Current clinical trials are mainly using viral vectors for gene delivery, however it is largely believed that non-viral gene therapy will be safer. The first clinical trial using PEI-mediated gene therapy was published in 2004: poly(ethylenimine) (PEI) complexed diphtheria toxin A-chain plasmid to treat bladder cancer (Ohana et al., 2004).

Targeting specific proteins on the surface of cells for drug delivery requires the engineering of a suitable carrier bearing the appropriate ligand. In targeted drug therapies, carriers such as liposomes (Zhang et al., 2002), antibodies (Ross et al., 2004) and polymers (Duncan, 2003) have been suggested. In this study the focus was on the design of water soluble cationic polymers for targeted gene delivery. The urokinase plasminogen activator receptor (uPAR) is over-expressed in many cancers and it has a high affinity for its ligand (Blasi, 1997).

In this project the development of a peptide targeted non-viral gene delivery system based on biocompatible polymers was investigated and the chosen target was uPAR. From potential polymers, chitosan was chosen as the delivery vector due to its biocompatibility (Corsi et al., 2003, Lee et al., 2001), good transfection efficiency (Thanou & Junginger, 2004), and potential for chemical modification. The following sections of the introduction outline the background to this research starting with the need for targeted cancer therapy.

1.2 The Need for Targeted Therapy of Cancer

According to the world health organisation (WHO) cancer is responsible for six million (12%) deaths worldwide (WHO, 2005). Cancer Research UK report that cancer has recently overtaken heart disease as the UK’s major killer (Cancer Research UK, 2005). With an aging population it is likely that the treatment of cancer will be increasingly important.

In 2001 breast and prostate cancers contributed 26% to the UK incidence of cancer and 14% of the mortality (Cancer Research UK, 2005). This large incidence and mortality shows the necessity for improvement in the treatment of these diseases. Both breast and prostate cancers have been reported to over-express uPAR (Blasi, 1997). This is one of the factors leading to the choice of this receptor as a target for non-viral gene delivery. The receptor and its function are described more fully in Section 1.4.

Great advances have been made in the treatment of cancer, but there remains much to accomplish. Current clinical anticancer drugs fall into two general categories:
cytotoxics and hormone based. Cytotoxins assault DNA at some level, either in its synthesis, replication or processing (Denny, 2001). Cytotoxins can be further split into: alkylating agents e.g. cyclophosphamide; antimetabolites e.g. methotrexate; cytotoxic antibiotics e.g. doxorubicin and vinca alkaloids e.g. taxol (Rang et al., 1996). When tumours are formed from hormone sensitive tissue they may be hormone-dependent and hormone antagonism (e.g. tamoxifen) can be used to delay the tumour growth. The main problems associated with the above mentioned therapies are their lack of specificity for tumour cells leading to non-specific toxicity and the development of resistance. Most small molecules are rapidly distributed throughout the body without selective accumulation in the tumour. They achieve their action due to the increased proliferation of cancer cells but have debilitating side effects and low efficiency. The use of a targeting method to deliver the therapy to cancer cells reduces non-specific action by localising cytotoxic drugs to the tumour.

Genetic therapies offer a new approach to the treatment of cancer. The main focus of gene therapy investigations is for the treatment of cancer (Fig. 1.2). It is considered that toxicity may even be abolished through the use of gene therapy. Indeed, adenovirus carrying p53 (Gendicine®) has been approved in China; 64 % of patients treated with radiotherapy and Gendicine® showed complete tumour regression compared with three times lower tumour regression in radiotherapy only patients (Surendran, 2004).

1.3 Targeting Therapeutics

Through targeting, scientists have tried to achieve greater success in the treatment of cancer. The word “Targeting” is used in this project to describe methods employed to achieve preferential localisation of a therapeutic in the region of disease and subsequently an increase of the local concentration. It was realised back in the 16th century “Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy” (Paracelsus, 1490-1541). Through targeting the delivery of a drug, and therefore increasing its concentration in the region of pathology, it is suggested that a lower total dose may be administered compared with a non-targeted drug. The lower concentrations at non-pathological sites would decrease the non-specific dose related toxicity of the therapeutic.