Breakthrough therapies designed to treat **blood disorders** not only benefit hematology patients, but also advance the care of patients with **other diseases**.
Hematology: A Critical Field For All of Health Care

The field of hematology has made significant contributions to human health over the last hundred years. With the advances gained through an increasingly sophisticated understanding of how the blood system functions, hematologists (both scientists and clinicians) have changed the face of medicine through their dedication to improving the lives of patients around the world.

More than a century ago, early hematologists laid the foundation for the field with the first descriptions of leukocyte phagocytosis, the coagulation system, and the lymphomas. In the last few decades, hematologists have pioneered uses for gene cloning, recombinant protein expression, and genome sequencing. Recently, leaders in hematology have applied these techniques to define novel treatments that have had a dramatic impact on patient survival. And today, hematologists are at the forefront of biomedical discovery, finding the precise DNA alterations that can determine whether a patient responds to a given therapy or not.

Importantly, many of the new treatments for blood disorders are applicable beyond the field of hematology and have already proved beneficial for many patients with other diseases. Examples of these applications are illustrated in the success stories below. Hematology research has advanced health care on many fronts, and small investments in this field have yielded large dividends for many other disciplines.

Despite impressive progress in understanding and treating hematologic disease, significant challenges remain, as each new discovery illustrates how much more we have yet to learn. The challenge now is to translate these new discoveries into patient care that delivers better survival, less toxicity, and even disease prevention.

The American Society of Hematology (ASH) Agenda for Hematology Research describes the valuable contributions of hematologists and illustrates the necessity of continuing to place this specialty among the top priorities for funding within the health-care community, both today and in the future. The first section describes stories of success in treating hematologic diseases, demonstrating the return on investment from past hematology research. The second half outlines the foremost challenges still confronting the field and identifies the highest priority scientific themes for the Society.
Hematology Advances Have Saved Lives

Success Story: Chronic Myeloid Leukemia Mortality Falls Significantly in a Generation

Just five decades ago, chronic myeloid leukemia (CML) was usually fatal. Because of a better understanding of the precise molecular basis for this disease, the mortality rate has decreased significantly, and fatalities from CML are now uncommon. This remarkable success story started in 1960, when a team of scientists in Philadelphia, using a simple desktop microscope, found that bone marrow cells from patients with CML had a unique chromosome. They called this abnormality the Philadelphia chromosome. It was later found to be the result of a translocation between chromosomes 9 and 22. Other hematologists uncovered the fusion gene formed by the translocated chromosome, known as BCR-ABL, which caused the myeloid cell proliferation that marks CML.

Despite that critical understanding of the disease biology, treatment advances for this disease took more than two decades of meticulous work. Bone marrow transplants were often used, but this treatment was costly, both economically and physically. Treatment of CML with the drug interferon could also produce remissions in some patients, but it was expensive, it had severe side effects, and the remissions were usually not long-lasting.

Many years later, the hematology community made a discovery that would forever change treatment and prognosis of this disease. A team of hematologists studying compounds that might prevent tumor cells from proliferating found one compound in particular that seemed to rapidly kill CML cells. Later studies confirmed that the compound, today known as imatinib, was remarkably effective in the treatment of CML and had very low toxicity.

The overall death rate from CML in the U.S. population decreased significantly after the introduction of imatinib.

The upper red line is elderly patients (80+ years old), the middle blue line is older patients (60-79), and the lower green line is younger patients (under 50). The downward inflection in each of these age groups indicates the marked decrease in death rate in the general population. American Journal of Medicine, 2010 Aug; 123(8):764-773.

\[\text{Patients 80+ years old} \quad \text{Patients 60-79 years old} \quad \text{Patients under 50 years old}\]
This hematology drug has since been used to treat a number of other types of cancer and has spawned a new generation of drugs known as the kinase inhibitors. There are now many distinct kinase inhibitors approved to treat a wide variety of cancers throughout the body. The success of imatinib did more than transform CML from a fatal cancer into a treatable disease; it also demonstrated that inhibition of kinase activity could be a successful cancer treatment strategy in general.

**Success Story: Anti-Platelet Drugs Prevent Heart Attacks**

Platelets are responsible for clotting and are also critical in wound healing. When the wall of a blood vessel is torn, platelets bind to the damaged area to form the primary plug that seals the hole. With a detailed understanding of the mechanisms that support platelet function, hematologists have markedly improved the treatment of several important clinical disorders. For example, this understanding of platelet function has improved the treatment of blockage in the arteries of the heart to help prevent and reduce deaths associated with myocardial infarction, one of the most common causes of death in America.

