

P&S

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COLUMBIA UNIVERSITY

College of Physicians
and Surgeons

Brain Tumors: Putting a Formidable Opponent in Check

MIGRATION INHIBITORS

VACCINES

CONVECTION ENHANCED DELIVERY

RADIATION

CHEMO

SURGERY

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NEUROLOGICAL
INSTITUTE
NEW CLINIC
FOR HARLEM'S
HOMELESS
GRADUATE STUDY
IN INFORMATICS

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Dear P&S Readers,

The day before the Neurological Institute opened on East 67th Street, the New York Times announced in a headline nearly 100 years ago, "NEW NERVE HOSPITAL TO OPEN TO-MORROW." Subheads further described the importance of the opening: "The Neurological Institute Will Have Wards and a Clinic to Treat

Patients Free"/"A New Departure Here"/"Modern Hospital Building Will Have Full Equipment for the Relief of All Forms of Nervous Disease."

The year was 1909, and this year we celebrate the centennial of what has become known as the Neurological Institute of New York, which moved to our medical center in 1929. This issue has two articles that launch the commemoration of the 100th anniversary of the Institute. One is a look back at one of the early practitioners of neurology, Dr. Moses Allen Starr. The article about Dr. Starr, a profile of him in context of the midtown architecture important in his time, was written by a Neurological Institute house staff alumnus.

The second article — our cover story in this issue — is more forward-looking and recounts the progress being made and soon to be made in brain cancer. Progress in treating brain tumors has made our researchers, surgeons, and physicians optimistic about what the next few years will bring. They are hopeful that they can move brain cancer from today's grim category to one of long-term management, similar to the way AIDS treatment has evolved.

Both articles instill pride in P&S, one in recalling the historical importance of Columbia medicine in New York City, the other sharing the optimism of our talented faculty as they work on a currently intractable disease in today's Neurological Institute.

With best wishes,

Lee Goldman, M.D., Dean
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ON THE COVER: Scientists, surgeons, and physicians are working together to make the right moves in treating brain tumors. Article, Page 14. Illustration by Sarah Knotz.

BRAIN TUMORS: GAINING ON A FORMIDABLE FOE



Brain cancer researchers and clinicians are optimistic that new ideas, animal models, delivery methods will soon improve survival

BY SUSAN CONOVA

EVERY THURSDAY, COLUMBIA'S BRAIN TUMOR BOARD GATHERS in the neuropathology conference room on the 15th floor of the P&S building to discuss the week's cases.

This morning, an MRI scan from a new patient is projected on the screen. The patient, an elderly man in his late 70s, went to the doctor feeling disoriented and lethargic. The cause was immediately clear from the scan's image: Amidst the dark grey brain tissue, an irregularly shaped white mass, vaguely resembling a galaxy, took up a large portion of the man's right temporal lobe. A classic sign of brain cancer, a bright white ring, representing a dense pack of malignant cells and tumor vessels, surrounded the mass.

The decision by the radiologists, oncologists, surgeons, and pathologists was made quickly. The tumor was most likely an aggressive glioblastoma, the most common type of brain cancer. Treat him.

Surgeons will remove the tumor, if possible, in most people diagnosed with glioblastoma, and several weeks of radiation and chemotherapy will follow in an attempt to kill any remaining cancer cells.

"But invariably, the cancer comes back, and we wonder what to try next," says neuropathologist Peter Canoll, M.D., Ph.D., assistant professor of clinical pathology. At Columbia, patients may be put on anti-angiogenesis therapy to disrupt the blood vessels fueling the tumor's growth. Or enter a trial testing a drug related to scorpion venom, which stops the migration of cancer cells through the brain. Some even have catheters inserted through their skulls to deliver chemotherapy directly to the brain tumor.

The options are experimental and though none are likely to add years to a patient's life, neuro-oncologist Steven Rosenfeld, M.D., Ph.D., director of the neuro-oncology program at the Herbert Irving Comprehensive Cancer Center, is optimistic that significant improvements in survival are around the corner.

"I've seen more progress in the last five years than in the last 50," Dr. Rosenfeld says, "and I think survival will begin to improve in the new few years. Already with anti-angiogenesis therapy, we routinely see people live one or even two years longer after their cancer returns, instead of the usual two or three months."

Progress in brain cancer research has accelerated, says Dr. Rosenfeld, because of an increase in funding that is attracting new talent to the field, a revolution in cancer therapeutics in general, and a growing interest from pharmaceutical companies.

At Columbia, where brain cancer research has increased in the past few years, surgeons, oncologists, and pathologists are casting a wide net for new treatments with the expectation that no one treatment can completely conquer brain cancer.

