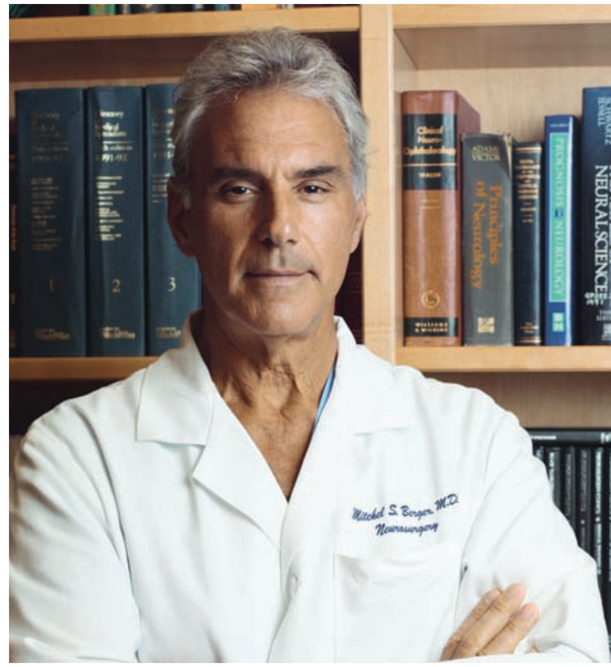
UCSF Brain Tumor Program

Stewardship Report 2011 Thank you

UCSF Helen Diller Family Comprehensive Cancer Center

Dear Friends,

The **UCSF Brain Tumor Program** continues to make great strides in the fight against brain cancer. From examining the factors that enable the proliferation of brain tumor cells to creating tools designed to destroy them, our talented scientists work tirelessly each day to understand the causes and progression of this devastating disease. Without you, our dedicated supporters, this important work would not be possible.



It is my pleasure to present in the following pages four research endeavors currently underway by leading investigators in the field. Joseph F. Costello, PhD, is involved in an ambitious, National Institutes of Health (NIH)-funded investigation to map the reference epigenomes of brain tissue and other human cells. Russell O. Pieper, PhD, is interested in understanding the metabolic processes responsible for the replication of tumors. C. David James, PhD, is participating in a California Institute of Regenerative Medicine (CIRM) project aimed at designing a stem cell that delivers a toxic agent to brain tumors. Finally, Daniel A. Lim, PhD, MD, with support from CIRM, is developing an innovative surgical device that delivers stem cell treatments to the brain with one injection.

Our analyses will surely yield new and improved therapies for patients, and I am confident that with each day, we are moving closer to a cure. Your support is vital to the success of these and other groundbreaking research studies being conducted in the UCSF Brain Tumor Program. On behalf of my colleagues, I thank you once again for your philanthropic vision.

Sincerely,

Mitchel S. Berger, MD
Chair, Department of Neurological Surgery
Kathleen M. Plant Distinguished Professor
Director, Brain Tumor Program

Examining Epigenetics

An ambitious project hopes to uncover the mechanisms responsible for brain tumor growth.

Joseph F. Costello, PhD

Professor in Residence, Neurological Surgery

Karen Osney Brownstein Endowed Chair in Molecular Neuro-Oncology

Principal Investigator, Roadmap Epigenomics Program

Joseph Costello

Much of Dr. Costello's research involves understanding the factors at work in the progression and resistance of brain tumors. He has most recently focused on the epigenetic modifications that result in the formation of brain tumor cells. Epigenetics concerns the set of reversible chemical instructions attached to DNA that help program the expression of genes. An epigenome is the full collection of these chemical instructions across our genome. The epigenome pattern differs in each cell type, allowing one genome to be programmed in many ways to create and maintain the diversity of cell types in the human body. Researchers believe that understanding the manner in which epigenetic processes control genes during different stages of development and throughout life will lead to more effective ways to prevent and treat disease.

To further the field's understanding of epigenetics, Dr. Costello is leading the Roadmap Epigenomics Program, a five-year National Institutes of Health-sponsored project. The purpose of the endeavor is to create epigenome maps of normal brain and other tissues. In turn, these maps will serve as references for disease studies, enabling scientists to investigate the mechanisms that may be responsible for triggering malignancies. The team's work to date can be found at vizhub.wustl.edu.