Acute coronary syndrome (ACS) affects more than one million people in the United States each year, almost half of whom will die from their condition, and the costs associated with ACS treatment now exceed $200 billion annually. Patients with ACS have a build-up of cholesterol plaque inside the coronary arteries. This plaque can rupture, causing injury to the vessels and stimulating the nearby platelets to form a clot over the ruptured plaque. But if the vessel area surrounding the ruptured plaque is already narrowed from significant cholesterol plaque build-up, platelet clotting can cause a sudden and complete interruption of blood flow to the heart, causing a myocardial infarction.

A detailed understanding of platelet activation has allowed hematology researchers to develop new anti-platelet drugs that have profoundly improved the management and treatment of ACS. Most of these drugs, including the long relied-upon aspirin, prevent platelets from being activated near injured tissue, while other drugs prevent platelets from sticking together within the coronary artery. When used in combination, these drugs have consistently reduced the risk of death and recurrent heart attacks associated with ACS.

So far, the use of these anti-platelet drugs to treat heart disease has decreased ACS-related deaths by about one-quarter, and similar improvements have been demonstrated when these drugs are used to prevent strokes. This is a tremendous achievement by hematologists that has improved cardiac care, but work

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**Research** on the function of platelets in blood clotting **resulted in the development of drugs for heart disease and stroke.**

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The peripheral blood from a patient with chronic myeloid leukemia.
remains to further improve the care of these patients. For example, the same drugs that reduce death from heart attack or stroke can inadvertently harm patients by increasing the risk of bleeding. Funding is critical for research to develop even more effective anti-platelet drugs that can block inappropriate blood clotting in coronary arteries while allowing platelets to control bleeding elsewhere in the body.

**Success Story: Multiple Myeloma Survival Doubles in 10 Years**

For many decades, multiple myeloma was an incurable bone marrow cancer with an average survival of just three years. This poor prognosis remained unchanged until the past decade, when survival rates have more than doubled, thanks to a significantly improved understanding of the disease.

This success has been the result of dedicated research on how myeloma cells are able to grow within the bone marrow environment. There have been three significant advances to achieve this remarkable success: the introduction of autologous stem cell transplantation, bone stabilizing drugs called bisphosphonates, and the discovery of several novel anti-myeloma drugs that are particularly effective when used in combination.

In the 1990s, the use of autologous stem cell transplantation increased survival in myeloma patients compared to conventional drug therapy, but the full effect of this procedure was not seen until the early 2000s, when it was vastly improved and a wider range of patients was made eligible for the procedure.

The discovery of several new drugs, including thalidomide, bortezomib, and lenalidomide, has had an even greater impact on survival rates of multiple myeloma. The use of these agents in both early and late stages of the disease has resulted in a paradigm shift in treatment protocols, as documented in numerous population-based databases worldwide. For example, a recent analysis of more than 250,000 myeloma patients found that the combination of stem cell transplantation and these new drugs has resulted in a significant improvement in survival. Thus, the remarkable synergy of combination treatments has resulted in even greater improvements in myeloma survival.

The future is even brighter, as innovative modifications of these novel drugs are currently in clinical trials. There is a long list of therapies being developed to target myeloma. The rapid pace of progress from basic research to clinical practice has not slowed, and the outlook for myeloma patients is exciting, as this once fatal disease becomes more and more treatable.

By combining new multiple myeloma drugs, **this previously incurable cancer's survival rate has doubled** in just 10 years.
Success Story: The Unlikely Cure of Acute Promyelocytic Leukemia

The success of the treatment of acute promyelocytic leukemia (APL) has undergone some of the most dramatic improvements, not only in the history of hematology, but in all of medicine. This rare disease was historically one of the most deadly forms of leukemia, with rapid proliferation and multiple complications (such as bleeding) that often killed patients within weeks of diagnosis.

In the 1970s, a regimen of cytotoxic chemotherapy helped cure up to one-third of APL patients, yet many patients still died from bleeding complications before the chemotherapy could take effect. Then in the mid-1980s, a natural product called retinoic acid, originally used to treat skin disorders, was found to differentiate APL cells into nearly normal mature neutrophils that rapidly died on their own. Retinoic acid also improved coagulation in this disease, thereby protecting patients from the hemorrhagic complications that often resulted in early mortality. Further research found that when used alone, the effect of retinoic acid was only temporary, but when combined with chemotherapy, it improved cure rates by up to 70 percent. Later, investigators found that arsenic trioxide, once used to treat syphilis, could also cure up to 70 percent of APL patients.

Evaluation of the mechanism of action of these two compounds found that they both directly degrade the oncogenic fusion protein PML-RARα, which results from the diagnostic chromosomal translocation of APL and is responsible for this disease. Because each of the drugs has different targets within that protein, clinical trials have demonstrated that greater than 90 percent of APL patients treated with a combination of these two agents are cured. In fact, many patients with APL who receive this regimen never need conventional cytotoxic chemotherapy.

