RESEARCH EDITION

Messageline

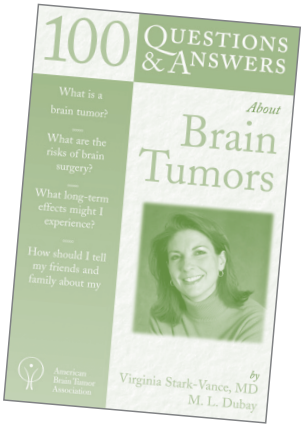
SUMMER 2003 VOLUME XXX, NUMBER 2

A PUBLICATION OF THE AMERICAN BRAIN TUMOR ASSOCIATION

MOVING CLOSER TO A CURE

The past year presented a financial challenge to all charities, but your unwavering dedication to the American Brain Tumor Association made it possible to fund the research that will eventually lead to a cure for brain tumors. Your support opened the door to 13 new research projects and the continuation of 9 existing studies. Additionally, 7 medical students were given the opportunity to spend their summers in a brain tumor research laboratory, and 30 scientists participated in a molecular biology training class – both unique programs offered through ABTA. Numerous awards were also given to promising researchers to encourage their career development in the field of neuro-oncology.

This issue highlights the scope of our research commitment; announces a research funding program for scientists sponsored by the National Institutes of Health and a research study focusing on familial brain tumors; and offers families a complimentary copy of 100 Questions and Answers About Brain Tumors.



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Message*line*

VOLUME XXX, 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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Naomi Berkowitz, Executive Director
Deneen Hesser, Editor

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Evanston Hospital
Evanston, Illinois

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UTMD Anderson Cancer Center
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Cross Cancer Institute
Edmonton, Alberta, Canada

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San Francisco, California

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American Brain Tumor Association
2720 River Road, Des Plaines, IL 60018 US
847.827.9910 TEL info@abta.org EMAIL
847.827.9918 FAX www.abta.org WEB
800.886.2282 PATIENT LINE

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.

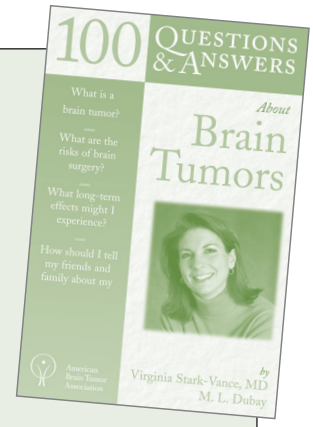
I. An ABTA **Fellowship** is a $70,000 two-year award for basic brain tumor research. The Fellowship is intended to provide salary support of $60,000 to a post-doctorate who has demonstrated the motivation and potential to conduct this research. The remaining $10,000 is to be expended at the discretion of the researcher for equipment/supplies or travel to an appropriate meeting, including a trip to Chicago, likely in the Summer of 2006, to present research results.

II. An ABTA **Translational Research Grant** is a one-year $50,000 award for neuro-oncology research. Our "translational" definition is on the application. The grant funds can be expended for salaries or supplies, but must include a trip to Chicago in May, 2005 to present research results.

The deadline for completed applications, *including all attachments* is January 7, 2004. Awards will be announced by April 1st for research work to commence July 1, 2004.

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

100 Questions & Answers *about Brain Tumors*



Complimentary Copies Now Available... an ABTA Exclusive!

A must-have for every family library, this 229 page book explains brain tumor basics, the process of diagnosing and treating the many types of brain tumors, medications and their effects, and clinical trials. *100 Questions & Answers About Brain Tumors* uses a novel approach to explain the day-to-day process of living with a brain tumor, coping with treatment side effects, talking to friends, changing priorities and everything in between.

Through a generous grant, we are able to provide free single copies of this publication to patients, families, and support groups. Please e-mail your name and mailing address to *info@abta.org*, or call us at 800-886-2282 to request a free copy.

2003 Research *Programs*

ABTA RESEARCH PROGRAMS

AN OVERVIEW

This year, we commemorate the 30th anniversary of the American Brain Tumor Association. Beginning as a small group of individuals who raised funds one research project at a time, ABTA is now a major force in the movement toward finding a cure for brain tumors. As research interest in brain tumors grew and the field of medicine called neuro-oncology evolved, we responded by expanding the scope of research supported by your generous donations. ABTA encouraged many of today's researchers by funding them early in their careers. We continue to look toward the research horizon for talented young investigators, new opportunities, and innovative approaches that will unlock the door to the cure.

If you are a researcher interested in learning more about any of these programs, please contact our office via e-mail: *info@abta.org*. If you are an individual donor, corporation, or foundation with the desire to support and encourage these programs, please call us at 847-827-9910. Working together, we can unlock the door.

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 for the 2004 awards are now available. Completed applications and all attachments due January 7, 2004.

Supported by the 2003-2004 ABTA Fellowship funding period are:

Ali Chahlavi, MD
Cleveland Clinic Foundation
Cleveland, Ohio

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UTMD Anderson Cancer Center
Houston, Texas

Faris Farassati, PhD
Mayo Clinic
Rochester, Minnesota

Giulia Fulci, PhD
Massachusetts General Hospital
Boston, Massachusetts

Chibo Hong, PhD
University of California
San Francisco, California

Rebecca Holmes Johnson, MD
Texas Children's Hospital
Houston, Texas

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

Eugene Chris Learn, PhD
Duke University Medical Center
Durham, North Carolina

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

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

Ajay Pandita, PhD
Mayo Clinic
Rochester, Minnesota &
University of Toronto, Canada

Beata Pyrzynska, PhD
Emory University
Atlanta, Georgia

Ravi D. Rao, MD
Mayo Clinic Rochester
Rochester, Minnesota

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

Dawid Schellingerhout, MBChB
Massachusetts General Hospital
Boston, Massachusetts

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

Continued on *page 4*

Continued from *page 3*

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 are available from the ABTA office at 847- 827-9910.

Recipients of ABTA Translational Research Grant funding are:

Bruce Frankel, MD
University of Tennessee
Memphis, Tennessee

Mahmet Fatih Okcu, MD
Baylor College of Medicine
Houston, Texas

Khalid Shah, PhD
Massachusetts General Hospital
Charlestown, MA

Hui-Kuo G. Shu, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Yinglin Wang, MD, PhD
University of California
Los Angeles, California

Radoslaw Zagozdzon MD, PhD
Beth Israel Deaconess
Boston, Massachusetts

YOUNG CLINICIAN INVESTIGATOR AWARD

ABTA offers, through the Neurosurgery Research and Education Foundation of the American Association of Neurological Surgeons, an annual $40,000 one-year 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 2003 Recipient of the NREF/ABTA award is:

John S. Kuo, MD, PhD
University of Toronto

Development of New Diagnostic and Therapeutic Strategies for Medulloblastoma Based on a Novel Tumor-Specific Gene, OPL.

JOHN S. KUO, MD, PHD

Studies of rare human tumor syndromes implicate Sonic Hedgehog activation of a transcriptional program involving the novel Odd-Paired-Like (OPL) protein. OPL is specifically expressed in both cerebellar granule cells and medulloblastoma, suggesting that granule cells give rise to these tumors. Dr. Kuo will use PCR-based subtractive cloning to discover OPL-activated genes that could serve as potential therapeutic targets. He will also develop an assay for use in tumor grading and detection of metastases.

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. Interested mentors should contact the ABTA office.

Participants in the 2003 Summer Fellowship Program are:

Columbia University
New York, NY
MENTOR: Jeffrey Bruce, MD
STUDENT: Michael Weicker
In memory of Paul Brazen

Johns Hopkins University
Baltimore, MD
MENTOR: Henry Brem, MD
STUDENT: Priscilla Brastianos
In memory of Bradley Benton Davis

Johns Hopkins University
Baltimore, MD
MENTOR: Alessandro Olivi, MD
STUDENT: Shaan M. Raza
In memory of Kerrie Gulczynski Long

St. Jude Children's Hospital
Memphis, TN
MENTOR: Richard Gilbertson, MD, PhD
STUDENT: Meredith Allen
In memory of Jackie Lippitz

University of California
San Francisco, CA
MENTOR: John W. Park, MD
STUDENT: Damon Tanner
In memory of Stephanie Kramer

University of California
San Francisco, CA
MENTOR: Tarik Tihan, MD, PhD
STUDENT: Justine Barletta
In memory of Bradley Benton Davis

University of Pittsburgh
Pittsburgh, PA
MENTOR: Kevin A. Walter, MD
STUDENT: Daniel M. Geynisman
In memory of David B. Anderson

COURSE ON MOLECULAR MECHANISMS IN BRAIN TUMORS

Supported by the American Brain Tumor Association in conjunction with the UTMD Anderson Cancer Center, this course offered a clinical overview of brain tumors and emphasized contemporary research in molecular mechanisms.

