RESEARCH EDITION

Messageline

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PARTNERS IN YOUR FUTURE

*This issue of the Message*line *celebrates an unprecedented milestone in our history. We proudly announce the granting of $1.5 million dollars for brain tumor research. This extraordinary achievement occurred because of your support and your dedication.*

These studies will explore the beginnings of glioblastoma multiforme, anaplastic astrocytoma, oligodendroglioma, medulloblastoma, ependymoma, and primitive neuroectodermal tumors. ABTA researchers will look at both adult and pediatric tumors – their origin, why they continue to grow, and how that growth might be stopped. Understanding these processes will be the first step toward prevention. It is an exciting window of opportunity, for which we are all grateful.

We used to say the future lies in nanotechnology, proteomics, and genetic research. The future is now! We are very excited to be here; thank you for joining us.

Message*line*
VOLUME XXXI, NUMBER 2

Our Mission: The American Brain Tumor Association exists to eliminate brain tumors through research and to meet the needs of brain tumor patients and their families.

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dear ABTA Supporters

Our research programs thrive because of your generosity, and others like you who have chosen to support these programs.

If you or a loved one has a brain tumor, consider making a donation. Donations can be made for any occasion – birthdays, anniversaries, end-of-treatment celebrations, or to honor someone special in your life. If you've lost someone to a brain tumor, commemorate the difference they made in your life with a memorial donation.

You can mail a check or charge your gift by using the enclosed envelope. For more immediate giving, call 800-886-2282 with your charge information or make a secure donation online at *www.abta.org*.

Together, with your support, we will walk into a future without brain tumors.

Thank you.

John Hipchen
President
American Brain Tumor Association

RESEARCH BREAKTHROUGH!

The presence of a ribbon of astrocytes along the walls of the lateral ventricle of the normal adult human brain was recently identified by researchers at the University of California San Francisco (UCSF) and the Institute Cavanilles of Valencia, Spain. The study's author, Nader Sanai, MD, began working on this project as an American Brain Tumor Association Medical Student Summer Fellow. Now a neurosurgical resident and researcher at UCSF, his continued work in this area lead to this breakthrough finding. The results were published as the cover story in the science journal, *Nature.* The study discusses the role these astrocytes may play as stem cells, perhaps capable of regeneration or even tumorigenesis.

Dr. Sanai's initial research grant was made possible by a donation in memory of David B. Anderson. Over the years, his wife, Mrs. Anderson, provided support for eight Medical Student Summer Fellowships – this investment in brain tumor research has certainly been rewarded.

To learn more about the ways *your* family can work together to support brain tumor research, please call Valerie in the ABTA office at 847-827-9910.

definitions of Research Terms

angiogenesis – the growth of new blood vessels around a tumor. The tumor uses this blood supply to feed itself.

angiogenesis inhibition – purposeful interference with the growth of new blood vessels around a tumor. Manipulating the genes involved in angiogenesis may be a way of controlling tumor growth.

apoptosis – normal, timely cell death. Healthy cells live and die in a predictable pattern. This pattern keeps the number of cells in our body balanced. Abnormal cells lose the ability to sense these natural cues, and go on needlessly reproducing. The unneeded cells eventually form a tumor.

basic research – laboratory studies that explore the ways in which cells live, grow, and die. Basic research helps scientists discover and learn how brain tumors begin and what makes them grow.

glioma – any tumor that arises out of the "glial" or gluey/supportive tissue of the brain. Astrocytes, oligodendrocytes, ependymal cells, and microglia are all glial cells. Astrocytomas, oligodendrogliomas, and ependymomas are specific types of gliomas.

growth factors – nutrients, found normally in the body, that help cells grow. Two growth factors currently of interest to brain tumor researchers are VEGFR (vascular epithelial growth factor receptor), a growth factor involved in starting and stopping angiogenesis, and EGFR (epidermal growth factor receptor), found in very high quantities on most glioblastoma cells.

hypoxia – lack of oxygen. Oxygen makes a tumor sensitive to radiation; oxygen is also needed for basic cellular functions. Researchers are looking at the effect of angiogenesis on oxygen levels, studying ways to cause hypoxia thus triggering intentional cell death, and at the possibility of manipulating hypoxia-related genes.

karyotyping – a technique for generating a "list," or profile, of the genetic contents of a given piece of tissue.

invasiveness/tumor invasion – a tumor cell's ability to spread into the normal tissue around it. It is this characteristic that makes malignant brain tumors difficult to control.

laser capture microdissection – a new technique for examining tumor tissue. It allows specific cells to be removed from a sample of tissue for detailed study.

microglia – tiny "scavenger" glial cells, found normally in the brain, which play a role in the immune functions of the brain. The observation that microglia around a tumor appear to have their scavenger-abilities turned off is of interest to researchers working with the immune system.

mouse model – a mouse breed genetically engineered to be missing particular genes. These mouse models are the closest science can come to duplicating the human tumor environment. A "spontaneous" mouse model is one engineered to eventually grow a brain tumor without any tumor cells being introduced into its body. This is done by altering genes in the breed.

p16, p53, etc. – the "p" preceding a number indicates this is a gene. Both p16 and p53 are two (of many) genes known to be altered in brain tumors. Studies underway are looking for abnormal genes, measuring the substances given off by those genes, looking at the impact of gene by-products on the patient's future; and studying the ways abnormal genes interact with the genes and proteins around them. Still, other studies explore the possibility of repairing abnormal genes via gene therapies.

signaling pathways – the molecular steps preceding and following an action by any gene or gene by-product. Several of our proposals explore the signaling pathways of proteins or enzymes found in elevated quantities in brain tumors. These studies look at "what came before" and "what happens after" the release of these substances.

stem cells – new cells capable of developing into one of a variety of different types of cells. Stem cells are of interest because they may be able to be "tweaked" into becoming a desired cell type, for their ability to replace injured cells, for their potential to grow into tumor cells, and for their potential therapeutic use.

translational research – studies that provide the bridge between basic research and human testing. Translational research provides the data to support the opening of a clinical trial, or it may provide additional scientific evidence as to how a substance in clinical trial works.

2004 Research *Programs*

ABOUT THE ABTA RESEARCH PROGRAMS

ANSWERS ARE FOUND IN RESEARCH

The American Brain Tumor Association is a leader in providing funding for innovative research that lays the groundwork upon which clinical studies are built. We are proud to have supported the career development of many current leaders in neuro-oncology, and look kindly upon the growing family of ABTA researchers.

If you wish to support and encourage these programs, please call us at 847-827-9910. If you are a researcher interested in learning more about any of these programs, contact our office via e-mail: *info@abta.org*. Working together, we will learn what causes brain tumors and how to cure them.

BASIC RESEARCH FELLOWSHIP AWARDS

The intent of the ABTA Fellowship program is to encourage talented scientists early in their careers to enter, or remain in, the field of brain tumor research. These awards help ensure a continuum of dedicated, well-trained brain tumor researchers. ABTA Fellowships are $70,000 awards payable over a two-year period. Criteria for selection include the quality of the individual applicant; the quality of the training program; and the research work being undertaken.

Supported by the 2004-2005 ABTA Fellowship funding period are:

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Applications for the 2005 awards are available from the ABTA office at 847-827-9910, with completed applications and all attachments due January 6, 2005.

TRANSLATIONAL RESEARCH AWARDS

The intent of these $50,000 one-year awards is to develop important research studies so they may move from the "bench" to the "bedside." Applications are reviewed by the Association's distinguished Scientific Advisory Council for research and researcher quality. Awards are determined by ABTA's Board of Directors based upon the Advisors' recommendations.

Applications for the next funding period are available from the ABTA office at 847- 827-9910.

Recipients of 2004-2005 ABTA Translational Research Grant funding are:

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Veteran's Administration
Medical Center
Los Angeles, CA

Amy Heimberger, MD
University of Texas
MD Anderson Cancer Center
Houston, TX

Jennifer Nelms, PhD
Brain Tumor Institute
Cleveland Clinic Foundation
Cleveland, OH

Khalid Shah, PhD
Massachusetts General Hospital
and Harvard Medical School
Charlestown, MA

Qian Xie, PhD
Van Andel Research Institute
Grand Rapids, MI

MEDICAL STUDENT AWARDS

Medical Student Summer Fellowships are intended to plant the seeds of neuro-oncology interest in bright, talented students. Mentors select appropriate students to receive the Fellowship. These are $2,500 Awards and the most outstanding student report receives the Lucien J. Rubinstein Memorial Award which provides an additional $1000, plus distinction. Interested mentors should contact the ABTA office.

If you are interested in mentoring a student, please e-mail us at info@abta.org.

Participants in the 2004 Summer Fellowship Program are:

MENTORS: Eric Bremer, PhD and Jeffrey Raizer, MD
STUDENT: Jessica Mellinger
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Chicago, IL
In memory of Stephanie Kramer

MENTOR: Jeffrey Bruce, MD
STUDENT: Richard Lochhead
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MENTOR: Howard L. Weiner, MD
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New York University School of Medicine
New York, NY
In memory of Bradley Benton Davis

PROJECT GRANT AWARDS

In keeping with our philosophy of flexibility to assure that the best research and the brightest researchers are funded, we instituted an additional grant program. The intent of this award is to provide up to $50,000 for one year for an exceptional research project if the investigator is just out of range for our other awards. As with our other grants, the work must be done at a recognized laboratory within the United States or Canada.

Recipients of 2004-2005 ABTA Project Grants are:

John Floyd, MD
Vanderbilt University
Nashville, TN

Corinne Grigeur, PhD
University of Alabama
Birmingham, AL

Continued on *page 6*

Continued from *page 5*

YOUNG INVESTIGATOR GRANTS

We offer three awards in recognition of achievement by young investigators. The awards are administered through the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) Joint Section on Tumors, as well as the Society for Neuro-Oncology. These professional society awards commend outstanding researchers for their contribution to the field of brain tumor research.

