

THE RESEARCH PROJECTS

The Cancer Vaccine Institute (CVI) is the only national charity in the UK devoted exclusively to funding research into the development of cancer vaccines and offering them to patients around the UK. The ultimate aim is that vaccines will increase survival rates and patients' quality of life. The CVI funds both laboratory research and clinical trials and is currently funding or will shortly start trials to develop dendritic cell based cancer vaccines for: malignant melanoma; brain; prostate; and childhood cancers. These cancers do not respond well to conventional treatments especially when they spread around the body (secondary cancers).

Research work is currently undertaken by Professor Angus Dalgleish and his team at St George's University of London Hospital. Laboratory work and early clinical studies for dendritic cell based vaccines, funded by the CVI and around the world, have demonstrated that good and occasional dramatic clinical responses can be achieved and that there are no significant side-effects.

Dendritic Cells in Cancer Vaccines Explained

In very simple terms, because cancer cells are produced from our own cells the immune system often has difficulty in recognising them as abnormal and harmful and does not respond to fight and destroy them. Cancer vaccines aim to stimulate the patient's immune system to recognise and fight these harmful cells. They are made by taking cancerous cells either from the patient or from somebody else's grown in the laboratory. These cells are then grown, made safe and manipulated so that when they are re-introduced into the body as a vaccine, the immune system is now able to recognise them as abnormal and can respond to destroy them.

Professor Dalgleish's research focuses on "dendritic cell" cancer vaccines. Dendritic cells are involved in the body's immune system and are known to be especially efficient at stimulating an immune response. It is hoped by adding them to the vaccine they will be able to overcome and stop the tumour cells multiplying and spreading and ultimately destroy them and eradicate the cancer.

The principle of dendritic cell immunotherapy is a simple one but in practice is hampered by technical difficulties. Much effort has gone into understanding what components can be added to the vaccine and at what stage that will generate the best immune response. In addition there is increasing consensus that immunotherapy should be used in combination with conventional therapies to boost their effectiveness, adding another layer of complexity. However, developments in dendritic cell vaccine research are encouraging and Professor Dalgleish stands at the forefront of this field.

THE CLINICAL TRIALS

The Aim of the Trials

The long term aim of all the trials funded by the CVI is to assess how well the vaccines work and how they can be further improved until an effective and safe vaccine is developed and becomes a standard treatment for a wide range of cancers.

For each trial the patients will be monitored to see how their tumour responds to treatment and to ascertain whether there are any adverse effects of the vaccine. Importantly, in order to determine the potency of the vaccine, the immune response to vaccine will be determined for each patient. It is hoped that the data accumulated by the end of each trial will show that patients can live longer or have delayed progression of their disease and that they have a better quality of life. Depending on the results of each of the trials the vaccines will either be ready for further, larger, randomized multi-centred trials or other variables will have been identified so that another similar trial can be conducted to further improve the vaccine.

Vaccine for Malignant Melanoma

The advent of package holidays sent millions of us to enjoy the novelty of blazing sunshine. As a result, incidence rates for malignant melanoma (skin cancer) are now climbing and are set to treble in thirty years time (*CRUK 2004*). Although there are now many different treatment approaches, unless the disease is caught early, there is currently no curative treatment available,

Trial One

In August 2007 a three year Phase I/II trial funded by the CVI to investigate the efficacy of treating thirty stage IV malignant melanoma patients who had failed chemotherapy, with a dendritic cell vaccine will end. The trial has already finished recruiting and data is being analysed to determine how well the vaccine has worked to stimulate immunity in these patients. Results so far indicate that patients who have low volume disease and who are largely fit and well, apart from their tumour, have responded well to dendritic cell therapy giving longer survival times than those treated by other therapies. Even patients who have progressed through maximum chemotherapy have responded with stable disease. Responses were most marked in metastases of the lung. Patients reported minimal side effects (common side effects including transient and mild flu-like symptoms and tenderness at the site of vaccination) and an improvement in quality of life with an increase in appetite and subsequent weight gain. Data from this trial will be collated and submitted as a manuscript to a peer-reviewed journal.

Trial Two

It is becoming clear that while some patients respond very well to vaccines, others do not. Further research is needed to pin down the best formulation of the vaccine and to identify who will respond and who is responding once treatment has begun. Using the data from trial one in combination with the recent laboratory research data on dendritic cell loading and maturation, a new more effective trial protocol will be developed.

The CVI has agreed to continue its funding for a new three year phase I/II melanoma trial anticipated to start in December 2007 treating a further thirty patients. Decisions about the final combination of treatments awaits the outcome of trial one. However, it is expected that it will involve some of the following approaches: increasing the effectiveness of dendritic cells; removing regulatory cells that damp down immune responses; increasing the effectiveness of the T cells that kill cancers; and combining the vaccine with chemotherapy. It is becoming apparent that vaccines could work much better in combination with other standard treatments and observations support this with marked unexpected responses to chemotherapy, radiotherapy, anti-angiogenic and anti-inflammatory treatments. Use of vaccine in combination with chemotherapy at lower doses may also have fewer toxic side effects for patients.

