Progress
Review
Groups

Report of the Brain Tumor Progress Review Group

November 2000

National Institute of Neurological Disorders and Stroke

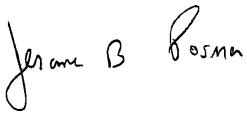
National Cancer Institute

From the Leadership:

It is a great pleasurdfce to submit this Report of the Brain Tumor Progress Review Group (BT-PRG) to the Director and Advisory Committee to the Director of the National Cancer Institute (NCI), and to the Director and National Advisory Neurological Disorders and Stroke Council of the National Institute of Neurological Disorders and Stroke (NINDS). At the beginning of 1999, the BT-PRG accepted the charge of Dr. Richard Klausner, Director of the NCI, and Dr. Gerald Fischbach, Director of the NINDS, to develop a national plan for the next decade of brain tumor research. Although this is the 4th in the series of PRGs, it is the first to be sponsored by 2 institutes, reflecting the importance of both cancer biology and neurobiology to the brain tumor field. The expertise and efficiency of the BT-PRG members and of the participants of the BT-PRG Roundtable Meeting have produced this exciting report in a ten-month period, reflecting the energy and enthusiasm of the clinical, research, industrial and advocacy communities for finding a cure for brain tumors.

The Report of the Brain Tumor Progress Review Group highlights the scientific research priorities that represent the next steps toward understanding the biological basis of brain tumors, and toward developing effective therapies for brain tumors. We look forward to discussing these priorities with the leadership of the NCI and NINDS.

Respectfully,

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

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Foreword

This report represents the collaborative efforts of scientists, clinicians, industry representatives, and patient advocates who were charged by the National Cancer Institute and the National Institute of Neurological Disorders and Stroke with the task of setting overall priorities for brain tumor research. The report and its appendices highlight those priorities in light of the biological and clinical complexity of brain tumors and the formidable challenges that have slowed progress toward their cure. Many priorities and directions need to be pursued in brain tumor research, and these are discussed in the appendices. Common themes emerge, however, and the Brain Tumor Progress Review Group considers the priorities delineated in this report to be the best guide to the future direction of brain tumor research. This report, and additional related information are available at the Brain Tumor Progress Review Group Web site (http://osp.nci.nih.gov/Prg_assess/PRG/BTPRG. The reader also is referred to the Web sites of the National Cancer Institute (www.nci.nih.gov) and the National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov).

Acknowledgments

The Report of the Brain Tumor Progress Review Group (BT-PRG) is the product of work carried out over the past 10 months by the BT-PRG, the participants at the BT-PRG Roundtable Meeting, and the staffs of the National Cancer Institute (NCI) and the National Institute of Neurological Disorders and Stroke (NINDS). The report is based on meetings of the BT-PRG Leadership in Bethesda, Maryland, in February 2000; of the BT-PRG in Bethesda in March 2000; of the Roundtable Meeting participants in Leesburg, Virginia, in July 2000; and of weekly conference calls of the BT-PRG Leadership and NCI staff from February through October 2000.

Special thanks are extended to the NCI Office of Science Planning and Assessment in the Office of Science Policy for their extraordinary organization and direction in all phases of the BT-PRG process. In particular, the guidance of Kate Nagy and Susan Rossi and the leadership of Cherie Nichols has been invaluable. The completion of the report was also greatly facilitated by Deborah Shuman, who served as lead science writer, and the breakout session reports by Deborah Shuman and the other expert science writers who attended the Roundtable Meeting.

Particular thanks are also due to the co-chairs of the Roundtable Meeting breakout sessions, who worked diligently with the BT-PRG members to plan the breakout sessions and formulate the individual breakout session reports.

Finally, the BT-PRG recognizes the tremendous efforts of brain tumor patient advocacy groups in strongly encouraging the NCI and NINDS to begin the BT-PRG process and in their invaluable participation in many aspects of the work.

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The National Cancer Institute (NCI) supports basic, clinical, and population-based research to identify and study the causes, biology, prevention, early detection, and treatment of cancer, while the National Institute of Neurological Disorders and Stroke (NINDS) is the Nation's leading supporter of biomedical research on disorders of the brain and nervous system. Through years of dedicated research, researchers supported by both Institutes have amassed a significant knowledge base about brain tumors, and this knowledge, coupled with new technologies, is providing a wealth of new scientific opportunities. At the same time, increasing research needs and scientific opportunities require that the Institutes determine the best uses for their resources. It is necessary to identify clear scientific priorities, both to provide guidance for the scientific community and to create a benchmark against which progress can be measured.

Progress Review Groups (PRGs) were originally established to assist the NCI in assessing the state of knowledge and identifying scientific opportunities and needs within its large, site-specific research programs. PRGs fit within the NCI's overall planning framework, which embraces the use of expert panels and includes the establishment of Working Groups, which are specifically focused on aspects of scientific discovery and technology, as well as more broadly focused Program Review Groups. The Brain Tumor Progress Review Group (BT-PRG) was the first PRG to be jointly established between NCI and another NIH Institute, in recognition of the importance of brain tumor research to both Institutes.

CHARGE TO THE PRG

The BT-PRG was charged with assisting NCI and NINDS in addressing the two Institutes' brain tumor research programs. PRG members were asked to take a broad view in identifying and prioritizing unmet scientific needs and opportunities that are critical to the advancement of the research field. The BT-PRG was specifically charged with the following:

1. Identify and prioritize scientific research opportunities and needs, and the scientific resources needed to address them, to advance medical progress.
2. Compare and contrast these priorities with an NCI-prepared analysis of its cancer research portfolio.
3. Develop a research plan of action that addresses unmet opportunities and needs.
4. Prepare a written report describing the PRG's findings and recommendations for deliberation by the Advisory Committee to the Director (ACD) of NCI.

This report is the final product of the Brain Tumor PRG's (BT-PRG) efforts and deliberations. This report describes the group's findings and recommendations for advancing brain tumor-related research. The following section details the process used in producing this and other PRG reports.

THE PRG PROCESS

The BT-PRG members were prominent scientists, clinicians, consumer advocates, and industry representatives from the U.S. and Canada who together represented the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's and NINDS's brain tumor research agenda. Members were also selected for their ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

In February 2000, the PRG Leadership finalized an agenda and process for the PRG Planning Meeting. At the Planning Meeting, participants were identified to take part in a subsequent Roundtable meeting. Topics were identified for Roundtable breakout sessions to which those participants were ultimately be assigned and for which the PRG members served as co-chairs.

The Brain Tumor PRG Roundtable Meeting (July 2000) brought together approximately 125 leading members of the cancer research and advocacy communities, representing diverse institutions and scientific disciplines. These experts met in an open forum in which they formulated key scientific questions and priorities for the next 5–10 years of brain tumor research. NCI and NINDS provided the PRG Roundtable with extensive information about their research programs for use in their review. The research priorities and resource needs that the Roundtable identified in the course of their deliberations are outlined in this report.

DEVELOPMENT OF THE PRG REPORT

After the Roundtable Meeting, an intermediate draft report was prepared, multiple iterations of which were reviewed by the PRG Leadership and PRG Members. Upon completion of the final draft, the report was submitted for deliberation and acceptance by the NCI Advisory Committee to the Director and the NINDS Council. The report will be widely disseminated and integrated into each Institute's planning activities. In Spring 2001, the PRG will meet with the NCI and NINDS Director to discuss the Institutes' response to the report.

PRG reports on breast, prostate, and colorectal cancer are available on line at osp.nci.nih.gov/Prg_assess. Other PRG reports currently in development or being planned include reports on pancreatic cancer; leukemia, lymphoma, and myeloma; gynecologic cancers; kidney and bladder cancer; stomach and esophageal cancers; liver and bile duct cancers; and skin cancer.

Report of the Brain Tumor Progress Review Group

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INTRODUCTION

Brain tumors represent a unique challenge in that they affect the organ that is the essence of the "self." Furthermore, because each area of the brain serves a different but vital function, the therapy that is most effective for other cancers—surgical removal of either the entire organ or the tumor with a generous surround of normal tissue—cannot be used to cure brain tumors. Unfortunately, most brain tumors are relatively insensitive to other cancer treatment, including radiation and chemotherapy.

Coupled with the difficulty in treating brain tumors is the unique biology of the brain:

- Brain tumors occur in an organ that is enclosed in a bony canal that allows little room for growth of the tumor without compressing and damaging normal brain.
- Many brain tumors extensively invade normally functioning brain, making complete surgical removal impossible.
- In their early stages, brain tumors are protected behind a blood-brain barrier; even when this barrier is disrupted in the bulk of the tumor, infiltrating tumor cells at the growing edge remain protected.
- Disruption of the blood-brain barrier leads to edema, which the brain tolerates poorly because of the limited intracranial space and the lack of lymphatics to rid itself of the products of edema and other debris.
- The brain itself is rich in expressed genes and therefore is a fertile field for the growth of both primary tumors and metastases.
- The brain and brain tumors appear to be less susceptible to attack by the immune system than are tumors in other organs.

Even the term *brain tumor,* which suggests a single type of tumor, can be misleading. There are a bewildering variety of central nervous system tumors; the World Health Organization lists 126. Many of these tumors are not, strictly speaking, in the brain but arise from structures intimately associated with that organ, such as tumors of the covering membranes (meningiomas) and adjacent cranial and paraspinal nerves (schwannomas). Brain tumors range from benign (most meningiomas) to highly aggressive (glioblastomas). They affect both adults and children (although the distribution of tumors varies) and are often highly resistant to treatment.

The term *brain cancer* is also misleading. Most cancers that arise elsewhere in the body cause damage by metastasizing to other organs (including the brain). Primary brain tumors, however, rarely metastasize, although they may widely infiltrate the nervous system. Conversely, many cancers metastasize to the brain, making metastatic brain tumors much more common than primary brain tumors.

Throughout this document, the term *brain tumor* is used to refer to all tumors that grow inside the skull. The issues discussed in this document, however, also extend to tumors growing within the spinal canal.

STRUCTURE AND PROCESS OF THE PRG MEETING

For the reasons described in the introduction to this report, the Brain Tumor Progress Review Group (BT-PRG) required input from participants with much more diverse expertise than was needed in previous PRGs. In addition to experts on cancer biology and genetics, the BT-PRG required

expertise in neurobiology, including areas such as progenitor cells, cellular migration, and blood-brain barrier function. Clinically, expertise was required from both oncology and the clinical neurosciences, including neurosurgery and neurology. In addition, to ensure inclusion of the wide diversity of brain tumors, breakout sessions were held not only for those topics that apply to all solid tumors, including brain tumors, but also (different from other PRGs) for specific types of brain tumors (i.e., intraaxial tumors, extraaxial tumors, pediatric tumors, and metastases). A total of 16 breakout groups were therefore convened (see box). Each participant attended three breakout sessions.

The participants in each of these 16 breakout sessions were asked to identify three important research priorities in their assigned areas. It was recognized that it might not be possible to place all of the research priorities formulated by the groups into an overall hierarchy. Although all of the priorities included in the appendices are important and meritorious, some arose in multiple breakout sessions and therefore appear to be of overarching importance. This report delineates those priorities considered by the BT-PRG to be overarching. The appendix contains the full reports of the individual breakout sessions and their priorities.

This report is divided into two sections. Section I, "Scientific Priorities," describes the overarching priorities in both the basic and the clinical sciences. These scientific research priorities are hypothesis driven. To meet them will require the scientific resources described in Section II. The resource priorities in Section II can be considered as hypothesis generating in that their development will generate hypotheses for further research.

STRUCTURE OF THE BT-PRG BREAKOUT GROUPS

Basic Biology	Clinical Biology	Specific Tumors
• Models • Cancer Biology and Etiology • Neurobiology: Progenitor Cells • Neurobiology: Migration and Trafficking • Cancer Genetics • Tumor Immunology	• Detection, Diagnosis, and Prognosis • Epidemiology, Prevention, and Outcomes • Imaging • Radiation Biology • Therapeutic Targeting: Blood-Brain Barrier, Gene Therapy, and Vascular Biology • Treatment	• Extraaxial Tumors • Intraaxial Tumors • Pediatric Tumors • Metastases

SECTION I: SCIENTIFIC PRIORITIES

Three separate sets of breakout sessions addressed the scientific priorities. One set was devoted to fundamental biology and included sessions on models, neurobiology of progenitor cells and of cellular migration and dispersal, cancer biology, immunobiology, and cancer genetics. Another set of sessions was related to clinical issues, ranging from detection and diagnosis to treatment and outcomes. A third set was devoted to specific tumors. Several overarching scientific priorities emerged from all of these sessions and are described here.

Basic Biology

Brain tumors are phenotypically and genotypically heterogeneous. Significant gaps exist in current understanding of the molecular pathways involved in the genesis, progression, and biological and clinical behavior of brain tumors. Brain tumors are unique among human cancers because of their complex interaction with the brain itself, which greatly complicates the use of existing therapies as well as the development of novel ones.

A cardinal feature of the most common malignant brain tumors—their diffuse infiltration into the surrounding brain—presents substantial barriers to the effective delivery of therapeutic agents and increases the possibility of therapeutic toxicity to a vital organ whose function greatly affects the patient's quality of life. Other obstacles to effective therapy include the blood-brain barrier and the difficulties it creates for therapeutic delivery, as well as the relative lack of information on the unique immunological aspects of brain tumors and the cerebral environment.

The biology of brain tumors is distinct from that of many other human tumors. Although tumors are named as though their lineage were understood (e.g., *astrocytoma* from *astrocytes*), the cells of origin for most human brain tumors remain enigmatic, complicating the interpretation of data that require a comparison between brain tumor cells and their "normal" counterparts. Highlighting these issues are childhood brain tumors, especially primitive neuroectodermal tumors that arise during brain development. Insights into the normal and aberrant regulation of neurodevelopmental genes may be significant in understanding the etiology of both childhood and adult brain tumors. Likewise, elucidating the genetic alterations in brain tumors may yield new insights into brain development. Achieving significant advances in the diagnosis, prognosis, therapy, and prevention of brain tumors requires unraveling and understanding many aspects of the cellular and molecular biology of brain tumors and their interactions with normal brain elements. These advances must proceed along a number of different fronts and will require the interaction of several disciplines in order to achieve the greatest chance of success (see "Communication" in Section II of this report).

Many of the priorities generated by the breakout sessions of the BT-PRG overlapped, particularly those concerning needed resources (see Section II). The highest scientific priorities in basic biology identified by such overlap are as follows:

- Understand the complex biology of brain tumors, both primary and metastatic, and their interaction with normal brain elements as they relate to oncogenesis, progression, tumor cell dispersal, and heterogeneity.

  - — Define the genetic changes and molecular pathways involved in brain tumor initiation and maintenance.
  - — Characterize the interactions of brain tumor cells with the normal brain.
- Provide a detailed molecular classification of the cells of origin for distinct tumor types and define their lineage associations, as well as the signal transduction pathways that regulate cell fate and the mechanisms by which the local environment of the brain influences cell migration and differentiation.
- Understand genotypic influences on phenotypic behavior, tumor type, age at onset, anatomical position, cell of origin, and cellular biology.
- Isolate the genes that predispose to human brain tumors and understand their relationship to the genes that regulate normal development.
- Identify the genes that regulate patients' responses to chemotherapy and radiotherapy and those that mediate tumor chemoresistance and radioresistance.
- Characterize both central nervous system and systemic immune responses in patients with brain tumors.
- Understand the blood-brain barrier and its regulation.
- Understand the mechanisms underlying the spread and establishment of metastases in the central nervous system.

Epidemiology

Little is known about the epidemiology of brain tumors. Germ line mutations (familial brain tumor syndromes) account for no more than 7% of patients. The only unequivocally established risk factors for nonfamilial brain tumors—therapeutic irradiation to the brain and chronic immunosuppression (e.g., AIDS)—are also infrequent causes of brain tumors. Other suggested etiologies, such as nonionizing radiation (e.g., from cellular telephones or high-tension wires), viral agents, household chemicals, or foods, have not been established as causal. In addition, little is known about the interaction of genetic factors and environmental toxins in the genesis of brain tumors.

Because identification of the risk factors for brain tumors may aid prevention and suggest effective treatments, high-quality epidemiological studies are extremely important. Factors that inhibit epidemiological studies include the relatively small number of patients affected by brain tumors and the large number of histopathological types of these tumors. These factors complicate the design of research protocols and limit the statistical power of the data collected. In addition, existing tumor registries are neither linked nor structured to facilitate the collection of large numbers of samples for meaningful epidemiological research. Important epidemiological scientific priorities, therefore, include the following:

- Support the linking of existing databases to provide larger numbers of samples for epidemiological studies.
- Expand and enhance databases to include all primary brain and spinal tumors—malignant and nonmalignant, adult and pediatric—and to have the flexibility to accommodate new histological and molecular classifications of tumors.
- Develop epidemiological studies of patients' susceptibility to the toxic effects of current treatment modalities and investigate risk and protective factors with study designs that incorporate biological measures.
- Use validated animal models (see "Models," Section II) to study the

potential causal factors of brain tumors and of treatment-induced neurotoxicity.

Detection and Diagnosis

Because brain tumors are an extraordinarily heterogeneous group of lesions, accurate diagnosis is essential to proper management. Current imaging techniques provide a sensitive means for delineating the anatomical features of brain tumors but have not provided an effective means for early detection. Early detection could also be complicated by the ethical problems created by presymptomatic diagnosis of tumors for which there may not be effective treatment, and in an organ whose proper function is essential to quality of life. Nonetheless, early detection of brain neoplasms, particularly in the pediatric population, where these lesions are often treatable, could be facilitated by appropriate education of pediatricians, parents, school officials, and other caregivers.

The diagnosis of brain tumors is currently based on histological examination of brain tumor tissues after radiological characterization and surgical biopsy. These approaches are successful in classifying and grading most cases, but in many situations they do not allow accurate prediction of therapeutic responses or of prognosis. The situation may be further complicated by the small size of some diagnostic biopsy samples. There is therefore a critical need to improve the diagnosis of brain tumors in order both to improve current therapeutic management strategies and to form a basis for the evaluation of novel approaches.

The ability to characterize tumors comprehensively at the molecular level raises the possibility that diagnosis could be based on molecular profiling, either alone or with histological examination, rather than on histological phenotype alone. Once such techniques become possible and practical, molecular profiling could be accomplished by tissue analysis or imaging. In the future, molecular markers could also form the basis for screening at-risk individuals or populations. In light of such possibilities, the following priorities in the detection and diagnosis of brain tumors were identified:

- Develop a molecular- and imaging-based classification scheme for brain tumors that can be used to predict tumor behavior and to guide treatment decisions more accurately and objectively than is possible with current histopathological methods.
- Develop techniques that can reliably detect brain injury related to tumor or treatment and use such techniques to assess the efficacy of neuroprotective interventions.

Treatment

Treatment options for patients with brain tumors have been limited and, for most types of tumors, have provided only modest benefits. Some of the likely reasons for these limitations (see “Introduction”) include the unique structural and physiological aspects of the central nervous system, especially its vulnerability to damage from many therapies as well as from neoplastic processes themselves. Research in the treatment of brain tumors has been hampered by the lack of clinically predictive model systems; by a minimal understanding, until quite recently, of fundamental tumor biology; and by a narrow range of available therapeutic agents for testing that have had little expected specificity for brain tumors. The major challenge for the future is to develop more effective techniques to treat brain tumors without damaging the brain.

Marked progress is currently being made in dissecting the molecular mechanisms of neoplasia in the brain and elsewhere. These advances are enabling the rapid identification of relevant molecular targets, and the result is a vast array of potential therapeutic approaches and agents in the development pipeline. At the same time, advances in neuroimaging are raising the tantalizing possibility of clinically assessing the capacity of an agent to alter its intended target. It therefore seems reasonable to expect an improved rate of success in research on the treatment of brain tumors. Because the special characteristics of these tumors will continue to present problems and challenges, however, the following priorities were identified:

- Facilitate the development of novel therapeutic agents and approaches for adult and pediatric brain tumors. These approaches should include, but not be limited to, chemotherapeutic, immunologic, antiangiogenic, genetic, and viral agents.
- Increase knowledge about the mechanisms of existing therapies for both adult and pediatric brain tumors.
- Improve the therapeutic index of new agents that are specifically relevant to the central nervous system.
- Enhance the therapeutic ratio for radiation therapy for brain tumors. (Overcome radioresistance of primary brain tumors; overcome normal tissue toxicity such as necrosis/edema and functional deficits.)
- Develop novel drug targeting systems that enhance the uptake by brain tumors of small- and large-molecule diagnostic and therapeutic agents.
- Develop clinical consortia for immunotherapy that are similar to those for radiation and chemotherapy.
- Develop therapies that are less toxic than existing therapies to both the mature and the immature nervous system.

Outcomes

Traditional outcome measurements used in brain tumor studies have included overall and recurrence-free patient survival and, in some instances, radiological response to therapy. Such measurements, however, largely ignore crucial issues relating to quality of life and biological endpoints of response. These issues are of particular importance in tumors for which effective therapies may not exist and in pediatric tumors, for which effective tumor control may be associated with significant long-term morbidity. For these reasons, there is an immediate and crucial need for better measurement tools and surrogate markers to assess patient quality of life and tumor response to therapy. Such outcome markers would facilitate the assessment of neurotoxicity, thereby providing an opportunity to discard potentially neurotoxic therapies sooner. They would also facilitate more accurate assessment of therapeutic response, thereby allowing effective therapies to be continued while ineffective therapies are discontinued. The following priorities were therefore identified:

- Improve techniques for measurement of quality of life and include such measurements in all clinical trials of brain tumor.
- Refine the ability to detect response to existing therapies, such as radiation, and to novel treatments, using surrogate markers measured either by imaging or in biological fluids (e.g., serum or cerebrospinal fluid).
- Establish clinical and imaging markers of neurotoxicity from existing therapies,

such as radiation, and from novel treatments.
- Extend the use of such markers to preclinical evaluations in animal models.

