Annual report : 2005 / Gene Therapy Advisory Committee.

GENE THERAPY ADVISORY COMMITTEE

TWELFTH ANNUAL REPORT

Covering the period from January 2005 to December 2005

Health Departments of the United Kingdom
2005

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FOREWORD

Welcome to the Twelfth Annual Report of the Gene Therapy Advisory Committee (GTAC) which covers the Committee's work from January to December 2005.

For well over a decade, GTAC has closely nurtured and supervised gene therapy clinical research in the UK, and has seen an increasing stream of high quality applications to undertake clinical trials in the NHS. The UK is the leader in the field of gene therapy in Europe. Following the trend of previous years, of the 15 applications discussed by the committee in 2005, most (over 70%) were for new treatments of a variety of life threatening cancers. However, there was also good news for sufferers of more rare conditions. GTAC approved two applications for gene therapy for autoimmune diseases (multiple sclerosis and myasthenia gravis). It is a tribute to the innovative minds of scientists and doctors that the technology is expanding to encompass novel treatments for ever more diverse conditions.

2005 was another busy year for tackling complex regulatory issues. The year began with the sad news that a third child in the French gene therapy trial for severe X-SCID had developed a complication. A joint working party of GTAC and the Committee on Safety of Medicines (CSM) met to review available data and to revise their recommendations of 2003 on the use of retrovirus based vectors. The recommendations, which were published in the journal Human Gene Therapy, exemplified once again the efficient workings of our regulatory framework in ensuring patient safety and high standards of clinical research. Associated with this issue and because of the legitimate concerns about the use of retroviruses as vectors, GTAC embarked on a consultation with scientists about the possibility of the use of alternative vectors. The outcome of the consultation is covered in section 3.4 of this report. I am very grateful to all those who responded with their views that enabled GTAC to formulate its advice.

There were a number of other interesting regulatory developments in 2005. I was delighted that GTAC's excellent work was acknowledged by the United Kingdom Ethics Committee Authority (UKECA) giving GTAC status as a recognised ethics committee for the purposes of the clinical trials regulations throughout the UK. This decision now gives GTAC the authority to consider, in addition to clinical trials of "classical" gene therapy, related applications of novel genetic medicines, for instance the use of oligonucleotides to affect gene modification. In fact, with the arrival of ever more diverse biological medicines, the boundaries between many technologies are being blurred or are disappearing altogether. In this regard, a significant development is the proposed EU regulation on Advanced Therapies which intends to group together gene therapy, somatic cell therapy and tissue engineered products. As far as the UK is concerned, the potential of novel cell therapies has long been recognised. Following the publication of the UK Stem Cell Initiative Report & Recommendations in December 2005, the Government asked GTAC to undertake the ethical oversight of relevant stem cell clinical trials and to act as a source of expert advice to researchers and other research ethics committees. I am excited by the prospect that the experience developed by GTAC in reviewing gene therapy trials may also benefit researchers of other advanced therapy strategies.

The 2005 public meeting "Demystifying Gene Therapy" in Manchester combined with the second annual conference of the British Society for Gene Therapy. This successful event covered all aspects of gene therapy from bench-top research to clinical applications to ethics review of clinical trials, including informed consent. Haemophilia, a common genetic disease, was used as an example for a condition potentially treatable by gene therapy. I was extremely pleased with the day, in particular the fostering of close relations between GTAC and the British Society for Gene Therapy.

Finally, I wish to warmly thank everyone who, during 2005, has helped to ensure that UK gene therapy continues to be conducted to a very high standard of ethics and patient safety. GTAC's work would not be possible without input from all our advisers, UK based and abroad, who have so generously contributed their time and expertise. Our relationship with experts is so important to maintaining GTAC's excellent reputation both on the national and international stages. Their expertise and advice is vital part in ensuring patient safety.

This will be my last report as Chairman of GTAC as I will retire from my post in June 2006. I will be handing over to my successor, Professor Martin Gore, who has an international reputation in the conduct of clinical trials involving patients with cancer. I am certain that he will provide first class leadership for GTAC and will ensure that the UK will maintain its prominent role in the field of gene therapy. I would like to thank retiring members: Professor James Neil and Dr Caroline Benjamin for their constructive contributions to GTAC. I would also like to thank the secretariat that supports the committee and in particular for the enormous assistance they have provided me as chairman over the past 12 years.

Everything that GTAC has done in my time on the committee has been to assist UK scientists and doctors to continue to conduct outstanding gene therapy research of international significance. However, in the development of new approaches to address the huge unmet clinical need, patient safety must remain a priority area. Whilst no UK gene therapy product has yet reached the market, it does not seem too far fetched to hope that there will be a product available throughout the NHS in the not too distant future. Gene therapy offers enormous potential to cure and alleviate single gene disorders, such as Duchenne muscular dystrophy and cystic fibrosis and common disease such as cancer and cardiovascular disease. I hope this day comes soon.

Professor Norman Nevin, OBE
Chairman of GTAC
April 2006

SUMMARY

In 2005, the Committee considered fifteen applications to do gene therapy clinical trials in the UK, in its role as the relevant national research ethics committee. Twelve applications were approved. As with previous years, the majority of applications focus on cancer, with eight of the approved applications covering prostate, kidney, blood (leukaemia), head & neck, and multiple cancers. Of the approved non-cancer protocols, there was one application for peripheral arterial disease and two applications for the autoimmune diseases multiple sclerosis and myasthena gravis. See Section 1 for details, as well as the summary and analysis chart (Section 6).

As well as considering protocols, an essential part of GTAC's work as a Department of Health ministerial advisory body is to provide advice and input into regulatory issues. The most significant area has been the definition of gene therapy and the review of clinical trials, which stems from the introduction in 2004 of the Medicines for Human Use (Clinical Trials) Regulations. See Section 2.

Related to its activities on regulatory issues, GTAC also provides guidance to the gene therapy community. The major area of work in 2005 was a consultation about whether GTAC should be encouraging applicants to do trials using self-inactivating ("SIN") vectors. See section 3.

The Committee held a well-received public-meeting, this year in Manchester on "Demystifying gene therapy" which attracted around 75 attendees. See Section 4.

In its lifetime the Committee has approved 113 trials, most of which are now closed for recruitment. Short summaries of some of these trials are given in Section 5, and show how results can help shape future trials.

The final section of this report details GTAC's terms of reference and membership, external expert advisers, and the summary of UK trials 1993-2005. Around 960 patients have been enrolled onto UK gene therapy trials by December 2005.

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2005

In 2005, GTAC received fifteen new applications (GTAC 100 to 114) to undertake gene therapy clinical trials in the NHS. Of these, twelve were approved and three applications were declined. The committee also received over 50 applications to amend ongoing protocols.

1.1 CANCER

Cancer is a multi-factorial disease where cells escape the body's control mechanisms and invade, erode and destroy normal tissue. The driving forces in the development of cancer are the cell's genes which can become damaged by a variety of factors such as the environment, diet and life-style. The chance of developing cancer can also be increased by an individual's genetic make-up, for example, in the case of familial breast and ovarian cancer, due to mutations in the BRCA and other genes. There are over 200 different types of cancer that can occur anywhere in the body. Surgery is usually the treatment of choice, however, cancer is less amenable to curative surgery once it has spread beyond the original tumour (metastasised). Gene therapy offers a new, but still experimental, potential treatment that could complement conventional treatments such as surgery, chemotherapy and radiotherapy. In fact, 72% of all gene therapy clinical trials in the UK aim to develop treatment for cancer (see Figure 3, Annex F).

1.1.1 Prostate cancer

Prostate cancer is a disease in which malignant (cancer) cells form in the tissues of the prostate. The prostate is a gland in the male reproductive system located just below the bladder (the organ that collects and empties urine) and in front of the rectum (the lower part of the intestine). Prostate cancer is found mainly in older men mostly over the age of 50. It can occur in younger men but this is very rare. Detected early, prostate cancer is a very treatable disease. Unfortunately, many men with prostate cancer are diagnosed at a late stage when the disease is less amendable to treatment.

GTAC 112: A phase III randomized, open-label study of docetaxel in combination with CG1940 and CG8711 versus docetaxel and drednisone in taxane-naïve patients with metastatic hormone-refractory prostate cancer with pain.

GTAC 113: A phase III randomized, open-label study of CG1940 and CG8711 versus docetaxel and prednisone in patients with metastatic hormone-refractory prostate cancer who are chemotherapy-naïve.

These are two related immunotherapy protocols for phase III trials in patients with prostate cancer. Immunotherapy for cancer is based on the premise that a patient's immune system can be activated to eradicate primary and metastatic tumours. The cellular immunotherapy product used in this trial is comprised of two prostate cancer cell lines (CG1940 and CG8711) that were genetically modified to secrete an immune-stimulating cytokine, granulocyte-macrophage colony stimulating factor (GM-CSF). The GM-CSF gene was introduced into the tumour cells *ex vivo* using a recombinant adeno-associated viral (AAV) vector.

GTAC 112 is a phase III clinical trial designed to evaluate cellular immunotherapy administered in combination with chemotherapy compared to chemotherapy alone in patients who are experiencing cancer-related pain. GTAC 113 is a phase III clinical trial designed to evaluate cellular immunotherapy compared to chemotherapy in patients who are asymptomatic for cancer-related pain. The main objective of both trials are to compare the duration of survival in the two treatment arms. Six hundred patients, at approximately 120 centres across Europe, the USA and Canada will be recruited. GTAC approved both studies in September.

1.1.2 Kidney cancer

The kidneys' function is to filter the blood and rid the body of excess water, salt, and waste products. The filtered waste products are concentrated into urine. Renal cell carcinoma is the most common type of kidney cancer. It accounts for more than 90% of malignant kidney tumours. There are five main types of renal cell carcinoma that are identified by examining the tumour under a microscope. Of these, clear cell renal cell carcinoma appears very pale or clear. This is the most common form of renal cell carcinoma. About 70% – 80% of people with renal cell carcinoma have this kind of cancer. Like all cancers, renal cell carcinoma begins small and grows larger over time. Although renal cell carcinoma usually grows as a single mass within the kidney, a kidney may contain more than one tumour. Sometimes tumours may be found in both kidneys at the same time. Some renal cell carcinomas are noticed only after they have become quite large; most are found before they metastasise (spread) to other organs through the bloodstream or lymph vessels. Like most cancers, renal cell carcinoma is difficult to treat once it has metastasised.

GTAC 104: Safety, immunology and efficacy evaluation of TroVax in patients with stage IV clear cell renal carcinoma.

TroVax has been used in a number of GTAC approved cancer trials. This is the first time it is used in patients with kidney cancer. TroVax is based on modified Vaccinia Ankara Virus (MVA) which carries the gene for "oncofoetal antigen" or "5T4" which is found on the surface of many cancer cells. The strategy is to immunise patients against 5T4 in an attempt to alert the immune system to the presence of the cancer cells. A single dose is tested in 10 evaluable patients. The primary objectives of the trial are to assess the safety and tolerability of TroVax injections in patients with renal cell carcinoma, and to assess the immune responses induced by TroVax. The study was conditionally approved in April.

1.1.3 Liver and colorectal cancer

Hepatoma, which is also known as hepatocellular carcinoma or HCC, is the most common type of primary liver cancer. It accounts for over 85% of all liver cancers. It is more likely to develop in men than in women and becomes more common with increasing age. HCC develops from the main liver cells called hepatocytes. It usually occurs in people who have a damaged liver from "cirrhosis". Cirrhosis is scarring of the liver due to previous damage. This scarring can cause problems with the functioning of the liver. Cirrhosis can be caused by virus infections such as hepatitis B or C. It can also be caused by alcohol, or by inherited diseases such as haemochromatosis (a rare genetic disease that results in the over-abundance of iron in body tissues) and antitrypsin deficiency (an inherited disorder that causes lung or liver disease).

Colorectal, or bowel, cancer can affect the large bowel (colon) and rectum. Colorectal cancer is responsible for about 10% of all new cases of cancer in the UK population. It is the third most common cancer in men (after prostate and lung cancer), and the second most common cancer in women (after breast cancer). Each year, there are over 18,700 new cases of colorectal cancer in men, and over 16,800 cases in women in the UK.

GTAC 101: An ascending dose trial of the safety, tolerability and biological effect of intra-arterial injection of the selectively replication-competent herpes simplex virus HSV1716 in patients with unresectable hepatocellular carcinoma.

HSV1716 is a modified HSV virus which cannot infect cells that are not themselves rapidly dividing. Tumour cells are rapidly dividing and HSV1716 should be able to selectively infect these cells and hopefully kill them. The same vector has been used in a number of GTAC approved studies such as the GTAC 018 series and more recently in a phase III trial in glioma patients (GTAC 74). Patients eligible for this new trial have unresectable hepatocellular carcinoma (HCC) that is unsuitable for liver resection or liver transplantation. The primary objective of the trial is to determine whether HSV1716 given by direct intra-arterial injection in patients with HCC is safe and well tolerated. GTAC considered this trial at its April meeting and judged that the application required some revision. The application was declined but the researchers were invited to submit a new application addressing GTAC's points.

GTAC 110: A single arm open-label phase I study of an injectable replication-incompetent adenoviral vector encoding a factor VII immunoconjugate to induce a cytolytic immune response against the vasculature of carcinoma of the bowel with metastatic lesions to the liver.

Tumour growth and the ability to metastasise are linked to the ability of the tumour to promote angiogenesis. The hypothesis is that if it were possible to cut off the blood supply, the tumour would die. The study seeks to exploit this by way of a molecule called the "Icon" protein which is designed to specifically target and mark up for destruction only tumour vessels (leaving normal vessels unscathed). The vector is a replication-incompetent adenovirus carrying the gene for the Icon protein. Subjects receive a single injection of the vector intratumourally into a liver lesion via ultrasound guided percutaneous (through the skin) injection. GTAC discussed this application in September and judged that the application required some revision. The application was declined but the applicants were invited to resubmit a new modified version of this study.

