

Project Title:	A novel anti-Wilms-Tumour-1 (WT1) vaccination strategy in haematological malignancy using DNA fusion vaccines delivered with electroporation
Project Ref:	08-99-24
Cost:	£973,304
Lead Applicant & Institution:	Professor Christian Ottensmeier Cancer Sciences Division Southampton University Hospitals
Start Date:	1 st January 2011
Plain English Summary:	<p>In many cancers of the blood such as chronic myeloid leukemia (CML) the outlook of patients remains limited. Imatinib is a new drug which is very effective in CML but the majority of patients have persisting disease and are therefore at risk of relapse. A treatment that offers a chance of cure is a bone marrow transplant. This works by stimulating immune control of the cancer but it is highly toxic and suitable only for younger patients. Additionally patients can only be treated with transplantation, if a suitable bone marrow donor is available. To exploit the benefit of immune therapy without its side effects, we propose to test a novel vaccine design. The study group includes the major UK clinical centre for treating CML (Hammersmith Hospital), and with the unique cancer vaccine expertise in Southampton is uniquely placed to undertake this trial.</p> <p>We have designed novel DNA fusion vaccines, which awaken the patient's immune system, generating killer T cells able to seek and destroy residual cancer cells. The vaccines are made specific for different cancers; we have tested our prostate-specific DNA vaccine with induction of immunity in ~60% of patients and no significant side effects. The DNA vaccines are injected into muscle and anti-cancer immunity remains visible over many months, suggesting that performance is superior to other vaccines.</p> <p>We are now proposing to take the DNA vaccine further by injecting two vaccines targeting different portions of a tumour protein named 'Wilms tumour antigen 1' (WT1). This is a found in residual tumour cells which persist in patients with CML even under continuous treatment with imatinib. Using an established sensitive laboratory test for a blood marker called BCR-ABL, we will measure objectively in the blood of the patients how effectively the vaccine can reduce or eliminate leukaemic cancer cells. We will evaluate how much WT1 can be found in the blood after vaccination and assess the benefits of vaccination on disease course, how long these last and if they go hand in hand with the immune responses. This latter is critical to be able to further improve the vaccines and their dosing over time. If successful, we intend to take the vaccines into larger, randomized trials.</p> <p>We have developed and validated (carefully defined and optimized for trial use) the key immune endpoints for a multi-centre setting, including validated sample collection, storage and transport.</p>

<p>Abstract:</p>	<p>In patients with chronic myeloid leukemia (CML), while outcome has improved with novel agents such as tyrosine kinase inhibitors, the only curative approach is with allogeneic transplantation. This exerts its benefit through immune control of the cancer, but is only suitable for a small number of patients. This study intends to examine whether DNA vaccination can exert measurable immune control of CML, by assessing disease with the established, clinically relevant monitoring of BCR-ABL transcripts and correlating reduction in BCR-ABL transcript levels (primary endpoint: molecular response rate at 6 months) with responses in WT1 transcript levels and immunological responses (secondary endpoints). We are in clinical testing with a strategy to raise epitope-specific immunity against cancer using a plasmid-DNA fusion vaccine platform. The unique design encodes an immune alert domain (DOM) from tetanus, linked to a tumour antigen-derived epitope (p-DOM-epitope). In the laboratory this design confers tumour protection, breaks immunological tolerance, and induces strong and durable cytotoxic CD8+ T cell immune responses, superior to peptide vaccines. In patients with prostate cancer, 60% (19/31) developed vaccine induced PSMA (prostate specific membrane antigen) specific T cells with excellent vaccine safety. In this same trial a novel delivery system (intramuscular electroporation) enhanced immune responses to the DNA vaccine.</p> <p>We now wish to show that DNA fusion vaccination can control haematological malignancies, specifically CML. Here, escape from cytotoxic T cell attack by loss of MHC I molecules is less likely and molecular markers are already used to guide clinical management. We intend to exploit the high expression of the WT1 antigen in CML and build on the observation that in spite of inducing only transient immunity, even the suboptimal vaccination with peptide vaccines against WT1 conferred some clinical benefit. Our strategy is to use double DNA vaccination targeting two separate WT1-derived peptides.</p> <p>In this phase I/II study we propose to vaccinate up to 37 HLA A0201+ patients with CML in cytogenetic remission (CCyR), stable on imatinib, with 6x 1-monthly doses of two WT1 vaccines, followed by maintenance vaccination up to 2 years in responders. As the vaccine can only work by stimulating the immune system, we intend to show that molecular clinical responses are related to a CD8+ T cell response induced by vaccination, measured by tetramer and ELISPOT analysis. Synchronously, a consented control group of up to 55 patients will be recruited, who are found to be HLA A2 negative at screening (genetic randomization). The generated data will assess the clinical response rate, validate WT1 measurement by qPCR as a biomarker for vaccine responses in CML and inform whether definitive Phase III testing of the vaccine is warranted.</p> <p>We expect to recruit 1-2 HLA A0201+ and 2-3 HLAA2- patients/ month with a follow up of 24 months, allowing completion of the study in the 4 years of funding requested.</p>
<p>ISRCTN: (if applicable)</p>	
<p>Project Protocol:</p>	<p>www.eme.ac.uk/projectfiles/089924protocol.pdf</p>
<p>Project website: (if applicable)</p>	
	<p>www.eme.ac.uk/projectfiles/089924info.pdf</p>

**URL of this
Page:**

--