Specific Tumors

Recognizing the remarkable diversity of human brain tumors and the distinct clinical questions associated with different tumor types, the PRG members were concerned that most of the general scientific sessions would concentrate on the more common tumors, such as malignant gliomas and medulloblastomas, to the exclusion of other brain tumor types. To address the possibility that research priorities might relate to different types of brain tumors, the PRG convened four special breakout sessions to focus on particular groups of brain tumors: pediatric brain tumors, intraaxial brain tumors (excluding malignant gliomas and medulloblastomas), extraaxial brain tumors, and metastases to the brain. These four special breakout sessions met after the 12 general scientific sessions had adjourned. The special sessions included attendees from the earlier, general discussions, thereby allowing important issues from the general sessions to be applied to discussions of the specific tumor groups.

Remarkably, the research priorities and needed resources identified by these special groups echoed those of the general sessions, although some different emphases were placed according to tumor type:

- The session on pediatric brain tumors emphasized clinical problems such as the need to study long-term outcomes for survivors of brain tumors, to investigate the impact of therapies on the developing brain, and to focus on some of the rarer, more primitive tumors occurring in children.
- The group addressing intraaxial brain tumors highlighted issues relating to low-grade gliomas, primary central nervous system lymphomas, and germ cell tumors.
- The session on extraaxial brain tumors emphasized the need for studies that incorporate careful long-term follow-up for these often slowly growing lesions.
- The group discussing metastatic tumors of the brain made the unique recommendation to convene a PRG devoted to the biology of metastasis.

The specific priorities from these sessions are detailed in the individual reports in Appendix A.

SECTION II: RESOURCE PRIORITIES

Although the scientific priorities set forth by the BT-PRG varied considerably across the different areas of scientific and clinical investigation, the resources required to accomplish those priorities were remarkably concordant. Indeed, nearly all of the five resource priorities listed below were deemed essential by most of the participants:

1. Models
2. Tissue banks and databases
3. Genomics and high-throughput screening
4. Communication
5. Training

These resources can be viewed as hypothesis generating because they will provide the information and abilities to accomplish the scientific and clinical priorities listed in Section I. The creation of these resources is deemed essential in order to develop new, effective therapies for brain tumors.

Models

Models are central to making the transition from developing scientific concepts to understanding human tumors within the context of the tissues that they affect. Models may be used for therapeutic screens, in preclinical trials, or to study the basic biology of tumors. However, because currently available cellular, tissue, and animal models do not accurately represent the biology of human brain tumors, it is vital to:

- Develop tissue and cell culture systems that replicate the biology of human brain tumors.
- Create genetically and behaviorally accurate models for brain tumors in mice and other animals.
- Generate tissue-based, imaging, and genomic methods to validate and compare animal models with their human counterparts.
- Improve the availability of the reagents needed to create new animal models of brain tumors, the sophisticated technologies used to evaluate and validate those models, and the animal models themselves.

To accomplish these priorities, a mechanism must be created to support the development and validation of model systems that more accurately reflect the biology of brain neoplasms. Although the National Cancer Institute (NCI) Mouse Models for Human Cancer Consortium (MMHCC) has been established to fund the development of mouse cancer models, additional mouse models of the various brain tumors that are not addressed through the MMHCC, as well as models in other animals, remain high priorities.

Tissue Banks and Databases

Addressing the complex biology of brain tumors requires innovative tumor banking and characterization facilities with relevant and appropriate clinical and radiological databases. Tissue banks linked to clinical databases are also vital for translating research discoveries into clinically relevant information. Because current tissue banks are typically institution based, they are limited in scope and amount of available specimens. These banks also process tissues in different ways, and their specimens are usually not sufficiently annotated with clinical and radiological information. Because of the rarity of many brain tumor types, including both adult and pediatric neoplasms, there is a great need for organized, interinstitutional approaches to banking and data management of both adult and pediatric neoplasms.

An effective tissue bank or database must do the following:

- Collect and bank tissue, blood, cerebrospinal fluid, and (when available) normal brain from patients with all varieties of brain tumors. In particular, attention should be paid to banking pediatric tumors; rarer intraaxial tumors, such as low-grade gliomas and lymphomas; tumors that follow long clinical courses, such as meningiomas; and metastases, when tissue from the primary tumor is also available. Specialized banks should also focus on acquiring clinical and radiological information and tissues from distinct populations, such as patients with neurofibromatosis 2, who provide unique opportunities to follow the natural history of particular tumors. Public and professional educational efforts will be required to ensure that

both common and rare brain tumors are submitted to the banks. In this regard, a challenge will be to alter the sociology of data sharing in order to make a concerted shift to a shared, distributed system.
- Maintain a comprehensive database of relevant clinical and demographic, pathologic, biologic, and therapeutic information on all patients whose tissue is banked. Develop links to population databases to enhance potential etiological and other epidemiological studies.
- Involve multidisciplinary participation of surgeons, pathologists, scientists, and other professionals, including neurooncologists, to ensure reliable and consistent tissue processing.
- Provide mechanisms to ensure access, on a competitive and open basis, by researchers to the material and data in the bank.
- Employ approved and ethical methodologies to protect patient confidentiality and ensure appropriate patient consent.
- Feature local and regional facilities and facilitate effective communication and collaboration among centers.
- Be supported by ongoing funding, potentially for longer than 5-year periods, to facilitate study of tumors with long clinical courses, such as meningiomas.

Genomics and High-Throughput Screening

The explosion of information in genomics, together with the promise of similar advances on the near horizon in proteomics, raise the need for technologies that allow high-throughput screens of brain tumors and related specimens (e.g., other tissues from patients with brain tumors). Such high-throughput screens would allow large amounts of information to be gleaned quickly and would facilitate further translational research toward more tailored therapeutic approaches. These screens can occur at the tissue level ex vivo or, in the future, at the molecular neuroimaging level in vivo. For such large-scale approaches to be functional, considerable emphasis will need to be placed on bioinformatics support. The need for high-throughput screening technologies was identified by a number of the different breakout sessions; the highest priorities were the following:

- Develop high-throughput laboratory approaches to understand gene function and to identify the targets and pathways that are critical to brain tumor biology.
- Develop high-throughput laboratory approaches to identify the genes and genetic variations that underlie tumor resistance to chemotherapy and radiation therapy, as well as the allelic variations that influence responses to therapy in individual patients.
- Develop high-throughput laboratory approaches to identify antigens that may be used to further understanding of the immunological features of brain tumors and to develop novel immunological therapies.
- Develop high-throughput neuroimaging approaches for the in vivo characterization of the molecular features of tumors and the surrounding brain that could monitor and influence therapies.
- Develop the bioinformatics support necessary for rapid and accurate analysis of data generated via these high-throughput approaches.
- Establish a consortium of brain tumor modeling laboratories for the purpose of testing novel therapies.

- Allocate resources for the generation of cDNA microarrays based on the mouse equivalent of the human sequences identified through the Brain Tumor Genome Anatomy Project (BT-GAP).
- Create a mechanism to ensure affordable access to these reagents and models.

Communication

The PRG Roundtable meeting provided a unique opportunity for scientists from different disciplines—including cancer biology and genetics, neurobiology, immunology, and radiation biology—to meet and discuss brain tumor biology. These stimulating interactions highlighted the potential for novel insights arising from such interdisciplinary interactions. A central goal that emerged from these discussions was the need for further communication among these various disciplines on the subject of brain tumor biology. Such enhanced communication would in turn lead to interdisciplinary collaborations that would approach problems in brain tumor research from a unified, and therefore novel, perspective.

It was recognized that one reason for the relative lack of such communication and collaboration among disciplines has been the historically different funding and oversight mechanisms that have supported such research. For example, neurobiology research is largely funded through the National Institute of Neurological Disorders and Stroke (NINDS), whereas cancer biology and immunology research is generally funded by NCI and other agencies. Recent attempts to bring together NCI and NINDS to address questions in brain tumor research—the BT-PRG, the BT-GAP, and the establishment of a combined NCI-NINDS Neurooncology Branch—have been widely applauded and further interinstitutional interactions strongly encouraged. The possible extension of such interactions to the grants review process was also deemed an important area for discussion.

Because the Center for Scientific Review (CSR) reviews most unsolicited brain tumor grant applications, the brain tumor research community believes that better coordination among the institutes and CSR is needed. Improved communication could prevent brain tumor biology from "falling between the cracks" among the various review groups that may have relatively few brain tumor biologists. It is anticipated that coordinated efforts by NINDS, NCI, and CSR on the referral, review, and funding of brain tumor research applications would facilitate the implementation of the national plan for brain tumor research.

Goals for improved communication extend to clinical problems as well. There is clearly a need for increased dissemination of information to patients, as well as to clinicians outside of neurooncology centers, with regard to the variety of available treatment options. The relatively low percentage of patients with adult malignant gliomas who are enrolled in clinical trials may reflect an inadequate knowledge of treatment options on the part of both patients and physicians. This area of need represents an ideal opportunity for patient advocacy groups to collaborate with physicians to develop strategies to educate patients and clinicians about treatment options, including clinical trials, as well as about the specialized expertise that is available at neurooncology centers. For these reasons, the following priorities were identified:

- Establish a set of interactive meetings involving scientists from different biological disciplines (cancer biologists

and geneticists, neurobiologists, immunologists, and radiation biologists) that focus specifically on important issues in brain tumor biology.
- Facilitate collaborations among different disciplines by encouraging interdisciplinary grant applications in brain tumor biology and etiology.
- Continue to develop combined programs in brain tumor research from NCI and NINDS and explore the possibility of revisions in the grant review process for brain tumor research.
- Encourage coordinated activities by advocacy groups toward further education of patients and clinicians about available treatment options for brain tumors.

Training

Achieving the goals for brain tumor research outlined in this report requires an adequately sized and well-trained scientific and clinical work force specializing in brain tumor research. Unfortunately, there is a dearth of basic scientists working in the field of brain tumors, which lacks sufficient numbers of clinicians who are cross-trained in brain tumor biology and scientists who are aware of the problems driving clinical neurooncology research. As is the case for biomedical science in general, there exists a true crisis caused by the small number of clinician-investigators now entering academic medicine. This issue has been discussed elsewhere and will not be recapitulated here, but its importance should not be underestimated. High priorities for brain tumor research are therefore as follows:

- Enhance training opportunities and support:
  - — Encourage funding for interdisciplinary and translational research.
  - — Recruit new talent and sustain proven talent in the field of brain tumor research.
- Create innovative public and private programs to stimulate promising young investigators to choose a career in clinical or laboratory brain tumor research through, for example, tuition loan payback or forgiveness and fellowships.
- Develop a joint NCI-NINDS campaign to encourage students to pursue interdisciplinary careers in the field of brain tumor research.
- Develop at NIH a model for a joint NCI-NINDS interdisciplinary training program in neurooncology at both the basic science and the clinical level. This program might include not only training at NIH for 2–3 years, but also additional support for the first 3 years of the individual's career as an independent investigator.

CONCLUSION

Although not among the most common of neoplasms, brain tumors are among the most devastating. Mental impairment, seizures, and paralysis afflict the very core of the person and have a demoralizing effect on loved ones. Added to these burdens is the knowledge that, for most brain tumors, adequate treatment is not available and the likelihood for long-term survival is poor. In children, even if they do survive, the devastating impact of disease and treatment often leaves permanent neurological damage.

Recent advances in the clinic, as well as in neuroscience and cancer biology, make the present an opportune time for a major attack

on brain tumors. As indicated in this report, progress has been made in the basic understanding of many aspects of brain tumor biology. These advances promise to provide new targets for therapies and more rational ways of delivering these novel therapies. In the clinic, new techniques in surgery and radiation therapy are just beginning to be exploited in the treatment of brain tumors. Other innovative approaches, such as gene and immunological therapies, are still in their infancy but represent substantial hopes for the future. Preventive factors identified in recent epidemiological studies, if replicated and understood at the biological level, may lead to intervention strategies.

The priorities outlined in this report provide a framework to guide progress in the field of brain tumor research. A concerted, interdisciplinary, and timely approach to addressing these priorities will allow the development of new diagnostic and therapeutic techniques that may ameliorate and, it is hoped, eventually cure brain tumors.

Appendix: Full Reports of the Brain Tumor Progress Review Group Roundtable Breakout Sessions

Cancer Biology and Etiology

Co-chairs: Francis Ali-Osman, D.Sc., and Tom Curran, Ph.D.

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STATEMENT OF THE PROBLEM

- Brain tumors are highly heterogeneous, both phenotypically and genotypically.
- Significant gaps exist in our knowledge and understanding of the genes, genetic changes, and pathways involved in the genesis, progression, and biological and clinical behavior of brain tumors.
- There is currently an inadequate understanding of brain tumor biology, particularly as it relates to the complex environment of the brain.
- The achievement of significant advances in diagnosis, prognosis, therapy, and prevention of brain tumors will require unraveling and understanding the cellular and molecular biology of brain tumors and their interactions with normal brain.

CHALLENGES AND QUESTIONS

- What are the genetic changes and pathways of oncogenesis and progression that account for the heterogeneity of brain tumors, and how can these be studied?
- Which genes, genetic changes, and pathways are important to the initiation, maintenance, and progression of brain tumors?
- Are the genetic changes and pathways that are required for initiation the same as those required for maintenance of the neoplastic phenotype and its biological behavior?
- What model systems and approaches are required to advance our study of these multigenetic changes and pathways?
- What are the interactions between the brain tumor and the normal brain?
- How do tumor-brain interactions contribute to oncogenesis and metastasis in the central nervous system?
- "Seed-soil" interactions: How does the spatial-anatomical site of the tumor against its specific genetic background determine the gene expression patterns and contribute to tumor heterogeneity, biological and clinical behavior, and therapeutic outcome?
- Are there genetic changes and pathways that are common to different brain tumor subtypes?
- What pathways, such as signaling, apoptosis, cell cycle, and migration, are involved in the response of brain tumors to intra- and extracellular stimuli such as growth factors or redox changes?

- What are the stem cells and progenitor cells of the different brain tumor subtypes?
- What model systems and approaches are required to advance the study of brain tumor biology and of the interactions between tumor cells and normal brain?
- If the genetic changes or lesions that initiate cancer are different from those required for progression and maintenance, could these be targeted in order to develop novel therapies?

BARRIERS

- Interdisciplinary barriers:
  — There is poor communication and collaboration between researchers in neurobiology and those in neurooncology, although expertise and advances in each field are essential to advancing understanding of brain tumor biology.
  — Current infrastructure and systems do not encourage or facilitate interdisciplinary interaction.
  — In the current grant review process, interdisciplinary grants that would encourage collaboration are often not reviewed favorably because of the existing review criteria.

- Tissue resource barriers: Existing tumor banks often do not have appropriate, relevant information, such as information on diagnosis, biological characteristics, natural history, and therapeutic outcome. The banks also often do not collect normal tissue or blood.

- Models: There is a lack of appropriate in vitro and in vivo models and systems with which to study the complex biology of brain tumors.

- Technological barriers: There is an inadequate application to brain tumor biology research of the latest technological advances, such as those in genomics and proteomics, structural biology, chemical biology, and high-throughput screening strategies.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Understand the complex biology of brain tumors and their interaction with the normal brain as it relates to oncogenesis, progression, and heterogeneity.

- Define the multigenetic changes and pathways involved in oncogenesis, progression, and maintenance of brain tumors, with particular attention to their heterogeneity.
- Identify the genes and pathways that are differentially involved in tumor initiation and maintenance.
- Characterize the interactions of the tumor cell with normal brain components as determinants of heterogeneity, gene expression, biological and clinical behavior, and therapeutic response within the context of the specific anatomical sites of the brain in which the tumor is located.
- Define and characterize the cells of origin of different brain tumor subtypes.

Priority 2:

Develop appropriate model systems for studying brain tumor biology that will allow for the following:

- Mimic the biological complexity of the brain, including brain matrix

- Facilitate comparative genetic studies in human brain tumors and animal brain tumor models
- Provide an interface between tumor cell and stem cell biology
- Study interactions and pathways between brain tumor cells and cellular components of normal brain
- Study molecular, cellular, and spatial heterogeneity in brain tumors
- Study the functional outcome of specific genetic lesions
- Evaluate novel therapies that target specific genes, gene products, and pathways

Priority 3:

Develop high-throughput approaches to understand gene function and to identify the targets and pathways that are critical to brain tumor biology and therapy.

RESOURCES NEEDED

Priority 1

- Address the complex biology of brain tumors requires innovative tumor banking and characterization facilities with relevant and appropriate databases. These facilities will enable the following:
  — Collect and bank tissue, blood, cerebrospinal fluid, and (when available) normal brain from patients with all varieties of brain tumors.
  — Maintain a comprehensive database of relevant clinical and demographic, pathological, biological, imaging, and therapeutic information on tumors.
  — Involve the multidisciplinary participation of surgeons, pathologists, scientists, and other professionals, including neurooncologists, for tissue processing.
  — Have mechanisms in place to ensure access by researchers to the material and data in the bank.
  — Include local (institutional) or regional centers and encourage communication and collaboration among centers.
  — Receive ongoing funding, specifically for longer than 5-year periods, because of the long-term nature of tissue banking

- Establish a centralized molecular profiling (cDNA and tissue array) resource with a strong bioinformatics component to profile gene expression patterns and genetic abnormalities in different brain tumor types. Such a facility could be located at NCI or NINDS or could be extramural.

- Develop the infrastructure and mechanisms to open up communication and collaboration among researchers in neuroscience, neurobiology, neurooncology, and cancer biology. Such an infrastructure would include:
  — Workshops and specialized meetings among these scientists
  — New funding mechanisms and grant review criteria appropriate for interdisciplinary research

Priority 2:

Targeted funding is needed for the development of model systems.

Priority 3:

Resources are needed to develop the following:

- Chemical and combinatorial libraries and high-throughput assays to

investigate molecular targets and pathways
- Structural and computational biology resources
- Functional genomics and proteomics
- Studies of ligand (drug)-protein interactions
- Targeted funding for high-throughput technologies

Therapeutic Targeting, Blood-Brain Barrier, Gene Therapy, and Vascular Biology

Co-chairs: William M. Pardridge, M.D., and Edward H. Oldfield, M.D.

Participants:	
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STATEMENT OF THE PROBLEM

An important problem in the treatment of human brain tumors is posed by the need to deliver therapeutic agents to specific regions of the brain, distributing them within and targeting them to brain tumors. The molecules that might otherwise be effective in diagnosis and therapy either do not cross the blood-brain barrier (BBB) in the brain adjacent to the tumor or do not cross the blood-tumor barrier (BTB) in adequate amounts. Improving our knowledge of the basic molecular and cellular biology of the brain microvasculature, which constitutes the BBB and BTB in vivo, could lead to innovative new strategies for drug targeting to human brain tumors.

The magnitude of this challenge stems from the lack of emphasis on BBB research in both academic neuroscience and the pharmaceutical industry. Knowledge of the basic functions of the BBB and research on cerebrovascular biology lag behind those of neuronal or glial biology. An improved understanding of the brain vasculature and the BBB will play a crucial role in the development of new therapeutic and diagnostic approaches for the treatment of human brain tumors. In addition, there is a need for novel delivery strategies that are unique to the brain and that bypass the vasculature.

At one time, the BBB was not been considered to present a problem in the diagnosis and treatment of brain tumors because early scans of human brain tumors suggested that the BTB was “leaky.” This leakiness is relative, however: as the size of the molecule increases, the rate of movement across the barrier decreases. Accordingly, antibodies that could be used as either diagnostic or therapeutic molecules do not cross the BTB in sufficient quantities to be effective. Anti-sense oligonucleotides, which could be used either to inhibit oncogenic signals or as anti-sense radiopharmaceuticals to image gene expression of the brain in vivo, also do not cross the BTB in sufficient amounts for activity. Gene therapies, whether of viral or nonviral formulations, are often too large to cross the BTB.

These problems are substantially greater for the BBB in the brain adjacent to the tumor, because even small molecules do not readily cross the BBB, which is the site of invasion of glioma cells into normal brain. Furthermore, the expression of drug-active efflux transporters, which are expressed at the BBB and the BTB, actively efflux chemotherapeutics from the brain back to the blood and may thereby prevent

significant distribution of chemotherapeutic agents in the brain. It is partly for these reasons that most of the classical chemotherapeutic molecules that have been used to treat cancer outside the central nervous system (CNS) are ineffective in the treatment of brain tumors.

CHALLENGES AND QUESTIONS

Chief among the challenges to be addressed in brain tumor research is limited knowledge about the basic biology of brain endothelial cells, about the cells of origin and the developmental changes in gene and protein expression in brain and endothelial cells, and about the proliferative potential, turnover rate, and regional differences of brain endothelial cells. There is also limited knowledge of the cell interactions among brain endothelial cells, tumor cells, and cells of hematopoietic origin. The role of angiogenesis in tumor development and anti-angiogenesis research are important avenues for future studies of brain tumor therapy.

Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery through the BBB entail disruption of the BBB, either by osmotic means or biochemically by the use of vasoactive substances such as bradykinin. The potential for using BBB opening to target specific agents to brain tumors has just begun to be explored. Other strategies to go through the BBB may entail the use of endogenous transport systems, including carrier-mediated transporters such as glucose and amino acid carriers; receptor-mediated transcytosis for insulin or transferrin; and active efflux transporters such as p-glycoprotein. Strategies for drug delivery behind the BBB include intracerebral implantation and convection-enhanced distribution. There is a need to determine which strategies are most effective and how they can be improved for patients with brain tumors.

Cerebral edema is a serious complication in many patients with brain tumors. The molecular and gene-related mechanisms underlying the formation of cerebral edema need to be identified. Also needed are more quantitative methods to measure flux or transfer rate constants as indicators of vascular permeability in patients and experimental animals. We also need to improve our understanding of how to reverse edema and to better understand the mechanisms underlying the effects of current therapies.

Current in vitro models of the BBB are inadequate. Although brain endothelial cells co-cultured with astrocytes have been used to study the BBB, better in vitro models that retain the phenotype of brain endothelial cells will be valuable, as would an in vitro model of the BTB. Basic research on brain tumors would be facilitated by the development of appropriate models that simulate the human condition in situ.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Develop strategies for delivering both small and large molecules to the CNS.

The transport of small molecules might be enhanced by designing drugs that have affinity for one of the carrier-mediated transporters within the BBB. Alternatively, drugs that inhibit the active efflux transporters may be useful as "co-drugs" to mediate the uptake of chemotherapeutic agents that are normally effluxed from brain to blood. Tumor-specific agents could be used with BBB disruption. Similar approaches might be used to develop new

diagnostics for human brain tumor imaging. Peptide or antisense radiopharmaceuticals could be developed as molecular "Trojan horses" that bind to endogenous receptor-mediated transporters in the BBB and are transferred across the BBB by this mechanism.

