Lipid Facilitated PDAC Stroma Transmission: Overcoming the Desmoplastic Stroma Through Advanced Drug Delivery, in vivo

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Constituting up to 90% of tumor volume in pancreatic ductal adenocarcinoma (PDAC), fibrotic tissue growth (desmoplasia) acts to inhibit chemotherapeutic drug delivery through physical blockage and non-porous structure. To overcome this inhibition, prior research has shown that controlled enzymatic degradation can improve drug penetration and activity, most notably of tyrosine kinase inhibitors (TKIs), although while risking substantial off-target damage. This study evaluated small unilamellar vesicle (SUV) encapsulation to: (1) minimize collateral effects, (2) extend therapeutic activity, and (3) enhance tissue specificity for mediating such side effects. In alignment with these factors, three tests were conducted in various PDAC models. In calcium alginate hydrogel models simulating desmoplastic tissue, pH-sensitive liposomes (DOPE:OA:cholesterol) selectively released lytic contents in acidic regions (pH 6.4), reducing non-target destruction by 72% compared to free molecule delivery. In decapitated planarian (Girardia tigrina) models, XAV-939-loaded liposomes inhibited tissue regeneration by 44% longer than free drug application at 144 hours, demonstrating prolonged activity. Glycine-functionalized fluorescent liposomes exhibited 8.5% higher peak concentration in targeted, neuron-rich structures of planarian models, mainly the cerebral ganglia, and 89% greater regional specificity compared to non-functionalized liposomes. Considering the tissue specific characteristics of PDAC tumors, most notably localized acidity and epidermal growth factor receptor (EGFR) overexpression, these factors outline strong potential for the efficient, targeted delivery of lytic enzymes to PDAC.

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