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A multicenter team led by Memorial Sloan Kettering neurologist and researcher [Ingo K. Mellinghoff](#) has uncovered the relationship between two proteins that play a critical role in glioblastoma, the most common form of brain cancer. The discovery may lead to better treatments for glioblastoma patients whose tumors have certain molecular changes.

The protein epidermal growth factor receptor (EGFR) is frequently overexpressed or mutated in glioblastoma, yet studies have shown that only a small percentage of glioblastoma patients (less than 10 percent) respond to drugs that target EGFR. These drugs, erlotinib (Tarceva®) and gefitinib (Iressa®), are used to treat certain forms of [lung cancer](#) that also are characterized by *EGFR* mutations.

In a study published in 2005, Dr. Mellinghoff found that in glioblastoma patients who did not respond to these drugs, a protein called PTEN was frequently inactivated by gene mutations in the tumors. PTEN belongs to a class of proteins known as tumor suppressors, because when functioning normally these proteins prevent tumors from forming. *PTEN* gene mutations are common in many types of cancer.

In the current work, published in April in the *Proceedings of the National Academy of Sciences*, Dr. Mellinghoff's team determined how PTEN and EGFR interact, demonstrating that PTEN plays a key role in the down-regulation (reduction) of EGFR inside cells. This means that when PTEN is lost, EGFR becomes more abundant and stable, making it harder to block with targeted drugs. The research was done in cultures of human cells and glioblastoma tumor samples. [\[PubMed Abstract\]](#)

"Erlotinib is currently in clinical trials for glioblastoma," Dr. Mellinghoff said. "Based on our findings, we have designed a clinical trial in which higher doses of erlotinib — given intermittently for safety reasons — will be used to try and overcome the resistance resulting from *PTEN* mutations." Future research will focus on pinpointing exactly how PTEN regulates EGFR. Understanding how this molecular mechanism works could lead to the development of new drugs.

Dr. Mellinghoff has been named a Leon Levy Foundation Young Investigator at Memorial Sloan Kettering for 2010-2011.



Ingo Mellinghoff

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