Targeted to those clinicians interested in building their knowledge of molecular biology as related to brain tumors, the seminar offered training in the growth and development of brain tumors with emphasis on molecular signaling mechanisms, neural stem cells, mouse models, genomics, imaging techniques, transgenic and knock-out mouse techniques, biobanks, and mechanism-based therapeutic strategies. Attendees were able to interact with senior investigators on a one-to-one basis in an informal environment. The course was limited to 30 learners, and was very highly regarded by those in attendance.

Those interested in notification of the next course can send an email message to the facilitator, Sadhan Majumder, PhD, MD at *majumder@mdanderson.org*.

YOUNG INVESTIGATOR GRANTS

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

This year's AANS award was given to Moneeb Ehteshan, MD, from Cedars Sinai Medical Center in Los Angeles, California. Dr. Ehteshan's award-winning research was entitled *Induction of Glioblastoma Apoptosis Using Neural Stem Cell Mediated Delivery of TRAIL* and was presented at the AANS annual meeting in San Diego. The recipient of the CNS award was given to Russell Lonser, MD, from the National Institutes of Health Neurologic Disorders & Stroke Surgical Neurology Branch. His award winning presentation was *Induction of Glioblastoma Multiforme After Whole Brain Irradiation in the Therapeutic Dose Range,* and was given at the CNS annual meeting in Philadelphia.

The Society for Neuro-Oncology Award is for Excellence in Basic Research - this grant was given to Erik J. Uhlmann, MD, Washington University School of Medicine in St. Louis, Missouri, for his research: *The Loss of Tuberous Sclerosis Complex-1 Gene Expression in Astrocytes, Results in Dysregulated Growth In-vitro and In-vivo.*

Erik Uhlmann, MD, and Naomi Berkowitz, Executive Director of the American Brain Tumor Association

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 Faith Davis, PhD and Serap Erdal, PhD, Department of Environmental and Occupational Health Sciences at the University of Illinois, Chicago, for their research: *Assessment of Human Exposure Profile of Known and Suspected Animal Neurocarcinogens.* To apply for this year's award, contact the Society at 713-745-2264 or www.soc-neuro-onc.org

The grant awarded to Jill Barnholtz-Sloan, PhD during 2002 continues into the 2003 funding period. Dr. Sloan's research, *The Role of Ethnicity in Survival of Patients with Primary Malignant Brain Tumors: A Molecular Epidemiology Pilot Study*, was generously funded by BP. An interim report on her work appears on page 15.

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GRANT TO CENTRAL BRAIN TUMOR REGISTRY OF THE UNITED STATES

Implementation of the mission of the Central Brain Tumor Registry of the United States (CBTRUS) will be facilitated by passage of the Benign Brain Tumor Cancer Registries Amendment Act. This bill amends the Public Health Service Act to add the collection of data on benign brain-related tumors.

One of the primary objectives in ABTA's founding and continuing support of CBTRUS is to ensure that data on ALL brain tumors – benign and malignant – is recorded. This year, ABTA increased its annual grant to CBTRUS to $50,000. This significant gift represents our commitment to the registry and conveys our understanding of the need for statistical data documenting the incidence and prevalence of this disease.

We continue to encourage the CBTRUS initiative of collecting data nationwide, and hope that families, healthcare professionals and industry will avail themselves of this resource. Visit the CBTRUS web site at www.cbtrus.org, or call them at 630-655-4786.

ANOTHER SOURCE OF RESEARCH FUNDS

National Institutes of Health (NIH) Loan Repayment Programs can repay up to $35,000 a year of qualified educational debt for health professionals pursuing careers in clinical, pediatric, contraception and infertility, or health disparities research. The programs also provide coverage for Federal and state tax liabilities.

Applicants must have a doctoral-level degree, devote 50% or more of their time to nonprofit or government-funded research, and have educational debt equaling at least 20% of their institutional base salary. US citizens, permanent residents, or US nationals may apply.

The NIH Loan Repayment Programs (LRP's) are a vital component of our nation's efforts to attract health professionals to research careers in areas of national need. The programs are the Clinical Research LRP, Pediatric Research LRP, Contraception and Infertility Research LRP, Clinical Research for Individuals from Disadvantaged Backgrounds LRP, and Health Disparities Research LRP.

All applications for 2004 awards must be submitted by December 31, 2003. Visit NIH's Loan Repayment web site at www.lrp.nih.gov for further information and to apply online.

2003-2005 Basic Research *Fellowships*

Seven researchers are recipients of the coveted ABTA Post-Doctoral Research Fellowships for this award period. These $70,000 awards are intended to encourage talented young researchers to enter, or remain in, the field of neuro-oncology. We welcome these future research leaders to the growing ABTA family.

OVERCOMING IMMUNE DYSFUNCTION IN GBM

Depressed immune cell function, resulting in ineffective anti-tumor responses, is common among cancer patients. The tumor microenvironment has a harmful effect on tumor infiltrating T cells (TILs), although the immunosuppressive effects extend into the periphery as well. Prior studies by others have shown that glioblastoma cells and possibly tumor-derived products may be responsible for the T cell dysfunction observed in people with glioblastoma (GBM). Gliomas appear to cause a broad range of immunological defects, including cutaneous anergy, depressed immunoglobulin production, impaired T cell responsiveness, defective hypersensitivity, and inability to generate interleukin-2. It is possible that gliomas secrete factors capable of distant immunosuppression by interfering with apoptosis, or natural cell death.

The proposed work should establish the proof of principle regarding the role of Bcl-2 in protecting T cells from apoptosis induced by brain tumors. Once the proof of principle is established with Jurkats and normal T cells, additional studies will then test whether a similar strategy can be effective in protecting T cells that have specificity for antigens expressed on GBM. Tumor antigens have been identified on GBM that can serve as targets for tumor specific T cells (eg ILI3R alpha chain peptides) and these antigens will likely be used as a vaccine approach for the treatment of brain tumors. Thus, it will be feasible to test whether GBM specific T cells are sensitive to tumor-induced apoptosis and if over-expression of Bcl-2 will provide protection.

Ali Chahlavi, MD
Cleveland Clinic Foundation
Cleveland, Ohio

SPONSOR
James Finke, PhD

AWARD
Laurie Deierlein/ ABTA Fellowship

RESEARCH APPLICABLE TO
glioblastoma multiforme (grade IV astrocytoma)

The American Brain Tumor Association offers two types of research funding awards: Fellowships and Translational Grants. Requests for guidelines and/or applications should be directed to *Linda@abta.org* or call 847-827-9910.

2003-2005 Basic Research *Fellowships*

John F. de Groot, MD
MD Anderson
Cancer Center
Houston, Texas

SPONSOR
W. K. Alfred Yung, MD

AWARD
Patricia J. Doyle/
ABTA Fellowship

RESEARCH APPLICABLE TO
low and high grade gliomas

GLUTAMATE EXCITOTOXICITY, CYSTINE AND GLIOMA GROWTH

New blood vessel formation, growth factor secretion and extracellular matrix destruction are important factors in glioma invasion. Exciting new data from our group and others suggest that glutamate may also play an important role in tumor dissemination.

Glutamate is the most abundant excitatory amino acid neurotransmitter in the central nervous system. (Please note this is not the same as monosodium glutamate, used in the food industry.) Several research groups have shown that some glioma cells release glutamate levels high enough to be toxic to normal neurons, and that rat tumors which secrete higher levels of glutamate grow faster.