The Joint Section on Tumors of the AANS and the CNS recognizes research performed by outstanding young investigators. This year's AANS award was given to Makoto Furuta, MD. Dr. Furuta's award-winning research was titled *Protein Patterns and Proteins That Identify Subtypes of Glioblastoma Multiforme* and was presented at the AANS annual meeting. The recipient of the CNS award was Qingze Wu, MD. His award winning presentation was *Local Release of Carboplatin via an Alzet Mini-osmotic Pump Prolongs Survival in Rat Brainstem Tumor Model,* and was given at the CNS annual meeting.

Stacey Ivanchuk, MSc (right) receives the ABTA/Society for Neuro-Oncology Award for Excellence in Basic Research from Mary Ellen Maher, MSN, Board member of the American Brain Tumor Association

The Society for Neuro-Oncology Award is for Excellence in Basic Research – this grant was given to Stacey Ivanchuk, MSc, The Hospital for Sick Children in Toronto, Ontario, Canada for her research titled *Characterization of an Interaction between p14ARF and Transcription Termination Factor-1 (TTF-1).*

EPIDEMIOLOGY RESEARCH AWARD

Given through the Society for Neuro-Oncology, this award recognizes contributions in the area of brain tumor epidemiology. This year's award was given to Edward Shaw, MD, Wake Forest Baptist Memorial Hospital, Wake Forest, North Carolina, for his research: *Ethnic Differences in Survival of Glioblastoma: a Secondary Analysis of the Radiation Therapy Oncology Group Recursive Partitioning Analysis Database.* To apply for this year's award, contact the Society at 713-745-2264 or *www.soc-neuro-onc.org.*

NEURO-ONCOLOGY NURSING RESEARCH GRANT

Quality of life, the impact of treatment on patients and their families, documenting outcomes and educational needs are all issues addressed by nurse researchers. We are proud to offer support with an annual neuro-oncology nursing research award through the Oncology Nursing Foundation of the Oncology Nursing Society. Nurses interested in applying for this $10,000 award should contact the Oncology Nursing Society at 866-257-4667.

The recipient of this year's award is Deborah Allen, RN, MSN, APRN, BC, a nurse practitioner at Duke University Medical Center in Durham, North Carolina. Ms. Allen's research is titled *Depression and Quality of Life in Patients With Glioma.*

The nurse members of the Neuro-Oncology Special Interest Group (SIG) at the Oncology Nursing Society invite you to learn more about this rapidly growing group. If you are a nurse caring for brain tumor patients in any way, and would like to become involved, please e-mail Shirley Entis at entissa@moffitt.usf.edu and introduce yourself!

COURSE ON MOLECULAR MECHANISMS IN BRAIN TUMORS

Supported by the American Brain Tumor Association in conjunction with the UTMD Anderson Cancer Center, the course is targeted to clinicians wishing to build their knowledge of molecular biology as related to brain tumors. Training is offered in molecular signaling mechanisms, neural stem cells, mouse models, genomics, imaging techniques, transgenic and knock-out mouse techniques, biobanks, and mechanism-based therapeutic strategies. Contact the facilitator, Sadhan Majumder, PhD, at majumder@mdanderson.org.

2004-2006 Basic Research *Fellowships*

This year, we are proud to announce *thirteen* new ABTA Post-Doctoral Research Fellowship Awards. We warmly welcome these bright leaders into the neuro-oncology community, and into the ever-growing ABTA family of researchers.

IDENTIFICATION OF NOVEL MOLECULAR THERAPEUTIC MARKERS IN GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme, one of the most aggressive brain tumors, represents up to 30% of all primary glial brain tumors. Like other major human tumors, glioblastoma is likely to result from a series of genetic alterations that initiate it and drive its progression. Two types of glioblastomas have been described in accordance to biological and clinical phenotypes. *De novo* primary glioblastoma account for the vast majority of cases in those 55 years of age and older. *Secondary* glioblastoma typically develop in younger patients, less than 45 years of age, through tumor progression from low grade astrocytomas. Both types of glioblastoma evolve through different genetic pathways, and result from multiple genetic factors.

Analysis of those genetic changes unique to glioblastoma will likely reveal potential novel molecular tumor markers. Unfortunately, very few markers have been identified for clinically useful therapies; therefore, the identification of novel tumor markers or antigens may have enormous clinical potential. We plan to use digital karyotyping, a recently developed state-of-the-art technology, to systematically analyze the genetic background of glioblastoma cells at a very high resolution to reveal the pathogenic basis of this disease and identify novel therapeutic targets. We believe that this technique will help reveal new cancer-causing genes that may be major contributors to glioblastoma multiforme.

David Cory Adamson MD, PhD
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In memory of Marie Becker

RESEARCH APPLICABLE TO
Glioblastoma multiforme (astrocytoma grade IV)

American Brain Tumor Association

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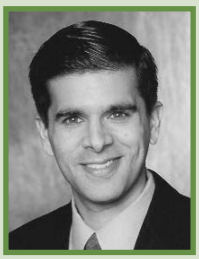
2004-2006 Basic Research *Fellowships*



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RESEARCH APPLICABLE TO
Glioblastoma multiforme
(astrocytoma grade IV)

ROLE OF ONCOGENE EXPRESSION OR TUMOR SUPPRESSOR MUTATIONS IN THE ABILITY OF MITOTIC AND ARRESTED GLIAL OR GLIOMA CELLS TO SUPPORT ONCOLYTIC HSV VECTOR REPLICATION

Although much of their molecular pathogenesis is understood, treatment for glioblastoma multiforme remains a challenge. The infiltrating nature of this tumor, along with the low number of cells replicating at any given time, limits the success of current therapies. This research will focus on developing a gene therapy that may be effective regardless of the replication status of the tumor cells.

Herpes simplex virus (HSV), genetically modified by deleting viral ribonucleotide reductase (RR), has been effective in experimental brain tumor models and presumably replicates only in dividing cells. If RR-HSV vectors only replicate in the small percentage of glioma cells replicating at the time of their inoculation, HSV glioma gene therapy would fail for the same reasons as most chemotherapies fail. However, we have shown that mitotically arrested glioma cells and arrested fetal astrocytes, deleted in tumor suppressor genes $p16^{INK4a}$ or p53, support RR-HSV vector replication. We propose to expand upon this data and determine if mutations in tumor suppressor genes $p16^{INK4a}$, $p19^{ARF}$, PTEN, p53, or oncogene EGFR allow infection of arrested astrocytes by RR-HSV vectors, and if such effects may be due to cell cycle-independent induction of mammalian RR in tumor cells. Identification of the factors promoting RR-HSV vector infection of arrested glioma cells will enable prediction of which glioma types may respond best to RR-HSV vector gene therapy.

Juan Arevalo, PhD
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New York, New York

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In memory of
Laurie Deierlein

RESEARCH APPLICABLE TO
Glioma

ROLE OF NEUROTROPHINS IN BRAIN CANCER

Approximately 50% of brain tumors are gliomas – tumors that arise out of the supportive, or "glial," tissue of the brain. Astrocytomas (pilocytic astrocytoma, low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme) account for the majority of gliomas.

Neurotrophins are small growth factors that play an important role in the development of the normal nervous system. They have also been implicated in pathological conditions, such as development of neuroblastoma and medulloblastoma brain tumors. However, the signaling pathways and mechanisms activated by neurotrophins, and their role in the development of gliomas, are not completely understood.

Our lab has identified a new substrate for neurotrophin receptors called ARMS (Ankyrin-Rich Membrane Spanning), which seems to be found in glioblastomas, but not in low-grade gliomas. We hypothesize that ARMS might be a marker of tumor progression and might participate in glial tumorigenesis. To explore this possibility we will investigate whether neurotrophins are involved with glial tumor formation. We will either overexpress or "knock-down" ARMS expression in these cells to analyze the effect upon cell growth and movement. We will also try to generate a glioma mouse model expressing ARMS, which may help us develop more effective treatments for these brain tumors.

MOLECULAR PATHOLOGICAL EXPRESSION PROFILING OF MALIGNANT GLIOMA CELLULAR INVASION

One of the key features of "diffuse" gliomas is local invasion. This invasive behavior causes difficulties in developing curative treatments. Given that cellular invasion is an essential component of malignant tumor behavior, it is likely that a better understanding of the mechanisms of tumor invasion will contribute to the development of novel and improved therapeutic strategies for patients with these tumors. We propose to use a technique called "laser capture microdissection" to micro-dissect tumor cells moving into surrounding normal brain as well as cells located at the "centers" of glioblastomas. RNA would be extracted from these cells and a profile of the growth factors and proteins released by these tumors will be created.

The RNA from these cells will be linearly amplified and hybridized to Affymetrix oligonucleotide chips. Those genes differentially expressed in invading cells would then be used for further analysis in a large series of gliomas. To test the hypothesis that gliomas with higher expression of invasion-related molecules are less amenable to current therapies, and will thus follow a more aggressive course, the expression results will then be correlated with patient survival. In the long run, identification of molecules involved in glioma invasion will likely contribute to the development of targeted therapies for people diagnosed with glioma.

Shumin Dong, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

SPONSOR
David Louis, MD

AWARD
In memory of George Kamberos

RESEARCH APPLICABLE TO
Glioblastoma multiforme (astrocytoma grade IV)

"SIGNAL-SMART" ONCOLYTIC VIRUS THERAPY FOR MALIGNANT GLIOMA

A balance between growth stimulatory and inhibitory signals is needed to provide the cell with appropriate capabilities for proliferation. Development of brain tumors, such as glioblastoma, is the result of a deregulation in such signaling. For example, a biochemical cascade called "Ras signaling" and its related molecules such as extracellular-signal-regulated kinase (Erk) induce proliferation in many cells such as glioma cells. Since the activity of the Ras pathway is significantly increased in glioma cells (as compared with normal cells), it seems logical that this characteristic could be used as a way to attack these cells.