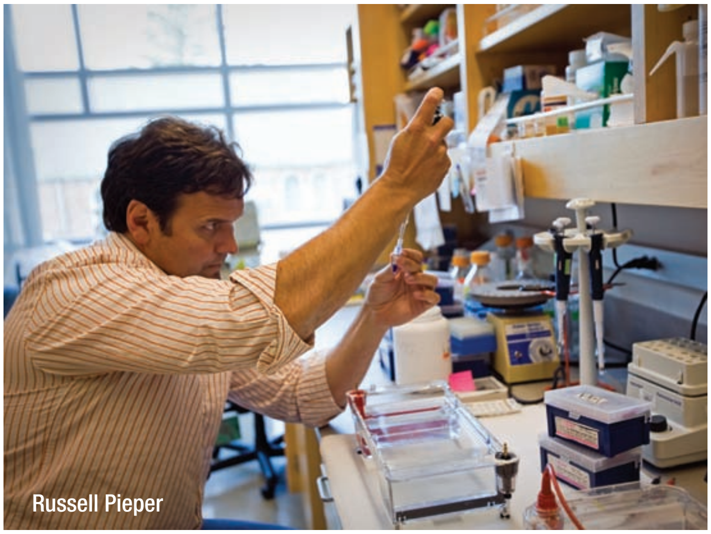
Together with his Roadmap partners from Washington University, University of Southern California, University of California Santa Cruz, and the British Columbia Genome Sciences Centre in Vancouver, Dr. Costello is utilizing a technique called next-generation sequencing to examine and document the expression levels of 25,000 genes present in the human genome and the epigenetic processes that maintain them in an expressed or unexpressed state. Their goal is to generate a clearer understanding of the epigenetic processes that influence the difference in genes with the aim of developing more targeted and effective therapeutic strategies for patients.

One component of the Roadmap Project is an analysis related to a specific area of the developing fetal brain, which is made up of cells that divide and migrate rapidly. While these characteristics are normal in the fetal brain, they are the primary signals of tumors in the adult brain (healthy cells in the adult brain are, for the most part, non-proliferative). Dr. Costello's hope is that by understanding and making reference catalogs of normal fetal brain tissue, he and his team will also be able to shed more light on the processes that reprogram healthy adult brain cells into proliferating, invading cells.

Brain Tumor Formation and Growth

An investigation seeks to disrupt the formation and growth of brain tumors.

Russell O. Pieper, PhD
Professor of Neurological Surgery
Suzanne Marie and Robert Vincent Haderle Endowed Chair in Molecular Neuro-Oncology
Director of Basic Science, Brain Tumor Research Center



Russell Pieper

As with all cells in the human body, brain tumor cells require energy. To generate the fuel necessary to grow and divide, they metabolize, or break down, glucose. Brain tumor cells, however, unlike normal cells, also need to create building blocks for cell growth and replication, including fatty acids for membranes and nucleic acids for new DNA. These building blocks are derived from glucose metabolism at the expense of energy production. Brain tumor cells therefore need to carefully regulate glucose usage, and it is this process that Dr. Pieper and his colleagues in the UCSF Brain Tumor Program are currently investigating.

An enzyme called pyruvate kinase (PK) plays a central role in determining how cells use glucose and, thereby, how well a tumor cell can replicate. PK exists in two forms: PKM1 is the predominant form in normal brain cells and favors the conversion of glucose to energy; PKM2 is abundant in brain tumor cells and prefers the conversion of glucose to cellular building blocks. The shift from PKM1 to PKM2 occurs early in tumor development, as even the lowest grade gliomas down-regulate PKM1 expression. The team is interested in how and why this shift happens and in the consequences of disrupting PKM expression in tumors. In tumor cells in culture that are growing rapidly in connection with PKM2 expression, the team is knocking down the levels of PKM2 expression to ascertain whether this action will slow down tumor cell growth. They will also overexpress PKM1 to determine if this might also curb growth or even prevent it altogether.

Concurrently, the Pieper lab is tracking the cells' reactions to chemotherapeutic agents to evaluate whether cells use shifts in glucose metabolism to increase their ability to survive exposure to the drugs, and if altering glucose metabolism could render cells sensitive to different therapeutic agents.

Key to this investigation is technology developed by Drs. Sarah Nelson and Sabrina Ronen in the UCSF Department of Radiology and Biomedical Imaging and Dr. Susan Chang in the Department of Neurological Surgery. Working collaboratively and using non-invasive magnetic resonance imaging techniques, the team can measure the flow of glucose and glucose byproducts through cells in real time and determine how this changes in response to drug therapy. Preliminary results reveal that cells that respond to temozolomide, an agent commonly used in the treatment of brain cancer, also exhibit decreased glucose metabolism. Magnetic resonance imaging of glucose metabolism may therefore be useful in predicting which patients will respond to temozolomide and in monitoring drug response in patients without the need for sampling of the tumor.

Dr. Pieper and his colleagues are hopeful that, in the next year, they will gain a better understanding of the factors regulating tumor cell metabolism. In doing so, they will have the critical information necessary to develop methods to monitor drug therapy and to devise new drug therapies that can improve outcomes for patients.

Stem Cell Research Targets

A collaborative effort is underway to design a stem cell that will eradicate brain tumors.

C. David James, PhD

Professor of Neurological Surgery

Berthold and Belle N. Guggenhime Endowed Chair

Associate Director and Principal Investigator, Brain Tumor Research Center

C. David James

Dr. James and his colleagues are in the second year of a collaborative project funded by the California Institute for Regenerative Medicine. The goal of his team, which includes scientists from UCSF, UCLA, UCSD, Sanford-Burnham Medical Research Institute, and the Salk Institute, is to engineer a stem cell that will deliver a brain tumor-killing therapeutic. To this end, the scientists set out to accomplish three main objectives:

1. Identify the most efficient way to administer therapeutic stem cells to patients.
2. Determine the best stem cell type to serve as a therapeutic delivery vehicle.
3. Select the therapeutic gene to deliver.