Multiple strategies developed from modern cancer molecular biology research are now used to target a once-incurable cancer, resulting in a more than 90 percent cure rate without the need of chemotherapy.
Important Unsolved Problems for the Next Era of Hematology Research

Stem Cells and Regenerative Medicine: Improving Current Technologies to Cure Blood Disorders

The field of stem cell biology was started by hematologists studying blood cell development. Hematologists have been studying the basic biology of stem cells for decades, exploring their extensive potential to repair damaged tissue, fight infections, and reduce autoimmune diseases. The techniques and principles used by hematologists in the blood system have been applied to stem cells from many other tissues with great success, spawning a huge stem cell research effort in many countries. Research in hematopoietic stem cells has led to significant clinical applications. For example, hematopoietic stem cell transplantation has been used for both genetic diseases and patients with hematologic malignancies. Since the introduction of this clinical procedure, cure rates in these diseases have steadily risen.

Future stem cell advances are highly dependent on the ability to transplant stem cells at high efficiencies and then have them perform well once transplanted. Investigators have examined methods to amplify hematopoietic stem cells in the bone marrow and in umbilical cord blood, and several preliminary mechanisms for stem cell amplification may help make transplantation much more efficient.

Recently, several research teams have made significant progress in re-programming adult cells into an undifferentiated embryonic stem cell state. These re-programmed cells, known as induced pluripotent stem (iPS) cells, can subsequently develop into any tissue of the body. The cell re-programming is accomplished by transducing the genes essential for embryonic stem cells, such as Oct-4, Sox2, and Nanog, into fibroblasts obtained from adult skin or bone marrow.

These iPS cells may ultimately be used as a transplantable source of stem cells for any number of diseases. They can be generated and used in patients who have genetic blood diseases as well as other complex diseases because they have several theoretical advantages: they do not require access to human eggs or embryos, they will not be attacked by a patient’s own immune system, they serve as a continuous source of cells, and they are amenable to genetic manipulation. However, several barriers remain that currently prevent the clinical translation of iPS cell technology. Compared to other sources of stem cells, iPS cells have slower growth kinetics, are more genomically unstable, and have decreased efficiency for differentiation. These barriers are important areas for future research, and a federally funded Request for Applications to investigate solutions to these problems would be an important step in bringing the promise of iPS cells to the clinic.

Recent research has suggested that iPS cells can be manipulated to become hematopoietic stem cells with sustained funding, blood stem cells will be among the first tissues to be derived from iPS cells and used clinically to treat hematologic diseases. This will set the stage for repair of other tissues and, eventually, regeneration of organs.
and be used as a transplant source for patients who do not have a matched donor. If recapitulating the blood system is successful, it may also be possible to transplant other organs, such as the kidney, heart, or brain. Creating blood stem cells from iPS cells means the community will have a new source for blood stem cells. This will have huge medical impact, because more than two-thirds of patients lack a human leukocyte antigen (HLA)-matched sibling for a marrow transplant. This will also generate significant financial savings, as there is a substantial morbidity to using poorly matched sources of blood stem cells, including bone marrow and cord blood stem cells. Closer to clinical application is the ability to generate personalized megakaryocytes for unlimited, patient-specific platelet production from iPS cells. Such donor platelets could be produced from a diverse set of HLA serotypes for transfusion, which would prevent the complication of the recipient immunologically destroying transfused platelets. Funding of these precedent-setting approaches is crucial to the future of regenerative medicine.

New uses for iPS cells could be implemented with existing technologies, but progress is limited due to insufficient funding. For example, iPS-generated red blood cells from rare blood types could be used in blood banking as reagents to identify allo-immunized patients and blood units suitable for transfusion. This is already feasible, as only small numbers of these red blood cells are needed. Also, iPS cells generated from diseases could serve as targets to test new drugs in rare conditions. Further, use of iPS technology to generate individual cancer stem cells for drug testing may be extremely valuable, since most relapse occurs from the small stem cell population within a malignancy. Additional funding from national blood banking organizations and the pharmaceutical industry could accelerate these important efforts.