Prostate Cancer Vaccine

In the UK 1 in 14 men will develop prostate cancer in their lifetime. Indeed, it is the most common form of cancer in men and is the second most common cause of death from cancer for men (*Prostate Research Campaign UK*). It is currently treated with radiotherapy and hormone therapy and if caught early enough surgery. However, patients that fail hormone therapy have little recourse to other treatment and there is a real need for other forms of intervention.

CVI's long term financial support has allowed a number of studies to proceed on whole tumour cell vaccination. Out of this original work a small biotech company, Onyvox, was born which has successfully developed a whole cell vaccine to a phase IIb clinical trial for prostate cancer in patients that have failed hormone treatment.

The CVI has agreed to fund a further two year phase I/II trial to investigate ways to improve the efficacy of the Onyvox vaccine. The trial will be conducted on thirty patients with prostate cancer and is due to start in August 2007. Onyvox Ltd will provide the necessary allogeneic tumour cell vaccine which will be combined with agents that should improve the outcome based on preclinical data. The agents include cyclophosphamide (which inhibits T regulatory cells and so aids the stimulation of the immune response) and doxycycline (which inhibits matrix metalloproteases, a class of enzyme involved in various aspects of tumour progression). There is currently no other trial of this kind in prostate cancer.

Vaccine for Childhood Cancers

Although cancer in children is rare, affecting about 1 in 500 children under the age of 15, it remains the most common cause of death from illness in childhood in the UK. Survival rates have improved dramatically but some children have a less than 10% chance of surviving two years. Furthermore, for many of these cancers the use of conventional chemotherapy has failed to make a significant impact on metastatic cancer (where a tumour spreads beyond its original site) or relapsed cancer (where a tumour comes back).

There is evidence from both human and mouse experiments that immunotherapy, and more specifically dendritic cell vaccines, might have an effect on these childhood cancers. Professor Dalglish has already treated six children on an 'informed consent' basis who had all failed standard therapies using their own resected tumour as a vaccine. In one test patient there has been a dramatic clinical response to vaccination which constitutes a dramatic response rate among patients whose prognosis is otherwise poor.

In August 2007, Professor Dalglish, in collaboration with two major childhood paediatric centres the Royal Marsden Hospital and Great Ormond Street, will embark on a two year phase I clinical trial to treat twenty patients with osteosarcoma followed later by other sarcoma types. The trial was peer reviewed through Cancer Research UK for funding of the Royal Marsden site and the CVI is providing co-funding for the work to be carried out at St George's University of London. Alongside this, unique to St Georges, Professor Dalglish will conduct off-trial treatment of other childhood cancers including neuroblastoma which is expected to provide basic information about the responsiveness of this cancer to the vaccine.

This will be the first trial of its kind in paediatric oncology. Patients will be treated with a course of about ten vaccinations of dendritic cells pulsed with autologous tumour lysate initially every two weeks but gradually dropping to every two months. It is hoped that this vaccine will stimulate an immune response against the tumour. To aid this process the patients will also be given a course of a drug called Interleukin-2 (IL-2) which has stimulatory effects on the immune response. The dose of IL-2 that will be used in this trial has minimal toxicity and is suitable for children.

Mycobacterium Vaccae (M vaccae) in Malignant Melanoma

The CVI recently funded a number of phase I, II and III clinical trials which demonstrated the effectiveness of vaccination with M vaccae in the treatment of melanoma, lung cancer and even breast cancer. M vaccae is similar to the bacterium that causes tuberculosis, but in this formulation (produced to clinical trial standard and heat killed) is completely safe for use in humans. The exact mechanism by which such the treatment works is unclear but it is likely that there is a non-specific recognition of M vaccae which stimulates the relatively suppressed immune system in cancer patients to respond to tumour antigens. Unfortunately, the company supplying the vaccae (SRL172™) have, until recently, discontinued production. However, an agreement has now been reached with SR Pharma to supply vaccine-quality M vaccae.

The CVI has agreed to fund a two year phase I trial, starting in September 2007, on thirty patients with malignant melanoma using M vaccae and where appropriate in combination with low dose IL-2. This initial trial will be done to batch test the SRL172™ for comparison with previous trials. However, unlike previous trials the aim is to follow immune responses in order to understand the underlying biology in these patients. There are currently no other trials of this kind being undertaken.

Aldara / IL-2 Trial – Malignant Melanoma

A phase I clinical trial, funded by the CVI has recently finished which determined the efficacy of Aldara cream topically applied to cutaneous (on the surface) and sub-cutaneous (under the skin) melanoma lesions. In some cases the Aldara cream was applied in conjunction with injections of IL-2 into the melanoma lesion. Clinical results for the trial have recently been submitted for publication and showed that Aldara treatment was effective in controlling the growth of about half of cutaneous melanoma lesions. The lessons learned from the Aldara trial will be applied to later studies, possibly in combination with vaccine therapy.