1.1.4 Blood cancer (leukaemia)

Leukaemia is a cancer of the white blood cells. White blood cells are produced by the bone marrow. There are two main types of white blood cell, lymphoid and myeloid, which are produced from different bone marrow populations. The lymphoid population includes all lymphocytes and plasma cells which are involved in antibody production and other roles in the immune system. All the other blood cells are grouped together as myeloid. The four main types of leukaemia are acute myeloblastic (AML), acute lymphoblastic (ALL), chronic lymphocytic (CLL) and chronic myeloid (CML).

GTAC 108: An open-labelled, international, multicenter, dose escalating, phase I/II study of SPC2996, an LNA antisense molecule against Bcl-2, in patients with relapsed or refractory chronic lymphocytic leukaemia.

This is a trial employing antisense technology. It was reviewed by GTAC in its function as a UKECA recognised research ethics committee (see section 2.3). The construct called SPC2996 is a 16-base oligonucleotide (short bit of single stranded nucleic acid) designed to bind to the messenger RNA of a gene called Bcl2 and in doing so prevents the RNA being "read" by the cells machinery. The aim is to stop production of the Bcl2 protein which, when elevated, prevents cancer cells from undergoing programmed cell death (apoptosis). The antisense product is injected intravenously into patients with CLL who have relapsed following treatment or whose disease does not respond to other therapy. The study was discussed in June and received conditional approval. Final approval was given in August.

1.1.5 Head and neck cancer

Squamous cell cancer of the head and neck is the sixth most common cancer worldwide. There are about 76,000 cases diagnosed in Western Europe each year. Treatment for advanced disease usually requires a multidisciplinary approach and may involve the use of radical radiotherapy with concomitant chemotherapy. In some patients this might be followed by radical neck dissection. There is some variation in the treatment of this cancer depending on the site and stage of the disease.

GTAC 105: A phase II exploratory study of the safety and biological activity of OncoVEX$^{GM\text{-}CSF}$ in combination with radiotherapy and cisplatin in the treatment of locally advanced epithelial cancer of the head and neck.

OncoVEX is a Herpes Simplex Virus (HSV) vector used as a potential treatment of solid tumours. OncoVEX results in death of infected cells, which causes the release of cancer proteins (antigens) from these cells. The antigens can then be recognised by the immune system. Once stimulated in this way, it is hoped that the immune system can mount an attack on the tumour tissue. The OncoVex construct combines oncolytic tumour therapy, which will destroy the tumour with the action of an immuno-stimulatory molecule, GM-CSF. This means it has the potential not only to induce a local anti-tumour effect but also a systemic anti-tumour immune response which may be effective in the treatment of metastatic disease. This study focuses on head and neck cancer. Delivery of the vector is by direct tumoral injection. The primary objective is to assess the safety of OncoVEX combined with chemo-radiotherapy in patients prior to radical neck dissection. The study was discussed in April when it received conditional approval in April. Full approval was given in August.

1.1.6 Multiple cancers

GTAC 100: A phase II study of NY-ESO-1 ISCOMATRIX vaccine and NY-ESO-1 ISCOMATRIX vaccine followed by recombinant fowlpox NY-ESO-1 (rF-NY-ESO-1) in patients with high-risk, resected NY-ESO-1 positive melanoma and prostate carcinoma.

NY-ESO-1 is a highly immunogenic, tumour specific antigen that is expressed in a variety of cancers including prostate and melanoma. This is a two arm study in which patients either receive six doses of the NY-ESO-1 protein mixed with the adjuvant lipid (ISCOMATRIX), or three doses of this followed by three doses of the recombinant fowlpox virus encoding the

NY-ESO-1 protein. A common problem encountered with viral tumour vaccines is that once patients have been immunised with the gene therapy virus, the immune system might subsequently elicit a greater immune response against the virus than the antigen itself. By injecting with protein first it is hoped that the immune response will be directed mainly towards the antigen (and thus the cancer). The study received conditional approval in February, followed by final approval in May.

GTAC 103: A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL-2 in patients with CD19 positive malignancy.

This study is similar to the GTAC 096 study approved by GTAC in November '04. It describes a complex scheme of gene therapy and chemotherapy for patients with CD19 positive cancers. CD19 is found in the majority of B cell derived malignancies as well as in Non-Hodgkin's lymphoma. The study product is a retroviral vector which carries three genes: a single chain antibody specific for CD19 (anti-CD19), a CD3 subunit protein which actives T cells, and a marker gene (truncated CD34) which allows for the selection of modified T cells which produce the transgene. This is an ex vivo study which involves the harvest of T cells from patients with CD19 positive cancers, exposure of these T cells to the study vector, and the re-infusion of the modified T cells back to the patient. The primary objectives are to evaluate the feasibility and safety of this approach and to determine survival and toxicity of modified cells given with pre-conditioning chemotherapy and intravenous IL2. The study was first discussed in April and received GTAC approval in June.

GTAC 102: A phase I study of intra-peritoneal Ad-hTR-NTR and CB1954, an adenovirus-delivered telomerase-directed enzyme-prodrug therapy, in patients with advanced intra-abdominal cancer.

A central cause for the immortality of cancer cells is known to be associated with high levels of activity of a cellular enzyme called "telomerase". This phenomenon can be exploited as a method to target a gene therapy agent to cancer cells with high telomerase activity. The study product is an adenoviral vector and contains as the transgene the sequence of the bacterial nitroreductase (NTR) enzyme. The production of NTR is driven by the telomerase promoter which restricts the production of NTR to cancer cells with high telomerase activity. NTR converts the relatively harmless prodrug CB1954 into its active, toxic, form which is hoped will kill the cancer cell (gene directed enzyme prodrug therapy). Patients eligible for this trial have advanced, inoperable, intra-abdominal carcinoma with ascites. Patients receive a single intra-peritoneal administration of one of an escalating dose of the gene therapy vector followed, 48 hours later, by a single intra-peritoneal administration of a fixed-dose of the pro-drug CB 1954. The study was discussed in April and received conditional approval.

GTAC 109: A phase I, dose-escalating trial of JX-594 (thymidine kinase-deleted vaccinia virus encoding GM-CSF) administered by intravenous infusion in patients with refractory solid tumours.

The study involves the use of an oncolytic vaccinia virus, deleted for the gene encoding the thymidine kinase enzyme, a modification that should restrict its replication and spread to dividing cells such as cancer cells. On destroying a cancer cell the virus should release cell

debris, a process which has the potential to stimulate an anti-cancer immune response. To maximise this effect the virus is carrying GM-CSF which is known to enhance the recruitment and activation of antigen-presenting cells and therefore is included to boost the immune response to the cell debris. The drug is given intravenously and all the patients enrolled have metastatic cancer. The main aim is to establish the maximally tolerated dose (MTD). The study received GTAC approval in June.

1.2 HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Bone marrow transplantation (BMT) is used to treat a wide range of conditions, including blood cell cancers, inherited abnormalities of the immune system and certain metabolic disorders. The process relies on the transfer of blood stem cells from a suitable donor to the patient. T cells, which are white blood cells, play a central role in helping the donor stem cells establish themselves in the recipient. T cells' job is to eliminate foreign molecules (viruses, cancerous cells etc). In recipients of bone marrow transplants this feature of T cells can become a problem. T cells recognise small differences between donor and the recipient, hence, donor T cells may start attacking normal tissues in their new host. This complication is called graft-versus-host-disease (GvHD). Thus, unless the donor and recipient are very closely matched, T cells have to be removed from the graft, or are heavily suppressed using drugs. Under these circumstances, T cells' beneficial effects are lost and the risk of graft failure or infective problems increases.

GTAC 106: A phase I/II clinical trial of T cell suicide gene therapy following allogeneic haematopoietic stem cell transplantation.

One way to harness the beneficial effects of T cells, whilst allowing their elimination in the event of GvHD, is to fit the cells with a suicide mechanism which can be turned on by giving a specific drug. This study utilises the Herpes simplex thymidine kinase (TK) as the suicide mechanism. Donor cells which are modified to carry the TK gene can be removed by giving patients the drug Gancilovir in case GvHD occurs. The donor T-cells are modified using a retrovirus that carries a suicide gene (thymidine kinase). This allows the modified donor T-cells to be destroyed by giving the antiviral Ganciclovir should the patient develop GvHD. GTAC considered this trial at its June meeting and judged that the protocol required some revision. The application was declined but the researchers were invited to resubmit the application addressing GTAC's points.

1.3 AUTOIMMUNE DISEASES

1.3.1 Multiple sclerosis

Multiple sclerosis (MS) is a condition of the central nervous system. It is the most common disabling neurological disease among young adults and affects around 85,000 people in the UK, 400,000 people in the US, and as many as 2.5 million individuals worldwide. MS is most often diagnosed between the ages of 20 and 40, and women are almost twice as likely to develop it as men. At present, there is no cure for MS.

The central nervous system is made up of the brain and spinal cord, which acts as the central message pathway from the brain to all parts of the body controlling both conscious and unconscious actions. Surrounding and protecting the nerve fibres of the central nervous system is an important protein called myelin, which helps messages travel quickly and smoothly between the brain and the rest of the body.

MS is an autoimmune condition. For reasons that are not fully understood, in MS, the immune system attacks myelin. This damages the myelin and strips it of the nerve fibres leaving scars known as lesions or plaques. This myelin damage disrupts messages travelling along nerve fibres – they can slow down, become distorted, pass from one nerve fibre to another (short circuiting), or not get through at all. As well as myelin loss, there can be damage to the actual nerve fibres. It is this nerve damage that causes the accumulation of disability that can occur over time. As the central nervous system links all bodily activities, many different types of symptoms can appear in MS. The specific symptoms that appear depend upon which part of the central nervous system is affected. Current therapy involves immunosuppressive agents such as corticosteroids and immune modulators such as beta interferon. Interferons are a family of immune-regulating proteins secreted by the immune system in response to infection. These drugs do not eliminate the disease, but work to reduce the severity of disease and its progression.

GTAC 107: A multicenter, randomized, double blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of BHT-3009 when administered intramuscularly to patients with relapsing remitting multiple sclerosis.

The strategy employed in this study is antigen-specific immunotherapy designed to decrease the autoimmune response that underlies MS. Several protein components of the myelin sheath are known to be targets of the autoimmune response ("auto-antigens"). These include myelin basic protein (MBP), proteolipid protein, and myelin oligodendrocyte glycoprotein. MBP is generally regarded as the predominant auto-antigen. The study product, called BHT-3009, is plasmid DNA which contains the gene for MBP. The hope is that BHT-3009 will tolerise and/or dampen the autoimmune response to MBP in myelin. The patient population for this trial are individuals with relapsing remitting MS who have low performance. Approximately 252 male and female patients with relapsing remitting MS will participate in this study. Eligible patients will be randomised to one of three blinded treatments, two doses of the product and one placebo. The study drug is administered intramuscularly into the arm. The study was discussed in June when it was approved.

1.3.2 Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune condition that causes weakness and fatigue in muscles. It can be fatal, and there is no cure. In order for a muscle to contract, the nerve ending carrying the signal to the muscle releases a chemical messenger called Acetylcholine (ACh). The ACh binds to the muscle cell causing its activation. Another chemical called Acetylcholinesterase (AChE) breaks down excess Ach and it is removed from the body. In patients with MG, the immune system produces antibodies that stop muscle cells from responding to ACh.

GTAC 111:A Phase II double blind, cross-over study to compare the safety and efficacy of 125, 250 and 500 ug/kg Monarsen (EN101) administered to patients with myasthenia gravis.

This antisense study was considered by GTAC in its function as UKECA recognised REC (see section 2.3). The product (called Monarsen) consists of an antisense oligonucleotide (20 bases long) that targets the production of AChE. This trial is "double blind" and therefore neither the investigator nor the patient will know what (randomly allocated) dose has been given to each patient until the end of the study. Three doses of Monarsen will be tested. The Monarsen will be given orally on a daily basis for one week followed by one week of treatment with Mestinon (a common treatment for MG) . On the third week of treatment patients will receive a second and different dose of Monarsen for a week. At the end of this week patients will receive again Mestinon for one week, followed by the third dose of Monarsen. The primary objective of the trial is to assess the efficacy and safety of Monarsen. The secondary objective is to assess the quality of life of patients using a questionnaire. The study was approved in September.

1.4 PERIPHERAL ARTERY DISEASE

Arteries are the blood vessels that take oxygen-rich blood from the heart to all parts of the body. Peripheral artery disease (PAD) is a common problem in late middle age, leading to severe pain on walking, tissue breakdown and ulceration, loss of toes due to gangrene, and limb amputation. This disease is caused by arteriosclerosis (fatty like deposits in the arteries) resulting in narrowing of the arteries reducing the amount of oxygen reaching the extremity of the limb. The decrease of oxygen supply to the tissues (ischemia) causes pain on exertion. People with PAD are also likely to have narrowing of other arteries in the body. If there is narrowing in the arteries which supply blood to the heart, it can cause angina or a heart attack. If the arteries to the neck are affected, it can interfere with the flow of blood to the brain and may cause a stroke.

GTAC 114:A phase II randomized, double-blind, placebo-controlled, parallel-Group, multi-center study of Ad2/Hypoxia inducible factor (HIF)-1alpha/VP16 administered by intramuscular injection to patients with no or poor option chronic critical Limb ischemia.

Patients with peripheral arterial disease and atherosclerosis frequently suffer critical limb ischemia which develops when the blood flow does not meet the metabolic demands of tissue at rest. This study proposes to administer hypoxia induced factor-1· (HIF-1alpha) via an adenoviral vector. HIF-1a affects the expression of a number of angiogenic growth factors which have the ability to stimulate the growth of new blood vessels. This chain reaction of events is hoped may increase the flow of oxygenated blood to ischemic cells. Patients with no or poor options for the treatment of chronic critical limb ischemia (CLI) will be randomised to receive either Ad/HIF-1a or placebo by way of a single treatment to the limb of patients in 20 injections. The study was approved at the December GTAC meeting.

1.5 AMENDMENTS TO ONGOING PROTOCOLS

In 2005, GTAC processed seven applications for approval of substantial amendments at committee meetings and almost fifty applications between committee meetings. GTAC and CSM also approved the enrolment of one patient each into the X-SCID (GTAC 045) and CGD (GTAC 046) clinical trials.

