus, OH
7. Johnathan J. Ledet  
   Louisiana State University School of Medicine, Shreveport, LA
8. Luz Juliana Barahona  
   Universidad Central del Caribe SDM, Bayamon, PR
9. Melissa Bent  
   Morehouse School of Medicine, Atlanta, GA
10. Nicole Jones  
    Wayne State University School of Medicine, Detroit, MI
11. Olabunni Agboola  
    University of Illinois at Chicago College of Medicine, Chicago, IL

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