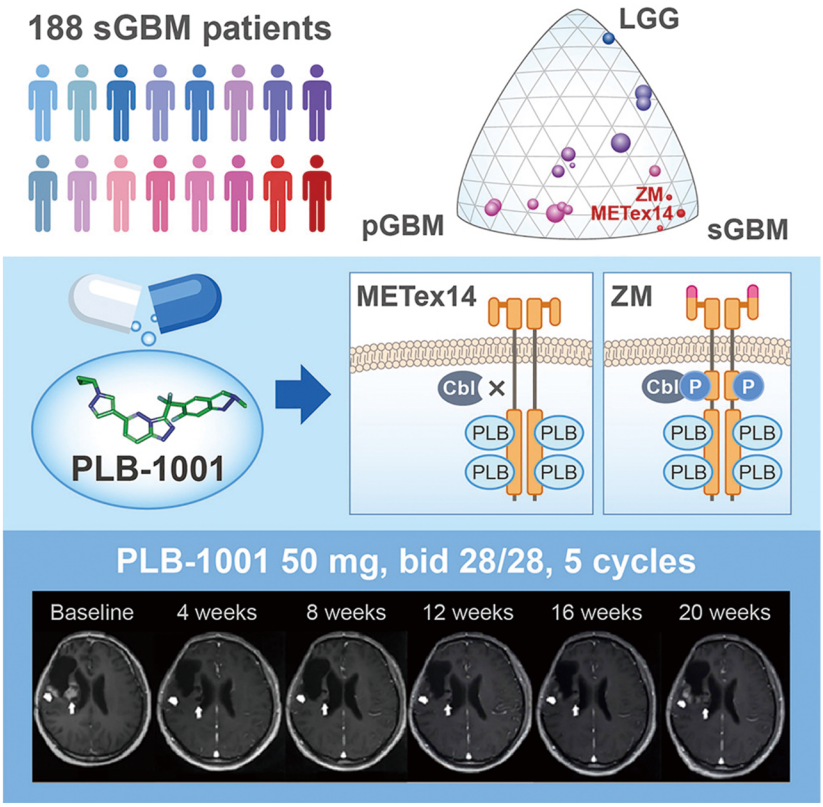
Published in Cell

Mutational Landscape of Secondary Glioblastoma Guides MET-Targeted Trial in Brain Tumor



Background

Grade IV gliomas, or glioblastoma(GBM), can be further classified into primary GBM (pGBM) and secondary GBM (sGBM). Mostly *IDH* wild-type, pGBM is *de novo* developed and commonly found in the elderly. In contrast, sGBM typically affects younger patients and progresses from low-grade diffuse astrocytoma or oligodendroglioma within 5–10 years of diagnosis. The limitations in current chemotherapy using temozolomide (TMZ), which functions by nonselective DNA damage, includes side effects and chemo-resistance. Under this therapy, almost all patients will recur, and the recurrent tumors usually carry distinct alterations that might lead to drug-resistance. To improve glioma treatment, it is essential to identify new oncogenic alterations and design therapies to specifically target them.

Research Pipeline

- 108 newly collected sGBM patient samples from AGGA
- 80 published datasets

1 Samples

- hWES libraries
- Targeted region sequencing libraries (272 genes)
- mRNA sequencing libraries

2 Library preparation

- Illumina Hiseq 4000 platform

3 Sequencing

- Copy number alteration analysis
- Hypermutation detection
- Detection of gene fusions from RNA sequencing
- Detection of *METex*14 from RNA sequencing
- Definition of sGBM specificity
- Gene expression analysis and GSEA
- Immune cell gene signature

4 Bioinformatics analysis

Substantial promotions for Human Whole Exome Sequencing and other services available. Contact us to find out more.

916-252-0068-383 inquiry_us@novogene.com en.novogene.com

Only for North and South America

Results

1. Comparing the mutational landscape of sGBM with that of LGG and pGBM reveals highly enriched *MET* alterations, including *MET* exon 14 skipping (*METex14*) and *PTPRZ1-MET* (ZM) fusion, in sGBM.

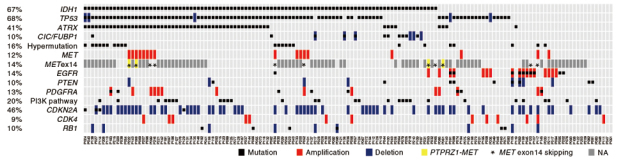


Figure 1. Mutational landscape of secondary glioblastoma

2. Functional studies of *MET* alterations in cell lines and xenografts demonstrated hyper-activation of MET signaling pathway and acceleration of tumor proliferation.

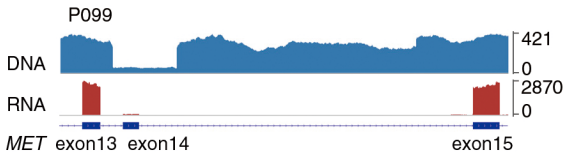


Figure 2. MET exon 14 skipping promote MET overexpression and hyperactication of MET signalling

3. A MET-specific inhibitor, PLB-1001, was characterized and demonstrated effective suppression of MET-induced glioma progression in cell lines and xenografts.

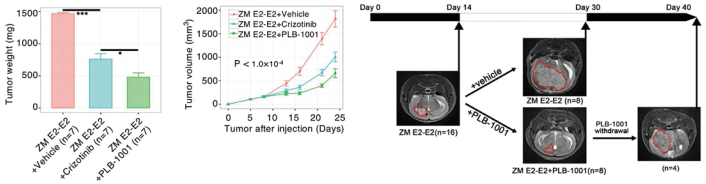


Figure 3. PLB-1001 treatment results in a significant reduction in the growth of ZM-harboring U87 MG xenografts

4. Phase I clinical trial of PLB-1001 monotherapy demonstrated a safety profile for patients with ZM fusion and/or *METex14*.

Conclusion

This collaborative study between Hu et al and Novogene describes the comprehensive somatic mutation landscape of sGBM and characterizes a small molecular inhibitor, PLB-1001, with high potency and specificity for the MET kinase domain as a promising therapeutic for patients with *MET* alterations.

Reference:

Hu et al., Mutational Landscape of Secondary Glioblastoma Guides MET-Targeted Trial in Brain Tumor [J]. Cell, 2018, 175: 1–14.

Other Novogene Powered Literature

Year	Journal	Title
2019	*BMC Genetics*	Characterization of the extra copy of TPOX locus with tri-allelic pattern
2018	*International Journal of Cancer*	Preliminary exploration of potential molecular therapeutic targets in recurrent and metastatic parathyroid carcinomas
2018	*PLoS One*	The genetic component of preeclampsia: A whole-exome sequencing study
2018	*European Respiratory Journal*	Germline BMP9 mutation causes idiopathic pulmonary arterial hypertension
2018	*Cancer Research*	Multiregion Sequencing Reveals the Genetic Heterogeneity and Evolutionary History of Osteosarcoma and Matched Pulmonary Metastases
2018	*International Journal of Cancer*	Characteristics of genomic alterations of lung adenocarcinoma in young never-smokers
2018	*PNAS*	Identification of genetic risk factors in the Chinese population implicates a role of immune system in Alzheimer's disease pathogenesis
2018	*Nature Communications*	Whole-exome sequencing reveals the origin and evolution of hepato-cholangiocarcinoma

Novogene Corporation Inc.
8801 Folsom Blvd #290, Sacramento, CA 95826
General Inquiry: 916-252-0068-383 Academic/Government Inquiry: inquiry_us@novogene.com