

CP-673451 for glioblastoma recurrence

CP-673451 is a potent inhibitor of platelet-derived growth factor beta-receptor (PDGFRB) kinase- and PDGF-BB-stimulated autophosphorylation of PDGFR-beta in cells ($IC_{50} = 1 \text{ nmol/L}$) being more than 450-fold selective for PDGFR-beta versus other angiogenic receptors (e.g., VEGF receptor 2, TIE-2, and fibroblast growth factor receptor 2). Multiple models have been used to evaluate in vivo activity of CP-673,451 and to understand the pharmacology of PDGFR-beta inhibition and the effect on tumor growth. These models include an ex vivo measure of PDGFR-beta phosphorylation in glioblastoma tumors, a sponge model to measure inhibition of angiogenesis, and multiple models of tumor growth inhibition. Inhibition of PDGFR-beta phosphorylation in tumors correlates with plasma and tumor levels of CP-673,451. A dose of 33 mg/kg was adequate to provide >50% inhibition of receptor for 4 hours corresponding to an EC_{50} of 120 ng/mL in plasma at $C(\max)$. In a sponge angiogenesis model, CP-673,451 inhibited 70% of PDGF-BB-stimulated angiogenesis at a dose of 3 mg/kg (q.d. x 5, p.o., corresponding to 5.5 ng/mL at $C(\max)$). The compound did not inhibit vascular endothelial growth factor- or basic fibroblast growth factor-induced angiogenesis at concentrations that inhibited tumor growth. The antitumor efficacy of CP-673,451 was evaluated in a number of human tumor xenografts grown s.c. in athymic mice, including H460 human lung carcinoma, Colo205 and LS174T human colon carcinomas, and U87MG human glioblastoma multiforme. Once-daily p.o. x 10 days dosing routinely inhibited tumor growth ($ED_{50} < \text{or } = 33 \text{ mg/kg}$). These data show that CP-673,451 is a pharmacologically selective PDGFR inhibitor, inhibits tumor PDGFR-beta phosphorylation, selectively inhibits PDGF-BB-stimulated angiogenesis in vivo, and causes significant tumor growth inhibition in multiple human xenograft models¹⁾.

Differentiation therapy has been proposed as an alternative for glioblastoma treatment, with the aim of bringing cancer cells into a post-mitotic/differentiated state, ultimately limiting tumor growth. As an integral component of cancer development and regulation of differentiation processes, kinases are potential targets of differentiation therapies.

Lane et al. in a study describe how the screening of a panel of kinase inhibitors (KIs) identified PDGF-R α/β inhibitor CP-673451 as a potential differentiation agent in glioblastoma. They show that targeting PDGF-R α/β with CP-673451 in vitro triggers the outgrowth of neurite-like processes in glioblastoma cell lines and glioblastoma stem cells (GSCs), suggesting differentiation into neural-like cells while reducing proliferation and invasion in 3D hyaluronic acid hydrogels. In addition, they report that treatment with CP-673451 improves the anti-tumor effects of temozolomide in vivo using a subcutaneous xenograft mouse model. RNA sequencing and follow-up proteomics revealed that upregulation of phosphatase DUSP1 and consecutive downregulation of phosphorylated-p38 mitogen-activated protein kinases can underlie the pro-differentiation effect of CP-673451 on Glioblastoma cells. Overall, the present study identifies a potential novel therapeutic option that could benefit Glioblastoma patients in the future, through differentiation of residual GSCs post-surgery, with the aim of glioblastoma recurrence treatment and improve quality of life²⁾.

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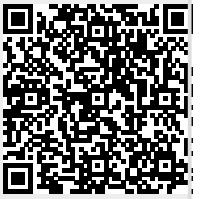
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