Report of the
Sarcoma Progress Review Group
A Roadmap for Sarcoma Research
January 2004

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute


SARCOMA PRG RECOMMENDATIONS
Develop sarcoma-specific animal model systems
Create a dedicated, sarcoma-specific organizational structure (Sarcoma Research Consortium) to serve as a focal point for sarcoma clinical trials and related clinical- and laboratory-based research, and to enhance networks of investigators and centers committed to sarcoma research
Develop toolkit of core reagents and access to technology platforms
Design prospective clinical trials of early surrogate (intermediate) markers
Fund and foster focused research on key areas of sarcoma biology
Fund/foster comprehensive approaches to sarcoma profiling and target discovery

FROM THE LEADERSHIP

We are pleased to submit this report to the Director of the National Cancer Institute (NCI), and to the Advisory Committee to the Director. The Sarcoma Progress Review Group (PRG) accepted the charge to develop a roadmap for the next 5 years of sarcoma research. This report represents the collaborative effort of scientists, clinicians, industry representatives, patient advocates, and other professionals who participated in the Sarcoma PRG Roundtable Meeting October 8-10, 2003. We look forward to discussing these priorities and the plan for their implementation with the leadership of the NCI.

We the undersigned members of the Sarcoma Progress Review Group concur with the enclosed report.

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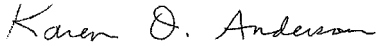

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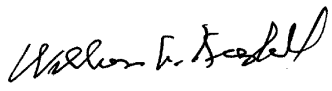

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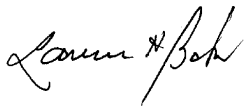

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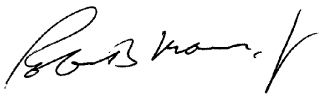

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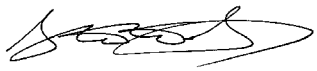

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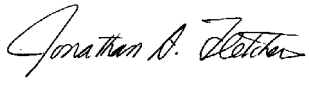

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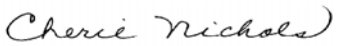

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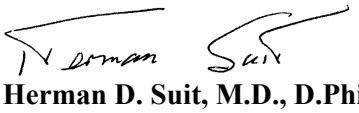

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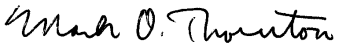

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ACKNOWLEDGMENTS

This report is the product of months of intense work and drew on the combined expertise and efforts of many individuals. The Sarcoma PRG particularly acknowledges the contributions of the following groups:

- The many scientists, clinicians, advocates, and other professionals who generously gave of their time and knowledge. Without their participation, this report would not have been possible. In particular, the 112 participants in our Sarcoma PRG Roundtable Meeting, including the individuals who served, along with PRG members, as Co-Chairs of our Roundtable Breakout Groups.
- The staff of the NCI Office of Science Planning and Assessment, under the leadership of Cherie Nichols, who provided ongoing guidance and technical support throughout the process of preparing this report. In particular, we acknowledge the hard work and dedication of Margaret Ames, who coordinated the full PRG process, as well as James Corrigan, Kevin Callahan, Stephanie Glezos Bell, Marilyn Duncan, DJ Joya, Annabelle Uy, Deborah Duran, and Julie Schneider.
- The staff of Science Applications International Corporation (SAIC) and the science writers who assisted in logistics, documentation, and report preparation. We thank Beth Mathews-Bradshaw for overall support; Nancy Volkers for serving as lead writer; Eric Levine and Glenn Bell for preparing of resource material; Catherine Kappel Hall for managing SAIC work; Rob Watson and Mary Ann Wood for conference support; and Debby Berlyne, Elaine Berry, Gregory Cole, Laura Janusik, Anita Sabourin, Maneesha Solanki, and Jeffrey Zalatoris for serving as science writers.

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THE CHALLENGES OF SARCOMA

Sarcomas comprise about 1 percent of adult and 15 percent of pediatric malignancies. It is estimated that in 2003, about 11,700 Americans were diagnosed with sarcoma and 5,200 died from the disease.[1] However, these figures are probably underestimates, and the number of Americans with each sarcoma subtype is unknown.

Current diagnostic coding systems categorize cancers by location and therefore make identification of sarcomas difficult. For example, physicians once viewed gastrointestinal stromal tumor (GIST) as one of the rarer subtypes of sarcoma. However, in a recent review of 1,500 intra-abdominal tumors for a genetic marker for GIST, researchers discovered 400 cases, of which only 100 had been diagnosed as GIST. (The other 300 had been diagnosed as other sarcoma subtypes.)

Diagnosis is delayed in many patients by the lack of experience of primary physicians, who often attribute the initial mass to common benign lesions. Once diagnosed, patients cannot rely on a uniform standard of care, resulting in wide variations in care and outcomes. New therapies are desperately needed, but the fragmentation of biological, translational, and clinical research makes it difficult to initiate innovative and timely studies.

Generally, a disease of younger adults and children, sarcoma's mortality rate is disproportionately high compared with other cancers common in these age groups, such as testicular cancer and Hodgkin's disease.

Several germline mutations confer a risk of sarcoma. High-risk groups include families with hereditary retinoblastoma, Li-Fraumeni syndrome, Werner's syndrome, neurofibromatosis, and other conditions. The downstream effects of these genes and the mechanism(s) of malignant transformation remain largely unknown. The tissue of origin for many sarcomas is defined (bone for osteosarcomas, smooth muscle for leiomyosarcomas, fat for liposarcomas, etc.), but for some subtypes, such as Ewing's sarcoma, it remains unclear.

In addition to radiation therapy for prior cancer (in both children and adults), other environmental risk associations include arsenic and polyvinyl chloride (plastics manufacturing) exposures and angiosarcoma, dioxin (Agent Orange) exposures in forestry workers and soft-tissue sarcomas, asbestos exposures and mesothelioma, and viral causes in immunosuppressed patients (HHV8 in Kaposi's sarcoma and EBV in leiomyoblastoma arising in the setting of immunosuppression).

However, in the vast majority of cases, specific risk factors are absent and there is also no evidence of germline predisposition. Genetic studies have found that sarcomas segregate into two major types: those with specific genetic translocations and simpler karyotypes, and those with complex karyotypes but without specific genetic alterations. The significance of these two major types and how these differences might translate into targeted treatments remains uncertain.

Since the 1950s, limb-sparing surgery, radiation therapy, and chemotherapy have improved sarcoma survival rates or reduced recurrence rates. Today, surgery—often coupled with radiation therapy—is usually the primary treatment for sarcoma, although some rhabdomyosarcomas and Ewing sarcomas can be cured with only radiation and chemotherapy. Most patients who die from sarcoma have

[1] http://www.cancer.org/docroot/STT/stt_0.asp

chemotherapy-resistant metastatic disease. Only a few chemotherapy drugs are effective, and the rarity and heterogeneity of sarcoma make testing new agents challenging.

Given the lack of a uniform standard of care, the difficulty in diagnosis, and the lack of new treatments (with the exception of imatinib for GIST, considered by many to be a model for tailored molecular therapy), most sarcoma patients have been underserved by the medical and research communities.

THE PROCESS

At a planning meeting in June 2003, the PRG organized a roundtable meeting to consider progress, identify gaps, and highlight research needs across the field of sarcoma research.

The meeting planners identified four cross-cutting areas and nine science-centric areas as the foci of breakout sessions. The four cross-cutting areas were Platforms for Discovery, Translation of Therapeutic Targets and Experimental Models to Clinical Settings, Innovative Clinical Trials, and Optimizing Existing Care. The science-centric areas were Better Biology and Discovery, Better Immunology, Better Access to Annotated Tissue, Better Models and Preclinical Testing, Better Prevention, Better Diagnosis and Prognostication, Better Imaging, Better Clinical Studies, and Better Communication and Outcomes.

The Roundtable Meeting, which included 112 participants, was held October 8-10, 2003, in Philadelphia. Each participant attended one cross-cutting group and one science-centric group. The cross-cutting groups met first; each group identified three priorities for sarcoma research over the next 5 years and presented them to the Roundtable. In the context of the cross-cutting groups' presentations, each science-centric group then met, identified three priorities, and presented them to the Roundtable.

Finally, the cross-cutting groups reconvened and revisited their original priorities in the context of the presentations from the science-centric groups. On the morning of the last day, the cross-cutting groups presented final priorities. The Roundtable participants reviewed these priorities and reached consensus on six high-priority recommendations.

THE PRIORITIES

Over the 3-day meeting, PRG Roundtable participants reiterated the need for some type of center or "governing body" to support sarcoma research. This struggle to organize the parts into a larger whole is not happening in a vacuum; both the NCI, in its Strategic Priorities for 2015,[2] and the National Institutes of Health (NIH), in its Roadmap,[3] have recognized the need for integrated and cooperative research plans. Furthermore, addressing these priorities for sarcoma may result in a framework that can serve as a model for research and treatment for other rare cancers and diseases.

The six high-priority recommendations are listed subsequently. Three of the four cross-cutting groups included a priority about centralization; thus, Priority 1 carries extra weight. Although Priorities 2-6 are numbered, they are not ranked in order of importance.

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[2] http://cancer.gov/directorscorner/directorsupdate-08-27-2003

[3] http://nihroadmap.nih.gov/

PRIORITY 1.

Create a dedicated, sarcoma-specific organizational structure—the Sarcoma Research Consortium (SRC)—to serve as a focal point for sarcoma clinical trials and related clinical- and laboratory-based research and to enhance networks of investigators and centers committed to sarcoma research.

Sarcomas are a heterogeneous and uncommon group of malignancies. Optimal treatment requires close collaboration among multiple disciplines with special expertise in the diagnosis and treatment of sarcomas. The current decentralized system does not support the effective interaction between experts or collaboration among interested researchers. Resources for studying the many subtypes of sarcoma are fragmented, resulting in a few small, inadequately powered studies. Centrally coordinated initiatives and strong networks will facilitate multidisciplinary research and data sharing, streamline the research process, and produce more reliable results per funding dollar spent. The resulting system also will be a model for studying other rare cancers and rare diseases.

A unifying theme of the PRG was the need to create a new organizational structure that would maximize the delivery of state-of-the-art clinical care to sarcoma patients and facilitate the conduct of clinical- and laboratory-based sarcoma research. Therefore, the Roundtable proposed the creation of an SRC.

Implicit in the creation of the SRC is the notion that specialized expertise in sarcoma patient care and/or sarcoma research is required to move the field forward. The intent is not, however, to create a structure that is exclusive. Rather, the SRC represents an organizational umbrella that can accommodate, and indeed welcomes, participation by any investigator or center committed to sarcoma research.

The concept of the SRC (**Figure 1**) resonates with both the NCI Strategic Priorities for 2015 and the National Institutes of Health (NIH) Roadmap themes. NCI's Strategic Priorities stress the need for an integrated clinical trials system and seamless integration of the elements of drug discovery from beginning to end. Similarly, the Roadmap's themes of "Research Teams of the Future" and "Re-engineering the Clinical Research Enterprise" recognize the need for new organizational models and partnerships to move research forward.

SRC funding may be drawn from cooperative groups, grants, the pharmaceutical industry, and philanthropy. Centralizing the sarcoma research enterprise will streamline the research process and make the SRC attractive to funding sources.

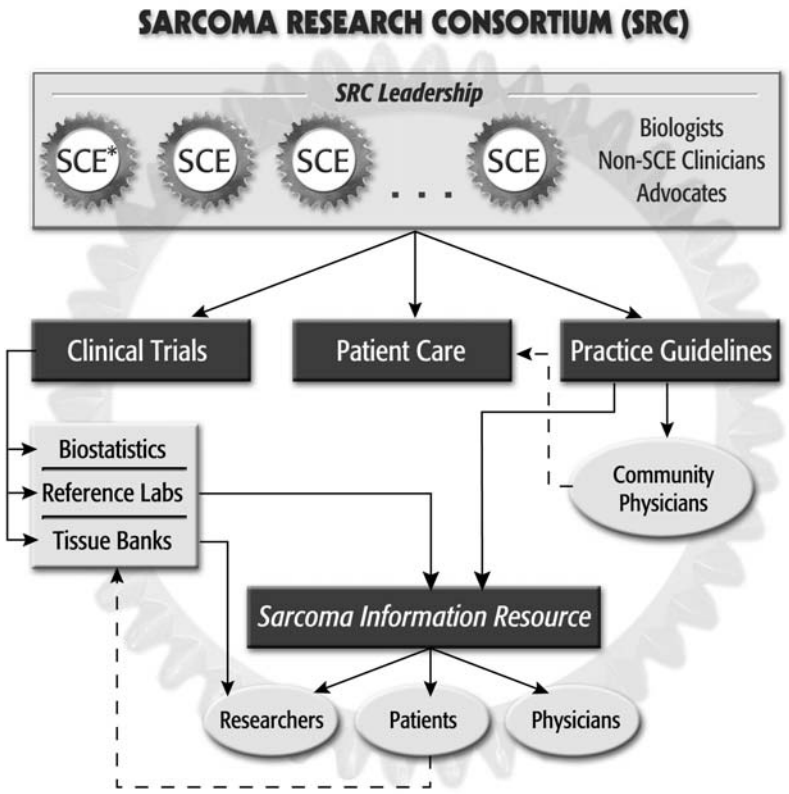

Figure 1. The Sarcoma Research Consortium

***SCE = Sarcoma Center of Excellence**

The SRC will consist of the following:

1. **A national, multidisciplinary group of investigators that provides leadership for sarcoma research**

   A critical aspect of the SRC is the integration of clinical and laboratory investigators committed to sarcoma research. SRC leadership will include clinicians and researchers at SCEs, as well as additional leaders elected on a regular basis (e.g., every 4 years). SRC leadership positions will not be restricted to SCE members; investigators interested in sarcoma biology research who may not reside within an SCE will be encouraged to participate. Leaders will come from all relevant disciplines (e.g., surgery, medical oncology, pediatric oncology, radiation therapy, radiology, pathology, cancer biology, and patient advocacy).

   The establishment of this national sarcoma leadership structure will ensure that the sarcoma research agenda receives adequate attention (which can be difficult for rare diseases within larger cooperative groups) and incorporates broad, multidisciplinary involvement of the sarcoma research community.

2. **Sarcoma Centers of Excellence**

   SCEs will have both multidisciplinary expertise in sarcoma patient care (surgery, medical oncology, pediatric oncology, radiation therapy, pathology, and radiology) and see a sufficient number of sarcoma patients on a regular basis (> 50 patients per year). The SRC will establish criteria for an SCE and

designate approximately 10 to 20 SCEs around the country. The seed money for the SCEs will come from money that is currently provided to cooperative groups for rare cancer research; funds will be augmented by money from other sources.

SCEs will conduct sarcoma clinical trials and serve as clearinghouses for annotated clinical data (with associated tissue/blood/serum samples). They will work with other sarcoma researchers, advocates, and physicians to elevate the standard of care for all sarcoma patients.

SCEs will provide care to as many sarcoma patients as is feasible, either in person or "virtually" through consultations and other interactions with community physicians. Using available evidence, the SRC will sanction treatment "best practices" and strongly encourage their use at SCEs.

3. **A common infrastructure to support and accelerate sarcoma research**

   Such infrastructure would likely include the following goals:

   - Establishing a centralized sarcoma tumor and tissue repository (possibly in coordination with the National Biospecimen Network). This repositioning will help rapidly achieve a "critical mass" of tissue for this collection of rare diseases, guarantee uniformity of pathological annotation, and facilitate the acquisition of material.
   - Generating renewable biological resources (e.g., cell lines, animal models, antibodies, and DNA constructs).
   - Generating selected data (e.g., DNA microarray data or molecular measurements in the context of clinical trials). This task would likely be contracted to experienced laboratories, and the guiding principle would be to make such data freely available to the public as rapidly as possible.

Within this framework, the SRC will take the following steps:

1. **Establish a national clinical trial agenda and oversee the conduct of such trials.**

   The SRC will schedule sarcoma clinical trials and assist in clinical trial design. This centralization will expedite testing of novel therapeutic approaches in this rare patient population; in addition, a more consistent approach to trial design will increase the comparability of clinical trial results. Clinical trials will continue to include both investigator-initiated and industry-sponsored trials and will be performed primarily, but not exclusively, at the SCEs. NCI Cancer Trials Support Unit members and cooperative groups will have access to these studies.

   The SRC will coordinate certain aspects of the clinical trials, including (1) centralized statistical services, (2) standardized data collection methods and data storage, (3) centralized pathology review, and (4) centralized sample collection and banking. When possible, these activities will leverage existing organizations if this can be achieved in a cost-effective manner and if the results will be of sufficiently high quality.

   Most patient samples will be obtained from SCEs, but a mechanism will be established whereby interested clinicians or patients can contribute available

tissue material even if patients are not being treated on a clinical trial or being seen at an SCE.

2. **Serve as an information resource for sarcoma researchers, clinicians, and patients.**

   Using existing electronic information resources of NCI, the SRC will partner with NCI to refine a subset of resources specific to sarcoma. For clinicians, this will include clinical trial information, referral information, clinical care best practice guidelines, and diagnostic information. For patients, it will include appropriately written information related to sarcoma, including background information, clinical trial information, contact information for nearby SCEs, and resource information such as patient support networks and advocacy groups. This information resource also will bring together valuable data relevant to sarcoma biology research (e.g., annotation of sarcoma cell lines, sources of useful reagents, biotechnology and pharmaceutical company contact information, and genomic data relevant to sarcoma, such as microarray data).

   The NCI's cancer biomedical informatics grid (CaBIG) – a common informatics platform integrating diverse data types and supporting analytic tools – will be an integral part of this effort.

   The SRC will partner with NCI surveillance to establish and maintain databases of NIH-funded sarcoma research and of accurate statistics on incidence and mortality (including optimization of coding and reporting methods identifying sarcoma diagnoses).