An important mission for the future, not only for brain tumors but for the field of neuroscience in general, is the ability to "image any gene in any person." This might be done with antisense radiopharmaceuticals that are made transportable through the BBB. This is a "barrier" problem, because to be successful, an antisense molecule targeted at an mRNA molecule within the tumor cell must be transported across not only the BTB but also the tumor cell and organelle membrane "barriers."

Priority 2:

Identify the genes and proteins expressed by the BBB and the BTB.

BBB genomics should be considered a high priority. Because only very abundant BBB-specific transcripts will be detected with whole-brain gene microarrays, BBB genomics research needs to start with the initial isolation of brain capillaries from animal or human brain, both normal and tumor derived. Comparison of capillaries from normal brain and brain tumor can help to elucidate the tissue-specific gene expression at the BTB and distinguish it from the tissue-specific gene expression at the BBB and normal brain. The elucidation of the pattern-specific tissue expression at the BBB or the BTB would provide the platform for further investigations on overall brain capillary biology and brain vasculature biology as they pertain to conditions such as angiogenesis, cell adhesion, antigen presentation, metastasis, and local inflammation.

Priority 3:

Develop novel viral and non-viral strategies for brain tumor gene therapy.

Viral strategies include the use of adenovirus, herpes simplex virus, adeno-associated virus, and other virus vectors. To date, investigators conducting trials in humans have used virus gene formulations administered invasively, through intracerebral implantation. Work in experimental animals, however, has demonstrated that both intra-arterial and intravenous delivery can be efficacious and safe. Some of the new conditionally replicating virus vectors have the added advantage of virus amplification within the tumor after passage through the BBB, thus increasing the treatment volume.

The developments in Priorities 1 and 2 should be applied to improve the delivery of virus and non-virus vectors to tumors and to target the BTB. Current problems include the lack of information on the role of the immune system in limiting virus replication, enhancing tumor rejection, and potentially causing brain inflammation. Limitations also exist in the methodologies available for targeting specific tumor cells in order to minimize potential toxicity to normal brain and vasculature. Studies have demonstrated the synergistic effects of virus vectors with other modes of therapy, such as radiotherapy, chemotherapy, and immunotherapy, but to date these approaches have not been applied in humans.

RESOURCES NEEDED

Priority 1

The development of novel drug targeting systems in the brain that enhance brain tumor uptake of either small- or large-molecule diagnostics or therapeutic molecules requires the following:

- Inclusion of lipid-soluble drugs that penetrate the BBB and of brain tumors in industrial and government antitumor drug development programs.
- Novel forms of BTB disruption
- Drugs that access BBB carrier-mediated transport systems
- Drugs that inhibit BBB active efflux transporters such as p-glycoprotein
- New vectors (ligands) that are transported across the BBB by receptor-mediated transcytosis systems, which can act as "molecular Trojan horses" for transporting drugs across the BBB and BTB

Priority 2

Isolated brain capillaries from either animal or human brain and human brain tumor should be used as the starting point for preparing BBB-specific gene arrays and cDNA libraries from BBB and BTB. BBB gene-specific proteomic programs can also be developed in parallel. The focus on these genomics or proteomic programs should be molecular-based strategies for investigation of the following:

- Tissue-specific gene expression of the BBB of normal brain
- Differences in capillaries perfusing normal brain BBB and tumor capillaries (BTB)
- New endogenous BBB or BTB transporters for targeted drug delivery to brain tumors
- Novel mechanisms of tumor angiogenesis, invasion, cell adhesion, metastasis, and antigen presentation

Priority 3

Development of vectors and strategies for gene/viral delivery to brain tumors, taking into account the unique character of brain vasculature, extracellular space, and cell diversity, will require the following:

- Novel adenovirus, herpes simplex virus, adeno-associated virus, or other virus vectors that specifically target tumor cells in the brain and do not cause brain toxicity
- Virus or non-virus vectors that target brain tumors upon intraarterial or intravenous administration. Such strategies may utilize the ability of some virus vectors to cross the brain vasculature and specifically multiply within the tumor or may follow the development of novel BBB/BTB drug targeting systems.
- Vectors or molecules that specifically target the tumor vasculature without harm to the normal brain vasculature
- Strategies that utilize the above vectors in combination with radiotherapy, chemotherapy, or immunotherapy

The NCI and the NINDS are urged to adopt all three of these priorities, as they are interconnected. Gene and viral therapy, use of recombinant proteins, monoclonal antibodies, or antisense therapy may be successful in patients with the adaptation of novel BTB drug targeting systems applied to brain tumors. However, the discovery of novel BBB drug targeting systems will be accelerated by the classification of the tissue-specific gene expression at the BBB through a BBB genomics program. Further, the use of any biological agent for brain tumor therapy could have immunological

problems that are different from those of similar therapies administered for non-CNS disease. Studies of this immunological response need to be supported in order to take these agents safely into clinical trial. Also needed are future training programs focusing on brain vascular biology in order to produce a generation of scientists who can integrate our knowledge of neuroscience and cerebrovascular biology.

Detection and Diagnosis

Co-Chairs: J. Gregory Cairncross, M.D., and Donna Neuberg, Sc.D.

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Greta Bunin	Bruce R. Korf	Malcolm Smith
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R. Edward Coleman	Ravi Menon	Mark Yarborough

STATEMENT OF THE PROBLEM

Brain tumors are a heterogeneous group of central nervous system neoplasms that arise within or adjacent to the brain. Some are curable by surgical resection, but many cannot be eradicated by current treatments, and, when they are, disabling neurological injury often ensues. Moreover, the location of the tumor within the brain has a profound effect on the patient's symptoms, surgical therapeutic options, and the likelihood of obtaining a definitive diagnosis. The location of the tumor in the brain also markedly alters the risk of neurological toxicities that alter the patient's quality of life.

At present, brain tumors are detected by imaging only after the onset of neurological symptoms. No early detection strategies are in use, even in individuals known to be at risk for specific types of brain tumors by virtue of their genetic makeup. Current histopathological classification systems, which are based on the tumor's presumed cell of origin, have been in place for nearly a century and were updated by the World Health Organization in 1999. Although satisfactory in many respects, they do not allow accurate prediction of tumor behavior in the individual patient, nor do they guide therapeutic decision-making as precisely as patients and physicians would hope and need. Current imaging techniques provide meticulous anatomical delineation and are the principal tools for establishing that neurological symptoms are the consequence of a brain tumor.

CHALLENGES

Detection

Early detection has not been an area of interest or focus in neurooncology. Because early treatment for many types of brain tumors does not improve quality or prolong length of life, early detection strategies have not been a priority and their use may not be ethical. In this respect, brain tumors are different from cancers of the breast, prostate, and colorectum, for which screening strategies are now broadly used in healthy populations. Moreover, because the causes of brain tumors are not known, it is not yet possible to identify special populations that are at increased risk due to environmental or occupational exposure.

Imaging, the obvious screening strategy for brain tumors, is extraordinarily costly, especially given the relative rarity of brain tumors in comparison with breast or prostate cancer. Genetic testing, a second option, is desirable as a screening tool because it is

based on a simple blood test, but this modality is not yet a reality for sporadically occurring brain tumors, which by far constitute the majority of brain tumors. Hence, the question arises as to whether there is a role for early detection strategies in neurooncology.

Detection can also be defined to include prompt diagnosis in symptomatic patients, early recognition of tumor recurrence in previously diagnosed or treated patients, and the ability to distinguish between recurrence and radionecrosis. In pediatric populations, early symptoms of brain tumor can be misdiagnosed as migraine, school phobia, anorexia, or other common pediatric problems. In very young children, the symptoms of brain tumor may be dismissed as minor developmental delays. An intense educational effort is required to ensure that children as well as adults receive prompt and thorough neurological assessment for lingering symptoms. Imaging methods need to be able to identify early recurrence and to distinguish recurrent disease from other pathologies.

Diagnosis and Prognosis

The current histopathological approach to the diagnosis and classification of brain tumors is satisfactory in many respects. In virtually all instances, brain tumors can be accurately placed into broad diagnostic categories, such as gliomas, meningiomas, or metastases. Within these categories, however, some tumors are not further classifiable; concordance in histological diagnoses between pathologists is sometimes poor; and tissue samples, when small, render confident classification difficult. Increasingly, tissue samples are small because stereotactic biopsy procedures are the preferred means to establish a diagnosis of brain tumor. In addition, when the tumor is located deep within the brain or adjacent to eloquent cortex, only stereotactic biopsies are feasible. Occasionally a brain tumor is treated in the absence of a histopathological diagnosis because its location precludes safe sampling.

Another limitation of the current histopathological basis of brain tumor classification is the inability to accurately predict tumor behavior or response to therapy . Tumors that look similar may behave quite differently, and conversely, tumors that look quite different may behave identically. Currently, when histopathological diagnosis is augmented by clinical and radiographic features such as patient age and tumor enhancement, prognostication for survival in individual patients improves but remains inexact. Predicting response to treatment by histologic, clinical, and radiographic features therefore remains elusive.

Given the rapid advances in gene expression profiling, the achievements in sequencing the human genome, and the continuing revolution in brain imaging, the question arises: What is the potential for molecular characterization and advanced imaging, alone or in combination, to augment or replace current histopathological diagnosis and tumor classification in neurooncology? More important, what is the potential of these approaches to predict tumor behavior and sensitivity to treatment? These possibilities are especially exciting because there are already suggestions that specific genetic alterations in glial tumors may predict survival outcomes after specific therapies.

A further exciting opportunity afforded by advances in molecular medicine and imaging might be the ability to predict response to existing and novel therapies, and to do so soon after administering the intervention. The ability to streamline the assessment of therapeutic maneuvers would permit ineffective therapies to be discarded

quickly. This would be especially welcome to patients, who perceive that the evaluation process is slow, inefficient, and imprecise. Having an earlier endpoint by which to declare a therapy ineffective would address these important concerns. Moreover, early identification of effective therapies quickly resets the clinical research agenda to include quality of life as well as efficacy.

RESEARCH AND SCIENTIFIC PRIORITIES

The successful achievement of the following priorities will require advances in brain tumor imaging and genetics and will have important implications for brain tumor treatment. epidemiology, and outcomes.

Priority 1:

Develop a molecular- and imaging-based classification for brain tumors that is capable of predicting tumor behavior and guiding treatment decisions more accurately and objectively than are current histopathological methods.

Corollary: Investigate whether imaging methods can be developed to capture the tumor's molecular signature. This is important because the amount of tumor tissue available at diagnosis may be limited, and tissue is not available for serial sampling after therapy.

Priority 2:

Refine the ability to detect response to novel treatments so that ineffective therapies can be discarded quickly while active compounds are evaluated fully in clinical trials that assess quality as well as length of life. Non-anatomical magnetic resonance signals, rather than change in tumor size, may have the potential to accurately detect early response.

Corollary: Refine the ability to predict response to existing treatments so that patients receive active agents prescribed optimally, and do not receive toxic ineffective therapies. Molecular markers or imaging signals may have the potential to accurately predict response.

Priority 3:

Identify serum markers of individual brain tumor types in preparation for screening programs in at-risk individuals or in populations. Screening, using serum markers, will be important and ethical only when it is clear that early treatment unequivocally improves patient outcomes.

RESOURCES NEEDED

Tissue banks linked to clinical databases are needed for both pediatric and adult brain tumors of all types. Tissue banks should include both paraffin-embedded and frozen tumor, serum, normal DNA from peripheral blood or buccal mucosa, and, in certain instances, cerebrospinal fluid. For frozen tissue, guidelines for quality assurance and tissue preparation need to be developed. The clinical database should contain information about patient characteristics, family history of brain tumor or unusual cancer susceptibility, imaging features (including tumor location), therapy administered, response to therapy, and survival.

A decentralized banking model is envisioned. Public and professional educational efforts will be required to ensure that both common and rare brain tumors are submitted to the banks. Large numbers of samples will be important to sustain a concerted research effort that can address the heterogeneity of these diseases and the many scientific questions that will arise. When available, serial samples should be banked on an individual basis. An oversight structure will be needed to control access to

this precious resource, and patient consent issues will need to be carefully considered.

Epidemiology, Prevention, and Outcomes

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Lisa DeAngelis	Scott Pomeroy	

EPIDEMIOLOGY

Statement of the Problem

Gaps in the fundamental understanding of brain tumors, from basic biological interactions to epidemiology, hinder systematic approaches to prevention. Although research exploiting new molecular and genetic technologies is attracting scientists and funds, epidemiological information about primary brain tumors remains scarce. The absence of high-quality epidemiological studies is an impediment to understanding who and how brain tumors arise in both children and adults.

Challenges and Barriers

The histopathological variability in brain tumors and the relatively small numbers of persons affected complicate the design of research protocols and historically have limited the statistical power of studies. Existing tumor registries and surveillance systems (including the Surveillance, Epidemiology, and End Results [SEER] Program and the North American Association of Central Cancer Registries [NAACCR]) are not linked or structured to allow rapid case ascertainment or case sample sizes adequate for meaningful epidemiological research of all brain tumor types. Although promising epidemiological clues have been uncovered in recent years, few are being pursued through funded studies.

Many previous epidemiological studies on primary brain tumors have significant methodological flaws. Methodological issues themselves warrant investigation to advance the field. Questions that need to be addressed include how to assess recall bias among study subjects who may have cognitive impairment; what types of exposures for which interview data and the potential for recall bias may be strong enough to result in spurious associations; how the interval between exposure and interview may affect recall bias; and whether there are feasible sources of control groups in the United States other than the current approach of random-digit dialing and interviews with hospital patients.

Most registries collect data only on malignant tumors, as defined by the *International Classification of Diseases*, 9th Edition (ICD-9). That registries are limited to malignant tumors artificially constrains epidemiological understanding of brain tumors. For example, the just-revised classification system used by all cancer registries now codes juvenile pilocytic astrocytomas as benign, and therefore registries—including SEER—are likely to stop collecting data on these tumors. Brain tumor specialists include and treat all neoplasia of the central nervous system as

cancer, and the rationale for including all brain tumors in population-based surveillance systems has been well documented.

Better surveillance tools are critical to facilitate epidemiological research. Two avenues of epidemiological investigation are especially compelling. In pediatrics, mechanisms are in development for a surveillance system that routinely collects biological samples of blood and tumor. A similar system is needed for adult tumors.

Research and Scientific Priorities

Priority 1:

Enhance and expand the existing infrastructure for a surveillance database that does the following:

- Includes all primary brain tumors (malignant and nonmalignant, central nervous system and extraaxial
- Is designed with enough flexibility to accommodate new histological and molecular classifications of tumors
- Gives individual investigators access to rapid case ascertainment for studies that require questionnaires, tissue samples, pathological review, and pooling of results to increase sample size.

SEER and state registries capture 50% or more of neuroepithelial tumors, and extraaxial tumors can be captured only through a central brain tumor registry. Approximately 52% of "quality" registries cover the U.S. population. If definitions were changed by consensus, data from diverse sources could be integrated into the database of the National Cancer Institute and other databases.

Priority 2:

Target funding to support basic science and population-based human studies to evaluate leads on animal neurocarcinogens, such as exposure to nitrosamines, viral agents, and polymorphisms. For known animal carcinogens, molecular exposure measures are needed to allow direct exposure measures for human studies.

Priority 3:

Investigate the epidemiology of neurotoxicity and other toxic effects of treatment, such as what makes some patients susceptible and what exerts a protective effect.

Resources Needed

- **Database of household carcinogens.** A database listing the major household sources of known carcinogens (e.g., dry-cleaned clothing, oven cleaner, specific types of paints, weed killer), including neurotoxins and neurocarcinogens, would be valuable for both brain tumor and cancer epidemiology in general.
- **Training.** Training in epidemiological methods is needed for researchers involved in etiological and outcome studies, including neurooncology and neurosurgery residents.

PREVENTION

Statement of the Problem

Although the literature and the current National Institutes of Health (NIH) research portfolio hold almost no information relevant to the prevention of primary brain tumors, factors that may reduce the risk of primary brain tumors are gradually being identified. Specifically, studies of pediatric

cancers suggest that maternal diets high in fruit and vegetable intake or maternal use of vitamin supplementation, particularly folates, during pregnancy may reduce tumor development. Other studies suggest a protective role for allergic conditions and selected infectious diseases in adult tumors. If these isolated results can be replicated and clarified and the underlying biological mechanisms understood, intervention and prevention strategies may become feasible.

Challenges

At this juncture, not enough is known about the basic epidemiology of primary brain tumors to guide research initiatives. For this reason, the most pressing challenge is to acquire data that will drive scientific inquiries in prevention.

Research and Scientific Priorities

Priority 1:

Because of the paucity of data and ideas about prevention, a request for proposals should be issued to stimulate new research approaches.

Priority 2:

For a subset of brain tumors, some information is available to suggest fruitful research directions. For example, it may be feasible to explore the prevention of certain familial cancers, such as neurofibromatosis or von Hippel–Lindau syndrome. In addition, data from patients treated in pediatric cancer cooperative groups may yield insights about prevention for patients at risk of second primary tumors resulting from previous cancer treatment.

OUTCOMES

Statement of the Problem

The endpoints of survival and disease-free survival, which traditionally have been used to assess outcome in patients with cancer, fall painfully short as measures of success in treating brain tumors. From the perspective of patients and families, "outcome" is a multidimensional, daily reality, and quality of life can be at least as important as survival. So, too, assessment of quality of life is increasingly used to evaluate the risks and benefits of new treatments.

Researchers who are not directly involved in patient care may lose sight of the importance of the functional impact of brain tumors and their treatment on survivors and the families who care for them. Because the current treatment armamentarium has little to offer many patients with brain tumors, saving a life can be a considerable achievement. Saving a life without considering future constraints on how life can be lived, however, may offer an unacceptable outcome. Parents want to normalize life for an affected child, and adult patients want to weigh the functional risks they face with each treatment option.

To allow patients and parents to make more informed treatment decisions, clinicians need more information on the expected functional outcomes of disease and treatment. Such assessment data can also contribute to the drug approval process, when the survival benefits of two treatments are not substantially different. Finally, greater understanding of the impact of treatment can lead to interventions that will allow parents and adult patients to rehabilitate damaged functioning and normalize their lives.

Posttreatment follow-up of brain tumor patients and survivors does not routinely include functional assessment, nor is patient

functioning routinely evaluated in clinical trials. This lack places a serious limitation on the ability to weigh the risks and benefits of new therapies and to develop strategies to improve functional outcomes. In this context, "function" includes neurocognitive status, symptoms, ability to perform activities of daily life, and psychosocial status. Another important but neglected aspect of assessment and intervention is the impact of brain tumor diagnosis and treatment on families. Because families are the primary caretakers of patients with brain tumors, families' functioning can have a profound and direct impact on patients' functioning and quality of life.

Challenges and Barriers

A major barrier to the conduct of functional assessments is a negative attitude among clinicians. Some feel that it should be sufficient for a treatment to avert a patient's death. Some clinicians interpret as presumptuous patients' wishes to have maximum levels of functioning and minimal damage to the central nervous system and loss of function. Further, clinicians may feel defensive when faced with a patient's serious or unexpected functional deficits. Finally, clinicians may be unfamiliar with the assessment process and may inappropriately feel that assessment is too costly and burdensome for patients.

To incorporate functional assessments into the design of clinical trials, two things are needed:

1. Criteria to determine which trials may be suitable (functional assessments are not an appropriate component of all clinical trials)
2. Identification of the appropriate time points during a clinical trial for administration of the assessments.

Research and Scientific Priorities

The goals in the area of outcomes are to be able to predict the impact of the tumor and treatment on a patient's functional status and to achieve the best possible outcome. Routine functional assessments and interventions are necessary to improve patients' functioning and quality of life and should become the standard of care for patients with primary brain tumors.

Priority 1:

Identify the pathogenesis of the injury related to the tumor (e.g., rapid versus slow growth, site of the tumor), treatment, and comorbid processes (for example, those involving the neuroendocrine and vascular systems and cytokines). To do this, the following are necessary:

- Correlate patient demographic characteristics, imaging, and cognitive/quality of life assessments.
- Develop animal models in tandem with human studies.
- Identify markers for patients at risk of developing toxic effects (e.g., the apolipoprotein E genotype).
- Develop and assess drugs that might offer neuroprotection during primary cancer therapy.

Priority 2:

Design and evaluate innovative interventions to ameliorate undesirable symptoms and functional deficits. Studies should include the following:

- Empirical investigations of what works—pharmacologic, behavioral, cognitive, or a combination of these approaches
- Mechanism-based interventions focused on cytokine antagonists, neurotransmitter agonists, and neuroprotective agents

Priority 3:

Alter primary therapy to reduce toxic effects while maintaining efficacy, such as conformal radiotherapy, local therapy, and reduced doses of radiotherapy.

To satisfy third-party payers, in anticipation of eventual coverage of the cost of such interventions, cost-effectiveness should be built into the research design prospectively. The efficacy of these interventions should be correlated with imaging measures, including functional magnetic resonance imaging, and with physiological correlates, such as levels of pro-inflammatory cytokines and neuroendocrine markers.

Resources Needed

Intra-institutional cooperative research initiatives, both within and outside NIH, should be fostered to address rehabilitation, education, and medical issues. Several working groups or consensus panels should be convened under NIH auspices to accomplish the following:

- **Standardize assessment tools.** The tools now used to assess patient function are not standardized across studies, sites, or patient populations. Standardized assessment instruments will enhance the generalization of findings; if a core of standard content exists, institutions can tailor aspects to specific studies. Tools need to be valid, reliable, easy to use, and inexpensive to administer.

  A panel of neuropsychologists, neurologists and patient advocates should select well established, user-friendly instruments from the literature to form a "practice guideline protocol" for use in evaluating patients in clinical trials. Such a protocol of assessment instruments can be constructed to allow the investigator to select the tools that will evaluate hypotheses related to, for example, memory, attention, language, and spatial deficits.

