1. EXECUTIVE SUMMARY

2. INTRODUCTION

3. HIGHEST PRIORITY SCIENTIFIC THEMES
   a. Hematopoietic Stem Cells
   b. Normal and Pathological Hematopoiesis
   c. Sickle Cell Disease
   d. Hematologic Malignancies
   e. Targeted, Cellular, and Genetic Therapies
   f. Immunobiology
   g. Thrombosis, Hemostasis, and Vascular Biology
   h. Hematology Outcomes and Society

4. RESEARCH INFRASTRUCTURE
   a. Training and Career Development
   b. Core Resources
Hematology research is intrinsically translational and transdisciplinary in nature, and innovations in hematology have repeatedly opened new frontiers in biomedical inquiry. To sustain this synergy, the American Society of Hematology (ASH) undertook a comprehensive strategic planning process in 2006 to identify and prioritize the most fertile areas of research in hematology. The “American Society of Hematology Agenda for Hematology Research” was always intended to be a living document, leading us toward new initiatives that build on the ongoing successes in the discipline. The current document represents a revision of the agenda that updates the critical research directions of the field, and that honors the 50th anniversary of the American Society of Hematology.

The ASH plan for hematology research is divided into two parts. The first section summarizes highest scientific priorities for future hematology research, and the second section recommends priorities for the development of research infrastructure to facilitate this research.

The highest priority scientific areas encompass some fields in which groundbreaking insights offer potential for clinical translation in the near future, and others that pursue basic biological questions that promise to ensure long-term progress toward improving clinical outcomes. These are structured around overarching themes that include hematopoietic stem cells, hematopoiesis, sickle cell disease, hematologic malignancies, targeted and gene therapies, immunobiology, thrombosis and vascular biology, and clinical outcomes research. Hematopoietic stem cells have served as models for understanding basic stem cell biology; the most promising lines of research in this area include better characterization of human hematopoietic stem cells and studies of the stem cell microenvironment, stem cells in aging, stem cell therapy, and stem cell tracking. Potentially important clinical benefits may derive from the further study of embryonic stem cells and from the reprogramming of adult somatic cells for the generation of hematopoietic and non-hematopoietic stem cells. Research on hematopoiesis should include: elucidation of the pathogenesis of the anemia of chronic inflammation; the actions of hematopoietic growth factors on hematopoietic and non-hematopoietic tissues; the therapeutic potential of hematopoietic cytokines and molecules that modulate cytokine production and action; further insight into the natural history and therapy of hemoglobinopathies; and studies of the regulation of hematopoiesis that will lead to new diagnostic and therapeutic opportunities in acute leukemia, and myeloproliferative and myelodysplastic disorders. Continued research on sickle cell disease should be directed at: better understanding of the predictors of disease complications; improved therapies; pain management and quality of life studies; organ disease and complications; and the improved collection of comprehensive patient data for phenotypic studies and risk prediction. Future research in hematologic malignancies...
should be directed at: molecular profiling of hematologic malignancies; studies of neoplastic stem cells; and treatment of hematologic malignancies, including immune therapies. Promising lines of research in targeted, cellular, and genetic therapies include the molecular targeting of neoplastic stem/progenitor cells, the development of cellular and genetic approaches to tissue regeneration, and the therapy of inherited disorders. Basic and applied research in immunobiology should include: studies of immune recognition; mechanisms of immune response; normal and abnormal immune regulation; transplantation immunology, including graft-versus-host disease, tissue rejection, and mechanisms of immune tolerance; innate immunity; lymphopoiesis; and immune cell trafficking. The highest priorities for research in thrombosis and vascular biology include: novel targets for antithrombotic therapy; mechanisms that initiate arterial and venous thrombosis; development of animal models of thrombotic disorders; genomics and proteomics of thrombosis; cancer-related thrombosis; thrombosis and vascular disease in women; age-related determinants of thrombotic risk; and hemostatic mechanisms in stroke. Finally, the importance of research on the improved delivery of care to patients with hematologic disorders is addressed in the section on Hematology Outcomes and Society.

The highest priorities for research infrastructure are in the areas of training and of institutional and national core resources. Training programs should address the declining numbers of physician scientists and trainees pursuing careers in non-malignant hematology. In addition to preserving the T32 training program mechanism, new programs should be developed for the combined training in hematology, laboratory, and related disciplines; for clinically oriented training of PhD scientists; and for the support of new investigators, with the top priorities being career development and investigator-initiated R01 grants. Core resources should include integrated institutional and translational research centers for blood disorders. These centers should support key resources such as tissue repositories and high-throughput sequencing facilities that are not readily available through individual investigator grants or institutional funds. Core resources should also include national resource centers, such as networks for rare hematologic disorders, and networks for the development and sharing of animal models of blood disorders.

The “American Society of Hematology Agenda for Hematology Research: 2009 – 2011” is a dynamic document that will be subject to ongoing review and revision. It is intended to provide a strategic framework for research in our discipline, which, we believe, will continue to make path-breaking advances in understanding, preventing, and treating human disease.
Hematology research is a paradigm for strategies aimed at elucidating fundamental biology and translating basic observations into advances in disease diagnosis, treatment, and prevention. Sickle cell disease was the first disorder to be understood at the molecular level; and early advances in our understanding of gene structure, function, and transcriptional regulation, as well as advancing technologies for prenatal diagnosis, developed with hemoglobin as a model system. Similarly, the understanding of the molecular pathogenesis of malignancy, and the resultant development of targeted therapies, has been driven by investigation of hematologic malignancy. The dissection of molecular translocations and specific mutations in chronic myeloid leukemia, acute promyelocytic leukemia, and the chronic myeloproliferative diseases has illuminated the importance of signaling molecules and transcription factors in the pathogenesis of malignant transformation while defining critical entry points for therapeutic intervention that can potentially cure these once-fatal diseases. Hematopoietic stem cells continue to provide the best models for understanding basic stem cell biology in other organs and tissues, and hematopoietic stem cell (bone marrow, mobilized peripheral blood, and cord blood) transplantation has been the impetus for clinical research on other forms of stem cell therapy. Genetic and cellular therapies involving hematopoietic cells have resulted in the successful treatment of several inherited and malignant diseases. As the hematopoietic stem cell was the first adult somatic stem cell to be described, the existence of cancer stem cells was likewise first described in the hematopoietic system. It has been the linkage of immunology with experimental and clinical hematology research (e.g., in transfusion medicine, the application of monoclonal antibodies, and research in immune-mediated blood diseases) that has served as a critical stimulus for understanding the molecular basis of the immune system. Fundamental hematology research in the area of thrombosis and hemostasis, including elucidation of the basic mechanisms of blood coagulation and platelet function, has revolutionized our understanding and treatment of ischemic cardiovascular disease.