SECTION 2: REGULATORY ISSUES

2.1 RECOMMENDATIONS OF THE GTAC/CSM WORKING PARTY ON RETROVIRUSES

In March 2005, GTAC and the Committee on Safety of Medicines (CSM) met to discuss the implications for the UK of a new serious adverse event in the French trial for X-linked severe combined immunodeficiency (X-SCID). The final report of GTAC/CSM was posted in May on the GTAC website (see http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm) and is published also in *Human Gene Therapy*, Recommendations of the Gene Therapy Advisory Committee/Committee on Safety of Medicines Working Party on Retroviruses, Oct 2005, Vol 16, 10:1237-1239.

2.2 FLAGGING PROJECT WORKSHOP

In September, a meeting took place of a GTAC working group on the long term monitoring of gene therapy volunteers. The meeting had the following aims:

- to review the current practice on the flagging of patients enrolled in gene therapy studies.
- to explore the clinical, scientific and ethical issues of long-term monitoring.
- to obtain input from interested parties on the flagging project.
- to make recommendations in relation to the future design and execution of the flagging project.

The group issued a report which contained a number of recommendations. This report, in particular Recommendation 4, was considered by GTAC at its September meeting. GTAC decided to grant exemption from the flagging project to trials that use low risk products, for instance those that have a very low risk of affecting vector integration and recombination (for instance: antisense oligonucleotides, plasmid DNA and vaccinia derived vectors). Volunteers in trials that use integrating vectors such as retroviruses and lentiviruses should be offered participation in the flagging project, as should be those receiving AVV and HSV derived vectors unless a convincing rationale to the contrary is given. In case of doubt, researchers are encouraged to contact the GTAC secretariat.

The full report is published on the GTAC website
http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm.

2.3 DEFINITION OF GENE THERAPY AND REVIEW OF CLINICAL TRIALS

GTAC is the UK national research ethics committee (REC) for gene therapy clinical research according to the Medicines for Human Use (Clinical Trials) Regulations 2004 (http://www.opsi.gov.uk/si/si2004/20041031.htm, see article 14(5)). It is the only UK ethics committee empowered to approve clinical trials of gene therapy products according to the definition given in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC):

L159/88 *"... [a] gene therapy medicinal product s mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell."*

Under the Clinical Trials Regulations, GTAC is required to provide an ethical opinion on applications for use of products that fall within the above definition within 90 days of receipt of a valid application. Some gene therapy trials are also subject to the "flagging project", please see http://www.advisorybodies.doh.gov.uk/genetics/gtac/flagging.htm.

GTAC's definition of gene therapy is as follows:

"The deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes."

This includes techniques for delivering synthetic or recombinant nucleic acids into humans:

- genetically modified biological vectors (such as viruses or plasmids)
- genetically modified stem cells
- oncolytic viruses
- nucleic acids associated with delivery vehicles
- naked nucleic acids
- antisense techniques (for example, gene silencing, gene correction or gene modification)
- Genetic vaccines
- DNA or RNA technologies such as RNA interference
- xenotransplantation of animal cells (but not solid organs).

This definition is slightly wider than that given in Directive 2003/63/EC. In order to cover this, GTAC is a UKECA recognised REC and wishes to approve clinical trials that use certain gene therapy related products that are not covered under the legal definition (for instance, antisense applications) but that are covered by the above definition. In these instances, GTAC is required to provide an ethical opinion within 60 days of receipt of a valid application. The flagging project does not apply.

In case of doubt, please contact the GTAC Secretariat.

2.4 RELEVANT LEGISLATION

The Medicines for Human Use (Clinical Trials) Regulations 2004

These regulations came into force on 1 May 2004 and name GTAC as the national research ethics committee for gene therapy research (Article 14(5), see: http://www.opsi.gov.uk/si/si2004/20041031.htm).

Draft regulation on advanced therapy medicinal products

A relevant initiative for gene therapy researchers is the new EU (draft) regulation on Advanced Therapies, published in May, which is intended to bring together **gene therapy** and somatic **cell therapy** and **tissue engineered products** as advanced therapy medicinal products. Details on this proposal for a regulation of the European Parliament and of the Council on Advanced Therapies and amending Regulation (EC) No 726/2004 can be found here: http://europa.eu.int/comm/enterprise/pharmaceuticals/index_en.htm.

EU Tissues and Cells Directive

From April 2006, anyone storing human tissue or cells for therapeutic use must be in possession of a licence from the Human Tissue Authority (http://www.hta.gov.uk/) which is when the EU Tissue and Cells Directive becomes law (for details see: http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2006/l_038/l_03820060209en00400052.pdf).

SECTION 3: GUIDANCE ISSUES

3.1 ADVICE TO RESEARCHERS

In its function as the national ethics committee for gene therapy research GTAC provides advice to researchers on issues of clinical trials of gene therapy, for instance, on the content of future proposals for gene therapy research on human subjects, on the appropriate design and conduct of the proposed research, on the facilities necessary for the proper conduct of the research and on arrangements necessary for appropriate patient information and consent. In the reporting year, GTAC invited the Cystic Fibrosis Consortium and the Muscular Dystrophy Campaign, to give presentations of their work, and gave advice on various aspects of future clinical trials for cystic fibrosis and Duchenne Muscular Dystrophy respectively.

3.2 HORIZON SCANNING ACTIVITIES

In order to be aware of different developments related to gene therapy and associated technologies, GTAC invites external speakers to brief members on new advances. In the reporting year, GTAC heard a presentation by Professor Stephen Minger (Centre of Age-Related Diseases, King's College London) who spoke about the latest advances and issues in stem cell biology and clinical research, Professor Manuel Grez who updated GTAC with findings in the clinical trial for CGD in Germany, and Dr Mike Themis (Imperial College London) on lentiviral vectors. GTAC is extremely grateful to Prof Minger, Prof Grez and Dr Themis for helping keep the committee informed of relevant developments.

3.3 GUIDANCE & APPLICATION FORM FOR NAMED PATIENT USE OF GENE THERAPY PRODUCTS

In October, GTAC issued Guidance and an application form for named patient use of gene therapy products, which can be found on the GTAC website:
http://www.advisorybodies.doh.gov.uk/genetics/gtac/applicform.htm.

3.4 CONSULTATION ON FUTURE DESIGN OF RETROVIRAL VECTORS

In October, GTAC sent an open letter to gene therapists and other regulatory bodies following the publication of the updated recommendations of the GTAC/CSM working party on retroviruses (Section 2.1). The working party had identified a number of advances in vector design that may be advantageous to pursue in the longer-term and for future generations of retroviral vectors. A key recommendation of the working party was that there be a move towards the use of self-inactivating (SIN) vectors and non-viral promoters to drive therapeutic genes (Recommendation 6). GTAC invited interested parties to contribute to its discussion on whether non-SIN vectors should be phased-out and if so by when.

This is a summary of comments received:

- Difficulties in evaluation of safer vectors remain considerable. Currently there are no validated systems in vitro or in vivo that are predictive of mutagenic potential.

- No rigorous comparisons of SIN and non-SIN vector configurations in any model of mutagenesis have been reported to date. Thus, the benefits of the non-SIN configuration have not yet been proven.
- Though there is evidence of the non-SIN configuration being involved in the leukaemia phenotype in humans, no evaluation on the safety of SIN vectors is available. There is no evidence of long-term non-SIN verses SIN configuration.
- There is currently no robust GMP process for the production of clinical grade SIN gamma-retroviral vectors in sufficient titre for clinical application though newer systems are under development. Premature withdrawal of non-SIN vectors could therefore impede the application of gamma-retroviral vectors to gene therapy.
- Non-SIN retroviruses have shown encouraging performance in clinical trials of SCID and CGD. Efficient GMP production of SIN vectors may take some considerable time and cost to develop, it would be wrong to phase out non-SIN vectors in the meantime since they may offer treatment options for patients without viable alternative.
- It is often difficult to manufacture SIN retroviral vectors, potentially making then an academic, rather than a practical option. If titres are low then this may lead to the use of higher risk protocols involving repeat transductions and amplification of transduced cell populations. This recommendation therefore, while superficially appealing maybe counter-productive.
- More basic research is needed to prove that non-SIN retroviral vectors really are more dangerous than SINs
- Patient safety is the central prerequisite for gene therapy vectors particularly for diseases that are not in themselves life threatening. Currently there is not enough evidence to phase out non-SIN vectors.
- Non-SIN retroviruses have shown encouraging performance in clinical trials of SCID and CGD. Efficient GMP production of SIN vectors may take some considerable time and cost to develop, it would be wrong to phase out non-SIN vectors in the meantime since they may offer treatment options for patients without viable alternative.
- With regards to CGD, new SIN vectors are very much in the development phase and they are not likely to come on-stream for a number of years. Until these vectors come on stream non-SIN retroviruses are being used to treat CGD patients with promising results.
- Moving towards SIN vectors could potentially negatively influence the perception of the gene therapy research community, investors and potential pharmaceutical partners.
- The recommendation is important in the context of X-SCID trials but the advice should be restricted to this specific therapy or to trials that are closely related.
- Observations have shown that even SIN configuration can be strongly associated with oncogenesis should be considered.

- Although most opinions are agreed that the SIN configuration in theory should be a safer option there appears to be issues on vector read through. This issue is still under investigation.
- If MLV vectors have been more thoroughly characterized with regards to promoter and enhancer effects these vectors in theory would be better suited to be used in the SIN configuration. This configuration appears still to be limited to promoter effects and does not address enhancer effects.
- It may not be desirable to suggest in detail how the basic recommendation might be achieved. This rather prescriptive advice that has been proposed would constrain the field, stifle innovation, may not be relevant for all protocols and may not be practical.
- Data is emerging, in one animal model that may have relevance to clinical protocols for human X-SCID, a SIN vector is less likely to induce tumours. However, a universal requirement for SIN vectors could block the development of even more useful vectors.
- Support evaluation of each application on the basis of vector configuration, transgene type, disease background, and the specific cell and patient population being studied.

After careful analysis of the comments received, GTAC considered that there was insufficient evidence at this time for a consensus on retroviral vectors to emerge. However, GTAC is keeping this issue under review and once more information is available on the use of SIN vectors and non-viral promoters this consultation may be repeated. Until such time, GTAC will continue to consider protocols utilising retroviral vectors by judging each application's respective merits and risks on a case-by-case basis. A letter to this effect went out to all respondents in December.

SECTION 4: GTAC PUBLIC MEETING – Demystifying Gene Therapy

GTAC's 2005 public meeting was held in Manchester and covered the process of gene therapy clinical trials, including informed consent, with Haemophilia as an example of a disease where gene therapists have been working to produce novel therapies. The full delegate pack of the meeting is available on the GTAC website: http://www.advisorybodies.doh.gov.uk/genetics/gtac/delegatepack3.pdf).

4.1 SUMMARY

Dr Christian Ottensmeier's talk on "demystifying gene therapy clinical trials" gave an overview of what gene therapy and genetic vaccination is and how various techniques work, the processes involved in obtaining permission to start a trial, and the typical timelines for bringing these new approaches to patients.

Dr John Ellis's spoke about "From molecule to market – developing a gene therapy drug". He sketched out the lengthy drug development process, and how it involves exhaustive testing of new medicines to ensure that licensed medicines are of high quality, as safe as possible, and will benefit patients.

Dr Tuija Takala and Dr Lisa Bortolotti, focussed on "research ethical issues in gene therapy".

GTAC member Mrs Debbie Beirne presented her views on "the process of informed consent in gene therapy research", which detailed how to gain the voluntary informed consent and cooperation of patients to participate in clinical trials, the most important consideration throughout being the protection of patients.

Mr Adam Jones talked about his personal experience of living with Haemophilia, and Dr Glenn Pierce then outlined "haemophilia gene transfer: solution to global treatment gaps."

Finally, Mrs Renée Watson, covered "awareness and involvement: BSGT, patients and the public", as the GTAC meeting was held before the annual BSGT meeting. For BSGT event details see: www.bsgt.org/

The audience then attended one of there possible parallel sessions, each chaired by a GTAC member.

Bishop Dr Lee Rayfield chaired a session on the report by the Science & Technology Select Committee on Human Reproductive Technologies and the Law, published on 24 March, following a year-long inquiry. The report made 104 recommendations to the Government on how the law in this area should be updated.

Mrs Fiona Sandford chaired a session about GTAC's decisions to do with the UK X-SCID gene therapy trial in light of the three cases of leukaemia, including one death, on the French X-SCID trial.

Dr Michael Waterhouse chaired a session called "Future developments in gene therapy?" where issues of gene therapy for genetic enhancements and germ-line gene therapy were discussed.

4.2 WHAT THE AUDIENCE THOUGHT OF THE PUBLIC MEETING

For GTAC's 2005 public meeting in Manchester, 36 feedback forms were received: a 48% response for an attendance of around 75 people. 33% of responders classified themselves as scientists, 19% as students, 11% as charity representatives, 5% as nurses, and 31% as "other". "Others" who provided an explanation included "LREC member/administrator" (3), "social scientist" (1), "pharmacist" (1), "patient" (1), and "Government representative" (1).

98% of delegates rated the event as Excellent (56%) or Good (42). Delegates rated the speakers as Excellent (50%) or good (44%), although some commented that the speakers were "very mixed". The delegate pack was rated as Excellent (50%) or Good (44%) & the promotional flyer as Excellent (36%) or Good (50%).

The three involvement sessions were overall rated as Excellent (25%) or Good (36%) although 31% did not provide a rating. The "Enhancement" session was clearly the most popular session, attracting the most attendees, and 14 people providing a rating (43% "excellent", 43% "good" and 14% "fair), but the other two sessions only received a handful of ratings: 5 for the X-SCID session (40% "excellent", 60% good) and 3 for the Select Committee Report session (33% "excellent", 66% "good").

In comparison with the last two events (in Cambridge in 2004, and in Edinburgh 2003), the attendance of 75 was a bit disappointing compared with previous years (2004: 88, 2003: 140). However, with an overall event rating of 56% "excellent", those who attended seemed to enjoy the event, although not quite as much as Cambridge (69% "excellent"), but a lot more than Edinburgh (33% "excellent").