"Ultimately, I think that treatment of brain cancer will be similar to HIV treatment," Dr. Canoll says. "We won't cure brain cancer, but by using an arsenal of drugs to hit multiple targets in malignant cells, we'll be able to transform it into something you can live with for a long time."

Turning to the Immune System

Today, neurosurgeons like Jeffrey Bruce, M.D., are responsible for what has been the mainstay of brain cancer treat-

ment since the early decades of the 20th century: physically removing the tumor.

Neurosurgeons know that removing the tumor will not save the patient's life. But evidence shows that if 95 percent or more of the tumor is removed, patients live longer and have a better quality of life. Today, removal of a tumor, combined with radiation and chemotherapy, increases survival from a few months to approximately one year.

These are still brutal odds, but despite computerized brain navigation technology that allows surgeons to cut out more cancer cells while preserving normal brain (a technique reportedly used during Sen. Ted Kennedy's surgery), neurosurgery has probably reached its limit in improving survival.



"Surgery isn't being limited by technology at this point but by the biological nature of the tumors," says Dr. Bruce, the Edgar M. Housepian Professor of Neurological Surgery.

"Ideally you want to remove everything you see on an MRI scan. But practically, one of the difficulties is distinguishing tumor from brain. At the edges of the tumor, cancer cells are mixed in with normal cells. If you push further, you'll remove normal parts of the brain. And even if you quote remove all of the tumor unquote, you know there are cells left behind that have already invaded other areas of the brain."

Neurosurgeons learned this early when they made a desperate attempt to cure some patients by removing the entire half of the brain containing the tumor. New tumors still popped up in the remaining hemisphere. For brain cancer treatment to be effective, it must be able to attack cancer cells that have already spread throughout the brain.

To chase down the remaining malignant cells, Dr. Bruce and fellow neurosurgeon Richard Anderson, M.D., assistant professor of neurological surgery, have turned to the immune system for help. "Most people know what the immune system does when you get a cold. It's there to recognize the things, like viruses, that are not supposed



to be in your body," says Dr. Bruce. "Although tumor cells are a part of your body, they are slightly different than normal cells and the immune system mounts a response against them."

Recent studies in the discipline have shown that cells of the immune system are constantly scanning the body for malignant cells and are sometimes capable of snuffing out cancer in its earliest stages. In animals without these cells, cancer is more common. Transplant recipients, for example, whose immune system is suppressed to prevent organ rejection, have a cancer rate seven times greater than the general population.



But many times cancer escapes destruction by thwarting the immune system's attack. Cytokines secreted from cancer cells seem to throw an invisibility cloak over the cancer and deceive immune cells into thinking nothing is there.

The trick is to use vaccines to educate the immune system to the cancer's deception. "Vaccines take the aspects of the malignant cell that will make the cells conspicuous to the immune system and amplify them," Dr. Bruce says.

Dr. Bruce thinks that even with a revved up immune system, a vaccine will not be able to eliminate an entire tumor. "We know the immune response against cancer is weak, and it won't work if there's too much tumor left. Ideally, chemotherapy will also improve and reduce the number of cells."

Improving Chemotherapy

Improvements in chemotherapy for brain cancer should come once scientists have a better understanding of what makes brain tumors malignant. That sounds obvious, but that tack wasn't always taken in the past. "We used to take drugs for other cancers and blindly try them in brain cancer," Dr. Rosenfeld says. "Now we're looking at unique targets, studying them in animals, and then moving drugs into the clinic."



One characteristic that sets glioma cells apart from other cancers is their remarkable ability to travel quickly through the brain.

“Gliomas are wildly infiltrative,” Dr. Rosenfeld says. “By the time a tumor is noticed, cancer cells have probably spread throughout the entire brain.”

Radiation therapy tries to kill these cells by zapping some of the normal brain tissue around the tumor. And the recently approved chemotherapy drug temozolomide, the only drug ever shown to improve survival in brain cancer, tries to kill by disrupting the cells’ DNA. Together the two treatments improve survival, but some cells always escape and provide the seed for new tumors. More rounds of surgery are possible, but the cancer acts faster so attempts to treat recurrences are quickly overwhelmed.

At Columbia, where brain cancer research has increased in the past few years, surgeons, oncologists, and pathologists are casting a wide net for new treatments with the expectation that no one treatment can completely conquer brain cancer.

Preventing cells from migrating, Drs. Rosenfeld and Canoll say, could help to confine the spread of tumors to a smaller area and improve the effectiveness of local techniques like surgery and radiation. Some studies also suggest that roving cells are more resistant to radiation and chemotherapy than less mobile cells. Stopping migration could potentially make these cells less dangerous and more susceptible to current therapies.

So far, however, trials of agents that aim to halt migrating cells have failed. Dr. Canoll thinks these failures can be traced back to laboratory studies that did not faithfully recreate the environment that glioma cells have to crawl through.

