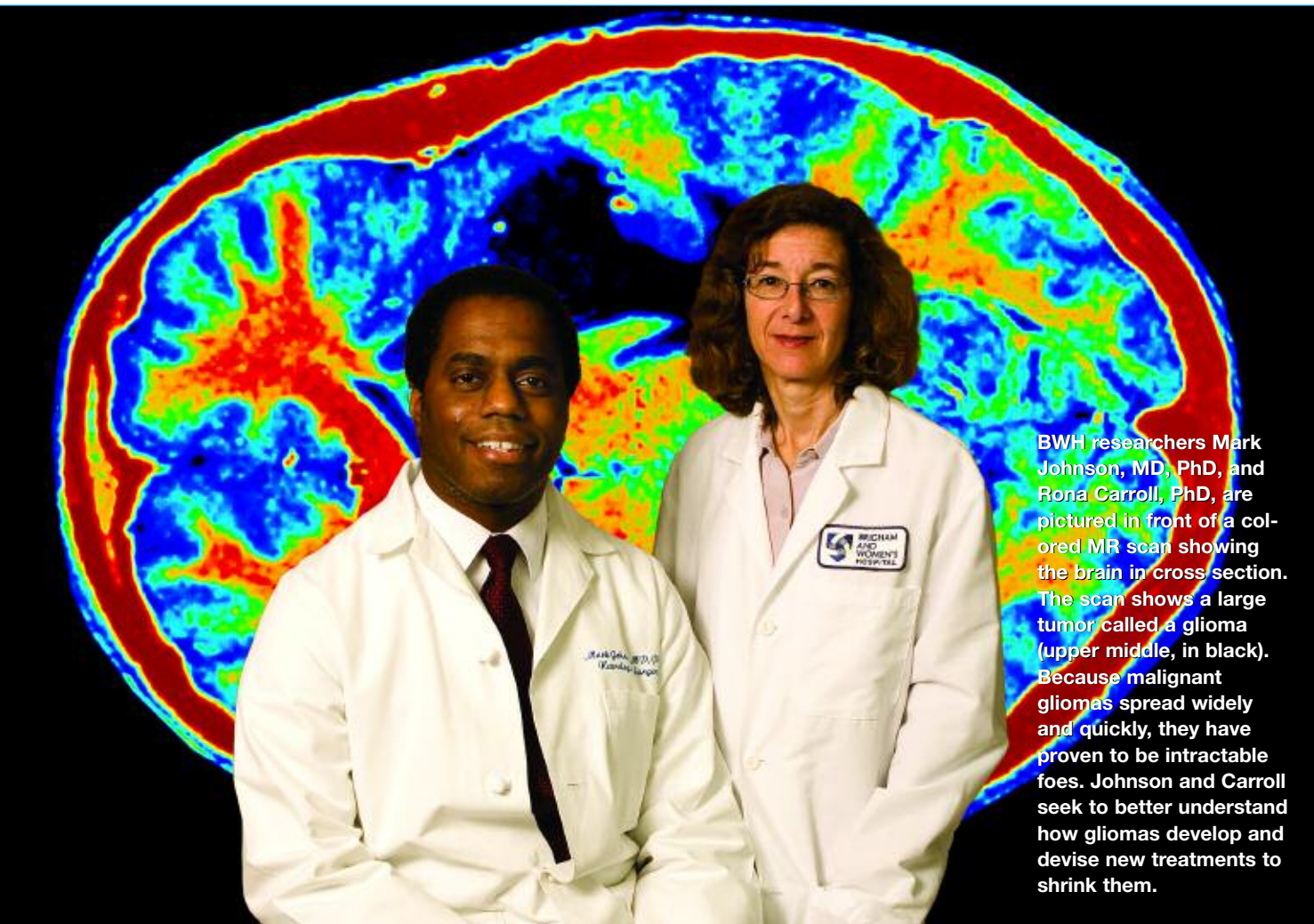


# David and Goliath

**CAN MICROPARTICLES AND OTHER SMALL-SCALE THERAPIES COMBAT ONE OF THE WORLD'S DEADLIEST BRAIN TUMORS?**



BWH researchers Mark Johnson, MD, PhD, and Rona Carroll, PhD, are pictured in front of a colored MR scan showing the brain in cross section. The scan shows a large tumor called a glioma (upper middle, in black). Because malignant gliomas spread widely and quickly, they have proven to be intractable foes. Johnson and Carroll seek to better understand how gliomas develop and devise new treatments to shrink them.

**K**ANSAS CITY ROYALS MANAGER DICK HOWSER. Cott beverage company CEO Gerry Pencer. ABC News correspondent Judd Rose. Baseball pitcher Dan Quisenberry.

