Rapidly proliferating tumour cells preferentially use aerobic glycolysis over oxidative phosphorylation (OXPHOS) to support growth and survive unfavorable microenvironment conditions. This metabolic reprogramming is referred to as the Warburg effect and offers a novel way to target cancer cells. We previously demonstrated that the glycolytic enzyme hexokinase 2 (HK2) is crucial for the Warburg effect in human glioblastoma multiforme (GBM), the most common malignant brain tumor. HK2 has little to no expression in normal brain making it an attractive target for targeting the Warburg effect. However, no direct inhibitor of HK2 exists so we explored whether a system biology approach to identify gene networks regulated by or associated with HK2 that could lead to promising treatment strategies. Using HK2 knockdown by siRNA in established GBM cell lines and primary GBM cultures we established gene signatures and networks associated with HK2 expression, identifying over 1000 genes with a 2 fold change with p-value <0.01. Loss of HK2 led to attenuation of several pro GBM signaling pathways affecting tumour cell invasion, glucose metabolism and proliferation. Using a small drug screen we identified the azole class of antifungals as inhibitors of tumour metabolism by reducing proliferation, lactate production, glucose uptake in GBM cells but not primary normal human astrocytes or normal neural stem cells. Interestingly, several antifungal Azole compounds were more potent at killing GBM cells in hypoxic conditions. Current work is focused on the in vivo efficacy of these azole compounds in pre-clinical orthotopic xenograft mouse models and transgenic models of GBM. In summary, the azole class of antifungals may represent a new way of targeting tumour metabolism in tumours dependent on aerobic glycolysis.