Strategic Plan For Addressing the Recommendations of the Leukemia, Lymphoma, and Myeloma Progress Review Group

Message From the Director

October 2002

In 2001, hematologic cancers-- as a group the fourth most common cancer -- claimed the lives of 60,300 Americans, drained the financial and emotional resources of hundreds of thousands, and continued to resist our best efforts to find a cure. Despite these tragic consequences, we are nevertheless increasing our scientific knowledge of this group of blood-related cancers and are using that knowledge to help reduce the burden. This year the death toll from hematologic cancers is expected to be 58,300 Americans. Continued scientific inquiry will yield unprecedented amounts of vital information essential to eliminating these diseases. I believe that in large part our increased success will be a direct result of the collaboration of dozens of America's most committed scientists, clinicians, planners, survivors, and advocates – a collaboration that produced the first report on progress and priorities for continued success against Leukemia, Lymphoma, and Myeloma (LLM).

This plan describes the National Cancer Institute's (NCI's) strategies, ongoing, new, and proposed, for carrying out the recommendations of the LLM Progress Review Group (LLM PRG). The plan reflects NCI's commitment to greatly reduce or eliminate these diseases with the continued expertise and guidance of the LLM PRG.

The LLM PRG and NCI's LLM Working Group have identified recommendations and strategies that will help us develop critical next steps. I want to thank them for an exceptional effort. Their work will help us close the gaps in NCI's and the Nation's current research effort with sound, productive science.

To help us reach our ultimate goal of better detection, diagnosis, treatment and prevention of LLM, the NCI will increase its efforts to:

- Understand the etiology and pathobiology of these diseases
- Support education, communication, and survivorship research
- Develop new treatments more rapidly and effectively through novel public-private partnerships and deliver those treatments where they are needed

Ultimately, this is not just a plan for NCI, but a call to action for the entire cancer research community. It begins the process of building the partnerships and collaborations necessary to successfully implement these strategies. By joining together, I am confident that we will continue to make substantial scientific and medical progress to achieve the one goal that matters most: the reduction and elimination of the burden of blood-related cancers for all who are in need.

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute

Table 1. New Activities and immediate strategies for LLM research

New Activities *Initiatives that NCI has started within the past year to address a recommendation.*			**Immediate Strategies** [1] *NCI is beginning to implement these strategies.*		
Name	**PRG Rec**[2]	**Page**	**Name**	**PRG Rec**[2]	**Page**
Designated the tumor microenvironment an Extraordinary Opportunity	3	18	Promote small grants program in behavioral research for cancer control to encourage research on LLM patients	6	30
New RFA "Molecular Interactions between Tumor Cells and Bone"	3	18	Target education programs to LLM patients and health care providers, including ethnic minority groups	6	30
Hosted workshop "Hematologic malignancies and the marrow microenvironment"	3	18	Encourage medical societies to discuss new certification programs for physicians	7	33
Hosted meeting on "Myelodyaspastic Syndromes and Acute Myeloid Leukemia"	4	22	Provide a regular forum for academia, government, and industry to discuss issues and barriers to drug approval in order to foster new partnerships	9	41
Developed a series of publications to help cancer survivors adapt to challenges encountered after treatment	6	29			
Developed an online continuing education program to educate physicians about clinical trials	7	32			
Requested proposals for a Phase IIb study of agents that may prevent multiple myeloma	8	36			

1 Speed of implementation will depend upon the availability of NCI staff to devote appropriate resources to the effort.
2 PRG Recommendations: The LLM PRG made 11 recommendations for future research.

Table 2. Short-, medium- and long-term proposed new strategies for LLM research

Short-term strategies[3] *NCI is currently developing these strategies further as a first step towards implementation.*			**Medium-term strategies**[4] *NCI has determined that it will develop these strategies further in the near term.*			**Long- term strategies**[5]		
Name	**PRG Rec**[6]	**Page**	**Name**	**PRG Rec**[6]	**Page**	**Name**	**PRG Rec**[6]	**Page**
Develop list of key targets for LLM prevention and therapy at an expert workshop, and fund research to evaluate them	4	22	Support case-control studies for parallel and joint studies in LLM	1	14	Expand cohort studies of LLM etiology to include more ethnic minority subjects	1	13
Evaluate the utility of molecular technology platforms in LLM diagnosis, prognosis and therapy	4	22	Co-sponsor grants with NHLBI on stem cell plasticity in hematopoietic and non-hematopoietic tissues	5	25	Expand cohort consortium to include hematological malignancies and larger and younger populations	1	13
Expand RAID, R*A*N*D and RAPID to accelerate the development of new treatments	9	41	Fund pilot studies to identify LLM patients at risk for long-term, adverse outcomes to foster future research	8	36	Fund new collaborative research for prevention, diagnosis and treatment tools	2	16
Encourage partnerships among NIH institutes, private and non-profit organizations in drugs/biologics development	9	41				Fund Tissue Resources for Research Initiative so that NCI-sponsored resources include specimens from all major tumor types	4	22
Hold a meeting with academic, government and industrial leaders to evaluate possible models to promote partnerships among these three sectors	10 11	45 47				Support NHLBI's Specialized Centers of Research, especially for stem cell research	5	25
						Expand CanCORS to conduct prospective studies in newly-diagnosed cohorts of LLM patients to identify patterns of care	6	30
						Initiate collaborations among SPORES to conduct long-term studies of LLM patient cohorts	8	37

3 Actual implementation will depend upon the availability of funds, the receipt of high-quality applications and a final determination that the strategy is feasible and scientifically sound.
4 Further consideration of these strategies will take place over the next several months.
5 While this strategy is important, NCI will not be able to implement it in the near future.
6 PRG Recommendations: The LLM PRG made 11 recommendations for future research.

Leukemia, Lymphoma, and Myeloma Progress Review Group Strategic Plan

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Strategic Plan for Addressing the Recommendations of the Leukemia, Lymphoma, and Myeloma Progress Review Group

The Leukemia, Lymphoma, and Myeloma Progress Review Group

The LLM PRG was charged with identifying and prioritizing areas of research that could advance progress against leukemia, lymphoma, and myeloma (LLM). At a planning meeting held in August 2000, the LLM PRG organized a Roundtable to review the state of the science and identify needs across the continuum of LLM research.

"The LLM PRG identified 10 areas for research that could revolutionize the prevention, diagnosis, treatment, and care of individuals with these cancers."

The LLM PRG Roundtable of approximately 180 participants met on December 13–15, 2000. Participants met in breakout groups organized around research topics, such as bone marrow and lymphoid tissue biology, partnership platforms and scientific infrastructure, diagnosis and prognosis, and preclinical therapeutics and outcomes research. Members of breakout groups identified top research priorities for the next 5–10 years. In support of the priority-setting process, the National Cancer Institute (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.

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

Implementation Approach

After the LLM PRG issued its report, the NCI Office of Science Planning and Assessment (OSPA) convened a working group to (1) identify NCI initiatives and projects that address the PRG's recommendations, and (2) develop potential strategies for filling gaps in the LLM research effort. This group met with the PRG in November 2001 to discuss the recommendations, the NCI initiatives and projects addressing them, and potential strategies for filling gaps. The PRG and NCI staff refined these strategies and identified additional ones. One of these additional strategies was to create a "champion" within NCI to oversee LLM research. This individual would oversee, coordinate, integrate, and seek synergies in LLM research to ensure rapid and effective implementation of the PRG's recommendations.

To develop a comprehensive implementation strategy, OSPA reconvened the NCI working group (see roster in Appendix A) to review and refine a draft implementation plan; identify additional opportunities for addressing the PRG's recommendations; and identify the resources, expertise, and strategies needed to implement the opportunities. Because of funding and other limitations, NCI cannot immediately address all issues and

recommendations raised by the LLM PRG (see Appendix B for a consolidated table of recommendations and strategies). Consequently, to make the best use of limited research dollars and to fully use NIH's existing infrastructure and funding mechanisms, the LLM PRG has chosen an implementation approach that:

- Focuses on investigator-initiated research and other mechanisms that provide critical research support;
- Builds on existing, broad-based initiatives, and leverages existing NCI funding mechanisms; and
- Addresses the highest priority areas and gaps between resources and needs.

Table 3. LLM PRG Recommendations that address gaps in current research.

Section 1 Research priorities in etiology and pathobiology	Section 2 Research priorities in education, communication, and survivorship	Sections 3 and 4 Research priorities in drug development and therapeutics
• Understand the interactions among genotype, immune function, infectious agents, environmental toxins, and lifestyle factors. • Identify the basic mechanisms responsible for genome instability, chromosome translocations, and other mutations. • Define the relationship between the tumor and the host biological environment. • Provide molecular characterization of hematological malignancies. • Further develop research on stem cells, both single- and multi-lineage.	• Determine how to provide accurate, timely, and tailored information to patients. • Develop education and training programs for certification of physicians and centers. • Identify and target individuals and populations at high risk for adverse long-term outcomes to define the biological basis of identified associations and to facilitate the design and testing of intervention and prevention strategies.	• Foster partnerships between the NCI and academia, advocates, cooperative groups, the Food and Drug Administration, and industry to expedite drug development and the availability of therapies. • Develop the required resources to translate "lead" structures and molecules into effective therapeutic agents. • Cancer Translational Research Allied Consortium.

This strategic plan is organized into four sections (See Table 1). The first section addresses priorities in the areas of *etiology and pathobiology*. The second section focuses on the key areas of *education, communication, and survivorship*. The third section addresses research priorities in *drug development and therapeutics*. Finally, the fourth section discusses a proposed new initiative: the *Cancer Translational Research Allied Consortium (C-TRAC)*, a novel alliance among academia, industry, government, and patients that would reduce drug development time from 5–10 years to 2 years.

For each priority area, the plan addresses the following:

- Introduction: a description of and justification for research
- Ongoing Activities: pre-existing NCI initiatives that address the priority;
- New Activities: initiatives that NCI has started within the past year to address the priority; and
- Proposed Strategies: initiatives that NCI is exploring as a means to fill gaps in the Institute's efforts to address the needs.

