Platelet-derived growth factor receptor

Platelet-derived growth factor receptors (PDGF-R) are cell surface Receptor tyrosine kinase for members of the platelet-derived growth factor (PDGF) family. PDGF subunits -A and -B are important factors regulating cell proliferation, cellular differentiation, cell growth, development and many diseases including cancer.

There are two forms of the PDGF-R, alpha and beta each encoded by a different gene.

see Platelet derived growth factor receptor A.

Depending on which growth factor is bound, PDGF-R homo- or heterodimerizes.

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 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) < or = 33 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 models [1)].

DNA Methylation of the PDGFD Gene Promoter Increases the Risk for Intracranial Aneurysms and Brain Arteriovenous Malformations [2)].

Current standard treatment for glioma patients is surgical removal followed by radiotherapy and adjuvant chemotherapy. Due to therapeutic resistance and tumor recurrence, efforts are ongoing to identify the molecules that are fundamental to regulate the tumor progression and provide additional methods for individual treatment of glioma patients. By studying the initiation and maintenance of glioma, studies focused on the targets of tyrosine kinase receptors including EGFR, PDGFR and other crucial signal pathways such as PI3K/AKT and RAS/RAF/MAPK pathway. Furthermore, recent advances in targeting immunotherapy and stem cell therapy also brought numerous strategies to glioma

treatment [3].

1)
Roberts WG, Whalen PM, Soderstrom E, Moraski G, Lyssikatos JP, Wang HF, Cooper B, Baker DA, Savage D, Dalvie D, Atherton JA, Ralston S, Szewc R, Kath JC, Lin J, Soderstrom C, Tkalcevic G, Cohen BD, Pollack V, Barth W, Hungerford W, Ung E. Antiangiogenic and antitumor activity of a selective PDGFR tyrosine kinase inhibitor, CP-673,451. Cancer Res. 2005 Feb 1;65(3):957-66. PMID: 15705896.
2)
Zhou S, Gao X, Sun J, Lin Z, Huang Y. DNA Methylation of the PDGFD Gene Promoter Increases the Risk for Intracranial Aneurysms and Brain Arteriovenous Malformations. DNA Cell Biol. 2017 Mar 27. doi: 10.1089/dna.2016.3499. [Epub ahead of print] PubMed PMID: 28346846.
3)
Lin L, Cai J, Jiang C. Recent advances in targeted therapy for glioma. Curr Med Chem. 2016 Dec 23. [Epub ahead of print] PubMed PMID: 28019637.