Hematology thus has a distinguished tradition of fostering new and groundbreaking approaches to biomedical inquiry. It was in recognition of this prominent role in establishing and furthering the biomedical research agenda that the American Society of Hematology undertook a strategic planning initiative to define and promote for our membership and for the research community at large the leading areas of active endeavor in hematologic research. The “American Society of Hematology Agenda for Hematology Research: 2006-2008” was initiated in the fall of 2005 by soliciting a wide input from all members of the 14 Scientific Committees of ASH. In a collaboration between the Executive Committee and the Scientific Committee Chairs, a draft was developed, edited, and revised to produce the first ASH Agenda. It was always
expected to evolve with the changing landscape of hematology research. This first revision of the Agenda, “American Society of Hematology Agenda for Hematology Research: 2009 – 2011” has been modified to reflect current trends in research and to celebrate the 50th anniversary of ASH. Although many aspects of the research trajectory remain the same, the document reflects new advances that have widened the field, including new breakthroughs in stem cell research, a renewed commitment to new strategies for understanding sickle cell disease, and disorders of hemostasis and thrombosis. The overriding message, however, remains the same: the recognition of the primacy of hematology research in forging new paradigms in basic, translational, and clinical research.

The following plan for hematology research is divided into two parts. First, we summarize highest scientific priorities, including the most promising directions for future hematology research in the areas of hematopoietic stem cells; hematopoiesis; sickle cell disease; hematologic malignancies; targeted, cellular, and genetic therapies; immunobiology; thrombosis and vascular biology; and clinical outcomes research. Second, we recommend the most important priorities for the development of research infrastructure to facilitate all areas of hematology research, emphasizing the needs for training and core facilities.
HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells have provided the best models for understanding basic stem cell biology, including pathways of lineage specification, differentiation, and self-renewal. Indeed, the stem cell field benefited immeasurably from the early clinical application of hematopoietic stem cell transplantation for the treatment of malignancies. Work on basic hematopoietic stem cell biology that began almost fifty years ago serves as the basis for the study of stem cells in diverse organs and tissues even today. To build on this impressive background in hematology research, there are several areas in which the study of hematopoietic stem cells should, and will, continue to lead advances in the field.

Characterization of human hematopoietic stem cells: In contrast to mouse stem cells, human hematopoietic stem cells remain poorly defined, both immunophenotypically and functionally. Efforts in this area are necessary to better define the hematopoietic stem cell content of tissues for transplantation, especially for umbilical cord blood. A more detailed delineation of the mechanisms of stem and progenitor cell self-renewal and proliferation will further enhance the clinical utility of hematopoietic cell transplantation.

Stem cell microenvironment: Research emphasis should highlight the importance of understanding the basic biology and the clinical applications of stem cells, including non-hematopoietic marrow-derived cells such as mesenchymal, stromal, bone, and endothelial progenitors. The identities and functions of various components of the stem cell “niche” are only now beginning to come into sharper focus. Since it is now recognized that signals emanating from the “niche” influence many of the functional properties of stem cells, studies of the stem cell microenvironment are key to a clearer understanding of stem cell biology.

Stem cells and aging: Since many, if not most, hematologic and non-hematologic malignancies manifest later in life, studies of the effects of aging on stem cells, and its role in malignant transformation, should be a high priority for stem cell research. Further understanding of aging tissue stem cells may provide important insight into age-related organ failure—a target for regenerative medicine.

Stem cell therapy: Cell-based therapy, using hematopoietic stem cell reconstitution for regeneration of non-hematopoietic tissues as well as hematopoietic cells, should continue to be a high research priority. Preclinical studies of stem cells to define their immunophenotype, gene expression profile, and functional capabilities require further investigation and validation. Improved methods for expansion of stem and progenitor cell populations, for their mobilization into the blood, and for enhancement of their engraftment potential, must be developed. The availability of stem cells for clinical transplantation, including cord blood stem cells and adult stem cells from minority populations, should be expanded, as this will facilitate the application of stem cell therapies to underserved populations.

Stem cell tracking: Advanced imaging technologies are needed to track transplanted cells...
after infusion. Research in this area will be best accomplished in collaboration with investigators with advanced expertise in imaging techniques. Such studies are needed in the immediate future to bolster our understanding of stem cell homing and trafficking and vital steps in the engraftment process.

**Immunomodulatory effects of stem cell therapy:** Modulation of immune function following stem cell therapy may reveal novel mechanisms for the treatment of malignant disorders. Studies aimed at preventing graft-versus-host disease, while at the same time optimizing graft-versus-leukemia effect, should be encouraged. Further research is required to realize the potential of vaccines and adoptive immunotherapy for the treatment of hematologic malignancies.

**Embryonic stem cells:** Embryonic stem (ES) cell research should also be promoted vigorously and receive high priority. Only with the ready availability of uncontaminated ES cell lines to the scientific community can critical studies be undertaken to compare the regenerative capacity of ES cells to that of adult stem cells in an attempt to develop new treatments for many debilitating and fatal diseases. In addition, genetic modification studies have demonstrated that the developmental properties of embryonic stem cells may be re-acquired by adult somatic cells. Thus, we strongly encourage the pursuit of studies to further the understanding of the most effective strategies for cell reprogramming for scientific and medical purposes. Such studies are of importance for understanding basic mechanisms of normal and malignant cell growth, and for the generation of large numbers of normal hematopoietic stem cells. Studies of reprogramming of adult somatic cells for generation of hematopoietic and non-hematopoietic stem cells are a rapidly growing field that should also have high priority.

