Progress
Review
Groups

Report of the Leukemia, Lymphoma, and Myeloma Progress Review Group

May 2001

NATIONAL® CANCER INSTITUTE

REPORT OF THE LEUKEMIA, LYMPHOMA, AND MYELOMA

PROGRESS REVIEW GROUP

May 2001

From the Leadership

We are pleased to submit this Report of the Leukemia, Lymphoma, and Myeloma Progress Review Group (PRG) to the Director and Advisory Committee to the Director of the National Cancer Institute (NCI). The PRG enthusiastically accepted its charge to identify scientific priorities and needs and create a national agenda for research on leukemia, lymphoma, and myeloma. We believe that this report provides a compelling strategy for progress against these diseases.

Rather than propose a long list of recommendations, the PRG has identified 10 areas of research that will transform the prevention, diagnosis, treatment, and care of individuals with hematological cancers. We believe that these areas truly represent the highest priorities in the field. Furthermore, because some aspects of these cancers are better understood than they are in other cancers, we hope that research in these areas will benefit patients with other cancers as well. We are delighted that the PRG was able to reach consensus on these priorities despite the many differences among the diseases.

We appreciate the NCI's decision to institute a PRG to address these challenging diseases. We look forward to assisting the NCI in implementing the PRG's recommendations and to following their progress.

Respectfully,

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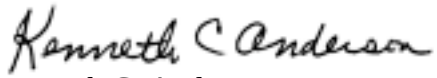

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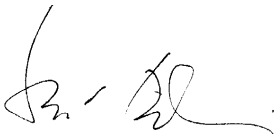

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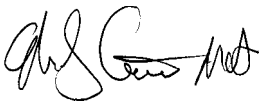

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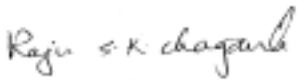

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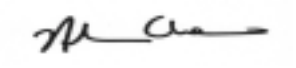

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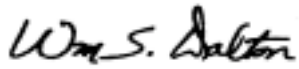

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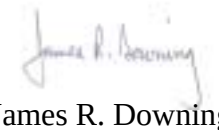

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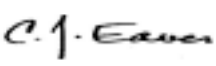

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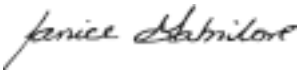

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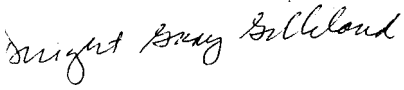

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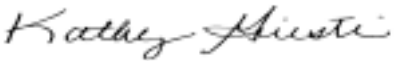

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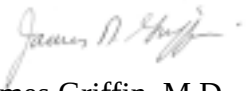

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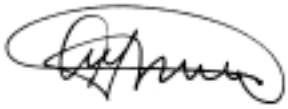

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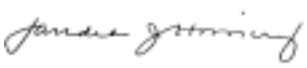

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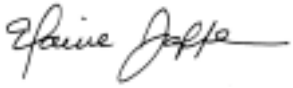

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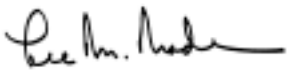

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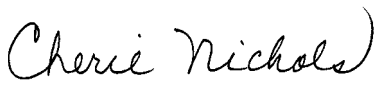

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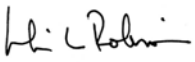

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Table of Contents

Section I: Executive Summary 1

Section II: Introduction 5

Overall State of the Science 5

Structure and Process of the LLM PRG 6

Section III: Top Research Priorities of the LLM PRG

Etiology 7

Pathobiology 9

Drug Development and Therapeutics 15

Education, Communication, and Survivorship Research 19

New Initiative: Cancer Translational Research Allied Consortium (C-TRAC) 23

Section IV: Appendices

A. About the National Cancer Institute's Progress Review Groups 25

B. Reports of the Roundtable Breakout Groups 27

Epidemiology 27

Biology of Normal and Neoplastic Tissue Targets: Bone Marrow 34

Biology of Normal and Neoplastic Tissue Targets: Lymphoid Tissue . . 39

Scientific Infrastructure 43

Diagnosis, Prognosis, and Disease Monitoring 46

Preclinical Therapeutics 49

Clinical Trials Methodology 55

Development of Therapeutics Directed Against Specific Targets in Hematological Malignancies 57

Optimization and Integration of Emerging Therapies and Conventional Treatments 60

Partnership Platforms 63

Education, Communication, and Behavioral Research 65

Outcomes Research 69

C. LLM PRG Member Roster 73

D. LLM PRG Roundtable Participant Roster 75

I. Executive Summary

Executive Summary

Taken together, leukemia, lymphoma, and myeloma (LLM) constitute the fourth most common form of cancer. More than 60,000 people will die of these diseases in 2001 alone. Unfortunately, the hematological malignancies are a daunting challenge to researchers and clinicians because they strike individuals of all ages and races and both men and women. These cancers actually represent a large number of diseases that vary in their cause, molecular makeup, pathophysiology, treatment, and care.

To help ensure the wise use of its resources in the fight against these challenging diseases, the National Cancer Institute (NCI) convened a Progress Review Group (PRG) to identify scientific priorities and needs. This report is the result of the PRG's 10-month effort.

The LLM PRG has identified 10 areas for research that will revolutionize the prevention, diagnosis, treatment, and care of individuals with these cancers.[1] A number of these research priorities can be achieved through a new initiative, the Cancer Translational Research Allied Consortium (C-TRAC), which can serve as a model for the rapid development of new therapies for many kinds of cancers. C-TRAC is a focused, new private-public partnership that will shorten drug development time from 5–10 years to 2 years.

[1]Other important research priorities are described in the reports of breakout groups convened at the PRG's Roundtable Meeting. These reports are included in the appendix to this report.

The priority areas for research identified by the PRG are as follows:

In Etiology:

- **Understand the interaction among genotype, immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to hematopoietic malignancy.** The etiology of LLM is not well understood, yet the development of behavioral and pharmacological interventions for prevention of these diseases requires that we know what causes them. Prior epidemiological research has focused almost entirely on a single or limited group of hematological cancers and precursor conditions. Case-control and cohort investigations are needed.

In Pathobiology:

- **Identify the basic mechanisms responsible for genome instability, chromosome translocations, and other mutations in hematological malignancies.** Reducing the incidence of LLM will require a better understanding of (1) how various types of DNA damage occur in hematopoietic cells, (2) the impact of various genetic factors on susceptibility to DNA damage, (3) repair capacity and other types of cellular responses to DNA damage, and (4) the role of environment in the broadest sense.

- **Define the relationship between the development of hematological malignancies and the host biological environment.** The stromal microenvironment and the overall host environment are critical determinants of tumor initiation, progression, migration,

and response to therapy. In light of the remarkable research tools that have been developed in the past few years and the considerable progress in understanding the biology of normal and tumor cells, it is time to make a major effort to study the complex problem of tumor-host interactions in hematological malignancies.

- **Provide molecular characterization of hematological malignancies, including the characterization of global patterns of genetic and epigenetic alterations and RNA and protein expression, as well as the validation of the molecular targets necessary for the survival, proliferation, and evolution of hematological malignancies.** Rapid migration to a molecular definition of cancer will have a dramatic impact on diagnosis and treatment. We recommend the expansion of several current NCI initiatives to promote the application of novel technologies to each of the hematological cancers, including both common and less prevalent subtypes.

- **Further develop research on stem cells, both multilineage and single lineage.** Our understanding of how specific outcomes are determined at a molecular level in different types of normal blood cell precursors is still limited. As a result, it is still not possible to anticipate how specific molecular changes produce disease. Such information is essential to designing therapies that are curative and nontoxic.

In Drug Development and Therapeutics:

- **Develop the required resources to translate "lead" structures and molecules into effective therapeutic agents. Hasten the translation of candidate validated targets to lead compounds and subsequent clinical trials and support the development of orphan therapeutic agents and diagnostics, including Food and Drug Administration (FDA) approval.** Target discovery, validation, and clinical translation for hematological diseases will form an important basis for future drug development in all cancer types. Consequently, the NCI needs to magnify its efforts to offset the cost of drug development for relatively rare cancers, including leukemia, lymphoma, and myeloma.

- **Foster partnerships between the NCI and academia, advocates, cooperative groups, FDA, and industry to expedite drug development and availability of therapies.** As lead agency for implementing the National Cancer Program, NCI should form a working group of equal partners to enhance cooperation and efficiency in developing new cancer treatments.

In Education, Communication, and Survivorship Research:

- **Determine how to provide accurate, timely, and tailored information to patients to improve medical decision-making, access to clinical trials, quality of care during active treatment and follow-up, and quality of life.** Effective health communication narrows the enormous gap between discovery and applications and reduces health disparities among our citizens. However, much of the available information on communicating with patients does not address the specific circumstances of those affected by the hematological cancers.

- **Develop education and training programs for certification of physicians and centers for diagnosis, treatment, and clinical trials in**

hematological malignancies. Certification will lead to significant improvement in the treatment of hematological cancers, not only through optimization of current treatment approaches but also through the channeling of patients to specialized physicians and centers where state-of-the-art treatments may be investigated and applied in Cooperative Group Trials.

- **Identify and target individuals and populations at high risk for adverse long-term outcomes to define the biological basis of identified associations and facilitate the design and testing of intervention and prevention strategies.** We do not know which patient populations are at high risk for adverse outcomes of treatment for LLM. Long-term outcomes research on these diseases has often been characterized by small sample sizes, lack of heterogeneity in the study populations to allow for adequate assessment of risks, and potential bias in study populations resulting from selection influences, such as incomplete follow-up. However, identification of high-risk individuals and populations is essential to the rational development and testing of intervention and prevention strategies.

A New Initiative: The Cancer Translational Research Allied Consortium:

- We propose a new initiative that will bring together experts across multiple disciplines and institutions to participate, within a formalized infrastructure, in the rapid discovery and development of cancer therapies. This initiative will encompass the whole spectrum of drug discovery and development: identifying, validating, and credentialing targets; discovery and preclinical testing of agents directed against these targets; and scale-up and testing of promising agents in clinical trials. The ultimate goal of the C-TRAC will be to shorten drug development time from 5–10 years to 2 years through a novel alliance among academia, industry, government, and patients.

Leukemia, lymphoma, and myeloma continue to have a significant impact on the lives of Americans, despite advances in diagnosis and treatment and improvements in patient survival. If implemented, the research priorities proposed here will dramatically accelerate progress against these diseases and will provide a bold new strategy for rapid translation of basic research into life-saving treatments.

II. Introduction

Introduction

OVERALL STATE OF THE SCIENCE

Despite advances in diagnosis and treatment and improvements in patient survival, the hematologic cancers continue to have a significant impact on the lives of Americans. Right now, almost 700,000 Americans are living with leukemia, lymphoma, or myeloma (LLM), and an estimated 100,000 new cases occur each year. Although mortality has declined and 5-year survival rates have increased among adults and children with certain forms of these diseases, an estimated 60,000 Americans will die of them in 2001. For all forms of leukemia, the 5-year survival rate is only 46%, for non-Hodgkins lymphoma it is 54.2%, and for multiple myeloma it is only 28%. Despite the significant decline in the death rate for children with leukemia, this disease still causes more deaths in children in the U.S. than any other disease. Furthermore, the death rates for non-Hodgkins lymphoma and multiple myeloma are increasing at a time when death rates for other cancers are dropping. Since the 1970s, incidence rates for non-Hodgkins lymphoma have increased dramatically, making it one of the fastest rising cancers in the United States. The hematologic cancers strike individuals of all ages, from children to the elderly; men and women; and all races.

The decreases in mortality that have occurred in recent decades reflect the progress that has been made in understanding and combating LLM. Disease pathogenesis and pathophysiology of the hematologic malignancies are better understood than in most other cancer subtypes. Standard radiation and chemotherapy can cure disease in a substantial fraction of patients with acute myeloid leukemia, acute lymphocytic leukemia, anaplastic large-cell and other lymphomas, and Hodgkins lymphoma.

Furthermore, it will soon be possible to achieve a molecular classification of myeloid and lymphoid malignancies that also incorporates a pathologic and clinical understanding of disease. New technologies, including genome-wide surveys of gene expression patterns and genetic alterations, have already resulted in changes to the classification of hematologic neoplasms and will result in the recognition of new disease entities and potential prognostic markers. In addition, a large number of potential targets for intervention are already available, and the development of treatments for the hematologic malignancies can serve as a prototype for the development of therapy for solid tumors.

The National Cancer Institute (NCI) has furthered this advancement through its programs and initiatives that facilitate drug discovery, development, and testing, including clinical evaluation of products and exploration of novel agents. The Institute's investment in developing molecularly targeted therapeutics has stemmed from a growing understanding of the basic pathobiology of specific hematologic malignancies, which in turn has permitted the identification and quantitation of selective targets within tumor cells. Findings from NCI-supported basic research have identified a plethora of potential therapeutic targets for further exploitation.

Perhaps the most striking example in any cancer of the benefit of molecularly targeted therapy is all-trans retinoic acid for acute promyelocytic leukemia (APL). The introduction of this agent, and systematic study of how to use it, has increased the cure rate of APL from a maximum of 40% to over 70% in just 10 years. More recently, targeted therapy for chronic myelogenous leukemia with an Abl-specific tyrosine kinase inhibitor, STI571, has shown

significant activity, including elimination of the causative genetic defect, in patients with advanced disease. As the application of chemotherapy in the hematologic malignancies led the way to improved chemotherapy for all cancers, so the development of these molecularly targeted therapies will serve as an important model for curing all cancers. Thus, a major expansion in translational research in the hematologic malignancies will provide a benefit for relieving the burden of cancer that far exceeds the frequency of these diseases.

STRUCTURE AND PROCESS OF THE LLM PRG

The LLM Progress Review Group (PRG) was charged with identifying and prioritizing areas of research that could advance progress against leukemia, lymphoma, and myeloma. At a Planning Meeting held in August 2000, the LLM PRG organized a Roundtable to consider progress and identify needs across the continuum of LLM research. Roundtable participants were chosen and topics were selected for breakout sessions, to which the Roundtable participants were assigned. PRG members served as co-chairs for the breakout sessions.

The LLM PRG Roundtable of approximately 180 participants met on December 13–15, 2000, in Chantilly, Virginia. Members of breakout groups were instructed to identify top research priorities for the next 5–10 years. The first sessions of breakout groups addressed bone marrow biology, lymphoid tissue biology, partnership platforms, and epidemiology. The second session addressed scientific infrastructure; clinical trials methodology; targeted therapeutics; and education, communication, and behavioral research. The final session addressed diagnosis, prognosis, and disease monitoring; preclinical therapeutics; outcomes research; and optimization and integration of emerging and conventional therapies. In support of the priority-setting process, NCI provided the Roundtable participants with analyses of its LLM research portfolio and extensive information about ongoing NCI initiatives and activities that might address some of the needs of the field.

Reports from the breakout groups showed a high degree of agreement on many of the crucial needs of the field. Using these reports, the PRG identified the highest priority areas for research and wrote descriptions and justifications for them. NCI provided information about relevant NCI initiatives so that the PRG could delineate how its priorities differed from already existing efforts. This report is the product of the PRG's 10-month effort.

The PRG's work is not yet done. The PRG will meet with the NCI Director to discuss the NCI's response to the report and to identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI will discuss a plan for implementing the most important research priorities of the PRG. This plan becomes the starting point for hastening progress against the hematologic cancers.

III. Top Research Priorities of the LLM PRG

Etiology

RESEARCH PRIORITY

1. **Understand the interaction among genotype, immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to hematopoietic malignancy.**

Our understanding of the etiology of leukemia, lymphoma, and multiple myeloma (LLM) and their precursors is extremely limited. These malignancies can serve as model systems to understand the molecular events that lead to carcinogenesis. Specifically, precursor disorders that lead to a high risk of developing frank LLM present model systems for the evaluation of the multi-step and progressive molecular events in the evolution of neoplastic transformation. These events have not been sufficiently exploited in previous research.

A major limitation in our ability to adequately identify the causal factors for these tumors results in part from their extreme biological heterogeneity and our previous inability to adequately characterize this heterogeneity. Recently developed gene and protein arrays provide powerful new tools to define hematopoietic and lymphoproliferative malignancy subtypes at the molecular level, to identify the specific biological effects of carcinogens, and to evaluate pathogenic mechanisms. These tools will improve our understanding of the causes of hematopoietic and lymphatic malignancies in the near future.

Another potentially fertile area for investigation is the contribution of other, less well recognized infectious agents or environmental toxins to the initiation or progression of these diseases. Detailed study is needed of the interactions between exogenous exposures and specific molecular loci, polymorphisms, and other genetic and host factors. Such study should be coupled with continuing improvements in technology to assess exposure and gene-environment interactions.

To overcome the limitations of previous research and to capitalize on existing opportunities, investment must be made in the investigations and infrastructure that are needed to establish national resources for the etiologic investigation of LLM and their precursors. Nearly all prior epidemiological research has focused on a narrow, single category or a limited group of LLM and precursor conditions. Resources consisting of case-control and cohort investigations are needed if new opportunities are to be provided. These investigations should incorporate the spectrum of LLM and precursor conditions in order to achieve the following objectives:

- Apply and compare newly developed classification systems with “current” classifications to determine how each performs in identifying and clarifying risk factor associations.

- Study the overlapping features as well as the differences in risk factor associations among the various hematopoietic and lymphoproliferative malignancies and their precursors.

- Include patients with precursor conditions to enable comparisons of risk factor associations across subgroups of patients, such as those with myelodysplastic syndromes and acute myeloid leukemia, to determine overlaps or differences in risk factors.

- Collect and utilize DNA and/or tumor tissue as a renewable resource.

- Evaluate risk factors among races and ethnic groups other than Caucasians to enable evaluation of the effect of genetic differences or gene-environment interactions in the etiology of LLM and precursor conditions.

- Provide in-depth exposure assessment, validating exposure by using alternative sources of exposure verification, newer methodologies for measuring external exposures, and/or biological effect measures for exposures.

- Assess underlying genetic aspects; the possible role of gene-environment interaction; and interaction among immune function, infectious agents, environmental toxins, and lifestyle factors; and investigate familial aggregations.

Rapid advancement in knowledge of the etiology of LLM clearly requires the engagement of a multidisciplinary group. This group should consist of epidemiologists, hematologists and oncologists, expert hematopathologists, geneticists, virologists, immunologists, exposure assessment specialists (including industrial hygienists, toxicologists, and others specializing in environmental measurements), molecular biologists, and statisticians. The data and specimens collected should include samples of fresh tumor tissue that are appropriately processed and stored to enable state-of-the-art molecular characterization. They also should include other biological specimens, such as paraffin blocks, genomic DNA and RNA, serum, urine, other appropriate biological samples, and appropriate environmental samples.