- **Survey successful interventions.** A review of cognitive-behavioral and psychopharmacological interventions used in other rehabilitation-related disciplines, such as special education and rehabilitative practices related to traumatic (acquired) brain injury, dementia and aging, and stroke, should be undertaken to determine whether successful strategies might be used successfully with brain tumor patients. This review should be comprehensive and include projects funded and/or conducted through the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, the National Institute of Mental Health, the National Institute of Dental and Craniofacial Research, and other NIH and Department of Health and Human Services institutions, centers, and working groups. Similarly, a review of family support interventions developed for traumatized families should be conducted to cull potentially effective interventions for families with a member affected by a brain tumor.

- **Develop assessment guidelines.** Guidelines are needed on what and when to assess in different types of clinical trials. Currently, questions about symptoms such as headaches are asked to determine side effects of treatment, but patients may also be asked questions such as how they feel about the symptoms they report. These questions are important for patient care but vary dramatically from person to person and may not be informative in clinical trials. It would also be helpful for guidelines to be framed with an

understanding of the World Health Organization's three-tiered level of analysis (impairment, disability, and handicap).

Cancer Genetics and Epidemiology

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STATEMENT OF THE PROBLEM

Concerted efforts over the past few years have shown that brain tumors, like other major human neoplasms, result from the accumulation of genetic lesions during tumor progression. Despite the extensive catalogue of these somatic tumor-associated lesions, significant gaps exist in our understanding of how such lesions initiate the process, how they influence therapeutic response, and the nature of their biological function. Clearly, such information will be required in order to harness the knowledge of genetics for improved diagnostic and therapeutic modalities. This is of particular importance for this group of tumors, given their unique biological and clinical characteristics and heterogeneity.

CHALLENGES AND QUESTIONS

- Little is known about brain tumor predisposition genes in humans. This situation reflects the scarcity of specimens, poor record-taking of family medical histories, insufficient clinical and pathological information on the samples, the lethality and late onset of many of these diseases, the inaccessibility of early lesions, and pedigrees that often do not lend themselves to mendelian analysis. In rare instances, autosomal dominant patterns indicative of "hard" primary mutations have been reported (e.g., Turcot syndrome, neurofibromatosis 1 and 2, and Li-Fraumeni syndrome). Family patterns are more commonly consistent with the possibility of multigenic inheritance ("soft" but interacting mutations), modifiers that alter the penetrance or expressivity of the genes, or epigenetic gene inactivation.
- A special feature of many malignant brain tumors is their innate resistance to existing chemo- and radiotherapeutic approaches. Little is known about the genetic mechanisms responsible for this resistance. For example, the impact of somatic or germline allelic variation on these mechanisms remains to be determined.
- Limited information exists on how specific lesions behave in cells of different lineages thought to represent precursors of distinct brain tumor types. Such information could be of importance in the design of therapeutic protocols targeting such lesions.
- Little is known of the interactions between predisposing/somatic mutations and external or internal environmental perturbations, such as hormonal influences, in utero exposures, and workplace carcinogens. This issue might be particularly relevant in explaining tumor emergence in different age groups

(pediatric versus adult) and their distinct clinical behaviors.

- The genetic basis of the unique biological features of brain tumors is largely not understood. This applies to integral and important features such as invasion, motility, angiogenesis, and necrosis, as well as tumor progression and maintenance.
- Existing genetic models and associated genomic infrastructure (particularly in mice) are inadequate to properly address the genetic and phenotypic aspects of the human diseases. In the absence of validated, refined models, rapid testing of candidate cancer genes and their therapeutic approaches is severely hampered.
- There is an inadequate compendium of gene expression profiles for precursor cells and their lineages and tumor derivatives. Little information exists on the nature of the physical and functional interactions of the gene products that are known to play a role in the development of brain neoplasia with other cellular components. Moreover, genome-wide genotypes have not been collected and so have not been tested for their correlation with tumor type or behavior.
- There exists a strong need for the development of genetic screens that will permit tumorigenesis. These screens need to be conducted on both the organism and cell levels. The latter will be depend on the development of in vitro systems that accurately reflect the in vivo process under investigation.
- There is no comprehensive tumor registry, tumor bank, and familial tissue bank. It is especially important that these be comprehensive and organized on a national level, given the rarity and heterogeneity of the most informative tumors and familial situations.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Isolate genes causing predisposition to human brain tumors.

It is important to search for predisposition genes in families with brain tumors as the primary identifier of genes relevant to brain tumors. Families whose members are prone to a variety of other tumors may represent additional opportunities to isolate genes that are also relevant to brain tumor pathogenesis. Elucidation of the interaction of such genes with environmental agents may also play a significant role in understanding the etiology of brain tumors.

Priority 2:

Identify the genes and genetic variations that underlie tumor resistance to chemotherapy and radiation therapy, as well as the allelic variations that influence responses to therapy in individual patients.

Priority 3:

Understand genotypic influences on phenotypic behavior, tumor type, age at onset, anatomical position, cell of origin, and cellular biology.

Priority 4:

Establish and refine genetically based model systems that can faithfully recapitulate the complexity, heterogeneity, and diversity of human brain tumors.

RESOURCES NEEDED

- There is a strong need for organized and coordinated brain tumor registries, including family histories and extensive clinical and pathological information. These registries should be coupled with tumor samples that are equally well characterized and with somatic noncancerous tissues from affected individuals and their family members. It would be particularly useful if such centralized resources maintained strong technical support to conduct routine genome-wide studies, including expression profiling, in situ hybridization of tissue arrays, and high-density genotyping and mutation analysis. Centralization of these technical efforts would provide for efficient and thorough utilization of these precious samples and enable investigators to obtain such information without the need to build or develop advanced capabilities themselves.
- It would be widely useful to establish a compendium of gene expression patterns and genome-wide genotypes of tumors of many different histologies to be used for correlative studies with regard to cell type, developmental stage, and their response to therapeutic agents. The Brain Tumor Genome Anatomy Project BT-GAP and the Cancer Genome Anatomy Project (CGAP) are making significant progress with regard to human tumors, but the genome infrastructure to analyze mice lags far behind. This is a serious problem in that it hampers the rapid isolation of genes based on interspecies sequence homologies.
- There is a strong need to support the design and development of novel and targeted genetic screens conducted on both the organism and cell culture levels. Particularly relevant is the need to fortify efforts for the development and refinement of mouse models of human brain tumors harboring commonly occurring genetic lesions. Such cancer-prone models will find great utility in the identification of pathways and their interactions, as well as for loci that modify the effects of these pathways. Significant emphasis should be placed on the development and design of mouse models that enable assessment of the role of genes in both tumor initiation and tumor maintenance.
- The interdisciplinary nature of neurooncology makes it essential to augment the opportunities for physicians to receive training in molecular oncology and developmental neurobiology. It is equally essential for basic scientist trainees to receive training that is medically relevant to molecular neurobiology. Similarly, there exists a need for programmatic funding mechanisms that can form a bridge between the activities of established investigators from different disciplines focused on common themes in neurooncology. The design of the peer review of such grants should consider the special needs and circumstances of such interdisciplinary efforts. Finally, the relative paucity of understanding of this dread disease underscores the desirability to develop rapid funding mechanisms emphasizing novel and, perhaps, preliminary ideas (cf. Department of Defense “concept grants”).

Imaging

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STATEMENT OF THE PROBLEM

The past 60 years have seen a progression in the field of imaging from the early use of cerebral angiography and pneumoencephalography to the development of early radionuclide techniques and the advent of X-ray computed tomography (CT) in the 1970s. The current era has seen the implementation of magnetic resonance imaging (MRI) in all its permutations (structural, functional [fMRI], perfusion, diffusion, and spectroscopy), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and intraoperative ultrasound. These techniques, now part of the clinical mainstream, are used individually or in combination to better understand the basic mechanisms, pathophysiology, and clinical features of brain tumors and their responses to therapy. They are also used to make therapy safer and more accurate, ultimately improving the quality and duration of life for patients.

Functional imaging—the visualization of physiologic, cellular, or molecular processes in living tissue—now provides insights into tumor blood flow, glucose or oxygen metabolism, and many other hemodynamic, physiologic, and biochemical processes. Such approaches may provide a means to identify molecular structures or receptors that cover the surface of a tumor and to help predict its natural history and response to certain treatments. Attempts are already being developed to use such strategies to examine gene expression, a strategy that will improve detection, staging, treatment selection, treatment monitoring, and prognosis. Imaging techniques are also now being linked to surgical and radiation therapies. Pre- and intraoperative imaging methods using CT, MRI, PET, and SPECT, as well as intraoperative methods such as radioisotope probes, optical imaging, and intraoperative MRI, are all finding a place in planning surgical or radiation therapy for patients and in sampling or targeting tissue for biopsy. These technologies also have a role in avoiding critical brain areas when destructive lesions or surgical resections are planned. They may also be important in evaluating the plasticity of normal brain tissue after such procedures, either during development in pediatric brain tumors or in adults.

The development of cellular- and molecular-based imaging will provide many new opportunities to assess brain tumors at a molecular level in animal and clinical models, as well as the ability to monitor gene therapy. As imaging techniques continue to evolve, it will be possible to visualize and quantitate changes as cells transform from normal to precancerous to cancerous. It may one day be possible to evaluate at-risk patients earlier in cancer pathogenesis, perhaps before a tumor becomes malignant. It is anticipated that, with the information obtained from the use

of such imaging techniques, it will be possible to visualize the actual molecular signatures of cancer in vivo. The ability to detect fundamental changes associated with a tumor cell will thus vastly improve our ability to detect and stage tumors, select appropriate treatments, monitor the effectiveness of a treatment, and determine prognosis.

For example, patients may be selected for a particular drug therapy on the basis of imaging before drug administration. A drug's effect on specific protein interactions, signal transduction, or metabolic pathways could be measured, thereby providing new endpoints for monitoring drug response. In all probability, nomograms of response could be created for populations receiving therapies. Clinicians would benefit from quantitative methods for the identification of "partial response" and "complete response." These would serve as endpoints to replace survival in clinical trials.

In imaging, as elsewhere in cancer research, animal models of cancer are making it possible to perform certain kinds of studies that are difficult, if not impossible, to perform in humans because of practical or ethical considerations. A distinct advantage of noninvasive imaging in animal models of cancer is the ability to perform repetitive, noninvasive observations of the biologic processes underlying cancer growth and development without sacrificing the animal. The development of small-animal imaging devices, which can produce serial images of experimental brain tumors in small animals and incorporate all of the functional strategies just described, should provide a powerful new tool for experimental studies of brain tumor behavior and response to treatments. Further development of targeted contrast agents, ligands, and imaging probes also need to be supported because they will provide better in vivo elucidation of the key metabolic pathways and specific cell cycle functions that become altered in cancer.

It is also clear that better use can be made of existing data derived from imaging techniques. Combining in vivo phenotypic information about tumor characteristics with ex vivo analysis at genetic, cellular, and chemical levels can provide better correlations among these variables and the patterns seen in images obtained in vivo. Four-dimensional (spatial and temporal) data analysis of these characteristics should provide new insights into the natural history of tumor growth, patterns of spread, and responses to therapy. When optimized into probabilistic data structures that account for variance, not only in normal brain structure but also in tumor behavior, these approaches should provide new and useful tools for optimizing clinical trials. Image analysis techniques that integrate information across modalities, spatial and temporal scales, subjects, trials, and species will require the development of new algorithms; an emphasis on neuroinformatics for the incorporation of images into clinical trial databases; and the incorporation of genetic, demographic, and clinical data sets.

CHALLENGES AND QUESTIONS

The goals of the National Cancer Institute's plan for Fiscal Year 2001 with regard to imaging are quite appropriate to the challenges associated with imaging brain tumors. These goals include the following:

- Develop and validate imaging technologies, probes, and radiocontrast agents that have the sensitivity to detect precancerous abnormalities and very small cancers.
- Develop imaging techniques that identify the biological properties of precancerous or cancerous cells that will predict clinical course and response to interventions.

- Develop minimally invasive imaging technologies that can be used in interventions and assessment of treatment outcomes.
- Foster interactions and collaboration among imaging scientists and basic biologists, chemists, and physicists to help advance imaging research.
- Create infrastructure to advance research in developing, assessing, and validating new imaging tools, techniques, and assessment methodologies.

Each of the goals listed above is associated with a set of challenges and questions. The major challenge for the imaging community is to accurately measure tumor burden and function (phenotype). This goal will be pursued by using different imaging technologies, probes, and paradigms (see Exhibit 1) in order to better characterize brain tumors before, during, and after treatment. A further challenge will be validation of the new imaging paradigms through animal experiments, in vivo versus ex vivo (molecular) analysis, and clinical correlations.

One goal of surrogate marker imaging is differentiating the cellular and molecular characteristics of tumor from those of normal brain tissue. Another goal is to image the biology (molecular biology) of brain tumors with new techniques and probes. A final goal is to arrive at non-lethal endpoints for the assessment of treatment and the natural course of tumor growth. This can be done with the development of four-dimensional nomograms specific for tumor and age of patient and with spatial-temporal measurements, using a multimodality, multispectral approach.

Image Outcome and Monitoring Interventions

Imaging has a role in monitoring both treatment progress and outcomes in addition to drug toxicity. Available radiographic endpoints are inadequate as treatment markers and endpoints. Efforts must be made to achieve realistic criteria ("cut points") for partial and complete response to therapy and to define criteria for assessing toxicity to white matter, cortex, and ventricular structures. In the case of treatment, there are several aspects under consideration, each with its own challenges. Drug effectiveness should be assessed within the context of tissue concentration (labeled drugs, etc.), drug delivery of small versus large molecules (i.e., blood-brain barrier, blood-tumor barrier), and biological effect (function) of the tumor.

Image-guided strategies include the following:

- Preoperative and intraoperative planning (e.g., image-guided stereotactic biopsy and resection using PET, MR, fMRI, magnetic resonance spectroscopy [MRS], and optical intrinsic signal [OIS] imaging)
- Radiation therapy (e.g., image-guided stereotactic radiosurgery using PET, MR, fMRI, MRS, and OIS)
- Development of multimodal image registration (e.g., MR, fMRI, MRS, OIS, and PET)
- Development and availability of improved instrumentation (e.g., high-field human MR systems) and hybrid imaging devices (e.g., combined CT-PET or MRI-PET tomographs)

Assessment of Treatment Toxicity

Radiation and chemotherapy can have toxic effects not only for the tumor they are intended to treat but for brain function as

well. Toxicity to brain white matter has received little attention in the past, and little is known regarding the mechanism (e.g., demyelination, axonopathy, edema) of this toxicity and its temporal course. Toxicity can also be gauged by imaging the vasculature of normal brain and tumor. Similarly, toxicity indices can be created for gray matter function and plasticity in treated children.

Transgene and Molecular-Based Therapies

Imaging at the molecular level (assuming a homogeneous region of interest) is on the horizon. The task will be to generate reporter gene constructs that can be imaged as markers for transgene delivery (e.g., viral vectors) and for markers of change in specific protein interactions, signal transduction, or metabolic pathways. These protein interactions and the specific steps in signaling pathways can be targeted by specific anti-tumor drugs, and drug efficacy assessments can be made by noninvasive imaging of the specific pathway. In the future, patients may be selected for therapy on the basis of imaging before drug administration. Response could be monitored by measuring changes in specific protein interactions, signal transduction, or metabolic pathways. In this way, new endpoints for monitoring drug response could be developed.

Development of Databases, Informatics, Standards, and Software Tools

The NCI has created brain tumor study groups offering Phase I and II studies that provide the basis for intergroup Phase III trials. Examples include the nationwide approaches to brain lymphoma and oligodendroglioma. It is important to translate the above-described imaging advances to serve clinical trials. Systems must be provided for sharing, accessing, archiving, and integrating information across all data types. Databases provided for these clinical trials must contain real-time imaging displays as well as quantitative data (e.g., volume, spectral ratios, diffusion ratios, and normalized cerebral blood flow [CBF] and volume [CBV] information). The field of informatics is growing rapidly in the biological sciences and can make a major impact in the area of brain tumor research. Unlike other organs in the body, the brain has a distinct and important architecture. Both the type and location of brain tumors are therefore important in understanding their causes, growth patterns, and response to therapy.

A logical framework for integrating information about these lesions would be to use the anatomical structure of the brain itself as the framework for an atlas that would store information about all patients, whether studied in scientific protocols or undergoing conventional clinical treatments. Imaging can provide this architecture for databases and atlases. It will be important to develop the tools and informatics methods to integrate imaging studies across modalities, spatial-temporal scales, subjects, trials, and species. Such databases and atlases should be four-dimensional (three in space and one in time, where the latter variable can be the age of the subject as well as the time course of tumor growth and treatment). Because brain anatomy is highly variable among individuals in a population, it is also advisable that such atlases be probabilistic in nature, thereby providing distribution estimates for the locations of regions and tumors. These four-dimensional, probabilistic, image-based databases can be linked to other data sets, including clinical, molecular, histological, and therapeutic variables.

To accomplish such an endeavor, it will be important to develop tools to normalize

image acquisition across sites and to develop a standardized core image analysis and feature-extraction pipeline for the quantitative processing of imaging studies from all modalities. For example, a nationwide trial for the therapy of brain lymphoma in 600 patients can provide seminal data on the rate of response, relationship between drug dose and volumetric diminution of tumor, changes in spectra of magnetic resonance, and diffusion parameters. The clinical trials format is the ideal mechanism by which reliance on individual data sets can be replaced while providing integration across laboratories and experimental trials. This important, final recommendation is critical and, based on experiences in other fields, will require appropriate funding to provide the force for data integration. It will be necessary to create data standards (e.g., voxel size, diffusion weighted imaging (DWI) software sharing) and communication pathways and brain atlases at nationwide meetings.

RESEARCH AND SCIENTIFIC PRIORITIES

The following research priorities were identified for brain tumor imaging and are further detailed in Table 1:

Priority 1:

Develop and validate new imaging markers and techniques to facilitate the spatial-temporal assessment of brain tumors. These will be applied to animal models, human phase I trials, and phase II–III clinical trials. (See Exhibit I for details of new probes, markers, and imaging techniques based on current imaging technology.)

Priority 2:

Develop imaging techniques for predicting outcome and for planning and monitoring interventions in patients with brain tumors.

Priority 3:

Develop databases, standards, and software tools that integrate demographic, clinical, and imaging information in a form that can be used to identify characteristics that are critical for managing brain tumors and tailoring therapy to individual patients.

RESOURCES NEEDED

Resources needed to address these challenges include the following:

- Continuation and expansion of the imaging research programs described in Exhibit II
- Development of a “shared” and “accepted” informatics and database infrastructure
- Meetings to facilitate relations among industry, academics, regulatory, and funding agents
- Research and training funds to support the scientific priorities

Table 1: Scientific priorities for imaging in the study of brain tumors

I. Develop and validate imaging markers for the spatial-temporal assessment of brain tumors for use in human research, clinical trials, animal models, and patient care.

- A. Assess tumor burden as non-lethal endpoints for treatment assessment and natural course.
- B. Develop tumor- and age-specific spatial-temporal nomograms (four dimensional).
- C. Multimodality, multispectral approach
- D. Validation via:
  1. Clinical correlation
  2. Molecular correlations
  3. In vivo vs. ex vivo analysis
- E. Validated for:
  1. Monitoring treatment
  2. Targeting biopsies
- F. Differentiating tumor from normal brain
  1. Preoperative planning
  2. Intraoperative planning
- G. Angiogenesis and tumor phenotype imaging

II. Image outcome and monitor therapy in patients with brain tumors.

- A. Treatment
  1. Drugs
     a. Tissue concentration—labeled drugs, etc.
     b. Drug delivery—blood-brain barrier, blood-tumor barrier
     c. Small vs. large molecule
  2. Image-guided strategies
     a. Preoperative and intraoperative planning
     b. Hybrid devices
     c. Small-animal imaging
  3. Molecular
     a. Reporter gene imaging
        i. Transcription of endogenous genes
        ii. Post-transcriptional modulation of mRNA
        iii. Protein interactions
     b. Genotypes—antisense imaging strategies
  4. Radiation
     a. Tumor
     b. Brain
     c. Vasculature
- B. Toxicity
  1. White matter
     a. Mechanism (demyelination, axonopathy, edema, etc.) as function of age and treatment plan
     b. Temporal course
  2. Vascular

a. Mechanisms
b. Temporal course

3. Gray matter
   a. Mechanisms
   b. Temporal course
   c. Plasticity

III. Develop databases, informatics, standards, and software tools to:

A. Integrate across modalities, spatial-temporal scales, subjects, trials, and species

B. Develop four-dimensional probabilistic image databases linked to databases of clinical, molecular, histological, and other variables

C. Develop tools to normalize across image acquisition sites and to standardize a core image analysis and feature extraction pipeline (e.g., post-processing, distribution, etc.)

D. Alter the sociology of data sharing

EXHIBIT I:
New Probes/Markers and Imaging Techniques Based on Current Imaging Technology

I. MRI

A. Surrogate markers:

1. Methods need to be developed for choosing among many options; for example, using MRI alone, one can assess tumor volume, hemodynamics (CBF, CBV, BBB permeability), tissue water diffusion, and blood O_2, as well as proton and ^{31}P-MRS. At present, it is impossible to perform all these imaging motifs/measurements well, and there is little standardization of techniques across sites.
2. An overall concern is how to pick and choose among the different MRI motifs (let alone nuclear, CT, and other imaging techniques), select targets for validation, and compare studies by using the different imaging methods in the study of different patient groups with different endpoints.
3. Priorities and challenges might include both technology development (needed to facilitate improved quantification, especially for MRS and fMRI) and basic clinical validation studies (although the challenge above holds true here).
4. Ways need to be found to to standardize acquisition across multicenter trials with industrial collaboration.

B. Toxicity:

1. There is an apparent clinical need for functional cognitive studies. Because other sessions, especially the Radiation Therapy session, identified the same need, this call should be heeded.
2. fMRI can be combined with anatomical, biological, and functional assessment of white matter changes. fMRI/DWI tomography would be one priority, and the other imaging modalities described below would also be involved.
3. Assessment of vascular toxicity/BBBs in this category will overlap with surrogate markers, especially for anti-angiogenic treatments. Hemodynamics is a near-term goal for MRI.

C. Imaging Therapeutic Effect:

1. It is difficult to precisely define the need for quantitative in vivo pharmacodynamics within the tumor. This issue seems largely relegated to nuclear imaging, but MRS is likely to play some role as well. The area of pharmacodynamics represents an opportunity for industrial collaboration (e.g., by major pharmaceutical corporations) in a national effort to radiolabel all prospective therapeutic drugs.
2. Gene expression presents a "grand challenge." MRI/MRS

is likely to play an important role in this new field of "molecular imaging"; it has the right elements and will be developed further in the decade ahead.