“The brain is a dense, dense jungle and glioma cells need to squeeze through spaces that are under a micron in diameter,” Dr. Canoll says. Such conditions had not

Building a Better Mouse

With high-profile patients in the news recently — Ted Kennedy, columnist Robert Novak, and Yankees outfielder Bobby Murcer — it may be easy to forget that glioblastoma is still a rare disease, affecting about 9,000 people in the United States each year.

But while researchers and clinicians are grateful that the cancer is not more widespread, the scarcity of patients makes the disease harder to study.

“People are the limiting factor, so we need to rely on animal models to mimic the human tumors,” says neuropathologist Peter Canoll, M.D., Ph.D., assistant professor of clinical pathology.

However, for 25 years, animal models of glioblastoma have proved powerless in predicting the effect of experimental therapies in human patients. Most brain tumors in animals develop from human glioma cells that have been maintained in culture and then implanted in the brain or under the animal’s skin. “They don’t resemble human tumors,” Dr. Canoll says. “They don’t infiltrate the brain like human gliomas do. And people can cure them. But none of the drugs that have been shown to cure these tumors work in people.”

In the past few years, Dr. Canoll and other researchers have been creating mouse models that more closely resemble human gliomas and which they hope will prove to be better predictors of treatment outcome.

In Dr. Canoll’s model, which is a spinoff of a previous model created by Eric Holland at Memorial Sloan-Kettering, mice are injected with viruses that express platelet-derived growth factor (PDGF), which is frequently expressed in human glioma cells. “We have combined PDGF with the genetic deletion of two tumor suppressor genes, PTEN and p53, which are frequently mutated or lost in human gliomas.” These molecular alterations cooperate to initiate tumor formation and 100 percent of the mice develop tumors that resemble human glioblastoma.

Though it’s too soon to say if the use of such models will be more powerful, Dr. Canoll is cautiously optimistic based on the model’s performance with drugs that have failed in human trials. “We tried the standard treatments, and they don’t work in our new model either. Now, we are using the model to test out new forms of therapy.”

“In the future, I see treatment coming in three phases. First surgery, then radiation combined with chemotherapy that breaks through the blood-brain barrier, and finally a treatment that harnesses the immune system,” Dr. Bruce says. “Am I optimistic that we’ll see big changes in the next 5 to 10 years? I wouldn’t be doing research if I wasn’t optimistic.”

been replicated in previous studies that looked at glioma migration using *in vitro* assays. Working with Dr. James Goldman, M.D., Ph.D., director of neuropathology, Dr. Canoll and Dr. Marcela Assanah, a postdoc in Dr. Bruce’s lab, have developed a system to study glioma cells migrating in slices of living brain tissue.

Faced with this jam-packed environment, the cells adopted a unique mode of migration that closely resembles the way normal neural progenitor cells migrate through brain tissue during brain development. Cells first sent out a long narrow projection that wedged itself into the pore but then paused. The normally round nucleus is too big to follow the projection, so the cell squeezed its nucleus into an hourglass shape and burst forward.

Dr. Canoll and Dr. Rosenfeld have used this system to test the effects of blocking a molecular motor called myosin II that is critical to this unique style. When faced with a flat surface, cancer cells could migrate just fine without myosin II, but when they needed to squeeze through tiny spaces, the cells stopped dead in their tracks.

“Molecular motors are particularly attractive therapeutic targets because they are at the end of the line,” Dr. Canoll says. “Many other things are needed to get a cell to move, but eventually cells must activate a molecular motor like myosin II in order to generate the forces needed to move.”

A drug already in use in Japan for pulmonary hypertension can block myosin II, and Dr. Rosenfeld says

Columbia researchers are trying to interest the company that makes the drug in brain cancer research. “We’re still far away from a myosin-based therapy but not as far as we used to think. Getting the drug companies interested in the concept is the first step.”

If such migration inhibitors work, they may have to be paired with other drugs that slow tumor growth, like angiogenesis inhibitors, to have the biggest effect. “If you block angiogenesis, you’ll still be left with migratory cells; if you just block migration, a big tumor may grow back near the original,” Dr. Canoll says. “People now realize that both these two things need to be targeted at the same time.”



