The Goldhirsh Foundation
Brain Tumor Research Awards Program
2009 Investigators

Recipients of Three-year Awards

Lara Collier, Ph.D.

University of Wisconsin-Madison

Genetic Approaches to Identify and Characterize Potential Drug Targets for High-grade Gliomas

Elucidating the genetic events that drive glioma formation is an important step toward designing better therapies. For this reason, we have been using the Sleeping Beauty (SB) transposon system in somatic cell mutagenesis screens for cancer gene discovery in mouse glioma models. By studying a limited number of SB-induced gliomas we have identified the cytokine Csfl as a candidate glioma oncogene. CSF1 and phosphorylated CSF1 receptor (CSF1R) have previously been detected in human gliomas, however the role of CSF1 signaling in gliomagenesis has not been thoroughly investigated. We hypothesize that CSF1 signal transduction is important in gliomagenesis and represents a potential treatment target. In addition, we hypothesize that the SB system can complement genomics studies of human glioma and discover additional candidate glioma genes. To test these hypotheses we will use genetic approaches employing mouse glioma models to determine if Csfl is required for glioma initiation or progression. The ability of Csfl and Csflr activation to promote or accelerate glioma formation will also be addressed. We will also investigate if Csfl impacts glioma development by signaling to the tumor cell or to macrophages/microglia. In addition, we will perform mutagenesis studies with SB in csfl deficient mice to identify additional candidate glioma genes. In summary, these experiments are designed to address if Csfl signaling is important for gliomagenesis and therefore a viable drug target for glioma therapy, and to use forward genetic approaches in murine models to identify additional candidate glioma genes.

Paul Mischel, M.D.

University of California Los Angeles

Identification of Malignant Glioma Cell Surface Markers and Molecular Characterization of Heterogenous Tumor Cell Populations to Guide Therapy

Glioblastoma is a molecularly heterogeneous disease. Cells within an individual patient's tumor may differ in their suite of molecular alterations. If an agent, or combination of agents, targets most of the tumor cells, but is ineffective against a subset of tumor cells, those cells will rapidly take over leading to resistance and tumor progression. Further, the heterotypic tumor microenvironrnent involves interactions between different types of cancer cells (i.e. stem cells and non-stem cells), between cancer cells and immune cells and support cells, all of which may be important for determining response to targeted therapy. We hypothesize that it is necessary to understand the signaling networks of multiple different component cells within each patient's tumor and use this information to guide combination therapies that anticipate and prevent resistance. The critical gap is our lack of cell surface markers with which to capture and characterize the defined tumor cell populations. Here we leverage a suite of powerful new technologies applied to well

characterized clinical samples to: 1) identify novel glioblastoma (GBM) cell surface markers and use them to define relative cell populations within heterogeneous tumors; 2) elucidate the signal transduction pathways activated within those defined tumor cell populations in clinical GBM samples and 3) examine the effect of small molecule inhibitors on signal transduction, proliferation and survival in defined tumor cell populations from clinical samples. Completion of this project will improve the care of GBM patients by: 1) identifying tumor cell populations promoting clinical resistance to therapies, including cancer stem cell populations; 2) defining more effective combination therapies that target the multiple populations within each tumor and 3) providing a pipeline of cell surface markers themselves that can serve as imaging and/or therapeutic targets.

Luis Parada, Ph.D.

University of Texas Southwestern Medical School

Physiologically Relevant Mouse Models of Human Glioma: A Powerful Tool for Therapeutic Target Identification by Parallel Chemical Genetics and Functional Genomics Analysis

Malignant astrocytomas are brain tumors that are locally infiltrative and incurable, with poor prognosis for the patient. Despite significant inroads into identifying the genetic mutations that lie at the root of tumor formation, the full spectrum of molecular events that occur during tumor initiation and progression have yet to be teased out. We previously reported mouse models based on conditional inactivation of human astrocytoma-relevant tumor suppressors p5S, Nfl, and Pten, wherein through somatic loss of heterozygosity, mutant mice develop tumors that histologically and molecularly resemble human astrocytomas with 100% penetrance. In addition, we have shown that these tumors arise from a neural stem/progenitor cell population located within a neurogenic niche of the brain. These cells can be propagated in culture as neurospheres and exhibit abnormal stem cell properties including increased self-renewal capacity and altered differentiation. They can also form tumors when transplanted into host mice. In the present application, our mouse models of human glioma will be utilized for experiments aimed at investigating the genes and signaling pathways that are involved in the tumorigenicity of these cells. Our research design employs the tumor-derived neurosphere-forming cells isolated from our mouse models for unbiased, large-scale chemical and genomic screening. We will exploit these self-renewable neurosphere cells to generate the large number of cells required for these comprehensive cell-based assays. Potentially interesting "hits" identified in our screens will be functionally pursued in both mouse and human cancer cells, using RNAi and overexpression techniques. We will evaluate the role of these genes on the growth and differentiation properties of mutant as well as wild-type neurosphere-forming cells, and analyze their affect on tumorigenic potential via transplantation techniques. Our fully penetrant glioma mouse models are clinically relevant and powerful tools and provide a cell population that is uniquely advantageous for these large-scale screens. It is our belief that these screens will identify novel compounds and genes that may be therapeutically tractable in human glioma.

