

NANOPARTICLES FOR TARGETED DELIVERY OF ANTICANCER AGENTS

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The first part of the lecture will be focused on the targeted delivery of glucocorticoids. Glucocorticoids are highly effective anti-inflammatory drugs, but have also been investigated as anti-angiogenic agents in the early '80s. Antitumor activity was observed in experimental animals, but only when the corticosteroids were administered frequently and in high doses. The need for such an intensive treatment schedule is associated with side effects, which has precluded further clinical development of corticosteroids as anti-angiogenic agents. As long-circulating liposomes can passively accumulate at sites of malignancy, their potential usefulness for the targeted delivery of glucocorticoids will be highlighted. The results obtained in a variety of animal models of cancer are promising and warrant further investigation of liposomal glucocorticoids as novel antitumor agents [Schiffelers, R.M. *et al.* **Neoplasia** 7 (2005) 118].

Vascular targeting offers therapeutic promise for the delivery of a broad spectrum of agents. An RDG peptide that targets alpha v beta 3 integrins overexpressed on angiogenic endothelial cells was coupled to the surface of poly (ethylene glycol) (PEG)-coated liposomes. We aimed at obtaining a stable multivalent nanoparticulate delivery system with a favorable pharmacokinetic profile and high drug payload capacity functioning as a platform for display of RGD peptides. Specific binding of the RGD-targeted liposomes to angiogenic endothelial cells was demonstrated *in vivo* in several animal models of cancer. Marked therapeutic effects were observed when the anthracycline doxorubicin or the corticosteroid prednisolone phosphate (PP) were encapsulated [Schiffelers, R.M. *et al.* **J. Contr. Release** 91 (2003) 115]. For the vascular targeting of siRNA [Schiffelers, R.M. *et al.* **Expert Opin. Biol. Ther.** 5 (2005) 359], RGD-peptide was coupled to the cationic polymer poly(ethylene) imine (PEI) via a PEG spacer. In the presence of siRNA, the RGD-PEG-PEI self-assembles into a nanoparticle with a core formed by an electrostatic complex between siRNA and PEI exposing RGD-peptide on the surface. Incorporated siRNA was specific for silencing of reporter genes or vascular endothelial growth factor receptor 2 (VEGFR2). Specific silencing effects and therapeutic efficacy mediated by this polymeric vascular targeting system were achieved *in vivo* [Schiffelers, R.M. *et al.* **Nucleic Acids Res.** 32 (2004) 149].

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