Brain Cancer Vaccine

In the UK 16,000 people are diagnosed with a brain tumour each year. It is the second most common cause of cancer mortality in the UK. Aside from primary tumours, 20% of all cancers go on to develop a secondary tumour in the brain. (*Brain Research Trust 2007*).

Reports in the scientific literature suggest that dendritic cell vaccines have clinical effects in the most common type of brain tumour, malignant glioma, with patients raising immune responses to the vaccines. There is also anecdotal data from Professor Dalglish's clinical work to suggest that dendritic cell vaccines give good control of the disease.

In January 2008 Professor Dalglish, in a multi-centre collaboration with the Royal Marsden University College London and a European colleague, Professor van Gool, aims to undertake a three year Phase I/II clinical trial to treat over 100 brain tumour patients using dendritic cells pulsed with lysate prepared from autologous tumour cells. The CVI will provide the funding for Professor Dalglish.

Off Trial Work

In addition to the clinical trials the CVI provides funding to treat a number of patients "off-trial" on an informed consent basis. Such patients are important to the development of treatments and are selected on the basis that they have clinical features which Professor Dalglish feels makes them amenable to dendritic cell vaccination. Responses in these patients can give vital clues to new areas of treatment and some of these may be written up as case studies in clinical journals.

THE PRE-CLINICAL RESEARCH

CVI funded staff are principally employed in the production of vaccines for clinical trials. However, they also carry out laboratory based pre-clinical research on vaccine formulation and ways to employ the immune system to destroy tumours.

Maturation of dendritic cells

The CVI is funding a project to investigate the optimal way in which to bring dendritic cells to maturity and at which stage of this process the dendritic cells can be loaded. There are a great range of variable factors which must be studied in order to provide the most optimal vaccine. Work in this area is progressing well and two publications in this area are expected to be submitted soon to scientific journals.

David Find Memorial Studentship

The CVI is currently funding a three year PhD studentship, which started in October 2006, to investigate chemicals released by tumour cells which have been induced to die by a process called "apoptosis". It is believed that such chemicals will have affects on the maturation of dendritic cells and that a better understanding of this process will help to improve the formulation of dendritic cell vaccines.

Biomarkers and Immune Response in Melanoma Patients

Later this year the CVI will fund a postdoctoral position to develop new strategies to utilise serum and tissue samples using samples taken from patients on clinical trials undertake studies on samples taken from Melanoma patients who are on the dendritic cell trial. It is hoped that the new scientist will develop new strategies. Clinical trials for vaccines, currently use a limited range of techniques to look at patients' immune responses and these do not consistently predict which patients are responding clinically to the treatment. It is hoped that by using a "biomics" approach that markers can be looked for which are more predictive of a clinical response and may also help to explain the underlying biology of these responses. Such studies are important not only because they improve our understanding of patient responses but also because they may provide non-clinical ways to monitor patient responses.

M vaccae

In parallel with the clinical trial for Mycobacterium vaccae the CVI will fund projects to understand how this treatment might work. One such project is to look at how the M vaccae stimulates other immune cells such as dendritic cells and gamma-delta cells (a type of T cell). Gamma-delta cells may be of particular interest since when stimulated in culture it may be possible to reintroduce them into patients to fight off their cancer.

Studies on the immunology of graft transplantation in the treatment of leukemia

The CVI has agreed to fund a two year study of leukaemia which will start in August 2007. The study will be undertaken as a collaboration between Professor Dalglish's group and Suparno Chakrabarti, Consultant in Haematology (BMT and Haematol-oncology at St George's Hospital, London.

Leukaemic patients are given Bone Marrow Transplantation because the chemotherapy that they receive kills their own bone marrow cells; these are the cells that are used to generate cells of the immune system. There is now the suggestion that transplantation of blood cells from umbilical cord will do the same task since the cord contains stem cells similar in nature to those of the bone marrow. Usually transplantation would be done from a donor with a closely matched tissue type. Recently, grafts from two partially matched cord bloods were shown to establish well (i.e. were not rejected) and to provide a source of functioning white blood cells.

The purpose of this study is to determine the importance of NK cells (a type of white blood cell) in the cord blood graft. NKs are known to be active against tumours and research has suggested that the NKs derived from the donor cord blood may aid in the destruction of residual tumour cells. In addition they may be of importance in the engraftment process i.e. to determine whether the graft is rejected or not.

The study will look for a correlation between the presence of NK cells and aspects of the engraftment and also to look at the involvement of donor NK cells in the anti-tumour response. Similar studies have been done for bone marrow transplants but this is a unique chance to study the effects of reconstitution by cord blood stem cells.

Ultimately, if Professor Dalglish can show the importance of NK cells, it may be possible to develop some immunotherapy to the cancer; most likely taking an "adoptive immunotherapy" approach where the NK cells are grown and activated in culture and are then reintroduced into the patient. It is hoped that this project will lead to clinical trials in humans.

Full details of the projects in either laymen's or scientific terms are available on request. Further information is also available on www.cancervaccine.org.uk or by contacting Emma Appleyard 0845 602 0662, emma@cancervaccine.org.uk