II. MRS has been a tool for examining the alterations in cellular metabolites associated with carcinogenesis and treatment response in animal and cell systems for more than 20 years. Recent developments in technology have allowed MRS to be increasingly routinely applied to patients with brain tumors in research and clinical studies.

There are three major areas for development:

A. **Single voxel water suppressed proton MRS** is the most widely available MRS technique for clinical applications. It has been shown to assist in characterizing tumor type and grade, distinguishing tumor from other mass lesions, and determining whether changes in lesion morphology correspond to tumor recurrence or treatment-induced necrosis. Challenges to this technology include the following:

1. Choosing the most appropriate region of the lesion to study
2. Developing databases of in vivo spectral characteristics and using pattern recognition techniques to identify fingerprints that are predictive of histology
3. Validating the in vivo findings by correlating them with results obtained by ex vivo analysis of molecular markers, histology, and nuclear magnetic resonance (NMR) spectroscopy of excised tissue
4. Educating radiologists and oncologists concerning the most appropriate applications of the technology and the interpretation of the biological significance of clinical MRS data

B. **Single-voxel proton MRS techniques** can only interrogate regions that are thought to be suspicious from morphological or other physiological criteria. Proton MRSI can be used to map out spatial heterogeneity in both the lesion and surrounding tissue for studies in animal tumor models and patients. Applications include directing tissue biopsies, planning surgical resection or other focal therapies, defining the extent of disease, and evaluating response to therapy. Challenges to this technology are as follows:

1. The need for improved data acquisition techniques for optimized shimming, more robust water and lipid suppression, more accurately tailoring the excitation to the region of interest, and improving signal-to-noise ratio by using either higher field magnets or more sensitive, custom-designed radiofrequency coils
2. Developing post-processing methods for displaying imaging and spectral data, registering serial data from follow-up examinations, and deriving quantitative indices describing the metabolic changes within the lesion and surrounding normal tissue that can be used for treatment

plannig and assessing response to therapy

3. Validation of the technology as a tool for routine clinical evaluation of brain tumor patients in both single and multi-institutional settings

C. **Multi-nuclear MRS:** At present, the applications of ^{31}P, ^{13}C, and ^{19}F MRS are limited by low sensitivity and mainly involve cell and animal model systems. In cases where specific drug therapies have a signature that can be detected using one of these methodologies, there is promise for noninvasive monitoring of drug delivery and function. More generally, it is possible to measure pH, cellular bioenergetics, and phospholipid metabolism. Challenges for this technology include the following:

1. Obtaining ^{13}C-labeled drugs at a price that is economic for routine basic and clinical research studies
2. Availability of high field human MRI scanners in order to obtain in vivo ^{13}C, ^{19}F, and ^{31}P data at adequate signal-to-noise and spatial resolution

III. Recent developments in CT merit its consideration as a relatively inexpensive and widely available method for assessing physiological responses to brain tumor therapy. The development of the helical scanning technique and, most recently, multi-detector technology permits the measurement of CBF at very high spatial resolution with high precision and accuracy. This technology is moving rapidly and is likely to become the predominant CT technique in the course of the next few years. This capability and widespread availability presents an opportunity for inexpensive and widely available functional imaging of brain tumors. It is expected that high-resolution, high-precision CBF and vascular permeability imaging will be most amenable for assessment of anti-angiogenic therapies. It is possible, perhaps likely, that it will be useful for evaluating a wide variety of novel therapies. For these reasons, it is prudent to encourage explorations in the use of this technology in the evaluation of brain tumors.

IV. Nuclear (PET, SPECT, gamma camera; special topics that require further development)

A. Cell proliferation (assessment within 5 years)

1. Established probe: ^{11}C-TdR
2. Developing probes: ^{18}F-3'FLT, ^{124}I-IUdR, ^{76}Br-FbrAU

B. Angiogenesis (validation of assays for monitoring anti-angiogenesis therapy, assessment within 5 years)

1. Blood flow (^{15}O-water, ^{99m}Tc-sestamibi, ^{201}Tl-thallium, ^{133}Xe-saline, etc.)
2. Blood volume (^{15}O- or ^{11}C-carbon monoxide–labeled erythrocytes [RBCs], or ^{99m}Tc-RBCs)
3. Capillary permeability (^{82}Rb-rubidium, ^{68}Ga-DTPA, ^{68}Ga-transferrin, ^{18}F-, ^{123}I-, ^{131}I-, ^{124}I- or ^{99m}Tc- labeled albumin)
4. Oxygen metabolism (^{15}O-oxygen)

C. Hypoxia (assessment within 5–7 years)

1. Established probe: ^{18}F-fluoromisonidazole
2. Developing probes: ^{61}Cu- or ^{64}Cu-ATSM, ^{18}F-EF1, ^{18}F-EF5, others

D. Transporter up-regulation (assessment within 5–7 years)
    1. Amino acid transporters (^{11}C-methionine, ^{18}F-FET, ^{18}F-FACBC, etc.)
    2. Nucleoside transporters (^{11}C-FMAU, etc.)
    3. Choline transporter (^{18}F-fluorocholine)
    4. Glucose transporter (^{11}C-3OMG, ^{18}F-FDG)
    5. Other substrates

E. Cell surface receptors/antigens (endothelial cells and tumor cells; assessments over next decade)
    1. Transferrin receptor (^{67}Ga-transferrin, ^{111}In-DTPA transferrin chelate, etc.)
    2. EGF receptor (radiolabeled antibody or peptide)
    3. Benzodiazepine receptor (iodinated-PK11195)
    4. Other cell surface receptors/antigens (e.g., Flt1 and Flk1/KDR receptors for VEGF)

F. Cell matrix antigens (assessments over next decade)
    1. Integrins (RGD- and other radiolabeled peptides

G. Molecular imaging strategies/issues (assessments over next decade)
    1. Reporter gene imaging (indirect assay; principle established)
    2. Enzymatic amplification vs. receptor binding and internalization
    3. Oligonucleotide/aptamer (direct binding/assay of mRNA/proteins; to be established)
    4. Probe/contrast agent delivery issues (small molecules vs. macromolecules)

H. Molecular imaging specifics (assessments over next decade)
    1. Endogenous gene expression (transcriptional activation/depression)
    2. Post-transcriptional modulation/stabilization of mRNA
    3. Protein-protein interactions of specific steps in selected signal transduction pathways

I. Gene therapy (assessments over next decade)
    1. Vector delivery and transgene expression (reporter transgene imaging established)
    2. Trafficking and targeting of genetically modified T cells

V. Optical intrinsic signal (OIS) imaging:

A. The development of more rapid, sensitive, and efficient optical instrumentation with multispectral capabilities, in order to observe the etiology of various functionally active cell types in normal and pathogenic tissues

B. Imaging systems compatible with interoperative MR environments

C. The ability to examine molecular concomitant to intraoperative optical measurements using probes and other markers

D. Compatibility between other intraoperative instrumentation and optical acquisition and display, such as microscopes, stereotactic localizers, etc.

E. Co-localization of multimodality displays, including optical, pre- and

intraoperative imaging, tomographic, and projection data

F. The ability to combine intrinsic and tracer-based optical images

G. New optical contrast agents to identify specific aspects of brain and brain tumor biochemistry. To a large extent these agents can be constructed as modifications of the nuclear probes.

EXHIBIT II:
NCI Imaging Research Priorities

Cellular and Molecular Imaging in Cancer: The Goals

Over the past several years, the National Cancer Institute (NCI) has been keenly aware of the potential power of imaging techniques and molecular imaging in particular. The Biomedical Imaging Program (BIP) (**http://cancer.gov/bip/default.htm**) of the Division of Cancer Treatment and Diagnosis is responsible for the extramural grant portfolio and programs related to oncologic imaging. Imaging has been identified as an area of "Extraordinary Opportunity" in the past several "NCI Bypass Budgets" (**http://2001.cancer.gov/imaging.htm**). The NCI Bypass Budget (**http://2001.cancer.gov/2001.htm**) is a public document produced annually by NCI to identify for the Administration and Congress those scientific priorities on which the budget appropriation will be spent. The imaging-related goals of the NCI include:

i. Develop and validate imaging technologies and agents (e.g., probes, radiocontrast agents) that have the sensitivity to detect precancerous abnormalities or very small cancers.

ii. Develop imaging techniques that identify the biological properties of precancerous or cancerous cells that will predict clinical course and response to interventions.

iii. Develop minimally invasive imaging technologies that can be used in interventions and in assessing treatment outcomes.

iv. Foster interaction and collaboration among imaging scientists and basic biologists, chemists, and physicists to help advance imaging research.

v. Create infrastructures to advance research in developing, assessing, and validating new imaging tools, techniques, and assessment methodologies.

The NCI has already made significant progress in the past several years toward reaching these goals with the introduction of various programs and initiatives:

- NCI has awarded three grants to support In-Vivo Cellular and Molecular Imaging Centers (ICMIC) (**http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-004.html**). The ICMIC grants will facilitate interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging. The integration of this breadth of expertise is still in its early stages.

- The NCI has also funded nine pre-ICMIC planning grants (**http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-002.html**) . The pre-ICMIC planning grants provide time and funds for investigators and institutions to prepare themselves, organizationally and scientifically, to establish an ICMIC

- Small animal models, particularly genetically engineered mice, are powerful discovery tools, but we have yet to capitalize fully on their potential in cancer research. NCI has funded five Small Animal Imaging Resource Programs (SAIRP) (**http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-98-023.html**). This initiative supports activities to develop and apply a wide variety of imaging modalities that focus on functional, quantitative imaging. Quantitating image data for small animals will lead the way to quantitative methods that can be applied in humans. An additional five SAIRPs will be funded in fiscal year 2001.

• New drug discovery programs are producing an increasing number of molecules for investigation, in turn stimulating a need for research that integrates imaging techniques into preclinical and clinical studies to assess newly developed therapeutic agents. NCI has set aside funding for the development and application of labeled therapeutic agents as compounds for imaging studies and imaging agents that serve as metabolic markers of response to newly developed therapeutic agents. The Development of Clinical Imaging Drugs and Enhancers (DCIDE)(**http://cancer.gov/bip/dcide.htm**) program will facilitate the development of novel imaging agents in preclinical development. A detailed overview of the newly approved DCIDE program will be presented at a future date in *Academic Radiology*.

Cellular and Molecular Imaging in Cancer: Meeting the Goals

To ensure that the initially defined goals for cellular and molecular imaging are met and completed in future years, the NCI has set forth in the 2001 Bypass Budget specific priorities and initiatives. These include:

1. Accelerate development of clinically useful technologies for detecting malignant and precancerous cells and for visualizing their functional characteristics.

• Expand the number of In-Vivo Cellular and Molecular Imaging Centers (ICMIC) in 2001, 2003, and 2004.

• Expand the Small Animal Imaging Resources Program (SAIRP) to improve access to researchers testing new approaches to diagnosis, treatment, and prevention in animal models of cancer. NCI will foster collaborations between this program and the Mouse Models of Human Cancers Consortium (MMHCC).

• Support multidisciplinary centers of expertise to develop optical technologies and perform clinical feasibility tests of instruments able to visualize epithelial tissue at risk for common cancers and recognize the optical signatures of precancerous abnormalities. This often involves molecularly oriented techniques.

2. Develop, synthesize, validate, and distribute to the research community novel imaging agents.

• Expand a program similar to NCI's Rapid Access to Intervention Development (RAID) initiative (which is designed to accelerate the movement of novel interventions from the laboratory to the clinic) specifically for imaging agent development. The Development of Clinical Imaging Drugs and Enhancers (DCIDE) program (**http://cancer.gov/bip/dcide.htm**) will facilitate and promote preclinical development and validation of important imaging agents and ligands. NCI will, on a competitive basis, synthesize, test, and distribute probes that image the physiological and functional status of tumor tissue in the human body. The DCIDE program will be described in detail in a future issue of *Academic Radiology*.

• Establish a publicly available database of agents available to the research community, together with information on their properties.

3. Expand and improve clinical studies of molecularly based imaging modalities and image-guided interventions.

4. Integrate molecular and functional imaging technologies into drug development and early clinical trials (**http://cancer.gov/bip/concepts.htm - c4**).

• Support the development of in-vivo and molecular clinical imaging research tools for assessing the biological effect of cancer drugs on their intended target or pathway.

• With this continued investment in the future of imaging research, it will soon

be possible to apply the techniques developed to image novel molecular targets, specific genetic pathways, signal transduction, cell cycle alterations, angiogenesis, apoptosis, and numerous other biologically relevant processes known to occur in cancer in routine clinical practice.

Cellular and Molecular Imaging in Cancer: The State of the Art

It is likely that the NCI goals and visions of cellular and molecular imaging in cancer research and patient care will be met. It is gratifying to note that the power of imaging with PET, nuclear medicine techniques, MRS, ultrasound, CT, optical imaging, and other techniques is being recognized and these techniques are becoming available in routine clinical practice. These modalities will allow for the molecular, functional, biochemical, and physiologic assessment of important aspects of malignancy. Many of these imaging techniques are already beginning to show their potential power in the management of the patient with cancer. With the continued advancements that are hoped to occur, imaging will assume a critical and essential role in the basic scientific understanding, diagnosis, staging, and monitoring of cancer.

In addition to the initiatives already in place and listed above, the resources required to address the challenges and opportunities for using imaging technologies in the study of brain tumor development and their treatment will require targeted funding in each of the areas detailed above. In addition, it is recommended that funds be provided for training in the areas of image analysis, tracer development, image methods development, and informatics systems. Funding should also be developed in a way that mandates integration of data across modalities, spatial-temporal domains, subjects, trials and species. This will require appropriate funding for the development of atlases and databases in which such complex and large-scale data sets (from patient outcomes to gene chip arrays) can be organized, archived, accessed, and distributed. Funding agencies should also provide opportunities for investigators to meet across disciplines to develop standards for communicating such information and to alter the sociological outlook of investigators from one of isolation and territoriality to integration and sharing. Finally, specific emphasis should be placed on funding programs that develop tools to standardize and normalize image acquisition across investigational sites and to develop core, quantitative analysis and feature extraction algorithms for the post-processing and distribution of imaging studies acquired from all imaging modalities in patients with brain tumors.

Tumor Immunology

Co-Chairs: Darell D. Bigner, M.D., Ph.D., and Richard M. Ransohoff, M.D.

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STATEMENT OF THE PROBLEM

There is a current lack of basic information concerning the functioning of the immune system within the central nervous system (CNS). It is imperative to narrow this sizeable gap in understanding of the interaction of these two systems in order to gain insight into the pathogenesis of primary brain tumors and the immunotherapeutic approaches that are most likely to produce successful outcomes in their treatment.

For broad purposes of discussion in this report, tumor immunotherapy may be considered to be both cell mediated (T-lymphocyte cell) and antibody mediated. Both types of immunotherapy are characterized by great specificity and low toxicity, as long as they are carefully administered. Current T-cell strategies involve recruiting tumor-reactive T-cells after exposure of autologous professional antigen-presenting cells to tumor antigens, and reinfusing them. Tumor-specific antibodies or their smaller fragments, such as single-fragment chains, are generated by hybrid technology from conventional or double-knockout/double-transgenic mice or from phage display systems. Antibodies may kill tumor cells in “unarmed” fashion or by directing drugs, radionuclides, or toxins to tumor cells.

CHALLENGES AND QUESTIONS

The areas in which further information would be most beneficial include the following:

- Identifying the antigen-presenting cell(s) (APC) of the CNS: For example, is there a CNS APC, or must we use APCs such as peripheral immune system dendritic cells?
- Determining the extent and pattern of the lymphoid drainage pathways of the CNS: Evidence for lymphoid drainage pathways in the CNS has been found in animals, but little is known of their existence or characteristics in humans.
- Elucidating the mechanisms or pathways by which marrow-derived immunocompetent cells traffic to the CNS: Chemokines, which are important in this process, are produced by resident neural cells, including glioma cells, and are essential for leukocyte recruitment to the normal and inflamed CNS. Chemokines also provide growth regulatory signals for glia during development and neoplasia and thus may play a complex role in the response of the CNS host organ to tumor.
- Identifying the important immune effector mechanisms in the CNS, both cell mediated and antibody mediated, and complement

- Identifying the antigens expressed on CNS tumors that also have encephalitogenic potential: Powerful immune responses underlie the relatively rare paraneoplastic syndromes, and immunotherapy targets potentially exist inside the CNS. However, unless directed appropriately, antigenic therapy bears the risk of extensive CNS destruction.
- Further understanding of the mechanisms by which CNS tissues and CNS tumors exert both local and systemic immunosuppressive effects: Although brain tumor–related immunosuppression is not severe enough to cause opportunistic infections, these effects may interfere with cell- and antibody-mediated tumor immune mechanisms.

BARRIERS

The development of predictive large and small animal models of primary CNS tumors is of great importance in the application of immunotherapy to primary brain tumors. Animal models have yielded disconcertingly little cross-species applicability in the treatment of brain tumors in the past; for example, the pharmaceuticals that have been found to be effective in mice with experimental allergic encephalomyelitis, a murine model of multiple sclerosis, have not proven effective in human trials. There are currently no predictive animal models for immunotherapy. However, the development of genetically modified mice provides promise of the ability to extrapolate the findings of mouse studies more effectively to human applications.

In mice, such models could be used to address critical problems, including the effector mechanisms by which immune responses to tumors can eliminate neoplastic cells. The creation of animal models of the paraneoplastic, immunologically mediated disorders of the CNS would also be advantageous for the examination of immunologic effector mechanisms.

Another barrier to optimal progress in tumor immunology is the lack of methodological consistency. Different immunotherapy groups use differing immunization strategies, thus diminishing the ability of clinicians to reach significant conclusions by comparing their results across trials. For example, at least four institutions are currently involved in dendritic cell trials, but each group uses a different method of cell preparation. Another area in which establishing a consistent methodology would be beneficial is the key investigative analyses of the immune responses of patients involved in clinical trials. Finally, although generation of CTL responses is not generally considered a gold standard for therapeutic success, it is an important technical outcome measure and should be determined in similar fashion by all investigators. Such is currently not the case.

There is a strongly felt need among immunotherapists that some outcome measures short of survival would be advantageous in evaluating investigative therapies rapidly and efficiently. Possible outcome measures could involve well-defined immunological endpoints and determination of toxicity or demonstration that the desired immune response has indeed been elicited.

An additional barrier to obtaining the maximal benefit from clinical trials of immunotherapy has been the lack of an optimal data set from all patients entered in those trials. For example, stratification for the degree of pre-treatment immunological suppression is not always done. It has been suggested that future initiatives should include, for instance, a complete proteomic analysis of the components of acid-washed membrane preparations used to pulse

dendritic cells, and ultimately molecular knowledge of each antigen employed.

A common theme of the preceding paragraphs, following but by no means eclipsing the discussion of animal models, is the need for consistency: in immunization strategies, in a consensus on the use of outcome models short of survival, and in obtaining the most complete and clinically-informative data set possible from patients in clinical trials.

RESEARCH AND SCIENTIFIC PRIORITIES

Among the areas of tumor immunology considered to be of greatest value and interest in the development of brain tumor immunotherapy, the following topics were selected by a consensus of the PRG participants as most deserving of research focus and funding:

Priority 1:

Develop techniques of antigen identification, resulting in a readily accessible source of information on the genes and gene products that produce antigens.

A preliminary database already exists containing information characterizing genes that are differentially expressed in tumor cells as opposed to those typically found in non-neoplastic tissue.

- To accomplish antigen identification, researchers will require high-throughput screens to define the antigens recognizable by T-cells.
- Similarly, high-throughput screens are needed to permit the identification of cell surface antigens and antigens located in the extracellular matrix, which may be approachable by antibody-targeted therapy.

Priority 2:

Characterize both CNS and systemic immune responses in patients with brain tumors.

Protective (tumor-destructive) responses are poorly understood. Deleterious reactions are frequently generated by interactions between neoplastic cells and the immune system response apparatus. These interactions are capable of generating tumor growth factors, angiogenic factors, and immunosuppressive components.
Tumor-associated immunosuppression is little understood, yet clinicians must learn to control this mechanism and develop means of dealing with it. Helpful investigatory areas would include characterization of the underlying mechanisms, implications for the natural history of the tumor, and consequences of the immunosuppressive reaction for the immunotherapy of the tumor.

Priority 3:

Consider the problems and challenges posed by patient and tumor heterogeneity.

Individual patients are heterogeneous, for both genetic (e.g., human leukocyte antigen) and epigenetic reasons, in their abilities to respond to immunotherapy. Tumors are heterogeneous with regard to antigen expression. Heterogeneity needs to be understood in each tumor so that as many as three or four individual molecular antigenic species may be targeted at one time. Target cells also display heterogeneity with regard to intracellular components that confer susceptibility to enzyme- or Fas-mediated programmed cell death.

RESOURCES NEEDED

- Brain Tumor Clinical Consortia for expediting chemotherapy and radiation therapy are funded by the National Cancer Institute (NCI) and are productive. Similar clinical consortia for immunotherapy, especially for Phase I and II trials, are needed to expedite and standardize approaches. There are enough institutions (five or six) ready to form the critical mass necessary for such consortia. Human trials are more important than animal studies. For example, cytokines are species specific, and human cytokines can be evaluated only in primate systems.
- Dedicated support from the National Institute of Neurological Disorders and Stroke (NINDS) to understand basic mechanisms of immune responses in the CNS is important for demyelinating and viral diseases as well as for brain tumors.
- The voluminous data from genomic differential displays have revealed many expressed genes in brain tumors not present in normal CNS. Before such findings can be used for immunotherapy, high-throughput screening must be developed and used to identify linear peptide T-cell and conformational antibody-targeted antigens. Workshops may be necessary for implementation.
- The NCI Rapid Access to Intervention Technology (RAID) program for biologics should be expanded to include NINDS investigators.
- Brain Tumor Immunotherapy Center Grants, Program Project Grants, and SPORES should be solicited by NCI and NINDS.
- Centralized transgenic and scientific model shared resources are needed. An especially important animal need is the availability of double-deletion/double-transgenic mice with murine immunoglobulin genes replaced with human immunoglobulin genes. Such mice can be used for production of fully human monoclonal antibodies for repetitive administration to patients with brain tumors and other cancers.
- Clinical trial support mechanisms are needed to cover the cost of research activities, including immunological assays, scanning, and autopsies, not covered by third-party payers. The National Institute on Aging successfully worked with investigators and advocates in dementia to obtain funding for research autopsies. Advocates should encourage federal legislation to provide a payment mechanism for research autopsies.
- Accessible proteomic facilities are needed to provide molecular characterization of antigens now presented in unpurified, crude form, such as cell lysates.