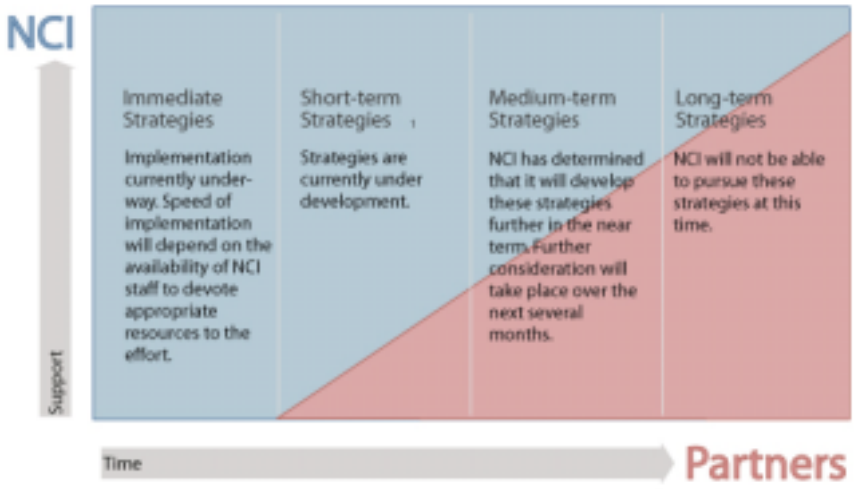
Strategic Plan to Address PRG Recommendations[1]

The NCI will do everything in its power to expedite progress against LLM. The Institutes will:

- implement as many of the proposed strategies in this document as it can
- pursue partnerships where they make sense
- encourage and assist other organizations to play a leading role in implementing those strategies that transcend NCI's mandate or resources
- seek collaborations and advice on all fronts as it implements this plan.

For each proposed strategy in this document, the Institute's plan of action is indicated in italics. There are four possible plans of action for each strategy.

Figure 1: Implementation Cycles for Proposed Strategies



[1] As always, the ability to implement any new strategy is dependent on: (1) a final determination that the strategy is vital, feasible, and sound; (2) the availability of funds; and (3) the receipt of high-quality

A table containing PRG priorities, the ongoing and new activities, and proposed strategies is included as Appendix B.

Section 1
Research priorities in etiology and pathobiology

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

Introduction

> *"Recently developed gene and protein arrays provide powerful new tools to define hematopoietic and lymphoproliferative malignancy subtypes at the molecular level, identify the specific biological effects of carcinogens, and evaluate pathogenic mechanisms."*

Our understanding of the etiology of 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 multistep and progressive molecular events in the evolution of neoplastic transformation. These events have not been sufficiently exploited in previous research.

Recently developed gene and protein arrays provide powerful new tools to define hematopoietic and lymphoproliferative malignancy subtypes at the molecular level, identify the specific biological effects of carcinogens, and evaluate pathogenic mechanisms. These tools will improve our understanding of the causes of hematopoietic and lymphatic malignancies in the near future.

Another area for investigation is the contribution of environmental toxins or infectious agents to the initiation or progression of LLM. Studies of the interactions between exogenous exposures and genetic and host factors should be coupled with evolving technology to assess exposure and gene-environment interactions.

To overcome the limitations of previous research and capitalize on existing opportunities, the LLM PRG recommended support for 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 to realize new opportunities.

The PRG recommended the following objectives as a means to understand the etiology of LLM:

- 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.

- Include patients with precursor conditions to compare risk factor associations across subgroups of patients, such as those with myelodysplastic syndromes and acute myeloid leukemia.
- Collect and use DNA and/or tumor tissue as a renewable resource.
- Evaluate risk factors among races and ethnic groups other than Caucasians to determine the effect of genetic differences or gene-environment interactions on the etiology of LLM and precursor conditions.
- Provide in-depth exposure assessment using alternative sources of exposure verification, newer methodologies for measuring external exposures, and/or biological effect measures for exposures.
- Investigate familial aggregations and assess underlying genetic aspects; the possible role of gene-environment interaction; and interactions among immune function, infectious agents, environmental toxins, and lifestyle factors.
- Invest in
    - 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, and
    - Animal studies to investigate the mechanistic aspects of environmental exposures.

Ongoing Activities Addressing the Priority

The following networks, consortia, and centers have ongoing projects in hematological cancers.

The **Case-Control Consortium** has assembled a large number of hematologic malignancy cases with available biospecimens and detailed data on relevant exposures. Two groups of investigators in the consortium are using the case-control approach to identify genetic and environmental determinants of non-Hodgkin's lymphoma.

The **Clinical Trials Cooperative Groups** are a national network of 12 consortia organized to test potential treatment advances in patients more rapidly. Each year, 1,700 institutions throughout the United States and Canada, including approximately 8,000 investigators, participate in these trials. Several intergroup trials are ongoing in adult leukemia and lymphoma.

The **Pharmacogenetics Research Network** is a network of multidisciplinary, collaborative research groups that support the development of a public pharmacogenetics knowledge base. These groups are studying the genetic variation contribution to inter-individual differences in drug responses by collecting comprehensive, integrative information about specific proteins and genes. The Pharmacogenetics of Anti-cancer Agents Research Group is addressing a hematological malignancy.

The following initiatives could potentially address leukemia, lymphoma, and myeloma:

The **Cohort Consortium** consists of investigators conducting 15 prospective studies of large population groups. Investigators are pooling their existing resources of high-quality exposure

data and biological specimens suitable for genetic analysis, with a combined total of 700,000 study participants.

Interdisciplinary Studies in the Genetic Epidemiology of Cancer supports collaborative, interdisciplinary, population-based investigations to identify and evaluate the interactions among genetic and epidemiologic risk factors leading to cancer susceptibility in individuals, families, and populations, as well as factors influencing the rate of increase with age in cancer susceptibility.

Diet, Lifestyle, and Cancer in U.S. Special Populations supports epidemiologic studies to elucidate causes of cancer and means of prevention in African Americans, American Indians, Alaska Natives, Asians and Pacific Islanders, Native Hawaiians, and Hispanics, as well as rural, older, low-income, and low-literacy groups.

The **Centers for Population Health and Cancer,** proposed for FY 2003, will support research to (1) expand understanding of the social and environmental determinants of cancer and the psychosocial, behavioral, and biologic factors that mediate them; (2) develop hypotheses for cancer control research at social, institutional, and policy levels; and (3) develop, apply, and evaluate interventions to improve cancer outcomes and reduce outcome disparities.

Proposed Strategies to Address Gaps

Rapid advancement in understanding the etiology of LLM clearly requires a large national effort involving multidisciplinary research and a national specimen bank, among other features. Strategies under consideration include:

- **Expand cohort studies investigating the etiology of LLM to include more minority (non-Caucasian) and underserved populations.** Supplement existing initiatives with additional funding to evaluate LLM-related risk factors in non-Caucasian populations and to explore differences in gene-environment interactions. [c]

- **Expand the Cohort Consortium to include hematological malignancies and include larger and younger populations in this effort.** Promote and coordinate one or more joint studies of LLM malignancy using information and biospecimens from large, general population cohorts in the United States and other developed countries. The consortium provides a powerful new approach to study the natural history of precancerous conditions. Consortium studies could identify predictive markers and intermediate endpoints in the etiology of LLM malignancies. [c]

- **Contribute resources to the Case-Control Consortium for parallel and joint studies of hematologic malignancies.** Support collaborative efforts by creating pooled datasets with common data dictionaries, exchanging samples for quality control, and coordinating central pathologic review, genotyping for combined analyses, and related activities. These additional resources will maximize the utility of extensive biospecimen and data collections for ongoing collaborative studies. [b]

[a] NCI is currently developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
[b] NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
[c] While this strategy is important, NCI will not be able to implement it in the near future.
[d] NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort

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

Introduction

LLM are caused by the sequential acquisition of mutations in the genome of immature hematopoietic cells. These mutations arise in any number of ways. Some patients are genetically predisposed to cancer because of inherited defects in genes involved in sensing or repairing DNA damage. Though these familial syndromes are not frequent causes 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.

"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."

Reducing the incidence of LLM will require a better understanding of:

- 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 environment in the broadest sense, and
- Strategies to reduce risk.

Ongoing Activities Addressing the Priority

The following initiatives are currently addressing LLM:

Applications of Innovative Technologies for the Molecular Analysis of Cancer supports projects to evaluate the utility and pilot the application of molecular analysis technologies in studies relevant to cancer research. Two funded applications focus on a hematological malignancy (see Appendix B).

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials promote translational and clinical research by supporting new therapeutic clinical trials or new correlative studies relevant to therapeutic clinical trials. Sixteen trials focus on a hematological malignancy.

***In Vivo* Cellular and Molecular Imaging Centers** foster interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging,

NCI has established five *In Vivo* Cellular and Molecular Imaging Centers. One center has a project entitled, "*In Vivo* Imaging of Bcl-2 Expression in Lymphoma."

The **Advanced Technology Center** is implementing novel technologies to address biological, clinical, and genetic questions pertinent to human cancers. Two large leukemia studies are under way with groups in Germany and Ireland. These studies are investigating the contribution of common genetic variants to pediatric and adult disease.

The **Cancer Genome Anatomy Project** was designed to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. Libraries include B cell, blood, bone marrow, lymph node, spleen, T cell, and thymus.

The **Mouse Models of Human Cancer Consortium** aims to derive or refine accurate, cancer-prone models of human malignancies; provide a comprehensive analysis of their phenotype and genotype; validate them for use by the cancer research community for a variety of investigations, which include testing of therapeutic, prevention, early detection, or imaging strategies; and ensure their availability to the research community. Several available and newly accepted strains are lymphoma models.

