# Strategic Plan for Addressing the Recommendations of the Brain Tumor Progress Review Group

October 2002

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

NATIONAL CANCER INSTITUTE

## Message From the NCI and NINDS Directors

October 2002

Each year, tumors take a devastating toll on the American people, and among the most feared are brain tumors. Five-year survival rates for adults are poor, and mortality rates have shown little change over the past 20 years. Even among children, where overall five-year survival rates have risen to 70 percent, and mortality rates have declined 25 percent since 1975, prognosis is still poor for those with certain types of brain tumors. Furthermore, while primary brain tumors are rare, metastatic brain tumors are more common because many other cancers metastasize to the brain.

Unfortunately, effective treatment of even early-stage brain tumors is difficult because many drugs cannot cross a blood-brain barrier that protects the brain from blood-borne pathogens. In addition, surgical removal of the tumor is often impossible, since each area of the brain serves a vital function. Even when treatment is effective, its side effects can cause life-long disability. Clearly, brain tumors constitute a considerable challenge.

In response to these sobering statistics and daunting challenges, the National Cancer Institute (NCI) and the National Institute of Neurological Disorders and Stroke (NINDS) convened the Brain Tumor Progress Review Group (PRG) to develop a national research agenda for overcoming brain tumors. This plan describes ongoing, new, and proposed strategies of the NCI and the NINDS for addressing the recommendations of the PRG. Our goal is nothing less than to reduce the suffering and death resulting from these cancers. This plan reflects the commitment of the NCI and the NINDS to achieving that goal.

In addition to describing strategies for advancing brain tumor treatment, this plan describes strategies for (1) understanding the unique biology of the brain and brain tumors, (2) identifying the causes of brain tumors, and (3) developing tools for better diagnosis. We at NCI and NINDS are grateful to the Brain Tumor PRG and the NCI/NINDS Working Group for their hard work and exceptional insights in helping to identify critical gaps and potential strategies for strengthening the Nation's research effort.

Our hope is that other organizations will join us in implementing these priorities. This plan is not just a plan for the NCI and NINDS, but a call to action to the entire research community. By working together, we are confident that substantial scientific and medical progress will be made against these terrible cancers.

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

Audrey S. Penn, M.D.
*Acting Director*
*National Institute of Neurological Disorders and Stroke*

# New activities and immediate strategies for brain tumor research

| New Activities<br>*Initiatives that NCI an/or NINDS have started within the past year to address a priority.* | | | Immediate Strategies[1]<br>*NCI and/or NINDS are beginning to implement these strategies.* | | |
|---|---|---|---|---|---|
| **Name** | **PRG Priority Area[2]** | **Page** | **Name** | **PRG Priority Area[2]** | **Page** |
| Supported glioma cell biology workshop | 1-1<br>2-1 | 12<br>16 | Establish working group to identify opportunities for improving review of brain tumor grant applications | 1-1 | 12 |
| Funded competing supplements for organotypic cancer models | 2-1 | 16 | Foster interdisciplinary NCI-NINDS workshops to promote collaboration | 1-1 | 12 |
| Supported annual meeting on BBB in CNS tumors | 2-2 | 19 | Establish NCI-NINDS brain tumor working group to facilitate implementation of PRG recommendations | 1-1 | 12 |
| Supported neurological disease brain banking workshop | 2-3<br>3-2 | 24<br>43 | Identify ways to improve access to investigational agents for pediatric clinical trials | 2-5 | 34 |
| Supported workshop on gene-environmental interactions in the etiology of childhood cancer | 2-3 | 24 | Better promote existing tissue resources | 3-2 | 45 |
| Supported workshop under the auspices of the Mouse Models of Human Cancer Consortium | 2-3 | 24 | Review existing training programs to identify important gaps in interdisciplinary research training | 3-4 | 52 |
| Established CNS/Brain Tumor Specialized Program of Research Excellence | 2-4<br>2-5 | 29<br>33 | | | |
| Funded grants for cancer-therapy related use of genetically engineered mice | 2-5 | 33 | | | |
| Integrated capacity for conducting immunotherapy trials into the Adult Brain Tumor Consortia | 2-5 | 34 | | | |
| Renegotiated agreement between NCI and pharmaceutical companies to provide drugs for testing | 2-5 | 34 | | | |

1 Speed of implementation will depend upon the availability of NCI staff to devote appropriate resources to the effort.
2 NCI organized Brain Tumor PRG recommendations that share a common theme or goal into 11 PRG Priority Areas.

# Short-, medium- and long-term proposed new strategies for brain tumor research

| Short-term strategies[3]<br>*NCI and/or NINDS are currently developing these strategies further as a first step towards implementation.* | | | Medium-term strategies[4]<br>*NCI and/or NINDS have determined that they will develop these strategies further in the near term.* | | | Long- term strategies[5] | | |
|---|---|---|---|---|---|---|---|---|
| **Name** | **PRG Priority Area[6]** | Page | **Name** | **PRG Priority Area[6]** | Page | **Name** | **PRG Priority Area[6]** | **Page** |
| Fund grants to understand mechanisms in glioma biology | 2-1 | 16 | Build case-control consortium to evaluate genetic and environmental risk factors | 2-3 | 24 | Link PRG report online to responsive initiatives | 1-1 | 12 |
| Fund grants to study the Blood-Brain-Barrier | 2-2 | 19 | Collect data on benign brain tumors | 2-3 | 25 | Extend APRC Program to fund collaborations among all NCI divisions | 1-1 | 12 |
| Expand the Glioma Molecular Diagnostic Initiative | 2-4<br>3-3 | 29<br>49 | Evaluate the feasibility and value of establishing a national children's registry to support etiology research | 2-3<br>3-2 | 25<br>45 | Fund the Tissue Resources for Cancer Research Initiative | 3-2 | 45 |
| Expand CMAP | 2-4<br>3-3 | 29<br>49 | Add an imaging component to the Adult Brain Tumor Consortia | 2-5 | 34 | | | |
| Develop standardized outcome measures for different tumor types and measures of quality of life | 2-6 | 37 | Develop and implement a plan to use pediatric preclinical models to evaluate new agents | 2-5<br>3-1 | 34<br>41 | | | |
| Fund grants to evaluate cognitive interventions that can address treatment-induced deficits | 2-6 | 38 | | | | | | |
| Revise CTC to improve reporting and evaluation of long-term effects of therapy | 2-6 | 38 | | | | | | |

3 Actual implementation will depend upon the availability of funds, the receipt of high-quality applications and a final determination that the strategy is feasible and scientifically sound.
4 Further consideration of these strategies will take place over the next several months.
5 While this strategy is important, NCI and/or NINDS will not be able to implement it in the near future.
6 NCI organized Brain Tumor PRG recommendations that share a common theme or goal into 11 PRG Priority Areas.

# Strategic Plan for Addressing the Recommendations of the Brain Tumor Progress Review Group

*Table of Contents*


Message from the NCI and NINDS Directors ..... 2

The Brain Tumor Progress Review Group ..... 6
Implementation Approach ..... 7

**Section 1: Crosscutting Priorities** ..... 10
1-1 Share Knowledge, Strengthen Interaction, and Improve Peer Review . 10

**Section 2: Research Priorities** ..... 14
2-1 Understand the Biology of Brain Tumors and Their Interaction with Normal Brain Elements as They Relate to Oncogenesis, Progression, Tumor Cell Dispersal, and Heterogeneity ..... 14

2-2 Expand Blood-Brain Barrier Research ..... 18

2-3 Improve our Understanding of the Genetic and Environmental Factors Related to Brain Tumors ..... 20

2-4 Characterize Tumors at the Molecular Level to Aid in Diagnosis, Treatment Choice, and Treatment Monitoring ..... 26

2-5 Develop Novel Therapies and Improve Support for Immunotherapy Trials ..... 30

2-6 Ensure that Brain Tumor Treatments are Safe and Effective ..... 35

**Section 3: Resource Priorities** ..... 39
3-1 Improve Models ..... 39

3-2 Improve Quality of and Access to Tissue Banks and Databases ..... 42

3-3 Develop High-Throughput Screening Approaches to Further the Understanding of Gene Function 46

3-4 Enhance Training Opportunities ..... 50

**Appendix A:** Roster of Brain Tumor Working Group ..... 53

**Appendix B:** Summary of Ongoing and New Activities and Proposed Strategies Addressing Brain Tumor PRG Priorities ..... 54

# Strategic Plan for Addressing the Recommendations of the Brain Tumor Progress Review Group

The National Cancer Institute (NCI) and the National Institute of Neurological Disorders and Stroke (NINDS) share a mutual and intense interest in advancing knowledge and understanding of brain tumors. NCI supports research on understanding normal brain function, causal factors of brain tumors, and other aspects of brain tumor biology and etiology, including early detection, prevention, and treatment. NINDS is the Nation's leading supporter of biomedical research on brain and nervous system disorders.

## The Brain Tumor Progress Review Group

In 1999, NCI and NINDS jointly established a progress review group (PRG) to assess past progress and identify future brain tumor research opportunities. The Brain Tumor Progress Review Group (BT-PRG) was the first jointly sponsored PRG, reflecting the importance of both cancer biology and neurobiology in brain tumor research. Its members identified and prioritized scientific research opportunities and needs, as well as the scientific resources required to address those needs.

***Progress Review Group Overview***

- *Composed of prominent scientists, clinicians, consumer advocates, and industry representatives*
- *Organized to assess state of knowledge and understanding*
- *Reviewed grant portfolio and other indicators*
- *Discussed current initiatives and strategies*
- *Developed specific recommendations*
- *Participated in follow-up session to review results and refine recommendations*

The BT-PRG was composed of approximately 25 prominent scientists, clinicians, consumer advocates, and industry representatives from the United States and Canada, representing a wide spectrum of scientific expertise. Members were selected for their ability to broadly identify and prioritize scientific needs and opportunities that are critical to advancing cancer research.

The progress review began in February 2000. The BT-PRG Roundtable, composed of over 100 neuroscientists, clinicians, and consumer advocates, was held in July 2000. Participants met in 16 breakout sessions organized around research topics such as basic biology, clinical biology, and specific tumors. As similar issues emerged from the breakout sessions, they were organized into more than 50 crosscutting recommendations, which were documented in the *Brain Tumor PRG Report*. A follow-up meeting with the NCI and NINDS directors was held in March 2001 to discuss the report and provide a framework for addressing the recommendations. The report, follow-up discussions, and an analysis of NCI's and NINDS's existing research initiatives served as key inputs in the development of this Strategic Plan.

## Implementation Approach

The recommendations of the BT-PRG fell into 11 priority areas:

- Share Knowledge, Strengthen Interaction, and Improve Peer Review

- Understand the Biology of Brain Tumors and Their Interaction with Normal Brain
- Elements as They Relate to Oncogenesis, Progression, Tumor Cell Dispersal, and Heterogeneity
- Expand Blood-Brain Barrier Research
- Improve our Understanding of the Genetic and Environmental Factors Related to Brain Tumors
- Characterize Tumors at the Molecular Level to Aid in Diagnosis, Treatment Choice, and Treatment Monitoring
- Develop Novel Therapies and Improve Support for Immunotherapy Trials
- Ensure that Brain Tumor Treatments are Safe and Effective
- Improve Models
- Improve Quality of and Access to Tissue Banks and Databases
- Develop High-Throughput Screening Approaches to Further Understanding of Gene Function
- Enhance Training Opportunities

*"The report, follow-up discussions, and an analysis of NCI's and NINDS's existing research initiatives served as key inputs to the development of this Strategic Plan."*

In order to develop a comprehensive implementation strategy, the NCI Office of Science Planning and Assessment compared the BT-PRG's priorities to existing initiatives. It also organized a working group (see roster in appendix A) to review and strengthen drafts of this document, map NCI and NINDS projects to the priorities, and develop strategies for addressing the most important needs and gaps. Due to funding and other limitations, NCI and NINDS cannot immediately address all issues raised and recommendations made by the BT-PRG. Consequently, to make the best use of limited research dollars and to fully utilize NIH's existing infrastructure and funding mechanisms, an implementation approach was chosen that:

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

This Strategic Plan is organized into three sections. The first section addresses *crosscutting* priorities. The second section addresses the key *research* priorities for expanding the understanding of brain tumors and identifying interventions for their prevention, diagnosis, and treatment. The third section addresses *resource* priorities—critical crosscutting infrastructures, such as models and tissue banks, required to support new research. For each priority area, the plan provides the following:

- Introduction: a description and justification that includes a list of relevant BT-PRG recommendations;
- Ongoing Activities: preexisting NCI and NINDS initiatives that either (1) currently fund BT-specific projects that address the recommendation or (2) are not yet funding such projects but are still accepting applications.
- New Activities: initiatives that NCI and NINDS have started within the past year to address the priority;
- Proposed Strategies: initiatives that NCI and NINDS are exploring as a means to fill gaps in the institutes' efforts to address the priority.

**The NCI and NINDS will do everything in their power to expedite progress against brain tumors. The institutes will implement as many of the proposed strategies in this document as they can, pursue partnerships where they make sense, and encourage and assist other organizations to play a leading role in implementing strategies that transcend the institutes' mandates and resources. Likewise, the NCI and the NINDS will seek advice on all fronts as they implement this plan. As always, the ability to implement a strategy is dependent on (1) a final determination that the strategy is vital, feasible, and sound; (2) the availability of funds; and (3) the receipt of high-quality applications or proposals. The institutes have determined one of the following courses of action for each of the proposed strategies in this plan:**

- This strategy is currently under development as a first step towards implementation.
- The NCI and/or NINDS have determined that they will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
- While this strategy is important, the NCI and NINDS will not be able to implement it in the near term.
- Implementation is currently underway. Speed of implementation will depend on the ability of NCI and NINDS staff to devote appropriate resources to the effort.