3. **Partner with NCI and other institutes in the conduct of sarcoma research, including efforts to increase the accuracy of sarcoma incidence and mortality data.**

   A range of federal research agencies should be invited to partner scientifically and financially with the SRC to minimize the need for new infrastructure. Other potential support agencies include the National Institute of Environmental and Health Sciences, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes & Digestive & Kidney Diseases, the National Institute of Nursing Research, the National Institute on Aging, the Department of Veterans Affairs, the Department of Defense, the Centers for Disease Control and Prevention, the Centers for Medicare & Medicaid Services, the Agency for Healthcare Research and Quality, and the Environmental Protection Agency.

   It is expected that Priorities 2-6 would be realized within the context of the SRC.

PRIORITY 2.

Fund and foster research focused on key areas of sarcoma biology most likely to advance the field.

The following areas are included:

- the developmental biology of mesenchymal tissues,

- mutational targets in growth signaling pathways,
- downstream targets of fusion proteins,
- cellular checkpoints and apoptotic pathways in the sarcoma context, and
- immunobiology of human sarcomas.

These areas represent the major knowledge gaps in sarcoma biology; bridging these gaps will advance the field at both the basic and translational levels.

A better understanding of mesenchymal developmental biology should allow for better transgenic models, help in interpretation of expression-profiling data, and identify shared mesenchymal differentiation pathways and antigens amenable to novel therapeutic approaches.

A focus on the mutational targets in growth signaling pathways should clarify the role of cooperating mutations in translocation sarcomas and may identify signaling pathways shared by diverse sarcomas.

A comprehensive analysis of fusion protein target genes will clarify the biology of translocation-associated sarcomas and may reveal common themes and pathways amenable to therapies with broad utility.

A better understanding of cellular checkpoints and apoptotic pathways in sarcomas may reveal new therapeutic targets.

Both the NCI and NIH emphasize the need to understand the complexity underlying biological systems and to provide new strategies for diagnosing, treating, and preventing disease.

PRIORITY 3.

Develop sarcoma-specific animal model systems (including new models and metastatic models).

Model systems are important for both understanding the biology of cancer and identifying potential treatments, as well as diagnostic and prognostic markers. Most patients who die from sarcomas die from metastatic disease, but research in metastasis is hindered by the dearth of models specifically addressing sarcoma metastasis. Many sarcomas are hypothesized to result from fewer genetic abnormalities than many carcinomas because of the diagnosis of many sarcomas in children. Therefore, recapitulating metastatic disease in sarcoma models may be easier and more accurate than for more complex carcinoma-derived metastatic tumors. The results of investigating sarcoma metastases can be applied to other cancers.

Both the NCI Strategic Priorities and the NIH Roadmap recognize the need for integrated approaches to biological research, including the use of models. The NIH Roadmap's "New Pathways to Discovery" theme recognizes that basic biological knowledge is tied to the development of useful models in any disease, including cancer. NCI's Integrative Cancer Biology priority has as its first objective to "generate models that recapitulate the interactive, dynamic, and spatial relationships between molecules in a cell, between cells, between cells and their microenvironment, and between the organism and the macroenvironment."

PRIORITY 4.

Fund and foster comprehensive approaches to sarcoma profiling and target discovery.

Approaches include the following:

- Comprehensive sarcoma profiling (genome, transcriptome, and proteome) to identify novel therapeutic targets, new markers for diagnosis, susceptibility, and prognosis, for prediction of treatment response and definition of intermediate endpoints.
- High-throughput screens and functional genomic approaches to identify novel therapeutic targets and critical pathways regulating sarcoma growth and survival.

Because targeted screening of specific pathways is limited by current knowledge of sarcoma biology, screening (compounds, RNAi, and functional genomics) may be essential to identify novel targets associated with pathways not currently implicated in sarcomagenesis. Sarcoma profiling is currently fragmented and focuses largely on expression profiling. Global understanding of specific sarcomas remains elusive.

Molecular profiling and targeted therapeutic interventions have the potential to alter the terrain of cancer research. The NCI and NIH have recognized these approaches as integral to future research and highlight them in their respective strategic plans.

PRIORITY 5.

Develop a centrally available toolkit of core reagents and access to technology platforms for sarcoma research including cell lines, model systems, annotated tissue banks, biomarkers, and imaging.

Current resources are inadequate for current or planned research endeavors. The toolkit will enable new technology to define novel and valid biomarkers, imaging, and surrogate markers to take advantage of the unique biology of sarcoma subsets and encourage rational, targeted, and timely clinical development.

In its "New Pathways to Discovery" theme, the NIH Roadmap highlights the need for a "toolbox" that consists of technologies, databases, and other scientific resources. NCI's Strategic Priorities include plans to establish a regional network of high-throughput laboratories for existing and emerging biomarkers of cancer risk, as well as to facilitate the collaborative development of a national, regulatory-compliant, privacy-protected, standardized network of annotated biological sample(s).

PRIORITY 6.

Design prospective clinical trials whose principal objective is to compare early surrogate (intermediate) markers to conventional endpoints. Such trials should be tightly linked to appropriate tissue banking and incorporate novel statistical methodologies appropriate to sarcomas. These trials should be conducted concurrently with a series of innovative therapeutic trials.

In areas where controversy exists as to optimal therapy, a trial focused on a surrogate (intermediate) endpoint may be viewed as innovative and therefore attractive to patients and their physicians. Furthermore, successful identification of a surrogate endpoint will allow more rapid conduct of clinical trials and will be very attractive to the pharmaceutical industry.

In its Strategic Priorities for 2015, one NCI objective is to develop, validate, and approve surrogate markers as endpoints to shorten the time necessary for conducting clinical trials. The need for improved assessment of clinical outcomes is highlighted in the NIH's "Re-engineering the Clinical Research Enterprise" Roadmap theme.

Appendix A

Cross-Cutting Breakout Group Reports

PLATFORMS FOR DISCOVERY

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INTRODUCTION

Cytogenetic and molecular genetic studies indicate that sarcomas have two broad types of biology. The first group of sarcomas, those with fusion genes due to reciprocal translocations, contains specific genetic alterations and, usually, simple karyotypes. The second group of tumors is defined by nonspecific genetic alterations and, typically, complex unbalanced karyotypes, representing numerous genetic losses and gains. These two classes of sarcomas differ in many fundamental areas, such as telomere maintenance mechanisms and in their incidence in p53-mutant or knockout mouse models, in bilateral retinoblastoma and Li-Fraumeni syndrome, and as radiation-induced sarcomas.

While this broad dichotomy crosses the boundaries between bone and soft-tissue or pediatric and adult sarcomas, awareness is increasing of the need to consider individual clinicopathologic entities separately in terms of prognostic markers and therapeutic targets. In the past, the relative uniformity or paucity of treatment options in sarcomas shaped a minimalist view of sarcoma classification, in which sarcomas were considered more by histologic grade, size, depth, and location than by specific histopathologic subtypes. This "lumping" approach may have hampered studies of biological prognostic markers because the power of certain markers may vary substantially among sarcoma subtypes. Likewise, low response rates to conventional or experimental therapies in studies combining multiple sequence tagged site types may have obscured higher response rates in individual unrecognized sarcoma types. Studies based on translocation analysis and, more recently, on global gene expression profiling have confirmed that the histopathologic classification of sarcomas corresponds with distinct biological entities, with some notable exceptions, such as the group of sarcomas historically termed "malignant fibrous histiocytomas."

Sarcomas with Specific Translocations and Simple Karyotypes

This molecular pathologic class of sarcomas is more often seen in children, adolescents, and young adults. In all, at least 12 types of sarcoma, accounting for about a third of all sarcomas, are characterized by specific translocations. In addition to providing very specific diagnostic markers, the fusion genes resulting from these translocations encode chimeric proteins central to the biology of these tumors, acting

as abnormal transcription factors that deregulate the transcription of multiple downstream genes and/or pathways.

The key role of these chimeric proteins in the pathogenesis of these cancers is supported by their demonstrated necessity for in vitro growth of the corresponding sarcoma cell lines and the impact of relatively minor variability in the structure of these chimeric proteins (due to cytogenetic or molecular variant breakpoints) on tumor phenotype and clinical behavior in some specific sarcomas. Potentially specific therapeutic targets include the resultant fusion proteins themselves as well as genes that are key downstream targets of these aberrant transcription factors. The latter may be more biologically accessible, but the current list of validated downstream target genes remains small.

Because the earliest known genetic lesion (the specific translocation) can be separated from late or secondary lesions, this group of sarcomas is amenable to a fairly simple model in which the earliest known genetic event is a specific chromosomal translocation in a specific precursor cell or stem cell. In most cases, this is an apparently random event, but in rare cases, it may be related to radiotherapy- or chemotherapy-induced DNA damage.

Whether secondary genetic alterations are necessary in the biology of this class of sarcomas (for instance, in kinase signaling pathways) remains unclear. The best studied secondary genetic alterations, p53 mutations and p16CDKN2A/p14ARF deletions, define small but clinically aggressive subsets in several of these sarcomas. However, no evidence is available to indicate that these two intersecting pathways are functionally altered in the remaining majority of cases. Highly prevalent (and therefore presumably necessary) secondary genetic alterations have so far not been identified in any of these sarcomas.

Certain translocation-associated sarcomas appear to be dependent on specific growth signaling pathways (insulin-like growth factor, platelet-derived growth factor receptor, and MET), but it generally remains unclear how much this relationship reflects their induction by the specific aberrant transcription factors versus pre-existing activation of these pathways in the precursor cells of these sarcomas. So far, the genes encoding these signaling molecules have not shown mutations or other structural alterations in translocation-associated sarcomas.

Sarcomas with Complex Karyotypes Lacking Specific Genetic Alterations

This second molecular pathologic group of sarcomas is characterized by complex, unbalanced karyotypes lacking specific translocations, with many genomic gains and losses. This group makes up approximately two-thirds of sarcomas. Prototypical tumors in this group include osteosarcoma, malignant fibrous histiocytoma, liposarcoma (other than myxoid type), angiosarcoma, leiomyosarcoma, adult fibrosarcoma, and skeletal chondrosarcoma. Their often complex and unbalanced karyotypes reflect a biology in which chromosomal instability associated with checkpoint defects (DNA damage and cell cycle checkpoints) plays a critical role, producing pathogenic gene copy number changes in tumor suppressor genes and oncogenes. The mechanisms of chromosomal instability may include chromosomal fusion-bridge-breakage cycles (secondary to dysfunctional eroded telomeres), impaired nonhomologous end joining, or increased centrosome numbers.

The degree of chromosomal or genomic instability in these sarcomas appears to correlate with p53 inactivation. Thus, in sarcomas with nonspecific genetic

alterations, p53 pathway inactivation may be a common early event, needed to overcome checkpoints triggered by senescence, telomere erosion, or double-strand breaks. The more widespread role of p53 inactivation in this class of sarcomas may also account for its limited ability to define distinct clinical subsets in these tumors. Unlike sarcomas with simple karyotypes, certain etiologic factors or predisposing conditions are well described in this class of sarcomas, notably, ionizing radiation and constitutional p53 or Rb mutations.

Gastrointestinal Stromal Tumors (GISTs): A Biologically Unique Sarcoma

Most GISTs show simple karyotypes and are unique in that they constitute the only sarcoma type with a specific recurrent activating mutation (in KIT) as the primary genetic abnormality. The success of therapeutic targeting of KIT in GISTs has demonstrated the importance of structural genetic alterations in credentialing targets, a notion also supported by the generally disappointing results of similar approaches on nonmutated kinase targets in other sarcomas.

PRIORITY 1.

Fund and foster focused research on key areas of sarcoma biology most likely to advance the field.

- **Developmental biology of mesenchymal tissues.**
- **Mutational target identification in growth signaling pathways.**
- **Downstream targets of fusion proteins.**
- **Cellular checkpoints and apoptotic pathways in the sarcoma context.**
- **Immunobiology of human sarcomas.**

Rationale

- These areas represent the major knowledge gaps in sarcoma biology. Bridging these gaps will advance the field at both the basic and translational levels.
- The stem cells or precursor cells that give rise to sarcomas are largely unknown and mouse models for sarcomagenesis remain limited. A better understanding of mesenchymal developmental biology should allow for more successful and more representative transgenic models; should help in interpretation of expression profiling data; and may identify shared mesenchymal differentiation pathways and antigens amenable to novel therapeutic approaches.
- A systematic focus on the tyrosine kinome of sarcomas should clarify the role of cooperating mutations in translocation sarcomas and may identify signaling pathways shared by diverse sarcomas.
- A comprehensive analysis of fusion protein target genes will be necessary to clarify the genesis of translocation-associated sarcomas and may reveal candidates for highly targeted therapies or common themes and pathways amenable to therapies with broader utility.
- A better functional understanding of cellular checkpoints (cell cycle, p53, and telomeres) and apoptotic pathways in sarcomas as they relate to the cellular response to fusion proteins or karyotypic complexity may aid in the understanding of and refine responses to conventional chemotherapies and may reveal further therapeutic targets.

- Sarcomas provide an important opportunity for the development of specific immunotherapies because many or most express differentiation antigens and/or tumor-specific fusion proteins. This opportunity is strengthened by recent progress in basic tumor immunology.

Proposed Mechanisms

- Requests for applications (RFAs) addressing these key areas.
- Other funding mechanisms attracting both junior investigators and current leaders in developmental, stem cell, and sarcoma biology to focus on these key areas of normal and neoplastic mesenchymal biology.
- Interdisciplinary symposia on mesenchymal development and differentiation and sarcoma biology.
- A centralized infrastructure at NCI to link investigators to specific inhibitory compounds currently available in the public or private sector with potential activity toward newly identified targets.

Issues of Importance

- Progress in understanding mesenchymal development and differentiation lags far behind that in the hematopoietic system. There remains a gulf between the data emerging from the studies of developmental biologists and the field of sarcoma cell and molecular biology.
- The current, piecemeal, gene-by-gene approach to gene discovery driven by multiple independent investigators has proven to be slow and inefficient in identifying new therapeutic targets among fusion protein transcriptional targets and growth signaling pathways.
- It remains difficult for investigators to identify sources of promising compounds under development that may be relevant to sarcoma biological systems under investigation in their laboratories.

PRIORITY 2.

Fund and foster comprehensive approaches to sarcoma profiling and target discovery.

- **Comprehensive profiling (genome, transcriptome, and proteome) of specimens from patients with sarcomas (including both neoplastic and non-neoplastic tissues) to identify novel therapeutic targets; identify new markers for diagnosis, susceptibility, and prognosis; predict treatment response; and define intermediate endpoints.**
- **High-throughput compound screens and functional genomic approaches to identify novel therapeutic targets and critical pathways regulating sarcoma growth and survival.**

Rationale

Because targeted screening of specific pathways is limited by current knowledge of sarcoma biology, broad-based screens (e.g., compounds, RNA interference, and functional genomics) may be essential to identify novel targets associated with pathways not currently implicated in sarcoma biology. Comprehensive sarcoma

profiling is presently fragmented and focuses largely on expression profiling. A global understanding of specific sarcomas remains elusive.

Proposed Mechanisms

- Provide support for integrating molecular profiling efforts to clinical trials so that the best available technologies are applied to the best annotated clinical specimens. This could be through RFAs or supplements to cooperative group awards, or through a newly established sarcoma clinical trials group.
- Fund center(s) to establish additional validated sarcoma cell lines to be deposited at the American Type Culture Collection (ATCC):
  - Select 10 sarcoma cell lines to add to the NCI 60-cell-line panel.
  - Review and validate sarcoma cell lines currently available at ATCC.
- Provide support and centralized infrastructure to link individual sarcoma investigators with promising disease-specific models to centers carrying out high-throughput compound and genomic screens.

Issues of Importance

- Suitable laboratory models and assays representing a full spectrum of sarcoma types must be developed. Focused research efforts are limited by current knowledge. Therefore, comprehensive, unbiased screens are needed to provide a more global understanding of the biology of sarcomas and to identify currently unanticipated targets and pathways.
- It is difficult for sarcoma investigators to interface with centers that have optimized screening technology platforms (e.g., RNA interference or small molecule) to bring these technologies to bear on sarcoma-specific systems.
- Current molecular profiling datasets do not include the full spectrum of sarcoma types or adequate numbers of clinically annotated specimens. In addition, the available datasets do not combine multiple modalities of profiling and molecular characterization, such as mutations in the p53 pathway and cell cycle checkpoints. Available molecular profiling data currently reside on disparate platforms in dispersed databases and are therefore difficult to mine and cross-reference.

PRIORITY 3.

Create a dedicated organizational structure to serve as a focal point for sarcoma clinical trials and related research, and enhance networks of investigators and centers committed to sarcoma research.

Rationale

Resources for studying the many forms of sarcoma are fragmented, resulting in many small, inadequately powered studies. Centrally coordinated initiatives and strong networks will facilitate multidisciplinary cooperative research and data sharing.

Proposed Mechanisms

- Foster central coordination of sarcoma clinical trials and related research in order to complete the following goals:
  - Develop shared bioinformatics resources to optimize data exchange and mining from existing and developing molecular profiling studies and

etiology/susceptibility studies, and increase representation of less common sarcomas.
  - Oversee the establishment of banks of tissues, cell lines, xenografts, and molecular resources for distribution to the sarcoma research community.
  - Link biological specimens to clinical trials and encourage collection of adequate frozen specimens from the majority of patients.

- Foster or enhance sarcoma research networks through new funding mechanisms including Specialized Programs of Research Excellence grants, RFAs for P01 awards, and philanthropic consortia.

Issues of Importance

The greatest challenge is to develop a coordinating organization with a structure and mission that would be acceptable to the sarcoma clinical and research community and would also meet the concerns of patient advocacy groups, while addressing regulatory compliance issues.

CONCLUSION

The preceding priorities are designed to build on recent progress in sarcoma research and new technologies in biomedical research. They are also designed to overcome organizational and scientific limitations that have impeded progress in this group of relatively uncommon cancers.

Based on a recognition that both highly specific targeting and wide spectrum approaches may be needed to advance the treatment of these cancers, these approaches should facilitate the identification of new sarcoma type-specific therapeutic targets, while also providing platforms for the discovery of broader therapeutic approaches related to shared underlying mechanisms of sarcomagenesis.