Experimental Models for Brain Tumor

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STATEMENT OF THE PROBLEM

Models are central to making the transition from scientific concepts to understanding the reality of a tumor in a person. They may be used for therapeutic screens, in preclinical trials, or to study the basic biology of tumors. Unfortunately, the available model systems, whether at the cellular, tissue, or animal level, do not accurately represent the biology of human brain tumors. Established glioma cell lines develop multiple genetic changes over time, so that they no longer reflect the biology of the tumor in the person. In addition, current primary tissue models cannot be maintained in a healthy condition for more than a few days. Finally, implantation animal models do not reflect the interaction between tumor and host that occurs in the human.

CHALLENGES AND QUESTIONS

Existing Models

- Conventionally used glioma-derived cell lines contain genetic and gene expression alterations that are ill defined and do not necessarily reflect the primary tumors from which they were derived. Therefore, data derived from them may not reflect the biology, heterogeneity, or therapeutic response of the primary tumors. The scientific community needs better cell culture and tissue models that more accurately reflect the biology of brain tumors.
- Traditional rodent models do not accurately reflect the growth, invasion, histology, gene expression profiling, vasculature, and stromal interactions of various intracranial tumors.
- No genetically defined brain tumor models exist in species other than in laboratory mice. Such animal models may offer additional insights into the biology of specific brain tumor types or may allow the testing of specific therapeutic modalities that is not possible in mice.

Future Models

- The gene expression profiles, controlling elements, pathways, and cells of origin for brain tumors remain largely unknown.
- Molecular reagents, such as tissue-specific promoters and enhancers, to create genetically accurate models of brain tumors are lacking. Further, it is necessary to identify to oncogenes and tumor suppressors, as well as to develop the technology needed to combine alterations in the appropriate cell types.
- There are no adequate mechanisms to correlate genetic alterations in mouse

tumors with their proposed human counterparts.
- There are no readily available and affordable noninvasive techniques to allow investigators to measure changes in tumor volume, growth pattern, gene expression, and other biological parameters of interest.

Model Availability

- Investigators who are not directly involved in the production of animal models lack easy and affordable access to these models.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Develop tissue and cell culture systems that replicate the biology of human brain tumors more adequately than do the currently available immortalized cell lines.

Specifically, there is a need to develop and validate primary tissue culture systems such as spheroids, brain slice cultures, primary cell cultures, and genetically defined immortalized cells, including stem cells. These systems need to be characterized as to their similarity to the brain tumors that they are designed to model.

Priority 2:

Create genetically accurate animal models for brain tumors.

An essential first step is to define and develop reagents, including tissue-specific promoters and enhancers, as well as to expand our capabilities for readily combining multiple genetic alterations in specific cell types.

The development of accurate mouse models is very important. In addition, the development of genetically defined brain tumor models in other species should be encouraged. Such species may include smaller animals, such as *Drosophila* or fish, as well as larger animals, such as pigs and dogs. These have the potential to be used to further understanding of the biology of the disease. In particular, the anatomical spatial dimensions of larger animal models may better allow for the testing of surgical interventions and novel delivery techniques.

Priority 3:

Generate methods to validate, compare, and contrast the animal model with its proposed human counterpart.

These methods should include standard methods such as histology, magnetic resonance imaging, anatomical imaging, and therapeutic response, as well as gene expression and genomic profiling. This will require the development of mouse arrays from the mouse counterparts to the human *BTGAP* sequences. In addition, methodologies such as BAC arrays or SKY analysis will be required to assess the acquired genomic alterations. Adequate bioinformatics support will be required in order to analyze these data.

Further development and use of noninvasive technology is necessary to measure aspects of tumor biology in these animal models. Specifically, there is a need for image analysis of gene expression, vascularity, tumor size, and invasiveness, and for other noninvasive techniques, such as serum or urine surrogate markers. These may require the generation of specific, genetically altered reporter mice.

Priority 4:

Improve access to and make available at reasonable cost to investigators:

- The reagents needed to create new animal models of brain tumors
- Sophisticated technologies used to evaluate and validate those models
- The animal models themselves

Expression cDNA microarray and BAC array technologies should be made available for analysis of these murine-derived tumors. Currently, access to these technologies is not readily available to all groups of investigators whose important scientific questions require these animal models. Moreover, investigators who have developed these animal models do not have the resources needed to provide and widely distribute them.

RESOURCES NEEDED

- Because of the lack of adequate cell, tissue, and animal model systems that reflect human brain tumors, and because grants to develop model systems traditionally have not been funded by the National Institutes of Health, a mechanism must be created specifically to fund the development and validation of model systems that more accurately reflect the biology of brain neoplasms. Although the National Cancer Institute (NCI) Mouse Models for Human Cancer Consortium (MMHCC) has been established to fund development of mouse cancer models in general, the National Institute of Neurological Disorders and Stroke (NINDS) needs to emphasize and coordinate with the NCI for the development of additional mouse models of the various brain tumors not addressed through the MMHCC and of models in other animals.
- Resources need to be allocated for the generation of cDNA microarrays based on the mouse equivalent of the human *BTGAP* sequences.
- A mechanism must be created to ensure affordable access to the reagents and models listed above to investigators. Furthermore, the NCI and NINDS should provide resources to establish a consortium of brain tumor modeling laboratories for the purpose of testing novel therapies.

Neurobiology: Cell Migration and Dispersal

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STATEMENT OF THE PROBLEM

A hallmark of primary neuroectodermal neoplasms is their infiltrative nature. By the time most such tumors are diagnosed, cells have spread beyond the neoplasm's identifiable mass and into surrounding tissues. These dispersed cells may contribute to tumor recurrence in situations in which the primary site can be controlled by surgery or other therapies. Rather little is known about the process of this spread.

The breakout group on Neurobiology: Cell Migration and Dispersal discussed the nomenclature used to describe cell movement from tumor masses into brain parenchyma. To avoid some implications of terms such as *migration, invasion,* and *infiltration,* it was agreed to use the word *dispersal* to describe the movement of tumor cells through the central nervous system (CNS).

CHALLENGES AND QUESTIONS

- The need to understand brain tumor dispersal through the CNS
- The need for more information on how tumor cells interact with normal cellular constituents of the brain. Emphasis should be placed on developing new models for studying tumor cell dispersal and tumor-CNS interactions.
- The need to consider how further knowledge of the first two phenomena could result in new therapies.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Define the molecular constituents required for dispersal.

Although redundancy in motility-based genes may make it problematic to isolate specific targets, there is evidence that cell-specific isoforms exist for some of these proteins. It would be valuable, therefore, to identify and determine the function of gene products that regulate motility in neuroectodermal tumors. The molecules include possible tumor- or tumor-type specific motors and cytoskeletal proteins; small GTPases that regulate interactions between external signals and internal cytoskeletal organization; cell surface receptors involved in cell migration, including those that may mediate start or stop signals or maintain cell polarity; components of extracellular matrix, including proteases involved in remodeling extracellular matrix molecules as cells

migrate; ion channels that may allow changes in cell shape or cell volume during migration; G protein–coupled receptors; and the extracellular matrix molecules produced by both tumor and CNS.

Resources needed:

- Use DNA chip technology to examine appropriate tumor cell types, preferably freshly isolated tumor cells rather than tumor cell lines. It may be worthwhile to search for differences among tumor types that display characteristic and different migratory patterns (e.g., juvenile pilocytic astrocytomas through white matter, oligodendrogliomas through white matter and into cortex, and medulloblastomas).

- This kind of search should also be carried out for normal glial and neuronal progenitors, because little is known about the specific molecular mechanisms underlying migration and because normal and tumor cells probably share many common regulatory mechanisms.

Priority 2:

Examine how tumor cells interact with the brain's normal cellular constituents.

Little is known about how tumor cells interact with normal neurons and glia. Several kinds of interactions are worthy of investigation, including gap-junction formation between tumors and normal astrocytes, altered potassium or neurotransmitter (glutamate) buffering produced by tumor cells in proximity to neurons, synaptic disruption, interactions between migrating tumor cells and the CNS extracellular matrix, and interactions with the immune system (Do tumors activate resting microglia? If so, how? Do tumors, which express a variety of cytokines, attract lymphocytes into the CNS?)

Emphasis should be placed on examining tumor-CNS interactions in appropriate in vivo and in vitro tumor models. It is important to design assays that determine the functional consequences of these interactions and whether the perturbations are reversible. Studies that integrate the anatomy and physiology of tumor-CNS interactions should receive highest priority.

Resources needed:

- New models are needed for studying tumor cell dispersal and tumor-CNS interactions

The group discussed existing models, including two- and three-dimensional models in vitro and co-culture experiments with tumor and normal brain, but focused on using existing models and on developing new models in which tumor cells could be studied moving through the normal CNS. This could be accomplished in brain slices or in whole animal models, from which slices could be used to examine tumor cell movements. These would be particularly useful if the models resulted in tumors whose cells disperse through the brain and are tagged to be clearly distinguishable from normal cells. It is hoped that such animal models would be freely available to investigators interested in tumor cell dispersal.

Priority 3:

Determine how we can best use the knowledge acquired through research described in the priorities above to define new therapeutic targets.

For example, can lymphocytes be directed toward dispersed tumor cells? Can other migratory cells (progenitors) expressing

therapeutic genes be directed toward dispersed tumor cells? Can chemoattractants be used to bring tumor cells back to the main tumor mass? Is there a way to stop migration so tumor dispersal is controlled? This may have the consequence of halting tumor spread without killing the tumor, thus turning a brain tumor into a chronic disease. Studies that emphasize controlling tumor dispersal should receive high priority. Interactions between cell movement and cell division must be carefully ascertained in various model systems. That is, what are the consequences of inhibiting cell motility in other cell functions, particularly proliferation?

Resources needed:

- A National Institutes of Health focus group in which researchers who study normal neuronal- and glial-progenitor migration interact with tumor biologists who study neoplastic cell movement. The two groups have a great deal to learn from each other, and such a meeting may result in beneficial collaborations.

- A consortium whose members work in established laboratories with expertise in various cell migration models, to allow new molecules that may be useful in blocking elements of tumor dispersal to be efficiently screened.

Neurobiology: Progenitor Cells

Co-Chairs: Robert H. Miller, Ph.D., and Scott Pomeroy, M.D., Ph.D.

Participants:		
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STATEMENT OF THE PROBLEM

The vertebrate central nervous system (CNS) is a unique tissue in terms of cell number and diversity. During development, the major classes of neural cells are derived from cells of the neuroepithelium. At present it is not known how these divergent cell types are specified and how they relate to highly heterogeneous brain tumors. There is also a current lack of understanding of the cells of origin and cell lineage associations for distinct tumor types. To design specific therapeutic approaches requires a detailed understanding of the signal transduction pathways utilized by different tumor cells in regulating cell fate, including cell proliferation and cell death and differentiation, as well as a comparison of these pathways with those utilized by normal neural progenitors.

An understanding of tumor cell biology depends on defining interactions between tumor cells and their immediate neural environment to elucidate how the environment influences tumor cell behavior and how tumor cells influence local neural function.

CHALLENGES AND QUESTIONS

- What are the cells of origin that give rise to distinct brain tumor types? How do distinct brain tumor types correlate with neural progenitors in the developing CNS? Are distinct tumor types derived from:
  - — Multipotent stem cells?
  - — Specified progenitor cells in the developing CNS?
  - — Specified progenitor cells in the adult CNS?
  - — Differentiated cells in the adult CNS?

- What approaches will yield a comprehensive molecular characterization of tumor and normal neural progenitor cells? What model systems are best suited to define tumor cell origins? Can human neural stem cells and their derivatives be used in defining tumor cell origins?

- What extracellular and intracellular signaling systems regulate the fate of brain tumor cells? How are the proliferation, differentiation, and survival of distinct tumor subtypes regulated? Are signaling pathways in tumor cells similar to those utilized by normal neural cells during development? Can specific molecular targets be identified in tumor signal transduction pathways for therapeutic treatments? What are the best cellular models with which to address signaling issues?

- What are the functionally significant cellular interactions between the founder cells of neural tumors and the local neural environment? What are the physiological properties of distinct tumor cell types? What is the influence of the local neural environment on tumor cells? How do influences of the immune system impinge on neural tumor cells? What interactions between the endothelium and tumor cells contribute to tumor expansion? What approaches are required to effectively address interactions between tumor cells and their environment?

BARRIERS

- There is extensive cellular diversity among neural cell types and brain tumor subtypes.
- There is a lack of understanding of the basic biology of neural cell fate determination, particularly within glial lineages.
- Insufficient research effort is being brought to bear on the cellular neurobiology of brain tumors.
- The lack of interaction between neurobiologists and neurooncologists has precluded the effective translation of progress in basic research to brain tumor research.
- There is a lack of appropriate molecular screening systems such as microchip arrays for further advancement of molecular classification and identification of specific signaling systems.
- There is a lack of appropriate models in which to study brain tumor biology
- There is a lack of representative cell lines in which to study the extrinsic and intrinsic signal systems that control normal and tumor progenitor cell fate.
- Current tissue banks are limited, and their existence or mode of access is not obvious to non–brain tumor neurobiologists.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Create a detailed characterization of the cell of origin of different brain tumor types.

This requires a clear definition of the cellular and molecular characteristics of neural cells during development. Basic biologic studies suggest that tumors might arise from multipotential stem cells, specified progenitor cells in the developing or adult central nervous system (CNS), or dedifferentiation of mature neural cells. To address this issue requires the following:

- Identification of new cell-surface markers and specific receptors for extracellular ligands
- Identification of lineage- and stage-specific transcription factors and other intracellular signaling molecules
- Application of these markers for molecular classification of brain tumors such that relationships between cells at distinct developmental stages of normal development and tumors become apparent
- Studies of tumor cellular biology provide a potentially important approach to defining molecular targets that could lead to further understanding of normal neural development
- Analyses of glial development and definition of glial progenitors in the vertebrate CNS. This reflects a high incidence of glial tumors and the relatively low emphasis on glial progenitor research by the neurobiology community.

Resources needed:

To define cellular origins of different brain tumor subtypes, the following resources are required:

- Model development: There is a shortage of effective cell-based models. Present emphasis is on mouse and rat models, but the use of other animals, including zebrafish, dogs, and others should not be excluded. New in vitro models also need to be developed. Emphasis could be placed on human stem cells/progenitor cells in this system, since species differences may exist. Progress in this area would be enhanced through the development and analyses of multiple model systems rather than a focus on a single or restricted number of models or cell lines.
- Development of microarrays to generate genetic, molecular, and biochemical information. Specifically, development of custom-designed neurodevelopment arrays are important.
- Tissue banking: Wide access to such tissue resources is critically important.
- Development of tissue arrays for further advancement of cellular classification
- Development of infrastructure to encourage interaction between scientists in basic neuroscience and neurooncology: These should include the development of new funding mechanisms that directly allow interdisciplinary teams of scientist to address cellular issues of brain tumor biology.

Priority 2:

Develop an understanding of the regulation of mitogenic and anti-mitogenic control of tumor and normal neural progenitor cells.

A thorough understanding of extracellular signaling systems and signal transduction pathways that control progression through the cell cycle and specific inhibitors of progression through the cell cycle is required. Studies should be directed at dissecting and identifying targets of cell growth, cell death and survival, and differentiation in normal and tumor progenitors. It seems likely that each distinct tumor type will utilize a different set of regulatory signaling pathways and share some common effector mechanisms. Comparison of regulatory signaling pathways will lead to enhanced understanding of neural tumors and the development of potential targets for specific intervention strategies. In addition, such studies are likely to provide molecular definitions of progenitor cells at critical developmental junctions and may characterize their derivative tumors.

Resources needed:

Defining the signaling systems involved in control of normal and tumor progenitor cell fate will require the following:

- Additional support for basic biological research in defining signal transduction pathways in neural progenitor cells, with particular emphasis on glial progenitors
- Facilitation of substantive interactions among scientists focused on normal developmental issues and those focused on glial tumor biology. Organization of specific workshops and the development of joint funding programs between basic and clinical research teams may accomplish this.
- Development of microarrays to identify novel signaling pathways in distinct cell types.

- Development of new in vivo and in vitro model systems in which to explore functional requirements for discrete signaling pathways. Specifically, given the limitation of cellular material from distinct tumor types, a need was recognized to develop new cell lines that more closely represent native tumor cells by using recently developed molecular techniques.

Priority 3:

Understand the interactions of brain tumors with their immediate neural environment. Studies directed at dissecting tumor-brain interactions should focus on the following areas:

- Further characterization of the physiological properties of tumor cells and the composition of the neural environment are needed. The ionic environment and activation of distinct channels in tumor cells may regulate cell morphology, proliferation, and motility. A broader understanding of interactions of tumor cells with microglial cells and cells of the immune system is warranted. Developmental studies have begun to provide evidence that neural cells respond to immune cells and their influences in a number of ways; these include control of cell morphology, migration, and proliferation. Defining tumor cell responses to immunological influences appears timely.
- Interactions between tumor cells and the local endothelium are poorly understood. Regulation of the blood-brain barrier, control of vessel formation, and other aspects of this interaction require additional analyses.

Resources Needed

The resources required to address this research priority include:

- Basic research in non-neuronal cell ion channel expression and function
- Models of neovascularization in vitro
- Identification of the distinct molecular properties of brain endothelium, perivascular astrocytes, and microglia
- Facilitation of interactions between neurobiologists, brain tumor biologists, and immunologists through the development of novel interdisciplinary funding programs and focused meetings or workshops

Radiation Biology

Co-chairs: Dennis Shrieve, M.D., Ph.D., and Philip J. Tofilon, Ph.D.

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STATEMENT OF THE PROBLEM

CLINICAL RADIORESISTANCE OF PRIMARY GLIAL TUMORS

Radiation therapy is a major component of the treatment of many primary and metastatic brain tumors. Standard therapy for glioblastoma multiforme and other primary malignant astrocytomas consists of radiotherapy after the fullest possible surgical resection has been performed. Radiotherapy has long been known to be the single most active treatment for these tumors; doses up to about 60 Gy yield dose-related increases in survival.

Despite this therapeutic benefit, however, in nearly all patients such tumors recur within the volume of tissue receiving high-dose radiation, and eventually these patients succumb to local disease within a median period of about 12 months. Attempts to escalate radiation doses above 60 Gy have not yielded a significant further advantage in survival, probably owing to toxicity related to the volumes of normal brain receiving doses in excess of tolerance. Conformal therapies (brachytherapy or radiosurgery), designed to "boost" the local dose, may allow increased survival. Even after these therapies, however, local failure is the rule and the risk of radionecrosis is extremely high in patients surviving for more than 6 months. Even in cases of "microscopic residual disease," these doses of radiation are inadequate to prevent progression of disease.

In vitro studies of the inherent radiosensitivity of cell lines derived from human glioblastoma multiforme have not demonstrated remarkable radioresistance of these cells. It is highly probable that the "neural environment" and microenvironment of the in situ tumors, and not just the special characteristics of tumor cells in culture, contribute to the remarkable radioinsensitivity of gliomas.

NORMAL TISSUE TOXICITY AFTER RADIATION

Necrosis and Edema

Radiation doses higher than 60 Gy may produce vasogenic edema and necrosis in some patients with glioblastoma multiforme. Escalation of the radiation dose above this level poses a significant risk of necrosis. These risks are greater than in patients with lower-grade astrocytic tumors or non-glial tumors, which are associated with better prognosis and longer survival.

Functional Deficits

Functional deficits in patients after radiotherapy are probably more common than is currently reported. These deficits include mental retardation in patients irradiated as infants, learning disabilities in

older pediatric patients, and memory or cognitive deficits in adults. Whole-brain radiotherapy for metastatic disease can result in a range of neurocognitive outcomes, ranging from little or no deficit to full-blown dementia. The factors contributing to the development of neurocognitive deficits are poorly understood. These deficits have severe effects on quality of life for patients and their families.

CHALLENGES AND QUESTIONS

- **Lack of understanding of mechanisms of tumor radioresistance and normal tissue toxicity—**Little is known of the basic mechanisms by which radiation kills brain tumor (or other) cells. Two main types of cell death, however, are thought to be important: mitotic, or clonogenic, death (loss of the ability to divide) and apoptosis (programmed cell death). There is evidence that malignant glioma cells do not undergo significant apoptosis after irradiation. Clearly, in patients, many cells escape both modes of cell killing after radiotherapy. The "neural environment" appears to play an important role in this clinical radioresistance, as may microenvironmental factors. In addition, the fundamental processes involved in the development of normal tissue toxicity after radiation are not understood.

- **Lack of integration of neurobiology with radiobiology—**There would be a great advantage to integration of basic and brain tumor neurobiology and brain tumor–related radiobiology.

- **Unavailability of appropriate models—**Appropriate animal models are not available, hindering progress. The brain is a unique organ, and its milieu is crucial to the behavior of central nervous system tumors. Cell culture studies are insufficient to allow understanding of the interactions between tumor and normal tissue, which is key to studying the mechanisms of resistance and thereby to improving treatment. It is important to describe in situ the physiology of these tumors, which is probably involved to a great degree in their resistance. Imaging is available, but interactions between normal and tumor cells must be described and modeled. Better models—specifically, orthotopic tumor models rather than subcutaneous models, and practical models for studying late damage to the brain—are necessary to study these interactions.

- **Low enthusiasm for development of drugs or modulators of radiosensitivity—**There is little enthusiasm within the pharmaceutical industry for the development of drugs or modulators of radiosensitivity for brain tumors. Incentives and encouragement for industry involvement in brain tumor research are needed. The National Cancer Institute (NCI) is planning to establish a screening program to test drugs in the clinic for their potential as radiosensitizers.