A table containing PRG priorities and the ongoing, new, and proposed strategies that address them is included as Appendix B. NCI and NINDS will use this information as a baseline for tracking and monitoring progress over the next 2-3 years.

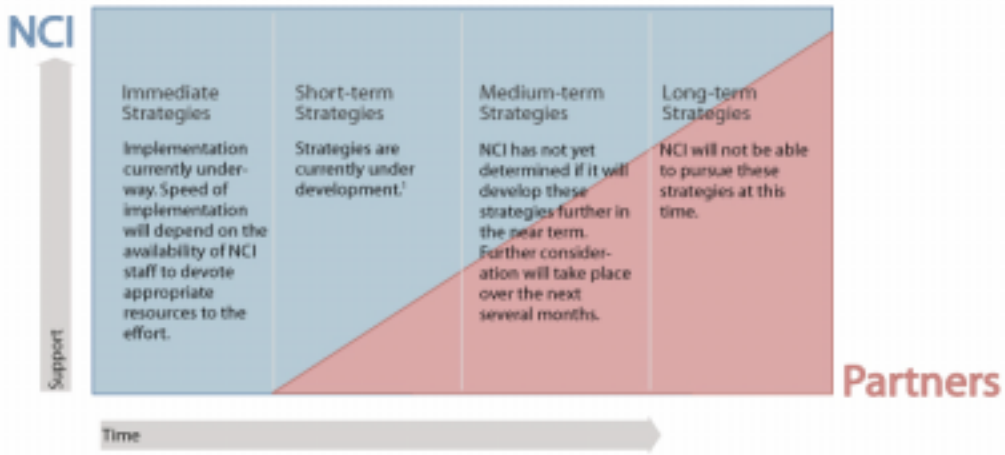
## Strategic Plan to Address PRG Recommendations[1]

The NCI will do everything in its power to expedite progress against Brain Tumor. The Institute will:

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

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

Figure 1: Implementation Phases for Proposed Strategies




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

# Section 1
## Crosscutting Priorities

The BT-PRG provided a unique opportunity for a wide range of scientists, clinicians, and advocates to help establish an agenda for brain tumor research. One of the key BT-PRG findings was the need to foster continued and sustained communication and collaboration, such as the dialog that took place during the joint BT-PRG Roundtable among researchers across a range of disciplines. Fostering such communication requires that NCI and NINDS support increased crossdisciplinary communication and collaboration, and remove barriers that inhibit joint research. This section describes strategies for doing so.

## Share Knowledge, Strengthen Interaction, and Improve Peer Review

### Introduction

The BT-PRG Roundtable provided a unique opportunity for scientists from different disciplines—including cancer biology and genetics, neurobiology, immunology, and radiation biology—to discuss brain tumor research issues. A central emergent objective was to foster more frequent communication, discussion, and sharing of ideas about brain tumors among scientists from a wide range of disciplines. Participants agreed that enhanced communication would foster interdisciplinary collaborations and new and unique approaches to confronting brain tumor research problems.

> *"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."*

Specific communication gaps were cited. For example, new research findings are emerging from the developmental neuroscience community, but few oncologists take advantage of this information. Closing these gaps requires identification of various research communities, such as neuroscience and oncology, developmental neurobiology and pediatric brain tumor, and specific strategies for encouraging dialog, sharing of knowledge, and collaborative opportunities. Major benefits are likely to emerge. Pediatric brain tumors, for example, provide excellent models, and linking them to developmental neurobiology, presents a tremendous opportunity to advance research in both fields.

The need for better mechanisms to support interdisciplinary communication and collaboration is a central theme in the BT-PRG report. The report made the following recommendations:

- Establish a series of meetings and interactions involving scientists from different biological disciplines (cancer biology and genetics, neurobiology, immunology, and radiation biology) 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; and
- Continue to develop combined NCI and NINDS brain tumor research initiatives and explore improvements in peer review of grant applications.

## Ongoing Activities Addressing the Priority

A number of workshops, Web sites, and working groups have already been established to communicate funding opportunities for brain tumor research and foster interaction between scientists from different biological disciplines.

**The Cancer Research Initiatives Web Site** (http://cri.nci.nih.gov/) provides information, organized by scientific area, about opportunities for support of brain tumor research. High-quality grant applications that are responsive to recommendations described in the PRG's report are eligible for "exception" funding. [NCI]

**The Brain Tumor Genome Anatomy Project (BTGAP)** and **The Cancer Molecular Analysis Program (CMAP)** are collaborative efforts between NCI and NINDS. BTGAP is a collaborative effort to develop a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy. CMAP enables researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. [NCI, NINDS]

**The Neuro-Oncology Models Forum**, initiated in 2000 by the Mouse Models of Human Cancers Consortium, includes basic and developmental neuroscientists, mouse modelers, neuro-oncologists, imaging scientists, surgeons, pathologists, and radiobiologists. The group meets regularly to discuss the status of efforts to develop mouse models of brain cancer, the outcome of human/mouse cancer comparative analysis, the emerging translational science applications and unmet needs for mouse cancer models, and priorities for collaborative pilot studies. [NCI]

## New Activities Addressing the Priority

In 2002, NINDS is hosting **Glioma Cell Biology Workshops** to explore the unique molecular and cellular characteristics of tumors in the brain environment. The meetings will focus on cell lineage and novel glial cell communication through gap junctions, cell-matrix interactions, and channel biology; unique signal transduction pathways in proliferating and migrating glioma cells; and unique immune mechanisms in normal brain and brain tumors. The objective of these workshops is to facilitate interaction among neuronal, immune, glial, and glioma cell biologists.

## Proposed Strategies to Address Gaps

One key benefit of the joint approach to the BT-PRG was the opportunity for interaction among experts from different disciplines. However, as noted in the BT-PRG report, the historically different funding and oversight mechanisms for supporting research in various disciplines has inhibited interdisciplinary communication and collaboration. Neurobiology, for example, is largely funded through NINDS, while cancer biology and immunology research is primarily funded by NCI. The NIH Center for Scientific Review (CSR), which reviews most unsolicited brain tumor grant applications, also does not review grant applications from an interdisciplinary perspective. PRG participants expressed concerns that CSR study sections may lack sufficient breadth in both neuroscience and oncology.

To strengthen communication and interdisciplinary collaboration and address funding concerns, NCI and NINDS propose to:

- ➔ Foster opportunities for development of interdisciplinary collaboration by integrating NINDS-supported neuroscientists into meetings and workshops of relevant crosscutting NCI initiatives such as the Director's Challenge Consortia, Brain Tumor SPOREs and Brain Tumor Consortia. Similar reciprocal arrangements will be made for NCI-funded oncologists to participate in workshops and symposia related to key NINDS neuroscience initiatives.[d]

- ➔ Link the BT-PRG report online to the responsive initiatives. The recommendations of the PRG (and their distillation as priorities in this strategic plan) will be linked to NCI and NINDS initiatives that address them.[d]

- ➔ Invite CSR staff to join a working group that will examine study sections' composition, behavior, and referral patterns for BT-related grant applications to determine whether equal and broad expertise exists in the areas of both neuroscience and oncology. Discuss the possibility of initiating an exchange program within neuroscience and oncology study sections to ensure fair review of applications.[d]

- ➔ Establish a brain tumor working group composed of NCI and NINDS staff, as well as CSR staff, that will, three times each year, review and report on each funding cycle's grant applications and review procedures, monitor outcomes, and identify gaps and problems that arise in implementing the PRG's recommendations.[d]

➔ Extend the Division of Cancer Biology's Activities to Promote Research Collaborations (APRC) Program to include other NCI divisions. Under this initiative, investigators can apply for funding for research collaborations and for organizing cross-disciplinary meetings/workshops. Providing funds to all NCI divisions will enable collaborations among basic, translational, and clinical scientists.[c]

---

[a] NCI and/or NINDS are currently developing this strategy further as a first step towards implementation. Actual implementation will depend upon the availability of funds, the receipt of high-quality applications and a final determination that the strategy is feasible and scientifically sound.

[b] NCI and/or NINDS have determined that they will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

[c] While this strategy is important, NCI and/or NINDS will not be able to implement it in the near future.

[d] NCI and/or NINDS are beginning to implement this strategy. Speed of implementation will depend upon the availability of NCI and/or NINDS staff to devote appropriate resources to the effort.

# Section 2
## Research Priorities

The PRG analyzed an array of issues affecting the advancement of brain tumor-related basic and clinical research. Among the important recommendations identified by the PRG, the following had the highest priority:

- Understand the biology of brain tumors and their interaction with normal brain elements as they relate to oncogenesis, progression, tumor cell dispersal, and heterogeneity;
- Expand blood-brain barrier (BBB) research;
- Improve our understanding of the genetic and environmental factors related to brain tumors;
- Characterize tumors at the molecular level to aid in diagnosis, treatment choice, and treatment monitoring;
- Develop novel therapies and improve support for clinical trials; and
- Ensure that brain tumor treatments are safe and effective.

Progress in these areas will substantially advance our understanding of tumor biology, diagnostic strategies, treatment approaches, and outcomes. Research in any one of these areas may well advance research in the others. For example, a better understanding of the BBB will aid in the development of novel therapies. Specific implementation strategies are discussed below.

## 2-1 Understand the Biology of Brain Tumors and Their Interaction with Normal Brain Elements as They Relate to Oncogenesis, Progression, Tumor Cell Dispersal, and Heterogeneity.

### Introduction

Brain tumors represent a large set of diseases that vary in their molecular makeup and pathophysiology. Significant gaps exist in our understanding of the molecular pathways involved in the genesis, progression, and biological and clinical behavior of brain tumors. In addition, a basic 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 patients' quality of life. Exemplifying these issues are childhood brain tumors, especially primitive neuroectodermal tumors that arise during brain development. Insights into the normal and aberrant regulation of genes during neurodevelopment may be important for 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.

The BT-PRG made the following recommendations in this area:

- 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; and
- Characterize the interactions of brain tumor cells with the normal brain.

## Ongoing Activities Addressing the Priority

Five initiatives seek the molecular characterization of cancer cells:

- **The Brain Tumor Genome Anatomy Project** is a collaborative effort to develop a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy. [NCI, NINDS]
- **The Cancer Genome Anatomy Project (CGAP)** is designed to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. CGAP provides gene expression profiles of normal, precancer, and cancer cells, including brain tumor cells. Clones and libraries are available to the scientific community, and the CGAP web site (http://cgap.nci.nih.gov/) provides access to all CGAP data and analysis tools. [NCI]
- **The Director's Challenge: Toward a Molecular Classification of Tumors** is developing novel tumor classification schemes based on profiles of molecular alterations in tumors. The Director's Challenge initiative is supporting three projects focused on brain tumors. [NCI]
- **The Zebrafish as an Animal Model for Development and Disease Research** will identify the genes and molecular and genetic mechanisms responsible for normal and defective development and disease. [NCI, NINDS]
- **The Innovative Technologies for the Molecular Analysis of Cancer Initiative** is developing novel technologies to support the molecular analysis of cancers and their host environment. This initiative is supporting one project focusing on brain tumors: "Genome-based Targeting of the Hedgehog Pathway in Cancer." [NCI]

**Molecular and Cellular Biology of Metastatic Tumor Cells** is a joint program announcement between NCI and the National Institute of Diabetes and Digestive and Kidney Disorders that will fund preliminary research projects which will form the basis of future R01 applications to investigate metastasis. The intent is to foster collaborative research between investigators with basic molecular and cellular biological and biochemical research experience and those with

experience in metastasis research, and increase the number of laboratories and investigators addressing issues of metastasis.[7] [NCI]

Several member groups of the **Mouse Models of Human Cancers Consortium** are testing the roles of key genetic alterations and molecular pathway perturbations in the genesis and progression of brain tumors. Using a variety of strategies, the mice are engineered to reflect the molecular signatures of human brain cancer, and the resulting tumors display many of the features of the relevant human diseases. Analysis of mouse tumor stages from the earliest manifestations of malignancy through invasive cancer reveals the additional genetic changes that characterize progression and distinguish among the various pathologies. Cross-species comparison is an ongoing activity to discover whether human tumors undergo similar changes that may have diagnostic or prognostic value. Analysis of the mouse tumors also provides evidence for the cells of origin for common brain tumors. [NCI]

## New Activities Addressing the Priority

In 2002, NCI issued a program announcement for **Support of Competing Supplements for Organotypic Cancer Models**, which invites applicants to develop and apply multicellular models that are more representative of the interactions among the various cell types in a tissue or organ than are cultures of single cell types.

In 2002, NINDS is hosting **Glioma Cell Biology Workshops** to explore the unique molecular and cellular characteristics of tumors in the brain environment. The meetings will focus on cell lineage and novel glial cell communication through gap junctions, cell-matrix interactions and channel biology, unique signal transduction pathways in proliferating and migrating glioma cells, and unique immune mechanisms in normal brain and brain tumors. The objective of these workshops is to facilitate interaction among neuronal, immune, glial, and glioma cell biologists.

## Proposed Strategies to Address Gaps

To address this priority, NCI and NINDS propose to:

- ➔ Issue a joint program announcement to encourage the application of new concepts in developmental neurosciences to understanding the unique organ-specific mechanisms of glioma biology in both pediatric and adult patients. Concepts aimed at understanding stem and precursor cell biology, and cell dispersal, differentiation, and signal transduction pathways as they relate to tumor cells within the central nervous system (CNS) will be emphasized through this initiative. Studies on the relationship of glial cells to brain tumors will be especially encouraged. Grantees may be required to attend at least one meeting a year to foster collaboration among basic neurobiologists, glial cell biologists, neuroimmunologists, neurologists, neurosurgeons, and neuro-oncologists and to address the bidirectional translation of basic and clinical science of brain tumor research.[a]

7 This initiative is not currently addressing this priority area but could do so if NCI receives competitive applications in response to it.

