

In a similar approach we hypothesise that peptides derived from the uPA ATF binding region may have ligand properties to uPAR. Therefore, the aim of this project was to use the u7 peptide, shown by Drapkin et al. (2000) to increase adenoviral uptake, and the u11 peptide, identified from the binding region determined by Appella et al. (1987), to target the over-expressed uPAR on cancer cells and hijack its entry into the cell as a means to internalise a non-viral gene therapy.

In the study by Drapkin et al. (2000) adenovirus was modified with bifunctional PEG and the u7 peptide conjugated. These surface modified adenoviruses were applied to the surface of excised human airway epithelia and β -galactosidase expression was found to be 10-fold higher than adenovirus coated with PEG or adenovirus coated with PEG and a mutated u7 peptide (Drapkin et al., 2000). The u11 sequence was proposed by Appella et al. (1987) as essential to the binding specificity of uPA whereas the u7 sequence has homology with the EGF growth factor domain (Appella et al., 1987).

1.5 Cancer Gene Therapy

Introducing a gene to correct a defect in the genetic makeup of a cell is an attractive strategy for the treatment of many diseases including cancer. The completion of the human genome project gives us a plethora of information from which we can source targets and design therapies against them (Venter et al., 2001). With increasing knowledge, the methods employed in gene therapy are almost as varied as the diseases under attack. These include: DNA immunisation (Toda et al., 1998), GDEPT/VDEPT (Chung-Faye et al., 2001, Martiniello-Wilks et al., 2004), restoration of a cell checkpoint protein (Dolivet et al., 2002), cytokine introduction, inhibition of tumour angiogenesis, gene silencing/antisense (Brooks, 2002, Lattime & Gerson, 1999). Through the last decade the main challenge in the above mentioned therapies has been difficulties in achieving successful delivery of the genetic material through the circulation to the target tissue and then to the correct compartment of the target cell.

1.5.1 Viral Vectors in Gene Therapy

The majority of gene therapy that has progressed to clinical trials is viral (69.2 %; Fig. 1.10; (Edelstein, 2005)) with polymeric delivery agents having just arrived at the clinical setting (Ohana et al., 2004).