Developing hyperbranched polyglycerol-based nanoparticles for targeted delivery of radiosensitizers

Mohamed K. Khan (MD Anderson Cancer Center, USA), Nelson K. Y. Wong (BC Cancer Research Centre, Canada), Ripen Misri (BC Cancer Research Centre, Canada), Rajesh A. Shenoi (University of British Columbia, Canada), Irina Chafeeva (University of British Columbia, Canada), Jayachandran N. Kizhakkedathu (University of British Columbia, Canada)

BACKGROUND: Radiosensitizers, such as taxanes and gemcitabine, are already used to enhance radiotherapy. The accumulation of small molecule radiosensitizers at the tumors is often limited by their pharmacokinetics and toxicity to normal tissues. We have developed a novel nanotechnology platform for tumor-targeted delivery of radiosensitizers to limit the toxicity of the delivered drug, enhance the drug accumulation at the tumors, and improve tumor cell kill. Hyperbranched polyglycerol-based nanoparticles (HPG NPs) were originally developed as plasma expanders. We developed this nanoplatform due to many favorable characteristics: including excellent safety profile, lack of immunogenecity, ease of synthesis, modifiable surface functional groups, and patent protection from our collaborators.

HYPOTHESIS: We hypothesize that chemical modifications of HPG NPs can affect their in vitro and in vivo behaviors and lead to the design of HPG NP as nanocarriers of chemo-radiosensitizers with greatly improve therapeutic ratio.

METHODS: Three HPG NP variants were synthesized and characterized. These include HPG-C_{10}-PEG that contains a hydrophobic core composed of C_{10} alkyl chains and a polyethylene glycol (PEG) shell, HPG-C_{10}-HPG that contains a similar C_{10} core with a hydrophilic HPG shell, and HPG-104 that is composed entirely of HPG with no hydrophobic core or PEG. These unimolecular nanoparticles are ~ 5-6 nm in hydrodynamic radius and ~ 100 kDa in molecular weight. The ability of the C_{10} core to hold and release a radiosensitizer, docetaxel (DTX), was assessed. The in vitro toxicities of these HPG NPs were assessed with primary human cell lines. The cytoxicities of the HPG NP drug formulations were also assessed with various human cancer cell lines. Tritium-labeled HPG NPs were also injected into tumor bearing mice to assess their biodistribution patterns.

RESULTS: The HPG NPs were well-tolerated by the primary cell lines. When DTX was loaded into HPG-C_{10}-PEG and HPG-C_{10}-HPG, slow and sustained release of the drug was observed at 37 ^{o}C in PBS. Results for cytotoxicity assays with DTX-loaded HPG NPs revealed that cancer cells were killed more effectively with the nanoparticle formulations, suggesting specific delivery of the drug to cancer cells. When injected intravenously in tumor-bearing mice, HPG-C_{10}-HPG accumulated substantially in the liver and the spleen, while the presence of PEG shell in HPG-C_{10}-PEG or absence of C_{10} in HPG-104 significantly decreased the levels of their accumulation at these organs. The accumulation of these HPG NPs in the tumors range from 3-5 % injected dose/g at 24 and 72 h post-injection. Tumor-to-normal tissue accumulation ratios of these HPG NPs indicate differential affinities to various organs, presenting a potential to widen the therapeutic index even more through organ-specific accumulation or avoidance. In conclusion, we have gained insights into how certain chemical modifications affect the in vivo distribution of these HPG NPs. Moreover, hydrophobically derivatized HPG NPs were able to hold and release DTX, a radiosensitizer with an excellent biodistribution profile. These observations support the development of HPG NPs as safe nanocarriers of chemo-radiosensitizers with greatly improved therapeutic ratios due to improved tumor/organ spatial localization as well as tumor/normal cell kill characteristics.