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

## 2-2 Expand Blood-Brain Barrier Research

### Introduction

> *"Improving our knowledge of the basic molecular and cellular biology of the brain microvasculature could lead to innovative new strategies for drug targeting to human brain tumors."*

An important problem in the treatment of human brain tumors (including brain tumors that are metastases of other cancers) is the difficulty of delivering therapeutic agents to specific regions of the brain, and distributing them within and targeting them to brain tumors. A consequence of the neuroprotective role of the BBB is to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. Molecules that might otherwise be effective in diagnosis and therapy either do not cross the 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 molecular and cellular biology of the brain microvasculature, which constitutes the BBB and BTB *in vivo*, could lead to innovative new strategies for targeting drugs to brain tumors. Additional research is needed, not only on tumor cell biology, but also on tumor endothelial cell biology, as well as research on BBB vascular genomics. Finally, research is needed on the role of the BBB in protecting the CNS from toxic agents and how damage to the BBB leads to long-term neurological toxicity.

The PRG made the following recommendation in this area:

- Understand the BBB and its regulation.

### Ongoing Activities Addressing the Priority

**The Cancer Genome Anatomy Project (CGAP)** is designed to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. CGAP provides gene expression profiles of normal, precancer, and cancer cells, including brain tumor cells. Clones and libraries are available to the scientific community, and the CGAP web site (http://cgap.nci.nih.gov/) provides access to all CGAP data and analysis tools. CGAP has expanded to include endothelial cells. NCI and Affymetrix have established an agreement to develop a total genome array analysis, which will replace traditional Cancer Genome Anatomy Project-type sequencing. [NCI]

**Cerebral Radiobiology and Neuroimaging of Brain Tumors** supports research to improve our knowledge of the biological basis of brain tumor cell function and surrounding normal brain cell injury and repair mechanisms induced by radiotherapy, including stereotactic radiosurgery, for brain tumor treatment, using state-of-the-art neurobiological and neuroimaging approaches. These investigations may provide opportunities for the development of novel and improved

therapies to enhance tumor cell death or reduce CNS injury in healthy brain cells adjacent to the targeted tumor cells.[8] [NCI, NINDS]

**Exploratory/Developmental Grant Programs (R21s)** support innovative, high-impact research projects. Such projects (1) generate pilot data to assess the feasibility of a novel avenue of investigation, (2) involve high-risk experiments that could lead to a breakthrough in a particular field, or (3) demonstrate the feasibility of new technologies that could have a major impact in a specific area. Applications focused on scientific and clinical issues in brain tumor and BBB research are responsive to these programs. [NCI, NINDS]

Investigators in the **Mouse Models of Human Cancers Consortium** employ functional imaging to follow angiogenesis during development of tumors in their models. The models can be engineered to enable the initiating genetic events to be turned on and off in specific cell types. When the mutant gene is turned on, neovascularization serves as evidence of early tumor formation; when it is turned off, the new blood supply disappears. Microarray analysis of endothelial cells isolated at various times during blood vessel development and regression can identify the gene profiles of the tumor-specific endothelial cells for comparison to normal brain endothelial cells. [NCI]

### New Activities Addressing the Priority

In 2002, NINDS and NCI supported **an annual meeting on the BBB in CNS tumors**.

### Proposed Strategies to Address Gaps

To address this priority, NCI and NINDS propose to:

- ➔ Issue a joint program announcement to support research in BBB regulation, transport biology, and potential targeted drug delivery strategies. It will support research aimed at understanding how neuroprotective barriers function and are compromised under disease conditions. Applications to study treatment-induced neurotoxicity also will be encouraged, as will applications to create an expression atlas for microvascular endothelial cells within gliomas and the normal brain. Finally, this announcement will support awards to provide endothelial cells to the research community.[a]

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

8 This initiative is not currently addressing this priority area but could do so if NCI or NINDS receives competitive applications in response to it..

## 2-3 Improve Our Understanding of the Genetic and Environmental Factors Related to Brain Tumors

### Introduction

In order to devise effective methods for preventing brain tumors, we must understand which factors, alone or in combination, raise the risk of triggering a tumor and which factors protect against such tumors. Although a few such factors have been identified, most brain tumors cannot be attributed to any of the known risk factors.

Familial brain tumor syndromes account for no more than seven percent of patients. The only unequivocably established risk factors for nonfamilial brain tumors (therapeutic irradiation to the brain and chronic immunosuppression) are also infrequent causes. Other suggested factors—such as nonionizing radiation, workplace and viral agents, household chemicals, or aspects of diet—have not been proven to have an association with the development of brain tumors.

Different types of brain tumor likely have different etiologies and should be evaluated separately; however, for uncommon subtypes, it is difficult for any one study to attain an adequate sample size. In addition, little is known about the interaction of genetic factors and environmental agents in understanding brain tumor etiology, and studies require large sample sizes. The BT-PRG made the following recommendations in these areas:

- Support the linking of existing databases to provide larger numbers of samples for epidemiological studies;
- Use validated animal models to study the potential causal factors of brain tumors and treatment-induced neurotoxicity;
- Isolate the genes that predispose individuals to human brain tumors and understand their relationship to the genes that regulate normal development; and
- Expand and enhance databases to include all primary brain and spinal tumors—malignant and nonmalignant, adult and pediatric—and to provide the flexibility to accommodate new histological and molecular classifications of tumors and give investigators access to rapidly ascertained cases.

### Ongoing Activities Addressing the Priority

**A Case-Control Study of Brain Tumors in Adults** is one of a number of intramural-extramural collaborations aimed at elucidating the risk factors and origins of brain tumors. This study is noteworthy for its large size (nearly 800 cases), patient interviews, and comprehensive data collection. Risk factors under study include workplace and home exposures, dietary history, family history, and medical history. It includes a family glioma study that will collect family histories and DNA samples from genetically related individuals. [NCI]

**The Diet, Lifestyle, and Cancer in U.S. Special Populations Initiative** supports epidemiologic studies to elucidate causes of cancer and means of prevention in African American, American Indian, Alaska Native, Asian and Pacific Islander, native Hawaiian, Hispanic, rural, older, low-income, and low-literacy groups. This initiative is supporting one project focusing on brain tumors: "Epidemiology of Cancer in a Cohort of Older Women." [NCI]

**Geographic-Based Research in Cancer Control and Epidemiology** encourages the use of the recently published *Atlas of Cancer Mortality in the United States, 1950-1994* (see http://www.nci.nih.gov/atlas), which displays the geographic patterns for various forms of cancer, as a catalyst for research in cancer etiology and control. Further epidemiologic research is needed to identify the reasons for the geographic variation of specific cancers, including the clustering of areas with high or low incidence and/or mortality rates. In addition, the geographic information system (GIS) (http://www.esri.com/gisforeveryone/) provides new tools for the exploration of such geographic patterns. The GIS can be used for assessment of environmental risk factors, identification of places and/or subpopulations where cancer surveillance and control programs are needed, statistical analysis of spatial patterns and presentation, and dissemination of information to the public. NCI wishes to stimulate research in three areas in order to encourage researchers to use the *Atlas* to speed up the process of scientific discovery and application: (1) epidemiologic research to study the determinants of the geographic patterns uncovered by the *Atlas*, (2) use of GIS for cancer research in response to the *Atlas*, and (3) methodologic GIS research needed to accomplish such research. This initiative is supporting one project focused on brain tumors: "Tests for Spatial Randomness in Cancer Maps." [NCI]

**Small Grants Program in Cancer Epidemiology** supports research on topics relevant to cancer etiology, which may lead to cancer control/prevention. Investigations may include: (1) planning a complex epidemiologic investigation; (2) developing or validating a laboratory or statistical procedure that has the potential to improve the quality of cancer epidemiologic research; (3) obtaining support to study a question relevant to cancer epidemiology in special situations, such as the availability of special personnel for limited time periods, rapidly evolving research, or limited access to an important resource; (4) analyzing previously collected data for epidemiologic purposes, such as combining data from several studies to examine consistency or strength of observed associations; (5) resolving methodologic problems, such as documenting the accuracy of a customary procedure in preparation for use in epidemiologic research, or evaluating the effect of cancer diagnosis and/or treatment on risk factor estimates derived from case-control studies; or (6) obtaining funding for investigations of urgent or emergent issues in cancer epidemiology.[9] [NCI]

**Fellowships in Cancer Epidemiology, Biostatistics, and Genetics** provide fellowship training for up to 5 years under the supervision of NCI senior scientists in the Division of Cancer Epidemiology and Genetics. Fellows design, carry out, and analyze research related to the etiology of cancer in human populations. They gain experience with interdisciplinary and/or multicenter collaborations. Research opportunities include the full range of cancer risk factors, such as nutrition, environmental exposures, radiation, occupation, infectious agents, and

9 This initiative is not currently addressing this priority area but could do so if NCI receives competitive applications in response to it.

hormones, as well as methods development (see http://www.dceg.cancer.gov/Fellowship.html). [NCI]

**The Exploratory Grants in Pediatric Brain Disorders: Integrating the Science Initiative** was established to: (1) focus the attention of neuroscientists on the detrimental processes that affect the developing brain, (2) promote the interaction of developmental neurobiologists and clinical scientists, and (3) provide the preliminary information necessary to unravel the complexities of developmental pathogenesis. The ultimate goal is to effect meaningful advances in understanding the pathogenesis of neurological dysfunction, and develop interventions and effective treatments that improve the quality of life for children and young adults. [NINDS]

These programs are developing animal models to help identify the genetic determinants of human cancers:

- The **Mouse Models of Human Cancers Consortium (MMHCC)** is comprised of multi-institutional, interdisciplinary groups focusing on mouse/human integrative biology. The consortium has approximately 12 brain cancer models in various stages of development. As the models are comprehensively analyzed for natural history, histopathology, gene expression, imaging features, and clinical course, the models and information about them are made available to the research community. In 2002, in collaboration with the Cancer Genetics Network and the Cancer Family Registries, the MMHCC plans disease-site-specific focus groups comprised of researchers from the human population research, bioinformatics, and mouse modeling communities. Their goal is to use the exceptional power of mouse genetics to identify and verify relevant human candidate genes much more rapidly. The groups will work collaboratively to define multigenic determinants of risk, and test hypotheses about gene/environment interactions in the etiology of cancer. [NCI]
- **The Tools for Insertional Mutagenesis in the Mouse Initiative** is developing tools and techniques to establish random and targeted sequence-tagged insertion libraries of embryonic stem (ES) cells to generate mutant mice that make it possible to scan the sequence database for genes of interest and order the corresponding targeted ES cell line. [NINDS]
- **Zebrafish as an Animal Model for Development and Disease Research** (see page 15)
- **Strategies for Germline Modification of the Rat** will establish methods for the efficient production of rat models containing germline mutations that will facilitate the transfer of biological concepts to human health problems. Development of rat embryonic stem cell technology by modification of current techniques or development of new approaches will meet the needs of researchers using the rat to study human health and disease.[10] [NCI, NINDS]

The following programs seek the molecular characterization of human cancers:

- **The Cancer Genome Anatomy Project** is designed to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. CGAP provides gene expression profiles of normal, precancer, and cancer cells, including brain tumor cells. Clones and libraries are available to the scientific community, and the CGAP web site (http://cgap.nci.nih.gov/) provides access to all CGAP data and analysis tools. CGAP includes **The Genetic Annotation Initiative**, which explores and applies technology to identify and characterize genetic variation in genes important in cancer, and **The Human Tumor Gene Index Initiative**, which will identify genes expressed during the development of human tumors, and discover new human genes. [NCI]

10 This initiative is not currently addressing this priority area but could do so if NCI or NINDS receives competitive applications in response to it..

Section 2

- **The Director's Challenge: Toward a Molecular Classification of Tumors** (see page 15)
- **The Mammalian Gene Collection Initiative** offers full-length, human, or mouse cDNAs for the study of individual genes, their protein products, and their roles in human diseases, including brain tumors. [NCI]

**The Brain Molecular Anatomy Program (BMAP)** is aimed at understanding gene expression and function in the nervous system. To address its two major scientific goals, gene discovery and gene expression analysis, BMAP has launched several initiatives to provide resources and funding opportunities for the scientific community. BMAP is also establishing physical and electronic resources for the community, including repositories of cDNA clones for nervous system genes, and databases of gene expression information for the nervous system. Most BMAP initiatives so far have focused on the mouse as a model species because of the ease of experimental and genetic manipulation of this organism, and because many models of human disease are available in the mouse. However, research in humans, other mammalian species, nonmammalian vertebrates, and invertebrates is also being funded through BMAP. [NCI, NINDS]

**The Molecular and Cellular Biology of Metastatic Tumor Cells Initiative** provides funds for preliminary research projects that will form the basis of future R01 applications to investigate metastasis. The intent is to (1) foster collaborative research between investigators with basic molecular and cellular biological and biochemical research experience, and those with experience in metastasis research; and (2) increase the number of laboratories and investigators addressing issues of metastasis.[11] [NCI]

**The Cancer Genetics Network** consists of eight centers and an informatics and information technology group that provides supporting informatics and logistics infrastructure. The network is a major national resource to support collaborative investigations into the genetic basis of cancer susceptibility; explore mechanisms to integrate this new knowledge into medical practice; and identify means of addressing the associated psychosocial, ethical, legal, and public health issues. [NCI]

**The Cooperative Human Tissue Network** collects, preserves, and distributes human tissues for research. Trained personnel coordinate the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies. Most specimens are collected prospectively to meet investigator protocol requirements; however, some previously collected specimens can be made available for immediate use. In addition to more common specimens that are provided from surgical resections to investigators on a regional basis, access to rare tumors, e.g., neuroendocrine tumors, is provided from all divisions via networking. Pediatric tumors, diseased and normal tissues are available nationwide. Normal tissues, including brain tissue, can be obtained from autopsies. [NCI]

**The Cancer Molecular Analysis Program** enables researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. [NCI]

**The CNS Tumor Animal Experimental Therapeutics Core** will provide intramural and extramural investigators with uniform, systematic pharmacological and antitumor analyses of new agents and delivery technologies for CNS malignancies. The core will also provide a platform to develop molecular and radiographic endpoints specific for antitumor agents, and evaluate the neurotoxic effects of new treatment modalities on the CNS. [NCI]

11 This initiative is not currently addressing this priority area but could do so if NCI receives competitive applications in response to it..