Studies with iPS cells have also provided new insights into how normal stem cells differentiate into mature lineages. Extensive studies of how hematopoietic stem cells regulate daughter cell fates have demonstrated that key transcription factor proteins in the nucleus of a cell can turn on an entire gene expression program. The hematology community is now keenly focused on understanding how these few key transcription factors alter a cell’s function and how they can modify the expression patterns of gene families. For example, recent research has found that regulating a single transcription factor can re-activate fetal hemoglobin

![Fluorescence representing the expression of fetal globin in differentiating human iPS-derived erythroid cells. Courtesy of Thalia Papayannopoulou, MD, DrSci](image-url)
in adult erythroid cells. This is a promising goal for therapy of sickle cell anemia. Results from these studies will also help to resolve other blood disorders like thalassemia, which carry a significant burden worldwide. Funding is absolutely critical to make progress in the discovery of compounds that target these regulatory transcription factors, particularly for chemical screening for modifiers of globin switching. This would provide a meaningful advance for the millions of people with sickle cell anemia and thalassemia around the world.

Myelodysplastic Syndrome and Acute Myeloid Leukemia: Finding an Effective and Personalized Treatment for the Elderly

More than 12,000 Americans of all ages are diagnosed with acute myeloid leukemia (AML) every year. If left untreated, this aggressive disease can lead to death within a matter of weeks. Fortunately, thanks to advances in hematology research, this disease can now be cured in up to 40 percent of patients.

A related condition, myelodysplastic syndrome (MDS), affects an additional 10,000 Americans annually, and although less aggressive than AML, it is ultimately fatal in the vast majority of patients as a result of bone marrow failure, immune deficiency, and, in some cases, transformation to AML. MDS can also be extremely difficult to diagnose; thus, the true incidence of MDS likely far exceeds current estimates.

Research successes have resulted in striking improvements in outcomes for younger patients with AML and MDS, but very few older patients have benefited from these improvements. These older patients have more frequent drug resistance, more co-morbidities that limit their tolerance of effective therapies or transplantation, and more frequent DNA mutations.

Outcomes for older patients with AML or MDS remain poor compared with younger patients and worsen with age.

Modified from Farag et al., 2006; Ma et al., 2007.
New treatment strategies are desperately needed for older patients with AML or MDS, but developing solutions will require a multi-faceted approach that includes basic, translational, clinical, and public health research across three primary areas:

1. First and foremost is the development of agents that specifically target common genetic mutations in older MDS or AML patients. Such agents will have to be derived from basic research into the mechanisms of this disease. Support is also needed for high-throughput screening, which has led to therapeutic advances in other cancers and should be applied to study MDS and AML in the elderly. Re-purposing existing drugs could be an inexpensive and effective method of finding less toxic and more effective agents. Further, using newly gained information about mutations in DNA methyltransferases, Tet genes, and splicing mechanisms will help focus study on the right targets for MDS and AML in the elderly.

2. Second, funding is critical for defined clinical trials studying specific groups of patients based on the biology of their disease. Identifying genetic or other biologic markers that predict a patient’s response to treatment will help facilitate more focused and less expensive clinical trials. Ancillary studies can help identify reasons why certain drugs fail, explain why leukemia cells become resistant to drugs, or describe tumor-host interactions that allow leukemia cells to survive therapy. Additionally, racial, ethnic, and socio-economic diversity is not sufficiently captured in most clinical trials, so support for more extensive, comprehensive patient inclusion (through cooperative groups, for example) will help ensure that the results can be applied to broader patient segments.

3. The third important priority is the development of a personalized approach to treatment based on the specific DNA mutations found in each patient. Genetic and clinical markers must be identified to help better inform treatment selection for each patient. Based on the personal leukemia DNA sequence or other biomarkers present, the individual’s treatment regimen may include a customized combination of intensive standard chemotherapy, stem cell transplantation, investigational drugs, or supportive care alone, tailored specifically to optimize patient outcomes. More research should also be invested in shared decision-making, in order to better understand how older individuals with MDS and AML choose their treatment. Identifying situations when treatment intervention may improve quality of life or prolong survival (or when it may not) is critical in choosing the right course of treatment.

Through these three defined approaches, older AML or MDS patients may achieve outcomes comparable to those of younger patients. This subject should be especially of interest to funding agencies or foundations focused on aging, and their participation in supporting these research efforts would be encouraged and valued.
Hematopoietic Stem Cell Transplantation: Increasing Success Rates by Improving Management of Graft vs. Host Disease

For patients with hematologic malignancies, allogeneic bone marrow or blood stem cell transplantation (SCT) is an effective treatment, and the frequency of transplants continues to increase worldwide. Unfortunately, almost half of all SCT patients develop graft-versus-host disease (GVHD), a condition in which the donor’s immune cells attack the patient’s skin, liver, or intestines. This is the single most important barrier to improving the success of this procedure, as about a quarter of these patients die from GVHD or its related complications. GVHD occurs more frequently following SCT from unrelated volunteer donors, a trend that has increased dramatically in the last 10 years as more transplants are conducted from unrelated donors. GVHD is also seen more commonly in older patients, and since older patients are more frequently undergoing SCT, there are now more patients with GVHD than ever before.

