American Brain Tumor Association®

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AMERICAN BRAIN TUMOR ASSOCIATION RESEARCH OUTCOMES 2013

BASIC RESEARCH FELLOWSHIPS (2011-2013)

The American Brain Tumor Association Basic Research Fellowship is a two-year fellowship designed to encourage talented scientists early in their careers to enter, or remain in, the field of brain tumor research.

CHRISTIAN BADR, PHD

Massachusetts General Hospital, Charleston, MA

American Brain Tumor Association Basic Research Fellowship in Honor of Susan Kramer

Project Title: "Multiplex Assay to Monitor Viability, Self-Renewal and Differentiation of Glioma Stem Cells"

Summary: Glioma stem cells (GSCs) represent a subset population within malignant gliomas. Recent evidence suggests that those cells might be responsible for tumor recurrence often observed in glioma patient following tumor resection and therapy. We have developed 3 different reporters which allow us to monitor the viability, differentiation and self-renewal of GSCs. Those reporters allow us to screen for thousands of small-molecules in order to identify compounds that can eradiate this malignant stem cell population. We have optimized our reporters and showed their potential in imaging 3 different biological processes *in vitro* and *in vivo*. We have so far screened part of our 20,000 small-molecules library and identified a natural compound, Obtusaquinone (OBT), which potentially kills GSCs and mature gliomas. OBT was well tolerated in mice with no signs of toxicity and its therapeutic efficacy was validated in subcutaneous and intracranial glioma tumor models. OBT slowed tumor growth and prolonged survival in treated mice compared to the control group. We will continue screening for the rest of our compound library as we validate OBT as a new potential drug candidate for glioblastoma.

MYRIAM CHAUMEIL, PHD

University of California San Francisco, San Francisco, CA

American Brain Tumor Association Basic Research Fellowship in Honor of Team Survivor

Project Title: Imaging Response to PI3K Inhibition in Glioblastoma Models

Summary: In healthy cells, genes create proteins and enzymes that communicate to perform specific functions. All brain tumors result from genetic mutations changing the way cells proliferate and communicate, altering tumor metabolism. Particularly, mutations in the isocitrate dehydrogenase 1 (IDH1) enzyme, found in <70% of gliomas and upgraded glioblastomas, play a crucial role in tumor development. Consequently, treatments specifically targeting such mutation are developed. Our goal was to develop innovative metabolic neuro-imaging techniques informing on, not tumor anatomy, but rather tumor function, thus giving information on treatment response at early time points. First, we developed a new 1H magnetic resonance spectroscopy (MRS) method to specifically look at lactate, a metabolite whose level is directly related to tumor status. We then combined 1H MRS with an innovative method, hyperpolarized (HP) 13C MRS imaging of pyruvate. Finally, we developed a new HP agent, α-ketoglutarate, to look at IDH1 status. Following HP α-ketoglutarate injection, production of HP 2-hydroxyglutarate by mutant IDH1 was detected in IDH1-mutated tumors, not in wild-type. This pioneer study demonstrates the use of HP αKG to non-invasively inform on mutant IDH1 activity. The methods developed during this fellowship should prove useful for monitoring response to targeted therapies. Consequently, treatment could be adjusted, if necessary, for better patient outcome.

KEVIN CHOE, MD, PHD
University of Texas Southwestern Medical Center, Dallas, TX
American Brain Tumor Association Basic Research Fellowship in Honor of Team Loving Life
Project Title: "A Genome-Wide Search for Mediators of Glioma Initiation and Progression"
Summary: Malignant gliomas are a common type of brain cancer. Depending on the histological grade, clinical outcomes and pathological characteristics are highly variable. In this study we modified the mouse model so that the initial formation and progression of brain tumors can be visualized in living animals, non-invasively. With mice, we were able to detect and localize small early-stage gliomas before they cause symptoms. By harvesting tumors of varying stages of malignancy and performing large-scale molecular analysis, we can determine the expression of every known gene in the entire genome. By comparing the gene expression patterns we are identifying key genetic changes involved in glioma development and therapeutic resistance. The findings from this study have the potential to make an immediate impact on the way we classify and treat glioma patients in the clinic. Using clinical relevance as a foundation, identification and characterization of key genes responsible for gliomagenesis and treatment resistance are ongoing.

