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Abstract - Master Thesis Project, the Pharmacy Programme

PEG-based paclitaxel brush polymer: a novel nanoscopic conjugate targeting breast cancer treatment

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Introduction: Nanoscopic drug delivery systems became eye-catching for cancer treatment due to their increased solubility and reduced toxicity, as well as improved accumulation in tumor tissue. Here we evaluated the cytotoxic and inhibitory effect of a pH-labile nanostructure made of a brush polymer (BP) with Paclitaxel (PTX) cytostatic moiety. We hypothesized that this nanomedicine will achieve greatly improved chemotherapeutic effect on breast cancer (BC) cells.
Methods: BP-PXTL was synthesized via ring-opening metathesis polymerization (ROMP) of norbornene (NB)-functionalized PTX and PEG (NB-PTX; NB-PEG). As control samples, PEG-based BP was prepared by ROMP of NB-PEG; fluorescent-labeled BP-PXTL and BP were similarly prepared. Solubility testing and the pH-induced PTX release behavior of BP-PXTL was monitored by chromatography, electrophoresis and UV fluorescence under different pH conditions. Hs578T human cells as well as various mouse cell lines (4T07, 67NR, 4TMiller, 4TMillerLP), all originating from BC, were used in the evaluation of drug penetration, and effect on viability, proliferation, and cytotoxicity.
Conclusions: Despite significantly increased drug-loading capacity (24 w%), expected water-solubility of >40mg/ml in aqueous solutions was not confirmed in our hands at room temperature. Our data show max drug accumulation after 5-9h exposure to 0.33µg/µl drug. Cytotoxicity and cell viability assays, measuring LDH release and respectively total ATP, showed enhanced toxic effects of BP-PTX on more aggressive, metastatic cancer cells (T4Miller) than non-metastatic cancer cells (Hs578T, 67NR, 4T07). Potentially, this enhanced nanoscopic structure may provide added benefit in treatment of aggressive or relapsed BC. Additional data are however needed and under current investigation