**The Shared Pathology Informatics Network** is creating a model Web-based system to access data from existing medical records that are related to archived human specimens at multiple institutions. The ability to access information automatically from medical databases is the first step toward the long-term goal of developing informatics systems to improve researchers' access to human specimens and clinical data. [NCI]

**The Surveillance, Epidemiology, and End Results (SEER) Program** currently collects and publishes cancer incidence and survival data from 11 population-based cancer registries and 3 supplemental registries covering approximately 26 percent of the U.S. population. Information on more than 2.5 million cancer cases is included in the SEER database, and approximately 160,000 new cases are accessioned each year within the SEER catchment areas. The SEER registries routinely collect data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. Most of the SEER registries have a mechanism for rapid reporting. [NCI]

## New Activities Addressing the Priority

NINDS sponsored a workshop to identify current problems, challenges, and emerging trends in brain banking, and to provide recommendations for establishing cooperative, multicenter networks for neural tissue banking, including brain tumors. This **Neurological Disease Brain Banking Workshop** was held in March 2002.

NCI is conducting a **Workshop on Gene-Environment Interactions in the Etiology of Childhood Cancer** that will bring together a multidisciplinary group of scientists and researchers to assess the current state of knowledge, identify gaps in understanding, and suggest promising research opportunities for etiologic studies of childhood cancer. A substantial portion of the meeting will be devoted to topics directly relevant to the etiology of childhood brain tumors. The intent of the meeting is to stimulate an interdisciplinary approach in which laboratory methods are applied to enrich and inform epidemiologic studies to clarify the importance of gene-environment interactions in childhood cancer etiology. This workshop took place in March 2002.

NCI is sponsoring **a workshop under the auspices of the Mouse Models of Human Cancers Consortium** to assess the status of engineered mouse models of pediatric malignancies, several of which are brain tumors; identify which models are most critical; and develop a plan for NCI to ensure that the necessary models are developed. This workshop is planned for 2002.

## Proposed Strategies to Address Gaps

To address this priority, the NCI proposes to:

- ➔ Build a case-control consortium to support pooled or parallel analyses concerning genetic and environmental risk factors in case-control studies of brain tumors. Based on recently completed and ongoing studies, 2,000-3,000 cases and a similar number of controls are expected to be available for study. A series of this size would have far greater statistical power than any previous study to evaluate possible gene-gene and gene-environment interactions contributing to the development and progression of brain tumors.[b]

- ➔ Continue to support a pilot study by the Children's Oncology Group to evaluate the feasibility of establishing a childhood cancer research network that would create a national registry of children with cancer, including a tissue bank for tumor and blood specimens, for identifying environmental and other causes of childhood cancer. This initiative would build upon the unique national clinical trials system for treating children with cancer. NCI will evaluate the results of the pilot study in FY 2003 to determine if this strategy has merit for supporting etiological research for childhood cancers (including tumors of the CNS).[b]

- ➔ Conduct a SEER special study to collect data on benign brain tumors.[b]

---

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

# 2-4 Characterize Tumors at the Molecular Level to Aid in Diagnosis, Treatment Choice, and Treatment Monitoring

## Introduction

Because brain tumors are an extraordinarily heterogeneous group of lesions, accurate diagnosis is essential to proper management. Current imaging techniques can delineate the anatomical features of brain tumors but have not provided an effective means for early detection.

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 often do not allow accurate prediction of therapeutic responses or reliable prognosis. The situation is further complicated by the small size of some diagnostic biopsy samples. The diagnosis of brain tumors must therefore be improved, both to advance current therapeutic management strategies and to form a basis for the evaluation of novel approaches.

*"The diagnosis of brain tumors must therefore be improved, both to advance 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, 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 BT-PRG identified the following priorities for the detection and diagnosis of brain tumors:

- 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;
- Provide a detailed molecular characterization 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; and
- Develop a molecular- and imaging-based classification scheme for brain tumors that can be used to predict tumor behavior and guide treatment decisions more accurately and objectively than is possible with current histopathological methods.

## Ongoing Activities Addressing the Priority

The following initiatives are designed to generate molecular profiles of human cancers:

- **The Brain Tumor Genome Anatomy Project** (see page 15)

- **The Cancer Genome Anatomy Project** (see page 15)
- **The Director's Challenge: Toward a Molecular Classification of Tumors** (see page 15)
- **The Innovative Technologies for the Molecular Analysis of Cancer Initiative** is developing novel technologies to support the molecular analysis of cancers and their host environment. This initiative is supporting one project focusing on brain tumors: "Genome-based Targeting of the Hedgehog Pathway in Cancer." A related initiative, **Applications of Innovative Technologies for the Molecular Analysis of Cancer**, also is supporting a project focused on brain tumors: "Molecular Analysis of Cancer—Imaging of Mass Spectrometry." [NCI]
- **Translation of Technologies to Detect Alterations in Tumors** analyzes the spectrum of molecular alterations in human tumor tissues to identify reliable molecular markers or targets for the detection, diagnosis, prognosis, and treatment of cancer. [NCI]
- **Gene Expression Profiling in the Nervous System** supports feasibility studies for profiling gene expression patterns in the mammalian nervous system. [NINDS]

A number of initiatives are developing new imaging techniques that build on the molecular fingerprints of cancer:

- **The Development and Application of Imaging in Therapeutic Studies** integrates and exploits, in clinical and preclinical settings, imaging techniques in the assessment of therapeutic agent development. This initiative is supporting three projects focusing on brain tumors: "Predicting Brain Tumor Chemosensitivity by in vivo MRS," "MRI Monitoring of Angiogenesis Inhibition," and "TNT Imaging to Monitor the Efficacy of Cancer Therapy." [NCI]
- **The Development of Clinical Imaging Drugs and Enhancers Program** (DCIDE) supports the development of promising imaging enhancers (contrast agents) or molecular probes (including probes that can get past the blood-brain barrier [BBB] and into the brain). DCIDE makes available to investigators, on a competitive basis, the preclinical development contract resources of NCI, including, for example, pharmacokinetics, dosimetry, and IND-directed toxicology. Assistance may also take the form of direction regarding regulatory affairs and access to probes for approved preclinical protocols. [NCI]
- **The Development of Novel Imaging Technologies** focuses on new image acquisition and enhancement methods and integrating these emerging technologies with traditional imaging modalities to yield more effective solutions for cancer and other diseases. This initiative is currently supporting one project focusing on brain tumors: "Antisense imaging of brain gene expression." [NCI]
- **Exploratory/Developmental Grants for Diagnostic Cancer Imaging** stimulate highly innovative research concepts in diagnostic cancer imaging. This initiative is supporting five projects focusing on brain tumors: "Low Cost, High Quality Prepolarized MRI Head Scanner," "Development of 1H Metabolite Imaging for Cancer," Diagnosis of Brain Tumor Recurrence by High-Field MRS," "NMR Detection of 13C Temozolomide in Canine Brain Tumors," "Assessing Tumor

Malignancy in vivo Using Sodium MRI," and Mutual Information Based Image Processing for FMRI."[NCI]

- **The Cerebral Radiology and Neuroimaging of Brain Tumors Program** supports research on the biological basis of brain tumor cell function and surrounding normal brain cell injury and repair mechanisms induced by radiotherapy treatment for brain tumors.[12] [NCI, NINDS]
- **The *In Vivo* Cellular and Molecular Imaging Centers** foster interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging. NCI has established 5 *in vivo* cellular and molecular imaging centers and additional centers will be funded in 2003. These centers narrow the gap between the discovery of new cancer genes and intracellular pathways, and the translation of these discoveries into clinically useful, minimally invasive imaging approaches to gaining a greater understanding of cancer. [NCI]

Two initiatives focus on strategies to assess cancer prognosis:

- **Exploratory Studies in Cancer Detection, Prognosis, and Prediction** evaluate new molecular or cellular characteristics of premalignant cells or tumors, or develop assays that are useful for cancer detection, diagnosis, and/or prognosis. This initiative is supporting two projects focusing on brain tumors: " SPARC—A Diagnostic Marker for Invasive Meningioma," and "Circulating SERBB1 Levels as Diagnostic Tumor Biomarkers." [NCI]
- **Phased Application Awards in Cancer Prognosis and Prediction** assess new strategies for determining prognosis or predicting response to therapy. This initiative is supporting one project focusing on brain tumors: "Genomic Profile-based Prognostic Markers for Ependymoma." [NCI]

**The Exploratory Grants in Pediatric Brain Disorders: Integrating the Science Initiative** (see page 22)

**Stem Cell Plasticity in Hematopoetic and Non-Hematopoeitic Tissue** promotes the thorough exploration and characterization of stem cell plasticity in hematopoietic and non-hematopoietic tissue. Research efforts are needed to test stem cell plasticity in a rigorous manner and, especially, characterize the cellular and molecular mechanisms that lead to the capacity of adult stem cells with hematopoietic potential to express other potentials and of precursor cells of adult non-hematopoietic tissues to express hematopoietic potential. Other areas of great interest include the ability of stem cells from nonneuronal tissues to differentiate along neuronal and glial lineages. [NINDS]

The highest priority item identified by the **Neuro-Oncology Models Forum** is to ensure that researchers incorporate imaging broadly during the derivation, evaluation, and application of all mouse brain tumor models. The **Mouse Models of Human Cancers Consortium**, in collaboration with the **Small Animal Imaging Research Program** and an alliance of instrument manufacturers, has now established an animal imaging roundtable to (1) work collaboratively to overcome the practical challenges of imaging mice with current modalities; (2) use the mouse to develop new modalities or additional applications of the presently available approaches; and (3) use mouse

12 This initiative is not currently addressing this priority area but could do so if NCI or NINDS receives competitive applications in response to it..

imaging to discover features of mouse cancer development that may be informative for human cancer etiology, treatment, early detection, or prevention. [NCI]

**The Glioma Marker Network**, though now supported as an investigator-initiated program project, was originally established through an NCI request for applications (RFA). This program analyzes the chromosomal and biochemical characteristics of cell lineages that give rise to different types of brain tumors and that determine prognosis and response to chemotherapy.

### New Activities Addressing the Priority

In 2002, NCI is funding a new **CNS/Brain Tumor Specialized Program of Research Excellence (SPORE)**.

### Proposed Strategies to Address Gaps

To address this priority, NCI and NINDS propose to:

- ➔ Provide additional support for the Glioma Molecular Diagnostic Initiative, a prospective, publicly available database containing data (including corollary clinical data) from molecularly characterized glioma specimens for the purpose of establishing a useful molecular classification scheme for gliomas.[a]

- ➔ Expand the Cancer Molecular Analysis Program (CMAP), which will enable researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. A Web site will provide access to molecular phenotypes that best fit a query and will offer information about clinical trials of molecularly targeted agents specific to the phenotypes. Gliomas will be the prototype for this initiative.[a]

---

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

# 2-5 Develop Novel Therapies and Improve Support for Immunotherapy Trials

## Introduction

Treatment options for patients with brain tumors are limited and, for most types of tumors, provide only modest benefits. These limitations are probably due to the unique structural and physiological aspects of the CNS, especially its vulnerability to damage from many therapies and the neoplastic processes themselves.

> *"The major challenge for the future is to develop more effective techniques to treat brain tumors without damaging the brain."*

Research in the treatment of brain tumors has been hampered by the lack of clinically predictive model systems; the minimal understanding, until recently, of fundamental tumor biology; and the narrow range and limited expected specificity for brain tumors of available therapeutic agents for testing. The major challenge is to develop more effective techniques to treat brain tumors without damaging the brain. Relevant recommendations of the BT-PRG are to:

- Increase support for immunotherapy trials similar to those for radiation and chemotherapy;
- Facilitate the development of novel therapeutic agents and approaches for adult and pediatric brain tumors, including chemotherapeutic, immunologic, antiangiogenic, genetic, and viral agents;
- 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;
- Develop techniques that can reliably detect brain injury related to tumor or treatment and use such techniques to assess the efficacy of neuroprotective interventions;
- Enhance the therapeutic ratio for radiation therapy for brain tumors (overcome radioresistance of primary brain tumors and normal tissue toxicity, such as necrosis/edema and functional deficits);
- Develop therapies that are less toxic than existing therapies to both the mature and the immature nervous system;
- Establish clinical and imaging markers of neurotoxicity from existing therapies, such as radiation, and from novel treatments;
- Study long-term outcomes for survivors of brain tumors, investigate the impact of therapies on the developing brain, and focus on some rarer, more primitive tumors occurring in children;
- Improve the therapeutic index of new agents that are specifically relevant to the CNS;

- Develop clinical consortia for immunotherapy that are similar to those for radiation and chemotherapy;
- Develop novel drug-targeting systems that enhance the uptake by brain tumors of small- and large-molecule diagnostic and therapeutic agents; and
- 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).