Research resources should allow for a focused assessment of families with two or more cases of LLM or precursors. Such an assessment would provide a better understanding of the roles of genetics and environmental exposure and interactions between the two. It would also allow for the identification and assembly of cohorts of subjects with high-risk precursor conditions (e.g., HIV-positive patients, myelodysplastic syndromes, solid organ transplant recipients, patients with monoclonal gammopathy of uncertain significance, and cancer survivors treated with chemotherapy and radiotherapy). Resources should be allotted to the assessment of existing large cohorts with serially collected sera and DNA for evaluation of past viral exposures, markers of susceptibility, and intermediate markers.

Investments are needed for the following:

- Further development and application of appropriate biological markers that accurately reflect pertinent environmental exposures

- Molecular studies on the role of endogenous and exogenous factors in the formation of chromosomal translocations

- Animal studies to investigate the mechanistic aspects of environmental exposures

Pathobiology

RESEARCH PRIORITIES

1. Identify the basic mechanisms responsible for genome instability, chromosome translocations, and other mutations in hematological malignancies.

LLM are caused by the sequential acquisition of mutations in the genome of immature hematopoietic cells. These mutations may arise from errors in replication of DNA, the intrinsic chemical instability of some DNA bases, or attack by free radicals generated endogenously within the cell or in response to certain stresses. DNA damage can also result from interactions with exogenous agents such as radiation or chemical carcinogens. To control this DNA damage, cells have evolved mechanisms to sense and repair different types of DNA damage and to undergo programmed cell death if the genomic damage is too extensive. In cancer cells, this repair process has failed, resulting in the accumulation of mutations that disrupt the normal ability of a cell to control its rate of growth, viability, motility, and stage of differentiation. Further, genetic damage continues to occur even after a cancer has formed, leading to a cell's continuously more "aggressive" behavior and drug resistance.

The mutations observed in the hematological malignancies may involve chromosome breakage and incorrect rejoining (chromosome translocations), deletions of variously sized segments of different genes, insertions of abnormal stretches of DNA, chemical modification of specific DNA bases, or changes of a single base to another base. Some patients are genetically predisposed to cancer because of inherited defects in the genes involved in sensing or repairing DNA damage. Although these familial syndromes, such as Bloom's syndrome, ataxia telangiectasia, Li-Fraumeni syndrome, and Fanconi's syndrome, are not a frequent cause of LLM, understanding their cause has been critical in identifying how DNA mutations are repaired in different tissues. Despite considerable recent progress in identifying the actual genes that are mutated in these disorders, there remains an inadequate level of understanding of how mutations occur, how they are repaired, and how malignant cells are able to escape surveillance mechanisms.

The ultimate goal in combating hematological malignancies is reducing their incidence, rather than merely improving therapy for patients with advanced disease. Reducing incidence is likely to require a more sophisticated understanding of the following:

- How various types of DNA damage occur in hematopoietic cells
- The impact of various genetic factors on susceptibility to DNA damage
- Repair capacity and other types of cellular responses to DNA damage
- The role of the environment in enabling DNA damage and cell survival
- Ultimately, strategies to reduce risk

It will also be important to understand the mechanisms that are unique to the various types of hematopoietic neoplasms. For example, the mechanism of transformation of B cells undergoing rearrangement of immunoglobulin loci is likely to differ in part from the mechanism of transformation of an erythroid precursor. A similar question

is why genome instability mechanisms, such as mismatch repair deficiency and microsatellite instability, are relatively uncommon in leukemias in comparison with colon cancers, whereas chromosome translocations are much more common.

The long-term value of understanding the mechanisms behind DNA damage will include the following:

- To prevent hematological malignancies by reducing exposure to environmental factors, ranging from toxins to viruses, that cause DNA damage

- To aid in identifying certain patients or families who are at particularly high risk and who may benefit from interventions to prevent or reduce their risk of disease

- To possibly lead to techniques to slow or prevent the progression of tumors into more aggressive forms

Further advances in understanding the basic pathogenesis of these disorders is directly applicable to many other tumors. Failure to understand pathogenesis at this level will adversely affect the goal to reduce the incidence, and not just the mortality, of all these diseases.

2. Define the relationship between the development of hematologic malignancies and the host biological environment.

Most research on hematopoietic tumors so far has focused on identifying genetic, epigenetic, and phenotypic properties of tumor cells. It is becoming increasingly apparent that the stromal microenvironment and the overall host environment are critical determinants of tumor initiation, progression, migration, and response to therapy. The following indicates how this is so important for hematopoietic malignancies:

- Myelodysplasia and immune dysregulation, both of which are associated with genetic factors, aging, environmental factors, exposure to drugs, etc., predispose individuals to a higher incidence of many kinds of leukemias and lymphomas, and perhaps to myeloma also.

- Specific stromal microenvironments are essential throughout the entire course of the disease for the survival, proliferation, and progression of most kinds of hematopoietic tumor cells.

- The stromal microenvironment is influenced by the tumor cells, which can directly affect the numbers, kinds (fibroblast, endothelial, inflammatory, osteoblast, osteoclast), and specific phenotypic gene expression pattern of stromal cells that are involved in the tumor. Ultimately, the tumor-induced phenotype of the stromal cells may become "fixed" through epigenetic changes, so that the microenvironment is relatively stable even when the tumor cells are temporarily eliminated.

- By virtue of reciprocal interactions mediated by direct contact and cytokines, tumor cells and stromal cells together cause the secondary manifestations of malignancy, including, for example, hematopoietic suppression, immunosuppression, and osteolytic lesions.

- Finally, host immunomodulatory effects within the microenvironment can regulate tumor cell growth and survival.

Much remains to be learned about the oncogenic events that occur within a tumor cell during tumorigenesis. However, in view

of the remarkable research tools that have been developed in the past few years and the considerable progress made in understanding the biology of normal and tumor cells, it seems timely to make a major effort to study the complex problem of tumor/host interactions in hematological malignancies. The therapeutic potential derived from this approach is illustrated by the clinical activity of thalidomide, even in drug refractory myeloma. This drug appears to act directly to induce apoptosis or growth arrest in myeloma cells. In addition, it inhibits tumor-stromal cell interactions, cytokine secretion, and angiogenesis in the bone marrow milieu, and also stimulates host antitumor immunity.

A comprehensive study of tumor-host interactions will require the effort of molecular and cell biologists, experts in bioinformatics, pathologists, clinicians, and others. Support for collaborative funding of investigators representing different disciplines and different institutions will be especially important in pursuing this priority. Specific research priorities include the following:

- Define the microenvironments of tumor and normal tissue counterparts in terms of kinds, numbers, and phenotypes of stromal cells.

- Determine the stability and mechanism of stability of phenotypes of various kinds of tumor stromal cells in the absence of tumor cells.

- Determine the kinds of interactions and their consequences between normal or tumor stromal cells and tumor cells or the normal counterpart of tumor cells.

- Develop animal models that fully mimic the human malignancies, including the roles of stromal cells so that both the tumor cells and stromal cells can be studied using a full array of genetic manipulations.

- Develop *ex vivo* models that use appropriate combinations of tumor and stromal cells.

- Develop and test therapies targeted against host cells or host cell/tumor cell interactions. These could include therapies that might revert the stromal cell phenotype or replace tumor stromal cells with normal stromal cells.

3. Provide molecular characterization of hematological malignancies, including the characterization of global patterns of genetic and epigenetic alterations and RNA and protein expression, as well as the validation of the molecular targets necessary for the survival, proliferation, and evolution of hematological malignancies.

One of the central challenges in cancer research is to define diverse hematological diseases in molecular terms. Currently, tumor cell morphology largely determines cancer diagnoses, so that multiple molecularly distinct diseases are often lumped together. This underlying molecular heterogeneity means that patients in the same diagnostic category may experience markedly different clinical courses and responses to treatment.

We must rapidly migrate to a molecular definition of cancer in which we make optimal use of our burgeoning knowledge of the genetic and epigenetic abnormalities in cancer and the profiles of gene, RNA, and protein expression in tumor cells. Ideally, a molecular diagnostic subtype of cancer would include only those patients whose cancers have a uniform pathogenesis. An optimal molecular diagnosis of cancer would identify which normal cell type gave rise to

a tumor and which molecular mechanisms resulted in the malignant transformation.

Such a paradigm shift in cancer diagnosis would have significant clinical utility. Cancer patients with the same molecular diagnosis would be likely to have much more homogeneous clinical behaviors and prognoses. A detailed understanding of the molecular abnormalities of a patient's tumor can be used to guide the patient to the treatment modality that is most likely to be effective. Most important, a molecular diagnosis of cancer will reveal new molecular targets for therapeutic development.

Hematological malignancies are an especially diverse group of cancers because nearly every stage of development of blood cells gives rise to a distinct type of cancer. Molecular definitions therefore must be developed for each of these many hematological malignancies. The National Cancer Institute (NCI) has established several initiatives, including the Cancer Genome Anatomy Project and the Director's Challenge, that foster the use of high-throughput molecular technologies to transform cancer diagnosis and treatment. These initiatives must be expanded to promote the application of these novel technologies to all hematological cancers, including both common and less prevalent subtypes.

Technologies of particular promise include genomic-scale gene expression profiling, proteomics, spectral karyotyping, and comparative genomic hybridization. These technologies are being separately applied to individual hematological cancers, but what is needed in the future is to study the same tumor specimens with all of these technologies in parallel and integrate the results to achieve a molecular portrait of each hematological cancer. An important adjunct to this work will be to fully understand gene and protein expression patterns during normal stages of blood cell development so that the normal cellular counterpart of each hematological malignancy can be identified. This approach will identify the molecular differences between normal and malignant cells. Relating genomic changes in cancer cells to changes in gene, RNA, and protein expression will allow a fuller understanding of how translocations, deletions, and amplifications of the cancer cell genome lead to changes in the cells' biological behavior. One of the most compelling scientific goals of this endeavor will be to identify the distinguishing molecular characteristics of hematological malignancies that are most vulnerable to therapeutic attack.

A critical component of the molecular characterization of hematological malignancies is identification of the mechanisms of action of molecular targets. Specific validation of molecular targets that are necessary for the survival, proliferation, and spread of cancer cells will be important for the development of new therapeutic, diagnostic, and preventive agents. New initiatives are required to create accurate models and systems with which to validate these targets as having causal or critical relationships to the proliferation or survival of the cancer cell. One such initiative is the Cancer Translational Research Allied Consortium (C-TRAC, discussed below), which will support target validation as a necessary step in expedited drug development.

4. Further develop research on stem cells, both multi lineage and single lineage.

Investigations into the production of normal blood cells have played a pivotal role in the development of modern understanding of

human leukemia. Such investigations also have been key to three decades of stepwise, dramatic improvements in the treatment of many of these diseases, which previously were rapidly and almost universally fatal. These improvements include the introduction of rationally based combination chemotherapy regimens, bone marrow transplantation, and more recently, the use of hematopoietic growth factors to enhance hematopoietic recovery and to mobilize stem cells to enable their collection in large numbers from the blood.

Seminal studies performed 40 years ago identified the presence of normal, multi-lineage, hematopoietic stem cells in mice. These studies also revealed the importance of quantitative functional assays for discriminating these cells from daughter, single-lineage stem cells that were subsequently characterized by a variety of *in vitro* and *in vivo* procedures. This insight enabled the development of procedures for purifying these different stem cell types to near homogeneity. These procedures, in turn, were essential for more rigorous investigations of the biological features of these cells.

Parallel studies of normal human hematopoietic stem cells are now underway, using analogous *in vitro* assays and the transplantation of human cells into xenogeneic hosts (fetal sheep and immunodeficient mice). The precise relationship of the human cell populations thus detected to similarly defined murine cells is not yet clear, and in neither case have the molecular mechanisms that govern their behavior and responses to molecular changes in the environment been well characterized. Because the clinical relevance of the human cells detected by different assays or defined by different phenotypes is not known, it is not possible to use any of these measurements to predict hematopoietic recovery patterns in patients. Experimental strategies to address these questions are no longer limited by technology but require the commitment of resources to support carefully designed, large-scale, preclinical and translational programs that could effectively combine efforts from multiple centers.

Much evidence now suggests that most malignancies of the blood-forming system result from the mutation of key genes that alter the growth control and differentiation behavior of multiple- or single-lineage stem cells. The hierarchical structure of such normal blood-forming cell populations has been assayed through *in vitro* and *in vivo* (xenotransplant) procedures. Using those same procedures, researchers have found that human leukemic populations preserve a similar structure within the leukemic cells. Within this structure, the leukemic stem cells are thought to be responsible for the initial, inappropriate expansion and evolution of clinically important clones of neoplastic cells. These leukemic stem cells are also likely to be responsible for disease relapse after treatment.

These developments point to exciting directions for a selected sampling of chronic and acute myeloid leukemias. Extension of these observations to larger patient populations and the exploitation and testing of these concepts to evaluate clinically relevant disease parameters and to develop new treatment strategies has only just begun.

Research in recent years has revealed exciting evidence of a common molecular signature of stem cells in multiple tissues and organs. Unanticipated and provocative examples of stem cell plasticity have also been described. These examples include the *in vivo* generation of liver and muscle cells from intravenously injected hematopoietic stem cell–enriched populations, the

generation of blood cells from intravenously transplanted neural stem cells, and the functional correction of infarcted heart tissue with marrow stem cell–enriched populations. Such studies have stimulated great interest in the therapeutic and regenerative applications suggested by these observations. They also raise new questions about epigenetic mechanisms that may regulate drug uptake properties, gene expression patterns, differentiation, and the migratory and invasive behavior of normal and malignant stem cell populations.

It is important to emphasize the recent explosion of information about the molecular control of basic cellular processes. In blood-forming stem cells, these controls are triggered by a multitude of growth factors and cytokines, many of which have now been identified along with their specific cell surface receptors. Many of the signaling intermediates that are activated by these receptors are also known, as are some of the transcription factors that direct the gene expression programs of these cells. It is also now known that many leukemia oncogenes disrupt these critical signaling pathways, thereby deregulating the mechanisms that control normal stem cell proliferation, viability, and differentiation. However, our understanding of how specific outcomes are determined at a molecular level in different types of normal blood cell precursors is still rudimentary, fragmented, and limited to a small proportion of the total gene expression program of these cells. As a result, it is still not possible to anticipate how specific molecular changes produce a leukemic behavior. Such information is essential to designing therapies that are not only curative but nontoxic. The potential for significant progress in these areas is now at hand through the exploitation of rapidly evolving high-throughput approaches, which will provide methods for analyzing gene and protein expression as well as new opportunities for large-scale investigations into functional genomics in a variety of model organisms.

The cardinal role stem cells are now thought to play, both in the pathogenesis of human malignancy and in its treatment, provides a compelling rationale for the creation of a strong innovative stem cell research initiative by the NCI, which currently has no specific programs to support this area. Hematopoietic stem cells and their derivative malignancies have served as the historic paradigm for such research and are particularly well suited for building a new interdisciplinary program in this subject with a recognized translational focus. Within such a program, the following should be considered:

- Create virtual interdisciplinary, inter-institutional “stem cell centers.” The mandate of these centers would be to obtain a complete minimal molecular characterization of the normal hematopoietic “stem cell state” and its alteration in leukemia and to apply this information to preclinical and clinical settings for validation and assessment of leads for new diagnostic and therapeutic strategies. Other areas requiring such a mechanism include the definition, manipulation and preclinical and clinical evaluation of stem cell plasticity, transdifferentiation, engraftment and genetic modification including investigations using embryonic as well as other sources of multi-potent stem cells.

- Support multi-center “trials” to develop and validate specific, quantitative and faithful assays and indicators of different types of normal and leukemic stem cells with different regenerative abilities that would include *in vivo* gene tracking studies in animals and patients.

Drug Development and Therapeutics

RESEARCH PRIORITIES

1. **Develop the required resources to translate "lead" structures and molecules into effective therapeutic agents. Hasten the translation of candidate validated targets to lead compounds and subsequent clinical trials and support the development of orphan therapeutic agents and diagnostics, including FDA approval.**

The explosion of knowledge relating to both the genetic basis and the molecular pathogenesis of leukemia has appropriately raised expectations of increased benefits for patients. In a recent example, an inhibitor of tyrosine kinase (STI571), which targets the *BCR-ABL*–induced fusion protein, has yielded promising clinical results in patients with chronic myeloid leukemia. Historically, other enzyme inhibitors have proved useful in treating patients with various forms of leukemia. In modern research, major resources are focused on rational drug development, and intense efforts are expended to define important molecular targets for therapeutics. Actual malignant cells from patients who are undergoing therapy can be retrieved for the specific purpose of validating that the new treatment is indeed having an impact on the proposed mechanism(s) of the targets. The development of targeted treatments for hematological malignancies represents a paradigm for similar approaches in other cancer types. Thus, advances in target discovery, validation, and clinical translation in hematological diseases will form an important basis for future drug development in all cancer types and should be fostered.

The NCI has issued important research initiatives to define appropriate molecular targets, develop assays to validate the impact of the therapeutic agent on the target, and fund extensive clinical trial networks to scientifically develop these agents. Indeed, the NCI has played a key role in the processes of drug discovery and development over the past 50 years. The National Cooperative Drug Discovery Groups have been funded to link scientists in academia to those in both the government and the pharmaceutical industry for the sole purpose of making therapeutic advances in the treatment of cancer. Currently, 16 awards are in existence. In addition, there are six NCI-sponsored Biology/Chemistry Centers dedicated to cancer drug discovery. In funding these efforts, the NCI is looking for new molecules evolving from advances in technology (e.g., robotics, computer science, genetic, and molecularly targeted hypotheses). In the past few years, the NCI has developed two new programs that will further facilitate therapeutic research by talented scientists. Non-government scientists can present their hypotheses with supporting preliminary data to gain assistance with the expensive processes of bringing new therapies to early clinical trial. Establishment of the Rapid Access to New Drug Discovery (RAND) program and the Rapid Access to Intervention Development (RAID) program have provided resources for both discovery and developmental tasks in hastening new agents to the clinic. It has been extremely important that computer access to extensive preclinical data at NCI is also now available for both extramural and intramural scientists dedicated to therapeutic research.

Despite the creation of these new initiatives by the Developmental Therapeutics Program at NCI, which will facilitate access to government resources in therapeutic

research, more work is desperately needed if the promise of rational therapeutics is to be fully realized. The pharmaceutical industry has often opted to pursue areas of therapeutic research in other areas (e.g., solid-tumor oncology) when considering the overall clinical market and the enormous costs involved with therapeutic product research.