TRANSLATION OF THERAPEUTIC TARGETS AND EXPERIMENTAL MODELS TO CLINICAL SETTINGS

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INTRODUCTION

For the patient, the process of scientific discovery is only effective if it is able to translate research results into effective new treatments. Advancing the field of sarcoma research requires redirecting the momentum of biological, biochemical, and molecular genetic understanding of mesenchymal tissues and mesenchymal neoplasia in a targeted and effective manner toward the needs of patients with sarcomas.

Sarcomas offer unique strengths as models of clinical translational research, and these strengths are disproportionately great compared to the relatively low incidence of these diseases. This is due to the specific molecular markers and targetable mechanisms of neoplasia that characterize specific subtypes of sarcomas. The translation of the molecular understanding of gastrointestinal stromal tumors (GISTs) into clinical practice, for example, has provided a crucial proof-of-concept that genetically simpler sarcomas should serve as models for hypothesis-driven translational investigations in patients.

Advances in the molecular understanding of sarcoma pathobiology have not always been optimally translated into new patient-oriented initiatives by the research and clinical communities. The field is currently hampered by small-scale, uncoordinated research conducted by investigators dispersed throughout the country, who may or may not have a particular interest in applying the results of fundamental research to sarcoma as a practical extension of their work. This dispersed and uncoordinated structure has resulted from (and is maintained by) certain logistical factors, such as the relatively uncommon incidence and prevalence of sarcomas across the country. The large-scale cooperative group mechanisms have traditionally failed to foster sarcoma research as well, resulting in a series of small-scale, unidisciplinary investigations throughout the country. This has led to an inefficient and ineffective dilution of expertise and a lack of focus on the key strengths of sarcoma as a powerful system for translational therapeutics research. Additionally, the current uncoordinated system often leaves care for sarcoma patients outside of optimal multidisciplinary approaches. The system also leaves researchers without a robust and reliable supply of sarcoma tissue samples with annotated connections to patient outcomes, which are necessary to understand this set of diseases more completely.

Establishing a novel NCI-funded scientific and clinical mechanism to focus on and enable sarcoma-directed research will actively facilitate the translation of basic research discoveries into new targeted therapeutic research studies to advance the field of research and patient care targeted to improving the lives of patients and families touched by sarcomas. The implications of this work will be far greater than for sarcomas alone, however, since this mechanism will serve as a model for research and clinical translational therapies in other orphan diseases of low incidence.

PRIORITY 1.

Create the Sarcoma Research Consortium (SRC) led by a steering committee comprised of sarcoma-focused scientific and clinical leaders. The SRC will develop strategy, implement plans, and influence the direction of translational research through resource allocation and coordination. Start-up funding from NCI will ensure rapid initiation of this effort. Other sources of funding to maintain the SRC and its activities will be developed into a robust funding model that will include support from the philanthropic sector, the biopharmaceutical industry, and other private sector sources.

Rationale

The currently decentralized system does not support effective interactions between sarcoma-focused experts or collaboration among interested researchers. Moreover, the centralized mechanisms currently in place, built around traditional oncology cooperative group mechanisms designed to study diseases of higher prevalence, are inadequate to foster optimal collaboration in this area. Setting up a multidisciplinary steering committee would allow sarcoma experts to develop strategies before implementing actions.

Issues of Importance

- Jump-start sarcoma research with a rapid infusion of funding that might be offered as supplements to sarcoma-focused cancer centers and as special requests for applications. These mechanisms can focus resources on sarcoma research and create an "affirmative action plan for sarcomas" to stipulate that a portion of the research and trials infrastructures will specifically support sarcoma research. This will maximize the impact from funding and focus on high-priority scientific initiatives in this important field.
- Develop aggressive and measurable metrics of success. For example, the number of adult sarcoma patients enrolled in protocols should be doubled within 1 year, the number of clinical trials should be tripled in 3 years, and an annotated tissue bank of 100 samples should be created in 1 year. A majority of patients with sarcoma should be enrolled into protocols, with an early emphasis on annotated tissue collection protocols.
- Construct the SRC to make sarcoma the paradigm for orphan disease translational research, as well as a model for collaboration across the age spectrum of pediatrics to adult care.
- Provide impetus and sustain momentum in sarcoma translational research through a responsible new funding model (to be started by rapid infusion of targeted government funding with the aim of acquiring and directing industrial

and philanthropic support toward this field) to enable more robust translational science.

PRIORITY 2.

Develop a centrally available tool kit of core reagents and access to technology platforms for sarcoma research, including cell lines, model systems, annotated tissue banks, biomarkers, and imaging.

Rationale

- Current resources are not adequate for current or planned research endeavors, and many important scientific and translational opportunities may go untapped. The tool kit will (1) interest the biopharmaceutical industry and basic science investigators and facilitate their translational research activities by focusing on the unique scientific strengths of sarcoma-selective targets, (2) enable new technology to define novel and valid biomarkers and imaging and surrogate markers to take advantage of the unique biology of sarcoma subsets, and (3) encourage rational clinical development with rapid speed and rational targeting.
- Existing cell lines are inadequately annotated. Many subtypes of sarcomas (especially those afflicting adults) are underrepresented by currently available cell lines.
- Sarcoma pathobiology may yield exceptionally clear answers to general questions of neoplastic disease mechanisms, and it is important to engage as broad a community as possible in research for which sarcoma would be an ideal translational model.

Issues of Importance

- Expand the NCI 60-cell-line panel to include at least five sarcoma cell lines, to be chosen by SRC.
- Collect and classify tissue in annotated repositories to be made available to researchers.
- Supplement existing NCI-funded cell culture core facilities to generate and characterize new cell lines. Make them available through a sustainable mechanism, such as American Type Culture Collection (ATCC), or explore collaborative interaction and expansion with the Cooperative Human Tissue Network.
- Optimize nonmurine models (e.g., sporadic canine sarcoma) through intramural comparative oncology programs and/or extramural veterinary collaborators.
- Expand the "Houghton model" for pediatric sarcomas to adult sarcomas as a preclinical screening and predictive framework.
- Evaluate preclinical molecules against robust standardized methods.

CONCLUSION

The discussions of this group led to consensus that the promise of sarcoma translational research can and should be optimized by developing a new mechanism to foster sarcoma-specific translational research as a model for orphan disease research. With sarcoma researchers dispersed around the country, this mechanism will require the formation of viable research collaborations between geographically distant sarcoma-focused researchers. Novel funding mechanisms need to support such collaborations across institutional boundaries to maintain and expand a critical mass of sarcoma translational science. Additionally, the heterogeneity of sarcoma and the rarity of distinct sarcomas require that a centrally available tool kit of sarcoma-specific core reagents and access to technology platforms for sarcoma research be developed to support basic and translational research. Together, these actions should not only bring about major advancements in sarcoma research but also provide insights that will extrapolate to many other more common forms of cancer as well.

INNOVATIVE CLINICAL TRIALS

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INTRODUCTION

While sarcomas as a group represent a significant proportion of all cancers, individual histologic entities are rare. This represents the principal obstacle to clinical trials for the treatment of sarcomas. Additionally, optimal clinical care and high-quality clinical research in these diseases require extensive collaboration from a broad array of medical specialties, but not all institutions that treat sarcomas have all the necessary specialties. Moreover, virtually all clinical trials of treatments for sarcomas rely on the endpoints of survival and event-free survival (EFS), so results have taken years to accrue and even longer to report.

Important priorities for clinical research in sarcoma are to lower the barriers to participation in clinical research trials and to develop surrogate endpoints that allow more rapid identification of promising therapies. In addition, because only a fraction of patients with sarcomas receive optimal treatment in their first encounter with a physician, the proportion of patients who are treated according to existing guidelines for the management of sarcomas must be increased, even if these patients do not participate in a clinical trial.

Barriers to Clinical Trial Participation

- Children and adults with sarcomas have different rates of participation in clinical trials. The Children's Oncology Group (COG) currently mounts clinical trials for the most common sarcomas in children—osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma. Participation by U.S. children younger than 21 in COG open trials averages 85 percent. Although participation in these trials is open to older patients, it drops sharply with age. Similarly, many trials designed to evaluate therapy in adults with soft-tissue sarcomas require that patients be 18 years or older, although little or no a priori biological reason exists to exclude children from participation in phase III trials.
- In most U.S. centers, children are treated in a freestanding children's hospital that does not accept older patients, who are typically seen by internal medicine oncologists at a university hospital. Some university hospitals collaborate closely with pediatric oncology groups and have open trials. However, at other

centers, the internal medicine oncology group may be unfamiliar with the trials or lack Institutional Review Board (IRB) approval for trial participation.

- Time gaps between open trials in the COG have sometimes been long. In the intervals between trials, trial participation obviously drops to zero.
- It is difficult for children's hospitals to open and maintain large numbers of trials with low accrual rates. It is also difficult for each group of oncologists to remain familiar with the many clinical trials so that they offer trial participation to every eligible patient. Moreover, data management resources and clinical trial regulatory groups are strained by the increase in the volume of trials, the heterogeneity of sarcoma trials, and the different data submission requirements for each cooperative group and trial.
- The principal loyalty of each group tends to be allied to a cooperative group. If the trial originates from a different group, data submission requirements may be different from those familiar to the institution and data managers may struggle to accommodate the requirements of an unfamiliar group.
- Several adult cooperative groups have sarcoma committees (Southwest Oncology Group [SWOG], Eastern Cooperative Oncology Group [ECOG], Cancer and Leukemia Group B, Radiation Therapy Oncology Group [RTOG], American College of Surgeons Oncology Group [ACOSOG], and National Cancer Institute of Canada Clinical Trials Group), and some of these have run competing studies. Where studies do not compete, multiple logistic and regulatory issues prevent the cross-group collaboration that could promote rapid accrual to studies. These logistical problems may also apply to collaborative development of new studies and have prevented the fostering of appropriate correlative biology studies.

Enhancing Collaboration for Sarcoma Clinical Research

Some steps have been taken to enhance collaboration for sarcoma clinical research:

- The very successful initiation and completion of the North American Intergroup study (S0033) of STI-571 (imatinib mesylate—Gleevec) in metastatic gastrointestinal stromal tumors (GISTs), with rapid accrual of more than 700 patients in 9 months, demonstrates a reservoir and prevalence of rare histology-specific sarcomas that could be accessed through cooperative groups. This study has also established patients' level of interest in participation in clinical trials of new modalities. Therefore, this study could be used as a model for intergroup collaboration on targeted therapies.
- Dr. Ernie Borden was appointed Chair of the SWOG Sarcoma Committee early in 2001 and, in collaboration with Dr. Murray Brennan from ACOSOG and representatives from all the cooperative groups, organized a multidisciplinary meeting on soft-tissue sarcomas of adults, with sponsorship from the Cancer Therapy Evaluation Program. The state of the science meeting took place in June 2002. (The meeting content can be viewed at www.webtie.org/sots/meetings/sarcoma.) The U.S./Canada Sarcoma Intergroup will focus on three of the many recommendations that came out of the meeting: (1) molecular and pathological redefinition; (2) evaluation of targeted biological therapies, both alone and in combination with chemotherapy and radiation; and (3) strengthening sarcoma clinical research collaborations with ACOSOG, RTOG, and COG. The U.S./Canada Intergroup has two specific aims:

  - To assess, in histology-specific trials, molecular targeted therapies—a number of protocols are in various stages of development.
  - To prospectively correlate pathologic diagnoses and clinical outcomes of soft-tissue sarcomas of adults with identification of novel gene clusters by DNA microarray.
- In the past 2 years, an organization has been formed of American institutions active in the Connective Tissue Oncology Society (CTOS). This organization has now launched three clinical trials enrolling several hundred patients, established a statistical center dedicated to sarcoma trials, and increased the interest of medical and pediatric oncologists in working together on those trials.

Improving Participation in Clinical Trials

Improving participation in clinical trials requires the following:

- High-quality trials asking important questions. This requires the convening of representatives of *all* relevant specialties to discuss new therapeutic options and set priorities for clinical trial development. Currently, the only venue that brings together representatives of pathology, surgery, radiation oncology, pediatric and medical oncology, and biology is CTOS.
- Widespread publicity about the availability of the trials to both practitioners and patients. This would require website development and maintenance, and e-mails and conventional mailings to physicians about trials. This type of education and publicity should improve both clinical care to all patients and participation in appropriate prospective trials for the treatment of sarcomas.
- Benefit to the patient and physician from participation in trials. Unique translocations have been identified for most sarcomas, and modern diagnosis of sarcomas will require molecular pathology. National or regional laboratories to perform molecular pathology of sarcomas would serve several purposes:
  - They would standardize and improve diagnosis of sarcomas, ensuring that clinical trials were applied to truly homogeneous groups of patients.
  - The centers would archive the material from patients, which could then be made available for basic research in sarcomas.
  - With appropriate informed consent, the biological resources would be linked to a clinical trial with all appropriate clinical information, including outcome data. This would dramatically improve the quality and quantity of information available to sarcoma researchers for correlation with biologic investigations.
- Availability of trials at centers that are geographically convenient to patients. This will require the development of an infrastructure to support clinical trials at many institutions. The COG model works for pediatric centers, and CTOS has had success at mounting and executing clinical trials, including imatinib mesylate for selected sarcomas.
- Increasing layers of review at every participating center makes the process of approval lengthy and cumbersome, and, in some cases, prevents participation. Data acquisition and management often receive no support.
- Participation in clinical trials must be made easier and more convenient for data management staff. Ideally, all data submission should be completed through electronic remote data entry, which could be filtered to improve quality and much closer to real time. Central data repositories could monitor delinquent

data reporting and seek redress much more quickly. The risk of error in data transmission and re-entry at the data center would be reduced, and availability of data to the statistician in usable form would be assured.

- Rapid dissemination of results in the medical literature. The most recently completed large national prospective trial for Ewing's sarcoma was reported in the literature 14 years after the trial opened.

Surrogate Endpoints

The only outcome variables currently considered to be reliable indicators of treatment efficacy are survival and EFS. Since median time to failure for some sarcomas is many years, trials run for years and results take years to accrue. For some of the diseases treated, novel techniques are available to assess response rapidly. For example, when patients with GIST are treated with imatinib mesylate, changes can be assessed in the tumor by positron emission tomography imaging within weeks of treatment initiation, and these changes correlate well with subsequent clinical response. Moreover, patients with osteosarcoma are typically treated initially with chemotherapy and then undergo definitive surgical resection of the primary tumor. Pathologic assessment of necrosis in the primary tumor strongly predicts subsequent EFS. In fact, the degree of necrosis observed after initial chemotherapy is the single strongest predictor of subsequent outcome. Similar results have been reported for Ewing's sarcoma. For most other sarcomas, information about earlier response indicators that predict outcome is not available. For all early response markers, we need adequate prospective data acquisition to ensure that they predict outcome robustly so that they can be used to assess response at an earlier stage of treatment. Each clinical trial that is designed for the treatment of sarcomas should include early measurements of response so that significant experience with these modalities can be accumulated in a prospective manner.

Novel Phase II Trial Design

New agents for sarcomas are traditionally evaluated with a phase II trial design, in which eligibility is restricted to patients with measurable disease. Response outcome is assessed by radiologic imaging, and only agents that result in complete or partial objective responses are considered valuable for additional investigation. This approach may not be ideally suited to investigation of novel biological agents. Some of these agents might not be capable of inducing regression of bulky tumors even though they have activity against microscopic residual disease. Thus, conventional phase II designs run the risk of discarding potentially valuable new therapies.

Novel trial designs are needed to evaluate novel therapies for sarcomas. These could include "adjuvant" phase II trials, where patients rendered clinically free of disease by surgery and/or radiotherapy would be eligible for entry. The relevant endpoint would be time to recurrence, measured through either randomization to treatment or observation, or comparison to an adequately robust historical control. Alternatively, the endpoint of interest could be survival from trial entry because stable disease with prolonged life is valuable to patients. The usual standard in phase II trials is to discard agents that do not result in measurable decrease in the size of tumors. However, investigators should be permitted to identify prolongation of life as a valuable endpoint, even if the therapy being tested does not result in objective shrinkage of the tumor.

The statistical design of phase II trials also needs attention. The current CTOS trial of imatinib mesylate for sarcomas incorporates a novel hierarchical Bayesian approach

to phase II trials to account for multiple subtypes of sarcomas. This approach, which was designed by Thall and colleagues (2003), allows improved use of limited numbers of patients to evaluate novel agents while minimizing the risk that the agents would be rejected as active.

PRIORITY 1.

Hypothesis: Treatment of sarcoma patients in a comprehensive sarcoma center results in better diagnosis and improved survival in comparison to diagnosis and treatment in a community setting.

Recommendation: Develop criteria to identify comprehensive sarcoma centers. Subsequently, complete a cohort study comparing patients treated in these centers with those who are not in terms of appropriateness of biopsy technique, diagnostic accuracy, appropriate use of diagnostic imaging, participation in clinical trials, collection and storage of appropriate tissues, local recurrence rates, and survival.

Rationale

Sarcomas are a heterogeneous and uncommon group of malignancies. Optimal treatment requires close collaboration among clinicians from multiple disciplines with special expertise in the diagnosis and treatment of sarcomas. These include pathologists, musculoskeletal radiologists, surgical and orthopedic oncologists, pediatric and medical oncologists, radiation oncologists, and other surgical subspecialists when appropriate.

In Ewing's sarcoma, German data (Paulussen et al., 2003) demonstrated a survival advantage to those patients treated at centers seeing 10 or more patients per year. While we presume that this experience factor is associated with other sarcoma types, data need to be gathered and evaluated to confirm the preceding hypothesis.

Issues of Importance

- For some sarcomas, such as localized Ewing's sarcoma and osteosarcoma, evidence clearly shows better outcomes for patients treated in experienced centers. Optimally, all patients with these sarcomas should be treated in sarcoma centers. For other sarcomas, the evidence is less clear; this question should be answered. In the interim, recognizing that not all patients will be able to receive care at a sarcoma center due to such issues as insurance, logistics, or cost, registration of such patients through the sarcoma centers, providing consultation and feedback to treating physicians regarding optimal care is encouraged.

PRIORITY 2.

Hypothesis: A more efficient clinical trials system will improve recruitment and generate the knowledge needed to modify standards of care in sarcomas.