Proposed Strategies to Address Gaps

- **Support expansion of Activities to Promote Research Collaborations (APRC) and R21 mechanisms for collaborations between investigators seeking new prevention, diagnosis, and treatment tools, and investigators who have innovative ideas for connecting what is known about basic mechanisms.** APRC gives supplements to existing grants so that principal investigators can broaden their teams and bring in new disciplines. The R21 mechanism encourages spontaneity by requiring fewer preliminary data. The review criteria for these applications should be shaped to address specific diseases. A sharper focus on LLM may forward all proposals to a single review at the Center for Scientific Review. [c]

[a] NCI is currently developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
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3 Define the relationship between the development of hematological malignancies and the host biological environment.

Introduction

Most research on hematopoietic tumors so far has focused on identifying genetic, epigenetic, and phenotypic properties of tumor cells. However, 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. A comprehensive study of tumor-host interactions will require the effort of molecular and cell biologists, experts in bioinformatics, pathologists, clinicians, and others.

"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."

Much remains to be learned about the oncogenic events that occur within a tumor cell during tumorigenesis. 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;
- Develop *ex vivo* models that use appropriate combinations of tumor and stromal cells; and
- Develop and test therapies targeted against host cells or host cell/tumor cell interactions.

Ongoing Activities Addressing the Priority

The following initiatives are currently addressing LLM:

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials (see page 15)

Innovative Technologies for the Molecular Analysis of Cancer funds research to develop novel technologies that will support the molecular analysis of cancers and their host environment. Four funded applications focus on a hematological malignancy.

Applications of Innovative Technologies for the Molecular Analysis of Cancer (See page 15)

Mouse Models of Human Cancer Consortium (See page 16)

Molecular and Cellular Biology of Metastatic Tumor Cells supports preliminary research projects that will form the basis of future R01 applications to investigate metastasis. The intent is to (1) foster collaborative research between investigators with basic molecular and cellular biological and biochemical research experience and those with experience in metastasis research, and (2) increase the number of laboratories and investigators addressing issues of metastasis.

New Activities Initiated Within the Past Year to Address the Gaps

- The **tumor microenvironment** has been incorporated into the Bypass Budget as an Extraordinary Opportunity area for NCI. There is ample evidence that the microenvironment is a critical factor in tumor development and that all of the clinical properties of a tumor, including response to therapy, depend heavily on the tumor stroma. However, we have much less understanding of the biology and genetics of stromal components than we do of tumor cells. This is the appropriate time to invest scientific effort and Institute resources to determine how tumors co-opt their own environment to ensure their survival and ability to progress. Specific objectives for this Extraordinary Opportunity range from the initiation of educational and communication initiatives, bringing together scientists from varying disciplines, to specific research initiatives that will help to define the molecular signatures of stromal cells and their communication with immune and cancer cells to promote tumor growth.

- **Molecular Interactions Between Tumor Cells and Bone** will highlight the role of bone metastases and multiple myeloma. This is a joint request for applications (RFA) with the National Institute of Diabetes and Digestive and Kidney Diseases. This RFA will use NIH R01 and R21 award mechanisms. The lead program is the Tumor Biology Branch within the Division of Cancer Biology.

- In September 2002, the Division of Cancer Biology hosted a workshop, **"Hematologic Malignancies and the Marrow Microenvironment."** Although much research has been done on transformed hematopoietic cells, far less research focuses on the marrow microenvironment. This workshop brought together researchers from Europe and the United States to assess the current state of knowledge, identify important areas for future research, and encouraged American investigators to become more active in this area. The lead program was the Division of Cancer Biology.

4 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.

Introduction

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. The underlying molecular heterogeneity means that patients in the same diagnostic category may experience markedly different clinical courses and responses to treatment.

"Hematological malignancies are an especially diverse group of cancers because nearly every stage of blood cell development can give rise to a distinct type of cancer."

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 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.

Hematological malignancies are an especially diverse group of cancers because nearly every stage of blood cell development can give rise to a distinct type of cancer. Molecular definitions therefore must be developed for each of these many hematological malignancies. The LLM PRG called for:

- Parallel study of tumor samples with promising technologies, including genomic-scale gene expression profiling, proteomics, spectral karyotyping, and comparative genomic hybridization, to integrate the results and achieve a molecular portrait of each hematological cancer.
- The use of promising new technologies to fully understand gene and protein expression patterns during normal stages of blood cell development.
- Identification of the mechanisms of action of molecular targets. New models and systems to validate these targets are also required.

Ongoing Activities Addressing the Priority

The following initiatives are designed to generate molecular profiles of human cancers and have ongoing projects addressing LLM.

Cancer Genome Anatomy Project (See page 16)

Director's Challenge: Toward a Molecular Classification of Tumors represents a challenge to the research community to revolutionize the classification of human tumors. The goal of this effort is to develop novel tumor classification schemes based on profiles of molecular alterations present in tumors. The Director's Challenge is supporting five groups developing molecular classification schemes for hematopoietic cancers. This initiative will be up for re-competition in 2004 and will focus, in part, on hematologic malignancies.

Innovative Technologies for the Molecular Analysis of Cancer (See page 18)

The **Advanced Technology Center** (See page 16)

Applications of Innovative Technologies for the Molecular Analysis of Cancer (See page 15).

The **Pharmacogenetics Research Network** (See page 12)

The **Tissue Array Research Program** is a joint program of NCI and the National Human Genome Research Institute to promote the development and application of tissue microarray technology. A variety of lymphoma samples are available on the slides, as well as normal lymph nodes, bone marrow, and spleen.

Interdisciplinary Research Teams for Molecular Target Assessment supports the development of methods to evaluate interventions directed at specific molecular targets that are directly or indirectly associated with the cancer phenotype. One project is examining survival targets in a hematological malignancy.

Molecular Target Drug Discovery for Cancer supports the discovery and validation of molecular targets for cancer prevention or treatment that can be developed into drug discovery assays. One project is looking into FLT3 as a target for treating leukemia, and another is looking at small molecule inhibitors of Bcl-X_L.

Non-Mammalian Organisms as Models for Anti-Cancer Drug Discovery is identifying key genes and gene products that are altered in human cancer and could be exploited as intervention points or targets for new cancer prevention or treatment. Three funded projects are examining hematological malignancies.

The **Cancer Prevention Research Small Grant Program** funds developmental research in chemoprevention agent development, biomarkers, early detection, and nutrition science. The program aids and facilitates the growth of a nationwide cohort of scientists with a high level of research expertise in cancer prevention research. The small grant programs may lead to the

submission of subsequent individual research project grants (R01). Two projects are focused on hematological malignancies.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials fosters collaborations and interactions between basic researchers, private industry, and clinical investigators to perform translational research on promising predictive and prognostic markers. The markers are assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. Nine funded projects are examining different types of leukemia.

***In Vivo* Cellular and Molecular Imaging Centers** (See page 15)

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials (See page 15)

The following initiatives have the potential to address LLM:

Translation of Technologies to Detect Alterations in Human Tumors analyzes the spectrum of molecular alterations in human tumor tissues to identify reliable molecular markers or targets for the detection, diagnosis, prognosis, and treatment of cancer.

Clinical Proteomics Program will identify and characterize the protein signatures of human cancer cells and tissues. A Basic Research Proteomics Program will emphasize the development of multidimensional techniques for the separation of cell and tissue proteins, as well as high-throughput, mass spectroscopy-based analytical approaches to support cancer research. This group will work in concert with the Clinical Proteomics Program, which will focus on translating proteomics technologies directly to patient diagnosis, toxicity monitoring, and therapeutic intervention.

Molecular and Cellular Biology of Metastatic Tumor Cells (See page 18)

Molecular Targets Laboratories (MTLs) are developing a resource of biological assays and chemical probes for biological studies of cancer. The MTLs will emphasize the need for collaboration between chemists and biologists to produce libraries of potential anti-cancer compounds for public distribution, develop screening assays suitable for high-throughput screening of chemical libraries of potential agents, and confirm a drug's initial ability to alter the drug target in cancer cells.

Phased Application Awards in Cancer Prognosis and Prediction support research in developing molecular profiles.

New Activities Initiated Within the Past Year to Address Gaps

- The Cancer Therapy Evaluation Program has hosted a state-of-the-science meeting on **Myelodyaspastic Syndromes and Acute Myeloid Leukemia.**

Proposed Strategies to Address Gaps

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.

- **Hold a workshop or consensus conference to determine the most promising targets for prevention of or therapy for LLM and develop a program announcement to address the prioritized list of targets.** LLM are unique, because many of the diseases have been characterized molecularly and many potential targets have been identified. NCI has the opportunity to take a leadership role in directing research and research funds toward the most promising of these targets. The proposed workshop would have as its outcome a prioritized list of the most pressing opportunities that the Institute can support. A second outcome of the workshop would be the development of a program announcement, tied to the existing Molecular Targets for Drug Development Program within the Division of Cancer Treatment and Diagnosis. The assembled group could craft a framework for a concept. [d]

- **Test various platforms (e.g., immunohistochemistry, mini-chip, quantitative polymerase chain reaction [PCR]) for applying molecular characterization to diagnosis, prognosis, and therapy.** Require diagnostics trials to use molecular techniques through the Program for Assessment of Clinical Cancer Tests (PACCT). PAACT, part of the Cancer Diagnosis Program in the Division of Cancer Treatment and Diagnosis, is addressing issues of marker validation, including assay development. PACCT is establishing the infrastructure to carry out diagnostic trials. A proposed clinical trial in diffuse large B cell lymphoma could serve as a paradigm for other prospective clinical trials. PACCT will emphasize hematopoietic cancers at a future time. [a]

- Reconsider support for the **Tissue Resources for Research initiative**, designed to expand the range of NCI-funded specimen resources and cover all major tumor types. Only multi-institutional organizations or pre-formed consortia would be allowed to apply, and they would be required to provide large numbers of cases (hundreds or thousands, depending on the research focus). The specimens would have to be made available to the research community, and the applicants would be required to propose policies to ensure equitable access. Investigators needing tissue would be required to submit a proposal for a defined study and would agree to deposit data on molecular characterization in a Web site that would make the information available to the larger research community. [c]

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

Introduction

The study and characterization of stem cells will enhance research in all areas of etiology and pathobiology previously mentioned in this plan. Investigations into the production of normal blood cells have played a pivotal role in our understanding of human leukemia. These 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. 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.

