Effective Evasion of Chemotherapeutic Resistance by Functionalized Viral Capsid QB

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Multidrug resistance (MDR) drastically curbs treatment success in cancers and other systemic diseases. A membrane pump overexpressed in tumors, Pgp, renders cancer cells ‘resistant’ to our world’s strongest chemotherapeutics by readily exporting them upon uptake. Nanomaterials functionalized with drugs, or nanocarriers, show first steps in evading MDR by entering cells via active mechanisms. However, they still critically lack in stealth from Pgp, intracellular trafficking to target sites, and drug release. Viral capsids, nanocarriers not used to bypass MDR, suggest a promising upgrade because of their innately distinct endocytic pathway. To test this proposal, bacteriophage QB’s capsid, chosen for its favorable uptake properties, was purified from E. coli, functionalized interiorly with ~360 chemotherapeutic doxorubicin molecules via an original, acid-sensitive linker, and characterized proteomically. To analyze this novel nanocarrier (fQB)’s distinction from 3 types of nanocarriers currently in use to combat MDR, AutoDockVina first concluded that fQB is the stealthiest of all tested, possessing a significantly less favorable binding energy and electrostatic affinity to Pgp. Custom-created spatiotemporal simulations modelling the carriers’ unique endocytic mechanisms then indicated that fQB’s trafficking into both an MCF-7 tumor cell and its nuclear target is more expedient than that of the other carriers, as derived through uptake rate. Solution-state-kinetics further revealed fQB’s impressive 90% drug release in ~15 minutes at a convenient endosomal pH. Cell studies are in progress to corroborate these encouraging findings. This developed viral nanocarrier is an incredibly promising drug-delivery platform for improved evasion of MDR in cancer and diseases beyond.

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