**NORMAL AND PATHOLOGICAL HEMATOPOIESIS**

Hematopoiesis provides a unique paradigm for many fundamental questions in biology, including embryonic development, stem cell expansion, and tissue differentiation. Studies of the genetic regulation of proliferation and maturation address key questions relevant to nearly all biological systems. The study of normal hematopoiesis is, therefore, of the highest priority; it will allow the translation of basic research into discoveries that elucidate disease processes and contribute to the development of new cellular therapies.

**The origin of blood:** A better understanding of how hematopoiesis develops, how it is controlled, and its relationship to vasculogenesis will translate into a better understanding of leukemia, bone marrow failure, and angiogenesis. In addition to the traditional embryonic stem cell and murine models, further research exploiting zebrafish, *Drosophila*, and *C. elegans* is critical to our long-term understanding of basic mechanisms of cellular development.

**Regulation of hematopoietic stem cells:** Stem cells have the capacity to self-renew, expand, differentiate into multiple tissue types, and survive for long periods of time in a quiescent state. Understanding the factors that regulate entry to and exit from quiescence, as well as lineage commitment and cellular maturation, requires delineation of the diverse roles of cytokines, transcription factors, and the microenvironment. In this context, novel regulators, such as microRNAs, offer an exciting new field of study. New avenues of research that define the role of telomere maintenance, DNA repair, ribosome biogenesis, and protein folding will provide clinically important insights into hematopoiesis in patients with inherited and acquired bone marrow failure.
Iron homeostasis: The discovery of hepcidin was a breakthrough in our understanding of iron metabolism. Further study of the regulation of iron balance may lead to a better understanding of the anemia of chronic inflammation, iron overload, and the anemia of aging.

Therapeutic use of cytokines/growth factors: Several cytokines, including granulocyte colony-stimulating factor, erythropoietin, and thrombopoietin mimetics, are now part of the standard therapeutic armamentarium for the hematologist. A better understanding of how erythropoietin acts in non-hematopoietic tissues is required to optimize the use of this powerful agent. More studies are also needed to determine the utility of recently developed peptides and small molecules that activate the thrombopoietin receptor in the treatment of thrombocytopenia associated with immune thrombocytopenia, chronic hepatitis, myelodysplasia, aplastic anemia, and following chemotherapy or transplantation.

SICKLE CELL DISEASE
The molecular and cellular basis for sickle cell disease (SCD) has been understood for over half a century, and advances in testing and supportive care have substantially improved life expectancy for SCD patients. With the improvement in early mortality has come a substantially increased burden of disease for those now surviving long enough to develop late disease complications. New therapies have been developed that modulate the clinical severity of SCD and may affect the evolution of organ damage. However, the application of these therapies – including hydroxyurea, acute and chronic exchange transfusion, and hematopoietic stem cell transplantation – has been hampered by the heterogeneity of the disorder. We have very limited understanding of the genetic modifiers and environmental factors governing the severity of disease manifestations and the development of late-end organ complications. While most patients will develop some complications, many of the most devastating disease-related manifestations – such as infection, stroke, and pulmonary hypertension – tend to affect only a subset of patients. Consequently, individualized effective therapy awaits new and better predictive techniques and treatment methods that can forecast the severity of illness, the response to therapy, and the likelihood of developing serious complications. The advent of genomic approaches and the development of strategies for evaluating clinical outcomes inform new opportunities for progress in sickle cell disease research. Future success will also be facilitated by the collection of comprehensive patient data using a well-funded long-term database/registry to perform phenotypic studies and assist with risk prediction.

Predictors of disease complications: Research should exploit newer techniques to identify genetic modifiers of disease severity and novel biomarkers that correlate with organ-specific late complications. Such studies would include Single Nucleotide Polymorphisms (SNPs), haplotype, and whole genome analyses, as well as development of improved imaging techniques and functional studies, such as transcranial Doppler and echocardiography.

Improved therapies: More and better drugs that increase fetal hemoglobin are needed. High-throughput small molecule screens should be used to identify agents that can achieve fetal hemoglobin levels of 30% or more in every red blood cell in every patient. Further studies are needed to improve outcome and availability of stem cell transplantation. Finally, groundbreaking gene therapy strategies in mouse models show promise for genetic correction.
of the disease using somatic cells; such studies should be promoted with a goal of translating them into humans. Implementation of new therapeutic strategies would be well-served by the establishment of a national clinical/translational patient network infrastructure to facilitate multicenter trials.

**Pain management/quality of life:** The supportive care of sickle cell patients reflects many shortcomings of the care to underserved populations. ASH supports collaboration of pain specialists and investigators in other disciplines to develop improved management standards and specific quality-of-life measures, including making the transition from pediatric to adult care for sickle cell patients more fluid and seamless.

**Organ disease and complications:** Further studies are needed to elucidate the mechanisms of end-stage disease, which has become more prevalent in the face of improved patient survival. Such research is required to develop interventions to prevent end-stage renal disease, to improve risk assessment and prevention of stroke and neurocognitive abnormalities, to understand and prevent pulmonary hypertension, and to manage and prevent late cardiac complications and sudden death.

**International outreach:** Sickle cell disease offers important opportunities to better understand the disease while contributing to the health of the international community. Africa offers a potential for better studies of the natural history of the disease, and as a comparative site for studying the benefits of hydroxyurea and other interventions in a new population of patients. Such international cooperation promises to improve sickle cell care and the quality of life for patients worldwide.

**HEMATOLOGIC MALIGNANCIES**

There has been an exponential increase in our knowledge about the genetic, biological, and molecular basis of transformation in hematologic malignancies. This has created unprecedented opportunities for identifying and targeting deregulated pathways as a potential therapy of these diseases. Importantly, the pathogenetic mechanisms elucidated in hematologic malignancies have relevance for cancer in general, including cell cycle, apoptosis, and signaling pathways. As discussed further under priorities for “Research Infrastructure,” this opportunity should be exploited by the development of multi-institutional translational research consortia focused on specific hematologic malignancies. Within these consortia, member institutions and their network of investigators would collaborate to create banks of tumor samples linked to bioinformatic platforms and outcome data. Molecular profiling and curating of tumor cells should result in a more comprehensive assessment of deregulated molecular pathways, and identify potentially “druggable” targets in hematologic malignancies.

