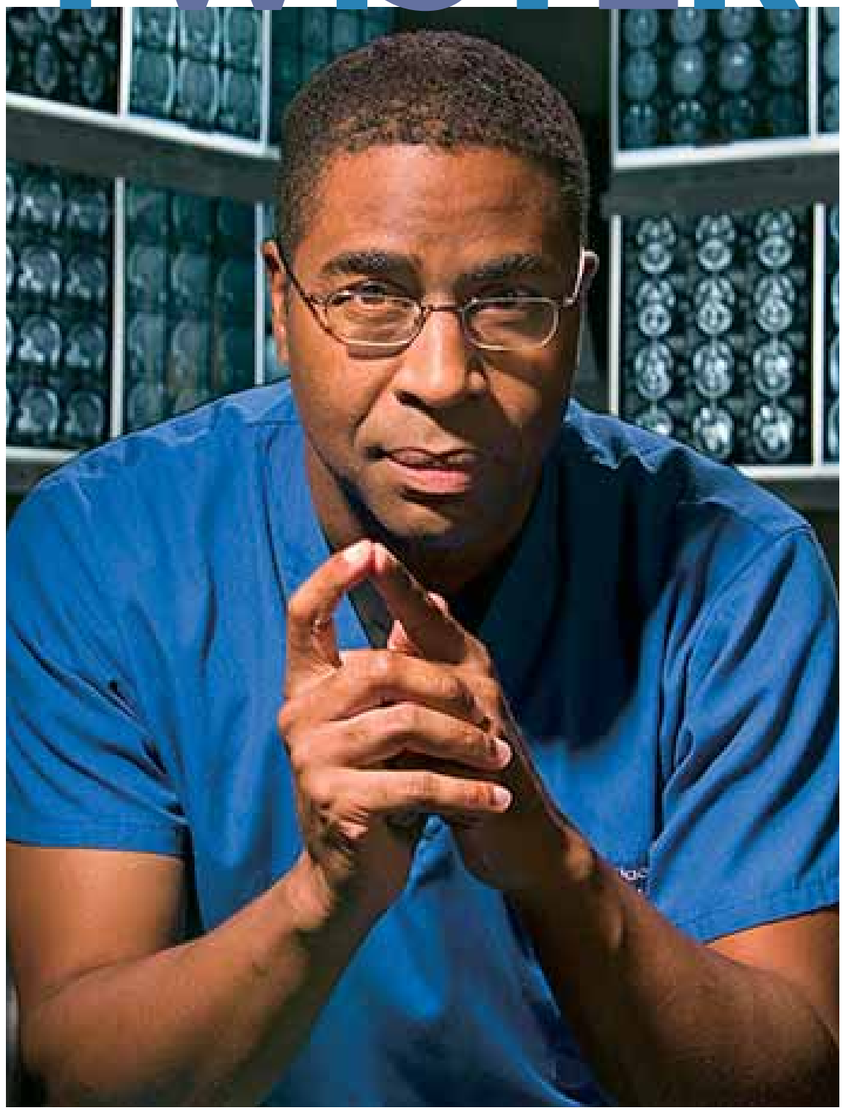
The BRAIN TWISTER



Brain cancer is the leading cause of cancer death in children and young adults under the age of 19 and is also on the rise in adults. Dr. Keith Black and his team at the Maxine Dunitz Neurosurgical Institute want to know why. Their quest is leading to lifesaving breakthroughs.

BY LAURA RANDALL

A LARGE TANK FULL OF FLOATING, luminescent jellyfish stands across from Dr. Keith Black's desk in his corner office overlooking the Beverly Center. There are other eye-catching items in the office: a photograph of Neil Armstrong and Buzz Aldrin walking on the moon that is signed by Aldrin, framed medical journals highlighting his discoveries over the past two decades, and photographs of the neurosurgeon with two U.S. presidents and other notable figures, including Nelson Mandela and Sidney Poitier. But it is the presence of the jellyfish that perhaps best illustrates Black's overall approach to work and life—one that is marked by an innate curiosity with unlimited breadth.

"I think they are amazing—here you have an organism with no brain, no skeleton, yet it is able to function and be very tranquil," he says.

The holder of the Ruth and Lawrence Harvey Chair in Neurosciences, he is also chairman of the Department of Neurosurgery at Cedars-Sinai. In 1997, the same year he started the Maxine Dunitz Neurosurgical Institute, he was featured on the cover of *Time* Magazine, above the headline, "Hero of Medicine" for his pioneering research on the blood-brain barrier.

Dr. Black's interest in science began as a small child growing up in Cleveland. "I remember watching tadpoles' tails fall off and asking why," he recalls. His fascination with the brain came a little later, when he was studying neurophysiology and anatomy as a medical student at the University of Michigan.

