RESEARCH EDITION

Messageline

SUMMER 2002 VOLUME XXIX, NUMBER 2

A PUBLICATION OF THE AMERICAN BRAIN TUMOR ASSOCIATION

ABTA FUNDS OVER ONE MILLION DOLLARS OF RESEARCH THIS YEAR

Despite our country's economic decline and terrorist attacks, we thank you for giving generously to help support a wide array of research programs. Funding awarded this year will be used to investigate the early steps in the development of glioblastoma, oligodendrogliomas, and low grade gliomas; explore the pathways by which malignant brain tumors form; study the growth of blood vessels that sustain a tumor; and learn more about the way in which tumor cells move into surrounding tissue. Looking toward the clinical area, researchers will study the development of a new radiosensitizing drug, a possible means of preventing radiation-induced injuries, several new imaging techniques, and a new drug delivery system. Inside are descriptions of the awards proudly funded by ABTA — and you.

Continued on *page 2*

Inside *this Issue*

Our Research Programs *continued* 2–4

In Memoriam... Jeffery A. Williams, MD 4

Basic Research Fellowships . . . 5–15

Translational Grants 16–18

Epidemiology Grant 19

Project Grants 20–21

Nursing Research 22

ACOSOG Neurosurgery Study 23

Research Summaries 24–28

Finding a Clinical Trial 29

Brain Tumor Action Week 30

Research Applications Available 31

In the News . . . . . Back Cover

Continued from *Cover*

Message*line*
VOLUME XXIX, 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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OUR RESEARCH PROGRAMS

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 Research 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. Applications are available in August and completed applications are due in early January.

2002-2003 ABTA Fellowships:

Peter Cannoll, MD, PhD
Columbia University
New York, New York

William Curry, Jr., MD
Massachusetts General Hospital
Charlestown, Massachusetts

Giulia Fulci, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

Kimmo J. Hatanpaa, MD, PhD
Johns Hopkins Hospital
Baltimore, Maryland

John Hill, MD, PhD
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Lebanon, New Hampshire

Andrew B. Lassman, MD
Memorial Sloan-Kettering Cancer Center
New York, New York

Mitsutoshi Nakada, MD, PhD
Barrow Neurological Institute
Phoenix, Arizona

Jean L. Nakamura, MD
University of California San Francisco
San Francisco, California

Ajay Pandita, PhD
Mayo Clinic, Rochester, Minnesota and University of Toronto, Ontario

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Toronto, Ontario

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Labatt Brain Tumor Research Centre
Hospital for Sick Children
Toronto, Ontario

Qing Zhao, MD, PhD
Dana-Farber Cancer Institute
Boston, Massachusetts

Your generosity made these research programs possible. Your renewed support ensures their continuance. Thank you!

TRANSLATIONAL RESEARCH AWARDS

The intent of these $50,000 one-year awards is to develop important research studies so they may move from the laboratory to the clinic. 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 are available in August from the ABTA office at 847-827-9910.

Recipients of ABTA Translational Research Grant funding are:

Richard A. Gemeinhart, PhD
University of Illinois

Burt Nabors, MD
University of Alabama at Birmingham

Khalid Shah, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

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 **James G. Guerny, MD**, University of Minnesota, Department of Pediatric Epidemiology. His significant research was titled, *Non-neurological late effects among childhood brain tumor survivors: a preliminary analysis from the childhood cancer survivors study.* To apply for this year's award, contact the Society at 713-745-2264 or *www.soc-neuro-onc.org.*

YOUNG CLINICIAN INVESTIGATOR AWARD

ABTA offers, through the Neurosurgery Research and Education Foundation of the American Association of Neurological Surgeons, an annual grant in support of young faculty pursuing careers as clinical investigators. The award funds clinical research which could provide preliminary data that may be used to strengthen applications for more permanent funding from other sources. Applications are available from the AANS office at 847-378-0500.

The recipient of this year's $50,000 award is **Sheila K. Singh, MD, PhD** at the University of Toronto, Hospital for Sick Children. Her research is *A Novel Assay of Stem Cells in Pediatric Brain Tumors.* Dr. Singh will explore the role of stem cells in the development of childhood brain tumors.

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. The current year's recipient is **Paula Riess Sherwood RN, MSN, CNRN** at Michigan State University. An explanation of her study appears on page 22. Nurses interested in applying for this $10,000 award should contact the Oncology Nursing Society at 412-921-7373.

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 carries an additional $1,000 plus distinction. Interested mentors should contact the ABTA office.

Participants in the 2002 Summer Fellowship Program are:

Cedars Sinai Medical Center
Los Angeles, California
MENTOR: Nagendra, Ningaraj, PhD
STUDENT: Paul Kaloostian

Columbia University
New York, New York
MENTOR: Jeffrey Bruce, MD
STUDENT: Gaetan Moise

Georgetown University
Washington, DC
MENTOR: Zofia Zukowska, MD, PhD
STUDENT: Edward W. Lee

Johns Hopkins University
Baltimore, Maryland
MENTOR: Henry Brem, MD
STUDENT: Jonathan Winter

Johns Hopkins University
Baltimore, Maryland
MENTOR: Alessandro Olivi, MD
STUDENT: John Ziewacz

Johns Hopkins University
Baltimore, Maryland
MENTOR: Jon Weingart, MD
STUDENT: Samantha Ford

Medical College of Virginia
Richmond, Virginia
MENTOR: William Broaddus, MD, PhD
STUDENT: Aaron Clark

St. Jude Children's Hospital
Memphis, Tennesse
MENTOR: Richard Gilbertson, MD, PhD
STUDENT: Amanda Mealer

Continued on *page 4*

Continued from *page 3*

OUR RESEARCH PROGRAMS

YOUNG INVESTIGATOR GRANTS

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

The award funded through the American Association of Neurological Surgeons and the Congress of Neurological Surgeons recognizes research performed by an outstanding young investigator. This year's award was given to **Howard Weiner, MD** of New York University Medical Center for his research titled *Retrovirus-Sonic Hedgehog Infection of Murine Embryonic Cerebellar Granule Cells Leads to Tumor Formation.* We're proud to reward Dr. Weiner's continued interest in neuro-oncology — he was a previous ABTA/Emily Dorfman Fellow and mentored an ABTA summer medical student.

HOWARD WEINER, MD

GUILIA FULCI, MD

The Society for Neuro-Oncology Award is for Excellence in Basic Research — this grant was given to **Guilia Fulci, PhD** for her work exploring the role of p53 loss in the development of malignant gliomas. Dr. Fulci is also a current ABTA Fellow.

CENTRAL BRAIN TUMOR REGISTRY OF THE UNITED STATES GRANT

Founded by ABTA to establish a registry where ALL brain tumors — benign and malignant — will be recorded, we continue our intense support of this organization. Our $ 30,000 2002 grant, part of a multi-year commitment to the registry, conveys our understanding and encouragement of the urgent need for statistical data documenting the incidence and prevalence of this disease. We continue to support the CBTRUS initiative of collecting nationwide data, and encourage patients, families, and healthcare professionals to access the wealth of information available to the public at their web site — *www.cbtrus.org.*

*In*Memoriam…

JEFFERY A. WILLIAMS, MD

The American Brain Tumor Association expresses our condolences to the family of Jeffery A. Williams, MD on his sudden passing. Dr. Williams was an associate professor of neurosurgery and oncology, and director of stereotactic radiosurgery at The Johns Hopkins School of Medicine in Baltimore, Maryland.

A renowned radiosurgeon, Dr. Williams was the only physician to be certified by both the American Board of Neurological Surgery and the American Board of Radiation Oncology. He was the author of numerous scientific papers and held 7 patents for innovative brain tumor treatments. Among Dr. Williams' many awards were a Clinical Investigator Development Award from the National Institutes of Health, and the Clinician Scientist Award from Johns Hopkins. He was a member of several professional societies and advisory committees, and was a founder and chairman of the medical advisory board of Proxima Therapeutics, Inc. His web site, the Johns Hopkins Brain Tumor Radiosurgery site, provided extensive resources to families and professionals alike. His contributions to the brain tumor community will be missed.

2002-2004 Basic Research *Fellowships*

NEW FELLOWSHIP AWARDS FOR 2002-2004

The following researchers are recipients of $70,000 ABTA Post-Doctoral Research Fellowships. These awards are intended to encourage talented young researchers to enter, or remain in, the field of neuro-oncology. We welcome these talented researchers to the ABTA family.