GVHD can occur soon after transplantation, which is termed “acute GVHD,” or more than three months later, which is called “chronic GVHD.” Chronic GVHD is an especially complex challenge. For many reasons, the hematology community has a limited understanding of the natural history of chronic GVHD. It normally occurs after patients have returned home and are no longer being closely followed at the transplant center. The onset can be so gradual that many patients do not even notice the subtle changes, and, by the time a definitive diagnosis is established, some effects may be irreversible. The few treatment options for chronic GVHD usually involve additional immunosuppression for patients who are already...
An increasing number of stem cell transplants have been performed each year worldwide for the last 40 years to treat and sometimes cure hematological diseases. However, **chronic graft-versus-host disease remains a challenge that spans many disciplines**, from hematology and pathology to immunology and blood banking.

depressed immunosuppressed, which increases the rate of infections in patients who are poorly equipped to fight them. Unfortunately, definitive clinical trials are lacking due to complicated logistics and a dearth of new drugs to treat GVHD.

The biology of chronic GVHD is also poorly understood, further challenging treatment. Few experimental models have been developed, in part because the chronic nature of the disease makes such experiments lengthy, labor-intensive, and prohibitively expensive. The biology of acute GVHD is better understood, not only because the models are better, but also because the disease occurs sooner after transplant, while a patient is still under the care of experienced transplant physicians. But even in the acute setting, progress has been agonizingly slow, and early studies have not yet translated into major clinical breakthroughs.

To accelerate progress and capitalize on relevant scientific advances, four broad areas should be targeted for additional funding. First, recent progress in cellular and molecular biology of GVHD target tissues offer opportunities to fund the identification of new treatments. Second, the interaction between the innate and adaptive immune systems is important in GVHD and will benefit from the study of new approaches in models and trials. Third, grading systems focusing on the severity of GVHD have not changed in 40 years and may not be as relevant as previously thought. Recently identified biomarkers should be more widely validated and incorporated into new grading systems to risk-stratify patients and better customize treatment. This would be particularly valuable for chronic GVHD, whose current consensus criteria are labor-intensive and still not validated prospectively. Finally, the percentage of SCT patients enrolled in trials remains small due to the substantial regulatory burdens and the prohibitive costs of clinical research, so the extension of the Bone Marrow Transplantation Clinical Trials Network should be a top priority for funding.

The technology available today could markedly increase the success of SCT, if it could be uniformly applied to GVHD research. Thus, support is needed today to translate this technology into new treatment options for GVHD in the near future, as it remains the major barrier to the success of SCT. Since GVHD research spans many disciplines, from hematology and pathology to immunology and blood banking, multi-investigator grants combining distinct approaches to combat this problem may be the most effective avenue through which progress can be achieved.
Sickle Cell Disease: Reducing the Barriers to Care, Burden of Pain, End-Organ Injury, and Premature Death

Sickle cell disease (SCD) is the most common inherited red blood cell disorder in the United States, affecting 70,000-90,000 Americans. Although the molecular basis of SCD was established several decades ago, it has been challenging to translate this knowledge into the development of novel targeted therapies. Nevertheless, enormous advances have been made. As recently as the 1960s, this disease was described as a disorder of childhood, because patients rarely survived their teenage years. Today, most sickle cell anemia patients can expect to live into adulthood, but the cost of care and the burden of pain, end-organ injury, and premature death remain high.

New approaches in managing this disease have improved diagnosis and disease maintenance over the last few decades, but many patients still have severe complications that have yet to be overcome. For example, the introduction of newborn screening has improved early management of the disease, and novel treatments have measurably reduced the disease burden. Oral penicillin prophylaxis, the impact of which was first seen thirty years ago, remains the primary method to prevent infection-related deaths during childhood, which are now rare. In addition, hydroxyurea, the only FDA-approved drug with a specific indication for SCD, has been shown to reduce hospitalizations for sickle cell pain and acute chest syndrome in adults and children. However, the drug is underused outside of academic centers, so understanding barriers to its use is an important area for health outcomes research.

Blood transfusions have also offered significant benefits for the prevention of stroke and other complications in SCD, and stem cell transplant efforts have led to cures in some children and adults. For patients who have matched donors, stem cell transplantation is likely underutilized and may improve quality of life, but since many patients lack HLA-matched stem cell donors, its use is still limited.

Adding to these clinical challenges is the worry that federal NIH funding will significantly decrease in coming years, resulting in fewer research initiatives, loss of infrastructure support, and fewer clinical trials. Research on the effect of psychosocial variables on SCD outcomes may be one of the first areas to be cut, even though it may significantly improve the health of this underserved patient population.

