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Dr Peter Searle PhD

Senior Lecturer

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School of Cancer Sciences

About

Peter Searle is a Senior Lecturer in the School of Cancer Sciences.

He has published over 70 research papers in scientific journals, and received grant funding from the Medical Research Council and Cancer Research UK.

He is keen to apply the advances from basic research to the development of novel therapies for cancer, and his research now has a focus on developing cancer gene/immuno therapies.

Qualifications

- PhD in Biochemistry, University of London, 1981
- BA in Natural Sciences, University of Cambridge, 1977

Biography

Peter Searle qualified with a BA in Natural Sciences from the University of Cambridge in 1977, where he specialised in Genetics in his final year. He went on to study for a PhD at the National Institute for Medical Research, Mill Hill, London, where his research focused on gene regulation. He subsequently took up a postdoctoral research position in the Department of Biochemistry, University of Washington, Seattle, USA, where his research continued the theme of gene regulation.

He returned to the UK with a Lectureship in the then Department of Cancer Studies, where he initially continued to work on gene regulation, while setting up model systems to investigate aspects of papillomavirus and Epstein Barr virus oncogenicity.

In the early 1990s he shifted his research interest to focus on development of cancer gene therapy, with particular interests both in prodrug activation gene therapy and immunotherapeutic approaches.

Teaching

- BMedSc
- MBChB
- Clinical Oncology MSc

Postgraduate supervision

Peter Searle is interested in supervising doctoral research students in the following area:

- Gene Therapy of Common Cancers: Immunological and Pharmacological Approaches to Cancer Treatment

Research

We are developing novel, gene-based therapies for cancer. One approach uses the enzyme nitroreductase, from E. coli, to activate prodrugs such as CB1954 to cytotoxic derivatives. Our labwork has progressed to early phase clinical trials, injecting an adenovirus vector expressing nitroreductase into tumours. These showed encouraging evidence of localised anti-tumour activity when combined with CB1954, and suggest that further optimisation could lead to an effective treatment for locally relapsed prostate cancer.

Towards this goal, we have developed improved nitroreductase mutants that activate CB1954 more efficiently than the natural enzyme, and collaborate with groups developing better prodrugs. We are also studying viruses that are engineered to replicate in cancer cells, but not in normal cells. Virus replication contributes direct anti-cancer activity, and can also improve the distribution of prodrug-activating enzyme through the cancer.

Stimulation of tumour-specific immune responses could allow a localized gene therapy to have a systemic benefit; we plan to test this by clinical trial of a vector that produces nitroreductase (for CB1954 activation) and the immunostimulatory cytokine GM-CSF. We are also interested in the potential of co-stimulatory proteins (e.g. CD80 and 4-1BBL) to overcome some of the factors that allow tumours to escape immune control.

Other activities

- Member of the Scientific Advisory Committee on Genetic Modification, a national committee which advises the Health and Safety Executive
- Member of the Biologicals and Vaccines Expert Advisory Group, a committee which advises the Medicines and Healthcare Products Regulatory Agency

Publications

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.

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.

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.

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.

Jarrom, D., Jaberipour, M., Guise, C.P., Daff, S., White, S.A., Searle, P.F., and Hyde, E.I. (2009). Steady-state and stopped-flow kinetic studies of three Escherichia coli NfsB mutants with enhanced activity for the prodrug CB1954. Biochemistry 48; 7665-7672.

Young, J.G., Green, N.K., Mautner, V., Searle, P.F., Young, L.S., and James, N.D. (2008). Combining gene and immunotherapy for prostate cancer. Prostate Cancer Prostatic Dis 11; 187-193.

Race, P.R., Lovering, A.L., White, S.A., Grove, J.I., Searle, P.F., Wrighton, C.W., and Hyde, E. (2007). Kinetic and Structural Characterisation of Escherichia coli Nitroreductase Mutants Showing Improved Efficacy for the Prodrug Substrate CB1954. J Mol Biol 368; 481-492.

Habib-Agahi, M., Phan, T.T., and Searle, P.F. (2007). Co-stimulation with 4-1BB ligand allows extended T-cell proliferation, synergizes with CD80/CD86 and can reactivate anergic T cells. Int Immunol 19; 1383-1394.

Expertise

Genetic manipulation/genetic modification; gene therapy; cancer gene therapy

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