INVESTIGATING THE ROLE OF EPH-EPHRIN INTERACTIONS IN GLIOMA MIGRATION

Glioma cells have a remarkable capacity to infiltrate the brain and migrate long distances along nerve fibers and blood vessels. This diffuse infiltration is the major reason glioblastomas, astrocytomas, and oligodendrogliomas are not curable by surgery. Even wide surgical resections inevitably leave some glioma cells behind, causing tumors to eventually recur. Our goal is to understand the molecular mechanisms that regulate glioma migration.

Toward this end, we developed an experimental system to monitor glioma cells migration using time-lapse videomicroscopy. We are using this system to test the effects of specific guidance molecules on glioma migration. Our initial analysis is focused on a group of molecules called Eph receptors and their binding partners, the ephrins. Eph-ephrin signaling mediates repulsive and adhesive mechanisms that guide migrating cells during embryonic development. We hypothesize that these molecules play a similar role in glioma migration.

To test this we will interfere with Eph-ephrin signaling using molecular and pharmacological techniques and then measure the effects on glioma migration in the rat model. We hope that this research will lead to the development of new strategies in glioma therapy.

SUMMARY

Ephs and ephrins are proteins involved in cell movement, patterning of cells within the nervous system, and development of the internal guidance systems that connects one neuron to another. During fetal development, Eph plays a role in the movement of cells as they form tissues and organs. Dr. Cannoll theorizes that Ephs and ephrins may also be involved when glioma cells begin to invade, or migrate, into surrounding brain. He proposes studying these molecules in tumor migration by recording the movements of individual tumor cells in brain tissue using digital video microscopy.

Peter Cannoll, MD, PhD
Columbia University
New York, New York

SPONSOR
James E. Goldman, MD, PhD

AWARD
The Sontag Foundation/ ABTA Fellowship

2002-2004 Basic Research *Fellowships*

Giulia Fulci, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

SPONSOR
E. Antonio Chiocca, MD, PhD

AWARD
Justin Porter/ABTA Fellowship

TARGETING TUMOR VASCULATURE USING BONE MARROW-DERIVED PRECURSOR ENDOTHELIAL CELLS EXPRESSING AN ANTI-TUMOR cDNA

Malignant gliomas are the most common type of primary brain tumors and remain very difficult to treat. One of the features of gliomas which renders them so challenging is their capacity to form blood vessels that carry nutrients to the tumor and prevent tumor cells from starving. This phenomenon, called angiogenesis, is essential for the growth and persistence of the tumor. Hence, the possibility of inhibiting tumor angiogenesis may represent an excellent means of controlling glioma growth.

In order to develop a therapy based on 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 differentiate into cells with different specificities) can migrate to the tumor and give origin to endothelial cells (blood vessel cells), which lead to tumor angiogenesis. If this is true, we can postulate the possibility of using stem cells as a means to destroy glioma vessels. These cells could be isolated and genetically engineered to carry proteins capable of killing these blood vessels. The engineered cells would then be administered back to the patient. The aim of our study is to evaluate to what extent stem cells participate specifically in glioma angiogenesis, make them express an antitumor protein, and test their therapeutic potential in the laboratory.

SUMMARY

It has long been assumed that the blood vessels providing nutrients to a tumor arise from blood vessels already present in the area of the tumor. Recent studies suggest that blood stem cells, rather than existing blood vessels, may be the actual origin of these new blood vessels. Dr. Fulci proposes to study the role of blood stem cells in angiogenesis (the growth of blood vessels around a tumor) and attempt to determine if these stem cells could be genetically altered to interfere with angiogenesis.

Dr. Fulci's sponsor, Antonio Chiocca, MD, PhD, was also the recipient of an ABTA Research Fellowship Award. He is now an ABTA Scientific Advisor. We are proud to offer Dr. Fulci this "second generation" research award, and to be part of this team's continued dedication to neuro-oncology.

CLINICAL SIGNIFICANCE OF LOSS OF CHROMOSOME ARMS 1P AND 19Q IN PEDIATRIC AND ADULT LOW-GRADE TUMORS

Distinguishing oligodendrogliomas from other gliomas is important because we now know that oligodendrogliomas can respond well to chemotherapy. We also know that oligodendrogliomas have a genetic alteration referred to as the "loss of heterozygosity on chromosome arms lp and 19q," abbreviated as "lp19q LOH". Thus, lp19q LOH testing may complement the often-challenging microscopic evaluation in the diagnosis of oligodendroglioma. Additionally, lp19q LOH has been shown to be a strong predictor of favorable chemotherapeutic response and prolonged survival in patients with high-grade (microscopically highly malignant) tumors.

The significance of lp19q LOH in low-grade gliomas, which affect approximately 12,000 Americans, is not known. Another group of tumors — dysembryoplastic neuroepithelial tumors (DNTs) — are benign but contain areas resembling low-grade gliomas, particularly oligodendrogliomas. Distinguishing these tumors is critical because they may be treated differently. Testing for lp19q LOH may help, as preliminary data indicate only oligodendrogliomas have lp19q LOH.

I have developed a lp19q LOH test that works on small areas of routine microscopic sections. Correlating the test results with clinical outcome, I will examine the clinical significance of lp19q LOH in low-grade gliomas, DNTs, and DNT-like tumors. This study will determine if patients with these tumors might benefit from lp19q LOH testing.

SUMMARY

Within the past few years, scientists have learned that oligodendroglioma tissue has an unusual characteristic — the loss of a small part of chromosomes lp and 19q. Tumors with this loss seem to be more sensitive to chemotherapy than tumors with these chromosomes intact. Dr. Hatanpaa will use his funding to screen low grade oligodendrogliomas, astrocytomas, DNTS, and a new group of DNT-like tumors for this loss so we can expand scientific knowledge of the importance of this unusual chromosomal change.

Kimmo J. Hatanpaa, MD, PhD
Johns Hopkins Hospital
Baltimore, Maryland

SPONSOR
Peter C. Burger, MD

AWARD
Bonnie Blair/Dallas Stars/ ABTA Fellowship

2002-2004 Basic Research *Fellowships*

Andrew B. Lassman, MD
Memorial Sloan-Kettering Cancer Center
New York, New York

SPONSOR
Eric Holland, MD, PhD

AWARD
Joel A. Gingras, Jr./ ABTA Fellowship

THE ROLE OF TRANSCRIPTION FACTOR 12 IN GLIOMA FORMATION

Some patients with brain tumors have poor prognoses partly because we don't understand the cause of their cancers. Understanding the first steps in the growth of a tumor may help physicians develop more effective therapies. In preliminary studies, my mentor and I discovered several apparently overactive genes in gliomas, including transcription factor 12 (TCF12). As TCF12 abnormalities are associated with other cancers, we believe TCF12 may contribute to glioma formation.

My project will study the potential role of TCF12 in gliomas. First, I will confirm TCF12 over-activity in human brain tumor specimens. Second, I will stimulate TCF12 production in cultured glial cells (those grown in a petri dish) to look for cancerous changes and then attempt to reverse those changes by inactivating TCF12. Third, I will identify other genes that TCF12 activates and determine whether they, too, are activated in gliomas. Fourth, I will stimulate TCF12 in transgenic mice — special laboratory models developed specifically for glioma research — to evaluate whether gliomas form. If so, I will then block TCF12 to determine whether the induced tumors shrink.

Finally, I will also study genetic combinations using TCF12 with other genes, to evaluate whether two genes may cause gliomas when neither alone is capable of causing tumor growth. My goal is to eventually discover whether TCF12 might be a target for new therapies.

SUMMARY

Gliomas, like all cancers, contain a collection of abnormal genes. Some of these genes appear in too great a quantity; others are absent or found in too small a quantity. To help identify the genes involved in glioma biology, this lab screened glioblastomas and low-grade gliomas for abnormally expressed genes. One of the genes found to be over-expressed was TCF12, a relatively unknown gene. Dr. Lassman will use his funding to study this gene to determine if it plays any role in the development of gliomas. He will look at TCF12 alone and in combination with other known genetic changes.

THE ANALYSIS OF THE MOLECULES THAT CONTRIBUTE TO GLIOMA INVASION AND THE ESTABLISHMENT OF A NEW STRATEGY TO TREAT GLIOMAS

Although a hallmark of malignant glial neoplasms is their heterogeneity, it is likely that similar genetic and biochemical aberrations underlie the phenotype of glioma invasion. The central hypotheses of this project is that the same genetic mediators affect glioma invasiveness under diverse conditions, and we will be looking for these shared targets to which new therapies could be aimed.