Unsurprisingly, 100% thought that the Government should continue to support UK gene therapy and clinical trials. 95% had discussed gene therapy with family and friends. 53% thought the event had changed their perception of gene therapy. 75% of delegates had heard of GTAC before attending the meeting. There were a number of comments about whether the event had changed the delegate's perception of gene therapy:

- [Yes] Better recognition of patient concerns/desires and technical issues.
- [No] Excellent talks from Glenn Pierce, Adam [Jones] and the nurse [Deborah Beirne].
- [No] Not my perception, but more the obvious need to communicate more to both patients and the general public.
- [Yes] Never heard of vaccines before and all the research in cancer field – really interesting.

- [Yes] Dr Ottensmeier exceptionally good and very easy to understand. Presentation on ethics disappointing and Finnish language problems could have contributed. There seemed to be a fundamental misunderstanding of issues or a disinclination to engage. Debbie Beirne was very good. Adam Jones made a very valuable contribution.
- [Yes] It has widened my knowledge and enabled me to see it is an extremely controversial issue.
- [Yes] The meeting was extremely informative and thought-provoking, and presented in a way accessible to "lay" people. I now have a better understanding and appreciation of the issues involved with gene therapy.
- [No] I feel much better informed and pleased to have my opinion confirmed.
- [Yes] The talk by Adam Jones made me think of gene therapy from the patient's point of view.
- [Yes] Better understanding of the whole process & how long it all takes. Patient views are a great incentive to keep going when it all gets difficult.
- [Yes] Very useful. I would recommend it to the patients I am in contact with (CF).
- [Yes] I strongly feel there should be more events like this throughout the country.
- [Yes] Now more informed after this event.
- [Yes] I already work in the field – it was good to hear about another disease – I attended the Edinburgh session on CF and it was good to hear about haemophilia this time.

And many additional comments:

- More members of the public should attend.
- There should be a systematic study of public understanding and attitudes. There should be panel of good medical communicators who would be prepared to answer any negative publicity. [Perhaps] BSGT or GTAC?
- Please continue all means of public engagement/interactions.
- Very useful and stimulating.
- A bit too short [the X-SCID involvement session] – would have liked more time for discussion.
- A longer involvement [X-SCID] session would be desirable.
- Speakers represented a good mix of "science" and practical/personal perspectives towards gene therapy.
- It's quite hard to contribute to the [Select Committee Report] debate when you don't have expertise in the area.

- I heard about the day via LREC – wider publicity to public would have brought in more people – maybe that would present organisational problems but there is a need for public to be better informed.
- Thanks to Adam Jones for presenting his very personal and moving testimony.
- Good discussion, multiple points of view, not enough time for discussion. Needed more focus. [Refers to Enhancement session].
- Some talks too long and detailed e.g. molecule to market. Not enough time for questions and discussions. Public involvement session [X-SCID] – not enough patients, still felt like scientists talking on behalf of patients – priorities are different for patients.
- Would be great to have two such [public involvement] sessions, and perhaps disease specific groups.
- Very enjoyable and informative.
- These session should be repeated in many locations around the UK.
- Excellent in every way (also good food and service).
- More "patients" please. Please GTAC introduce a feedback requirement (annual) for GT trials. Funding bodies could enforce this by asking for this to be done for continued funding. We need the information to be disseminated. Funding bodies can add "clout" to GTAC.
- Involve more patient groups?
- Very useful, try to increase number of "public" attendees, allocate more time to involvement sessions.

SECTION 5: UPDATE OF CLOSED UK CLINICAL TRIALS

The following are short summaries provided by researchers of closed gene therapy trials. GTAC would like to thank all researchers who have contributed to this section, which builds on an initiative of the 2004 report. The summaries are essentially unedited and reflect the views of the researchers.

5.1 CANCER GENE THERAPY TRIALS

5.1.1 Liver cancer

GTAC 32: A dose escalating study of gene directed enzyme prodrug therapy in liver cancer: intratumoural injection of CTL 102, a nitroreductase-encoding adenovirus, with intravenous administration of the prodrug, CB 1954.

Gene directed enzyme-prodrug therapy (GDEPT) seeks to accomplish tumour-targeted chemotherapy by the specific delivery and subsequent expression of a gene encoding an enzyme, that converts a relatively innocuous prodrug, into a potent cytotoxic agent. This trial was intended to evaluate GDEPT for liver cancer using CTL102, a replication-defective adenovirus encoding nitroreductase (NTR) and the prodrug CB1954. The enzyme NTR converts the prodrug, CB1954 into a bifunctional alkylating agent capable of cross-linking DNA and initiating cell death in dividing and non-dividing cells. The trial was designed with two stages:

Stage one (Operable Arm) involved the recruitment of patients with liver malignancies (primary or secondary) scheduled for surgery for injection of CTL102 without prodrug. A dose-escalating schedule covering 7 cohorts was devised from 1 x 108 up to 5 x 10^{11} viral particles with three patients per cohort. 2-5 days prior to surgery recruits received a single dose of virus by intratumoural injection. Following routine surgery histological sections from the injected tumour were examined by immunohistochemistry to identify NTR expression within the malignant and surrounding normal tissue. This data was used to determine the minimum dose of virus that was safe and that give an extent of NTR expression likely to give anti-tumour effects in combination with CB1954. Once this dose was determined the therapeutic arm was initiated.

Stage two (Inoperable – therapeutic arm) was aimed at patients with primary or secondary liver cancer who did not meet the criteria for surgery. These individuals received a single intratumoral injection of CTL102 followed 2 days later by an IV infusion of CB1954 prodrug. The viral dose was escalated to a maximum of 5 x 10^{11} viral particles. This stage of the trial aimed to assess safety and anti-tumour effects of the virus/prodrug combination.

This multi-centre study was initiated in 2000 and recruited 18 patients to the operable arm with no significant toxicity. The therapeutic arm of the trial was initiated at a viral dose of 1 x 10^{11} vps. 5 patients were recruited for administration of virus/prodrug up to a dose of 5 x 10^{11} vps. No significant toxicity was reported.

5.1.2 Head and neck cancer

GTAC 35: A phase II trial of pre-operative intratumoural injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours.

The above study was undertaken to see if a modified virus dl1520 (also known as Onyx-015) could be used to combat certain types of cancer. This virus is an adenovirus designed to selectively kill cells which are missing a protein called p53. The p53 protein is an important part of a normal cells defence against cancer, but if the protein is abnormal or absent from a cell, then cancer is much more likely. The p53 protein is commonly absent in mouth cancer. The dl1520 virus has been genetically modified so as to preferentially grow within, and therefore kill, cells which are missing this p53 protein.

Previous clinical trials involving patients with recurrent squamous cell carcinoma of the mouth have shown the dl1520 virus to have some clinical efficacy when the virus is injected into tumours. These studies did not however show any direct evidence as to whether the virus was targeting cells deficient in the p53 protein. We wanted to determine whether dl1520 is selective for survival and replication within tumour tissue after direct injection and whether this is determined by the levels of p53 protein in the tissues. We also wanted to ascertain whether the virus has any visible effect when injected into normal tissue.

A clinical trial was devised in which a fixed dose of the virus was administered to 15 patients via a direct intra-tumoural injection before surgery for untreated oral squamous cell carcinoma. The agent was also delivered into an area of adjacent normal tissue in the mouth. Specimens of the excised tumour and of biopsies of the injected normal tissue were assessed microscopically for viral presence and p53 status. We demonstrated that the virus replicates selectively in tumor as opposed to normal tissue after this direct injection. It was not possible to determine whether this selectivity was p53 related. No adverse effects of viral injection were noted.

This is the first report of injection of dl1520 into previously untreated squamous cell cancer. The data support the concept that dl1520 does not harm normal tissues when injected directly into them. Further evidence that the virus can survive in cancer tissues was demonstrated, although no shrinkage of these tumours was noted. This indicated that the dl1520 virus could be used in the future as a selective anti-cancer agent, although further research is required. (See: Morley S, et al. *Clinical Cancer Research*, 2004, 10(13):4357-62).

5.1.3 Blood cancer (leukaemia)

GTAC 29D: Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT).

The study was designed to test intramuscular application of idiotypic DNA vaccines as a way of stimulating anti-tumour immunity in patients with chronic lymphocytic leukaemia (CLL). The design is based on the observation that CLL cells express a unique immunoglobulin molecule, which can be used as a specific target for vaccination. Linkage of the unique part of these genes to a strong immune alert signal (Fragment C from Tetanus toxin) then allows the induction of anti tumour immunity.

Peripheral blood lymphocytes were used to produce a new vaccine for each patient. After assembly of the vaccine construct the production of clinical grade material was performed in the Clinical Biotechnology Centre, Bristol. Patients were vaccinated in Southampton University Hospitals and at the Royal Bournemouth Hospital. Key entry criteria were: untreated Binet Stage A CLL, good WHO performance status ($\leq$1) absence of autoimmune disease and other malignancy or serious comorbidity.

The study was open to recruitment from 2001 to 2003. 25 patients were screened and for 8 consenting patients a vaccine was assembled. There were no failures to identify the necessary sequences from the tumour cells and vaccine assembly. Of 5 patients a clinical grade vaccine was made and 3 of these patients were eligible for vaccination after manufacture was complete (1 patient withdrew, 1 patient had disease progression and required standard treatment).

The vaccines were well tolerated with mild side effects (WHO grade $\leq$1). All three patients completed the course of vaccination and are alive at follow up 3 years post vaccination.

The vaccine induced measurable anti-vaccine immunity in all patients and the data are being prepared for publication. No effect on the total white cell count was observed.

We closed the study in September 2003. An important reason was the lack of funding for vaccine production and production capacity. The second reason was limited laboratory capacity for sample processing and performing the endpoint assays. In the interim period since 2003 we have made enormous progress in the production of recombinant protein for the measurement of anti-idiotypic immune responses in the laboratory, as well as having established fully validated assays systems for the assessment of immune responses in patients after vaccination. We are in a position to extend the CLL programme and will consider this option once the current vaccine studies in patients with follicular lymphoma and multiple myeloma are completed and evaluated.

5.1.4 Multiple cancers

GTAC 062: First administration to man of an oncolytic herpesvirus vector containing a transgene for granulocyte macrophage colony stimulating factor (OncoVex$^{GM\text{-}CSF}$) – A study of its safety, biodistribution and biological activity.

In this trial, which evaluated safety, biodistribution and biological activity, OncoVEX$^{GM\text{-}CSF}$ was administered to 30 patients with stage IV solid tumours located in or just under the skin. The majority of patients were suffering from either adenocarcinoma of the breast, malignant melanoma or squamous cell carcinoma of the head and neck.

In Part 1 of the study, four patients received single doses of OncoVEX$^{GM\text{-}CSF}$ 10^6 pfu/mL, five patients received single doses of OncoVEX$^{GM\text{-}CSF}$ 10^7 pfu/mL and four patients received single doses of OncoVEX$^{GM\text{-}CSF}$ 10^8 pfu/mL. It turned out that, in the first two single dose groups (10^6 and 10^7 pfu/mL), the four patients who were seronegative to HSV1 at entry to the study all developed febrile influenza-like syndromes associated with malaise, rigors, erythematous skin rashes and, in some cases, transient small vesicles in the skin. Shedding of virus from some of the injected nodules also occurred. Patients were hospitalised while containment of

the virus was demonstrated. It was therefore concluded that seronegative patients should not be exposed initially to higher doses (10^8 pfu/mL) of OncoVEX^{GM-CSF}.

However, this part of the study did demonstrate that hGM-CSF could be detected in fine needle aspirations obtained 48 hours after injection, indicating biological activity of the virus. In addition, tumour necrosis was observed in some nodules after a single injection of OncoVEX^{GM-CSF}. Finally, OncoVEX^{GM-CSF} was found co-locating with areas of necrosis, thus demonstrating that such areas were the result of infection with the virus rather than due to other causes within the tumour.

In the highest dose group in Part 1 (10^8 pfu/mL), only seropositive patients were enrolled. A febrile response was observed in one patient, but rashes and rigors were absent.

In Part 2 of the study, three seronegative patients received a schedule of a single dose of 10^6 pfu/mL followed by two doses of 10^7 pfu/mL injected into a single nodule. Four seronegative patients received a single dose of 10^6 pfu/mL followed by two doses of 10^8 pfu/mL injected into a single nodule. This part of the study confirmed that both schedules were acceptably tolerated. Seroconversion occurred regularly within 2-3 weeks of the first injection. Importantly, the fine needle aspirations for the detection of hGM-CSF were abandoned. Following this, virus shedding from the tumour injection site was not detected.

Three seropositive patients received three injections of 10^8 pfu/mL injected into a single nodule. Finally, seven seropositive patients received a schedule of a single dose of 10^6 pfu/mL followed by two doses of 10^8 pfu/mL injected into a single nodule. Five of these patients completed dosing as planned, while two withdrew early. This schedule was well tolerated, confirming that it is an acceptable introductory schedule for Phase II clinical trials.

In common with many trials in late stage cancer patients, numerous adverse events were recorded, 16 of them being considered serious. Of these, nine were considered to be related to OncoVEX^{GM-CSF}. These included dyspnoea, skin reaction, pyrexia, injection site reaction and virus shedding, and diarrhoea. All of these resolved without sequelae, with the exception of the dyspnoea reported for one patient, which was ongoing at the time when she was withdrawn from the trial.

Injection site reactions ranged between CTC Grade 0 (no reaction) and Grade 3.

The results for the non-injected nodules showed that a number of patients experienced pain, inflammation and ulceration although OncoVEX^{GM-CSF} was not administered to these nodules. Prior to the first injection, four patients (13%) experienced pain, two patients (7%) experienced inflammation and one patient (3%) had an ulcerated nodule. Following OncoVEX^{GM-CSF} administration, six of the 30 patients (20%) experienced pain in a non-injected nodule, 10 (33%) experienced inflammation and five (17%) experienced mild ulceration of a non-injected nodule.

In this trial, there was no evidence of distant effects of OncoVEX^{GM-CSF} other than inflammatory responses in nearby nodules. This applied both to cutaneous nodules and CT scans. However, the brevity of the treatment schedule may account for this. Extensive data on immunological activation were not obtained. However, a variety of cytokines were detected in peripheral blood, although no characteristic pattern was observed.