- **Inability to test new drugs designed to work with radiation—**It is difficult to test new drugs designed to work with radiation. Combination development at preclinical stages currently does not occur. The Food and Drug Administration focuses on single agents rather than on combined-modality therapies. Furthermore, many companies are apprehensive about studying their agents in combination with radiation because of concern that toxicity could be, or appear to be,

enhanced. This means that, owing to regulatory complications, pharmaceutical companies will not study combined modalities as first-strike therapies.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Overcome radioresistance of primary brain tumors.

- Delineate the mechanisms of inherent radioresistance.
- Define the influence of the neural environment on radioresistance of brain tumors.
- Identify molecular targets for modulation of brain tumor radiosensitivity.
- Develop hypothesis-driven combinations of radiation therapy and modulators to overcome resistance in clinical practice.
- Develop and validate appropriate models.

Priority 2:

Overcome normal tissue toxicity (necrosis/edema versus functional deficits).

- Delineate the molecular, cellular, and physiological processes leading to radiation-induced toxicity.
- Define the influence of neurodevelopmental stage on these processes.
- Delineate the interactions between tumor and normal cells in the development of radionecrosis.
- Develop hypothesis-driven interventional strategies (radioprotection).
- Develop and validate appropriate models.

Priority 3:

Establish clinical indicators of radiation response of tumor and normal tissue.

- Develop imaging modalities to assess tumor response and early changes that are predictive of late sequelae.
- Identify serum, cerebrospinal fluid, or tissue markers of tumor or normal tissue response.
- Develop methods of target "credentialing"—identification of target molecules, evidence of modification of the target molecule, and measurement of desired effect.
- Develop high-throughput techniques to assess the efficacy of modulators of radiosensitivity (e.g., microarray technologies).
- Establish the use of clinical correlates to validate preclinical studies.
- Develop predictors of sensitivity (tumor versus normal tissue).

RESOURCES NEEDED

- NCI program for the development of drugs, sensitizers, and/or modulators of radiosensitivity
- Ability to test drugs in combination with radiation
- NCI-sponsored workshop bringing together neurobiologists and radiobiologists to discuss strategies for investigating brain tumor radioresistance and radiation-related toxicity

Treatment

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BACKGROUND: STATUS OF THE FIELD

Surgery

The tremendous evolution in surgical capabilities of recent decades has been driven by technology. The advantage of maximal resection has been documented in most primary central nervous system (CNS) tumor systems. At present, the state of the art in treatment for brain tumors is the incorporation of preoperative imaging, both metabolic and functional, with image-guided surgical techniques. For example, "navigation" technology allows imaging in a patient by using external landmarks before surgery, and during surgery, the surgeon is guided to the lesion and can appreciate its extent based on the preoperative image set. The newest technologies provide intraoperative imaging, allowing the neurosurgeon to realign the three-dimensional image set during surgery, further enhancing safe maximal resection. Surgery can also be important in local drug delivery, including the strategic placement of catheters to deliver small molecules. Careful and consistent mapping of tumor specimens allows coordination with imaging, drug delivery, and cellular/molecular correlates of disease characteristics and therapeutic response.

Radiation Oncology

Technology has also driven the field of radiation oncology. Radiation therapy has proven efficacy in many common tumor histiotypes. Trials in malignant gliomas in particular have provided opportunities to test altered fractionation and three-dimensional, image-guided delivery (including conformal photon irradiation, radiosurgery, and brachytherapy) to achieve substantial dose escalation. Unfortunately, however, there are few data encouraging additional explorations of dose escalation with radiation therapy alone for these inherently resistant tumors. Further studies of enhanced radiation dose are ongoing in other histiotypes (e.g., low-grade gliomas, and ependymomas).

Interactions of radiation with pharmacological and biological agents represents an important area for further development. Understanding ways to increase tumor response and potentially to limit normal tissue toxicities requires additional laboratory and clinical testing. Explorations of genetic radiosensitization

offer exciting research opportunities in the malignant gliomas.

In pediatric tumors, trials of restricted volumes of radiation therapy and dose reductions defined by response to chemotherapy seek to improve the therapeutic ratio in tumor types with known radioresponsiveness (e.g., medulloblastoma, other embryonal tumors, low-grade gliomas, intracranial germ cell tumors). Exquisite localization of radiation volume in ependymomas is the basis for ongoing and planned trials even in very young children. Image definition of tumor extent is important in guiding restricted radiation therapy volumes; better assessments of tumor volumes and margins are needed.

Chemotherapy

Chemotherapy has had a significant impact on the treatment of selected CNS tumors, such as primary CNS lymphomas, anaplastic oligodendrogliomas, and pediatric embryonal tumors. Nevertheless, the exact drug regimen, timing, and duration of treatment remain areas of uncertainty. Despite the clear benefits for these selective tumor types, the role of standard chemotherapy is limited for the majority of primary CNS tumors, particularly tumors of the astrocytic lineage. Identification of the role of chemotherapy has been hampered by relatively small numbers of many brain tumors other than glioblastoma multiforme, making large randomized trials problematic, and by the apparent poor responsiveness of glioblastoma multiforme to cytotoxic chemotherapy.

STATEMENT OF THE PROBLEM

The main problems in brain tumor treatment research listed below are addressed in detail in the following section (see “Challenges and Questions”).

- There are few active therapeutic approaches or agents for the treatment of brain tumors.
- There are no adequate or reliable preclinical screening systems.
- Few new agents are marked for CNS tumor development.
- There is little understanding of drug-radiation interactions in normal CNS tissue.

CHALLENGES AND QUESTIONS

Few Active Therapeutic Approaches or Agents for the Treatment of Brain Tumors

Generally, there have been few significant advances in the treatment of malignant gliomas over the last two decades. Difficulties in identifying effective approaches include heterogeneity of tumor types, the rarity of some tumors, and relative difficulties in accruing adult patients to clinical trials. All of these problems result in small patient populations for clinical study.

There are a myriad of biological reasons for the ineffectiveness of most current chemotherapeutic agents. These include inconsistent drug delivery secondary to issues related to the blood-brain and blood-tumor barriers, tumor hypoxia, intrinsic drug resistance, and acquired drug resistance through the variable exposure of tumor cells to different concentrations of delivered drug as a result of problems with drug delivery.

The “new biology” has led to the identification of a number of new signaling pathways that appear to be important for gliomagenesis, and with their identification has come the creation of a number of new and exciting molecular inhibitors of those pathways that appear to represent exciting therapeutic opportunities. There is significant concern, however, that the current drug development process, from

preclinical screening to clinical trial design, patient accrual, and endpoint assessment, may be suboptimal for studying newer cytostatic agents for brain tumors. As a result of this concern, there is reluctance from private industry (the source of the majority of the newer anti-tumor agents) to invest resources into exploring the utility of these agents in patients with brain tumors.

No Adequate or Reliable Preclinical Screening Systems

Preclinical screening of potential agents is currently time consuming and inefficient. Spontaneously occurring brain tumor animal models are not available at present, and there is a growing belief that currently utilized xenograft models do not accurately reproduce the biology of human tumors and therefore are generally nonpredictive for identifying active clinical agents. Therefore, the routine use of these models for screening agents for clinical development not only may have allowed inactive agents to enter clinical trials in the past, but may have inadvertently excluded potentially active drugs from ever having been evaluated clinically. This problem has become increasingly more important as the number of rationally designed agents with cytostatic rather than cytotoxic mechanisms of action are being developed (e.g. anti-angiogenic, differentiating, anti-invasion agents). Such agents can be adequately tested only in vivo, making the lack of reliable tumor models a major obstacle for preclinical development. Clearly reliable in vitro and/or tissue surrogate markers and/or assays of biological activity would be very helpful for the preclinical and clinical development of these agents (see "Few New Agents for CNS Tumor Development"). Coupled with the establishment of biological endpoints correlated with survival, improvements in preclinical screening may lead to innovative clinical trial designs, and ultimately the entire field of therapeutic development for brain tumors could move forward quickly and effectively.

Few New Agents Marked for CNS Tumor Development

Novel therapeutic development for CNS tumors is modest, and progress has been meager. Despite the exciting advances made in the identification of potentially active, selective, rationally designed anti-cancer agents, there has been significant reluctance on the part of the pharmaceutical industry to move these agents into the brain tumor population. The reason for this reluctance relates to the inherent characteristics of brain tumors and of patients with these tumors, which make them problematic as the focus of industry research. Examples include difficulties quantifying toxicities in patients with brain tumors, the altered pharmacology of many agents secondary to induction or inhibition of the hepatic P450 cytochrome system from concurrent administration of anti-epileptic agents, the heterogeneity of the patient population (particularly as it relates to heterogeneity of tumors), modest numbers of patients, and slow patient accrual, although this last issue has been addressed in part by the brain tumor consortia.

Low Rate of Patient Accrual to Clinical Trials

Patient accrual into clinical trials in general is lacking: less than 10% of adult patients with brain tumors enter clinical trials. Ways should be investigated to systematically increase adult patient accrual to trials. Even though there are at present few novel approaches that warrant large-scale Phase III trials, the infrastructure for speedy accrual needs to be in place in order to expedite testing when new agents appear promising in pilot studies. In addition, determining groups of molecularly homogeneous tumors would allow for more, and more effective, clinical trials.

Improvements in "response" criteria are needed. To advance the field of novel therapeutic agents for brain tumors, it will be necessary to identify and validate meaningful biological endpoints for evaluating novel therapies. There continues to be significant discussion within the neurooncology and neuroradiology community as to the appropriate criteria for measuring radiographic tumor "response." This discussion arises from the realization that abnormalities detected by magnetic resonance imaging and computed tomography and associated with tumors may be the result of pathophysiological processes other than the tumor mass itself. These abnormalities include treatment-related effects (e.g., radiation necrosis), cerebral edema, inflammation, and postsurgical changes. Routine criteria for measuring perpendicular diameters may be limited in reliability and accuracy by the fact that brain tumors often grow as irregular, asymmetrical processes in three dimensions, and by variability in head positioning in sequential imaging studies. The problem is further compounded by the realization that many of the novel agents entering clinical trials will not necessarily have cytotoxic mechanisms of action, so it might be difficult to assess therapeutic activity within the first several months of therapy, even with highly reliable measurement techniques. This difficulty in turn may complicate early (Phase I and II) trials, in which too few patients may be treated for a sufficient period to allow an accurate assessment of effects on progression-free and overall survival, the most accurate and important measures of biological activity for a cytostatic agent.

For this and other reasons outlined below, it would be ideal if, in early-phase studies, novel endpoints could be used as measures of biological activity of the tested agent. Such endpoints optimally would be related to the mechanisms of action of the agent or to modulation of the putative target (e.g., radiographic demonstration of diminished blood flow after administration of an antiangiogenic agent). Ideally, such endpoints will have correlates to preclinical screens (e.g., the same endpoint used to screen and select a biological agent for clinical testing can be demonstrated to be modulated in the treated patient). Such endpoints could include (but are not limited to) in vitro assays with patient material (blood, urine, cerebrospinal fluid, tumor tissue) and imaging methodologies such as magnetic resonance spectroscopy or positron emission tomography with appropriate probes. Early clinical trials could be designed to allow for agents that achieve a specific threshold effect in the predetermined endpoint evaluation to move forward into further clinical development, ultimately leading to a definitive Phase III trial.

The development of large, historical, clinical trials is important in order to evaluate the use of endpoints such as time to tumor progression and survival in early-phase trials. Such evaluations must be based on meaningful historical data used as controls against which activity and efficacy of the agent can be preliminarily inferred. Clinical endpoints for evaluating new agents must include quality of life measures in all Phase III and novel Phase II trials. The importance of quality of life endpoints is readily apparent in pediatric tumors but are also relevant for malignant gliomas in adults.

The development of such endpoints and objective response criteria will not only aid in the development of novel agents but also allow for the accrual of knowledge about current therapies. Furthermore, they will allow earlier identification of response in individual patients. Determining which patients are helped by current therapies and why will aid more rational and focused development of new therapeutics.

Novel clinical trial designs should be based on the demonstration that a new agent is able to reach and affect its intended target. The rarity of most CNS tumor types and the lack of meaningful short-term endpoints correlated with survival lead to difficulties in designing timely and effective brain tumor clinical trials. In order to focus more quickly on the highest-priority agents, especially for less common or slowly growing brain tumors, it would be helpful to be able to select them for further study based on demonstration of their ability to actually reach and alter their putative molecular targets in patients.

An additional issue relates to the delays often encountered in developing combinations of new agents. Rational combinations may be expected to be no less important for newer drug classes directed at defined molecular targets than they are for conventional cytotoxic chemotherapies. However, the current regulatory system requires that drugs can be licensed only if they are sufficiently useful individually, even when combinations may reasonably be expected to be considerably more efficacious. To substantially speed the development cycle for effective combinations would require a systematic plan for combination testing that begins at the preclinical and Phase I and II levels of the process, and when carried out with appropriate rigor, acceptance of such a strategy by the Food and Drug Administration.

The two adult and one pediatric brain tumor consortia offer excellent means to expedite testing of new agents, including in novel trial designs and in combinations. Further interactions with industry should be encouraged to provide pharmaceutical and biotechnology companies with access to tools (e.g., patient data, markers, validated endpoints) for evaluating potential new drugs. Study designs for new pharmacological agents should encourage pharmacokinetic and scientific endpoints, including collection of tumor and, where appropriate, adjacent normal neural tissue for pharmacological and genetic studies after drug delivery. Involvement of neurosurgeons and basic scientists in the design and analysis of clinical trial may facilitate this objective.

Little Understanding of Drug-Radiation Interactions in Normal CNS Tissue

An important challenge remains the development of interventions that might enhance radiosensitivity while diminishing neurotoxicity. Spatially defined radiation interactions with pharmacological and biological agents represent an exciting area for potential enhancement of the therapeutic ratio in brain tumor treatment. Further understanding of the interactions of chemotherapeutic agents and irradiation in normal CNS tissues should be sought.

New avenues to exploit radiation effects require intensive laboratory development prior to expedited clinical trials in malignant gliomas. Such approaches include the delivery of tumorsensitizing or -neuroprotective molecules via gene therapy coupled with focal radiation delivery. Exploration of radiation-induced promoters represents an additional focal biological effect that may be exploited in this tumor system. (See also the report of the Radiation Biology breakout session.)

RESEARCH PRIORITIES

Priority 1:

Facilitate novel therapeutic development and increase knowledge about the mechanisms of current therapies.

- Enhance preclinical screening:
  - — Recognize that currently existing brain tumor animal models are unreliable predictors of clinical drug activity.
  - — Develop a paradigm to move rationally developed new agents toward clinical trials primarily based on their ability to inhibit signaling pathways that are known to be important in the proliferation and/or survival of gliomas or other CNS tumors. Such a paradigm will require validation by experience, however, and perhaps could never displace entirely older designs, because our understanding of pathways and molecular targets is far from complete and will always be changing. Some agents will eventually be found to modulate pathways or inhibit targets in ways other than those originally assumed and intended.
  - — Support the development of new animal models that more faithfully model human tumors as validated both by molecular characterization and through their pharmacological interactions and response to new and known cytotoxic agents.
- Provide added resources to facilitate moving new therapeutic agents developed in the academic setting from laboratory compounds to clinical-grade drugs for therapeutic trials.
- Increase patient accrual into clinical trials.
  - — Increase patient awareness of clinical trials and the benefits of participation through advocacy groups.
  - — Support a systematic effort to determine barriers to adult enrollment in brain tumor clinical trials, the results of which effort should be incorporated into educational and informational efforts to increase enrollment.
  - — Facilitate the availability of innovative studies for less common CNS tumors or inclusion in ongoing trials of promising new therapies for more common CNS tumors in which patients can be analyzed as distinct subgroups.
- Identify meaningful biological endpoints for the evaluation of new therapeutic approaches.
  - — Develop and validate molecular and genetic endpoints (surrogate markers).
  - — Develop and validate imaging endpoint parameters (e.g., quantitative magnetic resonance imaging and magnetic resonance spectroscopy).
- Optimize study designs.
  - — Identify genetic and epigenetic markers that more accurately group patients

with biologically homogeneous tumors.
  - Formulate study designs by using specific biological endpoints that are relevant to the known mechanism of action of the agent(s) being tested.
  - Encourage study designs that incorporate tissue acquisition before and during treatment for assessment of drug delivery and measurement of biological endpoints.
  - Consider distinct designs appropriate to cytostatic and cytotoxic agents.
  - Encourage incorporation of functional and quality-of-life measures in adult and pediatric brain tumor studies.
  - Identify common data elements to facilitate the evaluation of new therapies across institutions and cooperative groups.
  - Establish a national data repository for clinical and genetic information to be available to investigators.

Priority 2:

Stimulate research on improving the therapeutic index of new agents specifically relevant to the CNS.

- Develop improved methodologies for drug delivery (e.g., blood-brain barrier disruption, convection) for both primary intraparenchymal tumors and leptomeningeal tumors.
- Develop new methodologies for assessing neuropharmacokinetics.
- Develop tools for assessing toxic effects of drugs on the CNS (neurotoxicology).
- Support enhanced research into potential means of neuroprotection.
- Support research to improve the design and delivery of conditionally replicating oncolytic viral vectors and other gene therapy vectors used either alone or in conjunction with chemotherapy and/or radiotherapy.

Priority 3:

Enhance research to improve the therapeutic ratio for radiation therapy for CNS tumors.

- Study means of enhancing radiosensitivity for malignant gliomas and other CNS tumors.
  - Develop gene transfer technologies providing radiosensitization or radioprotection.
  - Explore the role of radiation-inducible promoters as a means of enhancing temporal and spatially specific gene expression.

- Study outcomes in children treated with limited volume, high-technology radiation therapy, often at less than "conventional" dose levels.

RESOURCES NEEDED

- Resources to establish an Internet-based clinical/research database
- Incentives to encourage industry interactions with academic investigators to identify new endpoints and surrogate markers important to testing new CNS agents
- Increased access by academic scientists to centrally funded GMP capabilities in developing new CNS agents
- Funding for the development and validation of new animal models

specific for testing new agents in CNS tumors
- Increased funding for statistical support in developing novel study designs
- Funding for prospective assessment of imaging endpoints of therapeutic response based on collaborations between clinical investigators in neurooncology and neuroimaging
- Development of central core facilities for in vivo animal evaluation of new therapeutic approaches, including pharmacological imaging and biological endpoints for pharmacological and biological agents, neurosurgery, and radiation therapy
- Support for studies of genetically related alterations in radiation sensitivity and toxicity
- Support for development of radiation-inducible promoters to enhance temporal and spatial specificity of gene expression
- Support for an infrastructure of coordinated (central or linked) tumor banks that would be available on a competitive basis to researchers in academia or industry in order to expedite development of new therapies. These banks would need to contain specimens collected and maintained with appropriate quality assurance and associated (with appropriate privacy safeguards) with validated clinical data.

Extraaxial Brain Tumors

Co-chairs: Keith L. Black, M.D., Ph.D., and Stuart A. Grossman, M.D.

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STATEMENT OF THE PROBLEM

A wide variety of extraaxial tumors arise in the spinal and cranial nerves and sometimes affect the brain by compression. Extraaxial tumors are uniquely interesting for brain tumor research for a number of reasons:

- Extraaxial tumors tend to be more homogeneous than parenchymal brain neoplasms such as gliomas.
- The location of extraaxial tumors extrinsic to the brain encourages novel approaches to targeted therapy and facilitates acquisition of tissue for research.
- The early genetic changes underlying some extraaxial tumors are well characterized, including in hereditary syndromes, such as neurofibromatosis 2, that predispose to these lesions.

Extraaxial tumors that affect the brain and spinal cord include meningiomas, schwannomas, neurofibromas, and pituitary tumors, as well as mesenchymal tumors of the skull, spine, and dura mater. Although all of these entities may present problems in clinical management, two lesions, meningiomas and schwannomas, are priorities for further research because they are common and may be difficult to manage. Although surgical resection is a mainstay of treatment for these neoplasms, some cannot be resected and others may recur despite resection. Furthermore, some of these tumors remain dormant and do not require intervention, whereas others may grow and become refractory to standard therapy.

Unfortunately, current neuroimaging techniques do not provide substantial preoperative information about the predicted rate of tumor growth or the likelihood of tumor recurrence, and current histopathological classification and grading are not adequately predictive in many cases. Longitudinal studies of tumor growth are hampered by the sometimes long intervals between presentation and recurrence, and many standard registries do not capture information on these lesions. Finally, ancillary therapies are primarily restricted to radiation therapy, and few other options are available.

CHALLENGES AND QUESTIONS

- To predict which meningiomas and schwannomas will remain dormant and will not require surgical intervention—Such information will direct surgery toward those patients who are most likely to benefit from it and will spare potential complications for other patients.

- To predict which meningiomas and schwannomas will have a greater likelihood of recurrence after surgical resection—Such information would allow follow-up strategies and therapies to be directed toward those patients in need while sparing unnecessary therapy and potential complications for those patients whose tumors will not recur.
- To develop novel therapies for meningiomas and schwannomas that are not amenable to surgery or that recur after surgery—Current approaches are primarily restricted to radiation therapy, which also has potential neurotoxicity in extraaxial lesions.
- To identify clinical and neuroimaging endpoints for the evaluation of meningioma and schwannoma growth and of therapeutic efficacy—Current endpoints, such as tumor growth, time to recurrence, and survival, are problematic given the slow growth characteristics of many of these tumors.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Understand the natural history of meningiomas and schwannomas, as well as their response to therapies.

- Neuroimaging strategies should be developed that will allow prognostic information, anatomical or molecular, to be derived before surgical intervention.
- Tissue-based approaches should focus on refined diagnoses based on molecular profiling.
- Population-based studies must be enabled to allow follow-up of large numbers of patients over long periods and of unique populations of patients, such as those with neurofibromatosis 2.

Priority 2:

Develop outcome measurements for evaluating the efficacy of therapies for extraaxial tumors and the effects of tumor and therapy on quality of life.

Priority 3:

Develop novel therapies for extraaxial tumors on the basis of on their unique biological qualities.

- Molecular biological research should elucidate the pathways responsible for meningioma and schwannoma tumorigenesis. Initial avenues for research would include study of pathways regulated by merlin (the protein encoded by the neurofibromatosis 2 gene). Such information could contribute to biologically rational approaches to therapy.
- Targeted therapies should be investigated on the basis of the localized and physically separate nature of these tumors, as well as on their biological characteristics. A wide variety of therapeutic approaches could be of interest, from small-molecule inhibitors to antiangiogenesis to immunological to gene therapy.