Recipients of One-year Awards

Al Charest, Ph.D.

Tufts Medical Center

Targeting Cancer Stem Cells in a Pre-Clinical Mouse Model of Glioblastoma Multiforme Using Therapeutic Nanoparticles

The deadly nature of malignant gliomas is their intrinsic ability to invade surrounding, disease-free brain tissues. This leads to recurrence almost universally. It is thought that recurrence arise from a population of tumor cells known as cancer stem cells (CSCs). Also known as tumor-initiating cells, these cells represent the most therapy-resistant population within a tumor. Strategies designed to identify and eliminate CSCs therefore offer a highly promising approach toward finding a cure for this dreadful cancer. Our research centers on the utilization of mouse models of GBM to study molecular mechanisms of tumor initiation, maintenance and resistance to conventional therapies. In addition, we utilize these models to advance our knowledge on cutting-edge technologies. As such, we focus on the use of nanotechnology for the detection and treatment of primary malignant brain cancer. In this one-year pilot project proposal, we aim to target GBM cancer stem cells using nanoparticles capable of recognizing and binding the cancer stem cell surface marker CD133 and delivering a therapeutic cargo specifically to cancer stem cells. We will achieve these goals through the following specific aims. AIM 1. To measure the binding specificity and affinity of CD133-targeted nanoparticles to cancer stem cells in vitro. In this aim, we will isolate and characterize high affinities peptides against the CD133 marker protein by phage peptide library screening in vitro. Once identified, these peptides will be coupled to silk protein-derived nanoparticles loaded with therapeutic agents. This will be performed in collaboration with Professor David Kaplan's laboratory from the Department of Biomedical Engineering, Tufts University. Dr. Kaplan is a world renowed expert on biopolymer fabrication and use in biological systems. AIM 2. To ascertain bio-targeting abilities and bio-distribution of CD133-targeted silk-protein nanoparticles in vitro and in vivo. In this aim, we will measure the strength of CD133-targeted nanoformulations affinities and selectivities towards CD133 expressing and CD133-null cells in vitro and study uptake kinetics. We will then utilize these CD133-targeted nanoparticles to target human GBM CSC in vitro and in vivo and asses discriminate therapeutic efficacy.

Sean Morrison, Ph.D.

University of Michigan

Do Glioblastomas Follow a Cancer Stem Cell Model?

A number of studies have suggested that few human glioblastoma cells are capable of proliferating extensively or forming tumors in NOD/SCID mice. These tumorigenic glioblastoma stem cells were suggested to be intrinsically different from non-tumorigenic glioblastoma cells and distinguishable by CD133 expression. This conclusion has profound implications for treatment as it suggests that to cure glioblastoma it is necessary and sufficient to kill CD133+ glioblastoma stem cells. We have recently discovered that some cancers that appear to have rare tumorigenic cells in NOD/SCID mice actually have quite common tumorigenic cells when assayed under modified conditions (Nature 456:593). Melanoma had been suggested to follow a cancer stem cell model in which

only 0.0001% of cells were tumorigenic in NOD/SCID mice. In contrast, when assayed in more highly immunocompromised NOD/SCID IL2Rynu" mice, we found that approximately 25% of melanoma cells from several patients were capable of forming tumors (Nature 456:593). We have also started to address this issue in glioblastomas. We find glioblastomas from multiple patients that have extremely high frequencies of tumorigenic cells, and in which we have been unable to distinguish tumorigenic from non-tumorigenic cells based on CD133 expression. If many glioblastomas do not follow a cancer stem cell model it would have fundamental implications for research to develop new glioblastoma therapies as it will not be possible to improve the treatment of these tumors by targeting small subpopulations of cells. In Aim 1 we will test whether the use of more highly immunocompromised NOD/SCID IL2Rynu" mice or other assay modifications significantly increase the frequency of human glioblastoma cells that form tumors upon xenotransplantation. In Aim 2 we will perform limit dilution assays to determine the frequency of cells with tumorigenic potential within glioblastomas obtained from 10 patients. In Aim 3 we will test whether existing cancer stem cell markers distinguish tumorigenic from non-tumorigenic brain tumor cells when tested in an optimized xenotransplantation assay. These experiments will determine whether tumorigenic potential is a common attribute of glioblastoma cells or an attribute of a distinct subpopulation of cancer stem cells. The answer to this question has fundamental implications for therapeutic strategies.