Our initial data suggest that glutamate release from gliomas allows tumors to infiltrate the brain by destroying surrounding tissue. Furthermore, glutamate release is linked to cystine uptake. Cystine is an important precursor of glutathione, an antioxidant known to be important in tumor resistance to treatment. Blocking the release of glutamate or its receptors may prevent tumor invasion and enhance the effectiveness of chemotherapy.

The aim of this research will determine if glutamate transporters and glutamate receptors are important in human glioma growth and if treatments that block these glutamate receptors will enhance the effectiveness of traditional cytotoxic chemotherapy.

Faris Farassati, PhD
Mayo Clinic
Rochester, Minnesota

SPONSOR
Corey Raffel, MD and
Robert L. Martuza, MD

AWARD
Kyle S. Minor, Jr./
ABTA Fellowship

RESEARCH APPLICABLE TO
malignant glioma, glioblastoma multiforme (grade IV astrocytoma)

AN ALTERNATIVE HERPES VIRUS GENE THERAPY

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 network. For example, a biochemical cascade named "Ras signaling" and its related molecules, such as extracellular-signal-regulated kinase (Erk), work to induce proliferation in glioma cells. Since the activity of Ras pathway is significantly increased in glioma cells (as compared with non-neuronal cells), it seems logical that such a characteristic could be used as a way to attack these cells. This proposal 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.

In order to achieve this, the mutant-HSV-1 will be genetically modified in a way that the expression of a gene necessary for viral replication (named ICP4-gene, or alpha-4) will be under the control of Erk-pathway. Indeed, by designing the ICP4 gene to be induced in response to Erk, the mutant-HSV-1 will be "switched-on" in glioma cells, leading to their destruction. The rationale for designing such a virus is strengthened by the results of our studies proving that HSV-1, even without any genetic modifications, shows a preference toward infecting cells with over-activity in Ras/Erk.

Development of a "signal-smart" virus, which responds to such protein over-activity, should provide us with a more specific tool for treating glioma cells.

SEARCH FOR ABNORMAL GENES IN LOW GRADE OLIGODENDROGLIOMAS

The development of brain tumors is fueled by genetic and epigenetic changes that inactivate tumor suppressor genes (which normally inhibit cell growth). The interaction of these fundamental mechanisms is unknown. The current models used to explain tumor development are mainly based on the genetic approach. If the genes inactivated by DNA methylation are the same as those silenced by genetic mechanisms, then traditional genetic screening has identified most of these cancer genes. However, if methylation, which is not detectable by genetic screening methods, inactivates a different set of genes, the genetic model of brain tumor formation is far from complete, and there may be many more targets for therapy.

The combined effects of aberrant methylation and genetic mechanisms may be even more complex, since many gene pairs share a common gene regulator, or promoter, potentially allowing the silencing of two genes by inactivating only one promoter. I hypothesize that most genes silenced by DNA methylation are independent of those inactivated by genetic mechanisms, and that silencing of two genes at once results in an increasing loss of growth control. By testing this hypothesis, we will have a more complete understanding of the mechanisms of tumorigenesis that is not solely based on a genetic model, as has been our historical perspective. By knowing the predominant force(s) driving tumor growth at each stage or tumor grade, an appropriate clinical trial could be designed for each stage of tumor growth or specific aberrations found in the tumor.

Chibo Hong, PhD
University of California-San Francisco
San Francisco, California

SPONSOR
Joseph F. Costello, PhD

AWARD
Terri Yarbrough/ ABTA Fellowship

RESEARCH APPLICABLE TO
oligodendroglioma

CLINICAL STRATIFICATION OF PEDIATRIC EPENDYMOMA BY COMPREHENSIVE GENETIC PROFILING

Ependymoma is a malignant brain tumor whose treatment typically requires surgery and radiation. However, there is no reliable method to predict the outcome of patients with ependymoma. Thus, physicians are challenged to try to determine which patients would benefit from more aggressive therapies and which patients will do well without further treatment other than surgery.

My research will be performed in conjunction with ependymoma clinical trial ACNS-0121of the Children's Oncology Group, an NCI-funded cooperative group comprising 400 participating hospitals. This trial will be the largest investigation of ependymoma ever undertaken; it will set the standards of care for future patients with ependymoma. Using patient tumor samples, I will identify typical patterns of gain and loss, and classify tumors into clinically relevant groups or sub-types. We will compare the prognostic value of these subtypes to that of current standard histological classification. Clinical stratification by chromosomal profiling may then be used to improve outcome prediction for patients with ependymoma, help the clinician determine which patients are at highest risk and should therefore receive the most aggressive therapies, and create new prognostic markers for objective patient grouping in future clinical trials.

Rebecca Holmes Johnson, MD
Texas Children's Hospital and Baylor College of Medicine
Houston, Texas

SPONSOR
Ching C. Lau, MD, PhD

AWARD
Bonnie Blair/Dallas Stars/ ABTA Fellowship

RESEARCH APPLICABLE TO
ependymoma in children

2003-2005 Basic Research *Fellowships*

Eugene Chris Learn, PhD
Duke University
Medical Center
Durham, North Carolina

SPONSOR
Darell D. Bigner, MD, PhD

AWARD
Georgianne AuBuchon/ ABTA Fellowship

RESEARCH APPLICABLE TO
glioblastoma multiforme (grade IV astrocytoma)

THE EFFECTS OF EGFR MONOCLONAL ANTIBODY TREATMENT ON THE SIGNALING PATHWAYS IN GBM

Epidermal growth factor receptor (EGFR) is a normal protein that is overexpressed in many cancers of the brain. Overexpression of EGFR helps tumors grow. The most frequent mutation of this gene, EGFR variant III (EGFRvIII), encodes a membrane-bound protein that greatly enhances the tumorigenicity of cells containing this mutation. Since this mutation is found in approximately 40% of malignant gliomas, but not normal brain tissue, it makes an interesting target for tumor-specific immunotherapy. At this time, however, discrepancies exist as to which signaling pathways or molecular events are part of this transformation, which pathways may be redundant or dispensable, and what significance "cross-talk" between pathways has on development of this mutation.

Recent studies have shown that unlabeled monoclonal antibodies (mAbs) are relatively innocuous but potent therapeutic agents against specific tumor antigens. Our research group has developed an EGFRvIII tumor-specific monoclonal antibody, called Y10, that induces autonomous tumor cell death by altered signal transduction, resulting in decreased tumor growth and tumor cell death. Although YI0 has been shown in preliminary laboratory studies to have an effect on tumor growth, we do not know how it actually works. To this end, this study will investigate the molecular biology of brain tumors that express EGFRvIII and how these tumors are affected by Y10 therapy. It is our belief that treatment of tumors with monoclonal antibodies, such as Y10, has the potential for stopping the survival signals of a tumor cell while also affecting the tumor cell's inner workings and regulation.

Ravi D. Rao, MD
Mayo Clinic
Rochester, Minnesota

SPONSOR
C. David James, PhD

AWARD
Joel A. Gingras, Jr./ ABTA Fellowship

RESEARCH APPLICABLE TO
glioblastoma multiforme (grade IV astrocytoma)

THE EFFECT OF THE BACTERIAL EXTRACT IMMUNO-SUPPRESSANT, RAPAMYCIN, ON GLIOMA CELL GROWTH

Despite many advances in the battle against cancer, treatment for patients diagnosed with glioblastoma, a malignant brain tumor, remains challenging. Our research has shown that a combination of 2 new drugs, EKI-785 and rapamycin, may be effective in stopping the growth of these tumor cells.

EKI-785 is an inhibitor of epidermal growth factor receptor or (EGFR), a protein that promotes the growth of many glioblastomas. Rapamycin is an immunosuppressive drug that was first extracted from soil bacteria, and is known to be an inhibitor of mTOR, a protein also capable of promoting the growth of most glioblastomas. The combination seems to be more powerful than the use of either drug alone in stopping the growth of tumor cells, and also appears to overcome drug resistance.

