Title: Investigating the Dual Targeting Mechanism of Vorapaxar as a PAR1 Antagonist and GPR17 Agonist for Glioblastoma Multiforme Therapy

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Abstract
Vorapaxar is an FDA-approved antiplatelet medication that primarily acts as an antagonist of the protease-activated receptor 1 (PAR1). In Glioblastoma multiforme (GBM), the PAR1 receptor promotes tumor formation, invasion, and angiogenesis, whereas the G protein-coupled receptor 17 (GPR17) is associated with tumor recurrence. GBM is defined by the aberrant activation of several signaling pathways, including those controlled by PAR1 and GPR17. The present work aims to evaluate vorapaxar's binding selectivity to both receptors in GBM cells. We have shown that GPR17 and PAR1 are not only phylogenetically related, but also have structurally similar ligand binding sites, which leads to adenylyl cyclase inhibition and increased intracellular calcium. A docking model of Vorapaxar-PAR1 and Vorapaxar-GPR17 interaction was analyzed and validated using gene silencing. The release of cAMP and Ca^{+2} was monitored to confirm the dual binding activity in GBM cells. Vorapaxar acts as an agonist for GPR17, increasing the quantity of secondary messenger and activates cell death signalling pathway. The current research has uncovered a previously unknown dual function of vorapaxar, which also functions as an agonist of the GPR17. Overall, Vorapaxar's dual action has significant implications for its possible repurposing in the treatment of GBM.