All four incredibly talented men rose to the top in their respective professions. All four were diagnosed with brain tumors called malignant gliomas in the prime of their lives. And all four soon died of the disease.

Sadly, they aren't alone. Every year, nearly 12,000 Americans are diagnosed with these much-feared, fast-growing tumors; more than half die within 18 months.

Characterized by rapidly dividing cells that can migrate throughout the brain, gliomas are the Goliath of brain tumors. They almost always recur, and because of their ability to spread quickly and widely, they often outsmart traditional cancer treatments, such as surgery, radiation and chemotherapy.

Although they face an uphill battle, Brigham and Women's researchers Mark Johnson, MD, PhD, and Rona Carroll, PhD, are taking on Goliath in an effort to increase survival rates. They are pursuing different, yet complementary, tactics to better understand how gliomas develop and grow, and to devise treatments to shrink them while sparing healthy brain cells.

Researchers in Johnson's lab have identified many genetic abnormalities that determine glioma development and behavior. "There are hundreds of genetic defects in cancer," he says. "A few, maybe 30 or so, account for much of tumor biology."

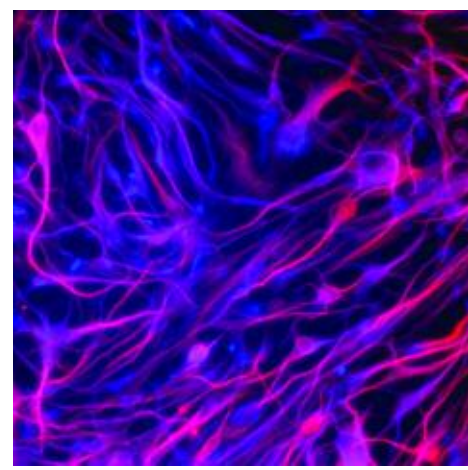
To determine which mutations play the most significant role, he and his colleagues recently developed a method of identifying clusters of functionally related genes within the cancer genome—the genetic makeup of a cancer cell. They then compare patients' glioma cells and pinpoint their genetic differences and similarities. (Their findings were published in *Cancer Research* in November.)

When they find the same genetic anomalies, they try to manipulate those genes and reproduce the tumors in mice. Then they try to interrupt the activity of the tumors' oncogenes, genes that can turn normal cells into cancerous ones, and augment the activity of tumor-suppressor genes.

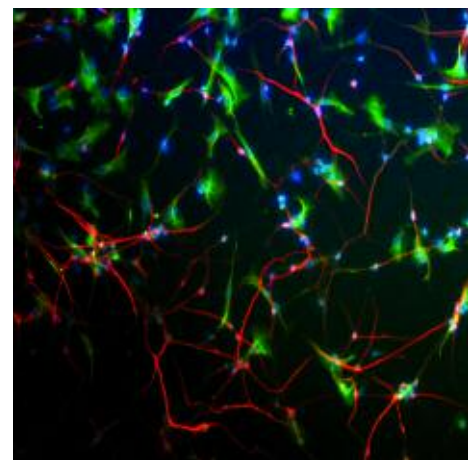
"We're focusing on identifying specific oncogene and tumor-suppressor gene pathways so pharmacologists can develop molecules that inhibit or augment them," explains Johnson.

That's where Carroll comes in. She focuses on developing methods to deliver therapeutic drugs to the tumor site while sparing healthy brain cells. Among the most promising: microparticle therapy and neural stem cells.

"When tumors grow in the brain," says Carroll, "they form the primary tumor and islands of cells in other areas of the brain. Microparticle therapy is designed to treat the islands that are left



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behind after the primary tumor is removed by surgery."

Microparticle therapy uses therapeutic drugs encased in polymers. When injected into the brain, the polymers slowly degrade and release their contents. The drugs Carroll uses include PEX, a powerful anti-tumor agent that she and a colleague identified in 1991, and platelet factor 4. Both prevent the growth of blood vessels that feed the tumor, inhibiting tumor growth.

In contrast, neural stem cells can track glioma cells that have migrated away from the main tumor mass. Carroll and her colleagues are exploiting this ability by injecting neural stem cells that have been genetically engineered to destroy tumor cells into the brain. Like bloodhounds tracking a scent, these cells find the primary tumor and then travel to satellites to complete their search-and-destroy mission.

What drives this behavior, however, is not fully understood, and much work remains before medical science can declare victory over gliomas. "In the meantime," she adds, "our goal is to shrink the tumors, prevent their recurrence and help patients live longer, richer lives."♦

Adult brain tumor stem cells (above) are being studied at BWH in the hopes of finding new treatments for malignant brain cancer. Glioma cells obtained from a patient during surgery (left). Each of the different cell types that make up the tumor is labeled with a marker of a different color.