This study explores the possibility of designing a mutant version of herpes simplex virus-1 (HSV-1) in a way that its replication would be restricted to cells with over-activity of Ras/Erk. To achieve this, the mutant herpes simplex virus will be genetically modified to be controlled by the Erk-pathway. Through this pathway the mutant-HSV-1 will be "switched-on" in glioma cells, leading to their destruction. The rationale for designing such virus is strengthened by the results of our studies proving that HSV-1, even without any genetic modifications, shows preference toward infecting cells with over-activity in Ras/Erk. However, the development of a "Signal-smart" virus, which responds to Erk-over-activity, should provide us with a more specific tool. Once the mutant is designed, its efficiency and specificity in attacking glioma cells will be tested by assaying for its replication in glioma cells in vitro and in laboratory models.

Faris Farassati, PhD, PharmD
Mayo Clinic
Rochester, Minnesota

SPONSOR
Corey Raffel, MD,PhD

AWARD
In honor of Kyle S. Minor, Jr.

RESEARCH APPLICABLE TO
Glioma

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In memory of Paul Brazen

RESEARCH APPLICABLE TO
Glioma
Astrocytoma

INVESTIGATING THE RELATIONSHIP BETWEEN NEURAL STEM CELLS AND BRAIN TUMORS

Gliomas are the most common brain tumors in adults, and brain tumors are the leading cause of solid tumor death in children. Gliomas are made of cells that have become immortal. These cells can divide extensively in an uncontrolled manner because they have mutations in genes that normally regulate cell proliferation and survival. It is not clear which cells in the brain acquire the mutations that allow them to form tumors, however, tumor cells share some characteristics with neural stem cells. Neural stem cells persist over a lifetime, so they are very long lived, and have the ability to divide extensively – but in a tightly controlled manner. An area of the brain, called the subventricular zone (SVZ), may hold the largest source of stem cells in the brain. Investigating the cells found in the SVZ is the focus of this study.

Why do tumor cells act like "out of control" stem cells? Do tumors arise from mutated stem cells, or do they appropriate the mechanisms of long-term survival and division normally used by stem cells? Many of the genes that are mutated in gliomas are known. Therefore, by mutating these genes in neural stem cells, we will determine if these cells can give rise to tumors. We will also mutate the same genes in other non-dividing brain cells to determine whether or not the stem cells have some predisposition to tumor formation. Finally, we will study the function of these commonly mutated genes in normal stem cells in an effort to better understand how tumor cells differ from the normal cells from which they arise.

Yvonne Kew, MD, PhD
UTMD Anderson
Cancer Center
Houston, Texas

SPONSOR
Timothy McDonnell, MD, PhD

AWARD
In memory of Justin Porter

RESEARCH APPLICABLE TO
Malignant glioma
Glioblastoma multiforme
(astrocytoma grade IV)

THE CONTRIBUTION OF PLEIOTROPHIN SIGNALING TO THE PROGRESSION AND THERAPEUTIC RESISTANCE OF MALIGNANT GLIOMA

In this study, we will learn the experimental approaches to studying the mechanisms of cell signaling, which are vital in the development of gliomas and in the local spread of lower grade and higher grade gliomas. We plan to develop innovative approaches that improve our understanding of the mutual interaction of glioma cells and their neighboring glial cells and neurons. We believe the mechanism of tumor dispersion, or invasion, differs between lower grade tumors and higher grade. Our preliminary research indicates that tumor cells expressing a growth factor called EGFRvIII show more malignant behavior and have markedly elevated levels of two proteins: pleiotrophin (PTN) and its receptor, anaplastic lymphoma kinase (ALK).

We will test the hypothesis that the PTN signaling pathway is important in conferring the malignant phenotype of GBM. Our experimental approaches will 1) define the mechanism of PTN upregulation associated with EGFR signaling in malignant glioma cells; 2) establish the functional role of PTN in tumor invasion and resistance to therapeutic cell death induction; 3) study the PTN/ALK and EGF/EGFR signaling pathways in glioblastoma. Our goal is to provide important new information regarding the molecular contributors to glioblastoma which can be applied to developing mechanism-based therapies.

GENERATION AND TREATMENT OF MOUSE MODELS FOR MALIGNANT GLIOMAS

Although several mouse models for well-developed glioma have been reported, there are no mouse models in which glioma generation and progression can be tracked down. Most of the models seem to be of well-developed high-grade tumors. Recently, Dr. Parada's lab created a mouse model for malignant gliomas by conditionally inactivating *Nf1* tumor suppressor in p53 null background. The *hGfap-cre; Nf1*$^{f/f}$*; p53*$^{-/-}$ mice developed from low-grade to high-grade gliomas with a complete penetrance. Histopathologically, these tumors mimicked human malignant gliomas.

In this proposal, we plan to easily visualize and trace the tumor cells by introducing a *Rosa26-GFP* allele into the *hGfap-cre; Nf1*$^{f/f}$*; p53*$^{-1-}$ mice. To see if PTEN inactivation is required for glioma progression, we will also introduce PTEN-deficiency into the mouse model. To chase the origin of gliomas, we will cross the *Nf1*$^{f/f}$*; p53*$^{-1-}$*Rosa26-GFP* mice with cre mice specific for either neural stem cells or mature glia. The second aim of this research is to evaluate several translational drugs for human gliomas by treating the mouse models. Experimental results from this study would provide insights into glioma genesis, its progression into malignancy, and its origin cell type(s). The results of translational study can be directly used for clinical settings.

Chang Hyuk Kwon, PhD
University of Texas Southwestern
Dallas, Texas

SPONSOR
Luis Parada, PhD

AWARD
In memory of Daniel J. Martinelli

RESEARCH APPLICABLE TO
Malignant glioma

INVOLVEMENT OF S1P RECEPTOR SUBTYPE-SPECIFIC RHO GTPASE SIGNALING IN HUMAN GLIOMA CELL PROLIFERATION AND MIGRATION

Little is known about the transformation of normal astroctyes, star-shaped cells found only in the brain and spine, into astrocytomas. Sphingosine-1-phosphate (S1P) is a compound formed in the brain in response to inflammation. S1P acts on specific cell surface receptors and activates Rho proteins. This research will help us understand more about how S1P influences astrocytoma growth and invasion.

We hypothesize that changing the ratio of S1P receptor subtypes would affect normal cell growth and migration and could thus contribute to invasion and uncontrolled proliferation. To determine whether normal astrocytic behavior can be altered by activation of, or deletion of, specific S1P receptor subtypes, we will examine proliferation and migration in astrocytes from mice lacking specific S1P receptor subtypes.

We also expect that specific patterns of Rho protein activation are part of astrocytic growth and invasion. S1P-Rho signaling will be correlated with invasiveness in human glioma cell lines. Information obtained about this growth and invasion process should provide potential new therapeutic targets to treat malignant astrocytomas.

Julie Radeff-Huang, PhD
University of California, San Diego
San Diego, California

SPONSOR
Joan Heller Brown, PhD

AWARD
In memory of Paul Fabbri

RESEARCH APPLICABLE TO
Astrocytoma
Malignant astrocytoma

2004-2006 Basic Research *Fellowships*

Yufang Shao, PhD
Memorial Sloan Kettering Cancer Center
New York, New York

SPONSOR
Xuejun Jiang, PhD

AWARD
In memory of Tiffany Townsend Daniels

RESEARCH APPLICABLE TO
Glioblastoma multiforme (astrocytoma grade IV)

IDENTIFICATION AND CHARACTERIZATION OF THE MOLECULAR BASIS OF APOPTOSIS DEFICIENCIES IN GLIOBLASTOMAS

It has been well documented that glioblastomas are resistant to many types of chemotherapy. Such pathological drug resistance could result in part from the development of resistance to apoptosis, or programmed cell death – a process that occurs in many types of cancer. The molecular mechanisms allowing tumor cell evasion of apoptosis remains elusive, and is the focus of this study.

We propose to identify potential abnormal components in apoptosis in glioblastoma. Apoptosis is a tightly regulated cellular process controlled by an orchestra of molecular players, among which are capsases, whose activation triggers apoptosis. Our preliminary data demonstrates that there is deficiency in the dATP apoptosis pathway in some glioblastoma cells. This deficiency may be corrected by components from another cell line, called HeLa cells. Thus, we plan to purify the rescuer(s) from HeLa cells using protein purification and expression cloning methods. The purified rescuers will be identified and characterized in all known glioma cell lines to explore whether the identified deficient player is a general phenomenon for all gliomas. The results of this research may provide a novel molecular basis for drug target for this form of brain tumor.

Sheila Singh, MD
The Hospital for Sick Children
Toronto, Canada

SPONSOR
Peter Dirks, MD, PhD

RESEARCH APPLICABLE TO
Medulloblastoma
Glioblastoma multiforme (astrocytoma grade IV)

ISOLATION AND CHARACTERIZATION OF A CANCER STEM CELL FROM HUMAN BRAIN TUMORS

In malignancies such as leukemia, multiple myeloma, and recently breast cancer, rare cells with remarkable potential for self-renewal have been isolated. These cells alone were found capable of driving the formation and growth of tumors. We recently discovered an abnormal stem cell that may drive the formation of brain tumors.

These tumor stem cells are rare, representing only a small fraction of the whole tumor, but these cells alone may be entirely responsible for continued tumor growth. Thus, therapies that focus on killing the tumor stem cell may provide better treatment and prognosis for patients with brain tumors. Our previous work represents the first isolation of cancer stem cells from the central nervous system. Our next goal in characterization of these brain tumor stem cells (BTSC) is to answer the following question: is the BTSC capable of initiating and maintaining a tumor when injected into a host? We will use a mouse model to test the capacity, potency and efficiency of the BTSC in brain tumor formation as a necessary validation of our previous findings. We will continue to study potential cell surface markers of the BTSC, and apply novel technology to explore the gene expression profile of the BTSC. In the future, these genes might then be targeted for therapeutic intervention.

