Development of Gefitinib Prodrugs Targeting Non-Small Cell Lung Cancer Brain Metastases via Inhibition of P-glycoprotein at the Blood-Brain Barrier

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The prognosis of non-small cell lung cancer (NSCLC) patients with brain metastases is very poor. Targeted therapeutic agents that are used as the first-line treatment of oncogene-driven NSCLC have limited effectiveness in treating brain metastases of mutant NSCLC due to efflux transporters, such as P-glycoprotein (P-gp), that limit drug penetration across the blood-brain barrier (BBB). To address this limitation, we present the development of a dimeric prodrug P-gp inhibitor based on the P-gp substrate and first-line NSCLC targeted therapeutic gefitinib. With the goal of improving gefitinib's therapeutic brain penetration, the gefitinib-based dimer **GFTB-Q** was designed to have a dual role: to inhibit P-gp efflux at the BBB and to regenerate the monomeric therapy within cellular reducing environments. **GFTB-Q** exhibited potent inhibition of P-gp-mediated efflux in cell culture, including for human brain endothelial cells. Additionally, reduction of **GFTB-Q** yielded the regeneration of its monomeric components, validating its design as a dimeric prodrug inhibitor of P-gp.