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2008 Investigators

Recipients of the Three-Year Awards ($600,000)

Keith Ligon, M.D., Ph.D.
Dana-Farber Cancer Institute
Stem and Progenitor Cell Transcription Factor Networks as Therapeutic Targets in Malignant Glioma

John Sampson, M.D., Ph.D.
Duke University Medical Center
Predicting Oncogenic Pathways driving Resistance to an EGFRvIII-targeted Vaccine using Signaling Pathway Gene Signatures

Erwin Van Meir, Ph.D.
Emory University
Mechanism of Action and Exploitation of Secreted Galectin-3 for Malignant Glioma Therapy

Wei Zhang, Ph.D.
The University of Texas M.D. Anderson Cancer Center
Validating the IGFBP2-ILK-NFkB Pathway in Glioma Development and Progression by a Glial Specific Mouse Model

Recipients of the One-Year Awards ($100,000)

Jef Boeke, Ph.D., D.Sc.
Johns Hopkins University School of Medicine
Retrotransposon Instability in Glioblastoma Multiforme

Joseph Costello, Ph.D.
University of California San Francisco
Deep-Sequencing of Glioblastoma Stem Cell Epigenomes

Calvin Kuo, M.D., Ph.D.
Stanford University School of Medicine
GPCR-Targeted Anti-angiogenic Therapy of Glioblastoma

Yael Mardor, Ph.D.
The Chaim Sheba Medical Center
Convection-Enhanced Delivery of High Viscosity Nano-Particles

Kyle Weaver, M.D.
Vanderbilt University
Biomarker Development using Absolute Copy Number of Methylated Tumor Suppressor Genes in the Plasma of Patients with Malignant Glioma

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2007 Investigators

Recipients of the Three-Year Awards ($600,000)

Ronald DePinho, M.D.
Dana-Farber Cancer Institute
Validation of Novel GBM Genes

Jeremy Rich, M.D.
Duke University Medical Center
Molecular Targeting of Glioma Cancer Stem Cells

Devanand Sarkar, MBBS, Ph.D.
Columbia University
Molecular Mechanism of Astrocyte Elevated Gene (AEG)-1 Function

Recipients of the One-Year Awards ($100,000)

Donald Durden, M.D., Ph.D.
Emory University School of Medicine
PI-3 Kinase Inhibitor Targeted Therapy for Glioma Therapeutics

Isabelle Germano, M.D.
Mount Sinai School of Medicine
Transgenic Embryonic Stem Cell Delivery of mda-7/IL-24 for Malignant Glioma Therapy

David Sabatini, M.D., Ph.D.
Whitehead Institute for Biomedical Research
Identification of Molecular Drivers of Human Brain Tumor Stem Cell Functions Using a Lentiviral RNAi Screen

Khalid Shah, M.Sc., Ph.D.
Massachusetts General Hospital
Targeted Embryonic Stem Cell based Therapies for Gliomas

Irving Weissman, M.D.
Stanford University
Identification and Isolation of Cancer Stem Cells from Glioblastoma Multiforme

David Zagzag, M.D., Ph.D.
New York University
Endothelial Progenitor Cell Recruitment

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2006 Investigators

Recipients of the Three-Year Awards ($600,000)

Robert Darnell, M.D., Ph.D.
Rockefeller University
Applying Naturally Occurring Tumor Immunity to the Treatment of Brain Tumors

Recipients of the One-Year Awards ($100,000)

Arnab Chakravarti, M.D.
Massachusetts General Hospital
The Role of Survivin in the Radiation Resistance of Glioblastomas

Lynda Chin, M.D.
Dana-Farber Cancer Institute
In Vitro and In Vivo Characterization of Small Molecule Inhibitors of Bcl2L12

Samira Guccione, Ph.D.
Stanford University
Vascular Targeted Therapeutics for Treatment and Imaging of Diffuse Gliomas

Alonzo Ross, Ph.D.
UMASS Medical School
RNAi Screen for Regulators of Brain Cancer Stem Cells

Devanand Sarkar, M.B.B.S., Ph.D.
Columbia University Medical Center
Astrocyte Elevated Gene (AEG)-1: Analysis of Function and Targeted Inhibition

Charles Stiles, Ph.D.
Dana-Farber Cancer Institute
OLIG2 Supression of P21 in Stem Cells for Human Glioma

Wei Zhang, Ph.D.
The University of Texas M. D. Anderson Cancer Center
Validating Glioma Genetic Regulatory Network by Glial Specific Mouse Model

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2005 Investigators

Recipients of the Three-Year Awards ($600,000)

Arturo Alvarez-Buylla, Ph.D.
University of California San Francisco
Are PDGFR+ Stem Cells a Source of Brain Tumors?

