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Extracellular vesicle/prodrug-mediated specific treatment of HER2+ve breast cancer xenografts in mice

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This talk is concerned with therapeutic uses of EVs (exosomes) and deals with gene-delivered enzyme prodrug therapy (GDEPT), which promises to confine drug generation to the tumor at a high concentration and mitigating off-target effects. A new prodrug [6-chloro-9-nitro-5-oxo-5Hbenzo-(a)-phenoxazine (CNOB)] and the Escherichia coli enzyme HChrR6 that we discovered, and improved, and our recent success in specifically targeting it to implanted orthotopic HER2+ve breast cancer (BC) tumors in mice will be discussed; HChrR6 converts the harmless CNOB to the highly cytotoxic drug, 9-p amino-6-chloro-5H-benzo[a]phenoxazine-5-one (MCHB). As mRNA is superior to DNA for gene delivery and EVs less subject to immune rejection, mRNA encoding the HCHrR6 enzyme-loaded EVs that displayed an anti-HER2 scFv antibody (on a chimeric protein termed EVHB) were used. These "EXO-DEPT" EVs–but not the non-directed, non-mRNA containing EVs-imparted CNOB activating capability specifically on the HER2+ve BT474 cells *in vitro* and caused the complete arrest of implanted orthotopic BT474 tumors in immunocompromised mice. This is the first time that foreign functional mRNA was successfully delivered using EVs4. As the anti-HER2 scFv in EVHB can be replaced by other targeting moieties, this approach can be employed to treat any disease overexpressing a specific marker. In vivo ablation of the tumor is a potent method for stimulating robust HER2-specific adaptive T- and B-cell responses. Results will be presented of ongoing work in collaboration with Dr Kim Lyerly (Duke University) on the reinforcing effect of this response on the efficacy of the EXODEPT/CNOB regimen. A BC mouse model driven by an oncogenic form of human HER2 (HER2Δ16) is being used. It relies on mammary-specific expression of HER2Δ16, leading to aggressive breast tumor development within weeks of induction, with strong central tolerance to the HER2Δ16 epitope. Measurements underway involve HER2-specific systemic T-cell responses (T-cell ELISPOT assays from harvested splenocytes; assessment of cytokine flow), tumor regression and mouse survival.

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