## Ongoing Activities Addressing the Priority

The following initiatives link institutions to carry out collaborative initial testing and clinical trials of new therapies for brain tumors:

- **Two Adult Brain Tumor Consortia** test novel agents and other new approaches to the therapy of high-grade brain tumors, especially gliomas. Designed to complete studies more efficiently than a single center or company, these highly specialized consortia have become the primary focus for clinical trials of new brain tumor agents in adults. Areas of emphasis in recent years include inhibiting signaling pathways that control cancer cell growth, inhibiting angiogenesis, optimizing treatments to specific areas of the brain, and integrating the evaluation of markers into clinical trials. [NCI]
- **The Pediatric Brain Tumor Consortium** rapidly conducts phase 1 and 2 clinical evaluations of new therapeutic drugs, intrathecal agents, delivery technologies, biological therapies, and radiation treatment strategies in children with primary brain tumors. Areas of emphasis include improving outcomes for young children with brain tumors and for children with brain stem gliomas, as well as the development of new approaches to providing localized treatments with fewer side effects. [NCI]
- **The Children's Oncology Group** (Brain Tumor Committee) designs and implements pilot and phase 2 and 3 trials for childhood brain tumors. [NCI]

These initiatives speed the translation of insights in cancer biology to therapeutic studies and early stage clinical trials:

- **Clinical Cancer Therapy Research** conducts clinical therapeutic studies/trials of cancer in humans. It encompasses a full range of studies employing drugs, biologics, radiation, and surgery. This initiative is supporting two projects focusing on brain tumors: "Gene-based Therapies and Imaging of Malignant Gliomas" and " Topotecan by Intracerebral Clysis for Brain Tumors."[NCI]
- **The Quick Trials for Novel Cancer Therapies Program** speeds the translation of ideas for novel cancer therapies developed in the laboratory to clinical trials by simplifying the grant application process. This initiative is supporting 10 projects focusing on brain tumors: " Intrathecal 131I 3FE for Leptomeningeal Malignancies," "Novel Tumor Antigen for Antibody Targeting, "ZD1839 Therapy of Gliobastoma Multimforme," "Phase I Study of Dendritic Cell Immunotherapy," "Assessment of Hypoxia in Malignant Gliomas Using EF5," "Cellular Immunotherapy for Neuroblastoma with CTL Clones," "Phase I/II Trial for Neutron Capture Therapy," "Beta Glucan Enhances Antibody

Section 2

Therapy for Neuroblastoma," "Correlative Trial of Fenretinide Against Glioblastomas," and "Biological Evaluation of CCI-779 in Brain Tumors."[NCI]

Two initiatives focus on the discovery and testing of drugs for cancer treatment:

- **The Innovative Toxicology Models for Drug Evaluation Initiative** supports new and innovative assays to determine specific organ toxicities of potential cancer therapeutic agents. [NCI]
- **The Rapid Access to Intervention Development Program** moves novel treatment interventions from academic settings into the clinic by making NCI's drug development resources available to investigators testing promising molecules for cancer treatment. This initiative is supporting four projects focusing on brain tumors: "Production of Non-Pathogenic Oncolytic Poliovirus Chimeras for the Treatment of Brain Tumors," "A Single Chain Variable Domain Fragment – Pseudomonas Exotoxin Construct for Treatment of Primary and Metastatic Brain Tumors and Neoplastic Meningitis," "Treatment of Malignant Gliomas with IGF-1R Antisense Oligodeoxy-nucleotides," and "A Study of Safety and Immunological Response of Immunotherapy in Patients with Solid Tumors."[NCI]

Several NCI initiatives are identifying strategies for cancer detection, diagnosis, and prognosis:

- **Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials** involve translational research on promising predictive and prognostic markers, focusing on correlations between biologic features of tissue specimens and patient outcomes. This initiative is supporting three projects focusing on brain tumors: "Genetic and Biologic Studies of 1P and 19Q in Gliomas," "Patterns of Ganglioside Expression in Neuroblastoma," and Significance of Genetic Alterations in Neuroblastoma."[NCI]
- **Exploratory Studies in Cancer Detection, Prognosis and Prediction** (see page 28)
- **Phased Application Awards in Cancer Prognosis and Prediction** assess new strategies for determining prognosis or predicting response to therapy. This initiative is supporting one project focusing on brain tumors: "Genomic Profile-based Prognostic Markers for Ependymoma." [NCI]
- **The Biomarkers and Clinical Endpoints in Pediatric Clinical Trials Initiative** supports mechanistic studies using patients, patient materials, or information from multisite pediatric drug trials, and determines biomarkers or surrogate endpoints. [NINDS]

The **Development and Application of Imaging in Therapeutic Studies** are integrating and exploiting, in clinical and preclinical settings, imaging techniques in the assessment of therapeutic agent development. Projects may address development and application of labeled therapeutic agents as compounds for imaging studies, or of imaging agents as metabolic markers of response to newly developed therapeutic agents. This initiative is supporting three projects focused on brain tumors: "Predicting Brain Tumor Chemosensitivity by In Vivo MRS," "MRI Imaging of Angiogenesis Inhibition," and "TNT Imaging to Monitor the Efficacy of Cancer Therapy." [NCI]

**Hyperaccelerated Awards/Mechanisms in Immunomodulation Trials** support mechanistic research studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including asthma and allergy, graft failure in solid organ and stem cell transplantation, and autoimmune diseases. Patients and patient materials from such trials are used to evaluate immunologic and other relevant parameters in order to study the underlying mechanisms of the intervention, mechanisms of disease pathogenesis, surrogate markers of disease activity and therapeutic effect, and mechanisms of human immunologic function. [NINDS]

**The Pilot Clinical Trial Grant for Neurological Disease Initiative** will obtain preliminary data and conduct studies to support the rationale for a subsequent full-scale clinical trial of an intervention to treat or prevent neurological disease. [NINDS]

**The CNS Barriers Initiative** supports additional research in BBB regulation, transport biology, and potential targeted drug delivery strategies. During FY 2002, a program announcement will be issued that will include set-aside funds for research focused on understanding how neuroprotective barriers function and are compromised under disease conditions. [NINDS]

**The Community Clinical Oncology Program** supports clinical trials for management of symptoms resulting from brain tumors and their treatment. Studies include assessments of methylphenidate and ginkgo biloba for treatment or prevention of cognitive dysfunction [NCI]

**Gene Therapy for Neurological Disorders** aims to to accelerate the translation of gene transfer methodologies into the clinic. [NINDS]

Five member groups of the **Mouse Models of Human Cancers Consortium** employ brain tumor models of medulloblastoma, glioblastoma, oligodendroglioma, astrocytoma, choroid plexus, and neurofibromatosis to explore new, molecularly targeted therapeutic agents singly or in combination. Several of the models are engineered to express molecules that enable the investigators to use imaging to follow delivery of the agents and tumor response, or are secreted to provide a measure of tumor burden. Some groups use novel delivery strategies, including gene therapy and tumor-targeted neural stem cells. [NCI]

The intramural **Neuro-Oncology Branch**, established by the NCI and the NINDS, is a collaborative effort to develop novel diagnostics and therapeutics for children and adults with brain and spinal cord tumors. [NCI, NINDS]

### New Activities Addressing the Priority

In 2002, NCI is funding a new **CNS/Brain Tumor Specialized Program of Research Excellence (SPORE)** that will support rapid funding for clinical trials.

NCI issued a program announcement entitled **Cancer Therapy-Related Use of Genetically Engineered Mice** early in 2002. It will support research to exploit mouse models to define molecular targets, test agents directed to such targets, identify the genetic determinants of response to therapy, determine the mechanisms that underlie recurrence, and achieve other therapy-related goals.

In 2002, NCI will integrate capacity for immunotherapy trials into the RFA for Adult Brain Tumor Consortia.

In 2002, NCI sponsored two meetings on access to drugs for preclinical testing. An outcome of these meetings was a renegotiation of agreements between NCI and pharmaceutical companies for provision of drugs for testing.

**Proposed Strategies to Address Gaps**

To address this priority, the NCI proposes to:

- ➔ Address the difficulty of obtaining access to investigational agents for clinical trials for children with brain tumors. NCI will collect data concerning recent pediatric group protocol applications (i.e., letters of intent) and agents for which applications were not submitted because of lack of access to the agent. Once the requisite data are collected, NCI will organize a workshop with relevant parties (e.g., researchers, pharmaceutical sponsors, the U.S. Food and Drug Administration, patient advocates) to identify factors limiting access to investigational agents and identify possible remedies. This effort will build on earlier NCI-sponsored meetings and NCI-negotiated agreements focused on improving access to investigational agents for preclinical testing.[d]

- ➔ Add an imaging component (or link the imaging component of another center) to the Adult Brain Tumor Consortia so the Consortia may assist in identifying non-invasive imaging techniques that can determine if a novel agent is actually altering its intended target within the brain tumor. This component also will enable the consortia to assist in identifying imaging surrogates for tumor response.[b]

- ➔ Develop and implement a plan for identifying and using preclinical models that can predict clinical activity of new agents against childhood cancers. In conformity with the Best Pharmaceuticals for Children Act, NCI (in FY 2002) will review the current capabilities of preclinical models to predict which therapies are likely to be effective for treating pediatric cancers (including brain cancers). A plan for using the models will be developed with input from the pediatric investigator community, and will require input from NCI's Developmental Therapeutics Program, the Cancer Therapy Evaluation Program, and Division of Cancer Biology (for mouse models of human cancers). Initial implementation of the plan could occur in FY 2003.[b]

---

[a] This strategy is currently under development as a first step towards implementation.
[b] The NCI and NINDS have determined that they will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
[c] While this strategy is important, the NCI and NINDS will not be able to pursue it at this time because of limited funds.
[d] Implementation is currently underway. Speed of implementation will depend on the ability of NCI and NINDS staff to devote appropriate resources to the effort.

## 2-6 Ensure that Brain Tumor Treatments are Safe and Effective

### Introduction

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.

*"Better measurement tools and surrogate markers are critically needed to assess patient quality of life and tumor response to therapy."*

For these reasons, better measurement tools and surrogate markers are critically needed to assess patient quality of life and tumor response to therapy. Such outcome measures 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.

In this priority area, the BT-PRG made the following recommendations:

- 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;
- Develop techniques for measurement of quality of life and include such measurements in key clinical trials of brain tumors;
- Develop techniques that can reliably detect brain injury related to tumor or treatment, and use such techniques to assess the efficacy of neuroprotective interventions;
- Refine the ability to detect responses 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;
- Investigate the impact of therapies on the developing brain; and
- Expand and enhance databases to include all primary brain and spinal tumors—malignant and nonmalignant, adult and pediatric—and to have the

Section 2

flexibility to accommodate new histological and molecular classifications of tumors and give investigators access to rapidly ascertained cases.

## Ongoing Initiatives Addressing the Priority

**The Clinical Trial Cooperative Groups Program** banks tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. Currently, six cooperative groups, including the Children's Oncology Group, provide brain tumor specimens and associated clinical treatment and outcomes data. These specimens, linked with clinical treatment and outcomes data, can be made available to other researchers. [NCI]

**The Biomarkers and Clinical Endpoints in Pediatric Clinical Trials Initiative** stimulates mechanistic studies using patients, patient materials, or information from multisite pediatric drug trials. Projects include ancillary mechanistic studies of disease pathogenesis and/or of results of therapeutic intervention, determination of biomarkers or surrogate endpoints, and development and validation of clinical endpoints in infants and older children. [NINDS]

**The Exploratory Grants in Pediatric Brain Disorders: Integrating the Science Initiative** (see page 22)

**The CNS Tumor Animal Experimental Therapeutics Core** will provide intramural and extramural investigators with uniform, systematic pharmacological and antitumor analyses of new agents and delivery technologies for CNS malignancies. The core will also provide a platform to develop molecular and radiographic endpoints specific for antitumor agents, and evaluate the neurotoxic effects of new treatment modalities on the CNS. [NCI, NINDS]

**The Childhood Cancer Survivor Study (CCSS)** was created to gain new knowledge about the long-term effects of cancer and therapy, which can then be used to help design treatment protocols and intervention strategies that will increase survival and minimize harmful health effects. Of the CCSS cohort of approximately 20,000 individuals who survived 5 or more years from their cancer diagnosis, approximately 1,800 are survivors of brain tumors. Evaluations of the neurological and nonneurological status of these brain tumor survivors are in progress. [NCI]

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

**Cerebral Radiobiology and Neuroimaging of Brain Tumors** (see page 18)

**Development and Application of Imaging in Therapeutic Studies** (see page 32)

Through these programs, researchers are developing new imaging techniques that can help determine prognosis and response to treatment:

- **American College of Radiology Imaging Network** manages clinical trials of imaging technologies as they relate to cancer.[13] [NCI]
- **The Development of Clinical Imaging Drugs and Enhancers Program** supports the development of promising imaging enhancers (contrast agents) or molecular probes (including probes that can get past the BBB and into the brain). [NCI]
- **Exploratory/Developmental Grants for Diagnostic Cancer Imaging** stimulates highly innovative research concepts in diagnostic cancer imaging. This initiative is supporting five projects focusing on brain tumors: "Low Cost, High Quality Prepolarized MRI Head Scanner," "Development of 1H Metabolite Imaging for Cancer," Diagnosis of Brain Tumor Recurrence by High-Field MRS," "NMR Detection of 13C Temozolomide in Canine Brain Tumors," "Assessing Tumor Malignancy in vivo Using Sodium MRI," and Mutual Information Based Image Processing for FMRI."[NCI]
- **The Development of Novel Imaging Technologies Initiative** focuses on new image acquisition and enhancement methods and integrating these emerging technologies with traditional imaging modalities for more effective solutions for cancer and other diseases. This initiative is currently supporting one project focusing on brain tumors: "Antisense imaging of brain gene expression." [NCI]
- **The Surveillance, Epidemiology, and End Results (SEER) Program** (see page 24)

## Proposed Strategies to Address Gaps

To address this priority, NCI and NINDS propose to:

➔ Revise the Common Toxicity Criteria (CTC) to allow for the capture and coding of information about the late effects of cancer therapy, including neurological sequelae of brain tumors and their therapy. The revised criteria will be developed collaboratively, under the leadership of NCI's Cancer Therapy Evaluation Program and outside groups, such as the Radiation Therapy Oncology Group, the Children's Oncology Group, and the American College of Surgeons Oncology Group. Enhancement of the CTC to include the grading of late effects of cancer therapy will facilitate systematic evaluations of the long-term effects of brain cancers and their treatment. In combination with the existing clinical trial resources of the Children's Oncology Group and the Pediatric Brain Tumor Consortium, the criteria may enable development of databases describing the long-term outcomes of children with brain tumors.[a]

13 This initiative is not currently addressing this priority area but could do so if NCI receives competitive applications in response to it..