Continued NCI support for preclinical research is also essential. Even after the discovery of a validated target, it takes 5–10 years to bring a new drug to a phase I clinical trial, and the cost is often measured in millions of dollars. Furthermore, given the extensive investments required to define promising molecular targets or support clinical trials, therapeutic agents that are tested must be optimal ones. Identification of a "lead" compound that interacts with an appropriate molecular target must be followed by optimization of its chemical structure and formulation. Lead optimization requires close collaboration between scientists in preclinical biology and chemistry. The iterative process requires an examination of the biological effects in relation to the structure of the modified lead agent. These structure investigations initially require the skills of a diverse team of preclinical scientists (e.g., medicinal, pharmaceutical, and formulation chemists; pharmacologists; and toxicologists) and, finally, physician scientists to execute the Phase I trial.

Important research efforts have focused on defining exciting therapeutic targets (e.g., signal transduction pathways mediated via tyrosine kinases emanating from fusion proteins, differentiating agents that induce selective apoptosis in myeloid leukemic cells, and new monoclonal antibodies directed at key targets on malignant cells). However, more resources must be directed toward the scientists who design and discover new therapeutic agents.

A potentially important barrier to the development of new agents is the relative rarity of hematological malignancies. Individually, leukemia, lymphoma, and myeloma afflict proportionately fewer patients than, for example, lung, breast, colon, and prostate cancers. For this reason, pharmaceutical companies have had uncertain interest in targeting the development of therapies specifically for patients with hematological neoplasms. They note that considerable expenditure for research and development might not translate into a product of value to a large number of patients. The NCI can step into this potential vacuum in drug discovery research by magnifying its efforts to offset the cost of drug development for relatively rare cancers, including leukemia, lymphoma, and myeloma. This situation is paradoxical, because (as noted in both the "Biology of Normal and Neoplastic Tissue Targets" and "Therapeutics I" Roundtable breakout groups) the hematological neoplasms constitute a signature example of an area in which science has both defined the molecular nature of the targets that are responsible for many of these diseases, and has produced initial "proofs of principle" that drugs directed against these targets (e.g., STI571 in chronic myeloid leukemia and all-trans retinoic acid in acute promyelocytic leukemia) are of clinical value. The NCI is therefore urged to align experts in drug discovery and development with scientists who are expert in the biology of the targets that are relevant to hematological neoplasms. The goal should be to produce a drug candidate for each of the biologically defined subsets of LLM over the next decade. The opportunity for progress exists to be seized.

The Orphan Drug Act was enacted in 1983 to stimulate the development of agents for

the treatment of diseases that afflict fewer than 200,000 Americans. This designation may be awarded to a therapeutic agent to provide incentives for its development. It includes granting of market exclusivity to sponsors of orphan drugs, tax incentives for clinical research, streamlined patient entry and access into clinical trials, and, potentially, grant funding to defray clinical testing. Since its enactment, more than 100 orphan drugs have been brought to market. Clearly, the proposed initiatives on drug development for hematological neoplasms will benefit from the incentives gained by orphan drug status, and these incentives should be vigorously pursued as part of the NCI's response to the LLM PRG's recommendations.

A Cancer Translational Research Allied Consortium (C-TRAC) is hereby proposed as a mechanism to rapidly develop novel therapies from discovery to treatment phases. It is expected that C-TRAC will provide the bridge for inter-institutional collaboration that targets chemistry efforts to identify and modify "lead" structures and to optimize existing investments in defining appropriate molecular targets. Indeed, the NCI could be a key arbiter of efforts to broker the efficient development of agents for hematological neoplasms through C-TRAC. This effort would expand and complement the NCI's long-standing capabilities in this area in a way that would invigorate extramural investigators and interest them in promoting the cause of therapeutics development for hematological neoplasms. The NCI would ensure scientific rigor and quality and would augment C-TRAC efforts by support with contracted research and development resources for studies on the synthesis, toxicology, pharmacology, and formulation of drugs and biological compounds emerging from these efforts and developed under Good Manufacturing Practices. In addition, the NCI would coordinate the further dissemination of agents emerging from C-TRAC through its clinical trials groups and would represent data emerging from C-TRAC and its associated clinical trials to the Food and Drug Administration (FDA) as a basis for continuing to pursue New Drug Application (NDA) status for suitable compounds and biological agents.

2. Foster partnerships between the NCI and academia, advocates, cooperative groups, FDA, and industry to expedite drug development and availability of therapies.

There is a widely recognized need to expedite the clinical development and regulatory approval of new therapies. In the period 1996–1998, this process took an average of 5.9 years across all therapeutic areas. Although this time represents an 18% decrease from that in 1993–1995, it is no faster than the average in 1984–1986. Anticancer agents in particular have an average clinical phase of 7.2 years—longer than that of antiviral, anti-infective, analgesic, cardiovascular, or respiratory drugs.

Among all cancers, hematological malignancies offer the best opportunity for therapeutic progress because they are better understood and are intrinsically sensitive diseases. However, each of them is also a rare disease, which may at times constitute a barrier to the development of new treatments.

Six groups are directly involved in the process of developing new cancer therapies: the NCI, the FDA, academia, patient advocacy organizations, the pharmaceutical industry, and NCI-funded Cooperative Clinical Trials Groups. It is critical for these six groups to work together in the most efficient manner so that new therapeutic products are developed and approved in the

most timely fashion. The NCI, as the lead agency for implementing the National Cancer Program, is in the best position to facilitate this partnership.

Currently, insufficient coordination between these groups makes the entire process highly inefficient. Academicians are hesitant to allow input on their research from the pharmaceutical industry. The NCI Cooperative Groups move at a slow pace. The designs of clinical trials often fail to meet the needs of the pharmaceutical industry. Study implementation needs to follow an expedited timeline. Patient enrollment can and must be enhanced. Study completion and reporting takes too long.

The FDA must reduce review and approval timelines in a real fashion. Recently those timelines were apparently shortened, but at the expense of lengthening the Phase I, II, and III timelines due to more stringent FDA requirements. In addition, the FDA appears to meet guidelines of the Prescription Drug User Fee Act by issuing a "completed review letter." However, this step must be followed by the review and approval of a package insert before final approval is granted for a new therapeutic agent. This review process requires months. Pharmaceutical companies find it more expedient to carry out their own studies, thus competing for patients with academia and the cooperative groups. Patient advocacy groups are often not included and are thus underutilized.

Meanwhile, a promising new therapy may not be available to the patients who need it and who could benefit from it. These patients do not have the luxury of time and cannot wait. Under the current system, a new therapy may have been proven useful as early as Phase II clinical trials but would not be widely available until it is approved and marketed. Expanded-access programs of many different types have been tried but will never substitute for actual approval, the only step at which a new therapy is truly available.

The NCI has an opportunity and a responsibility to exert its leadership and to take the initiative in developing a true and effective partnership among these agencies. The NCI should develop a working group with representatives from the FDA, academia, patient advocacy organizations, the pharmaceutical industry, and Clinical Cooperative Trials Groups to enhance cooperation and efficiency for the development of new cancer therapies. It is critical for the working group to be inclusive and a real partnership. All partners must be equally informed, have equal rights, develop a consensus strategy, work toward common goals, and participate with a voice and a vote in all committees and meetings. The development of a cooperative environment among these groups will greatly enhance the ability of C-TRAC and pharmaceutical companies to rapidly develop new agents for the treatment of hematological malignancies. The NCI must produce an implementation plan to address these pressing needs and to involve and truly facilitate a partnership of all six groups.

Education, Communication, and Survivorship Research

RESEARCH PRIORITIES

1. **Determine how to provide accurate, timely, and tailored information to patients to improve medical decision-making, access to clinical trials, quality of care during active treatment and follow-up, and quality of life.**

Effective health communication can help reduce cancer risk, incidence, morbidity, and mortality and improve quality of life. It narrows the enormous gap between discovery and applications and reduces health disparities among individuals. In fact, few other health interventions have a more immediate impact on the experience of individuals who are at risk for and who are living with cancer.

Unfortunately, much of the available information on communicating with patients does not address the specific circumstances of those affected by hematological malignancies. Furthermore, much of the information that does exist has been extrapolated from cross-cutting studies that include few if any patients with these diseases.

The time is ripe to identify and develop strategies for providing information to patients to improve medical decision-making, quality of care during active treatment and follow-up, and quality of life. The need is especially great for patients with hematological malignancies. First, the hematological malignancies affect a diverse patient population in terms of age, sex, and race. Second, short- and long-term side effects and complications vary by disease. For example, myeloma patients often experience severe bone pain, whereas leukemia and lymphoma patients face secondary cancers and the long-term health consequences of treatments. Third, treatments for hematological malignancies are evolving rapidly due to new scientific discoveries and advances. Recent research shows that hematological malignancies are even more diverse than previously thought and that tailoring treatment to the specific disease subtype can ensure that patients receive treatments that are more effective and less toxic than earlier ones. Finally, longer life for LLM survivors creates a need for more information about coping with cancer. This is especially true for the many LLM patients who are young and for those who are advised to "watch and wait" rather than pursue aggressive treatment. For all of these reasons, treatment and follow-up care information must be up to date, easily accessible, and tailored to the circumstances of the patient.

The NCI has a broad and expanding research program in education and communication. Some of this research focuses on patient and provider decision-making, clinical trial participation, quality of care, and social and psychological support, including research to develop persuasive message strategies and education for patients and providers on diagnostics and treatment. Gaps do exist, however. Little of this research addresses the specific needs of patients with hematological malignancies and their health care providers. Most current research focuses on long-term survivors, and relatively little focuses on patients who are undergoing or have recently completed treatment.

The NCI has in place a number of initiatives and activities that could identify and develop ways to provide information to LLM patients. For example, the Cancer Care

Outcomes Research and Surveillance Consortium (CanCORS) initiative, currently focused on breast, prostate, lung, and colorectal cancer, could be expanded to evaluate the impact of decision-making strategies on treatment course. Another example is the NCI's new initiative to support Centers of Excellence in Cancer Communications Research (CECCRs), which could play a pivotal role in addressing the recommendations proposed here.

Clearly, there is an urgent need to provide accurate, timely, and tailored information to patients to improve outcomes. A multifaceted program that addresses this need will undoubtedly build on existing NCI efforts. The NCI should consider support for the following:

- A survey that identifies and characterizes the primary information sources used by patients and providers to make decisions about LLM treatment and care

- An evaluation of the accuracy of this information. This evaluation should propose ways to improve the quality of and ease of access to the information

- The development of educational materials tailored to the numerous populations affected by these diseases. These materials should (1) reflect the best available treatment and care options, including information about participation in clinical trials; (2) be easy to update; and (3) give patients the information they want.

- The identification or development of effective ways to reach this diverse group of patients and their family caregivers, especially those that are underserved, such as the elderly and the poor, who do not have easy access to information. Exciting opportunities exist for building on recent dramatic developments in health communication, such as those made possible by the World Wide Web, two-way satellite linkages, high-speed transmission of high-resolution images and audio, and other multimedia technology.

- Training programs in education, communication, and behavioral research

Given the rarity of these diseases and the dearth of patients within individual centers, the NCI also should support multi-center collaborative studies for testing the effectiveness of messages and their delivery.

2. Develop education and training programs for certification of physicians and centers for diagnosis, treatment, and clinical trials in hematological malignancies.

Optimal diagnosis and treatment of hematological malignancies should be a necessary requirement for all physicians who treat patients with these diseases. This is particularly important when treating potentially curable malignancies, such as acute leukemias and aggressive lymphomas. There also exists a serious impediment to clinical investigation of hematological malignancies because so few patients are entered into clinical trials. The barriers to achieving these goals exist because, as a disease group, hematological malignancies are complex and their relative infrequency leads to limited experience among treating physicians. Furthermore, most patients are not treated by specialists in hematological malignancies and do not have the opportunity to participate in clinical trials. Although education is an important and necessary component of any solution, in the absence of experience it will not achieve optimal care. A solution to these barriers has been achieved with pediatric malignancies and may serve as a model for hematological malignancies. Presently in the United States,

the vast majority of pediatric malignancies are treated by limited groups, which are mostly aligned with cooperative groups and are treated according to state-of-the-art protocols. Similarly, in France, hematological malignancies are treated at designated centers that are members of a centralized cooperative group. Certification programs for other specialty care, such as heart surgery and bone marrow transplantation, have improved the care of their respective patient groups.

The development and ultimate implementation of a training and certification program for physicians and centers requires the engagement and participation of multiple groups, including academic centers and their training programs, medical societies, clinical cooperative groups, and physicians themselves. The NCI leadership can take a central role in the organization of a working group to further develop these concepts, including the conduct of a consensus conference. Implementation of this proposal will lead to significant improvement in the treatment of hematological malignancies, not only through optimization of current treatment approaches but also through the channeling of patients to specialized physicians and centers where state-of-the-art treatments may be investigated and applied through their participation in cooperative group trials.

3. Identify and target individuals and populations at high risk for adverse long-term outcomes to define the biological basis of identified associations and facilitate the design and testing of intervention and prevention strategies.

Each year in the United States, an estimated 17,000 patients with the diagnoses of LLM reach 5-year survival. Among this ever-growing population are subgroups of patients who are cured of their malignancy and will experience long-term survival. As advances in treatment continue, the number of LLM survivors will continue to increase. Little is known about which patient populations are at high risk for adverse outcomes of LLM treatment. This information is essential to the rational development and testing of intervention and prevention strategies.

The spectrum of outcomes that are in need of high-quality research include second malignancies, organ dysfunction (e.g., cardiac, pulmonary, and endocrine), neuropsychological, psychosocial, quality of life, and quality of care. Some high-priority populations are known and include survivors treated with chest irradiation (i.e., for Hodgkins lymphoma), exposed to anthracyclines, treated with bone marrow and stem cell transplants, or exposed to alkylating agents or topo-II inhibitors. Outcome issues are unknown for many populations, such as patients treated with novel therapies, those who may have unique genetic susceptibility traits, and those for whom extended periods have elapsed since treatment. Although some research has been conducted on treatment-related risks, very limited information is available regarding the potential impact of pre- and post-therapy health behaviors (e.g., smoking and diet).

Although a number of forums exist for the conduct of research on long-term outcomes, including single institutions, limited consortia, Cooperative Clinical Trials Groups, late-effects clinics, and health maintenance organizations, there are limitations inherent in these venues that have severely limited the conduct of high-quality research. Specifically, long-term outcomes research in LLM has often been characterized by limited sample size, lack of heterogeneity in the study

populations to allow for adequate assessment of patient- and treatment-specific risks, and potential bias in study populations resulting from selection influences, such as incomplete follow-up. The identification of factors that adversely affect long-term outcome, such as behavioral or treatment-based factors, should be used to design prospective studies directed at improving long-term outcomes.

To carry out research of the scope and quality required to understand the incidence, prevalence, and impact of adverse outcomes among LLM survivors, it will be essential to invest in the appropriate resources that will directly facilitate and enhance outcomes-based research at two distinct levels: the population level and the clinical level. Maximal yield from future population-level research will require investment in the establishment of research cohorts. Well-designed cohorts of LLM survivors would provide a dynamic resource with which to address a wide spectrum of high-priority outcomes, as well as provide a monitoring system for the identification of emerging outcomes-related issues among LLM survivors. It is essential that these future research cohorts overcome the limitations of previous and current research by including the following:

- A sufficiently large sample size that ensures demographic diversity and heterogeneity of disease characteristics and treatment exposures
- Utilization of extremely well-defined outcomes
- Collection of biological samples (e.g., genomic DNA and second tumors) to facilitate the evaluation of molecular genetic factors
- Appropriate support cores (e.g., biostatistics, tissue procurement and processing, and survey research)

To promote the conduct of high quality, clinically based research will require the establishment of an effective collaborative network consisting of clinical centers of excellence. Such a network, which could collaborate with existing institutional General Clinical Research Centers, would provide a clear and effective structure in which to conduct protocol-driven clinical investigations designed to test focused high-priority questions relating to the occurrence of adverse treatment-related outcomes among LLM survivors.

Finally, to be truly effective in moving forward in the area of outcomes-based research among LLM patients, investments must be made in each of three distinct areas: (1) identification and characterization of high-risk populations, (2) definition of the biological basis of identified associations, and (3) design and testing of innovative intervention and prevention strategies. There exists a critical need for the following:

- Establish the utility of biomarkers or surrogate markers for predicting the occurrence of specific outcomes.
- Develop and test psychological and behavioral strategies for education and prevention.
- Rigorously evaluate the impact of screening for early detection of adverse outcomes.
- Determine the effectiveness of late-effects clinics in modifying quality of life.
- Evaluate the effect of changes in lifestyle and behavior on health and quality of life.

New Initiative: Cancer Translational Research Allied Consortium (C-TRAC)

RATIONALE

Hematological malignancies serve as a model system for the discovery and development of targeted therapies. Understanding the pathogenesis and pathophysiology of hematological malignancies, which underlie the basis of discovery, has advanced at an extraordinary pace over the past decade. However, the identification and validation of potential molecular targets have only just begun, and more important, the therapeutic translation of these targets lags far behind our knowledge of the molecular basis of hematological malignancies. Indeed, even after the discovery of a validated target, it takes 5–10 years to bring a new drug to trial, and far too often, financial barriers prolong or prevent their translation. These barriers are multifaceted but ultimately are related to the absence of adequate infrastructure for the development of the therapeutics.

Although the pharmaceutical industry provides the broadest infrastructure for drug development, the often-limited financial rewards from targeted therapies for uncommon diseases and the risk of failure reduces access to this important source of drug development. Even with industrial interest, development often proceeds at an unacceptably slow pace. At the interface of clinical translation, there is also a critical shortage of trained investigators who understand the intricacies of *in vitro* assays and the development and application of the novel study designs that are increasingly necessary for targeted therapies.

The development of the C-TRAC mechanism arises as a solution to these concerns and can become a new paradigm for the study and treatment of cancers of all types. The intent of C-TRAC is to bring together experts across multiple disciplines and institutions to participate, within a formalized infrastructure, in the rapid discovery and development of cancer therapies. The intent of C-TRAC is not to replace the pharmaceutical infrastructure but rather to provide a parallel system that is capable of rapid translation. It is envisioned that, relevant to each C-TRAC, the broad enhancement of communication and collaboration among investigations within and between disciplines will produce important synergies.

The structure of each C-TRAC grant would be disease based, and separate platforms would provide cross-cutting infrastructures for tumor banks, animal model repositories, advanced technology centers (e.g., genomics and proteomics), and, importantly, for development capabilities such as high-throughput screening, drug synthesis and scale-up, and animal toxicology and pharmacokinetics.