In summary, 30 patients have been exposed to OncoVEX^{GM-CSF} in single and multidose treatment schedules. An introductory dosing schedule believed to be safe and tolerable has been developed for Phase II clinical trials. It has been shown that seroconversion occurs regularly two to three weeks after a single injection of 106 pfu/mL. Convincing local responses have been observed in injected nodules and the risk of virus shedding has been minimised. These data support the commencement of Phase II clinical trials.

5.2 CARDIOVASCULAR DISEASE

GTAC 051: A multinational multicenter, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of Ad5FGF-4 in patients with stable angina.

The study is closed to recruitment but is ongoing with the long term follow-up of participants according to the protocol. Patients are contacted by phone annually starting in November 2005 until November 2008. At each contact information about the health of each patient will be collected by the investigator. There are no final results available for publication at this time.

GTAC 36: The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD).

Arteriogenic Gene Therapy in Patients with unreconstructable Critical Limb Ischemia: A randomized, placebo-controlled clinical trial of Adenovirus 5 delivered FGF-4 (Manuscript accepted for publication).

Background: Critical limb ischemia is caused primarily by atherosclerosis that results in decreased blood flow to the lower limbs. Patients with this disease experience severe pain while walking. As the disease progresses these patients can develop pain while resting, leg ulcerations, and even gangrene necessitating amputation. One new approach for improving blood flow in patients with ischemic limbs is to stimulate the growth of blood vessels. The therapeutic approach used in this set of Phase I studies was to inject a gene known to regulate blood vessel growth into the leg muscles of patients in order to temporarily produce a vascular growth factor that would stimulate the growth of blood vessels and improve blood flow to the leg.

Objectives: The objective of the studies was to assess the safety and potential clinical efficacy of gene therapy in patients with critical limb ischemia after intramuscular injection of a vascular growth factor gene (fibroblast growth factor–4) that was packaged within a modified adenovirus vehicle.

Methods: This was a double-blinded, randomized, placebo-controlled examination with several dose groups. Thirteen patients with critical limb ischemia were randomized to either active drug (n=10) or placebo (n=3). Safety was evaluated and diagnostic measurements to assess the treatment's effectiveness were carrried out before the treatment and during the 12 weeks following the treatment.

Results: Gene therapy with fibroblast growth factor-4 was generally well tolerated and considered to be safe. The efficiency of the transfer of the packaged fibroblast growth factor–4 adenovirus to target cells may have been limited or local at the amounts injected. No firm conclusions about the effectiveness of the treatment could be drawn becuse of the small number of patients treated. However, diagnostics measurements showed a trend towards an increased number and slightly larger sized blood vessels.

Conclusions: Gene therapy of criticial limb ischemia patients with intramuscularly injected fibroblast growth factor–4 gene packaged into an adenovirus vehicle seemed safe but the gene transfer efficiency was limited at the doses assessed. No conclusions regarding clinical efficacy can drawn due to the small number of patients treated.

SECTION 6: ANNEXES

ANNEX A: GLOSSARY

Please see GTAC website:
http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm

ANNEX B: TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities – the Medicines and Healthcare products Regulatory Agency (MHRA), the Health and Safety Executive, and the Department for Environment Food and Rural Affairs (DEFRA);

(3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee has a responsibility for:

(a) Providing advice for applicants on:

  (i) The content of proposals, including the details of protocols, for gene therapy research on human subjects;

  (ii) The design and conduct of the research;

  (iii) The facilities necessary for the proper conduct of the research;

  (iv) The arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

  (i) The clinical status of the subjects;

  (ii) The scientific quality of the proposal;

  (iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;

  (iv) Whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable;

  (v) Sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);

  (vi) The potential benefits and risks for the subject of what is proposed.

ANNEX C: MEMBERSHIP OF GTAC

GTAC Members

- Professor Norman Nevin (Chairman),
  Emeritus Professor of Medical Genetics, Queen's University, Belfast.
- Dr Richard Ashcroft
  Medical Ethicist, Imperial College London
- Professor Andrew Baker (from December 2005)
  Professor of Molecular Medicine, University of Glasgow
- Mrs Deborah Beirne,
  Senior Research Nurse, St. James Hospital, Leeds
- Dr Caroline Benjamin (until December 2005),
  Macmillan Genetic Counsellor, Liverpool Women's Hospital NHS Trust
- Professor Mary Collins (from December 2005),
  Division of Infection and Immunity, Royal Free and University College Medical School
- Professor Martin Gore, vice Chairman
  Consultant Medical Oncologist, The Royal Marsden Hospital, London
- Professor Terence Hamblin,
  Consultant Haematologist, University of Southampton and
  Royal Bournemouth Hospital
- Dr Peter Harris,
  Development Director, KuDOS Pharmaceuticals Ltd.
- Professor David Harrison,
  Professor of Pathology and Medical Researcher, Department of Pathology,
  Edinburgh University
- Mr Michael Harrison, alternate vice Chairman
  arrister, London
- Professor Nicholas Lemoine,
  Professor of Molecular Pathology, Cancer Research UK Molecular Oncology Unit,
  Hammersmith Hospital, London
- Dr Adrian Lepper,
  Chartered engineer, Hertfordshire
- Professor Andrew Lever,
  Professor of Infectious Diseases, University of Cambridge

- Professor Alex Markham,
  Professor of Molecular Medicine, University of Leeds
- Professor James Neil (until December 2005)
  Professor of Virology and Molecular Oncology, University of Glasgow
- Right Reverend Dr Lee Rayfield,
  Bishop of Swindon and former immunologist
- Mrs Fiona Sandford
  Patient Advocate, Hertfordshire
- Dr Michael Waterhouse,
  Television Producer and Author, Southborough

Observers

Medicines and Healthcare products Regulatory Agency (MHRA):

- Dr Elizabeth Pollitt

Health and Safety Executive:

- Dr Paul Logan

Secretariat (Department of Health)

- Dr Monika Preuss
- Dr Jayne Spink (April to December 2005)
- Dr Cathleen Schulte (until April 2005)
- Ing. Daniel Gooch
- Miss Joanna Edwards (from November 2005)
- Mrs Margaret Straughan

ANNEX D: REGISTER OF MEMBERS INTERESTS

GTAC Member	Declared interests
Professor Norman Nevin	• None
Dr Richard Ashcroft	• None
Professor Andrew Baker	• None
Mrs Deborah Beirne	• Work involves gene therapy trials
Dr Caroline Benjamin	• Husband employed as Finance Manager for ConvaTec, Bristol Myers Squibb, UK Correct.
Professor Mary Collins	• None
Professor Martin Gore	• Companies who have paid honorariums, expenses and financial support of clinical trials and research include: Cobra Therapeutics Ltd., Genta Inc., ML Laboratoties PLC, Onyx. • Advisory Board of Onyx. • Advisor to Cambridge Antibody Technology
Professor Terence Hamblin	• Ad hoc consultant to Roche Pharmaceuticals.
Dr Peter Harris	• Employer: AstraZeneca
Professor David Harrison	• Shareholding The Forensic Institute. • Non Exec Chairman EMMS Nazareth – a healthcare charity. • Non Exec Director Emmanuel Healthcare – a healthcare charity.
Mr Michael Harrison	• Managing director of Bioethics Consulting Ltd. • Independent practising barrister working in the field, interests are declared as appropriate

Professor Nicholas Lemoine	• Consultant for IC-Vec and Medical Solutions Ltd. • Joint project funding for gene therapy agent with Cronos Therapeutics Limited from CR-UK Development Fund. • Principal investigator on trial with an agent from BioVex Limited.
Dr Adrian Lepper	• Secretary to the Board eLearning Holding company • Member of Corporation and Governor West Herts College • Independent consultancy assignments • Chair of Trustees – Care Co-ordination Network (UK) • Wife has a small shareholding in Glaxo Smith Kline.
Professor Andrew Lever	• None
Professor Alex Markham	• Chief Executive Officer, Cancer Research UK
Professor James Neil	• Ad hoc consultancy for Onwax Ltd
Bishop Dr Lee Rayfield	• None
Mrs Fiona Sandford	• Shares in Australian Mutual Provident
Dr Michael Waterhouse	• None

ANNEX E: EXTERNAL EXPERT ADVISERS TO GTAC

GTAC is extremely grateful to all its expert advisers for their support in the review of applications and for their input of expertise and advice in 2005. These included:

- Professor Andrew Baker, Division of Cardiovascular and Medical Sciences, Western Infirmary, University of Glasgow
- Professor David Beeson, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford
- Professor Finbarr Cotter, Department of Haematology, Barts and the London School of Medicine
- Dr Huw Davis, University of California at Irvine, Applied Immunology Laboratory, Centre for Virus Research
- Professor Farzin Farzaneh, Rayne Institute, King's College London
- Professor John Goldman, Hematology, NHLBI, NIH, US
- Professor Sir David Hall, Professor of community paediatrics, University of Sheffield
- Professor Barry Hancock, Cancer Research Centre, Weston Park Hospital
- Dr Phil Harrison, Department of Liver Studies and Transplantation, Division of Gene & Cell-Based Therapy Kings College London
- Dr Tim Helliwell, Department of Pathology, University of Liverpool
- Professor Ian Judson, Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research
- Dr Keith Leppard, Department of Biological Sciences, University of Warwick
- Professor Christopher Linington, Department of Medicine and Therapeutics, Institute of Medical Science, University of Aberdeen
- Dr Robert Marcus, Department of Haematology, Addenbrooke's Hospital, Cambridge
- Dr Amit Nathwani, Department of Haematology, University College London
- Dr Christian Ottensmeier, Cancer Research UK Oncology Unit, Southampton University Hospitals
- Dr Hardev Pandha, Department Medical Oncology, St George's Hospital Medical School
- Professor Maxine Partridge, Molecular Oncology, Maxillofacial Unit, Kings College Hospital
- Professor Neil Scolding, Institute of Clinical Neurosciences, Department of Neurology, University of Bristol
- Dr Peter Searle, University of Birmingham, CRC Institute for Cancer Studies

- Professor Peter Stern, Department of Molecular Biology, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester
- Professor Derrick Wade, Neurological Rehabilitation, Oxford Centre for Enablement
- Dr Dominic Wells, Gene targeting unit, Department of Cellular and Molecular Neuroscience, Imperial College London

ANNEX F: SUMMARY OF UK GENE THERAPY TRIALS 1993–2005

AN ANALYSIS OF UK CLINICAL GENE THERAPY: 1993 – 2005

Since 1993, when the first gene therapy study was conducted in the UK, GTAC has processed 126 applications to do clinical trials. Of these, 113 applications were approved (or conditionally approved) and five approved trials were subsequently withdrawn. The remaining 108 gene therapy trials, open and closed, are analysed below.

In these 108 trials, around 960 patients have been enrolled by December 2005 (894 patients by December 2004). The following three figures analyse the studies in terms of the year in which they were approved (Figure 1), the vector system used to deliver the therapeutic genes (Figure 2), and the disease (Figure 3). As shown in Figure 3, almost three quarters of all approved UK gene therapy trials, 78 in total, are for the treatment of cancers. Figure 4 breaks down this data in more detail.

Tables 1 and 2 show where UK gene therapy stands in relation to trials in Europe and worldwide, respectively (source: The Journal of Gene Medicine, March 2005).

Figure 1: GTAC approved trials (open and closed) by year (n = 108).

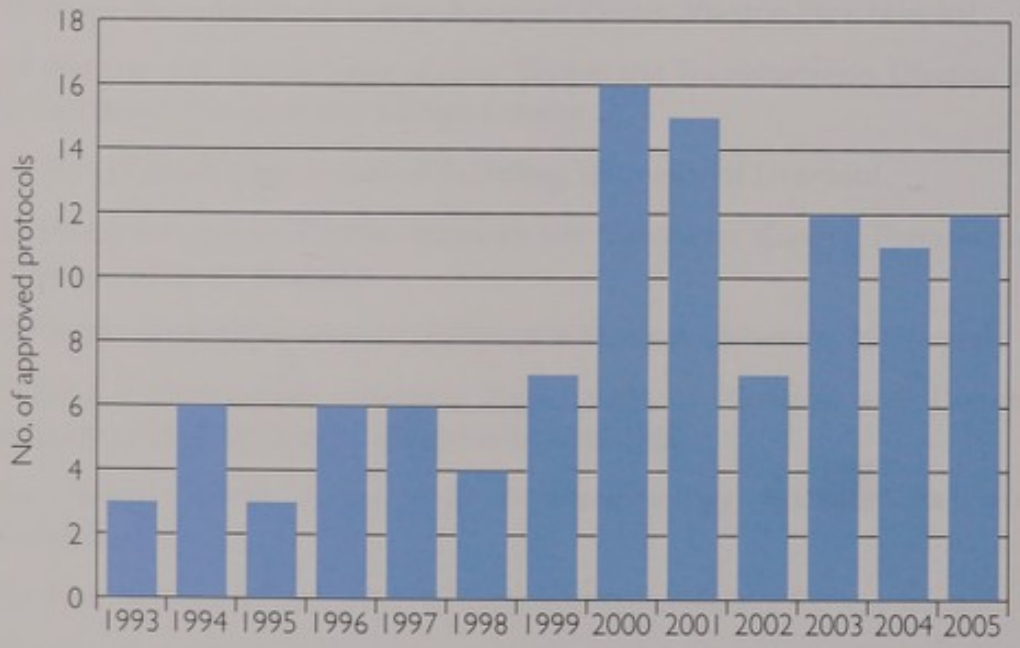

Figure 2: GTAC approved trials by vector system (n = 108).

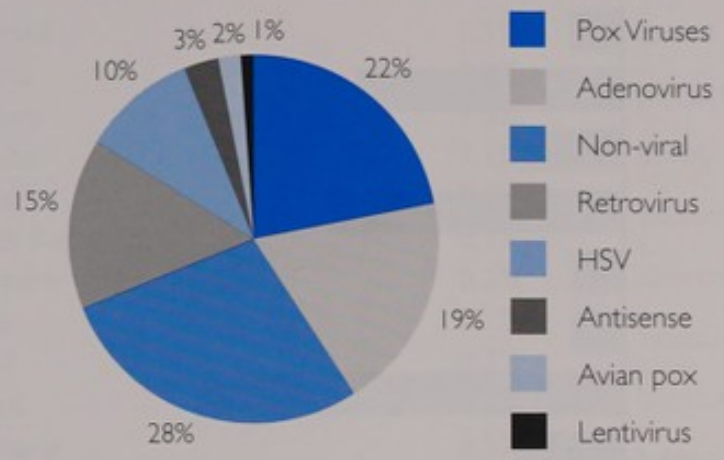

Figure 3: GTAC approved trials by disease (n = 108).