Recommendation: Develop a sarcoma-specific group to organize and conduct clinical trials to:

- **Foster constant, close communication with sarcoma biologists to design clinical trials based on promising preclinical results.**
- **Encourage the use of modern, translational scientific methods (tissue banking, gene expression, and modification).**
- **Further develop and refine a statistical design methodology to deal specifically with a disease category with multiple subtypes.**
- **Maximize the involvement of advocacy groups to promote and assist in recruitment to clinical trials.**
- **Monitor long-term effects of therapeutic interventions.**
- **Support development of a national IRB to decrease barriers to clinical trials participation.**

Rationale

Sarcomas are a unique group of diseases in which it has been difficult to make significant, consistent progress using the current clinical trials infrastructure.

Issues of Importance

- Current fragmentation of responsibility for sarcoma clinical research has failed to foster protocol development and conduct, and to support specimen acquisition and translational research.
- We should set metric goals for progress with a timetable to meet them.
- IRBs and scientific review committees need to be educated regarding novel statistical methodologies.

PRIORITY 3.

Hypothesis: Imaging or molecular biology studies can identify active therapies that will improve clinical outcomes earlier than conventional clinical endpoints.

Recommendation: Design prospective clinical trials whose principal objective is to compare early surrogate (intermediate) markers to conventional endpoints. Such trials should be tightly linked to appropriate tissue banking and incorporate novel statistical methodologies appropriate to sarcomas. These trials should be conducted concurrently with a series of innovative therapeutic trials.

Rationale

In areas where significant controversy exists surrounding optimal therapy (often based on limited data), a trial focused on a surrogate (intermediate) endpoint will be viewed as innovative and therefore attractive to patients and their physicians. Furthermore,

successful identification of a surrogate endpoint will allow more rapid conduct of clinical trials and will be very attractive to the pharmaceutical industry.

Issues of Importance

- A barrier of modern imaging is the lack of availability of dedicated imaging instruments, as well as related reimbursement issues.
- A second barrier is the method by which the diagnostic biopsy is performed. For example, fine needle aspirate biopsy often does not provide sufficient tissue.

CONCLUSION

Improving the clinical trials process not only will lead to better outcomes for patients but, equally important, will also provide materials, insight, and laboratory discoveries to permit the succeeding generation of clinical trials to have an even greater impact on outcomes.

A unifying theme of all of the breakout group's discussions was the need for a sarcoma-specific consortium. Such a consortium will overcome barriers to clinical research in sarcomas and enhance translational research.

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OPTIMIZING EXISTING CARE

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INTRODUCTION

The American Cancer Society has estimated that 8,300 soft-tissue sarcomas will be diagnosed in 2003. [1] Of these patients, 3,900 (45%) will die of their disease. The standard of care for these tumors varies by histologic type of sarcoma and location. For example, in this small group of tumors, appropriate management varies greatly for gastrointestinal stromal tumors, pediatric sarcomas, high-grade extremity sarcomas, and sarcomas of the retroperitoneum and uterus. Optimal care of these patients requires the multidisciplinary expertise of specialists with experience in the management of these tumors. Surgical, orthopedic, and medical oncologists; radiation therapists; and pathologists all have important roles in the management of these uncommon but complicated tumors.

Quality of care is a primary issue in the current management of sarcomas, but the rarity of these tumors prevents most practitioners from developing experience in their management. For example, the standard management of extremity and torso sarcomas requires a needle biopsy or incisional biopsy, and excisional biopsy by inexperienced surgeons may contaminate tissue planes and make further treatment more problematic as a result of inappropriate incisions. [2] Of 202 patients referred to Roswell Park Cancer Institute with biopsy-proven sarcomas of the extremity, 109 (more than 50 percent) underwent excisional biopsy. [3] Standards of care have been outlined by such groups as the National Comprehensive Cancer Network (NCCN). More objective assessments of what quality cancer care is for low-volume tumors, such as sarcomas, are difficult to obtain. [4] Most major assessments of quality of care, such as NCI's Cancer Care Quality Measures Project (CanQUAL) project, emphasize high-incidence tumors such as cancers of the breast, colon, lung, and prostate. Little is known about the quality of care in low-incidence tumors, such as sarcoma, primarily because most patients are treated by their primary providers and not by sarcoma specialists at multidisciplinary centers.

Multiple reasons exist for patients not being referred to or not choosing to be managed in multidisciplinary centers. Travel to centers of excellence is frequently inconvenient, bothersome, and expensive. Additionally, physicians and surgeons in small- and moderate-sized hospitals often want to maintain control of patients in their respective communities for economic and other reasons. However, many physicians do not appreciate how complex the care of sarcoma patients has become and are not aware of the many alternative care strategies available.

Many groups are beginning to address quality in meaningful ways. Specifically, the NCI's CanQUAL, in collaboration with the National Quality Forum and the Rand Corporation, is addressing quality issues in four high-incidence, nonsarcoma tumors. However, low-incidence and highly variable tumors, such as sarcomas, are not receiving the same attention.

PRIORITY 1A.

The standard of care for patients with sarcoma should be treatment at sarcoma multidisciplinary centers (SMCs).

Rationale

SMCs will improve patient outcomes, increase participation in translational research and clinical trials, and increase the availability of tissue for research.

Issues of Importance

- SMCs will set the standard for providing expert care to patients afflicted with sarcoma. Institutions that meet pre-defined requirements would qualify to become SMCs. (See Priority 2 for SMC qualification requirements.)
- Although optimal patient care would be provided at SMCs, patient barriers must be considered, such as insurance coverage, travel, and finances. For patients who are unable to overcome these barriers, alternatives must be established to optimize their care. Insurance companies should be advised of patient cost barriers and attempt to minimize/eliminate existing financial penalties. Increased provider awareness and education and improved communication between the treatment establishment and providers at SMCs would improve outcomes for patients unable to attend SMCs and enhance sarcoma trials and research activities. (This issue is further addressed in Priority 3.)
- Improved patient care would result from increased research on sarcomas. SMCs have the potential to assist and enhance clinical, translational, and basic research. Currently, only 1–2.5 percent of sarcoma patients are enrolled in clinical studies.

PRIORITY 1B.

Define sarcoma multidisciplinary centers.

Rationale

SMCs must be defined to identify the health care institutions that could provide optimal care to sarcoma patients.

Issues of Importance

Eligibility criteria would eliminate the possibility of misleading patients who seek optimal care.

The SMC requirements include the following:

- A sarcoma group consisting of physicians with special interest in all specialties, including surgical, orthopedic, and medical oncologists; radiologists; pathologists; and oncology nursing as well as rehabilitation services.
- One group member who is a member of a sarcoma-oriented medical organization, such as the Connective Tissue Oncology Society.

- Publications concerning sarcoma in peer-reviewed journals.
- Sarcoma conferences, where sarcoma group members meet at least once per month to discuss patient care issues.
- Approximately 50 newly diagnosed cases treated per year.
- Imaging (magnetic resonance imaging > 1.0 Tesla; positron emission tomography scan desired).
- Patient enrollment in clinical trials.
- Strong support personnel.

PRIORITY 2.

Design, implement, and study best practices in sarcoma management.

Rationale

The low incidence of sarcoma results in a lack of outcomes data and precludes objective assessment of end results of sarcomas.

Issues of Importance

- Investigate the potential role of payers and other groups (e.g., Leapfrog Group) in financially supporting the assessment of outcomes in sarcoma management. Sarcoma treatment costs may be significantly reduced if sarcoma is managed by SMCs. By decreasing the number of patient surgeries, costs could be reduced.
- Developing a registry would facilitate the availability of outcomes data.
- An international conference is needed to define the appropriate management of resected sarcoma specimens with respect to pathologic classification, grading, margin status, and treatment effect. Similar conferences have been held for lymphomas.
- Population-based studies are needed to evaluate the process of care and outcome results using retrospective data. This would provide a benchmark assessment of the quality of care and outcomes in patients from different populations and access to differing care providers. This could potentially be funded by supplements to NCCN Core Grants (P30).

PRIORITY 3.

Promote education among patients, providers, and payers concerning SMCs, treatment, and outcomes.

Rationale

Awareness of the advantages of referring sarcoma patients to SMCs should be increased.

Issues of Importance

- Educate and encourage pathologists and radiologists to facilitate referrals to SMCs.
- Expand patient information resources. For example, four or five on-line sources could be selected that provide information about sarcoma. These websites would be reviewed and evaluated by patient advocacy groups for content quality.
- Investigate potential additional roles of advocacy organizations.

CONCLUSION

Many if not most patients with sarcoma do not receive care that approaches what would currently be an acceptable standard. There are multiple reasons for this. Most primary care physicians, general surgeons, and general orthopedic surgeons have little or no experience in the management of these rare and complex tumors. There is a lack of broadly based outcomes data demonstrating the benefits of SMC care. Carefully obtained outcomes data will increase the pressure for improved care of sarcoma patients. Treatment at SMCs will result in specialized care to patients with sarcoma, better patient outcomes, and enhanced research efforts.

SMC designation requires that specific criteria be met. Supplements to core grants (P30 awards) could be used to fund population-based studies to evaluate processes of care and outcome results using retrospective data. Such studies would provide objective information concerning the current management and outcomes of soft-tissue sarcomas in different populations. Educating patients, providers, and payers concerning SMCs and sarcomas is important for optimizing patient outcomes and expanding research.

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Appendix B

Science-Centric Breakout Group Reports

BETTER BIOLOGY AND DISCOVERY

Co-Chairs:

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INTRODUCTION

In summarizing the known biology of sarcomas, one must be mindful that "sarcoma" is a complex disease category. Sarcomas can arise from, or differentiate toward, any of the many mesenchymal cell types that comprise the normal connective tissue structure, including fibroblasts, smooth and skeletal muscle, fat, nerve sheath, cartilage, and bone. In many cases, sarcomas evolve from more benign versions of the same tumors, and the biologic and clinical interface between benign and malignant can be difficult to define. In other sarcomas, such as Ewing's sarcoma and synovial sarcoma, no demonstrable benign precursors to the malignant tumor have been identified and, in fact, the precise tissues of origin remain to be defined.

For the most part, the identity and biological functions of the transformed progenitor cells in sarcomas have not been determined. The possibility of derivation from a mesenchymal stem cell, or at the least a noncommitted mesenchymal progenitor, is suggested by the examples of pulmonary chondroid hamartoma, triton tumor, and others. In pulmonary chondroid hamartoma, a transformed primitive mesenchymal cell can differentiate towards chondroid, adipose, smooth muscle, and skeletal muscle, and such components are typically admixed within an individual tumor. [1] However, in the more common types of sarcoma, the progenitor cell has not been identified. For example, the diagnosis of leiomyosarcoma is based on morphologic and immunophenotypic resemblance of the tumor cells to smooth muscle, but it is not clear whether the leiomyosarcoma progenitor cell is already committed to a smooth muscle differentiation pathway, or—alternately—whether it is a pluripotential mesenchymal cell in which smooth muscle differentiation results from the transforming mutations. Identification of sarcoma progenitor cells would greatly expedite the development of relevant in vitro and in vivo disease models.

Over the last decade, a considerable amount of the biologic headway toward understanding sarcoma pathogenesis has come from the study of tumor-associated genomic abnormalities (Table B.1). [2,3] Unlike some mutations that can found in a broad array of cancers, a one-to-one relationship frequently exists between a certain chromosomal rearrangement and a particular sarcoma. Many of the sarcoma chromosomal rearrangements are translocations that create fusion oncogenes, resulting in the production of chimeric transcripts and proteins. Because these sarcoma fusion oncogenes are specific for particular sarcoma subtypes, they serve essential roles as molecular markers in sarcoma diagnosis. They have also provided mechanistic insights into sarcoma oncogenesis.

Many fusion oncoproteins appear to function as aberrant transcriptional regulators, of which the PAX-FKHR oncoprotein in alveolar rhabdomyosarcoma and the EWS-ETS

oncoproteins in Ewing's sarcoma are well-characterized examples. [4-7] The transforming activity and biological consequences of these oncogenic transcription factors probably involve perturbations of proliferation and differentiation programs. [8,9] Although these transcription factor oncogenes appear to be essential to the development and maintenance of the corresponding types of sarcoma, it is unclear whether they are initiating oncogenic mutations or they are preceded by other mutations. Ectopic expression of fusion genes can be toxic in many cell types. This suggests that both additional genomic mutations and a compatible cell context are necessary for the genesis of most sarcomas.

Table B.1: Recurrent Molecular and Cytogenetic Aberrations in Soft-Tissue Sarcomas

Tumor	Cytogenetic Event	Molecular Event	Frequency	Diagnostic Utility?
Alveolar soft part sarcoma	t(X;17)(p11;q21)	*ASPL-TFE3* fusion	>90%	Yes
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*FUS-ATF1* fusion	?	Yes
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1* fusion	>75%	Yes
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1* fusion	>75%	Yes
Dermatofibrosarcoma protuberans	Ring form of chromosomes 17 and 22	*COL1A1-PDGFB* fusion	>75%	Yes
Endometrial stromal tumor	t(7;17)(p15;q21)	*JAZF1-JJAZ1* fusion	30%	Yes
Ewing's sarcoma	t(11;22)(q24;q12)	*EWS-FLI1* fusion	>80%	Yes
	t(21;22)(q12;q12)	*EWS-ERG* fusion	5–10%	Yes
	t(2;22)(q33;q12)	*EWS-FEV* fusion	<5%	Yes
	t(7;22)(p22;q12)	*EWS-ETV1* fusion	<5%	Yes
	t(17;22)(q12;q12)	*EWS-E1AF* fusion	<5%	Yes
Fibrosarcoma, infantile	t(12;15)(p13;q26)	*ETV6-NTRK3* fusion	>75%	Yes
Gastrointestinal stromal tumor		*KIT* or *PDGFRA* point mutation	>85%	Yes
	Monosomies 14 and 22		>75%	No
Inflammatory myofibroblastic tumor	2p23 rearrangement	*ALK* fusion genes	50%	Yes
Liposarcoma Well-diff/Dediff	Ring form of chromosome 12		>75%	Yes
Liposarcoma Myxoid/Round-cell	t(12;16)(q13;p11)	*TLS-CHOP* fusion	>75%	Yes
Rhabdoid tumor	Deletion of 22q	*INI1* inactivation	>90%	Yes
Rhabdomyosarcoma Alveolar	t(2;13)(q35;q14)	*PAX3-FKHR* fusion	>75%	Yes
	t(1;13)(p36;q14), double minutes	*PAX7-FKHR* fusion	10-20%	Yes
Rhabdomyosarcoma Embryonal	Trisomies 2q, 8 and 20		>75%	Yes
Synovial sarcoma	t(X;18)(p11;q11)	*SYT-SSX1* or *SYT-SSX2* fusion	>90%	Yes

Another functional class of sarcoma fusion oncogenes encode aberrant tyrosine kinases, resulting from fusion of an ectopic oligomerization domain to the catalytic domain of the tyrosine kinase protein. [10] The resultant fusion proteins function as

constitutively oligomerized and constitutively activated tyrosine kinases. Examples include the ALK fusion oncoproteins in inflammatory myofibroblastic tumor [11] and the ETV6-NTRK3 fusion oncoprotein in infantile fibrosarcoma. [12] In addition, aberrant activation of tyrosine kinase oncogenes can result from intragenic point mutations, as in the case of KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). [13,14] Tyrosine kinase oncogenes are strongly transforming in cell culture, and the tyrosine kinase transforming activity is dependent on signaling through the phosphatidylinositol 3 kinase/AKT survival pathway and through the RAS/mitogen activated protein kinase kinase/mitogen activated protein kinase proliferation pathway. Some evidence indicates that tyrosine kinase oncogenes can be initiating mutations, as demonstrated by the germline KIT mutations in GIST kindreds. [15,16]

Tumor suppressor genes also play essential roles in most, and perhaps all, sarcomas. Examples include p53 inactivation mutations in osteosarcoma [17] and SNF5/INI1 mutations in rhabdoid tumors. [18] Both of these mutations can be found as germline aberrations in patients with cancer syndromes [19,20], and in that context can be regarded as initiating mutations in the development of the associated sarcomas.

Several sarcoma oncogenes have already been used to advantage as therapeutic targets. Examples include the KIT and PDGFRA oncoproteins in GISTs [13,16,21] and activated PDGFRB—which results from oncogenic overexpression of the ligand PDGFB—in dermatofibrosarcoma protuberans. [22] Although essential oncogenes have been identified in many sarcomas, other oncogenes and tumor suppressor genes certainly remain to be identified in these tumors. Such genes probably play key roles in neoplastic progression, and their identification could provide additional therapeutic targets in sarcoma.

These observations prompt the following underlying questions:

- What are the progenitor cells that are transformed to give rise to different sarcomas?
- What are the dominant genetic pathways driving sarcoma development and maintenance?
- Which sarcoma oncogenic pathways are therapeutically tractable in the near future?

PRIORITY 1.

Enhance interactions among disciplines, including sarcoma biology, mesenchymal biology, and embryology, NIH should sponsor an annual or biennial symposium that is broadly inclusive of a range of scientific disciplines and industry. One objective would be to identify high-priority, cross-disciplinary research to be supported by request for application or program announcement mechanisms.

Rationale

Progress in sarcoma biology and in identifying new therapeutic targets will be enabled by greater interplay between researchers in the fields of sarcoma oncogenesis/biology and those studying normal mesenchymal development and embryogenesis. Furthermore, the public health benefits of sarcoma research will be maximized through interactions between scientists in this field and those working on other aspects

of mesenchymal pathology, such as atherosclerosis and osteoarthritis. Therefore, an active, prospective mechanism is needed to ensure progress in identifying sarcoma progenitor cells and generation of useful models for sarcomagenesis, and to expand the relevance of sarcoma research to other aspects of mesenchymal biology. Such a mechanism should not be limited to stimulating interaction among academic investigators but should also include fostering information exchange between sarcoma researchers and potential partners in the pharmaceutical or biotechnology industries.

Issues of Importance

- Commitment from NIH to support cross-cutting research symposia in sarcoma and mesenchymal biology.
- Commitment from NIH to support cross-cutting research in mesenchymal embryology, biology, and oncogenesis. This should ideally include solicitation of multiple investigator applications R01 or similar mechanisms, so as to promote multi-institutional collaborations.

