

## **Project title: Cancer therapy with gene modified T cells**

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The Tumour Immunology Research Lab at the Royal Free Hospital Campus of UCL Medical School is fully integrated with the Department of Clinical Immunology. Clinically the Department has the largest cohort of adult patients in the UK with inherited primary immune deficiencies. The two major research groups focus on Tumour Immunology (Hans Stauss and Emma Morris) with close links to the departments of Haematology and Oncology and the genetic basis of immune deficiencies (Bodo Grimbacher). In October 2009 Helen Baxendale joins the Department bringing a research group focussing on B cell responses to infectious pathogens.

Adoptive transfer of antigen-specific T cells is an effective form of immunotherapy for persistent virus infections and cancer. Major limitations of adoptive therapy are the inability to isolate antigen-specific T cells reproducibly and expand them to sufficient numbers *ex vivo*, whilst maintaining optimal function and specificity. Further, as the majority of identified target antigens expressed on tumour cells are over-expressed self antigens (tumour associated antigens, TAA) there is a requirement to overcome peripheral tolerance mechanisms that exist to limit unwanted self-reactive T cell responses. It is expected that low level expression of TAA in normal tissues may induce such tolerance affecting high avidity T cells that are specific for TAA.

Recently, we have developed gene therapy approaches to overcome the problems related to poor tumour immunogenicity and lack of specificity of allogeneic T cell therapy. Retroviral gene transfer is a potential strategy for generating large numbers of high avidity TAA-specific T cells. Recently, we and others have demonstrated that retroviral transfer of cloned T cell receptor (TCR) genes can reliably re-direct the antigen specificity of T cells. We have exploited the allo-reactive T cell repertoire to isolate high avidity T cells specific for the tumour-associated antigen WT1, which is highly expressed in MDS, AML, CML and ALL, together with a number of solid tumours. The genes encoding the T cell receptor of the WT1-specific, allo-restricted T cells were isolated and inserted into retroviral vectors for gene transfer into primary human T cells. *In vitro*, the gene modified T cells can kill primary human leukaemia cells and also autologous leukaemia cells expressing WT1 endogenously. Following adoptive transfer they can protect against the growth of autologous primary leukaemia cells in the xenogeneic NOD/SCID model. Currently, a clinical grade batch of the retroviral WT1-

TCR construct is in production, and we have final regulatory approval for a phase I/II clinical trial in leukaemia patients, due to open in 2009.

Other projects in the lab are aimed at improving the efficiency of TCR gene transfer and the subsequent in vivo function of TCR-transduced T cells. We have made a number of modifications to the alpha and beta TCR gene sequences together with alterations to the retroviral vectors in order to maximise preferential pairing between the introduced alpha and beta TCR chains and improve cell surface TCR expression. Other work is modifying the transduction procedures and/or target cells for transduction. It has recently been demonstrated that prolonged ex vivo manipulation of antigen-specific T cells generates cells with an 'exhausted' phenotype, impaired effector function and reduced persistence in vivo after adoptive transfer. We are evaluating the use of lentiviral vectors which can infect non-dividing cells and thus permit TCR gene transfer into minimally activated T cells, capable of retaining a naïve phenotype. It is possible to transfer TCR genes into CD34+ haematopoietic stem cells, which on differentiation into the T cell lineage, express the introduced TCR. We are currently exploring this approach as a mechanism to generate naïve TAA-specific T cells and investigate the effects of peripheral tolerance on in vivo function of T cells expressing the introduced TCR.

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