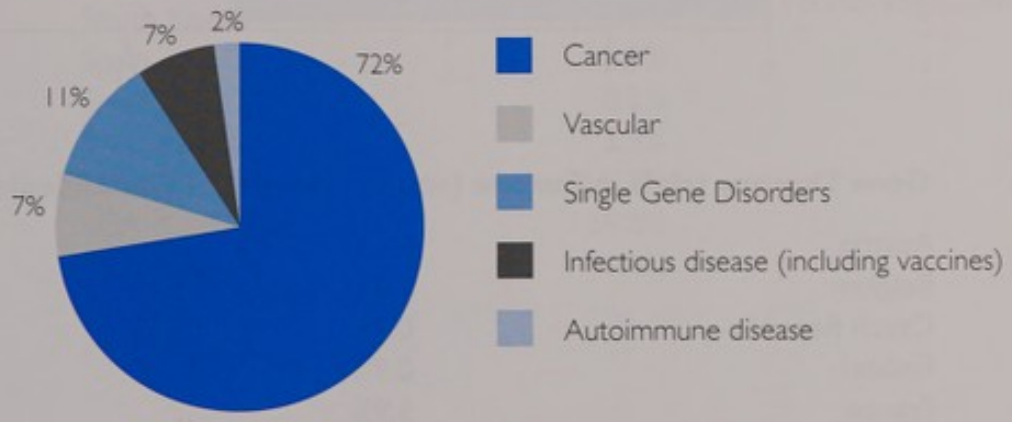

Figure 4: GTAC approved cancer trials (n = 78).

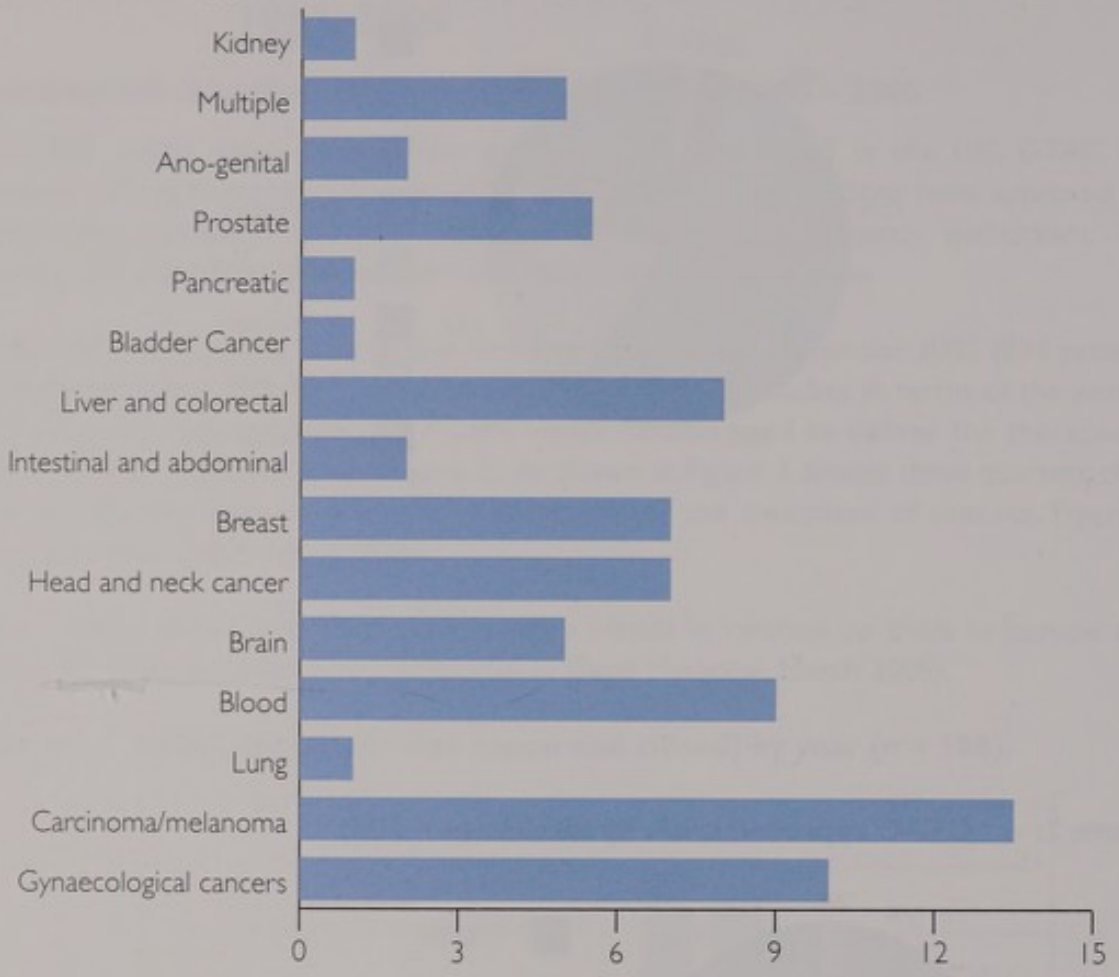

Table 1: Gene Therapy trials in Europe (source: Journal of Gene Medicine)

Austria	0.6%
Belgium	5.6%
Czech Republic	0.3%
Finland	0.9%
France	5.9%
Germany	22.8%
Italy	4.0%
Netherlands	2.2%
Norway	1.2%
Poland	0.9%
Spain	1.2%
Sweden	0.6%
Switzerland	12.3%
UK	**41.4%**

Table 2: Gene Therapy trials worldwide (source: Journal of Gene Medicine)

Australia	1.5%
Austria	0.2%
Belgium	1.6%
Canada	1.1%
China	0.3%
Czech Republic	0.1%
Denmark	0.2%
Egypt	0.1%
inland	0.3%
France	1.7%
Germany	6.5%
Israel	0.5%
Italy	1.1%
Japan	1.3%
Mexico	0.1%
Netherlands	0.6%
New Zealand	0.2%
Norway	0.3%
Poland	0.3%
Russia	0.1%
Singapore	0.2%
South Korea	0.3%
Spain	0.3%
Sweden	0.2%
Switzerland	3.5%
UK	**11.7%**
USA	64.8%
Multi-country	1.0%

LATEST UK GENE THERAPY RESEARCH 1993–2005 (JANUARY 2006)

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
01	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	SCID-ADA	Institute of Child Health/Great Ormond Street Hospital	1-93	Retrovirus	ADA	pOAM-P1	1 CLOSED
02	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Royal Brompton Hospital	3-93	Plasmid	CFTR	*E. coli* DM5α	15 CLOSED
03	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	MRC Cambridge	7-93	Plasmid	anti-idiotype immuno-globulin	*E. coli*	7 CLOSED
04	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	Neuroblastoma	ICRF Bristol	2-94	Retrovirus	LNL-6/neo G1N-neo	PA317	Trial withdrawn
05	Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	ICRF Oxford	5-94	plasmid	IL-2	*E. coli* JM109	23 CLOSED
06	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secrete IL-2	Metastatic melanoma	Institute of Cancer Research; Royal Marsden Hospital	2-94	Retrovirus	IL-2	GP+env AM12	12 CLOSED
07	Towards gene therapy for cystic fibrosis	CF Nasal trial	Oxford; Cambridge	2-94	Plasmid	CFTR	*E. coli*	18 CLOSED
08	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Edinburgh	5-94	Plasmid	CFTR	*E. coli*	16 CLOSED
09	Gene Therapy Research for Cystic Fibrosis	CF Lung trial	Royal Brompton Hospital	9-94	Plasmid	CFTR	*E. coli*	16 of 16 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
10	Transfer of the Human Multi-drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cell Transplantation for Malignant Lymphoma	Lymphoma	University College London Medical School	12-94	Retrovirus	MDR-1	AMI2M1	3 CLOSED
11	Genetic prodrug activation therapy for breast cancer	Breast Cancer	Hammersmith Hospital	10-95	plasmid	Cytosine deaminase	*E. coli*	12 CLOSED
12	Use of a recombinant vaccinia virus for therapy of cervical cancer	Cervical Carcinoma	University of Wales, Cardiff	6-95	Vaccinia	TA-HPV	MRC5	1+8 CLOSED
12A	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5-96	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
12B	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff; University of Manchester	8-97	Vaccinia	HPV E6 and E7	MRC5	8 CLOSED
12C	Use of recombinant Vaccinia vaccine (TA-HPV) to treat Vulval intraepithelial neoplasia III	Vulval Intraepithelial Neoplasia III	St Mary's Hospital, Manchester	1-00	Vaccinia	HPV E6 and E7	MRC5	18 CLOSED
12 D	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Ano-genital intraepithelial neoplasia III	Ano-genital intraepithelial neoplasia III	Addenbrooke's Hospital, Cambridge	4-00	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
13	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12-95	Retrovirus	pLX	GP+env AM12	3 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
14	Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoral Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(–) Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	1-96	Adenovirus	E1B deleted	HEK293	22 CLOSED
14A	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	7-97	Adenovirus	E1B deleted	HEK293	37 CLOSED
14 B	Phase I, Open-Label, Dose-Escalation Trial of Intraperitoneal Injection with an E1B Attenuated Adenovirus in patients with recurrent/refractory ovarian carcinomas	Recurrent/ refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2-97	Adenovirus	E1B deleted	HEK293	12 CLOSED
15	Towards gene therapy for Cystic Fibrosis	CF Nasal Trial	Oxford/Cambridge/ Leeds/Manchester Consortium	5-96	Plasmid	CFTR	*E. coli*	11 CLOSED
16	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Head and Neck Cancer	Institute of Cancer Research; Royal Marsden Hospital	9-96	Adenovirus	p53	HEK293	Trial never commenced in UK CLOSED
17	Gene therapy for Cystic Fibrosis Delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	Plasmid	CFTR # 67	*E. coli* TGI	16 CLOSED
18	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5–) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	12-96	HSV	ICP34.5 deleted	BHK 21/C13	9 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
18A	A Phase I dose-escalation study of intratumoral injection with modified HSV Type 1 (ICP 34.5–) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow; Institute of Neurological Sciences, Glasgow; Queen Elizabeth Hospital, Birmingham	7-99	HSV	ICP34.5 deleted	BHK 21/C13	12 CLOSED
18B	A study of the safety of the modified Herpes simplex virus (HSV 1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	11-00	HSV	ICP34.5 deleted	BHK 21/C13	8 CLOSED
19	GTI 0115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site).	Glioblastoma	Beatson Oncology Centre, Glasgow; Institute of Neurological Sciences, Glasgow	3-97	Retrovirus	TK	PA317	Trial withdrawn
20	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation	Gastrointestinal cancer, malignant cancer ascites	Royal Marsden Hospital, London	4-97	Adenovirus	P53	Hek293	1 CLOSED
21	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031)	Breast Cancer	Guy's Hospital, London	11-97	Vaccinia	MUC-1 IL2	–	14 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
22	A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of EIA-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu	Ovarian Cancer	The John Radcliffe Hospital, Oxford; Guy's and St Thomas's Cancer Centre, London; Royal Marsden Hospital, London; St George's Medical School, London	9-97	Plasmid	E1A HER2/neu	*E. coli* STBL2	22 CLOSED
23	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous)	Colorectal Cancer	Queen Elizabeth Hospital, Birmingham	3-98	Vaccinia	CEA	CV1	CLOSED with no patients recruited
24	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients	Ovarian Cancer	City Hospital NHS Trust and University Hospital NHS Trust Birmingham	3-98	Adenovirus	Nitroreductase	HEK-293	0 CLOSED
25	A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours	Head and Neck	Royal London Hospital; Charing Cross Hospital	Submission withdrawn	Plasmid	E1A	HEK293	Submission withdrawn
26	A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma	Malignant Melanoma	Glasgow Western Infirmary and Southern General Hospital, Glasgow	9-98	HSV	ICP34.5 deleted	BHK-21/C13	5 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
27	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral)	Breast Cancer	The Churchill Oxford	10-98	Retrovirus	Cytochrome P450	TEFLY-A	12 CLOSED
28	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours.	Liver Cancer	Hammersmith Hospital, London	Application Withdrawn	Adenovirus	p53	HEK293	Application withdrawn
29A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	Royal Bournemouth Hospital; Southampton General Hospital; Christie Hospital Manchester	5-99	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	25 of 25 Under review to extend numbers
29B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma "EDLI"	Multiple myeloma	Southampton General Hospital; Nottingham City Hospital; University College London	5-00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	3 of 15
29C	Phase I/II study of idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	Multiple myeloma	Royal Bournemouth Hospital; Southampton General Hospital; Nottingham City Hospital	4-00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	6 of 15 – 20
29D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT)	Chronic lymphocytic leukaemia	Royal Bournemouth Hospital; Southampton General Hospital	4-00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	2 of 10 CLOSED
30	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal).	Ovarian Cancer	Northern General Hospital, Sheffield	2-00	Retrovirus	Cytochrome P450	TEFLY-A	6 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
31	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoral)	Head and Neck Cancer	Queen Elizabeth Hospital, Birmingham; Royal Marsden Hospital, London	7-99	Adenovirus	Nitroreductase	PER-C6	7 of 30 CLOSED
32	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoral)	Liver Cancer	Queen Elizabeth Hospital, Birmingham	7-99	Adenovirus	Nitroreductase	Per-c6	25 of 30 CLOSED
33	Phase I trial of immunotherapy with adenovirus-interferon-Á in malignant melanoma (intratumoral)	Malignant Melanoma	St. George's Hospital	7-99	Adenovirus	IFN-Á	–	1 CLOSED
34	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	Ovarian Cancer	Royal Marsden Hospital, Christie Hospital/CRC Institute for Cancer Studies, John Radcliffe Hospital	7-99	Adenovirus	p53	HEK293	1 CLOSED
35	Phase II trial of pre-operative intratumoral injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	7-99	Adenovirus	E1B deleted	HEK293	15 CLOSED
36	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD)	Peripheral Arterial Occlusive Disease	St George's Hospital, London	10-00	Adenovirus	FGF-4	PER-C6	4 of 30 CLOSED
37	A Phase III study of quadruple HAART followed by double-blind randomisation to HIV vaccination with ALVAC-HIV and Remune or placebo	HIV	Chelsea & Westminster Hospital, Royal Free Hospital, Brighton General Hospital, University Hospital of Wales Cardiff	5-00	Canarypox	HIV-1 env, gag	AVIAN	8 of 15 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
38	A Phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with metastatic melanoma	Malignant melanoma	Churchill Hospital, Oxford Royal Marsden Hospital, London	5-00	HSV	hGMCSF	CR2C9 (Vero-derived)	10 CLOSED
39	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of TroVax in patients with metastatic colorectal cancer (Phase I i.m.)	Colorectal cancer	Christie Hospital NHS Trust, Manchester	10-00	Vaccinia	Human oncofoetal antigen 5T4	CEF	22 of 22 CLOSED
40	A Phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	Bladder cancer	St James's University Hospital, Leeds	Conditional Approval 7-00	Adenovirus	E1B deleted	HEK293	Trial not yet open for recruitment
41	Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (Phase II i.m.)	Breast cancer	Guy's Hospital, London	Application withdrawn	Vaccinia	MUC-1, IL-2	CEF	Application withdrawn
42	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	Melanoma	The Churchill Hospital, Oxford	7-00	Vaccinia DNA	Mel3 (melanoma antigens)	CEF	5 of 20
43	A phase I/II trial of polyHER2neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Breast cancer	St James's University Hospital, Leeds	Application Declined	Plasmid	HER-2 epitopes	*E. coli*	Application Declined
44	Treatment of leukaemic relapse after allogenic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions	Chronic myeloid leukaemia	Hammersmith Hospital, London	10-00	Retrovirus	HSV -tk	AM12	0 of 10-20

