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QUANTIFYING THE IMPACT OF FOCUSED ULTRASOUND INDUCED BLOOD-TUMOUR BARRIER DISRUPTION ON ANTICANCER AGENT TRANSPORT

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The blood-brain and blood-tumour barriers (BBB and BTB) constitute major obstacles to the transport of therapeutics in brain tumours [1]. In recent years, increased efforts have focused on identifying strategies to improve the delivery of therapeutics to them [2]. Mathematical modelling is an important tool for elucidating the mechanisms governing drug pharmacokinetics (PK) [3]. However, methods for proper integration of mathematical models and experimental data capable of quantifying both agent- and cell-line-specific parameters are limited. Here, we quantified the impact of focused ultrasound (FUS) therapy on the transport of doxorubicin (DOX) and ado-trastuzumab emtansine (T-DM1) across the BTB in an animal model of brain metastasis with attention to the effect of structural heterogeneity on transport.

A novel procedure was devised to parameterise PK models (reaction-convection-diffusion in a tumour cord) with experimentally measured drug PK for both agents. For DOX, only the vessel effective diffusion coefficient (4.3-fold increase, p=0.002) and the hydraulic conductivity (4.5-fold increase, p=0.006) were significantly increased after FUS-BTB disruption. The interstitial Peclet number increased from (Mean ± SEM) $Pe_{non\text{-}FUS} = 1.01\times10^{-1} \pm 2.75\times10^{-2}$ to $Pe_{FUS} = 22.15 \pm 15.45$ after treatment, providing quantitative confirmation of the shift from diffusive- to convective-dominated drug transport. For T-DM1, only the hydraulic conductivity (2.7-fold increase, p=0.003) was significantly increased post treatment.

To study the influence of tumour structural heterogeneity on drug transport after FUS-BTB disruption we employed a percolation model [3] parameterised with the previous agent- and cell-line-specific model parameters. In the FUS-treated group, apart from significantly higher drug penetration and uptake, we observed lower spatial drug gradients. The degree of perfusion in different parts of the network had a substantial impact on interstitial drug PK. Most notably, at low perfusion vessels, T-DM1 had very low extravasation (convection-dominated transport), whereas DOX had very high extravasation (diffusion-dominated).

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