PRIORITY 2.

Provide mechanisms of support to identify therapeutically relevant sarcoma mutations by genomic analysis of the sarcoma kinome and to identify sarcoma therapy response biomarkers by proteomic profiling of clinical specimens.

Rationale

While individual investigator-initiated studies will continue to reveal mechanisms of sarcoma oncogenesis, additional opportunities exist to hasten progress in identifying essential and therapeutically tractable sarcoma mechanisms. Such efforts may require expertise or infrastructure that is presently unavailable to most independent investigators. For example, substantial gains could potentially be made by applying current high-throughput genomic technologies to the search for tumor-associated mutations in sarcoma biopsy specimens or cell lines. Gain-of-function kinase mutations have been shown to play central roles in certain sarcomas. Pharmacological inhibitors of these protein kinases are under development by many drug companies and could prove to be a valuable source of new therapeutic agents for sarcomas harboring activating kinase mutations.

Issues of Importance

- Assemble and prioritize a representative panel of sarcoma cell lines and/or tumor samples for kinome analysis.
- Establish a coordinated system of specimen submission and publicly available data distribution for sarcoma kinome and other large-scale sarcoma genomic analyses.
- Identify and prioritize the sarcoma clinical models with the highest likelihood of being informative in proteomic marker screens.

PRIORITY 3.

Establish a central source of key resources to facilitate identification of essential aspects of sarcoma biology and enable their clinical translation. This should include both physical resources (cell lines, purified tumor-derived nucleic acids, viable cells, frozen tissue, tissue arrays, and expression constructs) and conduits to intellectual properties (expression microarray datasets and small molecule inhibitor "tool" compounds).

Rationale

Due to the rarity of individual sarcomas relative to other human malignancies, the lack of reagents can be a major impediment to established sarcoma researchers and, especially, to those trying to enter the field. A common resource for acquiring physical reagents would greatly benefit both groups. In addition, a mechanism for obtaining access to more restricted data (e.g., microarray data) or reagents (e.g., small molecule "tool" compounds) would be a boon. Up until now, obtaining these latter resources has been idiosyncratic and heavily reliant on establishing expedient interpersonal contacts. This has been particularly true for accessing small molecule inhibitors and other novel therapeutics developed by industry. Creation of web-based applications that offer initial contacts among investigators or conduits to pharmaceutical/biotechnology representatives could greatly enhance these potentially fruitful interactions.

Issues of Importance

- Infrastructure or support to create and distribute sarcoma tissue arrays, viable cells, frozen tumor, and sarcoma nucleic acid panels (both DNA and RNA), including at least 10 examples of each of the common types of benign and malignant mesenchymal tumors.
- Support for the creation and validation of a panel of sarcoma cell lines, including three-to-five representative examples of each of the common types of sarcoma, to be housed and distributed in an established facility, such as the American Type Culture Collection (ATCC).
- Collection and distribution of sarcoma oncogene expression constructs by a centralized resource, such as the ATCC.
- Determination of appropriate levels of accessibility to sarcoma datasets among investigators.
- Establishment of mechanisms, perhaps involving an NIH liaison, to facilitate interactions between the academic sarcoma research community and the pharmaceutical industry.

CONCLUSION

An urgent need exists to hasten the understanding of sarcoma biology and, in so doing, to identify novel therapeutic targets for these frequently disabling and/or lethal diseases. Although sarcomas are relatively uncommon and the sarcoma research field is commensurately small, much advantage can be gained by integrating sarcoma research with other disciplines in mesenchymal biology and pathology. A mesenchymal disease symposium should be initiated to highlight and promote such cross-disciplinary interactions and to identify high-impact research areas that warrant

targeted funding emphasis from NIH. In addition, progress in sarcoma biology and therapeutics must be hastened by supporting strategic larger scale genomic and proteomic surveys, which will provide the necessary infrastructure for subsequent biologic and preclinical studies within individual investigator research laboratories. The ability to conduct such studies efficiently and to generalize novel findings to different types of sarcomas will require substantial expansion of centralized sarcoma reagent and data resources. Although centralization of resources is desirable generally, given that many types of sarcoma are rare, it is particularly important that sarcoma tissue arrays, cell lines, tissue and nucleic acid samples, oncogene expression constructs, pathway inhibitors, and expression data be more widely available to those in the sarcoma research community.

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BETTER IMMUNOLOGY

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INTRODUCTION

Over the last decade, exponential advances in tumor immunology have provided a sound scientific basis for pursuing immunotherapy for cancer. What was once a marginal enterprise in cancer therapy is now becoming a reality. Within the next 5 years, the U.S. Food and Drug Administration is likely to approve new immune-based therapies for lymphoma, renal cell carcinoma, and melanoma.

The roots of many modern concepts in tumor immunobiology originated in murine models of sarcoma, including seminal findings on T-cell antigen recognition, the role of heat shock proteins in innate and adaptive immune interactions, and immune surveillance. The application of these principles to the study of the immunobiology of human sarcomas provides a compelling opportunity for the development of new, targeted immunotherapies. Classical studies of methacholanthrene-induced sarcomas in mice gave rise to the basic principle that the T-cell-mediated response to cancer is tumor specific. Further investigation identified heat shock proteins expressed by murine sarcomas as molecular chaperones capable of presenting immunogenic peptides to the adaptive immune system, thus providing a mechanism for the specificity of antigen recognition. More recent data have shown that the capacity for heat shock proteins expressed by sarcomas to activate innate immunity through dendritic cell interactions leads to cross-presentation of tumor antigens and the subsequent development of adaptive immune responses. Therefore, murine sarcoma studies have provided perhaps the most dramatic demonstration of the critical role of the interactions between innate and adaptive immunity in inducing antitumor immune responses. Further, extensive studies of methacholanthrene-induced sarcoma growth in genetically targeted T-cell-deficient mice have provided unequivocal evidence that immune surveillance plays a role in preventing tumors. Thus, murine models of sarcoma have not only clearly identified sarcomas as immune-responsive tumors, but they have also provided seminal insights into the host–tumor interface that have influenced current thinking regarding the larger field of tumor immunology.

To translate the insights gleaned from murine sarcomas into new immunotherapies for human sarcomas, specific targets of antigen recognition need to be identified. Tumor antigens have been identified primarily by dissecting the cell-mediated and humoral responses present in tumor-bearing patients that are directed toward autologous tumors or cDNA libraries derived from autologous tumors. Tumor antigens can be classified as belonging to one of the following groups:

- Tissue differentiation antigens that are highly expressed in embryonal tissues but have limited expression on normal adults tissues (e.g., carcinoembryonic antigen in colon carcinoma and melan-A/Mart-1 in melanoma).

- Cancer-testis antigens that are expressed on many neoplastic tissues and germ cells, presumably as a result of widespread genomic demethylation in neoplastic tissues (e.g., MAGE family).
- Mutated self-proteins that often occur as a result of the malignant process itself and contribute to the growth/survival pathways of the malignant cell (e.g., mutated Cdk4).
- Overexpressed self-proteins (e.g., n-MYC in neuroblastoma and HER2/neu in breast and ovarian cancer).
- Viral antigens expressed by virally associated tumors (e.g., human papilloma virus in cervical carcinoma and HHV-8 in Kaposi's).

Our current understanding of the biology of human sarcomas suggests that they are likely to express tumor antigens from each of these categories; however, very little is known regarding the extent of tumor antigen expression in the wide array of human sarcoma histologies. Further, it is not known whether endogenous immune responses exist in patients whose sarcomas express genes that are antigenic in other histologies. Therefore, while the results of murine studies and the identification of an array of tumor antigens likely to be expressed by sarcomas provide reasons to surmise that immune responses may be exploited in sarcoma patients, very few studies aimed at defining tumor antigens in human sarcomas have been performed.

Barriers to Progress

The primary barrier to research in the immunology of sarcomas is the *lack of a critical mass of investigators*. Most tumor immunologists are focused on melanoma and renal cell carcinoma, which are classically defined as "immune-responsive" tumors. However, evidence from murine models and the plethora of antigenic targets that are now identified as potential tumor antigens suggest that even in the absence of spontaneous tumor regressions in human sarcomas, opportunities exist for immunotherapy of sarcomas. The funding of studies designed specifically to address the immunobiology of human sarcomas is necessary to increase the number of investigators.

A second barrier to research in the field of immunology of sarcomas is the *lack of reagents* required to undertake basic studies to define tumor antigen expression in sarcomas; the critical first step in determining endogenous immune responses in patients with sarcoma. As tumor immunotherapy has become more antigen directed and molecularly targeted, sufficient quantities and accurately classified tissues for study from homogenous histologic groups must be available so that valid conclusions regarding antigen expression may be generated. Also necessary are viably cryopreserved cells from each of the sarcoma histologies to accurately determine whether molecular and immunohistochemical evidence for tumor antigen expression is accompanied by major histocompatibility complex-mediated *presentation* of tumor antigens. In addition, researchers must have access to immune effector cells from the patients from whom the tumors are derived in order to study patient responses. Peripheral blood mononuclear cells (PBMCs) are necessary in order to determine whether antigen expression in sarcomas leads to immune priming and whether immune responses directed toward a particular antigen can result in the killing of the sarcoma cell itself. HLA typing of patient samples and sarcoma cell lines is also required so that HLA restriction of candidate tumor antigens can be determined.

A third major barrier to research in the field of immunology of sarcomas is *the relative paucity of studies in human immunology* compared to murine immunology. A

plethora of information exists regarding immune responses toward murine sarcomas; however, this has not been translated to the biology, immunology, or clinical management of human sarcoma. To address this problem, general studies in human immunology and human tumor immunology need to be encouraged through funding mechanisms. Incentives for studies of human immunology and the availability of appropriate reagents for study will naturally lead more investigators to study the immunobiology of human sarcomas.

Opportunities for Progress

Sarcomas provide a *major opportunity for progress in immunotherapy* because the natural history of the disease results in a clinical scenario that is amenable to immune based therapy:

- The primary treatment for sarcomas is surgery, which provides an ample source of antigen. The ability to viably cryopreserve sarcoma tissues can potentially provide the research community with substantial amounts of tissue for study and a ready source for whole-cell approaches to tumor vaccination. Currently, several "patient-specific" immunotherapy approaches have progressed to phase III trials after good results in phase II trials that provided evidence that such approaches using patient-derived tissue as an immunogen are potentially clinically applicable.
- Chemotherapy is not effective for most histologies; therefore, patients with recurrent or progressive disease have not been heavily pretreated with cytotoxic agents and are therefore likely to be relatively immune competent compared to patients with other high-risk cancers.
- Incurable sarcomas are often readily reduced to a state of minimal residual disease by surgery alone.
- The lack of progress over at least two decades provides good historical controls for pilot studies. Optimization of such pilot studies in surgically resected high-risk patients could be guided by surrogate endpoints, such as the development of tumor-specific immune responses.
- The lack of good alternative treatments means that very little competition exists for innovative therapies for high-risk sarcomas. Because tumor vaccines in general are safe, high-risk patients with fully resected tumors may be reasonable candidates for immune-based therapy trials. For many of these patients, although their risk for recurrence approaches 100 percent, no reasonable alternative therapies are available.

PRIORITY 1.

Develop the centrally available core reagents necessary to begin addressing the immunobiology of human sarcomas. In addition to standard tissue banks and cell lines representing the wide variety of sarcoma histologies, viably cryopreserved tumor cells and PBMC and (where possible) aphaeresis specimens from patients with sarcoma should be made available.

Rationale

Standard tissue banks can only allow a very superficial screen for potential tumor antigens. Viably cryopreserved cells with matched lymphocytes are required to undertake immunologic studies.

Issues of Importance

Many tumor antigens have now been identified in other tumors, but the expression and immunogenicity of these molecules in sarcomas are largely unknown. Both (1) differentiation antigens and (2) mutated or amplified self-antigens that contribute to the neoplastic process are antigenic in other tumor models. Current understanding indicates that sarcomas represent an opportunity for rapid scientific progress based on the following:

- Differentiation antigens are likely to be highly expressed in sarcomas comprised of primitive mesenchymal tissues.
- Fusion proteins of sarcoma and their downstream transcriptional targets appear to be attractive candidates because of their critical role in the induction and maintenance of the relatively nonmutable transformed state. Such mutated or overexpressed transcription factors have been shown to be immunogenic in other model systems.

Investing in the development of procedures to generate viably cryopreserved specimens will advance sarcoma research beyond immunobiology alone. Procedures for preservation developed under Good Clinical Practice conditions can serve as the basis for subsequent Good Manufacturing Procedures for immune-based therapies using whole cell vaccines. In addition, the development of such standard operating procedures will also facilitate the pursuit of other preclinical studies in sarcoma that rely heavily on the availability of xenograft models.

PRIORITY 2.

Fund sarcoma-specific immunobiology studies so that established immunologists will have an incentive to apply their expertise to sarcomas.

Rationale

Immunotherapy is device independent. The investigators and technology are already available and the infrastructure exists within established immunology laboratories to rapidly identify whether antigens present in other human tumors are expressed and immunogenic in human sarcomas.

Applying state-of-the-art immunology reagents and expertise to the field of sarcoma biology can readily identify new immune-based therapies for sarcoma. Advances in knowledge have the potential for rapid translation to the clinic. Such studies are most likely to be successful if carried out by established human tumor immunologists;

unfortunately, these investigators are currently focused on other diseases. The success of this recommendation requires that sarcoma-specific mechanisms encourage investigators to study sarcoma immunobiology.

Issues of Importance

Dramatic progress has been made in identifying and measuring immune responses to target antigens in the last decade. Immunologists have a variety of reagents available to identify, quantify, and characterize immune responses to specific antigens. For instance, tetramers for the accurate identification and quantification of antigen-specific T cells are now available for essentially any molecularly identified antigen. After identification, the T cells can be characterized for function and phenotype and sorted for subsequent expansion for therapeutic studies. Similarly, peptide-based assays, such as enzyme-linked immunospot, intracellular cytokine staining, and bead arrays, are readily available to quantify extremely low-level immune responses that are characteristic of endogenous responses. Older technologies could not measure these marginal responses.

A plethora of human tumor antigens have now been defined. Access to standard tissue banks for use in microarray and immunohistochemical analyses will quickly identify the extent of sarcoma-specific antigen expression from antigens defined in other human tumors. Immunogenicity analyses of the same antigens in other human tumors and computer-based algorithms will allow prediction of epitopes that bind to unique HLA alleles.

Established investigators in human tumor immunology can readily apply state-of-the-art approaches to measure immune responses using peptides identified through tissue bank screening. Using PBMC from patients with sarcomas is relatively straightforward to determine whether endogenous immune responses exist toward these sarcoma-associated antigens. With the availability of viable cryopreserved tumor cells will come the validation of tumor antigen expression by demonstrating activation or lysis by peptide-specific T cells in response to sarcoma cells.

In summary, applying state-of-the-art immunology reagents and expertise to the field of sarcoma biology can readily identify new immune-based therapies for sarcoma. Advances in knowledge have the potential for rapid translation to the clinic. Such studies are most likely to be successful if carried out by established human tumor immunologists; unfortunately, these investigators are currently focused on other diseases. The success of this recommendation requires that sarcoma-specific mechanisms encourage investigators to study sarcoma immunobiology.

PRIORITY 3.

Provide incentives to young investigators to study the immunobiology of sarcomas for a long-term investment in this field.

Rationale

The time is ripe to exploit advances in developmental biology, molecular pathways, and immunobiology to translational progress in sarcomas. The rate-limiting step for capturing these opportunities is the lack of investigators; therefore, young investigators should be targeted. Addressing basic immunobiologic principles in sarcomas, such as the capacity for immune responses to occur in bone versus lung, could lead to important insights for immunotherapy in general.

Issues of Importance

- Modest NCI-based funding initiatives, such as K08 or K22 mechanisms, would foster the interest of young investigators. Supplements to existing funding mechanisms for sarcoma would also provide incentives.
- Exploring public–private partnerships (as exemplified by the Modell Foundation and the Leukemia Society) for funding young investigators could lead to significant increases in sarcoma researchers as well as funding. Partnering with the NCI would ensure a stringent peer-review process that would be valuable. The NCI would need to commit to working with private/philanthropic sources specifically interested in sarcomas.

CONCLUSION

The last decade has witnessed dramatic progress in understanding the immunobiology of and developing effective immunotherapies for cancer. There is every reason to believe that these advances in immune-based therapy for cancer in general could translate into effective immune-based therapies for sarcoma, since murine models of sarcoma have provided clear evidence that these are immune-responsive tumors. The cells of origin in sarcomas are likely to express candidate tumor antigens, and core technologies are now available to apply powerful immunologic reagents, such as tetramers and immunogenic peptides, for the rapid identification and characterization of tumor antigens in human sarcomas. Thus, relatively low-cost investments in young investigators, sarcoma-specific research incentives to current immunologists, and an optimized arsenal of reagents are highly likely to produce substantial, rapid, and long-term gains that will lead directly to clinical trials of novel, specific, nontoxic therapies for these many and varied tumors.

BETTER ACCESS TO ANNOTATED TISSUE

Co-Chairs:

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INTRODUCTION

With the recent increase in high-throughput technology, such as genome-wide expression profiling, comparative genomic hybridization, and the more detailed assessment of various molecular pathways within malignant cells, the need for access to tumor samples has increased. While obtaining sufficient specimens for most human neoplasms is difficult, this is especially difficult in the field of soft-tissue tumors.

Sarcomas are relatively rare neoplasms and individual surgical centers do not obtain sufficient materials for studies. Additionally, a wide variety (over 80) of different diagnoses exist in the field of soft-tissue tumors, and as a result, the already small number of soft-tissue tumors includes a multitude of subgroups with even smaller numbers of samples to examine per subgroup.

Several web-based patient groups have expressed an interest or have been instrumental in collecting these rare tissues, but a coordinated, centralized collection of samples—or at least a consensus approach to this issue—is desperately needed.