Access to the C-TRAC core facilities would be open to all members of the scientific community but would be funded and managed through the C-TRAC mechanism C-TRACs will encompass the whole spectrum of drug discovery and development: identifying, validating, and credentialing targets; discovery and preclinical testing of agents directed against these targets; and scale-up and testing of promising agents in clinical trials. The ultimate goal of the C-TRAC will be to shorten drug development time from 5–10 years to 2 years through a novel alliance among academia, industry, government, and patients.

Hematological malignancy C-TRACs:

- Leukemia (acute myeloid leukemia, myelodysplastic syndrome, acute lymphoid leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia)
- Lymphoma (Hodgkins and non-Hodgkins lymphoma)
- Plasma cell diseases (multiple myeloma, monoclonal gammopathy of undetermined significance, Waldenstrom's)

Essential features:

- Multi-institutional
- Basic and translational research
- Phase I and II clinical trial capabilities
- Outcomes research

Core facilities:

- Tumor bank
- Animal model repository
- Advanced technology centers (e.g., genomics and proteomics)
- Drug discovery and development capabilities (e.g., high-throughput screening, drug synthesis and scale-up, etc.) established through cooperation with government, industry, and academia, with the aim of rapid drug discovery and development

General aims:

- Rapid capabilities for identification and development of new therapies in hematological malignancies
- Identification and validation of biomarkers in specific diseases and pilot developmental diagnostics
- Drug discovery and development core facility that will establish and evaluate new standards in partnership with government and industry
- Development of new Phase I and II clinical trial models
- Support for standardized, interactive bioinformatics platforms and bioinformatics training, as well as training in proteomics, functional genomics, and translational research

IV. Appendices

Appendix A: About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that the Institute determine the best uses for its resources.

To help ensure the wise use of resources, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific priorities and needs for its large, site-specific research programs.

CHARGE TO THE PRGs

Each PRG is charged to:

- Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.
- Define the scientific resources needed to address these opportunities and needs.
- Compare and contrast these priorities with the current NCI research portfolio.
- Prepare a written report that describes findings and recommendations.
- Discuss a plan of action with NCI leaders to ensure that the priority areas are addressed.

The following section details the process used to execute these charges.

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100–180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next 5–10 years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable with an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the

Roundtable is used by the PRG in delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the PRG may solicit additional input from the research and advocacy communities through workshops, ad hoc groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. After the report is accepted, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is widely disseminated and integrated into the Institute's planning activities. At this meeting, the PRG and the NCI identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI discuss a plan for implementing the highest research priorities of the PRG. This plan becomes a blueprint for tracking and hastening progress against the relevant cancer.

PRG reports on breast cancer, prostate cancer, colorectal cancer, brain tumors, and pancreatic cancer, in addition to this PRG report on leukemia, lymphoma, and myeloma, are available online a http://osp.nci.nih.gov. Other PRG reports currently in development or planned include reports on lung cancer, gynecologic cancers, and kidney and bladder cancer.

Appendix B: Reports of the Roundtable Breakout Groups

EPIDEMIOLOGY

Co-Chairs: Julie A. Ross, PhD; Stella M. Davies, MD, PhD

State of the Science

Research developments in molecular biology have led to an increasingly detailed understanding of the biology of hematopoietic and lymphoproliferative malignancies. Although leukemias, lymphomas, and multiple myeloma and their precursors (hereafter abbreviated as "LLM and precursors") serve as model systems to understand the molecular events that lead to malignancy, our understanding of the etiology of these malignancies is extremely limited. A major limitation in our ability to adequately identify the causal factors for these tumors may be their extreme biological heterogeneity and the inability of the current International Classification of Diseases for Oncology, Second Revision (ICDO-2) and many other earlier diagnostic classification schemes to adequately characterize this heterogeneity. While the forthcoming ICDO-3 (currently being pilot tested) represents a substantial improvement, nevertheless ICDO-3 continues to focus mostly on histologically characterized categories, rather than on molecularly-defined subtypes. The extensive heterogeneity introduces classification error and diminishes statistical power. Investigations in the past have been too small to provide sufficient power to identify risk factors for specific subtypes. Recent development of gene and protein arrays provide powerful new tools to define hematopoietic and lymphoproliferative malignancy subtypes molecularly, identify specific biological effects of carcinogens, and evaluate pathogenic mechanisms to improve our understanding of the causes of hematopoietic and lymphatic malignancies in the near future. This, coupled with continuing improvements in exposure assessment and technologies to assess gene-environment interactions, indicates that multi-disciplinary investigations are now likely to provide information to greatly expand our understanding of the causes of these tumors.

Limitations of Prior Epidemiological Research

Epidemiological research of LLM and precursors has also been hampered by a general lack of understanding of important biological processes. There has been an insufficient focus of etiologic research on molecularly-defined subtypes of LLM and precursors. Epidemiological investigations have not given adequate attention to identifying polymorphisms of alleles that confer increased susceptibility, and the multistep and progressive molecular events in the evolution of neoplastic transformation. Thus, there are many gaps in knowledge about the specific molecular events (i.e., translocations, DNA methylation, gene mutations) that may contribute to the development of the LLM precursor disorders (i.e. myelodysplastic syndromes and aplastic anemia) and the frank LLM malignancies. The contribution of genetically derived (perhaps modified by exogenously influenced) immune dysfunction that is likely to be important in the etiology of many LLM and precursors is poorly understood. Similarly, the role of viral infection in the initiation and progression of these malignancies is unclear, as are any possible modifying effects of viral infection on other known or postulated risk factors for LLM or precursors. The critical

periods of exposure that may be important in etiology (e.g., *in utero* and, perhaps preconception exposures now appear to be important in childhood acute lymphoblastic leukemia) have not been delineated for most known or postulated risk factors for LLM or precursors. Overcoming these limitations requires large-scale, multidisciplinary efforts designed to exploit the recent biological and mechanistic advances from the laboratory by applying them in etiologically-based studies.

Research Priorities and Recommendations

1. **Conduct a very large case-control study that will serve as a national resource to systematically investigate the etiology of LLM and precursors.**

Problem and Rationale

Prior case-control and cohort epidemiological studies of LLM and precursors have virtually all focused on a narrow single category or a limited group of LLM and precursor conditions. The limited outcome(s) evaluated generally included some conditions not appropriately included due to misclassification (e.g., about 10% or perhaps more of Hodgkins disease diagnosed in the 1970s or earlier were actually forms of non-Hodgkins lymphoma). Another limitation was incomplete ascertainment of cases within an entity (e.g., many chronic lymphocytic leukemia cases present with no symptoms other than a high white blood count, and may not be immediately referred to a hematologist/oncologist, but initially managed by general internists with watchful waiting). Also, there was failure to separately evaluate different subtypes of a 'single' hematopoietic or lymphoproliferative disorder (e.g., many cases of prolymphocytic leukemia are, even now, not recognized as a separate entity). Finally, precursor forms, such as myelodysplastic syndromes (which may have some of the same stem cell or early myeloid precursor neoplastic origins as acute myeloid leukemia), have generally not been included in epidemiological studies evaluating etiology of acute myeloid leukemia.

As new understanding has developed of pathogenesis, clinical characteristics and etiology, the incomplete spectrum of myeloid, lymphoid, and hematopoietic stem cell origin outcomes evaluated in virtually all studies has limited the opportunity to: (1) apply and compare newly developed classification systems with 'current' classifications to determine how each performs in identifying and clarifying risk factor associations; (2) study the overlapping features as well as differences in risk factor associations among the various hematopoietic and lymphoproliferative malignancies and precursors; (3) include subjects with precursor conditions to enable comparison of risk factor associations across subgroups, such as myelodysplastic syndromes and acute myeloid leukemia to determine overlaps or differences in risk factors; (4) collect and utilize DNA and/or tumor tissue as renewable resource; (5) evaluate risk factors among races/ethnic groups other than Caucasians to enable evaluation of the effect of genetic differences or gene-environment interaction in the etiology of the LLM and precursors; (6) provide in-depth exposure assessment with validation of exposure using alternative sources of verification of exposure and/or newer methodologies for measuring external exposures, or biological effect measures for exposures; and (7) assess underlying genetic aspects and the possible role of gene-environment interaction within families of those cases in which two or more LLM malignancies or precursor conditions occurred among first-degree family members.

Proposal

A large case-control study of LLM and precursors should be undertaken to serve as a national resource. Such a case-control study should not only be very large, but also geographically, socioeconomically, and ethnically diverse. Inroads to understanding the etiology and mechanisms of these tumors can be accomplished through close interaction between laboratory scientists, clinicians, and epidemiologists to develop the best strategy for a major effort. The team should be led by a multidisciplinary group of epidemiologists, hematologists and oncologists, expert hematopathologists, geneticists, exposure assessment specialists (including industrial hygienists, toxicologists, and others specializing in environmental measurements), molecular biologists, and statisticians. Data and specimens collected should include samples of fresh tumor tissue processed and stored appropriately to enable state-of-the-art molecular characterization. Other biological specimens that should be collected would include samples obtained from paraffin blocks (particularly for subjects for whom fresh tissue is unavailable), genomic DNA and RNA, serum, urine, other appropriate biological samples, and appropriate environmental samples. The study should include focused assessment of families with two or more cases of LLM malignancies or precursors to better understand the roles of genetics, environmental exposures, and interactions between the two.

Advantages

A major advantage of such a very large case-control study would be the capacity to test and compare the 'current' classification with a proposed 'new' classification applied to all of the cases whenever a seemingly more refined approach is developed. This would provide an opportunity to evaluate and compare the relationship between putative risk factors and the 'current' vs. 'new' subtypes without the need to collect new information. This is rarely possible with studies completed so far because only a limited range of LLM malignancies (rarely including precursor disorders) were considered. In addition, few earlier studies were generally large enough to allow effective evaluation of relationships between risk factors and specific cancer subtypes. Earlier studies often did not collect biological specimens (either tumor tissue, blood, urine, or others) in sufficient amounts nor handle these in appropriate ways. Such a study would generate a resource of patients with contemporaneously collected exposure data in whom studies to identify and validate exposures in biological samples can be conducted as hypotheses are developed. The proposed study could be used almost like a renewable resource and, with modest additional investment, could take a look at old problems with new approaches to generate and test hypotheses.

2. **Generate the infrastructure and resources necessary to understand the interaction among immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to LLM and precursors.**

Problem and Rationale

Immune dysfunction is a potent and well-described risk factor for lymphoma and other LLM cancers and precursor disorders. For example, the association between lymphoma and HIV allows an opportunity to study co-factors, such as viral agents and genetic susceptibility factors that influence progression from asymptomatic infection to AIDS to lymphoma. A fertile area for investigation is the contribution of other, less well-recognized infectious agents or

environmental toxins in the initiation or progression of these. Precursor disorders that lead to a high risk of developing frank LLM cancers present model systems for evaluation of the multistep and progressive molecular events in the evolution of neoplastic transformation. Detailed follow-up of patients with such precursor disorders will enable researchers to identify many of the specific molecular events (i.e., translocations, DNA methylation, gene mutations) that may contribute to the development of frank LLM malignancies. Interactions of specific molecular loci, polymorphisms, and other genetic and host factors with exogenous exposures can be studied in detail.

Proposal

Cohorts of subjects with high-risk precursor conditions (e.g., HIV-positive patients, myelodysplastic syndromes, solid organ transplant recipients, patients with monoclonal gammopathy of uncertain significance, cancer survivors treated with chemotherapy and radiotherapy) should be assembled. While there have been some, mostly small investigations of such cohorts in the past, evaluation has generally been limited to estimating risk of transformation to frankly malignant end points, with no attempt to assess in detail the biological effects and subsequent pathogenic changes of specific or exogenous exposures (e.g., environmental exposures, occupational exposures, dietary factors, smoking) or endogenous factors (e.g., gender, racial/ethnic group, hormonal and immunological system characteristics) or the specific molecular and genetic changes underlying transformation of these high-risk states to frank LLM malignancies. The proposed cohort studies should include collection and assessment of appropriate biological specimens (obtained serially at appropriate intervals over time) to evaluate humoral and cellular immunity, genetic polymorphisms, and acquired mutations in conjunction with comprehensive lifestyle and exposure data. Information gleaned from these high-risk populations could be applied to the investigations of sporadic LLM or precursors of unknown etiology, such as most cases that would be included in the large, proposed case-control study. Longitudinal studies would allow the collection of serial samples that can be used to study the progress from premalignant to malignant disease, for example by using gene array technology to identify key genetic changes associated with disease progression.

Existing large cohorts (Nurses Health Studies I and II; the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial; and the Early Postmenopausal Interventional Cohort) of the general population could also be utilized to investigate incident LLM and precursors with serially collected sera and DNA for evaluation of past viral exposures (e.g., Epstein-Barr virus in Hodgkins disease), markers of susceptibility, and intermediate markers. Biological investigations of novel infectious agents that may contribute to etiology should also be undertaken. New strategies (involving diverse techniques, such as PCR, RDA, and others) could be applied within the high-risk cohorts, the general population cohorts, and the proposed large case-control study.

3. Improve methods to understand and better quantify the role of environmental exposures in the etiology of LLM malignancies and precursors.

Problem and Rationale

A critical role of environmental and lifestyle factors in the etiology of LLM and precursors is clearly indicated by the

worldwide geographic differences in cancer incidence and the rapid changes in risk that occur among migrants. Poor characterization of exposures hinders our understanding of causes of these cancers to the same or perhaps greater extent as imprecise classification of disease subtypes. Reliable and valid determinations of environmental exposures, such as pesticides, solvents, and polycyclic aromatic hydrocarbons, tobacco and alcohol, and dietary factors are essential, not only to determine the role these factors play in initiation and progress of the neoplastic process, but also to pinpoint exceptional risks faced by genetically-susceptible subgroups of the population. Timing of exposures is also important. For example, we know that many potentially hazardous substances cross the placenta, and that translocations occurring *in utero* can contribute to leukemogenesis during childhood. Thus, critical exposures may occur during development, childhood, and later. Yet, our understanding is rudimentary of the level of cancer risk in relation to the precise timing of specific exposures (i.e., effects on germ cells or other parental tissues during the preconception period, the different developmental stages occurring *in utero,* the perinatal period, lactation and early infancy, or the various components of the subsequent postnatal period on the occurrence of childhood leukemia, for example) is rudimentary.

Specific recommendations to address this issue include the following:

- Develop appropriate biological markers that accurately reflect pertinent environmental exposures.

- Develop and incorporate more valid and reliable measures to assess exposure (e.g., direct measurements of occupational and environmental agents such as pesticides, solvents, metals, and various physical, chemical, fibrous, and other types of agents; occupational records; medical records; and forms of indirect measurements that rely less heavily on subject recall).

- Conduct biological studies in children and adults to determine whether *in utero* acquisition of translocations plays a role in the subsequent occurrence of hematopoietic malignancy.

- Establish new cohorts and utilize existing cohorts of pregnant women enrolled in longitudinal studies to investigate intermediate biomarkers of *in utero* exposures on subsequent effects in their offspring; these cohorts should be followed with serial measures of exposure and biological effects to provide information regarding the importance of contributions from exposures during childhood, adolescence, and early adulthood.

- Conduct molecular studies investigating the role of endogenous and exogenous factors in the formation of chromosomal translocations, the hallmarks of LLM and some precursor disorders.

- Undertake animal studies to investigate the mechanistic aspects and etiological effects of the passage of potential carcinogens across the placenta, and to study similar aspects of preconception and prenatal exposures.

- Subclassify molecularly defined categories for case-case comparisons (e.g., infants with MLL rearrangements versus those without; patients with different forms of chemotherapy- or radiotherapy-induced, treatment-related acute myeloid leukemia/myelodysplastic syndromes [AML/MDS]).

- Develop and validate biomarkers to characterize host immune function (e.g., polarized TH1/TH2 types).

- Establish prospective cohorts of high-risk individuals, as discussed above.

Barriers to Implementation and Proposed Solutions

Barriers

1. **Slow case ascertainment**: For diseases such as multiple myeloma and some adult leukemias, life expectancy is short. Methods are needed to reduce the interval between diagnosis and ascertainment of this information by the investigators conducting epidemiological studies of LLM and precursors so that the investigators will be able to obtain biological specimens and to avoid the use of proxy interviews in exposure studies.

2. **Issues related to Institutional Review Board review of studies of LLM**: Careful and thorough review of an Institutional Review Board (IRB) is essential for the protection of human subjects in research projects and to insure full and complete consent. Critical aspects of epidemiological research involving LLM and precursors include the need to prevent coercion and pressure when collecting detailed interview data, as well as safety issues when collecting biological specimens. Paramount are the dual requirements for providing confidentiality and protecting privacy. Some aspects of current procedures required for obtaining institutional IRB approval of epidemiological research projects, however, are having a deleterious effect on research, without accompanying benefit to study participants. A major difficulty is the requirement that a duly constituted IRB from each institution with any involvement in a study must review and approve the research plan. In interdisciplinary, multi-center investigations this can require review by many, perhaps several hundred, IRBs. Multiple reviews may provide completely contradictory stipulations that can require enormous time and effort to resolve.

3. **Use of stored biological specimens**: Translation of new technologic developments to LLM research is currently hampered by narrow characterization of permissible consent. Currently, investigators are required to re-contact subjects and obtain approvals for any additional or new use of biological specimens subsequent to obtaining the initial consent. Such a requirement is burdensome to subjects; reduces the initial, often poor, participation rates even further; entails additional costs; and substantially extends the time required to test new findings in well-studied populations. The latter issue can delay resolution of a worrisome new finding, or prolong the period before a risk-reducing measure can be implemented.

Proposed Solutions

To decrease the interval between diagnosis and ascertainment of newly diagnosed LLM and precursor cases by epidemiologists, it is proposed that epidemiologists, hematologists, oncologists, and expert hematopathologists convene a small working group to consider alternative options for reducing this interval. We recommend development of special procedures for multi-centric investigations that can provide the critical review required to insure protection, privacy, and

maintenance of confidentiality of research subjects, yet minimize counter-productive duplication of effort. One approach might be for NIH to convene a panel to consider these issues and generate specific recommendations to the Office of Human Research Protection (OHRP) of the Department of Health and Human Services. Use of stored biological specimens for exposure assessment, *in vivo* markers of exposure effects, and characterization of genetic susceptibility as new methods are developed should be standard operating procedure, provided that appropriate consent is obtained initially and that there is no additional risk. The NIH panel should also develop specific recommendations for OHRP that would empower IRBs to approve more flexible consent procedures (assuming no increase in risk to subjects) in anticipation of technological developments. The panel should also provide recommendations to OHRP about dissemination of consistent guidelines to allow the repeated use of well-characterized, stored biological specimens with newly developed technologies.