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 recently detected human cell populations with 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 they require the commitment of resources to support carefully designed, large-scale, preclinical and translational programs that could effectively combine efforts from multiple centers. The LLM PRG concluded that the creation of a strong, innovative, stem cell research initiative by NCI, with a recognized translational focus, could help define the role of stem cells in both the pathogenesis of human malignancy and its treatment. The PRG said that such a program should include:

- Virtual, interdisciplinary, inter-institutional “stem cell centers” with a mandate to molecularly characterize the normal “stem cell state” and its alteration in leukemia, lymphoma, and myeloma.
- Support of 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.

Ongoing Activities Addressing the Priority

The following initiatives are currently addressing LLM.

Quick-Trials for Novel Cancer Therapies speeds the translation of ideas developed in the laboratory to early-stage clinical trials by simplifying the grant application process and

providing a rapid turnaround from application to funding. Sixteen projects focus on a hematological malignancy.

Clinical Cancer Therapy Research supports grant applications to conduct clinical therapeutic studies and trials. It encompasses a full range of studies employing drugs, biologics, radiation, and surgery. Three funded projects are focused on hematological malignancies.

The **Bone and Marrow Transplant Clinical Research Network,** a joint initiative between NCI and the National Heart, Lung, and Blood Institute (NHLBI), promotes the efficient comparison of novel treatment methods and management strategies for children and adults undergoing blood or marrow transplantation. The objective is to establish and maintain (1) the infrastructure required for a network of up to 20 core clinical centers to perform multiple clinical trials for persons undergoing a hematopoietic stem cell transplant, and (2) a data coordinating center for the network.

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials (See page 16)

Cancer Genome Anatomy Project (See page 16)

Novel Approaches to Enhance Animal Stem Cell Research supports research to enhance stem cells as a model biological system. Research is supported to isolate, characterize, and identify totipotent and multipotent stem cells from nonhuman biomedical research animal models, as well as to generate reagents and techniques to characterize and separate those stem cells from other cell types. Innovative approaches are stressed that make multipotent stem cells available from a variety of nonhuman sources and create reagents that will identify those stem cells across species and separate them from differentiated cell types.

Innovative Toxicology Models for Drug Evaluation Exploratory/Developmental Grants and Phased Innovation Award encourages the development, standardization, and validation of new and innovative assays that determine or predict specific organ toxicities, including hematologic cells.

Innovative Toxicology Models for Drug Evaluation: Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) Initiative encourages the small business community to develop, standardize, and validate new and innovative assays that determine or predict specific organ toxicities, including hematologic cells.

The following initiatives have the potential to address LLM.

Rapid Access to Intervention Development (RAID) moves novel treatment interventions from academic settings into the clinic by making NCI's drug development resources available to investigators testing promising molecules for cancer treatment. Products developed through RAID are returned directly to the originating laboratory for clinical trial testing. RAID currently analyzes the effect of therapies on stem cells.

The **Drug Development Group** prioritizes the use of NCI resources supporting pre-clinical agent development.

NIH is supporting the following initiatives in stem-cell research:

- Stem Cell Plasticity in Hematopoietic and Non-Hematopoietic Tissue
- NINDS and NHLBI Administrative Supplements for Research on Human Embryonic Stem Cells
- Basic Research on Mesenchymal Stem Cell Biology
- Career Enhancement Award for Stem Cell Research
- Stem Cells in Development/Repair of Orofacial Structures

Proposed Strategies to Address Gaps

- **Co-sponsor with NHLBI an RFA on stem cell plasticity in hematopoietic and non-hematopoietic tissues.** Currently, NCI is a co-sponsor with other institutes on various initiatives related to this recommendation. NHLBI, through the Stem Cell Plasticity in Hematopoietic and Non-Hematopoietic Tissue program, has already funded 20 R01 grants in this area. If NHLBI should re-issue this RFA, NCI and other interested institutes may want to co-sponsor it. This issue of stem cell plasticity is at the cutting edge of stem cell research and deserves attention from NCI. With the Juvenile Diabetes Fund International, NCI may co-fund grant applications related to stem cell research, such as those submitted under the Stem Cell Plasticity in Hematopoietic and Non-Hematopoietic Tissue program. [b]

- Explore the possibility of supplements to NHLBI's **Specialized Centers of Research** if NHLBI is interested and the expertise is present. [c]

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Section 2
Research priorities in education, communication, and survivorship research

6 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.

Introduction

Effective health communication can help reduce cancer risk, incidence, morbidity, and mortality, thereby improving 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 at risk for and 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. Moreover, much of the information that does exist has been extrapolated from cross-cutting studies that include few, if any, patients with hematologic malignancies. The time is ripe to identify and develop strategies for providing information to patients to improve medical decisionmaking, quality of care during active treatment and follow-up, and quality of life. The need is especially great for patients with hematological malignancies.

"Much of the available information on communicating with patients does not address the specific circumstances of those affected by hematological malignancies."

- Hematological malignancies affect a diverse patient population in terms of age, sex, and race.
- 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.
- Treatments for hematological malignancies are evolving rapidly because of new scientific discoveries and advances. Recent research shows that hematological malignancies are even more diverse than previously thought and tailoring treatment to the specific disease subtype can ensure that patients receive more effective and less toxic treatments.
- Finally, longer life for LLM survivors creates a need for more information about coping with cancer. This is especially true for the many young LLM patients and for those who are advised to "watch and wait" rather than pursue aggressive treatment.

The LLM PRG recommended that treatment and follow-up care information be up to date, easily accessible, and tailored to the circumstances of the patient.

Ongoing Activities Addressing the Priority

The following initiatives are addressing LLM.

Multimedia Technology/Health Communications Grants for Small Businesses/Nonprofit Organizations supports small businesses and nonprofit organizations that use media technology to facilitate the translation of cancer research into innovative programs, interventions, systems, networks, or products for healthcare professionals or the public. These tools can be used to reduce cancer risk, provide treatment options, or address the needs of cancer survivors. One funded project is a CD-ROM to educate pediatric patients with acute myeloid leukemia (AML) and acute lymphatic leukemia (ALL).

Small Grants Program for Behavioral Research in Cancer Control supports projects that address cancer control behavioral research. Two funded projects focus specifically on hematological malignancies. One focuses on quality of life in central nervous system (CNS) lymphoma patients and the other on steroid effects in pediatric ALL patients.

NCI's Redesigned Web Page provides new search features that will substantially enhance users' ability to retrieve patient information. From the home page, users can access to a great deal of patient information through CancerNet, CancerTrials, and the Cancer Information Service. The latter's publications locator provides easy access to a number of patient-oriented pamphlets and brochures focused on hematological malignancies.

Patterns of Care/Quality of Care Initiative aims to evaluate the dissemination of state-of-the-art therapy into community practice, disseminate findings in scientific journals and professional meetings, and work with professional organizations to develop relevant educational or training opportunities to improve the dissemination of state-of-the-art therapy into community practice. Currently, patterns of care studies in leukemia and multiple myeloma are underway.

The following initiatives have the potential to address LLM.

Making Quality Count for Consumers and Patients is a joint initiative between NCI and the Agency for Healthcare Research and Quality (AHRQ) to support demonstrations that facilitate consumer and patient use of information about quality. These demonstrations develop and test methods and models on quality for consumers and patients to use in healthcare decisions, and evaluate the impact of strategies to provide information about quality to consumers and patients.

Exploratory Grants for Behavioral Research in Cancer Control support developmental and formative behavioral, clinical, and culturally appropriate research approaches in cancer prevention and control. Studies may focus on assessment (instrumentation methods, measurement development), intervention (feasibility of new and innovative approaches, appropriateness for use in populations disproportionately burdened with cancer, or other clinical, organizational, and community settings), dissemination (applications, sustainability), surveillance (inclusion of minority populations, data-based linkage studies to monitor progress toward cancer prevention and control), psychological influences on cancer and the

biobehavioral mechanisms underlying cancer-related behaviors, and exploratory studies and interventions among cancer survivors and germane to survivorship research**.**

Health Communications in Cancer Control may include research on the use of "new media" (interactive digital media) in cancer prevention and control; message development including, but not limited to, their impact on primary and secondary cancer prevention and on cancer-related decisions; and refinement and evaluation of communications systems to deliver cancer control-related information. The program also supports research on cognition, message framing, and risk communication, as well as the development and evaluation of health communications in diverse populations (cultural, ethnic, and economic diversity).

Cancer Communication and Interactive Media Technology promotes and supports collaborations between nonprofit organizations and for-profit small businesses on research projects that address the translation of cancer research into interactive applications designed for specific population groups; the development of organizational infrastructures within healthcare settings or training programs that promote the use of media technologies to enhance communication between primary care professionals, oncologists, and their patients; the development of intervention strategies, tailoring models and tools to better inform the public about cancer prevention and control; or the development of traditional or distance-learning core competencies, training modules, evaluation modules, and tools needed to develop or expand a master's degree program in health communication and media technology.

Testing Interventions to Improve Adherence to Pharmacological Treatment involves 12 NIH institutes, including NCI, to stimulate research on promoting adherence to therapeutic regimens effective in the management of disease.

Centers for Population Health and Health Disparities supports research to expand our understanding of the social and environmental determinants of cancer and the psychosocial, behavioral, and biologic factors that mediate them; develop hypotheses for cancer control research at social, institutional, and policy levels; and develop, apply, and evaluate interventions to improve cancer outcomes and reduce outcome disparities.

Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) studies the impact of recently established, targeted interventions on patient-centered outcomes; investigates the dissemination of state-of-the-science therapies into community practice; examines the influence of modifiable risk factors; and analyzes disparities in the delivery of quality cancer care. This initiative currently focuses on the four most prevalent disease sites (breast, prostate, lung, and colorectal).

Informed Consent in Research Involving Human Participants develops and tests alternative strategies for obtaining informed consent in diverse populations and determines optimal ways to obtain informed consent for research participation. This is a joint initiative between nine NIH institutes (including NCI), the NIH Office of Extramural Research, the U.S. Department of Energy, and the U.S. Department of Veterans Affairs.