The team's first order of business was to investigate two routes through which the stem cells could be administered to patients. In mouse models, the team learned that very few cells reached brain tumors when they were injected intravenously. An alternative method requires injecting the cells into the area surrounding the cavity left by the removal of the tumor during surgery. Analyses conducted during the first year of the project helped the team determine that this latter approach — surgical administration of the stem cells to the tumor resection cavity — would increase the anti-tumor effect of therapeutic stem cells. Next, the research team needed to decide which of three stem cell types to choose: The first two, fetal and adult neural stem cells, originate from the brain; the third, mesenchymal stem cells, are derived from bone marrow. The team elected to use the mesenchymal cells due to their ready availability, as well as the ease with which they can be genetically modified and expanded in culture. The final task is to select which gene to utilize in developing therapeutic mesenchymal stem cells. Using bioluminescent imaging of tumors in mice, the team is conducting experiments to determine whether TNF-related apoptosis-inducing ligand (TRAIL) or cytosine deaminase (CD) is the most effective in eradicating tumors.

Once the final therapeutic stem cell is chosen, the team will begin working with cell therapy services company Progenitor Cell Therapy to produce a clinical-grade therapeutic stem cell. The ultimate goal of the four-year project will be to submit a successful application to the U.S. Food and Drug Administration for approval to begin clinical trials in brain tumor patients at UCSF.

Stem Cell Delivery Tool

A new surgical instrument is under development exclusively for the deployment of stem cell treatments to the brain.

Daniel A. Lim, MD, PhD

Assistant Professor in Residence of Neurological Surgery

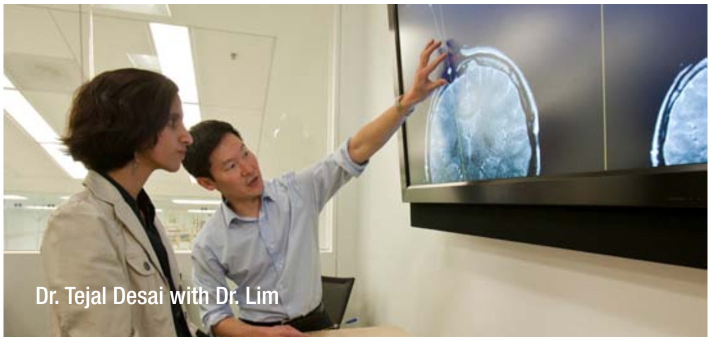
Director of Restorative Neurosurgery

Daniel Lim

Scientists in the UCSF Brain Tumor Program have made great strides in their efforts to create therapies for brain cancer patients. One of the most recent and exciting developments is the use of neural stem cells that have been modified to deliver toxic payloads to the brain tumor. While preclinical data in small animals with brain cancer appear to be very promising, the current unavailability of efficient surgical tools and techniques to deliver cell-based treatments to the human brain may lead to the failure of future clinical trials.

Why can't surgeons simply use a syringe and needle to deliver stem cell therapies to the brain? Pre-clinical experiments on mouse models with brain tumors have been carried out using standard needle and syringe-like devices, and this delivery method has resulted in successful cancer treatment. Why not just use a larger syringe and needle to deliver a larger number of cells to the human brain? One problem is the issue of scale. The human brain is at least 1,000 times larger than a mouse brain. The needle and syringe does not scale-up efficiently enough to address this 1000-fold difference in brain size.

Another issue is the need to efficiently distribute cells within the target area. In the case of brain tumor patients, stem cells must be disseminated widely to infiltrate even the most distant extent of the residual tumor rather than be deposited as a large, single clump. To achieve such wide distribution with a needle and syringe, surgeons would have to administer several injections, possibly dozens, each requiring a separate brain penetration. Each penetration carries risks to the patient such as bleeding or stroke. Numerous stem cell research projects are nearing their clinical trial stages, and so it is imperative to fill these translational gaps in research. With funding from the California Institute of Regenerative Medicine, Dr. Lim and his team, which includes Drs. Tejal Desai and Amy Herr of the California Institute for Quantitative Biosciences, are developing and refining a novel surgical device designed to disseminate human stem cell therapies to a large target through a single initial brain penetration. The first prototype device consisted of a titanium cannula that surrounded an angled inner tube to be used for cell deployment, and this basic design has since been refined to allow more precise cell delivery.



Dr. Tejal Desai with Dr. Lim

A primary aim of the project is to ensure the device's biocompatibility. To achieve this goal, the team will use FDA-approved, non-ferrous materials suitable for use with MRI techniques that can be used to track cell dispersal in the brain in real time during surgery. Additionally, Dr. Lim and his colleagues are taking great care to ensure that the new device will integrate seamlessly with the current crop of neurosurgical tools. The team is confident that, upon successful completion of the project, a new device and surgical techniques will be ready for inclusion in future clinical trials. With the closing of this translational gap, neural stem cell therapies for brain tumor treatments may work more effectively. By working collaboratively along this pipeline of therapeutic development – from the basic science to the surgical tools and techniques – we aim to provide the greatest hope to our brain tumor patients for treatments and an eventual cure.

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