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Discovery predicts patient sensitivity to important drug target in deadly brain cancer

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A recent discovery by Van Andel Research Institute (VARI) scientists enables the prediction of patient sensitivity to proposed drug therapies for glioblastoma - the most common and most aggressive malignant brain tumor in humans.

The study, published in January in the *Proceedings of the National Academy of Science*, investigated glioblastoma models characterized by cell signaling activation and gene amplification for their susceptibility to inhibitors of both the human MET oncogene and the epidermal growth factor receptor (EFGR).

An oncogene is a gene with the potential to cause cancer. In tumor cells, they are often mutated or expressed at high levels. High MET levels often occur in human tumors, and cells with inappropriate MET signaling produce activity that potently affects the spread of cancer. This signaling is implicated in most types of human cancers and high MET expression often correlates with poor prognosis. Mutations affecting EGFR expression or activity are also linked to cancer.

"Because oncogene MET and EGFR inhibitors are in clinical development against several types of cancer, including glioblastoma, it is important to identify predictive markers that indicate patient subgroups suitable for such therapies," said VARI Research Scientist Qian Xie, Ph.D., lead author of the study.

"Studies have shown that targeting MET signaling can have potent

antitumor effects," said Co-Author George F. Vande Woude, Ph.D., Head of the VARI Laboratory of Molecular Oncology. "Therefore, it is important to understand the mechanisms leading to HGF/MET sensitivity and to identify the patient subgroups most likely to benefit from MET-targeted therapeutics."

Dr. Vande Woude's career can be characterized by the uniquely broad scope of his work with MET and its molecular partner hepatocyte growth factor (HGF) -from the original cloning and characterization of the gene, through explaining the role of the HGF/ MET signaling pathway in human cancers, and then to applying that knowledge toward the identification of inhibitors of this important cancer pathway. Because MET and HGF play such an integral role in the process of cell survival, growth, blood vessel formation, and metastasis, they are a significant target in the development of anti-cancer drugs.

Dr. Vande Woude is also the co-author of an article published last week in *Nature Reviews Cancer* entitled "Targeting MET in cancer: rationale and progress," which updates the progress of MET and HGF as targets in the development of anti-cancer drugs.

"Progress in understanding this vital process has led to the successful development of blocking antibodies and a large number of small-molecule MET kinase inhibitors," said Vande Woude. "Results from recent clinical studies demonstrate that inhibiting MET signaling in several types of solid human tumors has major therapeutic value."

More information: Xie, Q. et al. (2012). Hepatocyte growth factor (HGF) autocrine activation predicts sensitivity to MET inhibition in glioblastoma. *Proceedings of the National Academy of Science*. 109: 570. www.pnas.org/content/109/2/570.full

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