SAHA AND 13-CIS RETINOIC ACID IN MEDULLOBLASTOMA

Suberoylanilide hydroxamic acid (SAHA) is a histone deacetylase inhibitor with efficacy in treating a variety of solid tumors in laboratory studies, but it has not been studied in medulloblastoma. Preliminary work in our laboratory indicates that SAHA is very effective against medulloblastoma, and other data suggests it has few side effects in humans. Retinoic acid (RA) has been shown to be very effective in causing cell death in medulloblastoma. We propose to combine SAHA with RA to improve the effectiveness of each drug, providing a better treatment for medulloblastoma. This study will look at whether or not these two agents will work together to enhance each other's effects. If successful in the lab, this study will lead to a clinical trial in children.

RA (a ligand) binds to the RA receptor forming a complex. This complex binds DNA, causing increased production of a gene product, BMP2, starting a cascade of events towards cell death. SAHA presumably allows DNA to relax, making gene promoters more accessible for ligand-receptor complexes to bind. This improved access increases transcription of gene products. An additional goal of this study is to determine whether SAHA improves RA's effectiveness by increasing access to the BMP2 gene promoter. Once the mechanism of action of SAHA is known, it can be exploited to treat medulloblastoma even more effectively.

Susan Spiller, MD
Fred Hutchinson Cancer Research Center
Seattle, Washington

SPONSOR
James Olson, MD, PhD

AWARD
Emily Dorfman Foundation for Children

RESEARCH APPLICABLE TO
Medulloblastoma

THE BRAIN EXTRACELLULAR MATRIX AS A TARGET IN BRAIN TUMOR THERAPY

Gliomas are brain tumors characterized by their ability to invade surrounding brain tissue. Understanding the mechanisms and molecules involved in glioma invasion is essential to designing new therapies.

Our previous work demonstrated that a brain-specific protein named BEHAB/brevican (B/b) may mediate the invasive ability of gliomas. Preliminary evidence of a novel variant of human B/b, $hB/b_{\Delta g}$ appears to show exclusive expression in glial tumors, suggesting a unique role for this variant in glioma progression. We propose to further elucidate the mechanisms of glioma invasion and to develop therapeutic strategies based on this glioma-specific variant.

Our first aim is to characterize $hB/b_{\Delta g}$ and determine the alterations in the protein structure that make it different from normal hB/b. Our second aim is to determine whether cells that express B/b on their surface can be selectively targeted by anti-B/b antibodies coupled to toxins. The final objective is to generate antibodies for the exclusive detection of the $_{hB/b\Delta g}$ variant. Our goal is to design novel glioma therapies tailored selectively to the cells expressing this unique B/b variant on their surface.

Mariano Viapiano, PhD
Yale University School of Medicine
New Haven, Connecticut

SPONSOR
Susan Hockfield, PhD

AWARD
Butler Family Foundation

RESEARCH APPLICABLE TO
Malignant gliomas

*dear*Researcher

The American Brain Tumor Association (ABTA) is seeking outstanding young researchers conducting quality brain tumor research. Additionally, we are interested in receiving innovative research proposals – those that incorporate new or original concepts.

While we recognize the importance of, and are committed to fostering the training of young, talented investigators in neuro-oncology, we are willing to divert some of our research funds for innovative research that has the potential to make a difference.

We are pleased to offer two types of American Brain Tumor Award Applications.

I. An ABTA **Fellowship** is a $70,000 two-year award for basic brain tumor research. The Fellowship is intended to provide salary support of $60,000 to a post-doctorate who has demonstrated the motivation and potential to conduct this research. The remaining $10,000 is to be expended at the discretion of the researcher for equipment/supplies or travel to an appropriate meeting, including a trip to Chicago, to present research results.

II. An ABTA **Translational Research Grant** is a one-year $50,000 award for neuro-oncology research. Translational is defined as pre-clinical research intended to evaluate the therapeutic potential of recent discoveries in the basic mechanisms of either brain tumor pathogenesis or experimental therapeutics. The grant funds can be expended for salaries or supplies, but must include a trip to Chicago to present research results.

The deadline for completed applications, *including all attachments* is January 6, 2005. Awards will be announced by April 1st for research work to commence July 1, 2005.

For criteria and applications, please e-mail *Linda@abta.org* or call 847-827-9910.

TIPS FOR WORKPLACE GIVING

Just a few short months from now, many giving campaigns will be underway in your workplace. United Way, Combined Federal Campaign, municipal solicitations…with so many choices, you may be confused about how to select the right organization for your donation. Below are a few reminders about the American Brain Tumor Association.

- We keep our overhead costs low, stretching your donated dollars further toward our goal of eliminating brain tumors.
- In fact, our Board of Directors just approved our largest sum ever for brain tumor research – $1.5 million for the upcoming fiscal year.
- Our education and support services reach thousands of patients and families each year. To learn more about our programs and services, please visit our website at www.abta.org.

As you make your donation selection, please remember:

- Review your campaign materials closely for the correct identification number – you may find us listed as **Brain Tumor Association, American (ABTA).**
- Give generously! Since we receive no government support, our research and patient service programs rely on your contributions.
- Call us at 847- 827-9910 if you have any questions about workplace giving.

Thank you for supporting the American Brain Tumor Association!

2004-2005 Translational *Grants*

Five $50,000 translational grants were awarded to help these researchers move their studies from the laboratory to the patient. These studies are the crucial steps needed before testing a new treatment in human beings. We applaud their years of diligent study, and the dedication that moved their work closer to the people living with this diagnosis.

EVALUATION OF GSK-3ß AND P38 MAP KINASE INHIBITORS IN PTEN-EXPRESSING GLIOBLASTOMAS

MTOR inhibitors, such as rapamycin and its variant CCI-779, are novel drugs with exciting and impressive antitumor activity in preclinical studies. These chemotherapeutic agents are currently in clinical trials to treat glioblastoma multiforme, the most common form of astrocytic tumors affecting adults today. Unfortunately, as with most chemotherapeutic agents, a subset of patients may be resistant to MTOR inhibitor therapy. It would thus be critical to discover the molecular mechanisms that regulate sensitivity of tumor cells to these agents so that individuals who might benefit can be easily identified.

Studies confirm a central role for the cell signaling protein molecule AKT in this regulation of sensitivity in glioblastomas and implicate the uncontrolled activation of AKT signaling in the tumor formation process. This proposal evaluates the ability of two targeted kinase inhibitors to interfere with the ability of PTEN-expressing glioblastomas to resist MTOR inhibition. We hope to evaluate the use of these inhibitors, and to develop a method of pre-determining PTEN status to define which people with glioblastomas may be sensitive to MTOR inhibitors and which will not respond. This biomarker information may then be used to help select appropriate therapies.

Joseph Gera, PhD
University of California,
Los Angeles
VA Medical Center
Los Angeles, California

AWARD
In memory of Bud Marvel

RESEARCH APPLICABLE TO
Glioblastoma multiforme
(astrocytoma grade IV)

Amy Heimberger, MD
University of Texas
MD Anderson Cancer Center
Houston, Texas

AWARD
In memory of Shawn Hansen

RESEARCH APPLICABLE TO
Unresectable astrocytoma
Glioblastoma multiforme
(astrocytoma grade IV)

GLIOMA INFILTRATING MICROGLIA: PHENOTYPIC AND FUNCTIONAL CHARACTERIZATION

Microglia are immune cells that reside within the central nervous system (CNS). Laboratory studies and cultured cell lines have shown that these cells do not function properly in brain tumors; however, no functional or phenotypic immunological data has been accumulated on microglia derived directly from human gliomas. There is clinical evidence that the systemic immune system has anti-glioma activity. However, this fails to eradicate or suppress the growth of malignant gliomas. The emerging evidence is highly suggestive that the immunological failure is within the intratumoral compartment.

The purpose of this project is to characterize the functional capabilities, or the lack thereof, of microglia and to investigate modulation techniques to improve the immunological responses against malignant gliomas. Microglia have distinct advantages compared to systemic immunological responses because of their proximity to CNS tumors and their ability to mediate antibody-dependent cellular cytotoxicity, which has been shown to be effective against CNS tumors. By investigating ways to optimize microglia immunological function directed against malignant gliomas, appropriate immunotherapy paradigms can be developed and/or existing immunotherapies improved. Furthermore, microglia could be developed for the delivery of agents to the CNS. Finally, although conventional chemotherapy is immunosuppressive, it may be therapeutically synergistic with the CNS-sequestered microglia in a combined therapy paradigm.

Jennifer Nelms, PhD
Brain Tumor Institute
Cleveland Clinic Foundation
Cleveland, Ohio

AWARD
In honor of Danielle O'Brien

RESEARCH APPLICABLE TO
Glioblastoma multiforme
(astrocytoma grade IV)

INVESTIGATION OF RATIONAL COMBINATIONS OF SIGNAL TRANSDUCTION INHIBITION IN MALIGNANT GLIOMAS

A recently implemented strategy in the treatment of glioblastoma is to specifically target and inhibit molecules within the signaling pathways that help tumor cells grow. This strategy has been used both in the laboratory and clinic, but no single agent has proven to have more durable efficacy than conventional therapies. We hypothesize that targeting multiple signal sites may be a more effective method of blocking cancer cell signaling.

This proposal focuses on the use of combinations of targeted agents in order to produce synergistic tumor inhibition. We will treat tumor cells grown in culture with combinations of targeted agents and monitor their growth over time. These drugs will be added, either at the same time or one after the other, in order to find the best treatment conditions. Additionally, we will examine the drug effects on different pathways by analyzing the signaling molecules. Our goal will be to determine the effective doses and combinations of the drugs necessary to maximize the therapeutic effect.

