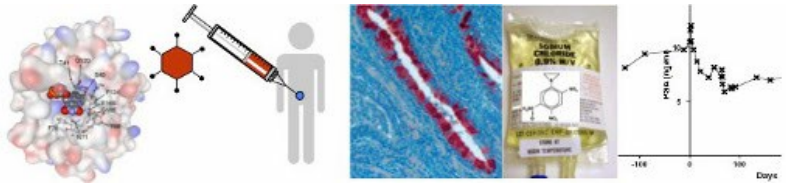
Gene Therapy Group



Group leader **Dr. Peter Searle (/staff/profiles/cancer/searle-peter.aspx)**

Overview

Genetically engineered viruses can be used to deliver genes into cells, providing a range of exciting new opportunities for treatment of a wide variety of diseases. We focus on the development of this technology to produce new therapies for cancer, using genes that will make the cancer more sensitive to specific drugs, or help stimulate immune responses able to attack the cancer.

Our research group

One approach to cancer gene therapy involves expression of a prodrug-activating enzyme in cancer cells; we have pioneered the use of nitroreductase to activate the prodrug CB1954 in cancer gene therapy. Through close collaboration with clinicians also in the School of Cancer Sciences, our laboratory studies of this prodrug activation gene therapy progressed to a series of clinical trials, first in liver cancer and then in prostate cancer, using a replication-defective adenovirus vector to express the enzyme following intratumoural injection. A further development is to co-express the cytokine GM-CSF with the prodrug-activating enzyme, so that the immune response could enhance the clinical benefit; we hope to start a clinical trial of this in men with locally recurrent prostate cancer during 2013.

The group investigates strategies to further optimise the prodrug activation gene therapy. These include engineering the nitroreductase enzyme for more efficient prodrug activation, collaboration with groups developing alternative prodrugs, and exploitation of replication-competent, oncolytic adenoviruses.

We are also interested in other strategies to promote immune responses against tumour cells, particularly expression of proteins such as CD80 and 4-1BBL that provide co-stimulatory signals to T-cells, or CD40L that has both pro-apoptotic and immunostimulatory functions.

Current projects

Open all sections

AdUP clinical trial of prodrug activation gene therapy with GM-CSF
(Searle, in collaboration with Patel, Viney, James, Porfiri)

The replication-defective adenovirus AdNRGM encodes both nitroreductase (prodrug-activating enzyme) and GM-CSF, for immune stimulation. We plan to test this by template-guided injection into the prostates of men with locally recurrent, hormone refractory prostate cancer, with subsequent administration of the prodrug CB1954. We will monitor the levels of the tumour marker PSA in the blood for up to a year following treatment, and monitor the induction of tumour-specific immune responses.

Investigation of CD40L for gene therapy of liver cancer
(Searle, in collaboration with Simon Afford [Centre for Liver Research, Infection & Immunity])

CD40L is a potent immunostimulatory ligand capable of maturing dendritic cells and licensing them for activation of cytotoxic T cells. It also exhibits direct pro-apoptotic activity in a number of tumours. In this project we will investigate the potential

for CD40L gene therapy of liver cancer, including evaluation of oncolytic adenovirus vectors that are able to replicate selectively in cancer cells, thus contributing to tumour-destruction while promoting immune attack of the cancer.

Recent publications

- **A.C. Dowell, K.A. Oldham, R.I. Bhatt, S.P. Lee and P.F. Searle.** (2012) Long-term proliferation of functional human NK cells, with conversion of CD56dim NK cells to a CD56bright phenotype, induced by carcinoma cells co-expressing 4-1BBL and IL-12. Cancer Immunology Immunotherapy 61, 615-628
- **Elmetwali, T., Searle, P.F., McNeish, I., Young, L.S., and Palmer, D.H.** (2010). CD40 ligand induced cytotoxicity in carcinoma cells is enhanced by inhibition of metalloproteinase cleavage and delivery via a conditionally-replicating adenovirus. Mol Cancer 9, 52.
- **Jaberipour, M., Vass, S.O., Guise, C.P., Grove, J.I., Knox, R.J., Hu, L., Hyde, E.I., and Searle, P.F.** (2010). Testing double mutants of the enzyme nitroreductase for enhanced cell sensitisation to prodrugs: Effects of combining beneficial single mutations. Biochem Pharmacol 79, 102-111.
- **Patel, P., Young, J.G., Mautner, V., Ashdown, D., Bonney, S., Pineda, R.G., Collins, S.I., Searle, P.F., Hull, D., Peers, E., et al.** (2009). A phase I/II clinical trial in localized prostate cancer of an adenovirus expressing nitroreductase with CB1954. Mol Ther 17, 1292-1299.
- **Vass, S.O., Jarrom, D., Wilson, W.R., Hyde, E.I., and Searle, P.F.** (2009). E. coli NfsA: an alternative nitroreductase for prodrug activation gene therapy in combination with CB1954. Br J Cancer 100, 1903-1911.

Staff

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