1.3.2.2 Proteins as Ligands in Targeted Delivery

For the purposes of this thesis a protein is defined as a chain of more than 20 amino acids (aa). The smallest protein described being a 20 aa Trp cage motif (Neidigh et al., 2002). Molecules with less aa are considered to be peptides, discussed in Section 1.3.2.4. Compared to antibodies proteins are easier to produce, store, are less likely to be immunogenic and are easier to specifically modify. However, many protein receptors investigated have a widespread expression in the body, e.g. the transferrin receptor (Qian et al., 2002). Protein-targeted therapy has similar problems to antibody-based targeting with their endogenous activity presenting an additional challenge.

Using transferrin-targeted poly(lactide-co-glycolide) (PLGA) paclitaxel containing nanoparticles Sahoo et al. (2004) found a greater reduction in tumour size (PC3 in mice) and increased survival compared with un-targeted nanoparticles or a paclitaxel formulation Cremophore® (Sahoo et al., 2004). In contrast, although greater tumour uptake was found using transferrin-targeted palmitoylated glycol chitosan vesicles containing doxorubicin compared with that seen using un-targeted vesicles, the targeted system was less effective in terms of antitumour activity than the free drug in vivo (Dufes et al., 2004). This suggests that, as tumour targeting was successful, the release of drug from the carrier must have been poor.

uPAR has been successfully targeted using a diphtheria toxin-urokinase fusion protein which showed selective toxicity in leukaemic cell lines expressing > 5000 receptors/cell (Ramage et al., 2003). This fusion protein was tested in mice against glioblastoma tumours and found to significantly regress tumours (Vallera et al., 2002). These successful studies targeting uPAR are promising indicators for this study. Protein-based targeting employed in non-viral gene delivery is discussed in Section 1.5.3.

1.3.2.3 Saccharide-Targeted Delivery

The term saccharide encompasses a wide range of molecules from simple sugars to complex polymers. Two saccharides widely employed as targeting ligands are mannose (to target the mannose receptor on macrophages (Ferkol et al., 1996)) and galactose (to target the asialoglycoprotein receptor (ASGR) on hepatocytes (Plank et al., 1992)). This targeting method has seen some success with the only actively targeted polymer-drug conjugate to reach clinical trial: PK2, an HPMA-doxorubicin-galactosamine copolymer,