VIVIAN GAMA, PHD
University of North Carolina at Chapel Hill, Chapel Hill, NC
American Brain Tumor Association Basic Research Fellowship
Project Title: "Cytochrome *c* Degradation as a Common Survival Mechanism of Neurons and Brain Tumors"
Summary: One million cells in our bodies die every second by a mechanism known as apoptosis. The realization that cells can actively kill themselves is perhaps one of the most remarkable discoveries of biomedical research in the last decades. This mechanism of cell suicide is essential during organismal development and is critical for eliminating cancer cells and therefore preventing the formation of tumors. It may seem paradoxical that neurons (non-dividing cells) and brain tumor cells (highly proliferating cells) will utilize similar mechanisms for survival, both cell types have the unique capacity of surviving long-term and this ability is in great part due to their ability to restrict apoptosis. In this study I characterized one of these mechanisms used by both neurons and brain tumor cells to evade apoptosis: the degradation of the pro-death protein cytochrome c (cyt c). I discovered that neurons and brain cancer cells have the acquired capacity to degrade cyt c once is released from the mitochondria preventing the subsequent cascade that leads to cell death. The degradation of proteins is a complex and highly regulated process, orchestrated by enzymes called E3 ligases. A siRNA screen in a glioblastoma cell line implicated an E3 ligase called PARC (Parkin-like cytoplasmic protein) in the degradation of cyt c. Our results identified a novel role of PARC in regulating apoptosis after the point of mitochondrial permeabilization in neurons and brain tumor cells, revealing a potential new target in the pathogenesis of cancer and neurodegeneration.

DAVID INFANGER, PHD
Cornell University, Ithaca, NY
American Brain Tumor Association Basic Research Fellowship in Honor of Team Will Power
Project Title: "Microenvironmental Control of Glioblastoma Stem Cells in the Perivascular Niche"
Summary: By utilizing engineered, three-dimensional (3D) cell culture models to mimic interactions between blood vessel-containing and glioblastoma cancer stem cells (CSCs), we discovered a critical signaling pathway which aids in CSC migration, growth, and ultimately tumor formation. Specifically, signaling cascades initiated by 3D culture conditions and factors secreted by CSCs robustly enhanced secretion of the pro-inflammatory cytokine interleukin-8 (IL-8), which maintained the undifferentiated stem-like character of CSCs in vitro and stimulated proliferation in culture. Signaling cues secreted by endothelial cells which were fed to CSC cultures enhanced the expression of the IL-8 receptors CXCR-1 and CXCR-2 on CSCs, which further stimulated these outcomes. In addition, IL-8 mediated CSC migration in vitro, which may partially explain the co-localization of CSCs and endothelial cells observed in clinical glioblastoma biopsies. When implanted, the presence of

endothelial cells dramatically accelerated glioblastoma formation, which was abolished by impairing CXCR-2 expression in implanted CSCs. Collectively, these findings demonstrate that signaling between endothelial cells and glioblastoma CSCs – within a 3D context – results in an enhanced sensitivity to IL-8 signaling which strongly participates in glioma pathogenesis. In a broader context, the utilization of engineered polymeric scaffolds as mimics of the 3D tumor microenvironment serve effectively to recapitulate signaling cascades which result in human glioblastoma tumor formation when these seeded scaffolds are implanted into mice. As such, this approach offers great promise in pursuit of a 'personalized approach' to brain cancer therapy.

SICHEN LI, PHD

University of California Los Angeles, Los Angeles, CA

American Brain Tumor Association Basic Research Fellowship in Honor of Naomi Berkowitz

Project Title: "Mechanism of Glioblastoma Radiosensitization by Mutant Isocitrate Dehydrogenase 1 (IDH1) and the Characterization of Aberrant Methylation Profiling in IDH1 Mutant Gliomas"

Summary: Isocitrate dehydrogenase 1(IDH1) is an enzyme that plays an important role in the citric acid cycle, which itself is a key part of the way the body generates energy from food. The mutation of IDH1 gene has been detected in most low grade and secondary brain tumors, and used as a molecular biomarker that categories brain tumor into two subtypes: IDH1 wild type or IDH1 mutant brain tumor. IDH1 mutant brain tumor has two distinguished characters: superior outcome for patients in clinic and global DNA hypermethylation (silencing of gene expression) at molecular level. To study the association between IDH1 mutation and improved patient survival, we introduced mutant IDH1 in brain tumor cells in vitro and found that reactive oxygen species (ROS) metabolism in these cells was affected and the cells became more sensitive to radiation, which suggests a mechanism for improved survival seen in patients with IDH1 mutation brain tumors. We characterized the high resolution DNA hyermethylation profiling in IDH1 mutant brain tumor using next generation sequencing technology and identified a set of tumor suppressor genes and microRNAs whose expression were specifically silenced by DNA hypermethylation in IDH1 mutant brain tumor, which may contribute to tumor formation. Our study provide key insights into the role of mutant IDH1 in the development or progression of tumors and the identification of silenced tumor suppressors will allow us to develop the target treatments towards those changes which are specific to brain tumors with mutant IDH1.

