Somatic mutations in SMARCAL1 in brain tumors and their role in telomere maintenance

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Value proposition

Glioblastoma (GBM) is the most common and deadly primary malignant brain tumor in adults with an incidence of 3 per 100,000 adults per year. Mutations in the *TERT* promoter (*TERTp)* and isocitrate dehydrogenase 1 or 2 (*IDH1/2*) can classify 80% of GBMs into molecular subgroups with distinct clinical courses. Approximately one in every five adult patients with GBM, the most common and deadly malignant brain tumor, has tumors that are wild type for *TERTp* and *IDH1/2*1,5. *TERTp*WT-*IDH*WT GBMs are a relatively poorly understood glioma subset defined by an absence of common biomarkers. One potential biomarker for this glioma subset is SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A-like 1 (SMARCAL1). Deficiency of SMARCAL1 enhances the anticancer activity of chemotherapy agents and reverses cancer cell resistance to these agents. Therefore, targeting SMARCAL1 is an attractive therapeutic approach for cancers, including GBM, with defects in DNA damage repair or cell cycle checkpoints. A novel GBM diagnostic and therapeutic would enter a rapidly growing glioblastoma treatment market projected to reach $3.3 billion by 2024.

Technology

The inventors claim the use of SMARCAL1 mutation status as a diagnostic for GBM. The inventors also claim to use SMARCAL1 as a therapeutic target for the telomere maintenance mechanism known as alternative lengthening of telomeres (ALT). Using whole exome sequencing, the inventors identified an ALT-positive group that is comprised equally of two distinct subgroups. One subgroup harbors mutations in *ATRX* (notably without *IDH* or *TP53* mutations), while the second subgroup harbors mutations in a newly ALT-associated gene, *SMARCAL1.* Their results demonstrate that SMARCAL1 expression suppresses the ALT phenotype, thus revealing an integral role of the *SMARCAL1* mutation in ALT-mediated telomere maintenance in human cancers. Collectively, their findings establish *SMARCAL1* mutations as a novel genetic mechanism of ALT.

Advantages

- Technology could be the first to use SMARCAL1 as a diagnostic indicator and therapeutic target for GBM.
- There is currently no pharmaceutical compound on the market or in clinical trials targeting SMARCAL1 in GMB patients.
- A therapeutic compound derived from invention would be a

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candidate orphan drug, benefiting from accelerated FDA approval.
- Technology presents novel GBM diagnostic aside from current expensive and laborious neuroimaging techniques
- Technology is able to diagnose *TERTp*WT-*IDH*WT GBMs previously unidentifiable with existing biomarkers
- Therapeutic compound targeting SMARCAL1 has the potential to treat other cancers

Publications

- Killela PJ, et al(2013) The genetic landscape of anaplastic astrocytoma. Oncotarget 5(6):1452-7.