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Cellular and Genetic Medicines Advancing the Treatment of Metastatic Prostate Cancer

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While early stage prostate cancer (PCa) can be cured with surgery, metastatic disease is currently incurable. The prostate is a non-essential organ for life making gene-directed enzyme prodrug therapy (GDEPT) a feasible option. GDEPT involves the transfer of a non-mammalian prodrug converting enzyme into the tumour microenvironment. This enzyme renders the prostate tumour sensitive to killing by a systemically administered non-toxic prodrug following its conversion to a toxin. GDEPT shows several advantages: prodrug activation in the tumour avoids systemic toxicity; the toxic metabolite readily diffuses across cell membranes killing 'local bystander' PCa cells that do not express the prodrug converting enzyme; stimulation of anti-PCa immune cells providing PCa metastases killing ('distant bystander effect').

We are currently exploring two GDEPT delivery methods for the treatment of metastatic PCa. The first method utilises the intratumoural injection of a sheep adenovirus to deliver the bacterial purine nucleoside phosphorylase gene (PNP) under the control of a prostate targeting promoter and in the presence of prodrug fludarabine phosphate (FP253; PCTAU03/00381). FP253 has been registered for a first-in-man Australian Phase I clinical trial (<http://ClinicalTrials.gov/NCT00625430>). We are now successfully engineering bone marrow-derived mesenchymal stem cells (BMSC) to deliver the yeast cytosine deaminase uracil phosphoribosyltransferase fusion gene (CDUPRT) to metastatic PCa in the presence of prodrug 5-fluorocytosine. BMSC have attracted much attention as cellular gene delivery vehicles due to their ability to: seek out cancer anywhere in the body; overcome issues of host immune responses allowing for allogeneic as well as autologous transplantation; avoid degradation by the immune system, a major limitation of most current gene delivery methods. These novel GDEPT delivery methods show promise for the development of novel therapeutics for PCa patients presenting with metastatic disease.