Memorial Sloan Kettering Cancer Center | GIVING

2023 Update

Advancing the Understanding and Treatment of Brain Tumors

The Challenge of Brain Tumor Treatment | Improving the Approach to Brain Tumor Research

Among people with cancer in the United States, primary brain tumors are relatively uncommon, with just over 25,000 individuals diagnosed annually. Though rare, these diseases continue to have an outsize impact. Current treatments, including surgery, chemotherapy, and radiation, can have side effects and generally do not provide a cure. The result: Fewer than one-third of people diagnosed with brain cancer live longer than five years.

Recognizing the urgent need for new approaches, the Brain Tumor Center at Memorial Sloan Kettering Cancer Center (MSK) brings together researchers and clinicians to promote the development of more effective therapies for brain cancer. Under the direction of Albert C. Foster Chair **Luis Parada, PhD**, MSK's team has become a world leader in brain tumor research. Dr. Parada collaborates with Scott M. and Lisa G. Stuart Chair **Lisa DeAngelis, MD**, MSK Physician-in-Chief and Chief Medical Officer, and is supported by Evnin Family Chair in Neuro-Oncology **Ingo Mellinghoff, MD,** Chief of the Brain Tumor Service and Chair of the Department of Neurology; Theresa Feng Chair in Neurosurgery **Viviane Tabar, MD**, Chair of the Department of Neurosurgery; and more than 70 faculty who focus their clinical and research activities on brain cancer. Together, they share a special focus on glioblastoma, the most prevalent type of brain cancer and one that remains incurable, as well as on cancers that have metastasized to the brain from other parts of the body.

The Brain Tumor Center's world-class research infrastructure includes a robust tissue bank, innovative laboratory models for the study of brain tumors and the evaluation of promising treatments, and a diverse and growing portfolio of clinical trials. It has the capacity to curate and analyze advanced genomic data. Senior faculty members have forged strong working relationships and are fostering the development of more junior faculty interested in taking on the challenge of brain tumors.

It is our pleasure to describe some of the Brain Tumor Center's achievements, as well as new projects that, with philanthropic support, have the potential to help even more people with brain cancer.

The Challenge of Brain Tumor Treatment

Brain cancer is especially difficult to treat because it often grows and spreads rapidly. Moreover, the blood-brain barrier — a natural defense against external invaders, such as viruses, bacteria, and toxins — presents a formidable obstacle for many anti-cancer medications. The Brain Tumor Center team is

engaged in research to develop innovative therapeutic strategies to deliver treatment directly into brain tissue. Highlights of these efforts include the following achievements:

A New Treatment for Glioma

A team of researchers led by Dr. Mellinghoff has discovered the first novel treatment option for low-grade glioma in more than 20 years. This type of cancer, also called grade 2 glioma, is the most common primary brain cancer in adults. Low-grade glioma gradually infiltrates healthy brain tissue and can cause serious symptoms; people with the disease have a poor long-term prognosis.

In a multicenter phase 3 clinical study published in *The New England Journal of Medicine*, the researchers showed that the oral drug vorasidenib significantly slowed the growth of low-grade glioma. Patients who received vorasidenib had an average progression-free survival (the length of time until the tumor started growing again) that was more than twice as long as the placebo group, at 27.7 months versus 11.1 months. And even after the tumors resumed growing, they did so more slowly — delaying the point when another treatment became necessary and reducing the need for more toxic therapies. Results were so impressive that the study was unblinded early so that people on a placebo had the opportunity to switch to vorasidenib.

Vorasidenib works because its chemical design enables it to cross the blood-brain barrier. The drug targets mutations in the *IDH* gene. Such mutations are present in 80% of low-grade gliomas and can cause tumor cells to produce abnormally high amounts of proteins that drive cancer growth. The study's results point to a blueprint for future precision medicine approaches in neuro-oncology and present an opportunity to change the standard of care for gliomas with *IDH* mutations.

Identifying Additional Therapeutic Targets

Building on the success of their previous studies, Dr. Mellinghoff and colleagues are identifying other signaling networks within brain tumors, with the aim of assessing novel drugs that target these pathways in various cancers, including glioma. Dr. Mellinghoff is directing clinical studies of these targeted medications:

- Ivosidenib (Tibsovo®) for glioma.
- Vorasidenib given with the immunotherapy drug pembrolizumab (Keytruda®) to treat astrocytoma (a type of glioma) that has an *IDH* mutation and has returned after previous treatments.
- RO7428731 and ERAS-801 for glioblastoma. Both take aim at a protein called EGFR, and each is being evaluated in its own clinical trial.
- Regorafenib (Stivarga®), VAL-083, and paxalisib for glioblastoma. Each of the three drugs has a different molecular target.

