Researchers from TGen, part of City of Hope, and from the University of California, San Diego have identified a set of genes that helps predict whether a patient's glioblastoma might respond to some promising drugs.
called neddylation (NAE) inhibitors.

The findings published in the journal *Neuro-Oncology Advances* will help Michael Berens, Ph.D., professor and head of the Glioma Research Lab, and his colleagues as they design clinical trials aimed at personalizing glioblastoma treatment.

New treatments for glioblastoma, the most common and most deadly primary brain tumor, are desperately needed. These tumors are characterized by a large and complex variety of molecular aberrations, such that a treatment that works against one patient's tumor may not work in another patient.

As a result, there have been more than 300 clinical trials for glioblastoma therapies that did not advance a drug to FDA approval, said Berens. "The pharmacopeia for treating brain tumors is abysmally slim," he added, "and new drug approvals for glioblastoma are tragically rare events."

NAE inhibitors, which affect protein turnover in cells, have shown impressive results against myeloma, and appear promising in glioblastoma models. But researchers need to know more about which glioblastomas are vulnerable to NAE inhibitor treatment, and why others may be resistant.

"This disease is too heterogeneous—you're not going to come up with a silver bullet against it," Berens explained, "But could you find some kind of a biomarker or molecular signature that differentiates between vulnerable and resistant tumors?"

The scientists studied genetic alterations and biological processes operating in human glioma cell lines and patient-derived xenografts, finding differences in signaling by the well-known tumor suppressor
protein PTEN and in pathways for DNA replication and repair. Based on these differences, the researchers developed an NAE Inhibition Response Gene Set—a set that could be used to predict which glioblastoma would be vulnerable to NAE inhibitors.

In particular, "these molecular signatures are a way for us to say which individual patients should get this drug in a clinical trial," Berens noted.

Berens and colleagues are designing just such a trial, called Glioblastoma Umbrella Signature Trial (GUST), named to convey the "gust of forward motion" that the team hopes the trial will give to personalized glioblastoma treatment, he said.

GUST will include at least six drugs, each associated with a molecular signature of vulnerability against glioblastoma. The idea is to profile 200 patients, Berens explained, "and test whether the signature of a patient's tumor demonstrates that this tumor will respond to a specific drug."

Umbrella trials may help speed up FDA approval of a drug that otherwise might get lost in the shuffle of a more traditional single drug clinical trial design, because patients are assigned to the new drug most likely to show activity, Berens explained.

For instance, the NAE gene set identified by the researchers is only found in 10% of patients—but getting NAE inhibitors approved for those 10 percent of patients could be a lifesaving effort.

And once a drug is FDA-approved, "then we can use those drugs in combination with other drugs like an immune checkpoint inhibitor or a DNA damage repair inhibitor, and that's where the big win is going to be for brain tumor patients," Berens said.

More information: Brett Taylor et al, Glioblastoma vulnerability to
neddylation inhibition is dependent on PTEN status, and dysregulation of the cell cycle and DNA replication, *Neuro-Oncology Advances* (2024). DOI: 10.1093/noajnl/vdae104

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