The second part of this proposal will examine drug combinations in a brain tumor model. Tumor growth following drug treatment will be monitored by magnetic resonance imaging, the same technique used clinically in patients. Together, these studies will determine whether combining drugs in order to target multiple parts of essential cancer cell growth pathways will be an effective treatment strategy, and if so, how best to implement the strategy in initial clinical trials.

ENHANCED ERADICATION OF GLIOMAS BY MIGRATING STEM CELLS EXPRESSING REGULATABLE COLLAGENASE AND TUMOR-SPECIFIC NOVEL SECRETED PROTEIN

The pressing needs in effective gene therapy for brain tumors remain an expanded range of therapeutic gene delivery and selective targeting of invasive tumor cells. Our studies will focus on evaluating the combined effect of Collagenase-3 and S-TRAIL on changes in glioma burden using neural stem cells (NSCs) as vehicles. We will engineer NSCs to stably express a) a firefly luciferase marker gene; b) a regulatable collagenase-3 (R-Colg), a collagen-degrading human enzyme to tumors that leads to matrix modification and increased diffusive transport within the tumors; and c) a secretable recombinant form of TRAIL (S-TRAIL), a novel therapeutic gene that specifically kills tumor cells in vivo. A human glioma cell line, Gli36 stably expressing Renilla luciferase marker gene will be implanted in the model, and then S-TRAIL bearing NSCs with or without R-Colg will be injected into the close proximity of the tumor. The migration of the NSCs into the gliomas will be monitored by Fluc imaging. To release R-Colg within the tumors, mice will be injected intravenously with CAD ligand. The changes in glioma burden over time will be followed by Rluc imaging. The effect of either apoptotic S-TRAIL or the combined effect of S-TRAIL and R-Colg by NSCs on gliomas will be monitored by the activation of caspase-3 that results in the bioluminescence of the caged DEVD-luciferin substrate, injected intraperitoneally. This research combines the use of novel therapeutic protein, modes of gene delivery and imaging modalities to optimize gene therapy for experimental brain tumors in a manner compatible with eventual clinical trials.

Khalid Shah, PhD
Massachusetts General Hospital and
Harvard Medical School
Charlestown, Massachusetts

AWARD
In memory of Lynne Batchelor

RESEARCH APPLICABLE TO
Glioma

EVALUATION OF GELDANAMYCIN AS A POTENTIAL THERAPEUTIC FOR BRAIN CANCER

Geldanamycin (GA) is a new anti-cancer drug. One of its analogues, 17-AAG (17-allylamino-17-demethoxygeldanamycin), is currently being tested in phase I/II clinical trials looking at its safety and effect on several different types of cancer. However, to my knowledge there are few studies that test GA drugs on brain tumor cells, and there are no published studies of the drug's potential in mouse models of human glioblastoma tumors. Recently, I discovered that GA and four GA derivatives, including 17-AAG, can block invasion of highly invasive glioblastoma cells. This inhibition of tumor cell invasion occurs at extremely low drug concentrations, suggesting these highly efficient GA drugs could be promising agents for treating glioblastoma brain cancers.

The purpose of this proposal is to systematically evaluate the therapeutic potential of GA drugs to inhibit human glioblastoma invasion and growth in mouse models. We have a unique model for testing the effect of GA drugs on cancer growth and imaging technologies that will allow monitoring of tumor growth and drug response during and after treatment. We will also develop a human brain cancer mouse model to test GA-based treatment. If GA drugs show efficacy in these tests, this could open the door to their potential use as a new agent for treating brain cancers.

Qian Xie, PhD
Van Andel Research Institute
Grand Rapids, Michigan

AWARD
In memory of Robert J. Lynch

RESEARCH APPLICABLE TO
Glioblastoma multiforme (astrocytoma grade IV)

2004-2005 Project*Grants*

Added to the eighteen Fellowship and Translational Awards are two new Project Grants. Your support through the past year allowed us to extend our funding even further through the awarding of these $50,000 special project grants. These studies look at innovative approaches to diagnostics and treatment.

John Floyd, MD
Vanderbilt University
Medical Center
Nashville, Tennessee

AWARD
Sontag Foundation

RESEARCH APPLICABLE TO
Glioblastoma multiforme
(astrocytoma grade IV)
Malignant glioma

THE INVASIVE PROTEOME: ANALYSIS OF THE PROTEINS IN THE INVASIVE MARGIN AND INFILTRATING TUMOR CELLS IN MALIGNANT GLIOMAS USING LASER CAPTURE MICRODISSECTION AND MALDI-TOF MS

Glioblastoma multiforme is a malignant brain tumor that affects approximately 30 of every 100,000 people. The challenge in treating this tumor arises from the unique ability of glioblastoma cells to invade the normal brain tissue surrounding the main tumor body. By the time of diagnosis, these cells, called infiltrate tumor cells (ITC's), are widely disseminated throughout the entire brain. Infiltrating tumor cells are particularly resistant to chemotherapy and radiation, as they do not replicate their DNA. Additionally, they are resistant to apoptosis – or natural cell death. This leads to recurrence of the tumor after surgery and further neurological decline.

The overall goal of this study is to selectively analyze these infiltrating tumor cells for the expression of unique proteins that enable invasiveness. If these proteins can be identified, then they can be used as markers for tumor growth and as targets for better chemotherapy.

ITCs will be identified within a brain biopsy sample, then laser capture microdissection (LCM) will be used to select these cells for study. This is accomplished by placing a glass slide under a unique microscope equipped with a laser that melts a plastic film over the cells of interest. This laser can be focused to the diameter of 1-2 cells. When the plastic film has melted over the cells, they can be lifted away from the rest of the sample. Once these invasive tumor cells have been isolated from the rest of the tissue, they will be analyzed with mass spectrometry. This technology will allow us to screen for the presence of several hundred proteins, from both normal and invasive cells, at the same time. Statistical methods are then used to determine the significant proteins found in the invasive tumor cells. Those proteins can then be developed to serve as tumor markers in a patient's blood, or as targets for drug therapy. Identification of these cells could help improve diagnosis, treatment, and the quality of life of people with malignant brain tumors.

PRECLINICAL EVALUATIONS OF OMX-2 FOR EXPERIMENTAL GLIOMA THERAPY

Metabolism is a universal process underlying all biological process. "Cross talk" between genetic and metabolic pathways regulates the bioenergetic potential of the cells. Therefore, modification of metabolism may potentially alter cell phenotype. Cancer cells produce more than 80% of the principal "fuel" for the cell, ATP, from glycolytic metabolism. About 20% of ATP is produced by oxidative phosphorylation. It has also been proposed that the ATP needed to support the most important cellular mechanisms, (i.e., protein synthesis, active ion transport) is produced by oxidative phosphorylation, with glycolysis playing a minor role. It is reasonable to assume that a partial and selective block of the oxidative respiration at the level of the electron respiratory chain would lower the production of ATP and therefore inhibit essential functions.

We designed and synthesized OMX-2, a novel, water-soluble organic compound that blocks ATP production by the aerobic pathway specifically in cancer cells, lowering the level of ATP production to a point where the cancer cells stop dividing. We will study the safety and toxicity of this compound in experimental mouse glioma model systems, define the maximally tolerated dose, determine its anti-tumor efficacy, and investigate its ability to act additively/synergistically with two established modalities of glioma therapy – temozolomide chemotherapy and radiotherapy. This preclinical development of OMX-2 is necessary groundwork for translation of these findings to human treatment of brain cancer.

Corinne Griguer, PhD
University of Alabama at Birmingham
Birmingham, Alabama

AWARD
In memory of Keith Marquart

RESEARCH APPLICABLE TO
Malignant glioma

KEEPING UP WITH RESEARCH AND TREATMENT OPTIONS

Just as research advances bring new information about the origins of brain tumors to the forefront, treatment advances bring new options to patients and their families. We offer two significant ways of staying abreast of these important changes:

The new, completely updated 8th edition of *A Primer of Brain Tumors* is now available online in its entirety at *www.abta.org*. This publication is key to understanding the brain, how brain tumors grow, diagnostic tests, and your treatment options.

Our *Sharing Knowledge, Sharing Hope* e-news offers timely treatment news, resources of interest to patients and their families, and suggestions for ways to make a difference in the brain tumor community. Subscribe to this free e-mail service at our web site, *www.abta.org*.

2004 Research *Results*

Jill Barnholtz-Sloan, PhD
Role of Ethnicity in Patients with Primary Malignant Brain Tumors

Peter Canoll, MD, PhD
Investigating the Role of Eph-Ephrin Interactlions in Glioma Migration

Bruce Frankel, MD
The Role of Interferon-Gamma as a Radiation Sensitizer in Glioblastoma Multiforme

Giulia Fulci, PhD
Characterization of the Cells Taking Part in Tumor Angiogenesis

Andrew Lassman, MD
The Helix-Loop-Helix Transcription Factor HEB in Gliomas

Mitsutoshi Nakada, MD, PhD
The Role of EPHB2 Tyrosine Kinase Receptor in Invasion of Glioblastoma

Jean Lee Nakamura, MD
Role of the Phosphoinositide 3-Kinase Signaling Pathway in the Radiation Response of Glioma

Mehmet Fatih Okcu, MD
Glutathione S-Transferase Polymorphisms and Outcomes in Central Nervous System Tumors in Childhood and Adolescence

Ajay Pandita, DVM, PhD
Contrasting In Vivo & In Vitro *Fates of Glioblastoma Cell Subpopulations with Ampliflied EGFR*

Beata Pyrzynska, PhD
Role of p53-Regulated Genes in Gliomagenesis

Dawid Schellingerhout, MBChB
Imaging Gene Therapy to Brain Tumors

Khalid Shah, PhD
NIRF Imaging & Selective Tumor Cell Apoptosis Using Viral Gene Delivery Vectors