"There is nothing more beautiful in the universe than the human brain," he says. "It is two-and-a-half pounds of tissue that gives us emotion, vision, language, the ability to create cities and bridges and jets and spaceships, and allows us to dream and to create. Who wouldn't be fascinated with it? It is ultimately who we are."

At Cedars-Sinai, Dr. Black performs more than 200 surgeries a year and is sought after by cancer patients around the world. Forty-eight-year-old JL is one patient who recently chose him over other neurosurgeons around the country to remove the colloid cyst that was discovered in her brain's third ventricle.

On the day of surgery, JL is prepped by assisting surgeon Ray Chu and half a dozen others in the operating room. The room is calm and hushed as Dr. Black uses a series of micro-dissection instruments to enter the narrow corridor between the brain's two hemispheres and smoothly extract the tumor without touching or harming healthy brain tissue.

The intention, the surgeon explains later, is to treat the brain as sacred territory. "We essentially want to be smooth criminals, like a thief in the night, going in and taking the tumor out and getting out of the brain before it ever realizes that we have been there."

Soon Dr. Black is washing up and striding to the waiting room to inform the patient's anxious mother that the surgery went well and that her daughter should be able to go home within the next two days.

As he prepares to leave the OR floor and return to his office to tackle the rest of the day's meetings, issues, and challenges, he smiles. "Beautiful anatomy, isn't it?" Indeed.

This beautiful anatomy is the center of attention at the Maxine Dunitz Neurosurgical Institute. Since launching in 1997 with Dr. Black as its leader, it has pushed many boundaries—and made crucial, lifesaving breakthroughs—in the treatment of brain cancer and other neurological diseases.

With his team of specialized researchers and physicians, Dr. Black is exploring innovative approaches to the treatment of glioblastoma, a highly aggressive form of brain cancer with a median survival rate of just one year, and diseases such as Parkinson's, Alzheimer's, and ALS. Among the team's discoveries: a vaccine that improves a patient's survival rate when combined with other treatments; stem cells that can be modified to secrete anti-cancer agents that track down and effectively kill brain tumors; and the development of technology that delivers lifesaving drugs past the blood-brain barrier.

Approximately 180,000 patients are diagnosed with brain tumors in the United States each year. Brain cancer recently replaced leukemia as the leading cause of cancer death in children and young adults under the age of 19. Its incidence is also on the rise in adults, a fact not lost on Dr. Black and his colleagues as they seek answers to what causes it.

"When we look at the impact of neurological disorders, I can tell you that almost everyone has a family member or close friend who is affected by one, be it a stroke, Parkinson's disease, Alzheimer's, or brain tumors," says Dr. Black. "As we develop technology to solve brain tumors, we are developing technology to solve other disorders that affect the human brain, and this will have broader implications for other diseases as well."

Dr. Keith Black performing brain surgery in the operating room

Among the significant discoveries made at the Institute is the development of an anticancer vaccine, known as dendritic-cell immunotherapy, which prompts the immune system to dispatch killer T-cells that track down and attack any renegade tumors left behind after surgery.

"Brain tumors spend a lot of time and energy trying to attack the immune system," Dr. Black explains. "So we felt that the highest impact we could make immediately was to teach the immune system how to fight the tumor."

For patients who received a combination of the dendritic-cell vaccine and chemotherapy in clinical trials, the two-year survival rate was 42 percent, compared with 8 percent for patients who did not receive the vaccine. "It appears that the vaccine actually works synergistically with chemotherapy in making the tumor more sensitive and much more receptive to chemotherapy, but more research is required," says Dr. Black.

For Dr. Chris Wheeler, a research immunologist recruited from Stanford to work on the vaccine, the results were stunning. "We could see that giant tumors were just melting away. That is something I had not only never seen before, but never even heard about," he says.

The research also led to the discovery that the vaccine improves survival in an age-dependant manner. "That means older patients are doing as well as the younger patients, whereas traditionally the older patients would do far worse," says Dr. Wheeler. "What we have shown, which is new so far in the field, is a link between the immune response to the tumor and the tumor's genetic characteristics." Now the team wants to take its findings to the next level. The Institute is working with the National Institutes of Health to launch a multi-institutional clinical trial, which could begin later this year.

Conducting and managing such essential clinical trials is the goal of the newly established Johnnie Cochran, Jr. Brain Tumor Center. "When a promising discovery is made in the laboratory, the Center will streamline the process of early clinical trials and help bridge the gap between research findings and patient care," says Dr. Black. Cochran was a friend of Black, who treated the renowned attorney for the glioblastoma multiforme that ultimately took his life in March 2005.