The future of care for SCD patients will be dependent on advanced and highly targeted approaches to research, discovery, and implementation of new interventions. Clinical research can make a dramatic difference in the SCD treatment paradigm with specific priority areas of focus. For example, in genetics, studies are needed to identify and validate genetic markers that predict disease severity, as SCD manifestations vary greatly among patients due to modified genes. There is an emerging body of evidence suggesting that some people with sickle cell trait are at increased risk for life-threatening medical conditions, such as...
Venous thromboembolism (VTE) is a common disease and is often preventable. Yet, it has become a public health crisis in the United States, costing healthcare providers more than $2 billion annually. **Understanding molecular mechanisms and identifying risk factors for VTE will lead to development of new targeted treatments.**

renal failure, so further studies are essential to identify the association between sickle cell trait and these conditions. Additional research is also needed to help identify markers of early progression in SCD, such as acute chest syndrome or sickle lung disease. Finally, studies to better understand the neurocognitive effects of SCD are critical, since neurocognitive defects (other than stroke-related disabilities) are not well understood and are difficult to prevent or treat.

New treatments for sickle cell disease to prevent pain, reduce severe anemia, and control inflammation are desperately needed. Studying pain in SCD may provide opportunities for hematologists to partner with investigators in the neurosciences to examine the neurobiology of pain and to consider more innovative and evidence-based approaches to pain management.

In addition, further research is needed concerning barriers to health care. For example, applying care models like the patient-centered medical home to SCD needs further study, as well as assessments of other innovative team systems that can ensure the availability of coordinated, comprehensive care to SCD patients. This issue is not unique to the United States: hemoglobin disorders should be high priorities for global health initiatives, as they represent opportunities for international collaborations that can improve sickle cell disease care worldwide.

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**Deep-Vein Thrombosis and Venous Thromboembolism: Understanding the Risk Factors and Developing Targeted Therapies**

Venous thromboembolism (VTE) comprises two related conditions, deep vein thrombosis and pulmonary embolism. This common disease, which is often preventable, has become a public health crisis in the United States, costing healthcare providers more than $2 billion annually. Even though between one-third and one-half of surviving patients develop recurrent thrombosis or long-term morbidity, the burden of VTE on society remains largely under-reported and under-
studied. Further, the disease impact increases dramatically with age, indicating that the societal burden will continue to increase in future years as the U.S. population ages. Significant research has been conducted in this area during the last decade, as studies have identified risk factors for a first or recurrent VTE. Tests have been developed to identify risk factors after an initial event, and physicians have been able to use this information to better manage the mortality and morbidity associated with the disease. Traditional therapies, such as warfarin, unfractionated heparin, and low-molecular-weight heparin, are being replaced by new oral clotting inhibitors, such as direct thrombin or factor Xa inhibitors, which reduce the need for constant monitoring of a patient’s coagulation function. While new options are in development, research is required to define who needs to be treated with a traditional or newer agent.

Despite these advances, substantial epidemiological, clinical, and basic science studies remain to be completed. Studies show that about one-third of patients will develop a recurrent VTE and may die if their anticoagulation therapies are interrupted. Yet it remains difficult to distinguish between patients whose clotting will recur and need prolonged anticoagulation therapy and those patients who will not have another blood clot and therefore should not be exposed to the hemorrhagic risk of prolonged anticoagulation therapy. Since the cause of at least half of VTE events cannot be determined through currently available testing, it is critical to understand the risk factors that contribute to the disease and its recurrence. This will require a number of investigative priorities, including new methods for identifying risk factors, better clarity about the molecular events that lead to venous thrombi, and defining the effects of VTE on systemic platelet function and clotting mechanisms.

With these insights, advanced modeling combined with in vitro and in vivo studies may eventually provide a more complete understanding of the mechanisms that cause thrombosis in order to develop and test targeted therapies. Collaborations between hematologists and scientists in other fields, such as epidemiologists, computer scientists, biomedical engineers, and behavioral psychologists, will also be essential in order to make advances toward reducing this significant public health problem. Progress in treating VTE will necessitate a number of important strategies that include:

1. Large clinical studies designed around treatment strategies, especially for patients who have suffered a single event. Essentially, who needs treatment and for how long?

2. Prediction models defining individuals who are at high risk for both initial and recurrent events.

Collaborations between hematologists and scientists in other fields, such as epidemiologists, computer scientists, biomedical engineers, and behavioral psychologists, will also be essential in order to make advances toward reducing this significant public health problem.
3. Studies of the new oral anticoagulants to define appropriate clinical settings for use, to develop effective methods to monitor efficacy, and to understand when and how to treat bleeding complications.