Bypassing the Blood-Brain Barrier

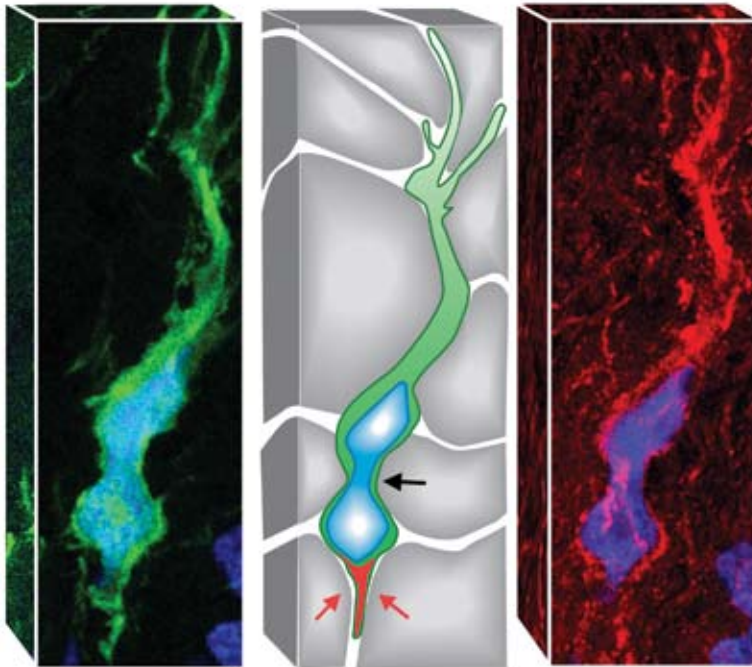
Despite a recent renaissance in brain cancer research and an increase in the number of compounds available for clinical testing, the field still faces obstacles that have stalled progress historically. What has looked promising in cell culture or animal studies hasn’t translated into patient survival, which essentially has remained the same for 20 years.

A big part of those failures can probably be attributed to the blood-brain barrier, which keeps most of the molecules in the bloodstream from getting into the brain.

“The barrier is not such a problem for the main bulk of the tumor and its outer margins, which are supplied by leaky blood vessels that even large drugs can pass through,” says Dr. Rosenfeld, “but the cancer cells that have migrated to other parts of the brain are next to normal, impermeable blood vessels. That’s where the blood-brain barrier is a problem.”

The blood-brain barrier is not just physical, although the tight seals between adjacent cells lining the brain’s blood vessels prevent most viruses, toxins, and other molecules from slipping through the joints. And pumps expel most things that try to gain entry by passing through the cells’ interiors.

Because of the barrier, most chemotherapeutics fail to penetrate the brain beyond the main tumor. “The problem with chemo is not that the drugs don’t work, it’s that you can’t get enough of it into the brain where you need it,” Dr. Bruce says. “If we could give as much of the drug as possible without worrying about side effects in other



Glioma cells need a push from behind to invade the brain. This image of a transplanted human glioblastoma cell squeezing through rat brain cortex shows that cancer cells use special machinery (myosin II, labeled red in the right image) to migrate through the brain's tight spaces. Columbia researchers are now investigating whether myosin inhibitors can stop brain cancer from spreading throughout the brain. The center image illustrates a model of how glioma cells migrate through brain tissue: First, the cell extends a long leading process followed by forward movement of the nucleus and cell body. To get the cell body through narrow points in the extracellular space, the nucleus deforms into an hourglass shape (black arrow). Actomyosin contraction at the rear (red arrows) generates force to push the cell forward.



parts of the body, we may be able to do better.”

After an encouraging phase I trial conducted at Columbia, Dr. Bruce thinks that bypassing the barrier completely and delivering chemotherapy directly to the brain may be one way to accomplish that.

The technique, called convection-enhanced delivery, slowly pumps chemotherapy into the brain through a catheter implanted surgically into the tumor and surrounding areas.

Delivery is slow to avoid putting the skull under more pressure, and patients remain connected to the system for four days. Though convection-enhanced delivery has not improved survival in recent phase III trials, the lack of success could be due to the drugs tested in those trials, Dr. Bruce says.

In a recently completed Columbia trial, Dr. Bruce chose to test topotecan, a drug commonly used to treat ovarian, cervical, and small cell lung cancer, based on his

laboratory experiments that showed it outperformed several other drugs at shrinking brain tumors in mice without affecting normal brain tissue. Topotecan selectively targets cancer cells but delivered through the bloodstream never reaches the brain because it is actively pumped out of the blood-brain barrier's cells.

Trial results were encouraging: Some tumors shrank and a few tumors disappeared, even though the trial was designed to evaluate safety, not effectiveness. “Nearly all patients, and particularly the ones who got higher doses, lived longer than expected, and none of them had side effects,” Dr. Bruce says.

In addition to planning a phase II trial to test the delivery system's effectiveness, Dr. Bruce is also looking at internal pumps that would free patients from the hospital during treatment and increase the dose by prolonging treatment time to two or three weeks.

“In the future, I see treatment coming in three phases. First surgery, then radiation combined with chemotherapy that breaks through the blood-brain barrier, and finally a treatment that harnesses the immune system,” Dr. Bruce says. “Am I optimistic that we'll see big changes in the next 5 to 10 years? I wouldn't be doing research if I wasn't optimistic.” ■