First, the profile of proteases produced by human glioma cells when they confront extracellular matrix proteins (laminin, fibronectin, vitronectin, tenascin, and brevican) will be determined. Microarray technology will be used to identify selected proteases at different anatomical sites and along different routes of invasion. Next, we will determine the gene expression profile of glioma cells under disparate invasive conditions *in vivo* and *in vitro*. LCM technology will be used to collect invading glioma cells from white matter tracts, perivascular spaces, and subventricular regions with a profile of cell migration and invasion determined. Consensus metabolic pathways will be assembled, addressing whether the patterns show concordance when glial cells invade different environments.

SUMMARY

A major impediment to improved management of patients with malignant brain tumors is the re-growth of tumor after surgery and radiation. This happens when tumor cells break away from the main tumor mass and invade normal surrounding brain, thereby escaping the surgeon's knife. These cells may then evade the focused beam of radiation, or even reside behind an intact blood-brain barrier to remain unexposed to chemotherapy. We speculate that in order for a brain tumor cell to invade, it must activate certain genetic pathways. This study is designed to determine these pathways, and learn whether they are the same for invasion into white matter of the brain, into spaces along blood vessels and/or under the brain's ventricles. A better understanding of the basis for glioma invasion is likely to identify ways that invading glioma cells may be vulnerable to new treatments that exploit invasion.

Mitsutoshi Nakada, MD, PhD
Barrow Neurological Institute
Phoenix, Arizona

SPONSOR
Michael E. Berens, PhD

AWARD
Harold Weinsheim/ ABTA Fellowship

2002-2004 Basic Research *Fellowships*

Jean L. Nakamura, MD
University of California San Francisco
San Francisco, California

SPONSOR
Daphne A. Haas-Kogan, MD

AWARD
Penny Stowell/ABTA Fellowship

THE ROLE OF THE PHOSPHOINOSITIDE3-KINASE SIGNALING PATHWAY IN THE RADIATION RESPONSE OF GLIOMA

As a class, gliomas present unique challenges due to their location and resistance to treatment. Radiation therapy is able to elicit varying responses in these tumors, depending on the type of glioma. While radiation treatment can help to control tumor growth, this control is often limited, particularly in those patients with high-grade gliomas. Radiation therapy is limited by the fact that only finite amounts of radiation can be delivered to any part of the body, including the brain, without irreparably harming normal tissues. Escalating radiation doses can produce serious neurologic complications, especially in the long term.

The results of recent studies show the phosphoinositide 3-kinase (PI3-kinase) pathway is abnormally active in glioma cells, leading to uncontrolled proliferation despite treatment with known anti-cancer agents such as radiation. I am interested in the role of the P13-kinase signaling pathway in modulating glioma resistance to conventional treatment modalities, including radiation. Understanding this mechanism may allow the development of drugs that disrupt glioma proliferation and possibly increase the effectiveness of radiation therapy. Sensitizing tumors to radiation could result in enhanced killing of tumor cells by radiation therapy, and perhaps less radiation would be required to achieve tumor control.

SUMMARY

Dr. Nakamura's funding will be used to explore the possibility of developing radiosensitizing drugs from agents which block the signals of an enzyme called P13-kinase. P13-kinase sends growth signals to tumor cells, which can cause tumor cells to proliferate. It is possible that the P13-kinase signal may help tumor cells to resist the toxic effects of chemotherapy and radiation. By studying how this enzyme controls a tumor cell's response to radiation, Dr. Nakamura hopes to develop better ways to combine drugs with radiation. She will also see if combining rapamycin, a drug capable of stopping signals given off by P13-kinase, with radiation can be more effective in killing tumor cells than radiation alone. Her work will be done in laboratory models.

Dr. Nakamura's sponsor, Daphne Haas-Kogan, MD, was also the recipient of an ABTA Research Fellowship Award. We proudly welcome Dr. Nakamura to the "ABTA family."

DEVELOPMENT OF MODEL SYSTEM FOR THE STUDY OF EGFR IN MALIGNANT GLIOMAS

Despite the overall progress in the battle against cancer, improving the prognosis for patients with glioblastoma remains a challenge. Epidermal growth factor receptor (EGFR) gene amplification is a common gene alteration in glioblastoma development occurring in approximately a third of these tumors. Unfortunately, the shortage in the availability of cell lines with which to study these important gene alterations has been a major roadblock in the understanding of the impact of this genetic aberration on the biology of glioblastoma. To date, the passage of tumor cells as xenografts represents the single established model system to maintain EGFR amplification/mutation and associated high levels of Egf receptor expression. While EGFR amplification is frequently observed *in vivo,* it is virtually never observed *in vitro.* This is in striking contrast to the other genetic alterations — such as TP53, CDKN2A, and PTEN — which are able to maintain stable amplification *in vitro.*

In this project we propose to establish stable tumor xenografts and cell lines in an effort to develop model systems for the study of EGFR amplification both, *in vivo* and *in vitro.* This will help us understand the mechanism and consequences of EGFR amplification in glioblastomas. This information may lead to new treatments that will hopefully improve the survival and quality of life of patients affected with this aggressive tumor.

SUMMARY

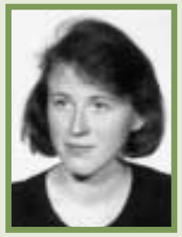
Approximately 40% of human glioblastomas contain the EGFR (epidermal growth factor receptor) gene in abnormally high quantities. However scientists have been unable to fully study the impact or pathway by which this works since this same over-expression does not seem to happen in laboratory *in vitro* models. Dr. Pandita theorizes that chemical conditions unique to the body may account for the difference in results obtained from *in vivo* (in the body) and *in vitro* (laboratory) models. He will use ABTA funding to create a new *in vitro* model which maintains EGFR amplification for future EGFR research.

Ajay Pandita, PhD
Mayo Clinic
Rochester, Minnesota and
University of Toronto
Toronto, Ontario

SPONSOR
C. David James, PhD
Abhijit Guha, MD, MSc, FRCS (C)

AWARD
Audley A. Ciamporcero, Jr./ ABTA Fellowship

2002-2004 Basic Research *Fellowships*



Beata Pyrzynska, PhD
Emory University
Atlanta, Georgia

SPONSOR
Erwin Van Meir, PhD

AWARD
Maryl Temkin/ABTA Fellowship

ROLE OF P53-REGULATED GENES IN GLIOMAGENESIS

Genetic mutations of the p53 gene or of the genes regulating p53 activity can lead to the loss of its tumor suppressor function. Furthermore, some mutations can induce the p53 protein to gain a new function. We hypothesize that mutant p53 in glioblastomas gains the ability to induce gliomagenesis, in particular blood vessel formation (angiogenesis), which is required for solid tumor growth and expansion of metastatic colonies.

P53 is a transcription factor that can up-regulate and down-regulate the expression of many genes. We plan to compare the gene expression pattern in the cells with normal "wild-type" and mutant p53, and to identify the putative targets of p53. We will use microarray technology that permits us to analyze at once a broad range of genes. In addition we propose to focus on those genes that may control gliomagenesis, in particular angiogenesis, and confirm their role in experimental models *in vitro* and *in vivo*.

The first two candidate genes to be examined in these experiments will be cathepsin-B and stromelysin-3. Cathepsin-B has been shown to correlate with the invasive nature of glioblastomas and to regulate angiogenesis by inhibition of tissue of matrix metalloproteinases. Stromelysin-3 is a member of the metalloproteinase family, involved in blood vessel formation. The identification of molecular events by which p53 alteration triggers gliomagenesis may potentially guide the design of novel therapeutic agents for brain cancer.

SUMMARY

The objective of this proposal is to identify genes involved in the growth of the blood vessels which feed a tumor and to examine the role of these genes in glioma development. The p53 gene is mutated in about 30-40% of all astrocytic tumors, and alterations of the p53 pathway are found in up to 80% of these tumors. The impact, however, of these p53 mutations is poorly understood. This study will explore our understanding of p53 and its products during the formation and malignant progression of astrocytomas — tumors that originate from glial cells and are one of the most vascularized tumors.

THE ROLE OF SHH-GLI PATHWAY IN THE INITIATION AND MAINTENANCE OF GLIOMAS

Deregulation of the Sonic Hedgehog (SHH) pathway, a cascade involved in several aspects of CNS development, has been implicated in different types of cancer including basal cell carcinomas, rhabdomyosarcomas, and medulloblastomas. A known transcription factor and mediator of the SHH signal, GLI is capable of mimicking the SHH effect.

