16P- How to translate what we learned from Gaucher's disease into new treatments for brain cancer

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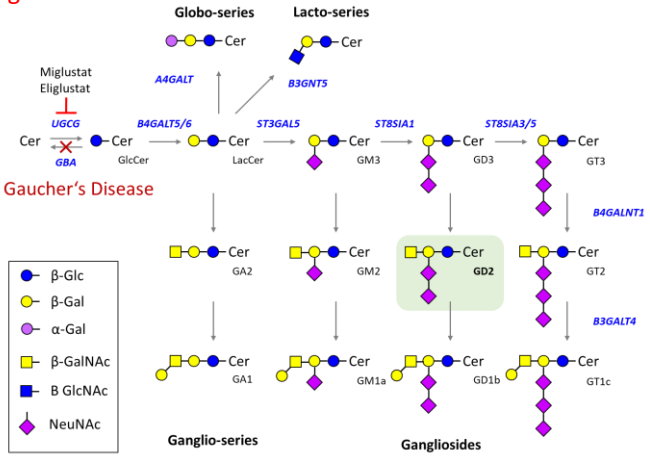
Hypothesis: H3K27M mutant diffuse midline glioma (H3K27M mut) is a lethal brain tumor entity affecting primarily children. Due to the major role of Glycosphingolipids (GSLs) in brain development and brain tumors, we hypothesized that GSLs are deregulated in H3K27M mut and represent a new therapeutic target.



Glycosphingolipids of the brain

Glycosphingolipids (GSLs) consist of a ceramide (Cer) backbone linked to a glycan moiety. Biosynthesis begins with the formation of glucosylceramide (GlcCer) from ceramide. This step is catalyzed by the glucosylceramide synthase (UGCG), which is inhibited by the small molecular compounds Eliglustat and Miglustat. Lysosomal degradation of GSLs is a stepwise process leading finally again to GlcCer, which is cleaved by lysosomal glucocerebrosidase (GBA). Deficiency of GBA causes the lysosmal storage disease Gaucher's Disease. Substrate deprivation therapy with Eliglustat or Miglustat by inhibiting UGCG is one possibility to treat Gaucher's Disease. It should also reduce brain tumor GSLs.

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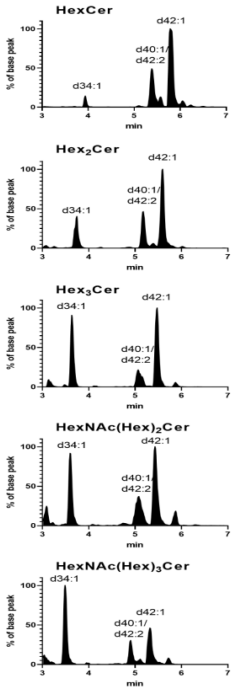
GSL composition suggests an embryonic origin of H3K27M mut

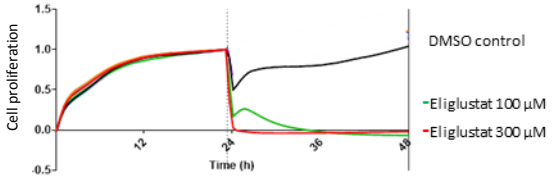


The composition of GSLs in H3K27M mut was analyzed by Mass spectrometry

	Embryo Brain	Adult Brain	H3K27M mut
GlcCer			
Globo-series			
Lacto-series			
Ganglio-series			
GM3/GD3			
GD2			
GT1b/GD1b			
GM1			

GSLs composition in normal brain and H3K27M mut. Red indicates high expression, green low expression

The inhibition of GSL synthesis via eliglustat is lethal



Primary H3K27M mut cells were incubated with eliglustat or vehicle. Proliferation was measured using the XCelligence device

Conclusions: H3K27M mut shows a GSL profile typical of proliferative embryonic cells. The inhibition of GSL synthesis is lethal for H3K27M mut primary cells. Because such inhibitors are already used for treating patients with Gaucher's disease, a rapid access of H3K27M mut patients to new innovative clinical studies is possible.