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Researchers to track tumor DNA through bloodstream

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Medical scientists know this about glioblastoma multiforme: the malignant brain tumor is aggressive, it is elusive, and it appears in different permutations.

In a novel effort to unravel the multiple identities of glioblastoma, a team of University of Cincinnati (UC) researchers has begun sequencing individual glioblastoma genomes and tracking abnormalities through the bloodstream. They hope that by mapping the various DNA rearrangements of glioblastoma tumors they will be able to establish biomarkers that will help them track the cancer's progress and guide their efforts to treat patients more effectively. They also hope the biomarkers will help them identify targets for new, improved therapies for the future.

The effort involves researchers from the UC Neuroscience Institute's Brain Tumor Center and the UC Cancer Institute.

"Glioblastoma tumors show some similarities under the microscope," explains Olivier Rixe, MD, PhD, director of the UC Experimental Therapeutics Program in and a neuro-oncologist with UC Health and the UC Brain Tumor Center. "But when we go deeper and deeper, we see some significant differences, especially in the DNA and chromosomes. So there is no one single glioblastoma. Each tumor is different."

During the next few months, the team will use a $50,000 grant from the Mayfield Education and Research Fund to map the DNA of

glioblastoma cancer cells taken from tumors that have been surgically removed from 10 study participants. The genome of each tumor can be sequenced for about $3,000.

Genome sequencing has been done previously for glioblastoma multiforme (GBM) by the National Institutes of Health (NIH). The Cincinnati study's innovation lies in its quest to identify genetic abnormalities in individual tumors and then follow those abnormalities through the bloodstream. Researchers at Johns Hopkins University have employed the technique for a limited number of patients diagnosed with colon and breast cancer.

Treatment of glioblastoma continues to present a major challenge to neurosurgeons and neuro-oncologists. "It is an aggressive, highly malignant tumor with unclear boundaries," says co-investigator Ronald Warnick, MD, director of the UC Brain Tumor Center and chairman of the Mayfield Clinic. "Because of its diffuse nature, surgeons are unable to remove it completely, and it will grow back in the majority of patients. Our ultimate aim is to find a way to keep the infiltrating glioblastoma cells from growing into adjacent, healthy tissue."

Following surgery to remove the maximum amount of tumor tissue possible, study participants will undergo the standard of care for glioblastoma, which includes radiation followed by chemotherapy.

Simultaneously, researchers will follow abnormalities in the study participants' blood, taking very small blood draws (15 milliliters) before and after surgery.

"There will be some circulating DNA in the blood coming from the tumor, and we will follow those very specific abnormalities," said Rixe, the study's principal investigator. "It is very much a personalized study, because we are not talking about the genetic abnormalities of other

patients. We are talking about the sequencing of a biopsy of a specific individual's tumor. And we are talking about tracking individualized, personalized abnormalities."

The study is important, Rixe said, because doctors do not currently have robust biomarkers to correlate with therapeutic activity.

Equally important, the discovery of biomarkers may provide scientists with new therapeutic targets. By identifying a specific genetic abnormality or mutation, for example, they can work to develop a future therapy that attacks that mutation.

Rixe foresees a time when the tumor DNA of every patient with GBM is sequenced to provide for optimal treatment monitoring.

The UC Brain Tumor Center is well positioned to lead the study because it is a regional destination for patients with brain tumors. The center treats approximately 100 individuals with glioblastoma every year and maintains a tumor bank containing approximately 1,000 tissue samples.

Sequencing of the GBM tumors will be performed by the department of genetics at Albert Einstein College of Medicine in New York with an Illumina GenomeAnalyzer.

In addition to Rixe and Warnick, the study's multi-disciplinary research team includes UC faculty Christopher McPherson, MD (neurosurgery), El Mustapha Bahassi, PhD, and Peter Stambrook, PhD (molecular genetics), and Muhammad Shaalan Beg, MD (hemotology-oncology) and Jan Vijg, PhD, Chair of the genetics department at Albert Einstein.

"It is a significant step for the UC Brain Tumor Center to embark on a novel study that involves genetic testing and molecular collaboration among surgeons, neuro-medical oncologists and basic scientists," Rixe

said. "This is a real translation medicine – from the operating room to the laboratory bench. This is the best way to investigate, and I hope we will have some truly relevant findings for our patients."

Provided by University of Cincinnati Academic Health Center