Hui-Kuo Shu, MD, PhD
Characterization of Resistance to Monospecific EGFR Inhibitors in Glioma Cell Lines

Yinglin Wang, MD, PhD
p53 Disruption Profoundly Alters the Response of Human Glioblastoma Cells to DNA Topoisomerase I Inhibition

Qingxia Wei, PhD
The Role and Interactions of PTEN and EGFR in the Development and Progression of Human Astrocytomas, Using Transgenic Mouse Models

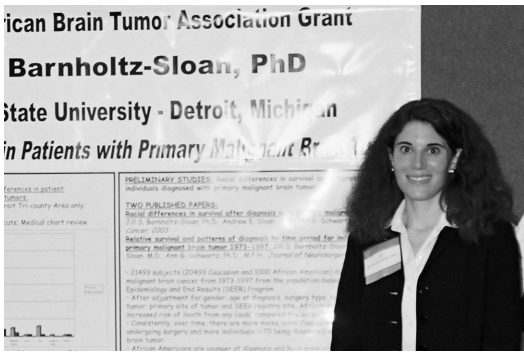
Radoslaw Zagozdzon, MD, PhD
Regulation of CHK Expression in Neural Tumors and Its Unique Role in ERK1/2 Activation Via SHP-2/ RAS-Mediated Signaling

Recipients of ABTA research awards are required to present the results of their work to the ABTA Board of Directors, as well as interested patients and family members. This year, those reports were presented in poster format at the Chicago Marriott O'Hare. Patients and their families visited with each researcher to ask questions and learn how the work applied to their disease. The evening's moderator was Nicholas Vick, MD, Professor of Neurology at Northwestern University and Chairman, Department of Neurology at Evanston Northwestern Healthcare. He led the discussion and interpreted the science so that it was a meaningful evening for all. We extend our thanks to Dr. Vick for graciously donating his time and his skills as an educator.

Jill Barnholtz-Sloan, PhD
Pilot Project Grant 2002 – 2004
Wayne State University & Karmanos Cancer Center, Detroit, Michigan
Award: BP (formerly BP Amoco)

ROLE OF ETHNICITY IN PATIENTS WITH PRIMARY MALIGNANT BRAIN TUMORS

The focus of this pilot project is to better characterize genetic differences by ethnicity in adults with primary, malignant brain tumors. United States cancer registry statistics demonstrate a two-fold or greater incidence of primary, malignant brain tumors in Caucasians compared to African Americans. We showed that survival also varies by ethnicity, in that African Americans have a 13% increased risk of death compared to Caucasians (JBS et al, *Cancer* 2003). Studies have also shown that genetic mutations occurring in specific genes varied between Caucasians and



Jill Barnholtz-Sloan, PhD

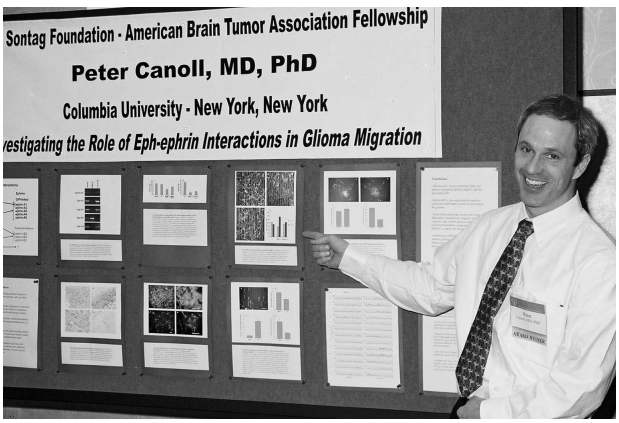
ABTA Board President, Larry Baerson (right), presents a plaque to Nicholas A. Vick, MD expressing our thanks for his ongoing commitment to our organization.

non-Caucasians with brain tumors, but these studies have been few. Therefore, we have been prospectively accruing samples of tumor and somatic DNA of individuals with a newly diagnosed primary, malignant brain tumor who reside in the Detroit Metropolitan area to further investigate ethnic differences in genes related to brain tumors. For each individual we obtain a blood and/or cheek swab sample (normal DNA), a re-cut of their tumor sample (tumor DNA), a copy of the medical record and risk factor information via a phone questionnaire. We will be using Affymetrix gene chips to look at mutations in 9 brain tumor candidate genes in each individual by comparing normal and tumor DNA. The design, laboratory methods and statistical analysis of these gene chips were discussed.

Peter Canoll, MD, PhD
Research Fellowship 2002 - 2003
Columbia University, New York, New York
Award: The Sontag Foundation

INVESTIGATING THE ROLE OF EPH-EPHRIN INTERACTIONS IN GLIOMA MIGRATION

Glioma cells have a remarkable ability to infiltrate the brain and migrate long distances from the tumor mass, making complete surgical resection impossible. Our goal is to understand the molecular mechanisms that regulate glioma migration and identify new targets for therapy. Towards this end, we have developed an experimental system to monitor glioma cells migrating through living slices of rodent brain using time-lapse video microscopy. Our results have shown that glioma cells infiltrate the brain by migrating along the outside surface of blood vessels. This finding has focused our studies on a group of molecules called Eph receptors and their binding partners the ephrins. Eph-ephrin signaling is known to play an important role in regulating cell migration and blood vessel formation during embryonic development. We hypothesize these molecules play a similar role in gliomas. To test this we are using molecular and pharmacological techniques to interfere with Eph-ephrin signaling and then measuring its effects on glioma migration in a variety of experimental systems. We hope this research will lead to the development of new strategies in glioma therapy.



Peter Canoll, MD, PhD

Bruce Frankel, MD
Translational Research Grant 2003 - 2004
University of Tennessee, Memphis, Tennessee
Award: In memory of John C. Carr, Jr.

THE ROLE OF INTERFERON-GAMMA AS A RADIATION SENSITIZER IN GLIOBLASTOMA MULTIFORME

Despite significant improvements in the field of neurosurgery, current modalities of treatment for high-grade gliomas are inadequate. Despite many improvements in other fields of oncology, the outlook for patients with these tumors remains a challenge in the 21st century, requiring that neuro-oncologists continue to explore novel therapeutics.

Currently, treatment of cancer patients is becoming more specific based on our increasing knowledge of malignancies. Through improved definition of molecular targets in cancer therapy, nonspecific toxicity can be reduced while increasing therapeutic efficacy. By utilizing the inherent ability of all cells, including cancerous ones, to undergo programmed cell death, tumor growth can be slowed or even arrested. The interaction of two important cellular factors, Fas and Fas ligand (FasL), results in cell death if both are present at high enough levels. By using a combination of treatments on GBM including interferon-gamma and radiation, both Fas and FasL can be increased resulting in tumor cell death via this pathway and subsequent increased host survival.

2004 Research *Results*

Giulia Fulci, PhD
Research Fellowship 2002 - 2004
Massachusetts General Hospital, Boston, Massachusetts
Award: In memory of Justin Porter

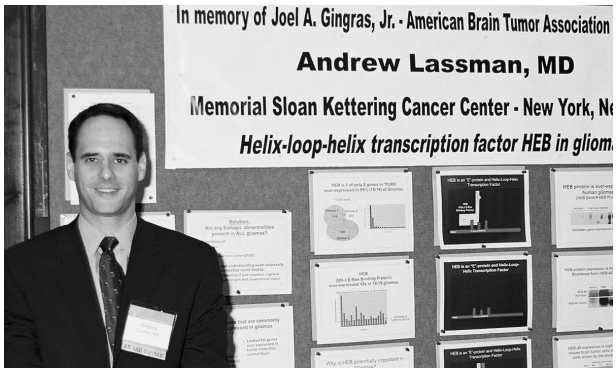
CHARACTERIZATION OF THE CELLS TAKING PART IN TUMOR ANGIOGENESIS

Malignant gliomas are the most common type of primary brain tumors and remain very difficult to treat. One of the features of gliomas is their capacity to induce the formation of blood vessels that prevent tumor cells from starving. This phenomenon, called *angiogenesis,* is essential for the growth and persistence of the tumor. Hence, the possibility to specifically inhibit tumor angiogenesis represents an excellent means for curing gliomas. In order to develop a therapy that specifically attacks tumor angiogenesis, it is essential to fully understand the molecular and cellular basis of this phenomenon. Recent data indicate that *stem cells* (pluripotent cells that can differentiate in cells with different specificities) can migrate to the tumor and give origin to *endothelial cells* (specific cells that constitute the blood vessels), that contribute to tumor angiogenesis. This hypothesis has significantly changed the previous opinions on tumor vascularization leading to the development of new research aimed at studying the characteristics of tumor vessels. We have contributed to these studies by evaluating to what extent stem cells participate specifically in glioma angiogenesis and what endothelial genes ("markers") are expressed in these malignant vessels. Altogether these studies are important for the development of new anti-cancer therapies that target tumor vessels.

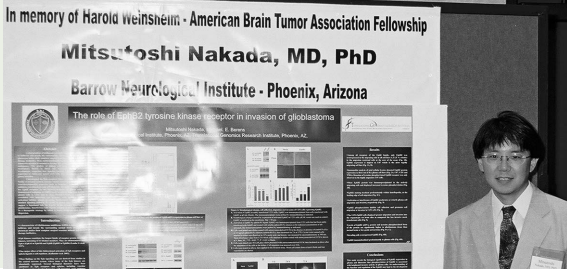
Andrew Lassman, MD
Research Fellowship 2002 - 2004
Memorial Sloan-Kettering Cancer Center,
New York, New York
Award: In memory of Joel A. Gingras, Jr.

