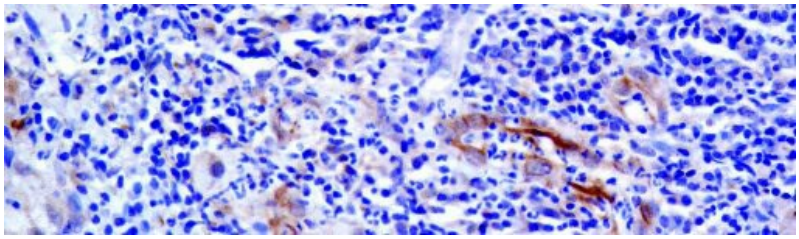
T cell-based therapies for cancer



Group leader: Dr **Steven P. Lee (/staff/profiles/cancer/lee-steven.aspx)**

Overview

Our laboratory is seeking to develop novel therapies for cancer that use the body's immune cells known as "T cells". T cells are normally very efficient at recognising viruses so we are studying cancers that carry such viruses to determine how these malignant cells have evaded the T cell response and how we might boost this response to clear the tumour. Lessons learnt are then being applied to develop effective T cell therapy for more common non-virus associated cancers.

Our research group

We have a particular interest in tumours that carry viruses such as the Epstein-Barr virus (EBV), a known target for the T cell response. By exploring T cell responses to such viruses and to the virus-associated malignant cells found in Nasopharyngeal carcinoma and Hodgkin's lymphoma, we are characterising T cells that naturally reside within the tumour tissue and seeking to define immune evasion mechanisms. A major focus for the group is developing T-cell based therapies for cancer and in this regard we are engineering T cells to make them more effective at recognising the tumour. We also have an interest in determining the mechanisms whereby such T cells can effectively home to the tumour site.Our work uses many in vivo and in vitro assays of T cell function, as well as flow cytometry, immunohistochemistry and molecular cloning. We work with collaborators both in the UK and overseas and have excellent links with local clinicians that enable us to access fresh material from cancer patients. As part of the Cancer Immunology and Immunotherapy Centre (CIIC) within the University, we also work closely with many other local groups interested in T cell responses to cancer.

Current projects

Open all sections

Immunology of virus-associated cancers:
Through collaborations with the Chinese University of Hong Kong (Prof. A.T.C. Chan, Prof. K.W. Lo) and University of Groningen, Holland (Dr A. Diepstra), we are investigating T cell responses to the EBV-associated cancers Nasopharyngeal carcinoma (NPC) and Hodgkin's Lymphoma respectively. As part of our basic research into the immunology of these cancers, we are exploring immune evasion mechanisms and the function of T cells that naturally reside within the tumour tissue.

Engineering T cells for adoptive therapy approaches:
Having established the use of adoptive T cell therapy in Birmingham through a pilot study in which 6 cancer patients were safely infused with tumour antigen-specific T cell clones, we are currently developing a rapid and reliable approach to generate therapeutic T cells using T cell receptor (TCR) gene transfer. We have successfully cloned a gene encoding a TCR specific for LMP2, a viral protein widely expressed in EBV-associated tumours. Using retroviral mediated gene transfer we have then delivered this TCR into T cells. The result is that within 3-5 days we can reliably generate large numbers of high avidity LMP2-specific effectors capable of recognising cells endogenously expressing physiological levels of this viral protein.

In order to target more common non-virus associated malignancies, we have recently begun a project to express a chimeric antigen receptor (CAR) in T cells that will enable them to selectively attack the blood vessels that supply many human cancers (including breast, prostate, kidney and bladder cancer).

Furthermore we are exploring the use of engineered T cells derived from cord blood as a source of more effective anti-cancer cells.

T cell homing to tumour tissues:
If T cells are to be effective in treating cancer, they must be capable of homing to the tumour site. But they will only be recruited to a tissue if they express the appropriate selectins, integrins and chemokine receptors for engaging molecules presented at this site. Since many tumours (e.g. NPC, Hodgkin's lymphoma and Renal cell carcinoma) are naturally infiltrated with T cells, another key area of our research is to define the mechanisms whereby these cells are recruited with a view to conferring the appropriate homing phenotype on tumour-specific effectors.

Recent publications

- **Frumento G, Zheng Y, Aubert G, Raeiszadeh M, Lansdorp PM, Moss P, Lee SP* and Chen FE*** (2012) Cord Blood T Cells Retain Early Differentiation Phenotype Suitable for Immunotherapy After TCR Gene Transfer to Confer EBV Specificity. *Am J Transplantation* in press. (* joint corresponding authors)
- **Parsonage G, Machado LR, Hui J, McLarnon A, Schmaler T, Balasothy M, To K-F, Vlantis AC, van Hasselt CA, Lo KW, Wong W-L, Hui EP, Chan A and Lee SP** (2012) CXCR6 and CCR5 localise T lymphocyte subsets in Nasopharyngeal Carcinoma. *Am J Pathol.* 180, 1215-22.
- **Oldham KA, Parsonage G, Bhatt RI, Wallace DMA, Deshmukh N, Chaudhri S, Adams DH and Lee SP** (2012) T lymphocyte recruitment into Renal Cell Carcinoma tissue: A role for chemokine receptors CXCR3, CXCR6, CCR5 and CCR6. *Eur Urol.* 61, 385-394.
- **Dowell AC, Oldham KA, Bhatt RI, Lee SP and Searle PF** (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 Immunol.* Immunother. 61, 615–628.
- **Fox CP, Haigh TA, Taylor GS, Long HM, Lee SP, Shannon-Lowe C, O'Connor S, Bollard CM, Iqbal J, Chan WC, Rickinson AB, Bell AI, Rowe M** (2010) A novel latent membrane 2 transcript expressed in Epstein-Barr virus-positive NK and T cell lymphoproliferative disease encodes a target for cellular immunotherapy. *Blood.* 116, 3695-3704.

Staff

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