➔ In conjunction with the effort to revise the CTC, develop a standardized set of outcome measures (including measures of dementia) to be adapted to different tumor types, and develop long-term follow up measures of quality of life in pediatric patients. It could be accomplished through groups such as the Children's Oncology Group and the Pediatric Brain Tumor Consortium, perhaps with existing funds. NCI could host a conference to catalyze the effort.[a]

➔ Sponsor additional studies of cognitive interventions to address treatment-induced deficits. This initiative could be undertaken through existing cooperative groups, consortia, and the brain tumor SPORE.[a]

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

# Section 3
Resource Priorities

To pursue the scientific research priorities discussed in the prior section, investigators and clinicians will need access to a host of crosscutting supporting resources. The BT-PRG identified specific improvements needed in the following areas:

- Models,
- Quality of and access to tissue banks and databases,
- High-throughput screening approaches, and
- Training.

Addressing these support issues is essential to furthering the understanding of tumor biology, prevention and early detection of brain tumors, and development of new effective therapies.

## 3-1 Improve Models

### Introduction

Models are central to making the transition from developing scientific concepts to understanding human tumors within the context of the tissues 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, the BT-PRG report called for:

*"Models are central to making the transition from developing scientific concepts to understanding human tumors within the context of the tissues they affect."*

- Developing tissue and cell culture systems that replicate the biology of human brain tumors;
- Creating genetically and behaviorally accurate models for brain tumors in mice and other animals;
- Generating tissue-based, imaging, and genomic methods to validate and compare animal models with their human counterparts; and
- Improving 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.

## Ongoing Activities Addressing the Priority

The **Mouse Models of Human Cancers Consortium** is designed to accelerate the pace at which well-designed and thoroughly characterized mouse cancer models are available to the cancer research community. With advice from the consortium, NCI established a **Mouse Cancer Models Repository** to receive mice, maintain and preserve them, and distribute them to the community. With support from the **NCI Center for Bioinformatics**, substantial descriptive information about models is maintained in a **cancer models database**. The ***e*MICE Web site** provides the community with information on all NCI mouse-related resources, including the many symposia, workshops, hands-on teaching laboratories, forum programs, and industry/academia roundtables organized by the consortium. [NCI]

**The Technologies to Improve the Utility of Animal Models Initiative** encourages the small business community to develop technologies, reagents, and equipment to improve the utility of animal models for biomedical research.[14] [NCI]

**The Innovative Technologies for the Molecular Analysis of Cancer Initiative** provides assistance for high-resolution cellular or molecular imaging research, access to tissue samples, development of preclinical models, and the conduct of clinical investigations as an important extension of molecular analysis methods.[15] [NCI]

**The Small Animals Imaging Resources Program (SAIRP)** speeds the development of new imaging methods for small animals. Currently, this initiative is supporting four projects focusing on brain tumors: "Interdisciplinary Small Animal Imaging in Oncology," "Small Animal Imaging Resource," "Development of Regional Tumor Imaging Resource," and "Small Animal Multimodality Imaging Center." SAIRP centers are developing and applying a wide variety of imaging modalities. [NCI]

14 This initiative is not currently addressing this priority area but could do so if NCI receives competitive applications in response to it..
15 This initiative is supporting one project focusing on brain tumors: "Genome-based Targeting of the Hedgehog Pathway in Cancer."

**Proposed Strategies to Address Gaps**

To address this priority, NCI proposes to:

➔ Develop and implement a plan for identifying and using preclinical models that can predict clinical activity of new agents against childhood cancers. In conformity with the Best Pharmaceuticals for Children Act, NCI (in FY 2002) will review the current capabilities of preclinical models to predict which therapies are likely to be effective for treating pediatric cancers (including brain cancers). A plan for using the models will be developed with input from the pediatric investigator community, and will require input from NCI's Developmental Therapeutics Program, the Cancer Therapy Evaluation Program, and Division of Cancer Biology (for mouse models of human cancers). Initial implementation of the plan could occur in FY 2003.[b]

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

# 3-2 Improve Quality of and Access to Tissue Banks and Databases

## Introduction

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 the 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, there is a great need for organized, inter-institutional approaches to banking and data management of both adult and pediatric neoplasms.

The BT-PRG made the following recommendations to improve tissue bank quality and access:

- Collect and bank tissue, blood, cerebrospinal fluid, and (when available) normal brain from patients with all varieties of brain tumors, paying particular attention to banking pediatric tumors; rare intra-axial tumors, such as low-grade gliomas and lymphomas; tumors that follow long clinical courses, such as meningiomas; metastases, when tissue from the primary tumor is also available; and acquiring clinical and radiological information and tissues from distinct populations;

*"Tissue banks linked to clinical databases are also vital for translating research discoveries into clinically relevant information."*

- Maintain a comprehensive database of relevant clinical, demographic, pathologic, biologic, and therapeutic information on all patients whose tissue is banked, and develop links to population databases to enhance potential etiological and other epidemiological studies;
- Involve multidisciplinary participation of surgeons, pathologists, scientists, and other professionals, including neuro-oncologists, 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;
- Feature local and regional facilities and facilitate effective communication and collaboration among centers; and
- Support the linking of existing databases to provide larger numbers of samples for epidemiological studies.

## Ongoing Activities Addressing the Priority

Through these programs, NCI collects, preserves, and distributes human tissues for research:

- **The Cooperative Human Tissue Network** collects, preserves, and distributes human tissues for research. Trained personnel coordinate the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies. Most specimens are collected prospectively to meet investigator protocol requirements; however, some previously collected specimens can be made available for immediate use. [NCI]
- **The Clinical Trials Cooperative Groups Human Tissues Resources Program** banks tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. Currently, six cooperative groups, including the Children's Oncology Group, provide brain tumor specimens and associated clinical treatment and outcomes data. These specimens, linked with clinical treatment and outcomes data, can be made available to other researchers. [NCI]
- **AIDS and Cancer Specimen Bank** provides tissue, cell, blood and fluid specimens, as well as clinical data from patients with AIDS and CNS cancers. The specimens and clinical data are available for research studies, particularly those that translate basic research findings to clinical application. [NCI]
- The **Tissue and Biological Fluid Banks of HIV-Related Malignancies** support consortia to bank tissue and biological fluids and to maintain associated clinical data from patients with HIV-associated malignancies. These cooperative efforts are identifying and improving access to tumor tissue, biological specimens, and associated clinical outcome data that the research community can use to study the pathogenesis of HIV-associated malignancies and development of more effective therapies.

The following programs help researchers identify and obtain tissues, including tissues with associated clinical data and tissues from rarer tumors:

- **The Specimen Resource Locator Web site** (http://www.cancer.gov/specimens/html) provides a database to help researchers locate appropriate sources of normal, benign, precancerous, and cancerous human tissue specimens for cancer research. [NCI]
- **The NCI Tissue Expediter** (e-mail: tissexp@mail.nih.gov) is a scientist who helps researchers locate additional sources of specimens and related data. [NCI]
- **The NCI Research Resources Web Site (http://resresources.nci.nih.gov/)** offers a centralized listing of animal resources; specimens; registries; and drugs, chemicals, and biologicals developed by NCI that are available to the research community. [NCI]

The following programs provide support to develop and increase the effectiveness of tissue specimen resources:

- **Shared Resources for Scientists Outside of the NCI Cancer Centers** provides groups of six or more NCI-funded investigators with additional shared support for shared resources, including tissue banks. This initiative is supporting at least two projects focusing on brain tumors: "A Multi-use Glioma Biorepository" and "Viral Vector Core Facility."[NCI]
- **The Shared Pathology Informatics Network** is creating a model Web-based system to access data related to archived human specimens at multiple institutions. The data to be accessed will be derived from existing medical records. The ability to automatically access information from medical databases is the first step toward the long-term goal of developing informatics systems to improve researchers' access to human specimens and clinical data. [NCI]

The BT-PRG expressed frustration with local institutional review boards (IRBs) that take a very conservative approach to tissue collection. While NCI is sympathetic to the needs of investigators, it has no authority over local IRBs. To facilitate a smoother approval process, **The NCI Resources Development Web Site** (http://www-cdp.ims.nci.nih.gov/rdb.html) provides:

- **Information on legal and ethical issues related to the use of human specimens in research**, including model consent forms and a brochure for investigators on how the Federal regulations for protection of human subjects in research apply to work with human tissues. [NCI]
- **Metrics for NCI evaluation of human specimen resources.** [NCI]

## New Activities Addressing the Priority

NINDS sponsored a workshop to identify current problems, challenges, and emerging trends in brain banking and provide recommendations for establishing cooperative, multicenter networks for neural tissue banking, including brain tumors. This **Neurological Disease Brain Banking Workshop** was held in March 2002.

In 2002, NCI launches a new **Research Resources Web Site** that includes information on how to establish and manage a tissue bank or other resource.

## Proposed Strategies to Address Gaps

While the preceding initiatives go a long way toward improving the availability of and access to brain tumor specimens, NCI and NINDS propose to:

- ➔ Better promote available tissue resources through workshops, publications, and Web sites.[d]

- ➔ Continue to support a pilot study by the Children's Oncology Group to evaluate the feasibility of establishing a childhood cancer research network that would create a national registry of children with cancer, including a tissue bank for tumor and blood specimens, for identifying environmental and other causes of childhood cancer. This initiative would build upon the unique national clinical trials system for treating children with cancer. NCI will evaluate the results of the pilot study in FY 2003 to determine if this strategy has merit for supporting etiological research for childhood cancers (including tumors of the CNS). A decision to support full implementation of the childhood cancer research network concept could be made late in FY 2003 or in FY 2004.[b]

- ➔ Fund the proposed Tissue Resources for Cancer Research, which is designed to expand the range of NCI-funded specimen resources and cover all major tumor types. Only multi-institutional organizations or preformed consortia may apply, and they must be able to provide large numbers of cases (hundreds or thousands, depending on the research focus). The specimens must be made available to the research community, and the applicants must propose policies to ensure equitable access.[c]

---

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

## 3-3 Develop High-Throughput Screening Approaches to Further the Understanding of Gene Function

### Introduction

The explosion of information in genomics, together with the promise of similar advances in proteomics, highlights 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 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.

Relevant recommendations in the BT-PRG's report are to:

*"The explosion of information in genomics, together with the promise of similar advances in proteomics, highlights the need for technologies that allow high-throughput screens of brain tumors and related specimens."*

- Develop high-throughput laboratory approaches to understand gene function and 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 the 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;
- 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; and
- Create a mechanism to ensure affordable access to these reagents and models.

## Ongoing Activities Addressing the Priority

Both NCI and the NINDS have an array of ongoing initiatives that support research in genomics and high-throughput screening and could be further used to address specific brain tumor research issues raised by the BT-PRG.

Several initiatives support the development of new technologies to explore gene expression in the nervous system:

- **The Tissue Array Research Program**, a joint effort of NCI and the National Human Genome Research Institute, develops and applies tissue microarray technology. [NCI]
- **Gene Expression Profiling in the Nervous System** supports feasibility studies for profiling gene expression patterns in the mammalian nervous system. [NINDS]
- **Technologies for Gene Expression Analysis in the Nervous System** supports research to develop new technologies or refine established technologies for gene discovery and gene expression analysis in the nervous system. [NINDS]
- **High-Throughput Analysis for Gene Expression Patterns in the Nervous System** supports high-throughput collection of gene expression patterns for the mouse nervous system. [NINDS]

These programs focus on molecular analysis and characterization of human cancers using high-throughput approaches:

- **The Cancer Genome Anatomy Project** is designed to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. CGAP provides gene expression profiles of normal, precancer, and cancer cells, including brain tumor cells. Clones and libraries are available to the scientific community, and the CGAP web site (http://cgap.nci.nih.gov/) provides access to all CGAP data and analysis tools. [NCI]
- **The Innovative Technologies for the Molecular Analysis of Cancer Initiative** is developing novel technologies to support the molecular analysis of cancers and their host environment. [NCI]
- **The Translation of Technologies to Detect Alterations in Human Tumors Initiative** analyzes the spectrum of molecular alterations in human tumor tissues to identify reliable molecular markers or targets for the detection, diagnosis, prognosis, and treatment of cancer. [NCI]

Two programs support research in biomedical information technology:

- **The Innovations in Biomedical Information Science and Technology Initiative** supports research in biomedical computing science and technology. [NCI, NINDS]
- **The National Programs of Excellence in Biomedical Computing Initiative** supports bioinformatics and biocomputational research and training that enables the advancement of biomedical research. [NCI, NINDS]

The following programs support the development of high-throughput approaches for cancer detection, diagnosis, and prognosis:

- **Exploratory Studies in Cancer Detection, Prognosis, and Prediction** evaluate new molecular or cellular characteristics of premalignant cells or tumors, or develop assays that are useful for cancer detection, diagnosis, and/or prognosis. This initiative is supporting two projects focusing on brain tumors: " SPARC—A Diagnostic Marker for Invasive Meningioma," and "Circulating SERBB1 Levels as Diagnostic Tumor Biomarkers." [NCI]
- **Phased Application Awards in Cancer Prognosis and Prediction** assess new strategies for determining prognosis or predicting response to therapy. This initiative is supporting one project focusing on brain tumors: "Genomic Profile-based Prognostic Markers for Ependymoma." [NCI]

**The Molecular Targets Laboratories Program** is developing a resource of biological assays and chemical probes for biological studies of cancer. The program emphasizes the need for collaboration between chemists and biologists in an effort to produce libraries of potential anticancer compounds for public distribution, develop screening assays suitable for high-throughput screening of chemical libraries of potential agents, and confirm the initial ability of certain drugs to alter the drug target in cancer cells. [NCI]

**The Translational Proteomics Program** is developing precise analytical approaches that are pertinent to cancer research to assess the proteins in biological tissues. [NCI]
**The Center for Bioinformatics** provides bioinformatics support for and integration of NCI-supported research initiatives. [NCI]

**The Advanced Technology Center (ATC)** implements novel technologies to address biological, clinical, and genetic questions pertinent to human cancers. The ATC houses investigators from NCI and the National Human Genome Research Institute whose research focuses on human cancer genetics, molecular epidemiology, and cell biology. This multidisciplinary center serves as the home of the **Cancer Genome Anatomy Project (CGAP)**, two high-throughput genotyping centers, two sequencing centers, and a microarray facility. The ATC will focus on the development of high-throughput, multiplex techniques for population-based studies, the analysis of expression states using expression array technology, and new gene discovery approaches. [NCI]

**Proposed Strategies to Address Gaps**

- ➔ Provide additional support for the Glioma Molecular Diagnostic Initiative, a prospective, publicly available database containing data (including corollary clinical data) from molecularly characterized glioma specimens for the purpose of establishing a useful molecular classification scheme for gliomas.[a]

- ➔ Expand the Cancer Molecular Analysis Program (CMAP), which will enable researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. A Web site will provide access to molecular phenotypes that best fit a query and will offer information about clinical trials of molecularly targeted agents specific to the phenotypes. NCI will prototype this effort using data gleaned from the Glioma Molecular Diagnostic Initiative.[a]

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

## 3-4 Enhance Training Opportunities

### Introduction

Achieving the goals for brain tumor research outlined in the BT-PRG report requires an adequately sized and well-trained scientific and clinical workforce specializing in brain tumor research. Unfortunately, there are insufficient numbers of scientists working in the field of brain tumors, clinicians who are cross-trained in brain tumor biology, and scientists who are aware of the problems driving clinical neuro-oncology research. As is the case for biomedical science in general, the small number of clinician-investigators now entering academic medicine compounds this problem.