THE HELIX-LOOP-HELIX TRANSCRIPTION FACTOR HEB IN GLIOMAS

Gliomas are the most common primary brain tumors in adults. Recently, other investigators identified abnormalities that characterize particular glioma subtypes or grades and predict prognosis or response to therapy. We took a different approach and asked whether there are any abnormalities common to all gliomas. We did this because understanding the role of such universally present abnormalities could fundamentally affect knowledge of glioma biology and have broad clinical impact. We identified HEB (HeLa E-box Binding protein) as 1 of only 2 such abnormalities in 10,000 analyzed that was expressed at significant levels in 95% of various glioma subtypes studied. HEB and related proteins are involved in cancers of other body organs, further suggesting a role in tumor formation. Notably, we found both normal and abnormally shortened forms of HEB in human glioma specimens, and are currently investigating the function and significance of these various sized HEB fragments. In addition, we discovered that the pathways important for the growth of human gliomas could also stimulate HEB synthesis when modeled in mice. Finally, we are testing whether forced overproduction of HEB causes mouse gliomas, both alone and in combination with other known tumor causing abnormalities. This project was made possible in part by the American Brain Tumor Association and the grant #CA009512 from the National Cancer Institute.



Andrew Lassman, MD



Mitsutoshi Nakada, MD, PhD

Mitsutoshi Nakada, MD, PhD
Research Fellowship 2002 - 2004
Barrow Neurological Institute, Phoenix, Arizona
Award: In memory of Harold Weinsheim

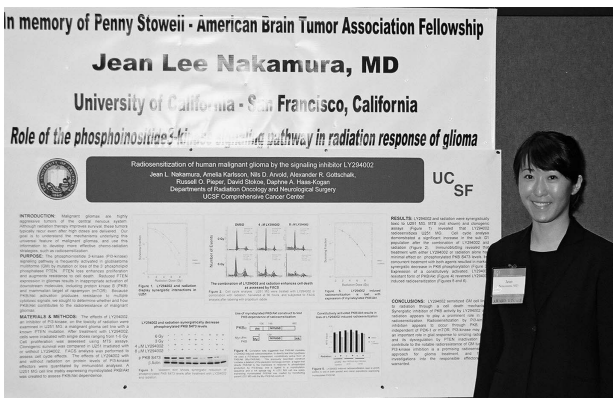
THE ROLE OF EPHB2 TYROSINE KINASE RECEPTOR IN INVASION OF GLIOBLASTOMA

A characteristic of malignant astrocytic tumors is their ability to infiltrate and invade the surrounding normal brain tissue. This phenotype makes their complete surgical resection difficult and focal therapy ineffective. Thus, understanding the mechanisms of astrocytic tumor cell invasion is essential to develop new strategies to control this malignancy. The process of glioma cell invasion may include mechanisms known to direct cell movement during neural development, suggesting that signaling proteins which contribute to migration of embryonic neural crest cells may be associated with glioma invasion. I investigated the Eph receptors which constitute the largest family of receptor protein tyrosine kinases and which mediate many neurodevelopmental processes, such as boundary formation, axon guidance, vasculogenesis and cell migration. My study revealed a role for EphB receptors in the invasive behavior of glioma cells. I demonstrated induction of EphB2 levels in actively migrating human glioma cells *in vitro* and *in vivo*. Phosphorylation of EphB2 is correlated with migration and invasion, while blocking EphB2 activation inhibits glioma invasion. Furthermore I explored the detailed signaling pathway of EphB2 in glioma cells. These results suggest a functional role for EphB2 in the invasive behavior of glioblastoma. Interference with EphB2 receptor or its signaling may be a therapeutic strategy by which to arrest malignant glial tumor dispersion.

Jean Lee Nakamura, MD
Research Fellowship 2002 - 2004
University of California, San Francisco, California
Award: In memory of Penny Stowell

ROLE OF THE PHOSPHOINOSITIDE 3-KINASE SIGNALING PATHWAY IN THE RADIATION RESPONSE OF GLIOMA

Gliomas are the most common tumor originating in the human brain. As a class, these tumors present unique challenges due to their location and resistance to treatment. Radiation can help to control tumor growth, however this control is often limited, particularly in those patients with high-grade gliomas. Despite the integral role of radiation therapy in the management of gliomas, the mechanisms underlying glioma response and resistance to radiation are poorly understood. Among the many known signaling aberrations harbored by glioma tumors, the phosphoinositide 3-kinase (PI3-kinase) pathway is abnormally active in glioma cells, leading to uncontrolled growth in the face of treatment with known anti-cancer agents, such as radiation. This work sought to identify the role of PI3-kinase in contributing to radiation resistance, with the aim of identifying novel molecular radiosensitizing strategies. We found that pharmacologic inhibition of PI3-kinase sensitizes extremely resistant human glioma cells to radiation. Further, we identified a commonly activated molecule, PKB/Akt, as the downstream molecule that mediates radiosensitization. Mutations and/or signaling aberrations which overactivate PI3-kinase may contribute to the notable radioresistance of GBM tumors, and inhibition of PKB/Akt offers an excellent target to enhance radiosensitivity.



Jean Lee Nakamura, MD

2004 Research *Results*

Mehmet Fatih Okcu, MD
Translational Research Grant 2003 - 2004
Baylor College of Medicine, Houston, Texas
Award: Emily Dorfman Foundation for Children

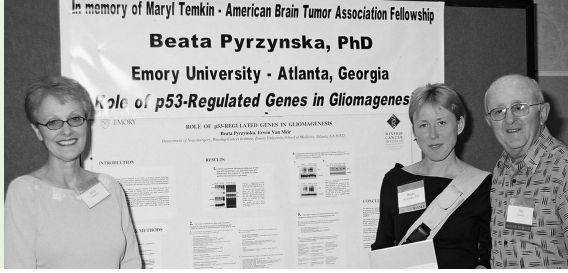
GLUTATHIONE S-TRANSFERASE POLYMORPHISMS AND OUTCOMES IN CENTRAL NERVOUS SYSTEM TUMORS IN CHILDHOOD AND ADOLESCENCE

With current therapy, approximately 50% of children and adolescents with brain tumors are cured. At the time of diagnosis it is impossible to predict which patients will benefit from therapy and which patients will experience significant toxicity. The Glutathione S-Transferase (GST) family of enzymes is responsible for clearance of chemotherapy agents including alkylating agents and platinum compounds used in brain tumor treatment. We hypothesized that GST polymorphisms may be responsible, in part, for individual differences in response to treatment hence determining the outcome for survival and toxicity. We conducted polymerase chain reaction (PCR) for GSTM1 and GSTT1 polymorphisms to investigate the relationship between GST genetic variations and survival in 45 patients with medulloblastoma. Results were analyzed for overall survival (OS) adjusting for age and risk group at diagnosis, and ethnicity. Patients with the GSTM1 null genotype had significantly shorter survival compared to patients with GSTM1 non-null. We observed a much higher rate of GSTT1 null genotype (31%) compared with the published frequency of this genotype in normal populations values (15-25%), possibly due to the high frequency of GSTT1 null genotype in the African American (AA) patients (83% n=5/6). These results indicate that GSTM1 polymorphisms may be a potential prognostic factor in children and adolescents with medulloblastoma. The GSTT1 genotype may be risk factor for development of medulloblastoma in the AA children.

Ajay Pandita, DVM, PhD
Research Fellowship 2002 - 2004
Mayo Clinic, Rochester, Minnesota &
University of Toronto, Toronto, Canada
Award: In memory of Audley A. Ciamporcero, Jr.,
The Audley Fund of the Philadelphia Foundation

CONTRASTING *IN VIVO* & *IN VITRO* FATES OF GLIOBLASTOMA CELL SUBPOPULATIONS WITH AMPLIFIED EGFR

Despite the high incidence of EGFR amplification in GBM tissues, only a single GBM cell line is known to maintain amplified EGFR. Because EGFR mutations manifest primarily in amplified form, hence the availability of cell lines with EGFR mutations are in short supply. In fact, there are no GBM cell lines harboring the common EGFR mutants described in GBM specimens. These observations suggest that in vivo environments select for EGFR amplification, whereas in vitro environment select against this gene alteration. To contrast directly the fates of EGFR amplification in vivo and in vitro, and to examine potential relationships between EGFR amplification and mutation, we established and maintained GBM explants as xenografts by growing in nude mice. Analysis of EGFR copy number and mutation status in 11 patient tumors and corresponding xenografts, as well as monitoring EGFR copy number during establishing a cell line from an EGFR amplified xenograft indicated that selection for EGFR amplification is an in vivo phenomenon. Our data indicated that EGFR mutation occurs only in tumors with EGFR amplification and that the selection of amplified mutant EGFR over amplified wild-type EGFR as a xenograft occurred rapidly and completely during tumor propagation. The reagents provided by the studies from this study will be helpful in directing research in areas that will further provide answers to the fundamental questions regarding the role of this GBM-associated gene alteration.



Beata Pyrzynska, PhD (center) with Alice and Hal Temkin

Beata Pyrzynska, PhD
Research Fellowship 2002 - 2004
Emory University, Atlanta, Georgia
Award: In memory of Maryl Temkin

ROLE OF P53-REGULATED GENES IN GLIOMAGENESIS

The objective of this project was to understand the impact of mutation of the p53 tumor suppressor in the formation and progression of glioblastoma – a highly malignant type of brain tumor. A human glioblastoma cell line lacking p53 genes was genetically engineered to express inducible p53, either wild-type or mutant. The three most common mutations found in human glioblastoma were tested. Using microarray technology, the whole genome was analyzed before and after p53 induction. This powerful approach allowed us to screen for all the genes regulated by wild-type and mutant p53. Wild-type p53 was able to up-regulate and down-regulate expression of many genes, including several genes previously unknown as p53 targets. In contrast, the mutant forms of p53 acted mainly to down-regulate expression of many genes. The cells were also exposed to hypoxia, mimicking the tumor growth conditions in vivo. Interestingly, some genes were found to be regulated by p53 only under hypoxia. The potential role of several new p53-target genes on the growth of glioblastoma as well as its ability to induce or inhibit formation of blood vessels (which feed the tumor) were discussed.

