

DEVELOPMENT OF IMPROVED 'ARMED' CONDITIONALLY REPLICATING ADENOVIRUSES FOR GENE THERAPY OF LOCALISED PROSTATE CANCER

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Abstract

Prostate cancer is the most frequent male malignancy in the UK with around 30,000 new cases diagnosed per year. 15-20% of prostate cancer patients develop local treatment failure without metastatic spread. These patients have limited treatment options and, given the localised nature of the disease, constitute suitable candidates for gene therapy. Several gene therapy strategies, particularly Virus Directed Enzyme Prodrug Therapy (VDEPT) and Conditionally Replicating Adenoviruses (CRAd's) have been studied in patients with locally relapsed prostate cancer. In our Institute we are developing VDEPT systems using *E. coli* nitroreductase (NTR) to activate the prodrug CB1954. In a clinical trial our group have shown that the intraprostatic injection of a replication defective adenovirus expressing NTR (CTL102) induces NTR expression, and in patients receiving virus followed by intravenous administration of the prodrug CB1954, there is preliminary evidence of efficacy as judged by decrease in PSA level. Similar observations have been made by other authors using different VDEPT systems or CRAd's, however in all studies the overall efficacy has been limited and the PSA responses short lived.

The research presented here describes improvements I have made on the already well established gene therapy vector CRAd-NTR in terms of increasing the catalytic activity of the prodrug activating enzyme and also the replication and spread of the virus. Having characterised new viruses in prostate cancer cell lines I have further assessed them *ex-vivo* in benign and malignant prostate specimens, in work described elsewhere.

We are now translating the information gained from these studies into possible therapeutic strategies for future gene therapy trials.

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