**Molecular profiling of hematologic malignancies:** A top priority for the research agenda is the accumulation of genetic, genomic, and proteomic profiles of hematologic malignancies. This should create a new molecular taxonomy that elucidates their molecular basis, facilitates the development of rapid clinical tests that will better delineate disease classification and prognosis, and contributes to the targeting of critical oncogenic pathways with novel, specific therapies. This initiative will be facilitated by the consortia proposed above.
**Neoplastic stem cells:** New observations about malignant stem cells as the origin of hematopoietic malignancies and solid tumors should be exploited to define the similarities and differences between normal and cancerous stem cells. Studies aimed at identifying the hallmark changes that accompany malignant stem cell transformation should be encouraged. This should include in vivo models where the biology, pathogenesis, and targeted therapeutics for the leukemia-initiating stem cells can be evaluated. A comprehensive molecular profile of these cells will also help identify deregulated pathways for future targeted therapeutics to eliminate stem cells and their progeny in hematologic malignancies. There is a growing sense in the field that epigenetic as well as genetic changes are important. Hematopoietic malignancies have been and will continue to be models for these studies, the goal of which is the development of targeted therapies. As also recommended in the section on “Stem Cells,” an important objective should be to support further research to elucidate the biology and the role of the bone marrow and lymph node microenvironment in sustaining hematologic malignancies. This effort is also likely to illuminate novel therapeutic options for hematologic malignancies.

**Treatment of hematologic malignancies:** Promising early results with novel therapeutic approaches should be extended. This includes a wide range of novel and developing therapies: 1) continued development of epigenetically targeted therapies based on elucidation of mechanisms of gene silencing; 2) exploration of the potential of RNA interference (RNAi)-based gene therapeutic approaches; 3) development of anti-angiogenesis therapies based on a clearer understanding of the relationship between angiogenesis and disease progression; 4) investigation of molecular therapeutics focused on drug resistance, apoptosis, and survival signaling; and 5) cell therapy with immune effector cells, especially in treating minimal residual disease. Molecular profiling, tissue array, and other correlative analyses should be incorporated into prospective clinical trials to identify biomarkers of response and resistance, with the ultimate goal of more individualized patient therapies.

**TARGETED, CELLULAR, AND GENETIC THERAPIES**

With the mobilization of appropriate resources, opportunities exist to exploit the considerable data generated by recent genomic, proteomic, and other basic science initiatives for translation into novel therapeutics. Progress in clinical gene transfer has helped to define the safety profiles of viral and non-viral gene delivery vehicles. Lentiviral and adeno-associated viral gene transfer vectors have emerged as particularly promising approaches for genetic modification. Further information on the safety of lentiviral, foamy viral, and other viral vectors is needed. Proposed projects in the functional genomics of cancer, especially the hematologic malignancies, will provide further valuable information and should be strongly supported. Moreover, the development of molecular probes to better understand biological pathways is likely to lead to the identification of potentially effective small chemical and peptidyl therapeutic molecules. The paradigm for such therapies is the successful treatment of chronic myeloid leukemia with imatinib. More recently, an acquired mutation leading to the activation of JAK2 kinase, the initiator of signaling for erythropoietin, thrombopoietin, and other factors, was discovered to be frequently present in myeloproliferative disorders, including polycythemia vera, essential thrombocytemia, and idiopathic myelofibrosis. The development of additional specific JAK2 kinase inhibitors with less toxicity for management of...
patients affected by these disorders should be pursued with alacrity. To help achieve the goal of bringing novel targeted agents to treat hematologic disorders to the clinic more quickly, resources must be deployed for the concerted promotion of studies in target identification and validation; in silico drug design; physical screening for lead compounds; preclinical investigations, including the design of the most appropriate animal models; medicinal chemistry; pharmacokinetics; and toxicology. For gene transfer, additional resources for pharmacology/toxicology testing and for production of clinical-grade vectors continue to be urgently needed.

**Targeting neoplastic stem cells:** Recent data support the importance of the concept of neoplastic stem cells. A high priority is the detailed investigation of malignant stem cells that will not only elucidate pathobiology but identify appropriate target cells for genomic, proteomic, and epigenetic studies and, ultimately, for the most appropriate targets for eradication by novel drugs and immunotherapeutics.

**Regenerative medicine:** Intensive research efforts are underway to study the regeneration of damaged tissue using bone marrow, peripheral, or cord blood-derived cells, as well as non-hematopoietic progenitor cells, including mesenchymal cells. It should now be a high priority to support basic and translational research aimed at better understanding the cell types and mechanisms leading to improvements in clinically relevant endpoints in both animal models and patients. Preclinical studies are essential to help design, as soon as possible, the most appropriate clinical trials with meaningful endpoints. The development of multidisciplinary teams with clinical and basic science expertise in stem cell biology, imaging and cell tracking studies rapidly applicable to clinical trials, cell transplantation methodology, clinical trials design, and organ-specific knowledge should be strongly encouraged.

**Cellular and genetic therapies:** The convergence of cellular and genetic therapies presents exciting opportunities for the management of benign and malignant hematologic diseases. Current investigation of cell-based therapies for hematologic and other malignancies with immune effector cells (adaptive and innate) should be strongly promoted. To enhance the safety and efficacy of such therapies, including mesenchymal stromal cells for immune suppression, high priority should be given to genetic modification to enhance biological function and, if necessary, to eliminate the cells in vivo with innovative gene suicide strategies. Furthermore, genetic manipulation of stem and progenitor cells, in particular, holds a considerable promise, especially with the newer generation of retroviral vectors, and should also be encouraged. Cures have resulted from genetic therapy of primary immunodeficiencies. Complications arising from insertional mutagenesis in X-linked Severe Combined Immunodeficiency (SCID) patients have led to re-engineered vectors in an attempt to avoid dangerous integration events. With these advances, additional preclinical and clinical studies need to focus on the thalassemias, sickle cell anemia, and hemophilia. The latter represents an excellent disease model for demonstrating proof of principle for different vector delivery systems. Success with any of these strategies (lentiviral, AAV vectors) will have immediate applicability in a wide range of diseases. Efforts are still required to enhance gene transduction, subsequent transgene expression, and more efficient engraftment of transduced cells. The continued availability of resources that enable clinical studies to be conducted, such as the centralized manufacture of clinical-grade vectors and genetically modified cells, as well as institutional clinical trials support, is
critical to the success of genetic therapies as a viable treatment option.