Another promising area of research absorbing the Institute's investigators is based on nanotechnology methods. It involves a new drug delivery system named Polycefin that is uniquely engineered to carry anticancer agents directly to the brain tumor cells without damaging healthy tissue. It was recently developed in the Department of Neurosurgery by Dr. Julia Ljubimova, working with biochemists at the University of Regensburg in Germany.

Acting on an earlier finding that a protein called Laminin-8 enables invasive tumor cells to spread and grow, Dr. Ljubimova used a nanocompound to effectively shut down Laminin-8 production by brain tumor cells. "By inhibiting the synthesis of this protein, we reduced

SCORPION VENOM TARGETS DEADLY BRAIN TUMORS

The giant yellow Israeli scorpion unleashes a sting that can cause fever, convulsions, and even death. But, oddly enough, that venom may also be key in prolonging the life of patients with malignant brain tumors. A compound that occurs naturally in the scorpion's venom displays an unusual property: it can cross the blood-brain barrier.

Researchers led by Dr. Adam Mamelak, a neurosurgeon at the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai, recently made a synthetic version of the compound known as TM-601. A single, low dose of TM-601, along with radioactive iodine, was injected in patients with glioma, the most aggressive form of brain cancer, following surgery to remove the tumor.

"The compound bound to the tumor, but it did not bind to normal cells elsewhere in the body," Dr. Mamelak explains. Traces not taken up by the tumor were apparently eliminated quickly from the body and did not accumulate in patients' organs.

While the study was not designed to evaluate efficacy, the treatment appeared to be encouraging and had an anti-tumor effect, said Dr. Mamelak.

Phase II studies of TM-601 are underway at Cedars-Sinai and other institutions. Researchers are also testing whether TM-601 will target and bind to other types of cancers as powerfully as it does to gliomas.

"Obviously, a scorpion has no interest in brain tumors," Dr. Mamelak says. "This is just an example of biological diversity at work, and it shows how medical research sometimes takes interesting turns for the better."

the number of brain tumor vessels by 75 percent, so the tumor grows more slowly," she explains.

The hope is that by taking the Polycefin alone or in combination with other drugs, cancer patients will develop fewer side effects than they would with conventional radiation and chemotherapy, and the survival rate will be higher, Dr. Ljubimova says.

Supported by a five-year grant from the National Cancer Institute, Dr. Ljubimova is also studying the effect of Laminin-8 on other invasive cancers such as metastasized breast cancer and the drug's effectiveness when combined with chemotherapy.

Headway is also being made in stem cell research. A team led by Dr. John Yu, co-director of the Comprehensive Brain Tumor Program at the Maxine Dunitz Neurosurgical Institute, engineered adult neural stem cells from bone marrow that will effectively attack brain tumors and improve survival rates. With the help of National Institutes of Health grants, Dr. Yu and his team are developing a clinical protocol using these adult stem cells to treat patients with brain tumors and neurodegenerative diseases such as Parkinson's disease and ALS.

"It is a very attractive therapy because instead of using stem cells obtained from fetuses or embryos, it can be obtained from the patient's own bone marrow," Dr. Yu explains. "These cells may be beneficial because there are no issues of rejection since they come from the patient's own body, and there is no risk of getting cancer from these cells."

The team's goal, Dr. Yu says, is to "dovetail this technology with ongoing dendritic cell vaccination trials to deliver a one-two punch."

Other investigators at the Institute are also involved in research involving stem cells. Dr. Dwain Morris-Irvin is studying their effectiveness in treating Parkinson's disease, a neurodegenerative disorder for which there is currently no cure. By isolating stem cells from the brain, engineering them to "become" the cells lost in Parkinson's, then transplanting them back into the patient, Morris-Irvin and his team hope to relieve the tremors symptomatic of the disease. "Presumably the cells will reintegrate into the system and re-establish lost functions," Morris-Irvin says. "If a patient is shaking uncontrollably, a typical symptom of Parkinson's, we should be able to relieve that symptom and get rid of that tremor." Morris-Irvin expects to bring these findings to early clinical trials within the next two years.

A NON-SURGICAL ALTERNATIVE

The latest Gamma Knife® technology is now available at Cedars-Sinai with the opening of the Gamma Knife Center at the Samuel Oschin Comprehensive Cancer Institute. The Center is one of only a handful of facilities in the Los Angeles area to offer Gamma Knife surgery to treat a range of lesions, tumors and conditions affecting the brain.

The Gamma Knife technology, a noninvasive alternative to traditional brain surgery, is designed to treat brain lesions that are smaller than four centimeters.