LISA MATLAF, PHD

California Pacific Medical Center Research Institute, San Francisco, CA

American Brain Tumor Association Basic Research Fellowship in Honor of Joel A. Gingras, Jr.

Project Title: "Identification and Characterization of a Potential HCMV Oncomodulatory Protein in Glioblastoma"

Summary: The human pathogen cytomegalovirus (HCMV) is highly associated with glioblastoma (GBM). We believe this virus can contribute to the growth of associated tumors by enhancing the vascularization and dispersal of tumor tissue. We found that the HCMV protein pp71 is present in a majority of human GBMs and is preferentially expressed in a specific population of cells with cancer stem-like properties which contribute to therapeutic resistance and recurrence. When we expressed pp71 in immature normal neural cells we observed a potent induction of the cytokine stem cell factor (SCF), which is highly expressed in forms of GBM and contributes to blood vessel growth required for the development of these tumors. Furthermore, we determined that pp71 can stimulate blood vessel formation in cell culture by activating an important receptor on the surface of specialized (endothelial) cells, causing them to grow and assemble into functional blood vessels. We found that pp71 induces SCF by promoting a pro-inflammatory response in tumor cells via activation of a specific pathway (NFKB) usually augmented in a subclass of GBMs. This suggests that HCMV pp71-induced signaling in the tumor microenvironment may contribute to the phenotype of this cancer. We found that treatment with the anti-HCMV drug cidofovir downregulated SCF expression and improved survival in a mouse model of GBM. We conclude that HCMV is a novel therapeutic target for brain tumor patients.

ILWOO PARK, PHD

University of California San Francisco, San Francisco, CA

American Brain Tumor Association Basic Research Fellowship in Honor of Theodore Sapper

Project Title: "Development of an Early Biomarker of MGMT Activity and Response to Temozolomide Treatment Using Hyperpolarized ^{13}C MR Metabolic Imaging"

Summary: Standard GBM treatment usually consists of surgical resection and post-operative radiation followed by chemotherapy. It has been shown that the high level of DNA damage repair protein MGMT predicts which patients with GBM are likely to be resistant to chemotherapy. There is currently no method for measuring MGMT activity in tumors non-invasively *in vivo* prior to and during therapy. Using a ^{13}C-labeled compound and a novel rapid imaging technique using hyperpolarized ^{13}C MR metabolic imaging, we have shown that early cell damage due to chemotherapy changes metabolism only when MGMT is absent. This effect was noticed as early as 24 hours after treatment, far earlier than any other previously measured events observed after exposure to chemotherapy. In addition, we have shown that this method enabled the differentiation of distinct ^{13}C metabolite patterns within abnormal tissues, and demonstrated the feasibility of using this technique for future human clinical trial by acquiring data from non-human primate brain. The results from these projects suggest that this technique have the potential to provide an early and reliable biomarker to monitor response to chemotherapy in patients with GBM. The ability to detect brain tumor response to chemotherapy early on would be valuable for neuro-oncologists to define criteria for continuing or modifying treatment strategies, thereby improving patient outcome.

MARIA SAMBADE, PHD

University of North Carolina at Chapel Hill, Chapel Hill, NC

American Brain Tumor Association Basic Research Fellowship in Honor of Mark Linder

Project Title: "Mechanisms of Melanoma Radio-Sensitization and its Impact on Therapy Against Melanoma Brain Metastases"

Summary: Radiation is the standard of care for most brain cancer, and the treatment of melanoma brain metastases, recognized as a therapy resistant cancer type, is an important clinical problem. The underlying idea of this grant is that over-expression of DNA damage and repair effectors support radio-resistance and that therefore, inhibition or knockdown of these effectors would significantly increase the effectiveness of radiotherapy against melanoma. To address the hypothesis, we proposed a bipartite methodology. First, we determined radio-resistance mechanism from gene expression analysis and testing it on human melanoma lines in vitro creates a rationale design schema that could be implemented next. Second, we generated the preclinical model for treatment regimen study, in which human melanoma cell lines representative of several melanoma subtypes, are surgically implanted intracranially in immunocompromised mice to recapitulate a human melanoma brain metastatic model. As an initial test of the preclinical models, we treated a BRAF mutant melanoma model with radiation and the pharmacological inhibitor combinations of well-known DNA maintenance proteins radio-sensitizers PARP1 and HDAC, which both cross the brain barrier. We have shown that inhibition of several DNA damage and repair response effectors radio-sensitize human melanoma cell lines, either through pharmacological inhibition or using shRNA knockdown technology. The development of the melanoma brain metastatic models has also been straightforward. We have started preliminary studies in non-tumor bearing mice with treatment combinations to balance combinatorial toxicities with greatest therapeutic impact against melanoma. I am eagerly anticipating the coming year, which will be a very exciting one for this preclinical research.