Unfortunately, the many barriers to a solution of the problem of tissue access include the following:

- Scattered and unfocused funding for sarcoma research and related tissue banking.
- Inadequate annotation and nonuniform diagnosis leading to inadequate treatment and research interpretation.
- Distribution and prioritization of the collected annotated tissue (legal issues dictate who actually has access to the tissues and how they may or may not be distributed).
- Tension between Health Insurance Portability and Accountability Act (HIPAA) and institutional review board (IRB) regulations, and patient groups and researchers.
- Patients' tension over their desire for access to research data.

The members of this breakout group agreed unanimously that the following priorities should be implemented to ensure access to these very important annotated tissues.

PRIORITY 1.

Establish an NCI-dedicated group for sarcoma.

Rationale

A dedicated group for sarcoma study will help focus the efforts on research and treatment, and facilitate the creation of the greatly needed centralized annotated sarcoma tissue bank.

Issues of Importance

- Sarcoma research cannot compete with the large number of more common tumor groups. Funding resources are currently fragmented among a multitude of institutions whose efforts are largely uncoordinated, leading to inadequate treatment and research interpretation. Integrating with large-scale tissue banking efforts is not likely to be a solution, as these efforts are not designed to address rare diseases like sarcomas.
- A focused effort would facilitate collaborations among patients, their physicians, the medical community, and industry.
- Centers of sarcoma expertise should comply with established criteria to include basic qualifications and ground rules for participation. Each group wishing to become a center of sarcoma expertise would have to satisfy certain criteria (such as seeing a minimum number of sarcoma patients and having adequate clinical support) and agree to certain ground rules pertaining to tissue and data collection and storage. As one ground rule, specimens collected at these centers would need to be cataloged according to set standards and be sent to the central bank with the appropriate clinical information and associated histology, as needed by the researchers.

PRIORITY 2.

Provide for the organization of a single, centralized, sarcoma-focused tissue bank.

Rationale

A centralized sarcoma-focused tissue bank would facilitate quality control and distribution of (accurately identified) specimens and provide access to frozen, paraffin-embedded, and viable material and serum

Issues of Importance

- Start with centers of sarcoma expertise, then move into the community. In theory, a center of sarcoma expertise would have access to a wider range of tumors and therefore be more likely to correctly diagnose a particular tumor. As the program grew, community centers would become a resource for the tumors they remove. Ideally, all centers would collect and send as much tissue as possible (i.e., more than one sample from each specimen) possibly reserving some for their own purposes.
- Develop NCI/NIH-sanctioned protocols for tissue collection and distribution that address scientific and regulatory issues (HIPAA, Clinical Laboratory Improvements Amendments, IRB, etc.). From a privacy standpoint, HIPAA protects the data associated with the collected tissue. A vast number of IRBs

(and medical professionals) are not comfortable with the provisions of HIPAA, which are often misunderstood. A statement by NCI or other organizations, such as the American Society of Clinical Oncologists (ASCO), to elucidate and solve the regulatory hurdles would greatly aid in the collection of tissues. Such a protocol would attempt to standardize collection, making it as simple and affordable as possible.

- Design a protocol to standardize the collection and storage processes, which would greatly improve the viability of the collected tumors, and help IRBs become more comfortable with the protection of patients.
- Map out a distribution system through a multi-sector committee. The competition for available samples could be fierce. A fair and balanced distribution of samples, not restricted to centers of sarcoma expertise, would be aided by a committee that includes patients, researchers, and representatives of industry and government.
- Use pre-existing large-scale tissue analysis and genomic and proteomic facilities. Existing national tissue banks may not have the focus necessary to accommodate the collection of these very rare tumors. A pilot study should be conducted to see how many samples are currently available for research through existing systems. The pediatric Cooperative Human Tissue Network (CHTN) could serve as a model for the development of a centralized sarcoma tissue bank.
- Address ownership issues, including ownership of data and related developments. Again, the provisions of HIPAA are largely misunderstood and need to be explored. The concerns of some patients regarding industry involvement (for-profit motivations versus novel therapies) need to be addressed.

PRIORITY 3.

Maintain and update clinical databases with outcome (survival/relapse) results.

Rationale

The ability to correlate outcomes of life, death, and recurrence with biological markers and treatment is critical.

Issues of Importance

- HIPAA and other regulatory issues are barriers to access, but these barriers are not insurmountable. A tension exists between HIPAA and the IRB regulations intended to protect patient rights and privacy, as well as patient groups seeking to contribute their tissues and researchers interested in studying these tissues. A centralized IRB approach would help quell concerns about the misunderstood HIPAA regulations and other patient privacy issues.
- A separate tension occurs between patients who want access to research results and physicians whose studies are not set up to handle patient inquiries.
- Researchers may lack adequate systems for quality control, such as those in clinical laboratories.
- Data collection, standardization, and quality still require a resolution. The current bone marrow registry is a good model.
- Information technology infrastructure and other support are needed.
- Follow-up can be extremely poor and should be ongoing.

CONCLUSION

The existence of an NCI-sanctioned group dedicated to sarcoma research and treatment, together with a centralized tissue bank collecting samples that are annotated with adequate clinical follow-up would promote progress in this field enormously. However, the current HIPAA regulations continue to present major barriers that must be overcome.

BETTER MODELS AND PRECLINICAL TESTING

Co-Chairs:

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INTRODUCTION

Human sarcomas are a histopathologically and clinically diverse group of solid tumors, and many of these tumor types affect both children and adults. Although sarcomas are relatively rare compared to many epithelial malignancies, they are significant causes of morbidity and mortality, as many patients with these cancers are not identified until the disease is advanced. Moreover, the rarity of sarcomas has made it difficult to conduct large, randomized treatment studies and has made this subgroup of solid tumors less attractive as a focus for drug development by pharmaceutical companies than more common epithelial malignancies. These are among the many compelling reasons for developing better in vitro and in vivo models of human sarcomas.

Models of human sarcomas have a number of key requirements:

- Models must recapitulate the in vivo disease as closely as possible.
- The use of models should be reproducible in many laboratories for validation purposes, and the models should be relatively easy to work with.
- Models should be amenable to the testing of potential therapeutic agents either alone or in combination.
- Ideally, models should represent tumor recurrence or metastasis with clinically relevant mechanisms of drug resistance.

Relevant models of sarcomas would permit experimental assessment of hypotheses derived from human clinical and epidemiological data, as well as the opportunity for preclinical testing that can accurately predict human clinical response to novel agents for these diseases. In particular, models will provide a means for investigators to develop and test new molecularly targeted approaches to treat sarcomas. Unfortunately, very few models of human sarcomas have been successfully designed for either biological or therapeutic investigations.

PRIORITY 1.

Establish a mechanism to create a repository of viable tissue for developing sarcoma models.

Rationale

Most of the current preclinical models of human sarcomas are inadequate for biology and therapy studies. While many human sarcoma cell lines are available for research purposes, a large proportion of these cell lines represent only a small subset of sarcomas, predominantly sarcomas that are more common in children. Additionally, the relevance of such cell lines to human tumors in vivo has been questioned, especially after multiple passages. Xenograft models of sarcomas, including orthotopic transplantation, have been used quite extensively in sarcoma research and have addressed some of these concerns. However, these systems still need to be rigorously validated for their relevance to human sarcomas, especially since most models use human sarcoma cell lines injected into murine hosts.

Issues of Importance

- A funding mechanism (e.g., request for applications [RFA]) should be initiated that will support research to generate in vitro and in vivo models of sarcomas for which very few or no models exist and to annotate and validate those models that currently exist. The development of new models will require a concerted effort to collect, annotate, and maintain viable tumor tissues that can be provided to researchers who are actively pursuing these aims.
- Existing and newly developed models need to be annotated. Existing models should be better characterized with respect to the molecular and genetic definition of the tumor cells and assessment of the cells' metastatic potential. Annotation of viable human tissues will require standardizing personal data (e.g., clinical data) collection, in addition to defining the same global biological characteristics as the existing models.
- Cell lines will be optimized by expanding to three-dimensional culture systems grown under physiological conditions (e.g., varying oxygen and nutrient content). Three-dimensional culture systems will enable cell cultures to be a closer representation of in vivo conditions. Growing cells on Matrigel™ or similar supports also enables studies to test the metastatic potential of cells, perform confocal microscopy, and examine the influence of additional cell types (e.g., fibroblasts) in the tumor microenvironment.
- Tissue collection, storage, and annotation should not be exclusive to human tissue but should include collection from other animal species for validation purposes. Comparative genetic expression or proteomic studies between human and animal models (e.g., spontaneous sarcomas in canines) would further define the similarities and differences between these model systems to better validate the use of specific models for specific research purposes.

PRIORITY 2.

Establish an integrated preclinical testing program for human sarcomas.

Rationale

Currently, no integrated mechanism exists to test sarcomas for therapeutic response to drugs.

Issues of Importance

- An RFA should be initiated that supplements an existing program in preclinical drug screening to support the inclusion of adult sarcomas, or a screening program could be developed as a new initiative.
- A proposal for a program already exists for preclinical drug screening in pediatric cancer (Pediatric Preclinical Testing Program). This program may be an intermediate step between in vitro studies and large animal studies and has been organized to examine drugs that have entered clinical trials or are likely candidates for clinical trials. The program uses a panel of distinct, disease-specific in vitro and in vivo models to examine the potential for agents for which maximally tolerated doses have been defined. Examining a sarcoma model panel will add a layer of analysis to confirm the potential for success of a particular intervention before advancing to longer term, more expensive preclinical and clinical trials. The program is currently designed to study common childhood tumors; however, the establishment of adult sarcoma tissue models will enable this program to expand into other sarcomas.
- Models should include, but not be limited to, cell lines, xenografts, orthotopic transplants, genetically engineered mice, and large animal models. Currently, the program, as developed for childhood cancers, relies mostly on xenograft models and some transgenic models. However, by supporting an infrastructure to develop novel cell models and animal models, these panels can be expanded.
- The current preclinical testing program itself is a prototype that needs to be critically examined and optimized. In addition to providing data about selective drugs, the program needs to be tested using panels of models for different diseases. By expanding the preclinical testing program to include adult sarcomas, this program can continue to be optimized while simultaneously providing much-needed preclinical data for potential agents to target sarcomas. In addition, for more rare diseases like sarcomas, the more preliminary testing to validate a drug's potential will improve the likelihood that partnerships will be developed with biopharmaceutical companies to advance the drug.

PRIORITY 3.

Focus on developing better models for metastatic sarcomas.

Rationale

Metastatic disease is the strongest prognostic factor for most human sarcomas. Most patients who die from sarcomas die from metastatic disease. Research in metastasis is mired by the dearth of models specifically addressing sarcoma metastasis. Fusion proteins are commonly associated with different sarcomas, and observed roles of fusion proteins in sarcomagenesis will offer a unique model in which to study mechanisms of tumor progression.

Issues of Importance

- Metastatic sarcoma cell lines and animal models need to be identified and/or established for subsequent biologic and preclinical studies. The availability of these reagents will permit detailed analysis of molecular pathways causally associated with metastasis, as well as provide a preclinical tool for assessment of the efficacy of novel therapeutic and preventive approaches. Metastatic cell lines should be derived from a variety of sources, including human, rodent, and large animal sarcoma. The identification and experimental analysis of metastatic cell lines would be facilitated through development of in vitro assays that are predictive of metastatic behavior in vivo. One example would be the use of invasion assays and other measures potentially related to metastatic capability of sarcoma cell lines. Cell lines to be used as metastatic models should be designed to incorporate imaging capability (e.g., luciferase, green fluorescent protein, and red fluorescent protein) to augment basic research efforts, as well as to expedite assessment of the efficacy of new therapeutic agents.
- Sarcomas should be considered as representing useful models for studying other metastatic tumors. At least subtypes of sarcomas are hypothesized to result from fewer genetic abnormalities than many carcinomas, particularly translocation-associated sarcomas of childhood. Therefore, recapitulating metastatic disease in sarcoma models may be easier and more accurate than for more cytogenetically complex carcinoma-derived metastatic tumors. As such, sarcomas should be rigorously explored to understand basic metastatic biology. Additionally, targeted therapeutics may be better examined preclinically in a less complex metastatic tumor. The results of investigating sarcoma metastases can provide a foundation that can be applied to other cancers.

CONCLUSION

A repository that collects and maintains primary tissues to establish in vitro and in vivo model systems will accelerate the biological studies of sarcomas and investigations of the therapeutic potential of drugs to treat human sarcomas. Through technical expertise, a centralized repository will be able to efficiently process, annotate, and maintain viable tissues and, from those tumors, develop both in vitro and in vivo models. The existence and support of a well-maintained sarcoma repository will enable the broadest community of basic and clinical sarcoma researchers to develop an integrated preclinical testing program and conduct biological studies that define the molecular characteristics of sarcomas. Such a repository will also facilitate the generation and study of in vitro metastatic models and the generation and study of better animal models of primary and metastatic sarcomas. Novel models will be applied to study not only broad issues of biology and therapeutic potential of drugs but also specific diagnostic technologies of imaging and surrogate (intermediate) biomarker identification and validation. As the molecular characteristics of sarcomas are better understood and the needs of the preclinical testing field are refined for specific sarcomas, this information may influence the development of later generation models.

BETTER PREVENTION

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INTRODUCTION

Sarcomas are relatively rare and very heterogeneous and, hence, as a group lack a uniform approach and visibility in research and clinical studies. The etiology of sarcomas is probably similarly heterogeneous, and few precursor lesions are known.

In general, prevention research focuses on primary prevention, identifying etiological factors that can be modified (e.g., smoking cessation for lung cancer), or on secondary prevention, identifying early or precursor lesions that can be removed or reversed to prevent progression to life-threatening cancer (e.g., screening for colon polyps that, if removed, reduce colon cancer risk). However, for sarcomas in general, neither clearly defined environmental risk factors nor precursor lesions exist. The results of this PRG must advance this work for sarcomas.

The best-defined environmental risk factor for sarcoma is therapeutic radiation for both soft-tissue sarcoma and osteosarcoma, with young age at exposure associated with increased risk. Thus, one identifiable high-risk group is childhood cancer survivors treated with radiation therapy. Newer forms of more targeted radiation therapy with less exposure of the surrounding normal tissue reduce this risk. Other epidemiologic studies have suggested that some agricultural groups may be at increased risk of soft-tissue sarcoma. However, but the relative risk is not large, and no specific causal agents have been identified. In addition, increased incidence of sarcoma may follow exposure to Agent Orange but, again, the risk is not sufficiently high to provide a high-risk group on which to focus prevention research or intervention. All of NIH's currently funded prevention research on sarcoma focuses on Kaposi's sarcoma and human herpes virus 8.

Additional considerations in prevention include understanding the basic biology of tumor development. Sarcomas are pathologically heterogeneous and include tumors attributable primarily to mutations in tumor suppressor genes; tumors attributable primarily to translocations, giving rise to new fusion oncoproteins; and tumors attributable to mutation, giving rise to constitutive activation of an oncogene. Hence, no single mechanism of tumor development exists on which to base prevention strategies. We suggest that different prevention strategies will be needed for these three mechanistic types of sarcoma development.

A number of rare hereditary syndromes predispose to sarcoma, some to sarcoma in general, others to specific types of sarcoma. These are as follows:

Hereditary Syndrome	Sarcomas
Li Fraumeni syndrome	General
Hereditary retinoblastoma	General
Neurofibromatosis (NF1)	Malignant peripheral nerve sheath tumor
Rothmund Thompson syndrome	Osteosarcoma
Werner syndrome	Soft-tissue sarcomas
Hereditary multiple exostoses	Chondrosarcoma
Lipomatosis	Liposarcoma
Paget's disease	Osteosarcoma
Familial gastrointestinal stromal tumor (GIST)	GIST

It is our judgment that prevention approaches using human studies for heterogeneous rare tumor type(s) must focus on very high-risk groups. Currently, for osteosarcoma and soft-tissue sarcoma, the only currently identifiable very high-risk groups are genetically susceptible individuals and long-term survivors of childhood cancer treated with therapeutic radiation.

In addition, both spontaneous and engineered animal models for sarcoma development may provide new information and the ability to carry out preclinical trials relevant to prevention of human sarcoma.

PRIORITY 1.

Develop, use, and validate preclinical models that mimic human high-risk genetic syndromes predisposing to sarcoma or spontaneous sarcoma, including recombinant mouse, dog (spontaneous), rat, cat, and zebrafish. Preclinical models will be used to identify precursor lesions and genetic and environmental risk modifiers, and test preventive strategies.

Rationale

Animal models can be engineered to develop predictable patterns of sarcoma, including specific histologic subtypes attributable to defined molecular mechanisms. Given the predictably of the sarcomas, these model systems can be used to identify the genetic pathways and precursor lesions. Mouse models offer unique opportunities to identify modifiers of high-risk genes by varying the host background or environment. These models then provide the opportunity to identify host and environmental factors that also reduce risk. Spontaneous models, including dog models, also allow studies of specific environmental and genetic modifiers of sarcoma development.

Issues of Importance

- Significant resources are available to address this priority. Achievement of the priority will include interaction with established consortia, especially the NCI-funded Mouse Models of Cancer Consortia, which has significant infrastructure but will need to develop a focus on the issues of sarcoma prevention.
- The needed focus will include collaboration between investigators of mouse models (or other model systems) and human cancer oncologists, prevention specialists, and geneticists. This effort requires validation of the mouse models' relevance to human sarcoma, such as demonstrating the causal mutation(s),

relevant histologic and molecular analysis, and biologic behavior. This model system may then be used not only to build models of tumor progression, but also to identify precursor lesions, demonstrate the relevant biologic imaging endpoints, and identify the relevant molecular changes that occur in cancer development that may be targets for intervention. These mouse (or other) validated models would be an ideal setting for initial "clinical prevention trials." Model systems can be developed that include models for the sarcomas attributable to tumor-suppressor gene mutations, chromosome translocations that produce new fusion proteins, and mutations in oncogenes leading to constitutive activation. Common and distinct pathways may be identified for the various mechanisms through which sarcomas develop and for which distinct prevention strategies may be needed.