Management of Symptoms Secondary to Treatment stimulates research that will lead to improved adherence to treatment regimens and better quality of life by developing and

testing strategies to decrease the negative impact of physical and psychosocial symptoms that are the secondary result of treatment or prevention regimens.

Management of Chronic Pain funds research on the management of chronic pain across the lifespan. Its objectives are to determine the best interventions to remove barriers to effective treatment; determine the most effective pharmacological and non-pharmacological therapies, including complementary and alternative therapies; identify assessment tools for patients unable to verbalize their pain; and identify effective pain management strategies for individuals with disabilities and underserved populations.

Centers of Excellence in Cancer Communications Research support research that will lead to major scientific advances in cancer communications and their translation into practice. These interdisciplinary centers will focus on the advancement of cancer communication science using new and/or improved syntheses, theories, methods, and interventions.

The Clinical Trials Education Series will address the varied educational needs of the public, patient groups, and healthcare professionals about clinical trials. The series includes a basic workbook, a textbook containing an in-depth program, a resource guide for developing specific clinical trial outreach and education activities, and a trainer's guide. This series is available at http://www.cancer.gov/publications.

The **Consumer Advocates in Research and Related Activities (CARRA)** program encourages people affected by cancer to provide their viewpoint and ideas directly to NCI staff so that the Institute can incorporate this perspective into its programs and activities. In addition to participating in NCI activities, CARRA members represent the opinions of their groups and play critical roles as two-way information links between their own communities and constituencies and NCI.

Special Populations Networks for Cancer Awareness Research and Training support the development and implementation of a variety of community-based cancer control and prevention activities. The initiative aims to establish a robust and sustainable infrastructure to promote cancer awareness within minority and medically underserved communities, thereby launching more research and cancer control activities aimed at specific population subgroups.

New Activities to Address Gaps

- The Office of Cancer Survivorship and the Office of Education and Special Initiatives have developed **Facing Forward: Life After Cancer Treatment** and **Making a Difference: Giving Back** survivor series.

Proposed Strategies to Address Gaps

- **Expand the CanCORS initiative to include LLM.** CanCORS will support the conduct of prospective studies in newly diagnosed cohorts of cancer patients to collect information about medical care practices used over the course of patients' disease, various outcomes associated with these practices, and information about patient and provider behaviors and perception. The information will be collected to address three goals reflecting major NCI research priorities:

  - Enhance monitoring and understanding of the process of cancer care and the patient-centered factors influencing prognosis in population-based cohorts of patients;
  - Establish a system for examining the relationship between the processes of care and clinical and patient-centered outcomes; and
  - Examine disparities in the receipt of state-of-the-science cancer care and factors that contribute to disparities in outcome.

  This initiative is being piloted for lung and colorectal patients. An expansion to LLM may be possible once CanCORS has demonstrated success in identifying patterns of care for the cancers currently under study. In the meantime, NCI can fund small studies in the hematological malignancies to establish the basis for a larger study under CanCORS. [c]

- **Promote the Small Grants Program in Behavioral Research in Cancer Control to address the specific circumstances of LLM patients.** This program can fund high-quality applications specifically targeted to the hematologic malignancies. For these grants, investigators may choose any of the full range of scientific approaches to their work. Although many of the research objectives are not applicable to LLM, investigators could focus on the testing of recruitment, intervention, or compliance procedures for participants, health communications message development research, survivorship, or health disparities issues. [d]

- **Target education programs to LLM patients and healthcare providers, and include information on the latest approved therapies, making sure to target minority and underserved populations.** Educational materials produced by the Office of Education and Special Initiatives would be reviewed by LLM patients, families, and survivors. All educational materials would include information directed toward LLM patients and survivors. The updating of existing publications and the development of new ones with specific LLM information would be included. [d]

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

Introduction

The LLM PRG noted that training in the diagnosis, treatment, and study of hematologic malignancies should be a necessary requirement for all physicians who treat patients with these diseases. This is particularly important when treating such potentially curable malignancies as acute leukemias and aggressive lymphomas. However, the hematological malignancies are complex, and their relative infrequency means that many treating physicians have limited experience. Furthermore, most patients are not treated by specialists in hematological malignancies and do not have the opportunity to participate in clinical trials.

"Following the example used for other cancers, hematological malignancies could be treated by limited groups, aligned with cooperative groups, and treated according to state-of-the-art protocols."

Following the example used for other cancers, hematological malignancies could be treated by limited groups, aligned with cooperative groups, and treated according to state-of-the-art protocols. This would provide an opportunity for specialized training, education, and certification in the treatment of these diseases. Developing and implementing a training and certification program for physicians and centers would require the engagement and participation of multiple groups, including academic centers and their training programs, medical societies, clinical cooperative groups, and physicians themselves.

The PRG suggested that NCI play a leading role in organizing 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 the 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.

Ongoing Activities Addressing the Priority

The following initiatives support (or have the potential to support) training in the care and study of patients with hematological malignancies.

Research Training and Career Development Opportunities for predoctoral candidates, postdoctoral candidates, junior faculty in independent research positions, and established investigators. NCI provides a continuum of opportunities as individuals proceed through these four stages of a career track.

The **Cancer Education Grant Program (CEGP)** is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will have an impact on reducing cancer incidence, mortality, and morbidity, as well as on improving the quality of life for cancer patients. The CEGP's education grants focus on education activities before, during, and after the completion of a doctoral-level degree that address a need that is not fulfilled adequately by any other grant mechanism available at NIH and are dedicated to areas of particular concern to the National Cancer Program.

Cancer Centers: Fifty-nine research-oriented institutions throughout the nation have been designated as NCI-supported cancer centers in recognition of their scientific excellence. Cancer centers are hubs of cutting-edge research, high-quality cancer care, and outreach and education for both healthcare professionals and the public.

The **Cancer Disparities Research Partnership** supports grants to initiate and establish priorities for stable, long-term collaborations and partnerships that will strengthen competitive cancer research, research training and career development, education, and outreach capabilities that address problems and issues relevant to the disproportionate cancer incidence and mortality.

The **Human Subjects Protection: Education for the Research Team Online NCI Tutorial** is intended for use by those involved in the design and conduct of research involving human participants, including biomedical and behavioral researchers, nurses, and data managers who are part of the research team. The tutorial presents common concepts, principles, and issues related to the protection of human participants. The tutorial helps researchers identify research activities and understand how to protect the rights and welfare of all human participants involved in research.

Special Populations Networks for Cancer Awareness Research and Training (See page 29)

New Activities Initiated Within the Past Year to Address the Priority

- **"Incorporating clinical trials into your practice"** is a new online program aimed at referring physicians, as well as physicians who are new to clinical trials and who would like to learn some of the practical side to conducting clinical trials in their practices. The program serves as a continuing education course.

Proposed Strategies to Address Gaps

- **Encourage medical societies to convene a meeting to discuss programs in certification.** To facilitate this meeting, NCI will contact the leadership of the American Society of Clinical Oncology, the American Society of Hematology, and the American Board of Internal Medicine to discuss their interest in programs for certification. If they are interested, NCI will encourage and promote a workshop or other vehicle to explore such programs in greater depth. NCI is beginning to implement this strategy. [d]

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Section 2

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

Introduction

"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."

Each year in the United States, an estimated 17,000 patients diagnosed with leukemia, lymphoma, or myeloma survive 5 years after their diagnosis. 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. Some high-priority populations include survivors treated with chest irradiation, exposed to anthracyclines, treated with bone marrow and stem cell transplants, or exposed to alkylating agents or topoisomerase II inhibitors. However, outcomes are unknown for many populations, including:

- Patients treated with novel therapies,
- Patients with unique genetic susceptibility traits, and
- People for whom extended periods have elapsed since treatment.

Furthermore, limited information is available regarding the impact of pre- and post-therapy health behaviors (e.g., smoking and diet).

Long-term–outcome 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 such selection influences 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. The establishment of an effective, collaborative network of clinical centers to conduct high-quality, clinically based research would allow protocol-driven clinical investigations to be carried out. This network could address the high-priority questions relating to the occurrence of adverse treatment-related outcomes among LLM survivors.

The LLM PRG recommended investments in each of three distinct areas:

- Identification and characterization of high-risk populations,
- Definition of the biological basis of identified associations, and
- Design and testing of innovative intervention and prevention strategies.

Ongoing Activities Addressing the Priority

The following networks, consortia, and groups are currently addressing outcomes in LLM patients.

The **Case-Control Consortium** has assembled a large number of hematologic malignancy cases with available biospecimens and detailed data on relevant exposures. Two groups of investigators in the consortium are using the case-control approach to identify genetic and environmental determinants of non-Hodgkin's lymphoma.

The **Clinical Trials Cooperative Groups** are a national network of 12 consortia organized to test potential treatment advances in patients more rapidly. Each year, 8,000 investigators in 1,700 institutions throughout the United States and Canada participate in these trials. Several intergroup trials are ongoing in adult leukemia and lymphoma.

Specialized Programs of Research Excellence (SPOREs) support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal). The SPORE program will be expanded to include LLM research.

The following initiatives have the potential to address outcomes in patients with hematological malignancies.

Special Populations Networks for Cancer Awareness Research and Training support the development and implementation of a variety of community-based cancer control and prevention activities. The initiative aims to establish a robust and sustainable infrastructure to promote cancer awareness within minority and medically underserved communities, thereby launching more research and cancer control activities aimed at specific population subgroups.

The **Cancer Genetics Network** supports collaborative investigations into the genetic basis of cancer susceptibility; explores mechanisms to integrate this new knowledge into medical practice; and identifies means of addressing the associated psychosocial, ethical, legal, and public health issues.

The **Cohort Consortium** consists of investigators from 15 ongoing prospective studies of large population groups. The investigators are pooling their existing resources of high-quality exposure data and biological specimens suitable for genetic analysis for a combined total of 700,000 study participants.