DAVID SCHONBERG, PHD
Cleveland Clinic Lerner Research Institute, Cleveland, OH
American Brain Tumor Association Basic Research Fellowship in Honor of Joel A. Gingras, Jr.
Project Title: "The Role of Iron Metabolism in Glioblastoma Stem Cells"
Summary: Improving survival for GBM patients will come from elevating our understanding of the key biological processes and cell types that make brain tumors grow and withstand current therapies. Proper iron metabolism is a vastly underappreciated requirement for normal cell function. Yet in various cancers, iron homeostasis is often dysregulated. I have found that within GBM, iron usage is upregulated in cells that have stem-like properties, referred to as GBM stem cells or GSCs. The significance of GSCs has been supported by studies from our group and others that these cells are resistant to chemo- and radiotherapy. Recent findings have linked elevated iron usage to chemoresistance, suggesting the importance of identifying how iron may be involved in controlling GSCs. I determined that depleting iron or the ability to safely use it causes significant damage to GSCs, decreasing their ability to grow and proliferate while increasing their production of toxic free radicals and rate of cell death. These results suggest that iron is a critical regulator for GSCs and their ability to form tumors. Current studies are ongoing to target this metabolic pathway in a way that can be easily translated to humans.

LEANNE WYBENGA-GROOT, PHD
Hospital for Sick Children, Toronto, Ontario, Canada
American Brain Tumor Association Basic Research Fellowship
Project Title: "Understanding LNX-Mediated Regulation of Oncogenic Signaling in Brain Tumors"
Summary: Cell signals control the fate of a cell, telling it when to grow, what type of cell to become, and when to die. Thus, cell signals must be tightly controlled to maintain a healthy, normal body. My research studies how E3 ligases turn cell signals off by targeting specific proteins for destruction through a process called ubiquitination, and how other proteins modify the activity of E3 ligases. For instance, an E3 ligase called LNX targets Numb for destruction, which itself turns off Hedgehog signaling. Abnormal Hedgehog signaling is tightly linked to medulloblastoma. My data reveals specific deregulation of LNX/NUMB in medulloblastomas belonging to the Sonic Hedgehog (SHH) subgroup. My research has advanced our understanding of how LNX interacts with Numb to target it for degradation, and how certain Mage proteins, which are expressed in tumor cells but not normal cells, bind to LNX to modify its activity. Another E3 ligase that I investigate, called Cbl, turns off signaling from the EGF receptor, which is prominent in glioma pathogenesis. I have uncovered a novel way in which Cbl activity is turned on by a protein called SLAP2. These findings represent significant progress in our understanding of the molecular events that underlie the initiation and progression of brain tumors, which is key to developing better, more specific therapeutic interventions.

JIAN ZHANG, PHD
Columbia University New York, New York, NY
American Brain Tumor Association Basic Research Fellowship in Honor of Denise Kimball
Project Title: "Role of mRNA Splicing Regulators in Glioblastoma"
Summary: This research aims at developing a novel mechanism of inhibiting GBM formation. We targeted three key proteins that are important for the regulation of tumor metabolism. In normal cells, glucose is metabolized mainly to generate energy. However, in tumor cells, glucose is metabolized mainly to generate biomass for making new cells, leading to tumor growth. The switch between these two different ways of glucose metabolism is regulated by three RNA splicing proteins called PTB, hnRNP A1 and hnRNP A2. In this study, we found that these three proteins are all present at higher than normal levels in human GBM samples as well as in GBM-like tumors developed from models. Reduction of these three proteins simultaneously using a technology called RNA interference greatly inhibits growth of GBM cells in vitro and impairs the ability of GBM cells to form tumors. These results will potentially lead to more effective treatments of GBMs in humans.