Managing Leptomeningeal Metastases

Cancer that has spread to the fluid and tissues of the brain and spinal cord is called leptomeningeal metastasis (LM), and it is very difficult to treat. This complication can have devastating effects, causing pain, seizures, difficulty thinking, and a loss of muscle control. Neurologist and Geoffrey Beene Junior Faculty Chair **Adrienne Boire, MD, PhD**, working with computational biologist and Alan and Sandra Gerry Endowed Chair **Dana Pe'er, PhD**, previously found that these cancer cells compete with other cells for the iron they need to grow and to disable the immune response that would normally destroy them. Dr. Boire is now directing an early-phase clinical trial of deferoxamine (Desferal®) in people with LM. Deferoxamine helps remove iron from the body and is given directly into the cerebrospinal fluid through a small plastic tube.

In June 2022, MSK researchers reported that proton therapy, a form of radiation therapy, is effective in controlling LM. Proton therapy uses charged particles called protons rather than the standard X-rays used in conventional radiation therapy, and it enables doctors to direct cancer-fighting energy to precise locations within the body. The phase 2 clinical trial results were presented at the American Society of Clinical Oncology Annual Meeting and showed that people with LM treated with proton therapy survived longer and had more stable disease than those treated with standard radiation.

The Role of Stem Cells in Glioblastoma's Return

Glioblastoma almost always comes back, even when it appears to have been completely surgically removed. In January 2022, Dr. Parada and his team reported in the journal *Developmental Cell* the existence of a small percentage of dormant, stem-like cells that resist treatment and reinitiate tumor development. The team demonstrated how the cells can leave their inactive state and begin dividing again, with the new tumors created from these cells possessing the same functional properties as the original cancer. The evaluation of new glioblastoma therapies will be best served by considering the response and status of these cancer stem cells. Researchers hope that learning more about them will lead to the design of new drugs that target glioblastoma stem cells based on their biology.

This work was possible due to patient-derived xenograft (PDX) models, laboratory constructs in which cells from a human tumor are transplanted into a research animal. The human cells grow into a new tumor and can then be studied on the microscopic level and used to assess potential drugs. The tumors used to create the models are collected from MSK patients who volunteer to donate their tissue for research after it has been removed during surgery. The Brain Tumor Center has more than 100 PDX research models.

Studying Central Nervous System Lymphoma Using Liquid Biopsy

Liquid biopsy detects the presence of cancer in the body by looking for evidence of tumor DNA (cell-free DNA) in the blood or cerebrospinal fluid. Neuro-oncologist and neurologist **Christian Grommes, MD**, and collaborators are using liquid biopsy to study the underlying genomic abnormalities of primary central nervous system lymphoma (PCNSL). The team has created laboratory models to assess a range of drugs before moving them into clinical trials. Dr. Grommes is now directing several clinical trials of innovative therapies for people with PCNSL, including:

- Ibrutinib (Imbruvica®), GB5121, and tirabrutinib (Velexbru®), all of which inhibit a protein called BTK, which drives PCNSL growth
- Copanlisib (Aliqopa™), an inhibitor of an enzyme called PI3K, given with ibrutinib for PCNSL or secondary central nervous system lymphoma (SCNSL)
- A targeted radiotherapy called CLR-131 for PCNSL or SCNSL
- Nivolumab (Opdivo®) immunotherapy to reduce the risk of cancer recurrence in people with PCNSL who have evidence of tumor DNA in their cerebrospinal fluid after completing initial chemotherapy with methotrexate

Boosting the Immune System to Fight Glioblastoma

Neuro-oncologist and neurologist **Thomas Kaley, MD**, is leading clinical trials evaluating immune-boosting therapies for glioblastoma. One of them is assessing the safety and effectiveness of nivolumab immunotherapy given alone or with ipilimumab (Yervoy®) immunotherapy before and after surgery in people whose glioblastoma came back after prior treatment. Both medications block proteins that inhibit the immune response. By targeting these proteins, nivolumab and ipilimumab boost the ability of the immune system to find and kill cancer cells.