Our study will investigate the mechanism of synergy between rapamycin and EKI-785 in glioma cells, and study mechanisms of cellular resistance and sensitivity to rapamycin. We will test the combination of these two drugs on glioblastoma cells in the laboratory, analyzing molecular changes in the growth inhibitory pathways involved in EGFR expression. The related goals of this research are to study the molecular basis of the synergistic anti-tumor effect of this treatment approach, and develop a way of predicting which patients will respond to this combination treatment.

2003-2005 Translational *Grants*

This award period, six scientists are recipients of grant support from ABTA. These $50,000 grants make possible the last phases of laboratory research needed to transition this research from "bench" to "bedside."

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

Despite improvements in other oncology fields, the outlook for patients with glioblastoma (GBM) still remains a challenge, requiring that neuro-oncologists continue to explore novel therapies. One of the major mechanisms by which cells die is apoptosis, a carefully regulated process involving several complex-signaling pathways. Because of the potential of utilizing apoptosis in cancer therapy, much attention has been directed toward the various factors composing these pathways. Two such factors, which play an important role in the regulation of cell death, include Fas and Fas ligand (FasL).

The interaction of Fas, and its natural ligand FasL, results in cellular apoptosis after subsequent caspase activation. In the nervous system, glia such as astrocytes, oligodendrocytes and ependymal cells express Fas under neoplastic conditions. Recent evidence indicates that 81% glioblastomas co-express Fas and FasL but are insensitive to Fas-mediated apoptosis.

Inhibition of the Fas signaling cascade occurs at a number of levels. At the receptor level "low" Fas expression can be increased by exposure of glioma cells to y-interferon. However, the addition of erogenous FasL is required for apoptosis to occur indicating yet another defect exists in this pathway. Flow cytometry analysis of FasL expression in over 10 GBM cell lines, indicates that FasL is located intracellulary. Irradiation of tumor cells results in extracellular translocation of FasL with subsequent FastFasL interactions resulting in apoptosis. This effect is potentiated by pre-exposure to γ-interferon, indicating that this cytokine is a potent radiation sensitizer, working through the FastFasL pathway.

The pre-clinical work proposed here will evaluate the therapeutic potential of γ-interferon as a radiation-sensitizing agent. Through the use of GBM cell lines (U87, U373), the therapeutic efficacy and CNS toxicity of combining γ-interferon with radiation will be studied in an ex vivo brain-slice culture model. This combination will then be studied in vivo, utilizing a GBM xenograft model.

Bruce Frankel, MD
University of Tennessee
Health Science Center
Memphis, Tennessee

AWARD
John C. Carr, Jr./ABTA Grant

RESEARCH APPLICABLE TO
glioblastoma multiforme
(grade IV astrocytoma)

2003-2005 Translational *Grants*

Mahmet Fatih Okcu, MD
Baylor College of Medicine
Houston, Texas

AWARD
Emily Dorfman Foundation for Children/ABTA Grant

RESEARCH APPLICABLE TO
malignant childhood brain tumors

GLUTATHIONE S-TRANSFERASE POLYMORPHISMS AND SURVIVAL IN CHILDHOOD MALIGNANT BRAIN TUMORS

Glutathione-s-transferase (GST) enzymes are responsible for the breakdown (metabolism) of a variety of substances including chemotherapy agents used in treatment of malignant brain tumors. The functions of these enzymes are determined by their genes. In the general population, variation for these genes exists, and metabolism of chemotherapy drugs varies from individual to individual significantly. We propose this variation may be responsible, in part, for individual differences in response to cancer treatment and different incidences of treatment effects from chemotherapy.

We will investigate the relationship between GST genetic variations and the survival and occurrence of toxicity secondary to chemotherapy in 175 children with malignant brain tumors. We will determine genetic variants for these enzymes, and will conduct Kaplan-Meier and Cox-proportional hazard analyses to examine if the GST polymorphisms are related to survival, and logistic regression analysis to explore if the GST polymorphisms are associated with toxicity secondary to chemotherapy.

If our study is successfully conducted, future treatment regimens may be tailored based on individual patient's genetic formation for enzymes that metabolize chemotherapy agents.

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

AWARD
Lynne Batchelor/ABTA Grant

RESEARCH APPLICABLE TO
malignant glioma

REAL TIME DUAL IN VIVO IMAGING OF STEM CELL MIGRATION TO, AND APOPTOSIS OF, GLIOMAS INDUCED BY TUMOR SPECIFIC NOVEL SECRETED PROTEIN

The studies proposed in this project fulfill the major themes of real time brain tumor imaging and apoptosis in vivo. The main goals are to: a) engineer a novel therapeutic gene that specifically kills tumor cells in vivo; b) develop an apoptosis activatable Renilla luciferase (Rluc) glioma cell line and a neural stem cell (NSC) line expressing firefly luciferase (Fluc) and secretable recombinant form of TRAIL and c) simultaneously monitor the migration of NSCs and selective apoptosis of malignant brain tumors induced by secreted TRAIL by dual bioluminescent imaging in vivo.

Specifically, we are interested in creating a NSC line stably expressing both Fluc and a recombinant secretable protein. This fusion protein will not be apoptotic in NSCs but will be highly apoptotic to glioma cells. The glioma cell line will be implanted in the models, and the migration of the NSCs across the corpus collusum into the gliomas overtime will be followed by bioluminescence imaging. The effect of the release of apoptotic HF-TRAIL by NSCs on the glioma tumor will be monitored by the activation of caspase-3 protease and the release of quenched Rluc activity. The bioluminescent signal emitted by both types of luciferase can be detected *in vivo* in subnanomolar quantities and at depths sufficient for experimental imaging and quantitation.

BLOCKADE OF EGFR FAMILY MEMBERS AS A THERAPEUTIC STRATEGY FOR MALIGNANT GLIOMAS

Research aimed at determining the underlying defect responsible for the development of these tumors has implicated abnormalities in the epidermal growth factor receptor (EGFR). Upon binding of the ligand epidermal growth factor to EGFR, its tyrosine kinase becomes activated which transmits multiple signals in the cell. Excessive or abnormal signaling by EGFR in cells is thought to be the basis for why EGFR contributes to the formation of various cancers including malignant gliomas. Recently, a new class of drugs have been developed that can specifically inhibit the function of this receptor. In testing some of these EGFR inhibitors in a glioma model system, we find that despite apparent inhibition of receptor tyrosine kinase activity, many of the downstream signals from this receptor continue to be activated. The reason for this effect remains unclear and is the topic of this research proposal. The main goal of this project is to further characterize this effect where receptor activity or autophosphorylation is no longer linked with activation of downstream signals. This phenomenon may represent a way by which tumors can become resistant to treatment by these agents.

Hui-Kuo G. Shu, MD
University of Pennsylvania
Philadelphia, Pennsylvania

AWARD
Paul Fabbri/ABTA Grant

RESEARCH APPLICABLE TO
malignant glioma

THE ROLE OF P53 DISRUPTION IN REGULATING GLIOBLASTOMA RESPONSE TO TARGETED THERAPY

A new approach to cancer therapy focuses on developing inhibitors that are targeted to specific genetic lesions. Glioblastoma contains a number of genetic lesions that are critical for the tumor development and their clinical behavior. P53 mutation occurs in nearly 1/3 to 1/2 of glioblastomas. However, p53 status is not currently used in guiding glioblastoma treatment. We have found that p53 disruption dramatically alters the response of glioblastoma cells to DNA topoisomerase I (Top 1) inhibition. We have shown that glioblastoma cells with mutant p53 die through apoptosis in response to SN-38 (the active metabolite of camptothecin analog CPT-11; DNA Top I inhibitor), whereas p53 wild-type tumor cells are growth arrested showing cell aging characteristics, but reversible after drug withdrawal. We will test this association by injecting tumor cells of different status of p53 then treating the cells with CPT-11. We will also analyze tumor tissues obtained before and after CPT-11 treatment and compare with each tumor's p53 status. More over, DNA Top I inhibitors and irradiation have recently been shown to have synergistic effect. We propose studies to determine whether DNA Top I inhibition enhances the effect of radiation therapy on glioblastoma cells and assess its dependence on p53 status using our unique cell line model. Our work will directly provide guidelines for selecting glioblastoma patients for CPT-11 treatment.