Cancer Surveillance Using Health Claims-Based Data Systems supports research entailing the use of health claims data for cancer surveillance, including cancer detection, treatment, and outcomes. Health claims include secondary data sources such as the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data; fee-for-service insurance bills for medical, rehabilitative, or other healthcare services; managed care encounter data; databases with multiple payers, such as the Healthcare Cost and Utilization Project database; and discharge summaries.

Long-Term Cancer Survivors: Research Initiatives supports projects focused on the incidence and scope of the effects of cancer and its treatment on survivors, as well as their relationship to treatment. Where appropriate, proposals to test interventions and the timing of interventions are supported to reduce the persistent and late physiological, psychosocial, and economic morbidity and to enhance the potential for both length and quality of survival from cancer and cancer therapy.

The **Centers for Mind/Body Interaction and Health** encourage behavioral, psychological, social, and biomedical research on the interrelationships among cognition, emotion, biological processes, and physical health. NCI is particularly interested in stimulating research with cancer patients and survivors that examines interactions among psychological factors; immune, neuroendocrine, genetic, and other potential biological mediators; and disease-related outcomes.

New Activities Initiated Within the Past Year to Address Gaps

- NCI is issuing a Request for Proposals (RFP) for **Multiple Myeloma Prevention Study**. This RFP is for a Phase IIb double-blind, placebo-controlled study of an NSAID (non-selective or selective agent) administered for the modulation of biomarkers associated with MGUS/smoldering myeloma. The lead program is the Division of Cancer Prevention.

Proposed Strategies to Address Gaps

- **Fund 2-year supplements to cancer centers to develop pilot data in the hematological malignancies so that investigators can apply for R01 or other, longer term funding.** Permit NCI-designated cancer centers to apply for developmental funds for innovative pilot research projects that focus on identifying individuals at high risk for adverse, long-term outcomes. This initiative aims to stimulate high-quality, innovative pilot research based on solid science in priority research areas articulated by the LLM PRG for survivorship outcomes. This initiative would provide pilot study support for new or established investigators as a supplement to a core cancer center grant. All LLM patients who have completed initial treatment would be eligible to participate in the study. Large, demographically diverse, and heterogeneous (vis-à-vis disease characteristics and treatment exposures) samples would be particularly encouraged. Furthermore, investigators would be asked to focus on well-defined outcomes and to combine self-report or clinical data with biological samples that would permit an examination of the biological bases of observed associations. This would be a substrate for a registry. [b]

- **Initiate a collaborative effort spanning several SPOREs or cancer centers to develop LLM cohorts.** Enroll and follow patients from cancer treatment trials to determine the incidence and predictors of long-term outcomes after LLM malignancy. Long-term survivor studies can provide information about additional malignant and benign outcomes of the interacting factors responsible for LLM malignancy. [c]

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Section 3
Research Priorities in Drug Development and Therapeutics

9 Foster partnerships between the NCI and academia, advocates, cooperative groups, U.S. Food and Drug Administration (FDA), and industry to expedite drug development and the availability of therapies.

Introduction

There is a widely recognized need to expedite the clinical development and regulatory approval of new therapies. In 1996–1998, this process took an average of 5.9 years across all therapeutic areas. Although this time represents an 18-percent decrease from 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."

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

Various stakeholders are directly involved in the process of developing new cancer therapies: NCI, the U.S. Food and Drug Administration (FDA), academia, patient advocacy organizations, the pharmaceutical industry, and NCI-funded cooperative clinical trials groups. The PRG noted that currently, insufficient coordination among these groups makes the entire process inefficient in the following ways:

- The NCI cooperative groups move slowly.
- Clinical trial designs often fail to meet the needs of the pharmaceutical industry, because they do not lead to drug approval.
- Study implementation should follow an expedited timeline.
- Patient enrollment can and must be enhanced.
- Study completion and reporting takes too long.

In addition, the FDA must reduce review and approval timelines in a realistic fashion. The review process requires months, prohibiting a promising new therapy from benefiting patients who do not have the time to wait.

The LLM PRG recommended that NCI take the initiative in developing effective partnerships among these groups. It is critical for this partnership to be inclusive, with all

partners being equally informed, possessing equal rights, developing a consensus strategy, working toward common goals, and participating with a voice and a vote in all committees and meetings.

Ongoing Activities Addressing the Priority

The following activities are currently addressing LLM.

The **Cancer Trials Support Unit** is a pilot project to support a national network of physicians and patients participating in NCI-sponsored phase III cancer treatment trials. The pilot project focuses on phase III trials in the adult population for leukemia and for genitourinary, lung, breast, and gastrointestinal cancers.

The **Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses** enables small businesses to bring their innovative efforts for drug discovery and development to clinical evaluation. Two funded applications focus on hematological malignancies.

The **Bone and Marrow Transplant Clinical Research Network,** a joint initiative between NCI and the National Heart, Lung, and Blood Institute, supports a network to promote the efficient comparison of novel treatment methods and management strategies for children and adults undergoing blood or marrow transplantation. This initiative aims to establish and maintain the infrastructure required for a network of up to 20 core clinical centers to perform multiple clinical trials for persons undergoing a hematopoietic stem cell transplant, as well as a data coordinating center for the network.

The **Chronic Lymphocytic Leukemia (CLL) Research Consortium** is a multi-institutional research program to study CLL in an entirely new way. The consortium brings together the nation's top scientists from different disciplines to conduct an integrated program of basic and clinical research focused on a single disease. Nine institutions are engaged in six research projects—five are laboratory based and the sixth is a multicenter clinical program conducting clinical trials of promising new agents.

The following activities have the potential to address LLM.

The **Rapid Access to Prevention Intervention Development (RAPID)** program makes available to academic investigators the preclinical and early clinical drug development contract resources of NCI's Division of Cancer Prevention.

Rapid Access to NCI Discovery Resources (R*A*N*D) provides NCI resources for the discovery and early preclinical development of anticancer drugs and biologics.

Rapid Access to Intervention Development (RAID) moves novel treatment interventions from academic settings into the clinic by making NCI's drug development resources available to investigators testing promising molecules for cancer treatment. Products developed through RAID are returned directly to the originating laboratory for clinical trial testing.

Cancer Clinical Trials: A New National System for the development, review, conduct, and support of cancer clinical trials has started. Several pilot projects are underway, and several more will soon be launched. NCI's efforts to build the new clinical trials system fall into five categories: generating new ideas, broadening access for physicians and patients, educating and communicating, streamlining procedures, and automating data systems.

Special Populations Networks for Cancer Awareness Research and Training supports the development and implementation of a variety of community-based cancer control and prevention activities. Cancer awareness activities appropriate for this project include health fairs, lectures to community groups, healthy cooking workshops, campaigns to encourage cancer screening, and the establishment of survivor support groups targeted within minority and medically underserved communities.

Cancer Disparities Research Partnership supports grants to initiate and establish priorities for stable, long-term collaborations and partnerships that will strengthen competitive cancer research, research training and career development, education, and outreach capabilities that address problems and issues relevant to the disproportionate cancer incidence and mortality.

Activities to Promote Research Collaborations provide supplements to existing research projects for collaborative activities that bring together ideas and approaches from disparate scientific disciplines. Collaborative activities include, but are not limited to, initiating new collaborative research projects, sharing resources and reagents, developing novel technologies, and organizing cross-disciplinary meetings/workshops.

The **Cancer Therapy Evaluation Program (CTEP)** currently holds monthly, informal meetings with the FDA to discuss pertinent issues on drug development, interacts with individual pharmaceutical and biotechnology companies and negotiates cooperative research and development agreements and clinical trial agreements with them, manages the National Clinical Trials Cooperative Groups, and is redesigning the National Clinical Trials System to eliminate inefficiencies. The redesign includes establishing a central institutional review board, which requires close collaboration with the Office of Human Research Protection and the Department of Health and Human Services. CTEP is intimately involved in the design and monitoring of the clinical trials performed by the Clinical Trials Cooperative Groups and has involved patient advocates in the review of these protocols. The Division of Cancer Treatment and Diagnosis staff has also worked diligently to expand insurance coverage for clinical trials.

Proposed Strategies to Address Gaps

- **Scale RAID, R*A*N*D, and RAPID according to need, merit, and available budget.** The scaling up of RAID, R*A*N*D, and RAPID could be achieved if the necessary funds for the contract are available. These initiatives are competitive, and the agents are not chosen on a disease-specific basis. [a]

- **Foster partnerships with other NIH institutes and private, nonprofit entities to support drug or biologics development.** Continue to try to leverage resources by cosponsoring or cofunding various initiatives in drug and biologics development with other NIH institutes. The Juvenile Diabetes Foundation International (JDFI) has approached NCI to collaborate on stem cell research as well as on drug and biologics development. Several drugs used to treat diabetes appear to have anticancer activity. The JDFI is willing to cofund research applications with NCI as they currently do with the National Institute of Allergy and Infectious Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases. [a]

- **Expand NCI's efforts in fostering partnerships by providing an open forum for stakeholders to discuss broad issues (such as policy) and barriers to drug approval.** This forum can meet once or twice per year. [d]

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10 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 U.S. Food and Drug Administration (FDA) approval.

Introduction

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 modern research, major resources are focused on rational drug development, and intense efforts are expended to define important molecular targets for therapeutics. 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.

"The identification of "lead" compounds that interact with an appropriate molecular target must be followed by the optimization of its chemical structure and formulation. This optimization process requires collaboration between scientists in preclinical biology and chemistry; medicinal, pharmaceutical, and formulation chemists; pharmacologists; and toxicologists."

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, NCI has roughly 300 treatment-related trials in both leukemia and lymphoma and about 130 in myeloma. Moreover, NCI has played a key role in drug discovery and development for 50 years. In the past few years, NCI has developed two new programs that will further facilitate therapeutic research by talented scientists. The Rapid Access to New Drug Discovery (R*A*N*D) and the Rapid Access to Intervention Development (RAID) programs have provided resources for both discovery and developmental tasks in hastening new agents to the clinic.