Dr. Kaley is also co-directing a study led by neuro-oncologist and neurologist **Lauren Schaff, MD**, to evaluate the safety and effectiveness of combining three drugs to treat people with an *IDH*-mutant glioma that came back after chemotherapy or surgery. The three medications are pembrolizumab (Keytruda®), which takes the brakes off the immune response; olaparib (Lynparza®), which blocks a protein called PARP that repairs damage to a cell's DNA before the cell divides and can make cancers more vulnerable to treatment; and temozolomide (Temodar®), the current standard of care for most gliomas, which prevents DNA repair in cancer cells.

Next Steps: Improving the Approach to Brain Tumor Research

While MSK investigators are making progress in understanding brain tumor treatment resistance, identifying new therapeutic targets, and evaluating promising drugs in clinical trials, significant challenges remain. Most phase 3 clinical trials fail to show that a new treatment is more effective than a standard therapy. These results are influenced by the complex molecular features of glioblastomas, which change over time and affect tumor behavior. There is also a need for better laboratory models to predict cancer behavior and patients' response to treatment.

Dr. Parada and the Brain Tumor Center team have proposed new strategies to bolster brain tumor research at its earliest stages of investigation so by the time a drug advances to later-stage clinical trials in patients, there is stronger evidence suggesting it is superior to existing treatments. These new strategies include:

Establishing a Prospective Longitudinal Collection of Glioblastoma Tissues

It is unknown if glioblastoma changes over time are due to the tumor environment, patient genetics, response to different treatments, or other variables. Previous studies that examined glioblastoma cells in blood or cerebrospinal fluid used data from patients treated in the past rather than a prospective approach. In addition to **using** the existing brain tumor tissue bank, the Brain Tumor Center team would like to prospectively enroll all patients newly diagnosed with glioblastoma into a nontherapeutic protocol to collect cerebrospinal fluid and blood at set time points, such as before and after surgery and every several months thereafter. Investigators would **then** be able to study cancer cells, cell-free DNA, proteins, changes in immune cells in the tumor environment, and other factors at various stages of tumor progression. This platform would provide researchers with a wealth of new data on the factors that influence tumors as they grow and open doors to **create** emerging technologies for monitoring the disease.

Creating a Glioblastoma Clinical Trial Team to Vet New Drugs in Phase 2 Studies

Phase 2 clinical trials are designed to assess a treatment's safety and effectiveness. While a drug may show promise at the phase 2 stage, it is not always known for certain if it is actually crossing the blood-brain barrier and if it is engaging its target. MSK researchers would like to design window-of-opportunity studies to see how a new drug is taken up in the body and to determine if it is reaching its target. One way to do this is to give the medication before brain tumor surgery. A tissue sample removed at the time of surgery can then be analyzed to see if the drug has reached the tumor. Another approach is to assess a new anti-cancer agent in a PDX model created for each phase 2 study participant to examine the ability of the agent to permeate the blood-brain barrier and engage with its target inside the tumor. These methods can fill a critical gap between phase 1 clinical trials and phase 3 studies that will help researchers choose the best therapies to move on to later-stage evaluation in patients and to eliminate drugs that are unlikely to prove effective.

Improving Organoids and PDX to Better Predict Patient Outcomes

Organoids are 3D, organlike cultures about a millimeter in size that are made from patients' tumor specimens. While they present enormous opportunities for better understanding the variety of cell states and behaviors in a tumor, as well as the vulnerability of a tumor to new treatments, their ability to predict outcomes in people with glioblastoma requires further evaluation. PDX models may hold the key to a cure for glioblastoma and other brain tumors, but they take a long time to create. Both models are very costly.

Brain Tumor Center scientists would like to compare organoid and PDX models from the same patient tumors to assess response to therapy and how well each model accurately reflects the behavior of a tumor in a patient. Their goal is to improve these models so they can be better used to guide and adjust treatments in patients in real time. Researchers would apply single-cell analysis to this endeavor to understand not only cancerous cells, but every type of cell in and around a tumor that supports its survival and growth. Gaining more knowledge about these cells may unlock the mystery of why immunotherapy and drugs that inhibit tumor blood vessel development have not been effective against brain cancer.

Looking Ahead

With a strong research infrastructure in place and advances propelling its momentum, the MSK Brain Tumor Center is poised to make impactful discoveries. But under its current budget, the center has reached a plateau. Renewed philanthropic investment will enable Dr. Parada and his team to recruit additional investigators and launch the laboratory and phase 2 clinical trial strategies outlined above. A transformational gift would allow this dynamic, multidisciplinary work to advance new, more effective brain tumor therapies for patients who desperately need novel treatment options. Thank you for your consideration.