Yinglin Wang, MD, PhD
University of California-
Los Angeles
Los Angeles, California

AWARD
Gabrielle Carteris/
ABTA Grant

RESEARCH APPLIABLE TO
glioblastoma multiforme
(grade IV astrocytoma)

2003-2005 Translational *Grants*

Radoslaw Zagozdzon, MD
Harvard Medical School
and
Beth Israel Deaconess
Medical Center
Boston, Massachusetts

AWARD
Linda Favero/ABTA Grant

RESEARCH APPLICABLE TO
malignant neuronal tumors

EVALUATION OF CHK-BASED TREATMENT IN BRAIN CANCER

Mechanism-based target identification and structure-based drugs are powerful tools in developing selective anticancer drugs. Natural antitumor proteins are very often the primary structures, upon which the new drugs are designed.

We and others previously identified a protein currently termed Csk Homologous Kinase (CHK). CHK is an enzyme inhibiting the activity of Src protein, which was shown to play a role in the development of brain tumors. We show the loss of CHK expression in brain tumors as compared to normal brain tissue. Our preliminary studies in neural cancer cells indicate CHK as a potent antitumor agent. To further strengthen the antitumor actions of CHK we plan to generate its more potent derivatives. In this project we will investigate the CHK derivative (named CHSK) possessing increased enzyme activity, while binding to same proteins within the cells as the natural form of CHK, and we hypothesize that purified CHSK protein conjugated with nine arginines would be capable of entering the cells directly. This would also allow us to study the effects of CHSK as a novel antineoplastic agent in a wide range of tumor cells both in cell culture and in animal models.

In summary, we propose to study the role of CHK as a novel tumor suppressor protein in neural cancer. We aim to study in detail the mechanisms of CHK inactivation in brain malignancies. Moreover, we wish to evaluate the therapeutic potential of CHK-based antitumor treatment by using the enhanced-activity CHK derivative along with a novel drug delivery system. We anticipate the results of our studies will provide new insight into the role of CHK in human cancer and will eventually constitute solid basis for generation of new class of antineoplastic agents based on mechanism of antitumor action of CHK in neural cancer.

GLIOMA FAMILY PROJECT

AT ALLEGHENY GENERAL HOSPITAL, PITTSBURGH

The vast majority of brain tumors appear to be of spontaneous origin due to local factors acting on cells. However a few families do exist in which two or more individuals are diagnosed with brain cancer, thereby suggesting a possible hereditary cause. Although these families are rare, they offer a unique opportunity to search for the genetic causes of malignant brain tumors which may underlie the origins of all of these tumors.

Researchers at Allegheny General Hospital are seeking your help, for a nationwide research project, to identify families which have two or more individuals who have been diagnosed with a biopsy-proven malignant glioma. At least one of the patients must be alive and be willing to participate in the study. Additional eligible participants are the first-degree relatives (parent, sibling, or child) of one of the patients.

Participation requires a brief discussion with the research coordinator, confirmation of diagnosis by review of pathology reports and collection of a small blood sample of each participant. Once family pedigree and pathology are confirmed, all identifying information is removed from the blood sample so that privacy is assured.

If you believe that your family is eligible and willing to participate, please call the research team at their toll-free number: 1-877-367-2444 (1-877-FOR-AGH4). This work is being conducted by the Department of Neurosurgery and Department of Human Genomics, Allegheny General Hospital, Pittsburgh, Pennsylvania and has received Institutional Review Board (IRB) approval.

2003 Research *Summaries*

Jill Barnholtz-Sloan, PhD
Role of Ethnicity in Survival of Patients with Primary Malignant Brain Tumors: A Molecular Epidemiology Pilot Study Interim report

Alice B. Brown, MD, PhD
Gene Therapy for Brain Tumors: "Novel Strategies for Delivery and Targeting of Therapeutic Cells to Tumors"

Lauren Bush, LCSW and Marguerite Wotoczek-Obadia, AHT
ABTA Resource Center at H. Lee Moffitt Cancer Center – Tampa, Florida

Chulhee Choi, MD, PhD
Role of the Ubiquitin/Proteasome Pathway on Death Receptor Signaling in Astroglioma

William Curry, Jr., MD
G207 Infection of Dendritic Cells: Effects on Maturation and Generation of Antitum or Immunity

Richard A. Gemeinhart, PhD
Microparticle-Drug Conjugates as Novel Chemotherapeutic Agents

John Hill, MD, PhD
Examining the Role of Growth Factor Signaling Pathways in Promoting the Growth and Survival of Medulloblastoma

L. Burt Nabors, MD
Targeted Imaging in the Mouse Brain Tumor Model

Michael E. C. Robbins, PhD
Role of the Cerebral Renin-Angiotensin System in Radiation-Induced Brain Injury

Khalid Shah, PhD
NIRF Imaging and Tumor Cell Apoptosis Using HSV Vector-Mediated Gene Delivery to Gliomas

Paula Riess Sherwood, PhD-c, CNRN
Family Care of Persons with a Brain Tumor

I-Mei Siu, PhD
Identification of the Role of c-Myc in Medulloblastoma Tumorigenesis

Gelareh Zadeh, MD
Functional Role(s) of Angiopoietins and Their Cognate Endothelial Cell Receptor Tie2, in the Vascularization and Growth of Malignant Astrocytomas

Qing Zhao, MD, PhD
Mechanisms of Hedgehog-Induced Neural Proliferation

A highlight of this year's Sharing Hope Family Weekend was the Research Reception at which recipients of ABTA funding reported on their work. These reports took the form of poster presentations, with verbal introductions to each study given by members of the ABTA Scientific Advisory Council. Our appreciation to those Advisors who served as discussants: G. Yancey Gillespie, PhD, University of Alabama Birmingham; Mark Israel, MD, Dartmouth-Hitchcock Medical Center; Lois Lampson, PhD, Harvard Medical School; and Stephen Tapscott, MD, PhD, Fred Hutchinson Cancer Research Center.

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

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

Background: Previous studies show that overall incidence of primary malignant brain tumor is highest in Caucasians, although survival is better in African Americans. The purpose of this study was to examine racial differences in survival after diagnosis with primary malignant brain tumor in a population-based sample of individuals, while adjusting for prognostic variables that differ by race.

Methods: 21,493 subjects (20,493 Caucasians and 1000 African Americans) diagnosed with primary malignant brain tumor from 1973-1997 (with follow-up through 1999) from the population-based Surveillance, Epidemiology and End Results (SEER) Program were used for analysis. Chi-square tests were used to determine statistical significance of prognostic variables and race (using two-sided p-values). Kaplan-Meier and Cox proportional hazard models were used to assess survival differences by race.

The univariable model for race showed no survival difference by race. The multivariable model demonstrated that African Americans were

at 13% increased risk of death from any cause compared to Caucasians. The racial difference was further explained by an interaction between race and surgery type, where there was an increased risk of death for African Americans with subtotal resections or surgery NOS compared to Caucasians.

Conclusion: There was a significant difference in risk of death from any cause for Caucasians and African Americans diagnosed with first primary brain tumor.

Alice B. Brown, MD, PhD
Massachusetts General Hospital
Charlestown, Massachusetts

GENE THERAPY FOR BRAIN TUMORS: NOVEL STRATEGIES FOR DELIVERY AND TARGETING OF THERAPEUTIC CELLS TO TUMORS

Glioblastoma multiforme is the most malignant tumor in humans, and the most common brain tumor. My ***long-range goal*** is to identify better therapeutic options for brain tumors, focusing on the development of promising gene therapy approaches which should complement and/or enhance the benefits derived from more traditional therapies, thereby increasing overall survival rates. The ***objective of this experimental plan*** is to explore the effect of intravascular delivery of "therapeutic" cells, genetically modified to express pro-drug activating enzymes and anti-angiogenic factors, on in vivo tumor growth. The ***central hypothesis*** is that delivery of therapeutic substances to tumor cells can be improved through intravascular administration of engineered "therapeutic" cells capable of defeating the blood-tumor barrier by incorporating into or traversing tumor endothelium. Preliminary data suggest that *endothelial cells, fibroblasts* and *neural stem cells* can be distributed throughout tumor parenchyma by intravenous administration, coming to lie within and in close association with the endothelium forming the blood-tumor barrier. This is an ideal location for the continued elaboration of therapeutic substances, alleviating the usual problems of limited access and the requirement of multiple, repeated administrations. The ***rationale*** derives from the observation that anti-angiogenic factors and pro-drug activating enzymes are promising anti-tumor strategies, which have shown only partial efficacy in the treatment of brain tumors, usually being administered either by direct implantation of cells or vectors into a few sites in the tumor bed or through systemic administration of drugs or molecules.