4. Inclusion of elderly and minority populations in clinical studies to expand the utility of the results.

5. Investigation of emerging findings that repurposing known drugs may prevent VTE. For example, several studies have suggested the statins may prevent VTE, and further research should identify the patient populations that are most likely to benefit from this intervention.

6. Study of thrombosis and stroke in children, as children suffer from the morbidity for these conditions substantially longer than adults.

This framework for future research will help the hematology community meet its goals of minimizing the burden of this disease and ultimately preventing VTE entirely. This disease represents a challenge that extends well beyond the hematology community, and fulfilling the research strategies above will require close collaboration with many other disciplines.

Childhood Leukemia: Improving Cure Rates by Performing Coordinated Research on Novel Targeted Therapies

Relapsed B-lineage acute lymphocytic leukemia (ALL) is a leading cause of cancer death in children. Recent genomic analyses have identified a unique subtype of high-risk ALL that has high rates of relapse. This type of ALL has mutations in the CRLF2, IKZF1, and/or JAK genes. Proteins coded by these genes function in the same pathway, which is associated with increased
survival and proliferation of B-lymphoid cells. Strategies to block this signaling pathway are needed to prevent relapse and enhance patient survival where current therapies are insufficient.

Acute leukemia in infants is another type of childhood leukemia that is prone to frequent relapse. One of the most common forms of infant leukemia, characterized by a rearrangement of the MLL gene, still has particularly poor outcomes. Research has identified several factors that may predispose some infants to MLL leukemogenesis even before birth. Genomic investigation has also defined molecular abnormalities that are associated with more aggressive disease, pinpointing several molecular causes for infant leukemia and offering important insight into the biology of the disease. In addition, insights gained from gene expression profiling have identified possible therapeutic targets, and drugs for those targets are now under development. Yet one of the primary challenges today is to effectively integrate this genomic information into novel treatment strategies.

Several ongoing clinical trials will soon answer critical questions about infant leukemia. One important advance occurred in 2008, when the kinase inhibitor drug lestaurtinib was added to an ongoing infant leukemia clinical trial, making it the first trial to evaluate a targeted agent in this young population. Then in 2009, a phase I trial was initiated to test a targeted therapy for relapsed pediatric cancers and infant leukemia called obatoclax, which inhibits the proteins that prevent leukemia cell death. Despite these advances, leukemia in infants remains a formidable challenge, with the youngest patients suffering the worst survival rates, so there remains a dire need for more effective and safer treatments.

In order to prevent relapse in all types of pediatric acute leukemia, coordinated research that addresses discovery of targets, preclinical testing, and clinical trials of novel targeted agents would be an efficient strategy to achieve measurable progress in this disease. It is critical that research programs are interdependent and multi-disciplinary in order to overcome drug resistance and further reduce toxicity. For example, program project grants may be especially effective to integrate biological advances into therapy, as the insights gained will likely translate into other areas of cancer research and treatment, especially for infant cancers.

Preclinical work is also desperately needed to meet new regulatory standards requiring that targeted agent combinations must inhibit specific targets and overcome resistance mechanisms. Furthermore, funding is essential to improve clinical trial designs in order to gain information on adult and pediatric leukemias that share similar underlying molecular abnormalities. It may be possible to leverage information between adults and children to help streamline research progress and accelerate introduction of new drugs into the clinic. Pharmaceutical industry partners should be sought to assist in achieving this goal.
Translating Laboratory Advances into the Clinic: Using Novel Genomic Technologies to Improve Treatment of Hematologic Diseases

Dedicated laboratory and epidemiologic research in an array of hematologic disorders has led to the discovery of important new genetic and biologic markers that define disease susceptibility, etiology, and treatment responsiveness. However, there has been limited success in translating these discoveries into improved patient care, and there is now an urgent need to clinically apply these findings.

While many treatments used for malignant and non-malignant hematologic diseases are fairly effective, they are commonly based on empiric discoveries, with limited knowledge of the basic biology of the disease. Unfortunately, many hematologic diseases still lack effective therapy, and the resulting patient burden is great, so novel therapies directed against therapeutic targets are urgently needed. Recently it has been shown that a patient’s responsiveness to different treatments and susceptibility to adverse treatment reactions are heavily influenced by both the genetics of the disease and the inherited genetics of the patient. Thus, new research priorities addressing these specific insights should be implemented to ensure that patients receive the right treatment protocols to maximize their opportunities for successful outcomes.

Many recent advances have stemmed from the use of advanced DNA sequencing technologies, including sequencing of entire cancer genomes. This has helped explain the changes in diseased cells, how these sequences relate to cells in other tissues in the body, and how they may help identify targets for new therapies to improve patients’ responsiveness.
Research teams are working to determine the best mechanism to use these technologies to influence the course of hematologic diseases. Genome studies are still in their infancy, and additional studies are needed in large cohorts of patients before widespread individual genetic testing can be implemented in the clinical setting.