BIOLOGY OF NORMAL AND NEOPLASTIC TISSUE TARGETS: BONE MARROW

Co-Chairs: James D. Griffin, MD; Connie Eaves, PhD; Malcolm A.S. Moore, MD

State of the Science

Investigations of myelopoiesis and the myeloid leukemias have served as the lead paradigm for establishing most of our current concepts of cellular hierarchies in tissues characterized by rapid turnover. Normal hematopoietic stem cells were identified 40 years ago, and technologies for their reproducible isolation, purification to near homogeneity, and quantitation in murine models are now well advanced. Rapid progress is also now occurring in parallel studies of normal human hematopoietic stem cells, using analogous *in vitro* assays and *in vivo* transplantation into xenogeneic hosts (fetal sheep and immunodeficient mice). Much evidence now suggests that most leukemogenic mutations occur in these stem cells or their immediate progeny, which then become the leukemic stem cells that are responsible for the initial development and maintenance of the expanded clone of neoplastic cells. They may also be responsible for disease relapse after treatment.

The past two decades have seen an explosion of information about more than a dozen growth factors and cytokines that maintain the viability and stimulate the growth and differentiation of normal myeloid stem and progenitor cells. These responses are triggered by the activation of specific receptors and their downstream signaling pathways, ultimately targeting many transcription factors that together direct the gene expression programs of these cells. We now know that many leukemia oncogenes disrupt these critical signaling pathways and lead to unregulated proliferation, prolonged viability, and differentiation blocks.

The first evidence of a consistent gene mutation associated with a particular cancer was provided about 40 years ago by the recognition of the Ph chromosome in chronic myeloid leukemia (CML). This was followed 20 years later by the identification of a unique fusion gene, the *BCR-ABL* oncogene, and the eventual development 5 years ago of one of the first oncogene-targeted drugs, STI571. This compound is directed at the *BCR-ABL* gene product and is currently showing remarkable promise in the treatment of chronic-phase CML. Cytogenetic and molecular analyses of other types of leukemia have now enabled the identification of more than 100 additional oncogene targets that may be accessible to similar drug development strategies. Nevertheless, for over 45% of all leukemias, very little is known about the biological abnormalities that characterize and may contribute to the generation of an abnormal, dominant clone, and nothing is known about the gene mutations involved.

Breakthroughs have also occurred in the molecular characterization of the pathways that regulate cell cycle control, apoptosis, and cell adhesion, as well as in the identification of "master genes" regulating morphogenesis and the activation of tissue differentiation programs. These key regulatory pathways have been found to be highly evolutionarily conserved and to involve genes that serve as key targets for leukemogenic changes. However, recent technological developments allowing high-throughput analysis of gene expression in normal and leukemic cells are revealing an enormous additional complexity in the transcript profiles of these cells. These complexities pose new challenges to understanding those genes whose expression is essential to the display of a leukemic

phenotype, particularly at the level of the stem cell compartment. Parallel advances in genetic strategies for manipulating the genomes of model organisms and for introducing abnormal genes into normal murine and human hematopoietic stem cells are making possible the creation of new experimental systems for addressing specific questions about gene function. Of significant interest are the consequences of overexpressing candidate oncogenes alone or in combination in various cellular contexts, including the very primary human cell types in which these genes are believed to act first in the clonal hierarchy of leukemic cells.

In the last 2–3 years, researchers have revealed exciting evidence of a common molecular signature of stem cells in multiple tissues and organs. Unanticipated and provocative examples of stem cell plasticity have also been described. These examples include the *in vivo* generation of liver and muscle cells from intravenously injected hematopoietic stem cell–enriched populations, and the generation of blood cells from intravenously transplanted neural stem cells. Such studies have stimulated great interest in the therapeutic and regenerative applications suggested by these observations. They also raise new questions about the epigenetic mechanisms that may regulate drug uptake, gene expression patterns, differentiation, and the migratory/invasive properties of normal and leukemic stem cell populations.

In summary, oncogene-targeted therapy as a new, nontoxic approach to the treatment of a single human malignancy is on the horizon. It is clear, however, that larger-scale, interdisciplinary, and cooperative efforts are required to extend this approach to other myeloid leukemias, and in a faster time frame. In many other forms of leukemia, such as myelodysplastic syndromes (MDS), the genetic targets are currently unknown, prognosis is poor, and there are essentially no effective treatments for most patients by the time of their diagnosis. In addition, there is an urgent need to obtain comprehensive and clinically relevant knowledge about normal as well as malignant human hematopoietic stem cells, to devise definitive ways of measuring these cells and to exploit them for testing new therapeutic approaches.

Goals

- Obtain definitive and clinically useful assays for normal and malignant human hematopoietic stem cells and understand their relation to cells with other tissue potentialities.
- Define the molecular basis of the stem cell state and understand the processes and regulation of stem cell developmental changes, self-renewal, commitment, differentiation, mobilization, homing, aging, senescence.
- Understand the pathogenesis of all myeloid leukemias, preleukemias, and related disorders.
- Identify cellular and molecular targets for diagnostic and therapeutic (drug, biological, immunotherapeutic) agents.
- Generate valid animal and *ex vivo* models for all leukemias.
- Understand the genetic and epigenetic mechanisms of progression, predisposition, and causes of mutations.
- Use this information to develop nontoxic, definitive therapies.

Barriers and Opportunities

- Progress is good in some areas (e.g., chromosome translocations) but not in others, such as MDS, acute myeloid leukemia (AML) in the elderly, secondary AML, and myeloproliferative syndromes other than CML.

- Leukemic stem cells are likely to be critically important for relapse, drug resistance, and expression of unique genes, but they are rare and not well characterized.

- The genetic factors that predispose to leukemia and modify response and resistance are not known.

- Promising targets are currently mostly enzymes, but known AML oncogenes interfere mostly with protein-protein or protein-DNA interactions.

- There is a lack of people with multiple disciplinary skills in the field, and the training of entry-level and established investigators in multidisciplinary science poses many challenges.

- There is a lack of prospective epidemiological studies to obtain access to material that is characteristic of the preclinical stages of primary and secondary hematopoietic malignancies.

- Technology to characterize the function of genes in hematopoietic cells is currently slow, cumbersome, and resource intensive.

- There is limited access to large numbers of primary, viable leukemic cells associated with high-quality clinical data.

Research Priorities

1. **Develop integrated, multi-institutional, multidisciplinary, multi-site, and possibly multi-national consortia to create the type of critical mass of collaborating investigators that is necessary to achieve major and more rapid progress in the poorly understood myeloid malignancies.**

Recommended for initial focus:

- Preleukemic states (primary and secondary MDS and myeloproliferative syndromes other than CML)

- AML in the elderly

These consortia should assemble the resources necessary to address major unanswered questions in the biology of the myeloid malignancies and to provide the information needed to initiate significant translational research through approaches such as the following:

- Identification of the genes that initiate a preleukemic state and that promote progression to full-blown leukemia

- Creation of better animal models

- Definition and validation of diagnostic and drug targets

Disciplines required include:

- Cellular and molecular biology

- Developmental biology

- Engineering

- Proteomics, genetics, and bioinformatics

- Cytogenetics

- Mathematics and biostatistics
- Epidemiology
- Clinical investigation and hematopathology of leukemia
- Immunology
- Virology
- Chemistry
- Pharmacology

2. Foster new, faster, and innovative strategies to obtain a complete molecular characterization of normal and leukemic stem cells.

- Develop standardized technologies to isolate, measure, clinically validate, and immortalize *in vitro* leukemic and normal stem cells and to undertake gene expression and proteomic analyses in these cells.
- Use animal models (e.g., mice, zebrafish, Drosophila) to characterize the function of certain genes that are essential to the normal and leukemic stem cell phenotype.
- Identify the genetic differences between normal and leukemic stem cells that might be exploited for their differential detection and isolation and/or for therapy.
- Understand the interactions of leukemic stem cells with hematopoietic microenvironments (cytokines, endothelial cells, stromal cells, extracellular matrix immune cells).
- Understand the potential replicative life span of stem cells, their plasticity at a molecular level, and their relationship to leukemic stem cells.
- Understand stem cell adhesion, migration, and homing.
- Create new technology to exploit the enormous therapeutic potential of homologous recombination at useful frequencies in stem cells (from any source) that have hematopoietic potential.

3. Develop comprehensive mechanisms to support the investigation of the basic mechanisms responsible for genome instability, chromosome translocations, and other mutations in the leukemias and preleukemias.

- Identify the pathways and genes involved in congenital DNA repair syndromes that lead to leukemia.
- Identify environmental factors that promote genetic lesions that cause leukemia.
- Encourage interaction between leukemia biologists and investigators in DNA synthesis, DNA repair, and mechanisms of DNA mutations in other model systems, such as bacteria and yeast.

4. Develop multidisciplinary approaches to identify and validate molecular targets.

- Develop strategies to make small-molecule drugs that target protein-protein or protein-DNA interactions.
- Identify targets for immunotherapeutic intervention.

- Increase support for the identification of common downstream and/or overlapping targets.

- Support efforts to identify mutations in viability genes, especially those that encode kinases, in all leukemias.

- Validate targets using biochemical, *in vitro*, and *in vivo* models.

- Develop faithful and novel models for accurately predicting primary leukemic cell responses to improve the efficiency and speed of promising drug selection.

5. Develop new mechanisms to attract and optimize involvement of the best minds.

- Provide support for the education of multidisciplinary and translational investigators at both entry and more senior levels.

- Create new opportunities for fostering leadership among new investigators by challenging them to take on big questions supported by larger grants and through greater involvement in policy-making bodies within the structure of the National Cancer Institute.

- Develop new mechanisms of support for short-term training in specific, rapidly evolving technologies, such as bioinformatics, mass spectrometry, functional genomics, and model organisms.

- Devise mechanisms to support networking of existing investigators at different sites and in different fields to promote the rapid creation of new groups.

Linkages to Other Subcommittee Recommendations

Several synergies and overlapping themes suggested by other subcommittees were identified. These include the use of consortia to address other large problems and the exploitation of a novel opportunity to link with the epidemiological proposal for long-term follow-up of defined patient cohorts, which will include sample collection.

The priorities listed here will be greatly enhanced by the creation of Regional Proteomics Centers, a National Animal Model Laboratory, and a National Biomedical Development Center, as recommended by the Scientific Infrastructure subcommittee. These initiatives will also enhance, and be enhanced by, parallel initiatives proposed by the Lymphoid Biology subcommittee.

BIOLOGY OF NORMAL AND NEOPLASTIC TISSUE TARGETS: LYMPHOID TISSUE

Co-Chairs: Louis Staudt, MD, PhD; Thomas Kipps, MD, PhD

Introduction

Given the richness of our current knowledge of lymphoid biology, many potential therapeutic targets have been defined in the lymphoid malignancies. To validate and exploit these targets, and to identify new targets, it is critical to promote fundamental investigations into the genetics, biochemistry, and function of normal and malignant lymphocytes. The application of exciting new technologies (e.g., genomics, proteomics, and spectral karyotyping [SKY]) to this problem will enable the comprehensive and systemic classification of lymphoid malignancies as they relate to normal lymphoid biology. It is envisioned that we can now achieve a molecular classification of lymphoid malignancies that also incorporates a pathologic and clinical understanding of disease. Inevitably, such an endeavor will require an interdisciplinary agenda aided by the talents and resources of investigators from diverse backgrounds to achieve a broad consensus on disease definition. It is therefore important to develop novel initiatives that focus the diverse research community on this timely and important issue.

Lymphocytes have several features that are not inherent in other cell lineages. Through the process of lymphocyte differentiation, several unique mechanisms are used to rearrange and mutate the genome. These mechanisms account for the immune system's rich diversity, but they also present distinct challenges to the lymphocyte to maintain genomic integrity. For this reason, several checkpoints have evolved to test and clear cells that have incurred deleterious genetic alterations that can predispose to or cause neoplasia. Genetic, viral, or environmental factors may mitigate these checkpoints and contribute to the increasing incidence of lymphoid malignancies now witnessed in the United States.

The immune system is highly interactive. The immune response is predicated on orderly, coordinated communication between disparate lymphocytes and non-lymphoid cells. These interactions are critical for developing immune responses and can be used to monitor the fitness of cells that are engaged in the immune response. They also are critical in controlling the differentiation, proliferation, and survival of lymphoid cells and may be usurped by neoplastic cells, giving them a way to enhance their survival or to resist therapeutic interventions. Host-tumor interactions can contribute to the pathophysiology (e.g., immune suppression, autoimmunity, hematopoietic suppression, osteolytic changes) of lymphoid diseases. For these reasons, understanding the interactions of tumor cells with non-neoplastic lymphocytes or other cell types will illuminate novel targets for disease intervention.

Through traditional molecular genetic and novel genomic techniques, several provocative targets have been identified that could contribute to pathogenesis. New initiatives are required, however, to advance models and systems with which to validate these targets as having causal or critical relationships to the proliferation or survival of the neoplastic cell. Applying new technologies can help generate and test the capacity of the models to accurately mimic clinical disease. Standardizing such model systems will provide the reagents necessary for achieving a systematic understanding of the biochemical signaling pathways and immunologic factors that contribute to pathogenesis. It is envisioned that the

research community will share such model systems through this new initiative. This will provide for a systematic and comparative evaluation of disease targets and will lead to a basic understanding of the critical signaling pathways that are involved in disease pathogenesis.

The study of lymphoid malignancies and normal lymphoid biology will provide important information that transcends the problem of lymphoid malignancies. Lymphocytes are central mediators of immune effector function and biology. Understanding the basic principles of lymphoid biology will allow better manipulation of the immune system in treating other malignancies or diseases that are associated with autoimmunity and aging. The biology of lymphocytes incorporates all of the mechanisms that are fundamental to cell differentiation, interaction, and survival.

Research Priorities

1. **Develop molecular definitions of lymphoid disease entities, using integrative molecular technologies.**

Rationale

Clearly defined disease entities will enable interpretable functional analyses of the malignant phenotype, identification of molecular and immunologic targets, and functional validations of novel therapeutic targets. A broad initiative is required to achieve consensus on a molecular definition of disease for the community involved in studying and developing new treatments for lymphoid malignancies.

Approach

- Develop a comprehensive molecular definition of neoplastic phenotype vis-à-vis normal lymphoid differentiation.
- Use high-throughput RNA and protein expression technologies.
- Use genomic analyses involving fluorescent *in situ* hybridization (FISH), SKY, and assays for genetic polymorphism.
- Incorporate consideration of clinical and pathological features in the disease definition.

This initiative must make use of other proposed initiatives involving shared tissue and clinical data resources in order to achieve a consensus on a molecular definition of diagnostic entities.

- Define differences and similarities between neoplastic cells and their presumed normal counterparts.
- Define genomic events in tumor evolution via longitudinal analyses of cells in patients with defined diseases.
- Use comprehensive molecular analyses of the malignant cell to gain insight into neoplastic alterations in biochemical pathways and immune function.
- Use insights from the molecular definitions of human lymphoid malignancies to create and validate animal models and *in vitro* models.

2. **Evaluate host-tumor interactions.**

Rationale

Lymphoid malignancies interact with other immune cells and other cell types, such as stromal cells, osteoclasts, and other hematopoietic cells. Understanding these interactions will provide insight into the pathophysiology of disease, the survival of neoplastic cells, and resistance to therapy.

Approach

- Develop and disseminate *ex vivo* models of human lymphoid malignancies.
- Use long-term cell culture models.
- Develop models in immunodeficient mice (orthotopic model systems).
- Use model systems to examine the clonigenic potential of cell subsets within a given tumor population.
- Relate to cell-cell interactions of normal lymphoid cells.
- Define the molecules and biochemical pathways involved in cognate interactions leading to differentiation, survival, or clearance of normal and malignant lymphocytes.
- Define the molecular changes in the tumor cell as a consequence of its interaction with host cells.

3. Validate the molecular targets that are critical for the survival, proliferation, and evolution of lymphoid malignancies.

Rationale

Priorities 1 and 2 will provide a host of potential molecular and immunologic targets for future therapy. These targets must be validated by using functional analyses in model systems before they can be used to develop novel therapies.

Approach

- Define cell line models of each lymphoid malignancy that mimic the native tumor cell. Use genomic approaches to validate these models as accurate reflections of the native tumor cell.
- Develop methods for systematic somatic cell genetics to generate cells that express targeted genes that can be activated or deleted in an inducible fashion. Progress has been made in other cell types, such as embryonic stem cells, and it is envisioned that similar embryonic stem cell manipulation techniques can be used with these model cell systems.
- Assess the consequences of inducing gene deletion or activation defined in priorities 1 and 2 as influencing the malignant phenotype (cell death, cell cycle arrest, or modulation of critical signaling pathways).
- Use validated mouse models of lymphoid malignancies to study the effect of targeted genetic alterations that contribute to lymphoid malignancy.

The results of these validation studies will be used to order priorities for developing new therapies and to provide surrogate endpoints with which to evaluate their efficacy.

4. Evaluate mechanisms of genomic instability in normal and malignant lymphocytes.

Rationale

Understanding the mechanisms that lead to genomic instability will provide insight into the factors that can predispose to lymphoid malignancy or operate in the progression of disease. These factors may be influenced by viral and environmental factors that can predispose to lymphoid malignancies.

Approach

- Evaluate the normal and pathologic processes involved in genetic recombination and somatic mutation of

genes during lymphoid differentiation and malignancies.

- Examine the checkpoints involved in the clearance of cells that have incurred genetic alterations that can predispose to malignancy.

- Examine the role of DNA damage checkpoints in controlling the fidelity of recombination and mutation in normal and diseased lymphocytes.

- Examine the influence of environmental factors (e.g., pesticides, viruses).