These new initiatives facilitate access to government resources for therapeutic research. However, more work is desperately needed if the promise of rational therapeutics is to be fully realized. Continued NCI support for preclinical research is also essential. Because of the extensive investments required to define promising molecular targets or support clinical trials, the therapeutic agents that are tested must be optimal ones. The identification of "lead" compounds that interact with an appropriate molecular target must be followed by the optimization of its chemical structure and formulation. This optimization process requires collaboration between scientists in preclinical biology and chemistry; medicinal, pharmaceutical, and formulation chemists; pharmacologists; and toxicologists. More

resources must be directed toward the scientists who design and discover new therapeutic agents.

Ongoing Activities Addressing the Priority

(NCI initiatives focusing specifically on the development of new diagnostics are not included in this list.)

The following activities are addressing LLM.

The **Interdisciplinary Research Teams for Molecular Target Assessment** program supports teams developing methods to evaluate interventions directed at specific molecular targets associated with the cancer phenotype. One funded project is examining survival targets in a hematological malignancy.

Molecular Target Drug Discovery for Cancer supports the discovery and validation of molecular targets that can be developed into drug discovery assays. One project is studying FLT3 as a target for treating leukemia, and another is examining small molecule inhibitors of Bcl-X_L.

The **Quick-Trials for Novel Cancer Therapies** program speeds the translation of ideas developed in the laboratory to early-stage clinical trials by simplifying the grant application process and providing a rapid turnaround from application to funding. Sixteen funded applications focus on a hematological malignancy.

Cancer Drug Discovery: Diversity Generation and Smart Assays supports innovative approaches to the generation of structural diversity (such as combinatorial synthesis, parallel synthesis, or genetic manipulation of biosynthetic pathways in producer organisms) and smart assay development for cancer drug discovery. One funded project focuses on a hematological malignancy.

Cancer Trials Support Unit (See page 39)

Flexible System to Advance Innovative Research for Cancer Drug Discovery By Small Businesses (See page 39)

Rapid Access to Intervention Development (RAID) (See page 39)

Early Therapeutics Development with a Phase II Emphasis provides a resource for the conduct of phase II and early clinical trials of NCI-sponsored agents. This resource can also be used to evaluate biologic effects of these agents on their molecular targets, to evaluate other relevant biologic effects, and to determine clinically relevant outcomes and correlates. Major emphasis is on phase II studies, pilot protocols that explore promising combination therapies, and high-priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting.

The **Development and Application of Imaging in Therapeutic Studies** enable the integration and exploitation, in clinical and preclinical settings, of imaging techniques in the assessment of therapeutic agent development. Projects may address the development and

application of labeled therapeutic agents as compounds for imaging studies, or they may facilitate the development and application of imaging agents as metabolic markers of response to newly developed therapeutic agents.

The **Clinical Trials Cooperative Groups** are a national network of 12 consortia organized to test potential treatment advances in patients more rapidly. Each year, approximately 8,000 investigators in 1,700 institutions throughout the United States and Canada participate in these trials. Several intergroup trials are ongoing in adult leukemia and lymphoma.

The **Mouse Models of Human Cancer Consortium** derives or refines accurate, cancer-prone models of human malignancies; provides a comprehensive analysis of their phenotype and genotype; validates them for their use by the cancer research community for a variety of investigations (such as testing therapeutic, prevention, early detection, or imaging strategies); and ensures their availability to the research community. Several available and newly accepted strains are lymphoma models.

The **Clinical Cancer Therapy Research** program conducts clinical therapeutic studies and trials in humans. It encompasses a full range of studies employing drugs, biologics, radiation, and surgery. Three funded projects focus on hematological malignancies.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials foster collaborations and interactions among basic researchers, private industry, and clinical investigators to perform translational research on promising predictive and prognostic markers. The markers should be assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. Nine funded projects are examining different types of leukemia.

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials promote translational and clinical research by supporting new therapeutic clinical trials or new correlative studies relevant to therapeutic clinical trials. Sixteen trials focus on a hematological malignancy.

The **Community Clinical Oncology Program (CCOP)** is a network of 49 central offices in 31 states that provides the infrastructure to link more than 2,500 community cancer specialists and primary care physicians with clinical cooperative groups and cancer centers. Combining the expertise of community physicians and other healthcare professionals with NCI-approved cancer treatment and prevention and control clinical trials provides the opportunity for the transfer of the latest research findings to the community level. The CCOP is evaluating a number of therapeutics aimed at reducing the symptoms of hematological malignancies and the side effects of their treatment. It is also evaluating drugs for the prevention of second cancers.

The following activities have the potential to address LLM.

Molecular Targets Laboratories (MTLs) are developing a resource of biological assays and chemical probes for biological studies of cancer. The MTLs will emphasize the need for collaboration between chemists and biologists in an effort to produce libraries of potential anticancer compounds for public distribution, develop screening assays suitable for high-

throughput screening for potential agents, and confirm a drug's initial ability to alter the drug target in cancer cells.

Innovative Toxicology Models for Drug Evaluation supports new and innovative assays to determine specific organ toxicities of potential cancer therapeutic agents.

Phase I Trials of Anti-Cancer Agents provides funding to assess novel agents available through NCI in early clinical, dose-finding trials. This initiative primarily aims for the timely completion of trials of promising anticancer agents and combinations of agents to establish safe and biologically active treatment schedules for patients with cancer and to establish proof of principle for new agents directed at novel molecular targets.

Proposed Strategies to Address Gaps

- **Convene a meeting of leaders from academia, industry, and government to examine models for establishing public-private partnerships for drug discovery.** The group will look at a model from the National Science Foundation and the Industry/University Cooperative Research Centers, as well as the proposed Cancer Translational Research Allied Consortium (C-TRAC) model. From these models and other information shared at the meeting, the group will create a framework for funding novel partnerships to expedite cancer drug development. Once a concept is developed and approved, planning grant support would be offered for potential partnerships. Successful planning grant applicants could then apply for center grants if they have the appropriate private sponsorship. [a]

See Section 4 for details on this new initiative.

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Section 4
A New Initiative

11 The Cancer Translational Research Allied Consortium (C-TRAC).

Introduction

A number of the research priorities outlined by the LLM PRG 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. 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.

"The identification and validation of potential molecular targets has just begun and, more importantly, the therapeutic translation of these targets lags far behind our knowledge of the molecular basis of hematological malignancies."

The identification and validation of potential molecular targets has just begun and, more importantly, the therapeutic translation of these targets lags far behind our knowledge of the molecular basis of hematological malignancies. 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.

General aims of C-TRAC are:

- Development of capability of rapid identification and development of new therapies in hematological malignancies;
- Identification and validation of biomarkers in specific diseases and pilot developmental diagnostics;
- Establishment of a drug discovery and a development core facility that will create and evaluate new standards in partnership with government and industry;
- Development of new phase I and II clinical trial models; and
- Support for standardized, interactive bioinformatics platforms and bioinformatics training, as well as training in proteomics, functional genomics, and translational research.

C-TRAC includes credentialing of targets in animals, validation of surrogate endpoints for markers, development of a therapeutic strategy, and proof of targeting. It is intended to be a government-university-industry collaboration, because each of these partners has unique strengths. C-TRAC will pull together the components that already exist within NCI and elsewhere to help speed the process along.

C-TRAC will support multiple institutions with phase I and II clinical trial capabilities to conduct basic, translational, and outcomes research. Core facilities include:

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

A project management team would be responsible for allocating human and fiscal resources, selecting and prioritizing projects, creating modules and finding expertise quickly, defining benchmarks, and ensuring accountability and progress. Informatics, Web sites, and virtual meetings will be critical to this endeavor.

Ongoing Activities Addressing the Priority

No NCI initiative addresses this recommendation in its entirety, but the following initiatives may contribute to any future effort by NCI.

Specialized Programs of Research Excellence (SPOREs) support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal). The SPORE program will be expanded to include LLM research.

Cancer Centers: Fifty-nine research-oriented institutions throughout the nation have been designated as NCI-supported cancer centers in recognition of their scientific excellence. Cancer centers are hubs of cutting-edge research, high-quality cancer care, and outreach and education for both healthcare professionals and the public

Proposed Strategies to Address Gaps

- **Convene a meeting of leaders from academia, industry, and government to examine models for establishing public-private partnerships for drug discovery**. The group will look at a model from the National Science Foundation and the Industry/University Cooperative Research Centers, as well as the proposed C-TRAC model. From these models and other information shared at the meeting, the group will create a framework for funding novel partnerships to expedite cancer drug development. Once a concept is developed and approved, planning grant support would be offered for potential partnerships. Successful planning grant applicants could then apply for center grants if they have the appropriate private sponsorship. [a]

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Appendix A
Roster of Leukemia, Lymphoma, and Myeloma Working Group

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Division of Cancer Control
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Appendix B
Table of Ongoing and New Activities and Proposed Strategies

Recommendation 1 Understand the interaction among genotype, immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to hematopoietic malignancy.	
Ongoing Activities	**Page**
Case-Control Consortium	12
Clinical Trials Cooperative Groups	12
Pharmacogenetics Research Network	12
Cohort Consortium	12
Interdisciplinary Studies in the Genetic Epidemiology of Cancer	13
Diet, Lifestyle, and Cancer in U.S. Special Populations	13
The Centers for Population Health and Cancer	13
Proposed Strategies	
Expand cohort studies investigating the etiology of leukemia, lymphoma, and myeloma (LLM) to include more minority (non-Caucasian) and underserved populations.[c]	13
Expand the Cohort Consortium to include hematological malignancies and include larger and younger populations in this effort.[c]	13
Contribute resources to the Case-Control Consortium for parallel and joint studies of hematologic malignancies.[b]	14