Some challenges remain in the proper identification of the genetic alterations through these technologies, such as the distinction between changes specifically acquired by a malignancy or those that are simply inherited by the patient. These obstacles must be resolved before the genomic technologies can be used confidently and broadly. Thus, investment is required to comprehensively identify acquired molecular alterations underlying disease biology and inherited genetic alterations that predispose to cancer or influence toxicity and efficacy of therapy. Such an investment would improve the applicability of sequencing technology to the diagnosis and treatment of patients.

To shift this early success in genomic research into routine diagnostic testing, five specific challenges must be addressed:

1. Identify all important inherited and acquired genetic alterations that contribute to the development of hematologic disease.

2. Determine whether patients will be best served by testing limited numbers of genes or whole-genome approaches. While single-gene testing is already underway and is much more rapid, whole-genome sequencing will likely eventually become routine. Associated standards of quality control, and FDA or CLIA accreditation are issues that have not yet been addressed for many genomic profiling approaches.

3. Work to ensure that whole-genome sequence data or data subsets are not exploited by third parties to the detriment of patients, such as by denying health insurance. Some protections are in place in current federal policies, but additional measures will be required to fully protect patient rights.

4. Agree on the management of the unprecedented large amounts of data that are generated by whole-genome sequencing. Unlike single-gene tests, genome-wide sequencing produces massive amounts of data that will need novel informatics approaches for rapid analysis, and the data will need to be stored for a currently undetermined period of time. This may lead to better patient stratification and new drugs targeted to specific new disease targets.

5. Rationally prioritize these data for development of targeted drugs. There is already a flood of information based on limited years of study, and selecting the best targets in an era of limited resources will be essential for translation into clinical relevance. This might be an appropriate area for funding mechanisms such as Small Business Innovation Research grants.

It is critical to identify all important inherited and acquired genetic alterations that contribute to the development of hematologic diseases in order to develop personalized treatment for each patient.
Hematologists Are Committed to Working Together with Other Disciplines for the Future of All Medicine

The acceleration of progress throughout the medical community, not just in hematology, has been striking in the last decade. Demands for support come from every biomedical research area. However, few other fields can state with as much robust evidence as hematology that their research contributions not only support their own stakeholders, but deliver relevant insights that improve the care of patients in many other specialties.

The successes generated by hematologists have been leveraged successfully by physicians around the world, from improving the care of patients with hemoglobinopathies in Africa to curing a high proportion of acute promyelocytic leukemia (APL) cases in Brazil, where APL is common. Further, the successes generated in other fields can be incorporated into hematology. This is perhaps best seen in the interface between immunology and hematology, where findings in immunology, such as defining an immune function of platelets, generated a greater understanding of the role platelets play in vascular integrity and tissue regeneration. Hematology research serves as a bridge between many clinical disciplines and generates collaborations not possible without hematology research advances.

The return on discovery achieved in the last decade in hematology research can be replicated in the future if investigation continues to be supported. It is crucial for hematologists to educate patients and the public about the impact hematology research has had on the nation’s health. Indeed, hematologists can play the role of health-care ambassadors globally, and particularly in the developing world, given their achievements in improving international health. The impact of
hematology research on health care has been crucial in many areas outside of hematologic disease, such as solid tumor oncology, cardiovascular disease, and lung disease. Past successes demonstrate how well hematology research findings can be applied to other areas of medicine. These advances not only have led to increases in the success rates in treating many diseases, but also have spawned multiple biotechnology and pharmaceutical ventures that increase employment, and export of goods and services, at a time when both are sorely needed.

Funding for hematology research is an investment in the nation’s health. It is vital that research funding is increased to allow investigators to address the difficult problems facing the field described in this document. This will permit the major advances in understanding the molecular defects behind a hematologic disease to be translated into novel diagnostics and targeted therapeutics. Given the diverse array of public health interests that will benefit from this research, federal agencies should coordinate their hematology funding in order to produce the greatest impact on specific high-need areas. A multi-agency approach would deliver advances faster, more economically, and more efficiently, in that duplication of effort would be decreased. Thus, Requests for Applications in the areas listed here, co-sponsored by multiple agencies, will be important for future progress.

For hematologists, the status quo is simply not acceptable. Despite the notable successes discussed previously, there is much to be done. Too many patients still suffer from and die from hematologic diseases, and hematologists remain committed to investigation, treatment, and cure of these diseases.
Support for the field of *hematology* should be among the *top priorities* in health care because it will have a dramatic impact on the *future of health care* in America and around the world in all areas of medicine.