Immune therapy: Monoclonal antibodies are now commonly used in the treatment of malignancies, and many additional antibody-based therapies are being developed. Cellular elements of tumor immunity play a major role in the success of graft-versus-tumor responses after allogeneic hematopoietic stem cell transplantation; they also have a great potential for treatment and prevention of cancer in autologous settings. Increasingly, novel approaches based on basic advances in tumor immunology are being tested in animal models and evaluated in clinical trials. Identification of critical tumor antigens, methods to enhance effective cellular responses, and methods to maintain immune responses over time will facilitate the development of more effective immune therapies for hematopoietic and non-hematopoietic malignancies.

Immunobiology
Hematology research over the past 20 years has substantively contributed to the remarkable advances in our understanding of the mechanisms of innate and adaptive immune recognition, response, and regulation. These basic advances in immunobiology have already led to the development of many new therapies for a variety of autoimmune, inflammatory, and neoplastic diseases. Further research in this area should lead to new approaches to improve the outcome of hematopoietic and solid organ transplantation, to treat autoimmune diseases, to induce effective tumor immunity, to develop more effective vaccines, and to limit tissue damage from inflammation. To foster advances in immunobiology, the following areas of basic and applied research should be highlighted.

Lymphopoiesis: The mechanisms whereby hematopoietic stem cells give rise to a diverse set of immune cells are not well understood. Identification of critical genes, epigenetic elements, and microenvironmental signals that regulate normal stages of lymphopoiesis will lead to novel approaches for enhancing immune reconstitution in vivo after cytotoxic chemotherapy or hematopoietic stem cell transplantation, following infection with Human Immunodeficiency Virus (HIV), and with aging, as well as the potential generation of functional immune cells ex vivo. Research in normal lymphopoiesis will also improve our understanding of mechanisms that contribute to malignant transformation of lymphoid cells, and potentially lead to new therapies for lymphoid cancers.

Innate immunity: It is now appreciated that various components of innate immunity play important roles in the response to infectious agents, malignant transformation, and tissue injury. These components, including monocyte/macrophages, neutrophils, dendritic cells, γδ-T cells, and natural killer cells, also interact with the adaptive immune system to initiate and amplify productive T- and B-cell responses. Research defining mechanisms that regulate innate responses, such as Toll-like receptors, killer immunoglobulin-like receptors, leukocyte inhibitory receptors, and the interactive networks with adaptive immune cells, will provide new opportunities for manipulating immune responses to external pathogens, malignant cells, and normal tissues.

Adaptive immunity: The structural basis for antigen recognition by specific T- and B-cell receptors is becoming increasingly clear. Mechanisms for development and maintenance of a diverse repertoire of T and B cells capable of distinguishing “self” from “non-self” and maintenance of immunologic memory are also
being elucidated. Aberrations in these pathways lead to autoimmunity or immune deficiency. Research in these areas will improve our understanding of the pathogenesis and treatment of autoimmune diseases, which, in turn, will lead to the development of more effective immune therapies for hematologic and non-hematologic malignancies.

**Mechanisms of immune response:** Many intracellular pathways that mediate critical elements of immune function, such as cell membrane receptor signaling, lymphocyte maturation, clonal selection, antigen processing, and apoptosis, have been described, and new interactive elements continue to be identified. Further studies will be able to determine how large networks of positive and negative signals are continuously integrated to modulate and maintain effective immune responses in different cell types.

**Immune cell trafficking:** The elucidation of mechanisms of immune cell adhesion and homing has already led to new opportunities for manipulation of immune responses in diseases of autoimmunity and inflammation. Recent advances in live cell imaging within the immune system in animal models have greatly expanded our knowledge of cellular dynamics within the lymphoid tissue. Research in this area will likely identify many novel ways of directing and modulating immune responses in vivo.

**Immune regulation:** Recent advances have highlighted the critical role of immune regulatory cells in the maintenance of immune homeostasis. Deficient immune regulation leads to autoimmunity, while excessive immune suppression induces functional immune deficiency and an inability to develop effective immune responses to infectious agents and transformed cells. Further studies of mechanisms of immune regulation and how these pathways interact to maintain immunologic control will identify critical checkpoints that contribute to the disease. Such pathways could be therapeutic targets for restoring immunity against cancer or inducing immunologic tolerance in autoimmune disorders and transplantation.

**Transplantation immunology:** Advances in transplantation of hematopoietic stem cells and solid organs continue to improve the outcomes for patients with a variety of congenital, degenerative, and malignant diseases. Nonetheless, immunologic barriers resulting in tissue rejection or graft-versus-host disease (GVHD) remain critical obstacles to the development of new allogeneic cell-based therapies for many diseases. Research into mechanisms of immune tolerance and other aspects of transplantation immunology will have a considerable impact on the development of new approaches to prevent rejection of allogeneic cells and tissues. Studies aimed at preventing GVHD while at the same time optimizing graft-versus-leukemia should be encouraged.

**Aging and the immune system:** Aging of the immune system can lead to changes in lymphoid cell dynamics, autoimmunity, and lymphomagenesis. Although little is known about the biological changes associated with aging, it seems likely that epigenetic and genetic influences may alter the normal differentiation pathways of lymphoid cells and favor clonal abnormalities in response to certain antigenic stimuli. Research in this area could greatly improve our understanding of how interactions with the environment can alter the host immune system over time, and potentially lead to therapeutic approaches to correct abnormal control mechanisms that can occur during aging.
THROMBOSIS, HEMOSTASIS, AND VASCULAR BIOLOGY

In the U.S., about 500,000 venous thromboembolic (VTE) events, 1.1 million myocardial infarctions (MIs), and more than 150,000 stroke deaths occur every year. Atherothrombosis is central to the pathogenesis of thrombosis, as it is the dominant cause of morbidity and mortality in the Western world. In hemostasis research, there are numerous potential opportunities for the translation of recent basic science advances into clinical benefits. Important and timely areas of investigation in thrombosis, hemostasis, and vascular biology are summarized below.

