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Developing Tumor-Targeted Peripherally Cross-Linked Core-Shell Polymer Micelles to Improve Cytotoxic Chemotherapy of High-Risk Neuroblastoma

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Neuroblastoma (NB) is a relatively rare, solid tumor that is the primary cause of death for pediatric cancer patients between the ages 1 and 5. Children with high-risk NB make up at least half of the ~600 newly diagnosed cases each year with long-term survival of ~40 to 50% despite aggressive treatment. Children that survive after aggressive treatment are also at higher risk for treatment-related complications later in life. Thus, there is an urgent need to improve the safety and efficacy of therapies for high-risk NB. High dose cytotoxic chemotherapy is a critical part of induction and consolidation therapy for high-risk NB. The optimal dose intensity (mg/m2/week), however, is often decreased by drug-related side effects and inadequate patient recovery between treatments. Physical encapsulation in core-shell polymer micelles is a promising approach to potentially decrease drug toxicity and increase drug potency in solid pediatric and adult tumors. Physically encapsulated drug, however, may be prematurely released from polymer micelles after i.v. administration. We previously found that cross-linking peripheral functional groups on the surface of F127 core-shell polymer micelles ("peripheral cross-linking") decreases premature release of physically loaded Combretastatin A4 in human whole blood, decreases distribution to the heart, liver, lungs, and kidneys, and increases potency against primary murine syngeneic 4T1 breast tumors after i.v. administration. As such, encapsulation in peripherally cross-linked core-shell polymer micelles (PX-PM) is expected to improve high dose cytotoxic chemotherapy. Historically, nitrogen mustard alkylating agents have been used to treat high risk NB. Here, we encapsulated the hydrophobic mustard alkylating agent, chlorambucil (CLB), at 25 wt% in F127 polymer micelles (PM) or in F127 PX-PM peripherally cross-linked at 66%. We found that peripheral cross linking did not increase the hydrodynamic diameter, whereas CLB loading increased the hydrodynamic diameter of both PM and PX-PM. Our lyophilized formulations were found to be most stable after being brought to room temperature, stirred, and then equilibrated to physiological temperature for 1 hour. Peripheral cross-linking decreased potency of encapsulated CLB slightly in MDA-MB-231 cell lines compared to unencapsulated CLB from 6 uM (CLB) to 30 uM (PX-PM). In the future, we will do work on how peripherally cross-linking polymer micelles affects toxicity.