TRANSLATIONAL GRANTS (2012-2013)

The American Brain Tumor Association Translational Grant is a one year award for pre-clinical research that critically evaluates the diagnostic and/or therapeutic potential of recent discoveries for advancement to clinical application.

ALBERT LAI, MD, PHD

David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA

American Brain Tumor Association Translational Grant in Honor of Justin Porter

Project Title: "Non-Invasive Circulating Free DNA Methylation Based Biomarkers for Glioma Diagnosis and Surveillance"

Summary: Diffuse gliomas constitute a common primary brain cancer in adults. Due to the justified reluctance to subject glioma patients to multiple resections/biopsies, glioma tumor tissue is generally only available at initial diagnosis, and almost never during ongoing treatment. Based on the need for molecular surveillance, the goal of this proposal is to develop non-invasive molecular markers that can be used to track and understand treatment response and resistance. By analyzing tumors, we have identified several promising candidates demonstrating methylation changes with malignant transformation and treatment resistance. We have made significant progress in developing DNA methylation based markers to help us monitor tumor behavior without subjecting the patient to an additional surgeries. These DNA methylation markers will aid in non-invasive molecular surveillance to guide treatment.

G. PRAVEEN RAJU, MD, PHD

Weill Medical College of Cornell University, New York, NY

American Brain Tumor Association Translational Grant Supported by the Humor to Fight the Tumor Volunteer Event Committee

Project Title: "Preclinical Assessment of Arsenic Trioxide and Resistance Mechanisms in a Novel Mouse Model of Sporadic Medulloblastoma"

Summary: There are two significant findings from this research. Previous work has suggested that the mechanism of ATO action is through GLI protein inhibition which is predicted to result in either decreased cellular proliferation or increased cellular differentiation for medulloblastoma tumor cells. However, our results testing ATO treatment on cerebellar granule cell precursors, the cell of origin for Sonic hedgehog-driven medulloblastoma, suggest that the effects of ATO result primarily in cell death, or apoptosis. Based on these findings we continue testing the efficacy and toxicity of ATO in vivo using our novel genetically relevant medulloblastoma animal model with the goal of identifying a therapeutic window for this drug. A second significant finding shows that we can identify the two subtypes of Sonic hedgehog-driven medulloblastoma that are found in children in our animal model using MRI techniques. This is particularly important because we can specifically assess whether one subtype of Sonic hedgehog-driven medulloblastoma might be more responsive to a particular treatment than the other subtype. The support of the ABTA has allowed the development of this novel drug testing platform which can be used by other brain tumor researchers to test additional novel therapies for medulloblastoma.

DISCOVERY GRANTS (2012-2013)

The American Brain Tumor Association Discovery Grant is a one year award supporting high risk/high impact projects that have the potential to change current diagnostic or treatment paradigms for either adult or pediatric brain tumors.

AKEMI KOSAKA, PHD
University of Pittsburgh, School of Medicine, Pittsburgh, PA
American Brain Tumor Association Discovery Grant
Project Title: "Immunological Soil in the Brain-Strategies for Prevention of Breast Cancer Brain Metastasis"
Summary: We seek to understand how breast cancer spreads to the brain and to develop the means to predict, prevent, and treat brain metastases. We found markedly up-regulated production of the inflammatory chemokines S100A8 and S100A9 (S100A8/A9) in the brains of mice with 4T1 tumors just before cancer metastases arrive. Treatment of 4T1-bearing mice with anti-Gr1 monoclonal antibody reduces accumulation of $CD11b^{+}Gr1^{+}$ cells in the day 14 premetastatic brain as well as subsequent brain metastasis of 4T1 tumors detected on day 30. Furthermore, when we gave the mice an anti-inflammatory drug, celecoxib, we did not find as many $CD11b^{+}Gr1^{+}$ cells or as much S100A8/A9 in the pre-metastatic brain and subsequent formation of brain metastasis. Our results strongly suggest that the primary tumor induces accumulation of $CD11b^{+}Gr1^{+}$ cells in the brain to form "premetastatic soil" and inflammation mediators, such as S100A8/A9, that attract additional myeloid cells as well as metastatic tumor cells. These studies could help us to identify biomarkers that predict metastasis and to develop strategies to prevent the metastatic spread of breast cancer.