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
45	Phase I clinical gene therapy protocol for X-SCID	X-SCID	Institute of Child Health, London	01-01	Retrovirus	Common gamma chain	PG13	7 of 20
46	Phase I gene therapy protocol for X-CGD	X-CGD	Institute of Child Health, London; Royal Free Hospital, London	12-00	Retrovirus	Gp91-phox	HEK293	3 of 5
47	A phase I, Randomised, Double-blind, Placebo Controlled, Escalating Dose, Multicentre Study of Ad2/Hypoxia Inducible Factor Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting Surgery in Patients with Incomplete Revascularisation	Coronary artery disease	John Radcliffe Hospital, Oxford; King's College Hospital, London	12-00	Adenovirus	HIF-1a/VP16	HEK293	9 of 12
48	A randomised phase I trial of intravenous CI-1042 with or without entanercept in patients with metastatic carcinoma	Metastatic carcinoma	Hammersmith Hospital, London	12-00	Adenovirus	p53	HEK293	Application withdrawn
49	A phase I/II Study of Immunotherapy for Patients with Metastatic Melanoma Using Dendritic Cells Transfected with a Plasmid Encoding Two Melanoma Antigens	Metastatic Melanoma	CRC Institute for Cancer Studies, Birmingham	02-01	Plasmid complexed with peptide	MART-1 gp-100	*E. coli*	Trial never opened CLOSED
50	A Phase II Trial of Preoperative intratumoural Injection with HSV1716 in Patients with Resectable Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Southern General Hospital, Glasgow	05-01	HSV	ICP34.5 deleted	BHK-21/C13	20 of 20 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
51	A multinational multicenter, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of Ad5FGF-4 in patients with stable angina	Coronary Artery Disease	Papworth Hospital NHS Trust; Royal Sussex County Hospital; Royal Infirmary of Edinburgh; Hammersmith Hospital, London; King's College Hospital, London; Royal Free Hospital, London; St Thomas' Hospital, London; The London Chest Hospital; Wythenshawe Hospital, Manchester; Nottingham City Hospital; University Hospital Wales, Cardiff; Queen Elizabeth Hospital, Birmingham (to be confirmed)	05-01	Adenovirus	FGF-4	HEK293	17 of 60 in UK 116 of 450 world-wide CLOSED
52	A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	Hepatitis B Vaccine Trial	TNO BIBRA International, Surrey; University of Oxford; Central Middlesex Hospital	08-01	Vaccinia & plasmid	HBsAg	MVA: Chicken embryo fibroblasts; Plasmid in *E. coli*	18 of 18 CLOSED
53	A pilot study of the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV-1-seropositive subjects receiving highly active anti-retroviral therapy	AIDS	John Radcliffe Hospital, Oxford	05-01	Plasmid	HIV-1 clade A *gag* and 25 HIV-1 *gag, pol, env, nef* CTL epitopes	1 DH1	10 of 10 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
54	A Phase II, Randomised, double-blind, Placebo-controlled, Parallel Group, Efficacy and Safety Study of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease	Peripheral Artery Occlusive Disease	St. George's Hospital, London; Royal Bournemouth Hospital; Leicester Royal Infirmary; Wythenshawe Hospital, Manchester; Freeman Hospital, Newcastle; Royal Free Hospital, London; Bristol Royal Infirmary (CLOSED); Leeds General Infirmary; Southampton General Hospital	08-01	Plasmid	FGF-1	1XAC-1	11 CLOSED
55	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoral)	Prostate Cancer	Queen Elizabeth Hospital, Birmingham; Freeman Hospital Newcastle; St James's University Hospital, Leeds	04-01	Adenovirus	Nitro reductase	PER-C6	32 of 44 CLOSED
56	A Phase II, Multicentre, double-blinded, Placebo-Controlled, Dose-Finding Study of ZYC101a in the Treatment of high-grade Squamous Intra-Epithelial Lesions of the Uterine Cervix	Ano-genital Neoplasia III	Hammersmith Hospital, London	11-01	Plasmid	HPV E6 & E7	*E. coli*	0 of 5 CLOSED
57	A Phase I, Multidose Study to Evaluate the Safety of Intramuscular Injections of HER-2 DNA in Patients with Metastatic Breast Cancer	Breast Cancer	Hammersmith Hospital, London	11-01	Plasmid	HER-2	*E. coli*	27 of 27 CLOSED
58	The Use of a cDNA Vaccine Encoding the Human MUC1 Gene in the Treatment of Patients with Advanced Breast Cancer – A Phase I/II Study	Breast Cancer	ICRF, Guy's Hospital, London	08-01	Plasmid	MUC-1	*E. coli*	6 of 12-28

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
59	A phase IIa, open label trial to assess the safety, immunogenicity and efficacy of a prime-boost strategy of TA-CIN administered in associated with TA-HPV to patients with high grade ano-genital intraepithelial neoplasia (AGIN)	Cervical Cancer	University of Wales, Cardiff; St. Mary's Manchester; Addenbrooke's, Cambridge	07-01	Vaccinia	E6 & E7 HPV	MR-5	29 CLOSED
60	Study of Transfection Efficacy and Safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast Cancer	Churchill Hospital, Oxford; Queen Elizabeth Hospital, Birmingham	07-01	Retrovirus	P450	TEFLYRD	8 of 8 CLOSED
61	An upward titration study of transfection efficacy and safety of Metxia-OB83 in patients with adenocarcinoma of the prostate	Prostate Cancer	The Churchill Hospital, Oxford	08-01	Retrovirus	P450	TEFLYRD	CLOSED
62	First Administration to Man of an Oncolytic Herpesvirus Vector Containing a Transgene for Granulocyte Macrophage Colony Stimulating Factor (OncoVexGM-CSF) – A Study of its Safety, Biodistribution and Biological Activity	Melanoma, Breast, Head & Neck, cancer, Non-Hodgkins Lymphoma	ammersmith Hospital, London; St George's Hospital, London; CR-UK Institute for Cancer Studies, University of Birmingham	11-01	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	30 CLOSED
63	VTP-1/01: A Phase I/II Trial of Intravenous vs. Hepatic Arterial Infusion of an E1A-CR2 Deleted Adenovirus (VTP-1) in Patients with Inoperable, Metastatic Colorectal Carcinoma	Metastatic colorectal carcinoma	Hammersmith Hospital, London	Application withdrawn	E1A conserved region 2 deleted & E3B RID gene region deleted	N/a	HEK-293	Application withdrawn
64	A Phase I trial of replication-competent herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma	Malignant pleural mesothelioma	University of Glasgow, Beatson Oncology Centre, Glasgow	02-02	HSV HSV1716	ICP34.5 deleted	BHK-21/C13	0 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
65	A Phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients	Melanoma	St James Hospital, Leeds	01-02	Plasmid DNA (polyMEL)	Multiple melanoma epitopes	*E. coli*	4 of 12
66	A recombinant vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr Virus target antigens: phase I dose escalation trial to determine immunogenicity and toxicity in patients with EBV+ malignancy. EuraCT: 2004-001931-46	Naso-Pharyngeal carcinoma	Institute of Cancer Studies, Birmingham; Royal Marsden Hospital, London	02-02	DNA plus MVA	EBV epitopes (EBNA1 and LMP2A)	CEF	2 of 15
67	Percutaneous Intramyocardial Gene Therapy against myocardial ischaemia with phVEGF-A165SR – A double-blind placebo controlled study	Coronary Artery Disease	Wythenshawe Hospital, Manchester	Application Pending	plasmid	VEGF	*E. coli*	Application withdrawn
68	A Phase I trial of polyHER2neu – a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer	Breast Cancer	St James Hospital, Leeds	01-02	Plasmid DNA	Poly epitopes of HER-2	*E. coli*	0 of 12 Trial not yet open
69	A phase I/II study of vaccination with a DNA fusion gene containing an epitope of CMV in allograft donors and patients awaiting renal transplantation	CMV infection following transplant	Southampton General Hospital; Royal Free Hospital London; University College London Hospital	02-02	Plasmid DNA (pcDNA3)	Peptide from pp65 from CMV	*E. coli*	4 of 15 pairs (8 patients)
70	NUMBER NOT ALLOCATED							

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
71	A Phase I/II prospective study of immunogene therapy with a liposomally encapsulated replication incompetent Semliki Forest Virus (SFV) vector carrying the human interleukin-12 gene and administered intratumorally in patients with recurrent or progressing glioblastoma multiforme	Glioma	University of Liverpool	Application withdrawn	Replication disabled Semliki Forest Virus, liposome encapsulated	Human IL-2	Baby hamster kidney (BHK)	Trial withdrawn
72	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine, involving pSG2.Mel3 and MVA.Mel3, in patients with Stage III or Stage IV metastatic melanoma	Metastatic melanoma	Christie Hospital, Manchester; Churchill Hospital Oxford; Western General, Edinburgh; Southampton General Hospital	09-02	DNA and MVA	Multiple melanoma epitopes	CEF	41 of 41 Closed to recruitment
73	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	Severe Combined Immunodeficiency	Great Ormond Street Hospital, London	12-02	Retrovirus (spleen focus forming virus)	Adenosine Deaminase	PG13	1 of 5
74	A Randomised Efficacy Trial of Herpes Simplex Virus HSV1716 in Recurrent Glioblastoma Multiforme (EudraCT: 2004-000097-32)	Glioblastoma multiforme	Queen Elizabeth Hospital, Birmingham; Southern General Hospital, Glasgow; Royal Hallamshire Hospital, Sheffield; Derriford Hospital, Plymouth; and Hurstwood Park Neurological Centre, Haywards Health	07-04	HSV	ICP34.5 deleted	BHK21.c13	0 of 100 Trial due to open in February 2006
75	A Phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01)	HIV-1	Imperial College London	02-03	MVA	HIV-1 Clade C *gag, pol, nef, env,* (NYVAC C)	Chick Embryo Fibroblasts	12 of 12 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
76	A phase I/II study of DNA vaccination with a CEA/pDOM fusion gene in patients with carcinoma expressing CEA	Carcinoma	Southampton General Hospital	02-03	Plasmid DNA (pcDNA3)	CAP-1 peptide from CEA	*E. coli*	0 of 30
77	Gene therapy protocol for the evaluation of the safety and efficacy of TroVax in conjunction with chemotherapy in patients with metastatic colorectal cancer	Metastatic colorectal cancer	Christie Hospital Manchester; Queen Elizabeth Hospital, Birmingham	02-03	MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Fibroblasts	19 of 19 CLOSED to recruitment
78	A phase I clinical gene therapy trial for X-SCID using umbilical cord blood	X-SCID	Institute of Child Health, London	02-03	Retrovirus (Moloney murine leukaemia virus)	Common gamma chain	PG13	0 of 10
79	A pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA delivered to HIV-1 sero-positive adults receiving HAART	HIV-1	MRC Human Immunology Unit, John Radcliffe Hospital, Oxford	07-03	MVA	HIV-1 clade A *gag, pol, nef* and *env*	CEF	10 of 20 Closed to new recruitment
80	Phase I/II study – first administration of Dendritic cells transduced with ImmunoVEXTRI-Melan to patients with metastatic or inoperable melanoma	metastatic or inoperable melanoma	St George's Hospital Medical School, London	Application declined	HSV	hTyrosinase, hMART1, hGP100	Vero *(MEVP16/M4 F6A)*	Application declined
81	An open label study of TroVax given in conjunction with 5-Fluorouracil/ Leukovorin/Oxaliplatin: safety and immunogenicity before, during and after chemotherapy (TV2)	Colorectal cancer	University of Leeds School of Medicine; Hammersmith Hospital, London	05-03	MVA	Human oncofoetal antigen 5T4	CEF	17 of 17 CLOSED to recruitment