It is our ***expectation*** that improved tumor uptake through intravascular administration of potent, long-lived genetically engineered cells, delivering sole or synergistic therapy for brain tumors, will impove efficacy and survival in experimental tumor models, and that treatment paradigms incorporating this novel approach will make significant contributions to the management of both intracranial and systemic/metastatic tumors. This technique also has important implications as a gene replacement strategy for benign, but devasting, neurological disease.

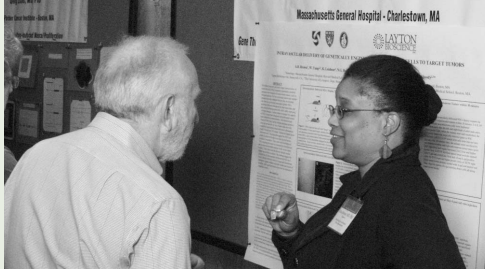
Lauren Bush, LCSW and Marguerite Wotoczek-Obadia, AHT
H. Lee Moffitt Cancer Center
Tampa, Florida

ABTA RESOURCE CENTER

A brain tumor or brain metastasis can be devastating due to the physical, cognitive and psychological side effects that often result. There is a need for accessible, credible and comprehensive information to help individuals understand and cope with this complex diagnosis. The American Brain Tumor Association responded by providing a generous grant to the H. Lee Moffitt Cancer Center & Research Institute to establish a brain tumor resource center for patients and their families.

Since opening in February of 2002, the **American Brain Tumor Association Resource Center at H. Lee Moffitt Cancer Center & Research Institute** has been administered by the Patient Education Department with oversight and clinical leadership

Alice B. Brown, MD, PhD
Massachusetts General Hospital
Charlestown, Massachusetts



provided by the Neuro-Oncology Program. It was intended to benefit brain tumor patients, family members and loved ones by empowering them with the tools needed to make informed decisions and to enhance coping through education and support. A wide range of multi-media resources are available including: medical software, Internet access, brochures, reference books, inspirational books, videos, magazines, newsletters, anatomical charts/models and personal guidance in answering brain tumor questions. Volunteers who have been affected by a brain tumor diagnosis staff the Center for a minimum of 10 hours each week.

In an effort to increase visibility of the Center, a monthly educational series, **Brain Tumor Talks,** was developed to inform the public about the many aspects of brain tumors and to foster an informal support network for the exchange of experiences. This presentation reviews the scope of services provided by a brain tumor resource center at an NCI Comprehensive Cancer Center with a large brain tumor population. Current utilization statistics are discussed as well as the success of the **Brain Tumor Talks** series.

Marguerite Wotoczek-Obadia, AHT and Lauren Bush, LCSW
H. Lee Moffitt Cancer Center
Tampa, Florida

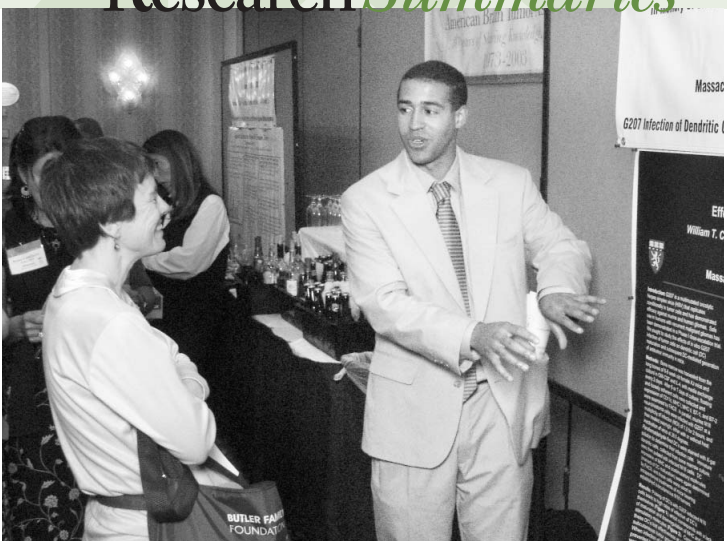
Recognizing that more brain tumor patients and families could benefit from available services, the Center is currently serving this population well by having a wide range of educational tools and programs. Ongoing efforts will continue to focus on raising awareness of this disease and highlighting the unique and valuable service the **ABTA Resource Center at Moffitt Cancer Center** is offering the brain tumor community.

Chulhee Choi, MD, PhD
University of Alabama at Birmingham
Birmingham, Alabama

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

Glioblastoma multiforme (GBM) is the most common and malignant form of primary brain tumors in adults. Development of effective treatments will be tremendously beneficial for patients with GBMs. Although TRAIL has been considered as a magic bullet for treatment of malignant human tumors including GBMs, we have recently shown that human GBM cells can utilize this ligand 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 cell§§ is determined upon TRAIL ligation.

This study focused on the role of the ubiquitin (Ub)/proteasome pathway and reactive oxygen species (ROS) as modulators of ligand-mediated signaling in two functional outcomes, apoptotic cell death and IL-6/IL-8 expression. The research suggests that the Ub/proteasome pathway promotes survival of cells by enhancing inflammatory/angiogenic signals (NF-kB 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 TRAIL in GBMs. Furthermore, TRAIL increases the intracellular level of ROS, which functions surprisingly as a



survival factor. ROS has been regarded as cytotoxic byproducts of oxidative phosphorylation and functions as an inducer of inflammation by activating the NF-kB pathway. However, TRAIL-mediated expression of IL-8 is not suppressed by inhibition of ROS production, suggesting that ROS is not involved in TRAIL-mediated inflammatory signaling.

Given the two distinct signal transduction pathways of TRAIL, my work will re-evaluate the role of the Ub/proteasome pathway and ROS 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 these pathways on death ligand signaling, and the background to develop better therapeutic strategies for human brain tumors.

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

G207 INFECTION OF DENDRITIC CELLS: EFFECTS ON MATURATION AND GENERATION OF ANTITUMOR IMMUNITY

Introduction: G207 is a multimutated oncolytic herpes simplex virus (HSV) that replicates conditionally in tumor cells and has demonstrated efficacy against murine and human gliomas. Safe use in humans with recurrent malignant gliomas has been demonstrated in

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

a Phase I dose-escalation trial. We sought to study the effects of *in vitro* G207 infection of tumor cells on dendritic cell (DC) maturation and subsequent DC-mediated generation of antitumor immunity in mice.

Methods: Bone marrow was harvested from the long bones of 6-8 week old female AJ mice and cultured in GM-CSF and IL-4, with media exchange every 2 days. After 6 or 7 days of culture, floating and loosely adherent cells were collected and expression of CD11c, MHC I, MHC II, B7-1, and B7-2 examined by FACS. In parallel, murine N18 neuroblastoma cells were infected with G207 at a multiplicity of infection (MOI) of 1.0 for 2 hours, and then treated overnight, either with or without heat inactivation of virus at 39.5 degrees. Immature dendritic cells, collected from bone marrow culture, were then pulsed with infected N18 cells. DC expression of MHC and costimulatory molecules were again determined by FACS, and these cells were used in intraperitoneal treatments of mice bearing established subcutaneous N18 tumors.

Results: Pulsing of DC's with G207-infected N18 cells leads to high rates of infection of DC's themselves, which corresponded with a lack of maturation and downregulation of MHC and co-stimulatory molecules. Correspondingly, these DC's lost effectiveness at inhibiting subcutaneous tumor growth in mice. When infection of dendritic cells themselves was prevented by heat-inactivation of virus, maturation was regained.