Antithrombotic therapy: Despite the recent therapeutic advances with low-molecular-weight heparins, pentasaccharides, and direct thrombin inhibitors, bleeding remains a significant complication of anticoagulant therapy; and agents with a better risk/benefit ratio are needed in the management of VTE. The therapeutic armamentarium for preventing and managing arterial thrombosis remains limited. For both venous and arterial thrombosis, new and better agents, especially oral drugs, are needed. The development of novel targets for antithrombotic therapy will require a more detailed understanding of the physiology and pathophysiology of thrombus formation. Characterization of predictors of drug benefit or risk will also translate into better therapy.

Early mechanisms of arterial and venous thrombosis: The initiating cellular and molecular factors in most venous thromboses are unknown. It remains unknown why venous stasis contributes to thrombosis. Similarly, what triggers clot formation in patients with known thrombophilia also remains to be defined, as does the relationship between increasing age and thrombotic risk. A better understanding of the role of platelets, endothelial cells, inflammation, and innate immunity in these processes is crucial, and integrating these systems into existing information regarding hemostasis and fibrinolysis will help define the early mechanisms in thrombosis. Basic research is also required to elucidate the roles of platelets and vascular biology in the atherothrombotic complications of obesity, diabetes, and aging.

Thrombophilia and risk modification: Counseling patients and families regarding genetic risk factors for first or recurrent thrombosis has become a standard part of hematology practice. Many of these patients are seen in consultation in primary clinical settings outside of hematology. Large clinical studies are needed to establish norms for screening and risk modification of patients that are at risk.

Animal models for venous and arterial thrombotic disorders: Although there are a number of animal models of arterial thrombosis, most are not representative of atherothrombosis, and good models of venous thrombosis are similarly lacking. Consequently, novel animal models that more closely mimic human disease are needed to better define the pathophysiology of thrombotic disorders.

Genomics and proteomics: Easy access to blood has facilitated advances in our understanding of the biochemistry and physiology of coagulation, fibrinolysis, and platelet function. The identification of common modest-risk genetic variants influencing platelet reactivity, coagulation, and fibrinolysis will help to elucidate the factors contributing to thrombotic risk. Other polymorphisms, such as those correlated with warfarin metabolism, will have an important impact on therapy.
**Cancer-related thrombosis:** VTE is a leading cause of morbidity and mortality in cancer patients. Nevertheless, VTE in cancer remains under-diagnosed and under-treated, and its mechanisms are poorly understood. The association of VTE with specific tumor types, including mucin-secreting adenocarcinomas, suggests there are mechanisms of VTE in cancer that may be different from those in patients without cancer. The roles of tissue factors, prothrombotic microvesicles, platelets, and novel tumor procoagulant molecules need to be further investigated, as does the role of inflammatory factors, such as Tumor Necrosis Factor (TNF) and vascular endothelial growth factor. The mechanism of cancer-related thrombosis should be better defined in animal models. The potential anti-tumor, anti-metastatic, anti-angiogenic, and anti-inflammatory effects of heparins and other antithrombotic agents need additional study, particularly at a cellular and molecular level.

**Thrombosis and vascular disease unique to women:** Much but not all of the gender-specific thrombotic risk in women reflects hormonal changes associated with pregnancy, oral contraceptives, and therapeutic hormone administration, but the factors contributing to increased risk in any individual are poorly understood. Elucidation of the pathophysiology of thrombotic microangiopathy in the setting of eclampsia and pregnancy may permit more rational interventions for prevention. They may further provide insight into the overall increased risk for these syndromes in non-pregnant women. Finally, further studies aiming to understand gender differences in the response to anti-platelet therapy may improve treatment.

**Stroke:** Greater attention needs to be focused on the basic hemostatic mechanisms in the cerebrovascular circulation, including the role of platelets, coagulation, and fibrinolysis in the pathogenesis of stroke. This should be coupled with translational investigations into appropriate and novel antithrombotic treatments. Appropriate animal models need to be developed to enhance progress in this area.

**Inherited coagulopathies:** The hemophilias remain excellent candidate diseases for the application of innovative genetic and cell-based therapies. Progress has been made in the pre-clinical evaluation of various viral vector-mediated approaches to the gene therapy of hemophilia, but obstacles such as host innate and adaptive immune responses need to be overcome if clinical success is to be achieved. Other therapeutic advances that show promise and should be encouraged include development of clotting factor molecules that demonstrate enhanced biological and therapeutic characteristics such as prolongation of the circulating half-life and reduction of immunogenicity. Finally, our knowledge of the molecular pathogenesis of von Willebrand disease and less common inherited coagulopathies continues to improve, and small animal models of these pathological hemostatic states are now required to enable detailed in vivo investigation.

**Acquired coagulopathies:** In the hospital setting, most bleeding problems related to acquired coagulopathies are caused by liver disease, various pathologies causing Disseminated Intravascular Coagulation (DIC), and poorly controlled anticoagulation. In each of these situations, current blood component therapies are sub-optimal, and further investigation is required to develop targeted procoagulant molecules that can treat bleeding and reverse the type of anticoagulation associated with the new generation of direct thrombin and factor Xa inhibitors. Some of these novel molecules will also have the potential to provide hemostatic benefit to patients with factor VIII and IX antibodies.
HEMATOLOGY OUTCOMES AND SOCIETY

Molecular research and discovery can lead to novel and improved diagnostic and therapeutic approaches to hematologic disease. The American Society of Hematology also supports and seeks to further stimulate investigation aimed at improving health care delivery and patient outcomes. Nevertheless, clinical quality improvement and related research domains remain relatively new areas of investigation in hematology that deserve attention. This recognition is in alignment with the major policy-making institutions such as the National Institutes of Health (NIH), the Institute of Medicine (IOM), and the National Science Foundation (NSF).

Quality: There is a need to better understand the quality and outcomes of care that is received by patients with hematologic diseases. One priority is to identify clinically significant gaps in hematologic care and address sub-optimal use of evidence-based interventions. A more challenging priority is to develop new metrics and to show definitively that they can be linked to improved clinical outcomes.

Delivery of care: The challenge of improving the availability and cost-effectiveness of clinical care for patients with chronic hematologic disease is another priority. Sickle cell disease management continues to be particularly important because it affects children and young adults, and because optimal care requires multidisciplinary approaches. Management of patients with sickle cell disease is particularly challenging in the face of our current fragmented and ineffective system of health insurance and medical financing. Important research remains to be done on the most cost-effective way of serving this patient population and their families. Models for delivering excellent and cost-effective care for other significant patient groups also require study, including individuals with chronic diseases such as myelodysplasia and anemia in the elderly.

