Immunotherapy for Brain Cancer

Each year, more than 200,000 people in the United States receive the chilling diagnosis of a primary or metastatic brain tumor. The sheer number of these cases makes central nervous system tumors one of the most common and deadly malignancies.

Despite the use of aggressive treatments, including surgery, external beam radiation and prolonged chemotherapy, the survival of a patient with a malignant brain tumor is typically less than 12 to 18 months after diagnosis. Moreover, the intensive and nonspecific treatments routinely used in these patients can often result in considerable and irreversible neurologic deficits.

Duane Mitchell, M.D., Ph.D., Phyllis Kottler Friedman professor of neurosurgery and director of the UF Brain Tumor Immunotherapy Program.

To address the urgent need for the development of safe and more targeted therapies for patients with malignant brain tumors, Duane Mitchell, M.D., Ph.D., and his colleagues are developing novel treatments using immunotherapy, a strategy that helps patients fight cancer with their own defenses. In 2013, Dr. Mitchell joined the University of Florida as the Phyllis Kottler Friedman professor of neurosurgery and director of the UF Brain Tumor Immunotherapy Program in the newly created Preston A. Wells, Jr. Center for Brain Tumor Therapy. Earlier this month, his paper in the March 19, 2015 issue of Nature, reporting on

promising immunotherapy strategies for brain cancer, was recognized by the Clinical Research Forum as one of the top 10 papers in clinical and translational science appearing in the scientific literature during 2015.

In their Nature paper, Dr. Mitchell and colleagues from the University of Florida and Duke University report on the results of a first-in-human randomized trial of immunotherapy for patients with glioblastoma, including parallel mechanistic studies in mice. Glioblastoma, a very aggressive brain cancer, is highly resistant to standard treatment. In an exploratory randomized trial of 12 glioblastoma patients, Mitchell and his colleagues showed that adults with glioblastoma receiving a new and enhanced cancer vaccine that they developed showed a remarkable improvement in overall survival length. The research was funded by the National Institute of Neurological Disorders and Stroke as well as the National Cancer Institute, which are part of the National Institutes of Health.

Dr. Mitchell's interest in brain tumor immunotherapy has its roots in an early interest as a high school student in neurobiology and computer science. Dr. Mitchell thought at the time that he'd combine these interests in pursuing studies in computer programming and artificial intelligence research as an undergraduate student. While enrolled in a summer college preparatory program for engineering and science students at MIT, Dr. Mitchell came across a few articles about the newly emerging concept of gene therapy and its applications in medicine to treat intractable diseases. Up until that point, Dr. Mitchell felt he was deciding between whether he wanted to apply his strong interests in the biological sciences toward the creative aspects of research and development of new technologies, or follow in the footsteps of his older sister and become a physician who applied existing scientific knowledge in the medical management of patients. The articles he read during high school on the potential of emerging gene therapy applications in medicine raised an awareness for Dr. Mitchell of the concept of translational research involving the application of scientific discovery in the development of new treatments for patients.

A few years later, Dr. Mitchell read the book "The Transformed Cell" by Dr. Steven Rosenberg, chief of the Surgical Oncology Branch at the National Cancer Institute. In his book, Dr. Rosenberg chronicled his quest to apply the power of the immune system to the development of new treatments for patients with metastatic melanoma. The book was pivotal in crystallizing in Dr. Mitchell's mind a mental picture of what a career path as a translational physician-scientist could look like, and he became captivated by the personal pursuit of such a career.

It was with this background and experience that Dr. Mitchell decided to focus on immunotherapy for brain cancer. While cancer immunotherapy has emerged as a highly effective approach for the treatment of several types of advanced cancers, including metastatic melanoma, advanced lung cancer and refractory lymphoma, brain cancer has remained a significant challenge due to the blood-brain barrier exclusion of many immune cells from the central nervous system and the profoundly immunosuppressive brain tumor microenvironment.

