105. Development of Radiolabeled Antibody-Targeted Gemini Nanoparticles for Melanoma

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Purpose: Malignant melanoma is the sixth most commonly diagnosed cancer and the most lethal form of skin cancer with limited treatment options. Nanotechnology is of one of the promising options to improve diagnosis and therapeutic outcome for melanoma. Gemini surfactants self-assemble into nanoparticles which can be decorated with monoclonal antibodies to selectively deliver alpha emitters (theoretically the most cytotoxic form of radiation) to tumour cells that overexpress the targeted surface antigens.
Methods: A pair of radiopharmaceuticals was selected to conjugate to the nanoparticles using the same chelating moiety: Actinium 225 as the alpha emitter and Indium 111 as radiotracer for SPECT/CT monitoring. The serum stability of the Indium 111 nanoparticles was measured by radiometry. Cellular binding and uptake in melanoma cell line were determined by flow cytometry and radiometry. Pharmacokinetic parameters were measured in nude mice.
Results: Indium 111-labeled nanoparticles show high stability in biological environment; less than 10% radionuclide dissociated in a week.
Cellular targeting studies showed that the cellular uptake of the antibody labeled nanoparticles is a specific uptake, as it could be blocked by pretreatment with free antibody. The non-targeted nanoparticles attached non-specifically to the cell surface and showed no difference from the targeted nanoparticles in binding. However, cellular internalization of the targeted nanoparticles was significantly higher than the non-targeted nanoparticles. Pharmacokinetic study in nude mice revealed a significant difference ($P < 0.05$) in the AUC, Vd and Cl_s of the antibody targeted 111In nanoparticles compared to the non-targeted nanoparticles. The half-lives were not significantly different.
Conclusion: The antibody-conjugated gemini nanoparticles are more effective in binding to the cell surface, internalizing, and penetrating the nucleus of melanoma cells than the non-targeted nanoparticles. They also show promising pharmacokinetic properties when used on nude mice models.
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106. Aptamer-based Liposomes to Improve the Specificity, the Drug Loading and the Release

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Purpose: Liposome technology is limited by poor encapsulation of the drugs. In this study, we demonstrate that drug-binding aptamers can actively load drugs into liposomes (Figure 1). We designed a series of DNA aptamer sequences specific to doxorubicin, displaying multiple binding sites and various binding affinities. The impact on drug loading, drug release and therapeutic efficacy was investigated. This proof-of-concept was first demonstrated with doxorubicin and applied to tobramycin, a hydrophilic drug suffering from low encapsulation into liposomes.
Methods: Cationic liposomes (DOTAP/cholesterol/ DSPE-PEG_{2000}) were incubated with designed aptamers at various charge ratios to form lipoplexes. Aptamer encapsulation efficiency and stability was determined by fluorescence assay. The drug loading capacity was determined by fluorescence after incubation at various aptamer/drug ratios, for doxorubicin and tobramycin-Cy5, respectively. In *vitro* release of doxorubicin from lipoplexes was studied at pH 5 and pH 7.4. *In vitro* therapeutic efficiency was evaluated by cell viability measurements on HeLa cells.
Results: The aptamers displayed an affinity constants ranging from 68 to 380 nM for doxorubicin, and 1.15 μM for tobramycin, showing the specificity of the aptamer sequence to the drug. The binding ability of aptamers was preserved when incorporated into cationic liposomes, and resulted in a 16 and 6-fold improvement of encapsulation