Survivorship: It is important to continue to study how the treatment of clinical hematologic disease such as lymphoma and leukemia in children and young adults influences the quality of life of patients and the risks of secondary disease. One priority is to establish and test algorithms for follow-up of known risks to learn if late complications can be mitigated and quality of life improved.

Hematology in developing countries: The challenge of introducing known standards of care into the population of developing nations is familiar to ASH. Another research priority is to identify specific areas of hematologic research that promise the greatest impact on helping health care systems evolve in developing nations. The ASH International Consortium for Acute Promyelocytic Leukemia (IC-APL) has brought together hematologists from several developing nations to model a clinical research program along the guidelines of current standard of care for APL. This highly successful endeavor serves as a model for how the clinical and scientific expertise of the ASH membership can foster international cooperation and guide the development of clinical research strategies to improve outcomes for patients worldwide. Such programs should be embraced and expanded.
There is a current projected shortage in the overall physician workforce that is augmented by a specific decline in physicians choosing to specialize in adult and pediatric hematology. The American Board of Internal Medicine statistics reveal that, in the 1970s, an approximately equal number of candidates sought certification for hematology and medical oncology. Since then, the number of hematology certifications has declined; in contrast, the number of physicians certified in medical oncology has steadily risen. In 2006, 200 more graduates of adult training programs were certified in medical oncology than in hematology. A published survey of training program directors conducted by ASH raised concern “over the small number of trainees who opt for single-board eligibility in hematology (10%) and pursue careers in non-malignant hematology (<6% of graduates of adult training programs)” (Blood 2004;103:4383). Graduates of training programs report increasing difficulty in financially supporting a practice without including the care of patients with malignancy; hence, malignant disease experiences during training are often maximized at the expense of benign hematologic disorders. Other external factors, including a lack of visibility among other physicians, the lay public, policy-makers, and elected officials, have also contributed to “the apparent wholesale incorporation of hematology into mainstream oncology” (The Hematologist 2004: vol. 1, issue 4). This decline in trainees endangers clinical care and the future of hematology research, especially in non-malignant disorders.

Despite declining numbers of trainees pursuing careers in non-malignant hematology, the need for hematologists in academic health centers, in specialized centers (e.g., hemophilia, sickle cell disease), and in the wider medical community is expanding. Moreover, in private practice, there are increasing pressures to restrict the delivery of subspecialty care for non-malignant hematology disorders to those with hematology certification (The Hematologist 2007: vol. 4, issue 6). Training programs and agencies supporting career development must therefore intensify their efforts to preserve the continued availability of talented hematologists in the physician workforce. The following training initiatives are considered to be of the highest priority:

Training programs: Collaboration among fellowship training programs and undergraduate, medical, and residency programs must be encouraged to foster early exposure to the broad opportunities available in hematology and to promote physician-scientist training. For fellows opting for hematology training, combined fellowship programs should emphasize training in benign hematology and related fields. Formal training in both hematology and a related discipline may stimulate more young investigators to pursue, and to remain in, academic careers. Practical examples of such programs include combined training in a) non-malignant hematology and laboratory medicine; (b) non-malignant hematology and transfusion medicine; (c) adult and pediatric hematology emphasizing the diseases that extend from childhood to adulthood; (d) hematology and geriatrics; and (e) hematology and training for leadership positions for non-malignant hematology.
public health careers. ASH welcomes the opportunity to collaborate in setting curriculum development, developing trainee evaluation tools, and determining benchmarking goals.

The NIH physician-scientist T32 training grant program must be preserved. Recent limitations of NIH funding endanger financial support for T32 grants. Not only has the overall number of these grants declined, but the laudable desire to provide funding to less-developed training programs has eroded support for successful, more mature programs. Training grants focused on non-malignant hematology should be encouraged, as such programs help offset the trend toward the focus on malignant diseases within hematology/oncology training programs and promote the development of careers in under-represented areas of hematology. Areas of focus should include stem cells, molecular therapeutics, hematopoiesis, myelodysplastic and myeloproliferative disorders, vascular biology, transfusion medicine, thrombosis and hemostasis, and hematologic consequences of non-hematologic disorders. Successful training demands dedicated multidisciplinary mentors who provide both scientific guidance and career direction. To attract skilled and dedicated mentors, T32 awards should provide for financial support commensurate with mentoring effort.

Another continuing priority is to promote the career development of post-doctoral level PhD scientists pursuing hematology-based careers. Training grants should support a cadre of PhD scientists to integrate into the curriculum with clinical trainees to provide basic science support for understanding normal and abnormal hematopoietic mechanisms, and to facilitate the effective translation of scientific discoveries to the clinic, especially in clinical trials.

Despite an anticipated shortage of hematologists, funding for all physicians in training, including hematologists, is at risk of being cut from the Centers for Medicare and Medicaid Services (CMS) budget. The loss of indirect and direct medical education (IME and DME) dollars to academic hospitals will decrease the number of training program positions these hospitals can afford. ASH will continue to work with members of Congress, and others, to promote an environment that adequately addresses hematology training and workforce needs.

Transitional awards: For the continued career development of scientists at the crucial transition from a trainee to junior faculty, we advocate the continuation and enhancement of the mentored career development awards already offered by the NIH, such as the NRSA, K, and K99/R00 awards. We support the continuation of awards specifically aimed toward non-malignant hematology that require career development activities and curricula devoted to developing academic careers in non-malignant hematology. As with the T32s, financial support should be provided for K award mentors commensurate with effort. Increasingly, young physician-scientists are attempting to balance family and work responsibilities during a critical time in their careers. To improve the viability of the physician-scientist pathway, the NIH should consider modifying the part-time eligibility rules for its Research Career Development Awards to open eligibility and increase flexibility.
Support of new investigators: ASH believes that a top priority during this time of fiscal constraint is to support first R01 applications by new investigators. R01s are the backbone of the research enterprise and an essential element to protection of the field from further losses. The new K99/R00 provides a nice transition, but does not eliminate the hurdle of achieving a first independent research grant. NIH initiatives to provide special consideration to new investigators are applauded. Furthermore, as research becomes increasingly collaborative, the value of new investigators in a multidisciplinary research team should be recognized through the NIH grant funding mechanisms, as well as in academic promotion.