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Recommendation 2 Identify the basic mechanisms responsible for genome instability, chromosome translocations, and other mutations in hematological malignancies.	
Ongoing Activities	**Page**
Applications of Innovative Technologies for the Molecular Analysis of Cancer	15
Exploratory Grants for Correlative Laboratory Studies and Clinical Trials	15
In Vivo Cellular and Molecular Imaging Centers	15
Advanced Technology Center	16
Cancer Genome Anatomy Project	16
The Mouse Models of Human Cancer Consortium	16
Proposed Strategies	
Support expansion of Activities to Promote Research Collaborations and R21 mechanisms for collaborations between investigators seeking new prevention, diagnosis, and treatment tools and investigators who have innovative ideas for connecting what is known about basic mechanisms.[c]	16

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Recommendation 3 Define the relationship between the development of hematological malignancies and the host biological environment.	
Ongoing Activities	**Page**
Exploratory Grants for Correlative Laboratory Studies and Clinical Trials	17 (15)
Innovative Technologies for the Molecular Analysis of Cancer	18 (15)
Applications of Innovative Technologies for the Molecular Analysis of Cancer	18
The Mouse Models of Human Cancer Consortium	18 (16)
Molecular and Cellular Biology of Metastatic Tumor Cells	18
New Activities	
The tumor microenvironment has been incorporated into the Bypass Budget as an Extraordinary Opportunity area for NCI.	18
A new request for applications, "Molecular Interactions Between Tumor Cells and Bone."	18
In September 2002, the Division of Cancer Biology hosted a workshop on "Hematologic Malignancies and the Marrow Microenvironment."	18

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Recommendation 4 **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.**	
Ongoing Activities	**Page**
Cancer Genome Anatomy Project	20
Director's Challenge: Toward a Molecular Classification of Tumor	20
Innovative Technologies for the Molecular Analysis of Cancer	20
The Advanced Technology Center	20
Applications of Innovative Technologies for the Molecular Analysis of Cancer	20
Pharmacogenetics Research Network	20
The Tissue Array Research Program	20
Interdisciplinary Research Teams for Molecular Target Assessment	20
Molecular Target Drug Discovery for Cancer	20
Non-Mammalian Organisms as Models for Anti-Cancer Drug Discovery	20
Cancer Prevention Research Small Grant Program	20
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	21
In Vivo Cellular and Molecular Imaging Centers	21
Exploratory Grants for Correlative Laboratory Studies and Clinical Trials	21
Translation of Technologies to Detect Alterations in Human Tumors	21
Clinical Proteomics Program	21
Molecular and Cellular Biology of Metastatic Tumor Cells	21
Molecular Targets Laboratories	21
Phased Application Awards in Cancer Prognosis and Prediction	21
New Activities	
The Cancer Therapy Evaluation Program hosted a state-of-the-science meeting on "Myelodyaspastic Syndromes and Acute Myeloid Leukemia."	21

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Recommendation 4 **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. (*continued)***	
Proposed Strategies	**Page**
Hold a workshop or consensus conference to determine the most promising targets for prevention of, or therapy for, LLM and develop a program announcement to address the prioritized list of targets.[a]	22
Test various platforms (e.g., immunohistochemistry, mini-chip, quantitative polymerase chain reaction) for applying molecular characterization to diagnosis, prognosis, and therapy.[a]	22
Fund the Tissue Resources for Research initiative.[b]	22

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Recommendation 5 **Further develop research on stem cells, both multi-lineage and single lineage.**	
Ongoing Activities	**Page**
Quick-Trials for Novel Cancer Therapies	23
Clinical Cancer Therapy Research	24
The Bone and Marrow Transplant Clinical Research Network	24
Exploratory Grants for Correlative Laboratory Studies and Clinical Trials	24
Cancer Genome Anatomy Project	24
Novel Approaches to Enhance Animal Stem Cell Research	24
Innovative Toxicology Models for Drug Evaluation Exploratory/ Developmental Grants and Phased Innovation Award	24
Innovative Toxicology Models for Drug Evaluation: Small Business Innovation Research/Small Business Technology Transfer Initiative	24
Rapid Access to Intervention Development (RAID)	25
Drug Development Group	25
Proposed Strategies	
NCI should cosponsor with the National Heart, Lung, and Blood Institute (NHLBI) a request for applications on stem cell plasticity in hematopoietic and non-hematopoietic tissues.[b]	25
NCI may explore the possibility of supplements to NHLBI's Specialized Centers of Research.[c]	25

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Recommendation 6 **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.**	
Ongoing Activities	**Page**
Multimedia Technology/Health Communications Grants for Small Businesses/Non-Profit Organizations	27
Small Grants Program for Behavioral Research in Cancer Control	27
NCI's Redesigned Web Page	27
Patterns of Care/Quality of Care	27
Making Quality Count for Consumers and Patients	27
Exploratory Grants for Behavioral Research in Cancer Control	27
Health Communications in Cancer Control	28
Cancer Communication and Interactive Media Technology	28
Testing Interventions to Improve Adherence to Pharmacological Treatment	28
Centers for Population Health and Cancer	28
Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)	28
Informed Consent in Research Involving Human Participants	28
Management of Symptoms Secondary to Treatment	29
Management of Chronic Pain	29
Centers of Excellence in Cancer Communications Research	29
The Clinical Trials Education Series	29
Consumer Advocates in Research and Related Activities	29
Special Populations Networks for Cancer Awareness Research and Training	29
New Activities	
"Facing Forward: Life After Cancer Treatment" and "Making a Difference: Giving Back" survivor series.	29

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Recommendation 6 **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. (*continued*).**	
Proposed Strategies	**Page**
Expand the CanCORS initiative to include LLM.[c]	30
Promote the Small Grants Program in Behavioral Research in Cancer Control to address the specific circumstances of LLM patients.[d]	30
Target education programs to LLM patients and health care providers, and include information on the latest approved therapies, making sure to target minority and underserved populations.[d]	30
Recommendation 7 **Develop education and training programs for certification of physicians and centers for diagnosis, treatment, and clinical trials in hematological malignancies.**	
Ongoing Activities	**Page**
Research Training and Career Development Opportunities	31
The Cancer Education Grant Program	32
Cancer Centers	32
Cancer Disparities Research Partnership	32
The Human Subjects Protection: Education for the Research Team Online NCI Tutorial	32
Special Populations Networks for Cancer Awareness Research and Training	32
New Activities	
"Incorporating clinical trials into your practice" is a new online program aimed at referring physicians, as well as physicians who are new to clinical trials and who would like to learn some of the practical side to conducting clinical trials in their practices.	32
Proposed Strategies	
NCI will encourage medical societies to convene a meeting to discuss programs in certification.[d]	33

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[d] NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

Recommendation 8 **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.**	
Ongoing Activities	**Page**
Case-Control Consortium	35
Clinical Trials Cooperative Groups	35
Specialized Programs of Research Excellence (SPOREs)	35
Special Populations Networks for Cancer Awareness Research and Training	35
Cancer Genetics Network	35
Cohort Consortium	35
Cancer Surveillance Using Health Claims-Based Data Systems	36
Long-Term Cancer Survivors: Research Initiatives	36
Centers for Mind/Body Interaction and Health	36
New Activities	
Multiple Myeloma Prevention Study	36
Proposed Strategies	
Fund 2-year supplements to cancer centers to develop pilot data in the hematological malignancies so that investigators can apply for R01 or other, longer term funding.[b]	36
Initiate a collaborative effort spanning several SPOREs or cancer centers to develop LLM cohorts.[c]	37

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Recommendation 9 **Foster partnerships between the NCI and academia, advocates, cooperative groups, U.S. Food and Drug Administration (FDA), and industry to expedite drug development and availability of therapies.**	
Ongoing Activities	**Page**
The Cancer Trials Support Unit	39
Flexible System to Advance Innovative Research for Cancer Drug Discovery By Small Businesses	39
The Bone and Marrow Transplant Clinical Research Network	39
The Chronic Lymphocytic Leukemia Research Consortium	39
Rapid Access to Prevention Intervention Development (RAPID)	39
Rapid Access to NCI Discovery Resources (R*A*N*D)	39
Rapid Access to Intervention Development (RAID)	39
Cancer Clinical Trials: A New National System	40
Special Populations Networks for Cancer Awareness Research and Training	40
Cancer Disparities Research Partnership	40
Activities to Promote Research Collaborations	40
Cancer Therapy Evaluation Program	40
Proposed Strategies	
Scale RAID, R*A*N*D, and RAPID according to need, merit, and available budget.[a]	41
Foster partnerships with other NIH institutes and private, non-profit entities to support drug or biologics development.[a]	41
Expand NCI's efforts in fostering partnerships by providing an open forum for stakeholders to discuss broad issues (such as policy) and barriers to drug approval.[d]	41

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Recommendation 10 **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 U.S. Food and Drug Administration (FDA) approval.**	
Ongoing Activities	**Page**
Interdisciplinary Research Teams for Molecular Target Assessment	43
Molecular Target Drug Discovery for Cancer	43
The Quick-Trials for Novel Cancer Therapies	43
Cancer Drug Discovery: Diversity Generation and Smart Assays	43
The Cancer Trials Support Unit	43
Flexible System to Advance Innovative Research for Cancer Drug Discovery By Small Businesses	43
Rapid Access to Intervention Development	43
Early Therapeutics Development with a Phase II Emphasis	43
The Development and Application of Imaging in Therapeutic Studies	43
The Clinical Trials Cooperative Groups	44
The Mouse Models of Human Cancer Consortium	44
Clinical Cancer Therapy Research	44
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	44
Exploratory Grants for Correlative Laboratory Studies and Clinical Trials	44
Community Clinical Oncology Program	44
Molecular Targets Laboratories	44
Innovative Toxicology Models for Drug Evaluation	45
Phase I Trials of Anti-Cancer Agents	45
Proposed Strategies	
Convene a meeting of leaders from academia, industry, and government to examine models for establishing public-private partnerships for drug discovery. Develop a concept to fund drug development centers.[a]	45

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Recommendation 11 The Cancer Translational Research Allied Consortium	
Ongoing Activities	**Page**
Specialized Programs of Research Excellence	47
Cancer Centers	47
Proposed Strategies	
Convene a meeting of leaders from academia, industry, and government to examine models for establishing public-private partnerships for drug discovery. Develop a concept to fund drug development centers.[a]	47

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