MICHAEL OLIN, PHD
University of Minnesota, Minneapolis, MN
American Brain Tumor Association Discovery Grant
Project Title: "Discovery of the Link between Central Nervous System Tumors and Cervical Lymph Node-Mediated Immune Suppression"
Summary: Utilizing tumors as a source of vaccination antigens in immunotherapy has demonstrated promising results. However, researchers have failed to overcome the suppressive effects of the tumor microenvironment. We demonstrated that proximity of vaccination injection site to the primary tumor site dictates CD8 T-cell priming within the draining lymph node. These results were due to suppressive effects of the tumor and its microenvironment. Using proteomic techniques, we discovered an excess of soluble CD200 protein in the cerebral spinal fluid and cervical lymph nodes in tumor bearing mice. CD200 is immunosuppressive in multiple graft rejection models, but has not been clearly defined as a factor in tumor-induced suppression. However, specific peptide domains within the CD200 have antagonist activity (act as competitive inhibitors for CD200). Preliminary data show that these inhibitors reverse immune suppression within lymph nodes, significantly extending survival of vaccinated GL261-bearing and breast carcinoma mice. These findings have major implications for the design of translational research approaches and future clinical trials. If our hypothesis is correct, the use of a competitive inhibitor may overcome the suppressive properties of the tumor in both the sentinel lymph nodes as well within the tumor microenvironment ultimately leading to the development of novel therapeutics that increase the efficacy of cancer immunotherapy.

KAI TAN, PHD
University of Iowa, Iowa City, IA
American Brain Tumor Association Discovery Grant
Project Title: "Multi-Analyte Network Markers for Brain Tumor Prognosis"
Summary: Understanding the molecular pathways that distinguish GBM long-term survivors from short-term survivors could ultimately lead to more accurate diagnosis and personalized therapies for subgroups of GBM patients. Our results highlight the critical role of two novel pathways in the prognosis of GBM patients, small GTPase-mediated protein trafficking and ubiquitination-dependent protein degradation. A better understanding of these two pathways could lead to personalized therapies for subgroups of GBM patients.

MINGYAO YING, PHD

Hugo W. Moser Research Institute at Kennedy Krieger, Inc., Baltimore, MD

American Brain Tumor Association Discovery Grant

Project Title: "Hyaluronan-Mediated Motility Receptor as a Novel Target for Inhibiting Glioblastoma Stem Cells"

Summary: Considerable evidence has demonstrated that glioblastoma (GBM) stem cells interact with tumor microenvironment to promote tumor angiogenesis, immune evasion, therapeutic resistance and tumor recurrence. It is becoming increasingly important to understand the stem-cell-supporting signaling in GBM stem cells and develop novel therapeutic strategies to efficiently inhibit GBM stem cells. Here, we study the function of hyaluronan-mediated motility receptor (HMMR) in human GBM stem cells and human GBM tumors. HMMR is an oncogene that plays essential roles in the tumor initiation and migration of a variety of human tumors, including GBM. We found that HMMR shows higher expression in GBM tumors than normal brain tissues. We found for the first time that HMMR is essential for the self-renewal and tumor formation ability of GBM stem cells. Moreover, HMMR level positively correlates with the activity of GBM-stem-cell-supporting signaling in human GBM tumors. These findings lay a solid foundation for the development of HMMR-targeted therapy. Our discoveries also identify HMMR as a biomarker for measuring the activity of stem-cell-supporting signaling in human GBM tumors. This project helps us to establish an efficient system for drug target identification aiming at targeting cancer stem cells in brain tumors.

WILLIAM C. ZAMBONI, PHARMD, PHD

University of North Carolina at Chapel Hill, Eshelman School of Pharmacy, Chapel Hill, NC

American Brain Tumor Association Discovery Grant

Project Title: "Nanoparticle Agents for the Treatment of Metastatic Central Nervous System Malignancies"

Summary: We evaluated the exposure and efficacy of a novel PEGylated liposomal formulation of cisplatin (PLC-E180-248; PLC) and a novel polymeric nanoparticle formulation of cisplatin (PSQ-cisplatin) compared with standard cisplatin in intracranial models of SUM149 triple negative breast cancer (TNBC) and A549 NSCLC. The data suggests that the cisplatin was not readily released from the liposome and into the tumor matrix. Ongoing studies are evaluating methods to enhance the release of drug (e.g. cisplatin) from liposomes within the tumor matrix. The low response of PLC and cisplatin in mice bearing A549 NSCLC tumors is consistent with the lower exposure of both agents in the intracranial tumors. These results highlight the rationale for performing detailed PK studies in tumors, the need to develop novel methods to induce and evaluate the release of drug from liposomes in tumors and the need to determine the factors that affect the tumor delivery of small molecule and nanoparticle agents to intracranial and other solid tumors. The PSQ-cisplatin studies are ongoing.