Mid-career transitional awards: Physician-scientists with heavy service responsibilities and researchers in other fields of hematology should be encouraged to devote more of their time to the study of hematologic disorders. Many of these investigators have an in-depth understanding of the molecular basis of hematologic diseases and the combined experience in the laboratory with care of patients with hematologic disease. Moreover, although much of the emphasis and funding in hematology has been on malignant diseases, there is a potential to attract researchers to non-malignant hematologic diseases and to increase awareness of funding opportunities such as NIH K22 and K24 (and other) programs that are specifically targeted for hematology.

Part-time and shared academic faculty positions: As the demands of career and personal life increase, many academic physicians wish to pursue non-traditional employment models. Academic institutions are struggling to define how to accommodate a desire to better balance career and personal life through part-time or shared employment positions. Specifically, ASH supports and will continue to work to modify the corresponding criteria for academic promotion, job expectations and responsibilities, and salary and benefits structure.

CORE RESOURCES

Integrated institutional basic and translational research centers: The future of hematology requires that research in diverse areas of basic science be integrated and translated into novel, decisive therapies that will effectively prevent or cure serious blood and vascular diseases. Integrated multidisciplinary institutional research centers can provide invaluable synergies at many stages in the translational cycle, from efficiently stimulating the most important basic research within individual investigators’ laboratories to encouraging active collaboration between multiple investigators around common themes to supporting novel clinical trials. Such trials can, in turn, circle back to the bench by providing the basis for further hypothesis-driven basic investigation. We, therefore, consider it a high priority to create such integrated multidisciplinary institutional research centers, with the specific goal of accelerating progress from discovery to prevention and cure of hematologic disorders.

Based on the experience of elements of other center programs that work well (e.g., cancer centers), as well as those that do not, we believe that these institutional centers for hematologic disorders should support key resources that are not readily available through individual investigator grants or institutional funds, including:
1. Basic research cores supporting sophisticated technical capabilities that are not easily duplicated within individual laboratories, but are in high demand. These might include: stem cell production, in vivo xenogeneic transplant assays, bioinformatics, live animal bioimaging and cell tracking, in vitro vascular modeling and vascular dynamics, tissue engineering, and nanotechnology.

2. Translational and clinical research cores, including genomics and proteomics cores, small molecule discovery facilities, pharmacokinetic and pharmacodynamics units, clinical trial support and monitoring units, and biostatistical cores. For early phase clinical trials in humans, core facilities must be able to provide “clinical-grade” reagents and regulatory support, and facilitate the combined use of therapeutic agents from different sources.

3. Seed funds for novel research, including pilot project awards, collaborative research proposals bridging multiple investigators from diverse scientific disciplines, and translational research proposals testing new reagents in proof-of-concept clinical trials.

4. Prevention/outreach education materials should be readily available. One of the most important missions of the public health/research community is the promulgation of information about disease prevention, screening, and health education. We believe that academic centers should serve as an organized and efficient agent of communication with the public about these issues while conducting appropriate clinical trials. Integrated institutional research centers should, therefore, support key infrastructure for such efforts in hematologic disorders, including genetic screening programs, clinical trial recruitment cores, and public information resources.

Note that none of these areas overlap with essential programs such as individual and multi-investigator projects, fellowships, or new and translational investigator awards, each of which, we feel, is most appropriately managed under their current highly efficient and effective structures.

National resource centers: National resource centers focusing on blood diseases would have an important impact on research of these disorders. Given advances in information storage and technology, these may be “virtual centers” rather than localized or centralized institutional centers. These collaborative networks of multiple academic medical centers would: (1) establish centralized disease-based registries and databases for both common and rare hematologic disorders; (2) collaborate to design and prioritize clinical trials; (3) collect and store biological specimens for future researchers; and (4) coordinate the prospective recruitment and registration of patients with hematologic disorders into available clinical trials at the national level.

Particular examples of such national resource centers would include networks for rare hematologic disorders and hematologic malignancies. For rare blood disorders, the national resource centers would provide detailed phenotyping. The maintenance of detailed databases and easy access to these databases would facilitate clinical studies of patient populations whose prevalence is too low to allow single-
institution clinical trials. For example, thrombotic thrombocytic purpura (TTP) is a disorder whose etiology has been almost completely identified. The development of diagnostic and treatment strategies requires access to numerous patients to support clinical trials, but a disorder like TTP requires pooling of patient data, since no one center sees sufficient numbers. Large patient populations could be characterized over decades, as hematology equivalents to the Framingham study model. Patient data and materials would be deposited, and investigators would have access to these data to explore new hypotheses. These data could provide phenotyping for long-term epidemiologic outcome studies, which are critical for defining the role of genetic variation in the development and progression of disease, and are not typically funded in investigator-initiated grant proposals. These national resources could also collaborate with the National Marrow Donor Program and a national cord blood facility to supply well-characterized stem cells to support individual research projects. A national central Institutional Review Board (IRB) would facilitate conduct of research in rare diseases, rather than requiring each center to obtain local IRB approval to submit information and samples to the national center.

The creation and activities of multi-institutional translational research consortia focused on specific hematologic malignancies would help create banks of tumor samples, which should be linked to accessible bioinformatic platforms, including clinical profiles and outcomes. The consortia would also perform molecular profiling and curating of the tumor cells aided by high-density genomic arrays, as well as epigenome, proteome, and phosphoproteome analyses. This effort should result in a more comprehensive assessment of the deregulated molecular pathways and identify potentially “druggable” targets in hematologic malignancies.

National centers could also be a resource for the development of animal models not currently available to study disease pathogenesis. Examples are the absence of adequate animal models to study the pathogenesis of thrombotic disorders, such as venous thromboembolism, atherosclerotic plaque development, stroke, the role of platelets in angiogenesis, and the absence of a mouse model for atherothrombosis. Given the importance of animal models in the study of vascular biology, these genetically modified animals would be available to the research community. Furthermore, multidisciplinary efforts to develop novel technology for exploiting these animal models could be shared with the general research community or made available in regional or centralized facilities.