Previous results from our lab have shown that the SHH-GLI pathway regulates dorsal brain growth and is deregulated in brain tumors, including PNETs and gliomas, possibly being a cause for their initiation and maintenance. We propose to study these issues by testing whether forced expression of GLI1 in GFAP- or in Nestin-positive cells in two transgenic mouse models results in brain tumor formation. We also have recently demonstrated the ability of cyclopamine, a plant compound derived from lilies, to inhibit the proliferation of brain tumor cells, which suggests that the SHH pathway is also required for tumor maintenance.

To further investigate the action of cyclopamine, we will study what happens to cells that stop proliferating and whether they re-enter the cell cycle upon cessation of the cyclopamine treatment. Since GLI function could be required for tumor maintenance, we will attempt to inhibit brain tumor growth by specifically inhibiting GLI function. We are very enthusiastic about the possibility that our work on the SHH-GLI pathway in normal development and tumorigenesis will reveal important aspects of brain precursor regulation, as well as potential rational therapeutic agents.

SUMMARY

Dr. Sanchez has been studying the role of the SHH-GLI cascade in the normal growth and development of the brain. The laboratory in which she works has previously shown that this pathway regulates dorsal brain growth and that it is deregulated in brain tumors. Dr. Sanchez will use her funding to study the effect of the expression of GLI in tumor formation and the results of inhibiting the pathway.

Maria-Pilar Sanchez, PhD
New York University
New York, New York

SPONSOR
Ariel Ruiz i Altaba, PhD

AWARD
Emily Dorfman Foundation for Children/ABTA Fellowship

2002-2004 Basic Research *Fellowships*

Dawid Schellingerhout, MBChB
Massachusetts General Hospital
Boston, Massachusetts

SPONSOR
Ralph Weissleder, MD, PhD

AWARD
Laurie Deierlein/ABTA Fellowship

VIRAL GENE THERAPY TO BRAIN TUMORS: DEVELOPING THE IMAGING TOOLS TO OPTIMIZE GENE DELIVERY AND NON-INVASIVELY DETECT GENE EXPRESSION

Gene therapy is a promising modality of treatment for brain tumors, but difficulties in vector delivery and expression have so far hampered the translation of this therapy into clinical practice. All gene therapy approaches have these features in common: genetic materials need to be delivered to their target tissue, and therapeutic genes need to be expressed in these tissues. These basic steps have also been the stumbling blocks in advancing gene therapy from cell culture to intact organisms — and both are amenable to imaging strategies to allow their optimization.

This study will explore novel imaging techniques that may be useful in assessing the delivery and effects of viral gene therapy. Imaging the virus will allow the formulation of strategies to overcome these difficulties, and will lay the groundwork for successfully getting this novel therapy to work in patients. We propose a variety of strategies that could be used to improve viral delivery using an imaging technique specific for viral delivery, which for the first time allows the assessment of the efficacy of such manipulations. We further propose to detect and quantify gene expression using a novel optical imaging technique, and to provide a comprehensive set of innovative imaging tools to allow the further development of the field of viral gene therapy for brain cancer.

SUMMARY

The goal of this study is to use imaging technology to maximize the delivery of viral gene therapy. This lab recently developed a radionuclide-based imaging technique to track the distribution of viral vectors used in gene therapy. More recently, they have developed an optical imaging system that allows researchers to visualize the expression of marker genes. Dr. Schellingerhout will use these imaging techniques to study the effects of manipulating the blood brain barrier and the immune system during gene therapy, hoping to optimize viral delivery and gene expression.

TRANSGENIC MOUSE MODEL ASTROCYTE-SPECIFIC KNOCKOUT OF PTEN/MMAC1

Therapies against human astrocytomas based on encouraging pre-clinical results in current *in vitro* and xenograft-based astrocytoma models have not shown efficacy in clinical trials. This may be due to our incomplete molecular understanding of these tumors and/or testing therapies in less than ideal models. This project will develop and characterize models with astrocyte-specific loss of the tumor suppressor PTEN/MMAC 1, which is the most common molecular signature of glioblastoma multiforme. In a study assessing the frequency of PTEN mutations in de-novo glioblastomas vs. secondary glioblastomas, 32% of de-novo tumors contained a PTEN mutation while only 4% of secondary tumors contained the mutation.

My project will concentrate on astrocyte-specific knockout of PTEN/MMAC1. Two strategies will be used. The first is knockout of PTEN in embryonic astrocytes or glial cell precursors, which may promote astrocytomas and perhaps tumors of other glioma lineages. The second is PTEN knockout in adult astrocytes, which can overcome embryonic lethality possibly caused by the first strategy. These strategies will allow us to understand the role of PTEN by itself and in the context of other genetic alterations towards astrocytoma development. These models may also serve to test novel biologicals as they more closely resemble the pathological and molecular profiles of human astrocytomas, compared to currently available xenograft based models.

SUMMARY

Currently, there are two known pathways by which glioblastomas are thought to develop: they may arise from a lower grade astrocytoma (and thus are called "secondary" glioblastoma), or they may start as a grade IV tumor ("de novo" glioblastoma.) Laboratory studies show that each has unique molecular markers as well as markers that are shared between the two types. This laboratory is working toward development of mouse models of each of these glioblastomas to help researchers learn if these molecular findings have any significance. Dr. Wei will work on development of a model of the glioblastoma that arises from lower grade astrocytoma, and the role of the PTEN gene in creating that model.

Qingxia Wei, PhD
The Hospital for Sick Children
Toronto, Ontario

SPONSOR
Abhijit Guha, MD, MSc, FRCS (C)

AWARD
Emily Dorfman Foundation for Children/ABTA Fellowship

2002-2003 Translational *Grants*

This year we proudly announce three $50,000 grants for translational research. Support for these projects will assist these researchers in bringing their work from the "bench" to the "bedside." These studies provide a link between the molecular-level laboratory research and the data necessary to move this work into human clinical trials — new research treatments for people with brain tumors.

Richard A. Gemeinhart, PhD
University of Illinois—Chicago

AWARD
Kathy Murphy/ABTA Grant

Please note: This work will be done in the laboratory. If successful, it may one day lead to a clinical trial in humans.

MICROPARTICLE-DRUG CONJUGATES AS NOVEL CHEMOTHERAPEUTIC AGENTS

Brain tumors are one of the largest categories of malignant tumors in humans and at the same time, one of the most difficult to treat. Even when surgery is possible, there is typically a short remission time followed by re-emergence of the cancer at the site of resection or distant from that site. Controlled drug delivery devices are currently available, but these devices do not selectively treat recurring cancer nor do they treat distant recurrence. This research will test the hypothesis that targeted chemotherapy delivery increases the effectiveness of conventional chemotherapeutic agents. The delivery devices can be injected in the brain following surgery and will be free to move throughout the brain. However, they will be designed to only deliver the active agent in the presence of actively growing cancer cells.

To accomplish the goal of producing chemotherapeutic agents that target brain tumors, three specific aims will be investigated:

- to synthesize targeted microparticle-drug conjugates,
- to determine the *in vitro* release rate from microparticle-drug conjugates,
- to determine the effectiveness of microparticle-drug conjugates *in vitro.*

The chosen method of targeting is an enzyme naturally secreted from cells but selectively overexpressed in brain tumors. The enzyme cleaves the chemotherapeutic agent from the microparticle. Since these enzymes are naturally present in actively growing brain tumor tissue, the drug cleavage will be concentrated at the site where the cancer cells are the most active.

Chemical and physical analysis of the microparticles will be conducted, followed by *in vitro* delivery studies to determine the selectivity and rate of release of the model chemotherapeutic agent, camptothecin. *In vitro* cytotoxicity will be examined using human glioblastoma cells that are known to exhibit similar traits to those tumors *in vivo.* Finally, the post-release condition of the microparticles will be examined using fluorescent microscopy.

Upon completion of the project, novel methods for delivering chemotherapeutic agents will have been examined that will allow targeted delivery of anti-cancer drugs for people undergoing brain tumor resection.

TARGETED IMAGING IN THE MOUSE BRAIN TUMOR MODEL

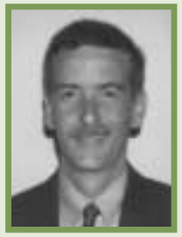
Astrocytic tumors are the most common primary central nervous system neoplasm. Glioblastoma multiforme is the most common of the astrocytic tumors, primarily affecting individuals over age 45. Advancement in the treatment of these tumors is dependent upon an understanding of the events that lead to neoplastic conversion.

The shift in the angiogenic balance or ability of a tumor to make its own blood vessels is seen as a critical threshold in the promotion and progression of malignancy. Malignant brain tumors are one of the most angiogenic forms of cancer, thus highly dependent upon their ability to produce blood vessels. As our understanding of the molecular processes that support the ability of tumors to make blood vessels advances, novel therapies are becoming available for patients.