SCIENTIFIC INFRASTRUCTURE

Co-Chairs: Gary Gilliland, MD, PhD; Robert Hromas, MD

The guiding principles for development of the initiatives proposed here are as follows:

- Benefit investigation of all hematological malignancies, including lymphoma, myeloma, and leukemia
- Represent infrastructure that does not currently exist or is inadequate
- Are unlikely to be funded by other sources
- Stand alone and yet are highly interactive and synergistic
- Driven by substantive advances in the understanding of the molecular basis of hematological malignancies
- Would enhance the productivity of individual investigators
- Are highly compatible with initiatives from other subcommittees, including the Cancer Translational Research Allied Consortium (C-TRAC) initiative proposed at this LLM PRG Roundtable (see "Therapeutics I" report)
- Allow opportunities for collaboration and interaction with the international community

Research Priorities

1. Create Proteomics Centers for Hematological Malignancies.

Goal: To characterize global patterns of protein expression and post-translational modification in sample sets of hematological malignancies

- There would be three to five regional centers.
- All samples would be submitted with complete clinical history and would be updated as new clinical data become available. This will allow correlation of the clinical history with the fingerprint of protein expression. Appropriate informed consent will be obtained, and patient confidentiality will be strictly maintained.
- Investigator-initiated projects will be reviewed and funded by the Proteomics Centers.
- Investigators would be required to deposit tissue in the National Animal Model Laboratory described in Priority 2. This will allow for maintenance of primary human tumors in NOD/SCID mice as a renewable source of material for subsequent analysis by other investigators that could be correlated with proteomic outputs.
- Investigators can publish their research, but their data will also be placed into a public interactive database on the Web.

2. Create a National Animal Model Laboratory.

Goal 1: To make validated animal models of hematological malignancy freely available to individual investigators

- Facilitate drug screens or targeted therapeutic approaches.
- Facilitate the generation of appropriate knock-in and knock-out mouse strains

through investigator-initiated and peer-reviewed proposals.

- Facilitate analysis of modifying genetic and environmental influences that modify disease phenotype.

- Backcross into genetic backgrounds appropriate for specific experimental strategies. This could include both immunologic studies and assessment of transgenic, knock-out or knock-in mice to obtain a specific genotype for phenotypic studies.

- Centralized histopathologic analysis and other core resources would be available for phenotype analysis.

- The laboratory could interact closely with or be incorporated into the C-TRAC proposal from this LLM PRG Roundtable (see "Therapeutics I" report).

Goal 2: To generate renewable sources of primary human hematological tumors in NOD/SCID or nude mice

- Clinical specimens will be obtained from patients with the full spectrum of hematological malignancies. These specimens will be accompanied by a complete clinical history. Informed consent will be obtained, and strict patient confidentiality will be maintained.

- These samples would be used to generate replicate sets of well-characterized, renewable hematological tumor samples for different investigators. This will allow for correlation of molecular and cellular studies with the clinical history on the same set of tumor specimens.

- Applications could include expression arrays, tissue arrays, and proteomic studies.

- Data obtained from these replicate sets of samples would be maintained in a public-domain database on the Web.

- This resource would be augmented by contributions from investigators whose samples have been analyzed at the National Proteomic Centers. Therefore proteomic data would be available on replicate sets of tumor samples accessible here.

- This resource will be expanded to include zebrafish and other vertebrate models of hematopoietic malignancy as they become available.

3. Create a National Biomedical Development Center.

Goal: To support the development of orphan therapeutic agents and diagnostics, including Food and Drug Administration (FDA) approval

- This concept was derived independently but overlaps with the C-TRAC proposal in this LLM PRG Roundtable (see "Therapeutics I" report).

- Resources would include the following:

  — Systematic production of humanized monoclonal antibodies against multiple targets in hematopoietic malignancies
  — Large-scale screening of small molecules with potential activity in hematological malignancy
  — Development of lead compounds with optimized biological activity and pharmacokinetic properties

- This center could perform, as necessary, preclinical and clinical testing leading to FDA approval.

- The effort could incorporate and significantly expand existing NCI programs for therapeutic development.

- Novel targets for small-molecule screening could be identified through interfaces with the National Proteomics Centers.

- These orphan therapeutics also could be validated by using models from the National Animal Model Laboratory.

4. Increase support for ongoing NCI initiatives in:

- Standardized interactive bioinformatics platforms and bioinformatics training.

- Improved accrual for clinical trials and specimen acquisition, including the mobilization of patient advocacy groups to improve public acceptance of participation in clinical trials. This initiative also could include increased NCI efforts in direct patient education for high-priority clinical trials in cooperative groups and at the NCI.

- Developing technologies to make expression and tissue arrays standardized, inexpensive, and widely available.

- Increasing financial support for trainees in research on the hematological malignancies.

DIAGNOSIS, PROGNOSIS, AND DISEASE MONITORING

Co-Chairs: Randy D. Gascoyne, MD; Peter Leif Bergsagel, MD

State of the Science

In the current practice of pathology, morphologic assessment, immunophenotypic analysis, and molecular cytogenetics are used to identify specific disease entities. Accurate diagnoses are required to plan appropriate therapy and predict outcome. New technologies, including genome-wide surveys of gene expression patterns and genetic alterations, have already resulted in changes to the classification of lymphoma and leukemia and are poised to significantly modify current classification schemes for all hematological neoplasms. These discoveries will result in the recognition of new disease entities and potential prognostic markers.

The challenge for the future is to incorporate these insights into clinical practice. The current approach to analyzing biological prognostic markers typically involves measuring single parameters assessed in combination with clinical variables. This approach will dramatically change as a result of newer technologies and a significant increase in novel gene discovery. There is currently in North America no model of collaboration to investigate clinical-pathologic insights into the biology of hematological neoplasms based on inter-institutional studies.

Research Priorities

Translational diagnostics plays a critical role in identifying molecularly defined disease entities and relevant biological prognostic factors that will provide the basis for identifying homogeneous populations of patients who may benefit from targeted therapies. The recent delineation of disease entities with specific ectopic protein expression—for example, PML-RARA in acute promyelocytic leukemia, ALK in anaplastic large-cell lymphoma, and FGFR3 in t(4;14) multiple myeloma—provide a paradigm that must be expanded in the future. The NCI does not currently fund core programs that facilitate some types of translational research, in particular the development and validation of diagnostic reagents resulting from the identification of novel pathogenic mechanisms. These efforts will be required to identify new molecular targets and to implement novel therapies based on new gene discovery. Funding and academic recognition of pathologists as translational researchers are essential for applying pathogenetic insights to clinical disease definition.

1. Implement developmental diagnostics.

Genome-wide surveys of gene expression and genetic abnormalities will generate numerous new targets. Some will specifically define diseases, whereas others will be important prognostic markers to guide therapy. It will be important to rapidly translate findings from marker discovery to clinically applicable reagents.

<u>Resource Needs</u>

- Affordable investigational reagents (subsidize M–fluorescent *in situ* hybridization, spectral karyotyping probes)
- National core facility for rapidly generating monoclonal antibody reagents, including reagents active in paraffin-embedded material
- Infrastructure to validate gene expression observations at the protein level

- Infrastructure to support validation of clinical relevance and rapid determination of prognostic significance

A unique opportunity exists in hematological neoplasms to build on an elaborate understanding of normal and malignant molecular biology with novel technologies. In the past, individual investigators have undertaken the responsibility of producing useful diagnostic and/or prognostic reagents but in an inefficient and under-funded fashion. The wave of new gene discovery mandates a "ramping up" of this process to meet projected demands. Thus, an NCI-funded core facility is urgently needed to develop diagnostics that move novel gene discovery from expressed sequence tag to full-length sequence and finally to protein structure and diagnostic reagent.

2. Establish a national consortium for biomarker evaluation and testing.

Resource Needs

- A large database of extremely well-characterized clinical specimens; a "virtual repository"
- Inclusion of tissue, clinical data, phenotype, genotype, sequential samples
- Core facility or an inter-institutional, interdisciplinary model to promote collaboration among investigators
- Statistical support, including outcome analysis

In contrast to that of solid tumors, the molecular characterization of hematological neoplasms has made significant advances in the last few years. The ease of novel gene discovery in this group of tumors results from several factors, including the ability to study purified tumor cells in suspension, the relative lack of cytogenetic and molecular complexity in LLM, and finally, the fact that many of these diseases result from translocation-based mechanisms that lead to deregulated gene expression. Opportunities in LLM lie in the number of recently identified biologically and clinically important genetic markers, in addition to the many more that will result from genome-wide surveys. Current approaches to the analysis of novel biomarkers are limited by small sample sizes, single-institution bias, lack of available fresh tissue samples, and a dearth of accompanying genetic information in the current structure of clinical trial groups. The timely validation of new insights into the biology of these diseases, in addition to the clinical importance of specific gene expression patterns, will be important to designing novel and risk-adjusted therapies. Expert pathologists will play a central role in the evaluation of new biomarkers, having the requisite skill set needed to interpret these data in the light of conventional histology and existing immunophenotypic and genotypic data. Infrastructural support will be needed to create and maintain such expert panels.

3. Establish a comprehensive tissue archive.

Resource Needs

- National strategy to enhance the acquisition of adequate diagnostic biopsy material on patients with complete clinical information, uniform therapy, and follow-up
- Tissue bank that includes fresh-frozen biopsy specimens, cell suspensions of enriched tumor cells, normal cells and stromal elements, and serum
- A core facility to produce tissue arrays of normal tissues, neoplastic diseases, and

consecutive patients enrolled in clinical trials

- Infrastructural support for the creation and maintenance of expert pathology panels with disease-specific focus

- A universal plan to prospectively address all aspects of patient consent and ethical issues for research in which clinical samples are used

Tissue banks are absolutely required to validate the diagnostic accuracy of new reagents and to determine the clinical relevance of all new gene discoveries. Blinded retrospective analysis of stored samples will be required to rapidly move these discoveries from the bench to the bedside. Current trends in pathology are resulting in ever-decreasing sizes of diagnostic biopsy samples. If a change is not mandated, the current archive of clinical material will soon be depleted. A comprehensive tissue archive is therefore necessary to ensure adequate numbers of samples for subsequent analysis. The present technology for analyzing diagnostic reagents and prognostic biomarkers makes use of paraffin-embedded biopsy specimens from individual patients. A tissue array facility will greatly improve this approach by reducing costs and preserving the archive.

PRECLINICAL THERAPEUTICS

Co-Chairs: Michael Grever, MD; Ed Sausville, MD, PhD; John Reed, MD, PhD

Introduction

Therapeutic research in the treatment of patients with hematological malignancies has made enormous progress over the past 50 years. The NCI has facilitated this important mission for many decades. The initial National Service Center was established by the NCI to enable basic scientists to design and test chemical agents for evidence of anti-tumor activity. In addition to pioneering cancer drug screening, the government funded an entire preclinical drug discovery and development program. The NCI also established and funded investigators to pursue all phases of clinical evaluation of products emanating from their own discovery and developmental efforts, as well as interacting with the pharmaceutical industry and academic institutions to explore their novel agents. In the last decade, there has been an enormous investment in defining molecular targeted agents in cancer chemotherapy. Understanding the basic pathobiology of specific hematological malignancies has permitted the identification and quantitation of selective targets within tumor cells. Basic research findings have identified a plethora of potential therapeutic targets for further exploitation.

Many of the therapeutic agents of current use in treating cancer patients are enzyme inhibitors. The NCI was responsible for the identification and developmental support of pentostatin, a potent inhibitor of the ubiquitously expressed enzyme adenosine deaminase. The pharmaceutical sponsor who had initially isolated pentostatin lost interest in this agent as the period of patent protection dwindled, and the target patient population was small (patients with a rare hematological malignant disease). Hairy cell leukemia, described in 1958 by Bouroncle and colleagues, had been essentially unresponsive to standard chemotherapeutic agents. In the mid-1980s, investigators at M. D. Anderson showed that alpha-interferon produced hematological remissions but noted infrequent complete remissions. In contrast, pentostatin induced complete remission in more than 75% of patients. Recent data have confirmed that this discovery has now changed the natural history of this otherwise fatal indolent leukemia.

Twenty years later, another enzyme inhibitor (STI571) was introduced as an effective therapeutic agent for another form of chronic leukemia, chronic myeloid leukemia (CML). This disease had also been essentially refractory to standard chemotherapeutic agents. Again, alpha-interferon induced hematological remissions in most patients with this disease, but the frequency of achieving a true complete remission with interferon was quite modest (in the range of 10% of patients with CML). The development of STI571, a small-molecule drug synthesized by scientists at Ciba-Geigy Pharmaceuticals (now Novartis), represents a stellar example of successful drug development based on molecular targeted screening. STI571, a specific inhibitor of the *BCR-ABL*–associated tyrosine kinase, represents the product of lead optimization by medicinal chemists. The original "lead" compounds resulting from screening efforts of natural products and synthetic compounds against a tyrosine kinase target were modified in light of the structure of natural product lead bound to a protein kinase core structure. This modification yielded a molecule that was both orally bioavailable and effective in inhibition of the target enzyme. It was believed that this target enzyme was responsible for drug resistance in patients with CML.

Thus, empirical screening of natural products for enzyme inhibitors, plus rationally guided modification of lead structures, ultimately resulted in impressive clinical results for patients with CML. Of the 54 patients with the chronic phase of this leukemia, 53 achieved a hematological remission once therapeutic dose levels were achieved. With prolonged therapy, 53% of the patients achieved a cytogenetic response. Thirteen percent achieved a complete cytogenetic remission, with disappearance of the Philadelphia chromosome. This result is particularly impressive because patients who were previously treated still showed evidence of response to this new agent. STI571 also has activity in the blast crisis of this disease, suggesting that even the most resistant of leukemias can show temporary evidence of response to this enzyme inhibitor. Thus, this developmental story has attracted substantial attention and provides further evidence that drug optimization based on identifying a lead structure is capable of providing a useful agent in the treatment of leukemia. This story provides hope that future success will result from scientific collaborations surrounding the molecular targeted approach to drug discovery and development.

In addition to advances linked to small molecules, enormous efforts have been successfully introduced in biological approaches to therapy. Monoclonal antibodies (e.g., Rituxan, Campath-1H, and others) have shown great promise in the treatment of both leukemia and lymphoma. Increased recognition that the mode of inducing a clinical response involves more than antibody-mediated cytotoxicity has sparked further investment in defining the impact of these agents on the modulation of anti-apoptotic molecules in leukemic cells. In addition, new efforts in introducing gene therapy for patients with chronic lymphocytic leukemia and vaccines for those with an indolent lymphoma emphasize the need to provide resources in the newer therapeutic strategies. Enormous interest in the use of "old agents," such as thalidomide and arsenic, for patients with multiple myeloma and refractory forms of leukemia, respectively, emphasize the necessity to fully explore the utility of diverse agents in these diseases. Finally, recent data have shown that the proteosome may be a useful target in the treatment of multiple myeloma.

These encouraging examples highlight the need for the additional resources described in the following sections. Major new initiatives will be necessary to fully exploit the multiple new targets that have been described in the neoplastic cells obtained from patients with a hematological malignancy. The development of therapeutic products (particularly in the areas of medicinal, pharmaceutical, and protein chemistry) is a major focus of the recommendations that follow. However, other resources for the full development of biological products are equally important. The major mission in translational research to propel the best ideas from bench to bedside will require the investment of adequate resources from the government, the pharmaceutical industry, academia, and patient advocacy groups. New partnerships are needed. The time for maximal collaboration has arrived.

Research Priorities

1. **Consistent with the extensive definition of relevant molecular targets in hematological malignancies, markedly enhanced resources are required to translate the lead structures and molecules into effective therapeutic agents. Therefore, we propose the following:**

- Inter-institutional collaborative research agreements specifically targeting chemistry for lead optimization

- Enhancement of financial resources for the proposed Rapid Access to New Drug Discovery (RAND) program and the existing Rapid Access to Intervention Development (RAID) program

- Creation of new resources to engage the scientists whose expertise is needed for the development of therapeutic products (e.g., a special study section for medicinal, pharmaceutical, protein chemistries, formulation research, and animal models development designated for therapeutic studies of new agents and combinations based on specific molecular targets)

If the promise of molecular targeted therapies is to be realized, validation of the approach to rational drug development must be tested. It is impossible to validate the investment in defining molecular targets without following through with development of the therapeutic agents. The extensive processes involved in drug discovery and development involves the following:

- Identification of the lead

- Lead optimization and scale-up production for additional testing

- Assessment of the therapeutic index

- Definition of optimal dose and schedule of administration prior to entry into a clinical trial (development of small-animal models is critical)

- Development of analytical methods for pharmacokinetics and pharmacodynamic studies

- Preclinical pharmacology and toxicology

- Formulation research

- Large scale-up production for initial clinical trials in humans

The process of preclinical drug development is both time and resource intensive. In general, it takes 5–10 years from validation of a clinical target to a Phase I trial in humans. This time is potentially shortened with additional resources, but safety and speed of development are always critically important to the ultimate outcome for patients with fatal diseases. In particular, patients with hematological malignancies should be considered for early evaluation of molecular targeted therapies. A unique opportunity exists to serially sample the tumor in patients with these diseases. This opportunity is rarely possible with a solid tumor. The serial tumor assessment enables confirmation that the desired pharmacodynamic event actually occurred. Coupling the molecular assessment of the desired endpoint in the tumor cell with the plasma concentration of the anti-tumor agent (or its major metabolites) through pharmacokinetics provides a tremendous opportunity for modifying the therapeutic strategy. It is also critically important that the extensive studies described are conducted with the optimal therapeutic agent. Optimization of the chemical structure or biological properties of the proposed new agent involves an iterative process that is best accomplished by extremely close collaboration between chemist and biologist. The scientist who discovers the lead must have intellectual engagement with the chemist who can modify and optimize the product.

Academic credit often eludes the chemist who modifies a chemical structure for enhanced bioavailability or ease of drug administration. However, the scientific contributions of these scientists are critically important for the outcome of the therapeutic strategy. It is strongly recommended that chemists be encouraged with tangible

incentives (e.g., access to structure-activity data in national data banks, funding opportunities, authorization to publish results, and academic promotion and other financial rewards) to participate in this mission.

The NCI funds limited projects through the National Cooperative Drug Discovery Group (NCDDG) program. A broader opportunity is needed for inter-institutional program projects and master agreements to maximize the use of existing talent in academic centers. Considering the long-standing and understandable track record of cautious investment by the pharmaceutical industry, the government must continue to play a critical role in therapeutic research for patients with hematological malignancies. The progress made in the past validates that much can be learned from studying new agents in these uncommon diseases, and the information gained will continue to be important for patients with solid tumors. The resources of both RAND (research initiatives in early new drug development) and RAID (research initiatives in later drug development) should be expanded to fully support therapeutic research ideas emanating from small molecules, biological agents, anti-sense molecules, vaccines, and gene therapies.

In funding these opportunities to foster inter-institutional collaboration, the NCI should identify the leading experts, regardless of their geographic location. In this era of rapid communication, virtual laboratory meetings can occur successfully over long distances. The time has arrived for optimal cooperation. Access to government and intramural resources should link to extramural investigators who are committed to the development of therapeutic agents (e.g., access to Human Genome Project data, investigators for collaboration, and training of new investigators interested in structural and functional biology). Previous impediments to collaboration among government, industry, academic institutions, and advocacy groups must be surmounted. Investment in the discovery and development of therapeutic products is expensive but rewarding. The explosion in molecular and genetic information should be translated into benefits for those who have supported the research. This goal can be accomplished by optimizing the agents for both preclinical and clinical evaluation in patients with hematological malignancies.