In the area of training, the BT-PRG made the following recommendations:

- 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 that 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 brain tumor research; and
- Develop at NIH a model for a joint NCI-NINDS interdisciplinary training program in neuro-oncology at both the basic science and clinical levels; this program might include not only training at NIH for 2-3 years, but also support for the first 3 years of the individual's career as an independent investigator.

> *"Unfortunately, there are insufficient numbers of scientists working in the field of brain tumors, clinicians who are crosstrained in brain tumor biology, and scientists who are aware of the problems driving clinical neuro-oncology research."*

### Ongoing Activities Addressing the Priority

NIH sponsors a wide range of training initiatives that support new researchers and cross-disciplinary approaches. **NCI's Cancer Training Branch** manages the institute's research training, career development, and education programs for U.S. citizens, providing guidance to the extramural biomedical research community and administration of awards. Award mechanisms supported by NCI and NINDS include the following.

**The Mentored Quantitative Research Career Development Award** supports the career development of investigators with quantitative scientific and engineering

backgrounds outside of biology or medicine who have made a commitment to focus their research on behavioral and biomedical research. The award supports a period of supervised study and research for professionals who have the potential to integrate their expertise with biomedicine and become productive investigators. [NCI, NINDS]

**The Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences** is sponsored by NINDS and eight other institutes to encourage and support broad early-stage training by offering institutions a single comprehensive training grant. This training program is expected to enhance basic and disease-related neuroscience research. [NINDS]

**Cancer Education Grant Program** is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that will ultimately help reduce cancer incidence, mortality, and morbidity, as well as improve the quality of life of cancer patients. Projects range from the development of new curricula in academic institutions, national forums, seminar series, and workshops, to short-term research experiences designed to motivate high school, college, medical, dental, and other health professional students to pursue careers in cancer research. [NCI]

**The National Research Service Award (NRSA) Institutional Research Training Program** develops or enhances research-training opportunities for individuals who are training for careers in biomedical, behavioral, and clinical research. The program helps ensure that a diverse and highly trained workforce is available to assume leadership roles in the Nation's biomedical and behavioral research. Accordingly, the NRSA program supports predoctoral, postdoctoral, and short-term research training experiences. [NCI, NINDS]

**The Transition Career Development Award** is for individuals who have been educated as clinician-scientists (e.g., M.D. or doctoral-level oncology nurse) or as prevention control, behavior, or population scientists (e.g., Ph.D., D.P.H., M.D.), and are ready to pursue an independent research career. The award provides protected time for newly independent investigators to develop and receive support for their initial cancer research programs. [NCI, NINDS]

**The NCI Scholars Program** provides support for up to 4 years at NCI, followed by 2 years of support at an extramural institution. [NCI]

## Proposed Strategies to Address Gaps

As demonstrated by the number and diversity of training programs listed above, NCI and NINDS have a strong training infrastructure that can be used to foster interdisciplinary and translational research. To ensure that these programs are adequate to meet BT-PRG concerns and to encourage their use, NCI and NINDS propose to:

➔ Review existing training programs to identify interdisciplinary research needs that are not covered adequately.[a]

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

# Appendix A
## Roster of Brain Tumor Working Group

**Kevin Callahan, Ph.D.**
Office of Science Planning and Assessment
Office of the Director

**Norman Coleman, M.D.**
Radiation Research Program
Division of Cancer Treatment and Diagnosis
Center for Cancer Research

**Howard Fine, M.D.**
Neuro-Oncology Branch
Center for Cancer Research

**Jorge Gomez, M.D., Ph.D.**
Office of Centers, Training and Resources
Office of the Director

**Peter Inskip, Sc.D.**
Radiation Epidemiology Branch
Epidemiology and Biostatics Program
Division of Cancer Epidemiology and Genetics

**Tom Jacobs, Ph.D.**
Neural Environment Program
Division of Extramural Research
NINDS

**Richard Kaplan, M.D.**
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis

**Joseph Kelaghan, M.D., M.P.H.**
Community Oncology and Prevention Trials Research Group
Division of Cancer Prevention

**Tracy Lugo, Ph.D.**
Cancer Diagnosis Program
Division of Cancer Treatment and Diagnosis

**Cheryl Marks, Ph.D.**
Office of the Director
Division of Cancer Biology

**Judy Mietz, Ph.D.**
Cancer Cell Biology Branch
Division of Cancer Biology

**Cherie Nichols, M.B.A**
Office of Science Planning and Assessment
Office of the Director

**Lynn Ries, M.S.**
Surveillance Research Program
Division of Cancer Control and Population Sciences

**Malcolm Smith, M.D., Ph.D.**
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis

**Roy Wu, Ph.D.**
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis

# Appendix B

## Summary of Ongoing and New Activities and Proposed Strategies Addressing Brain Tumor PRG Priorities

| **Section 1**<br>**1-1 Share Knowledge, Strengthen Interaction, and Improve Peer Review** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Cancer Research Initiatives Web Site | **11** |
| Brain Tumor Genome Anatomy Project and the Cancer Molecular Analysis Program | **11** |
| Neuro-Oncology Models Forum | **11** |
| **New Activities** | |
| Glioma Cell Biology Workshops | **11** |
| **Proposed Strategies** | |
| Foster opportunities for development of interdisciplinary collaboration by integrating NINDS-supported neuroscientists into meetings and workshops of relevant crosscutting NCI initiatives such as the Director's Challenge Consortia, Brain Tumor SPOREs and Brain Tumor Consortia. Similar reciprocal arrangements will be made for NCI-funded oncologists to participate in workshops and symposia related to key NINDS neuroscience initiatives.[d] | **12** |
| Invite CSR staff to join a working group that will examine study sections' composition, behavior, and referral patterns for BT-related grant applications to determine whether equal and broad expertise exists in the areas of both neuroscience and oncology. Discuss the possibility of initiating an exchange program within neuroscience and oncology study sections to ensure fair review of applications.[d] | **12** |
| Establish a brain tumor working group composed of NCI and NINDS staff, as well as CSR staff, that will, three times each year, review and report on each funding cycle's grant applications and review procedures, monitor outcomes, and identify gaps and problems that arise in implementing the PRG's recommendations.[d] | **12** |
| Link the Brain Tumor PRG Report online to the responsive initiatives. The recommendations of the PRG (and their distillation as priorities in this strategic plan) will be linked to NCI initiatives that address them.[c] | **12** |
| Extend the Division of Cancer Biology's Activities to Promote Research Collaborations (APRC) Program to include other NCI divisions. Under this initiative, investigators can apply for funding for research collaborations and for organizing cross-disciplinary meetings/workshops. Providing funds to all NCI divisions will enable collaborations among basic, translational, and clinical scientists.[c] | **12** |

[a] NCI and/or NINDS are currently developing this strategy further as a first step towards implementation. Actual implementation will depend upon the availability of funds, the receipt of high-quality applications and a final determination that the strategy is feasible and scientifically sound.

[b] NCI and/or NINDS have determined that they will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

[c] While this strategy is important, NCI and/or NINDS will not be able to implement it in the near future.

[d] NCI and/or NINDS are beginning to implement this strategy. Speed of implementation will depend upon the availability of NCI and/or NINDS staff to devote appropriate resources to the effort.

| **Section 2**<br>**2-1 Understand the Biology of Brain Tumors and Their Interaction with Normal Brain Elements as They Related to Oncogenesis, Progression, Tumor Cell Dispersal, and Heterogeneity** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Brain Tumor Genome Anatomy Project | **15** |
| Cancer Genome Anatomy Project | **15** |
| Director's Challenge | **15** |
| Zebrafish as an Animal Model for Development and Disease Research | **15** |
| Innovative Technologies for the Molecular Analysis of Cancer | **15** |
| Molecular and Cellular Biology of Metastatic Tumor Cells | **15** |
| Mouse Models of Human Cancers Consortium | **16** |
| **New Activities** | |
| Support of Competing Supplements for Organotypic Cancer Models | **16** |
| Glioma Cell Biology Workshops | **16** |
| **Proposed Strategies** | |
| Issue a joint program announcement to encourage the application of new concepts in developmental neurosciences to understanding the unique organ-specific mechanisms of glioma biology in both pediatric and adult patients. Concepts aimed at understanding stem and precursor cell biology, and cell dispersal, differentiation, and signal transduction pathways as they relate to tumor cells within the central nervous system (CNS) will be emphasized through this initiative. Studies on the relationship of glial cells to brain tumors will be especially encouraged. Grantees may be required to attend at least one meeting a year to foster collaboration among basic neurobiologists, glial cell biologists, neuroimmunologists, neurologists, neurosurgeons, and neuro-oncologists and to address the bidirectional translation of basic and clinical science of brain tumor research.[a] | **16** |

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

| **Section 2**<br>**2-2 Expand Blood-Brain Barrier Research** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Cancer Genome Anatomy Project | **18** |
| Cerebral Radiobiology and Neuroimaging of Brain Tumors | **18** |
| Exploratory/Developmental Grant Programs | **19** |
| Mouse Models of Human Cancers Consortium | **19** |
| **New Activities** | |
| Annual Meeting on the BBB in CNS Tumors | **19** |
| **Proposed Strategies** | |
| Issue a joint program announcement to support research in BBB regulation, transport biology, and potential targeted drug delivery strategies. It will support research aimed at understanding how neuroprotective barriers function and are compromised under disease conditions. Applications to study treatment-induced neurotoxicity also will be encouraged, as will applications to create an expression atlas for microvascular endothelial cells within gliomas and the normal brain. Finally, this announcement will support awards to provide endothelial cells to the research community.[a] | **19** |

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

| **Section 2**<br>**2-3 Improve Our Understanding of the Genetic and Environmental Factors Related to Brain Tumors.** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Case-Control Study of Brain Tumors in Adults | **20** |
| Diet, Lifestyle, and Cancer in U.S. Special Populations | **21** |
| Geographic Based Research in Cancer Control and Epidemiology | **21** |
| Small Grants Program in Cancer Epidemiology | **21** |
| Fellowships in Cancer Epidemiology, Biostatistics, and Genetics | **21** |
| Exploratory Grants in Pediatric Brain Disorders: Integrating the Science | **22** |
| Mouse Models of Human Cancers Consortium | **22** |
| Tools for Insertional Mutagenesis in the Mouse | **22** |
| Zebrafish as an Animal Model for Development and Disease Research | **22** |
| Strategies for Germline Mutation of the Rat | **22** |
| Cancer Genome Anatomy Project | **22** |
| Genetic Annotation Initiative | **22** |
| Tumor Gene Index | **22** |
| Director's Challenge | **23** |
| Mammalian Gene Collection | **23** |
| Brain Molecular Anatomy Program | **23** |
| Molecular and Cellular Biology of Metastatic Tumor Cells | **23** |
| Cancer Genetics Network | **23** |
| Cooperative Human Tissue Network | **23** |
| Cancer Molecular Analysis Program | **23** |
| CNS Tumor Animal Experimental Therapeutics Core | **23** |
| Shared Pathology Informatics Network | **24** |
| Surveillance, Epidemiology, and End Results (SEER) Program | **24** |
| **New Activities** | |
| Neurological Disease Brain Banking Workshop | **24** |
| Workshop on Gene-Environmental Interactions in the Etiology of Childhood Cancer | **24** |
| Workshop under the auspices of the Mouse Models of Human Cancers Consortium | **24** |


