**DUAL TARGETING OF EPH-EPHRIN SYSTEM AND VEGFR INHIBITS TUMOR GROWTH AND INCREASES SURVIVAL IN GLIOBLASTOMA**

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The Eph receptors represent the largest family of receptor tyrosine kinases (RTK) in humans. They are divided in 2 classes, EphAs and EphBs, based on sequence homology of extracellular domain and their affinity for ephrin ligands, proteins tethered to the cell membrane by either glycosylphosphatidyl-inositol linkage (ephrin-As) or a transmembrane domain and cytoplasmic tail (ephrin-Bs). In the last two decades several Eph receptors and ephrin ligands have been found deregulated in many solid tumors including gliomas, where signaling mediated by this system was shown to keep tumor propagating cells (TPC) in a stem-like state. Moreover Eph-ephrin signaling has a key role in tumor angiogenesis and is involved in the main mechanisms of the tumor antiangiogenic therapy escape: vascular co option and vasculogenic mimicry (VM). Finally, antiangiogenic therapies, exacerbating hypoxia in tumor microenvironment, may drive tumor progression toward a more aggressive and metastatic phenotype in which ephrin system plays a prominent role. For all these reasons Eph receptors and ephrin ligands represent a promising target in cancer therapy. Since 2009 our research group has been discovering and developing molecules able to interfere with this system and UniPR1331, an aminoacid conjugate of 3β-hydroxy-Δ5-cholenic acid, represent the most promising molecule identified so far. Here we evaluated the efficacy of UniPr1331 in the treatment of glioblastoma (GBM), in which antiangiogenic therapy has shown to be promising but of insufficient efficacy. Then we validated UniPr1331 as anti-vasculogenic molecule by using in vitro and in vivo assays such as HUVEC and U87MG tube formation assays and chick chorioallantoic membrane assay (CAM). Next pharmacokinetic studies showed UniPR1331 oral bioavailability and its ability to reach the central nervous system. Therefore UniPR1331 was tested in xenografts and in an orthotopic tumor model of GBM using U87MG and TPC cells. Daily orally administration of UniPR1331 30mg/kg was able to inhibit tumor growth in both models. Notably Disease Free Survival and Overall Survival were synergistically increased when UniPR1331 was tested in combination with bevacizumab or sunitinib. In conclusion our data showed that UniPR1331 may represent a novel and promising therapeutic strategy in GBM treatment increasing the efficacy of standard VEGF- based anti-angiogenetic therapies.