Conclusion: HSV infection of dendritic cells prevents their maturation and may depress anti-tumor immunity, an important consideration as we explore the immune effects of viral oncolytic therapies for malignant gliomas.

Richard A. Gemeinhart, PhD
University of Illinois
Chicago, Illinois

Richard A. Gemeinhart, PhD
University of Illinois
Chicago, Illinois

MICROPARTICLE-DRUG CONJUGATES AS NOVEL CHEMOTHERAPEUTIC AGENTS

We are testing the hypothesis that targeted chemotherapy delivery increases the effectiveness of conventional chemotherapeutic agents. The long term goal of this project is to design devices that can be injected in the brain following surgery and will be free to move throughout the brain while only delivering the active agent (drug) in the presence of growing and invading cancer cells, while having no toxicity for normal cells. To produce devices that can deliver chemotherapy to sites locally and distant from the site of injection, three specific aims are being investigated: to synthesize microparticle-drug conjugates, to determine the *in vitro* release rate from microparticle-drug conjugates, and to determine efficacy of microparticle-drug conjugates in vitro. The chosen method of targeting is an enzyme naturally secreted from cells, but that is selectively overexpressed in brain tumors. The enzymes cleave the chemotherapeutic agent from the microparticle. Since the enzymes are present in close proximity to the cancer cells that are actively growing and invading other tissue, the drug will be cleaved from the microparticles predominantly at the site where cancer cells are most active. Microparticles, unlike other conjugated drug delivery devices, have many molecules of the chemotherapeutic agent within one particle; large amounts of the chemotherapeutic agent can be delivered to the local environment of the cancer with little or no free drug present in solution.

This type of chemotherapy would be beneficial to cancer patients as it would extend the remission period following surgery for patients that are injected at the time of surgery, while decreasing the side-effects of the chemotherapeutic agent. It is too early to indicate if these devices are effective at treating gliomas, but studies are underway that continue this work with microparticulate devices.

John Hill, MD, PhD
Dartmouth Medical School, Lebanon
New Hampshire

EXAMINING THE ROLE OF GROWTH FACTOR SIGNALING PATHWAYS IN PROMOTING THE GROWTH AND SURVIVAL OF MEDULLOBLASTOMA

Medulloblastoma is the most common malignant brain tumor of childhood affecting approximately 500 children per year. Despite combination therapy including surgery, irradiation, and chemotherapy, significant numbers of patients succumb to medulloblastoma. Of those that survive, many suffer long term sequela from the treatment including impaired cognitive function and learning disabilities.

To identify molecular pathways that could be targeted to enhance current therapies with the goal of reducing mortality and morbidity, I am examining growth factor signaling pathways that appear to be active in medulloblastoma and required for its growth and survival. These include the ErbB and IGF signaling pathways.

Common to both these pathways is the protein kinase Akt, which appears to promote both cell survival and cell proliferation through regulation of various molecular pathways. I am attempting to block Akt expression using RNA interference. I will then determine if this inhibition of Akt expression renders medulloblastoma derived cells more susceptible to either radiation or chemotherapy.

L. Burt Nabors, MD
University of Alabama at Birmingham
Birmingham, Alabama

TARGETED IMAGING IN THE MOUSE BRAIN TUMOR MODEL

Anti-angiogenesis therapies that target specific mechanisms of tumor neovascularization present difficult problems in assessing their relative efficacy. Since the anti-angiogenesis effect may result in a significantly delayed or clinically in-apparent anti-tumor effect when compared with that seen in therapies that target tumor

cells directly, the most appropriate methods to assess an anti-angiogenesis effect need to be identified and validated. In patients with malignant brain tumors, it is procedurally high-risk, infeasible and unethical to obtain routine multiple tissue biopsies on a longitudinal basis to verify, at histopathological, cellular and molecular levels, that tumor vasculature is being appropriately targeted and adversely affected. The overall objective of this project will be to evaluate the capacity of a labeled, targeted compound to reproducibly and effectively evaluate alterations in a specific biologic endpoint, tumor angiogenesis. We propose to: (1) determine the binding affinity of a labeled, targeted nanoparticle (PM-PV) for the integrins, $\alpha v\beta 3$ and $\alpha v\beta 5$; (2) determine the distribution and clearance of the compound in an animal brain tumor model and, (3) explore the utility of a gadolinium-labeled imaging compound (PM-GAD-PV) targeted to glioma vasculature through the $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins. Data from these studies will be critically important in developing, refining and validating non-invasive methodologies for timely assessment of specific anti-angiogenic therapies for malignant brain tumors in patients. The proposal addresses concerns raised by the recent NCI Brain Tumor Progress and Review Report on the need for targeted imaging modalities in clinical trials of novel therapies.

Michael E. C. Robbins, PhD
Wake Forest University School of Medicine
Winston-Salem, North Carolina

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

The identity of the specific biological mediators involved in the development of radiation-induced brain injury remains unknown. We purpose a novel, provocative hypothesis, namely that Ang II, produced intracerebrally by the brain RAS, is involved, in part, in the development and progression of radiation-induced brain injury. We are currently testing this hypothesis by using *in vivo* and *in vitro* approaches. While we have failed to observe any radiation-induced increase in renin or angiotensinogen, components of the RAS, we have observed a 2-fold increase in levels of the Ang II type 1 receptor (AT1R) in astrocytes 24 h after irradiation with a single dose of 10 Gy. In addition, we have preliminary data to suggest that ANG II may play a role in the radiation-induced increase in PAI-1 observed in astrocytes. For the *in vivo* studies we are using a gene targeting approach to generate mice transgenic for both the human renin and angiotensinogen (AGT) genes; these mice express elevated intracerebral levels of locally generated Ang II. We are testing the hypothesis that these double transgenic mice will exhibit enhanced radiation-induced injury following whole brain irradiation as compared with mice expressing a single human transgene. These studies are currently ongoing.

Defining the putative role of 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, both types of Ang II inhibitors, either angiotensin converting enzyme inhibitors or Ang II receptor antagonists, have been routinely prescribed as antihypertensive drugs for a number of years, and are well tolerated. Thus, the establishment of a pathogenic role for Ang II in radiation-induced brain injury will lead to the rapid translation of these findings to the clinic, with the promise of thereby inceasing the therapeutic window for glioma patients and impacting both their quality of life and long-term survival.

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

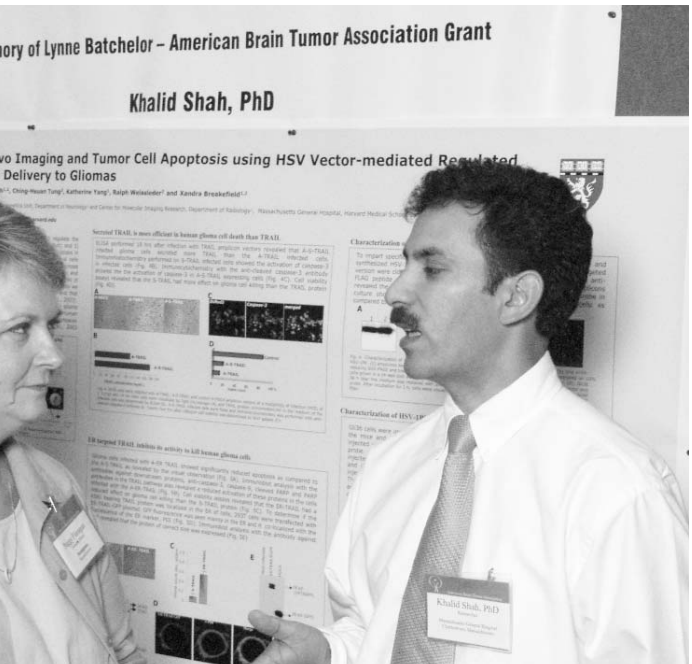
John Hill, MD, PhD
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Khalid Shah, Ph.D.
Massachusetts General Hospital, Harvard Medical School
Charlestown, Massachusetts

NIRF IMAGING AND TUMOR CELL APOPTOSIS USING HSV VECTOR-MEDIATED GENE DELIVERY TO GLIOMAS

The aim of the study was to fulfill the major themes of brain tumor imaging and apoptosis: 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 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.