One of the challenges researchers face when screening drugs for effectiveness is developing an understanding of how the drug works. By learning whether a drug's action is targeted at a specific biologic process, we are hopeful of developing specific methods of determining if the drug is doing what we hope it will do in patients once it begins clinical trials.

This research project is novel in that it focuses on the pre-clinical study of a new targeted imaging agent, called PM-PV, being developed by a biotechnology company. Our research has three aims: we plan to determine the apparent binding affinity of the drug in human glioma and endothelial cell lines, determine the distribution and clearance of the drug through our brain model, and determine the utility of this drug for quantitative MR imaging. This work will be performed in the laboratory and will hopefully provide the basis for future human testing of this imaging agent.

Our ability to non-invasively evaluate the neovascularization of malignant brain tumors and follow this process during anti-angiogenic therapy will advance the care of patients with malignant brain tumors and identify agents which are effective against this aggressive form of cancer.



Burt Nabors, MD
University of Alabama at Birmingham

AWARD
George Kamberos/ABTA Grant

2002-2003 Translational *Grants*

Khalid Shah, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

AWARD
Lynne Batchelor/ABTA Grant

NIRF IMAGING AND SELECTIVE TUMOR CELL APOPTOSIS USING VIRAL GENE DELIVERY VECTORS TO GLIOMAS

In order to compare and optimize different therapeutic genes and delivery modalities it is imperative to be able to non-invasively image therapeutic gene expression in models and human patients. Our goals are to develop technology that can be widely applied to brain tumor paradigms in order to affect on-site visualization of gene therapy *in vivo*. The aims of this project are:

1. to develop novel probes, tools and imaging strategies through use of HSV amplicon vectors and non-invasive optical imaging
2. to visualize novel therapies at the molecular level through delivery of a protease which triggers cellular apoptosis by release of non-active endoplasmic reticulum (ER)-bound protein to the cell surface, in addition to activating fluorescence of optically quenched near infrared fluorescent (NIRF) probe in targeted tumor cells.

We are interested in combining protease-activated noninvasive optical imaging with protease-controlled release of apoptotic proteins to visualize both transgene delivery and expression. Our research will consist of three components: the HIV-1 (Human immunodeficiency virus-1) or HSV-1 (Herpes Simplex virus-1) protease, depending on which one confers more specificity; the apoptotic protein TRAIL (tumor necrosis factor apoptosis inducing ligand); and the NIRF probe.

We will develop peptide-caged NIRF probes specific for HIV- I and HSV- I proteases and use them in imaging gene delivery to glioma cells in culture and in models. The apoptotic properties and the bystander effect of TRAIL and truncated TRAIL proteins will also be compared. Tumor cell apoptosis will be controlled by targeting the TRAIL protein to the ER using HSV amplicon vectors. The infection of the tumor cells by HIV-1 or HSV-1 protease bearing amplicon vectors is intended to release the TRAIL protein from the ER and result in cell death. This will enable us to monitor the transgene delivery and expression *in vivo* by administering and imaging long circulating, synthetic, optically quenched NIRF probes. The intracellular release of NIRF probes by specific protease will result in a fluorescent signal that can be detected *in vivo* in subnanomolar quantities and at depths sufficient for experimental or clinical imaging.

Epidemiology *Grant*

Funding continues for our largest ever research grant. This $200,000 project grant was made possible by special sponsorship provided by BP Amoco.

ROLE OF ETHNICITY IN SURVIVAL OF PATIENTS WITH PRIMARY MALIGNANT BRAIN TUMORS: A MOLECULAR EPIDEMIOLOGY PILOT STUDY

PRINCIPAL INVESTIGATOR
Jill Barnholtz-Sloan, PhD
Karmanos Cancer Institute and
Wayne State University
Detroit, Michigan

AWARD
BP Amoco/ABTA Grant

Two previous studies suggest that malignant brain tumors undergo different oncogenic pathways in Caucasians and non-Caucasians. However, one study included only 6 African-Americans in the 172 study subjects and the other did not include any. To date, there has not been any investigation of the molecular epidemiology of malignant primary brain tumors specifically in African-Americans. Since this population comprises 25% of the Metro-Detroit SEER registry, and because this registry supplies about 35% of data on African-Americans nationally, the investigators are uniquely suited to address this issue. A better understanding of these genetic differences between ethnic groups may lead to identification of new targets and strategies for prevention and/or cure.

The investigators are conducting a prospective, population-based pilot study utilizing the SEER rapid reporting mechanism, to identify Caucasian and African-American patients with newly diagnosed primary malignant brain tumors. Dr. Barnholtz-Sloan assesses clinical and epidemiologic variables using a chart-review and by interviewing participating patients using a clinical instrument designed and pioneered by Dr. Margaret Wrench. Dr. Andrew Sloan screens for p53 mutations and loss of heterozygosity at three chromosomal locations of known significance in glioma oncogenesis.

This proposal fits well with objectives of the National Cancer Institute strategic plan to reduce cancer-related health disparities. It also ties in with the epidemiologic priorities of the recently established brain tumor progress review group (BT-PRG). Therefore, it is believed that this pilot study has a high likelihood of leading to future funding from the National Institutes of Health.

Andrew Sloan, MD, Wayne State University is the co-investigator on the study. Margaret Wrensch, PhD, University of California San Francisco, Ann Schwartz, PhD, MPH, Director of the Detroit SEER Registry at Wayne State University and Mark Hughes, MD, PhD, Director of the Center for Molecular Medicine and Genetics at Wayne State University serve as consultants.

2002-2003 Project *Grants*

This year two $50,000 grants were awarded to researchers for pre-clinical work. It is hoped the funding for these projects will assist these researchers in subsequently qualifying for substantial funding opportunities in government or industry.

Chulhee Choi, MD, PhD
University of Alabama at Birmingham

AWARD
Catherine Leigh O'Rourke/ ABTA Grant

ROLE OF THE UBIQUITIN/PROTEASOME PATHWAY ON DEATH RECEPTOR SIGNALING IN ASTROGLIOMA

Glioblastoma multiforme (GBM) is the most common form of primary brain tumors in adults and can be resistant to therapeutic approaches. Therefore, development of effective treatments will be tremendously beneficial for patients with GBMs. Although FasL and TRAIL are considered potential "magic bullets" for treatment of GBMs, we have recently shown that human GBM cells can utilize these ligands to transduce inflammatory and angiogenic signals, which are crucial for tumor growth and invasion. The proposed research is designed to investigate further the molecular mechanisms by which the fate of these cells is determined upon FasL and/or TRAIL ligation.

This study will focus on the role of the ubiquitin (Ub)/proteasome pathway as a modulator of ligand-mediated signaling in the aspect of two functional outcomes, apoptotic cell death and IL-6/IL-8 expression. The research we propose suggests that the Ub/proteasome pathway promotes survival of cells by enhancing inflammatory/ angiogenic signals (NF-κB pathway) and suppressing apoptotic cascades (caspase pathway), so that inhibition of this pathway renders cells more susceptible to ligand-mediated cytotoxicity and can be used to potentiate the efficacy of FasL and/or TRAIL in GBMs. My preliminary data provides support for this hypothesis by demonstrating that inhibition of the Ub/proteasome pathway markedly enhances ligand-mediated cell death of human glioma cells via several distinct mechanisms; suppression of NF-κB activation and stabilization of active caspases.

Given the two distinct signal transduction pathways of FasL and TRAIL, my work will re-evaluate the role of the Ub/proteasome pathway on two functionally distinct outcomes of FasL and TRAIL ligation and the molecular events responsible for these outcomes. This novel approach will provide us with a more complete picture of the role of the Ub/proteasome pathway on death ligand signaling, and the background to develop better therapeutic strategies for human brain tumors.

ROLE OF THE CEREBRAL RENIN-ANGIOTENSIN SYSTEM IN RADIATION-INDUCED BRAIN INJURY

Despite the combined use of surgery, radiation therapy and chemotherapy, the long-term survival for people with malignant brain tumors remains challenging. The inability to kill all tumor cells reflects the inability to use enough radiation due to concerns over damaging too much normal brain tissue. Exposing normal brain tissue to excess radiation can lead to devastating functional deficits several months to years after irradiation. Recent data suggest that dementia occurs in 30-50% of brain tumor patients who are long-term survivors after receiving brain irradiation.