RESOURCES NEEDED

- Integrated registries, tissue banks, and databases for meningiomas and schwannomas, including neurofibromatosis 2
- Funding mechanisms to support long-term (e.g., >10-year) longitudinal studies of tumor growth rates and the natural history of tumors in specific patient populations (such as those with neurofibromatosis 2). Current

Department of Defense grants address only vestibular schwannoma growth in patients with neurofibromatosis 2.

Intraaxial Tumors

Co-Chairs: Faith Davis, Ph.D., and Lisa DeAngelis, M.D.

Participants:		
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STATEMENT OF THE PROBLEM

Intraaxial tumors comprise a complex mixture of low- and high-grade lesions occurring in both children and adults. This report restricts its discussion to adult tumors other than malignant gliomas, specifically low-grade gliomas, lymphomas, and germ cell tumors.

Low-grade gliomas can be divided into two general categories: infiltrating and localized. Infiltrating tumors include, but are not limited to, fibrillary astrocytomas, oligodendrogliomas, and ependymomas. Non-infiltrating tumors include pleomorphic xanthoastrocytomas, pilocytic astrocytomas, and dysembryoplastic neuroepithelial tumors. Despite their rarity, primary central nervous system (CNS) lymphomas and germ cell tumors are also important because some patients are cured of their tumors. However, not all patients are cured, and some of those who are suffer long-term neurotoxicity.

CHALLENGES

Although numerous in the aggregate, each tumor type is uncommon. Patient numbers are small, and no single institution acquires adequate numbers to answer important questions.

Tissue for study is limited. Often only a needle biopsy is available, and sometimes, as in infiltrating low-grade gliomas, no tissue is available. This creates particular challenges for molecular studies. Imaging techniques may provide an alternative approach for the investigators to non-invasively "examine" the entire tumor. Development of biological and molecular imaging technologies is essential for further understanding of these less common intraaxial neoplasms.

RESEARCH AND SCIENTIFIC PRIORITIES

Low-Grade Gliomas

Priority 1:

Better understand the natural history of low-grade gliomas with an emphasis on mechanisms of progression, infiltration or lack of it in non-invasive diagnosis.

Imaging strategies should be developed to:

- Identify the extent of infiltrating tumor
- Predict progression
- Identify heterogeneity prior to surgery or biopsy

Priority 2:

Develop techniques to molecularly characterize tumors on small biopsy samples.

- Particular emphasis should be placed on the molecular signature of tumors that infiltrate and progress to higher grade.
- Conduct population-based studies to allow assessment of etiology and new treatment strategies, including their toxicity and patients' quality of life.

Primary CNS Lymphoma and Germ Cell Tumors

Priority 3:

Understand the natural history of primary CNS lymphomas.

- Epidemiologic studies are needed to identify environmental factors other than immune suppression that appear to be leading to an increased incidence of lymphomas.
- Molecular characterization of CNS lymphomas is required to determine how they differ from systemic lymphoma, identify the cell of origin, and predict prognosis. Molecular characterization of germinomas is needed for prognostic prediction.

Priority 4:

Develop more effective therapies.

- Conduct long-term studies on dose intensity for the treatment of lymphomas and determination of optimum volume for radiation therapy for germinomas.
- Determine the relationship between molecular characterization of the tumor and response to therapy is required.
- Long-term studies of neurotoxicity require development of quantitative quality of life and neurocognitive instruments, development of treatment strategies to improve cognition, and further study on how the tumor itself may affect brain function.

RESOURCES NEEDED

- Funding for the establishment of cell lines of each of these tumor types is necessary to learn more about the biology of these tumors.
- A central repository for tissue banking for genetic analysis of tumors should be established to draw samples from all over the country.
- A central registry or database should be established to accumulate clinical information on diagnosis, response to treatment, neurotoxicity, and long-term follow-up of patients with these tumors. Support should be provided for long-term longitudinal studies.

Metastasis

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STATEMENT OF THE PROBLEM

Central nervous system (CNS) metastases are a serious and common problem in patients with systemic cancer. Brain metastases are at least 10 times more frequent than primary brain tumors. Leptomeningeal metastasis affects about 5% of cancer patients, and spinal cord compression due to metastases occurs in 5–10% of patients with systemic malignancies. Despite refinements in surgery and radiotherapy, many patients die from CNS metastases, and long-term survivors often suffer devastating side effects of their treatment.

Despite the large number of patients affected, metastatic disease to the nervous system is an area that has been largely neglected by investigators. CNS metastases are an "orphan" area falling between the classic areas of tumor biology/medical oncology and neuroscience, as shown by the dearth of extramurally funded grants in the National Cancer Institute (NCI) and National Institute of Neurological Disorders and Stroke (NINDS) portfolios. As a result, understanding of the general cellular and molecular mechanisms involved in metastasis has lagged behind that of other advances in the basic sciences related to oncology and neuroscience.

CHALLENGES

The main problem in the area of CNS metastatic disease is the scarcity of data on the biology of the disease that can be applied to clinical approaches to prevention and treatment. Other challenges are as follows:

- Obtaining tissue from both the primary tumor and the CNS metastasis in order to understand the fundamental biology of metastases to the nervous system.
- Including patients with CNS metastasis in protocols for treatment of systemic disease. All too often, innovative protocols for the treatment of cancer specifically exclude brain and other CNS metastases because of the belief that metastases in the CNS do not respond to treatments that affect the cancer elsewhere in the body.
- Increasing the interest of the neuroscience and neuro-oncological community in the biology and treatment of CNS metastases.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Identify genetic/cellular/molecular factors that allow metastatic disease to establish itself in the CNS. These factors include:

- Biology of the CNS microenvironment
- Basement membrane biology
- Interaction of genotypic/phenotypic metastatic cells with the CNS microenvironment
- Immune system interactions within the phenotype of metastatic cells into the nervous system

Priority 2:

Identify factors that may prevent metastases to the nervous system:

- Develop new animal models of de novo metastatic disease to the CNS.
- Evaluate potential markers in systemic cancers that predict CNS metastasis.
- Develop agents to prevent CNS metastasis.

Priority 3:

Identify targets of established disease:

- Develop new imaging techniques to identify CNS metastases earlier than is presently possible.
- Develop appropriate clinical endpoints for clinical trials of prevention and therapy as well as instruments to measure quality of life.

RESOURCES NEEDED

- A tissue bank to include tissue from a primary tumor and tissue from its CNS metastases.
- New animal models for brain and leptomeningeal metastasis.
- A Progress Review Group that deals exclusively with metastasis.
- Specific NIH initiatives to study metastatic disease to the nervous system.

Pediatric Brain Tumors

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STATEMENT OF THE PROBLEM

Childhood brain tumors are the second most frequent malignancy of childhood and the most common form of solid tumor. Tumors of the central nervous system (CNS) comprise 22% of all malignancies occurring among children up to 14 years of age and 10% of tumors occurring among 15–19-year-olds. Although rapid progress has been made in the treatment of some forms of childhood cancer, such as acute lymphatic leukemia, the outcome for children with primary CNS tumors has remained poor and for most tumors has not changed over the past decade. Brain tumors are now the leading cause of death from childhood cancer, accounting for 24% of cancer-related deaths in 1997 among persons up to 19 years of age. In addition, due to either the effects of the tumor or the treatment required to control it, survivors of childhood brain tumors often have severe neurologic, neurocognitive, and psychosocial sequelae.

Tumors in childhood differ significantly from adult lesions in their sites of origin, histological features, clinical presentations, and proclivity to disseminate throughout the nervous system early in the course of illness. Whereas 90% of adult tumors arise in the cerebral cortex, 50% of childhood brain tumors originate infratentorially, in the cerebellum, brain stem, or fourth ventricular region. A large proportion of brain tumors in adults are the result of metastatic lesions from nonprimary brain sites, and the primary tumors are for the most part glial tumors and meningiomas. In contrast, childhood brain tumors mainly represent primary CNS lesions and, although gliomas make up the majority of childhood neoplasms, other tumor type,s such as medulloblastomas, primitive neuroectodermal tumors, pineoblastomas, atypical teratoid tumors, and other embryonal neoplasms, contribute a significant proportion.

The biological behavior and management of childhood tumors depends on not only the histological character of the tumor but also its location within the nervous system. For example, childhood low-grade cerebellar gliomas may be curable in over 90% of patients with surgery alone, whereas brain stem gliomas (even if “low-grade”) carry the dismal prognosis of death for most child patients within 18 months of diagnosis. The

aspects of tumor dissemination are extremely important for childhood brain tumors. Control of local disease remains problematic for many forms of childhood brain tumors; however, specific types of tumors, especially embryonal tumors, have a high proclivity for early dissemination within the nervous system and treatment approaches must take into account this tendency for early tumor spread. The neurobiological underpinnings of these differences are largely unknown: the importance of the relationship between tumor type and location is poorly studied; the reasons why tumors primarily arise at certain ages and have proclivity to specific areas of brain are unclear; and the ways to utilize these differences to alter management and improve outcome require further investigation.

The histological heterogeneity of childhood brain tumors makes it necessary to develop separate lines of investigation into the molecular mechanisms of each type of tumor, the effect of the surrounding milieu on the tumor, and the development of effective treatment approaches. A variety of different classification systems have been utilized for childhood brain tumors, and controversy still exists concerning the most appropriate nomenclature for some tumors. The classification systems in use are still based on relatively subjective criteria, making comparison across different studies difficult. Although some subtypes of childhood brain tumors are relatively rare, such as primitive neuroectodermal tumors (excluding medulloblastoma), atypical teratoid tumors, medulloepitheliomas, dysembryoplastic neuroepithelial tumors, desmoplastic infantile gangliogliomas, and superficial cerebral astrocytomas of infancy, together they constitute a significant percentage of childhood brain tumors and a major cause of morbidity and mortality. Studies focusing on the more frequent adult and pediatric CNS tumors often do not include such rare tumors, which results in missed opportunities to understand these tumors' biology and create more effective treatment regimens.

Even within the tumor types commonly found in both children and adults, studies focusing on tumors occurring in adults may not result in new insights for pediatric tumors. The molecular aspects of glial neoplasia in children, for example, appear to differ substantially from those in adults. Most childhood low-grade gliomas are pilocytic astrocytomas, whereas this tumor type is relatively infrequent in adults. Pilocytic astrocytomas have a different biology than fibrillary or other grade 2 lesions. For example, one major difference is that pilocytic astrocytomas rarely mutate into higher-grade lesions, whereas fibrillary astrocytomas often do so. Furthermore, even fibrillary low-grade gliomas in childhood rarely mutate into higher-grade tumors in the childhood years, despite this common occurrence in adults. For progress to be made in this subset of tumors, research must be focused directly on pediatric low-grade gliomas.

The differences between the neurobiological features of glial neoplasia in children and those of the disease in adults are not limited to low-grade tumors. Approximately 40% of grade IV gliomas in adults exhibit amplification of epidermal growth factor receptor, whereas this change is less commonly detected in childhood glioblastomas. In addition, P53 mutations, which are observed in 50% of grade III and grade IV gliomas in adults, are rarely seen in high-grade gliomas in children. These differences may at least partly account for the somewhat better prognosis for childhood high-grade gliomas; a subset of children with high-grade glial tumors, including glioblastoma multiforme (as high as 20% in some studies), survive after treatment. In addition, evidence from randomized

prospective studies shows that long-term survival for childhood glioblastoma multiforme is improved by the addition of chemotherapy to radiotherapy; such data are lacking in adults.

A focused effort to define relevant molecular markers for prognosis in childhood glial tumors may facilitate improved diagnostic and therapeutic stratification of patients and more appropriate treatment. Treatment strategies may also need to differ for childhood and adult high-grade gliomas. Also needed are innovative classification systems that integrate molecular, neurobiological, and neuroimaging aspects with histological diagnosis to develop more clinically relevant nomenclatures for these tumors; this will guide epidemiological research, biological studies, and treatment approaches.

The molecular pathways involved in the development of primitive neuroectodermal tumors are just being unraveled. Research focused on the glial tumors that predominate in adults may not lead to a better understanding of these primitive embryonal tumors. Although such tumors are not unique to childhood, they are substantially more common in children than in adults. There has been significant controversy over the most appropriate classification of childhood primitive neuroectodermal tumors, primarily whether all such tumors should be grouped into one category or better subdivided based purely on tumor location. Recent studies have suggested, although not proven, that although these tumors share histological similarities, molecular features of the lesions occurring outside the posterior fossa are distinct from those arising in the posterior fossa. In addition, studies have recently shown that other molecular features, such as TrkC expression, correlate with outcome in medulloblastoma and may lead to better stratification systems. Other neurobiological abnormalities have been noted in these primitive neuroectodermal tumors, and research into the molecular pathways involved in tumor development and growth is needed.

Infants and very young children with primary CNS tumors often harbor lesions that are apparently unique to the early childhood years. Some of these tumors, such as atypical teratoid tumors and medulloepithelioma, although rare, are a significant problem in the pediatric age range. More global investigations into brain tumors, especially research focusing on more common adult tumors, will fail to address these important lesions. Many of these embryonal tumors are apparently true congenital tumors, and studies of the mechanism of their development may also lead to important insights into general brain development. Similarly, studies of brain development may lead to insights into the neurobiological aspects of these and other embryonal tumors.

Also related to age are the effects of therapy on the developing nervous system. As stated previously, some childhood brain tumors are true congenital lesions, whereas others, such as medulloblastoma and ependymoma, peak in incidence before age 5 years. Given the proclivity of primitive tumors to disseminate within the nervous system early in the course of disease, treatment approaches must focus on controlling not only local disease but also disease in all sites of the nervous system. This often requires treatment to be aimed at the entire nervous system in the young child and heightens the likelihood of treatment-related brain injury.

The long-term effects of the tumor and its treatment on outcome are extremely important issues in both children and adults with brain tumors, but because of the above-mentioned reasons, they take on even more significance in childhood. It has been well

documented that young children with brain tumors, independent of the form of treatment they receive, have significant neurological and cognitive sequelae. Furthermore, for older children and adolescents, treatment may result in permanent long-term sequelae, especially neurocognitive difficulties. Other common sequelae include endocrinological dysfunction, focal neurological deficits, and psychosocial sequelae.

In a recent retrospective questionnaire review of 1,845 children with brain tumors who survived for at least 5 years, it was noted that seizures, convulsions, or blackouts occurred in 28% of survivors; headaches, including migraines, were a problem in 37% of patients; and motor disabilities, such as balance problems, weakness of the arms of legs, or tremors, were noted in over 50% of children. A sizeable minority of patients had blindness in one or both eyes, double vision, hearing loss, or persistent tinnitus. Over 50% of those surviving for 5 years from the date of diagnosis of their childhood brain tumors required special education or learning-disabled classroom settings, including 70% of those less than 3 years of age and 62% of those between 3 and 9 years of age. The incidence of secondary brain tumors in long-term survivors of childhood brain tumors is rising, and second malignancies are almost always fatal for this patient population. These sobering numbers highlight the problems faced by survivors of childhood brain tumors and the need for further research into means to reduce long-term sequelae and remediate such problems when they arise.

CHALLENGES AND QUESTIONS

On the largest scale, the overriding challenge for research into pediatric brain tumors is to improve outcome for children with a host of different types of brain tumors. The predominant barriers are the relative infrequency of any individual tumor type, the presence of embryonal/primitive tumors that often disseminate to the leptomeninges, and the lack of interest in, focus on, and funding for research on these primitive tumors. Specific challenges associated with improving outcomes for children with pediatric brain tumors and barriers to meeting these challenges are grouped below into four categories: Tumor Biology, Epidemiology, Treatment, and Long-Term Sequelae.

TUMOR BIOLOGY

Challenges

- Improved understanding of the genetic and environmental factors involved in the development of childhood CNS tumors
- Increased understanding of the cellular origin of different types of pediatric brain tumors
- Greater insight into the relationship between normal brain development and the neurogenetic/biologic underpinnings of childhood nervous system tumors
- Determination of factors responsible for the proclivity of some childhood brain tumors to disseminate within the nervous system early in the course of illness
- Clarification of the relationship between age, development, and outcome of childhood brain tumors
- Enhanced understanding of the biologic differences between childhood and adult gliomas and the development of treatment approaches that take advantage of such differences
- Better understanding of the neurobiology of childhood primitive neuroectodermal tumors (including medulloblastoma) and other less common embryonal tumors

- Development of better animal models that mimic human pediatric brain tumors, including those primarily occurring in children, such as PNETs and other rarer pediatric tumors (e.g., atypical teratoid tumors)
- Definition of relevant molecular markers for the prognosis of the diverse forms of childhood brain tumors

Barriers

- Insufficient appreciation of the important distinction between research required for childhood brain tumors and research required for adult tumors
- Lack of emphasis placed on the defining biologic differences between histologically identical tumors occurring in children and adults, especially the low- and high-grade gliomas
- Paucity of investigations focused on the molecular, genetic, and biologic aspects of embryonal childhood brain tumors, including primitive neuroectodermal tumors
- Lack of understanding of the relationship between normal brain development and aberrations of such development in the etiology of childhood brain tumors
- Lack of understanding of the uniqueness of the rarer childhood brain tumors; their overall importance, in total; and the need to study these types of neoplasms individually
- Lack of usable surrogate markers to determine the prognosis of childhood brain tumors and to evaluate the potential efficacy of agents used to treat such tumors

EPIDEMIOLOGY

Challenges

- Creation of a biologically-based classification of childhood brain tumors that integrates molecular aspects, neurobiological parameters and other neurodiagnostic findings
- Determination of the incidence of individual types of childhood brain tumors, including low grade neoplasms, congenital tumors, and embryonal neoplasms

Barriers

- Variability in the classification of rare childhood brain tumors, especially congenital and embryonal lesions
- Lack of methods to study individual tumor types that occur less commonly
- New coding of low-grade gliomas as "benign" tumors, which could increase the likelihood that children with these diagnoses will not be included in cancer registries
- Lack of funding for epidemiological research, especially for the less common, but critically important, childhood brain tumor subtypes

TREATMENT

Challenges

- Development of more effective treatments for childhood low- and high-grade gliomas
- Development of more effective and safer treatment approaches for childhood embryonal and primitive tumors
- Development of immunotherapeutic approaches aimed at improving control of localized and disseminated pediatric brain tumor disease
- Development of new, safer approaches to control CNS disseminated disease

- Development of innovative biologically-based treatments for childhood brain tumors

Barriers

- Reluctance of industry to focus on developing drugs for pediatric brain tumors because of the relative rarity of childhood brain tumors
- Difficulty in performing clinical trials for specific brain tumor subtypes because of the relative infrequency of specific types of childhood brain tumors
- Insufficient development of novel therapeutics designed for childhood brain tumors such as primitive neuroectodermal tumors
- Hesitancy to apply new therapies early in their development, especially biologically-based treatments, to childhood brain tumors
- Paucity of research into the impact of new neurobiological treatments, such as anti-growth factor agents and anti-angiogenesis agents, on the developing nervous system
- Limited scope of research focused on the immunocompetence of children with brain tumors and the potential utility of different immunotherapeutic approaches for children with brain tumors

LONG-TERM SEQUELAE

Challenges

- Detection of long-term neurologic, cognitive, endocrinologic, systemic and psychosocial sequelae of childhood brain tumors and their treatments, and determination of the incidence of these sequelae
- Investigation into factors that are involved in the development of neurotoxicity and host neurobiological/genetic characteristics that underlie the variable severity of neurologic compromise in an individual child
- Development of new strategies to prevent, ameliorate and remediate neurocognitive and psychosocial sequelae of childhood brain tumors and their treatment
- Evaluation of the impact of innovative biologically-based therapies on the developing nervous system
- Research into factors involved in the development of secondary tumors in long-term survivors of pediatric brain tumors and more effective means to treat such secondary malignancies.
- Research into the effects of the diagnosis of a brain tumor on the family unit, especially parental relationships and the impact on other children in the family

Barriers

- Lack of appreciation of the severe long-term sequelae suffered by children who have brain tumors, either due to their tumor or its treatment
- Lack of emphasis on the psychosocial sequelae of these tumors on the child and the family
- Lack of information concerning the development and treatment of second malignancies in childhood brain tumor survivors
- Lack of neuro-investigative techniques which take into account the developing nervous system and the differences required in evaluation between adults and children

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Understand the signaling systems involved in mitogenesis, survival, and cell death for pediatric tumors.

- Understand how these signaling systems relate to those in developmental neurobiology
- Use this understanding to identify new targets for pediatric brain tumor therapy.

Priority 2:

Fully characterize the phenotypic and genetic alterations that are unique to benign and malignant pediatric brain tumors.

- Develop novel in vitro and animal models that faithfully recapitulate the biology of these tumors.
- Use these models for the identification and prioritization of targeted therapeutic strategies for pediatric brain tumors.

Priority 3:

Investigate in detail the impact of the tumor and its treatment on long-term neurological, cognitive, and psychological functional outcome, and develop new means to prevent, ameliorate, and remediate such dysfunction.

Priority 4:

Conduct pediatric clinical trials of novel therapeutic agents at an appropriately early stage in their development; include in these trials comprehensive and noninvasive assessments (including innovative imaging and biological studies) of the short- and long-term effects of such agents on the child and on the developing nervous system.

RESOURCES NEEDED

- Tumor banking of pediatric brain tumor tissues
- DNA microarrays applicable to pediatric brain tumors and nervous system development
- Tissue arrays for pediatric CNS tumors
- Development of in vitro model systems for pediatric brain tumors
- Animal model systems for pediatric brain tumors
- Greater availability of well-characterized and validated clones or lines of stem cells
- Imaging techniques for identifying tumors in situ for animal models of pediatric tumors
- Coordinated effort, on a national basis, of core facilities or coordinated individual laboratories with specific expertise and models (both academic and private industry) to facilitate the development of new drugs, biological agents, or other treatment approaches
- Funding for neuropsychological testing
- Validated, user-friendly, pediatric instrument for measuring quality of life
- Development of neuroimaging techniques that correlate with subclinical and clinical neurotoxicity.

Appendix 2: Rosters

Brain Tumor Progress Review Group

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Brain Tumor Progress Review Group Roundtable Meeting

July 5–7, 2000

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