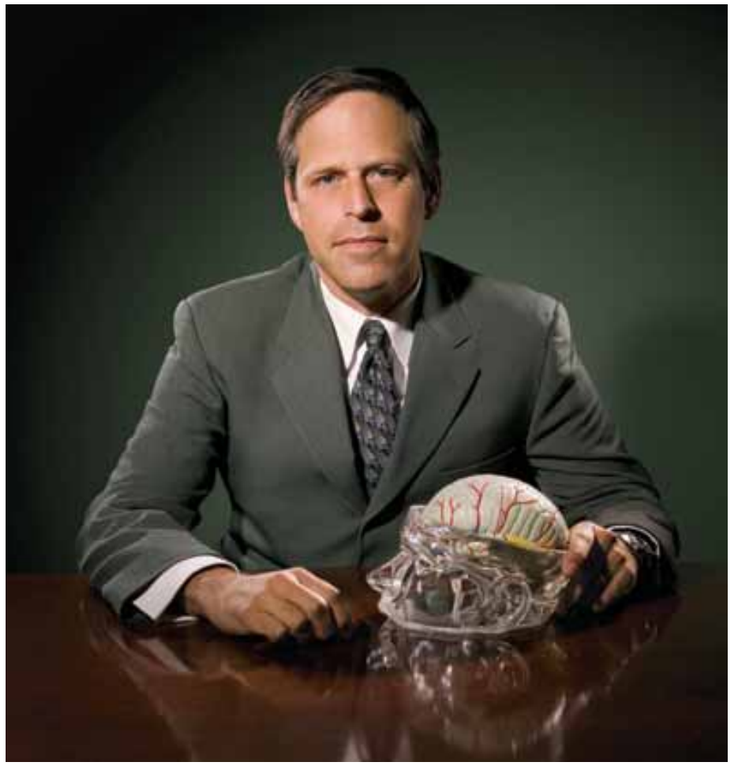
Treatment using the Gamma Knife is painless, accurate and effective. The Gamma Knife is not a knife in the normal sense of the word. No incision is made. The Gamma Knife uses up to 201 separate beams of radiation that converge at a single target point. The shape and dose of the radiation is optimized to hit the target with unparalleled accuracy, without damaging surrounding healthy tissue.

"The Gamma Knife delivers a full dose of radiation in one session. It is a fixed system that is extremely precise, which makes it an excellent choice for treating trigeminal neuralgias and other 'functional' abnormalities," says Keith Black, MD, chairman of the Department of Neurosurgery at Cedars-Sinai and director of the Maxine Dunitz Neurosurgical Institute.

THE GAMMA KNIFE CAN BE USED TO TREAT:

Benign brain tumors, including acoustic neuromas, meningiomas and pituitary adenomas ▲ Primary brain tumors, including hemangiomas, meningiomas, schwannomas, hemangioblastomas, and all forms of cancer that have spread to the brain ▲ Arteriovenous malformations ▲ Trigeminal neuralgia ▲ Thalamic pain syndrome ▲ Pineal tumors

> "We are expanding what you can do with the endoscope in terms of taking out other tumors at the base of skull. The same technology can be applied to other tumor types, such as gliomas and meningiomas."
> — Dr. Adam Mamelak



CEDARS-SINAI IS A NATIONAL LEADER in pituitary disease research and treatment, offering the most advanced treatment options through the Pituitary Center. The pituitary is the kidney-bean-shaped gland attached to the base of the brain that controls the secretion of hormones. The Center's surgical co-director, Dr. Adam Mamelak, is developing novel therapies for pituitary tumors through the technological advancement of endoscopic surgery. Currently, surgeons typically remove a pituitary tumor by entering through the upper lip, an effective yet destructive method that requires painful nose packs and a long, uncomfortable recovery. By using a very small endoscope, the tumor can be removed through the nasal cavity. The chances of eliminating all malignant tissue are greatly improved, says Dr. Mamelak.

The hope is that the same method can eventually be applied to other tumors. "We are expanding what you can do with the endoscope in terms of taking out tumors at the base of skull," Dr. Mamelak says. "The same technology can be applied to other tumor types, such as gliomas and meningiomas."

Dr. Mamelak, who is also widely known for his advancements in epilepsy research, was invited to the Maxine Dunitz Neurosurgical Institute in November 2006, attracted by its emphasis on translational research, which promotes the free flow of information between research laboratories and clinical work and practice.

"Dr. Black has built a very strong, deep, and diverse group here," he says, "and the ability to be part and parcel of that group was very appealing."

That group, which Dr. Black refers to as his "mini-Manhattan project," includes more than two dozen scientists and physicians recruited from Stanford, Harvard, and other top institutions around the world.

"We found the best and the brightest basic scientists and physicians and put them together to find unique opportunities to make a real impact on disease," Dr. Black says. "It is the ability to make what I call the odd observation in the right supportive environment that can allow us to make major medical discoveries that ultimately lead to cures."