- At present, mouse models seem to offer the greatest potential; however, the initiative would support development of other sarcoma-related model systems as well, particularly in organisms such as zebrafish.
- In some instances, dogs may serve as a preferred model because some species are prone to spontaneous osteosarcomas. Veterinarians have developed cancer prevention efforts in dogs but these may not be sarcoma specific. Some species (wolfhounds) have a very high risk and in some lines, the tumor susceptibility appears to segregate as a recessive condition. Other than rapid growth in long bones, no sarcoma risk factors have been identified in dogs. The incidence of sarcoma in most dogs may not be high enough to enable them to serve as model systems, but high-risk species may serve as "sentinels" for response to exposure to suspected environmental agents. Resources may include the NCI Comparative Oncology Program and the Dog Genome Project at the National Human Genome Research Institute.

PRIORITY 2.

Identify a cohort of individuals at high risk for sarcoma for longitudinal prevention studies to identify precursor lesions and biomarkers associated with risk, test new imaging or early detection techniques, identify risk modifiers, and, ultimately, test preventive agents found through the preclinical studies. Identifiable high-risk individuals include those with hereditary cancer susceptibility syndromes and those with prior radiation therapy exposure in childhood.

Rationale

High-risk groups provide the greatest opportunity in humans to understand the molecular pathways that lead to sarcomas and identify the genetic mechanisms. They also provide the greatest opportunity to develop prevention studies, given their increased risk and the frequent identification of these individuals' years before they are at greatest risk for developing sarcomas. Their increased risk significantly affects the risk/benefit analysis when designing human prevention trials. Given that the hereditary syndromes are rare, a variety of groups must be contacted to identify sufficient numbers of individuals willing to enroll in sarcoma studies. These groups may include the Cancer Genetics Network, NIH Office of Rare Diseases, National Organization of Rare Diseases (NORD), Childhood Cancer Survivor Study (CCSS), and Sarcoma Foundation of America.

This cohort is a high-risk group for sarcoma that will allow the testing of hypotheses related to various genetic and environment risk modifiers, early or evolving biomarkers, effective diagnostic imaging, and chemoprevention.

Issues of Importance

- This defined cohort provides the best opportunity to develop strategies for prevention in humans. The findings from the mouse or other model systems described in Priority 1 should directly interact with and affect the study of the human hereditary cancer susceptibility syndromes.
- A bank with biospecimens, including longitudinal plasma and serum samples, DNAs, and tissue (fibroblasts, other) for ongoing and future studies to identify changes prior to tumor development or to precursor lesions should be established from these high-risk patients.
- This priority requires the collection of longitudinal data and samples to allow testing of new hypotheses. As in the mouse models system described earlier, the study of the high-risk tissue for the general and specific sarcomas may reveal common and distinct pathways for the various sarcomas.
- Available resources include an international NF1 database with voluntary participation. The CCSS includes some 15,000 five-year survivors of childhood cancer treated between 1970 and 1986, who are well characterized by radiation and chemotherapy and (to some extent) family history of cancer. These individuals have been followed longitudinally for late effects of cancer, including additional malignant neoplasms. This group could be targeted for collection of samples for proteomics, markers of risk, imaging studies, etc. Hereditary retinoblastoma cohorts have been developed for the study of additional malignant neoplasms that perhaps could be recruited for these studies. A number of individual investigators are studying some of the hereditary cancer syndromes. In addition, recruitment could proceed through the patient advocacy groups, including the Sarcoma Foundation of America, Life Raft Group, and NORD.
- Identification of the genetic high-risk groups may provide additional information on risk factors for sarcoma in the general population. To date, studies of genetic high-risk groups suggest that they may be at increased risk following exposure to agents that cause sarcoma in the general population (e.g., therapeutic radiation). Hence, they may be able to provide evidence for environmental risk factors. For example, the risk of sarcoma could be determined in genetic high-risk groups residing in agricultural areas.
- The hereditary syndromes cited are experienced primarily by individuals at high risk of sarcoma attributable to mutations in tumor suppressor genes (not including familial GIST) and hence may not be relevant to prevention strategies for the translocation-based sarcomas described in Priority 3.

PRIORITY 3.

Include epidemiologic, ethnic, and family history of cancer data in the sarcoma tissue bank registry.

Rationale

This registry could facilitate a better understanding of etiology at the molecular, cellular, and epidemiologic level to develop prevention strategies. Sarcomas of different etiologies may have different molecular signatures, different expression profiles, etc. Investigators should consider stratifying tumors by etiologic factors. We are further motivated to consider opportunities to understand sarcoma etiology when extreme differences in exposure groups or ethnic groups are observed. Specifically, highly significant differences in the incidence of Ewing's sarcoma exist in African Americans and others; Ewing's sarcoma represents one of the tumors attributable to chromosome translocations. In the African American population, specific DNA sequences might be resistant to the specific Ewing's translocation. Further, epidemiologic studies indicate that agricultural exposure may be associated with increased risk of soft-tissue sarcoma, and sarcoma shows an increased incidence in the farming belt in the middle of the United States. Research (expression profiling, etc.) that classified these tumors by exposure might provide new clues to etiology that might lead to the identification of specific carcinogens and, ultimately, to primary prevention by reducing the exposure.

If epidemiology information is not included in the sarcoma registry, these studies will be essentially prohibited.

Issues of Importance

- An epidemiologic questionnaire and database must be developed to characterize the specimens in the tissue bank. Epidemiologic studies in general would be facilitated by consistent coding developed to capture sarcomas currently coded to site of origin.

CONCLUSION

We have outlined a set of priorities to develop the knowledge on etiology and mechanisms required for the development of programs in prevention of sarcoma. These include collaborating with animal models groups to focus on sarcoma prevention, developing a cohort of high-risk individuals based on genetic susceptibility or environmental exposure, and characterizing the proposed sarcoma tissue bank by genetic and epidemiologic risk factors. These studies, when combined, should greatly advance the possibility of sarcoma prevention.

BETTER DIAGNOSIS AND PROGNOSTICATION

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INTRODUCTION

Better diagnosis of bone and soft-tissue sarcomas implies both an improvement in the traditional morphologic diagnosis as well as development and implementation of novel markers to enhance diagnosis and predict behavior.

Traditionally, the morphologic diagnosis of sarcomas has been problematic. This is due to several interrelated factors including the rarity of the disease, limited experience of most pathologists, increasingly smaller biopsy specimens (e.g., core needle biopsy), and lack of consensus among pathologists themselves concerning both the classification and grading of sarcomas. These issues are underscored by the fact that a 30 percent error rate is found in the diagnosis of sarcomas referred to clinical protocols and approximately 40-70 percent of surgical pathology reports lack information critical to patient staging (e.g., size, and grade).

Although without a doubt immunohistochemistry has improved the accuracy of sarcoma diagnosis, it has largely addressed the identification of structural cytoplasmic proteins, in an attempt to classify sarcomas more precisely. Few, if any, current markers are totally specific for any one tumor type, and there are essentially no prognostic or predictive markers used in daily practice. Thus, there is both a need and mandate to utilize new technologies to identify diagnostic, prognostic, and predictive markers.

Development of such markers would take advantage of advances in the field of molecular genetics and high-throughput technologies. The observations of chromosomal translocation, point mutations, and tumor-specific proteins have served as the source of "first-generation markers" in sarcomas. Application of these molecular assays can impact the diagnosis and management of sarcomas at several levels. The consistent presence of unique gene fusions within specific sarcoma types provides valuable markers for diagnosis and in some cases the presence of alternative gene fusions resulting from variant translocations offers the promise of defining subsets with distinct outcomes. Finally, the ability of polymerase chain reaction-based technology to detect rare fusion-positive cells has provided approaches for high-sensitivity detection of submicroscopic disease, such as metastatic spread to the bone marrow.

Despite the promise of the "first-generation markers" there remains a large category of sarcomas that to date have no diagnostic or prognostic markers (e.g., malignant fibrous histiocytoma or undifferentiated pleomorphic sarcomas of adults). Newer approaches that take advantage of high-throughput screening methodologies offer the best promise of marker identification.

PRIORITY 1.

Develop and promote best practice pathology guidelines. It is recommended that such guidelines be developed by a group of pathology experts working in close conjunction with appropriate organizations (e.g., College of American Pathologists) to encourage acceptance and dissemination of this information.

Rationale

There is a need to establish and/or endorse the following:

- Clinical and imaging information essential for pathologic interpretation.
- Minimum diagnostic criteria for certain sarcoma types.
- Appropriate allocation of tissues for diagnosis, research, and tissue banking.
- Grading system and its applicability or nonapplicability to needle biopsy specimens.
- Definitions of margin status (e.g., positive margin).
- Criteria for evaluating treatment effects.
- Algorithmic decision-making process for application of immunohistochemistry.

A discussion of problems related to immunohistochemical methods may comprise a part of these deliberations.

Issues of Importance

A critical issue will be to define an "expert" pathologist and appoint an appropriate group of such individuals to work constructively and objectively with various constituencies.

Development of standards for application of immunohistochemistry will be challenging since it infringes on the practice of large commercial laboratories who typically perform numerous immunostains largely for profit.

PRIORITY 2.

Studies need to be developed to test the diagnostic, prognostic, and/or predictive utility of recognized and novel molecular markers on large numbers of appropriate subsets of sarcoma cases.

Rationale

Studies of translocation-associated sarcomas have in several tumor categories detected one or more variant translocations as well as tumors without detectable translocations. Similarly, recent studies of gastrointestinal stromal tumors have provided evidence that KIT point mutations in different exons and point mutations in other tyrosine kinases (PDGFRA) are associated with different treatment outcomes. These findings provide evidence of molecular heterogeneity among cases with histologic homogeneity and that this molecular heterogeneity results in the presence of significant phenotypic heterogeneity. Therefore, these and other molecular markers provide the opportunity to identify unappreciated biological subsets within these sarcoma categories.

In addition, numerous studies of various molecular markers, most notably gene fusions in leukemias, have demonstrated the potential of sensitive molecular assays to detect these signposts of tumor cells even when the tumor cells are present in only the minority within a cellular population. Therefore, these assays provide the potential to monitor the presence of tumor cells at distal sites and at various time points during a patient's clinical course. Such analysis will have potential utility as a tool for molecular staging at the time of diagnosis, for monitoring response to therapy, and for assessing relapse.

Issues of Importance

These studies are contingent on the availability of a bank(s) of well-categorized, clinically annotated samples. These samples should include tissue from the primary tumor, sites of metastasis, and biological fluids.

Even though retrospectively collected tissue will permit focused studies of specific diagnostic issues, in many cases these tissues will not have annotated clinical data because of lack of appropriate informed consent necessitating delinking of the patient and much of the clinical data. In addition, in many cases, patients will be pooled from different sources; thus, the dataset will suffer from a lack of uniform treatment and clinical care. It is envisioned that, following institution of appropriate informed consent mechanisms, prospective collection of tissue, preferably from a cohort of uniformly treated patients, with the accompanying collection of clinical follow-up data will provide the optimal data for these studies.

PRIORITY 3.

Efforts need to be coordinated to apply high-throughput discovery approaches (including expression profiling, array comparative genomic hybridization, mutation screening, and proteomics) on selected subsets of sarcomas.

Rationale

New markers need to be identified that will enhance diagnostic, prognostic, and predictive capabilities. For various sarcoma subsets, analyses will provide data that will either confirm the homogeneity of these categories or detect unappreciated heterogeneity in these categories. In the case of homogeneous categories, the data will provide potential surrogate diagnostic markers that can be tested in subsequent directed studies. In the cases of heterogeneous categories, the data will provide markers that will enable novel subsets to be distinguished and the properties of these subsets to be compared in subsequent studies in which these markers of prognosis can be directly tested. Finally, based on the hypothesis that some aspects for the capability for eventual metastasis can be predicted from the properties of the primary tumor, it is believed that in some categories, markers that are associated with the propensity for metastasis may be identified.

Issues of Importance

The availability of tissue samples is crucial to the success of these ventures, at the levels of both the number of samples of a particular type of sarcoma as well as the amount of tissue of each sample. Therefore, judicious choices must be made concerning the specific studies for each tissue sample to maximize the benefit of limited tissue resources.

Based on the cost of the high-throughput approaches, consideration must also be made concerning the likely utility of each high-throughput approach to maximize the benefit of limited financial resources.

As in the previous priority, tissue collected retrospectively will provide only limited utility because of the likely absence of a full set of annotated clinical data. Therefore, it is likely that the most fruitful studies will be those that use tissues collected in a prospective manner from patients who are appropriately approached with informed consent in order to accumulate the full range of clinical follow-up data.

For several of these approaches, the availability of matched normal tissue from the patients will provide valuable controls for the precancerous genomic state of the patient.

CONCLUSION

Accurate pathologic diagnosis of sarcomas represents the cornerstone for subsequent scientific discovery and innovative clinical trials. Efforts to address issues related to inconsistent and incomplete reporting of sarcomas should be addressed immediately by knowledgeable individuals capable of interfacing with appropriate national and international organizations. Despite efforts on development of current markers, there remains significant work to definitively establish their role in clinical diagnosis and management. New methodologies represent the most promising means to identify urgently needed diagnostic, prognostic, and predictive markers. All of these efforts are contingent upon the availability of collections of well-annotated and uniformly diagnosed tissues.

BETTER IMAGING

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INTRODUCTION

Sarcoma tumors derived from mesenchymal tissue elements have traditionally been imaged using standard radiological techniques such as plain film, computed tomography (CT) scanning, and magnetic resonance imaging (MRI). More recently, positron emission tomography (PET) scanning has added significant functional information in a noninvasive and quantitative manner that correlates with histopathologic findings and clinical outcome. These imaging modalities can specify the tumor diagnosis based on anatomic and functional imaging information and correlation with histopathological data. In some sarcoma subtypes, the anatomic image may be pathognomonic for a specific tumor. However, these modalities have varying sensitivity to specific clinical information regarding the extent of disease, response to chemotherapy/radiotherapy, and diagnosis of recurrence.

Recently, PET imaging of tumor metabolism (and limited use of more specific biological tracers) has been explored and is becoming an important complement to conventional anatomic imaging and histopathological techniques in patient diagnosis and treatment planning. In limited studies, PET scanning has been shown to be useful in determining diagnostic biopsy site, assessing tumor grade, characterizing response to neoadjuvant/radiotherapy and site-directed drugs, and predicting patient outcome. PET scanning of a variety of tumors is also being investigated by a number of groups for use in treatment planning in conjunction with anatomic imaging data in radiation oncology.

Combined imaging modality use has demonstrated significant utility in identifying treatment response in experimental therapy protocols. However, sarcoma biological and experimental therapy research and clinical care still have not exploited the full capabilities of imaging to contribute to improved patient survival. Imaging is underused and often not performed properly at the basic science, translational, and clinical research levels. Properly designed imaging studies need to be incorporated into all levels of research to provide noninvasive, real-time biological data on tumor biology, effectiveness of new treatment strategies in animal models, and clinical trial design.

Imaging is often underused and sometimes overused in everyday clinical care due to the widespread lack of knowledge of imaging techniques and recommendations for imaging sarcoma patients, as well as the lack of recognition by third-party payers that patients with sarcoma have the same imaging requirements for their diagnosis, treatment planning, and response evaluation as patients with other cancer histologies. The information that can be provided by including appropriate imaging techniques in prospective studies and clinical care can significantly contribute to answering a wide array of questions regarding how to increase the survival of patients with sarcoma.

Barriers to the widespread use of imaging techniques in basic biology studies, animal studies, translational clinical studies, and larger scale clinical trials design include the following:

- Lack of input from imaging experts to study protocols at all levels of investigation.
- Underuse of functional and anatomic imaging techniques in patient diagnosis, treatment planning, and treatment response assessment.
- Lack of hypothesis-driven imaging studies in sarcoma.
- Lack of insurance reimbursement for functional imaging studies of proven clinical utility.
- Resources needed to achieve the priorities are as follows:
- Inclusion of imaging experts at all levels of investigation, with a demand for hypothesis-driven studies.
- Provision of adequate funding to include imaging in existing studies.
- Inclusion of anatomic and functional imaging modalities in prospective studies to justify Centers for Medicare and Medicaid Services and third-party reimbursement.
- Opportunities for stand-alone studies on the efficacy of imaging and new imaging techniques to determine treatment response and patient outcome.

PRIORITY 1.

Regional multidisciplinary sarcoma centers must include the following imaging resources:

- **Dedicated imaging coordinator**
- **State-of-the-art hardware, including a high-field MRI (1.0 Tesla or above) and a dedicated PET scanner.**
- **Patient care coordinator.**
- **Data analysis and imaging processing (information technology) capability.**
- **Ability to access intramural images and receive extramural images for interpretation and analysis.**
- **Access to clinical outcome data.**
- **Access to tissue samples and validation studies.**

Regional sarcoma centers should establish imaging guidelines to define best practices.

Rationale

Anatomic and functional imaging is a critical component of a high standard of care and specialized capability for sarcoma diagnosis, evaluation, treatment, and research.

Issues of Importance

- Imaging capabilities must be a component of qualification for designation of a regional sarcoma center of expertise.

PRIORITY 2.

Provide imaging input into clinical trial design and care planning. Imaging should be involved in all phases of trials (preclinical; phases I, II, and III; and translation). Imaging data analysis should be integrated into the statistical design of the study.

Rationale

Imaging is underused and not always completed properly. Existing imaging techniques, including anatomic and functional imaging modalities, can make significant contributions to all levels of research. Considerable imaging data are acquired but not analyzed in trial results.

Issues of Importance

- Study budgets must include funding for imaging and image analyses, as well as support for an imaging expert to conduct these studies.

PRIORITY 3.

Identify imaging research issues in sarcoma, including the following:

- **Identification of surrogate endpoints using imaging.**
- **Prospective validated imaging studies.**
- **Development of new imaging agents and imaging modalities.**
- **Incorporation of innovative uses of imaging protocols in radiation therapy planning.**
- **Participation in preclinical studies examining the mechanism of response and effectiveness of therapy.**

Institute collaboration among academia, the pharmaceutical industry, the private sector, and NCI to share knowledge, provide advice on the use of appropriate new technology, and supply more funding.