Frank Furnari, Ph.D.
Ludwig Institute for Cancer Research, UCSD
The Role of EGF Receptor Heterogeneity in Driving Glioma Development and Therapeutic Responsiveness

Recipients of the One-Year Awards ($100,000)

Robert Bachoo, M.D., Ph.D.
Dana-Farber Cancer Institute
Validation of Promoters Targeting the Mature Astrocyte Compartment In Vivo

Maria-Magdalena Georgescu, M.D., Ph.D.
Department of Neuro-Oncology and Department of Molecular Gentics, Brain Tumor Center and The University of Texas MD Anderson Cancer Center
Understanding the Dispersal of Glioblastoma Cells

Qing Richard Lu, Ph.D.
U. T. Southwestern Medical Center at Dallas
The Role of bHLH Transcription Factor Olig2 in Glioma Formation

William A. Weiss, M.D., Ph.D.
University of California, San Francisco
Inhibition of P110α in Glioma

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2004 Investigators

Recipients of the Three-year Awards ($600,000)

Charles L. Sawyers, M.D.
University of California
Optimal deployment of kinase inhibitors for glioma therapy

Elizabeth Maher, M.D., Ph.D.
Dana-Farber Cancer Institute
Identifying the genetic switches driving glioma initiation and progression

Recipients of the One-year Awards ($100,000)

R. Jude Samulski, Ph.D.
University of North Carolina at Chapel Hill
In vitro evolution of viral vectors with targeting capability for human astrocytic tumors

Gabriele Bergers, Ph.D.
University of California – San Francisco
Understanding perivascular invasion mechanisms in glioblastoma

Arturo Alvarez-Buylla, Ph.D.
University of California – San Francisco
Do brain tumors originate from adult neural stem cells?

Harald W. Sontheimer, Ph.D.
University of Alabama at Birmingham
Role of amino-acid transport in growth control and invasion of astrocyte derived tumors

Terry A. Van Dyke, Ph.D.
University of North Carolina at Chapel Hill
Development and imaging of preclinical mouse models of high grade astrocytoma

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2003 Investigators

Recipients of the Three-year Awards ($600,000)

Xandra O. Breakefield, Ph.D.
Massachusetts General Hospital
Co-ordinated imaging and apoptosis of experimental brain tumors

Arnab Chakravarti, M.D.
Brigham and Women's Hospital
Enhancing radiation response of malignant gliomas through molecular targeting of phosphatidylinositol 3-kinase

Daniel G. Jay, Ph.D.
Tufts University School of Medicine
Function-based identification and validation of proteins required for GBM dispersal and survival

Recipients of the One-year Awards ($100,000)

Bruce R. Ksander, Ph.D.
Schepens Eye Research Institute
Eliminating brain tumors by membrane Fas Ligand vesicles: A Novel immunotherapy

Andreas C. Kurtz, Ph.D.
Massachusetts General Hospital
Secreted protein profiles of astrocytic tumors for classification and therapy

Elizabeth A. Maher, M.D., Ph.D
Dana-Farber Cancer Institute
Identifying the genetic changes in the transition from low-grade astrocytoma to glioblastoma

Vladimir P. Torchilin, Ph.D., D.Sc.
Northeastern University
Antibody-mediated targeting of pharmaceutical agents to astrocytic tumors

The Goldhirsh Foundation
Brain Tumor Research Awards Program
2002 Investigators

Recipients of the Three-year Awards ($600,000)

Bob S. Carter, M.D., Ph.D.
Massachusetts General Hospital
Cytotoxic T-lymphocytes genetically engineered to attack the EGFRvIII mutation in human glioma

Lynda Chin, M.D.
Dana-Farber Cancer Institute
Identification and characterization of novel glioma-relevant genes

Rakesh K. Jain, Ph.D.
Massachusetts General Hospital
Optimizing combination anti-Angiogenic and radiation therapy for glioblastoma multiforme

Recipients of the One-year Awards ($100,000)

Xandra O. Breakefield, Ph.D.
Massachusetts General Hospital
Co-ordinated imaging and apoptosis of experimental brain tumors

Andrew L. Kung, M.D., Ph.D.
Joshua Rubin, M.D., Ph.D.
Dana-Farber Cancer Institute
Improved in-vivo models for discovery of new anti-brain tumor therapies

Lois A. Lampson, Ph.D.
Brigham and Women's Hospital
A small molecule inhibitor of glioma invasion

David N. Louis, M.D.
Massachusetts General Hospital
Molecular profile-based classification of adult astrocytic tumors: Defining a novel subtype

Pamela A. Silver, Ph.D.
Dana-Farber Cancer Institute
RNA binding proteins in the progression of adult astrocytic tumors