Radiation-induced injury was thought to be irreversible and untreatable. In recent years, however, a number of kidney, lung and heart studies demonstrated that blocking the function of a growth factor called angiotensin II (Ang II) reduces the severity of radiation-induced injury. Ang II is produced in the blood and distributed throughout the body, but it is also made in a number of tissues including the kidney, lung, heart and brain. Its function in the normal or damaged brain is still unclear. We propose that brain radiation leads to increased Ang II production, resulting in the development of radiation-induced injury.

Our studies will be carried out using cultured cells grown in rats and genetically altered mice. Astrocytes will be isolated from rat brain tissue then grown in culture to determine how they respond to radiation and Ang II. At the same time, we will study the radiation response of mice that produce normal amounts of Ang II with mice that produce increased amounts of Ang II. The mice will be followed for a period of up to 300 days after irradiation — a time period comparable to many years in the life of a person.

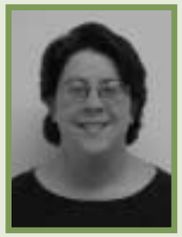
Identifying a role for Ang II in radiation-induced brain injury offers the promise of developing rational interventional therapies aimed at selectively reducing the severity of radiation-induced injury. Of note, drugs that block the affect of Ang II have been routinely prescribed as anti-hypertensive drugs for a number of years, and are well tolerated. Thus, the establishment of a role for Ang II in radiation-induced brain injury will lead to the rapid translation of these findings to the clinic. The hope of protecting normal brain from radiation injury, leading to the possibility of increased, more effective radiation doses to the tumor may be able to impact both the quality of life and long-term survival of glioma patients.

Michael Robbins, PhD
Wake Forest University School of Medicine
Wake Forest, North Carolina

AWARD
Butler Family Foundation/ ABTA Grant

2002 Nursing *Research*

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 of this evidence-based research with an annual neuro-oncology nursing research award through the Oncology Nursing Foundation of the Oncology Nursing Society. Nurses interested in applying for this award should contact the Oncology Nursing Society at 412-921-7373.



Paula Riess, RN, MSN, CNRN
Michigan State University
East Lansing, Michigan

MENTOR
Barbara Given, RN, PhD, FAAN

AWARD
ABTA and ONS Research Award

FAMILY CARE OF BRAIN TUMOR PATIENTS

Changes in health care reimbursement often make family members responsible for providing care, even though they may not feel prepared to deliver this care. Researchers have documented the effects of providing care for a person with an illness such as cancer and for a person with cognitive and behavioral problems such as the dementia patient. However, there have been minimal efforts to describe the impact of providing care for persons who may suffer from the trajectory of illness associated with having cancer and a deterioration in cognitive and behavioral status.

The purpose of this study is to identify factors that are associated with the burden and depression of family caregivers of persons with brain tumors. The specific aims of the project are:

1. to describe the association between the patient's functional, cognitive, and behavioral status and the burden and depression of caregivers of persons with a brain tumor; and
2. to describe the moderating relationship of mastery and perceived adequacy of information to care on the burden and depression of these caregivers.

During this project, caregivers of patients with a primary malignant brain tumor will participate in a one-time telephone interview, where they will be asked questions about the patient's status and about the caregiver's feelings and opinions of the challenges involved in providing care. Study results will enhance both clinical practice and research. In the area of clinical practice, study results will help health care practitioners identify characteristics of caregivers of persons with a brain tumor that may place them at risk for burden and depression. If interventions can be aimed at meeting the needs of these caregivers, caregiver health can be improved. In the area of research, results will help to identify factors that may be amenable to future intervention studies, and add to the generalizability of findings from studies to caregivers at large.

Sharing *Knowledge*

THE AMERICAN COLLEGE OF SURGEONS ONCOLOGY GROUP OPENS Z0300, GROUP'S FIRST NEUROSURGERY STUDY

The American College of Surgeons Oncology Group (ACOSOG) has activated study Z0300, "A phase III randomized trial of the role of whole brain radiation therapy in addition to radiosurgery in the management of patients with one to three cerebral metastases." Z0300 is the first study opened by the Group's Brain and Central Nervous System Organ Site Committee.

Participating patients will receive either radiosurgery (RS) alone (Arm 1) or RS combined with whole brain radiation therapy (Arm 2). The primary objective of the study is to ascertain if one treatment, compared to the other, is associated with better overall survival. Secondary objectives will compare time to local failure, quality of life, duration of functional independence, long-term neurocognitive status, and post-treatment toxicity.

The study provides an opportunity to gain critical comparative data about therapeutic options for patients with cerebral metastases arising from an extra-cerebral primary tumor. Anthony Asher, MD, Director of the Brain Tumor Program at Carolinas Medical Center in Charlotte, North Carolina, is the study chair for ACOSOG Z0300.

Physician investigators interested in participating in Z0300 can find membership applications and other information about the study on the Group's web site at *www.acosog.org*. Patients interested in the study can learn more at the National Cancer Institute's web site, *www.cancer.gov*.

For more information about Z0300 or other ACOSOG trials, please contact Meggan Monroe, ACOSOG Public Relations Coordinator, at 919-668-8156 or via e-mail to *monro015@surgerytrials.duke.edu*.

Sharing *Knowledge*

RESEARCH RECEPTION

ABTA Research Award recipients completing their research term in 2002 met in Chicago to report their results to the ABTA Board of Directors, medical professionals, patients and families. A poster reception provided a forum for face-to-face interaction between the researchers and those attending. Following the poster presentations, each researcher presented a short oral summary of their work and answered questions.

Our appreciation to Jan Buckner, MD, Medical Oncologist, Mayo Clinic in Rochester, Minnesota for moderating this session. Dr. Buckner chairs the North Central Cancer Treatment Group, serves on the Editorial Board of "Neuro-Oncology," consults for the FDA Center for Drug Evaluation and Research, Division of Oncology Drug Products and their Oncologic Drug Advisory Committee. He is also a past officer of the Society for Neuro-Oncology, a member of the American Society of Clinical Oncology and of the American Association of Cancer Research. And, most importantly to us, Dr. Buckner is a highly regarded member of our distinguished Scientific Advisory Council.

JAN BUCKNER, MD

RESEARCH SUMMARIES

Christine E. Fuller, MD
Washington University
St. Louis, Missouri

AWARD
Laurie Deierlein/ABTA Fellowship

MIXED OLIGOASTROCYTOMAS (MOAS) AND OTHER MORPHOLOGICALLY AMBIGUOUS GLIOMAS: A COMBINED HISTOLOGIC AND GENOTYPIC APPROACH TO DIAGNOSIS

Mixed oligoastrocytomas (MOAs) are notoriously difficult to define and our ability to effectively stratify such tumors into prognostically significant groups is limited. Although a few histologically biphasic MOAs have been genetically characterized, studies of MOAs in which the two cell types are intimately admixed or exhibit hybrid astrocytic/oligodendroglial features are lacking.

From roughly 900 diffuse gliomas from the files at Washington University (1987-2000), 155 admixed/hybrid MOA candidates were independently classified and graded by five neuropathologists, with consensus-derived (3/5 pathologists) pure oligodendrogliomas and astrocytomas excluded from further study. The 89 remaining cases (MOA grades II=28, III=44, IV= 17) were analyzed. EGFR amplification was found in 11%. Patients were followed for a mean of 4.4 years. Prolonged median survival (8 years) was associated with 19q deletion or lp/19q co-deletion, whereas EGFR amplification or deletions of PTEN, DMBT], or p16 were all encountered in patients with shorter median survival.

We conclude that: 1) intermixed MOAs are genetically heterogeneous, and distinct subsets may be identified using FISH on routine paraffin-embedded tissue, 2) both histologic grading and FISH analysis yield prognostically useful, non-overlapping information, and 3) the wide biologic variability in this challenging group of tumors warrants a combined histologic and genotypic approach for improved patient stratification and management.

Research *Summaries*

BAX PROTEIN METABOLISM: A NOVEL MECHANISM FOR THERAPEUTIC RESISTANCE IN GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme (GBM) is a malignant brain tumor that accounts for approximately 23% of tumors of the central nervous system (CNS). Although the primary treatment for these tumors is radiation therapy, they are relatively resistant to such treatment. Cells derived from GBM do not undergo apoptosis, a form of cell death, following radiation treatment. An apoptotic response is critical for any cytotoxic therapy to be effective.