2. Expand animal model research to complement therapeutic initiatives.

- The models that have been developed are providing extensive information on the molecular pathogenesis and progression of hematological diseases. The biological data are extremely valuable, but the models must also be available for therapeutic testing and evaluation of both new agents and combination strategies that are based on molecular leads.

- Small-animal models may be useful for the production of humanized monoclonal antibodies and other experimental reagents.

- Small-animal models may be valuable to enhance our understanding of the toxicity and effectiveness of new therapeutic agents targeted to tumor models with well-characterized molecular features (e.g., pharmacogenomics).

Additional support for this recommendation was voiced by other breakout groups, including that on myeloid biology. We endorse this recommendation because it provides a vehicle for evaluating therapeutic agents in an *in vivo* setting. Traditional human tumor xenograft models have been appropriately criticized because neither the

biology of the model nor the immortalized tumor cell lines reflect the clinical setting of patients. In contrast, SCID/NOD models and others have enabled primary human tumor cells to be examined in an animal model that provides data reflecting the agent's activity when confronted with a systemic environment. Furthermore, molecularly engineered animal models provide extremely valuable information relative to specific molecular and genetic profiles. The necessity for the model to be based on a "small animal" reflects the practical limitations of scale-up synthesis for many products. Lead optimization will also be facilitated by increased access to these resources. In addition, the small-animal models will also be useful for examining therapeutic strategies that involve combinations of agents and modalities.

Training opportunities for postdoctoral fellows should be supported to increase the expert pool of investigators who specialize in this area of research. These individuals will be extremely valuable for molecular and genetic research. Increasing access to training will facilitate the future development of therapeutic products.

3. To fully exploit advances in biologically based therapies, the following substantial new resources are needed:

- Increased access to resources for monoclonal antibody production
- Increased effort to develop new vectors for gene therapy
- Increased identification of tumor antigens for vaccines
- Increased resources for vaccine reagents
- Support for assay design, implementation, and validation to support vaccine development

The explosive growth of clinical research in monoclonal antibody therapies mandates increased access to resources to make humanized monoclonal antibodies. This production is extremely expensive. Currently, there is a suggestion to use available murine antibodies for initial "proof of principle," or "boutique," studies before committing the resources for production of the humanized product. However, murine antibodies are not being developed for clinical studies. Research to expedite the production capabilities of these reagents should be funded through a separate Request for Applications to explore new strategies for enhanced production of humanized monoclonal antibodies.

Optimization of vaccine strategies in cancer therapy will require funding for core Good Manufacturing Practice (GMP) facilities to produce clinical-grade material. Investigators must have access to experts in formulation research as well as those with knowledge in basic immunology. The construction of the optimal vaccine will need to be a collaborative effort of those who can identify the optimal tumor antigen, incorporate the cellular immunology to maximize the host's ability to respond, and then develop the assay to validate that effective immunization has occurred. Furthermore, the development of appropriate surrogate endpoints will facilitate eventual clinical trials for confirmation of response. Agents that limit T-cell apoptosis (e.g., IL15 and others) must be explored, with an ultimate goal of generating T cells that do not undergo apoptosis. Thus, research is needed that is targeted not solely to the vaccine but also to the maximal survival and function of the patient's immune effector cells.

In dealing with the promise of gene therapy, substantial work must be done to regain the trust of the scientific and clinical investigative community. The NCI and advocacy groups, working with knowledgeable investigators, can develop strategies for close monitoring of pioneering projects. Careful assessment of preclinical toxicology and follow-up with early clinical trials is necessary. New strategies for viral vector development with adequate facilities for cellular transduction must be provided if this new approach is to be successful.

We need to support further development of vectors; not many virologists are addressing the issue of how viruses may infect hematopoietic cells. In addition, we must support research to enhance the transport of the viral vector efficiently and reliably. Gene expression must be monitored carefully. The use of *ex vivo* modification presents unique challenges. Thus, GMP facilities are needed to transduce cells and conduct quality assurance and monitoring as well as vector development. Investigators often do not have access to the high-quality reagents needed to lead into clinical studies. Furthermore, regulatory issues are also key; because medical centers are not well equipped to provide the necessary oversight, the infrastructure needed to do this must be strengthened.

CLINICAL TRIALS METHODOLOGY

Co-Chairs: Sandra Horning, MD; Richard Larson, MD

Introduction

Advancements in the molecular classification of hematological malignancies are subdividing these diseases into biologically distinct subsets, each with smaller patient numbers. As a result, more patients are required to participate in clinical trials in order for adequate numbers of patients to be included within each disease subtype.

Currently, only a small minority of adult patients with LLM in the United States are referred to centers for initial care of hematological malignancies. Conversely, nearly all U.S. children with hematological malignancies are referred to specialized centers, and most are enrolled in prospective clinical trials. Some European countries, including France and Germany, have been more successful than the United States in accruing adults to clinical trials in a timely fashion.

Pediatric and European clinical trial models have several commonalities. Both have a highly centralized distribution of physicians; private-practice oncologists cannot exist successfully in either the pediatric or the European environment, resulting in necessary centralization and a lack of competition with private practices for patients. Because of their employment situations, clinicians in pediatric and many European trials are not under pressure to generate revenue. In addition, there is little competition from off-label use in either the pediatric or the European setting, so potential patients are not drawn away from participation in clinical trials.

Currently, about half of patients enrolled in NCI-sponsored cooperative group trials come from the community. The 1999 American Society of Clinical Oncology Clinical Trials Survey found that community physicians are interested in participating in trials but cite several barriers, including complex and time-consuming paperwork for patient enrollment, informed consent, and data management and a lack of time. Successful models of clinical trials participation in the community have the following common elements:

- Interested physicians
- Affiliation with a cancer center or academic center
- Dedicated research nurses for administering informed consent
- On-site data managers

There is increased community participation in pharmaceutical-sponsored studies relative to NCI-funded studies, despite a preference for the latter. This is apparently due to increased per-case reimbursement offered by industry-sponsored studies, as well as streamlined and/or reduced paperwork for industry trial participation. The U.S. health care system provides incentives for private-practice physicians to treat patients with off-label investigational approaches rather than referring them to studies. Research priorities for clinical trials methodology would ideally surmount the current barriers to patient participation as well as result in more comprehensive, standardized results across trials.

Research Priorities

1. Define new clinical trial models.

Increased participation by the community is a necessary goal for any new clinical trial model. Enhancements in the methodology and infrastructure of clinical trials are likely to increase participation in trials in the community. Required resources include funding to provide research nurses and/or data managers on site to community physicians, which would eliminate the time constraints that many physicians cite as a barrier to participation in clinical trials. These personnel could be dedicated to specific practices or could travel among several smaller practices that may not need their services on a full-time basis. Additional funding should be provided to reimburse participating physicians at levels comparable to those offered by industry-sponsored trials.

New models could include interaction with existing cooperative groups and regional cancer centers. Other models may include consortia on rare diseases and/or international cooperative efforts to study rare diseases.

Key to this recommendation is increased training and support for the clinical investigators who will lead these efforts. This support is needed at all career levels, from young investigators to senior researchers, to provide the funding and time necessary to devote full attention to clinical research.

2. Establish a tissue bank for untreated LLM patients that is linked to clinical databases and prospective trials with long-term follow-up.

Methods to establish tissue banks from untreated patients, many of whom are initially diagnosed in community hospitals, should be tested. It is of critical importance that the tissue be linked to clinical databases and prospective trials providing long-term follow-up data. These samples should be available to peer-reviewed projects for molecular genetic studies, microarray and other technologies, and proteomics and animal model research. Samples would be subject to expert hematological review to provide resources to test diagnostic technology. Incentives for physicians and patients to provide initial diagnostic biopsy material could include access to the newest diagnostics, as well as tailored information on clinical trials aimed at each patient's specific diagnosis and demographics. Broad-based consent for use of these tissues on a long-term, repetitive basis is needed.

3. Establish and evaluate new standards for LLM clinical trials in partnership with government and industry.

Clinical trials methodology would benefit enormously from the standardization of study endpoints. In addition, surrogate markers will be needed for the evaluation of new therapeutics. Quality-of-life endpoints deserve greater emphasis, particularly for patients with pediatric malignancies with high rates of long-term survival and patients who undergo non-ablative allotransplantation. Clinical trials endpoints, including surrogate endpoints, must be clinically meaningful and acceptable to patients, clinical investigators, the NCI, and regulatory agencies. An initiative is hereby recommended in order to achieve this goal. In addition, centralized Institutional Review Boards and simplified consent forms (these forms are as short as two pages in Germany and one page in France), simplified case-report forms, and Web-based data management will increase participation in clinical trials.

DEVELOPMENT OF THERAPEUTICS DIRECTED AGAINST SPECIFIC TARGETS IN HEMATOLOGICAL MALIGNANCIES

Co-Chairs: Lee M. Nadler, MD; Stanley Korsmeyer, MD

Introduction

Understanding of the pathogenesis and pathophysiology of the hematologic malignancies has advanced at an extraordinary pace during the past decade. However, the definition, validation, and credentialing of molecular targets that might facilitate the development of target-specific therapeutics have only just begun. More important, the translation of such validated targets to clinical trials has lagged far behind understanding of the molecular basis of hematological malignancies. Even after the identification of a validated target, it takes 5–10 years to bring a new drug to trial. Investigators have struggled, and frequently failed, to translate their laboratory-based observations to the development of lead compounds and then drugs. Most important among the barriers to this task is a critical shortage of trained translational investigators to lead these efforts. In addition to regulatory hurdles, other obstacles to the development of therapeutics against molecular targets include the lack of the following:

- Availability of "tool" compounds to validate each target
- Availability of faithful models for target credentialing and preclinical investigation
- Capacity to produce Good Manufacturing Practices (GMP)-quality drugs for human trials
- Cores to support the trials

Compared with research in other cancer subtypes, research in hematological malignancies is the most advanced in its understanding of disease pathogenesis and pathophysiology. A large number of potential targets for intervention are already available. The challenge is to create an entity that will provide the structure and emphasis necessary to overcome most of the obstacles that now impede the development of new drugs and diagnostics. Successful translational research requires the following:

- Robust basic science
- Disease-oriented research
- Development of rational therapeutic strategies
- A robust clinical research system
- A core of talented, trained translational investigators

Priority

1. **Create a new entity, the Cancer Translational Research Allied Consortium (C-TRAC), the mission of which will be to significantly hasten the translation of candidate validated targets to lead compounds and then clinical trials.**

The objective of C-TRAC will be to shorten drug development time from 5–10 years to 2 years. Achievement of this objective will require the building of a novel alliance among academia, industry, government, and patients.

Scope

Each C-TRAC will be comprised of nationally designated centers for translational cancer research that are affiliated with academic institutions but

employ a business model emphasizing dynamic leadership and rapid results. Any designated C-TRAC center will be required to fulfill well defined criteria and to compete for designation. The goal of C-TRAC will be to successfully develop and bring to the clinic five to ten new drugs directed against specific cancer targets. In addition, C-TRAC centers will foster the development of new diagnostic tests that will aid in patient stratification and prediction of outcomes. Collectively, C-TRAC centers will be responsible for the following:

- Discovery of new molecular targets and their validation
- Discovery of lead compound drugs
- Discovery of biomarkers
- Preparing and/or obtaining drugs for clinical trials
- Conducting phase I and phase II clinical trials
- Managing intellectual property, regulatory, and technology transfer issues
- Developing models and providing support for career pathways in translational investigation
- Providing training and mentorship for the development of new translational investigators
- Developing and maintaining cores to support the myriad needs of translational research

Discovery of lead compounds for drugs will be central to the mission of C-TRAC. Agents will include small molecules, monoclonal antibodies, cytokines, vaccines, therapies involving cellular and gene modification, and proteins that inhibit cellular contact, receptor-ligand interactions, and angiogenesis. Such compounds will be directed to the following targets:

- Pathogenetic mechanisms for each subtype of cancer
- Host-tumor cell interactions
- Cell death pathways
- Therapeutic resistance
- Metastasis

Training programs and transitional support for translational investigators will be an important element of C-TRAC. The shortage of trained translational investigators is nothing short of a national emergency. Many factors contribute to investigators' reluctance to pursue this career path, including the length of training required, the shortage of training programs and mentors, and the length of time required to publish and obtain promotion. To overcome these barriers, C-TRAC will provide the following support for translational investigators:

- Committed mentors
- Suggested promotional criteria
- Start-up funds for trainee and mentor
- Mid-career support for extended training of translational investigators
- Protected time for translational investigators at all career stages

Regulation and Evaluation

Because of its national agenda, hematological C-TRACs will be governed by a National Leadership Group and a National Governing Board. The National

Leadership Group will include the principal investigators of the C-TRAC centers and a full time national director. This group will monitor the daily functioning and collaborations of the C-TRAC centers. The Governing Board will consist of Cancer Center Directors, industry leaders, and representatives of patient and advocacy organizations. The Governing Board will be responsible for developing criteria for success and appointing an independent committee for evaluation of each appointed C-TRAC institution on a regular basis.

OPTIMIZATION AND INTEGRATION OF EMERGING THERAPIES AND CONVENTIONAL TREATMENTS

Chair: Richard Champlin, MD

State of the Science

The treatment of hematological malignancies is the most successful area in oncology and serves as the prototype for the development of therapy for solid tumors. Standard radiation and chemotherapy can cure disease in a substantial fraction of patients with acute lymphoid leukemia, acute myeloid leukemia, anaplastic large-cell and other lymphomas, and Hodgkins disease. Prognostic groups may guide therapy, including clinical, cytogenetic, and molecular characteristics. Therapy is not ideal in any diagnosis, however, and is unsatisfactory in many areas. Treatment is limited by toxicity that is severe in relation to that associated with therapy of nonmalignant diseases. There is a general need to develop safer, more effective treatments.

Antineoplastic drugs have evolved from toxic drugs with some differential effects on malignant versus normal cells to more selective agents that target the cell lineage or tumor type, augment immunity, or interfere with host-tumor interactions. Advances in therapy depend on the following:

- Fundamental advances in defining the critical molecular events (stimulatory pathways or regulatory defects) that are responsible for the malignant phenotype

- Development of therapeutic agents to disrupt these pathways, induce effective immune response, or interfere with the host-tumor interactions that are necessary to maintain the malignancy

No patients will be cured without translational research to take these advances into preclinical and clinical trials. There is an urgent need for better therapy.

How can we most rapidly advance the standard of care for treating hematological malignancies? A prototype of success is targeted therapy to a critical molecular signaling pathway, defect, or unique phenotype. Examples include the following:

- STI571-tyrosine kinase inhibitor targeting the critical transforming enzyme encoded by *BCR-ABL* in chronic myeloid leukemia

- All-trans retinoic acid targeting the molecular defect t(15;17) of acute promyelocytic leukemia

- Rituximab-monoclonal antibody targeting CD20 expressed by most B-cell malignancies

All of these therapies are highly active, have minimal toxicity, and have a selective effect on malignancy. However, the molecular heterogeneity of lymphoma, leukemia, and myeloma means that critical molecular targets are unknown in other hematological malignancies. Thus, there is a need to identify targets and common pathways. Also needed are molecular correlates of response—diagnostic and classification systems that relate directly to therapy and that guide specific therapy molecularly and immunologically.

Other therapeutic approaches, such as interferon and monoclonal antibodies, pose several problems: their mechanisms of action are not completely defined, and their target antigens are largely unknown. Immunologic tolerance and/or unresponsive states need to be overcome. Further, there is a need to definitively demonstrate the efficacy of specific immunotherapy with

vaccines or adoptive cellular therapies and antigen-specific approaches.

How do we develop novel therapies and integrate them into the overall treatment of lymphoma, leukemia, and myeloma?

Research Priorities

1. Form a Transplant Trials Group.

Multicenter collaborative clinical trials are necessary to address many important issues in hematopoietic transplantation. A Transplant Trials Group should focus on transplant-specific research issues and should coordinate its efforts with those of existing cooperative groups. Major research issues in hematopoietic transplantation include determination of targets for immune antimalignancy responses, approaches to distinguish graft-versus-leukemia and graft-versus-host disease, and the potential for antitumor responses after autologous hematopoietic transplants. The function and therapeutic uses of stem cells, including cells derived from bone marrow, peripheral blood, and cord blood, is a high-priority area of research. Areas requiring further study include the potential of stem cells for differentiation for tissue restoration and their potential for oncogenesis. Also important are studies to reduce toxicities and treatment-related morbidity and mortality. The biology and role of nonmyeloablative transplants and studies to improve the results of unrelated and human leukocyte antigen nonidentical transplants are a high priority, as are assessment of late effects and quality-of-life issues. NCI and the National Heart, Lung, and Blood Institute have collaborated on a Request for Applications (RFA) that will support a national Transplant Trials Group. This RFA may address some of the needs identified above.

2. Support the development of promising new anticancer therapeutic agents that have been dropped or are not being developed by the pharmaceutical industry.

Some promising anticancer drugs and biological agents are not taken forward in development by the pharmaceutical industry, often because of economic considerations and perceptions of a small ultimate market. The NCI should expand its mechanism to support the development of such agents. Acquiring agents for direct development or provision of financial assistance is necessary to support the development of promising anticancer agents for "orphan" indications.

A major barrier to research involving immunotherapy and gene therapy of malignancy is the lack of access to critical reagents that have been prepared under Good Manufacturing Practices for *ex vivo* cellular manipulations and human clinical trials, including dendritic cell preparation, gene transfer, and cell expansion. In many cases, multiple required factors are controlled by competing companies that will not support their use in the desired combination. Many of these factors and reagents may not have the potential for systemic use and may not be considered for development as potential products, and the companies that produce them are reluctant to continue their production.

The NCI should establish a national source for selected cytokines, reagents, and vectors prepared under Good Manufacturing Practices and a mechanism for access for investigator-initiated clinical research. Examples include IL-4, TNF-alpha, CD40 ligand, kit ligand, flt-3 ligand, and control peptides. Drug master files should be maintained and should allow cross-referencing by investigators to facilitate submissions to the Food and Drug Administration (FDA) of Investigational

New Drug and Investigational Device applications. A steering committee comprising representatives of investigators, including internal and external scientists and translational clinical investigators, and NCI representatives should determine which agents shall be obtained and stored and should establish policies for distribution of these agents to investigators.