Dawid Schellingerhout, MBChB
Research Fellowship 2002 - 2004
Massachusetts General Hospital, Boston, Massachusetts
Award: In memory of Laurie Deierlein

IMAGING GENE THERAPY TO BRAIN TUMORS

Our goal was to use imaging to gain a better understanding of the delivery of Gene Therapy vectors to brain tumors. We studied the following areas: a) the bio-distribution of Herpes Simplex viral vectors (HSV), and the manipulation of vector bio-distribution with pharmacological and physical interventions, b) novel imaging technologies to image vector distribution, and c) novel imaging technologies to image gene expression. We had modest success in improving HSV delivery to brain with pharmacological manipulations, but unfortunately viral delivery with vascular administration was low, and remained so despite our interventions. Thus we attempted physical disruption of the blood brain barrier (BBB) by means of therapeutic focused ultrasound. We showed proof of concept that vector delivery to selected focal sites in the brain was achievable. We developed a novel imaging technique to show vectors administered stereotactically using Coded Aperture nuclear imaging. We demonstrated the superiority of this technology to traditional imaging. We showed proof of concept that luciferase could be imaged as a marker gene for the assessment of gene expression. In summary, we believe that imaging will be useful in the further development of gene therapy, and will likely contribute to its eventual success in the clinic.

Dawid Schellingerhout, MBChB

Khalid Shah, PhD
Translational Research Grant 2003 - 2004
Massachusetts General Hospital,
Charlestown, Massachusetts
Award: In memory of Lynne Batchelor

NIRF IMAGING & SELECTIVE TUMOR CELL APOPTOSIS USING VIRAL GENE DELIVERY VECTORS

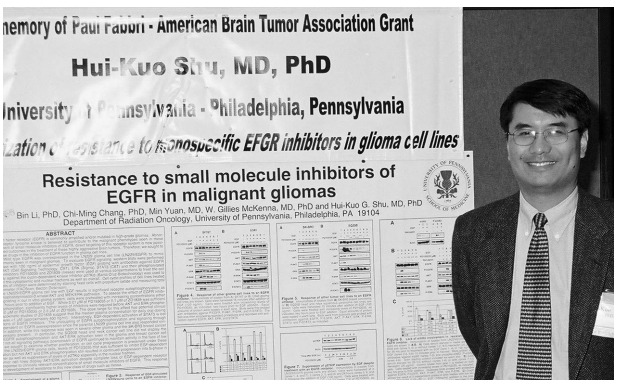
Despite many refinements in current therapeutic strategies the overall prognosis for patients with glioblastomas still needs to be improved. Neural precursor cells (NPCs) are capable of tracking to glioma tumors and could thus be utilized to deliver

therapeutic molecules. We have engineered immortalized mouse NPCs to deliver a novel secreted form of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), S-TRAIL optimized to selectively kill neoplastic cells. NPC-FL-sTRAILs secreted 140 ng/ml S-TRAIL protein per 10^6 cells, expressed firefly luciferase (FL) and retained tumor migratory properties in the brain as revealed by bioluminescence imaging. Using a highly malignant human glioma model expressing Renilla luciferase (RL), intracranially implanted NPC-FL-sTRAIL were found to have profound anti-tumor effects as confirmed by real time imaging and histology. These studies reveal the potential of NPCs as therapeutically effective delivery vehicles for the treatment of gliomas, and also provide important tools to evaluate the migration of NPCs and changes in glioma-burden *in vivo*.

Hui-Kuo Shu, MD, PhD
Translational Research Grant 2003 - 2004
University of Pennsylvania, Philadelphia, Pennsylvania
Award: In memory of Paul Fabbri

CHARACTERIZATION OF RESISTANCE TO MONOSPECIFIC EGFR INHIBITORS IN GLIOMA CELL LINES

The epidermal growth factor receptor (EGFR) has been shown to be important in the development of malignant gliomas and how aggressively they behave. Specific EGFR inhibitors have now been developed that may potentially improve the outcomes of patients treated for this disease. However, our lab has recently found that a glioma cell line can display resistance to these drugs. This response may potentially limit efficacy of these new drugs. We studied how widespread this problem is and the underlying mechanism responsible for this response. We found that resistance to these agents is seen in a number of glioma cell lines irrespective of EGFR expression levels. In addition, assessment of signaling pathways downstream of EGFR has revealed that some but not all signals are resistant to these agents. Based on these results and what is known about the mechanism of EGFR activation, we theorized that the resistant downstream signals were maintained through similar receptors that interact with EGFR such as erbB2, or HER2. Preliminary data now suggest that this is indeed the case with partial transfer of signal to erbB2 when low levels of drug are used. If these results hold up, it is possible that dual inhibition of EGFR and erbB2 will be more effective than inhibition of either receptor alone.



Hui-Kuo Shu, MD, PhD

Yinglin Wang, MD, PhD
Translational Research Grant 2003 - 2004
University of California at Los Angeles,
Los Angeles, California
Award: In honor of Gabrielle Carteris

p53 DISRUPTION PROFOUNDLY ALTERS THE RESPONSE OF HUMAN GLIOBLASTOMA CELLS TO DNA TOPOISOMERASE I INHIBITION

A critical challenge in cancer research is to identify genetic lesions that sensitize patients to chemotherapy. Tumor suppressor gene p53, which is mutated in nearly one-third to one-half of glioblastomas, may be such a lesion. In this study, we demonstrate that p53 disruption dramatically sensitizes glioblastoma cells to DNA topoisomerase I inhibitor-mediated apoptosis (programmed cell death). Using 19 glioblastoma cell lines, including 15 low-passage primary culture derived from patients, we show that clinically achievable levels of SN-38 (the active metabolite of chemotherapy agent CPT-11) potently induce cell cycle arrest and temporary senescence (cell aging) in glioblastoma cells with wild-type p53 while causing massive apoptosis in p53-deficient cells ($P<0.0002$). We demonstrate that glioblastoma cells with wild-type p53 proliferate when recultured in drug-free medium,

Qingxia Wei, PhD (center) with
Beth and Steve Dorfman

whereas p53-deficient cells do not. We also show that tumor suppressor gene p16 is neither necessary nor sufficient for initiation and/or maintenance of SN-38-induced arrest/senescence. These results indicate that p53 disruption has a dramatic effect on how glioblastoma cells process topoisomerase I inhibitor-mediated DNA damage. This study further suggests that patients with p53-deficient glioblastomas would benefit the most from topoisomerase I inhibitor therapy.

Qingxia Wei, PhD
Research Fellowship 2002 - 2004
The Hospital for Sick Children, Toronto, Canada
Award: Emily Dorfman Foundation for Children

THE ROLE AND INTERACTIONS OF PTEN AND EGFR IN THE DEVELOPMENT AND PROGRESSION OF HUMAN ASTROCYTOMAS, USING TRANSGENIC MOUSE MODELS

Glioblastoma multiforme (GBM) are the most malignant, common and incurable form of primary human adult brain tumors with mean survival less than 12 months. They are classified in four grades of increasing malignancy based on the pathological features by the World Health Organization. GBM, or grade4 astrocytomas, are characterized by invasion, necrosis and increased vascularity. Molecular signatures not found in lower grades of astrocytomas, include loss of the tumor suppressor gene PTEN and over expression, amplification and mutations of Epidermal Growth Factor Receptors (EGFRVIII). Transgenic models to date have demonstrated that neither of these genetic alterations by themselves in astrocytes is sufficient for astrocytoma formation. My interest is to determine the role and interactions of these genetic alterations in the progression and development of astrocytomas with mouse models. I have taken advantage of existing transgenic mouse glioma models developed in our lab and by others, to create these two GBM-associated genetic alterations specifically in astrocytes of varying developmental age, in combination with each other or with other relevant genetic alterations in these tumors. My experiments to date already demonstrate that these genetic alterations are involved in glioma progression in conjunction with additional genetic alterations and that the sub-type of brain tumors that are formed depends on the developmental expression profile. Development of these models will not only increase our knowledge of the molecular pathogenesis of brain tumors, but also provide pre-clinical spontaneous models more representative of human brain tumors for examining potential therapies.

Radoslaw Zagozdzon, MD, PhD
Translational Research Grant 2003 - 2004
Beth Israel Deaconess Medical Center,
Boston, Massachusetts
Award: In memory of Linda Favero

REGULATION OF CHK EXPRESSION IN NEURAL TUMORS AND ITS UNIQUE ROLE IN ERK1/2 ACTIVATION VIA SHP-2/RAS-MEDIATED SIGNALING

CHK and Csk are members of Csk-family kinases, and their common function is to phosphorylate the inhibitory C-terminal tyrosine in Src-family kinases. In central nervous system, Csk and CHK exhibit opposite temporal expression during embryonal development – expression of CHK increases, while that of Csk decreases along with maturation of the neural tissue. In this study, we show that the expression of CHK in human neural tumors is dramatically down-regulated, while expression of Csk is significantly increased. Overexpression of wild-type CHK, but not Csk or dead-kinase mutant of CHK, resulted in the increase of Erk1/2 phosphorylation and neurite outgrowth in PC12 cells. CHK induced MAPK activation independently from inhibition of Src kinase, and formed a complex with SHP-2 resulting in SHP-2 phosphorylation. Subsequently, SHP-2 associated with Grb2 leading to increased activity of Ras and Erk1/2 activation via Raf/MEK1/2 pathway. In addition, an amplification and prolongation of EGFR signaling by CHK was observed in PC12 cells, resulting in stimulation of neurite outgrowth by EGF, which strongly suggests that CHK act as a molecular switch promoting differentiation mediated by EGFR signaling instead of mitogenic effects. Taken together, this study provides novel insights into the CHK expression and function in neural malignancies.

American Brain Tumor Association

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For program and hotel information, send an email to *info@abta.org*, or call Linda at 800-886-2282.

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