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
82	A phase II trial to evaluate efficacy and safety of intramuscular injections of HER-2 DNA Autovac™ in patients with metastatic or locally advanced breast cancer	Breast cancer	Hammersmith Hospital	07-03	Plasmid	HER-2 with T cell epitopes P2 and P30 derived from tetanus toxin	*E. coli*	Trial withdrawn
83	A Phase I/II safety study of MetXia-OB83 in patients with pancreatic cancer	Pancreatic cancer	Royal Liverpool University Hospital; Christie Hospital, Manchester; Hammersmith Hospitals, London	10-03	Retrovirus (Moloney murine leukaemia virus)	cytochrome P450	FLY RD83	14 of 27
84	A Phase I study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	Malignant melanoma	CRUK, Birmingham	07-03	Plasmid DNA	MART-1 and gp-100	*E. coli*	9 of 10
85	A phase I trial to assess the safety of DNA C, and the safety and immunogenicity of DNA C followed by NYVAC C in an open, randomised comparison to NYVAC C alone in healthy volunteers at low risk of HIV infection (EV02) (EudraCT: 2004-001802-28)	HIV-1	Imperial College London, St's Mary's Hospital	10-03	Plasmid pORT1 And MVA	HIV-1 clade C *gag, pol, nef, env*	*E. coli*	0 of 20 Trial due to open in early 2005
86	First administration of dendritic cells transduced with ImmunoVEX$^{Tri\text{-}Melan}$ to patients with metastatic or inoperable melanoma, preliminary assessment of safety, biodistribution and indicators of efficacy	metastatic or inoperable melanoma	University of Surrey, Guildford; Southampton General Hospital; Sites in Canada	10-03	HSV	hTyrosinase, hMART1, hGP100	Vero (MEVP16/ M4 F6A)	6 UK patients, 14 patients in Canada (total number of 60)

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
87	A Phase II Study Immunologically Evaluating 5T4-MVA (TroVax) in Patients undergoing Surgical Resection of Colorectal Liver Metastases	Metastatic colorectal cancer	Christie Research Centre, Manchester; North Manchester General Hospital	01-04	MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Fibroblasts	20 of 20 Closed for recruitment
88	A Cancer Research UK Phase I Trial of AEG35156/GEM640 (XIAP antisense) administered as a 7 day continuous intravenous infusion in patients with advanced tumours	Advanced tumours	Christie Hospital NHS Trust, Edinburgh Royal Infirmary	12-03	N/a	Antisense DNA to human X-linked inhibitor of apoptosis	N/a	11 of 18-46
89	A Phase I/II Trial of a DNA vaccine with a PSMA27/ pDom fusion gene given by intramuscular injection in HLA A2+ patients with prostate carcinomas with or without electroporation	Prostate cancer	Southampton General Hospital; Royal Marsden Hospital, London	02-04	DNA with and without electro-poration	1st domain of Tetanus toxin fragment C, 9 amino acid peptide from PSMA	*E. coli*	8 of 30
90	A Controlled, Randomised, Parallel Group, Multicentre Study of the Efficacy and Safety of Herpes Simplex Virus-Thymidine Kinase Gene Therapy (Cerepro™), with Subsequent Ganciclovir, for the Treatment of Patients with Operable High Grade Glioma	Operable primary or recurrent high grade glioma	Walton Centre for Neurology and Neurosurgery, Liverpool (withdrawn); Western General Hospital, Edinburgh; Addenbrooks Hospital, Cambridge; Queen's Medical Centre, Nottingham; Hope Hospital, Salford	04-04	Adenovirus type 5, E1 and E3 deleted	Herpes simplex virus-thymidine kinase gene (HSV-tk)	HEK293	Target: 250 world-wide 0 of 50 patients in UK
91	Double-blind, randomised, placebo-controlled, parallel group and dose-finding, multicentric, safety and efficacy study with intramuscular injections of NV1FGF in subjects with intermittent claudication	Peripheral artery occlusive disease in patients with intermittent claudication	Royal Bournemouth Hospital; Freeman Hospital Newcastle; Gloucestershire Royal Hospital	03-04	Plasmid	FGF-1	*E coli* XAC-1	0 patients in UK, 118 subjects world-wide. The trial is closed for recruitment

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
92	A 2 x 2 Factorial Randomised Phase II Trial Assessing Anti-CEA, Anti-MUC-1 Vaccination +/– Chemotherapy +/– GM-CSF after Surgery in Patients with Stage II Colorectal Cancer (EudraCT: 2004-001734-16)	Colorectal Cancer	Churchill Hospital, Oxford	06-04	Vaccinia and fowlpox virus	carcinoembryonic antigen, Mucin-1, B7-1, ICAM-1 and LFA-3		0 of 40
93	An open, randomised, parallel group study to evaluate the safety, tolerability and immunogenicity of the GW825780 DNA immunotherapeutic when delivered using the PowderJect ND5.5 device to healthy adult volunteer subjects (EudraCT: 2004-000251-41)	HIV	Addenbrooke's Hospital Cambridge; Chiltern International, Slough	06-04	Plasmid on gold particles	Reverse transcriptase, nef, gag of HIV-1	*E. coli* DH1	37 Closed to recruitment
94	A Phase II exploratory study of the efficacy and safety of OncoVEX GM-CSF in combination with Arimidex in the neoadjuvant treatment of breast cancer in post menopausal women with oestrogen receptor positive tumours (EudraCT: 2004 –01938-16)	Breast Cancer	Hammersmith Hospitals NHS Trust	Application declined	HSV	CP34.5-deleted IICP47-deleted Human GM-CSF	BHK 21c13	– of 20
95	Safety and immunology evaluation of TroVax produced by the Baxter synthetic route in patients with stage IV colorectal cancer (EudraCT: 2004-002251-13)	Colorectal cancer	Christie Research Centre, Manchester; University of Leeds School of Medicine	11/04	MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Cells	Trial withdrawn
96	A Phase I Study of Adoptive Transfer of Autologous Tumour Antigen-Specific T Cells with Pre-conditioning Chemotherapy and Intravenous IL2 in Patients with Advanced CEA Positive Tumours. EudraCT: 2005-004085-16	CEA positive malignancies	Christie Research Centre, Manchester	11-04	Retrovirus	MFE23 specific for carcinoembryonic antigen; CD3ζ	Murine PG13	0 – 15

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
97	A multicenter, randomised, double-blind, placebo-controlled study evaluating the efficacy of BIOBYPASS (ADGVVEGF121.10NH) delivered by NOGATM -Guided/myostar catheter in no option patients with class II-IV stable angina EudraCT: 2004-001250-91	Stable angina	King's College Hospital, Southampton University Hospital	11-04	Adenovirus type 5	VEGF	human embryonic retinoblasts (PER.C6)	6 of 129
98	A pilot study of lentivirus transduced acute myeloid leukaemia (AML) blasts expressing B7.1 (CD80) and IL-2, for the induction of graft verses leukaemia (GVL) effect in poor prognosis, relapsed AML	Acute myeloid leukaemia	King's College London	11-04	Lentivirus (HIV-1)	CD80 (B7.1) and IL-2	human embryonic kidney 293T	– of 10
99	A Phase 2, Randomized, Double-blind, Placebo controlled, Parallel-group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor HIF-1·/VP16 in Patients with Intermittent Claudication EudraCT: 2004-002508-13	Peripheral artery disease: Intermittent Claudication	Ninewells Hospital, Dundee; St George's Hospital and Medical School; Freeman Hospital, Newcastle; Belfast City Hospital	11-04	Adenovirus (E1 and E4 deleted)	HIF-1α (Hypoxia-Inducible Factor-1)	human 293 cells	– of 75
100	A phase II study of NY-ESO-1 ISCOMATRIX® vaccine followed by recombinant fowlpox NY-ESO-1 (rF-NY-ESO-1) or NY-ESO-1 ISCOMATRIX® vaccine alone in patients with high risk resected NY-ESO-1 positive melanoma and prostate cancer EudraCT: 2004-004991-36	Melanoma or prostate carcinoma	Churchill Hospital, Oxford	Conditional approval, 03-05; Approval 05-05	Recombinant fowlpox virus	NY-ESO-1 tumour specific antigen	Chicken embryo dermal (CED) cells	– of 40

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
101	An Ascending Dose Trial of the Safety, Tolerability and Biological Effect of intra-arterial Injection of the Selectively Replication-Competent Herpes Simplex Virus HSV1716 in Patients with Unresectable Hepatocellular Carcinoma EudraCT: 2005-000133-38	Hepatocellular Carcinoma	Royal Infirmary of Edinburgh	Declined	HSV1716	HSV deleted in both copies of RL1 gene	BHK21.c13	Declined
102	A Phase I Trial of Intra-Peritoneal Ad-hTR-NTR and CB 1954, an Adenovirus-Delivered Telomerase-Directed Enzyme-Prodrug Therapy, in Patients with Advanced Intra-Abdominal Cancer EudraCT: 2005-003294-24	Intra-Abdominal Cancer	Cancer Research UK Beatson Laboratories, Glasgow; Radcliffe Infirmary, Oxford	Conditional approval, 04-05	Adenovirus (E1/E3 deleted)	Bacterial nitroreductase gene	Human 293 cells	– of 8-12
103	A Phase I Study of Adoptive Transfer of Autologous Tumour Antigen-Specific T Cells with Pre-conditioning Chemotherapy and Intravenous IL2 in Patients with CD19 Positive Malignancy	CD19 positive cancer	Christie Research Center, Manchester	06-05	Retrovirus	Chimeric Immune Receptor CD19-z cDNA	Murine PG13	– of 22
104	Safety, Immunology And Efficacy Evaluation Of Trovax In Patients With Stage IV Clear Cell Renal Carcinoma (TV2) EudraCT: 2005-000088-24	Renal carcinoma	Christie Research Centre, Manchester; Institute for cancer studies, Birmingham	Conditional approval, 04-05	Attenuated vaccinia virus vector MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Cells (CECs)	0 of 10
105	An exploratory study of the safety and biological activity of OncoVexGM-CSF in combination with radiotherapy and cisplatin in the treatment of locally advance epithelial cancer of the head and neck EudraCT: 2005-000777-21	Head and Neck cancer	Royal Marsden Hospital, London	Conditional approval, 04-05; Approval 08-05	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	1 of 20

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
106	Phase I/II clinical trial of T cell suicide gene therapy following allogeneic haematopoietic stem cell transplantation EudraCT: 2005-001925-27	To prevent GvHD in children and adults undergoing DLI after bone marrow transplant	Great Ormond Street Hospital NHS Trust; Royal Free Hospital, London	Declined	Retrovirus	HSV-TK (herpes simplex thymidine kinase – splice corrected version)	PG13	Declined
107	A multicenter, randomized, double blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of BHT-3009 when administered intramuscularly to patients with relapsing remitting multiple sclerosis (Protocol No. BHT-3009-03) EudraCT: 2005-001340-22	Multiple Sclerosis	Guy's, kings and St Thomas' School of Medicine; Walton Neurology Centre, Liverpool; Royal Hallamshire Hospital, Sheffield; Essex Neuroscience Centre, Oldchurch Hospital, Romford; Royal Victoria Infirmary, Newcastle; Queens Medical Centre, Nottingham	06-05	Plasmid DNA	human myelin basic protein (hMBP)	*E. coli*	250 worldwide
108	An open-labelled, international, multicenter, dose escalating, phase I/II Study of SPC2996, an LNA antisense molecule against Bcl-2, in patients with relapsed or refractory Chronic Lymphocytic Leukaemia EudraCT: 2004-004741-17	Chronic lymphocytic leukaemia	Christie Hospital NHS Trust, Manchester; Royal Marsden Hospital, London; Barts and the London, London; Leeds General Infirmary; Leicester University Hospital	Conditional approval 06-05; Approval 08-05	n/a	Antisense DNA binding to mRNA of Bcl-2	n/a	– of 42
109	A phase I, dose-escalating trial of JX-594 (thymidine kinase-deleted vaccinia virus encoding GM-CSF) administered by intravenous infusion in patients with refractory solid tumours EudraCT: 2005-002015-25	Solid tumours	Radcliffe Infirmary, Oxford	06-05	Replication-selective oncolytic vaccinia virus (TK depleted)	GM-CSF	Vero cells	0 of 20-30 Trial not yet open

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
110	A Single Arm Open-Label Phase I study of an injectable replication-incompetent adenoviral vector encoding a factor VII immunoconjugate to induce a cytolytic immune response against the vasculature of carcinoma of the bowel with metastatic lesions to the liver	Liver and colorectal cancer	Hammersmith Hopsital, London	Declined	Adenovirus	Factor VII		Declined
111	A Phase II Double Blind, Cross?Over Study to Compare the Safety and Efficacy of 125, 250 and 500 ug/kg Monarsen (EN101) administered to Patients with Myasthenia Gravis. EudraCT: 2005-002740-26	Myasthenia Gravis	Hope Hospital, Salford	09/05	N/a	antisense oligodeoxynucl eotide against Acetylcholinest erase	N/a	– 18
112	A Phase III Randomized, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane-Naïve Patients with Metastatic Hormone-Refractory Prostate Cancer With Pain EudraCT: 2005-003275-20	Prostate cancer	Royal Marsden Hospital London; Institute of Cancer Research and Royal Marsden NHS Trust, Sutton	09/05	AAV	Granulocyte macrophage colony stimulating factor (hgGM-CSF	human kidney cells	– of approx 60 (600 worldwide)

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
113	A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer who are Chemotherapy-Naïve. EuraCT: 2005-002738-36	Prostate cancer	Beatson Oncology Centre, Glasgow; Freeman Hospital, Newcastle; St James' University Hospital, Leeds; Hammersmith Hospital London; Churchill Hospital, Oxford; Belfast City Hospital; Addenbook's Hospital, Cambridge; Royal Hallamshire Hospital, Sheffield; Mount Vernon Hospital, Northwood; Nottingham City Hospital	09/05	AAV	Granulocyte macrophage colony stimulating factor (hgGM-CSF)	human kidney cells	– of approx 60 (600 worldwide)
114	A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-/VP16 Administered by Intramuscular Injection to Patients with No or Poor Option Chronic Critical Limb Ischemia EudraCT: 2005-004068-21	Critical Limb Ischemia	Ninewells Hospital, Dundee	12/05	Adenovirus (E1 and E4 deleted)	HIF-1α (Hypoxia-Inducible Factor-1)	human 293 cells	– of 90

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