TRAIL (Tumor necrosis factor related apoptosis-inducing 1igand) induces apoptosis in neoplastic cells and its controlled induction could thus be used in tumor therapy. We have developed a system that simultaneously allows a specific viral protease to control the secretion of TRAIL and to perform real time near infrared imaging (NIRF) *in vivo*. The cDNA for two variants of TRAIL, the secreted one and the one that is targeted to ER and the cDNA for ER targeted HSV-1 protease, were cloned into HSV amplicons and packaged into helper virus-free vectors. Human glioma cells (Gli36) infected with the HSV amplicons bearing recombinant TRAIL showed that ER tagged form of recombinant TRAIL had a significantly reduced apoptotic effect as compared to the secreted TRAIL. The co-infection of the ER tagged TRAIL with the HSV-1 protease resulted in the release of the TRAIL from ER and the induction of apoptosis in glioma cells. We have also shown that transfer of the HSV-1 protease could be directly imaged *in vivo* following intratumoral delivery of the HSV-amplicon. The simultaneous regulation of both the TRAIL mediated apoptosis and protease dependent NIRF imaging should be useful for controlled induction of apoptosis and for real-time non-invasive imaging of brain tumors *in vivo*.



Paula Riess Sherwood, RN, PhD-c, CNRN
Michigan State University
East Lansing, Michigan

FAMILY CARE OF PERSONS WITH A BRAIN TUMOR

Researchers have documented the effects of providing care to the caregiver of a person with cancer, and for a person with a neurodegenerative disorder such as dementia. However, there have been few efforts to describe the impact of providing care for caregivers of persons with a brain tumor.

The purpose of this study is to identify the effect of the care recipient's functional and mental status on the burden and depression of caregivers, and to identify the role of caregiver characteristics in burden and depression, such as mastery and having access to information to assist in providing care. This project is gathering information via telephone interviews with 120 caregivers of persons with a primary malignant brain tumor from local, statewide and national brain tumor databases.

2003 Research *Summaries*

For clinical practice, study results will help health care practitioners identify characteristics that may place caregivers of persons with a brain tumor at risk for burden and depression, in order to generate interventions to improve caregiver health. In the area of research, results will help identify factors that may be amenable to future intervention studies and add to the generalizability of findings from studies to caregivers at large.

I-Mei Siu, PhD
Duke Univeristy
Durham, North Carolina

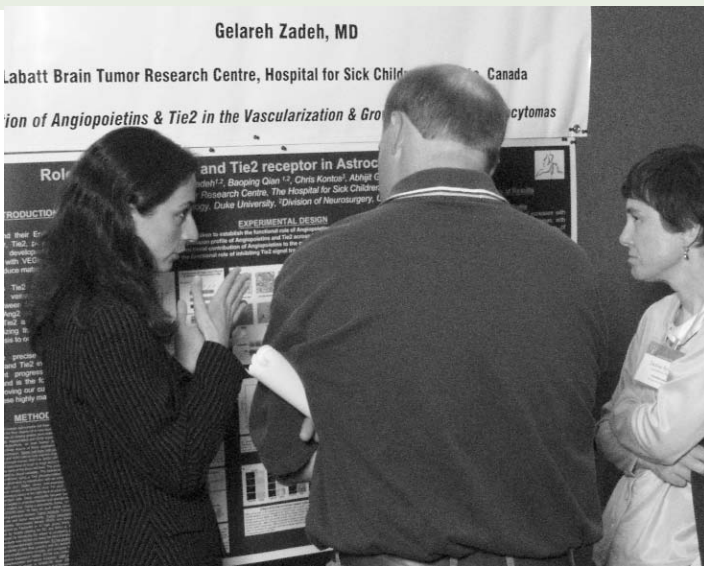
IDENTIFICATION OF THE ROLE OF C-MYC IN MEDULLOBLASTOMA TUMORIGENESIS

Medulloblastomas are the most common type of malignant pediatric brain tumors. However, only a few of the genetic alterations involved in medulloblastoma progression have been identified. In order to identify candidate medulloblastoma markers, we used digital expression profiling to identify and quantify messenger transcripts in two medulloblastomas, two normal cerebella and two medulloblastoma cell lines. This technique, Serial Analysis of Gene Expressions (SAGE), produced 240,180 ten base pair transcript tags.

Bioinformatic analysis of this data indicated transcripts expressed in primary tumors, but not normal cerebella resulting in a list of medulloblastoma associated transcripts. Expression of these genes in cancer, but not normal brain, was further confirmed by real-time PCR and immunohistochemistry.

The candidate markers are involved in a wide range of functions, such as growth (early growth response 1), signaling cascades (bmk1a/ERK5), transcription (serum response factor), and translation (eukaryotic translation initiation factor 4 gamma 2).

From the list of confirmed candidates, we selected developmentally related genes for further investigation into their involvement and possible oncongenic function in medulloblastoma using a retroviral system.



Gelareh Zadeh, MD
Labatt Brain Tumor Research Centre,
The Hospital for Sick Children
Toronto, Ontario

Gelareh Zadeh, MD
Labatt Brain Tumor Research Centre,
The Hospital for Sick Children
Toronto, Ontario

FUNCTIONAL ROLE(S) OF ANGIOPOIETINS AND THEIR COGNATE ENDOTHELIAL CELL RECEPTOR TIE2, IN THE VASCULARIZATION AND GROWTH OF MALIGNANT ASTROCYTOMAS

Malignant astrocytomas are the most common primary adult brain tumors, and are characterized by florid vascularization, which are abnormal in many regions leading to vascular shunting, tumor hemorrhage, and edema. Angiogenesis involves sprouting of new vessels from pre-existing ones. Important positive and negative regulators contribute to this process and amongst them are two specific angiogenic growth factors, since their receptors are expressed mainly by the vascular endothelium.

Vascular Endothelial Growth Factor (VEGF) and VEGF receptors are well established as important regulators of astrocytoma angiogenesis and growth,

I-Mei Siu, PhD
Duke Univeristy
Durham, North Carolina

while very little is known about the more recently discovered Angiopoietins and their receptor, Tie2. To follow up on the expression study of Angiopoietins/Tie2 in human astrocytomas, this proposal asks what role(s) if any do they have in astrocytoma vascularization and growth. I will use molecular biological techniques to induce or attenuate Angiopoietin activation of Tie2, on cell lines and astrocytoma explant xenografts models, and also a transgenic mouse astrocytoma model established in our lab. This increased understanding of the molecular mechanisms of astrocytoma vascularization will hopefully lead to novel anti-angiogenic therapeutic interventions for this human cancer.

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

MECHANISMS OF HEDGEHOG-INDUCED NEURAL PROLIFERATION

The sonic hedgehog protein is responsible for growth of the cerebellum, a part of the brain involved in coordinating movement and balance control. However, human genetic mutations (primarily in children) are known in which the Sonic hedgehog signal is overly active, resulting in the cerebellar tumor, medulloblastoma.

To accomplish these, first, we will combine primary culture and animal model systems using techniques ("chips") that allow for a high-throughput screening of 11,000 mouse genes potentially regulated by Sonic hedgehog; secondly, we will study mouse homologues of the differentially expressed gene profiles from published human medulloblastoma chips (Pomeroy SL. Nature 2002).

The identification of Sonic hedgehog downstream proliferative targets and genes up or down regulated in the medulloblastoma patients will shed light on fundamental mechanisms during cerebellar development, and may potentially guide the design of novel therapeutic agents for human cancer.

Nursing RESEARCH AWARD

We are proud to support an annual neuro-oncology nursing research award through the Oncology Nursing Foundation of the Oncology Nursing Society. The current year's recipient is Terri Armstrong, MS, APRN, BC at the MD Anderson Cancer Center in Houston, Texas. Ms. Armstrong will develop a symptom inventory module for evaluating brain tumor patients. Nurses interested in applying for this award should contact the Oncology Nursing Society at 412-921-7373.

American Brain Tumor Association

2720 River Road, Suite 146
Des Plaines, Illinois 60018

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