Rationale

Imaging data can provide surrogate endpoints that will increase the speed of development and significance of current and new therapies. Use of validated imaging techniques can also increase the speed of clinical trial outcome analysis.

Issues of Importance

- An imaging research agenda for sarcoma is needed that leads to hypothesis-driven prospective studies at all levels.
- Patients with sarcoma are ideal research imaging subjects, as the majority of their tumors are in the extremities and thus easily accessible for early clinical evaluation of new imaging technologies.

CONCLUSION

The development of regional multidisciplinary sarcoma centers will provide a high standard of care and specialized capability for sarcoma diagnosis, evaluation, treatment, and research. Inclusion of anatomic and functional imaging in clinical trial design is essential to evaluate the role and cost-effectiveness of these techniques as surrogate markers of response to therapy and as prognostic markers. Imaging data may help speed the development and clinical application of new therapeutic agents and determine the effectiveness of current therapeutic protocols.

BETTER CLINICAL STUDIES

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INTRODUCTION

The management of patients with sarcomas requires a multidisciplinary team that specializes in basic and translational research on sarcomas and the care of patients with this group of tumors. The multidisciplinary expertise at the special sarcoma centers recommended by the Sarcoma PRG is expected to provide higher success rates in diagnosis, surgery, medical/pediatric oncology, and radiation oncology.

The efficacy of surgery and radiation therapy has strong potential for improvement, resulting in higher likelihood of local tumor control and reduced frequency and severity of late treatment-associated morbidity, which remains a serious problem for sarcomas at many anatomic sites and for certain sarcoma types. Even though local control can be achieved, the late sequelae often constitute serious problems for patients and their physicians.

Despite many important advances, the majority of deaths in patients with sarcoma is due to metastatic disease because currently available chemotherapeutic and other systemic agents are not uniformly successful in eradicating microscopic or macroscopic metastatic disease. Chemotherapeutic studies have been limited by the small numbers of patients with particular sarcoma subtypes, the lack of widely accepted diagnostic criteria for sarcomas, and the small number of patients seen in centers other than those specializing in sarcomas. These factors severely lessen the experience with sarcomas of the oncologists at most institutions.

The current U.S. adult cooperative groups have been very effective at conducting studies in common tumors, but have not had similar success for sarcomas. This may be due to the following:

- The fact that sarcomas make up a small portion of all cancers treated by these groups and, hence, are not given sufficiently high priority for clinical study.
- The lack of sufficient expertise and/or interest in these tumors among group members.
- The fact that sarcomas have not been given high priority by the NCI Cancer Therapy Evaluation Program.

The Intergroup mechanism is unlikely to provide greater success because it shares the bottlenecks and problems experienced by the cooperative groups that are part of it.

Because all soft-tissue sarcomas are typically lumped together in chemotherapy trials, most studies have failed to identify the drugs or combinations of drugs that are active in particular sarcoma subtypes. For example, myxoid liposarcomas are highly

responsive to doxorubicin and ifosfamide, while gastrointestinal stromal tumors (GISTs) have been found to be unresponsive. The high prevalence of GIST in previous metastatic sarcoma trials has heretofore diluted the overall effects of the regimens tried. The best regimen for synovial sarcoma may not be the best regimen for leiomyosarcoma, and the best regimen for angiosarcoma may be entirely different. The best currently available regimens for Ewing's sarcoma are different from the best regimens for osteosarcoma, and these tumors are never lumped together in studies. Certainly, the best regimen for GIST is different from those for other sarcomas.

For effective studies to be mounted in specific sarcomas, specific diagnoses are required, and these can be made reliably only by expert sarcoma pathologists. Consequently, patients must be diagnosed at centers with sufficient expertise in the pathology of these rare tumors. Alternatively, a few referral centers should be established for the smaller centers, and pathologists at referring hospitals must be willing to share sufficient material for diagnosis and, hopefully, additional studies. Specifically, this means that physicians at smaller centers need to submit blocks or multiple unstained slides.

The diverse group of diseases known as "soft-tissue sarcomas" includes several subtypes that may be optimal for approaches of targeted therapy because they have specific translocations. To study these tumors effectively, cytogenetic studies or, preferably, molecular genetic studies must be performed to ensure correct target identification.

To study these diseases in scientifically reliable clinical trials, patients must be brought to the experts across North America for national trials. Trials should also be performed internationally to identify the best therapies for specific sarcomas and then strategies must be devised to test the integration of these therapies into multidisciplinary therapy.

Standard clinical trial designs requiring large numbers of patients, such as conventional phase III trials, are not well suited to dealing with a rare disease having multiple subtypes. New strategies must therefore be devised, and reliable intermediate therapeutic outcomes must be developed for assessing the activity of new treatments. Imaging has come a long way since current response criteria were developed and, ideally, should provide such outcomes. Functional imaging adds a new dimension, but due to the small numbers of patients, the database is inadequate for Medicare reimbursement for positron emission tomography.

At present, an international multidisciplinary forum for sarcomas exists but is not funded as a clinical trials organization. Interestingly, European investigators are organized to conduct sarcoma studies; cooperative groups exist in Scandinavia, Italy, Spain, and France that are specifically focused on sarcomas. The European Organization for Research and Treatment of Cancer (EORTC) has a specific and very strong soft-tissue and bone group, and members of this group are the only ones who perform EORTC studies of sarcomas. Both North American and European investigators would like to see a group coordinating multicenter North American or, better still, international trials. However, the obstacles for European participation in U.S. trials, especially those related to ethical issues, need to be resolved to have true, international collaboration.

In the United States, a small group of investigators has come together to form a consortium that includes some of the major sarcoma centers in the country. Other centers with an interest in sarcomas, including European investigators, would like to

participate in studies if an international sarcoma trial consortium with adequate funding were developed. The advantages of such a strategy would be multiple:

- Since only investigators with a major interest in sarcomas would participate in the consortium, internal competition with studies of more common tumors would be prevented and studies of high priority to investigators in the field could be conducted.
- Exceptionally rare tumors, such as alveolar soft part sarcoma, that could never be studied at a single institution could be studied with international cooperation. If North American investigators joined forces with European investigators, the number of patients available for study would be doubled.
- Only investigators interested in studying sarcoma would participate in an international sarcoma trial consortium. This would ensure a high level of expertise in sarcoma management and a focus on sarcoma biology that does not exist in the current adult cooperative groups. New trial designs addressing accrual of small numbers of patients could be used. Multidisciplinary studies could be performed because the membership would be multidisciplinary. Since the consortium would offer a forum for basic scientists as well as clinicians, translational studies would be encouraged.

PRIORITY 1.

Form a sarcoma-specific group to organize clinical trials that will be integrated into a multidisciplinary society focused on sarcomas that will conduct diagnostic, therapeutic, basic, and translational research.

- **Dissociate from existing adult cooperative groups.**
- **Prioritize and facilitate translation of new approaches.**
- **Establish representation at FDA and NCI.**

Rationale

Previous cooperative group mechanisms have worked well for common tumors but have not served the sarcoma community effectively.

Issues of Importance

- Facilitate rapid recruitment, efficient trial conduct, and rapid translation of innovative therapies.
- Concentrate patients into a single clinical trial group focused on sarcomas.
- Bring clinicians of different disciplines and basic scientists into a single forum to facilitate translational research.
- Provide a mechanism for international participation in collaborative clinical trials.

PRIORITY 2.

Use innovative clinical trial designs.

Rationale

- Sarcoma research is poorly served by traditional statistical paradigms for clinical trial design and conduct.
- Many sarcoma subtypes exist, some of which are quite rare.
- Rapidly emerging technologies are producing new experimental treatments at an ever-increasing rate.
- Actual medical treatment is sequentially adaptive, with multiple stages.
- Patient outcome typically is complex.
- Translational science and imaging studies should be incorporated into trial design whenever feasible.

Issues of Importance

- Use adaptive decision rules.
- Use Bayesian hierarchical models and regression methods to borrow strength across patient subgroups and between clinical trials.
- Account for complex treatment-outcome structure.
- Account for multiple sources of variability.
- Conduct many small-to-moderate-scale trials instead of a few large-scale trials.
- Conduct long-term follow-up to assess late morbidities and survival.

PRIORITY 3.

Implement high-quality information systems.

Rationale

- To optimize the reliability of the data that are the basis for statistical analyses and medical decision making.
- To optimize the linkage between statistical software, user interfaces, and databases.

Issues of Importance

- Database design and management, including data from clinical trials, genomics, proteomics, and other translational research studies.
- User-friendly interfaces.
- Statistical software development.

CONCLUSION

To enhance the ability to conduct better clinical trials in this group of rare tumors, a sarcoma-specific collaborative group is essential. It might be possible to base such a group on an already-established voluntary collaboration.

Innovative clinical trial designs maximizing the information from small numbers of patients are also required. The methodologies developed for these sarcoma trials could then be applied to other rare diseases.

Achieving these priorities requires dedicated funding for the proposed collaborative group with the responsibility for conducting the proposed clinical trials. This funding could be appropriately obtained by redistributing the funding for the existing cooperative groups to a newly formed sarcoma-specific collaborative group.

BETTER COMMUNICATION AND OUTCOMES

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INTRODUCTION

Sarcomas are rare neoplasms and, given the current fragmentation of care for these uncommon and diverse tumors, information about their management and outcomes is not readily accessible. At the time of initial diagnosis, many clinicians often are not knowledgeable about appropriate referrals, optimal management, and the need for follow-up care. Many treated patients, even those enrolled in clinical trials, have unknown outcomes. Treatment practices are poorly defined and have unclear relationships to outcomes. The ability to obtain long-term information, other than vital status and/or local control, is hindered by a mobile population, lack of access to medical records, and a gap in patients' self-knowledge about the details of their diagnoses and subsequent treatments, particularly among long-term survivors of childhood cancers. Appropriate short, intermediate, and long-term outcomes, as well as the tools for their measurement, are not standardized. Mechanisms for follow-up need definition, as do methods for managing barriers such as Health Insurance Portability and Accountability Act regulations.

Researchers, medical providers, patients, and others lack knowledge due to communication barriers. In particular, researchers do not share with each other relevant sarcoma research activities. Physicians who make the initial diagnosis often seem unaware of opportunities for referral for both optimal initial management (including radiologic assessment, diagnostic accuracy, and surgical management) and for tumor banking and evaluation of eligibility for clinical trials. Pathologists and/or diagnostic radiologists often do not recognize the importance and value of their role as facilitators of referrals to regional centers of excellence. Physicians who follow patients after completion of therapy typically are not familiar with guidelines for follow-up of late effects. Patients lack access to comprehensive information concerning their tumors, treatment, and critically important long-term follow-up. Third-party payers, the public, and legislators lack information regarding the disease and its care.

In NCI's current portfolio, approximately 20 projects and 4 clinical trials address survivorship, outcomes research, and cancer-control issues related to sarcomas. The majority of these studies focus on Kaposi's sarcoma, and only four projects and four clinical trials focus on bone sarcoma and/or soft-tissue sarcomas. One observational outcome study is evaluating the late effects of prior treatment for pediatric sarcoma. Additionally, one communication project is directed at children with solid tumors including, but not limited to, sarcomas. No projects directly address communication issues related specifically to sarcomas.

In terms of outcomes, effective multimodal treatments have improved the prognosis of many sarcomas in children, adolescents, and adults. The newer surgical techniques for sarcomas focus on preserving tissue and limb function; thus, amputations are performed less frequently. However, these preservation techniques are usually associated with the need for radiotherapy and potential late morbidity, including second cancers. Longer follow-up of these patients is needed to assess both medical risks and functional and psychological sequelae of local resection or amputation. The intensity of treatments required for most sarcomas is associated with the potential for increased toxicities. Patients typically experience multiple symptoms and impaired quality of life during the treatment phase. Effective communication with patients and their families is critical to minimize symptom distress and provide the necessary supportive care.

For sarcoma survivors, the late effects of treatment can include second malignancies and functional musculoskeletal impairment, as well as cardiac, gonadal, renal, metabolic, and immune dysfunction. Depending on the site of involvement, specific problems relating to deformity, risk of bone fracture, tissue fibrosis, and edema also may result. In addition to the medical sequelae, many children, adolescents, and adults must cope with long-term effects relating to education, occupation, and multiple other psychosocial changes. Sarcoma survivors may report chronic symptoms such as pain, fatigue, sleep disturbance, or emotional distress.

Clinical research on late effects and other outcomes experienced by sarcoma survivors has focused on incidences of significant medical outcomes such as second malignancies and cardiac toxicities. Some studies have addressed the physical, functional, and occupational outcomes associated with sarcomas and their treatment. Very little research has focused on quality of life or other psychosocial outcomes that affect survivors and their families, and very few patients have been followed for more than 20 years.

Despite the fact that survivors of sarcoma appear to be at great risk for adverse health outcomes over the long term, few outcomes models exist. Among them is that of the Pediatric Brain Tumor Consortium, which studies second tumors in childhood cancer survivors. The Childhood Cancer Survivor Study[1] recently focused on adult survivors of childhood cancer to determine their health status. Further opportunities exist to gain an understanding of some short- and long-term outcomes and patterns of care using administrative data, such as Medicaid, Medicare, third-party payer data, and Canadian provincial health databases.

Finally, the young mobile population of survivors with a multitude of possible outcomes, often manifested many years later, presents prodigious barriers to outcome capture and assessment. As recommended subsequently, as many sarcoma patients as possible should be enrolled in a long-term registry that, in its best form, would play several roles. For those in the registry contributing tissue specimens, the registry would allow exploration of underlying biologic processes, different treatment modalities, and long-term outcomes. Furthermore, such a registry could provide a formal process for long-term research and serve as a repository of sarcoma treatment details. This registry also would provide an accessible medical record resource for patients, who could then share this information with their future care providers to support their management over the longer term.

PRIORITY 1.

Evaluate patterns of care, including short- and long-term outcomes, in retrospective data on sarcoma patients in population-based studies.

Rationale

Information is lacking on the natural history of sarcoma diagnosis, initial treatment (and modalities), portals of care, physician specialty, cancer treatment, center types, short- and long-term management, and outcomes.

Issues of Importance

- Reliable data on short-term processes and outcomes are needed, including baseline imaging, accuracy of histologic diagnosis and grading, open biopsy versus fine needle aspiration, definitive primary resection versus need for re-excision, marginal resection versus negative margins, referral for radiotherapy, enrollment in clinical trials and follow-up, and submission of tissue to repositories.
- Information is also needed on long-term follow-up of treated sarcoma patients with respect to process of care, occurrence of late toxicity (e.g., cardiotoxicity), and secondary tumors.
- Determinations are needed of whether disparities in care exist by geographic region, ethnic and social group, age, and/or sarcoma type, and whether any disparities translate into differences in outcomes.

PRIORITY 2.

Prospectively register all newly diagnosed patients and compare short- and long-term outcomes of those treated at community hospitals and those treated at sarcoma centers of excellence.

Rationale

It must be demonstrated that patients can be registered and followed for short- and long-term outcomes to determine whether a relationship exists between outcomes and specific care interventions. This registry is also needed to allow correlation of pathological specimens collected at the time of registration with long-term follow-up and prognosis of patients.

Issues of Importance

- The development of this registry would provide an opportunity to develop a consensus on standard definitions of sarcomas and short- and long-term outcomes.
- The development of this registry would provide an important foundation for a database for research as well as summaries of patient treatment and outcomes. The latter function would be important for research, but could also serve as a resource for patients to access, via password, their own medical record of treatment for their long-term care.
- This registry would also be linked to pathological specimen data, if collected, and would allow linkage of biological studies to long-term outcomes.

PRIORITY 3.

Target a communication campaign to diagnostic radiologists and pathologists to ensure an optimal portal of entry to multidisciplinary centers.

Rationale

These two types of specialists provide initial diagnostic information and are thus uniquely positioned to facilitate optimal care.

Issues of Importance

- Diagnostic radiologists and pathologists may not be aware of their critical role in facilitating appropriate patient referrals and educating referring physicians.

CONCLUSION

Population-based studies of sarcoma patients and the development of a sarcoma patient registry are recommended strategies for meeting the urgent need for increased outcomes research. Additionally, increasing effective communication with community pathologists and diagnostic radiologists is critical for increasing referrals to multidisciplinary sarcoma treatment centers.

The current state of sarcoma outcome assessment remains unsatisfactory due to the rarity, diverse histology, and clinical behavior of these tumors; the numerous interventions required; the varied practitioners who provide care for these patients; and the overall fragmentation of care. The process of care from the time of diagnosis to that of ultimate follow-up is inherently susceptible to aberrant and disjointed practice.

Unfortunately, many patients are not referred to centers of excellence, and their outcomes remain largely unknown. More effective communication between diagnostic gatekeepers, such as pathologists and diagnostic radiologists, and sarcoma specialists, the medical community, and the broader public is needed to improve access to optimal care in specialized centers of excellence, increase tumor specimen acquisition, and increase enrollment in clinical trials.

Therefore, the extent of fragmentation in care delivery and communication to patients diagnosed with sarcomas must be understood. The medical community must begin to assess the feasibility of registration and data collection for established sarcoma centers of excellence and community practice.

REFERENCE

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Appendix C

About the NCI's Progress Review Groups

INTRODUCTION

The NCI supports basic, clinical, and population-based research to elucidate the biology; etiology; prevention; early detection, diagnosis, and prognosis; cancer control, survivorship, and outcomes; treatment; and scientific model systems of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that provides a wealth of new scientific opportunities for further advancing our knowledge and progress against these diseases, but this plentitude has also dictated that the Institute focus on the best use of its resources.

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

CHARGE TO THE PRGS

Each PRG is charged with the following:

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

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

THE PRG PROCESS

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

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

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

the research and advocacy communities through workshops and ad hoc groups or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

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

PRG reports on breast cancer; prostate cancer; colorectal cancer; pancreatic cancer; lung cancer; brain tumors; leukemia, lymphoma, and myeloma; gynecologic cancers; kidney/bladder cancers, and stomach/esophageal cancers, in addition to this PRG report on sarcoma are available online at http://planning.cancer.gov.

Appendix D

Sarcoma PRG Membership Roster

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Appendix E

Sarcoma PRG Roundtable Participants Roster

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