Dr. Mitchell's team at UF and his collaborators have developed several approaches to the immunologic

treatment of pediatric and adult malignant brain tumors. They have developed a system of cellular immunotherapy in which a unique subset of hematopoietic stem cells, when injected intravenously, migrate specifically to areas of invasive brain tumor growth and co-localize with tumor cells that are sequestered deep within the normal brain. Strikingly, these stem cells recruit large numbers of tumor-specific cytotoxic T cells to the areas of tumor growth, and alter the immunosuppressive landscape such that these killer T cells retain their function for a prolonged period within the tumor microenvironment. Given the fact that even the most effective immunotherapies to date (which have been highlighted as breakthrough successes) still only achieve complete clinical responses in roughly 30 percent of treated patients, the capacity to restore immunotherapy responsiveness in a refractory cancer holds tremendous potential significance. Dr. Mitchell is leading a first-in-human cellular immunotherapy trial in children with recurrent medulloblastoma, an aggressive and common brain tumor in pediatric patients. These children are often treated with intensive chemotherapy, including high-dose chemotherapy and stem cell transplant, and Dr. Mitchell and collaborators are applying cellular immunotherapy following hematopoietic stem cell rescue in patients with relapsed disease to determine if the enhancing effects of hematopoietic stem cells can be harnessed in patients receiving cellular immunotherapy. A first-in-human phase 1/2 clinical trial (Re-MATCH trial, UF IRB# 201500502) is underway at UF.

Dr. Mitchell along with Dr. Catherine Flores (assistant professor in the Department of Neurosurgery and principal investigator of the Hematopoietic Stem Cell Engineering Laboratory within the Preston A. Wells, Jr. Center for Brain Tumor Therapy and UF Brain Tumor Immunotherapy Program) and Dr. Elias Sayour (assistant professor of neurosurgery and pediatrics and principal investigator of the RNA Engineering Laboratory within the Preston A. Wells, Jr. Center for Brain Tumor Therapy and UF Brain Tumor Immunotherapy Program).

In the Nature study, Dr. Mitchell and his collaborators created their targeted therapeutic strategy based on earlier findings that glioblastoma tumors harbor a strain of cytomegalovirus, or CMV, that is not present in the surrounding brain tissue, creating a natural target for an immune therapy. One such targeted approach uses the patient’s own peripheral blood-derived dendritic cells, loaded with viral antigens as a cellular therapeutic cancer vaccine. Dendritic cells are specialized immune cells that normally capture microorganisms, and then migrate to the lymph nodes to prepare other immune players, such as T cells, to

fight off the invaders. In this case, when the antigen-loaded dendritic cells are injected back into the patient's bloodstream, they travel to lymph nodes and signal the immune fighter cells to search and attack the CMV-laden glioblastoma tumor.

Members of the Preston A. Wells, Jr. Center for Brain Tumor Therapy at the University of Florida gather outside the McKnight Brain Institute at UF. (Copyright: University of Florida)

This immunotherapy worked well, but the research team sought additional gains. Specifically, they hypothesized that the use of tetanus/diphtheria toxoid — which is widely available and safe as a clinically approved vaccine — would prime the immune system to be on high alert prior to the infusion of dendritic cells, thus potentially enhancing the efficiency and effectiveness of the immunotherapy. To test this hypothesis, the investigators enrolled 12 glioblastoma patients, with half randomly assigned to receive a tetanus primer and the other half a control vaccine. The next day, patients in both groups were given the dendritic cell immunotherapy. Patients who received the tetanus primer showed a significant increase in survival from the time of pre-conditioning compared with patients receiving just the dendritic cell therapy, with half living from 51 to 101 months, compared with 11.6 months for the comparison group. Half the patients in the tetanus group have lived five years or longer, and one patient continues to have no tumor growth and is still alive eight years after the treatment.

The publication in Nature garnered significant interest due to the impressive clinical outcomes in patients with glioblastoma (a particularly deadly form of brain cancer), the novelty of the dendritic cell vaccine, and the implications for improving the efficacy of such a vaccine against glioblastoma and potentially other cancers through targeting of the dendritic cell migration. Dr. Mitchell and his collaborator Dr. John Sampson at Duke have received a multiple PI investigator award to support a large randomized and blinded phase 2 study to confirm these results, which will involve 120 patients. Future clinical studies under development within the UF brain tumor immunotherapy program will explore harnessing the effects of hematopoietic stem cells to enhance other forms of immunotherapy, the use of nanotechnology to overcome immunosuppression in brain tumor patients and the implementation of genetically engineered dendritic cells and T cells with improved tumor-killing potency.

The Power of Together,

David S. Guzick, M.D., Ph.D.
Senior Vice President for Health Affairs
President, UF Health