3. Optimize the efficiency of clinical trials.

The NCI and the FDA should support novel statistical study designs and procedures to improve the efficiency of clinical trials of novel agents. The use of validated surrogate markers and endpoints should be encouraged to allow earlier assessment of efficacy. Determination of "optimal" doses of biological agents may involve surrogate endpoints but should correlate with response. Statistical designs are needed to more rapidly define maximally tolerated doses and optimal biological doses in Phase I studies and to combine Phase I and II evaluations to assess both toxicity and response. Rapid transition from Phase I to Phase II evaluation is needed to minimize delays in study completion. Criteria under which trials shall be discontinued should be used to rapidly terminate studies of toxic or ineffective agents. Surrogate markers that are predictive for response and survival should be sought and validated. Designs should be flexible in terms of allowable toxicities, particularly for "high-risk, high-reward" therapies such as human leukocyte antigen nonidentical transplants or cord blood transplants. Finally, the NCI should continue its vigorous advocacy efforts with Medicare and third-party medical insurance providers to ensure patient access to participation in Phase I, II, and III clinical trials of innovative cancer therapies, as well as the eligibility and access of pediatric patients to participation in clinical trials.

4. Establish a national tissue bank.

Rational drug development requires a detailed understanding of the molecular signaling pathways that are responsible for the malignant phenotype. A high priority is to develop a system for large-scale collection of tissue for molecular analysis, using arrays, proteomics, and other methods to assess pathogenesis and classify malignancies in relation to their prognosis and response to various therapies. This approach should ultimately provide effective guidance in the selection of treatments. Tissue as well as clinical history, treatment, and response and survival data should be available to investigators throughout the country for analysis. Also required is funding for collection and processing of specimens and relevant clinical data.

A national tissue bank should be developed involving cooperative groups and NIH-sponsored investigators and institutions to provide cells and DNA for research studies from patients with clinical data regarding diagnosis, prognostic factors, and clinical response to treatment. A steering committee should be formed to develop the plan for implementation and the procedures for distribution of samples.

PARTNERSHIP PLATFORMS

Co-Chairs: Antonio Grillo-López, MD; Frederick Appelbaum, MD; Robert DeLap, MD, PhD

Introduction

There is a widely recognized need to expedite the time required for clinical development and regulatory approval of new therapies. In 1996–1998, across all therapeutic areas, this process took an average of 5.9 years. Although this length of time represents an 18% drop from that in 1993–1995, it is no faster than the average in 1984–1986. Anticancer agents in particular have an average clinical phase of 7.2 years—longer than that of antiviral, anti-infective, analgesic, cardiovascular, or respiratory drugs. Among all cancers, hematological malignancies offer the best opportunity for progress because they are better understood and are intrinsically sensitive diseases. However, they are also rare diseases, and that rarity may at times constitute a barrier to the development of new treatments.

For the purposes of this report, "partnering" is considered as interaction among seven groups: the NCI, the FDA, academia, the corporate community, patient advocacy organizations, the pharmaceutical industry, and reimbursement entities. It is critical for these seven groups to work together in the most efficient manner possible so that new therapeutic products may be evaluated in the most timely fashion. The NCI must take the initiative to make that happen. Its leadership in the development of a true and effective partnership in this area is most important because of the sore need for improvement in the length of time that is required for the development of new cancer therapies.

Research Priorities

1. **The NCI should partner with the FDA, academia, the corporate community, patient advocacy organizations, the pharmaceutical industry, and reimbursement entities to continue to strengthen its commitment to expedite drug development and to make new therapies available and approved through the following:**

- Increasing support for translational research (e.g., expanding on the current Rapid Access to Intervention Development [RAID] concept to draw on the expertise and resources of all partners)

- Considering novel strategies for ensuring continued dialogue among all partners during clinical drug development (e.g., creating a "chaperoning" group of independent experts [one person from each partnering entity] who can provide institutional memory, input from community, etc.)

- Taking the initiative for developing and obtaining consensus among partners on criteria for response, data collection, monitoring, auditing, toxicity, study endpoints, and development of expert panels, as appropriate, to ensure consistency among studies

- Creating a process for identifying, funding, and completing novel, high-priority clinical trials

2. **The NCI, working with the FDA, academia, the corporate community, patient advocacy organizations, the pharmaceutical industry, and reimbursement entities, should foster the discussion and resolution of legal and regulatory issues that impede the**

progress of cancer research through the following:

- Developing standards for interactions between pharmaceutical industry and academia with regard to intellectual property rights, including research data and inventions

- Developing broad-based consent forms for access to patient data and clinical samples

- Developing uniform contracts for interactions between study sites and sponsors

- Encouraging the continued development of centralized Institutional Review Boards

3. **The NCI should take the initiative to improve communication and to facilitate interactions among the FDA, academia, the corporate community, patient advocacy organizations, the pharmaceutical industry, and reimbursement entities through the following:**

- Broadening "state-of-the-science" meetings to include partner participation at all levels, including international representation

- Establishing fellowship programs between agencies and organizations (e.g., FDA, patient advocates, industry, NCI)

- Broadening Internet resources (e.g., include research areas of interest to NCI scientists, a comprehensive listing of available clinical trials from all partners)

EDUCATION, COMMUNICATION, AND BEHAVIORAL RESEARCH

Co-Chairs: Ilene Penn Miller, JD; Kathy Giusti; Paul Jacobsen, PhD

Introduction

Only $6 million has been spent on survivorship research in the hematological malignancies by the NCI's Division of Cancer Control and Population Sciences. Of the 16 grants funded to date, the majority (7) have focused on bone marrow transplantation, which is being used less frequently in the treatment of these diseases. The remaining studies have focused on various aspects of Hodgkins disease (1), lymphoma (1), leukemia and non-Hodgkins lymphoma (2), and leukemia (5). No grants have been awarded in myeloma.

At the same time, treatments for leukemia, lymphoma, and myeloma (LLM) are undergoing dramatic changes due to new scientific discoveries and molecular advances. As treatments evolve, research on education, communication, and behavior must keep pace so that patients can achieve maximum benefit in terms of both quality and quantity of life. The time is ripe for the NCI to undertake a comprehensive survey of practitioners, researchers, patients, and caregivers to identify and develop much-needed psychosocial, education, and communication interventions, from the early symptoms of these diseases through diagnosis, treatment, and long-term follow-up and care.

Unmet and Urgent Needs

Although many of the most common cancers are declining in incidence and mortality, the statistics for lymphoma and myeloma are on the rise. The incidence of lymphoma is increasing by 1.1% each year, making it the second fastest-rising cancer incidence in the United States today. New lymphoma cases have doubled since the 1970s. At the same time, the number of deaths from lymphoma is increasing, and the 5-year survival rate for non-Hodgkins lymphoma hovers at 50%. The incidence of myeloma is increasing by 0.8% each year. The rate of death from myeloma is similarly increasing, by 1.3% annually. The survival median for myeloma patients is a short 3 years, making this one of the most devastating cancers for patients and their families.

Unlike many other forms of cancer, the hematological malignancies span a wide range of patient populations that must be reached through diverse forms of communication. The incidence of multiple myeloma is skewed toward African Americans at a ratio of 2:1. Historically a disease of the elderly, myeloma is now affecting younger patients in their 20s, 30s, and 40s. Leukemia strikes 10 times as many adults as children. It is also the leading cause of death in children under age 15. Lymphoma comprises more than 30 disease subtypes that affect all ages, from children to the elderly. The incidences of all three diseases are skewed toward men, and leukemia and lymphoma are the leading fatal diseases in men under age 35.

Also unlike other forms of cancer, there are no proven methods of prevention, screening, or early detection for these diseases. They are difficult to diagnose because symptoms such as fatigue, weight loss, and compromised immune systems are often confused with those of other illnesses. As a result, patients are often misdiagnosed and/or diagnosed late in the course of their disease. Yet early and accurate diagnosis of the hematological malignancies is critical to the successful treatment of these patients. Diagnostic tools on the horizon, such as the Lymphochip, promise to improve the diagnosis of these diseases at the molecular

level, enabling doctors to specifically target therapies and improve outcomes for patients.

Advancements in the field of molecular profiling have increased the importance of obtaining pretreatment tissue samples to better classify patients by disease type and to help monitor patients over time. These same tissue samples can be stored to facilitate long-term research and to help in the identification of targeted therapies. Patients must be educated about the importance of providing samples. All oncologists and surgeons, including those at NCI-designated cancer centers and those at community practices, where most blood cancer patients are evaluated, must be educated and motivated to obtain, analyze, and distribute tissue samples to ensure accurate diagnosis by disease subtype and to enhance future research.

Once a diagnosis is confirmed, many patients with hematological malignancies face difficult treatment decisions. A segment of patients with myeloma and non-Hodgkins lymphoma are asked to "watch and wait," putting off treatment until symptoms require intervention. These patients must learn to live with chronic cancer and manage their lives accordingly. Other patients are diagnosed with late-stage, aggressive disease that requires immediate intervention. Both scenarios evoke anxiety and frustration as patients strive to understand the complexities of their disease.

The emergence of new compounds and trials in hematological malignancies brings hope to patients; however, understanding the advantages and accessibility of new, emerging treatments can be overwhelming. Although many patients rely on their community oncologist for guidance, the community oncologist may not be current on the latest approaches for each specific disease. Easy access to up-to-date information about treatment options is critical to ensure that appropriate medical decisions are made.

Over the longer term, patients' quality of life must be optimized. As patients with hematological malignancies face anemia, persistent infections, and, with myeloma, severe bone pain, their treatment plans require continual evaluation. Furthermore, many patients with leukemia and lymphoma also face secondary cancers and long-term health consequences of treatment, including heart disease, infertility, and compromised immune systems. Due to the high mortality associated with AML, MDS, Adult ALL, non-Hodgkins lymphoma and multiple myeloma, clinicians must also evaluate patients for anxiety and depression.

Research Priorities

What little research has been conducted on the hematological malignancies has been predominantly initiated by investigators and conducted on an ad hoc basis. The NCI must initiate a comprehensive and coordinated series of national studies to identify and develop behavioral, education, and communication interventions at the four critical stages in the progression of hematological disease. The studies would focus on understanding and establishing behavioral, communication, and education interventions for the following purposes:

- To expedite the diagnosis of hematological cancers through better identification of risks and symptoms
- To ensure a timely and thorough diagnosis of these cancers through all available diagnostic tools
- To facilitate optimal treatment and management decisions for patients with chronic and aggressive disease

- To optimize the quality of life and quality of care for patients who are cured, who are living with chronic disease, or who are terminally ill.

Centers of Excellence in LLM should be motivated to pool resources and collaborate on multi-site studies. Priorities 1–4 below further delineate areas of study and intervention that serve as the basis of this request.

1. **Identify interventions and develop educational materials and communications for the public to better identify the early symptoms of the hematological malignancies through the establishment of a National Hematological Surveillance Program that provides a system for collecting and analyzing data relating to diagnosis, treatment, side effects, and short- and long-term follow-up of patients by disease subtype. Develop a public health program to increase awareness of risks and symptoms, similar to programs that have been conducted to raise awareness of early signs and symptoms of ovarian cancer.**

2. **Identify behavioral, education, and communication interventions to ensure that patients and practitioners understand the importance of retrieving, distributing, analyzing, and storing pretreatment tissue samples for evaluation, monitoring, and clinical research. Obtaining sufficient and appropriate biopsies at diagnosis is critical to supporting the treatment choices and long-term follow-up of blood cancer patients.**

3. **Identify and implement programs that facilitate informed doctor–patient decision-making at the time of treatment for aggressive and indolent patients.**

With the rapid development of novel therapies, patients and practitioners must stay abreast of new trials and enrollment criteria. They need to understand that initiating one treatment may reduce eventual access to another treatment. Interventions must identify ways to disseminate accurate state-of-the-art information to both patients and medical communities (including internists), taking into consideration the diverse ages, genders, races, educational levels, and socioeconomic status of patients affected by the hematological malignancies. Easy, centralized access to information on hematological malignancies, standard treatment options, emerging treatments, and available trials must be facilitated. Outreach programs to community oncologists and patients encouraging participation in clinical trials are needed at the earliest possible stage. New interventions must be promulgated that respond to the changing nature of treatments and that help patients manage the administration and side effects of vaccines, monoclonal antibodies, and radioimmunotherapies.

4. **Identify and implement methods of improving quality of life and quality of care as patients move through treatment and maintenance.**

New interventions must be identified to help patients and caregivers cope with chronic cancers that may span a lifetime. Similarly, younger patients with leukemia, Hodgkins disease, and myeloma need coping mechanisms to live their lives as long-term cancer survivors once cured. Guidelines should be established to screen patients for pain, depression, fatigue, and common symptoms of these diseases and their treatments. Treatments to alleviate these symptoms must be identified, and patients and health care professionals must be educated about these treatments. Patients and health care professionals must also be educated about the availability and benefits

of psychosocial support. Guidelines and support resources should be prepared for caregivers who monitor symptoms, deliver care, and provide emotional support. Finally, quality-of-life issues facing patients and families living with hematological cancers must be identified and prioritized, especially as new treatments emerge and, hopefully, survival is extended.

OUTCOMES RESEARCH

Co-Chairs: Leslie L. Robison, PhD; Charles Sklar, MD

Introduction

Data from the NCI-supported Surveillance, Epidemiology, and End Results (SEER) program indicate 5-year relative survival rates of 43% for leukemia, 82% for Hodgkins lymphoma, 51% for non-Hodgkins lymphoma, and 28% for myeloma. Nationally, these figures translate into the following estimates of new 5-year survivors in the United States: 4,900 for leukemia, 4,300 for Hodgkins lymphoma, 7,600 for non-Hodgkins lymphoma, and 860 for myeloma. Given these numbers, active research programs are needed to address the spectrum of outcomes within these populations of survivors who have been treated with a variety of therapeutic modalities, often including radiation therapy and multi-agent chemotherapy.

Research Priorities

1. **Establish the following:**

- A collaborative network of Centers of Excellence consisting of follow-up clinics with the capacity, expertise, and patient populations to participate in protocol-driven outcomes research in leukemia, lymphoma, and myeloma (LLM)

- LLM cohorts, consisting of patients who have achieved a set survival point, for prospective surveillance of the occurrence of high-priority outcomes

Rationale

Although a number of venues exist for the conduct of outcomes research within LLM populations, serious limitations inherent in these venues have severely limited the conduct of high-quality outcomes research. Venues for outcomes research include single institutions, limited consortia, cooperative clinical trials groups, late-effects clinics, and health maintenance organizations. Outcomes research in LLM has often been characterized by limited sample size, lack of heterogeneity in the study populations to allow for adequate assessment of patient- and treatment-specific risks, and potential bias in study populations resulting from selection influences, such as incomplete follow-up.

Investment in the proposed resources would provide opportunities to facilitate and enhance outcomes research at two distinct levels: the population level and the clinical level. The clinically based resource, consisting of the collaborative network of clinical Centers of Excellence, would provide a clear and effective structure in which to conduct protocol-driven clinical investigations designed to test focused, high-priority questions. Investment in the establishment of research cohorts will yield a dynamic resource with which to address a wide spectrum of high-priority outcomes and will serve as a monitoring system for the identification of emerging issues among LLM survivors. The research cohorts must overcome the limitations of previous and current research by having the following characteristics:

- Sufficiently large sample sizes

- Demographic diversity

- Heterogeneity of treatment exposures

- Extremely well-characterized disease, therapy, and defined outcomes

- Collection of biological samples (e.g., genomic DNA and second tumors) to

facilitate evaluation of molecular genetic factors

- Support cores (e.g., biostatistics, tissue procurement and processing, survey research)

2. Using the established research cohorts, clinical networks, and other appropriate resources to institute an aggressive mechanism of support for high-priority research directed toward the identification and characterization of patient-, disease-, and treatment-related associations and outcomes of interest:

- Identify and characterize high-risk populations.

- Define the biological basis of identified associations.

- Design and test innovative intervention and prevention strategies.

Rationale

Little is known about which patient populations are at high risk for adverse outcomes of treatment for LLM, yet this information is essential to the rational development and testing of intervention and prevention strategies. The spectrum of outcomes that are in need of high-quality research include second malignancies, organ dysfunction (e.g., cardiac, pulmonary, endocrine), neuropsychological and psychosocial aspects, quality of life, and quality of care. Some high-priority populations are known and include survivors who have been treated with chest irradiation (i.e., for Hodgkins lymphoma), exposed to anthracyclines, treated with bone marrow and stem cell transplants, or exposed to alkylating agents/topo-II inhibitors. Moreover, the outcomes issues are unknown for many populations, such as patients treated with novel therapies, those who may have unique genetic susceptibility traits, and those for whom extended periods have elapsed since treatment. Additionally, the potential impact of pre- and post-therapy health behaviors is not known.

Similarly, to move toward prevention and intervention, it is important to understand the induction mechanisms for adverse outcomes related to disease or treatment or both. Accordingly, support is needed for research to elucidate the basis of associations identified through clinical- and population-level research.

There are rare examples of well-designed and adequately evaluated interventions that use innovative strategies to prevent or modify adverse outcomes within LLM patient populations. These interventions need to encompass strategies to assess the following:

- The utility of biomarkers or surrogate markers for predicting the occurrence of outcomes

- Psychological and behavioral strategies

- The impact of screening for early detection of adverse outcomes

- The effectiveness of late-effects clinics in modifying quality of life

- The effect of changes in lifestyle and behavior on health and quality of life

3. Develop educational materials and programs for health care professionals involved in the follow-up care of LLM survivors and establish mechanisms for training of researchers in outcomes-based research of these patient populations.

Rationale

Only a limited number of specialists have adequate training in the care of LLM survivors. There is a pressing need to develop effective and efficient ways to educate a diverse group of health care providers (e.g., oncologists, internists, family practitioners, psychologists, nurse clinicians, social workers) about comprehensive and appropriate medical follow-up for survivors. Such education should include the medical, psychological, and social consequences of these diseases and their therapies. Research is needed to determine how best to provide this education.

Similarly, there is a paucity of adequately trained professionals who are capable of conducting high-quality outcomes research. Funding is required to support specific training of investigators who are interested in pursuing a career in outcomes research in these populations of LLM survivors.

Barriers

Inadequate resources and training programs, addressed above, are primary barriers to the implementation of highly productive activities directed toward outcomes research. Another critical issue is the increase in restrictions imposed by Institutional Review Boards. These restrictions seriously limit the ongoing monitoring of survivors through collection of health-related information and biological specimens.

Appendix C: LLM PRG Member Roster

Kenneth C. Anderson, M.D.
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Co-Chair

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Riccardo Dalla-Favera, M.D.
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