The expression of BAX, a molecule that is normally induced by DNA damage and causes apoptosis in numerous cell types, does not increase in GBM following radiation. In addition, GBM cells have high levels of BAX. It has been previously shown that forced over-expression of BAX in GBM cells results in apoptosis. We hypothesized that alterations in the regulation of BAX expression or modifications of the BAX protein prevent GBM cells from undergoing radiation-induced apoptosis. To investigate these possibilities, we studied the promoter region of the BAX gene, the cellular localization of BAX, and other proteins that may bind to the BAX protein.

Arlene Hwang, PhD
University of California
San Francisco, California
Case Western Reserve University
Cleveland, Ohio

AWARD
Joel A. Gingras, Jr./
ABTA Fellowship

INTRACRANIAL CHEMO-IMMUNOTHERAPY FOR MALIGNANT GLIOMAS

This research was aimed at developing a combined chemo-immunotherapy protocol for the treatment of malignant brain tumors. Dr. Lesniak has been able to show a powerful synergistic effect between BCNU (Gliadel) and a cytokine, interleukin-2 (IL-2), in experimental brain tumors. Over 80% of animals treated with this form of therapy are long-term survivors of malignant brain tumors.

Indeed, this research has sparked a strong interest among the pharmaceutical industry and plans are currently underway for designing a phase I clinical trial involving BCNU with IL-2.

Maciej S. Lesniak, MD
Johns Hopkins Hospital
Baltimore, Maryland

AWARD
Mickey Gitlitz/ABTA Fellowship

Research*Summaries*

Patrick B. Senatus, MD, PhD
Columbia-Presbyterian Medical Center
New York, New York

AWARD
Catherine Leigh O'Rourke/ ABTA Fellowship

Dr. Senatus met Rosemary O'Rourke, Catherine's mom and founder of Cathy's Connection.

INTRACEREBRAL CLYSIS IN A RAT GLIOMA MODEL USING A P53-DERIVED C-TERMINAL PEPTIDE

My work in the Bartoli Brain Tumor Laboratory has focused on a novel molecular mechanism of tumor suppression. Within each cell there exists a common innate protective process that controls that cell's ability to divide and propagate its genetic material. This mechanism is activated when the cell is injured by toxins, carcinogens, or metabolic stresses that suggest violation of cellular genetic integrity.

Cells with malignant potential are thereby eliminated from the genetic pool. When this protective process is intact, the cellular protein p53 initiates a self-destruct sequence that eliminates defective cells from the propagating pool by a process called apoptosis.

In brain tumors, although p53 is present (often in increased quantities), p53 function is defective. Through genetic analysis of the p53 molecule the most common reasons for p53 dysfunction have been identified and peptides designed to rescue function have constructed. With the support of the American Brain Tumor Association, I have used malignant glioma cell lines derived from murine and human sources to demonstrate the efficacy of novel chimeric peptides in the control of malignant cell propagation.

Laurence Cooper, MD, PhD
City of Hope National Medical Center
Duarte, California

AWARD
Nancy Mattison/ABTA Grant

Nancy Mattison's parents, Ray and Diane, meet with Dr. Cooper.

STUDY OF PEDIATRIC BRAIN TUMOR AS A POTENTIAL T-CELL TARGET: IMPLICATIONS FOR ADOPTIVE IMMUNOTHERAPY OF MEDULLOBLASTOMA

Medulloblastoma is a malignant brain tumor that usually develops in young children. Some cannot be cured using conventional treatment, so additional therapeutic options are desperately needed. Moreover, the remedies now used to achieve a cure can damage a child, raising the need for therapies that reduce the side effects of current treatments. Therapy using specialized immune cells is a new approach that may not only improve overall survival, but might improve the quality of life of the survivors.

We are conducting research into how T-cells, the immune system cells responsible for defending against disease, can be genetically modified and introduced back into the body to combat brain tumors, such as medulloblastoma. This research focuses on the process of reprogramming a patient's own T-cells to provide a supply of potent tumor-specific cells that can be used for therapy. Combining the power of immunotherapy and gene therapy may improve the treatment for children and adults who have cancer in or out of the central nervous system.

A NOVEL CANDIDATE PROTO-ONCOGENE OVEREXPRESSED IN HUMAN BRAIN CANCER

Glioblastoma multiforme is the most common primary neoplasm of the central nervous system. To identify genes that may be involved in the malignant progression of these brain tumors, representational difference analysis (RDA) and differential immuno-absorption (DIA) were performed between glioblastoma multiforme tumors and normal brain tissues. Candidate clones were then screened using CDNA microarray analysis.

Here we report the identification of a novel CDNA that we designated L17, which was independently isolated from both subtractive approaches. Tumor-associated expression was confirmed. Sequence analysis showed no significant homology to any known genes, although homology was detected with an uncharacterized expressed sequence tag (EST). This novel gene mapped to chromosome Xp I 1.3. Transfection of a murine glial cell line and human glioblastoma cells with sense CDNA for L17 resulted in a dramatic increase in cell proliferation, while transfection with antisense L17 CDNA resulted in significant growth arrest and morphological changes.

We then hypothesized that antibodies targeted to the L17 gene product may have antitumor effects on human glioblastoma cells *in vitro*. Phase-contrast microscopy indicated that the tumor cells treated with the L17 antibody did not spread as well as the control cells and maintained a more rounded morphology. Furthermore, the L17 antibody-treated cells exhibited a dose-dependent decrease in cellular proliferation.

These results suggest a potentially important role for L17 in the malignant transformation and/or progression of human brain cancer.

An explanation of the import of the L17 gene was provided by Dr. Liau.

Linda Liau, MD, PhD
UCLA School of Medicine
Los Angeles, California

AWARD
BP Amoco/ABTA Grant

Dr. Liau shares results of her work with colleague, Hiro Yamamoto, PhD.

Research *Summaries*

Joon Uhm, MD
Mayo Clinic
Rochester, Minnesota

AWARD
The Sontag Foundation/ ABTA Grant

Details of this clinical trial can be found at www.cancer.gov. *Look for Protocol ID: NCCTG-N0074.*

THE ROLE OF ABERRANT EPIDERMAL GROWTH FACTOR RECEPTOR SIGNALING IN THE INVASIVE PHENOTYPE OF MALIGNANT GLIOMAS

Genetic alterations of EGFR (epidermal growth factor receptor) constitute one of the most frequent oncogenic changes in malignant gliomas. While the importance of aberrant epidermal growth factor receptor (EGFR) activity in glioma proliferation has been well demonstrated, much less is known about the impact of this receptor protein tyrosine kinase on the invasive behavior of gliomas, a feature which underlies the poor prognosis associated with these tumors. Our laboratory has pursued the hypothesis that mutations of EGFR that occur frequently in glioma enhance tumor invasiveness and that this biologic property can be inhibited by drugs that target EGFR signaling.

Over the last year, we have shown that EGFR activity enhances invasion by two mechanisms. First, integrins, which provide tumor cells with the traction necessary for motility, are translocated to the plasma membrane, where they are biologically active. Second, EGFR activity increases the expression of matrix metalloproteinase-1 (MMP-1) by glioma cells both *in vitro* and *in vivo*. And, preliminary data indicates MMP-1 expression *in vivo* may be restricted to tumors harboring EGFR gene rearrangements.

Given the pleiotropic effects of EGFR signaling on multiple facets of glioma biology, encompassing proliferation, chemoresistance, as well as invasiveness, EGFR represents a viable target for therapeutics to enhance patient care. In this regard, we are performing a phase II clinical trial of the EGFR inhibitor ZD1839 in newly diagnosed glioblastoma patients. This clinical study also incorporates laboratory correlative studies to determine the effect of EGFR mutations on the response/resistance of patient tumors to ZD1839. Taken together, our laboratory studies, meshed with the ongoing clinical trial that targets EGFR, constitute a translational program directed towards delineating the effect of EGFR signaling in glioma biology, which will hopefully lead to advances in the care of our patients.

Sharing *Knowledge*

FINDING A CLINICAL TRIAL

When searching for a clinical trial (a research treatment) patients and families have several databases available to them. The past few years have seen a surge in these resources — and the majority are easily accessed online. Be aware, however, that none of the databases contain every trial, thus, you'll need to look closely at each site. You'll want to find out how each database obtains their trial information, if there is a posting fee involved, or if the site accepts listings from non-sponsoring institutions. You'll also want to carefully read the site's privacy policy to learn if they pass along your personal information to research sites or to the companies sponsoring the listed trials. (Many sites also offer the option of providing information anonymously.) Here are some suggestions to begin your search:

THE NATIONAL CANCER INSTITUTE'S PDQ CLINICAL TRIALS DATABASE

http://cancer.gov/search/clinical_trials/
PDQ contains several files, one of which is a list of clinical trials. That database includes over 160 brain tumor trials which can be searched by tumor type, treatment type, sponsor type, patient age, or geographic region. Both US and international trials are listed. Trial information is also available by phone for those without Internet access — call 800-422-6237 and choose the option of speaking to a Cancer Information Specialist. This service is available in both English and Spanish.