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

| **Section 2**<br>**2-3 Improve Our Understanding of the Genetic and Environmental Factors Related to Brain Tumors. (*continued*)** | |
|---|---|
| **Proposed Strategies** | **Page** |
| Build a case-control consortium to support pooled or parallel analyses concerning genetic and environmental risk factors in case-control studies of brain tumors. Based on recently completed and ongoing studies, 2,000-3,000 cases and a similar number of controls are expected to be available for study. A series of this size would have far greater statistical power than any previous study to evaluate possible gene-gene and gene-environment interactions contributing to the development and progression of brain tumors.[b] | **24** |
| Conduct a SEER special study to collect data on benign brain tumors.[b] | **25** |
| Continue to support a pilot study by the Children's Oncology Group to evaluate the feasibility of establishing a childhood cancer research network that would create a national registry of children with cancer, including a tissue bank for tumor and blood specimens, for identifying environmental and other causes of childhood cancer. This initiative would build upon the unique national clinical trials system for treating children with cancer. NCI will evaluate the results of the pilot study in FY 2003 to determine if this strategy has merit for supporting etiological research for childhood cancers (including tumors of the CNS). A decision to support full implementation of the childhood cancer research network concept could be made late in FY 2003 or in FY 2004.[b] | **25** |

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

| **Section 2**<br>**2-4 Characterize Tumors at the Molecular Level to Aid in Diagnosis, Treatment Choice, and Treatment Monitoring** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Brain Tumor Genome Anatomy Project | **27** |
| Cancer Genome Anatomy Project | **27** |
| Director's Challenge | **27** |
| Innovative Technologies for the Molecular Analysis of Cancer | **27** |
| Applications of Innovative Technologies for the Molecular Analysis of Cancer | **27** |
| Translation of Technologies to Detect Alterations in Tumors | **27** |
| Gene Expression Profiling in the Nervous System | **27** |
| Development and Application of Imaging in Therapeutic Studies | **27** |
| Develop of Clinical Imaging Drugs and Enhancers | **27** |
| Development of Novel Imaging Technologies | **27** |
| Exploratory/Developmental Grants for Diagnostic Cancer Imaging | **27** |
| Cerebral Radiobiology and Neuroimaging of Brain Tumors | **28** |
| In Vivo Cellular and Molecular Imaging Centers | **28** |
| Phased Application Awards in Cancer Prognosis and Prediction | **28** |
| Exploratory Grants in Pediatric Brain Disorders: Integrating the Science | **28** |
| Stem Cell Plasticity in Hematopoetic and Non-Hemopoetic Tissue | **28** |
| Neuro-Oncology Models Forum | **28** |
| Mouse Models of Human Cancers Consortium | **28** |
| Small Animal Imaging Research Program | **28** |
| Glioma Marker Network | **29** |
| **New Activities** | |
| CNS/Brain Tumor Specialized Program of Research Excellence | **29** |
| **Proposed Strategies** | |
| Provide additional support for the Glioma Molecular Diagnostic Initiative, a prospective, publicly available database containing data (including corollary clinical data) from molecularly characterized glioma specimens for the purpose of establishing a useful molecular classification scheme for gliomas.[a] | **29** |
| Expand the Cancer Molecular Analysis Program (CMAP), which will enable researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. A Web site will provide access to molecular phenotypes that best fit a query and will offer information about clinical trials of molecularly targeted agents specific to the phenotypes. NCI will prototype this effort using data gleaned from the Glioma Molecular Diagnostic Initiative.[a] | **29** |

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

| **Section 2**<br>**2-5 Develop Novel Therapies and Improve Support for Clinical Trials.** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Adult Brain Tumor Consortium | **31** |
| Pediatric Brain Tumor Clinical Trials Consortium | **31** |
| Children's Oncology Group (Brain Tumor Committee) | **31** |
| Clinical Cancer Therapy Research | **31** |
| Quick Trials for Novel Cancer Therapies | **31** |
| Innovative Toxicology Models for Drug Evaluation | **32** |
| Rapid Access to Intervention Development Program | **32** |
| Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials | **32** |
| Exploratory Studies in Cancer Detection, Prognosis, and Prediction | **32** |
| Phased Application Awards in Cancer Prognosis and Prediction | **32** |
| Biomarkers and Clinical Endpoints in Pediatric Clinical Trials | **32** |
| Development and Application of Imaging in Therapeutic Studies | **32** |
| Hyperaccelerated Awards/Mechanisms in Immunomodulation Trials | **33** |
| Pilot Clinical Trial Grants for Neurological Diseases | **33** |
| CNS Barriers Initiative | **33** |
| Community Clinical Oncology Program | **33** |
| Gene Therapy for Neurological Disorders | **33** |
| Mouse Models of Human Cancers Consortium | **33** |
| **New Activities** | |
| CNS/Brain Tumor Specialized Program of Research Excellence | **33** |
| Cancer Therapy-Related Use of Genetically Engineered Mice | **33** |
| Integrate capacity for conducting immunotherapy trials into the Adult Brain Tumor Consortia | **34** |
| Renegotiate agreement between NCI and pharmaceutical companies to provide drugs for testing | **34** |


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

| **Section 2**<br>**2-5 Develop Novel Therapies and Improve Support for Clinical Trials. (*continued*)** | |
|---|---|
| **Proposed Strategies** | **Page** |
| Address the difficulty of obtaining access to investigational agents for clinical trials for children with brain tumors. NCI will collect data concerning recent pediatric group protocol applications (i.e., letters of intent) and agents for which applications were not submitted because of lack of access to the agent. Once the requisite data are collected, NCI will organize a workshop with relevant parties (e.g., researchers, pharmaceutical sponsors, the U.S. Food and Drug Administration, patient advocates) to identify factors limiting access to investigational agents and identify possible remedies. This effort will build on earlier NCI-sponsored meetings and NCI-negotiated agreements focused on improving access to investigational agents for *preclinical* testing.[d] | **34** |
| Add an imaging component (or link the imaging component of another center) to the Adult Brain Tumor Consortia so the Consortia may assist in identifying non-invasive imaging techniques that can determine if a novel agent is actually altering its intended target within the brain tumor. This component also will enable the consortia to assist in identifying imaging surrogates for tumor response.[b] | **34** |
| Develop and implement a plan for identifying and using preclinical models that can predict clinical activity of new agents against childhood cancers. In conformity with the Best Pharmaceuticals for Children Act, NCI (in FY 2002) will review the current capabilities of preclinical models to predict which therapies are likely to be effective for treating pediatric cancers (including brain cancers). A plan for using the models will be developed with input from the pediatric investigator community, and will require input from NCI's Developmental Therapeutics Program, the Cancer Therapy Evaluation Program, and Division of Cancer Biology (for mouse models of human cancers). Initial implementation of the plan could occur in FY 2003.[b] | **34** |

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

| **Section 2**<br>**2-6 Ensure that Brain Tumor Treatments are Safe and Effective** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Clinical Trial Cooperative Groups Program | **36** |
| Biomarkers and Clinical Endpoints in Pediatric Clinical Trials | **36** |
| Exploratory Grants in Pediatric Brain Disorders: Integrating the Science | **36** |
| CNS Tumor Animal Experimental Therapeutics Core | **36** |
| Childhood Cancer Survivor Study | **36** |
| Cancer Clinical Trials: A New National System | **36** |
| Cerebral Radiobiology and Neuroimaging of Brain Tumors | **36** |
| Development and Application of Imaging in Therapeutic Studies | **36** |
| American College of Radiology Imaging Network | **37** |
| Development of Clinical Imaging Drugs and Enhancers | **37** |
| Exploratory/Developmental Grants for Diagnostic Cancer Imaging | **37** |
| Development of Novel Imaging Technologies | **37** |
| Surveillance, Epidemiology, and End Results (SEER) Program | **37** |
| **Proposed Strategies** | |
| Sponsor additional studies of cognitive interventions to address treatment-induced deficits. This initiative could be undertaken through existing cooperative groups, consortia, and the brain tumor SPOREs.[a] | **38** |
| Revise the Common Toxicity Criteria (CTC) to allow for the capture and coding of information about the late effects of cancer therapy, including neurological sequelae of brain tumors and their therapy. The revised criteria will be developed collaboratively, under the leadership of NCI's Cancer Therapy Evaluation Program and outside groups, such as the Radiation Therapy Oncology Group, the Children's Oncology Group, and the American College of Surgeons Oncology Group. Enhancement of the CTC to include the grading of late effects of cancer therapy will facilitate systematic evaluations of the long-term effects of brain cancers and their treatment. In combination with the existing clinical trial resources of the Children's Oncology Group and the Pediatric Brain Tumor Consortium, the criteria may enable development of databases describing the long-term outcomes of children with brain tumors. Planning for revision of the CTC has begun, and a major workshop addressing the coding of late effects took place in April 2002. Project completion, including implementation of the Common Toxicity Version 3.0, is anticipated for FY 2004.[a] | **37** |
| In conjunction with the effort to revise the CTC, develop a standardized set of outcome measures (including measures of dementia) to be adapted to different tumor types, and develop long-term follow up measures of quality of life in pediatric patients. This could be accomplished through groups such as the Children's Oncology Group and the Pediatric Brain Tumor Consortium, perhaps with existing funds. NCI could host a conference to catalyze the effort.[a] | **37** |

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

| **Section 3**<br>**3-1 Improve models.** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Mouse Models of Human Cancers Consortium | **40** |
| Mouse Cancer Models Repository | **40** |
| EMice Web Site | **40** |
| Technologies to Improve the Utility of Animal Models | **40** |
| Innovative Technologies for the Molecular Analysis of Cancer | **40** |
| Small Animal Imaging Resources Program | **40** |
| **Proposed Strategies** | |
| Develop and implement a plan for identifying and using preclinical models that can predict clinical activity of new agents against childhood cancers. In conformity with the Best Pharmaceuticals for Children Act, NCI (in FY 2002) will review the current capabilities of preclinical models to predict which therapies are likely to be effective for treating pediatric cancers (including brain cancers). A plan for using the models will be developed with input from the pediatric investigator community, and will require input from NCI's Developmental Therapeutics Program, the Cancer Therapy Evaluation Program, and Division of Cancer Biology (for mouse models of human cancers). Initial implementation of the plan could occur in FY 2003.[b] | **41** |

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

| **Section 3**<br>**3-2 Improve Quality of and Access to Tissue Banks and Databases** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Cooperative Human Tissue Network | **43** |
| Clinical Trials Cooperative Groups Human Tissue Resources Program | **43** |
| AIDS and Cancer Specimen Bank | **43** |
| Tissue and Biological Fluid Banks of HIV-Related Malignancies | **43** |
| Specimen Resource Locator Web Site | **43** |
| NCI Tissue Expediter | **43** |
| NCI Research Resources Web Site | **43** |
| Shared Resources for Scientists Outside of NCI Cancer Centers | **43** |
| Improving DNA, RNA, and Protein Availability in Fixed Tissue | **43** |
| Shared Pathology Informatics Network | **43** |
| NCI Resources Development Web Site | **43** |
| **New Activities** | |
| Neurological Disease Brain Banking Workshop | **44** |
| **Proposed Strategies** | |
| Continue to support a pilot study by the Children's Oncology Group to evaluate the feasibility of establishing a childhood cancer research network that would create a national registry of children with cancer, including a tissue bank for tumor and blood specimens, for identifying environmental and other causes of childhood cancer. This initiative would build upon the unique national clinical trials system for treating children with cancer. NCI will evaluate the results of the pilot study in FY 2003 to determine if this strategy has merit for supporting etiological research for childhood cancers (including tumors of the CNS). A decision to support full implementation of the childhood cancer research network concept could be made late in FY 2003 or in FY 2004.[b] | **45** |
| Better promote available tissue resources through workshops, publications, and Web sites.[d] | **45** |
| Fund the proposed Tissue Resources for Cancer Research, which is designed to expand the range of NCI-funded specimen resources and cover all major tumor types. Only multi-institutional organizations or preformed consortia may apply, and they must be able to provide large numbers of cases (hundreds or thousands, depending on the research focus). The specimens must be made available to the research community, and the applicants must propose policies to ensure equitable access. [c] | **45** |

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

| **Section 3**<br>**3-3 Develop High-Throughput Screening Approaches to Further Understanding of Gene Function** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Tissue Array Research Program | **47** |
| Gene Expression Profiling in the Nervous System | **47** |
| Technologies for Gene Expression Analysis in the Nervous System | **47** |
| High-Throughput Analysis for Gene Expression Patterns in the Nervous System | **47** |
| Cancer Genome Anatomy Project | **47** |
| Innovative Technologies for the Molecular Analysis of Cancer | **47** |
| Translation of Technologies to Detect Alterations in Human Tumors | **47** |
| Innovations in Biomedical Information Science and Technology | **48** |
| National Programs of Excellence in Biomedical Computing | **48** |
| Exploratory Studies in Cancer Detection, Prognosis and Prediction | **48** |
| Phased Application Awards in Cancer Prognosis and Prediction | **48** |
| Molecular Targets Laboratories Program | **48** |
| Translational Proteomics Program | **48** |
| Center for Bioinformatics | **48** |
| Advanced Technology Center | **48** |
| **Proposed Strategies** | |
| Provide additional support for the Glioma Molecular Diagnostic Initiative, a prospective, publicly available database containing data (including corollary clinical data) from molecularly characterized glioma specimens for the purpose of establishing a useful molecular classification scheme for gliomas.[a] | **49** |
| Expand the Cancer Molecular Analysis Program (CMAP), which will enable researchers to identify and evaluate molecular targets in cancer through integration of basic and clinical cancer research programs. A Web site will provide access to molecular phenotypes that best fit a query and will offer information about clinical trials of molecularly targeted agents specific to the phenotypes. NCI will prototype this effort using data gleaned from the Glioma Molecular Diagnostic Initiative.[a] | **49** |

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

| **Section 3**<br>**3-4 Enhance Training Opportunities** | |
|---|---|
| **Ongoing Activities** | **Page** |
| Mentored Quantitative Research Career Development Award | **50** |
| Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences | **51** |
| Cancer Education Grant Program | **51** |
| National Research Service Award Institutional Research Training Program | **51** |
| Transition Career Development Award | **51** |
| NCI Scholars Program | **51** |
| **Proposed Strategies** | **51** |
| Review existing training programs to identify interdisciplinary research needs that are not covered adequately. [d] | **52** |


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