CLINICAL TRIALS AND NOTEWORTHY TREATMENTS FOR BRAIN TUMORS

www.virtualtrials.com
Maintained by Al Musella, DPM, this site offers a database of both clinical trials and new, conventional treatments for brain tumors. The database can be searched by treatment category, by state, or by tumor type. Also offers access to the Emerging Med database referenced below.

CENTERWATCH — CLINICAL TRIALS LISTING SERVICE

www.centerwatch.com
These trials are posted by physicians conducting research at major medical centers and private research centers. Patients can use this site to learn about investigational therapies and identify ongoing clinical research trials. The information is provided by a publishing company covering clinical research as an information source to patients. Also links to the National Cancer Institute's PDQ database.

EMERGINGMED

www.emergingmed.com
A single, short, secure questionnaire matches patients to enrollment criteria for over 100 brain tumor clinical trials. EmergingMed staff then help patients connect to the right trial coordinators.

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

www.phrma.org
PhRMA represents approximately 100 US companies involved in pharmaceutical research. Site includes industry information as well lists of members' new drugs in development.

VERITAS MEDICINE

www.veritasmedicine.com
The Veritas Medicine website clinical trials database allows patients to be matched to clinical trials based on information submitted confidentially. The clinical trial matching tool is supplemented with original information about current and investigational treatments developed by physicians.

Sharing *Knowledge*

NORTH AMERICAN BRAIN TUMOR COALITION

BRAIN TUMOR ACTION WEEK 2002

This year, the week of May 5th was designated Brain Tumor Action Week (BTAW) by the North American Brain Tumor Coalition (NABTC), a network of thirteen brain tumor organizations. Patients/survivors, family members, and their friends came to Washington to honor the survivors, remember those that have been lost, and advocate before our elected representatives for issues of importance to the brain tumor community.

MONDAY, MAY 6:

BTAW activities began with Advocacy Education Day.

- We learned about the NABTC advocacy positions.
- We heard about the rationale for benign brain tumor data collection from Jeffrey Wisoff, MD; a member of Senator Jack Reed's staff (D-RI) informed us about the outlook for introducing such a bill in the Senate to assure that data collection.
- Dr. Howard Fine reported on the NCI/NINDS Neuro-Oncology Branch.
- An in-depth discussion of clinical trials was presented by oncology nurse Anita Nirenberg, MS; Jeffrey Sherman, MD, Chief Medical Officer/ Executive Vice President, NeoPharm, Inc.; Richard Pazdur, MD, Director, Oncology Drug Products Division, Food and Drug Administration; and Howard Fine, MD, Chief, NCI/NINDS Neuro-Oncology Branch.

Hats donated by families who lost a loved one to a brain tumor were displayed around the fountain across the street from the Capitol. This unique, touching memorial was initiated and organized by Marcia Jacobs, whose daughter Anjuli lost her battle to a brain tumor a year ago at age four and one-half.

TUESDAY, MAY 7

Brain tumor constituents, representing twenty-one states, visited with the healthcare legislative aides of our Congressmen and Senators to bring our message. We urged them to:

1. Require implementation of the Brain Tumor Progress Review Group's recommendations
2. Pass the "Benign Brain Tumor Cancer Registries Amendment Act" in the House and introduce a companion bill in the Senate *(see sidebar)*
3. Take actions to ensure a Patient's Bill of Rights, which would guarantee, among other provisions, access to specialty care, clinical trials, and continuity of care

A poignant candlelight vigil, honoring patients and survivors and remembering those who have been lost was held that evening near Arlington National Cemetery. Everyone who attended was emotionally touched by this special event.

As we said our goodbyes, we vowed to expand our efforts to make a positive difference in the lives of brain tumor patients.

WE DID IT!

Thanks to the enormous efforts of our dedicated members, S.2558 was introduced. Senator Jack Reed (D-RI) with original co-sponsors Senators Fitzgerald (R-IL), Cantwell (D-WA), and DeWine (R-OH) introduced the "Benign Brain Tumor Cancer Registries Amendment Act" on May 23rd.

Additional information and detailed instructions on how you can participate in assuring passage of this crucial legislation is available online at the NABTC website *www.nabraintumor.org*. If you don't have access to the Internet, contact our office at 1-800-886-2282 and we'll provide the names and contact information for your Senators, instructions, and a sample letter.

Together, we can help researchers by assuring they will have the information needed to develop successful treatment strategies.

Advocate, Thom Kennedy, traveled from Illinois to participate in BTAW 2002.

Hats Memorial was organized by Marcia Jacobs as a tribute to her daughter, Anjuli.

American Brain Tumor Association

August, 2002

Dear Researcher:

We invite you to join the ABTA Family. We welcome your application for conducting post-doctoral brain tumor research beginning July 1, 2003.

Specifically, we seek:

1.) Investigators, early in their careers, to apply for Fellowship funding for basic brain tumor research. These are two-year $70,000 awards. Eligible candidates are MDs within two years of pre- or post-residency completion, or PhDs with no more than 30 months of postdoctoral laboratory experience.

2.) Junior faculty investigators to apply for translational brain tumor research grants. These are one-year $50,000 awards. Eligible candidates are MDs who are up to five years post-residency and have attained Junior Faculty to Assistant Professor status or PhDs with no more than five years post-doctoral laboratory experience.

3.) Also, project applications for pediatric brain tumors, benign and low-grade brain tumors, epidemiology, genetics and heredity factors, new drug delivery systems and neuroprotective interventions are encouraged.

4.) Mentors for our Medical Student Summer Fellowship program — $2,500 student awards for basic research.

ABTA's Scientific Advisory Council will review all qualified applications. The Board of Directors will determine awards based upon the Advisors' recommendations. Completed applications are due January 8, 2003.

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

Dear ABTA Supporters:

Our research awards can continue because of your generosity, and others like you. If you or a loved one has a brain tumor, consider making a research gift. Donations can be made for birthdays, anniversaries, end-of-treatment celebrations, or any special occasion. If you've lost someone to a brain tumor, commemorate the difference they made in your life. Donations can be made using the enclosed envelope, or call us at 800-886-2282. You can also make a secure donation online at www.abta.org.

Thank you, one and all!

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In the *News*

A new National Cancer Institute brochure, *If You Have Cancer and Have Medicare…You Should Know About Clinical Trials,* addresses patient rights, costs covered by Medicare, and other issues important to patients considering treatment options. To receive a free copy in either English or Spanish, call the Cancer Information Service at 800-422-6237.

If you've not yet seen it, we've greatly expanded our *Dictionary for Brain Tumor Patients.* This newly updated book provides patients and families with over 130 pages of brain tumor terms, explained in everyday language. Single copies are free. Send your e-mail request to *info@abta.org.* Be sure to include your name and mailing address. Please let us know if you are a healthcare professional so we can include instructions for obtaining the Dictionary in quantity.

The Oncology Nursing Society Neuro-Oncology Focus Group is looking for nurses who would like to meet other colleagues caring for people with central nervous system tumors. This focus group offers the opportunity for neuro-oncology nurses to make poster and podium presentations, participate in networking sessions held during the ONS meetings, network with colleagues, increase nursing awareness of the special needs of people with brain tumors, and help build this group into a Special Interest Group within the ONS. If you are interested in learning more, please contact Shirley Entis at *entissa@moffitt.usf.edu* (Moffitt Cancer Center/Florida) or Deneen Hesser at *deneen@abta.org* (American Brain Tumor Association).

YOUR MAIL PREFERENCES

The Message*line* is available in several formats — in print copy via regular mail, electronically as a text e-mail file, and/or as a PDF file at our web site. If you would like to receive your newsletter in a different format, please send a message to us at *info@abta.org.* If you do not specify a preference, your newsletter will be sent via regular mail.

Likewise, should you no longer wish to receive this mail, please let us know. We appreciate your interest in saving postage wherever practical and realize that your information needs may change over time.

Remember, we never give or sell our mailing list. If you ever have any questions about the mail you receive from ABTA, either print or electronic, feel free to call our office at 847-827-9910.

Save the Date July 18-20, 2003

The 6th biennial Sharing Hope Family Weekend will be held at Marriott's Lincolnshire Resort about 30 minutes from Chicago's O'Hare Airport. Watch the Spring issue of the Message*line* for program details.